National Report on Medicines use in Italy

Year 2022

THE MEDICINES UTILISATION MONITORING CENTRE

AIFA
ITALIAN MEDICINES AGENCY

National Report on Medicines use in Italy Year 2022

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Summary

This Report provides an analytical description of the use of medicines, in the national and regional context, during 2022, through the elaboration of various information flows that allow to obtain a comprehensive picture of pharmaceutical care in the local and hospital settings, both borne by the National Health Service (SSN) and through private purchases by the citizen.

OsMed flows have been used for analysing consumption under the approved care regime, whereas the medicine traceability flows have been used to analyse the consumption of medicines purchased by health facilities.

In addition, for analysing prescriptions by age and gender and exposure and for estimating adherence and persistence, data from all Italian Regions, collected through the information flow of pharmaceutical prescriptions reimbursed by the NHS (Tessera Sanitaria) have been analysed.

For assessing purchases by citizens, data collected through the Medicine Traceability flow for medicinal products delivered to public and private local pharmacies have been used.

Finally, regional flows were used to analyse expenditure and consumption of medicines delivered through direct distribution and distribution in name and "on behalf".

SECTION 1 - General characteristics of medicines use in Italy

In 2022 the **overall national pharmaceutical expenditure** (public and private) amounted to 34.1 billion euros, increasing by 6.0% compared to 2021. It represents an important component of the national health expenditure accounting for 1.8% of gross domestic product (GDP). **Public pharmaceutical expenditure**, worth 23.5 billion euros, accounts for 68.9% of total pharmaceutical expenditure and 17.9% of public health expenditure, increasing compared to 2021 (+5.5%) (**Table 1.1.1**).

In 2022 the **overall local pharmaceutical expenditure**, both public and private, amounted to 22.5 billion euros, increasing by 6.5% over the previous year.

Public local expenditure, including expenditure on Class A medicines provided under approved care regime and direct and "on behalf" distribution, was equal to 12.5 billion

euros, recording an increasing trend (+ 5.7 %), mainly driven by the increase in the expenditure of Class A medicines supplied in direct distribution (+ 15.4 %) and Class A medicines supplied through distribution "on behalf"(+ 11.5 %; **Table 1.2.1**).

The **citizen pharmaceutical expenditure**, including cost-sharing (regional tickets and difference between the price of off-patent medicine and reference price), the private purchase of class A medicines and expenditure for class C medicines, totalled 9.9 billion euros, increasing by 7.6% compared to 2021. This trend was influenced by the increase in private expenditure on Class A medicines (+ 16.1 %), the increase in expenditure on self-medication medicines (+ 13.9 %) and those dispensed in stores (+ 13.7 %).

In 2022, **18 packages** per citizen and **1140.6 doses** per 1,000 inhabitants were consumed every day under approved care regime (+0,9% compared to 2021; **Table 1.2.2**).

Within local care, both public and private, **about 1.9 billion packages** were dispensed, with an increase compared to the previous year (+3.5%). It can be noted that, also this year, the number of packages dispensed by direct distribution fell (-0.8%), while the rising trend of those dispensed "on behalf" continues (+3.8%).

The **main components of the change in gross pharmaceutical expenditure** under approved care regime, compared to the previous year, show stability in consumption of prescribed medicines (+0.4% in terms of DDD), a slight reduction in average prices (-1.4%), partially linked to an increase in the use of expired patent medicines and, finally, a shift in prescription towards more expensive medicines (mix effect: +2.1%) (**Table 1.2.6**).

The **Region with the highest per capita gross expenditure** for class A-NHS medicines was Campania with 197.9 euros per capita, while the lowest value was found in the A.P. of Bolzano (115.3 euros per capita), with a 71.6% difference between the two Regions (**Table 1.2.4**). As regards **consumption**, the Region with the highest levels was Campania (1293.4 DDD/1000 inhabitants per day), while the lowest consumption was found in the A.P. of Bolzano (843.8 DDD/1000 inhabitants per day).

Expenditure on medicines purchased by public health facilities was around 15.0 billion euros (253.6 euros per capita), rising compared to 2021 (+8.6%), with an increase in consumption by 5.7% (**Table 1.3.1**).

Regions with the highest expenditure were Campania (290.3 euros per capita) and Marche (288.3 euros per capita); conversely, Valle d'Aosta (189.3 euros per capita) and the A.P. of Trento (217.1 euros per capita) showed the lowest values. The increase in expenditure, compared to 2021, was recorded in all the Regions, with the greatest variations in Veneto (+13.7%) and Marche (+12.1%).

In 2022, **66.3% of patients received at least one medicine prescription**, with a per capita expenditure of 203 euros and a consumption of 1,182 DDD/1000 inhabitants per day; there is a slight difference in drug exposure between males and females, with a prevalence of 62.0 % in males and 70.4 % in females (**Table 1.4.1** and **Figure 1.4.1**). Per capita expenditure and consumption increase with age, particularly the population over 64 accounts for almost 65 % of spending and 70 % of doses. The Northern Regions have a lower prevalence (63.1 %) than Central (68.6 %) and Southern Regions (69.5 %) (**Table 1.4.2**); for each user a higher expenditure was incurred in the South (325.0 euros) compared to the Centre (308.2 euros) and to the North (290.5 euros).

In 2022, **almost 4.2 million children and adolescents**, equal to 45.0% of the overall paediatric population, received at least one pharmaceutical prescription, with a slightly higher prevalence in males than females (46.1 % vs 43.8 %) (**Table 1.5.1** and **Figure 1.5.2**). Compared to 2021, there is an increase in packages per capita in both males and females and, when analysing age groups, it is noticeable that the increase was concentrated more in children between 6 and 11 years of age, although an increase in consumption affected all age groups (**Table 1.5.2**). **Anti-infective for systemic use** are confirmed as the therapeutic category with higher consumption in paediatric age followed by medicines for the respiratory system; for both categories a strong increase in consumption can be observed compared to the previous year, by 53.3 % and 36.9 % respectively. Central nervous system medicines rank fourth among the most prescribed medicines, accounting for 8.8% of the total consumption, confirming the growing trend of the packages dispensed (+6.9% compared to 2021; **Figure 1.5.3** and **Table 1.5.3**).

In the **elderly population**, the average expenditure per user was equal to 556.2 euros (601.5 euros for men and 520.8 euros for women) and almost all the population (98.4%) received at least one pharmacological prescription during the year (**Table 1.6.1**). On average, each user consumed more than 3.5 doses per day (with higher levels recorded among men than women) and took 7.6 different substances, with the lowest rate (6.0 substances per user) recorded in the 65-69 age group, and the highest rate (8.7 substances per user) recorded in the ≥85 age group (**Table 1.6.2**). For both genders the number of different active ingredients taken increased with age. In 2022, 68.1% of users aged ≥65 years received prescriptions for at least 5 different substances (i.e. polypharmacy) and approximately one person in four (28.6%) took at least 10 different active ingredients (**Figure 1.6.2**).

In order to analyse the level of spending and consumption of the elderly population over time, for the first time data on use in the elderly population in 2018-2022 were compared to the population under 65 years of age. The incidence of gross local pharmaceutical expenditure by age group (**Figure 1.6.4**) shows that in 2022 the over 65-year-olds account for more than 63 % of the total, with a rather constant trend over time. Compared to the population under 65, it is highlighted that a greater use of medicines is associated with a lower average DDD cost, probably due to a greater use of drugs that have lost patent coverage (**Figure 1.6.13**). In the period 2018-2022 there is an increase in expenditure per capita in the over 90 age group and in persons aged 75 to 79 (**Table 1.6.5**); these developments are attributable to the increase in the number of users, given that the use intensity (DDD per user) and the average DDD cost remained stable over the period analysed.

The **time trend of the monthly consumption** of medicines shows a growth in class A medicines under approved care regime and in medicines purchased by public health facilities; for Class C medicines requiring a prescription a decreasing trend is recorded in the period 2006-2017, while in the last 5 years (2018-2022) an increase in consumption is observed (**Figure 1.7.1**, **Figure 1.7.2** and **Figure 1.7.3**).

The analysis of the **time trend of prices** for medicines reveals a reduction in the average price per dose for class A medicines under approved care regime (**Figure 1.8.1**) and a corresponding increase in outpatient class C medicines requiring prescription (**Figure 1.8.5**). The in-depth analysis of medicines provided under the agreed care regime analysed the trend in the average cost per DDD and per package of medicines included in the Transparency list, showing an increasing trend in the price per package for both generic and former-originator drugs, while the price trend per DDD remains stable. This trend could be determined by the entry on the Transparency list of medicines with a higher price than the average prices of medicines included in the list (**Figure 1.8.2**). The analysis also concerned drugs not on the Transparency list, distinguishing molecules with only one specialty and those with a number of specialties greater than one. As expected, molecules with only one specialty have both an average cost per package and per DDD higher than the active ingredients that have more than one specialty on the market (**Figure 1.8.3**).

In the context of the approved care regime, the price trend of medicines dispensed under approved care regime that entered the transparency list after 1 January 2018 was analysed, showing how the expiry of the patent and consequently the entry into the market of generic medicines is able to affect the reduction in prices (**Figure 1.8.4**); similarly, on the direct purchasing side, it is possible to note the effect of price reduction given by the introduction on the market of new medicines, in addition to the former-originator, following the patent expiry (**Figure 1.8.6**).

The **international comparison** section compares the Italian pharmaceutical assistance with 9 other European countries, both for drugs distributed at local level and for those in the hospital setting. Considering these two different settings, a profound diversity emerges in the use of specific categories of medicines, which can also depend on the specific distribution regime used in Italy (Law No 405/2001).

The total Italian pharmaceutical expenditure, including local public and private expenditure and hospital expenditure, was equal to 555 euros per capita, lower than that of Germany (640 euros), Austria (620 euros) ,Belgium (635 euros), France (557 euros) and Spain (558 euros),), while it is well above the values of Poland (221 euros), Portugal (410 euros), UK (454 euros), Sweden (451 euros) and the average of the European countries, which is equal to 359 euros (**Figure 1.9.3**).

Italy ranks first in incidence of local consumption of cardiovascular system drugs (26.9%) (**Table 1.9.3**), followed by Germany (24.3%) and Portugal (23.5%), while the percentage of SU consumed in Italy for central nervous system drugs (15.1%) is lower than nearly all countries considered except Poland (14.8%). The analysis of the rate of similarity in the ranking of the first 20 active ingredients by expenditure and consumption in the various supply channels revealed that the differences in the various countries are attributable, in addition to the different prescribing patterns, also to the different methods of drug supply (**Table 1.9.13**, **Table 1.9.14**, **Table 1.9.15** and **Table 1.9.16**).

There is still a low incidence of expenditure on generic medicines (**Figure 1.9.8**) compared to other European countries, although Italy ranks first in the incidence of spending (76.4%) and consumption (66.1%) of biosimilars, respectively (**Figure 1.9.9** and **Figure 1.9.10**). Through the Herfindhal-Hirschman index, the penetration of biosimilars and the level of market concentration for single molecules were analysed (**Table 1.9.20).** When looking at the average cost per dose unit, Italy with 0.22 euros has in the local context a 21% lower value than the average (0.28 euros) of the 10 countries analysed (**Figure 1.9.5**), while in hospital settings (**Figure 1.9.6**), Italy has an average cost SU (5.90 euros) higher than the average of the countries analysed (4.24 euros).

Italy, with 31.2 euros per capita, ranks 5th for expenditure on orphan drugs, after Austria (62.3 euros), France (62.0 euros), Belgium (50.3 euros) and Germany (49.3 euros); all countries show an increasing trend in orphan drug expenditure in 2021 and 2022 (**Figure 1.9.12**). Finally, an analysis was conducted comparing prices of medicinal products that are identical or have a similar packaging to those marketed in Italy. For Italy and Germany, the analysis was conducted using actual purchasing prices. Considering territorial medicines (**Figure 1.9.13**), it is noted that all countries have higher average prices than Italy;

in the hospital setting Belgium, France, Portugal and Germany have lower prices than those applied in Italy, with differences ranging between -56.8 % in Germany and -31.0 % in Belgium (**Figure 1.9.14**). If we consider the overall market, including medicines supplied both in the territorial and in the hospital setting, Italy has lower prices than Belgium (+ 91.5 %), Germany (+ 86.5 %), Austria (+ 33.8 %), Sweden (+ 25.9 %), Great Britain (+ 14.4 %) and Spain (+ 11.3 %), while France (16.5 %), Portugal (-37.2 %) and Poland (-38.9 %) have lower prices than Italy (**Figure 1.9.15**).

SECTION 2 - Detailed analysis of expenditure and consumption of medicines

In 2022, off-patent medicines accounted for 71.6% of expenditure and 86.2% of consumption of class A medicines under approved care regime. The percentage share of generic medicines, excluding those with patent coverage, accounted for 21.9% of expenditure and 30.3% of consumption (**Figure 2.1.1** and **Figure 2.1.2**).

The therapeutic categories with a higher incidence of expenditure on expired patent drugs are cardiovascular drugs (93.3 %), drugs acting on the genito-urinary system (91.0 %) and Antiinfectives for systemic use (89.2 %; **Table 2.1.3**).

Citizen cost-sharing for the amount exceeding the reference price of off-patent medicines (hereinafter “cost-sharing”) was equal to 18.4 euros per capita (approximately 1.1 billion euros), representing 73.1% of the total citizen cost sharing and showing a higher per capita value in the South and the Islands (23.9 euros) compared to the Centre (20.3 euros) and the North (13.7 euros; **Table 2.1.15**) of Italy. An analysis of the correlation between cost-sharing and regional per capita income shows that the Regions with the lowest income are those with the highest cost-sharing (**Figure 2.1.11**).

As regards **biosimilars**, an increase in the consumption of medicinal products that have been available for a longer time and a positive trend for more recent ones (**Table 2.1.12**) are confirmed, although a certain regional variability in consumption and incidence of expenditure remains; in particular, Lombardy, Calabria, Molise and Abruzzo tend to consume more former-originators, while Marche, Tuscany, Piedmont, Basilicata, Veneto, Campania, Liguria and the AP of Trento are the Regions with the highest consumption of biosimilars (**Figure 2.1.28**).

Total expenditure on class C-NN medicines amounted to approximately 127.6 million euros, corresponding to a per capita expenditure of 2.16 euros, which overall decreased by 29.6% compared to the previous year (**Table 2.2.1**).

Regarding **class C medicines dispensed directly by public health facilities**, per capita expenditure was equal to 11.29 euros, increasing by 12.1% compared to the previous year (**Table 2.2.8**).

In 2022 expenditure for medicines dispensed via **direct (DD) and “on behalf” (DPC) distribution** equalled 9.5 billion euros (160.9 euros per capita), of which 75.3% attributable to DD and 24.7% to DPC (**Table 2.3.1**). As far as direct distribution is concerned, class H medicines account for the largest share of expenditure (66.7%), while in the distribution "on behalf" all expenditure is absorbed by class A medicines (**Table 2.3.2** and **Table 2.3.3**).

In 2022, the total per capita expenditure for **medicines dispensed in hospital and local settings** amounted to 189.21 euros per capita (11.4 billion euros), increasing by 7.4% compared to 2021. Pembrolizumab is the main active ingredient by expenditure dispensed in the hospital and local setting, followed by daratumumab and ibrutinib (**Table 2.4.1** and **Table 2.4.4**).

Expenditure for **class C medicines** reached approximately 6.5 billion euros in 2022, showing a 6.9% increase over 2021; 54% (3.5 billion euros) of this amount relates to prescription medicines whereas 46% (2.99 billion euros) relates to self-medication medicines (SOP and OTC), including those sold in shops (**Table 1.1.1**). Also for this year, benzodiazepines, contraceptives and medicines used to treat erectile dysfunction are the categories with the highest incidence on expenditure.

Among **class A medicines privately purchased by citizens**, ibuprofen, amoxicillin in combination with clavulanic acid and cholecalciferol ranked in the top three places in 2022, all showing an increase in expenditure of 3.6 %, 3.5 % and 3.2 % respectively (**Table 2.6.13**).

Among **self-medication medicines**, propionic acid derivatives account for 12.3% of total expenditure, with a value of 364 million euros, increasing by 36.5 % compared to 2021 (Table 2.6.5); the first active principles by expenditure are ibuprofen, with a substantial increase in consumption (+ 51.9 %) and diclofenac, despite the latter a contraction in consumption was observed (-9.8 %; **Table 2.6.7** and **Table 2.6.8**).

SECTION 3 - Consumption and expenditure by therapeutic class

In 2022, the **pharmaceutical expenditure borne by the NHS** expressed as a per capita value was 419.37 euros, increasing by 5.7% compared to the previous year (**Table 3.1**). This trend was mainly determined by the increase by 8.6% of expenditure for public health facilities (253.59 euros, equal to 60% of total expenditure), while the expenditure for class A drugs under approved care regime showed a lower increase (+1.5%; 165.78 euros). Consumption is equal to 1325.21 DDD/1000 inhabitants per day, increasing by 1.6%, compared to 2021, with consumption under approved care regime (Table 3.2) accounting for 86% of total doses (**Table 3.2**).

Cardiovascular medicines represent the therapeutic category with the highest expenditure (50.29 euros per capita) and consumption (487.39 DDD) **under the approved care regime**, whereas, **antineoplastic and immunomodulating agents** as well as **medicines for blood and blood forming organs** show the **highest expenditure** (113.04 euros per capita) and **consumption** (52.97 DDD) among medicines **purchased directly by public health facilities**.

Under the approved care regime, the top active ingredients per expenditure are atorvastatin (276 million euros), pantoprazole (266.3 million euros) and cholecalciferol (239 million euros; **Table 3.11**).

The molecules with the highest variation in expenditure compared to the previous year are: semaglutide, dulaglutide, ezetimibe/rosuvastatin, and clarithromycin. Cholecalciferol, ramipril and atorvastatin are the most consumed active substances (**Table 3.15** and **Table 3.17**).

Taking into account medicines purchased by public health facilities, the top active ingredients by expenditure are cancer drugs, such as pembrolizumab (445 million euros) and daratumumab (391 million euros; **Table 3.21**). The Varicella Zoster vaccine and tafamidis, a medicine of recent approval, indicated for the treatment of cardiomyopathy caused by transthyretin mediated amyloidosis (ATTR-CM) in adults, show the greatest variation in expenditure compared to 2021 (**Table 3.23**).

For each level I ATC, after presenting the overall data on expenditure, consumption and exposure, insights are given for the mostly prescribed therapeutic categories, including the time trend of consumption and expenditure, national and regional data and, where possible, indicators of exposure, also at subgroup level, and adherence to pharmacological treatment in the population.

The assessment of adherence and persistence indicators was carried out using the flow data of the Tessera sanitaria for the following categories of pharmaceuticals: antidiabetics, anticoagulants, antiaggregants, lipid-lowering agents, antihypertensives, antidepressants, medicines for benign prostate hypertrophy, osteoporosis, and obstructive respiratory tract disorders (asthma COPD). The therapeutic category with the highest percentage of subjects with **treatment coverage** greater than or equal to 80% of the observed period is the treatment with medicines for osteoporosis (67.3%) followed, for the male population alone, by medicines for genito-urinary disorders (63.4%) and finally by antiplatelet drugs (61.1%). Conversely, the therapeutic categories with the highest percentages of subjects with treatment coverage lower than 40% of the observed period are the treatments with medicines for obstructive respiratory disorders (53.6%), antidepressants (27.7%) and antidiabetics (27.1%).

As regards persistence, the therapeutic categories reaching the highest levels of persistence at 12 months are anticoagulants (65.1%), antiplatelets (52.9%) and antihypertensives (52%).

SECTION 4 - Monitoring registries and conditional reimbursement agreements

In 2022, 283 registers were active (at least 1 day of monitoring), increasing by 17.4% compared to 2021 (**Table 4.1.1**). Specifically, the number of Registries activated during the year was 80 while the registries closed in the previous year (2021) had been 38 equal to an increase of 42 new monitoring registries.

In 2022, the ATC category A "*Alimentary tract and metabolism*" recorded a sharp increase from 165 patients initiated in 2021 to 43,317 patients initiated in 2022. This increase is due in particular to the release of two registries in 2022 for Forxiga and Jardiance in the indication for the treatment of chronic heart failure. The second most growing ATC category in terms of number of monitored treatments was J, related to antiinfective medicines, while

R class "*Respiratory system*" recorded for the second year in a row a relative increase of more than 50 % (**Table 4.1.2**). The category B "*Blood and blood forming organs*" still remains the category that collects the highest number of patients within the platform of the Monitoring Registries (**Table 4.1.3** and **Table 4.1.4**), although, given the closure of NVAF therapeutic plans, the relative increase 2022-2021 was low, around 5 %.

Finally, data on reimbursements paid by companies in 2022, following the application of conditional reimbursement agreements, are reported, both for those falling within the scope of Registries (for example, payment by result agreement) and for those managed through the information flows on the monitoring of expenditure and consumption (i.e., expenditure ceilings per product and price-volume agreements). Total reimbursements amount to 213 million euros, with a financial impact of Managed Entry Agreements (MEAs) on the NHS expenditure of approximately 1%.

SECTION 5 - New therapeutic entities and orphan medicines

The **new therapeutic entities** selected from class A and H medicines marketed in the period 2014-2022 increased from 208 to 287 (incident and prevalent). The new therapeutic entities marketed since 2022 (incident) were 41 (**Table 5.1.1** and **Table 5.1.2**) with an expenditure of 151,1 million euros. The **expenditure for new incident and prevalent therapeutic entities increased from around 5,174 million euros in 2014 to around 8,540 million euros in 2022**; the impact of the expenditure for new therapeutic entities on the total NHS expenditure also increased over the years from 25.3 % in 2014 to 34.3 % in 2022 (**Table 5.1.2**). The ATC L category "Antineoplastic and immunomodulatory drugs", is not only the one with the highest number of new therapeutic entities but also the one with the highest expenditure, increasing over the period 2014-2022 (from 2,621 million euros to 4,752 million euros, increasing by 81 %); the second category, ATC A, increased from 2014 to 2022 (CAGR 2014-2022 of 3.95 %) reaching 645 million euros in 2022 (**Table and Figure 5.1.3**).

Orphan medicines are medicinal products used for the diagnosis, prevention and treatment of rare diseases. During 2022, the European Medicines Agency (EMA) granted the authorisation to a total of 24 new orphan medicines: of these, 16 have entered the price and reimbursement negotiation process and 3 are already on the market. The remaining 8 medicines did not apply for price and reimbursement.

As of 31 December 2022, out of a total of 159 orphan medicines authorised by EMA, 135 were available in Italy (**Figure 5.2.1** and **Figure 5.2.2**), of which 76 in Class H (56.3%) and 25 in Class A (18.5%). The expenditure for orphan medicines, including the purchase by public health structures and the provision under the approved care regime, **recorded an increase by 29.2% compared to 2021, reaching 1.98 billion euros in 2022**, corresponding to 6.0% of the pharmaceutical expenditure borne by the NHS (**Table 5.2.1**). The therapeutic category that ranks first in both expenditure and consumption is antineoplastic and immunomodulatory medicines (47.6% and 52.7% respectively) (**Figure 5.2.3**).

The highest incidence on expenditure is found for medicines intended for the treatment of lymphomas, myelomas and genetic diseases (32% and 25.6% respectively), in line with the trend of the previous year. On the consumption side, the first in the ranking are medicines used in lymphomas, myelomas and other oncohaematologic diseases, followed, with much lower values, by those for genetic diseases and inherited metabolic diseases (**Table and Figure 5.2.11**).

SECTION 7 - Environmental impact of medicines

This new section, dedicated to the analysis of the potential environmental impact of a series of high-use or high-toxicity active substances aims to provide an informative overview and to raise public awareness of the emerging problem of the impact of medicines on the environment. The results obtained on the 90 active substances analysed, selected on the basis of environmental toxicity criteria, inclusion in European water monitoring programmes and increased consumption at Italian level, reveal a **high or moderate risk for most of the therapeutic classes** considered (**Figure 7.1**, **Figure 7.2** and **Figure 7.3**).

With regard to the analyses by geographical area, differences in use, and therefore in environmental risk, between North, Central and Southern areas were observed, suggesting that the difference in local consumption may result in different environmental risks according to the geographical areas.

Section 1

General characteristics of medicines use in Italy

1.1 General data on expenditure and consumption

In 2022 the overall pharmaceutical expenditure (both public and private) amounted to 34.1 billion euros, with an increase of 6.0% compared to 2021. This expenditure represents an important part of healthcare expenditure, accounting for 1.8% of the gross domestic product (GDP) at current prices. Gross public pharmaceutical expenditure, equal to 23.5 billion euros, accounts for 68.9% of total pharmaceutical expenditure and for 17.9% of public health expenditure and has increased compared to 2021 (+5.5%). The most impacting item is related to local health authorities, hospitals, healthcare residences and prisons (43.9% of public health expenditure). Private expenditure, including citizen cost-sharing, amounts to 9.9 billion euros and mainly concern class C prescription medicines (35.5% of private expenditure). The increase in total pharmaceutical expenditure recorded in comparison with 2021 is mainly due to the trend in expenditure on medicines supplied by the local health authorities, hospitals, healthcare residences and prisons (+5.5%), accounting for 30.3% of total expenditure. An increase was also recorded for class A medicines supplied in direct distribution (+15.4%), in distribution “on behalf” (+11.5%), for self-medication medicines (+13.9%) and the private purchase of class A medicines (+16.1%) Different from 2021, there is a slight increase in net expenditure under approved care regime (+1.2%) and a reduction in expenditure on imported medicines (-12.5%) and galenic preparations (-27.6%) (Table 1.1.1). Similar trends are found when looking at the period 2020-2022 (Figure 1.1.2). As regards public expenditure, €2,088 million refer to expenditure that does not contribute to the pharmaceutical expenditure ceiling, which is mainly related to class C medicines, including C-NN (€815 million) and vaccines (€639 million; Figure 1.1.1). Table 1.1.2 shows the composition of the total regional pharmaceutical expenditure by distribution channel and reimbursement regime. In Central and Southern Regions, a higher incidence of gross expenditure under approved care regime and of medicines purchased by public health facilities is observed, whereas expenditure for self-medication medicines and class C medicines requiring a medical prescription is smaller compared to Northern Regions. The share of class A medicines purchased privately by citizens is higher in the Centre than in the South and in the North (Table 1.1.2 and Figure 1.1.2). The regional variability in expenditure and consumption under approved care regime is confirmed in the period 2018-2022, presenting increasing coefficient of variation (CV) values. In contrast, on the direct purchasing side, a reduction in regional variability in both expenditure and consumption is observed (Figure 1.1.4).

Figure 1.1.5 shows that public territorial expenditure has been decreasing over the period 2017-2020; conversely, hospital expenditure and for class A medicines purchased privately by citizens is constantly growing. Figure 1.1.6 shows the comparison between the National Healthcare Fund (NHF), current public health expenditure, public pharmaceutical expenditure, pharmaceutical expenditure borne by the NHS calculated for the purpose of monitoring compliance with the pharmaceutical ceilings (hereafter, NHS pharmaceutical expenditure) and the planned funding for pharmaceutical care, which is the sum of the pharmaceutical expenditure ceilings as defined by the various regulations (including funds for innovative medicines), over the period 2014-2022. To cope with the emergency related to the spread of the SARS-COV-2 virus, there was a 6.1% increase in healthcare expenditure in 2020 compared to 2019, whereas until 2019 the rates of change had not exceeded 2%.

In 2022, healthcare expenditure amounted to EUR 131,103 million, a rate of increase of 2.9% compared to 2021. This development is driven by two important components of healthcare expenditure, which are employee income (EUR 40,377 million) and intermediate consumption expenditure (EUR 44,426 million). These items showed an increase of 5.7% and 3.7%, respectively, compared to 2021. Intermediate consumption expenditure includes the purchase of medicines, which increased by 9.6% compared to 2021. The cross-time comparison between the NHF and health expenditure shows that the greatest differences between the two values were found in 2022, the year in which the NHF was EUR 6,201 million lower than health expenditure.[1]

Comparing, on the other hand, the financing of pharmaceutical expenditure and NHS pharmaceutical expenditure, we see that the greatest difference was found in 2016, then decreased sharply in 2017 and increased again in 2018, remaining stable in the following years. In 2022, an excess of NHS expenditure over funding of 4.3% was observed, lower than the average for the period 2014-2022, which was 8%. However, it should be stressed that this figure could deviate from the overrun, especially for direct purchases, given the presence of separate caps for the approved care regime and direct purchases. In addition, it is possible to compare the trend of NHS pharmaceutical expenditure and public pharmaceutical expenditure that includes other components of pharmaceutical care charged to the NHS that do not fall within the definition of the ceilings (class C and C-non-negotiated medicines purchased by public health facilities, foreign medicines, vaccines, galenic preparations, and extra DRGs). Public pharmaceutical expenditure in 2022 amounted to EUR 23.5 billion compared to EUR 20.5 billion of NHS expenditure for the purposes of monitoring pharmaceutical expenditure ceilings; both show a slight increase compared to 2021, by 6.0% and 6.2% respectively.

The incidence of health expenditure in relation to GDP peaked in 2020 at 7.4%, due to both an increase in health expenditure of 6% and a reduction in GDP of about 7% (Figure 1.1.7). From 2021 onwards, the incidence decreases to a forecast for 2026 of 6.2%. Both the incidence of public pharmaceutical expenditure and of pharmaceutical expenditure for monitoring purposes remain almost stable in the period 2019-2022, with a slight increase in 2020. Similar to the incidence of health expenditure on GDP, the incidence of pharmaceutical expenditure financing shows a decreasing trend, although with very small variations; indeed, it decreases from 1.0% in 2023 to 0.9% in 2026.

The incidence of public pharmaceutical expenditure over GDP is higher in Southern Regions (2.3%) compared to the Centre (1.3%) and the North (1.1%) of Italy, with a national percentage of 1.4%. The incidence of public pharmaceutical expenditure over GDP in Calabria (2.6%) is more than 3 times higher than in the Autonomous Province (AP) of Bolzano (0.7%; Table 1.1.3).

From 2017 to 2022, resources for pharmaceuticals were increased in absolute terms by EUR 2.1 billion, corresponding to a change of 12.3% (Table 1.1.4). At the same time, an increase in the gap between NHS expenditure (net of payback) and funding was observed, rising from €726 million in 2017 to €1.6 billion in 2022 (15% ceiling assumption). The overrun in direct

[1] Documento di Economia e Finanza 2023
https://www.rgs.mef.gov.it/_Documenti/VERSIONE-I/Attivit--i/Contabilit_e_finanza_pubblica/DEF/2023/DEF2023-Sez-II-AnalisiETendenzeDellaFinanzaPubblica.pdf

purchases rose from €1,652 million in 2017 to €2,506 million in 2022, while expenditure under approved care regime showed a surplus compared to the programmed ceiling during the same period, with a surplus of €706 million in 2022 (Figure 1.1.9). Expenditure on innovative medicines was always in surplus compared to the funds for innovations with the exception of the year 2018, when there was a slight deficit in the fund for oncology innovations of EUR 86 million (Figure 1.1.11). Expenditure on innovative medicines is growing and, in 2022 compared to 2021, an increase of 30 per cent was recorded, showing a surplus of EUR 172 million compared to the fund for innovative medicines (EUR 1,100 million). In 2021, the surplus was larger (EUR 286 million), although the fund for innovations was less sizeable (EUR 1,000 million; Figure 1.1.11). The value of the 2022 payback of €1.3 billion affects the expenditure of direct purchases (class A and H) by 11.1% and 6.1% of total NHS expenditure. Both incidences have shown a decreasing trend, also as a result of the increase in the resources allocated to the financing of pharmaceuticals (Figure 1.1.10).
Analysing the distribution of the number of companies according to the incidence of the payback on the turnover, it is observed that for 32% of the companies the payback accounts for between 5% and 10% of the turnover and for only 15% of the companies the payback accounts for less than 1% (Table 1.1.6).
From 2013 to 2021, payments by pharmaceutical companies doubled in relation to the payback, and the number of days for payment assessment also decreased drastically, from 1977 in 2013 to 47 in 2021: the simplification of the relevant regulations, but also the increased transparency of the procedures as well as the timely communication to the companies, have led to a reduction in litigation and therefore to an increase in the percentage of payments by companies of the amount due (Table 1.1.5).
By analysing the correlation between regional *per capita* income and pharmaceutical expenditure borne by the NHS, Regions with lower *per capita* income appear to have higher pharmaceutical expenditure (Figure 1.1.12). Analysing, instead, the correlation between regional *per capita* income and private *per capita* expenditure, no real correlation between the two variables emerges. Moreover, it can be seen that Campania, among the Regions with the lowest income, has the highest private expenditure, and, on the contrary, the Province of Bolzano, the one with the highest income, records after Molise, Basilicata and Friuli Venezia Giulia the lowest expenditure (Figure 1.1.13).
With regard to consumption, an upward trend can be observed for class A-NHS pharmaceuticals supplied under the approved care regime until 2020, when a 4% reduction in consumption was recorded with respect to 2019 (1,098.4 DDD/1000 inhabitants per day in 2020 compared to 1,143.9 in 2019), probably attributable to the effect of the pandemic, while in 2021 and 2022 an increase was observed that brought consumption levels back to pre-pandemic levels (1,131 DDD in 2021 and 1,141 in 2022). Medicines purchased by public health facilities show an upward trend in consumption from 2006 to 2013, after which they are stable, while in 2022 an increase of approximately 6% is observed compared to 2021. Regarding consumption of class C medicines with prescription, no significant changes were recorded in the period 2004-2020. In the years 2021-2022, an upward trend is recorded with a change in 2022 compared to 2021 of 13.6% (Figure 1.1.14).

Table 1.1.1 Composition of pharmaceutical expenditure: 2022-2021 comparison (Table and Figure)

	Expenditure *(million)*	**Δ % 22-21**	**%°**	**%°°**
Net expenditure under approved care regime^	7,675.2	1.2	22.5	32.6
of which oxygen and vaccines	85.2	3.9	0.2	0.4
Direct distribution Class A	2,517.3	15.4	7.4	10.7
Class A - distribution "on behalf"	2,357.7	11.5	6.9	10.0
Local health authorities, Hospitals, Healthcare residences and prisons*	10,333.4	5.5	30.3	43.9
of which oxygen and vaccines	887.7	1.2	2.6	3.8
Import	41.7	-12.5	0.1	0.2
Galenic preparations	30.8	-27.6	0.1	0.1
Extra tariff	560.5	6.4	1.6	2.4
Public expenditure	**23,516.7**	**5.5**	**68.9**	**100.0**
Fixed co-payment (ticket)	417.1	4.7	1.2	4.2
Reference price share	1,083.8	0.1	3.2	10.9
A private	1,907.9	16.1	5.6	19.2
C with prescription	3,523.1	1.6	10.3	35.5
OTC	2,660.9	13.9	7.8	26.8
Shops	326.3	13.7	1.0	3.3
Private expenditure	**9,919.2**	**7.6**	**29.1**	**100.0**
Discounts	704.1	-0.6	2.1	
Total	**34,140.0**	**6.0**	**100.0**	
COVID-19 medicines expenditure (monoclonal and antiviral)	664.2			
Expenditure COVID-19 vaccines	2,359.1			

^ including expenditure for class C reimbursed medicines (19 million euros)
* Does not include expenditure for class A medicines under direct and "on behalf" distribution
° calculated on the total
°° calculated on subtotals (public and private expenditure)

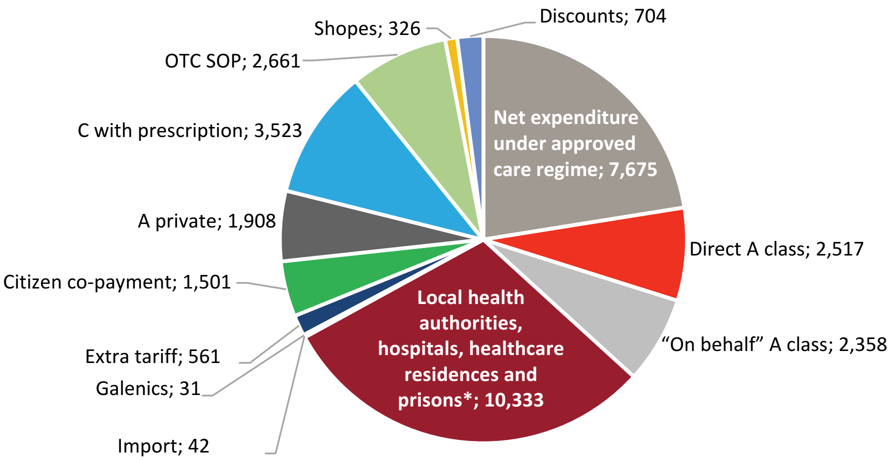


Figure 1.1.1 Breakdown of public pharmaceutical expenditure and public pharmaceutical expenditure not related to the ceiling of pharmaceutical expenditure (2022)

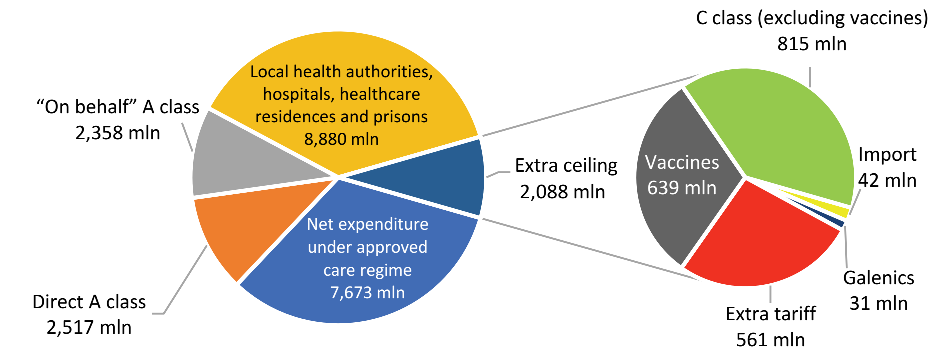


Figure 1.1.2 2020-2022 % change in pharmaceutical expenditure components

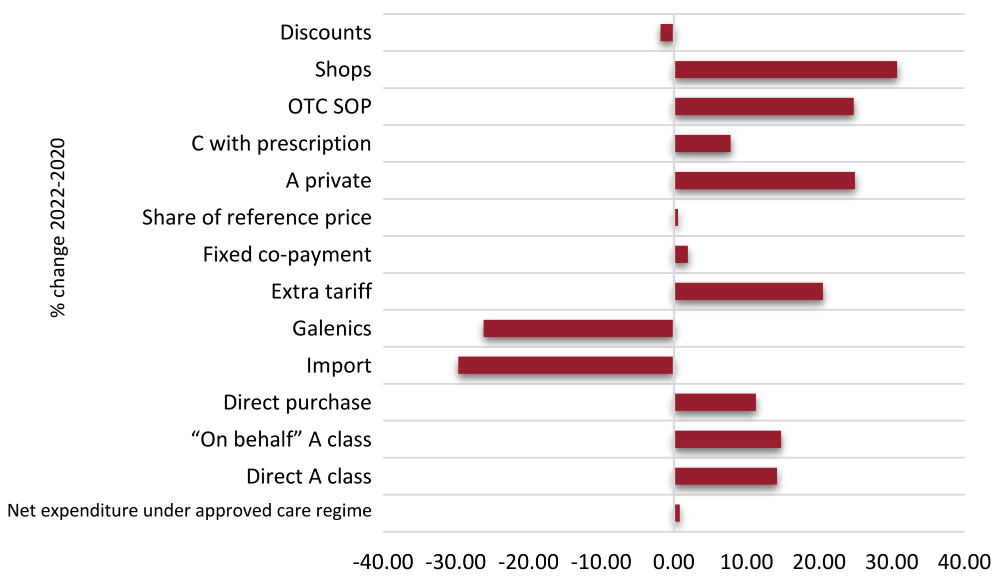


Table 1.1.2 Composition of total pharmaceutical expenditure by Region (year 2022)

Region	Expenditure under approved care regime lorda[1]		Class A private		Class C with prescription		Self-medication (public and private pharmacies)		Shops		Public health facilities		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°	%	€°
Piedmont	624	25.7	186	7.6	281	11.6	209	8.6	25	1.0	1,107	45.5	2,432
Valle d'Aosta	17	25.5	10	15.0	7	10.5	7	10.5	1	1.5	25	36.9	67
Lombardy	1,854	33.8	270	4.9	633	11.5	480	8.7	59	1.1	2,196	40.0	5,492
A.P. of Bolzano	57	23.5	12	5.0	23	9.5	28	11.6	0	—	122	50.5	242
A.P. of Trento	76	28.6	17	6.4	26	9.8	29	10.9	2	0.8	116	43.6	266
Veneto	651	25.5	131	5.1	275	10.8	239	9.4	22	0.9	1,237	48.4	2,555
Friuli VG	184	27.7	28	4.2	65	9.8	57	8.6	5	0.8	324	48.9	663
Liguria	241	24.8	61	6.3	123	12.6	92	9.5	10	1.0	446	45.8	973
Emilia Romagna	588	23.8	95	3.8	263	10.7	215	8.7	35	1.4	1,273	51.6	2,469
Tuscany	530	26.0	90	4.4	235	11.5	187	9.2	28	1.4	970	47.5	2,040
Umbria	141	27.1	27	5.2	57	11.0	36	6.9	5	1.0	253	48.8	519
Marche	246	27.0	47	5.2	95	10.4	67	7.4	7	0.8	448	49.2	910
Lazio	1,034	30.8	261	7.8	358	10.7	273	8.1	20	0.6	1,410	42.0	3,356
Abruzzo	241	28.8	91	10.9	71	8.5	53	6.3	7	0.8	374	44.7	837
Molise	51	32.3	4	2.5	14	8.9	10	6.3	1	0.6	78	49.4	158
Campania	1,044	30.7	171	5.0	358	10.5	256	7.5	40	1.2	1,530	45.0	3,399
Puglia	726	32.1	80	3.5	207	9.1	147	6.5	19	0.8	1,084	47.9	2,263
Basilicata	105	34.5	5	1.6	23	7.5	18	5.9	3	1.0	151	49.5	305
Calabria	352	32.5	50	4.6	98	9.0	62	5.7	10	0.9	511	47.2	1,083
Sicily	838	33.9	156	6.3	220	8.9	137	5.5	13	0.5	1,105	44.7	2,469
Sardinia	282	27.9	116	11.5	90	8.9	60	5.9	14	1.4	447	44.3	1,009
Italy	**9,880**	**29.5**	**1,908**	**5.7**	**3,523**	**10.5**	**2,661**	**7.9**	**326**	**1.0**	**15,208**	**45.4**	**33,506**
North	4,291	28.3	810	5.3	1,696	11.2	1,355	8.9	159	1.0	6,846	45.2	15,157
Centre	1,951	28.6	425	6.2	745	10.9	564	8.3	60	0.9	3,081	45.1	6,826
South and Islands	3,639	31.6	673	5.8	1,082	9.4	742	6.4	108	0.9	5,281	45.8	11,525

[1] The expenditure refers to class A-NHS medicines and class C medicines reimbursed by the NHS. Expenditure on reimbursed class C medicines is EUR 19 million.

°Million euros

* Calculated on overall regional expenditure

Figure 1.1.3 Regional variability in expenditure and consumption under approved care regime, direct purchasing and private purchasing (year 2022)

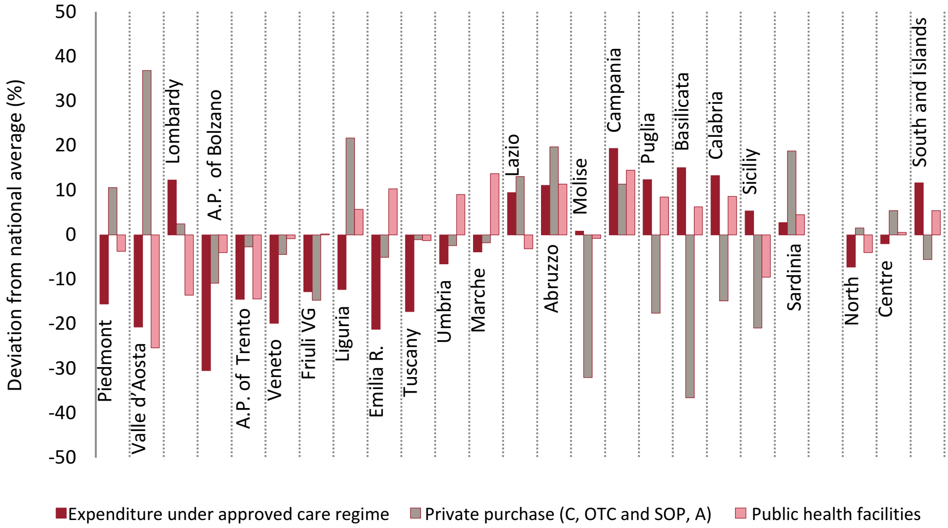


Figure 1.1.4 Regional variability trend in expenditure and consumption under approved care regime and for direct purchasing (2018-2022)

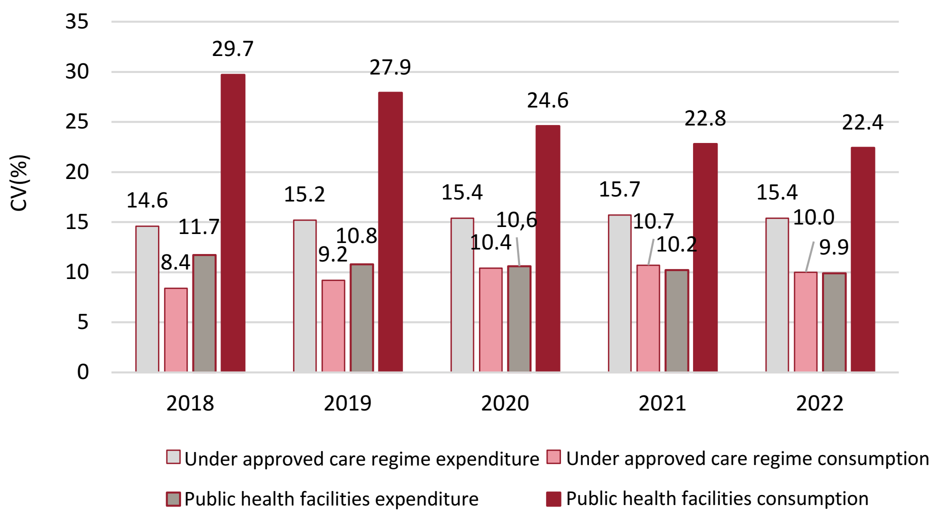
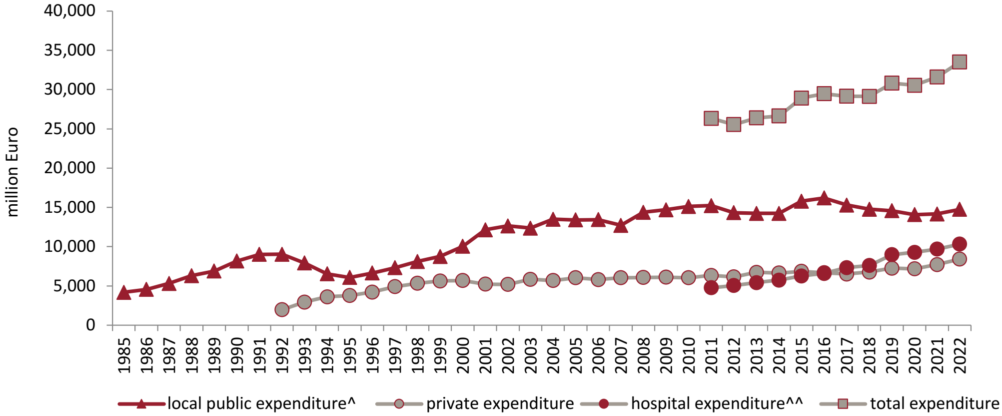


Figure 1.1.5 Pharmaceutical expenditure in the period 1985-2022 (Figure and Table)



Year	Gross expenditure under approved care regime*	Class A direct and "on behalf" distribution	Public local expenditure^ (1)	Private expenditure (2)	Public health facilities	Hospital expenditure^^ (3)	Total expenditure (1+2+3)
1995	6,087		6,087	3,785			
1996	6,638		6,638	4,216			
1997	7,321		7,321	4,919			
1998	8,113		8,113	5,332			
1999	8,760		8,760	5,640			
2000	10,041		10,041	5,684			
2001	12,154		12,154	5,232			
2002	12,644		12,644	5,204			
2003	12,354		12,354	5,849			
2004	13,491		13,491	5,694			
2005	13,408		13,408	6,046			
2006	13,440		13,440	5,814			
2007	12,712		12,712	6,046			
2008	12,724	1,651	14,375	6,088			
2009	12,928	1,767	14,695	6,122			
2010	12,985	2,144	15,129	6,046			
2011	12,387	2,832	15,219	6,346	7,606	4,774	26,339
2012	11,488	2,837	14,325	6,152	7,892	5,055	25,532
2013	11,226	3,003	14,229	6,732	8,425	5,421	26,383
2014	10,988	3,250	14,238	6,648	8,994	5,744	26,630
2015	10,863	4,921	15,784	6,859	11,203	6,282	28,926
2016	10,638	5,556	16,194	6,681	12,143	6,587	29,461
2017	10,499	4,792	15,291	6,526	12,124	7,332	29,149
2018	10,141	4,620	14,761	6,771	12,214	7,594	29,126
2019	10,089	4,481	14,570	7,261	13,461	8,980	30,811
2020	9,820	4,259	14,080	7,180	13,544	9,284	30,544
2021	9,772	4,295	14,067	7,734	14,089	9,794	31,595
2022	**9,880**	**4,875**	**14,755**	**8,418**	**15,208**	**10,333**	**33,507**

^ inclusive of the reimbursed pharmaceutical expense (gross of the pay-back and discount) and of the direct and "on behalf" distribution of the class A-NHS, including the share paid by the citizen; ^^ expenditure of public health facilities (gross of payback) net of direct and "on behalf" distribution of band A-NHS

Figure 1.1.6 Trend of the National Health Fund, health expenditure, pharmaceutical expenditure and pharmaceutical expenditure borne by the NHS over the period 2014-2022

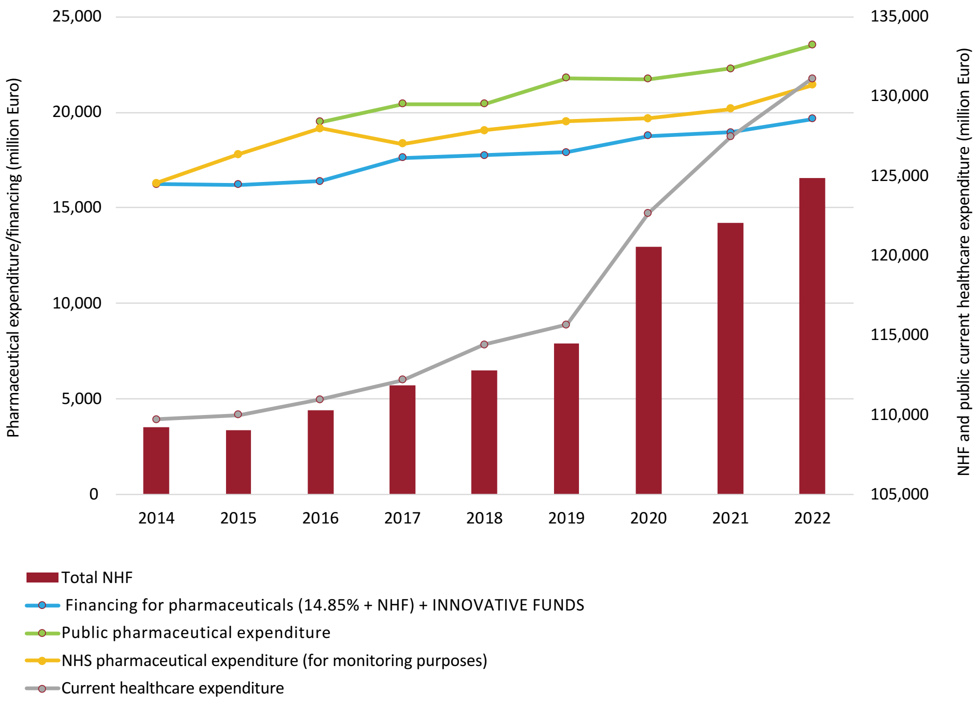
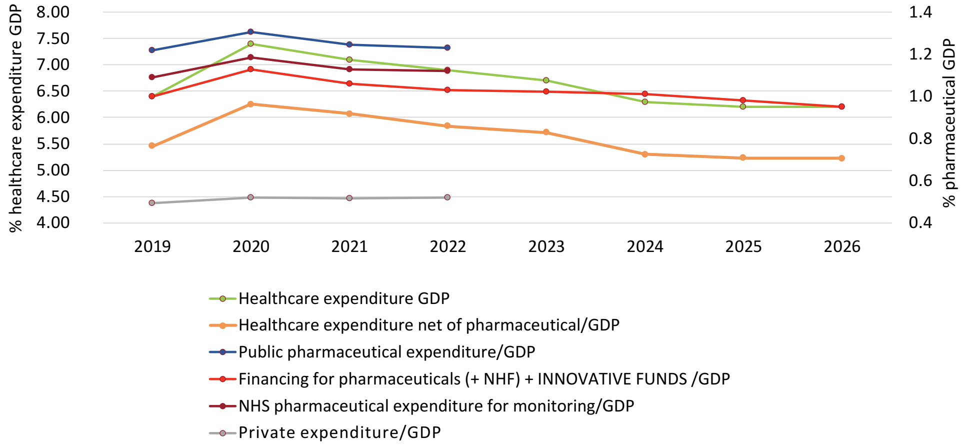


Figure 1.1.7 Trend in the ratio of healthcare expenditure to GDP and pharmaceutical expenditure to GDP (2019-2026)



Source: Source: For healthcare expenditure 2014-2018 AIFA processing of data from: MEF-Monitoraggio della spesa sanitaria-Rapporto N.9. For the years 2019-2026 the data published in DEF 2023 was used.
For national healthcare fund (FSN) AIFA processing of data from: MEF-Monitoraggio della spesa sanitaria-Rapporto N.8
NHS pharmaceutical expenditure for the purposes of monitoring includes: net expenditure under approved care regime, that is, net of discounts paid by pharmacies, of the 1.83% payback paid to the regions gross of regional co-payments; of the expenditure for direct purchases of band A and H medicines net of vaccines and paybacks, including expenditure on innovative medicines.
Public pharmaceutical expenditure includes net contracted expenditure, purchases by public health facilities including oxygen and vaccines, class C and C-NN medicines, medicines imported from abroad, galenic preparations and non DRG expenditure.

Table 1.1.3 Regional incidence of public pharmaceutical expenditure over GDP: period 2017-2022

Region	Incidence (%)					
	2017	2018	2019	2020	2021	2022
Piedmont	1.15	1.11	1.18	1.27	1.26	1.27
Valle d'Aosta	0.77	0.76	0.80	0.86	0.84	0.87
Lombardy	0.90	0.87	0.93	1.00	1.01	1.00
A.P. of Bolzano	0.64	0.61	0.65	0.71	0.69	0.70
A.P. of Trento	0.80	0.78	0.82	0.89	0.89	0.88
Veneto	1.00	0.96	1.01	1.11	1.13	1.15
Friuli VG	1.26	1.19	1.27	1.36	1.31	1.30
Liguria	1.23	1.24	1.25	1.36	1.38	1.76
Emilia Romagna	0.99	0.98	1.01	1.08	1.15	1.14
Tuscany	1.25	1.17	1.21	1.34	1.30	1.31
Umbria	1.60	1.59	1.64	1.79	1.84	1.73
Marche	1.53	1.47	1.52	1.64	1.63	1.64
Lazio	1.16	1.14	1.18	1.25	1.26	1.24
Abruzzo	1.66	1.68	1.71	1.85	1.86	1.89
Molise	1.84	1.80	1.94	2.07	1.98	2.03
Campania	2.16	2.11	2.25	2.38	2.37	2.34
Puglia	2.38	2.30	2.32	2.45	2.45	2.37
Basilicata	1.91	1.80	1.91	2.04	2.08	2.00
Calabria	2.40	2.39	2.46	2.56	2.62	2.64
Sicily	2.08	2.02	2.12	2.22	2.25	2.20
Sardinia	2.14	1.93	1.95	2.13	2.13	2.11
Italy	**1.30**	**1.26**	**1.32**	**1.41**	**1.42**	**1.41**
North	0.99	0.96	1.01	1.09	1.11	1.11
Centre	1.26	1.21	1.25	1.35	1.35	1.33
South and Islands	2.15	2.09	2.17	2.29	2.30	2.27

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Table 1.1.4 Direct expenditure and expenditure under approved care regime from 2017 to 2022 (in millions)

Year	Expenditure Direct purchases (A, H and innovatives net of payback)	Expenditure under approved care regime (net of payback)	NHS Expenditure total (net of Payback)	National Heathcare Fund (NHF)	Overall resources: %NHF + innovative fund	Total resources	Total deviation in case of full utilisation of all available resources for pharmaceuticals
2017	9,907	8,435	18,342	111,892	14.85% FSN + 1,000	17,616	726
2018	10,964	8,174	19,138	112,774	14.85% FSN + 1,000	17,747	1,485
2019	11,383	8,144	19,527	113,792	14.85% FSN + 1,000	17,898	1,629
2020	11,741	7,939	19,680	119,573	14.85% FSN + 1,000	18,757	923
2021	12,275	7,904	20,179	120,924	14.85% FSN + 1,000	18,957	1,222
2022	13,407	8,017	21,425	124,614	15% FSN + 1,100	19,792	1,633

Table 1.1.5 Closure of monitoring, payback and related payments (2013 to 2021)

Year to which the payback refers	Share of payments made vs. the overrun (%)^	Days for final payback§	Days for payment assessment*
2013	54	1025	1977
2014	54	660	1612
2015	54	295	1247
2016	54	396	881
2017	54	390	516
2018	83	756	388
2019	98	346	249
2020	99	325	50
2021	99	317	47

^Source: AIFA determinations
§from the first of January of the year following the year of reference of the payback
* from the day following the deadline for making payments until the last publication of payments on the website of Agenzia Italiana del Farmaco

Figure 1.1.8 Trend of direct expenditure and expenditure under approved care regime from 2017 to 2022

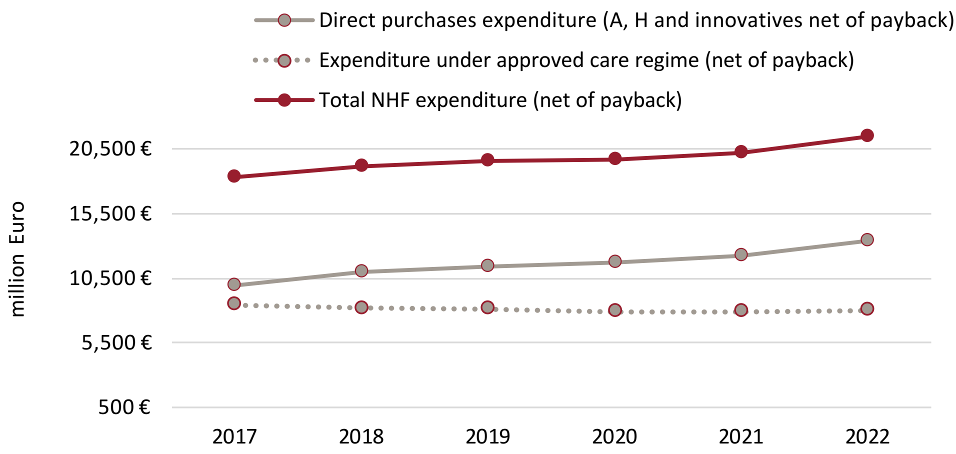


Figure 1.1.9 Trend of direct expenditure and expenditure under approved care regime from 2017 to 2022

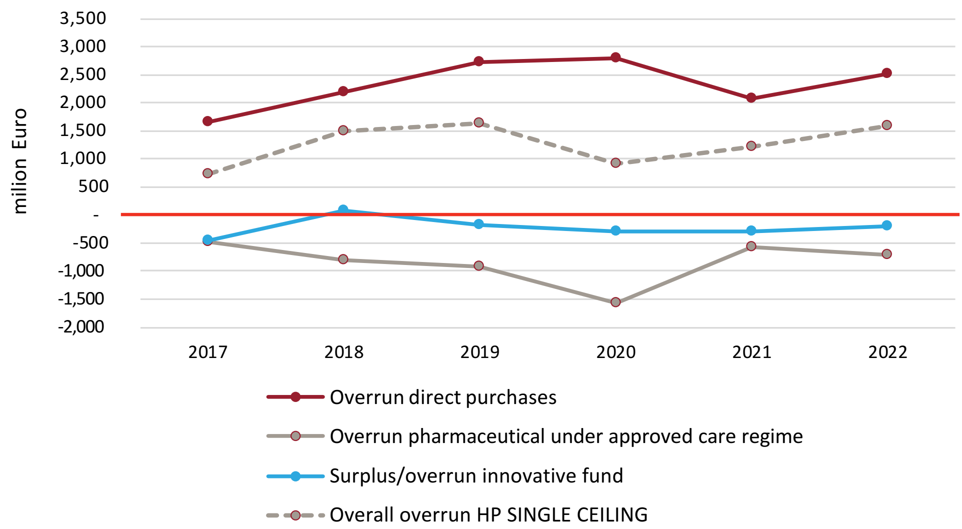


Table 1.1.6 Distribution of the number of companies by the incidence of payback on turnover (2022)

Incidence of payback on total turnover* (a, H, C, Cnn)	Companies		Payback	
	N°	%	€	%
<1%	22	15%	17,777,786	1%
1%-5%	45	31%	82,060,386	6%
5%-10%	47	32%	539,245,971	40%
10%-15%	32	22%	713,820,244	53%
Total	**146**	**100%**	**1,352,904,386**	**100%**

Figure 1.1.10 Incidence of payback (A and H) on the expenditure for direct purchases (A and H) and NHS expenditure in the period 2018-2022

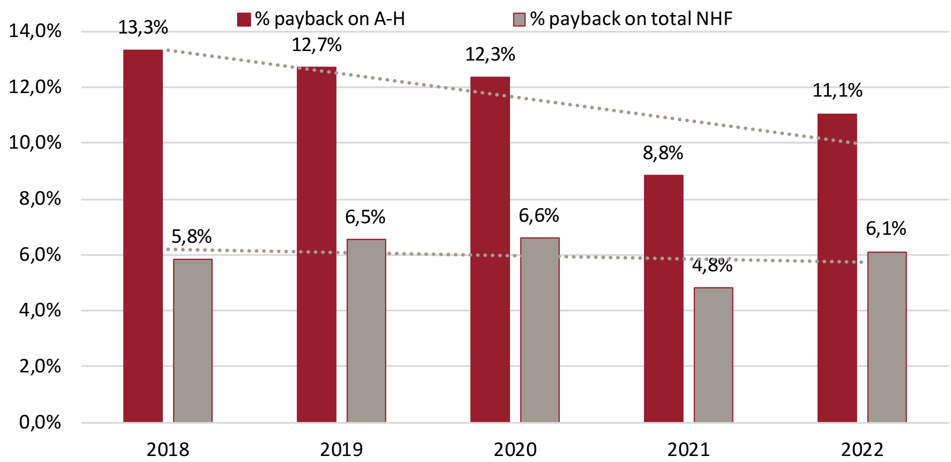
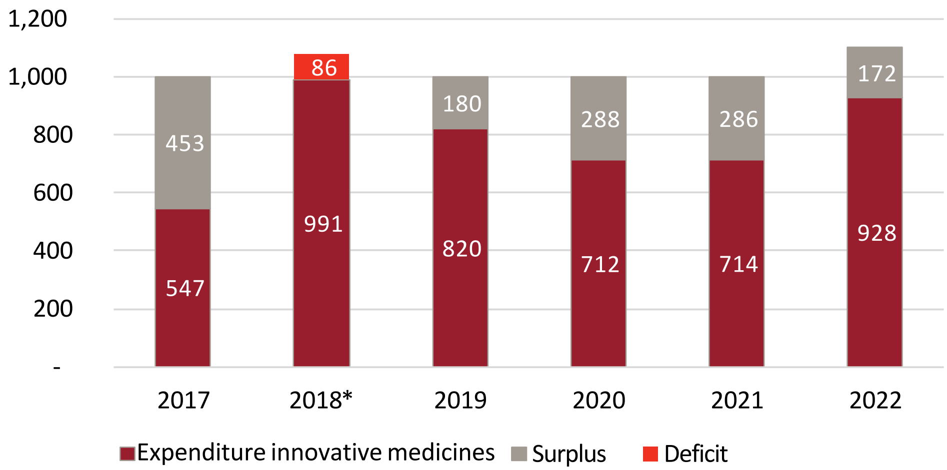


Figure 1.1.11 List of innovative medicines in the period 2017-2022



* Overrun is only related to innovative oncology medicines

Figure 1.1.12 Relationship between *per capita* public pharmaceutical expenditure and *per capita* regional income in 2022

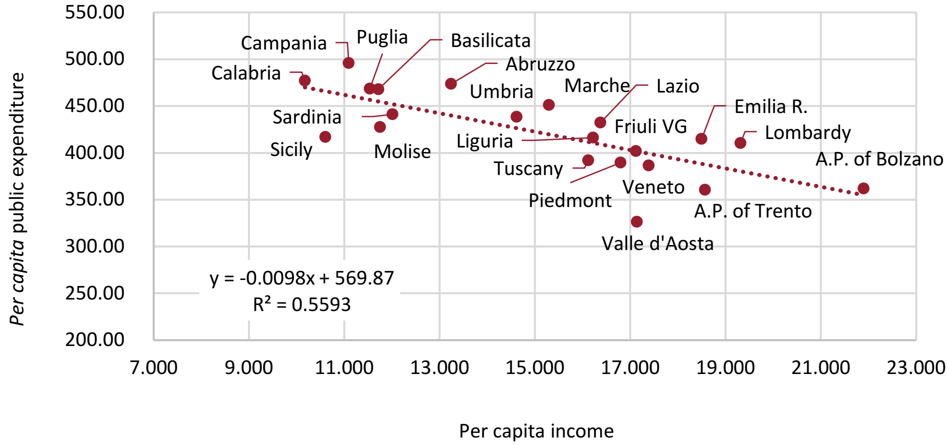


Figure 1.1.13 Relationship between *per capita* private pharmaceutical expenditure and *per capita* regional income in 2022

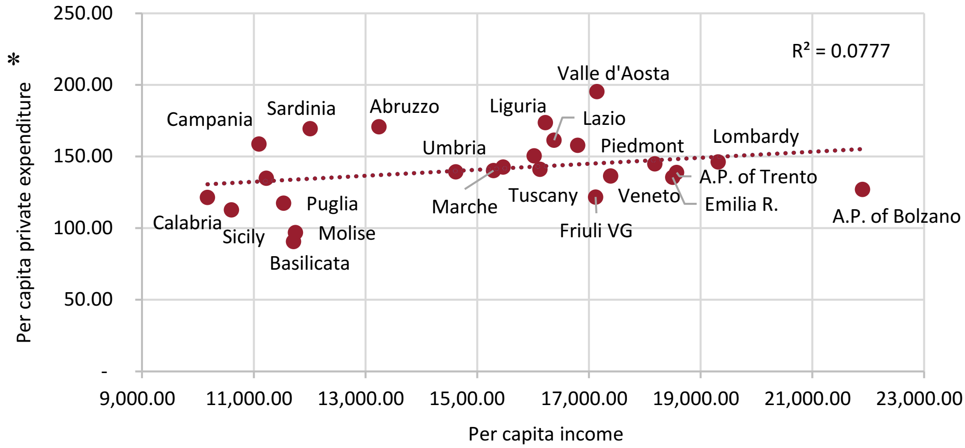
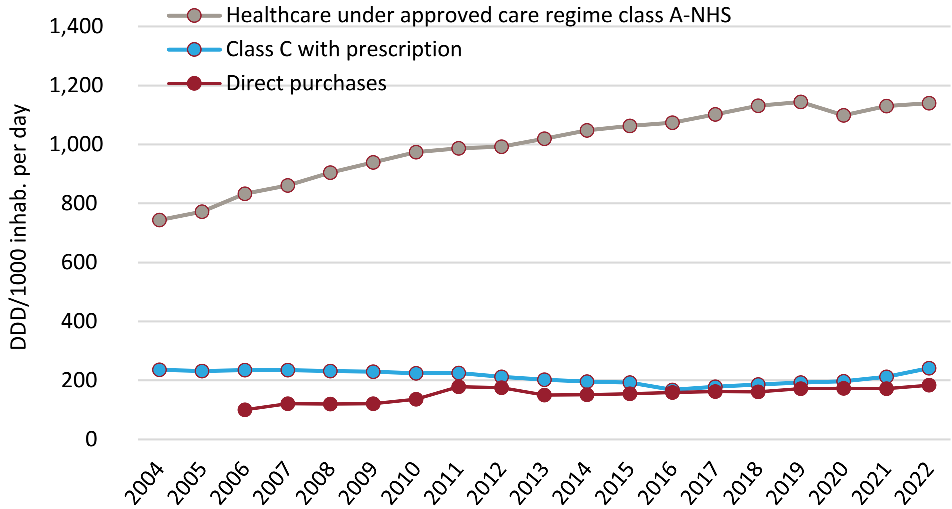


Figure 1.1.14 Consumption (DDD/1,000 inhabitants per day) in the period 2004-2022 (Figure and Table)



Year	DDD/1000 inhab. per day					
	Approved care regime Class A-NHS	Δ % vs previous year	Class C with prescription	Δ % vs previous year	Direct purchases	Δ % vs previous year
2004	743.6		235.9			
2005	771.9	3.8	231.7	-1.8		
2006	833.0	7.9	235.4	1.6	100.6	
2007	861.6	3.4	235.0	-0.2	121.7	21.0
2008	904.9	5.0	231.9	-1.3	120.4	-1.1
2009	939.4	3.8	229.6	-1.0	120.9	0.4
2010	973.9	3.7	223.8	-2.5	136.5	12.9
2011	987.0	1.3	225.7	0.8	178.8	31.0
2012	992.3	0.5	212.2	-6.0	175.1	-2.1
2013	1019.2	2.7	202.4	-4.6	150.9	-13.8
2014	1047.9	2.8	195.8	-3.3	151.2	0.2
2015	1062.4	1.4	193.0	-1.4	154.3	2.1
2016	1074.3	1.1	168.2	-12.8	159.1	3.1
2017	1101.6	2.5	178.8	6.3	162.1	1.9
2018	1130.8	2.7	186.0	4.0	161.5	-0.4
2019	1143.9	1.2	193.2	3.9	171.8	6.4
2020	1098.4	-4.0	196.7	1.8	174.7	0.7
2021	1130.8	2.9	212.8	8.1	172.7	0.9
2022	**1140.6**	**0.9**	**241.7**	**13.6**	**184.6**	**5.7**

1.2 Outpatient pharmaceutical expenditure and consumption

In 2022 the overall outpatient pharmaceutical expenditure, both public and private, amounted to 22,470 million euros, with an increase of 6.5% compared to the previous year (Table 1.2.1). The NHS outpatient pharmaceutical expenditure includes medicines supplied under the approved care regime (7,675 million) and class A medicines supplied through direct and "on behalf" distribution channels (2,517 million and 2,358 million euro respectively) (Table 1.2.1). Public outpatient expenditure amounted to 12,550 million euros (213 euros *per capita*), which, compared to 2021, showed an increasing trend (+5.7%), in the face of a slight increase in expenditure under approved care regime (+1.2%), a strong increase in expenditure on class A medicines supplied in direct distribution (+15.4%) and class A medicines supplied "on behalf" (+11.5%). In 2022 public local expenditure represented 55.9% of the total local pharmaceutical expenditure; this incidence in the last 6 years has shown a decreasing trend due to the increase in private expenditure.
The expenditure borne by the citizen (Table 1.2.1 and Figure 1.2.1), comprising expenditure for citizen cost-sharing (regional co-payments and the difference between the price of the expired patent medicine and the corresponding reference price), expenditure for class A medicines purchased privately and expenditure for class C medicines amounted to €9,919 million, with an increase of 7.6% compared to 2021. This trend was influenced by the increase in private expenditure on class A medicines (+16.1%), the increase in expenditure on self-medication medicines (+13.9%) and medicines supplied in shops (+13.7%), while the increase in expenditure on class C medicines with prescriptions shows a less significant change (+1.6%). There is also a slight increase in expenditure for citizen cost-sharing (+1.4%) with a value of €1,501 million (about €25.0 *per capita*) and an incidence on gross pharmaceutical expenditure under approved care regime of 15.2%. Compared to 2021, the change in expenditure related to total citizen cost-sharing (+1.4%) was essentially brought about by the increase in expenditure related to the per-prescription/package cost-sharing (+4.8%), while citizen cost-sharing for the share exceeding the reference price of patent expired medicines remained stable (+0.1%). The incidence of citizen cost-sharing on gross expenditure, after increasing in 2018 compared to 2017, showed a decreasing trend in the years 2018-2020 and then remained stable in the last two years. The incidence of citizen cost-sharing for the share exceeding the reference price, after increasing in 2018 compared to 2017, remained almost stable in the years 2019-2022, at around 15%. The incidence of the fixed co-payment (ticket) is also stable in the period 2019-2022, at about 11% (Figure 1.2.2).
During 2022 (Table 1.2.2), an average of 1140.6 daily doses per 1000 inhabitants (hereinafter DDD) of NHS reimbursed class A medicines were consumed, with a stable trend compared to 2021 (+0.9). The average cost per day of therapy, EUR 0.40 in 2022, is stable compared to the previous year, unlike previous years when a decreasing trend was observed. With regard to the purchase of class C medicines, the packages of medicines requiring prescription remain stable, while self-medication medicines increase sharply (+19.3%), reflecting the trend in expenditure, which grows by 13.9% (Tables 1.2.1 and 1.2.2).
At national level, net expenditure amounted to €7,675 million (Table 1.2.3), with the highest levels, in absolute terms, recorded in Lombardy (€1,432.2 million), Lazio (€795.0 million) and Campania (€764.0 million). The Regions with the highest expenditure in absolute terms for fixed co-payments (ticket) are Lombardy (€127.7 million), Campania (€73.9 million) and

Veneto (€58.4 million). All the Regions, with the exception of Basilicata and Lazio, have recorded increases in the fixed co-payment ticket, with the greatest variations in Emilia Romagna (+28.1%), in the A.P. of Trento (+27.8%) and in Tuscany (+26.7%). With regard to citizen cost-sharing for the portion exceeding the reference price, Lazio (€ 143.1 million), Lombardy (€ 138.3 million), Campania (€ 130.7 million) and Sicily (€ 111.2 million) show the highest expenditure in absolute terms. The largest reduction compared to 2021 was recorded in Umbria (-5.2%), while the largest increase was recorded in Basilicata (+2.0%).

The region with the highest *per capita* gross expenditure for A-NHS medicines was Campania with 197.9 euros *per capita*, while the lowest value was recorded in the A.P. of Bolzano (115.3 euros *per capita*), with a 71.6% difference between the two regions (Table 1.2.4). Regarding consumption, the region with the highest levels was again Campania with 1,293.4 DDD/1000 inhabitants per day, while the lowest consumption was found in the A.P. of Bolzano (843.8 DDD/1000 inhabitants per day). In general, on average, Southern Regions consume and spend more than Northern and Central Regions as regards medicines provided under approved care regime. Analysis of the trend in expenditure and consumption compared to the previous year shows how the North (+2.8% in expenditure and +2.0% in consumption) records the greatest increases due, in particular, to Lombardy and Emilia Romagna, compared to the Regions of the Centre and the South, which show broadly stable expenditure and consumption values. At national level, citizen expenditure for self-medication pharmaceuticals, class C medicines with prescription and class A medicines amounted to 142.7 euros *per capita*. A fair variability across Italian Regions emerges, with Valle d'Aosta registering the highest value (195.3 euros *per capita*) and Basilicata registering the minimum value (90.6 euros) (Table 1.2.4). Contrary to what was found for class A medicines reimbursed by the NHS, Regions in the centre of Italy showed higher private expenditure than Northern and Southern Regions. The Centre registers the greatest increase in terms of expenditure with respect to the previous year (+18.7%), double that of the Italian average (+9.3%); the North is substantially in line with the Italian average (+8.2%), while the South shows increases lower than the Italian average (+5.3%).

An analysis of the relationship between average cost and consumption under approved care regime (Table and Figure 1.2.5) shows that Campania, Basilicata, Puglia, Calabria, Lazio, Abruzzo and Sicily are the regions with a consumption and an average cost per DDD higher than the national average. Conversely, Emilia Romagna, Tuscany, A.P. of Trento, Friuli Venezia Giulia, Veneto, Piedmont, Valle d'Aosta and A.P. of Bolzano are those with the lowest consumption and average cost compared to the national average.

Gross expenditure in 2022 increased slightly compared to the previous year, by 1.1% at national level. The greatest increases were found in Lombardy (+4.8%) and in the A.P. of Trento (+3.7%), while Umbria (-6.0%) and Campania (-1.4%) showed the greatest decreases in expenditure (Table 1.2.6). The main components of the variation in gross pharmaceutical expenditure under approved care regime (i.e. quantity, prices and mix effect) (Figure 1.2.3 and Table 1.2.6) show, with respect to the previous year, an increase in the consumption of pharmaceuticals requiring prescription (+0.4% in terms of DDD), a slight reduction in average prices (-1.4%), linked in part to an increasing use of patent-expired products, and finally to the prescription of more expensive products (mix effect: +2.1%). In contrast to 2021, 2022 shows stability of the average DDD cost (+0.7%). Against these national average values, regional variability is very broad: change in prices compared to the previous year

ranges between -4.7% in Valle d'Aosta to -1.4% in Campania and Puglia. The mix effect varies between +0.8% in Umbria to +4.9% in Molise. The variation in consumption ranges between -4.4% in Umbria and +2.9% in A.P. of Bolzano. There is wide variability also in the variation, compared to 2021, of the average DDD cost, in particular the Regions of the North present an increase of 1.2%, while in the other geographical areas a stability in the average cost is found. The increase in the North is mainly due to the variation recorded in the Lombardy Region (+2.8%), driven mainly by the shift in prescription towards more expensive molecules (mix effect: +4.4%).
Table 1.2.7 shows data on class A local expenditure (approved care regime and direct and "on behalf" distribution) and private expenditure (class A, class C, self-medication). The A.P. of Bolzano has the lowest local public expenditure (174.9 euros *per capita*), while Campania, Puglia and Basilicata are the regions with the highest local public expenditure (295.3, 285.5 and 285.4 euros *per capita*, respectively). Considering also private expenditure, the A.P. of Bolzano and Campania are, respectively, the regions with the lowest and highest level of expenditure (315.9 and 454.2 euros *per capita*, respectively) (Table and Figure 1.2.7).

Table 1.2.1 Public and private local pharmaceutical expenditure: comparison 2017-2022

		2017 *(million)*	2018 *(million)*	2019 *(million)*	2020 *(million)*	2021 *(million)*	2022 *(million)*	Δ % 18-17	Δ % 19-18	Δ % 20-19	Δ % 21-20	Δ % 22-21
1	**Gross expenditure under approved care regime**	**10,499**	**10,141**	**10,089**	**9,820**	**9,772**	**9,880**	**-3.4**	**-0.5**	**-2.7**	**-0.5**	**1.1**
2	Citizen cost-sharing	1,549	1,608	1,582	1,487	1,481	1,501	3.8	-1.6	-6.0	-0.4	1.4
3	Fixed co-payment (ticket)	499	482	459	409	398	417	-3.4	-4.7	-10.9	-2.7	4.8
4	Reference price share	1,050	1,126	1,123	1,078	1,083	1084	7.2	-0.3	-4.0	0.4	0.1
5	Discount^	830	751	743	717	709	704	-9.5	-1.1	-3.4	-1.2	-0.7
6=1-2-5	**Net expenditure under approved care regime**	**8,120**	**7,781**	**7,764**	**7,616**	**7,583**	**7,675**	**-4.2**	**-0.2**	**-1.9**	**-0.4**	**1.2**
7	Class A direct distribution	3,171	2,829	2,541	2,205	2,181	2,517	-10.8	-10.2	-13.2	-1.1	15.4
8	Class A - distribution “on behalf”	1,622	1,794	1,939	2,055	2,214	2,358	10.6	8.1	6.0	2.9	11.5
9=6+7+8	**Local expenditure expenditure**	**12,913**	**12,404**	**12,244**	**11,875**	**11,878**	**12,550**	**-3.9**	**-1.3**	**-3.0**	**0.0**	**5.7**
10	Citizen cost-sharing	1,549	1,608	1,582	1,487	1,481	1,501	3.8	-1.6	-6.0	-0.4	1.4
11	Private purchase of class A medicines	1,317	1,360	1,544	1,528	1,644	1,908	3.3	13.5	-1.1	7.6	16.1
12	Class C medicines with prescription	2,813	2,875	3,066	3,269	3,466	3,523	2.2	6.6	6.6	6.0	1.6
13	Self-medication pharmaceuticals	2,109	2,270	2,392	2,134	2,337	2,661	7.6	5.4	-10.8	9.5	13.9
14	Shops	286	266	259	250	287	326	-7	-2.5	-3.7	14.9	13.7
15=10+11+ 12+13+14	**Total private expenditure**	**8,074**	**8,379**	**8,843**	**8,668**	**9,215**	**9,919**	**3.8**	**5.5**	**-2.0**	**6.3**	**7.6**
16=9+15	**Total pharmaceutical expenditure**	**20,987**	**20,783**	**21,087**	**20,543**	**21,093**	**22,470**	**-1.0**	**1.5**	**-2.6**	**2.7**	**6.5**
9/16	Share (%) borne by the NHS	**61.5**	**59.7**	**58.1**	**57.8**	**56.3**	**55.9**					

^including the discount per price ranges charged to pharmacies, the extra-discount following AIFA Resolution of June 15, 2012 and art. 15, paragraph 2 of Law 135/2012 and -charged to the industry- both the discount from AIFA Resolution of 30 December 2005, and the pay-back under the approved care regime under art. 11, paragraph 6, of Law 122/2010, temporarily modified by Law 135/2012 ° Expenditure for Class A medicines by direct and “on behalf” distribution, including - in the case of Regions with missing data - the value of 40% of pharmaceutical expenditure outside the approved care regime recorded through the flow of the “Traceability of medicines”, pursuant to Law 222/2007. In 2022 this condition was not applied to any Region; *Source: OsMed analysis from NSIS data*

Figure 1.2.1 Composition of local pharmaceutical expenditure: comparison 2014-2022

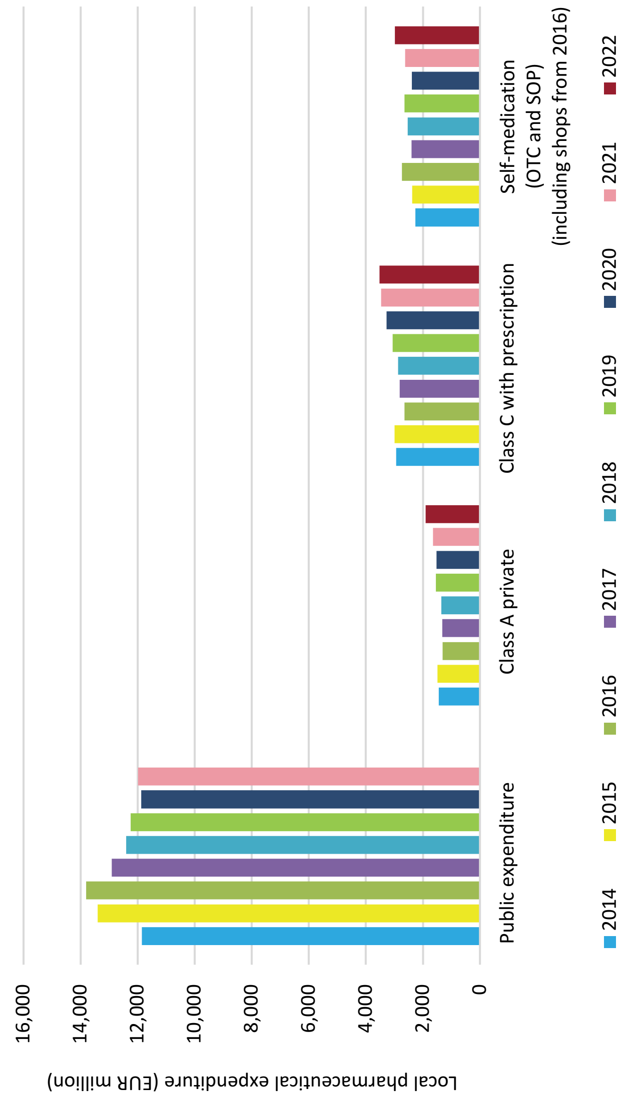


Table 1.2.2 Consumption for public and private local pharmaceutical care: comparison 2017-2022

		2017 (million)^	2018 (million)^	2019 (million)^	2020 (million)^	2021 (million)^	2022 (million)^	Δ % 18-17	Δ % 19-18	Δ % 20-19	Δ % 21-20	Δ % 22-21
1	Approved care regime	1,110	1,102	1,083	1,034	1,029	1,039	-0.7	-1.7	-4.6	-0.4	1.0
2	Class A - Private*	216	162	190	215	227	232	-25.0	17.4	13.3	5.3	2.1
3	Direct distribution of class A medicines	66	175	64	50	44	44	164.7	-63.2	-22.9	-12.0	-0.8
4	"On behalf" distribution of class A medicines	38	44	47	52	55	57	15.2	7.3	8.7	7.1	3.8
5=1+2+3+4	**Total packages class A**	**1,431**	**1,484**	**1,385**	**1,350**	**1,355**	**1,371**	**3.7**	**-6.6**	**-2.5**	**0.4**	**1.2**
6	Class C medicines with prescription	222	229	234	243	244	248	3.2	2.1	4.1	0.4	1.6
7	Self-medication pharmaceuticals (Self-medication SOP and OTC)	231	241	242	248	215	256	4.3	0.6	2.2	-13.4	19.3
8	Shops	30	29	28	27	28	32	-3.3	-4.0	-1.9	2.0	13.4
9=6+7+8	**Total packages class C**	**484**	**498**	**504**	**519**	**487**	**536**	**2.9**	**1.2**	**2.9**	**-6.1**	**10.1**
10=5+9	**Total packages**	**1,915**	**1,982**	**1,889**	**1,869**	**1,842**	**1,907**	**3.5**	**-4.6**	**-1.1**	**-1.4**	**3.5**
	DDD/1000 inhab. per day#	1,101.6	1,130.8	1,143.9	1,098.4	1,130.8	1140.6	2.7	1.2	-4.0	2.9	0.9
	Average DDD cost#	0.43	0.41	0.40	0.41	0.39	0.40	-5.7	-1.5	0.9	-2.6	0.7
	Prescriptions #	581	576	570	541	552	564	-0.9	-1.0	-5.2	2.2	2.2

^ only the number of recipes and packages is expressed in millions of units
* the data relating to the private expenditure of medicines reimbursable by the NHS is obtained by the difference between total expenditure (estimated through the data from the "Traceability of medicines" flow) and the expense borne by NHS (obtained from OsMed data)
# related to the consumption of Class A medicines provided under the approved care regime

Table 1.2.3 Expenditure and consumption of medicines supplied under approved care regime in 2022

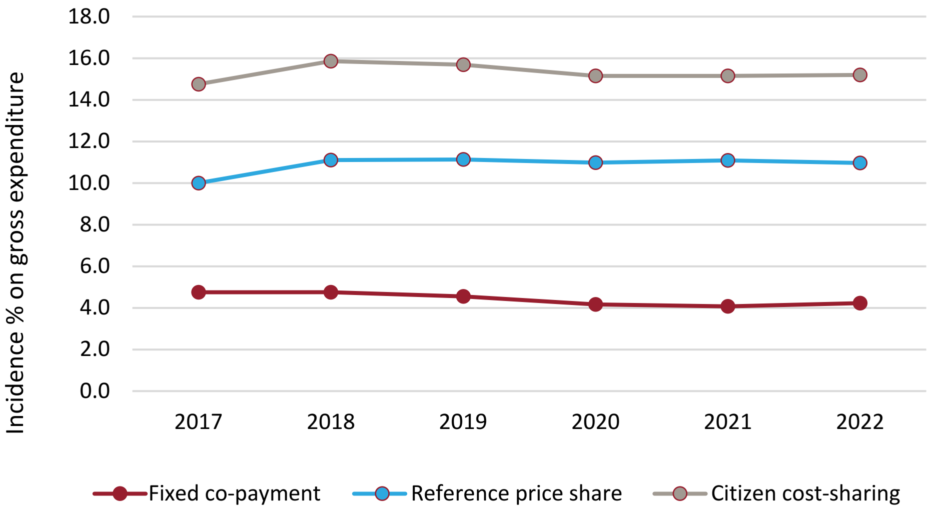
Region	Gross expenditure *(million)*	Citizen cost-sharing				Discount^ *(million)*	Net expenditure^^ *(million)*
		Fixed co-payment (ticket) *(million)*	Δ % 22-21	Reference price *(million)*	Δ % 22-21		
Piedmont	623.9	0.4	22.3	61.7	-0.7	39.1	522.7
Valle d'Aosta	16.6	1.4	3.5	1.6	-0.5	0.9	12.5
Lombardy	1853.9	127.7	7.4	138.3	0.7	155.7	1432.2
A.P. of Bolzano	57.3	4.5	5.6	6.0	1.3	3.9	42.9
A.P. of Trento	75.5	0.1	27.8	6.9	1.8	4.8	63.7
Veneto	651.0	58.4	5.0	68.9	0.6	41.0	482.7
Friuli VG	183.6			18.2	-0.9	11.8	153.6
Liguria	241.0	19.0	5.8	24.8	0.4	15.0	182.3
Emilia Romagna	587.8	0.4	28.1	66.6	1.6	34.8	486.0
Tuscany	530.1	0.3	26.7	52.5	-0.6	35.2	442.1
Umbria	140.5	0.0	19.9	17.0	-5.2	8.9	114.5
Marche	245.6			29.1	-0.6	16.4	200.0
Lazio	1034.4	19.3	-6.4	143.1	1.0	76.9	795.0
Abruzzo	241.0	7.1	4.0	27.4	0.5	15.6	190.8
Molise	51.2	2.7	3.7	6.6	0.8	3.0	39.0
Campania	1043.6	73.9	2.5	130.7	-0.7	74.9	764.0
Puglia	726.5	43.9	0.6	85.2	0.2	52.6	544.8
Basilicata	104.8	0.1	-38.0	13.1	2.0	6.8	84.9
Calabria	351.8	10.4	12.3	46.3	0.3	21.8	273.3
Sicily	837.9	47.0	6.9	111.2	-0.5	66.1	613.6
Sardinia	282.3	0.2		28.6	-0.5	18.7	234.7
Italy	**9880.5**	**417.1**	**4.7**	**1083.8**	**0.1**	**704.1**	**7675.2**
North	4290.7	212.0	6.6	393.0	0.5	307.0	3378.6
Centre	1950.6	19.7	-5.9	241.8	0.0	137.5	1551.6
South and Islands	3639.1	185.4	3.8	449.0	-0.2	259.6	2745.0

^including the discount per price ranges charged to pharmacies, the extra-discount following AIFA Resolution of June 15, 2012 and art. 15, paragraph 2 of Law 135/2012 and -charged to the industry- both the discount from AIFA Determination of 30 December 2005, and the pay-back under the approved care regime under art. 11, paragraph 6, of Law 122/2010, temporarily modified by Law 135/2012

^^ Net expenditure is obtained by subtracting the discount and the patient's co-payment from gross expenditure

Source: Italian Medicines Agency DCR (Distinte Contabili Riepilogative - Summary Accounting Statement)

Figure 1.2.2 Time trend (2017-2022) of the incidence of citizen total citizen cost-sharing, fixed co-payment (ticket) and reference price share on gross expenditure



The data in the following tables are calculated net of oxygen

Table 1.2.4 Regional variability of pharmaceutical consumption supplied through local public and private pharmacies: year 2022 (Table and Figure)

Region	Class A medicines reimbursed by the NHS					Private purchase of class A, class C, self-medication SOP and OTC medicines	
	Gross expenditure A-NHS^	Weighted gross *per capita* expenditure	Δ % 22-21	DDD 1000 inhab. per day	Δ % 22-21	*Per capita* expenditure	Δ % 22-21
Piedmont	622	140.1	0.8	1,051.3	2.1	157.8	10.1
Valle d'Aosta	17	131.5	0.8	929.9	1.7	195.3	59.8
Lombardy	1,837	186.2	4.8	1,099.3	2.1	146.2	3.3
A.P. of Bolzano	57	115.3	1.7	843.8	2.8	127.2	26.1
A.P. of Trento	75	141.9	3.7	1,069.4	2.6	138.8	37.4
Veneto	649	132.9	1.3	1,004.5	0.3	136.4	12.4
Friuli VG	183	144.7	0.4	1,104.7	2.4	121.8	13.6
Liguria	240	145.5	0.4	1,002.2	2.1	173.7	8.1
Emilia Romagna	586	130.7	2.7	1,134.3	3.0	135.5	6.6
Tuscany	525	137.3	1.3	1,094.0	0.4	141.2	7.9
Umbria	139	155	-6.0	1,187.0	-3.6	139.3	26.1
Marche	245	159.5	0.4	1,126.5	1.2	140.2	12.8
Lazio	1,026	181.5	-0.2	1,185.1	0.3	161.4	26.7
Abruzzo	239	184.2	2.2	1,214.8	2.7	170.9	63.2
Molise	51	167.2	2.7	1,169.4	1.9	97	0.6
Campania	1,027	197.9	-1.4	1,293.4	-2.8	158.9	-5.8
Puglia	720	186.3	0.4	1,258.1	0.5	117.6	9
Basilicata	104	190.8	1.4	1,282.1	2.8	90.6	-6.1
Calabria	340	187.8	-0.7	1,217.6	0.6	121.6	8.9
Sicily	814	174.7	-0.8	1,188.4	0.7	112.9	-8.6
Sardinia	282	170.3	1.8	1,197.8	1.5	169.5	50.3
Italy	**9,778**	**165.8**	**1.1**	**1,140.6**	**0.9**	**142.7**	**9.3**
North	4,266	153.8	2.8	1,069.2	2.0	144.9	8.2
Centre	1,936	162.5	-0.2	1,148.5	0.1	150.5	18.7
South and Islands	3,577	185.1	-0.2	1,238.2	-0.1	134.8	5.3

Amounts in million euros
^Expenditure for class A medicines net of class C reimbursed medicines (19 million euros) and oxygen including expenditure for vaccines

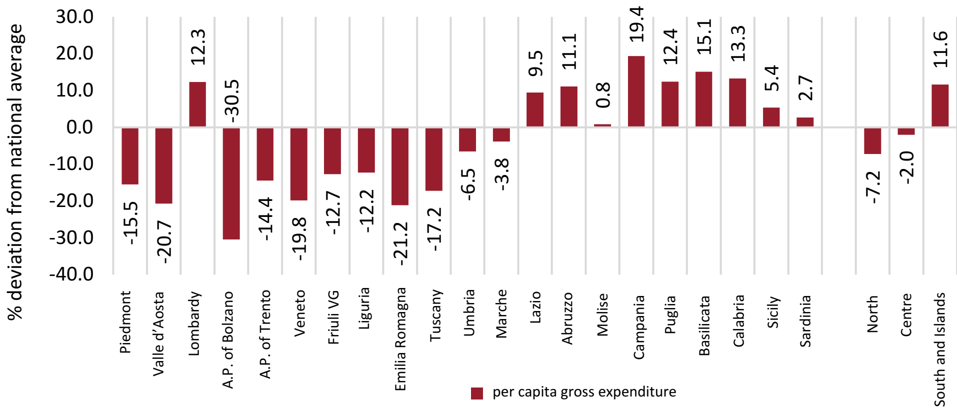


Table 1.2.5 Regional variability of 2022 pharmaceutical consumption under approved care regime by quantity, average cost per day of therapy and expenditure (% deviations from national average) (Table and Figure)

Region	% deviation from national average			Expenditure rank 2022
	DDD/1000 inhab. per day	DDD average cost	Gross *per capita* expenditure	
Campania	13	5	19	1
Basilicata	12	2	15	2
Calabria	7	6	13	3
Lombardy	-4	17	13	4
Puglia	10	2	12	5
Abruzzo	6	4	11	6
Lazio	4	5	9	7
Sicily	4	1	5	8
Sardinia	5	-2	3	9
Molise	2	-2	1	10
Marche	-1	-3	-4	11
Umbria	4	-10	-7	12
Liguria	-12	0	-12	13
Friuli VG	-3	-10	-13	14
A.P. of Trento	-6	-9	-15	15
Piedmont	-8	-8	-16	16
Tuscany	-4	-14	-17	17
Veneto	-12	-9	-20	18
Valle d'Aosta	-19	-3	-21	19
Emilia Romagna	-1	-21	-21	20
A.P. of Bolzano	-26	-6	-31	21
North	0	0	0	0
Centre	-6	-1	-7	0
South and Islands	1	-3	-2	0

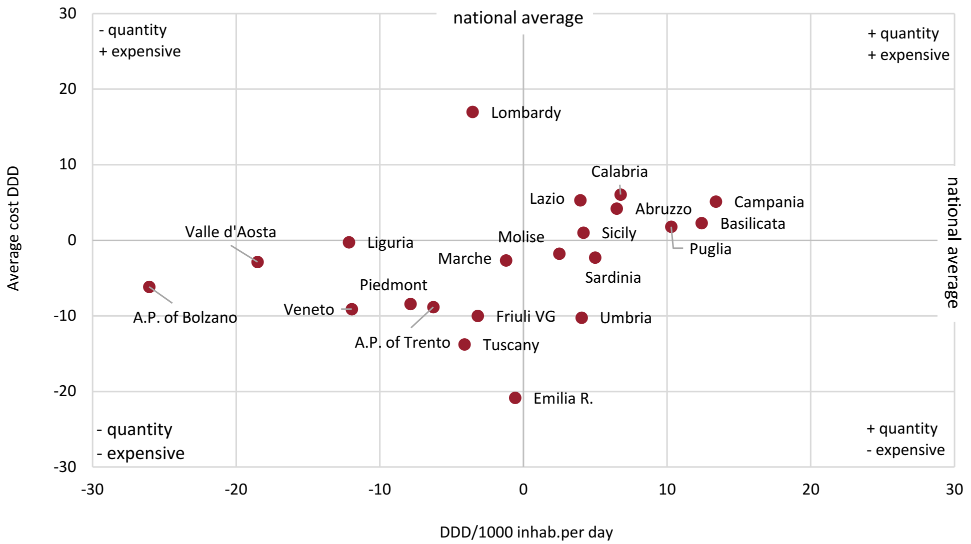


Figure 1.2.3 Trend of class A-NHS pharmaceutical expenditure under approved care regime in the period 2010-2022: consumption, price and mix effect

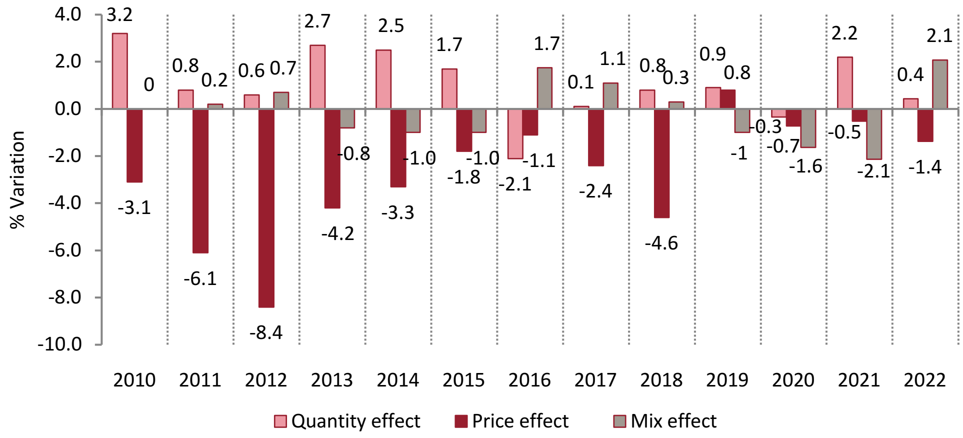


Table 1.2.6 Consumption, price and mix effect on the variation in class A-NHS pharmaceutical expenditure under approved care regime: comparison 2022-2021

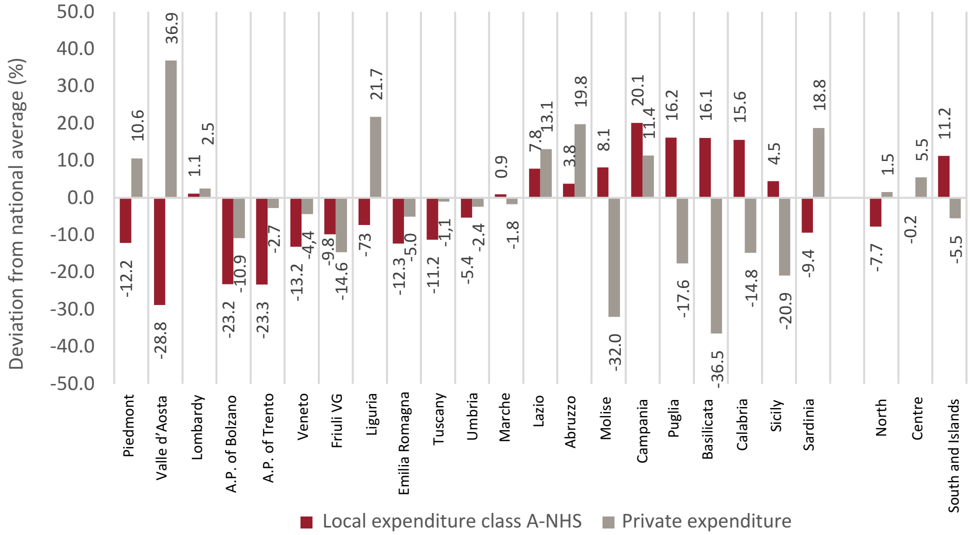
Region	Gross expenditure 2022 *(million)*	Δ % 2022-2021				DDD Average cost 2022	Δ % Average cost DDD
		expenditure	DDD	prices	mix		
Piedmont	622.4	0.8	1.4	-1.8	1.2	0.4	-0.6
Valle d'Aosta	16.6	0.8	1.0	-4.7	4.8	0.4	-0.2
Lombardy	1,836.9	4.8	2.0	-1.5	4.4	0.5	2.8
A.P. of Bolzano	57.2	1.7	2.9	-2.9	1.8	0.4	-1.1
A.P. of Trento	75.3	3.7	2.6	-2.4	3.5	0.4	1.0
Veneto	648.6	1.3	0.1	-1.7	3.0	0.4	1.2
Friuli VG	182.9	0.4	1.7	-2.3	1.0	0.4	-1.3
Liguria	240.0	0.4	1.0	-2.0	1.5	0.4	-0.5
Emilia Romagna	586.0	2.7	2.6	-1.7	1.8	0.3	0.1
Tuscany	525.2	1.3	-0.3	-1.8	3.4	0.3	1.6
Umbria	139.3	-6.0	-4.4	-2.5	0.8	0.4	-1.7
Marche	245.2	0.4	0.5	-1.7	1.6	0.4	-0.2
Lazio	1,025.9	-0.2	0.1	-1.9	1.5	0.4	-0.4
Abruzzo	239.4	2.2	2.1	-1.7	1.9	0.4	0.1
Molise	50.6	2.7	0.6	-2.8	4.9	0.4	2.0
Campania	1,027.1	-1.4	-3.2	-1.4	3.2	0.4	1.8
Puglia	720.2	0.4	0.0	-1.4	1.8	0.4	0.3
Basilicata	104.2	1.4	2.1	-2.3	1.7	0.4	-0.7
Calabria	339.8	-0.7	-0.1	-2.1	1.6	0.4	-0.6
Sicily	813.9	-0.8	0.1	-1.9	1.1	0.4	-0.9
Sardinia	281.6	1.8	1.2	-2.0	2.6	0.4	0.6
Italy	**9,778.4**	**1.1**	**0.4**	**-1.4**	**2.1**	**0.4**	**0.7**
North	4,266.0	2.8	1.6	-1.5	2.8	0.4	1.2
Centre	1,935.6	-0.2	-0.3	-1.6	1.7	0.4	0.1
South and Islands	3,576.8	-0.2	-0.6	-1.4	1.8	0.4	0.4

Note: expenditure is net of reimbursed class C medicines, vaccines and oxygen

Table 1.2.7 *Per capita* local pharmaceutical expenditure (public and private) in 2022 (weighted population) (Table). % deviation from national average (Figure)

Region	Total local expenditure^ class A-NHS *per capita*	Private expenditure *per capita* (A, C, SOP and OTC)	Local pharmaceutical expenditure total *per capita*
Piedmont	215.9	157.8	373.7
Valle d'Aosta	174.9	195.3	370.2
Lombardy	248.6	146.2	394.8
A.P. of Bolzano	188.7	127.2	315.9
A.P. of Trento	188.5	138.8	327.3
Veneto	213.4	136.4	349.8
Friuli VG	221.7	121.8	343.5
Liguria	227.9	173.7	401.6
Emilia Romagna	215.6	135.5	351.0
Tuscany	218.2	141.2	359.5
Umbria	232.6	139.3	371.9
Marche	248.1	140.2	388.3
Lazio	265.0	161.4	426.4
Abruzzo	255.1	170.9	426.0
Molise	265.8	97.0	362.8
Campania	295.3	158.9	454.2
Puglia	285.5	117.6	403.0
Basilicata	285.4	90.6	376.0
Calabria	284.1	121.6	405.7
Sicily	256.8	112.9	369.7
Sardinia	222.8	169.5	392.3
Italy	**245.8**	**142.7**	**388.5**
North	226.8	144.9	371.7
Centre	245.3	150.5	395.9
South and Islands	273.4	134.8	408.2

^Gross class A expenditure under approved care regime, net of reimbursed class C medicines, to which expenditure for direct and "on behalf" distribution of class A medicines has been added. It does not include oxygen



1.3 Medicines purchased by public health facilities

Expenditure for the purchase of medicines by public health facilities (hospitals, direct and "on behalf" distribution) amounted to approximately €15.0 billion (€253.6 *per capita*) (Table 1.3.1) and registered an increase of 8.6% compared to 2021, against an increase in consumption (+5.7%; 184.6 DDD/1000 inhab.die) and an increase in the average cost per DDD of 6.8%. It should be highlighted that, although the DDD approach allows a useful parameterization at different levels (geographical and temporal) of the consumption of medicines purchased by public health facilities, it does not represent the actual pharmaceutical dose administered to the patient. Although this assumption is also valid in cases where DDD is used to parametrize local consumption (for example in the paediatric population), it becomes even more valid in a hospital setting, where the dose of a medicine varies considerably depending on the patient's care needs. The southern regions have the highest *per capita* expenditure (267.3 DDD) and the lowest consumption (163.9 DDD). Therefore, the higher expenditure is mainly attributable to the higher average DDD cost of 4.47 euro, compared to the North (3.34 euro) and the Centre (3.81 euro).
The Regions with the highest expenditure values are Campania (290.3 euros *per capita*) and Marche (288.3 euros *per capita*); on the contrary, Valle d'Aosta (189.3 euros *per capita*) and the A.P. of Trento (217.1 euros *per capita*) have the lowest values. The increase in expenditure, compared to 2021, was recorded in all regions, with the largest variations in Veneto (+13.7%) and Marche (+12.1%).
In terms of consumption, Emilia Romagna (317.5 DDD) and Lombardy (117.9 DDD) represent the regions with the highest and lowest levels of consumption, respectively. The regions registering the largest increases in consumption compared to the year 2021 are Molise (+15.3%) and Campania (+15.1%), while Tuscany is the only region to register a decrease (-2.6%).
An analysis of the relationship between average cost per DDD and the purchase of pharmaceuticals by public health facilities (Table and Figure 1.3.2) reveals that only Sardinia consumes greater quantities and slightly more expensive active ingredients, and no Region consumes fewer quantities at a lower cost than the national average. Lombardy, Abruzzo, Puglia, Lazio, Calabria, Basilicata, Molise, Campania, and Sicily registered lower consumption, but with an average cost per DDD higher than the national average. Emilia Romagna, Valle d'Aosta, Friuli Venezia Giulia, Marche, Veneto, Tuscany, Umbria, Liguria, Piedmont, A.P. of Bolzano and A.P. of Trento consumed higher quantities but with a lower average cost per DDD. Table 1.3.3 analyses the elements that contributed to the change in expenditure for purchases by public health facilities. In 2022, expenditure increased by 8.3% at national level, driven by a shift towards more expensive molecules (mix effect: +7.6%), an increase in consumption (+6.0%) and a 5.1% reduction in prices. However, the average cost per DDD increased by 6.8%, with the greatest changes recorded in Emilia Romagna (+17.0%) and Veneto (+14.4%), while it decreased in Molise (-4.3%), Friuli VG (-4.0%), Basilicata (-3.0%) and Campania (-2.6%).

Table 1.3.1 Expenditure and consumption for medicines purchased by public health facilities: comparison 2022-2021 (weighted population) (Table and Figure)

Region	NHS Expenditure *(million)*	NHS Expenditure *per capita*		DDD/1000 inhab. per day		DDD Average cost	
		€	Δ % 22-21	No.	Δ % 22-21	€	Δ % 22-21
Piedmont	1,085.4	244.3	12.0	218.3	9.5	3.07	3.0
Valle d'Aosta	23.9	189.3	7.6	200.1	7.9	2.59	6.6
Lombardy	2,163.1	219.2	12.0	117.9	5.7	5.10	9.9
A.P. of Bolzano	120.9	243.5	10.6	217.3	8.3	3.07	5.1
A.P. of Trento	115.2	217.1	9.7	203.4	6.0	2.92	9.4
Veneto	1,227.3	251.4	13.7	227.7	3.3	3.02	14.4
Friuli VG	321.1	254.0	7.8	204.9	13.7	3.40	-4.0
Liguria	442.3	268.0	12.5	225.6	3.0	3.26	13.2
Emilia Romagna	1,255.0	279.9	8.8	317.5	2.5	2.41	17.0
Tuscany	957.6	250.3	4.0	209.4	-2.6	3.28	5.8
Umbria	248.4	276.5	2.6	234.0	5.2	3.24	3.8
Marche	443.2	288.3	12.1	232.5	1.8	3.40	13.0
Lazio	1,388.7	245.6	5.3	144.0	6.4	4.67	2.9
Abruzzo	367.0	282.4	10.0	159.2	5.4	4.86	7.0
Molise	76.1	251.7	9.7	154.1	15.3	4.47	-4.3
Campania	1,507.0	290.3	8.8	177.9	15.1	4.47	-2.6
Puglia	1,063.1	275.1	5.7	156.3	1.7	4.82	8.8
Basilicata	147.2	269.6	9.0	164.7	11.2	4.48	-3.0
Calabria	498.4	275.5	8.7	162.2	13.3	4.65	1.3
Sicily	1,068.8	229.4	2.6	147.5	6.9	4.26	5.2
Sardinia	438.1	265.0	7.6	191.3	11.3	3.80	-0.3
Italy	**14,957.6**	**253.6**	**8.6**	**184.6**	**5.7**	**3.76**	**6.8**
North	6,754.0	243.5	11.4	199.7	5.2	3.34	10.6
Centre	3,037.9	255.0	5.6	183.2	2.0	3.81	5.8
South and Islands	5,165.6	267.3	6.8	163.9	9.3	4.47	2.5

Source: OsMed analysis on NSIS data related to the "Traceability of medicines" - Ministerial Decree 15 July 2004

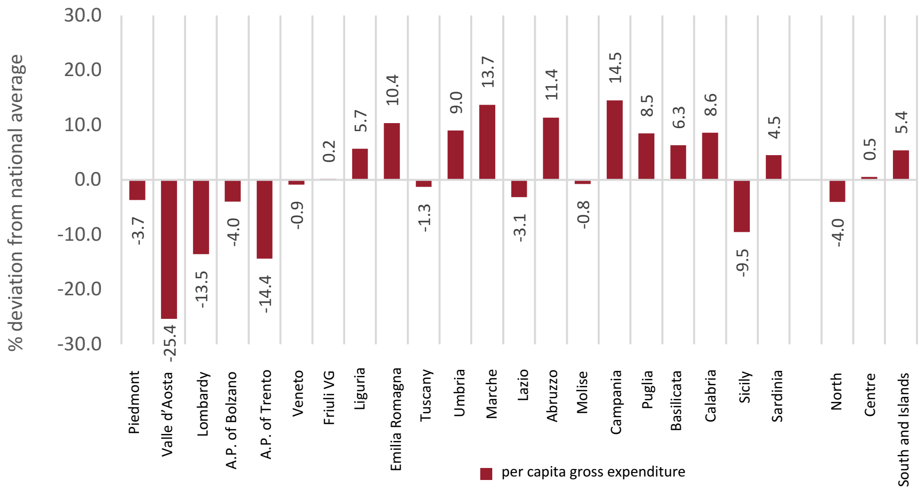


Table 1.3.2 Regional variability of consumption of medicines purchased by public health facilities in 2022 by quantity, average cost per day of therapy and expenditure (% deviations from national average) (Table and Figure)

Region	% deviation from national average			Expenditure rank
	DDD/1000 inhab. per day	DDD Average cost	Gross *per capita* expenditure	
Campania	-4	19	14	1
Marche	26	-10	14	2
Abruzzo	-14	30	11	3
Emilia Romagna	72	-36	10	4
Umbria	27	-14	9	5
Calabria	-12	24	9	6
Puglia	-16	29	8	7
Basilicata	-11	19	6	8
Liguria	22	-14	6	9
Sardinia	4	1	4	10
Friuli VG	11	-10	0	11
Molise	-17	19	-1	12
Veneto	23	-20	-1	13
Tuscany	13	-13	-1	14
Lazio	-22	25	-3	15
Piedmont	18	-18	-4	16
A.P. of Bolzano	18	-19	-4	17
Sicily	-20	13	-10	18
Lombardy	-36	35	-14	19
A.P. of Trento	10	-22	-14	20
Valle d'Aosta	9	-31	-25	21
North	8	-11	-4	
Centre	-1	1	1	
South and Islands	-11	19	5	

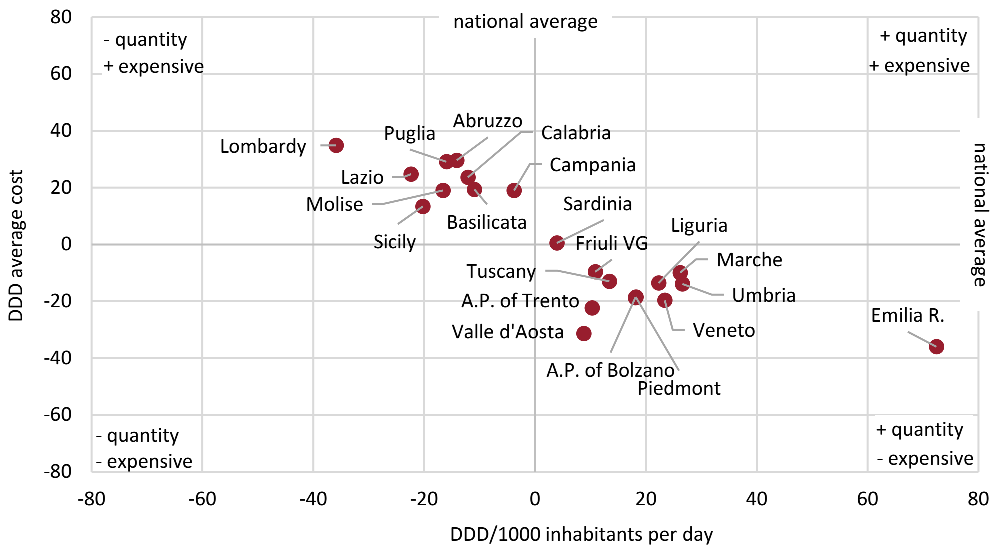


Table 1.3.3 Consumption, price and mix effect on the variation of expenditure for medicines purchased by public health facilities: comparison 2022-2021

Region	Gross expenditure 2022 *(million)*	Δ % 2022-2021				DDD Average cost 2022	Δ % 22-21
		expenditure	DDD	prices	mix		
Piedmont	1,039.7	10.2	14.1	-10.1	7.4	3.07	3.0
Valle d'Aosta	22.9	7.2	9.7	-28.5	36.7	2.59	6.6
Lombardy	2,049.6	11.9	5.9	-6.1	12.5	5.10	9.9
A.P. of Bolzano	114.9	10.3	10.5	-27.8	38.2	3.07	5.1
A.P. of Trento	107.3	8.6	2.4	-23.1	37.9	2.92	9.4
Veneto	1,157.4	12.5	7.8	-7.9	13.3	3.02	14.4
Friuli VG	307.5	7.7	5.0	-26.7	40.0	3.40	-4.0
Liguria	422.5	10.7	7.3	-11.3	16.3	3.26	13.2
Emilia Romagna	1,200.9	9.1	4.8	-9.8	15.4	2.41	17.0
Tuscany	919.5	2.8	1.4	-13.5	17.2	3.28	5.8
Umbria	238.4	2.2	4.0	-14.6	15.1	3.24	3.8
Marche	429.3	11.7	3.1	-10.2	20.7	3.40	13.0
Lazio	1,333.7	5.9	8.8	-8.7	6.6	4.67	2.9
Abruzzo	355.0	9.9	14.4	-13.6	11.2	4.86	7.0
Molise	73.1	9.1	5.4	-23.3	35.0	4.47	-4.3
Campania	1,454.4	9.3	12.0	-9.3	7.6	4.47	-2.6
Puglia	1,021.1	5.9	1.0	-10.2	16.7	4.82	8.8
Basilicata	141.3	7.6	10.7	-16.4	16.3	4.48	-3.0
Calabria	480.7	8.6	8.1	-39.9	67.0	4.65	1.3
Sicily	1,017.3	2.6	-5.6	-10.5	21.6	4.26	5.2
Sardinia	425.1	7.5	5.9	-11.8	15.1	3.80	-0.3
Italy	**14,311.6**	**8.3**	**6.0**	**-5.1**	**7.6**	**3.76**	**6.8**
North	6,422.7	10.8	7.4	-5.1	8.7	3.34	10.6
Centre	2,920.9	5.4	4.6	-6.5	7.8	3.81	5.8
South and Islands	4,968.0	6.9	4.7	-5.8	8.5	4.47	2.5

Note: expenditure is net of vaccines and oxygen

1.4 Pharmaceutical consumption by age and gender

The use of pharmaceuticals in the population may depend on different factors, including socio-demographic characteristics, epidemiological profiles of the populations, a variety of healthcare settings and the different prescribing attitudes of physicians. The aim of this section is to provide, within the approved care regime and the "on behalf" distribution, a description of consumption and expenditure, as well as of the prevalence of use of medicines by age and sex in the general population. Data for this analysis derive from the information flow of prescriptions of medicines charged to the NHS (*tessera sanitaria*) and provided through public and private pharmacies. This flow covers the whole Italian population.
Overall, in 2022, 66.3% of the population received at least one pharmaceutical prescription, with a *per capita* expenditure of €203 and a consumption of 1,182 DDD/1000 inhabitants per day (this suggests that on average every Italian citizen received slightly more than one dose of medicine every day of the year) (Tables 1.4.1 and 1.4.2).
There is a slight difference in the exposure to medicines between the two sexes, with a prevalence of 62.0% in males and of 70.4% in females. As far as consumption and expenditure are concerned, the number of doses registered are 1,111 DDD in males and 1,250 in females, whereas pharmaceutical expenditure is equal to 200.9 euros *per capita* in males and 205.5 euros *per capita* in females (Table 1.4.1 and Figure 1.4.1).
As expected, the trend of pharmaceutical expenditure and consumption increases with the ageing of population. The *per capita* pharmaceutical expenditure borne by the NHS is three times higher in the +75 age group compared to the national average value. Moreover, for citizens older than 64, the pharmaceutical expenditure is six times higher than the average expenditure for people younger than 40 (Table 1.4.1). This result is due to change both in the prevalence of use and in consumption. The prevalence of use ranges from about 50% in children and adults up to 49 years of age, to over 90% in the elderly population up to 74 years, and to 100% in the population aged +74 years. Consumption is between 313.8 and 475.9 DDD/1000 inhabitants per day in the 40-49 age group and reaches over 4,000 in the population over 75 years of age (Figure 1.4.1 and 1.4.2, Table 1.4.1). This shows that each person in this age group has taken at least 4 doses of medicine every day of the year. The population over 64 years of age accounts for more than 60% of expenditure and DDD (Table 1.4.1).
Sex differences can be seen especially in the 15-69 age group, where females show a higher prevalence of use than male (Figure 1.4.1). Compared to a prevalence of use of 66.3% at a national level in 2022, the values of the different Regions vary between 52.8% in the P.A. of Bolzano and 74.0% in Abruzzo (Table 1.4.2). Generally, Northern Regions have a lower prevalence (63.1%) compared to Central (68.6%) and Southern (69.5%) ones. An expenditure of €325.0 per user was incurred in the South (+6.2% compared to the national average of €306.4), compared to €290.5 in the North and €308.2 in the Centre. These differences are mainly due to increased consumption, to the prescription of more expensive products and to a reduced use of generic medicines. As a matter of fact, more doses per user are dispensed in the South (662.1 DDD) than in the Centre (651.1 DDD) and in the North (640.9 DDD), which could reflect a different epidemiological distribution of the pathologies, both in terms of severity and the presence of comorbidity, and a different prescriptive attitude of doctors. Compared to 2021, the prevalence of use increased, while both doses per user and expenditure per user reported a decrease, by 5.2 % and 4.5 % respectively,

with the greatest reductions in the Centre. In relation to the two sexes (Table 1.4.3), there are no differences in the average age of the users, which is equal to 51 and 54 years in men and women respectively, while there are differences in consumption, which is higher in men in terms of DDD per user (653.7 in men and 647.8 in women) and in terms of packages per user (28.2 in men and 27.0 in women). At regional level, Friuli VG records the highest DDDs per user in both males and females (723.1 and 678.6 DDDs respectively), while in the A.P. of Bolzano the lowest number of doses and packages per user is observed in both males and females (Table 1.4.3).

This consumption trend is also reflected in the expenditure sustained per user, which is equal to €323.8 in males and €291.8 in females; with a maximum value for males in Lazio (€368.13) and in Calabria for females (€334.66) (Table 1.4.3).

The greatest differences in prevalence of use between the two sexes are found in the ATCs A-Gastrointestinal system, G-Genitourinary system, H-Systemic hormonal preparations, excluding sex hormones and insulin, and N-Central nervous system (Table 1.4.4).

With the exception of ATC G, the prevalence of use of these ATCs is higher in women than in men. These differences are also reflected in the indicators of consumption (DDD/1000 inhab. per day) and expenditure *per capita*. For example, for ATC N, where the prevalence of use in females is 16.6% and in males it is 10.3%, consumption in females is 91.0 DDD/1000 inhab. per day and in males 58.2 DDD/1000 inhab. per day, and similarly, *per capita* expenditure is higher in females at € 28.2 compared to € 20.5 in males. Conversely, analysing the indicators by user, both higher consumption and expenditure are observed in males than in females.

Assessing the highest-consumption ATC level IV categories, the greatest differences between the two sexes in terms of consumption are recorded for the group relating to vitamin D and analogues, thyroid hormones and alpha-adrenergic receptor antagonists. For all these groups, consumption is higher in females than in males, with the exception of alpha-adrenergic receptor antagonists, which are used almost exclusively in males (Table 1.4.5). Looking at the ATC level IV categories with the highest *per capita* expenditure, on the other hand, the highest differences between the two sexes were recorded for the group relating to vitamin D and analogues, other antidepressants, selective serotonin reuptake inhibitors and alpha-adrenergic receptor antagonists; only for the latter category was there a higher expenditure for males than for females (Table 1.4.6). In addition, it is noted that for men there is generally a greater intensity of use of medicines, especially for the categories relating to chronic diseases, probably due to the higher dosages to take account of weight differences.

Among the first 20 active ingredients by consumption, important differences between the two sexes are observed for cholecalciferol and levothyroxine, used more in females, and for tamsulosin, the latter being used almost exclusively in males. Higher consumption in males is also recorded for ramipril, acetylsalicylic acid, amlodipine, metformin and atorvastatin (Table 1.4.7). For the other statins, there is higher consumption in females for simvastatin and almost similar consumption between males and females for rosuvastatin. Among the first 20 active ingredients by expenditure (Table 1.4.8), important differences between the two sexes can be observed on the one hand for dulaglutide, semaglutide and omega-3, which show a higher expenditure among males, and on the other hand for cholecalciferol and enoxaparin, which show the highest expenditure among females.

Table 1.4.1 Breakdown of local expenditure and consumption by age group and sex (year 2022)

Age group	*Per capita* gross expenditure			Total expenditure		DDD/1000 inhab. per day			Total DDD	
	males	females	total	%	cum. %	males	females	total	%	cum. %
0-4	23.2	19.8	21.5	0.4	0.4	110.5	101.1	105.9	0.3	0.3
5-9	24.5	21.8	23.2	0.5	0.9	65.9	58.2	62.2	0.2	0.6
10-14	31.1	24.2	27.8	0.7	1.5	67.1	59.0	63.2	0.3	0.8
15-19	40.3	28.6	34.6	0.8	2.4	90.9	102.1	96.3	0.4	1.2
20-24	34.1	36.5	35.3	0.9	3.2	104.5	140.1	121.5	0.5	1.7
25-29	39.8	42.7	41.2	1.1	4.3	119.1	165.7	141.7	0.6	2.3
30-34	43.9	56.2	50.0	1.4	5.6	145.7	214.9	179.9	0.8	3.2
35-39	53.5	71.5	62.5	1.8	7.4	192.6	266.3	229.3	1.1	4.3
40-44	68.4	85.2	76.8	2.6	10.0	281.4	346.0	313.8	1.8	6.1
45-49	94.5	103.1	98.8	3.8	13.8	447.9	503.6	475.9	3.2	9.3
50-54	138.2	143.0	140.6	5.6	19.5	725.5	796.8	761.7	5.2	14.5
55-59	207.7	196.9	202.2	7.8	27.3	1,164.8	1,204.1	1,184.9	7.8	22.4
60-64	307.7	270.6	288.5	9.5	36.8	1,771.1	1,719.1	1,744.2	9.9	32.3
65-69	426.1	361.5	392.2	11.3	48.1	2,498.8	2,353.3	2,422.5	12.0	44.3
70-74	517.5	437.2	474.8	13.5	61.6	3,064.8	2,871.5	2,961.9	14.5	58.8
75-79	703.8	589.0	640.4	13.5	75.1	4,180.9	3,861.5	4,004.4	14.5	73.3
80-84	720.2	605.0	653.2	12.3	87.4	4,275.1	3,948.2	4,085.0	13.2	86.5
85+	799.6	629.4	686.4	12.6	100.0	4,718.2	4,050.4	4,274.0	13.5	100.0
Total	**200.9**	**205.5**	**203.2**	**100.0**	**0.0**	**1,111.1**	**1,250.0**	**1,182.3**	**100.0**	

Figure 1.4.1 Trend in prevalence of use of local pharmaceuticals by age and sex (year 2022)

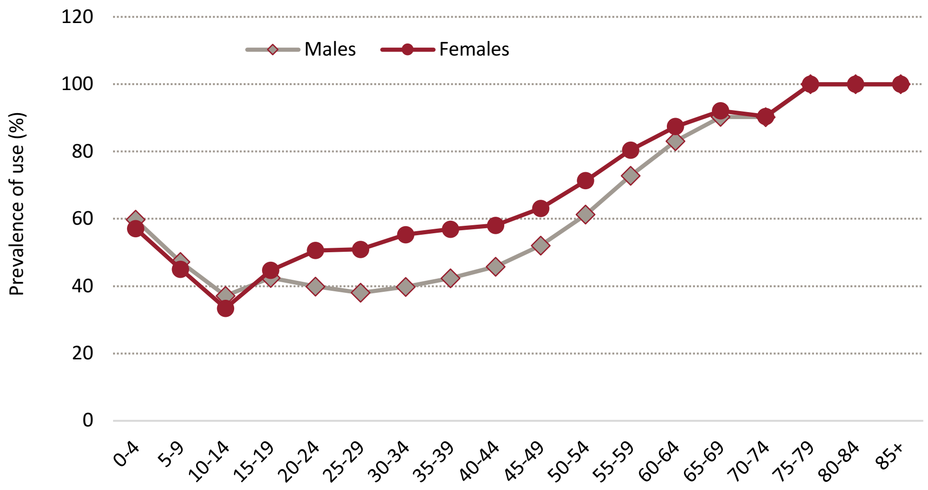


Figure 1.4.2 Trend in local DDD/1000 inhabitants per day by age and sex (year 2022)

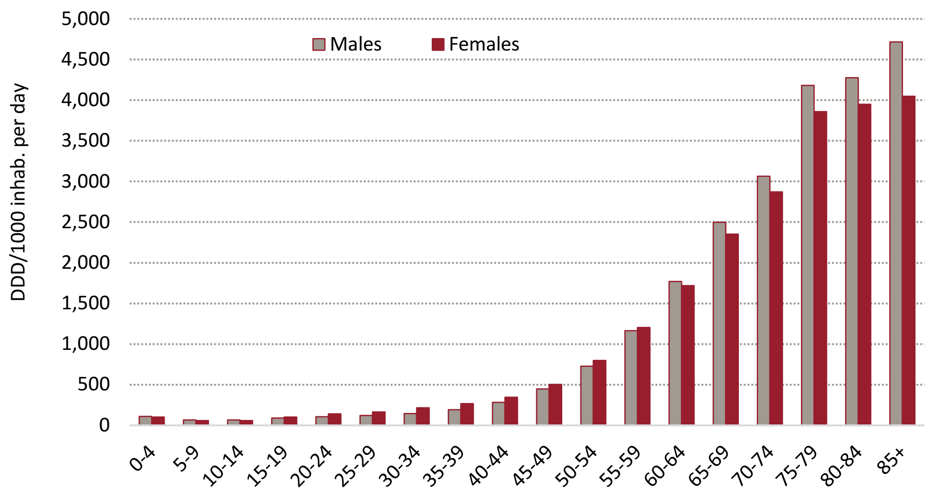


Table 1.4.2 Prevalence and intensity of use in local setting by Region (2020-2022)

Region	Prevalence of use (%)				Expenditure per user				DDD per user			
	2020	2021	2022	Δ % 21-22	2020	2021	2022	Δ % 21-22	2020	2021	2022	Δ % 21-22
Piedmont	60.8	61.7	65.4	6.0	293.04	294.31	284.72	-3.3	666.4	677.0	648.2	-4.3
Valle d'Aosta	58.0	57.7	60.7	5.2	276.29	271.71	265.69	-2.2	606.9	615.0	589.0	-4.2
Lombardy	57.4	57.9	61.4	6.1	348.63	349.18	332.09	-4.9	672.6	685.5	636.7	-7.1
A.P. of Bolzano	47.6	48.1	52.8	9.8	266.10	271.90	251.99	-7.3	595.6	604.9	570.2	-5.7
A.P. of Trento	61.6	62.1	66.0	6.2	259.62	264.81	258.77	-2.3	605.7	617.1	593.2	-3.9
Veneto	57.2	57.3	61.2	6.8	277.57	281.01	271.23	-3.5	665.2	672.1	634.3	-5.6
Friuli VG	60.6	61.1	64.2	5.1	315.55	313.67	305.51	-2.6	705.8	715.7	698.5	-2.4
Liguria	60.4	60.8	65.2	7.3	322.76	318.32	303.20	-4.7	686.2	691.4	654.9	-5.3
Emilia Romagna	62.0	62.5	66.7	6.7	224.54	229.95	229.52	-0.2	639.4	659.6	643.6	-2.4
Tuscany	62.2	62.8	66.9	6.6	273.48	280.39	263.88	-5.9	681.0	694.9	650.6	-6.4
Umbria	67.0	67.0	70.5	5.3	337.02	336.86	298.89	-11.3	730.9	745.9	684.0	-8.3
Marche	66.3	66.9	70.7	5.7	304.56	306.59	294.83	-3.8	651.4	667.4	637.4	-4.5
Lazio	64.7	64.8	68.9	6.3	353.22	355.55	340.85	-4.1	672.4	686.2	650.1	-5.3
Abruzzo	69.3	69.7	74.0	6.2	317.87	319.41	308.36	-3.5	639.3	657.4	622.3	-5.3
Molise	68.0	69.0	71.4	3.4	328.60	330.04	309.25	-6.3	653.3	683.1	647.6	-5.2
Campania	65.3	66.9	69.0	3.1	350.70	356.91	339.89	-4.8	692.6	711.4	667.5	-6.2
Puglia	68.8	69.4	72.3	4.3	330.87	342.42	317.59	-7.2	660.2	675.7	647.0	-4.2
Basilicata	67.4	69.4	73.0	5.1	331.09	340.63	326.55	-4.1	672.4	695.4	673.9	-3.1
Calabria	61.6	63.2	66.1	4.6	382.14	369.37	360.41	-2.4	705.6	719.9	692.3	-3.8
Sicily	63.0	64.0	67.1	4.9	324.00	326.96	311.55	-4.7	684.0	690.9	661.7	-4.2
Sardinia	66.0	67.1	69.6	3.8	321.90	318.14	308.26	-3.1	693.2	705.9	681.2	-3.5
Italy	**62.2**	**62.8**	**66.3**	**5.6**	**317.83**	**320.66**	**306.37**	**-4.5**	**672.5**	**685.9**	**650.5**	**-5.2**
North	58.8	59.3	63.1	6.4	299.91	300.75	290.51	-3.4	664.0	676.1	640.9	-5.2
Centre	64.3	64.6	68.6	6.2	321.48	324.51	308.21	-5.0	676.7	690.9	651.1	-5.8
South and Islands	65.5	66.7	69.5	4.2	337.76	339.52	325.03	-4.3	680.4	695.1	662.1	-4.8

Table 1.4.3 Prevalence and intensity of use in local setting by Region and sex (year 2022)

Region	Prevalence of use (%)		Average age		Expenditure per user		DDD per user		Packages per user	
	M	F	M	F	M	F	M	F	M	F
Piedmont	60.6	69.8	53	55	301.38	271.04	662.9	636.1	28.1	26.1
Valle d'Aosta	55.9	65.4	53	55	285.50	249.50	608.0	573.5	26.5	24.2
Lombardy	57.2	65.3	51	53	358.47	309.90	643.4	631.0	26.7	24.9
A.P. of Bolzano	48.3	57.2	50	52	270.54	236.63	576.6	564.9	23.2	21.3
A.P. of Trento	61.6	70.3	50	52	271.15	248.28	603.9	584.1	26.0	24.5
Veneto	57.4	64.9	52	54	290.43	254.89	655.0	616.6	26.7	24.0
Friuli VG	59.2	69.0	54	56	329.07	286.37	723.1	678.6	30.0	27.3
Liguria	61.0	69.1	55	58	316.24	292.60	649.2	659.4	27.7	27.0
Emilia Romagna	62.2	70.9	51	54	240.18	220.64	646.0	641.7	27.0	25.9
Tuscany	62.7	70.8	53	55	279.23	251.17	659.9	642.9	27.6	26.4
Umbria	66.3	74.5	53	55	317.99	283.03	706.1	665.6	30.0	28.2
Marche	66.9	74.3	52	54	311.75	280.39	654.8	622.5	28.4	26.6
Lazio	64.3	73.2	51	53	368.13	318.46	650.2	649.9	29.1	28.5
Abruzzo	69.9	78.0	51	53	319.29	299.02	621.1	623.3	27.6	27.1
Molise	67.0	75.6	52	55	326.51	294.45	641.4	653.0	29.0	28.3
Campania	65.1	72.8	49	51	348.82	332.29	657.1	676.4	29.5	29.1
Puglia	68.0	76.4	51	53	328.91	308.04	638.9	653.8	28.8	28.3
Basilicata	68.5	77.3	51	53	340.04	314.98	656.9	688.5	29.9	29.7
Calabria	61.9	70.2	51	53	391.00	334.55	697.3	688.0	32.2	31.1
Sicily	62.8	71.3	51	53	321.75	303.05	658.3	664.6	29.0	28.5
Sardinia	64.2	74.8	53	55	319.95	298.59	661.8	697.2	28.6	28.1
Italy	**62.0**	**70.4**	**51**	**54**	**323.80**	**291.79**	**653.7**	**647.8**	**28.2**	**27.0**
North	58.8	67.2	52	54	310.10	274.14	650.7	632.7	27.1	25.3
Centre	64.3	72.7	52	54	329.75	290.38	658.0	645.4	28.6	27.6
South and Islands	65.2	73.5	50	52	337.34	314.65	654.9	668.1	29.3	28.8

Figure 1.4.3 Distribution of local consumption by age group and ATC 1st level (Males - year 2022)

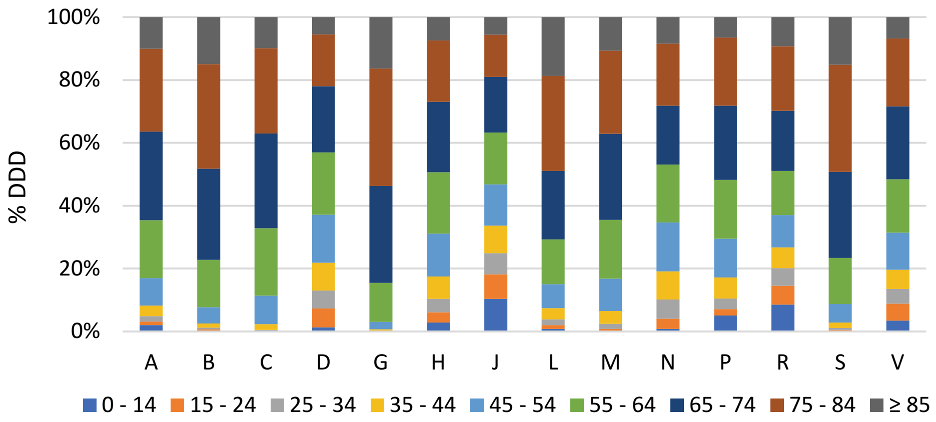


Figure 1.4.4 Distribution of local consumption by age group and ATC 1st level (Females - year 2022)

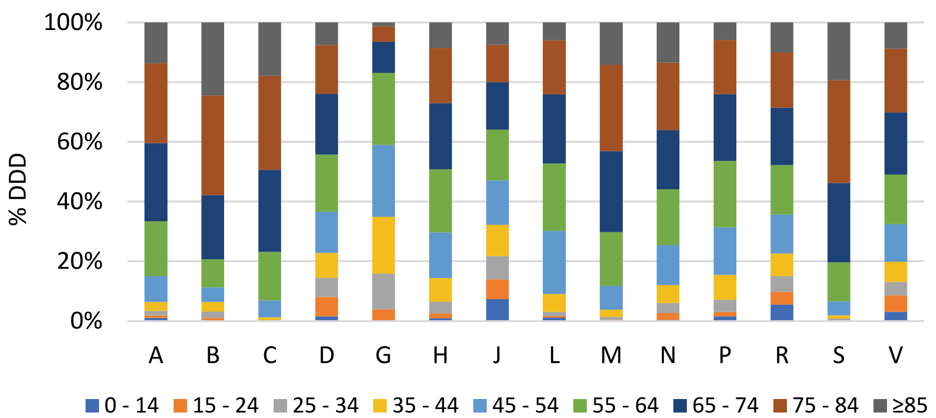


Table 1.4.4 Prevalence, expenditure, consumption and intensity of use in local setting by ATC 1st level and sex (year 2022)

ATC 1st level	Prevalence of use (%)			*Per capita* expenditure			DDD/1000 inhab. per day			Expenditure per user			DDD per user		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
A	25.8	35.3	30.7	43.70	44.41	44.07	211.8	374.2	295.1	169.44	125.69	143.60	299.7	386.5	351.0
B	16.0	18.4	17.3	23.08	19.46	21.22	120.1	112.8	116.4	144.02	105.59	122.97	273.6	223.4	246.1
C	29.1	30.9	30.0	54.08	49.27	51.61	500.7	461.5	480.6	185.94	159.32	171.88	628.3	544.8	584.2
D	1.6	1.4	1.5	1.63	1.04	1.33	5.8	4.1	4.9	104.20	75.65	90.51	134.8	109.3	122.6
G	8.9	2.3	5.5	9.90	2.90	6.31	81.1	9.3	44.2	111.46	123.72	114.13	333.2	144.1	292.1
H	12.7	20.3	16.6	4.60	7.22	5.95	23.1	53.2	38.6	36.20	35.52	35.78	66.2	95.6	84.6
J	33.2	40.0	36.7	10.43	11.83	11.15	14.1	16.3	15.3	31.45	29.60	30.41	15.5	14.9	15.2
L	1.2	2.0	1.6	7.02	10.65	8.88	5.4	12.6	9.1	605.86	521.04	550.72	169.8	225.3	205.9
M	16.6	21.4	19.1	3.66	8.74	6.26	30.6	50.9	41.0	22.07	40.79	32.87	67.3	86.7	78.5
N	10.3	16.6	13.5	20.49	28.22	24.46	58.2	91.0	75.0	198.86	169.70	180.50	206.1	199.7	202.1
P	0.6	1.1	0.9	0.12	0.32	0.23	0.4	1.5	1.0	19.05	28.39	25.16	25.1	48.9	40.7
R	14.0	15.3	14.7	16.85	15.83	16.33	39.9	40.5	40.2	120.23	103.27	111.16	103.9	96.4	99.9
S	2.1	2.4	2.2	3.39	3.77	3.59	19.8	22.0	21.0	165.11	156.36	160.27	352.8	333.2	342.0
V	0.6	0.7	0.7	1.96	1.85	1.91	0.3	0.2	0.2	303.24	269.09	285.17	17.9	9.7	13.6

Table 1.4.5 Prevalence, expenditure, consumption and intensity of use at local level by sex for the top 20 ATC 4th level by consumption (year 2022)

Subgroups (level IV ATC)	Prevalence of use (%)			Expenditure *per capita*			DDD/1000 inhab. per day			Expenditure per user			DDD per user		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Vitamin D and analogues	5.1	18.1	11.8	1.78	7.30	4.61	53.1	215.7	136.51	34.61	40.39	39.16	377.6	435.6	423.3
HMG-CoA reductase inhibitors	11.1	11.5	11.3	8.25	7.75	7.99	88.8	72.9	80.67	73.99	67.54	70.64	290.9	232.0	260.2
ACE inhibitors, not in combination	6.7	5.6	6.1	3.83	3.17	3.49	89.0	69.2	78.86	57.32	56.44	56.91	486.9	449.3	469.2
Proton pump inhibitors	16.3	19.8	18.1	10.26	12.05	11.18	69.9	81.8	76.00	62.80	60.98	61.78	156.1	151.1	153.3
Platelet aggregation inhibitors, excluding heparin	9.8	8.6	9.1	4.95	3.08	3.99	74.9	59.7	67.14	50.68	36.03	43.65	280.2	254.8	268.0
Angiotensin II (ARBS) receptor blockers, not in combination	5.7	6.0	5.8	4.67	4.96	4.82	56.3	57.5	56.90	82.23	82.66	82.45	361.6	349.4	355.2
Dihydropyridine derivatives	5.7	5.5	5.6	4.11	3.87	3.99	52.2	45.0	48.47	72.20	70.01	71.10	334.5	296.8	315.4
Beta blockers, selective	9.4	11.0	10.2	4.41	5.34	4.89	36.3	44.4	40.41	46.89	48.65	47.86	140.8	147.4	144.4
Angiotensin II (ARBS) and diuretics receptor blockers	3.6	4.7	4.2	3.16	4.23	3.71	26.7	35.4	31.15	87.75	89.66	88.86	270.3	273.6	272.2
Selective serotonin reuptake inhibitors	2.8	5.9	4.4	2.03	4.54	3.32	18.5	40.6	29.85	73.83	76.78	75.87	245.3	250.5	248.9
Alpha-2 adrenergic receptor antagonists	7.8	0.1	3.8	5.93	0.02	2.90	57.6	0.1	28.11	76.20	17.43	75.48	270.1	56.6	267.5
Sulfonamides, not in combination	4.0	5.2	4.6	0.76	0.84	0.80	23.9	24.1	23.97	18.84	16.22	17.33	216.8	169.9	189.8
Biguanides	4.7	3.9	4.3	1.80	1.47	1.63	25.6	19.9	22.65	38.58	37.72	38.18	200.5	186.2	193.8
Thyroid hormones	1.7	7.9	4.9	0.51	2.25	1.40	8.8	35.1	22.30	29.56	28.29	28.51	185.4	161.4	165.5

continued

Table 1.4.5 – *continued*

Subgroups (level IV ATC)	Prevalence of use (%)			Expenditure *per capita*			DDD/1000 inhab. per day			Expenditure per user			DDD per user		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
ACE inhibitors and diuretics	2.4	2.8	2.6	2.08	2.55	2.32	16.6	19.8	18.23	88.16	90.26	89.33	256.7	255.7	256.2
HMG-CoA reductase inhibitors with other lipid modifying agents	2.9	2.3	2.6	3.24	2.49	2.86	18.7	14.1	16.37	111.98	106.10	109.27	235.6	219.9	228.4
Glycocorticoids	11.0	13.6	12.3	1.33	1.65	1.50	12.8	15.6	14.26	12.05	12.17	12.12	42.4	42.0	42.2
Vitamine B12 (cyanocobalamin and derivatives)	0.5	0.8	0.7	0.09	0.12	0.11	11.4	15.4	13.45	16.88	15.97	16.34	779.0	738.1	754.6
Direct Xa factor inhibitors	2.2	2.0	2.1	8.40	7.97	8.18	14.1	12.4	13.20	384.98	391.44	388.18	235.4	222.0	228.8
Adrenergic in combination with corticosteroids or others, excluding anticolinergics	3.2	3.5	3.3	6.81	7.26	7.04	11.8	12.5	12.14	215.55	208.55	211.79	136.1	130.9	133.3

Table 1.4.6 Prevalence, expenditure, consumption and intensity of use at local level by sex for the top 20 ATC 4th level by expenditure (year 2022)

Subgroups (level IV ATC)	Prevalence of use (%)			Expenditure *per capita*			DDD/1000 inhab. per day			Expenditure per user			DDD per user		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Proton pump inhibitors	16.3	19.8	18.1	10.26	12.05	11.18	69.9	81.8	76.0	62.80	60.98	61.78	156.1	151.1	153.3
Direct Xa factor inhibitors	2.2	2.0	2.1	8.40	7.97	8.18	14.1	12.4	13.2	384.98	391.44	388.18	235.4	222.0	228.8
HMG-CoA reductase inhibitors	11.1	11.5	11.3	8.25	7.75	7.99	88.8	72.9	80.7	73.99	67.54	70.64	290.9	232.0	260.2
Adrenergic in combination with corticosteroids or other, excluding anticholinergic	3.2	3.5	3.3	6.81	7.26	7.04	11.8	12.5	12.1	215.55	208.55	211.79	136.0	130.9	133.3
GLP-1 receptor analogues (glucagon-like peptide-1)	1.0	0.6	0.8	7.88	5.05	6.43	7.1	4.5	5.8	815.16	798.69	808.44	268.8	262.1	266.1
Beta blockers, selective	9.4	11.0	10.2	4.41	5.34	4.89	36.3	44.4	40.4	46.89	48.65	47.86	140.8	147.4	144.4
Angiotensin II (ARBS) receptor blockers, not in combination	5.7	6.0	5.8	4.67	4.96	4.82	56.3	57.5	56.9	82.23	82.66	82.45	361.6	349.4	355.2
Vitamin D and analogues	5.1	18.1	11.8	1.78	7.30	4.61	53.1	215.7	136.5	34.61	40.39	39.16	377.5	435.6	423.3
Platelet aggregation inhibitors, excl. heparin	9.8	8.6	9.1	4.95	3.08	3.99	74.9	59.7	67.1	50.68	36.03	43.65	280.2	254.8	268.0
Dihydropyridine derivatives	5.7	5.5	5.6	4.11	3.87	3.99	52.2	45.0	48.5	72.20	70.01	71.10	334.5	296.8	315.4
Other lipid modifying subtances	2.5	1.8	2.1	4.69	2.94	3.79	10.2	7.4	8.8	191.00	167.22	180.78	151.6	154.2	152.7

continued

Table 1.4.6 – *continued*

Subgroups (level IV ATC)	**Prevalence of use (%)**			**Expenditure *per capita***			**DDD/1000 inhab. per day**			**Expenditure per user**			**DDD per user**		
	M	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**
Angiotensin II (ARBS) receptor blockers and diuretics	3.6	4.7	4.2	3.16	4.23	3.71	26.7	35.4	31.1	87.75	89.66	88.86	270.3	273.7	272.2
ACE inhibitors, not in combination	6.7	5.6	6.1	3.83	3.17	3.49	89.0	69.2	78.9	57.32	56.44	56.91	486.9	449.3	469.2
Other antiepileptics	0.6	0.9	0.7	3.24	3.62	3.43	4.0	4.6	4.3	518.63	417.64	458.70	233.2	192.7	209.2
Other antidepressants	1.8	3.3	2.6	2.21	4.43	3.35	7.7	16.1	12.0	124.47	132.42	129.76	159.5	175.3	170.0
Selective serotonin reuptake inhibitors	2.8	5.9	4.4	2.03	4.54	3.32	18.5	40.6	29.8	73.83	76.78	75.87	245.3	250.5	248.9
Insulins and injectable analogues, fast-acting	1.1	0.9	1.0	3.69	2.77	3.22	8.2	6.2	7.2	333.00	295.57	315.37	271.4	240.7	256.9
Insulins and injectable analogues, slow-acting	1.5	1.2	1.4	3.65	2.71	3.17	5.6	4.2	4.9	238.98	220.66	230.58	132.8	124.7	129.1
Heparins	2.7	3.5	3.1	2.61	3.48	3.06	4.5	5.9	5.2	97.02	98.78	98.04	61.1	61.6	61.4
Alpha-adrenergic receptor antagonists	7.8	0.1	3.8	5.93	0.02	2.90	57.6	0.1	28.1	76.20	17.43	75.48	270.1	56.6	267.4

Table 1.4.7 Prevalence, expenditure and intensity of use by sex for the top 20 substances by consumption (year 2022)

Substance	Prevalence of use (%)			Expenditure *per capita*			DDD/1000 inhab. per day			Expenditure per user			DDD per user		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
cholecalciferol	4.2	15.2	9.8	1.46	6.35	3.97	52.0	212.2	134.2	35.05	41.74	40.36	454.4	508.8	497.6
ramipril	4.5	3.6	4.0	2.18	1.66	1.91	69.6	51.4	60.3	48.21	46.15	47.27	562.3	522.3	544.1
atorvastatin	6.7	6.0	6.3	5.14	4.07	4.59	59.5	40.8	49.9	76.53	68.30	72.56	322.9	249.9	287.6
Acetylsalicylic acid	7.1	5.9	6.5	1.30	1.05	1.17	50.3	39.6	44.8	18.38	17.86	18.14	259.1	245.8	252.9
pantoprazole	7.8	9.0	8.4	4.25	4.58	4.42	27.4	29.3	28.4	54.58	50.91	52.56	128.3	119.0	123.2
amlodipine	3.7	3.1	3.4	1.79	1.36	1.57	31.7	23.3	27.4	48.77	43.32	46.18	315.6	270.6	294.3
furosemide	3.7	4.6	4.2	0.67	0.69	0.68	23.1	22.6	22.8	18.01	14.86	16.23	224.9	178.0	198.3
metformin	4.7	3.9	4.3	1.80	1.47	1.63	25.6	19.9	22.6	38.58	37.72	38.18	200.5	186.2	193.8
levothyroxine	1.7	7.9	4.9	0.50	2.19	1.37	8.8	35.0	22.3	28.86	27.66	27.86	185.5	161.3	165.5
omeprazole	3.6	4.6	4.1	1.91	2.32	2.12	15.6	18.9	17.3	53.01	51.05	51.89	157.9	151.5	154.3
nebivolol	2.1	3.1	2.6	1.23	1.81	1.53	13.4	19.5	16.5	57.17	58.13	57.75	227.7	228.4	228.1
olmesartan	2.3	2.4	2.4	1.82	1.94	1.88	16.0	16.7	16.4	79.71	80.11	79.92	256.8	251.5	254.0
esomeprazole	3.1	4.2	3.7	1.86	2.51	2.19	13.1	17.7	15.5	59.53	60.26	59.96	153.3	155.3	154.5
rosuvastatin	2.1	2.3	2.2	1.44	1.47	1.46	15.9	15.0	15.4	69.02	64.85	66.79	279.2	240.8	258.6
lansoprazole	2.9	3.5	3.2	1.98	2.28	2.14	12.3	13.9	13.1	69.26	66.11	67.49	156.9	146.8	151.3
bisoprolol	5.8	6.3	6.0	2.62	2.91	2.77	12.2	12.8	12.5	45.46	46.36	45.94	77.4	74.6	75.9
cyanocobalamin	0.5	0.7	0.6	0.07	0.10	0.09	10.1	13.8	12.0	14.44	13.99	14.17	738.6	710.4	721.7
simvastatin	2.0	2.6	2.3	1.18	1.48	1.33	10.0	12.3	11.2	59.06	56.99	57.86	184.0	172.5	177.4
tamsulosin	3.6	0.1	1.8	2.29	0.01	1.12	22.4	0.1	10.9	64.23	12.56	63.32	229.3	44.0	226.0
clopidogrel	1.8	1.4	1.6	1.43	1.14	1.28	12.1	9.3	10.7	81.09	83.52	82.18	250.1	250.4	250.2

Table 1.4.8 Prevalence, expenditure, consumption and intensity of use at local level by sex for the top 20 substances by expenditure (year 2022)

Substance	Prevalence of use (%)			Expenditure *per capita*			DDD/1000 inhab. per day			Expenditure per user			DDD per user		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
atorvastatin	6.7	6.0	6.3	5.14	4.07	4.59	59.5	40.8	49.9	76.5	68.3	72.6	322.9	249.9	287.6
pantoprazole	7.8	9.0	8.4	4.25	4.58	4.42	27.4	29.3	28.4	54.6	50.9	52.6	128.3	119.0	123.2
cholecalciferol	4.2	15.2	9.8	1.46	6.35	3.97	52.0	212.2	134.2	35.1	41.7	40.4	454.4	508.8	497.6
dulaglutide	0.6	0.3	0.4	4.61	2.77	3.67	4.7	2.8	3.7	833.6	820.8	828.6	309.1	302.3	306.5
apixaban	0.8	0.8	0.8	3.24	3.22	3.23	5.2	4.8	5.0	385.4	389.1	387.3	227.4	212.0	219.5
rivaroxaban	0.9	0.7	0.8	3.29	2.70	2.99	5.8	4.7	5.2	386.9	397.1	391.5	248.6	250.1	249.3
enoxaparin	2.5	3.2	2.8	2.37	3.15	2.77	4.2	5.5	4.9	96.6	99.2	98.1	62.6	63.7	63.2
bisoprolol	5.8	6.3	6.0	2.62	2.91	2.77	12.2	12.8	12.5	45.5	46.4	45.9	77.4	74.6	75.9
amoxicillin/ Clavulanic acid	15.2	16.7	15.9	2.42	2.66	2.54	4.8	5.4	5.1	16.0	15.9	16.0	11.7	11.7	11.7
formoterol/ beclomethasone	1.1	1.3	1.2	2.30	2.65	2.48	3.7	4.2	4.0	209.8	199.6	204.1	122.2	116.3	118.9
semaglutide	0.4	0.3	0.3	2.74	1.87	2.29	1.8	1.3	1.5	760.0	740.0	751.5	184.8	182.7	183.9
esomeprazole	3.1	4.2	3.7	1.86	2.51	2.19	13.1	17.7	15.5	59.5	60.3	60.0	153.3	155.3	154.5
lansoprazole	2.9	3.5	3.2	1.98	2.28	2.14	12.3	13.9	13.1	69.3	66.1	67.5	156.9	146.8	151.3
omeprazole	3.6	4.6	4.1	1.91	2.32	2.12	15.6	18.9	17.3	53.0	51.0	51.9	157.9	151.5	154.3
omega 3	1.5	0.9	1.2	2.88	1.38	2.11	3.4	1.6	2.5	187.9	162.0	178.3	81.5	69.2	77.0
mesalazine	1.0	1.0	1.0	2.29	1.89	2.09	5.7	4.8	5.3	239.4	186.5	211.5	217.8	173.2	194.3
vilanterol/ fluticasone furoate	0.8	0.8	0.8	2.05	2.09	2.07	3.5	3.6	3.5	272.5	258.2	264.9	169.7	160.8	164.9
edoxaban	0.5	0.6	0.5	1.86	2.05	1.96	3.0	2.9	3.0	354.6	362.0	358.5	210.6	188.2	198.7
ramipril	4.5	3.6	4.0	2.18	1.66	1.91	69.6	51.4	60.3	48.2	46.2	47.3	562.3	522.3	544.1
olmesartan	2.3	2.4	2.4	1.82	1.94	1.88	16.0	16.7	16.4	79.7	80.1	79.9	256.8	251.5	254.0

1.5 Use of pharmaceuticals in the paediatric age

This section presents an analysis of the use of pharmaceuticals in the paediatric age taking into consideration data from all Italian regions, with a resident paediatric population (age <18 years) of 9.1 million individuals in 2022.
In 2022 almost 4.2 million children and adolescents received at least one pharmaceutical prescription, representing 45.0% of the general paediatric population, with a slightly higher prevalence in males than females (46.1% vs. 43.8%) (Table 1.5.1). Furthermore, in the same year, 17.4 million prescriptions were issued, for a total of 17.7 million packages (approximately 1.9 packs per user) and a total expenditure of €244.5 million euros (€26.4 *per capita* and €58.63 per user). As in 2021, an increase in consumption in terms of both prescriptions (+31.7%) and packages (+31.0%) as well as *per capita* expenditure (+18.7%) can be observed in 2022, while expenditure per user decreases (-7.4%).
During the year, each child received 1.9 prescriptions and 1.9 packages of pharmaceuticals, without significant differences between males and females (Table 1.5.1).
At regional level there is a marked variability in the use of medicines in the paediatric age, with an increasing North-South gradient in the prevalence of use; in particular, the prevalence level varies from a minimum of 36% in the Province of Bolzano to a maximum of 55% in Abruzzo (Figure 1.5.1).
The prevalence of use peaks in the pre-school age group (1-5 years) (61.4%), and then gradually decreases in the following years to reach a value of 38.4% in the 12-17 age group (Figure 1.5.2). A similar trend by age concerns consumption, with the number of packs *per capita* going from 2.7 in pre-school children (1-5 years) to 1.6 in school children (6-11 years) to 1.7 in adolescents (12-17 years), with a negligible difference by sex: 2.0 packages for males versus 1.8 packages for females (Table 1.5.2). Compared to the year 2021, there was an increase in the number of packages *per capita* in both males and females, and when analysing the age groups, it can be noticed that the increase was more concentrated in children between 6 and 11 years of age, although an increase in consumption affected all age groups (Table 1.5.2).
As expected, antimicrobials for systemic use are the medicines with the highest consumption (39.3% of the total number of packages prescribed in the Italian paediatric population), followed by medicines for the respiratory system (27.3%) (Figure 1.5.3).
The analysis of distribution of consumption by sex shows a higher use in males than in females for all therapeutic categories, with the exception of medicines for the genito-urinary system and sexual hormones (females 65.5% vs males 34.5%), anti-neoplastic and immunomodulatory medicines (females 64.0% vs males 36.0%), anti-parasitics, insecticides and repellents (females 52.9% vs males 47.1%) and medicines belonging to the blood and haemopoietic organs category (females 50.2% vs males 49.8%) (Figure 1.5.4).
Antimicrobials for systemic use are confirmed as the therapeutic category with the highest consumption in the paediatric age group, with a prevalence of 444.2 per 1000 children and a number of packs per 1000 children of 752.4, with an increase of 53.3% compared to 2021 (Table 1.5.3), despite the downward trend observed in previous years (2021-2020: -4.0% and 2020-2019: -46.0%). In 2022, the prescribing pattern of antibiotics in the Italian paediatric population was again confirmed: the combination amoxicillin/clavulanic acid was the most prescribed medicine in the category (281.7 packs per 1000 children), up by 57.2%

compared to 2021, confirming its position in the first place among the 30 active ingredients with the highest consumption in 2022 (Table 1.5.4). It is followed by amoxicillin alone (117.3 packs per 1,000 children, +67.5% compared to 2021), the antibiotic of first choice in the treatment of the most common paediatric infections according to the guidelines (and therefore to be preferred over the combination with clavulanic acid), which ranks third in the ranking of the top 30 active ingredients by consumption, and azithromycin (92.2 packs per 1,000 children, +28.8% compared to 2021), which ranks sixth.

In the list of the most prescribed categories, respiratory system medicines follow, with a prevalence of 286.2 per 1000 children and 522.9 packs per 1000 children. After the significant reduction in packages observed in 2020 (-30.3%), there was a recovery in consumption in 2021 and 2022, with an increase of 13.4% and 36.9%, respectively, over the previous year. Medications indicated for the treatment of bronchial asthma, such as inhaled corticosteroids, beclomethasone and budesonide, and salbutamol, a selective beta-2 adrenergic receptor agonist, show higher prevalence of use and consumption values within the category, with strong increases in prescriptions compared to 2021 (from +37.2% for salbutamol to +76.9% for budesonide) (Table 1.5.3). The antihistamine cetirizine ranks fourth in terms of prevalence of use (92.3 per 1,000 children) and in terms of number of packages per 1,000 children (63.0, registering an increase of 10.5%), placing tenth among the top 30 active ingredients by consumption in the paediatric age in 2022 (Tables 1.5.3 and 1.5.4).

The third category by consumption is systemic hormonal preparations, excluding sex and insulin, with a prevalence of 130.7 per 1,000 children and a consumption of 189.8 packs per 1,000 children, showing a significant increase in 2022 (+33.2%), following that observed in 2021 (+16.2%). Betamethasone, a corticosteroid indicated in the treatment of complications related to upper respiratory tract infections in children, is the most prescribed medicine (123.6 packs per 1000 children), followed by growth hormone somatropin, with 21.3 packs per 1000 children, and both active ingredients rank among the top 30 for paediatric consumption in 2022, in second and seventeenth place respectively.

In the fourth most prescribed category are medicines for the central nervous system, with a prevalence of 14.0 per 1000 children and a consumption of 167.5 packs per 1000 children, which continues to increase in 2022 (+6.9% compared to 2021), following the increase recorded in 2021 (+6.0% compared to 2020). Valproic acid appears to be the most prescribed active ingredient in the category, with a prevalence of 153.3 per 1000 children and a consumption of 51.6 packs per 1000 children, followed by two other antiepileptic medicines (carbamazepine and levetiracetam); these active ingredients are placed twelfth, twenty-first and twenty-fourth, respectively, in the list of the top 30 active ingredients by paediatric consumption in 2022.

If, together with these three active ingredients, we also consider other anti-epileptic medicines lamotrigine and ethosuximide, in fifth and ninth position by consumption within the category, these active ingredients cover more than half of the consumption of the nervous system medicines category. In fourth place within the category is aripiprazole, a medicine indicated for the treatment of schizophrenia from the age of 15 and bipolar disorder from the age of 13; although it registers lower consumption than the other medicines in the category (10.6 packs per 1,000 children), it confirms an upward trend in 2022 (+29.2%), following that observed in 2021 (+32.9%). The active ingredient with the greatest increase in consumption (+33.1%) is sertraline, an antidepressant serotonin reuptake inhibitor (SSRI) authorised for the treatment of obsessive-compulsive disorder (OCD) in children and adolescents aged 6-17 years (Table 1.5.3).

The use of methylphenidate and risperidone is reported to be higher in males than in females, consistent with the epidemiological data in the literature that show a higher prevalence of certain neuropsychiatric disorders in males than in females; in particular, the use of methylphenidate, a psychostimulant still considered the pharmacological therapy of reference, in cases where psycho-social interventions or psycho-therapies alone are not sufficient, is still considered to be the most appropriate treatment in males in a ratio of 6:1, as is risperidone, an antipsychotic authorised for the short-term treatment (up to 6 weeks) of persistent aggression in conduct disorders in 5-year-old children and adolescents with intellectual functioning below the average or intellectual disability and in children and adolescents with autism spectrum disorders, is used more in males in a ratio of 3:1.

The use of cardiovascular medicines, indicated in the treatment of congenital or acquired paediatric heart disease, is slightly higher in males than in females, although for some active ingredients the use is greater in females, as in the case of propranolol, whose greater use in females could be associated with the treatment of infantile haemangiomas, which occur more frequently in females.

Among the antineoplastics and immunomodulators, triptorelin, a medicine indicated in the paediatric population in the treatment of precocious puberty, appears to be the most widely used medicine, with a ratio of 10:1 in favour of females over males. The other active ingredients in this group are instead used mainly in the treatment of paediatric rheumatological diseases.

Also, the use of isotretinoin, a medicine authorised for the treatment of prepubertal acne, is twice as high in males as in females. Its use in females appears limited due to the known teratogenic effects of the molecule.

Among the top 30 active ingredients with the highest level of consumption in the paediatric population in 2022 (Table 1.5.4), we find 10 belonging to the category of respiratory system medicines, 8 antibiotics, 4 in the category of hormones (excluding sex hormones), 4 of the central nervous system (3 antiepileptics and one antipsychotic), two belonging to the category of gastrointestinal tract medicines (cholecalciferol and insulin lispro) and one belonging to the category of pesticides, insecticides and repellents (mebendazole). After the combination amoxicillin/clavulanic acid, betamethasone, amoxicillin and beclomethasone are in the top positions in terms of consumption with 123.6, 117.3 and 101.0 packs per 1000 patients, respectively. All these active ingredients show an increase compared to 2021, ranging from 43.2 % for beclomethasone to 67.5 % for amoxicillin. Among all the active ingredients with the highest consumption, higher consumption is recorded in females than in males only for cholecalciferol, levothyroxine (a medicine indicated in forms of hypothyroidism), carbamazepine, levetiracetam, mebendazole and sertraline (Table 1.5.4).

Furthermore, the type of formulation prescribed for the top five active ingredients with the highest paediatric consumption in 2022 is appropriate for the child's age group (Table 1.5.5). Indeed, as expected, the most frequently prescribed formulations for amoxicillin alone or in combination with clavulanic acid, antibiotics indicated in children of all age groups, are liquid formulations for oral use, predominantly used by pre-school children (1-5 years), 60%

and 70% respectively, while tablets are mostly prescribed to adolescents aged 12-17 years (89%). For the respiratory medicines to be taken by inhalation (budesonide and beclomethasone), suspensions by nebuliser are more commonly used than formulations requiring the use of a device (e.g., pressurised suspension for inhalation). For betamethasone, a corticosteroid for systemic use, the effervescent tablet formulation is the most commonly used compared to injectable ampoules, with a higher proportion in children aged between 1 and 5 years (47%).

Table 1.5.1 General prescription data in the paediatric population in 2022

	Males	Females	Total
Users	**2,200,458**	**1,970,421**	**4,170,879**
Prevalence (%)	46.1	43.8	45.0
Prescriptions	**9,493,980**	**7,892,306**	**17,386,286**
Per capita	1.99	1.75	**1.88**
Δ % 21-20	5.8	7.4	6.5
Δ % 22-21	31.7	31.8	31.7
Packages	**9,689,556**	**8,049,072**	**17,738,628**
Per capita	2.03	1.79	**1.91**
Δ % 21-20	4.6	6.3	5.4
Δ % 22-21	30.9	31.1	31.0
Expenditure	**140,944,371**	**103,581,739**	**244,526,110**
Per capita	29.53	23.02	**26.37**
Δ % 21-20	0.6	4.4	2.1
Δ % 22-21	16.5	21.9	18.7
Per user	64.05	52.57	**58.63**
Δ % 21-20	4.0	6.9	5.1
Δ % 22-21	-9.3	-4.7	-7.4

Figure 1.5.1 Regional trend in prescriptions in the paediatric population in 2022

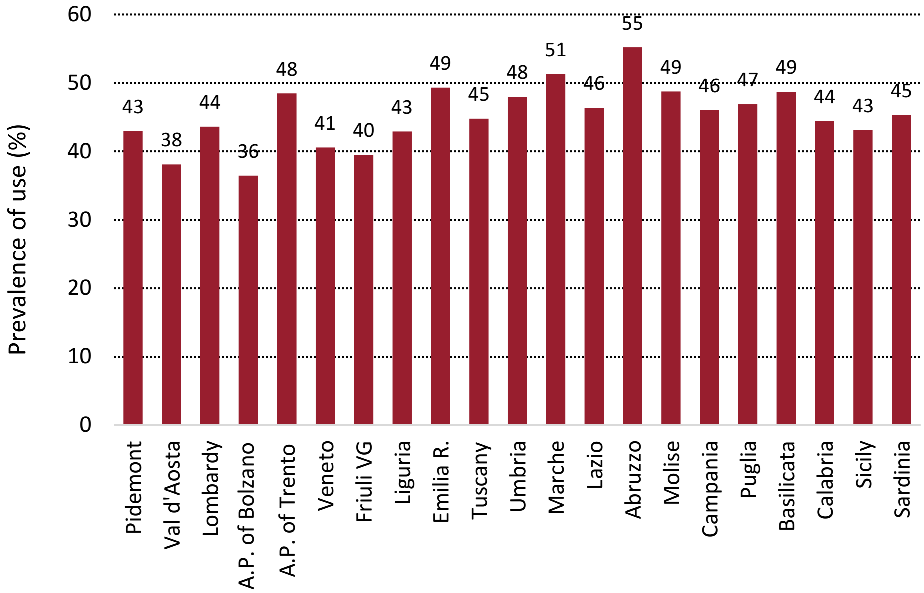


Figure 1.5.2 Trend in the prevalence of use and prescriptions in the paediatric population by age in 2022

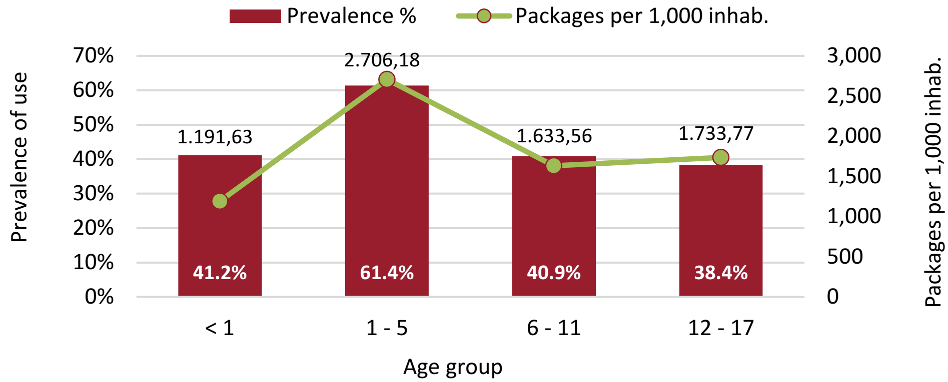


Table 1.5.2 Distribution of consumption (packages) by age and gender in the paediatric population in 2022

Age group	*Per capita* packages					
	Males	Δ % 22-21	Females	Δ % 22-21	Total	Δ % 22-21
< 1	1.29	3.4	1.08	1.0	1.19	2.3
1 - 5	2.87	29.0	2.54	29.4	2.71	29.2
6 - 11	1.75	45.2	1.51	50.6	1.63	47.6
12 - 17	1.82	25.1	1.64	22.6	1.73	23.9
Total	**2.03**	**30.9**	**1.79**	**31.1**	**1.91**	**31.0**

Figure 1.5.3 Percentage distribution of consumption (packages) in the paediatric age by ATC I level in 2022

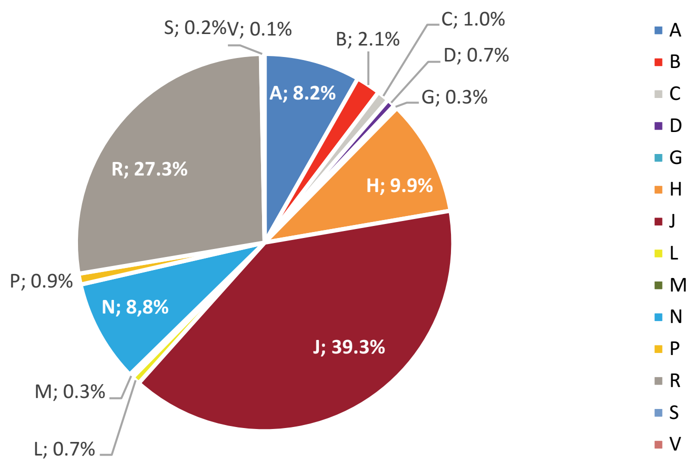
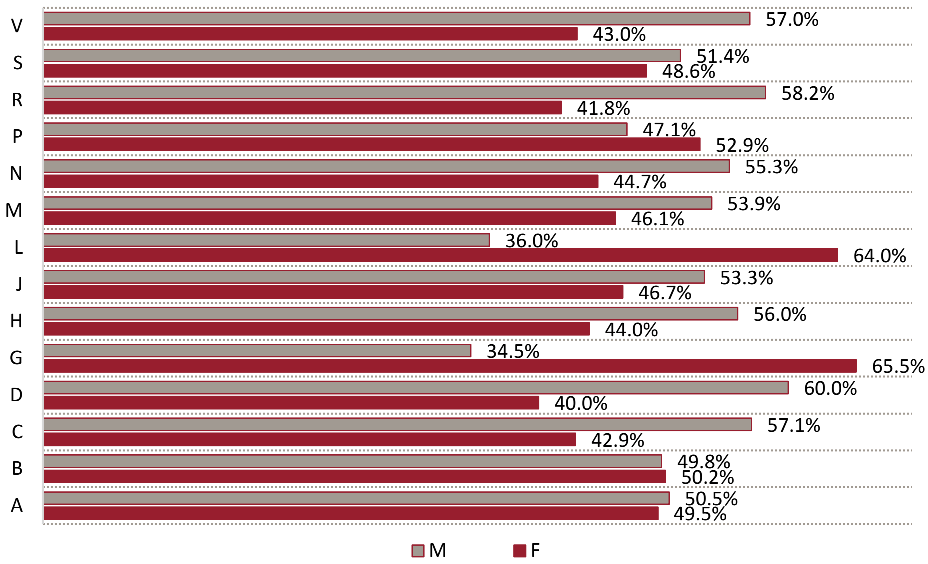


Figure 1.5.4 Percentage distribution of consumption (packages) in the paediatric age by ATC I level and gender in 2022



A	Gastrointestinal tract and metabolism
B	Blood and blood-forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Hormones (excl. sex hormones)
J	Antimicrobials for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products
R	Respiratory system
S	Sensory organs
V	Various

Table 1.5.3 Most prescribed substances in the paediatric age by therapeutic category (75% of packages) in 2022

Therapeutic category/substance	Packages (per 1000 inhab.)	Δ % 22-21	Δ % 21-20	Prevalence (per 1000 inhab.)	Ratio M/F
J - Anti-infectives for systemic use	**752.4**	**53.3**	**-4.0**	**444.2**	**1.1**
amoxicillin/clavulanic acid	281.7	57.2	-5.8	371.9	1.1
amoxicillin	117.3	67.5	-7.4	138.1	1.1
azithromicyn	92.2	28.8	19.5	139.8	1.2
cefixime	90.6	69.7	2.8	137.5	1.1
R- Respiratory system	**522.9**	**36.9**	**13.4**	**286.2**	**1.2**
beclomethasone	101.0	43.2	30.6	225.3	1.2
budesonide	100.8	76.9	49.0	211.0	1.2
salbutamol	83.3	37.2	15.8	172.3	1.4
cetirizine	63.0	10.5	3.7	92.3	1.4
salbutamol/ipratropium	34.4	33.4	40.4	86.9	1.2
fluticasone	33.5	26.3	-0.9	57.4	1.6
H - Systemic hormonal preparations, excl. sex ones and insulins	**189.8**	**33.2**	**16.2**	**130.7**	**1.3**
betamethasone	123.6	52.3	30.7	829.4	1.3
somatropin	21.3	1.5	-5.2	9.6	1.5
N- Central nervous system	**167.5**	**6.9**	**6.0**	**14.0**	**1.1**
valproic acid	51.6	0.0	-1.3	153.3	2.0
carbamazepine	15.3	2.9	4.1	52.0	1.2
levetiracetam	14.1	5.1	-0.1	77.3	0.8
aripiprazole	10.6	29.2	32.9	78.2	0.9
sertraline	8.6	33.1	49.8	76.5	0.4
lamotrigin	7.6	6.2	4.3	26.9	0.6
methylphenidate	7.2	14.8	24.3	52.3	5.8
risperidon	4.7	7.3	5.2	70.0	2.7
ethosuximide	4.6	6.8	1.2	20.8	0.7
phenobarbital	4.6	-5.0	-7.3	14.3	1.2
A - Gastrointestinal tract and metabolism	**157.3**	**-0.7**	**13.3**	**71.3**	**1.0**
cholecalciferol	80.0	-5.1	22.0	630.1	1.0
insulin lispro	9.5	14.4	12.3	18.1	1.2
lansoprazole	8.3	-0.3	1.8	32.8	1.0
insulin aspart	7.1	3.5	3.9	10.2	1.1
esomeprazole	6.3	4.1	5.9	33.2	1.0
ursodeoxycholic acid	5.0	0.4	8.0	7.0	1.0
omeprazole	4.1	-4.8	1.5	25.5	0.9
B - Blood and blood-forming organs	**40.0**	**6.5**	**25.4**	**18.9**	**0.8**
enoxaparin	7.4	11.2	30.8	158.6	1.8
ferrous sulfate	5.3	7.6	32.2	180.0	0.3
folic acid	4.9	5.5	25.9	185.2	0.5
polymaltosate iron	4.3	1.0	0.0	130.8	1.2
electrolytes for intravenous solutions	4.5	0.0	0.0	51.3	1.2
tranexamic acid	2.4	8.7	3.8	92.2	1.0
sodium ferric gluconate	1.5	4.0	13.7	46.8	1.2

continued

Table 1.5.3 – ***continued***

Therapeutic category/substance	Packages (per 1000 inhab.)	Δ % 22-21	Δ % 21-20	Prevalence (per 1000 inhab.)	Ratio M/F
C - Cardiovascular system	**20.0**	**0.7**	**-0.4**	**3.2**	**1.2**
ramipril	2.0	2.4	-1.6	80.0	1.6
enalapril	1.9	-2.9	-1.4	73.0	1.5
flecainide	1.6	4.1	4.6	50.5	1.1
bisoprolol	1.4	5.4	4.9	75.9	1.2
furosemide	1.4	-4.7	-0.8	83.2	1.2
losartan	1.3	1.5	-0.5	33.9	2.0
carvedilol	1.3	-4.1	2.0	34.4	1.4
amlodipine	1.1	9.3	-5.4	55.8	1.4
spironolactone	1.0	4.4	8.6	31.6	0.7
propranolol	0.8	-2.4	9.9	45.5	0.6
adrenaline	0.6	70.2	21.6	80.6	1.5
omega 3	0.4	-2.7	21.2	20.9	1.3
pravastatin	0.4	-10.1	5.0	10.7	0.9
P - Antiparasitic, insecticide and repellent pharmaceuticals	**17.8**	**-2.5**	**-4.8**	**14.5**	**0.9**
mebendazole	15.1	7.6	-6.0	865.0	0.9
L - Antineoplastic and immunomodulating agents	**13.6**	**0.7**	**9.0**	**1.9**	**0.4**
triptorelin	4.0	10.8	39.6	310.5	0.1
methotrexate	2.8	-7.0	-0.6	258.4	0.5
tacrolimus	2.2	-1.9	0.4	65.6	1.2
azathioprine	1.2	9.0	8.5	100.7	1.0
ciclosporin	0.7	-12.4	-11.8	63.6	1.0
D - Dermatologicals	**13.3**	**-0.4**	**18.0**	**6.3**	**1.3**
isotretinoin	7.7	1.0	29.2	346.6	2.0
calcipotriol/betamethasone	1.1	-4.0	-8.2	112.3	0.9
methylprednisolone	1.0	3.9	8.1	143.5	1.2
clobetasol	0.9	-1.1	15.1	89.9	0.9
M - Musculo-skeletal system	**6.4**	**29.1**	**9.8**	**5.6**	**1.1**
ibuprofen	1.9	111.5	51.2	374.0	1.1
ketoprofen	1.3	30.9	11.1	249.0	1.1
baclofen	0.7	1.9	-3.7	19.7	1.5
allopurinol	0.4	4.7	3.2	30.0	2.0
diclofenac	0.4	6.9	4.5	76.4	1.2
colchicine	0.3	15.0	11.6	22.6	1.3
G - Genito-urinary system and sex hormones	**6.0**	**1.8**	**8.5**	**2.0**	**0.3**
oxybutynin	2.1	5.4	7.7	209.3	1.8
cyproterone/ethinylestradiol	0.8	-8.7	1.3	80.8	0.0
estradiol	0.5	6.5	4.8	44.2	0.0
dydrogesterone	0.5	-6.0	14.2	112.9	0.0
cabergoline	0.3	-7.3	9.9	55.7	0.1
nomegestrol	0.3	1.7	30.0	99.2	0.0
progesterone	0.2	1.3	7.6	82.2	0.0
S-Sensory organs	**4.0**	**-2.5**	**-3.7**	**0.6**	**0.9**
acetazolamide	1.1	-6.5	1.9	112.9	1.0
timolol	0.7	-1.3	13.0	323.7	0.6
dorzolamide/timolol	0.5	-0.3	-0.1	126.3	1.3

continued

Table 1.5.3 – *continued*

Therapeutic category/ substance	Packages (per 1000 inhab.)	Δ % 22-21	Δ % 21-20	Prevalence (per 1000 inhab.)	Ratio M/F
timolol/brinzolamide	0.2	-7.5	-12.1	40.9	1.4
dorzolamide	0.2	8.6	5.3	53.7	1.1
brinzolamide	0.2	-12.2	-1.7	35.0	1.9
latanoprost	0.2	6.0	0.6	40.0	1.4
V - Miscellaneous	**1.9**	**-2.2**	**-7.6**	**0.5**	**1.4**
oxygen	0.6	-2.6	-5.1	410.5	1.2
deferasirox	0.3	8.5	4.2	55.9	1.2
pollen of phleum pratense/dactylis glomerata/ anthoxanthum odoratum/lolium perenne/poa pratensis	0.3	16.5	-12.0	228.0	1.8
grass pollen (phleum pratense)	0.3	47.0	-6.9	172.4	1.8
deferoxamine	0.1	-29.4	2.7	10.4	1.4

Table 1.5.4 Top 30 active ingredients by consumption in the paediatric age in 2022

ATC I	Active ingredient	Packages (per 1000 inhab.)	Δ % 22-21	Δ % 21-20	Consumption (%)*		Inc. % tot**%
					males	females	
J	amoxicillin/clavulanic acid	281.7	57.2	-5.8	54.1	45.9	18.0
H	betamethasone	123.6	52.3	30.7	56.9	43.1	25.8
J	amoxicillin	117.3	67.5	-7.4	53.1	46.9	33.3
R	beclomethasone	101.0	43.2	30.6	55.1	44.9	39.8
R	budesonide	100.8	76.9	49.0	55.4	44.6	46.2
J	azithromicyn	92.2	28.8	19.5	53.8	46.2	52.1
J	cefixime	90.6	69.7	2.8	51.3	48.7	57.8
R	salbutamol	83.3	37.2	15.8	59.9	40.1	63.2
A	cholecalciferol	80.0	-5.1	22.0	49.3	50.7	68.3
R	cetirizine	63.0	10.5	3.7	60.9	39.1	72.3
J	clarithromycin	55.7	86.6	-23.5	54.8	45.2	75.8
N	valproic acid	51.6	0.0	-1.3	67.3	32.7	79.1
J	cefpodoxime	36.4	72.6	-10.8	53.5	46.5	81.4
R	salbutamol/ipratropium	34.4	33.4	40.4	55.2	44.8	83.6
R	fluticasone	33.5	26.3	-0.9	62.6	37.4	85.8
R	montelukast	25.4	5.7	-19.9	63.2	36.8	87.4
H	somatropin	21.3	1.5	-5.2	60.6	39.4	88.7
R	flunisolide	20.6	54.9	8.7	54.3	45.7	90.0
J	ceftriaxone	17.4	35.8	-16.6	55.2	44.8	91.2
H	levothyroxine	15.7	1.6	2.0	39.0	61.0	92.2
N	carbamazepine	15.3	2.9	4.1	56.3	43.7	93.1
P	mebendazole	15.1	7.6	-6.0	47.2	52.8	94.1
H	prednisone	14.2	24.6	1.5	55.5	44.5	95.0
N	levetiracetam	14.1	5.1	-0.1	44.7	55.3	95.9
J	cefaclor	13.7	64.6	-13.9	50.9	49.1	96.8
R	levocetirizine	11.9	5.5	-2.6	62.8	37.2	97.5
N	aripiprazole	10.6	29.2	32.9	50.4	49.6	98.2
R	salmeterol/fluticasone	10.0	14.8	-15.8	65.8	34.2	98.8
A	insulin lispro	9.5	14.4	12.3	53.7	46.3	99.5
N	sertraline	8.6	33.1	49.8	30.8	69.2	100.0
	Total of top 30	**1568.4**	**38.6**	**6.0**	**55.1**	**44.9**	**100.0**
	Total	**1913.1**	**31.9**	**6.0**	**54.6**	**45.4**	

* calculated with reference to the overall consumption of the molecule in the paediatric age

** calculated with reference to the overall consumption in the paediatric age

Table 1.5.5 Percentage distribution of packages for the top five active ingredients with the highest paediatric consumption in the year 2022

ATC 1st level	Active ingredient	Formulation	<1		1 - 5		6 - 11		12 - 17		Total (0 -17)	
			No.packs	%	No.packs	%	No.packs	%	No.packs	%	No.packs	%
J	amoxicillin/ clavulanic acid	syrup	57,458	3.15	1,094,579	59.96	620,343	33.98	53,041	2.91	1,825,421	100
		tablets	64	0.01	2,002	0.44	49,125	10.90	399,420	88.64	450,611	100
		sachets	43	0.01	5,578	1.66	123,650	36.77	207,006	61.56	336,277	100
H	betamethasone	tablets	41,122	3.62	529,234	46.56	334,528	29.43	231,688	20.38	1,136,572	100
		injectable ampoules	28	0.30	1,336	14.14	1,352	14.31	6,733	71.26	9,449	100
J	amoxicillin	syrup	42,284	4.65	632,400	69.59	221,872	24.42	12,153	1.34	908,709	100
		tablets 1 g	33	0.02	2,321	1.60	51,357	35.51	90,904	62.86	144,615	100
		tablets 500 mg	12	0.04	3,449	10.13	22,596	66.36	7,994	23.48	34,051	100
R	budesonide	suspension for nebulizer	40,366	4.38	513,868	55.78	287,091	31.16	79,921	8.68	921,246	100
		pressurized suspension for inhalation	91	0.74	4,459	36.22	4,696	38.14	3,065	24.90	12,311	100
		powder for inhalation	1	0.17	48	8.03	192	32.11	357	59.70	598	100
		capsules	—	—	3	3.75	23	28.75	54	67.50	80	100
		nasal spray	—	—	7	16.67	20	47.62	15	35.71	42	100
R	beclomethasone	suspension for nebulizer	40,503	4.80	411,925	48.86	257,703	30.57	132,910	15.77	843,041	100
		pressurized suspension for inhalation	1,673	1.79	48,576	51.96	32,590	34.86	10,657	11.40	93,496	100
		nasal spray	—	—	3	13.64	7	31.82	12	54.55	22	100

1.6 Pharmaceutical use in the geriatric age

In Italy, the population aged 65 and overreached about 13.9 million people in 2022, or 24% of the Italian population. Women are about 7.8 million, representing 56.3% of this age group.

As expected, medicines use increases with age up to the 80-84 yrs. group and then slightly decreases among those aged 85 and over (Figure 1.6.1). The highest level of pharmaceutical consumption was recorded in the 80-84 and ≥85 age groups (4071.2 and 3843.5 DDD/1000 users per day, respectively), with a per user expenditure equal to 651.0 euros and 617.2 euros, respectively (Table 1.6.1).

Overall, the average expenditure per user was 556.2 euros (601.5 in men and 520.8 in women), stable compared to 2021 (-0.3%). The analysis of medicine consumption in individuals who received at least one prescription in 2022 showed that the number of DDD/1000 users per day was higher in the male population than in the female population (3,557.1 vs. 3,394.2) and a stability of the doses dispensed per user in 2022 compared to 2021 (-0.8%) (Table 1.6.1).

Analysing the prevalence of use, almost the entire population (98.4%) received at least one medicine prescription during the year, with no particular differences between the two sexes and a slight increase (+1.3%) compared to 2021. Evaluating the incidence of use, on the other hand, shows an increase of 14.6% over the previous year. The increase in the number of incident patients in 2022 follows the positive trend of the previous year, showing a probable catch-up in the number of new diagnoses, compared to the years 2019-2020, which were more affected by the health emergency. These percentages are higher in the 75-79 age group (+20.82%) and in the over-85s (18.8%).

In the geriatric population, polypharmacy was also studied using the average number of substances prescribed per user as a proxy (Table 1.6.2).

In 2022, each user used 7.6 different substances, with a lower value (6.0 substances per user) recorded in the 65-69 years age group and the highest figure (8.7 substances per user) in people aged 85 and over. For both sexes, there was a progressive increase in the number of different active substances taken with increasing age, from 6.0 substances in males aged 65 to 69 to 8.9 in males aged 85 and over. A similar trend was also found in women, with 6.1 different substances taken in the 65-69 age group and 8.6 different active ingredients taken by women aged 85 years or over.

Moreover, the distribution of users by number of different active ingredients (Figure 1.6.2) showed that around 68.1% of elderly users received prescriptions for at least 5 different substances (i.e., polypharmacy) during the reference year and that more than one subject in 4 (28.6%) aged 65 years or older took at least 10 different active ingredients. These data show that polypharmacy is very frequent in people aged 65 years and over, with a higher risk of pharmacological interactions. The presence of a high number of active substances in the very elderly population (>85 years) also indicates the need to incentivise pharmacological deprescribing activities within general medicine.

An analysis of the prevalence of use by region and geographical area (Table 1.6.3) shows a prevalence higher than the national average, relating to the use of more than ten substances, for the regions of the Centre (30.1%) and the South (39.4%). For less than 7

substances, on the other hand, a higher prevalence of use can be noted in the northern regions, compared to the national average.
Observing the combinations of the most frequently prescribed therapeutic categories in persons taking more than one substance (Table 1.6.4), the combination of antihypertensives, hypolipidemic and peptic ulcer medicines can frequently be noticed. For patients on polypharmacy with more than 10 medicines, it is necessary to emphasise the constant presence of an antibiotic in each combination. It is therefore becoming increasingly evident that there is a need for increased activities to assess prescribing appropriateness, as well as medicine reconciliation and deprescribing in the elderly population.

Table 1.6.1 Distribution by age and sex of pharmaceutical prescription in the population aged ≥65 years in 2022

Age group	Expenditure per user				DDD/1000 users per day				Prevalence of use (%)				Incidence of use (%)			
	M	F	T	Δ % 22-21	M	F	T	Δ % 22-21	M	F	T	Δ % 22-21	M	F	T	Δ % 22-21
65-69	471.7	392.3	429.7	-0.17	2,766.5	2,553.8	2,654.0	-1.7	90.3	92.2	91.3	2.5	6.6	5.9	6.2	15.3
70-74	573.3	483.2	525.3	0.06	3,395.3	3,173.8	3,277.2	-1.2	90.3	90.5	90.4	-1.2	3.9	3.5	3.7	8.9
75-79	655.2	563.1	604.9	-0.29	3,892.1	3,691.7	3,782.7	-0.8	107.4	104.6	105.9	4.7	3.1	2.7	2.9	20.8
80-84	704.1	611.5	651.0	-0.22	4,179.6	3,990.5	4,071.2	-0.2	102.3	98.9	100.3	-0.5	2.1	1.9	2.0	13.6
85+	681.2	582.2	617.2	-0.62	4,019.8	3,747.1	3,843.5	-0.1	117.4	108.1	111.2	1.3	2.3	2.3	2.3	18.8
Total	**601.5**	**520.8**	**556.2**	**-0.28**	**3,557.1**	**3,394.2**	**3,465.6**	**-0.8**	**98.7**	**98.1**	**98.4**	**1.3**	**4.0**	**3.4**	**3.7**	**14.6**

Figure 1.6.1 Prescription trend in the population aged ≥65 years (DDD/1000 users per day and gross expenditure per user) in 2022

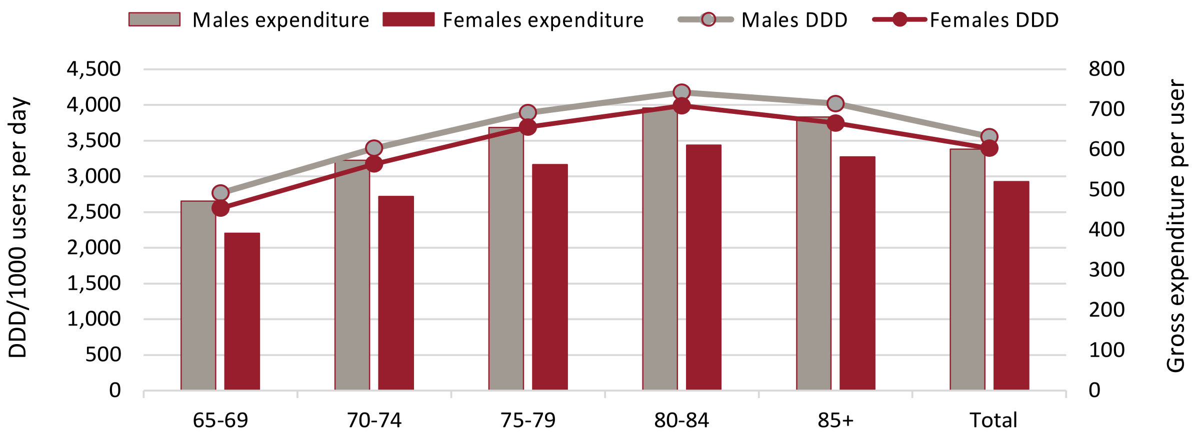


Table 1.6.2 Average number of substances by age and sex in 2022

Age group	Average number of substances			Average last 5 years
	Males	Females	Total	
65-69	6.0	6.1	6.0	6.0
70-74	7.0	7.0	7.0	7.0
75-79	7.9	7.9	7.9	7.7
80-84	8.5	8.4	8.4	8.3
≥85 years	8.9	8.6	8.7	8.4
Total	**7.6**	**7.6**	**7.6**	**7.5**

Figure 1.6.2 Percentage distribution of users in the population ≥ 65 years by number of different substances in 2022

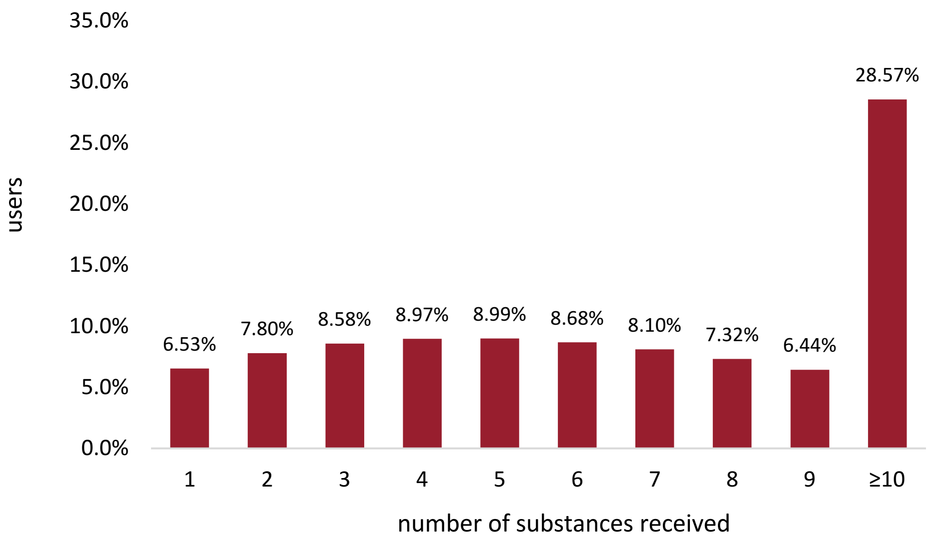


Table 1.6.3 Prevalence of use by Region and number of different substances (year 2022)

Region	Number of different substances				
	1	2-4	5-7	8-9	10+
Piedmont	7.4	27.6	26.2	13.0	22.4
Valle d'Aosta	9.3	30.8	25.4	11.8	17.4
Lombardy	8.0	29.0	25.7	12.1	19.1
A.P. of Bolzano	11.2	32.2	24.1	10.2	13.1
A.P. of Trento	8.6	28.5	26.0	12.3	20.0
Veneto	9.0	31.5	26.1	11.5	16.6
Friuli VG	8.1	29.4	26.6	12.3	18.4
Liguria	7.4	26.6	25.6	12.8	22.6
Emilia Romagna	7.0	27.4	27.2	13.5	21.4
Tuscany	7.1	26.1	25.8	13.3	25.7
Umbria	5.5	24.0	26.6	14.7	29.4
Marche	5.8	24.5	26.8	14.7	28.1
Lazio	5.3	21.7	25.0	14.8	34.1
Abruzzo	4.8	21.7	26.0	15.3	33.4
Molise	5.0	22.0	25.5	14.8	33.0
Campania	3.8	17.9	23.1	14.8	43.5
Puglia	4.5	21.0	25.4	15.3	37.1
Basilicata	4.6	20.7	25.2	15.4	36.5
Calabria	4.3	17.6	21.3	13.7	44.3
Sicily	4.3	18.7	23.0	14.6	42.5
Sardinia	6.3	26.2	27.5	14.5	26.3
Italy	**6.4**	**24.9**	**25.4**	**13.5**	**28.1**
North	6.0	23.7	25.6	14.2	30.1
Centre	7.9	28.8	26.1	12.4	19.7
South and Islands	4.5	19.9	24.1	14.8	39.4

Table 1.6.4 Frequency of the main combinations of therapeutic categories by number of substances received in 2022

Number of substances received	Combinations of therapeutic categories (OsMed - National Observatory on the Use of Medicinals - groups)	Number of users	% of users
1	Antihypertensives	254,182	28.4
	Antibiotics	132,935	14.9
	Medicines for osteoporosis	65,574	7.3
2	Antihypertensives (2 categories)	109,088	10.2
	Antihypertensives — Lipid lowering agents	58,628	5.5
	Antibiotics — Antihypertensives	54,430	5.1
3	Antihypertensives (2 categories) — Lipid-lowering agents	32,932	2.8
	Antihypertensives (3 categories)	26,124	2.2
	Antibiotics — Antihypertensives (2 categories)	24,247	2.1
4	Antiplatelets — Antihypertensives (2 categories) — Lipid lowering agents	17,141	1.4
	Antiplatelets — Antihypertensives — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	13,714	1.1
	Antihypertensives (3 categories) — Lipid-lowering agents	9,637	0.8
5	Platelet aggregation inhibitors — Antihypertensives (2 categories) — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	17,531	1.4
	Platelet aggregation inhibitors — Antihypertensives (3 categories) — Lipid-lowering agents	6,542	0.5
	Platelet aggregation inhibitors - Antibiotics - Antihypertensives — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	4,227	0.3
6	Platelet aggregation inhibitors — Antihypertensives (3 categories) — Medicines for peptic ulcer — Lipid-lowering agents	8,129	0.7
	Platelet aggregation inhibitors - Antibiotics — Antihypertensives (2 categories) — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	5,323	0.4
	Platelet aggregation inhibitors — Antihypertensives (2 categories) — Medicines for osteoporosis - Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	3,714	0.3
7	Platelet aggregation inhibitors — Antihypertensives (4 categories) — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	2,540	0.2
	Platelet aggregation inhibitors — Antidiabetics - Antihypertensives (3 categories) — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	2,499	0.2
	Platelet aggregation inhibitors — Antidiabetic agents (2 categories) — Antihypertensives (2 categories) — Medicines for peptic ulcer and GERD — Lipid-lowering agents	2,337	0.2

continued

Table 1.6.4 – *continued*

Number of substances received	Combinations of therapeutic categories	Number of users	% of users
8	Platelet aggregation inhibitors — Antidiabetic agents (2 categories) — Antihypertensives (3 categories) — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	1,271	0.1
	Platelet aggregation inhibitors — Antidiabetic agents (3 categories) — Antihypertensives (2 categories) — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	1,114	0.1
	Platelet aggregation inhibitors - Antibiotics — Antihypertensives (4 categories) — Medicines for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	817	0.1

*calculated on the total number of users taking *n* different substances

Consumption and expenditure trend by age group

Analysing the values of *per capita* expenditure over the last five years, stratified by age group (Table 1.6.5 and Figure 1.6.3) it is evident how the population of the over 65-year-olds registers values that are markedly higher than those of the younger ones (≤64 years). The value of *per capita* spending tends to increase with age, showing a maximum in the 85-90 age group, which in 2022 recorded a value of 704.5 euros, and then decreasing slightly in the very old (>90 years; 640.2 euros). This trend can be observed for all the years considered. Of special interest is the figure for the over-90s, which rose from a value of €513.5 in 2018 to €640.2 in 2022, with an average annual increase index of 4.5%, the highest shown for the years considered. People aged between 75 and 79 record the second highest annual increase (CAGR: +2.1%) and the highest year-on-year increase (+4.35%). The greatest decrease is instead recorded for the 70–74-year-olds (CAGR: -1.60%), who dropped from a value of € 514.8 in 2018 to € 474.8 in 2022. The incidence of gross local pharmaceutical expenditure by age group (Figure 1.6.4) shows that in 2022, the over-65s account for more than 63% of the total, with a rather steady trend over time. The highest percentage value is found for the 70-74 and 75-79 age group (both at 13.5%), and the lowest for the over-90s (3.3%). The incidence values also show a progressive increase in the expenditure of the over-90s and a change in the maximum values in the 70-79 age group. Analysing the differences by sex (Figures 1.6.5. and 1.6.6), it may be noted that females show higher percentage values, compared to males: in 2022 females show an incidence of 64.1% and males of 62.3%. In 2022, differences between the two populations can be seen in the age group with the highest uptake, which for females is represented by those aged between 80 and 84 years (12.8%) and for males by those aged between 75 and 79 years (13.8%).
Analysing the trend in expenditure per user (Table 1.6.6 and Figure 1.6.7), it is possible to note an increase in values with increasing age up to the 80-84 age group and a slight decrease for people over 85. Over the years 2018-2022, on the other hand, the greatest increases are observed in the 85-90 age group (CAGR 0.68%), albeit to a lesser extent than in the under-64 population (CAGR: +1.43%). The historical series of the number of users (Figure 1.6.8) shows a slight increase in the number of people over 65 taking medicines and a marked increase in the over-90s (CAGR 6.0%), from 541,627 in 2018 to 725,117 in 2022. Thus, although the expenditure per user of the over-90s has remained rather constant, an increase in the number of users can be evidenced, which can justify the noted increase in *per capita* expenditure.
The consumption, expressed as DDD/1000 inhabitants per day (Table 1.6.2 and Figure 1.6.8), once again reflects the trends of the expenditure values, both in the maximum values (4,388.8 DDD in the 85-90 years old band), and in the increase trends (CAGR 4.56% in the over-90 years old group). An increase in consumption with increasing age is shown up to the 90-year-old group, who in 2022 record a value of 4,388.8 DDD (85-90 years). The over-90s, however, show the greatest increases in consumption over time, rising from 3,185.6 DDD in 2018 to 3,982 DDD in 2022 (CAGR: +4.56%) (Table 1.6.7 and Figure 1.6.9).
The percentage incidence of the number of doses (Figure 1.6.10) shows that the weight of the over-65s has increased from a value of 66.7% in 2018 to one of 67.7% in 2022. It is those aged between 70 and 79 years who register the highest percentage with a value of about 14.5%. In all age groups, there is a difference by gender, with males consuming more than

females (Figure 1.6.11). In particular, the greatest difference is found in the 65-69 age group, where males have 8% more doses than females (Figure 1.6.12).
Overall, the *per capita* expenditure of the elderly population tends to increase in the over-90s and in the 75-79 age group, but expenditure per user tends to remain steady for all age groups. These trends can be attributed to the increase in the number of users, which is particularly evident in the over-90s and in the 75-79 age group. The average DDD cost of the over-65s, on the other hand, tends to remain steady over time (Figure 1.6.13), despite an increase in the doses used. These trends indicate that the elderly show a higher consumption of medicines with a lower DDD cost than those under 64 years of age.

Table 1.6.5 *Per capita* expenditure by age in the period 2018-2022

Age group	*Per capita* expenditure							
	2018	2019	2020	2021	2022	Δ % 22-21	Δ % 22-18	CAGR %
0-64	92.87	94.19	92.67	95.89	97.69	1.9	5.2	1.0
65 - 69	377.17	380.19	378.64	383.50	392.26	2.3	4.0	0.8
70 - 74	514.77	508.54	509.61	480.14	474.78	-1.1	-7.8	-1.6
75 - 79	578.07	575.39	574.21	613.67	640.39	4.4	10.8	2.1
80 - 84	676.64	676.58	678.71	657.99	653.21	-0.7	-3.5	-0.7
85 - 90	722.70	718.95	723.98	701.59	704.52	0.4	-2.5	-0.5
>90	513.52	550.93	590.53	631.25	640.20	1.4	24.7	4.5
Total	**193.73**	**196.31**	**197.62**	**200.74**	**203.27**	**1.3**	**4.9**	**1.0**

Figure 1.6.3 Trend in *per capita* expenditure by age over the period 2018-2022

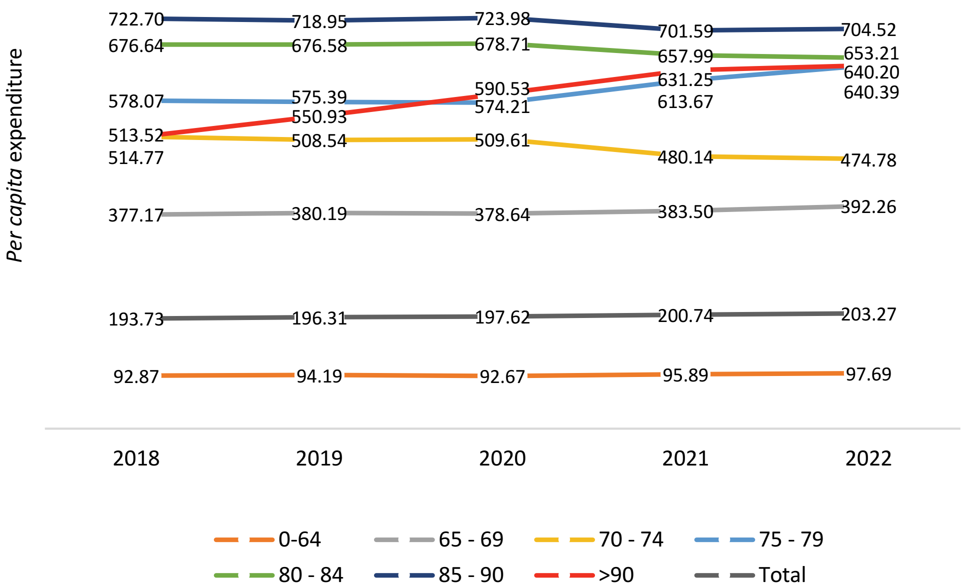


Figure 1.6.4 Incidence of local gross pharmaceutical expenditure by age over the period 2018-2022

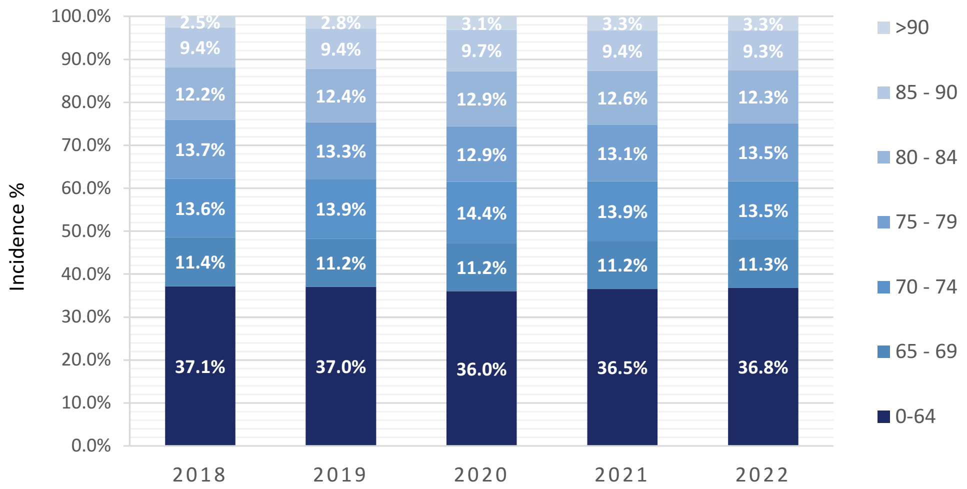


Figure 1.6.5 Incidence of local gross pharmaceutical expenditure by age for females over the period 2018-2022

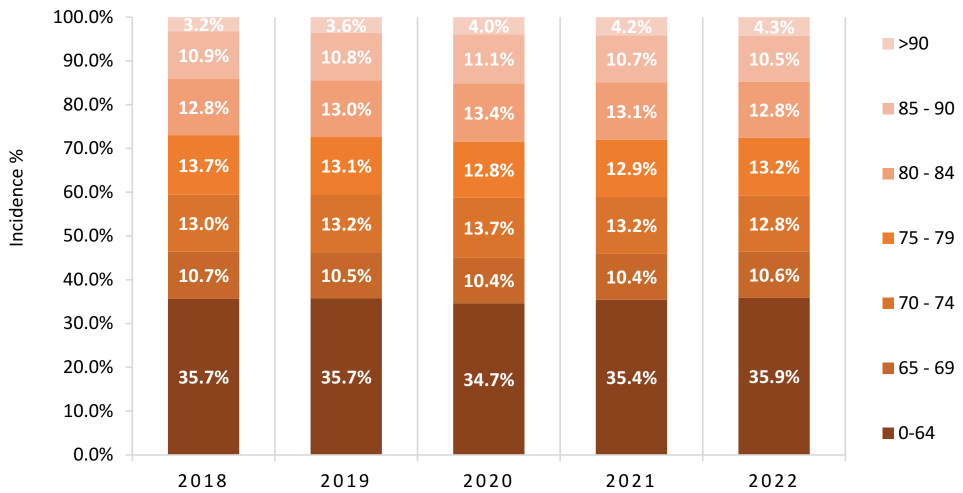


Figure 1.6.6 Incidence of local gross pharmaceutical expenditure by age for males over the period 2018-2022

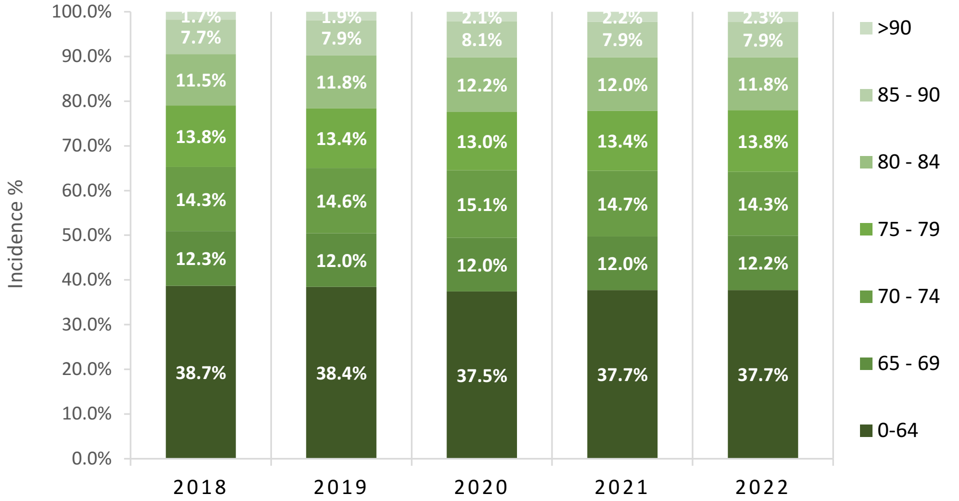


Table 1.6.6 Expenditure per user per age group in the period 2018-2022

Age group	Expenditure per user							
	2018	2019	2020	2021	2022	Δ % 22-21	Δ % 22-18	CAGR %
0-64	160.99	164.08	179.41	183.36	172.85	-5.7	7.4	1.4
65 - 69	428.48	425.95	431.88	430.44	429.70	-0.2	0.3	0.1
70 - 74	522.26	521.77	528.26	524.98	525.30	0.1	0.6	0.1
75 - 79	603.37	605.35	613.07	606.68	604.92	-0.3	0.3	0.1
80 - 84	652.18	652.87	659.16	652.41	651.00	-0.2	-0.2	0.0
85 - 90	623.69	634.23	648.89	647.34	645.20	-0.3	3.4	0.7
>90	544.15	544.60	553.76	556.13	550.46	-1.0	1.2	0.2
Total	**290.29**	**294.59**	**317.83**	**319.47**	**306.37**	**-4.1**	**5.5**	**1.1**

Figure 1.6.7 Trend in per user expenditure by age over the period 2018-2022

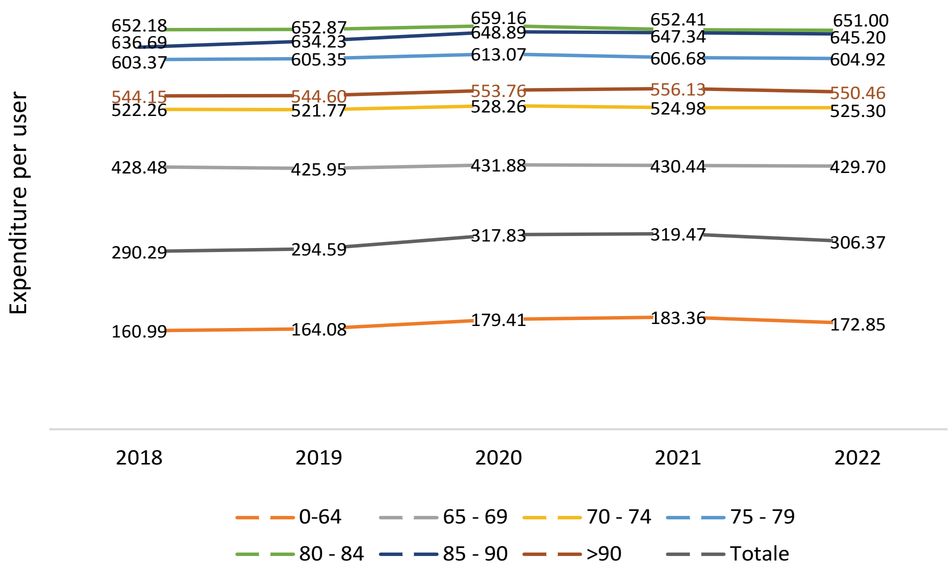


Figure 1.6.8 Number of users over 65 per age group in the period 2018-2022

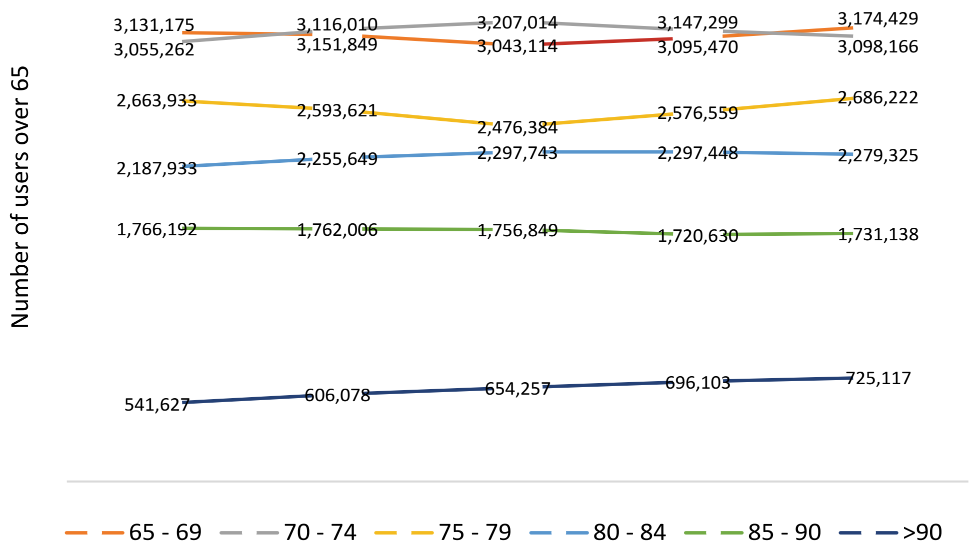


Table 1.6.7 Consumption of medicines (DDD/1000 inhabitants per day) by age in the period 2018-2022

Age group	DDD/1000 inhab. per day							
	2018	2019	2020	2021	2022	Δ % 22-21	Δ % 22-18	CAGR %
0-64	493.21	500.95	474.86	500.17	498.71	-0.3	1.1	0.2
65 - 69	2,409.54	2,446.65	2,351.41	2,406.11	2,422.74	0.7	0.5	0.1
70 - 74	3,285.77	3,273.90	3,182.22	3,032.68	2,962.03	-2.3	-9.9	-2.1
75 - 79	3,645.40	3,660.23	3,555.30	3,857.45	4,004.53	3.8	9.9	1.9
80 - 84	4,204.31	4,242.95	4,165.28	4,114.16	4,085.07	-0.7	-2.8	-0.6
85 - 90	4,447.46	4,452.93	4,397.65	4,346.34	4,388.82	1.0	-1.3	-0.3
>90	3,185.61	3,440.41	3,616.95	3,915.90	3,982.06	1.7	25.0	4.6
Total	**1,148.52**	**1,170.75**	**1,145.51**	**1,180.86**	**1,182.44**	**0.1**	**3.0**	**0.6**

Figure 1.6.9 Trend in the consumption of medicines (DDD/1000 inhabitants per day) by age in the period 2018-2022

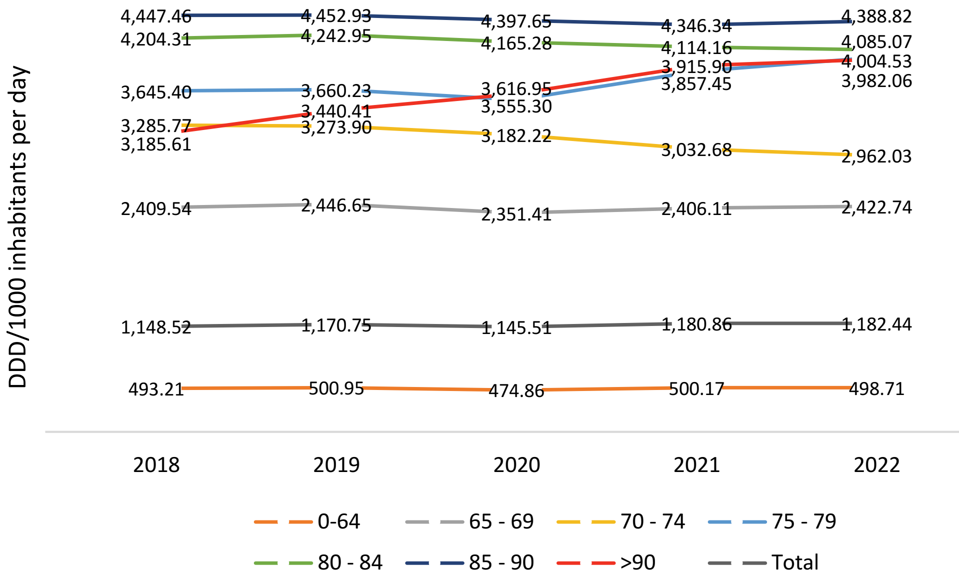


Figure 1.6.10 Incidence of local consumption (number of doses) of medicines by age in the period 2018-2022

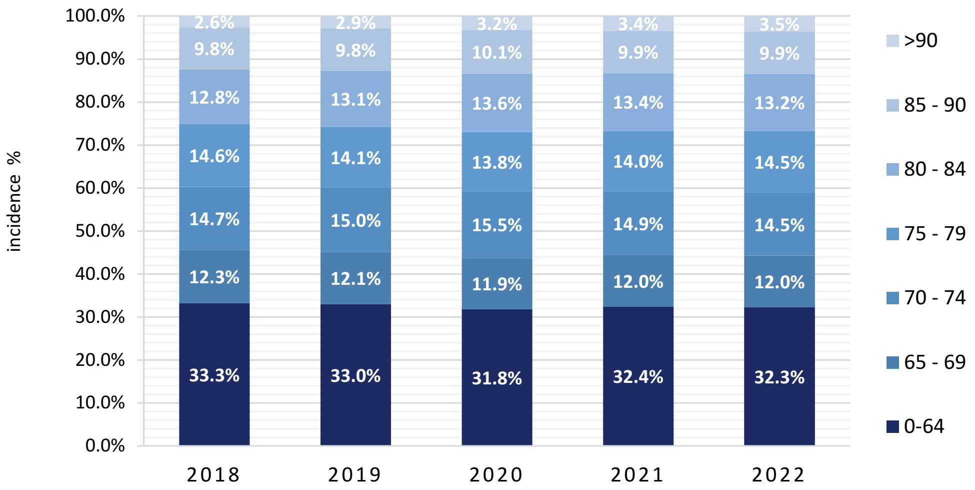


Figure 1.6.11 Incidence of local consumption (number of doses) of medicines by age of females in the period 2018-2022

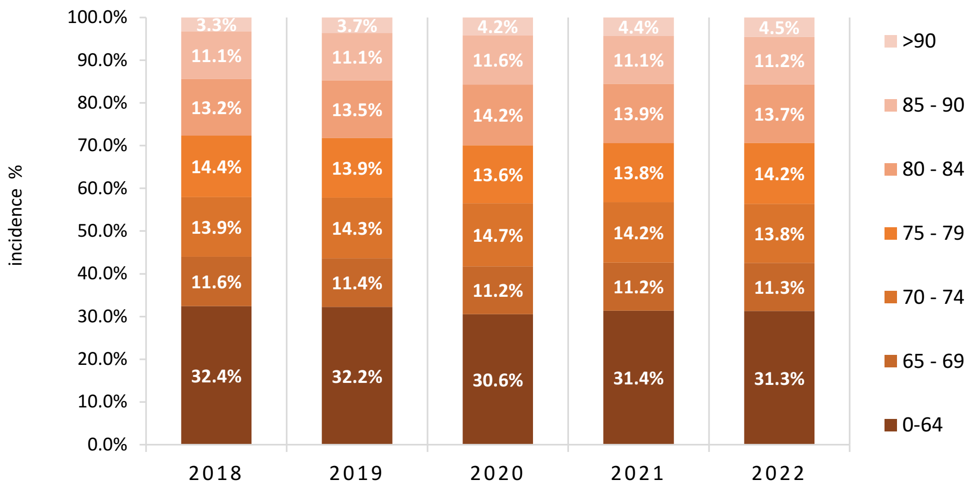


Figure 1.6.12 Incidence of local consumption (number of doses) of medicines by age of males in the period 2018-2022

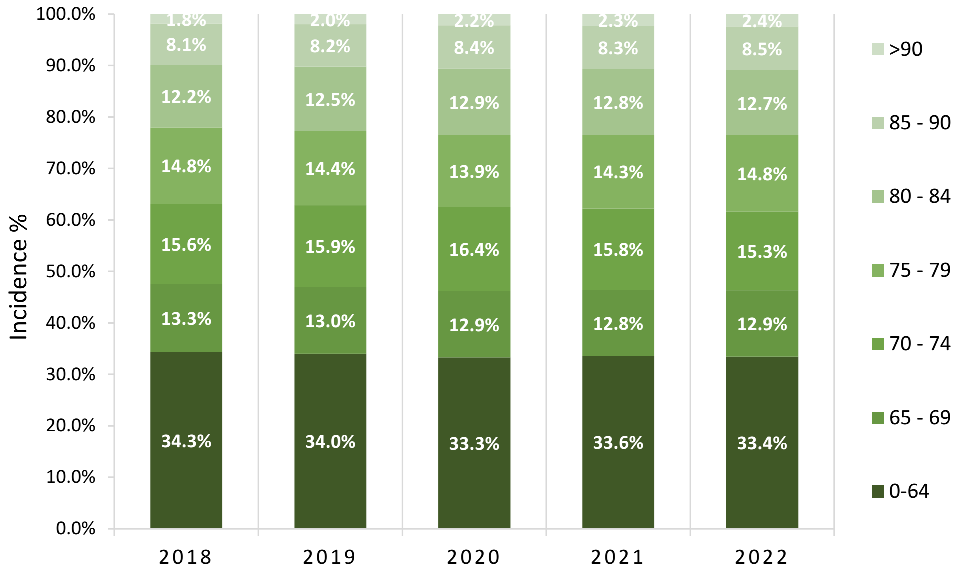
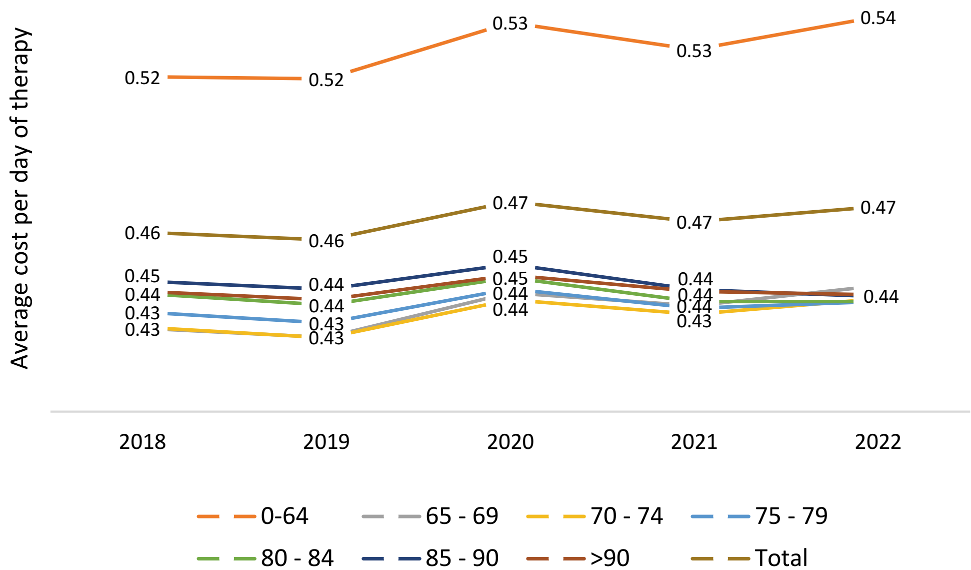


Figure 1.6.13 Trend of average cost for day of therapy by age group in the period 2018-2022



1.7 Temporal trend of monthly pharmaceuticals consumption

Approved care regime Class A-NHS

Figure 1.7.1 shows the consumption trend, expressed in DDD/1000 inhabitants per day, of class A-SSN medicines over the period 2003-2022.
The consumption of medicines in this period showed an increasing trend, rising from 715.3 DDD/1000 inhabitants per day in January 2003 to 1147.4 DDD in December 2022.
Besides being characterised by an increasing trend, the consumption of medicines is associated with a seasonal periodicity, as shown by the regularity of the monthly consumption peaks shown in Figure 1.7.1. Generally, systemic antimicrobials and respiratory medicines are the therapeutic categories on which consumption seasonality has the highest impact.
Examining the trend by four-year period, it shows how consumption slightly increased in the period 2003-2006 (CAGR: +0.2%) and in the period 2007-2010 (CAGR: +0.2%), and how it was more stable in the subsequent periods and slightly decreased in the last period 2019-2022 (CAGR: -0.1%). The trend in the last period was influenced by the reduction in consumption recorded in 2020 following the SARS-CoV-2 pandemic, which led to a reduction in the consumption of certain categories of medicines that are mainly supplied under approved care regime, such as antibiotics.

Class C medicines with prescription

Figure 1.7.2 shows the temporal trend of DDD/1000 inhabitants per day of class C medicines with prescription starting from January 2007. It should be taken into account that trends in consumption might be influenced by regulatory decisions that over time have resulted in the inclusion or exclusion of medicines from compulsory prescription and price updating every two years. In the periods 2007-2010, 2011-2014 and 2015-2018, consumption decreased with an average annual variation of -0.4%, -0.5% and -0.1%, respectively; instead, in the last four years, consumption has increased, rising from an annual average of 193.3 DDD in 2019 to an average of 241.9 DDD in 2022, an increase of 25.1% and with an average annual variation of +0.5% (for further details, Section 2.6). In 2022, the months with the highest average consumption are February and March (260.2 and 261.2 DDD); in contrast, August has the lowest consumption (201.2 DDD).

Medicines purchased by public health facilities

Figure 1.7.3 shows the trend in consumption of medicines purchased by public health facilities in the period 2007-2022. Consumption shows an increasing trend from an average of 121.8 DDD in 2007 to an average of 184.6 DDD in 2022 (+51.6%). The chart shows that the largest increase in consumption was recorded in the period 2010-2011; consumption was fairly stable over subsequent periods. In 2022, when an increase compared to 2021 of 6.4% was recorded, the lowest consumption levels were observed in August with 129.9 DDD and December with 145.0 DDD, while July with 214.5 DDD and November with 215.2 DDD show the highest consumption levels.
For a correct interpretation of monthly consumption of medicines purchased by public

health facilities, it should be noted that, unlike annual consumption trends, such trend cannot be strictly interpreted in terms of monthly consumption and seasonality since it is impacted by the purchase procedures of public health facilities. This clarification can be verified on the basis of irregularities in the size of monthly purchases made by public health facilities in the past 15 years.

Figure 1.7.1 Time series 2003-2022 of total DDD/1000 inhabitants per day of class A-NHS medicines under approved care regime

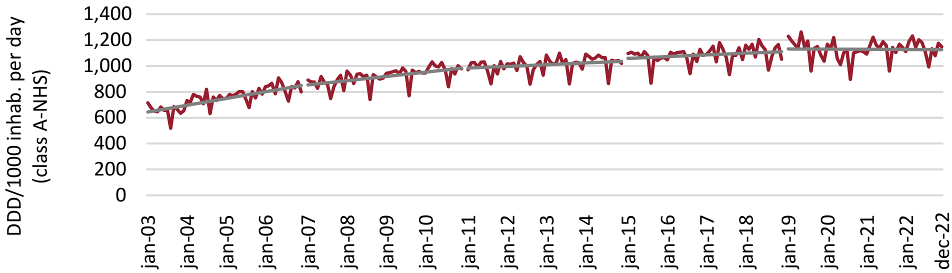


Figure 1.7.2 Time series 2007-2022 of total DDD/1000 inhabitants per day of class C medicines with prescription

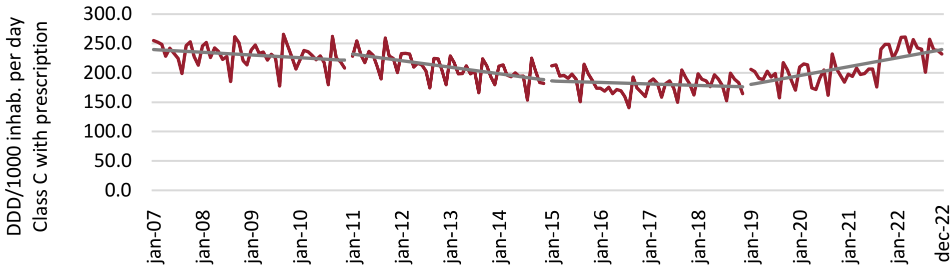
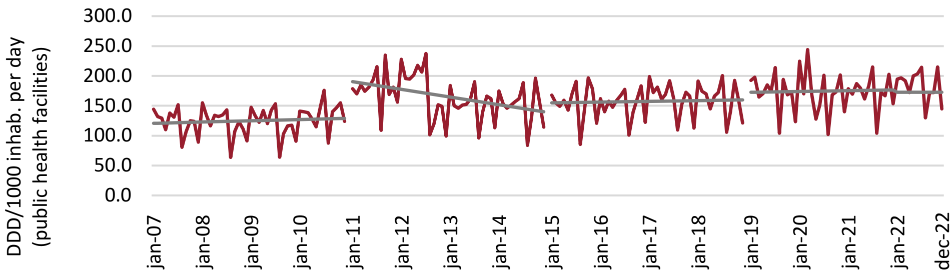


Figure 1.7.3 Time series 2007-2022 of DDD/1000 inhabitants per day of medicines purchased by public health facilities



1.8 Temporal trend of medicines prices

Approved care regime - Class A-NHS

The data in Figure 1.8.1 show the development of the weighted average price per DDD for class A-NHS medicines over the period from January 2003 to December 2022. The historical series shows a decreasing trend, especially in the periods 2003-2006 (CAGR: -0.4%), 2007-2010 (CAGR: -0.3%), 2011-2014 (CAGR: -0.5%) and in the period 2015-2018 (CAGR: -0.3%). This reduction was mainly driven by the patent expiration of important molecules that occurred during this period (e.g. valsartan and atorvastatin), the price reduction measures implemented during the renegotiation years and the activities to promote the Transparency List. In the latest period (2019-2022), the trend has remained substantially stable.
Figure 1.8.2 compares the trends in the package-weighted average price and the DDD-weighted average price of the medicines included in the transparency list, distinguishing generic medicines from ex-originator medicines over the period 2017-2022. Both generic and ex-originator medicines show an increase in prices per pack over the analysed period, while the price trend per DDD was stable. This trend could be due to the entry of medicines with a higher price than the average price of the medicines on the transparency list. As expected, the average price of generic medicines is well below that of ex-originators; in fact, in 2022 the average price per pack of generic medicines differed from that of ex-originators by approximately EUR 1.6.

Figure 1.8.1 2003-2022 trend of average price of class A-NHS medicines under approved care regime

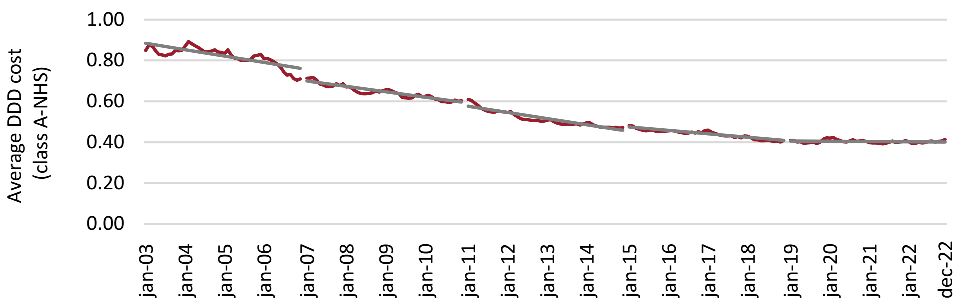


Figure 1.8.2 2017-2022 trend of average price for medicines included in the transparency list by patent coverage (approved care regime)

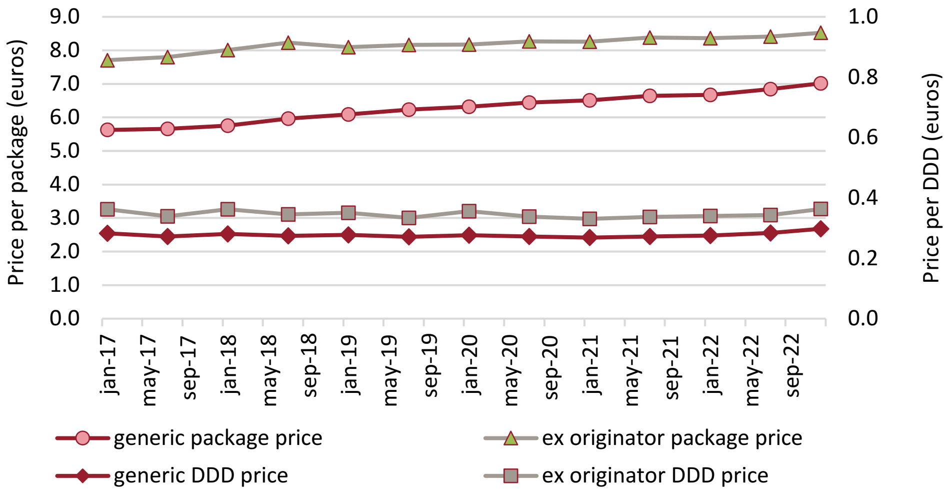


Figure 1.8.3 shows the development of the average price per pack and the weighted average price per DDD of medicines not on the transparency list, distinguishing between molecules with only one speciality and those with more than one speciality. As expected, molecules with only one speciality have both a higher average cost per pack and per DDD than active ingredients with more than one speciality. Medicines with only one speciality have a stable price per pack over the period 2017-2022 of approximately EUR 20, while those with more than one speciality have a price of approximately EUR 17 over the same period. Similar trends are found when looking at the price per DDD.

Figure 1.8.3 2017-2022 trend of average price for medicines not included in the transparency list (with 1 speciality and ≥2 specialities) under approved care regime

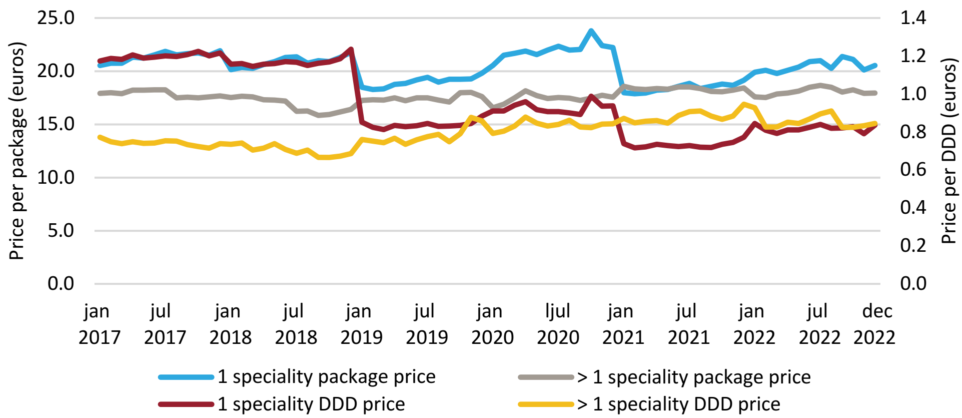
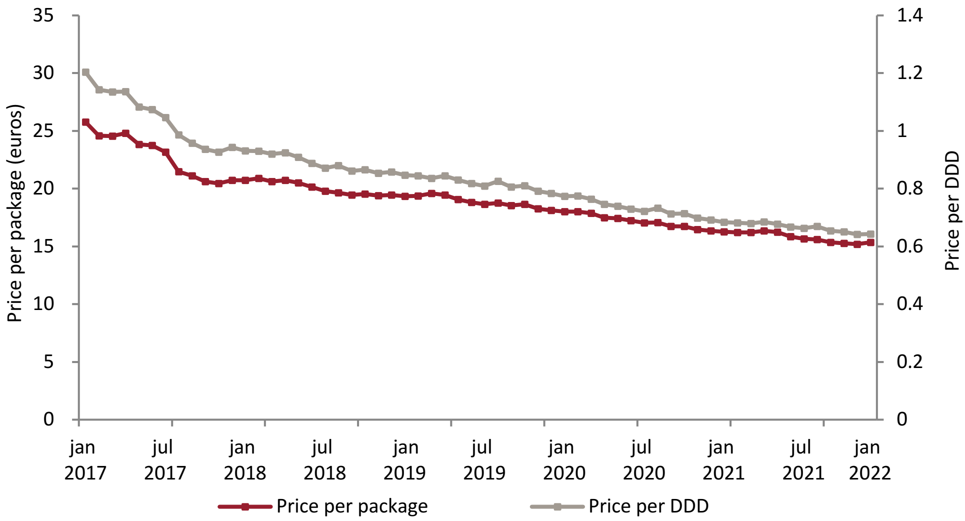


Figure 1.8.4 shows average price trends over the period January 2017 - December 2022 for medicines included in the transparency list as of 1 January 2018. The effect of entry on the transparency list on the price reduction is evident, with the price reduction falling sharply compared to the previous year in the years 2018 and 2019, while the reduction in price has been smaller in the last three years.

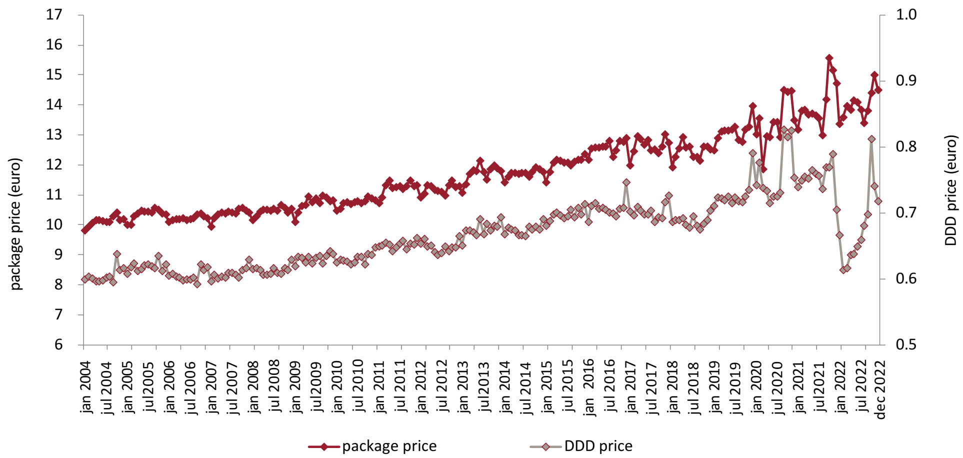
Figure 1.8.4 2017-2022 trend of average price for medicines included in the transparency list after 1 January 2018 (approved care regime)



Class C medicines with prescription

Figure 1.8.5 shows the trend in average weighted price per package and per DDD of class C medicines with prescription in the period 2004-2022. Looking at the monthly data of the time series, trends between these two indexes show regular growth from 10.13 euros per package (and 0.60 euros per DDD) in 2004 to 14.5 euros per package (and 0.72 euros per DDD) in 2022, up by respectively 43% and 20%, compared to 2004. In 2022, an even year when pharmaceutical companies could not change the price of these medicines, a stability of prices was recorded compared to the previous year, when prices had increased by 3.8% (see Section 2.6 for further details).

Figure 1.8.5 2004-2022 trend of average price for class C medicines with prescription (local pharmacies)



Medicines purchased by public health facilities

Figure 1.8.6 shows the trend of average cost per package and DDD of medicines purchased by public health facilities in the period 2006-2022. The price trend increased from 2006 to 2009, then stabilised in the period 2010-2013 and increased again from 2014 to 2017. An analysis was carried out of medicines that have lost market exclusivity since January 2017. As a proxy for the loss of exclusivity, the marketisation was used of at least one other specialty based on the same active ingredient. Figure 1.8.7 shows with evidence the effect on the price due to entry into the market of the competitors. Comparing the average price per DDD and per package at the beginning of the period with the 2022 period, there was a reduction by over 50%. The average price per package goes from 247.6 euros in 2016 to 110.0 euros in 2022, while the price for DDD shifts from 19.70 euros to 9.14 euros. During this period, various generics and biosimilars of molecules entered the market, mainly purchased by public health facilities.

Figure 1.8.6 2007-2022 trend of average price for medicines purchased by public health facilities

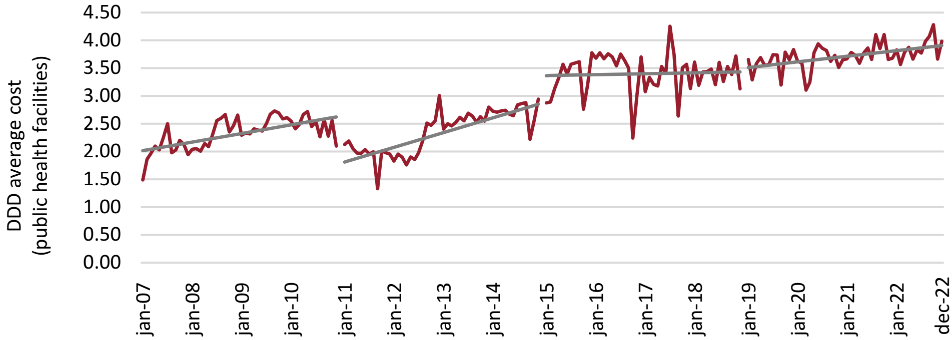
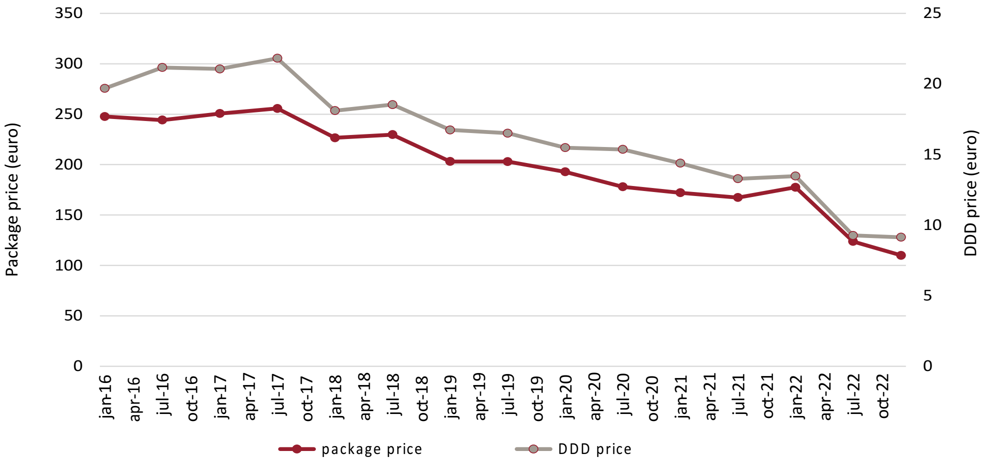
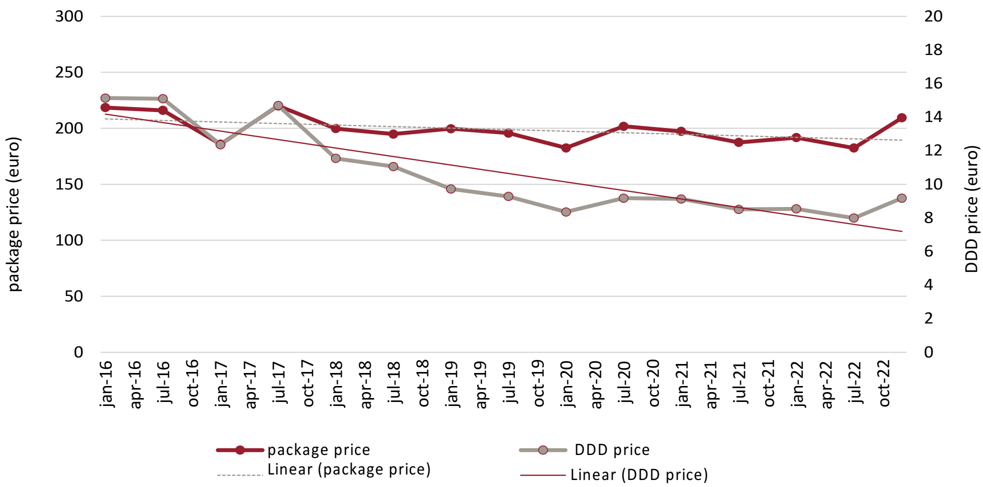


Figure 1.8.7 2016-2022 trend of average price for medicines having lost market exclusivity as of 1 January 2017 (public health facilities)



If we consider the medicines that have only one specialty on the market each year (Figure 1.8.8), we can see that both the price per DDD and per package have decreased in the period 2016-2022. In detail, the price per pack goes from 218.60 euros in 2016 to 209.48 euros in 2022 while the price for DDD goes from 15.14 euros in 2016 to 9.18 euros in 2022. These values are well above the prices of all medicines purchased by public health facilities (Figure 1.8.6), since the effects of competition do not apply to these medicines.

Figure 1.8.8 2016-2022 trend of average price for medicines with only one specialty in the market (public health facilities)



Percentage distribution of consumption and expenditure per price band under approved care regime and within public health facilities

The percentage distribution of expenditure under approved care regime of the medicines included in the transparency list by price band shows that a little more than half is concentrated on medicines with a price up to € 9.94 and the remainder on medicines with a higher price. The situation is different if consumption is taken into consideration; almost 70% of the doses relate to medicines with a price up to 9.94 euros, and the remaining 30% to medicines with a higher price (Tables 1.8 1 and 1.8.2). If we consider the medicines not on the transparency list we observe that only 12% of the expenditure concerns medicines with a price up to € 8.30, 18% medicines with a price from € 8.40 to € 17.50 and over 70% medicines with a price above € 17.50. If, on the other hand, consumption is considered, 48% of it relates to medicines priced up to 8.30 euros, 23% to medicines in the price range 8.40-17.50 euros and 29% to medicines priced above 17.50 euros (Tables 1.8.3 and 1.8.4). Taking into consideration the pharmaceuticals purchased by public health facilities, only 5% of the expenditure relates to pharmaceuticals with a NHS price falling within the first three quartiles (up to 24.80 euros), while 94.5% of the expenditure relates to pharmaceuticals with a price above 24.80 euros. On the consumption side, the majority of these (57.6%) relate to pharmaceuticals with a price falling within the first three quartiles (up to €24.80), while 42.4% relate to pharmaceuticals with a price above €24.80 (Tables 1.8.5 and 1.8.6).

Table 1.8.1 Percentage distribution by price band of the expenditure under approved care regime on medicines in the Transparency list by Region (year 2022)

Region	% First quartile (price ≤4,35)	% Second quartile (price 4.35-6.72)	% Third quartile (price 6,72-9.94)	% Fourth quartile (price >9,94)
Piedmont	9.6	18.8	25.8	45.8
Valle d'Aosta	9.4	16.9	25.4	48.4
Lombardy	7.5	15.5	24.9	52.1
A.P. of Bolzano	8.8	15.2	22.4	53.6
A.P. of Trento	11.0	16.1	24.3	48.6
Veneto	9.0	16.5	24.2	50.3
Friuli VG	10.1	17.7	24.3	47.8
Liguria	6.7	16.4	25.5	51.5
Emilia Romagna	12.0	20.5	26.0	41.5
Tuscany	11.2	20.5	25.7	42.7
Umbria	10.1	18.8	25.2	45.9
Marche	8.2	17.6	25.3	48.9
Lazio	7.9	16.4	23.7	52.0
Abruzzo	7.7	16.0	24.6	51.7
Molise	8.9	17.1	25.6	48.3
Campania	6.4	16.8	27.7	49.1
Puglia	8.6	16.6	25.4	49.4
Basilicata	8.3	16.7	27.3	47.7
Calabria	7.9	16.5	27.2	48.4
Sicily	7.9	16.0	27.4	48.8
Sardinia	8.8	15.4	24.7	51.1
Italy	**8.3**	**17.1**	**25.6**	**49.0**
North	8.7	17.3	24.8	49.3
Centre	9.0	17.8	24.6	48.7
South and Islands	7.5	16.4	26.5	49.6

Table 1.8.2 Percentage distribution by price band of consumption under approved care regime on medicines in the Transparency list by Region (year 2022)

Region	% First quartile (price ≤4,35)	% Second quartile (price 4.35-6.72)	% Third quartile (price 6,72-9.94)	% Fourth quartile (price >9,94)
Piedmont	22.0	25.7	27.2	25.1
Valle d'Aosta	22.0	22.6	27.9	27.5
Lombardy	17.5	22.2	29.2	31.1
A.P. of Bolzano	20.5	22.0	23.6	33.9
A.P. of Trento	24.9	22.6	24.7	27.9
Veneto	20.8	24.3	24.9	30.0
Friuli VG	23.5	22.4	25.9	28.1
Liguria	14.9	21.7	29.8	33.7
Emilia Romagna	25.6	27.5	24.0	23.0
Tuscany	24.1	26.1	24.7	25.1
Umbria	23.1	23.9	26.1	26.9
Marche	20.3	21.6	27.1	31.1
Lazio	19.3	21.1	26.9	32.6
Abruzzo	19.3	20.5	26.8	33.4
Molise	20.9	19.6	27.8	31.7
Campania	14.4	19.6	31.4	34.6
Puglia	19.6	21.9	27.4	31.1
Basilicata	19.3	19.4	30.7	30.6
Calabria	18.7	19.1	30.9	31.4
Sicily	18.0	18.4	30.8	32.7
Sardinia	21.0	20.4	25.5	33.1
Italy	**19.5**	**22.4**	**27.8**	**30.3**
North	20.3	24.2	26.9	28.6
Centre	21.2	22.9	26.2	29.8
South and Islands	17.6	19.9	29.6	32.9

Table 1.8.3 Percentage distribution by price band of the expenditure under approved care regime on medicines not in the Transparency list by Region (year 2022)

Region	% First quartile (price ≤4,79)	% Second quartile (price 4.79 -8.3)	% Third quartile (price 8.3- 17.47)	% Fourth quartile (price >17.47)
Piedmont	6.2	13.4	16.8	63.6
Valle d'Aosta	5.3	12.3	16.1	66.3
Lombardy	2.6	6.0	8.6	82.9
A.P. of Bolzano	4.4	8.6	16.3	70.6
A.P. of Trento	5.8	8.8	19.9	65.6
Veneto	5.6	13.2	18.6	62.7
Friuli VG	4.9	8.2	18.8	68.1
Liguria	5.3	11.9	16.8	66.0
Emilia Romagna	8.5	16.9	20.5	54.2
Tuscany	5.7	12.9	15.3	66.2
Umbria	6.3	11.5	16.5	65.7
Marche	5.7	13.5	18.6	62.3
Lazio	3.5	11.7	16.0	68.7
Abruzzo	4.5	8.8	19.7	67.0
Molise	6.2	10.8	17.9	65.2
Campania	3.8	11.3	15.5	69.4
Puglia	4.1	12.7	16.2	67.0
Basilicata	5.5	12.7	15.8	66.0
Calabria	3.6	10.6	15.0	70.8
Sicily	4.3	9.2	16.3	70.1
Sardinia	5.2	11.5	16.2	67.1
Italy	**3.9**	**7.8**	**17.6**	**70.7**
North	4.4	9.3	12.9	73.5
Centre	4.3	12.5	16.1	67.1
South and Islands	4.4	7.5	19.3	68.8

Table 1.8.4 Percentage distribution by price band of consumption under approved care regime on medicines not included in the Transparency list by Region (year 2022)

Region	% First quartile (price ≤4,79)	% Second quartile (price 4.79 -8.3)	% Third quartile (price 8.3- 17.47)	% Fourth quartile (price >17,47)
Piedmont	39.5	15.1	19.9	25.5
Valle d'Aosta	29.0	16.9	22.8	31.3
Lombardy	33.4	12.9	17.3	36.3
A.P. of Bolzano	45.4	12.0	17.3	25.3
A.P. of Trento	31.1	14.4	27.1	27.5
Veneto	47.0	12.6	19.7	20.6
Friuli VG	36.3	12.8	22.9	27.9
Liguria	34.4	13.6	22.8	29.3
Emilia Romagna	48.1	13.7	19.7	18.6
Tuscany	50.9	11.7	15.7	21.8
Umbria	37.4	13.6	21.3	27.7
Marche	30.2	15.6	25.1	29.1
Lazio	25.1	16.2	25.5	33.1
Abruzzo	29.1	15.0	25.7	30.1
Molise	34.6	14.6	25.6	25.2
Campania	19.5	17.2	28.7	34.6
Puglia	31.2	15.9	24.1	28.8
Basilicata	28.5	17.0	24.4	30.0
Calabria	25.2	16.7	26.9	31.2
Sicily	21.7	14.7	29.8	33.8
Sardinia	42.7	12.1	19.5	25.7
Italy	**34.0**	**13.6**	**23.3**	**29.1**
North	39.7	13.3	19.2	27.9
Centre	35.9	14.5	21.5	28.1
South and Islands	26.9	14.0	27.8	31.4

Table 1.8.5 Percentage distribution by NHS price band of expenditure on medicines purchased by public health facilities by Region (year 2022)

Region	% First quartile (price ≤0.68)	% Second quartile (price 0.68 -2.47)	% Third quartile (price 2.47- 24.79)	% Fourth quartile (price >24,79)
Piedmont	0.5	0.8	5.2	93.5
Valle d'Aosta	0.8	3.0	6.1	90.2
Lombardy	0.4	0.6	3.9	95.1
A.P. of Bolzano	0.4	1.1	4.6	93.9
A.P. of Trento	0.4	0.8	7.1	91.7
Veneto	0.5	1.0	5.2	93.4
Friuli VG	0.5	0.7	3.8	95.0
Liguria	0.4	0.7	4.9	94.1
Emilia Romagna	0.7	0.9	6.2	92.2
Tuscany	0.6	0.8	5.6	93.0
Umbria	0.7	1.0	4.3	94.1
Marche	0.5	0.7	6.4	92.5
Lazio	0.4	0.5	3.5	95.7
Abruzzo	0.8	0.5	3.9	94.9
Molise	0.1	1.0	3.7	95.2
Campania	0.4	0.6	3.4	95.7
Puglia	0.4	0.7	3.7	95.3
Basilicata	0.6	0.5	4.4	94.6
Calabria	0.3	1.0	4.0	94.7
Sicily	0.5	0.9	3.7	94.9
Sardinia	0.3	1.4	4.3	94.1
Italy	**0.6**	**0.7**	**4.2**	**94.5**
North	0.5	0.8	4.8	93.9
Centre	0.5	0.7	4.6	94.2
South and Islands	0.4	0.8	3.7	95.1

Table 1.8.6 Percentage distribution by NHS price band of consumption of medicines purchased by public health facilities by Region (year 2022)

Region	% First quartile (price ≤0,68)	% Second quartile (price 0.68 -2.47)	% Third quartile (price 2.47- 24.79)	% Fourth quartile (price >24,79)
Piedmont	19.4	22.1	23.6	34.9
Valle d'Aosta	18.7	21.9	26.8	32.6
Lombardy	14.6	13.8	22.4	49.1
A.P. of Bolzano	17.7	26.8	25.0	30.5
A.P. of Trento	14.8	19.8	27.3	38.2
Veneto	16.2	25.4	26.1	32.2
Friuli VG	21.1	22.1	19.1	37.8
Liguria	15.9	23.9	24.9	35.4
Emilia Romagna	23.9	22.0	26.1	28.0
Tuscany	12.5	21.2	29.5	36.9
Umbria	13.9	22.6	25.4	38.1
Marche	17.6	16.6	30.1	35.8
Lazio	11.9	12.0	22.5	53.6
Abruzzo	12.9	13.1	21.1	53.0
Molise	8.0	16.0	23.1	52.9
Campania	8.9	14.0	25.5	51.6
Puglia	7.8	9.8	26.3	56.1
Basilicata	10.2	9.1	29.5	51.1
Calabria	4.0	10.8	31.9	53.3
Sicily	9.1	21.9	20.3	48.6
Sardinia	11.0	16.2	25.5	47.3
Italy	**14.4**	**19.2**	**24.0**	**42.4**
North	18.0	21.9	24.1	36.0
Centre	11.9	19.1	25.9	43.1
South and Islands	8.9	14.4	25.0	51.8

1.9 International comparison

This section presents an international comparison of pharmaceutical consumption and expenditure. Several in-depth studies have been carried out on:

- the impact of pharmaceutical expenditure on Gross Domestic Product (GDP);
- the relationship between *per capita* GDP and *per capita* expenditure;
- the distribution of consumption and expenditure in the different supply channels, by therapeutic category and by active ingredient;
- the international comparison in the average cost per Standard Unit;
- the penetration of generic and biosimilar medicines;
- the level of market concentration in relation to patent-expired biological medicinal products;
- the expenditure for orphan medicines;
- a price comparison analysis in 2022;
- a time analysis (2014-2022) comparing ex factory prices against the European average for products covered and not covered by patents;
- a comparison analysis of ex factory prices in Italy during 2014-2022 against the European average for baskets of pharmaceuticals, defined on the basis of their launch date.
- a comparison analysis of ex factory prices in Italy against the European average by therapeutic category.

The source of the international comparison is the IQVIA MIDAS® database. The data collected in the different countries, both in the inpatient and outpatient settings, are standardised (language, currency, company name, product name and packaging). Information was gathered on launch dates, patent coverage, specialty, biological/biosimilar classification and orphan drug designation. Data on inpatient treatments include accredited private health care facilities. Community data include private purchases by citizens, net of direct and "on-behalf" distribution. Besides Italy, 9 countries were considered for the purposes of the international comparison: Germany, Belgium, Austria, Spain, France, Sweden, Portugal, UK, Poland (EU 10) and the average of European countries (Europe).

Comparison of expenditure and consumption

In Italy in 2022 the incidence of total pharmaceutical expenditure on GDP was 1.7%, lower only to Spain (2.0%) and Portugal (1.8%). Significantly lower percentages were recorded in Sweden (0.8%) and UK (1.0%) (Figure 1.9.1). All countries showed an increase from 2019 to 2020 in the proportion of pharmaceutical expenditure over GDP. This trend is essentially due to a decrease in GDP recorded in all countries, against an increase in pharmaceutical expenditure. In 2021 and 2022, a substantial stability is instead recorded in the incidence of total pharmaceutical expenditure on GDP. No correlation emerges between expenditure and GDP *per capita*, although there is a tendency for expenditure *per capita* to rise as GDP *per capita* increases (Figure 1.9.2).

Figure 1.9.1 International comparison: incidence of total pharmaceutical expenditure on GDP in the period 2018-2022

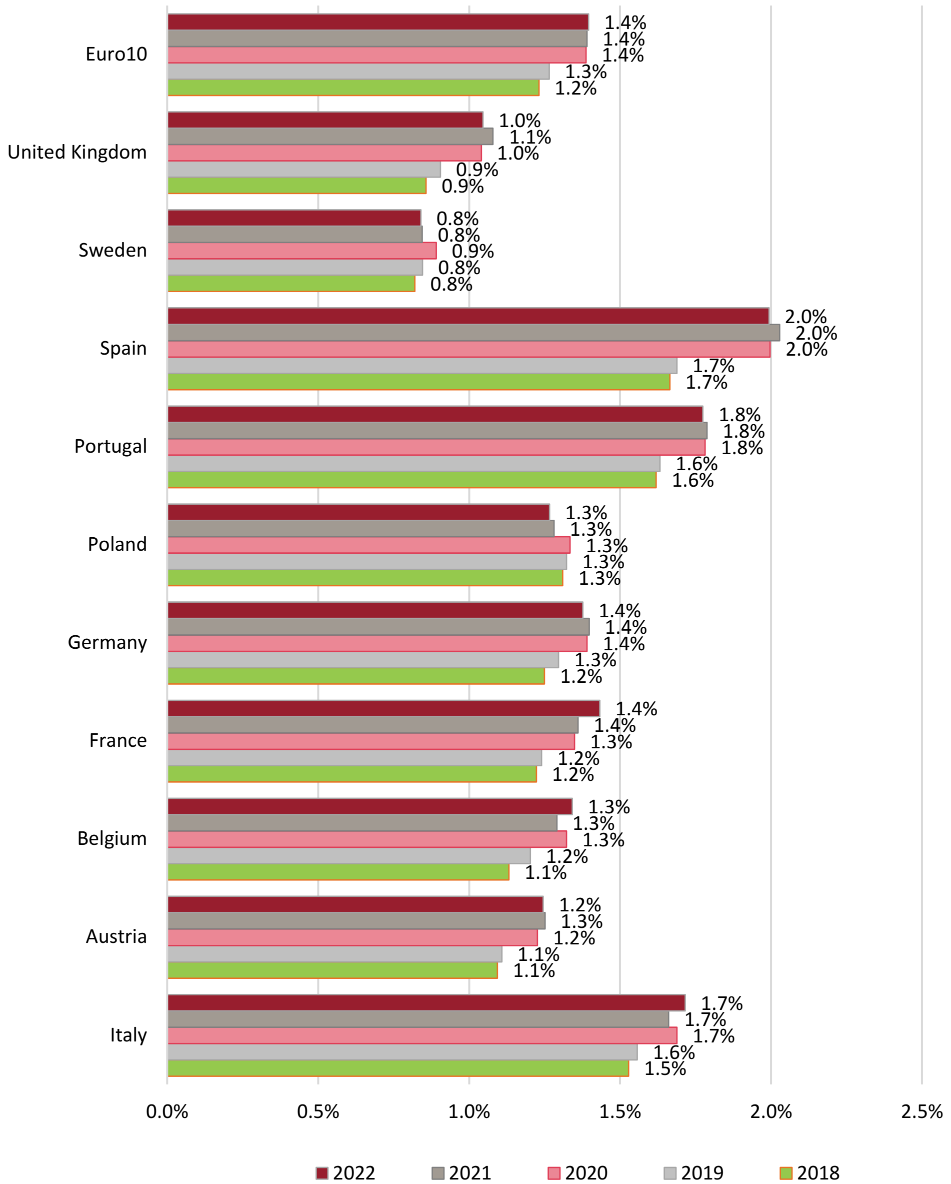
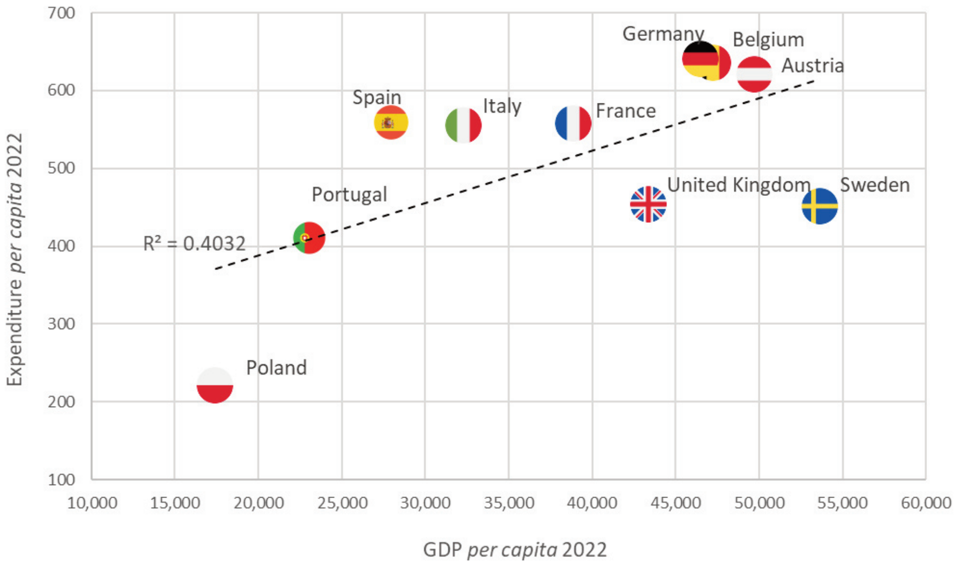


Figure 1.9.2 The relationship between *per capita* pharmaceutical expenditure and *per capita* GDP (Year 2022)



The total Italian pharmaceutical expenditure, including local public and private expenditure and hospital expenditure, was equal to 555 euros *per capita*, lower than in Germany (640 euros), Austria (620 euros), Belgium (635 euros), France (557 euros) and Spain (558 euros), while it is well above the values of Poland (221 euros), Portugal (410 euros), UK (454 euros), Sweden (451 euros) and the average of the European countries, which is equal to 359 euros (Figure 1.9.3).

The international comparison was also made in terms of Standard Unit (standard unit - SU), i.e. the elementary units contained in each package. Standard units can be easily defined in the case of solid forms (typically tablets, capsules, etc.) or liquid forms that have been already pre-packaged in minimum units (e.g. pre-filled syringes). In the case of other forms (e.g. syrups or aerosols), criteria are identified for the identification of the minimum standard minimum unit (e.g. inhalation).

The comparison by Standard Unit shows a *per capita* consumption of 832 SU in Italy (Figure 1.9.4), lower than all countries considered (average countries analysed (EU 10) 1.083 SU *per capita* and average Europe 1.059 SU). It is worth highlighting that consumption refers to supplied Standard Units and not to those actually consumed by the patient, therefore the different packaging or the number of dose units within the individual packages may have an impact on the consumption levels detected. If the treatment adherence is the same, a country that has on average a smaller number of dose units per package will report a lower consumption than a country with higher number of dose units per package, given by the lower number of dose units not taken by the single patient. The difference found in consumption in Italy compared to the European average can therefore also be attributed to the fact that in Italy the packages delivered at a local level contain on average a lower number of SU and DDD than the European average.

Figure 1.9.3 International comparison of total *per capita* pharmaceutical expenditure 2015-2022

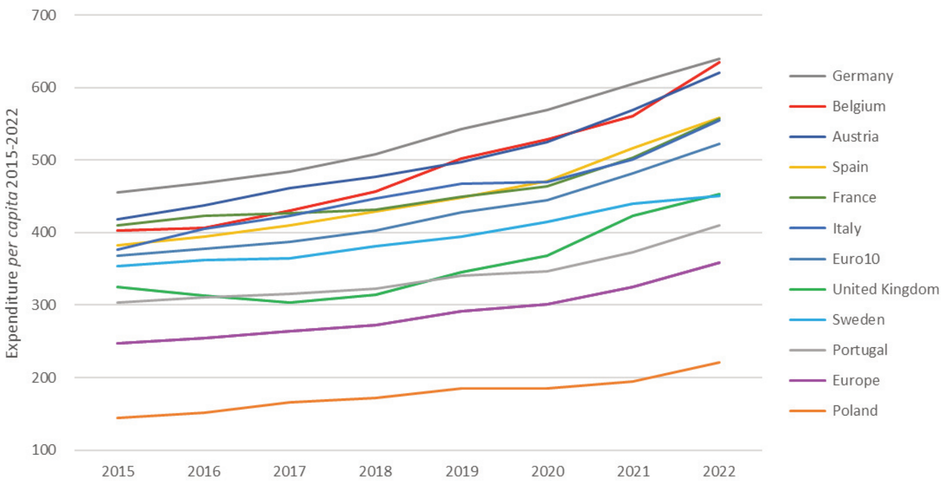
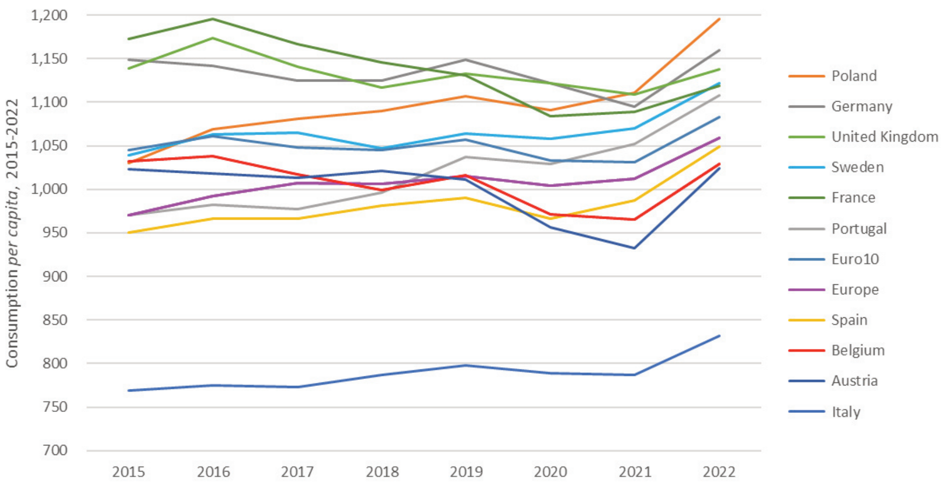
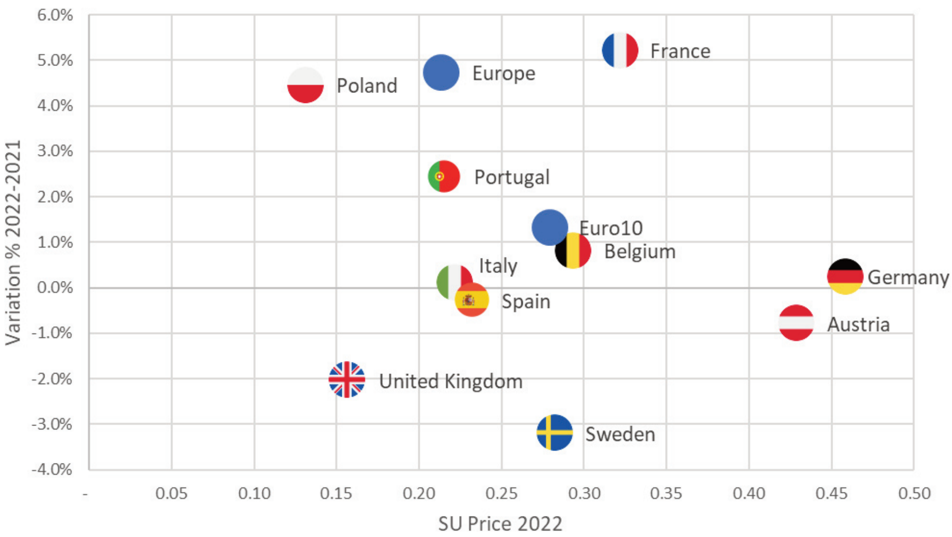


Figure 1.9.4 International comparison of total *per capita* consumption (Standard Unit per inhabitant) 2015-2022



When looking at the average cost per dose unit, Italy with 0.22 euros has a 21% lower value in the area than the average (0.28 euros) of the 10 countries analysed (Figure 1.9.5). In Italy, the average cost is fairly stable compared with 2021, with the largest variation found in Poland (+4.4%) and France (+5.2%).

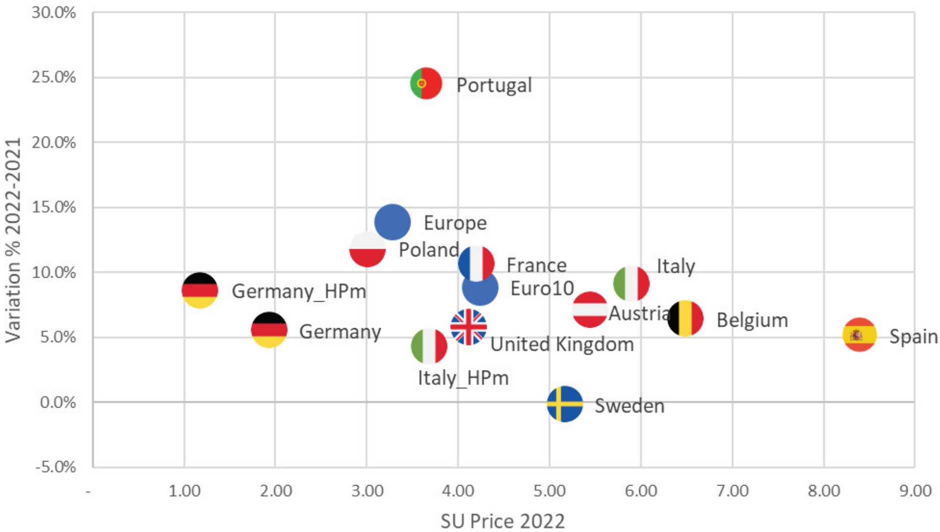
Figure 1.9.5 International comparison of the average cost by Standard Unit at local level in 2022 and 2022-2021 variation



In hospital settings (Figure 1.9.6), Italy has an average cost for Standard Unit (5.90 euros) higher than the average of the countries analysed (4.24 euros), with a 39% percentage difference. It is important to underline that the comparison is not conducted on a common basket of medicines and that the different packaging (number of dose units contained) could affect the definition of the cost per dose unit, due to a potential price/volume effect. In all the analysed countries there is an increase compared to 2021, with the highest values in Portugal (+24.5%) and Poland (+11.8%). Considering the purchase prices for Italy and Germany, the only countries for which such a price is available, the price per SU is 3.70 euro and 1.20 euro, respectively.

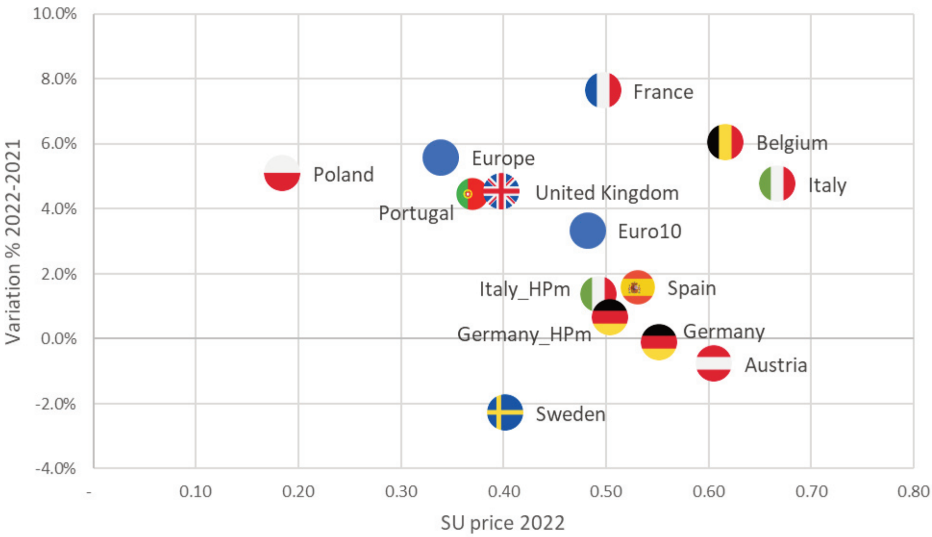
Considering altogether the territorial and hospital setting and the purchase price, the values for Italy and Germany are aligned (respectively 0.49 and 0.50 euro per SU; Figure 1.9.7).

Figure 1.9.6 International comparison of average cost by Standard Unit in hospital setting in 2022 and 2022-2021 variation



For Italy and Germany both the cost per standard unit was included using the base auction price and the tender price (HPm).

Figure 1.9.7 International comparison of average cost by Standard Unit in local/community care and in hospital setting in 2022 and 2022-2021 variation with tender price in hospital setting (HPm)



For Italy and Germany both the cost per standard unit was included using the base auction price and the tender price (HPm).

In the context of local care, in Italy the largest share of expenditure, equal to 20.0%, is represented by medicines of the cardiovascular system, which is higher than that recorded in the other countries; for example, in Sweden, only 5.9% of the local expenditure is represented by this category of medicines. Great Britain and Spain, with a value of 22.0% and 22.8% respectively, have the highest incidence of expenditure on central nervous system medicines. Poland (15.3%) and Great Britain (12.8%) are the countries with the highest incidence of expenditure on respiratory system medicines. Finally, gastro-intestinal medicines account for a very large share of expenditure in Portugal (24.1%), Great Britain (23.3%) and Spain (21.9%). Sweden (10.6%), France (8.9%), Germany (8.6%), Belgium (8.2%) and Austria (5.6%) report a considerably higher proportion of antimicrobial expenditure than Italy (4.8%) (Table 1.9.1).

Table 1.9.1 International comparison of percentage distribution of local pharmaceutical expenditure* in 2022 by ATC 1st level

ATC 1st level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
C - Cardiovascular system	20.0	9.8	10.6	9.7	7.5	15.5	18.7	14.8	5.9	11.5	11.5	10.9
N - CNS	19.6	15.6	17.5	12.7	13.8	14.8	18.5	22.8	16.3	22.0	15.2	16.1
A - Gastrointestinal tract	18.1	10.2	15.1	11.2	12.5	20.3	24.1	21.9	14.5	23.3	16.3	15.4
R - Respiratory system	12.1	10.3	11.1	10.1	8.9	15.3	9.1	10.0	8.8	12.8	10.6	10.4
G - Genito-urinary system and sex hormones	7.1	2.0	4.4	3.1	2.3	5.9	5.3	6.0	3.9	5.8	4.2	3.9
M — Musculo-skeletal system	6.1	4.8	4.2	2.8	3.9	4.8	5.5	4.2	3.2	1.9	4.3	3.8
J - Antimicrobials for systemic use	4.8	5.6	8.2	8.9	8.6	4.5	3.6	2.8	10.6	2.6	6.8	6.8
D - Dermatological	3.3	2.4	2.7	1.6	3.2	2.6	2.3	2.2	1.7	2.7	2.6	2.6
B - Blood and blood forming organs	3.1	8.0	10.4	9.0	9.1	11.8	9.7	7.9	9.1	10.7	8.6	8.8
H - Systemic hormones	2.1	1.5	2.1	2.4	1.9	1.3	0.9	2.1	2.9	2.3	1.9	2.1
S - Sensory organs	1.7	0.3	0.9	4.8	2.2	0.8	0.9	1.2	1.1	1.2	1.9	2.3
L - Antineoplastic	1.5	28.0	12.3	22.9	24.0	1.5	0.5	3.4	21.3	2.8	14.8	15.9
V - Various	0.3	1.4	0.3	0.6	1.8	0.6	0.8	0.5	0.6	0.2	1.1	1.0
P - Antiparasitic products	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2

Table 1.9.2 shows the average annual change (CAGR) in local expenditure for ATC 1st level over the period 2019-2022. In Italy, the largest increases were recorded for ATC P (Antiparasitic), N (Central Nervous System), M (Musculoskeletal System) and R (Respiratory), while at the level of the 10 countries analysed, the largest increases were observed for ATC B (Haematological), L (Antineoplastics) and R (Respiratory System).

Table 1.9.2 International comparison of the 4-year CAGR on local pharmaceutical expenditure* 2022 by ATC 1st level

ATC I level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	United Kingdom	Europe	EU10
P - Antiparasitic	2.4%	-9.8%	-0.9%	-3.2%	-5.0%	4.0%	-3.8%	19.0%	2.4%	-2.2%	0.3%	-1.8%
N - SNC	2.0%	6.0%	0.0%	0.0%	1.3%	2.9%	2.4%	1.8%	0.0%	0.4%	2.2%	1.3%
M - Musculoskeletal	1.9%	4.2%	0.8%	2.3%	5.1%	2.0%	1.2%	1.1%	2.3%	-7.3%	3.3%	2.4%
R - Respiratory	1.6%	11.0%	2.1%	9.6%	7.9%	5.5%	2.3%	0.6%	3.2%	1.9%	5.7%	5.4%
S - Sense Organs	1.5%	4.4%	12.8%	4.3%	3.2%	2.7%	0.8%	3.1%	1.3%	5.1%	4.1%	3.7%
C - Cardiovascular	1.3%	1.0%	-0.8%	6.1%	3.7%	0.9%	3.8%	1.5%	5.9%	0.7%	3.0%	2.7%
L - Antineoplastic	1.3%	7.8%	2.7%	7.4%	5.1%	-0.3%	-0.3%	1.0%	2.5%	1.6%	6.1%	5.6%
A - Gastrointestinal	0.8%	4.3%	3.9%	2.3%	5.5%	7.6%	7.3%	5.4%	6.6%	6.2%	5.3%	4.7%
H - Systemic hormones	0.5%	-2.4%	-2.1%	-1.4%	1.3%	0.3%	1.7%	1.8%	5.8%	-3.4%	0.5%	0.1%
G - Genitourinary and sex hormones	0.4%	-0.4%	-1.1%	-2.0%	-1.6%	2.3%	0.2%	0.1%	-0.3%	-0.1%	0.6%	-0.5%
D - Dermatological	0.2%	14.9%	5.6%	5.4%	8.9%	1.9%	1.6%	1.1%	6.4%	1.0%	5.5%	5.3%
V - Various	-0.1%	5.7%	14.1%	1.5%	0.4%	-0.9%	7.2%	6.0%	10.9%	-5.2%	2.5%	1.2%
B - Haematological	-1.8%	5.3%	3.1%	6.9%	8.0%	4.2%	3.6%	4.9%	5.4%	7.6%	6.6%	6.4%
J - Antimicrobial	-2.4%	-2.4%	-2.5%	-0.6%	5.1%	1.4%	-2.8%	-3.1%	-0.1%	-4.1%	1.2%	1.3%

*Medicines supplied by local pharmacies, excluding distribution “on behalf”

Italy ranks first in terms of the incidence of local consumption of cardiovascular system medicines (26.9%) (Table 1.9.3), followed immediately by Germany (24.3%) and Portugal (23.5%). The percentage of SU consumed for medicines of the central nervous system (15.1%) is lower in almost all the countries considered with the exception of Poland (14.8%). The percentage of consumption of respiratory system medicines also shows a low value in Italy (14.2%), lower than all the other countries analysed, with the exception of Portugal (11.9%). As for antimicrobials for systemic use, represented at the local/community level mainly by antibiotics (J01), Italy shows the largest share of consumption, lower only than France. Analysing the CAGR of local consumption over the period 2019-2022 (Table 1.9.4), the most important variations in Italy were observed for pesticides (+3.6%), for medicines of the musculoskeletal system (+2.3%), of the respiratory system (+2.0%), for systemic hormones (+2.0%) and for medicines of the genito-urinary system (+2.0%), while in the European countries analysed the greatest increases were recorded for medicines of the genito-urinary system (+1.8%) and for those of the central nervous system (+1.5%).

Table 1.9.3 International comparison of the percentage distribution of local/community consumption* in 2022 by ATC 1st level

ATC 1st level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
C - Cardiovascular system	26.9	19.2	17.9	16.6	24.3	21.3	23.5	18.1	18.2	17.7	19.0	20.6
A - Gastrointestinal tract	17.4	14.4	15.6	18.1	14.2	22.7	15.4	15.5	17.9	18.0	17.3	17.1
N - Nervous system	15.1	16.5	22.3	24.1	15.4	14.8	24.7	27.9	26.5	22.9	17.1	20.3
R - Respiratory system	14.2	26.6	22.1	17.3	19.7	18.7	11.9	15.5	17.9	20.3	22.3	18.1
M — Musculo-skeletal system	6.9	7.5	5.2	4.8	6.0	6.7	8.1	6.0	3.8	3.2	5.7	5.5
B - Blood and blood forming organs	5.4	4.8	5.4	4.7	5.6	4.5	4.8	4.7	5.0	4.6	4.7	5.0
H - Systemic hormones	4.0	3.3	2.5	2.9	4.3	2.6	2.3	2.9	3.0	2.9	2.7	3.3
G - Genito-urinary system and sex hormones	2.9	1.9	2.6	2.3	2.6	2.6	2.8	2.2	2.1	2.8	2.4	2.5
S - Sensory organs	2.6	1.4	2.1	4.0	2.6	1.8	2.0	2.7	2.3	1.8	2.7	2.6
D - Dermatological	2.3	2.5	1.8	2.1	2.6	1.8	2.6	2.2	1.5	3.5	3.0	2.4
J - Antimicrobials for systemic use	1.7	1.0	1.6	2.0	0.8	1.7	1.2	1.5	0.9	1.6	1.7	1.5
L - Antineoplastic and immunomodulating agents	0.4	0.6	0.7	0.6	0.6	0.3	0.2	0.6	0.8	0.5	0.7	0.5
V - Various	0.2	0.4	0.1	0.6	0.9	0.4	0.4	0.1	0.1	0.1	0.5	0.4
P - Antiparasitic products	0.0	0.1	0.1	0.1	0.4	0.1	0.2	0.1	0.1	0.2	0.2	0.2

Table 1.9.4 International comparison of the 4-year CAGR on local pharmaceutical consumption* 2022 by ATC 1st level

ATC I level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	United Kingdom	Europe	EU10
P - Antiparasitic	3.6%	-12.7%	8.7%	-5.6%	-11.2%	1.4%	-5.1%	21.8%	-0.5%	-5.8%	-2.2%	-7.0%
M - Musculoskeletal	2.3%	-1.6%	-1.8%	-3.7%	-0.8%	0.9%	-1.3%	-1.9%	-1.6%	-0.7%	-0.7%	-0.9%
R - Respiratory	2.0%	0.5%	1.7%	0.5%	0.1%	4.2%	1.0%	0.9%	1.8%	-0.4%	1.7%	0.9%
H - Systemic hormones	2.0%	1.5%	-0.7%	-0.3%	0.5%	2.0%	2.6%	2.2%	3.6%	-0.6%	2.1%	0.8%
G - Genitourinary and sex hormones	2.0%	-0.1%	-0.1%	0.1%	0.1%	1.5%	1.2%	1.9%	1.7%	6.6%	1.6%	1.8%
N - SNC	1.8%	2.3%	0.8%	0.1%	2.1%	2.8%	3.1%	3.3%	1.8%	0.3%	1.6%	1.5%
C - Cardiovascular	1.3%	0.6%	-0.3%	-0.3%	1.6%	0.4%	1.6%	1.1%	1.9%	0.6%	1.1%	0.9%
S - Sense Organs	1.3%	0.2%	-0.4%	0.3%	-0.3%	1.4%	0.0%	3.0%	1.7%	1.0%	0.8%	0.8%
D - Dermatological	0.3%	-1.8%	-2.8%	-2.0%	-1.5%	-4.1%	-1.0%	-0.4%	-0.3%	-2.1%	-0.5%	-1.6%
L - Antineoplastic	0.2%	3.2%	-0.3%	1.2%	3.1%	2.1%	-0.7%	0.5%	1.0%	-0.9%	7.2%	1.2%
A - Gastrointestinal	0.0%	-0.6%	-0.9%	-0.9%	0.4%	2.6%	2.2%	1.1%	0.5%	0.6%	0.9%	0.5%
B - Haematological	-0.1%	1.3%	-2.3%	2.1%	1.7%	0.8%	1.1%	1.4%	0.4%	0.6%	2.1%	1.1%
J - Antimicrobial	-2.0%	-1.5%	-1.0%	-1.6%	-0.1%	1.3%	-0.9%	-2.6%	-2.4%	0.5%	0.5%	-0.8%
V - Various	-4.1%	-5.6%	-1.4%	-2.3%	-7.7%	-0.4%	4.6%	-1.6%	3.3%	-1.5%	-3.5%	-4.9%

*Medicines supplied by local pharmacies, excluding distribution "on behalf"

On the hospital care side (Table 1.9.5), in Italy the first expenditure item is represented by antineoplastic medicines (43.1%), although higher percentages are observed in almost all the countries considered, with the exception of Germany (40.0%) and Portugal (42.0%). For antimicrobials, Germany (21.9%), Portugal (17.8%), Spain (16.2%) and Italy (14.6%) have the highest incidence of expenditure compared to other countries. This incidence in Italy is gradually decreasing, in fact in 2019 it was 22.8%, in 2020 17.6%, in 2021 15.6% and in 2022 14.6%. Italy has the highest incidence (12.3%), followed immediately by Sweden (12.2%), of spending on haematological medicines compared to the countries considered in the analysis (average 8.8%) and the European average (8.5%). Even for ATC A (gastrointestinal system and metabolism) Italy presents the highest incidence of expenditure (7.6% compared to the EU10 average of 5.4%); this could be attributable to the different supply of antidiabetics, which in Italy are mainly supplied "on behalf". The highest increases (CAGR 2019-2022) were observed for Italy for dermatological medicines (+52.0%), for medicines of the respiratory system (+19.7%), of the cardiovascular system (+11.9%), for antineoplastics (+10.3%) and for medicines of the gastrointestinal system (+9.8%; Table 1.9.6). The increase recorded in Italy for ATC A, which is higher than the EU10 average (+6.6%), could be driven by the trend in antidiabetics. At the level of the 10 countries analysed, the largest increases were for medicines of the respiratory system (+23.6%), for dermatological medicines (+23.2%), for antineoplastics (+10.4%), for medicines of the central nervous system (+6.8%) and of the gastrointestinal system (+6.6%).

Table 1.9.5 International comparison of percentage distribution of 2022 hospital pharmaceutical expenditure by 1st level

ATC 1st level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
L - Antineoplastic	43.1	59.5	57.0	54.3	40.0	52.4	42.0	49.9	44.8	46.1	47.1	47.3
J - Antimicrobials for systemic use	14.6	14.5	7.3	10.8	21.9	9.4	17.8	16.2	12.1	14.1	15.6	14.7
B - Blood and blood forming organs	12.3	8.2	9.6	9.0	9.8	4.4	5.7	6.1	12.2	6.6	8.5	8.8
N - Nervous system	9.4	6.5	6.3	11.8	13.8	17.0	14.6	9.2	8.4	7.7	9.9	10.0
A - Gastrointestinal tract	7.6	3.6	5.8	5.7	4.5	1.8	6.3	4.1	5.3	4.4	5.3	5.4
R - Respiratory system	3.9	0.8	4.4	1.0	1.1	5.4	4.8	5.1	1.1	9.2	4.0	4.3
C - Cardiovascular system	3.0	2.0	3.5	2.1	2.0	3.1	1.7	1.8	1.5	1.5	2.1	2.2
M — Musculo-skeletal system	1.6	1.4	1.2	1.8	1.9	1.6	1.6	1.6	4.3	2.7	2.0	1.9
H - Systemic hormones	1.4	0.7	0.7	0.8	0.9	1.6	1.1	1.1	0.6	1.0	1.0	1.1
S - Sensory organs	1.1	1.5	3.0	0.4	1.4	2.5	2.0	3.2	8.4	5.1	2.5	2.5
D - Dermatological	0.9	0.2	0.1	1.0	0.9	0.3	1.6	1.1	0.1	0.8	0.8	0.9
V - Various	0.6	0.6	0.5	0.5	1.3	0.3	0.7	0.2	0.8	0.4	0.6	0.6
G - Genito-urinary system and sex hormones	0.4	0.6	0.5	0.8	0.4	0.2	0.2	0.3	0.3	0.5	0.5	0.4
P - Antiparasitic products	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0

Table 1.9.6 International comparison of the 4-year CAGR on hospital pharmaceutical expenditure 2022 by ATC 1st level

ATC I level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	United Kingdom	Europe	EU10
D - Dermatological	52.0%	6.5%	5.7%	3.4%	7.0%	14.9%	39.8%	64.6%	-5.9%	22.7%	23.2%	23.2%
R - Respiratory	19.7%	-5.1%	29.2%	-12.6%	-0.8%	38.7%	28.7%	21.2%	-3.6%	42.0%	22.4%	23.6%
C - Cardiovascular	11.9%	1.5%	31.1%	-1.3%	0.2%	2.4%	6.4%	4.1%	-0.1%	8.3%	5.8%	6.4%
L - Antineoplastic	10.3%	11.1%	12.1%	13.6%	6.1%	10.3%	5.7%	10.2%	7.7%	10.9%	10.6%	10.4%
A - Gastrointestinal	9.8%	-2.9%	9.6%	4.8%	-0.9%	-0.4%	3.0%	8.7%	3.2%	8.4%	6.9%	6.6%
M - Musculoskeletal	7.4%	-1.9%	3.3%	1.0%	0.2%	8.4%	6.0%	10.3%	4.7%	7.3%	7.0%	5.4%
N - SNC	5.3%	2.8%	8.6%	5.7%	4.0%	8.6%	13.9%	9.7%	0.2%	11.0%	7.1%	6.8%
B - Haematological	4.8%	-0.1%	10.3%	2.9%	-3.7%	2.8%	4.4%	8.7%	2.3%	13.9%	4.7%	4.5%
V - Various	1.7%	-5.5%	5.1%	2.0%	6.4%	4.6%	7.6%	19.1%	8.0%	2.5%	4.1%	4.0%
S - Sense Organs	0.8%	5.5%	6.0%	1.6%	-1.2%	10.6%	14.0%	19.3%	4.4%	4.4%	6.0%	6.2%
H - Systemic hormones	-0.7%	0.1%	7.5%	3.1%	0.9%	-9.2%	-6.2%	-0.1%	0.5%	2.9%	0.4%	0.2%
P - Antiparasitic	-2.6%	-35.2%	9.0%	-2.4%	-1.9%	-4.8%	-2.1%	3.8%	-0.1%	13.7%	2.9%	2.6%
G - Genitourinary and sex hormones	-3.0%	-1.7%	4.8%	19.3%	11.7%	-3.3%	-8.2%	-0.2%	3.5%	-3.9%	2.1%	2.8%
J - Antimicrobial	-5.2%	2.7%	0.1%	2.6%	1.4%	-10.4%	1.8%	-0.4%	2.9%	2.8%	0.9%	-0.6%

Blood medicines rank first in terms of incidence on hospital consumption (25.7%), much higher than the average of the countries considered in the analysis (7.7%) and the European average (6.8%; Table 1.9.7). These differences may be attributable to the different methods of supplying certain medicines belonging to this category, such as the new oral anticoagulants, which in Italy are mainly supplied by direct distribution and “on behalf”. Even for medicines of the gastrointestinal system, Italy has the highest incidence on hospital consumption (19.1% vs EU10 average: 14.4% and European average: 14.3%), mainly due to the distribution “on behalf” of antidiabetics in Italy. On the other hand, the percentage of SU consumed in hospital for respiratory system medicines is low, amounting to 3.0% compared to the percentage of consumption in all the analysed countries (EU10 average: 11.7% and European average: 11.1%). Increases (CAGR 2019-2022) in hospital consumption for Italy were recorded for haematological medicines (+5.4%), antineoplastics (+2.9%) and medicines of the gastrointestinal system (+0.6%). All other categories recorded a decrease. At the level of the 10 countries analysed, likewise, only haematological medicines (+3.0%) and antineoplastics (+4.0%) recorded increases in consumption (Table 1.9.8). When taking into consideration overall territorial and hospital expenditure, for Italy and for all the countries considered, antineoplastics and central nervous system medicines are the first and second, respectively, in terms of incidence. In Italy the third in terms of incidence are the antimicrobials with a value on the total expenditure of 11.6%, higher than that of the 10 countries analysed (10.4%) and than the European average (10.3%) (Table 1.9.9). Increases (CAGR 2019-2022) in total expenditure for Italy were recorded for antineoplastics (+10.1%), dermatological medicines (+9.6%) and respiratory medicines (+7.5%). At the level of the 10 countries, there was a similar increase for antineoplastics (+8.9%), dermatological medicines (+8.1%) and for respiratory medicines (+8.9%) (Table 1.9.10).

Table 1.9.7 International comparison of percentage distribution of 2022 hospital consumption by ATC 1st level

ATC 1st level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
B - Blood and blood forming organs	25.7	4.8	4.8	4.5	3.0	6.3	1.9	3.4	5.2	4.9	6.8	7.7
N - CNS	25.3	27.6	39.9	35.4	17.9	29.4	14.1	28.1	41.4	21.4	22.6	24.8
A - Gastrointestinal tract	19.1	13.5	12.1	15.8	12.9	17.8	6.8	8.8	16.0	14.3	14.3	14.4
C - Cardiovascular system	10.5	12.3	8.7	8.2	8.9	14.1	5.2	7.3	8.8	6.2	10.2	8.5
L - Antineoplastic	5.2	0.7	3.8	0.8	0.3	3.3	9.3	4.5	1.2	5.0	3.8	3.0
J - Antimicrobials for systemic use	4.6	4.4	4.9	3.5	2.7	6.6	7.5	7.9	6.0	8.0	9.5	5.0
R - Respiratory system	3.0	16.4	12.2	13.3	10.6	7.2	30.3	19.5	7.1	14.8	11.1	11.7
D - Dermatological	1.8	5.2	4.1	5.3	26.9	1.8	15.9	5.6	1.7	5.3	8.3	10.6
H - Systemic hormones	1.5	2.2	1.6	2.0	1.6	2.6	1.8	2.4	5.5	3.3	2.2	2.2
M — Musculo-skeletal system	1.1	6.5	2.7	1.9	4.0	5.1	1.3	2.6	2.2	1.9	2.7	2.6
V - Various	1.0	1.8	0.7	3.1	7.6	0.4	1.5	0.3	0.7	1.1	3.1	3.1
S - Sensory organs	0.6	3.6	3.7	5.1	3.1	4.1	3.3	8.9	2.9	12.1	4.4	5.4
G - Genito-urinary system and sex hormones	0.6	1.0	1.0	0.9	0.6	1.2	0.9	0.6	1.2	1.6	0.9	0.9
P - Antiparasitic products	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.0	0.0	0.1	0.1	0.1

Table 1.9.8 International comparison of the 4-year CAGR on hospital pharmaceutical consumption 2022 by ATC 1st level

ATC I level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	United Kingdom	Europe	EU10
B - Haematological	5.4%	-2.1%	6.2%	1.4%	-1.1%	2.1%	-0.5%	0.1%	-0.2%	0.8%	3.2%	3.0%
L - Antineoplastic	2.9%	0.7%	12.7%	5.8%	-0.9%	7.9%	3.0%	7.6%	1.8%	3.3%	13.9%	4.0%
A - Gastrointestinal	0.6%	-2.4%	6.4%	1.8%	-1.9%	-0.2%	-0.5%	-2.3%	-1.9%	0.1%	-1.8%	-0.1%
V - Various	-1.8%	-10.8%	13.7%	11.4%	-12.9%	-30.3%	1.9%	-3.2%	-4.1%	-4.5%	-12.0%	-9.3%
N - SNC	-2.1%	-1.6%	6.1%	0.0%	-6.9%	0.5%	0.8%	0.8%	0.7%	-1.9%	-2.3%	-2.0%
P - Antiparasitic	-2.1%	-44.1%	-12.8%	2.0%	-8.2%	-2.2%	6.4%	6.1%	-8.2%	-3.1%	-3.7%	-3.6%
M - Musculoskeletal	-3.6%	-3.5%	9.2%	-0.7%	-2.3%	-0.2%	-1.1%	-2.8%	2.9%	-1.2%	-2.7%	-1.7%
C - Cardiovascular	-3.6%	-4.8%	7.1%	0.1%	-1.7%	-0.3%	-0.3%	-0.2%	2.5%	0.8%	-1.6%	-1.2%
H - Systemic hormones	-4.5%	-1.2%	8.3%	1.3%	-1.4%	0.0%	1.4%	-0.1%	4.4%	-1.6%	-0.2%	-0.9%
J - Antimicrobial	-4.9%	-1.9%	6.1%	-0.5%	-1.8%	-0.7%	-1.6%	-1.2%	2.3%	-0.8%	0.7%	-1.5%
D - Dermatological	-5.4%	-6.1%	9.2%	-4.0%	-3.5%	-5.6%	-2.2%	-3.6%	-2.3%	-6.8%	-3.5%	-3.9%
R - Respiratory	-7.7%	-0.6%	6.8%	-1.4%	-6.4%	-0.4%	21.3%	11.4%	8.7%	-4.5%	-2.0%	-1.5%
S - Sense Organs	-8.0%	-0.4%	-2.6%	1.0%	-2.0%	1.4%	6.7%	-2.7%	3.8%	-7.3%	-4.2%	-4.2%
G - Genitourinary and sex hormones	-9.6%	-2.8%	7.4%	1.6%	-2.1%	-4.5%	-0.4%	-3.0%	2.7%	-1.5%	-3.7%	-2.3%

Table 1.9.9 International comparison of percentage distribution of 2022 total expenditure by ATC 1st level

ATC 1st level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
L - Antineoplastic	30.4	38.0	36.8	34.9	27.5	16.9	18.9	30.4	28.7	30.1	27.6	30.1
N - Nervous system	12.5	12.8	11.4	12.4	13.8	15.5	16.7	14.9	13.8	12.9	13.1	13.4
J - Antimicrobials for systemic use	11.6	8.4	7.7	9.6	11.5	6.0	9.9	10.6	11.0	9.9	10.3	10.4
A - Gastrointestinal tract	10.9	8.1	10.0	9.1	10.7	14.7	16.2	11.6	11.6	11.4	11.9	10.9
B - Blood and blood forming organs	9.5	8.0	10.0	9.0	9.3	9.6	7.9	6.9	10.1	8.1	8.6	8.8
C - Cardiovascular system	8.2	7.3	6.7	6.8	6.3	11.8	11.2	7.3	4.5	5.2	7.8	7.0
R - Respiratory system	6.4	7.3	7.4	6.6	7.2	12.4	7.2	7.2	6.4	10.5	8.0	7.6
M — Musculo-skeletal system	3.0	3.7	2.5	2.4	3.5	3.8	3.8	2.7	3.6	2.4	3.4	2.9
G - Genito-urinary system and sex hormones	2.5	1.6	2.3	2.2	1.9	4.2	3.0	2.7	2.7	2.4	2.7	2.4
D - Dermatological	1.6	1.7	1.3	1.4	2.7	1.9	1.9	1.6	1.2	1.5	1.9	1.8
H - Systemic hormones	1.6	1.2	1.3	1.8	1.7	1.4	1.0	1.5	2.2	1.5	1.5	1.6
S - Sensory organs	1.3	0.7	2.0	3.1	2.1	1.3	1.4	2.4	3.4	3.7	2.2	2.4
V - Various	0.6	1.1	0.4	0.5	1.7	0.5	0.7	0.4	0.7	0.3	0.9	0.8
P - Antiparasitic products	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table 1.9.10 International comparison of the 4-year CAGR on total expenditure 2022 by ATC 1st level

ATC I level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	United Kingdom	Europe	EU10
L - Antineoplastic	10.1%	9.4%	10.4%	10.9%	5.5%	9.5%	5.6%	9.6%	4.9%	10.5%	9.1%	8.9%
D - Dermatological	9.6%	14.5%	5.6%	4.8%	8.8%	2.3%	9.4%	13.0%	5.9%	6.0%	7.6%	8.1%
R - Respiratory	7.5%	10.1%	7.9%	7.4%	7.5%	7.9%	7.5%	6.9%	2.8%	16.0%	8.1%	8.9%
A - Gastrointestinal	4.8%	3.2%	5.6%	2.9%	4.8%	7.3%	6.5%	6.0%	6.1%	6.7%	5.6%	5.1%
B - Haematological	4.0%	3.4%	6.6%	5.3%	4.6%	4.0%	3.9%	6.7%	4.1%	10.6%	5.8%	5.5%
M - Musculoskeletal	3.8%	3.4%	1.4%	1.9%	4.4%	2.7%	2.0%	3.8%	3.2%	1.8%	4.1%	3.3%
N - SNC	3.6%	5.5%	2.2%	1.9%	1.9%	4.6%	6.2%	4.3%	0.0%	3.7%	3.6%	3.0%
C - Cardiovascular	3.5%	1.1%	4.6%	5.1%	3.5%	1.1%	3.9%	1.9%	5.2%	1.9%	3.3%	3.2%
P - Antiparasitic	1.7%	-10.5%	-0.6%	-3.1%	-4.9%	3.8%	-3.4%	18.3%	2.3%	1.1%	0.5%	-1.4%
V - Various	1.3%	3.4%	8.0%	1.6%	1.3%	-0.1%	7.4%	9.8%	9.8%	0.4%	2.9%	2.1%
S - Sense Organs	1.1%	5.1%	7.2%	4.2%	2.5%	7.0%	8.3%	14.9%	3.6%	4.5%	5.0%	4.9%
G - Genitourinary and sex hormones	-0.1%	-0.6%	-0.5%	-0.2%	-1.1%	2.2%	-0.1%	0.1%	-0.2%	-0.6%	0.7%	-0.2%
H - Systemic hormones	-0.2%	-2.0%	0.3%	-0.7%	1.2%	-3.6%	-2.5%	1.0%	5.2%	-0.9%	0.5%	0.1%
J - Antimicrobial	-4.9%	0.2%	-1.2%	0.7%	3.5%	-5.1%	0.8%	-0.8%	0.9%	2.1%	1.0%	0.1%

On the consumption side, medicines of the cardiovascular system, the gastrointestinal system and the central nervous system account for the largest share in Italy, 25.6%, 17.5% and 15.9% respectively. For medicines of the central nervous system and the gastrointestinal system, similar percentages are observed in the 10 European countries analysed, whereas for medicines of the cardiovascular system, a lower percentage is found than in Italy (Table 1.9.11). Increases (CAGR 2019-2022) in total consumption for Italy were recorded for antiparasitic (+3.3%), musculoskeletal (+2.2%) and respiratory medicines (+1.8%). At the 10-country level, increases were recorded for antineoplastics (+1.8%), genito-urinary (+1.7%) and central nervous system medicines (+1.3%) (Table 1.9.12).

Table 1.9.11 International comparison of the percentage distribution of total consumption in 2022 by ATC 1st level

ATC 1st level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
C - Cardiovascular system	25.6	18.9	17.4	16.2	23.3	21.1	22.7	17.7	18.0	17.0	18.6	20.0
A - Gastrointestinal tract	17.5	14.4	15.4	18.0	14.1	22.6	15.0	15.3	17.8	17.8	17.2	17.0
N - Nervous system	15.9	16.8	23.2	24.6	15.5	15.1	24.2	28.0	26.8	22.8	17.4	20.6
R - Respiratory system	13.3	26.2	21.5	17.1	19.1	18.5	12.7	15.6	17.6	19.9	21.9	17.8
B - Blood and blood forming organs	7.0	4.8	5.4	4.7	5.4	4.6	4.6	4.6	5.0	4.6	4.8	5.1
M — Musculo-skeletal system	6.5	7.4	5.1	4.6	5.9	6.7	7.8	5.9	3.7	3.2	5.6	5.3
H - Systemic hormones	3.8	3.3	2.5	2.8	4.2	2.6	2.2	2.9	3.0	2.9	2.6	3.2
G - Genito-urinary system and sex hormones	2.7	1.9	2.6	2.2	2.5	2.6	2.7	2.1	2.1	2.7	2.3	2.4
S - Sensory organs	2.4	1.5	2.2	4.1	2.7	1.9	2.1	2.9	2.3	2.4	2.8	2.7
D - Dermatological	2.2	2.6	2.0	2.2	4.1	1.8	3.2	2.3	1.5	3.6	3.2	2.9
J - Antimicrobials for systemic use	1.9	1.1	1.7	2.1	1.0	1.8	1.5	1.8	1.0	2.0	2.0	1.7
L - Antineoplastic	0.8	0.6	0.8	0.6	0.6	0.4	0.6	0.7	0.8	0.7	0.9	0.6
V - Various	0.2	0.4	0.1	0.7	1.3	0.4	0.4	0.1	0.1	0.1	0.6	0.5
P - Antiparasitic products	0.0	0.1	0.1	0.1	0.4	0.1	0.2	0.1	0.1	0.2	0.2	0.2

Table 1.9.12 International comparison of the 4-year CAGR on total consumption 2022 by ATC 1st level

ATC I level	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	United Kingdom	Europe	EU10
P - Antiparasitic	3.3%	-13.9%	8.4%	-5.4%	-11.2%	1.2%	-4.8%	21.5%	-0.6%	-5.7%	-2.2%	-6.9%
M - Musculoskeletal	2.2%	-1.7%	-1.6%	-3.7%	-0.9%	0.9%	-1.3%	-1.9%	-1.5%	-0.7%	-0.8%	-0.9%
R - Respiratory	1.8%	0.4%	1.9%	0.5%	-0.1%	4.2%	2.5%	1.3%	1.9%	-0.6%	1.6%	0.8%
H - Systemic hormones	1.8%	1.5%	-0.4%	-0.3%	0.4%	2.0%	2.5%	2.1%	3.7%	-0.7%	2.1%	0.7%
G - Genitourinary and sex hormones	1.7%	-0.2%	0.0%	0.1%	0.1%	1.4%	1.1%	1.9%	1.7%	6.3%	1.5%	1.7%
L - Antineoplastic	1.6%	3.1%	2.1%	1.5%	2.9%	2.9%	1.6%	1.9%	1.1%	0.7%	8.2%	1.8%
B - Haematological	1.3%	1.2%	-1.9%	2.0%	1.6%	0.8%	1.0%	1.4%	0.4%	0.6%	2.2%	1.2%
N - SNC	1.3%	2.1%	1.3%	0.1%	1.2%	2.7%	3.0%	3.2%	1.7%	0.1%	1.4%	1.3%
C - Cardiovascular	1.1%	0.5%	-0.1%	-0.3%	1.5%	0.4%	1.6%	1.1%	1.9%	0.7%	1.0%	0.8%
S - Sense Organs	1.0%	0.1%	-0.6%	0.4%	-0.4%	1.4%	0.4%	2.2%	1.8%	-1.9%	0.4%	0.2%
A - Gastrointestinal	0.0%	-0.7%	-0.6%	-0.8%	0.2%	2.5%	2.1%	1.0%	0.4%	0.6%	0.8%	0.5%
D - Dermatological	-0.1%	-2.2%	-1.8%	-2.2%	-2.3%	-4.2%	-1.3%	-0.7%	-0.4%	-2.5%	-0.9%	-2.1%
J - Antimicrobial	-2.6%	-1.5%	-0.1%	-1.6%	-0.4%	1.2%	-1.1%	-2.4%	-1.8%	0.2%	0.6%	-0.9%
V - Various	-3.3%	-6.5%	2.2%	-0.2%	-9.7%	-2.0%	4.1%	-1.7%	2.2%	-3.2%	-5.5%	-6.3%

Large differences are found in the ranks of the 20 active substances with the highest expenditure in the local area (Table 1.9.13), where the highest similarity rate, calculated as the percentage of countries which include a given substance in their ranking, is found for paracetamol (56%), ibuprofen (44%) and atorvastatin (44%). For 7 active substances the similarity rate is 0%, indicating that in no country other than Italy are these medicines included in the top 20 active substances by expenditure. Among these is the combination amoxicillin-clavulanic acid, confirming that Italy has a higher consumption and expenditure than other countries. For the remaining 10 active ingredients, the similarity rate does not exceed 22%. The similarity rate per country does not exceed 30%. Less variability is found if we analyse the first 30 active ingredients by local consumption (Table 1.9.14); indeed, for 5 active ingredients a similarity rate of 100% is found, indicating that the active ingredient is present in the ranking of the first 20 in all the countries analysed.

Table 1.9.13 International comparison of the first 20 active ingredients in Italy: ranking by local expenditure 2022

Active ingredient	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe	Similarity rate
paracetamol	1	136	4	187	2	24	12	9	13	28	4	56%
ibuprofen	2	32	14	27	77	3	8	18	43	104	6	44%
cholecalciferol	3	121	33	82	86	14	56	58	128	47	24	11%
pantoprazole	4	53	8	58	87	25	33	31	466	411	23	11%
diclofenac	5	34	18	46	68	6	26	68	86	82	15	22%
atorvastatin	6	58	22	111	38	13	11	1	85	2	5	44%
amoxicillin/clavulanic acid	7	93	71	114	73	37	28	76	502	346	43	0%
ketoprofen	8	925	460	1,824	211	35	381	586	461	559	146	0%
bisoprolol	9	78	83	196	49	7	36	86	171	86	41	11%
esomeprazole	10	149	120	303	33	125	20	21	132	97	54	11%
beclomethasone/formoterol	11	60	23	33	64	40		25	91	3	16	11%
omeprazole	12	328	24	201	109	33	38	15	73	18	40	22%
lansoprazole	13	304	447	1,295	190	712	152	87	498	48	153	0%
alprazolam	14	501	45	1,121	275	170	48	141	558	978	201	0%
flurbiprofen	15	170	268	345	451	98	61	403	441	858	196	0%
omega 3	16	853	823	977	862	921	705	265		395	355	0%
enoxaparin	17	51	31	70	35	5	46	10	366	114	26	22%
mesalazine	18	115	107	101	145	65	45	44	33	16	45	11%
tadalafil	19	167	70	191	57	195	37	84	119	230	81	0%
fluticasone furoate/vilanterol	20	317	17	153	80	1,780	44	46	282	52	76	11%
Similarity rate		0%	25%	0%	5%	30%	20%	25%	5%	20%	25%	

Table 1.9.14 International comparison of the first 20 active ingredients in Italy: ranking by local consumption 2022

Active ingredient	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe	Similarity rate
metformin	1	12	3	12	3	1	4	8	2	3	4	100%
acetylsalicylic acid	2	5	5	4	4	4	5	7	14	19	5	100%
levothyroxine	3	4	6	3	5	6	10	5	12	8	6	100%
bisoprolol	4	10	8	6	10	7	7	14	25	14	8	89%
pantoprazole	5	6	4	8	17	15	8	36	117	142	13	67%
diclofenac	6	3	9	9	6	5	9	16	29	48	9	78%
atorvastatin	7	14	10	15	7	13	3	9	6	5	10	100%
paracetamol	8	11	1	20	1	16	1	1	1	2	2	100%
ibuprofen	9	9	7	2	9	11	2	4	9	22	7	89%
ketoprofen	10	417	198	899	63	29	589	177	180	281	48	0%
furosemide	11	35	110	114	15	63	14	23	30	35	28	22%
ramipril	12	37	112	5	21	14	39	52	53	10	16	33%
salbutamol	13	13	12	7	2	27	11	3	11	1	3	89%
flurbiprofen	14	62	182	104	225	148	136	452	250	765	58	0%
amlodipine	15	17	27	14	30	24	34	25	10	9	14	44%
omeprazole	16	193	17	30	20	35	13	2	7	7	12	67%
esomeprazole	17	58	36	91	12	37	15	42	45	94	30	22%
lansoprazole	18	175	273	542	68	512	86	95	255	11	46	11%
naphazoline	19	80	450	1,159		534		1,163			11	0%
alprazolam	20	93	21	446	14	133	6	21	194	646	41	22%
Similarity rate		55%	55%	60%	70%	50%	70%	50%	45%	55%	70%	

With regard to expenditure in the hospital setting (Table 1.9.15), it can be seen that the first three molecules in Italy (pembrolizumab, daratumumab and nivolumab) are present in the rankings of the top 20 in all the countries analysed. Apixaban and rivaroxaban, ranked eighth and ninth by hospital expenditure in Italy, are not in the top 20 in any other country. These differences may also be attributed to the different methods of medicine distribution, together with the different epidemiology of the disease in the various countries. As a matter of fact, since oral anticoagulant medicines in Italy are distributed directly and “on behalf”, they fall within the hospital channel, whereas in other countries these medicines are considered in the local channel. The same consideration can be made for the antidiabetic medicine dulaglutide, which ranks 14th in Italy and is not among the top 20 in any other country.

Table 1.9.15 International comparison of the first 20 active substances in Italy: ranking by hospital expenditure 2022

Active ingredient	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe	Similarity rate
pembrolizumab	1	1	1	1	1	2	1	1	3	5	1	100%
daratumumab	2	2	4	5	2	18	5	5	2	13	3	100%
nivolumab	3	3	2	6	4	3	8	8	6	19	2	100%
lenalidomide	4	290	6	352	14	26	41	10	282	8	8	44%
adalimumab	5	169	318	130	396	71	22	2	362	1	5	22%
epoetin alfa	6	224	53	153	106	125	224	76	965	125	45	0%
ibrutinib	7	268	5	347	393	15	6	6	357	17	13	56%
apixaban	8	147	210	99	92	242	549	371	122	138	54	0%
rivaroxaban	9	173	242	144	187	150	708	428	308	223	62	0%
sofosbuvir/ velpatasvir	10	577	55	433	235	14	85	11	98	20	25	33%
immunoglobulin base	11	7	7	2	3	25	2	9	4	7	4	89%
enzalutamide	12	211	17	291	315	4	15	25	317	9	19	44%
dulaglutide	13	485	649	436	467	715		892	696	684	112	0%
bictegravir/ emtricitabine/ tenofovir alafenamide	14	603	232	498	135		12	4	265	35	22	22%
ivacaftor	15	999	9	622	165	20	53	50	620	3	17	33%
pertuzumab	16	18	20	20	25	6	14	15	79	195	20	67%
osimertinib	17	171	32	459	161	28	10	17	213	34	30	22%
dimethyl fumarate	18	764	1,039	734	984	5	35	37	998	18	34	22%
edoxaban	19	225	262	280			793	486	490	309	132	0%
trastuzumab	20	8	14	34	13	21	16	18	13	44	15	67%
Similarity rate		30%	50%	25%	30%	45%	50%	60%	25%	55%	55%	

Wide variability is found in the ranks of the active ingredients with the highest hospital consumption (Table 1.9.16): as many as 11 have a similarity rate of 0%, i.e. rivaroxaban, dabigatran, clopidogrel, edoxaban, ranolazine, metformin/sitagliptin, ticagrelor, dapagliflozin/metformin, olanzapine, methadone and sacubitril/valsartan. These differences may be attributable to the different ways of supplying these medicines, which are mainly supplied in direct distribution and on behalf in Italy, whereas in other countries they are supplied in a local context. As a matter of fact, analysing the first 20 active ingredients by overall expenditure and consumption, at local and hospital level (Table 1.9.17 and Table 1.9.18 respectively), the similarity rates are higher: the first 5 active ingredients by expenditure and by consumption in Italy present a similarity rate always higher than 65%, with the only exception of lenalidomide.

Table 1.9.16 International comparison of the first 20 active substances in Italy: ranking by hospital consumption 2022

Active ingredient	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe	Similarity rate
apixaban	1	45	69	48	15	98	231	113	28	33	7	11%
quetiapine	2	12	23	49	118	8	51	16	63	113	21	33%
rivaroxaban	3	144	149	152	135	77	416	236	193	105	31	0%
dabigatran etexilate	4	208	179	365	269	145	621	288	267	461	41	0%
clopidogrel	5	114	92	123	138	122	240	136	117	76	36	0%
edoxaban	6	164	180	246			487	329	334	182	68	0%
ranolazine	7	361		299		1,443	967	560		256	78	0%
lidocaine	8	7	1	18	5	9	12	72	2	84	6	78%
metformin/ sitagliptin	9	209	785	298	337	1,068		475	616	1,346	122	0%
enoxaparin	10	10	21	64	13	12	27	22	168	38	28	33%
pantoprazole	11	6	7	9	8	2	22	45	130	308	11	56%
ticagrelor	12	276	250	264	316	202	326	354	206	187	108	0%
dapagliflozin/ metformin	13	385	1,092	736	1,049	809	1,029	840	1,100	1,682	149	0%
furosemide	14	17	76	52	11	5	20	13	11	41	20	67%
olanzapine	15	139	58	119	126	52	111	62	55	152	69	0%
carbidopa/ levodopa	16	266	4	145	28	37	52	7	177	46	37	22%
methadone	17	978	555	567	116	59	163	52	59	139	88	0%
sacubitril/ valsartan	18	163	316	149	248	306	356	306	225	209	132	0%
sevoflurane	19	4	2	17	3	11	17	4	8	10	4	100%
salbutamol	20	13	11	19	4	56	2	5	5	3	3	89%
Similarity rate		35%	25%	20%	35%	30%	20%	25%	20%	10%	30%	

Table 1.9.17 International comparison of the first 20 active substances in Italy: ranking by total expenditure 2022

Active ingredient	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe	Similarity rate
pembrolizumab	1	1	1	3	1	3	2	1	4	6	1	100%
daratumumab	2	2	4	14	2	49	11	5	2	17	6	89%
nivolumab	3	3	2	25	5	4	17	8	10	25	7	78%
lenalidomide	4	29	8	22	32	89	85	10	109	11	14	33%
adalimumab	5	6	13	4	8	253	43	2	9	1	3	78%
epoetin alfa	6	196	112	121	92	488	569	139	1,086	210	81	0%
apixaban	7	8	12	1	4	5	1	14	1	5	2	100%
ibrutinib	8	13	6	12	15	41	13	6	22	22	10	67%
rivaroxaban	9	11	18	5	14	1	4	38	20	14	5	89%
sofosbuvir/ velpatasvir	10	70	122	236	141	39	184	12	32	24	51	11%
immunoglobulin	11	9	7	2	3	85	3	9	5	9	4	89%
Paracetamol	12	105	14	196	6	38	20	29	18	55	16	44%
Dulaglutide	13	111	62	40	30	50	22	47	81	53	32	0%
enoxaparin	14	19	40	33	17	6	48	24	362	50	17	33%
Pantoprazole	15	52	26	41	68	37	63	75	573	586	46	0%
Enzalutamide	16	16	25	9	16	10	30	33	13	10	11	67%
bictegravir/ emtricitabine/ tenofovir alafenamide	17	58	35	84	39		26	4	162	56	27	11%
Ibuprofen	18	48	45	35	121	7	16	60	60	251	23	22%
Ivacaftor	19	17	9	37	24	54	100	77	455	3	15	33%
Pertuzumab	20	60	29	89	63	15	27	18	293	340	45	22%
Similarity rate		55%	55%	40%	55%	40%	45%	55%	45%	45%	65%	

Table 1.9.18 International comparison of the first 20 active substances in Italy: ranking by total consumption 2022

Active ingredient	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe	Similarity rate
metformin	1	12	4	12	1	4	8	2	3	4	3	100%
acetylsalicylic acid	2	6	5	4	4	6	7	14	19	5	4	100%
levothyroxine	3	4	6	3	6	11	5	12	8	6	5	100%
bisoprolol	4	9	8	6	7	9	15	25	14	8	8	89%
pantoprazole	5	5	3	7	15	8	36	117	152	13	16	67%
diclofenac	6	3	9	9	5	10	17	29	50	9	6	78%
paracetamol	7	11	1	20	16	1	1	1	2	2	1	100%
atorvastatin	8	14	11	15	13	3	10	7	5	10	7	100%
ibuprofen	9	10	7	2	11	2	4	9	22	7	9	89%
furosemide	10	32	106	107	54	14	22	30	35	27	15	22%
ketoprofen	11	411	167	953	28	627	181	180	296	49	62	0%
salbutamol	12	13	12	8	27	5	3	11	1	3	2	89%
ramipril	13	38	117	5	14	39	55	53	10	15	21	33%
flurbiprofen	14	65	189	108	150	141	469	258	912	62	233	0%
amlodipine	15	17	25	14	24	34	26	10	9	14	29	44%
omeprazole	16	201	19	31	35	13	2	6	7	12	24	56%
esomeprazole	17	57	38	92	37	15	42	44	100	33	12	22%
lansoprazole	18	180	289	577	519	87	96	261	11	46	64	11%
alprazolam	19	94	21	470	132	7	23	196	763	41	14	22%
naphazoline	20	78	466	1,221	539		1,530			11		0%
Similarity rate		55%	55%	60%	65%	50%	70%	50%	45%	55%	70%	

Patent-expired medicines and biosimilars

In Italy there is still a low incidence of expenditure for generic medicines compared to the other European countries, standing - with a percentage of 43.4% - third last in the ranking of the 10 countries. The average percentage of local expenditure for generic medicines in the countries analysed is 47.6% (European average: 48.3%) and ranges between 34.7% in Belgium and 68.6% in Poland (Figure 1.9.8); also, the percentage of consumption ranges between 50.6% in Belgium and 81.8% in Great Britain (Figure 1.9.9) with Italy in third last place with an incidence of generics of 54.9%, in a similar way as for expenditure.
The penetration of biosimilar medicines in terms of expenditure and consumption was also investigated (Figures 1.9.10 and 1.9.11). Italy ranks first in the incidence of, respectively, expenditure (76.4%) and consumption (66.1%) of biosimilar medicines compared to a European average of 60.2% for expenditure and 33.2% for consumption. Figure 1.9.19 illustrates the penetration of biosimilars in terms of consumption by single molecule. At European level, the highest percentage of biosimilar medicine consumption is recorded for filgrastim, epoetin, rituximab, infliximab, bevacizumab and pegfilgrastim. The incidence of bevacizumab biosimilar consumption increased in all countries, reaching a European coverage of 81% (in 2021 it was 58%). Low biosimilar penetration rates are observed in all countries for insulins and low molecular weight heparin. In Italy, the low biosimilar incidence of insulins could be attributable to the fact that they are supplied under approved care regime, where there is no effect of tenders. Teriparatide, which had a low incidence (34%) of biosimilar consumption in Europe in 2021, increased to 52%.

Figure 1.9.8 International comparison of the percentage distribution of 2022 local pharmaceutical expenditure on patent-expired medicines

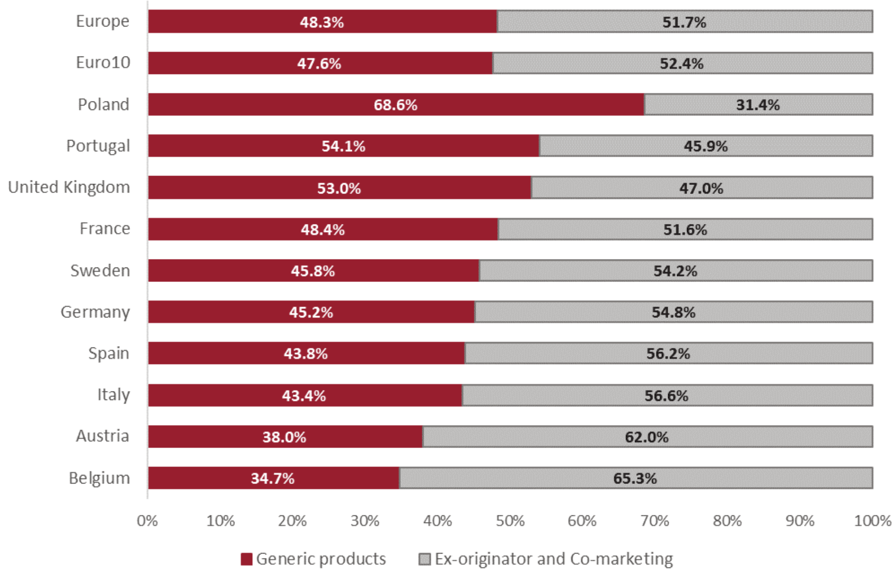


Figure 1.9.9 International comparison of the percentage distribution of 2022 local consumption on patent-expired medicines

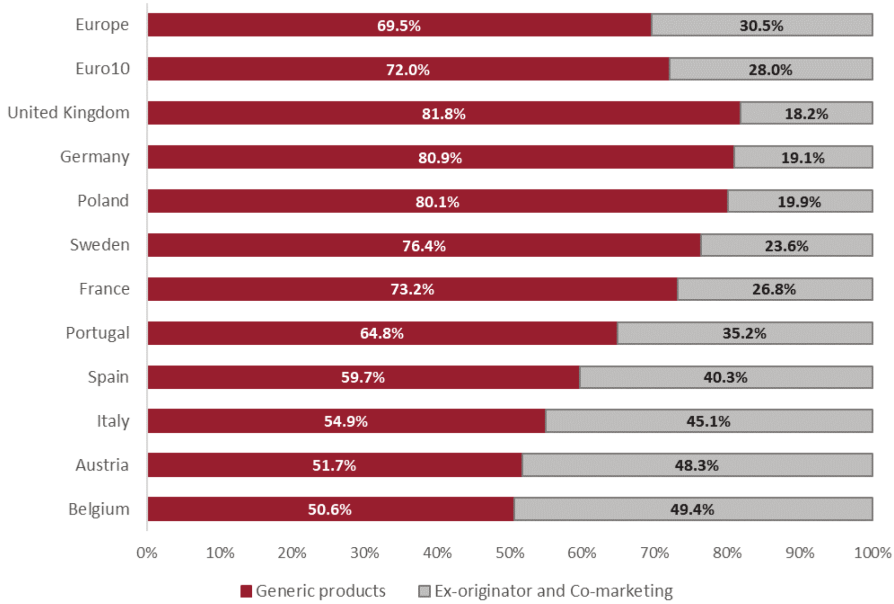


Figure 1.9.10 International comparison of the percentage distribution of 2022 expenditure on biosimilars

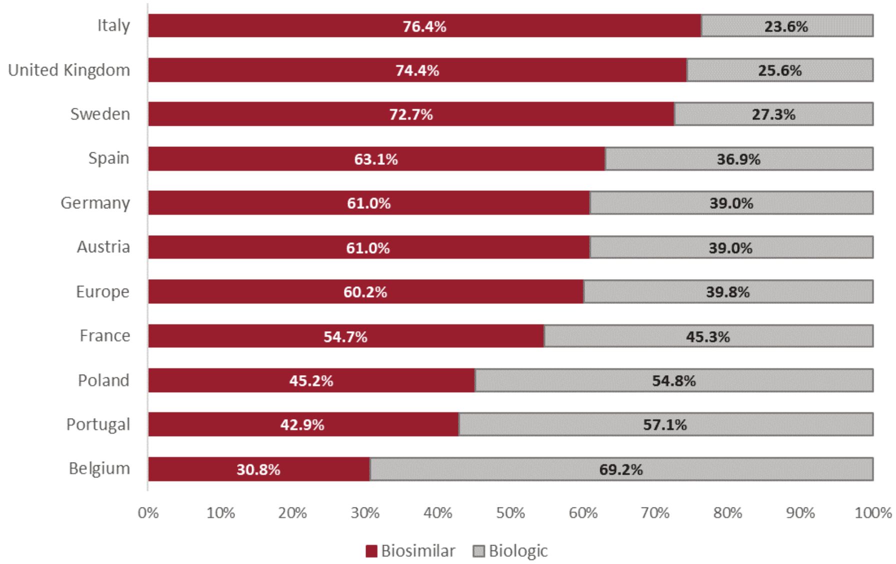


Figure 1.9.11 International comparison of the percentage distribution of 2022 consumption of biosimilar medicinal products

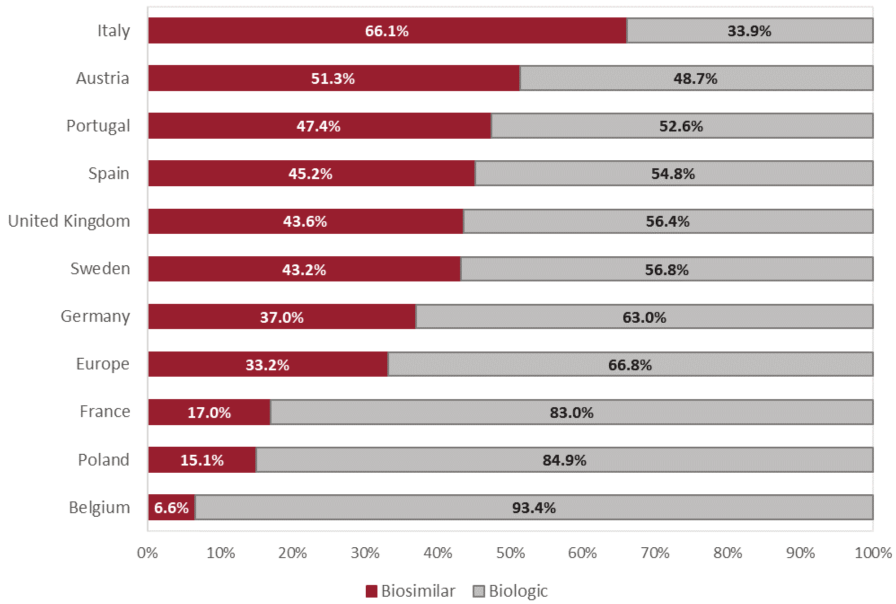


Table 1.9.19 Percentage distribution of biosimilar consumption (Standard Unit) by country and molecules

Molecules	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe
adalimumab	81%	19%	31%	45%	76%	99%	65%	66%	88%	86%	63%
bevacizumab	91%	97%	34%	97%	85%	96%	76%	81%	79%	22%	81%
low molecular weight heparins	77%	60%	4%	7%	46%	0%	59%	51%	0%	70%	39%
epoetin	94%	67%	4%	63%	94%	100%	93%	92%	98%	13%	87%
etanercept	76%	26%	27%	48%	79%	79%	52%	52%	85%	85%	60%
filgrastim	98%	100%	29%	97%	84%	99%	95%	96%	97%	100%	94%
follitropin	55%	40%	76%	68%	63%	76%	70%	75%	55%	49%	45%
infliximab	95%	94%	55%	83%	80%	100%	89%	82%	94%	97%	81%
insulin aspart	1%			2%	1%	14%			5%	0%	3%
insulin glargine	30%	34%	7%	42%	26%	44%	21%	33%	55%	20%	24%
insulin lispro	12%	0%			10%	56%			52%	1%	10%
pegfilgrastim	86%	49%	24%	80%	54%	100%	99%	90%	99%	95%	73%
rituximab	91%	92%	27%	87%	86%	99%	77%	89%	91%	95%	87%
somatropin	21%	35%	41%	38%	34%	99%	61%	11%	30%	29%	26%
teriparatide	70%	74%		48%	43%		7%	52%	67%	91%	52%
trastuzumab	86%	82%	13%	48%	63%	46%	56%	77%	89%	41%	55%

Table 1.9.20 shows, by means of the Herfindhal-Hirschman index (HHI), the concentration and market shares of competitors of individual patent-expired biological products by country. This index is commonly used to quantify the level of market competition and is defined as the sum of the squares of the market shares. The index takes values ranging between 0 and 1, where the maximum value corresponds to a situation of complete monopoly, while very low values are obtained in markets in which there is a large number of competing actors, each holding a small market share. Insuline lispro, insuline aspart and insuline glargine have a high concentration index in most countries, since in addition to the reference product, a single biosimilar is present with still very small market shares. In Italy, the high market concentration recorded for insulins could be attributable to the fact that they are supplied under approved care regime, where there is no effect on competition from tenders. For teriparatide, a reduction in the concentration index was observed, in parallel with the increased incidence of biosimilar use and given the availability of several biosimilar specialities. Low molecular weight heparins are characterised by a high concentration index in several countries (European average: 0.5), despite the fact that several biosimilars have been authorised for a long time now.

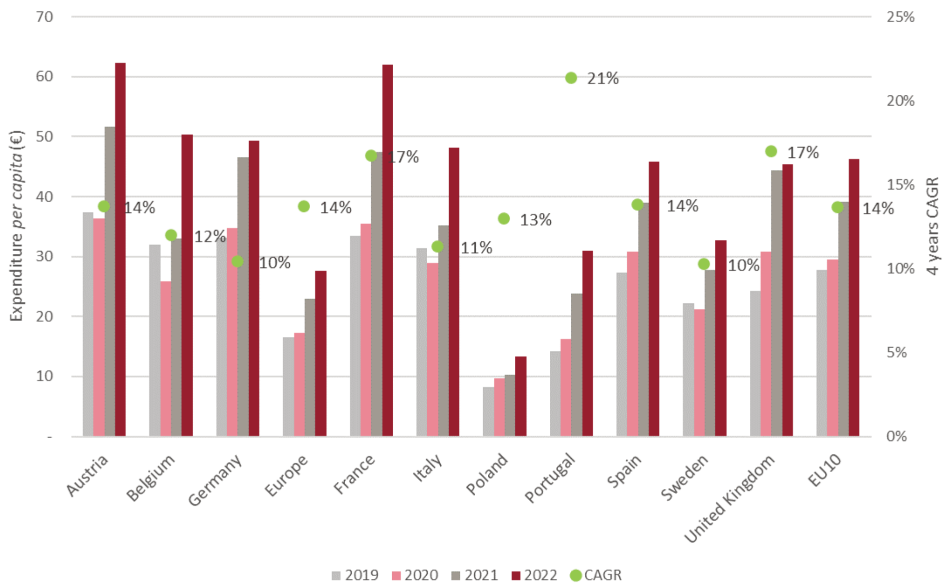
Table 1.9.20 Patent-expired biologic medicines: Herfindahl-Hirschman Index (HHI) by country (year 2022)

Molecules	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe
adalimumab	0.2	0.7	0.5	0.4	0.2	0.5	0.4	0.3	0.2	0.3	0.2
bevacizumab	0.3	0.3	0.5	0.3	0.3	0.8	0.3	0.2	0.4	0.6	0.2
low molecular weight heparins	0.3	0.5	0.9	0.9	0.5	1.0	0.4	0.4	1.0	0.5	0.5
epoetin	0.5	0.4	0.9	0.4	0.2	1.0	0.6	0.8	1.0	0.8	0.3
etanercept	0.4	0.6	0.6	0.4	0.4	0.6	0.5	0.4	0.5	0.6	0.3
filgrastim	0.4	0.5	0.5	0.4	0.4	0.5	0.5	0.4	0.3	0.3	0.2
follitropin	0.5	0.6	0.5	0.4	0.4	0.4	0.5	0.4	0.6	0.5	0.3
infliximab	0.3	0.4	0.3	0.4	0.3	0.5	0.4	0.3	0.3	0.4	0.2
insulin aspart	1.0	1.0	1.0	1.0	1.0	0.8	1.0	1.0	0.9	1.0	0.8
insulin glargine	0.6	0.6	0.9	0.5	0.6	0.5	0.7	0.5	0.4	0.7	0.5
insulin lispro	0.8	1.0	1.0	1.0	0.9	0.5	1.0	1.0	0.5	1.0	0.8
pegfilgrastim	0.3	0.4	0.6	0.2	0.3	0.8	0.5	0.4	0.6	0.6	0.2
rituximab	0.4	0.3	0.6	0.3	0.4	1.0	0.4	0.4	0.5	0.4	0.3
somatropin	0.5	0.5	0.5	0.5	0.5	0.9	0.5	0.5	0.5	0.5	0.5
teriparatide	0.3	0.3	1.0	0.4	0.5	1.0	0.9	0.3	0.5	0.4	0.3
trastuzumab	0.2	0.2	0.8	0.5	0.4	0.7	0.7	0.3	0.2	0.7	0.3

Orphan medicinal products

Italy, with EUR 48.2 *per capita*, ranks 5th for orphan drug expenditure, after Austria (EUR 62.3), France (EUR 62.0), Belgium (EUR 50.3) and Germany (EUR 49.3; Figure 1.9.12). All countries show an increasing expenditure trend in the years 2021 and 2022. In 2022, the expenditure *per capita* at the European level was EUR 27.6 with a variation compared to 2021 of +20%. The countries with the largest variations compared to 2021 were Belgium (+52.4%), France (+30.5%) and Italy (+37.0%). The average annual change (CAGR) over the period 2019-2022 at European level was +14% and the countries with the highest variations were Portugal (+21%), Great Britain (+17%) and France (+17%).

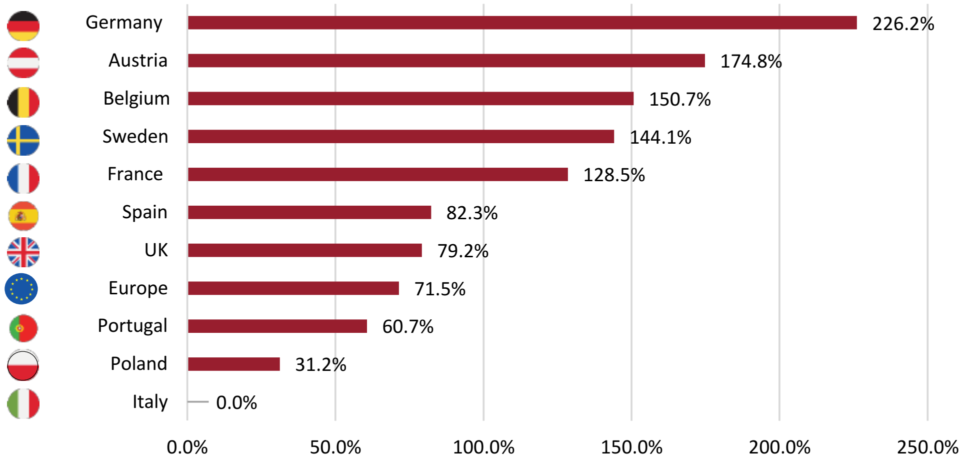
Figure 1.9.12 Trend in *per capita* expenditure for orphan drugs in the period 2019-2022



European price comparison

Figures 1.9.13 and 1.9.14 show the comparison of the weighted average ex-factory price for 2022 consumption, relating separately to medicines dispensed by local pharmacies and medicines dispensed by hospitals. Figure 1.9.15 shows a comparison of prices in the overall market, including both local and hospital medicines. The analysis considered medicinal products that are identical or have a similar packaging to those marketed in Italy. The percentage of expenditure on products in common with the comparator country (Italy) was therefore calculated on the total expenditure recorded in the country concerned and on the total amount of expenditure recorded in Italy. The average price in this basket was calculated as the ratio between the expenditure and the dose units supplied in each country. This approach makes it possible to overcome the problem of the different ways of delivering medicines in the various countries. The Italian local/community distribution channel does not include medicines supplied via direct and “on-behalf” distribution. Conversely, they are included in the hospital channel. For example, unlike other countries, the Italian local/community channel does not include new oral anticoagulants and more recently marketed antidiabetics (e.g. glyphozines), which are included in the hospital channel. The comparison should be made only between Italy (reference country) and the other countries considered, as the analysed basket changes each time based on the country selected. A further element to consider when interpreting the results is the lack of an impact evaluation of conditional reimbursement agreements, including confidential discounts, which may be applied differently in different countries, as well as the effect of tenders. An attempt was made to partially overcome this limitation by applying actual purchase prices for Italy and Germany, i.e. the countries for which they were available. Taking the local/community-delivered medicines into account, Figure 1.9.13 shows that all countries have average prices higher than those in Italy, with a variable range between the minimum difference of +31.2% with Poland, to the maximum of +226.2% with Germany. On average in Europe prices are 71.5% higher than in Italy. The situation is different when looking at medicines dispensed through the hospital pharmacies, as Belgium, France, Portugal and Germany have lower prices than Italy, with differences ranging from -56.8% in Germany to -31.0% in Belgium. Italy has lower prices than Sweden (+681.8%), UK (+444.4%), Austria (+354.4%), Poland (+ +281.7%) and Spain (+13.5%) (Figure 1.9.14). Looking at the European average, as for the shared basket, hospital prices are 87.6% higher than in Italy. Applying purchase prices for Italy and Germany, the difference in prices between the two countries remains almost the same (Germany -51% compared to Italy), indicating that the effect of tenders or conditional reimbursability agreements in the basket considered is similar in the two countries. Considering the overall market, covering both medicines delivered at a local level and in hospital settings, Italy reports lower prices than Belgium (+91.5%), Germany (+86.5%), Austria (+33.8%), Sweden (+25.9%), Great Britain (+14.4%) and Spain (+11.3%), while the following counties have lower prices than Italy: France (-16.5%), Portugal (-37.2%) and Poland (-38.9%) (Figure 1.9.15). Considering the European average, both local/community and hospital prices are 61.4% higher than in Italy. Applying purchase prices, Germany shows prices that are 131.9% higher than Italy, a greater difference than when using basic auction prices. This could be due to the effect of tenders for the purchase of medicines which are dispensed in Italy in direct distribution and “on behalf” while in Germany they are purchased and dispensed by local/territorial pharmacies. When interpreting the results, it is important to consider the corresponding medicines between Italy and other countries, in particular their coverage on the country's pharmaceutical expenditure. In the total market, the largest expenditure coverage is observed in Spain (70%) and the lowest in Germany (25%).

Figure 1.9.13 International comparison of pharmaceutical prices (ex-factory prices) in 2022: local/community care



	Germany	Austria	Belgium	Sweden	France	Spain	UK	Europe	Portugal	Poland	Italy
Coverage (%) of the country's expenditure	6	29	19	15	27	43	35	25	39	21	100
Coverage (%) of Italy's expenditure	25	23	22	13	22	29	18	100	23	19	100

(with tender prices)

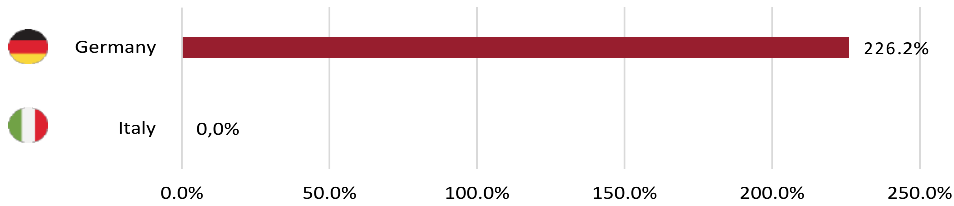
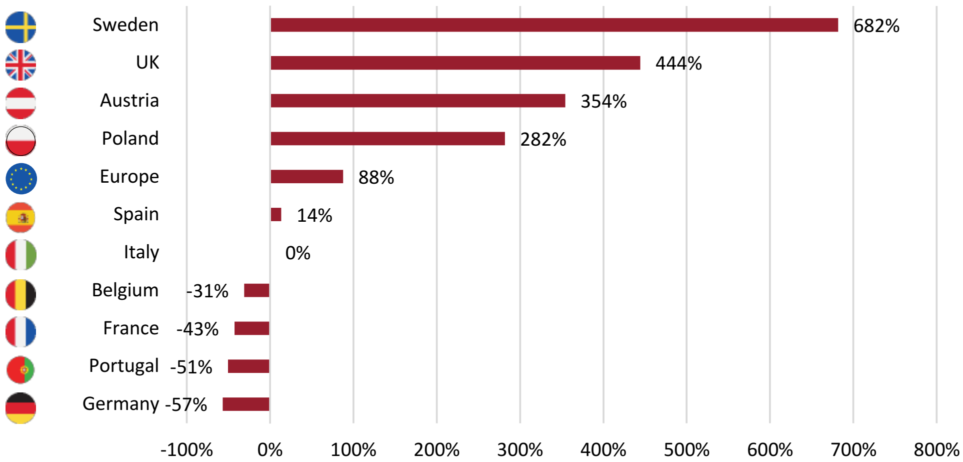


Figure 1.9.14 International comparison of pharmaceutical prices (ex-factory prices) in 2022: hospital care*



	Sweden	UK	Austria	Poland	Europe	Spain	Italy	Belgium	France	Portugal	Germany
Coverage (%) of the country's expenditure	64	36	67	51	69	88	100	86	76	82	62
Coverage (%) of Italy's expenditure	40	45	44	32	100	70	100	66	69	62	74

(with tender prices)

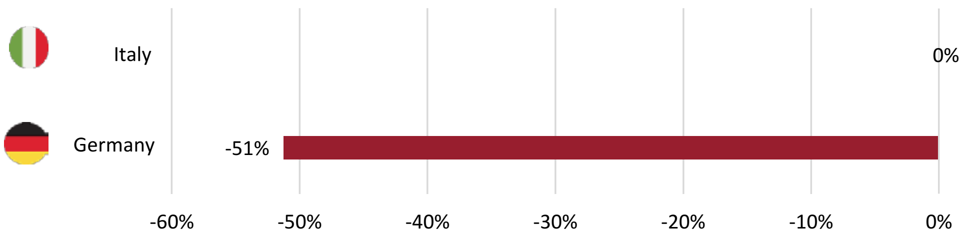
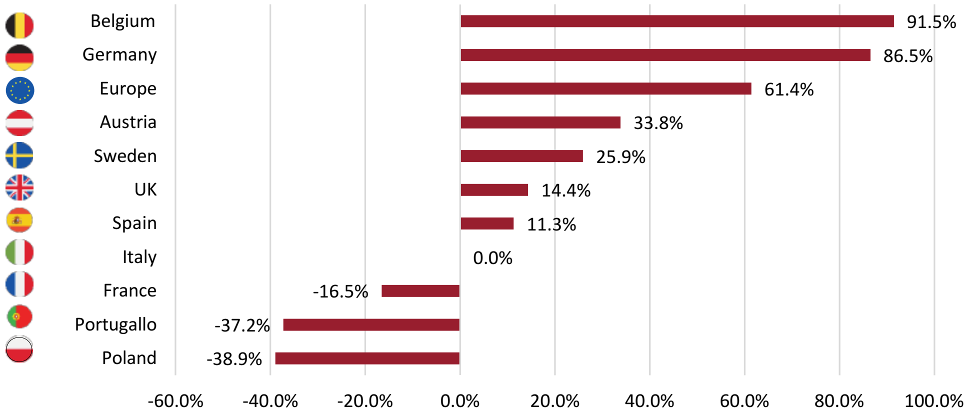
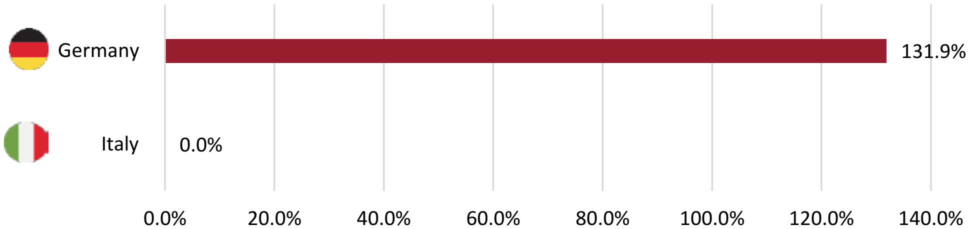


Figure 1.9.15 International comparison of pharmaceutical prices (ex-factory prices) in 2022: local/community and hospital care



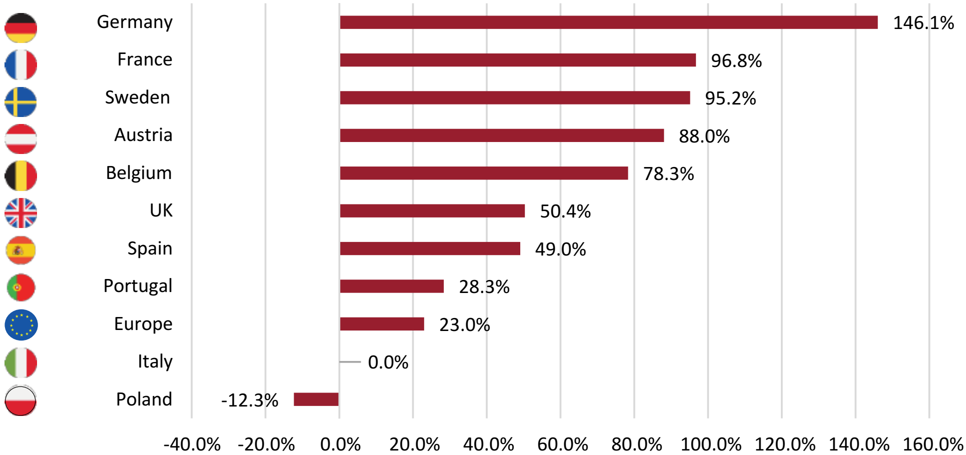
	Belgium	Germany	Europe	Austria	Sweden	UK	Spain	Italy	France	Portugal	Poland
Coverage (%) of the country's expenditure	60	25	46	47	34	38	70	100	51	58	31
Coverage (%) of Italy's expenditure	58	66	100	40	33	38	64	100	61	56	29

(with tender prices)



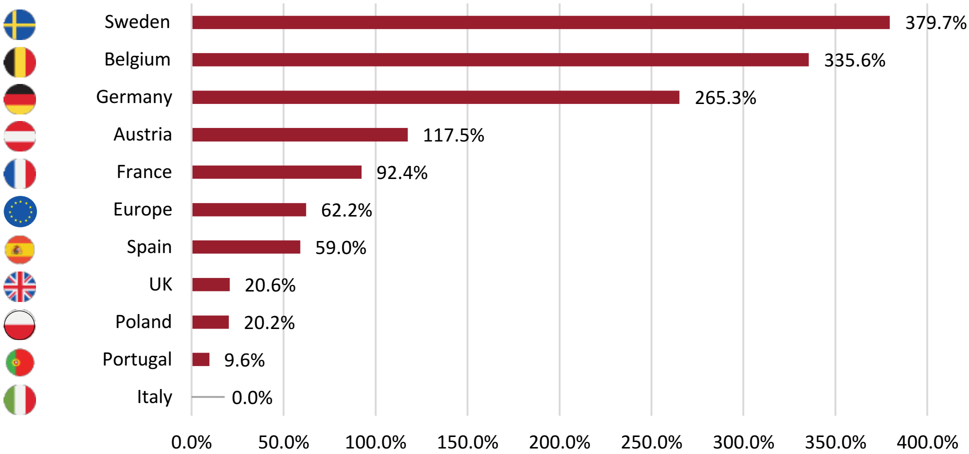
A price comparison was also conducted, distinguishing between medicines with competition (off-patent) and those without competition (on-patent). In the territorial area, Italy presents lower prices than all the countries considered in the market without competition (Figure 1.9.17), while in the market with competition only Poland presents lower prices than Italy (-12.3%) (Figure 1.9.16). In the hospital market, in the market with competition, Italy has higher prices than Poland (-7.2%), Belgium (-21.4%), France (-42.7%), Germany (-51.3%) and Portugal (-59.2%) (Figure 1.9.18). As already emphasised, this analysis does not take into account the effect of tenders, which occur precisely in the market with competition in the hospital sector. Instead, in the market without competition, only Germany and Portugal show lower prices than Italy, respectively 5.4% and 18.0% (Figure 1.9.19).

Figure 1.9.16 International comparison of pharmaceutical prices (ex-factory prices) in 2022 WITH COMPETITION: local/community care



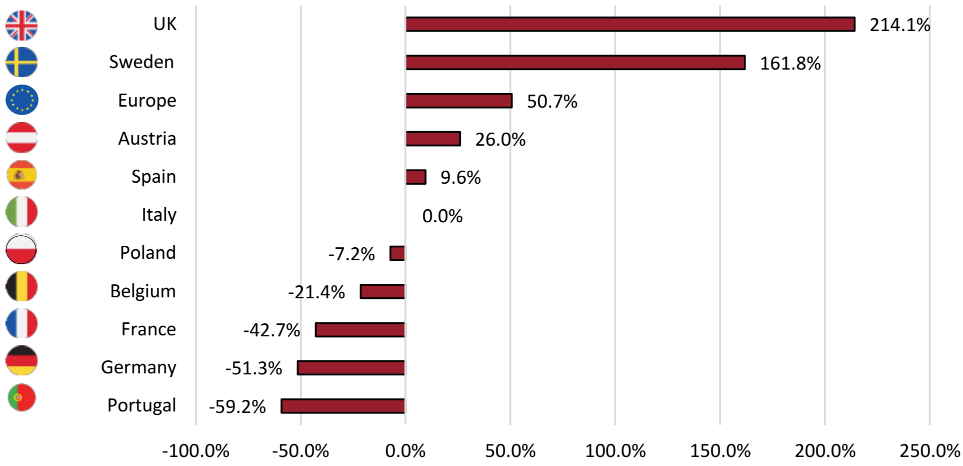
	Germany	France	Sweden	Austria	Belgium	UK	Spain	Portugal	Europe	Italy	Poland
Coverage (%) of the country's expenditure	6	28	14	24	17	17	31	24	20	100	12
Coverage (%) of Italy's expenditure	21	18	8	19	19	13	25	18	95	100	16

Figure 1.9.17 International comparison of pharmaceutical prices (ex-factory prices) in 2022 WITHOUT COMPETITION: local/community care



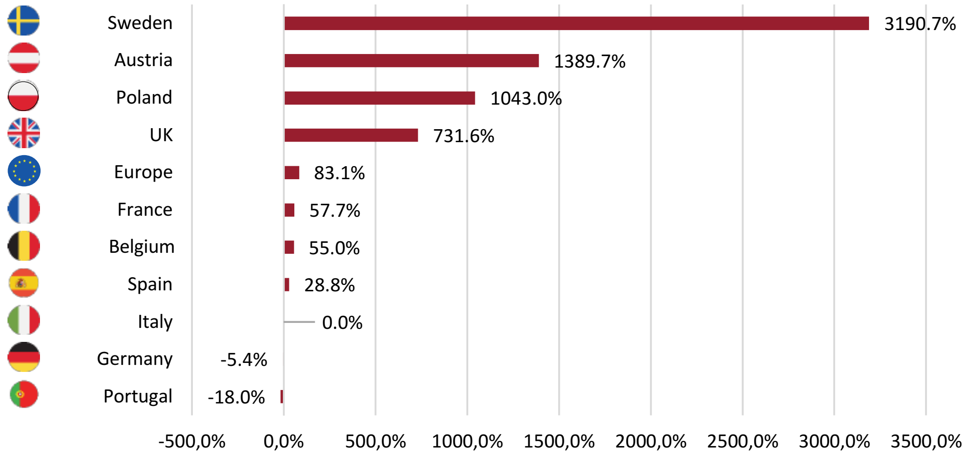
	Sweden	Belgium	Germany	Austria	France	Europe	Spain	UK	Poland	Portugal	Italy
Coverage (%) of the country's expenditure	16	21	5	32	25	11	71	78	62	71	99
Coverage (%) of Italy's expenditure	51	44	52	54	44	49	60	55	29	49	99

Figure 1.9.18 International comparison of pharmaceutical prices (ex-factory prices) in 2022 WITH COMPETITION: hospital care



	UK	Sweden	Europe	Austria	Spain	Italy	Poland	Belgium	France	Germany	Portugal
Coverage (%) of the country's expenditure	25	32	47	40	74	100	37	69	53	40	65
Coverage (%) of Italy's expenditure	36	32	93	32	59	100	25	43	52	62	48

Figure 1.9.19 International comparison of pharmaceutical prices (ex-factory prices) in 2022 WITHOUT COMPETITION: hospital care

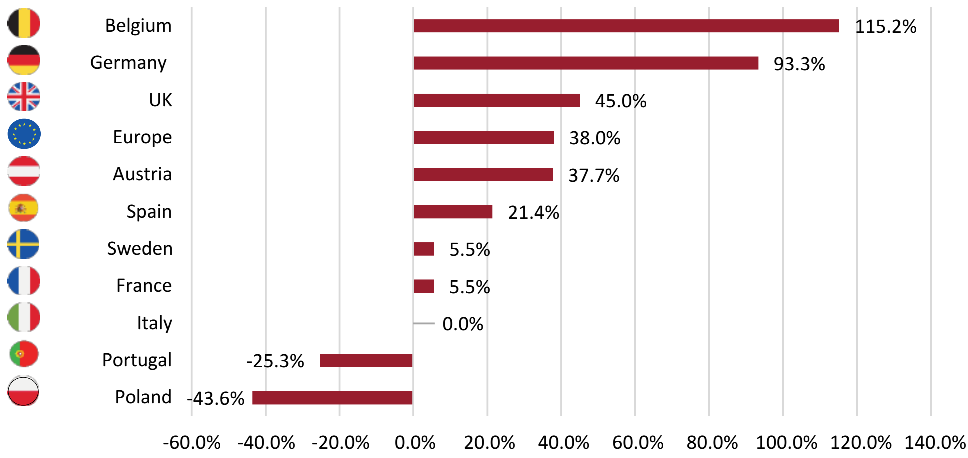


	Sweden	Austria	Poland	UK	Europe	France	Belgium	Spain	Italy	Germany	Portugal
Coverage (%) of the country's expenditure	91	91	55	43	44	93	94	93	100	89	87
Coverage (%) of Italy's expenditure	43	48	34	48	65	77	77	72	100	76	66

Figures 1.9.20 and 1.9.21 show price comparisons in the market with competition and in the market without competition, respectively, considering local and hospital care together. In the market with competition only Portugal (-25.3%) and Poland (-43.6%) have lower prices than Italy; in the market without competition, all the countries, with the exception of Belgium (+186.6%), Sweden (+170.8%) and Germany (+118.2%), have lower prices than Italy. Comparing prices at a local level and considering only medicines reimbursable in Italy, all the countries have prices higher than Italy with the widest difference for Germany (+797%) and the smallest for Poland (+10%) (Table 1.9.22).
An analysis was conducted of the trends in the period 2015-2022 of prices in Italy compared to the other countries, separately in the patented medicines market and in the patent-expired medicines market (Figure 1.9.23). Information was collected relating to the 9 countries (EU 9) included in the analysis per single package on patent protection, expenditure and consumption. Only products showing the same patent coverage in the various countries that were marketed in Italy were included in the analysis. In order to compare the price in Italy with the average price of the countries considered, an annual comparison index was calculated between the average prices in Italy and the EU9 average prices for patented medicines and off-patent medicines. It can be noted that in Italy the

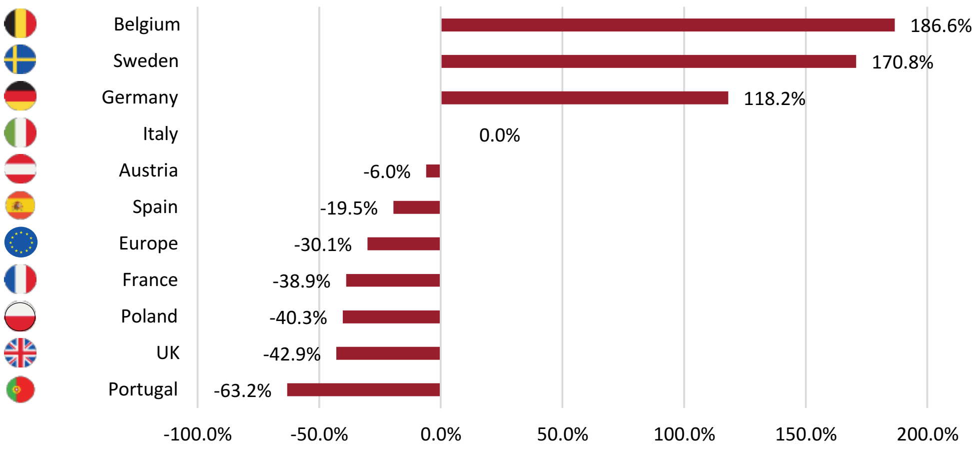
price of patent-expired medicines is 35.0% lower than the EU9 average in 2015 and 36.6% than 2022, noting that in the period considered, the price of patent-expired medicines has further decreased compared to the EU9 average. By contrast, if we consider the market of patented medicines, up to 2017, prices in Italy were below the EU9 average, while since 2018 prices in Italy have been slightly above the EU9 average. Over the last three years, the difference is gradually narrowing, from +12.7% in 2019 to +6.7% in 2022.

Figure 1.9.20 International comparison of pharmaceutical prices (ex-factory prices) in 2022 WITH COMPETITION: local/community care and hospital care



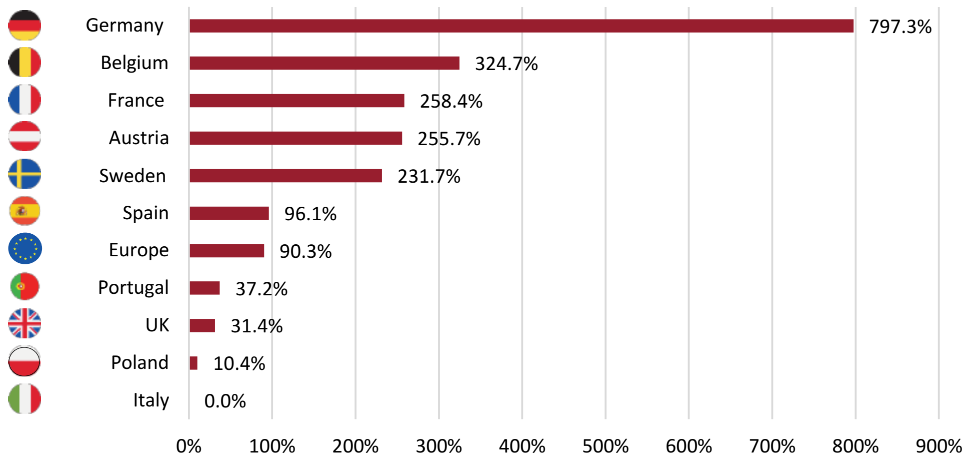
	Belgium	Germany	UK	Europe	Austria	Spain	Sweden	France	Italy	Portugal	Poland
Coverage (%) of the country's expenditure	75	34	51	29	60	89	46	64	100	82	59
Coverage (%) of Italy's expenditure	84	85	49	62	50	82	45	83	100	73	35

Figure 1.9.21 International comparison of pharmaceutical prices (ex-factory prices) in 2022 WITHOUT COMPETITION: local/community and hospital care



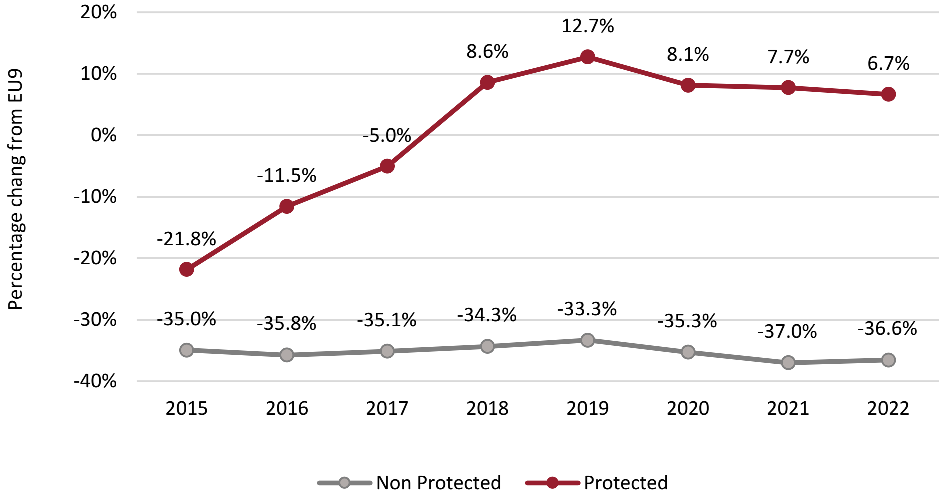
	Belgium	Sweden	Germany	Italy	Austria	Spain	Europe	France	Poland	UK	Portugal
Coverage (%) of the country's expenditure	41	21	16	100	31	48	29	37	16	23	36
Coverage (%) of Italy's expenditure	32	20	43	100	27	44	94	37	20	25	35

Figure 1.9.22 International comparison of pharmaceutical prices (ex-factory prices) reimbursable in Italy in 2022: local/community care



	Germany	Belgium	France	Austria	Sweden	Spain	Europe	Portugal	UK	Poland	Italy
Coverage (%) of the country's expenditure	3	8	11	12	6	16	10	12	11	6	41
Coverage (%) of Italy's expenditure	11	10	9	11	6	14	41	11	9	10	41

Figure 1.9.23 International comparison of prices of patent-expired medicines and patent-covered medicines between 2015 and 2022 (ex-factory prices): local/community care and hospital care



The same analysis was conducted including only those medicines that are classified in band H in Italy and it was observed that the price in Italy of patent-expired medicines is 30.8% lower than the EU9 average in 2015 and 19.0% lower in 2022, highlighting how the prices of patent-expired medicines have moved closer to the EU9 average over the period considered. By contrast, the price of patent-covered medicines in Italy was 40.0% lower than the EU9 average in 2015 and 42.3% lower in 2022, widening the gap with the EU9 average (Figure 1.9.24). For C-range medicines in hospital setting, Italy's prices are also below the EU9 average (Figure 1.9.25). For patent-expired medicines in the period 2015-2020, the difference in Italian prices compared to the EU9 average widened from -20.7% in 2015 to -28.6% in 2020. In the period 2021-2022, the price difference narrowed slightly. For patent-covered medicines, Italian prices in 2015 were 23.3% lower than the EU average while in 2022 they were 34.9% lower, highlighting how Italian prices have further decreased compared to the EU9 average.

Figure 1.9.24 Sub-analysis class H medicines hospital care: international comparison of the price of patent-expired and patent-covered medicines between 2015 and 2022 (ex-factory prices)

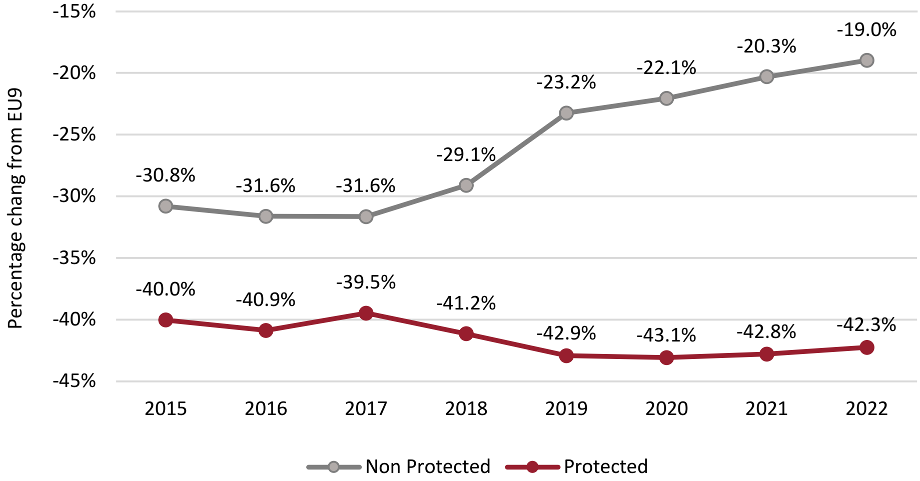
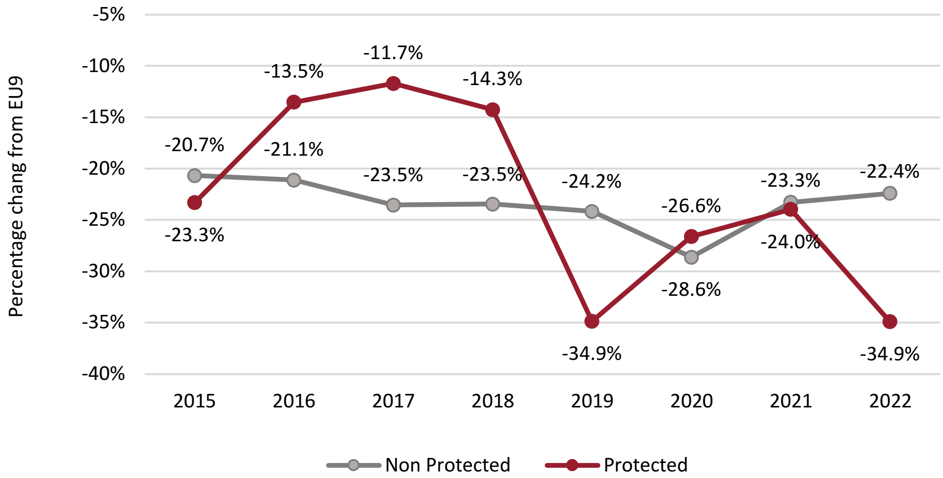


Figure 1.9.25 Sub-analysis class C medicines hospital care: international comparison of the price of patent-expired and patent-covered medicines between 2015 and 2022 (ex-factory prices)

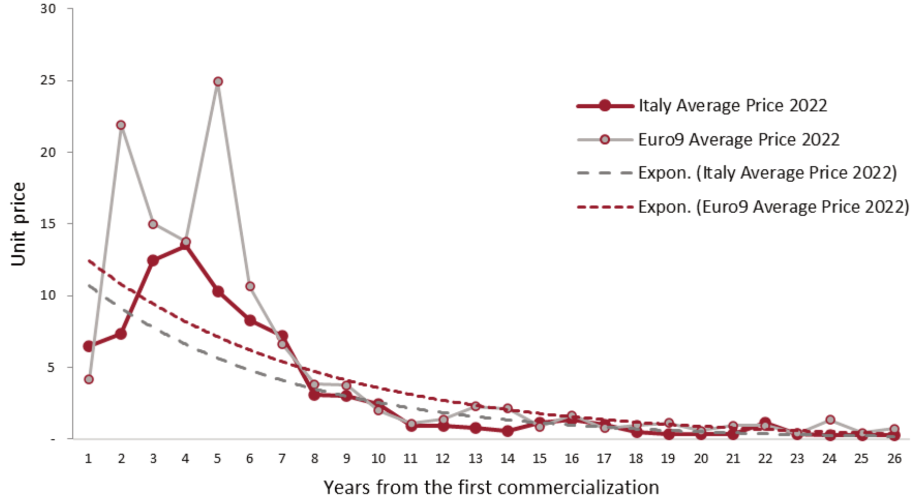


Finally, a comparison of prices was conducted in Italy compared to the EU9 average based on the launch date of the products. After pooling data from 9 countries (EU9) per product and package size, packages were classified according to the first marketing start date in Europe (10 countries). The analysis was carried out by launch year comparing the average price in Italy with the average European price by selecting the package sizes consumed in Italy and at least in another of the 9 European countries. For the comparison, the average was used over the eight years from 2015 to 2022. Should a product be marketed for a shorter period, the average price for the years on sale shall be applied. As years since the first market launch increase, both the average price in Italy and in the 9 countries considered decreases (Figure 1.9.26a). Based on a comparison index of average prices in Italy with average prices in the nine countries, it can be noted that the difference increases with years since first marketing (Figure 1.9.26b). Finally, a price comparison was conducted for certain categories of medicines with respect to the European average (Figures 1.9.27 and 1.9.28). For medicines indicated for diseases with impaired cell metabolism function, there is a price variation in Italy compared to Europe of more than 100%, while for multiple sclerosis medicines prices in Italy are 60% below the European average (Figure 1.9.27).

For medicines belonging to ATC L (antineoplastics), the largest differences are found for ACM PD-1/PD-L1 antineoplastics with a difference of +50.4% and for interleukin inhibitors with a difference of -33.6% (Figure 1.9.28).

Figure 1.9.26 International comparison of the average price calculated over 8 years (2015-2022), for medicines marketed on the same year (ex-factory prices): local/community care and hospital care

a) comparison on unit price



b) ratio between price in Italy and in EU9

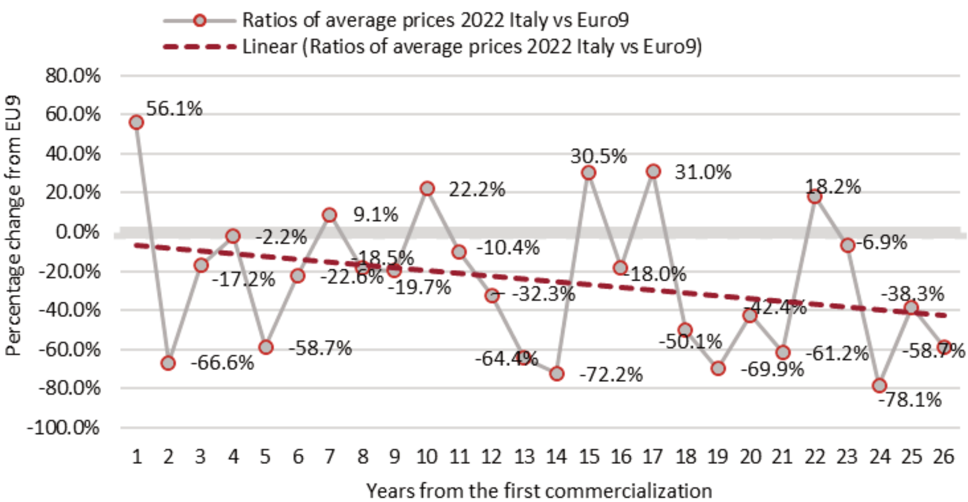


Figure 1.9.27 International price comparison by therapeutic category in 2022: local/community and hospital care

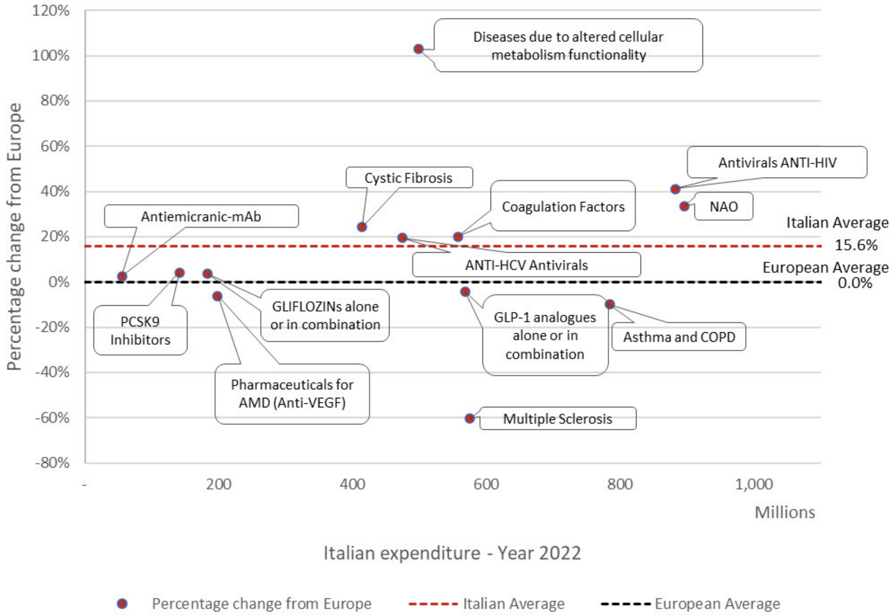
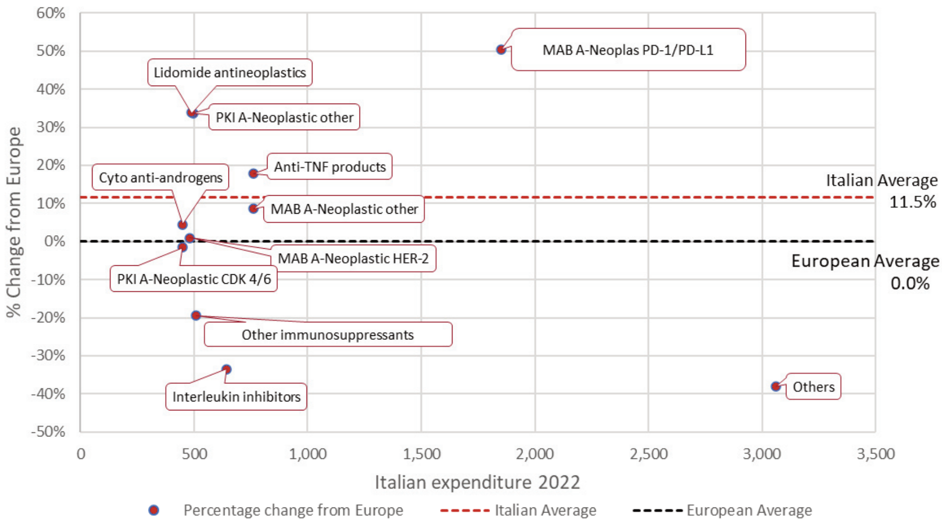


Figure 1.9.28 International price comparison for ATC level IV under ATC L in 2022: local/community and hospital care



Abbreviations: MAB (Monoclonal Antibodies), CDK (Cyclin-Dependent Kinase), HER-2 (Receptor 2 for the epithelial growth factor), PKI (Protein Kinase Inhibitors), PD-1 (Programmed Death-1), PDL-1 (Programmed Death-1 Ligand), TNF (Tumour Necrosis Factor)

References

- Dave C, Kesselheim A, Fox E et al. High generic drug studies and market competition. ANN Intern Med 2017; 167: 145-51

Section 2

Detailed analysis of pharmaceutical expenditure and consumption of medicines

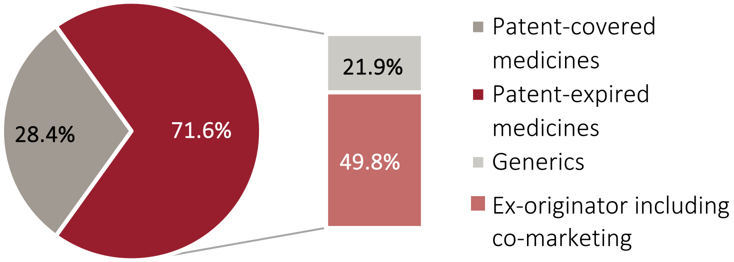
2.1 Patent expired medicines and biosimilars

Patent-expired medicines under approved care regime

In 2022, patent-expired medicines accounted for 71.6% of expenditure and 86.2% of consumption under class A approved care regime. The percentage share of generic medicines (unbranded), i.e. medicines based on active ingredients with expired patents, excluding those with patent coverage, accounted for 21.9% of expenditure and 30.3% of consumption (Figure 2.1.1 and Figure 2.1.2). This confirms the growing trend in both expenditure and consumption of these medicines, although it has been relatively moderate over the past two years (Figure 2.1.3 and 2.1.4).
At national level, *per capita* expenditure on patent-expired medicines amounted to EUR 118.8 in 2022, up by 5.9% from 2021, and with the percentage share of total spending rising from 68.7% in 2021 to 71.6% in 2022. Taking into account the last two years, the percentage of expenditure on generic medicines has remained nearly stable, rising from 30.4% to 30.5% (Table 2.1.1). The regions in the South (73.9%) and in the Centre (73.1%) have the highest share of expenditure on patent-expired medicines, both in comparison with the Northern Regions (69.1%) and the Italian average (71.6%). As a matter of fact, the lowest value was recorded in the Province of Bolzano (EUR 82.8), while the highest one in Campania (EUR 147.7). An opposite trend is observed when considering the percentage of expenditure on generic medicines: the Northern Regions show higher values (39.2%) compared to the Central (28.1%) and Southern Regions (22.1%).
In 2022, 983.3 daily doses per 1000 inhabitants were consumed of patent-expired medicines, with an increase of more than 2.9% compared to the previous year, corresponding to 86.2% of total DDD. The percentage of use of generic medicines, which was 35.2% in 2022, has slightly increased (Table 2.1.2). The Northern Regions consume a greater percentage of generic medicines (44.5%), compared to the Central (33.2%) and Southern Regions (24.8%). As a matter of fact, the highest value was recorded in the Province of Trento (49.6%), while the lowest one in Basilicata (21.1%).
In the use of patent-expired medicines, the regional heterogeneity in terms of both expenditure and consumption is plain to see. The composition of expenditure on medicines under approved care regime (Figure 2.1.5) shows that the use of generic medicines is lower in Campania, Calabria and Basilicata (19-20%), whereas the highest values are recorded in the Province of Trento and Lombardy (43-44%) In the northern regions, the consumption of generic medicines is higher than the national average, with 45%. In the Centre and the South and Islands the consumption of the ex-originator medicines prevails with 67% and 75% respectively. The A.P. of Trento shows an equal consumption between ex originator and generic medicines (50%). By contrast, Calabria and Basilicata are the regions with the lowest share of consumption of generic medicines (21%) (Figure 2.1.6).
The three therapeutic categories with a higher incidence of expenditure on patent-expired medicines (Table 2.1.3) are cardiovascular medications (93.3%), as well as medications acting on the genitourinary system (91.0%) and anti-infective for systemic use (89.2%). For the category of miscellaneous (V), oncology and immunosuppressants (L), medicines active on the genito-urinary system (G), cardiovascular medicines (C), medicines active on the gastrointestinal tract and metabolism (A) and medicines of the central nervous system (N),

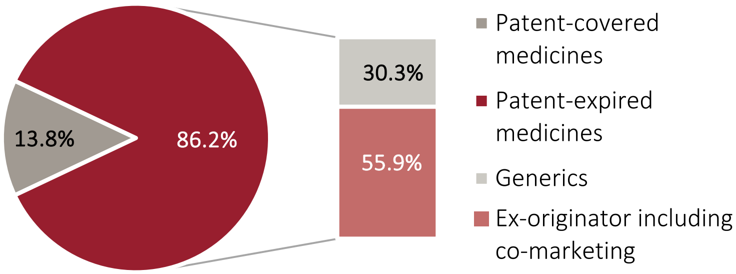
the highest percentages of expenditure on generics were recorded, respectively 42.4%, 29.8%, 27.6%, 27.2%, 25.3% and 24.9%. When looking at consumption, medicines acting on the cardiovascular system (96.0%) and on the genitourinary system (93.8%) as well as anti-infective for systemic use (92.8%) confirm the trend shown for expenditure. The category of systemic hormones, excluding sex hormones and insulins (H), on the other hand, has a higher incidence of consumption (83%) compared to that of expenditure (48%). Categories with the highest incidence of consumption of generic medicines are: ATC L (39%), N (38.2%), C (36.4%), G (33.0%), A (30.5%), and V (29.7%).
As for expenditure on the top 20 active ingredients of class A-NHS (private purchase) with expired patent, more than half belong to cardiovascular medications, followed by medicines acting on the gastrointestinal system and metabolism (Table 2.1.4). In 2022, atorvastatin is the most expensive active substance, with an absolute value of EUR 276.0 million, up by 0.9% compared to the previous year, and a percentage incidence of generics equal to 39.0%, followed by pantoprazole (EUR 266.3 million) and cholecalciferol (EUR 232.9 million). The active substances with the highest incidence of expenditure on generic medicines are lansoprazole (71.3%) and pantoprazole (56.7%). In contrast, the incidence of spending on generics for the combination ezetimibe/rosuvastatine (5.7%), olmesartan/amlodipine (16.9%), and amoxicillin/clavulanic acid (18.5%) is very low; the latter, together with the ezetimibe/rosuvastatine combination, shows the greatest increase in spending in 2022, +25.1% and +62.7% respectively, amounting to an expenditure of 152.8 and 85.5 million euros. However, cholecalciferol and ramipril show a reduction in expenditure of -3.6% and -3.3% respectively.
Considering the active substances with high consumption, cholecalciferol records the highest values (115.0 DDD/1000 inhabitants per day), followed by three substances acting on the cardiovascular system and three on the gastrointestinal system and metabolism, respectively: ramipril (61.5 DDD/1000 inhabitants per day), atorvastatin (50.9 DDD/1000 inhabitants per day), amlodipine (28.0 DDD/1000 inhabitants per day) acting on the cardiovascular system; pantoprazole (29 DDD/1000 inhabitants per day), metformin (23.1 DDD/1000 inhabitants per day), and omeprazole (17.6 DDD/1000 inhabitants per day) acting on the gastrointestinal system.
In public health facilities almost 77% of the expenditure concerned medicines with one speciality. All regions and geographic areas show the same trend (Figure 2.1.7). On a national level, more than 60% of the consumption concerns medicines with more than one speciality. This share is highest in the Northern regions (66.7%) and reaches its highest value in Emilia Romagna with 69%. In the regions of the South and the Islands, the consumption of medicines with more than one speciality is around 51%, with the lowest value in Basilicata (41%) (Figure 2.1.8). Regarding the temporal trend, over the period 2016-2022, the consumption of medicines with more than one speciality decreased from 79.4% in 2016 to 66.4% in 2022. In a complementary way, from 2016 to 2022 the consumption of medicines with only one speciality increased from 20.7% in 2016 to 33.6% in 2022 (Figure 2.1.9). Also, the expenditure trend remained stable over the period 2016-2022, both for medicines with only one speciality (about 75% of expenditure) and for medicines with more than one speciality (about 25%) (Figure 2.1.10).

Figure 2.1.1 Expenditure on medicines supplied under approved care regime (class A-NHS) and broken down by patent coverage in 2022



Generic medicinal products are medicinal products containing active substances with expired patents, with the exception of those which have benefited from patent cover, pursuant to Article 1(bis) of Decree-Law No 87 of 27 May 2005, converted with amendments by Law No 149 of 26 July 2005.

Figure 2.1.2 Consumption of medicines supplied under approved care regime (class A-NHS) and broken down by patent coverage in 2022



Generic medicinal products are medicinal products containing active substances with expired patents, with the exception of those which have benefited from patent cover, pursuant to Article 1(bis) of Decree-Law No 87 of 27 May 2005, converted with amendments by Law No 149 of 26 July 2005.

Figure 2.1.3 Trends in the impact of expenditure on generic and patent-expired medicines on the total spending on medicines under approved care regime (class A-NHS): comparison 2011-2022

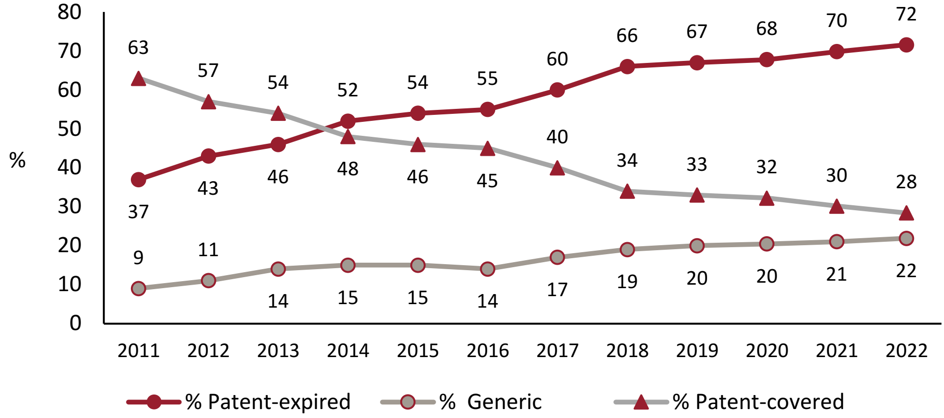


Table 2.1.1 Regional expenditure under approved care regime of medicinal products with expired patent* (class A-NHS): comparison 2022-2020

Region	*Per capita* expenditure (euro)			% on overall expenditure			% of expenditure on generics**		
	2020	2021	2022	2020	2021	2022	2020	2021	2022
Piedmont	94.75	95.40	102.2	68.5	69.1	72.9	37.1	37.8	38.1
Valle d'Aosta	88.77	88.13	94.4	67.1	68.0	71.8	36.3	36.9	37.4
Lombardy	106.55	107.83	115.0	60.2	60.8	61.8	42.3	42.9	42.9
A.P. of Bolzano	77.08	77.57	82.8	67.3	68.4	71.8	36.6	36.9	36.5
A.P. of Trento	96.97	98.66	106.3	71.3	72.1	74.9	43.4	43.9	43.5
Veneto	91.98	92.72	98.8	70.0	70.9	74.4	35.9	36.0	35.7
Friuli V.G.	98.02	99.58	106.0	67.5	69.6	73.3	41.5	38.6	38.7
Liguria	100.06	100.26	107.7	69.2	70.0	74.0	34.7	34.6	34.8
Emilia R.	90.97	94.16	101.2	73.4	74.3	77.5	36.6	36.7	36.4
Tuscany	90.29	90.98	98.0	66.5	67.5	71.4	36.9	37.5	38.1
Umbria	118.27	118.17	117.5	72.1	72.2	75.8	27.5	27.6	28.1
Marche	111.18	112.82	118.8	70.5	71.5	74.5	25.3	25.6	25.9
Lazio	126.11	126.65	133.0	68.9	69.7	73.3	23.6	23.8	23.7
Abruzzo	124.90	126.57	136.0	69.8	70.6	73.8	26.9	27.2	27.4
Molise	117.46	116.64	125.6	71.3	72.5	75.1	24.2	23.1	24.1
Campania	140.52	142.69	147.7	70.3	71.4	74.7	19.2	18.8	18.8
Puglia	130.29	130.21	136.7	69.9	70.4	73.4	24.1	24.5	24.8
Basilicata	125.69	131.64	140.7	69.0	70.5	73.7	18.9	20.3	20.4
Calabria	134.84	133.76	139.7	71.0	71.2	74.4	19.1	19.1	19.1
Sicily	123.18	122.62	128.9	67.5	70.1	73.8	20.8	20.8	20.8
Sardinia	113.88	114.25	123.1	67.8	68.4	72.3	30.5	30.6	31.1
Italy	**111.21**	**112.19**	**118.8**	**67.8**	**68.7**	**71.6**	**30.2**	**30.4**	**30.5**
North	98.01	99.33	106.2	65.9	66.7	69.1	39.0	39.2	39.2
Centre	112.06	112.74	118.8	68.7	69.6	73.1	27.6	27.9	28.1
South and Islands	129.67	130.28	136.8	69.4	70.6	73.9	21.9	22.0	22.1

* transparency lists published by AIFA over the years 2020-2022 have been used
** calculated on the expenditure of patent-expired medicines

Figure 2.1.4 Trend in the incidence of consumption (doses) of patent-expired medicines and generic medicines on total consumption of medicines under approved care regime (class A-NHS): comparison 2011-2022

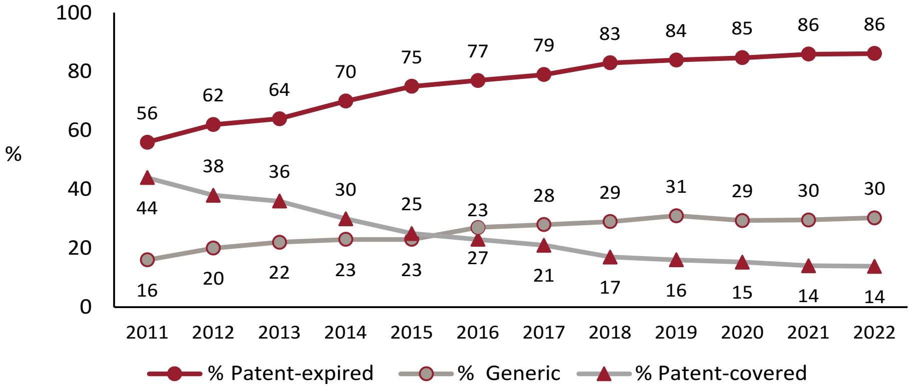


Table 2.1.2 Regional expenditure under approved care regime of medicinal products with patent-expired medicines* (class A-NHS): comparison 2022-2020

Region	DDD/1000 inhabitants per day			% of total DDDs			% of expenditure on generics**		
	2020	2021	2022	2020	2021	2022	2020	2021	2022
Piedmont	845.5	865.1	901.4	84.5	84.0	85.7	43.1	43.5	44.3
Valle d'Aosta	772.9	780.5	807.8	84.9	85.3	86.9	42.0	42.4	43.5
Lombardy	875.9	903.1	939.3	84.0	84.0	85.5	46.4	46.6	47.2
A.P. of Bolzano	669.0	681.2	712.5	83.1	83.0	84.4	41.7	41.4	41.7
A.P. of Trento	874.2	901.8	941.0	86.5	86.5	88.0	48.9	49.0	49.6
Veneto	807.4	817.2	846.0	81.6	81.6	84.2	41.5	41.1	41.5
Friuli V.G.	900.5	923.5	963.8	85.1	85.6	87.2	47.8	44.1	44.7
Liguria	815.3	829.1	863.5	84.7	84.5	86.2	39.8	39.6	40.3
Emilia R.	895.8	942.3	984.9	85.9	85.6	86.8	42.7	42.4	43.0
Tuscany	850.8	872.2	908.1	80.3	80.0	83.0	44.2	44.3	45.4
Umbria	1,050.1	1062.7	1,039.9	86.7	86.3	87.6	31.6	31.1	32.5
Marche	925.6	954.8	981.4	85.9	85.8	87.1	29.3	29.2	29.8
Lazio	1,003.3	1,013.9	1,036.5	86.1	85.8	87.5	27.0	26.6	26.9
Abruzzo	977.4	1007.5	1052.5	85.3	85.2	86.6	29.3	29.2	29.6
Molise	946.7	982.6	1017.5	85.6	85.6	87.0	25.2	24.9	25.9
Campania	1,112.0	1148.8	1,133.2	86.9	86.3	87.6	22.2	21.7	21.9
Puglia	1,047.8	1063.3	1,088.5	85.4	84.9	86.5	26.0	25.7	26.1
Basilicata	1,009.5	1,068.8	1,118.0	85.9	85.7	87.2	20.7	20.8	21.1
Calabria	1,024.0	1,032.3	1,057.4	85.8	85.3	86.8	21.3	21.2	21.4
Sicily	1,009.7	1,016.7	1,043.1	86.4	86.2	87.8	23.7	23.5	24.0
Sardinia	933.5	953.1	1,001.4	80.7	80.7	83.6	34.7	34.7	35.1
Italy	**933.4**	**955.4**	**983.3**	**84.7**	**84.5**	**86.2**	**34.7**	**34.5**	**35.2**
North	855.5	880.2	916.2	84.1	84.0	85.7	44.1	43.9	44.5
Centre	947.7	964.4	988.4	84.4	84.1	86.1	32.6	32.5	33.2
South and Islands	1,036.5	1,057.8	1,076.5	85.7	85.4	86.9	24.6	24.4	24.8

* transparency lists published by AIFA over the years 2020-2022 have been used
** calculated on the expenditure of patent-expired medicines

Figure 2.1.5 Composition by Region of 2022 expenditure on patent-expired medicines under approved care regime (class A-NHS)

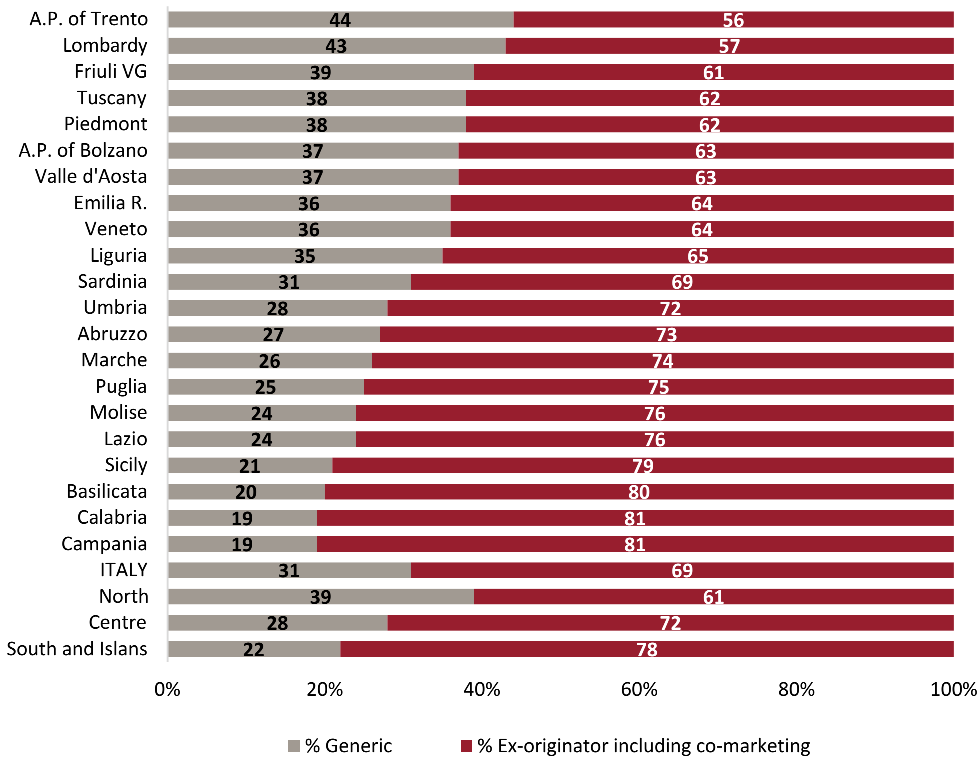


Figure 2.1.6 Composition by Region of 2022 consumption of patent-expired medicines under approved care regime (class A-NHS)

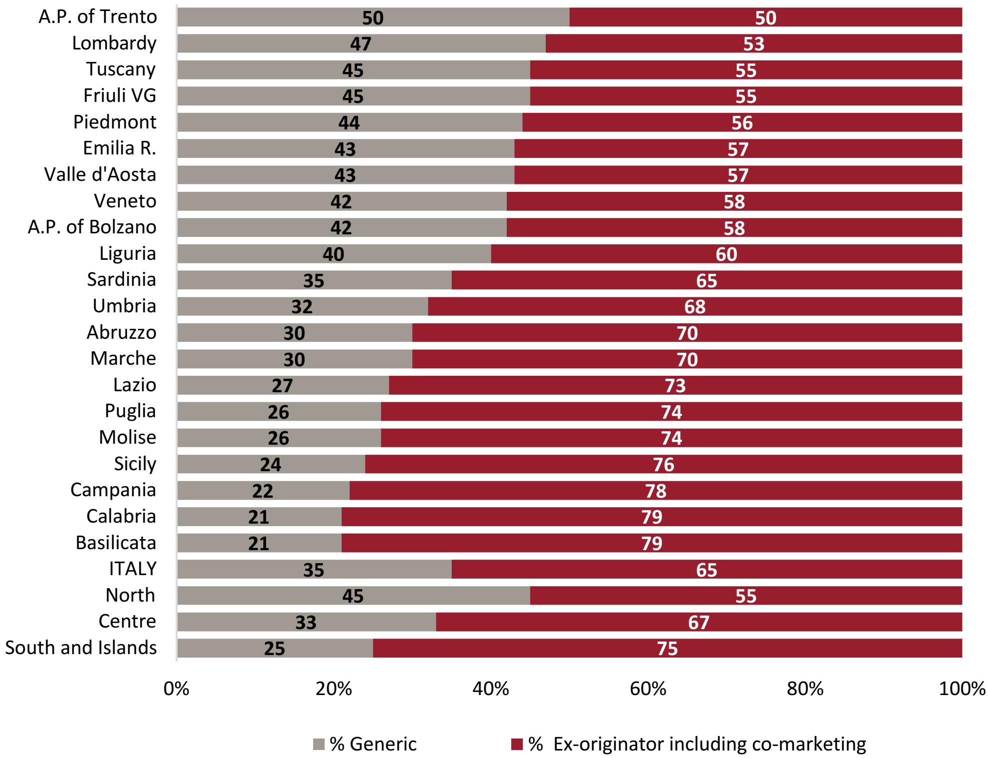


Table 2.1.3 Incidence of 2022 expenditure and consumption of patent-expired medicines under approved care regime (class A-NHS) by ATC 1st level

ATC 1st level	Expenditure under approved care regime		Consumption (DDDs) under approved care regime	
	% patent expired	% generic**	% patent expired	% generic**
A	65.2	25.3	84.8	30.5
B	47.0	12.9	67.3	16.5
C	93.3	27.2	96.0	36.4
D	36.9	5.6	33.0	3.1
G	91.0	27.6	93.8	33.0
H	48.0	3.5	83.0	5.0
J	89.2	21.8	92.8	24.6
L	85.2	29.8	87.2	39.0
M	80.6	18.8	83.6	27.6
N	60.8	24.9	76.7	38.2
P	79.0	2.5	91.3	3.9
R	32.1	3.8	54.1	12.0
S	49.3	6.6	56.5	10.9
V	48.1	42.4	31.5	29.7

* transparency lists published by AIFA over the years 2020-2022 have been used
** calculated on overall expenditure and consumption of patent-expired medicines

Table 2.1.4 Expenditure and consumption of the top 20 active substances with expired patent* under approved care regime (class A-NHS) with higher consumption: comparison 2022-2021

ATC	Active substance	Expenditure *(million)*	Inc. %^	Δ % 22-21	% generic**	DDD/1000 inhab. per day	Average cost DDD
C	atorvastatin	276.0	2.9	0.9	39.0	50.9	0.3
A	pantoprazole	266.3	2.8	8.7	56.7	29.0	0.4
A	cholecalciferol	232.9	2.4	-3.6	22.0	115.0	0.1
C	bisoprolol	166.5	1.7	3.5	32.8	12.8	0.6
J	amoxicillin/clavulanic acid	152.8	1.6	25.1	18.5	5.2	1.4
A	esomeprazole	130.9	1.4	6.0	35.0	15.8	0.4
A	lansoprazole	128.2	1.3	-0.4	71.3	13.3	0.5
A	omeprazole	127.5	1.3	1.8	41.2	17.6	0.3
C	omega-3	126.9	1.3	2.8	42.4	2.5	2.3
C	ramipril	115.0	1.2	-3.3	40.4	61.5	0.1
C	olmesartan	113.0	1.2	7.3	22.1	16.7	0.3
C	ezetimibe	99.6	1.0	8.3	43.3	6.3	0.7
A	metformin	98.0	1.0	1.9	30.9	23.1	0.2
N	levetiracetam	96.6	1.0	3.1	39.6	2.2	2.0
C	amlodipine	94.4	1.0	-1.3	34.7	28.0	0.2
C	nebivolol	91.8	1.0	1.4	23.9	16.9	0.3
L	letrozole	89.0	0.9	6.4	46.0	1.8	2.3
C	rosuvastatin	87.6	0.9	4.7	34.0	15.8	0.3
C	olmesartan/amlodipine	85.8	0.9	10.4	16.9	9.9	0.4
C	ezetimibe/rosuvastatin	85.5	0.9	62.7	5.7	10.1	0.4
	Total of the first 20	**2,664.1**	**27.6**	**5.1**	**36.2**	**454.3**	**0.3**
	Total	**7,005.0**	**72.5**	**5.4**	**30.5**	**983.3**	**0.3**

* transparency lists published by AIFA over the years 2021 and 2022 have been used
^ calculated on overall expenditure under approved care regime
** calculated on overall expenditure of the active substance

Public health facilities

Figure 2.1.7 Composition by Region of expenditure on medicines purchased by public health facilities 2022 with one speciality and medicines with at least two specialities (AIC 6 digits)

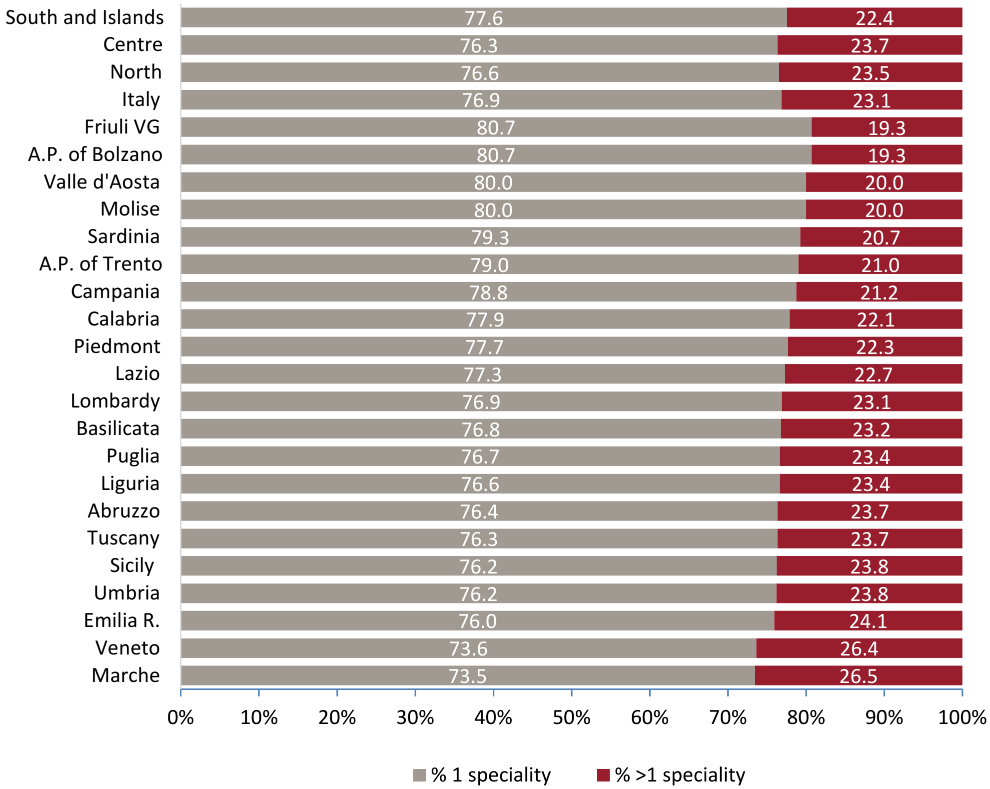


Figure 2.1.8 Composition by Region of consumption of medicines purchased by public health facilities 2022 with one speciality and medicines with at least two specialities (AIC 6 digits)

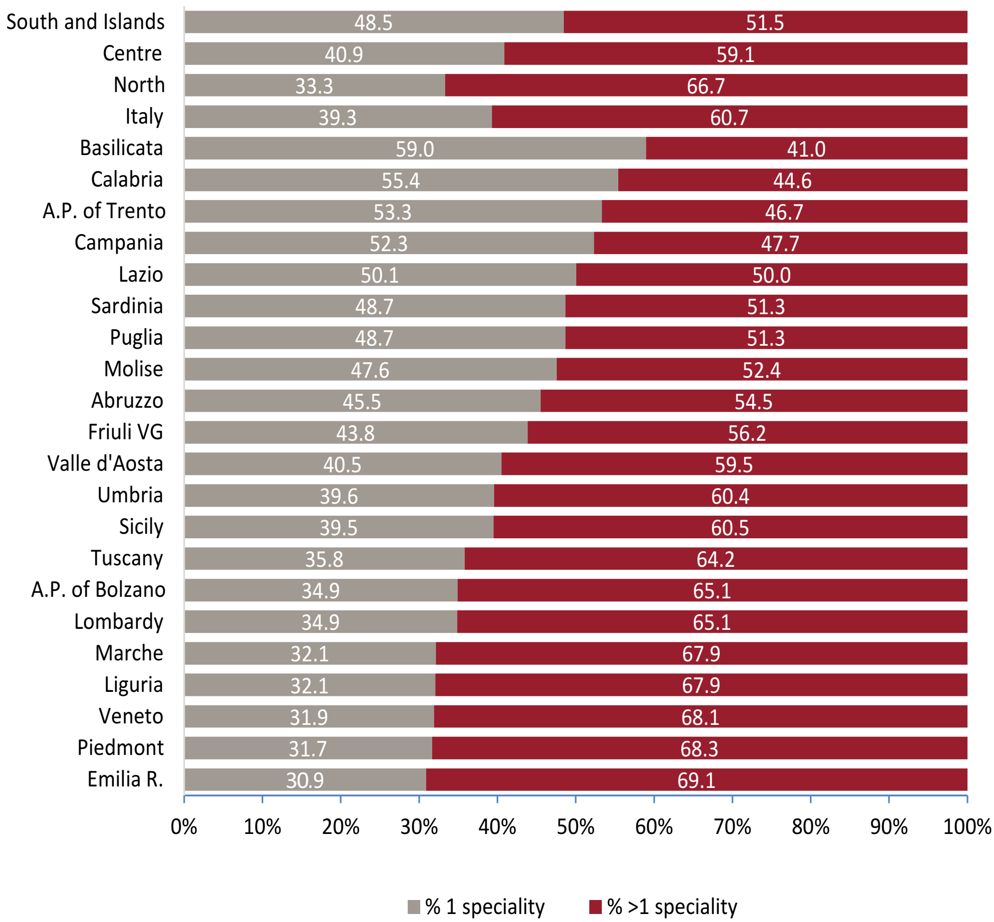


Figure 2.1.9 Time trend (2016-2022) of the percentage distribution of consumption of medicines purchased by public health facilities with one speciality and medicines with at least two specialities

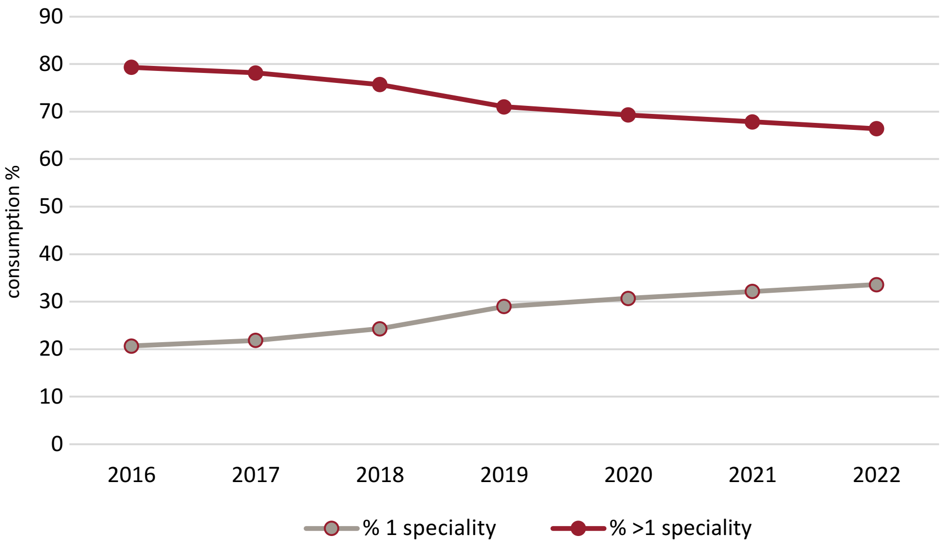
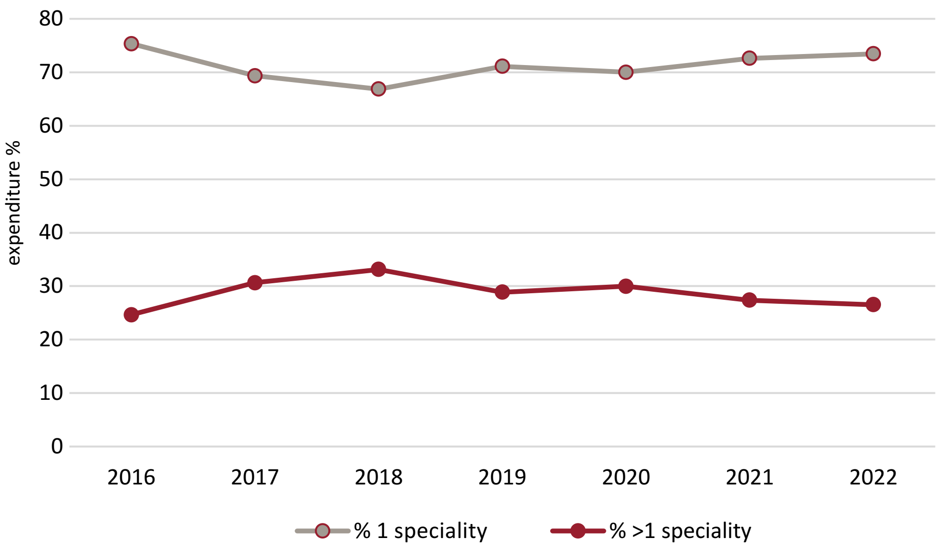


Figure 2.1.10 Time trend (2016-2022) of the percentage distribution of expenditure on medicines purchased by public health facilities with one speciality and medicines with at least two specialities



Expenditure for citizen cost-sharing on the reference price of patent-expired medicines

In 2022, spending on citizen cost-sharing for the share exceeding the reference price of patent-expired medicines (hereafter cost-sharing) was 18.4 euros *per capita* (about 1.1 billion euros). This value represents 73.1% of the total citizen cost-sharing (including the ticket per prescription and/or packaging) and has shown an increase of 0.1% compared to the previous year (Table 2.1.5) and a CAGR of +1.2% since 2017.
Expenditure *per capita* on citizen cost-sharing is higher in the South and the Islands (EUR 23.9), while the lowest is in the North with EUR 13.7 (Figure and Table 2.1.5), deviating from the national average of +30.1% and -25.4% respectively. Calabria, Lazio and Campania are the regions with the highest spending values (EUR 25.6, EUR 25.3 and EUR 25.2 respectively), while Bolzano, Trento and Valle d'Aosta have the lowest values of EUR 12, EUR 13.1 and EUR 12.9 respectively.
An analysis of the correlation between expenditure on citizen cost-sharing and regional *per capita* income shows that Regions with the lowest income are those with the highest citizen cost-sharing. In particular, for Calabria, Campania, Sicily and Puglia which have a *per capita* income slightly above EUR 10.000, there is a higher citizen cost-sharing compared to the national average (>20 euros) (Figure 2.1.11). The top 5 therapeutic categories with the highest level of citizen cost-sharing concern cardiovascular medications, in particular lipid modifying substances, not in combination (8.6%), beta-blockers (7.5%), angiotensin II receptor antagonists, in combination (6.0%), ACE-inhibitors in combination (5.5%) and angiotensin II receptor antagonists, alone (5.0%). These categories make up about one third of total expenditure (Table 2.1.6).
Compared to 2021, the value of citizen cost-sharing for other beta-lactam antibacterials (+27.2%), beta-lactam antibacterials, penicillins (+18.3%) and antiepileptics (+14.6%) increased (Table 2.1.6). For the first two categories, this trend is mainly determined by the increase in consumption (+33% for other antibacterials and +25.3% for penicillins) compared to the previous year. The same trend can also be found at the level of active ingredients, where an increase in expenditure per cost-sharing can be observed for amoxicillin/clavulanic acid (+19.6%), cefixime (+43.7%) and ceftriaxone (+11.3%) (Tables 2.1.6 and 2.1.7). On the contrary, expenditure on peptic ulcer medicines continued to decrease (-21.3%) and cost-sharing expenditure for vitamin A and D, including combinations, also decreased in 2022 (-10.3%), mainly due to a reduction in cost-sharing for cholecalciferol (-11.2%) (Table 2.1.7). Both of these categories showed a decrease in consumption, which may have had an impact on the reduction in cost-sharing expenditure.
Among the top 30 active ingredients with the greatest impact on the reference price, more than half relate to the category of medicines acting on the cardiovascular system; in particular, bisoprolol and atorvastatin cover almost 9% of total cost-sharing expenditure (Table 2.1.7). The top 30 active ingredients showing the greatest absolute change in cost-sharing expenditure in 2022 were magaldrate, bisoprolol and the combination amlodipine/olmesartan. The change for magaldrate is due to the entry on the transparency list in 2022, showing an absolute difference between 2022 and 2021 of about € 6.6 million (Table 2.1.8). For bisoprolol and for the combination amlodipine/olmesartan the increase in citizen cost-sharing is due to the increase in consumption of 3.8 % and 11.2 %,

respectively. Among the top 30 active ingredients with the greatest difference between the retail price and the reference price, those with a difference of more than € 25 did not have approved pharmacies as the predominant distribution channel (Table 2.1.9).
When considering the average difference between the public price and the reference price and the share of expenditure in relation to the distribution channel (Table 2.1.10), it is noted that the majority of products with an average difference of less than 3 euros are supplied through the channel under approved care regime (71.4%), accounting for more than half (64.6%) of total cost-sharing expenditure. Only 0.7% of products with a difference of more than 20 euros are distributed under approved care regime.
It is evident from Figure 2.1.12 that there is no correlation between the average difference between the retail price and the reference price and the incidence of consumption of the generic medicines; in fact, most generic medicines have a differential below EUR 3 (Figure 2.1.12).
Thus, while for expenditure on tickets per package and/or prescription the regional variability is due to the different ways in which the ticket is applied, for citizen cost-sharing in the reference price of patent-expired medicines, the regional differences are essentially due to the different use of generic medicines. This highlights the need for further information and education policies at both national and regional level in order to promote wider use of generic medicines.
By taking into account the top 10 therapeutic categories (ATC 3rd level) with a higher share of spending on the reference price, it is observed that in the North generic medicines are more used than in the Centre and the South (Table 2.1.11), with the largest difference for the category of beta blockers (C07A). Males tend to rely on generic medicines more than females. Overall, age-layered analysis shows a different use of generic medicines, according to the categories considered. As for medicines used to treat benign prostatic hypertrophy (G04C), it is observed that the use of generic medicines increases with age; on the contrary, for calcium channel blockers used in the management of cardiovascular diseases (C08C) and angiotensin II antagonists (C09C), the use of generics decreases with age.

Table 2.1.5 Distribution of share on reference price by Region (Table and Figure) (year 2022)

Region	Weighted *per capita* expenditure	Δ % 22-21	CAGR % 2017-2022	Δ % national average
Piedmont	13.9	-0.7	-0.8	-24.5
Valle d'Aosta	12.9	-0.5	1.1	-29.7
Lombardy	14.0	0.7	1.1	-23.7
A.P. of Bolzano	12.0	1.3	1.6	-34.7
A.P. of Trento	13.1	1.8	2.4	-28.9
Veneto	14.1	0.6	1.1	-23.2
Friuli V.G.	14.4	-0.9	0.0	-21.7
Liguria	15.0	0.4	0.6	-18.1
Emilia R.	14.9	1.6	2.0	-19.2
Tuscany	13.7	-0.6	0.2	-25.3
Umbria	19.0	-5.2	0.8	3.2
Marche	19.0	-0.6	1.3	3.2
Lazio	25.3	1.0	1.7	37.7
Abruzzo	21.1	0.5	1.9	14.7
Molise	21.7	0.8	1.7	18.0
Campania	25.2	-0.7	2.0	37.1
Puglia	22.0	0.2	0.8	19.9
Basilicata	24.0	2.0	2.9	30.8
Calabria	25.6	0.3	3.0	39.1
Sicily	23.9	-0.5	0.6	29.9
Sardinia	17.3	-0.5	0.7	-5.7
Italy	**18.4**	**0.1**	**1.2**	**-**
North	13.7	0.5	0.8	-25.4
Centre	20.3	0.0	1.3	10.4
South and Islands	23.9	-0.2	1.5	30.1

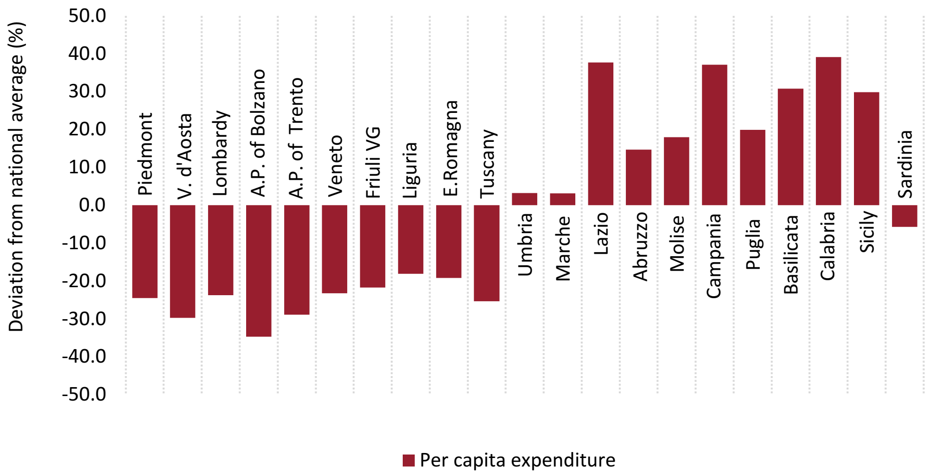


Figure 2.1.11 Correlation analysis between citizen cost-sharing and *per capita* income (year 2022)

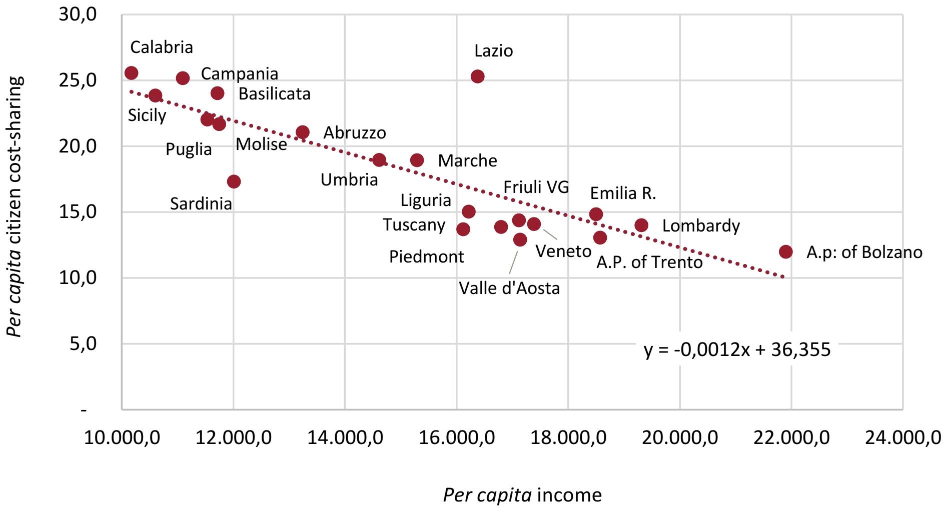


Table 2.1.6 Top 20 therapeutic categories with the largest share of expenditure on reference price (year 2022)

ATC 3rd level	Therapeutic category	DDD/1000 inhab. per day	Δ % 22-21	% generic	Total expenditure^	Δ % 22-21	Cost-sharing	Δ % 22-21	%*	% cum.
C10A	Lipid modifying substances, not associated	94.2	1.4	46.1	733.7	1.5	92.5	-3.5	8.6	8.6
C07A	Beta blockers	45.4	1.0	40.6	329.1	1.3	80.1	1.1	7.5	16.1
C09D	Angiotensin II antagonists, in combination	42.4	1.2	22.6	343.3	2.9	64.1	-1.1	6.0	22.1
C09B	Angiotensin-converting enzyme inhibitors (ACE), in combination	36.5	-0.6	22.5	281.5	-2.6	59.3	-5.4	5.5	27.6
C09C	Angiotensin II antagonists	58.0	0.1	30.8	289.8	0.3	53.8	-1.6	5.0	32.6
N06A	Antidepressants	43.7	2.4	48.1	410.4	1.9	50.4	-3.2	4.7	37.3
G04C	Medicines used in benign prostatic hypertrophy	39.6	2.7	35.5	267.1	0.9	47.0	-1.3	4.4	41.7
C09A	Angiotensin-converting enzyme inhibitors (ACE), not in combination	80.4	-2.4	52.2	209.9	-4.5	44.3	-5.8	4.1	45.8
B01A	Antithrombotics	66.6	-0.6	20.0	338.9	-2.9	43.0	-1.6	4.0	49.8
C08C	Selective calcium channel blockers with prevalent vascular effect	49.5	-1.2	37.1	239.8	-2.6	33.7	-3.7	3.1	52.9
M01A	Non-steroidal anti-inflammatory and anti-rheumatic medicines	18.1	6.5	18.5	152.6	6.2	33.5	7.4	3.1	56.0
A11C	Vitamins A and D, including their combinations	139.2	-2.3	20.3	277.3	-2.8	28.4	-10.3	2.6	58.6
A10B	Oral hypoglycemic agents	34.0	-3.2	39.0	333.0	18.2	26.1	-5.2	2.4	61.0
S01E	Antiglaucoma and miotic preparations	20.9	2.2	11.1	213.4	-2.0	25.7	-3.8	2.4	63.4
A02B	Treatments for peptic ulcer	79.7	-1.2	51.7	703.0	-4.9	24.1	-21.3	2.2	65.6
J01C	Beta-lactam antibacterials, penicillins	6.1	25.3	23.8	171.5	23.8	22.3	18.3	2.1	67.7
J01D	Other beta-lactam antibacterials	1.9	33.0	13.4	152.2	24.0	20.9	27.2	1.9	69.6
N03A	Anti-epileptics	9.6	1.0	17.4	285.0	1.7	18.7	14.6	1.7	71.3
C10B	Other lipid modifying agents, in combination	16.9	47.8	12.5	173.6	29.7	16.5	1.5	1.5	72.8
R06A	Antihistamines for systemic use	10.3	2.2	32.0	64.2	1.7	16.1	0.7	1.5	74.3
	Top 20 therapeutic categories	**893.1**	**0.6**	**34.0**	**5,969.4**	**2.1**	**800.5**	**-1.7**	**74.3**	
	Total citizen cost-sharing	**1,140.4**	**0.9**	**30.3**	**9,778.4**	**1.1**	**1,083.8**	**0.1**	**100**	

^gross expenditure including expenditure on citizen cost-sharing
* calculated on overall citizen cost-sharing

Table 2.1.7 Top 30 substances with the largest share of expenditure on the reference price (year 2022)

ATC 5th level	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	% generic	Expenditure total^	Δ % 22-21	Citizen cost-sharing	Δ % 22-21	%*	% cum.	Average difference between retail price and reference price
C07AB07	bisoprolol	12.8	3.8	47.0	166.5	3.5	54.7	2.6	5.1	5.1	1.35
C10AA05	atorvastatin	50.9	1.3	46.5	276.0	0.9	40.5	-1.4	3.8	8.9	1.27
A11CC05	cholecalciferol	136.8	-2.3	20.2	239.0	-3.2	25.7	-11.2	2.4	11.3	0.87
C09AA05	ramipril	61.5	-1.5	52.7	115.0	-3.9	25.7	-3.9	2.4	13.7	0.88
B01AC06	acetylsalicylic acid	45.6	1.5	21.3	70.4	1.0	24.2	0.8	2.3	16.0	0.74
J01CR02	amoxicillin/clavulanic acid	5.2	25.4	21.8	153.4	25.2	20.0	19.6	1.9	17.9	1.20
C08CA01	amlodipine	28.0	-0.3	45.1	94.4	-1.6	19.8	-4.0	1.8	19.7	0.97
C09CA08	olmesartan	16.7	7.7	26.6	113.0	7.3	18.4	5.7	1.7	21.4	1.44
C09DA08	olmesartan/ hydrochlorothiazide	10.4	3.8	19.0	74.5	3.1	15.8	2.1	1.5	22.9	1.97
A10BA02	metformin	23.1	0.5	42.4	98.0	1.4	15.7	0.4	1.5	24.4	0.55
C10AX06	omega-3	2.5	4.4	48.3	127.1	3.0	15.5	-3.8	1.4	25.8	1.41
G04CA02	tamsulosin	11.2	3.0	42.2	67.3	1.6	15.1	0.3	1.4	27.2	1.32
C09DB02	olmesartan/ amlodipine	9.9	11.2	20.5	85.8	10.4	15.1	9.5	1.4	28.6	1.99
B01AC04	clopidogrel	6.0	6.1	41.5	71.6	4.0	14.8	-1.7	1.4	30	3.23
A05AA02	ursodeoxycholic acid	2.7	3.9	38.5	53.5	3.5	13.6	3.9	1.3	31.3	2.18
C07AB12	nebivolol	16.9	2.0	27.7	91.8	1.3	12.8	0.0	1.2	32.5	0.99
C09BB04	perindopril/ amlodipine	5.3	-0.8	28.6	48.3	-2.1	12.5	-4.3	1.2	33.7	3.28
G04CB02	dutasteride	8.4	0.6	32.3	60.9	-1.0	11.6	-3.4	1.1	34.8	2.02
C10AA07	rosuvastatin	15.8	6.1	39.6	87.6	4.8	11.5	-6.1	1.1	35.9	1.03
N02BF02	pregabalin	2.4	6.1	37.5	80.3	4.6	11.3	-2.9	1.0	36.9	1.4
C02CA04	doxazosin	7.5	-1.1	36.2	72.5	-1.8	11.2	-2.0	1.0	37.9	1.27
N06AB10	escitalopram	7.6	0.6	38.7	57.1	-0.3	11.2	-2.2	1.0	38.9	2.28

continued

Table 2.1.7 – *continued*

ATC 5th level	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	% generic	Total expenditure	Δ % 22-21	Citizen cost-sharing	Δ % 22-21	%*	% cum.	Average difference between retail price and reference price
C09BX01	perindopril/ indapamide/ amlodipine	4.7	11.5	2.1	37.5	3.4	11.1	-2.7	1.0	39.9	3.31
J01XX01	fosfomycin	0.4	1.3	39.3	37.5	0.7	11.1	0.2	1.0	40.9	2.72
H03AA01	levothyroxine	22.7	4.9	2.4	82.1	13.6	10.9	1.4	1.0	41.9	0.53
C10AA01	simvastatin	11.4	-6.1	60.8	80.2	-6.8	10.1	-9.0	0.9	42.8	0.79
J01DD08	cefixime	1.2	42.8	15.9	58.7	42.5	9.9	43.7	0.9	43.7	1.97
C01BC04	flecainide	3.1	4.2	18.3	54.4	3.0	9.8	-1.9	0.9	44.6	1.84
G04CA04	silodosin	6.5	4.3	24.1	43.3	3.0	9.4	0.1	0.9	45.5	1.90
J01DD04	ceftriaxone	0.2	15.1	24.8	55.3	14.0	9.3	11.3	0.9	46.4	1.00
	Total of top 30	**537.2**	**1.0**	**32.1**	**2,753.0**	**3.5**	**498.4**	**0.3**	**46.4**		
	Total	**1,140.4**	**0.9**	**30.3**	**9,778.4**	**1.1**	**1,083.8**	**0.1**	**100**		

^gross expenditure including expenditure on citizen cost-sharing
* calculated on overall citizen cost-sharing

Table 2.1.8 Top 30 active substances by change (2022-2021) in citizen cost-sharing for the share exceeding the reference price

ATC	Active ingredient	Expenditure 2022^ *(million)*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21	DDD/1000 inhab.per day generic	Δ % 22-21	Citizen cost-sharing *(million)*	Δ 22-21 *(million)*
A02AD02	magaldrate	33.14	36.0	2.5	35.7			6.6	6.6
C07AB07	bisoprolol	166.47	3.5	12.8	3.8	6.0	6.1	54.7	1.4
C09DB02	olmesartan/amlodipine	85.76	10.4	9.9	11.2	2.0	15.7	15.1	1.3
A07EC02	mesalazine	125.60	2.3	5.4	2.6	0.5	0.2	4.9	1.2
C09CA08	olmesartan	113.03	7.3	16.7	7.7	4.4	13.7	18.4	1.0
A05AA02	ursodeoxycholic acid	53.53	3.5	2.7	3.9	1.0	3.8	13.6	0.5
C09DA08	olmesartan/hydrochlorothiazide	74.47	3.1	10.4	3.8	2.0	10.4	15.8	0.3
C10BA06	ezetimibe/rosuvastatin	91.15	49.5	10.6	69.0	0.6	198.8	8.6	0.3
C03DA01	spironolactone	5.63	-9.3	0.7	-1.5			0.3	0.3
B01AC06	acetylsalicylic acid	70.43	1.0	45.6	1.5	9.7	2.5	24.2	0.2
C09DB07	candesartan/amlodipine	3.83	21.6	0.5	22.3			0.1	0.1
C09BB07	ramipril/amlodipine	22.02	5.8	3.6	7.1	0.1	166.7	3.7	0.1
A10BH01	sitagliptin	0.76	8.6	0.0	42.2	0.0		0.1	0.1
C07AB02	metoprolol	16.21	3.6	4.5	4.9	2.2	9.2	3.4	0.1
C07BB12	nebivolol/hydrochlorothiazide	28.70	1.8	4.7	2.5	0.7	9.4	6.9	0.1
A10BA02	metformin	97.96	1.4	23.1	0.5	9.8	-3.9	15.7	0.1
C01BD07	dronedarone	0.19	>100	0.0	> 100	0.0	> 100	0.1	0.0
A10BD05	pioglitazone/metformin	5.95	-4.7	0.3	-5.5	0.2	-16.1	0.5	0.0
C03AA03	hydrochlorothiazide	1.31	-4.7	0.7	-4.3	0.0	-11.7	0.3	0.0
C02KX01	bosentan	0.10	67.5	0.0	14.4	0.0	14.4	0.0	0.0
B01AC22	prasugrel	0.68	33.1	0.0	31.0	0.0	28.1	0.1	0.0
C10AX09	ezetimibe	100.99	9.0	6.4	10.1	2.8	18.9	4.3	0.0
C03DA04	eplerenone	3.68	26.6	0.1	27.5	0.1	27.1	0.1	0.0
D01BA02	terbinafine	2.97	-0.1	0.1	-0.1	0.1	-1.3	0.4	0.0
C02KX02	ambrisentan	0.08	28.5	0.0	29.6	0.0	-33.0	0.0	0.0
A02BX02	sucralfate	2.02	1.2	0.2	-0.5	0.0	-1.4	0.4	0.0
A03FA01	metoclopramide	0.57	2.9	0.0	3.4	0.0	40.1	0.1	0.0
A16AA01	levocarnitine	0.35	-0.4	0.0	-1.2			0.1	0.0
C02CA	terazosine	0.16	12.0	0.0	9.5			0.0	0.0
A10BH02	vildagliptin	34.90	1.0	0.6	1.9			7.6	0.3

^gross expenditure including expenditure on citizen cost-sharing

Table 2.1.9 Top 30 active ingredients by difference between retail price and reference price (2022)

ATC	Active ingredient	Difference between the public price and the reference price	Expenditure 2022 *(million)*	Δ % 22-21	% expenditure under approved care regime	DDD/1000 inhab. per day	Δ % 22-21	DDD/1000 inhab. per day generic	Citizen cost-sharing *(million)*	Δ 22-21 *(million)*
C02KX02	ambrisentan	1,553.22	0.08	28.5	2.0	0.0	29.6	0.0	0.04	0.0
C02KX01	bosentan	380.86	0.10	67.5	3.8	0.0	14.4	0.0	0.05	0.0
J02AC03	voriconazole	285.49	0.03	-42.1	5.2	0.0	-15.7	0.0	0.01	-0.0
L03AX13	glatiramer	250.08	0.07	33.3	0.6	0.0	26.7		0.02	0.0
H01CB03	lanreotide	129.59	0.53	>100	1.2	0.0	>100		0.05	0.1
J02AC04	posaconazole	105.66	0.13	-6.6	2.0	0.0	35.6	0.0	0.02	-0.0
J01XX08	linezolid	72.38	0.04	-14.8	6.7	0.0	-20.1	0.0	0.01	0.0
V03AC03	deferasirox	47.04	0.24	>100	0.4	0.0	>100	0.0	0.03	0.0
H05BX02	paracalcitol	35.37	0.53	-24.0	29.4	0.0	-39.3	0.0	0.15	0.1
L01AX03	temozolomide	35.09	0.03	-48.5	2.0	0.0	-36.9	0.0	0.00	-0.0
N03AF04	eslicarbazepine	34.59	0.25	6.5	16.3	0.0	11.9	0.0	0.06	0.1
V03AC02	deferiprone	31.48	0.01	17.6	0.3	0.0	21.0	0.0	0.00	0.0
J05AF10	entecavir	24.90	0.51	>100	7.1	0.0	147.1	0.0	0.06	0.0
C01BD07	dronedarone	21.66	0.19	>100	11.8	0.0	>100	0.0	0.05	0.0
L04AD01	ciclosporin	21.65	26.45	-6.2	90.2	0.2	-5.6		8.06	-0.5
L01EA01	imatinib	17.28	0.03	25.4	0.1	0.0	>100	0.0	0.00	-0.0
J05AB14	valganciclovir	14.55	2.08	11.5	59.1	0.0	12.4	0.0	0.03	0.0
N04BA03	levodopa/carbidopa/entacapone	9.49	1.23	-19.8	62.5	0.0	-18.1	0.0	0.18	-0.1
H05BX01	cinacalcet	9.23	0.98	39.5	12.4	0.0	39.0	0.0	0.24	0.1
J05AB15	brivudine	8.83	7.83	-12.0	99.3	0.0	6.9	0.0	1.18	-0.1
L04AA06	mycophenolate	6.78	0.15	73.7	0.8	0.0	84.2	0.0	0.01	0.0
L04AD02	tacrolimus	6.58	4.80	7.3	9.5	0.0	-0.1		0.36	0.2
L02AB01	megestrol	6.10	2.47	20.0	98.7	0.1	20.5		0.23	0.0
M05BA02	clodronic acid	5.60	0.36	0.8	98.6	0.0	5.4	0.0	0.06	0.0
A10BH01	sitagliptin	5.00	0.76	8.6	2.3	0.0	42.2	0.0	0.08	0.1
N03AX18	lacosamide	4.79	38.74	-3.4	86.7	0.4	11.8	0.0	2.04	2.0
H01CB02	octreotide	4.68	0.62	-7.3	1.7	0.0	-3.5	0.0	0.01	-0.0
B01AC22	prasugrel	4.60	0.68	33.1	32.7	0.0	31.0	0.0	0.07	0.0
N05AX13	paliperidone	4.38	2.59	3.1	5.2	0.0	5.5	0.0	0.16	-0.0
B01AC30	clopidogrel/acetylsalicylic acid	4.27	11.07	-4.0	59.5	0.9	0.4	0.2	2.80	-0.5

Table 2.1.10 Average difference between the public price and the reference price and share of expenditure under approved care regime and in direct and "on behalf" distribution (year 2022)

Average difference between retail price and reference price (€)	% expenditure under approved care regime*	% expenditure in direct and "on behalf" distribution**	% citizen cost-sharing on total cost-sharing
<1	10.6	0.8	7.4
≥1-<2	30.2	2.6	25.6
≥2-<3	30.6	2.6	31.6
≥3-<5	18.0	4.9	22.5
≥5-<10	8.7	11.3	9.8
≥10<20	1.3	5.1	1.8
≥20	0.7	72.8	1.4

** calculated on overall expenditure under approved care regime*
*** calculated on expenditure in direct distribution and "on behalf" distribution*

Figure 2.1.12 Correlation between average difference (between retail price and reference price) and consumption of generics by molecule (year 2022)

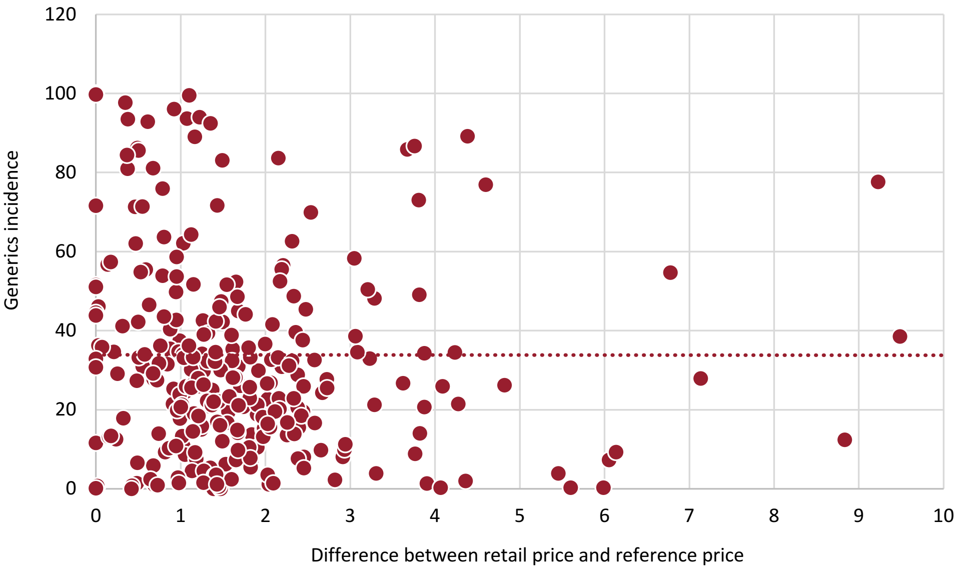


Table 2.1.11 Distribution by geographical area, gender and age of patients using generic medicines for the top 10 therapeutic categories (ATC 3rd level) with the largest share of expenditure on the reference price (year 2022)

	C10A	C07A	C09D	C09B	C09C	N06A	G04C	C09A	B01A	C08C
Geographical Area										
North	62.7	59.8	34.0	33.5	45.7	57.2	55.1	65.8	23.2	51.7
Centre	51.4	44.0	25.9	24.8	35.4	49.1	45.0	52.9	21.2	38.6
South and Islands	42.4	33.9	20.0	18.0	25.1	37.5	35.4	38.9	17.6	27.5
Gender										
Females	50.6	44.1	25.5	25.5	33.7	49.2	40.2	53.2	17.9	38.8
Males	55.0	51.2	28.2	26.6	37.4	50.1	45.9	56.1	23.6	44.0
Age class										
<50	55.4	44.9	28.8	24.0	38.5	50.8	39.9	57.5	8.1	46.8
50-60	56.3	46.6	29.5	26.4	38.0	51.5	43.0	57.8	20.9	46.1
60-70	54.7	47.0	28.3	26.9	36.6	50.8	46.3	55.9	24.0	43.6
70-80	51.3	46.3	25.3	25.5	33.7	49.1	46.3	53.0	22.1	39.6
>80	49.9	49.4	24.8	25.9	33.9	46.4	46.3	52.8	20.5	39.0
Total	**52.8**	**47.3**	**26.7**	**26.0**	**35.4**	**49.5**	**45.8**	**54.7**	**20.7**	**41.4**

C10A: Lipid modifying substances, not associated
C07A: Beta blockers
C09D: Angiotensin II antagonists associated
C09B: Angiotensin-converting enzyme inhibitors associated
C09C: Angiotensin II antagonists
N06A: Antidepressants
G04C: Medicines for benign prostatic hypertrophy
C09A: Angiotensin-converting enzyme (ACE) inhibitors not associated
B01A: Antithrombotics
C08C: Selective calcium channel blockers with prevalent vascular effect

Patent-expired biologic medicines

Analysing the level of competition in the biosimilars market (HHI) and the market shares per competitor (Figure 2.1.13), insulin aspart, whose biosimilar entered the market in 2022, and insulin lispro are the active ingredients with the highest market concentration, presenting an HHI value of 0.98 and 0.71, respectively, as the largest market share belongs to the ex-originator, which competes with only one type of biosimilar. The situation is different for somatropin (HHI=0.61), for which the largest market share is made of a single biosimilar on the market.
Follitropin alfa (HHI 0.48), teriparatide (HHI 0.58), and epoetin (HHI 0.52) have greater competitiveness; as a matter of fact, there are two other competitors in addition to the originator, although the originator still holds the largest market share. In the case of enoxaparin (HHI=0.50), filgrastim (HHI=0.37) and pegfilgrastim (HHI=0.39) the competitiveness is even greater; as a matter of fact, the ex-originator market represents a small share (very small in the case of filgrastim) compared with that of the 3 available biosimilars. Etanercept (HHI=0.37) e infliximab (HHI=0.32) have a low market concentration, although the largest share is held by a biosimilar. In the case of rituximab (HHI=0.36), the largest market share is held by one of the three biosimilars, with the ex-originator and the other two sharing the remaining share equally. For bevacizumab (HHI=0.31), two of the five available biosimilars account for about 75% of the market share, with the remaining share split between the other biosimilars and the ex-originator. Finally, trastuzumab and adalimumab, have the lowest HHI value (0.26 and 0.22), an indication of high competition, where there are at least four competitors.
Analysing the trend in expenditure and consumption of expired biological medicines for ATC 4th level (Table 2.1.12), it is noted that for follitropin, fast acting insulin and somatropin, the greatest incidence of expenditure and consumption is represented by the therapeutic category of other biologicals, i.e. those medicines that do not fall either within the definition of reference product nor biosimilar, which reach percentages ranging between 60% and 67% (Figure 2.1.19, 2.1.20 and 2.1.24).
In the case of anti-TNF-alpha therapies, although the highest incidence of expenditure is attributable to golimumab and certolizumab (other anti-TNF-alpha therapies, 36%), the highest percentage of consumption is attributable to adalimumab biosimilar (51.9%), increasing by +32.1% over 2021 (Table 2.1.12).
Analysing the trend over the last decade it can be observed a clear reduction in reference product expenditure for both adalimumab and etanercept (Figure 2.1.14). Also in the case of growth factors, it is possible to note that although there is a higher incidence of expenditure for the other growth factors (Table 2.1.12 and Figure 2.1.18), which has been declining sharply in recent years (-54.9% between 2017 and 2022), in the case of consumption, the highest incidence is attributable to the filgrastim biosimilar (44.1%), which shows an increase of 8.4% over the previous year. For long-acting insulins, insulin glargine (ex-originator, biosimilar and other insulin glargine) accounts for more than 70% of the category's expenditure, while other long-acting insulins account for almost a third of expenditure and consumption (Figure 2.1.21). For intermediate-acting and mixed (long or intermediate acting with fast acting) insulins, the ex-originator is responsible for almost all spending and consumption.

Rituximab, trastuzumab and infliximab, that are the only three molecules with two different formulations available, subcutaneous and intravenous, show a high incidence of both expenditure and consumption of the biosimilar (Figures 2.1.23, 2.1.26 and 2.1.27); moreover, for all three medicines a reduction in expenditure for the biosimilar can be observed against an increase in consumption. In contrast, intravenous ex-originators show the largest contractions in both spending and consumption compared with the previous year.

As low molecular weight heparins and epoetins, there is a higher incidence of both consumption and expenditure on biosimilars (Figures 2.1.16 and 2.1.17).

Bevacizumab, whose biosimilar was first marketed in Italy in 2020, has a high percentage of both expenditure (88.2%) and consumption (96.2%) on the biosimilar, showing a high increase for both indicators in 2022, of 16.1% and 55.3% respectively (Figure 2.1.15). For teriparatide, there is a similar trend, with biosimilars accounting for 89.6% in spending and 93.9% in consumption, with major increases (+46.6% and +60.5%) over the previous year (Figure 2.1.25).

Analysing the regional variability of the consumption of patent-expired biological medicines (Figure 2.1.28), Lombardy, Calabria, Molise and Abruzzo tend to consume more ex-originator, while Marche, Tuscany, Piedmont, Basilicata, Veneto, Campania, Liguria and the A.P. of Trento are the regions with the highest consumption of biosimilars.

Analysing the regional variability in terms of biosimilar consumption and the average DDD cost of patent-expired biologics in direct purchases (Figure 2.1.29), it is shown that in Emilia Romagna, the Province of Trento, Veneto, Tuscany, Piedmont, Sardinia and Umbria the higher consumption of biosimilar corresponds to an average DDD cost lower than the national average. On the contrary, Basilicata, Marche and Campania have a higher cost of patent expired biologics, despite a higher consumption of biosimilars. Liguria consumes more biosimilars than the national average at an average cost per DDD in line with the national average. Lombardy, Calabria, Lazio, Molise, A.P. of Bolzano, Abruzzo, Friuli Venezia Giulia and Puglia have the highest values of cost per day of therapy compared to a lower consumption of biosimilars.

Figure 2.1.30, on the other hand, shows a linear correlation between the incidence of biosimilar consumption on the total consumption of patent-expired biologics and the average cost per day of therapy of all medicines purchased by public facilities. The regions with the highest biosimilar consumption that record a lower DDD cost are: Emilia Romagna, Piedmont, the A.P. of Trento, Valle d’Aosta, Liguria, Friuli VG, Veneto, Tuscany and Campania; while Lombardy and Calabria show low incidence of biosimilar and higher DDD cost.

Figure 2.1.13 Expired-Patent Biologics: Herfindahl-Hirschman Index (HHI) and market shares by competitor (year 2022)

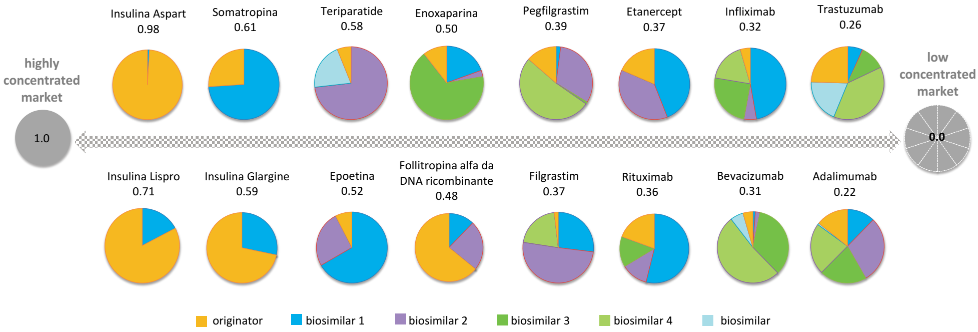


Table 2.1.12 Biosimilars, provision through public health facilities and NHS prescriptions (year 2022)

Group and subgroup	Total *per capita*	Incidence %	Δ % 22-21	Δ % 22-17	DDD/1000 inhab. per day	Incidence %	Δ % 22-21	Δ % 22-17	Average cost	Δ % 22-21	Δ % 22-17
Anti-TNF alpha	**4.15**	**100.0**	**-7.6**	**-56.0**	**1.3**	**100.0**	**13.3**	**56.0**	**8.86**	**-18.4**	**-71.8**
Biosimilar adalimumab	0.82	19.8	13.3	—	0.7	51.9	32.1	—	3.38	-14.3	—
Biosimilar etanercept	0.69	16.7	-11.1	129.4	0.2	19.2	14.1	613.9	7.70	-22.0	-67.9
Originator adalimumab	0.63	15.1	-24.6	-86.7	0.1	8.6	-22.1	-71.3	15.50	-3.3	-53.6
Originator etanercept	0.52	12.4	-28.6	-81.0	0.1	4.4	-25.1	-76.9	25.19	-4.7	-17.8
Other anti-TNF alpha	1.50	36.0	4.1	-12.5	0.2	16.0	4.2	27.9	20.03	-0.1	-31.5
Bevacizumab	**0.73**	**100.0**	**-26.6**	**-80.1**	**0.1**	**100.0**	**23.2**	**-11.5**	**17.57**	**-40.4**	**-77.5**
Biosimilar	0.65	88.2	16.1	—	0.1	96.2	55.3	—	16.11	-25.2	—
Originator	0.09	11.8	-80.4	-97.7	0.0	3.8	-80.3	-96.6	54.60	-0.8	-30.1
Low molecular weight heparins	**2.27**	**100.0**	**2.4**	**5.2**	**6.6**	**100.0**	**-1.6**	**-0.8**	**0.94**	**4.0**	**6.0**
Biosimilar	1.63	71.8	10.1	—	5.1	77.5	10.6	—	0.88	-0.4	—
Fondaparinux	0.27	12.0	-8.6	12.6	0.5	7.4	-7.0	5.7	1.53	-1.7	6.5
Originator	0.17	7.7	-21.9	-88.4	0.6	9.1	-43.2	-88.2	0.79	37.5	-1.9
Other low molecular weight heparin	0.19	8.5	-10.2	-53.1	0.4	5.9	-20.3	-63.5	1.35	12.7	28.3
Epoetins	**2.48**	**100.0**	**-1.1**	**-31.8**	**3.8**	**100.0**	**5.4**	**20.5**	**1.77**	**-6.1**	**-43.4**
Biosimilar	1.27	51.0	2.4	21.2	3.1	81.1	8.0	90.0	1.11	-5.1	-36.2
Originator	0.25	10.1	-7.4	-71.4	0.3	6.6	-3.8	-61.1	2.68	-3.8	-26.5
Other epoetins	0.96	38.9	-3.7	-43.9	0.5	12.3	-4.7	-47.1	5.60	1.0	6.0
Growth factors	**0.35**	**100.0**	**-12.1**	**-61.4**	**0.1**	**100.0**	**9.5**	**21.5**	**8.65**	**-19.7**	**-68.2**
Biosimilar filgrastim	0.10	27.3	-7.9	-32.1	0.0	44.1	8.4	36.5	5.37	-15.0	-50.3
Biosimilar pegfilgrastim	0.07	20.1	6.1	—	0.0	41.2	15.6	—	4.22	-8.2	—
Originator filgrastim	0.02	6.4	13.0	-58.6	0.0	0.8	18.7	-54.0	67.71	-4.8	-10.0
Originator pegfilgrastim	0.05	13.5	-32.4	-89.7	0.0	6.5	16.7	-81.1	17.91	-42.0	-45.6
Other growth factors	0.11	32.7	-17.2	-54.9	0.0	7.4	-15.5	-46.8	38.31	-2.0	-15.1

continued

Table 2.1.12 – *continued*

Group and subgroup	Expenditure *per capita*	Incidence %	Δ % 22-21	Δ % 22-17	DDD/1000 inhab. per day	Incidence %	Δ % 22-21	Δ % 22-17	Average cost	Δ % 22-21	Δ % 22-17
Follitropins	**0.88**	**100.0**	**-4.2**	**-12.6**	**0.1**	**100.0**	**-12.9**	**-16.9**	**22.46**	**10.0**	**5.1**
Biosimilar	0.08	9.2	-3.0	110.2	0.0	15.1	1.3	163.7	13.70	-4.2	-20.3
Originator	0.20	23.1	-28.2	-55.4	0.0	27.0	-25.1	-43.4	19.14	-4.1	-21.4
Other follitropin	0.60	67.7	7.9	16.1	0.1	57.8	-9.3	-13.5	26.30	19.0	34.3
Infliximab	**0.51**	**100.0**	**-5.7**	**-66.0**	**0.4**	**100.0**	**8.2**	**38.6**	**3.40**	**-12.9**	**-75.5**
Biosimilar infliximab IV	0.38	75.3	-14.3	-40.0	0.4	90.1	4.2	124.5	2.84	-17.7	-73.3
Biosimilar infliximab SC	0.05	10.4	1,275.9	—	0.0	5.4	1,227.1	—	6.51	3.7	—
Originator infliximab IV	0.07	14.3	-18.2	-91.5	0.0	4.5	-18.2	-85.9	10.75	0.1	-40.0
Fast acting insulins	**0.16**	**100.0**	**-3.5**	**-30.4**	**0.9**	**100.0**	**4.4**	**2.2**	**0.49**	**-7.6**	**-31.9**
Biosimilar insulin aspart	0.00	0.3	—	—	0.0	0.2	—	—	0.64	—	—
Biosimilar insulin lispro	0.02	11.0	-23.1	—	0.1	9.1	-31.7	—	0.60	12.6	—
Originator Insulin aspart	0.06	37.4	-10.7	-23.7	0.2	24.4	1.8	-11.7	0.76	-12.3	-13.6
Originator Insulin lispro	0.04	25.7	17.8	-63.4	0.4	42.4	25.6	-6.6	0.30	-6.2	-60.9
Other long acting insulins	0.04	25.6	-0.3	5.8	0.2	23.9	-3.6	-3.7	0.53	3.4	9.9
Long acting insulins	**2.26**	**100.0**	**-4.5**	**-1.4**	**4.7**	**100.0**	**-5.5**	**-14.0**	**1.31**	**1.0**	**14.6**
Biosimilar	0.20	9.1	-15.0	3.1	0.7	14.0	-14.6	12.4	0.85	-0.5	-8.3
Originator	0.59	26.0	-13.9	-53.3	1.7	35.5	-12.1	-49.0	0.96	-2.0	-8.5
Other insulin glargine	0.71	31.3	11.6	707.8	0.7	15.8	11.8	718.7	2.61	-0.2	-1.3
Other long acting insulins	0.76	33.6	-6.2	1.4	1.6	34.7	-0.5	7.3	1.27	-5.8	-5.5
Rituximab	**0.74**	**100.0**	**-32.5**	**-76.1**	**0.4**	**100.0**	**-1.0**	**-20.0**	**4.56**	**-31.8**	**-70.1**
Biosimilar IV	0.50	68.4	-35.3	527.1	0.4	80.6	6.0	2,119.0	3.87	-39.0	-71.7
Originator IV	0.02	2.5	-63.7	-99.2	0.0	1.1	-54.1	-98.5	10.18	-20.9	-48.5
Originator SC	0.21	29.2	-18.3	-70.5	0.1	18.3	-19.0	-63.7	7.25	0.8	-18.8
Somatropin	**1.15**	**100.0**	**-4.0**	**-18.4**	**0.3**	**100.0**	**2.5**	**5.9**	**11.42**	**-6.3**	**-22.9**
Biosimilar	0.25	21.7	-0.6	41.5	0.1	28.5	9.8	73.3	8.71	-9.4	-18.3
Originator	0.16	14.0	-8.3	-41.3	0.0	10.0	-7.1	-34.6	15.89	-1.3	-10.3
Other somatropin	0.74	64.3	-4.1	-22.8	0.2	61.5	1.1	-1.9	11.94	-5.2	-21.4

continued

Table 2.1.12 – *continued*

Group and subgroup	Expenditure *per capita*	Incidence %	Δ % 22-21	Δ % 22-17	DDD/1000 inhab. per day	Incidence %	Δ % 22-21	Δ % 22-17	Average cost	Δ % 22-21	Δ % 22-17
Teriparatide	**0.09**	**100.0**	**-4.4**	**-64.7**	**0.0**	**100.0**	**21.1**	**-30.2**	**6.38**	**-21.0**	**-49.4**
Biosimilar	0.08	89.6	46.6	—	0.0	93.9	60.5	—	6.09	-8.7	—
Originator	0.01	10.4	-76.1	-96.3	0.0	6.1	-74.5	-95.7	10.80	-6.2	-14.4
Trastuzumab	**0.81**	**100.0**	**-27.1**	**-82.4**	**0.2**	**100.0**	**-3.4**	**-20.0**	**13.28**	**-24.5**	**-78.0**
Biosimilar IV	0.46	56.1	-24.7	—	0.1	75.5	3.9	—	9.87	-27.5	—
Originator IV	0.02	2.0	-75.4	-99.3	0.0	0.6	-71.5	-98.7	44.34	-13.8	-46.5
Originator SC	0.34	41.9	-22.9	-84.7	0.0	23.9	-16.9	-69.1	23.25	-7.3	-50.3
Total	**16.58**	**100.0**	**-8.4**	**-51.5**	**19.0**	**100.0**	**0.3**	**1.4**	**2.40**	**-8.7**	**-52.2**
Biosimilar	7.25	43.7	-2.5	176.4	11.1	58.4	8.8	337.8	1.79	-10.3	-36.9
Originator	3.44	20.8	-27.7	-86.2	3.5	18.5	-17.5	-69.5	2.69	-12.4	-54.6
Other	5.89	35.5	-0.2	-11.9	4.4	23.2	-2.0	-6.1	3.67	1.9	-6.1

Figure 2.1.14 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): anti-TNF alpha

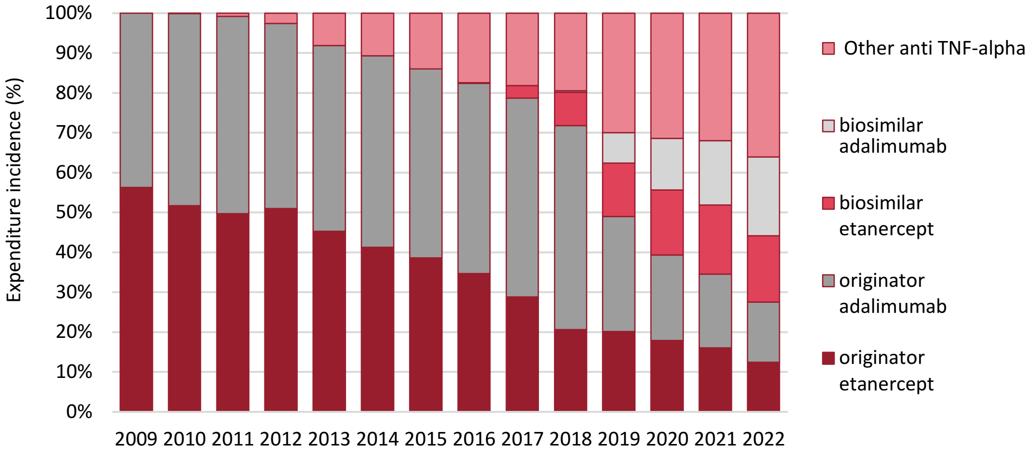


Figure 2.1.15 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category: bevacizumab

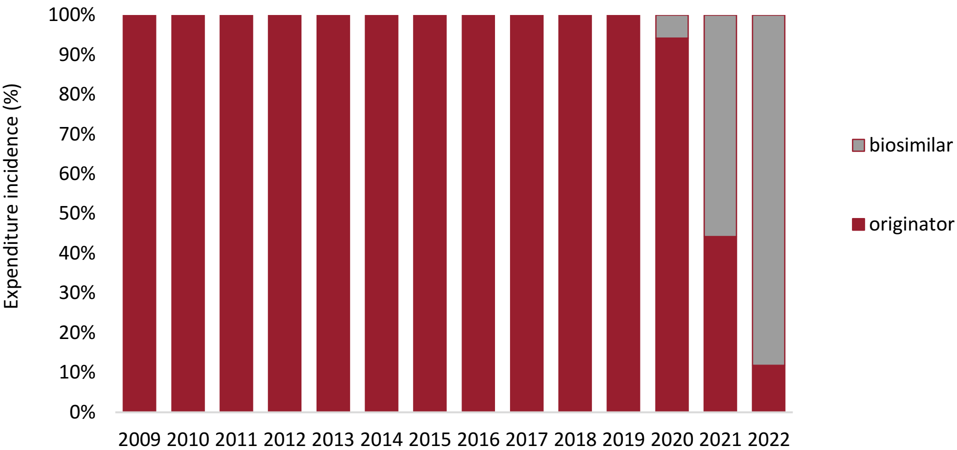


Figure 2.1.16 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): low molecular weight heparins

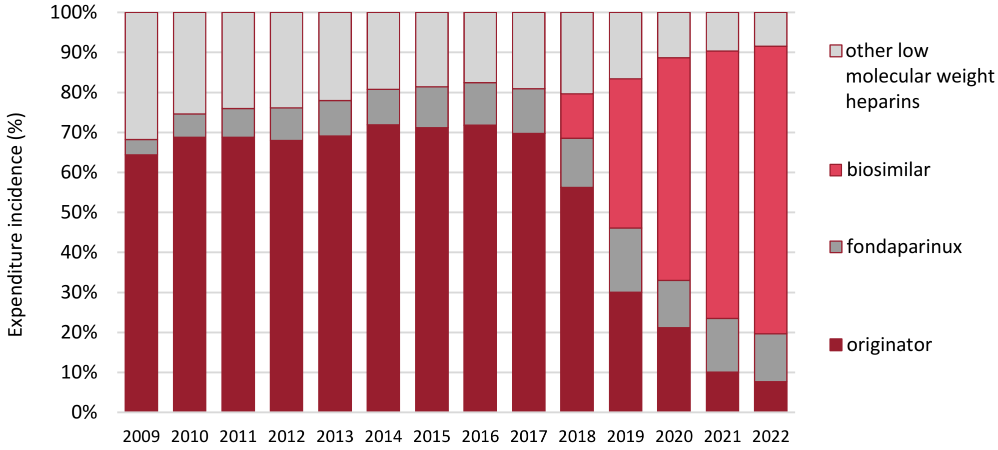


Figure 2.1.17 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): epoetin

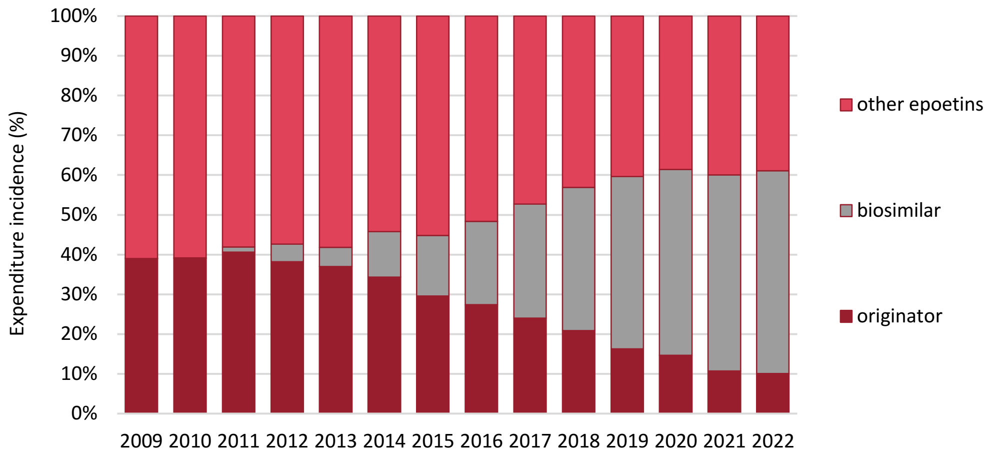


Figure 2.1.18 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): growth factors

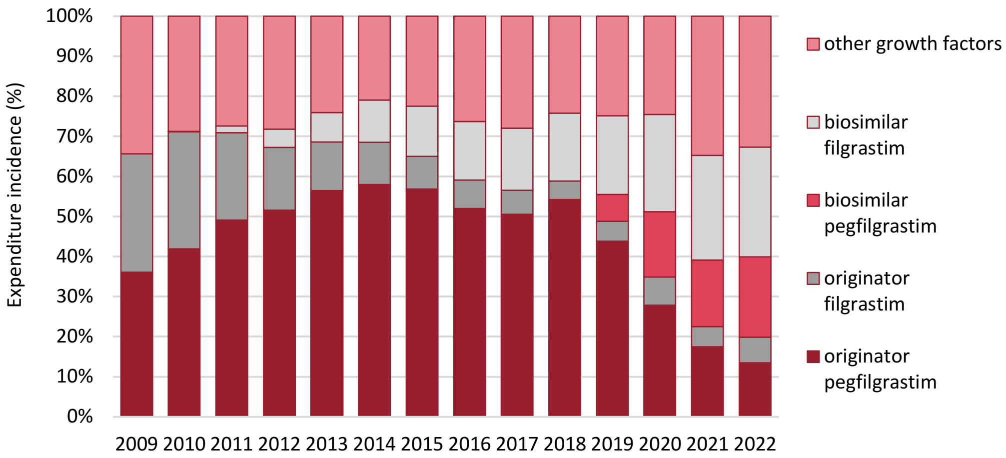


Figure 2.1.19 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): follitropin

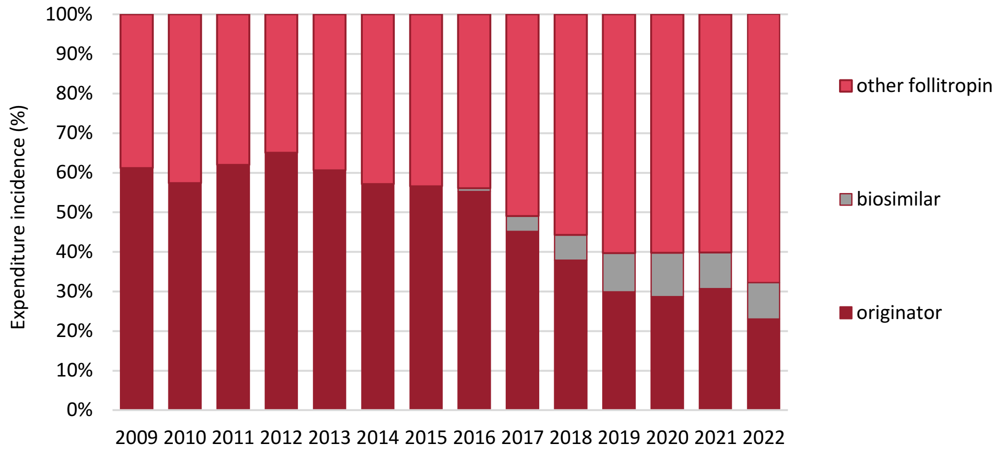


Figure 2.1.20 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): fast acting insulins

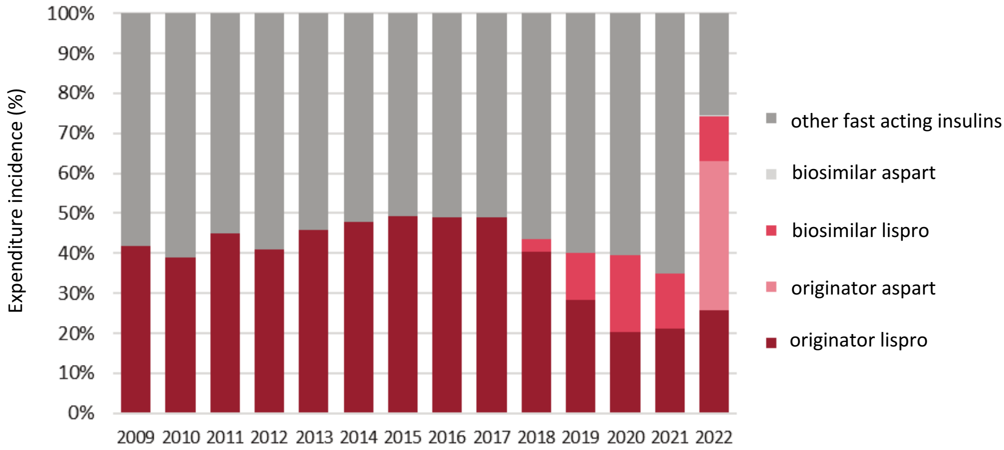


Figure 2.1.21 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): long acting insulins

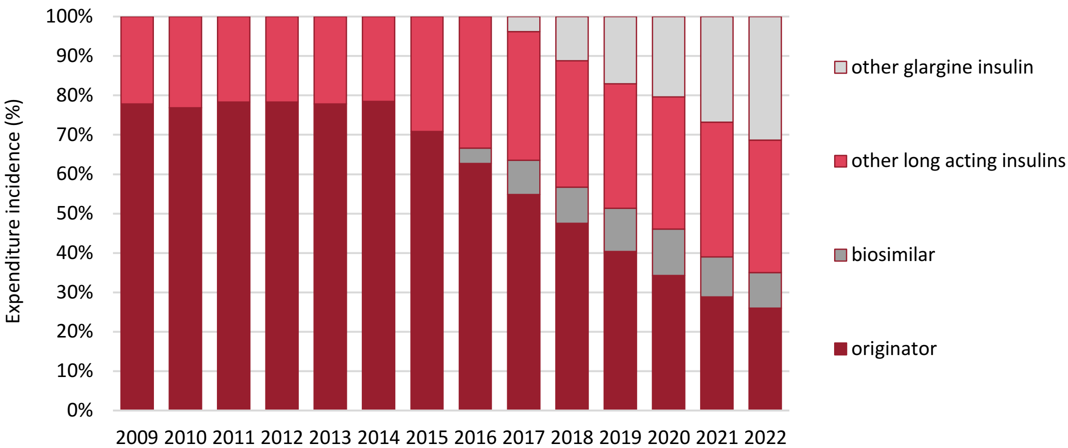


Figure 2.1.22 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category (ATC 4th level): combined (long/intermediate acting with fast acting) insulins

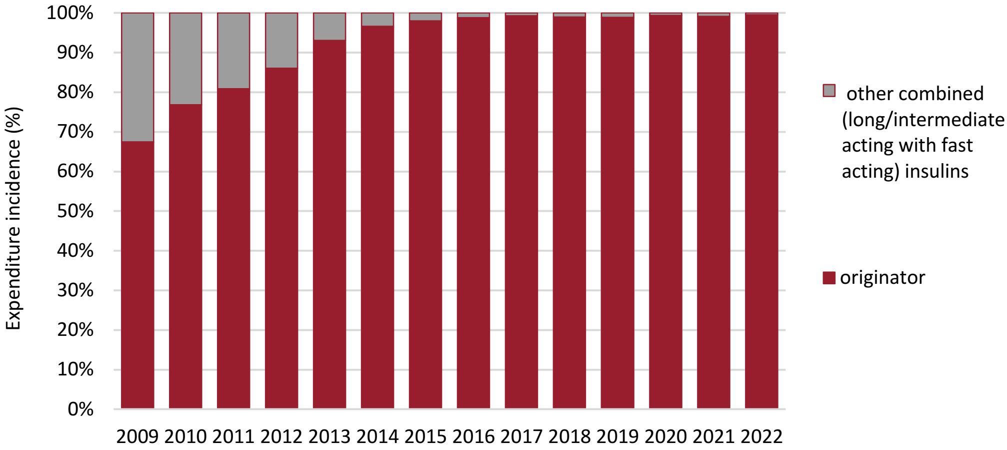


Figure 2.1.23 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category: rituximab

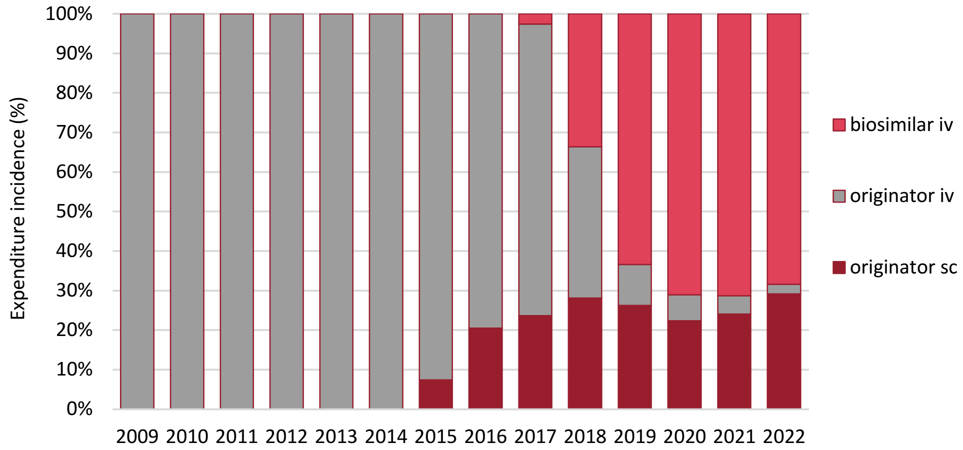


Figure 2.1.24 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category: somatropin

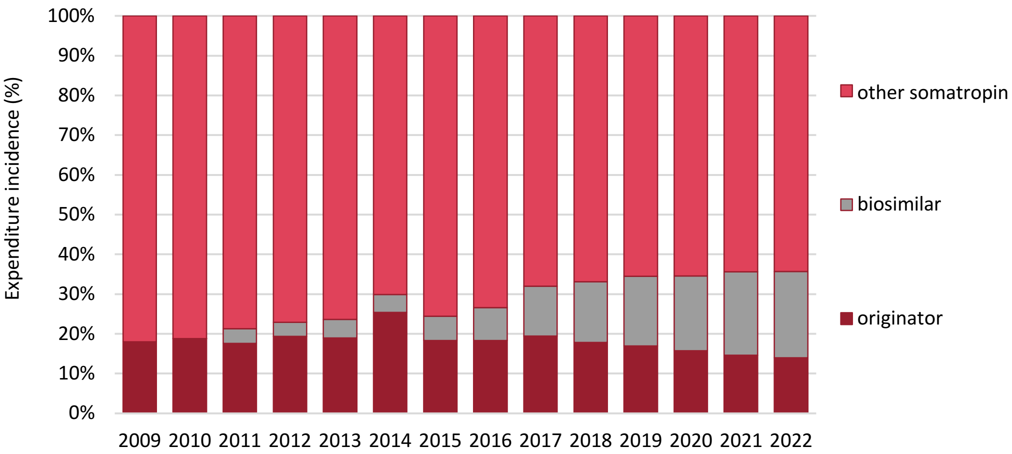


Figure 2.1.25 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category: teriparatide

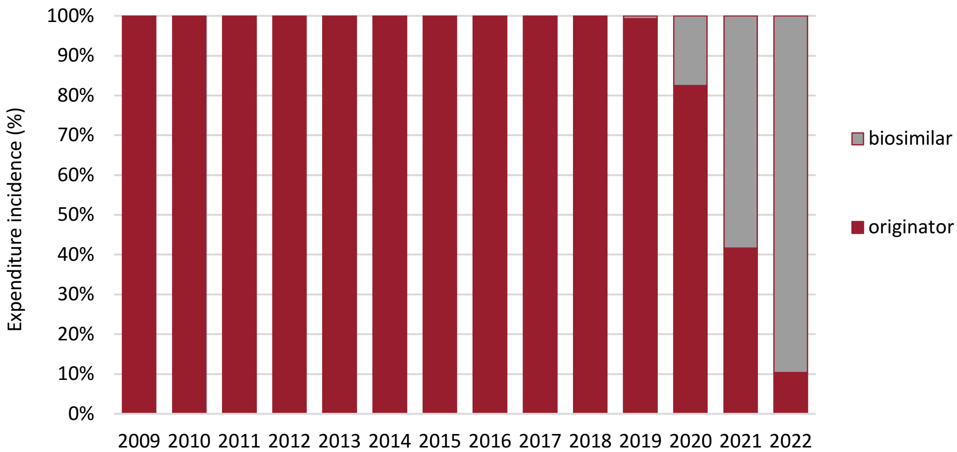


Figure 2.1.26 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category: trastuzumab

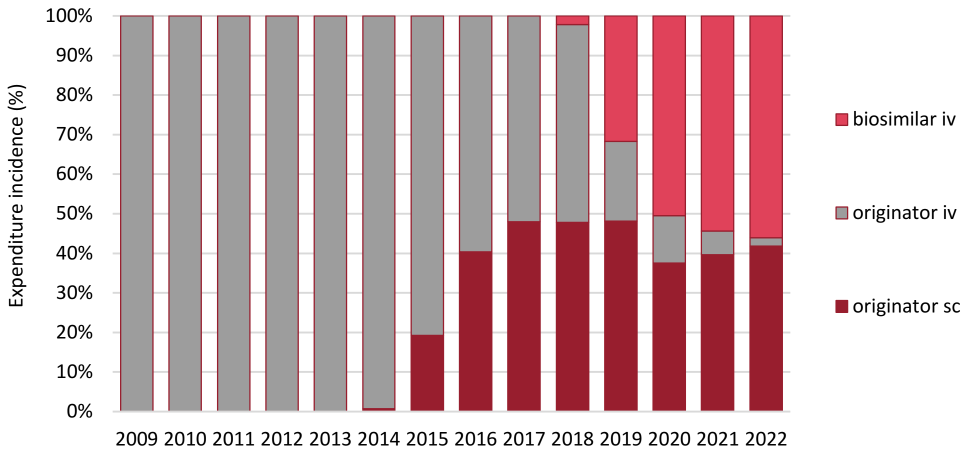


Figure 2.1.27 Incidence (%) of expenditure on biosimilar medicines compared to total expenditure for the therapeutic category: infliximab

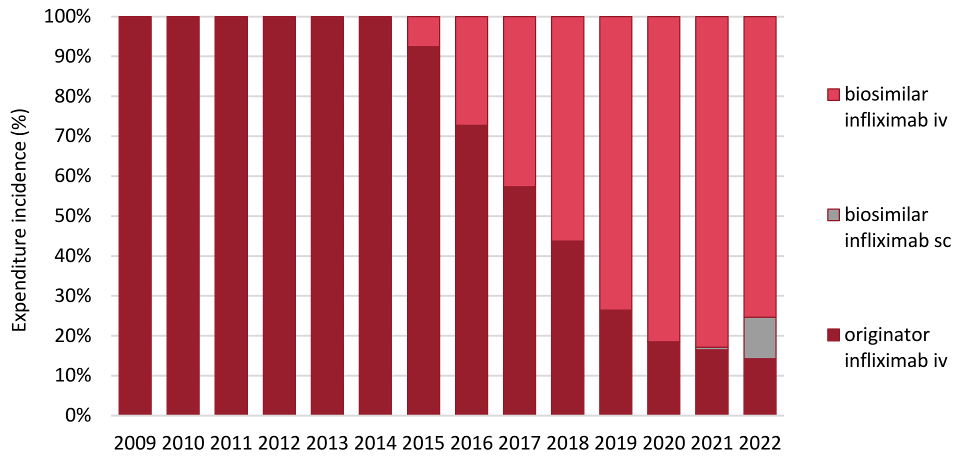


Figure 2.1.28 Consumption (DDD/1000 inhab. per day) of biosimilar vs originator medicines compared to the national average (year 2022)

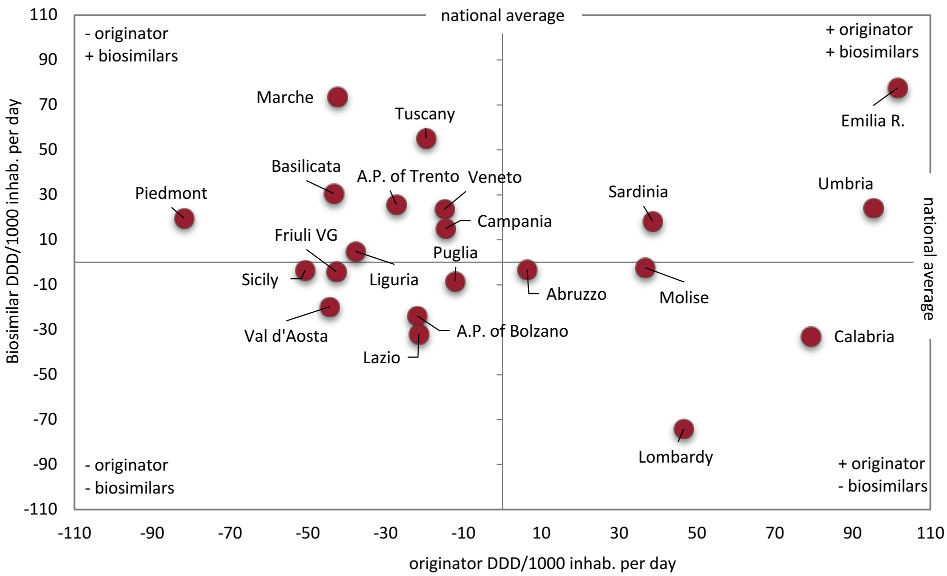


Figure 2.1.29 Regional variability in biosimilar medicines consumption and average DDD cost of patent-expired biologics in 2022 (% deviations from national average)

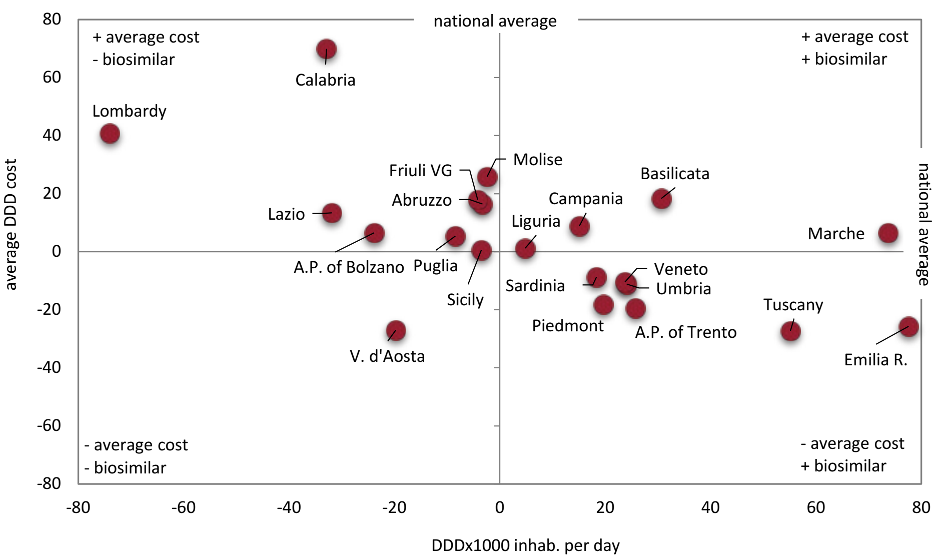
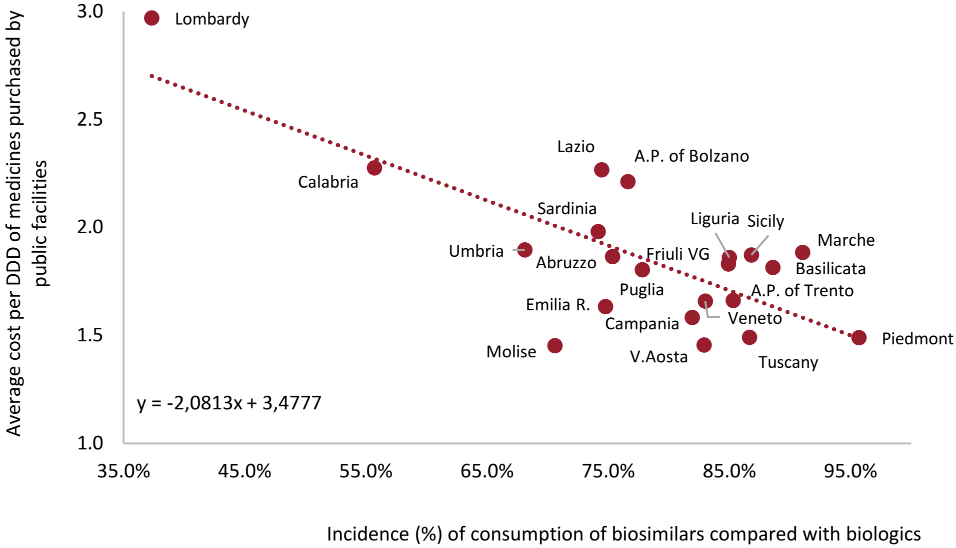


Figure 2.1.30 Correlation analysis between the incidence of biosimilar consumption on patent-expired biologics and average DDD cost in direct purchases (year 2022)



2.6 Out-of-pocket medicines consumption

In 2022, expenditure on class C medicines exceeded €6.5 billion, an increase of 6.9% compared to 2021; of this, 54% (€3.5 billion) related to prescription medicines and 46% (€2.99 billion) to self-medication medicines (SOP and OTC), including those supplied in shops (Table 1.1.1).
The 1.6% year-on-year increase in expenditure on class C prescription medicines was mainly due to an increase in quantities (+13.0%), while prices remained stable (price effect +0.1%, mix effect: +0.4%) (Figure 2.6.1). Among the top 20 highest-spending class C therapeutic categories with prescription in 2022 (Table 2.6.1), six belong to ATC N, half of which are benzodiazepine derivatives (both anxiolytic and hypnotic-sedating) and benzodiazepine analogues, which therefore present themselves as the highest-purchasing category with 17% of expenditure and 22% of prescription class C DDDs. Benzodiazepine derivatives with anxiolytic activity are the category with the highest expenditure with € 379.3 million, and with the highest consumption with 26.1 DDD per 1000 inhabitants per day, although both indicators are decreasing compared to 2021 (expenditure -5.4%, consumption -4.4%) (Table 2.6.1). The second category with the highest expenditure is anilides, with €272.6 million or 7.7% of total expenditure, showing an increase in consumption (+6.7%) and a decrease in expenditure compared to 2021 (-14.6%). Other categories with an expenditure level of more than €200 million are medicines used in erectile dysfunction, which show an increase in consumption (+9.5%) and expenditure (+1.2%) compared to 2021, and fixed oestrogen-progestin combinations (+0.7% expenditure and -0.5% doses). Significant adherence to the influenza vaccination campaign in the 2022-2023 season led to a 6.3% increase in expenditure, compared to 2021, for influenza vaccines (for a total expenditure of EUR 79.6 million) purchased in pharmacies by citizens. Among the top 20 therapeutic categories with the highest consumption, we find non-steroidal anti-inflammatory drugs with 38.8 doses dispensed per 1000 inhabitants per day, followed by vitamin B12 with 29.1 DDD, anxiolytics with 26.1 DDD and hypnotics and sedatives with 21.6 DDD per 1000 inhabitants per day (Table 2.6.2).
Among the top 10 categories with the highest expenditure, it can be observed that influenza vaccines are those with the highest cost per DDD, although decreasing in the period 2021-2022, followed by medicines used in erectile dysfunction, which instead present a decreasing trend in the period 2018-2020, to then remain stable in the following years (Figure 2.6.2).
The top six active ingredients with the highest expenditure (Table 2.6. 3) remain unchanged from the previous year: paracetamol, with an expenditure of €260 million, equal to 7.4% of the total class C prescription, ranks first although it shows a decrease in expenditure of 16% accompanied, however, by an increase in consumption of 5.6% compared to 2021; this drug, mainly used in paediatric settings for its analgesic and antipyretic action, has been included in protocols for the home treatment of patients with COVID-19 in the event of fever or joint or muscle pain. These are followed by two benzodiazepines (alprazolam: € 132.7 million and lorazepam: € 108.8 million), although both showed a slight reduction in consumption, and two phospho-diesterase type 5 (PDE5I) inhibitors (tadalafil: € 120.2 million and sildenafil: € 94.8 million) used in the treatment of erectile dysfunction, whose expenditure increased by 5.1% and decreased by 1.0% respectively. In addition to alprazolam and lorazepam, among

the most expensive substances there are several benzodiazepines placed as follows: 7th zolpidem, 9th lormetazepan, 13th delorazepam, 14th bromazepam, and 17th triazolam. There was a marked increase in the purchase of acetylcysteine-based specialities, recording, for this molecule, an increase in expenditure and consumption of over 60% compared to last year (expenditure +71.4%, consumption +67.6%); specialities containing *Clostridium botulinum* toxin type A also recorded an increase in expenditure of 10.3%. Among the top 30 active class C prescription ingredients with the highest consumption (Table 2.6.4), we find diclofenac in ophthalmic formulation in first place, with 37.7 DDD per 1000 population per day and an increase over the previous year of more than 200%, followed by cyanocobalamin with 28.8 DDD per 1000 population per day, a decrease of -4.3%, and three benzodiazepines (lormetazepam, alprazolam and lorazepam). The most important increases in consumption compared to 2021 are for acetylcysteine (+67.6%), cholecalciferol (+16.7%), mometasone in an inhaled formulation (+23.5%), bilastine (+14.3%) and tobramycin (+25%). Among self-medication medicines, propionic acid derivatives account for 12.3% of total expenditure and are worth EUR 364 million, up 36.5% compared to 2021 (Table 2.6.5). These are also among the top 20 most consumed self-medication categories, together with sympathomimetics and non-steroidal anti-inflammatory drugs for topical use (Table 2.6.6). Topical non-steroidal anti-inflammatories are the second highest spending category (233.7 million euro, -7.1% compared to 2021), followed by anilides with 221.8 million euro. Mucolytics, other cough suppressants, other substances for local oral treatment and sympathomimetics are the categories that show the most significant increases in both expenditure and consumption (Table 2.6.5). Ibuprofen is the molecule with the highest expenditure at €252.8 million, a sharp increase over 2021 (+52.5%), together with diclofenac, which has an expenditure of €183.8 million, decreasing by 4.1%. At the same time, ibuprofen recorded an important growth in consumption (+51.9%) probably due to the fact that it was prescribed as an antipyretic and anti-inflammatory in the home treatment of Sars-Cov-2 infection (Table 2.6.7). On the consumption side, we find diclofenac, naphazoline and flurbiprofen in the top three positions. While diclofenac shows a reduction in consumption compared with the previous year of 9.8%, naphazoline and flurbiprofen show a strong increase, of 32.1% and 85.7% respectively (Table 2.6.8). All the Regions record an increase in the consumption of class C prescription medicines, and consequently, an increase in the volume of expenditure, with the exception of Campania, Sicily and Sardinia in which a reduction in expenditure is recorded compared to last year; while for self-medication medicines in all the Regions an upward trend is observed for both expenditure and consumption. At regional level there is a moderate variability in expenditure and consumption for self-medication medicines and for class C prescription medicines; this trend can be explained mainly by differences in income between the Regions but also by a different attitude of doctors and patients in using these medicines. For prescription medicines, the North and the Centre spend about 10% more than in the South. The greatest increases in the consumption of class C medicines were recorded in Umbria (+100%) and Veneto (+28.6%), while for self-medication medicines, they were observed in the A.P. of Bolzano (+23.5%) and Trento (+22%) (Table and Figure 2.6.9).

The widest differences between the Regions emerge from the analysis of the private purchase of band A pharmaceuticals, with Valle d'Aosta holding the record, with a *per capita* expenditure of €76.40, more than 8 times higher than Basilicata (€9.70 *per capita*) and, in general, with the expenditure of the Regions of the Centre (€35.40 *per capita*), which grew during the last year by 60%, greater than that of the Regions of the North and the South (€29.00 and €29.80 respectively) (Table and Figure 2. 6.10). The Valle d'Aosta, Abruzzo, Sardinia, A.P. of Trento and Latium Regions record a significant (>100%) increase in *per capita* expenditure with respect to 2021. Overall, in Italy there is an increase in the expenditure of band A medicines purchased privately (+19.5% in expenditure) accompanied by a weak reduction in consumption (-1.8%) (Table 2.6.10). The first therapeutic categories of class A purchased by the citizen, with the highest expenditure are proton pump inhibitors with over 145 million euros, propionic acid derivatives with 129 million euros, the combination of penicillins including beta-lactamase inhibitors with 65 million euros and vitamin D and analogues with 62.3 million, representing over a fifth (22.4%) of the total expenditure of class A medicines purchased privately by the citizen (Table 2.6.11). Three of these are also among the therapeutic class A categories purchased by the citizen with the highest consumption: vitamin D and analogues (54.1 DDD per 1000 inhabitants per day), propionic acid derivatives (18 DDD) and proton pump inhibitors (16.2 DDD), followed by the category of platelet aggregation inhibitors, excluding heparin (23.5 DDD per 1000 inhabitants per day) (Table 2.6.12). Among the class A active ingredients purchased privately by the citizen, ibuprofen, the combination amoxicillin/clavulanic acid, cholecalciferol, pantoprazole and ketoprofen rank at the top with an expenditure of more than EUR 50 million. Ketoprofen (77.8%) and ibuprofen (70.8%) are the substances with the highest percentage of private expenditure, calculated on the total expenditure on the molecule. As for pump inhibitors, in addition to the aforementioned pantoprazole, among the top 20 active ingredients at the highest expense, there are also esomeprazole, lansoprazole and omeprazole, whose share of private expenditure is around 17% (Table 2.6.13). The percentage of private purchase for the combination amoxicillin/clavulanic acid, which reaches almost one third of the expenditure of the active substance, could be a wake-up call suggesting an inappropriate use of antibiotics. Among the first 30 class A active ingredients purchased privately by the citizen, those with the highest consumption are cholecalciferol with 53.9 DDD, acetylsalicylic acid with 21.6 DDD, up by about 30 per cent compared to last year, and ketoprofen with 9.9 DDD per 1000 population days (Table 2.6.14).

A closer look at the breakdown of the consumption of class A medicines by price range shows that approximately two thirds of private purchases relate to medicines with a price below EUR 6 (61.3%) and only 14.8% relate to medicines with a price above EUR 10. There is, however, a wide regional variability in the distribution of consumption, mainly in the price range above EUR 10, which peaks in the central regions with 17.2% of consumption. The consumption of medicines with a price below EUR 6 accounted for about 65% of consumption in the southern regions (Table 2.6.15).

In 2022, expenditure on self-medication medicines dispensed by commercial shops amounted to €326.3 million, increasing by 13.7% over the previous year. The highest *per capita* expenditure is recorded in Sardinia (EUR 8.7) and Campania (EUR 7.8), while in the A.P. of Bolzano and Sicily the lowest values are observed (EUR 0.80 and EUR 2.70 respectively). There are no specific differences in expenditure between different geographical areas, ranging from EUR 5.00 *per capita* in Centre to EUR 5.70 in the North (Table 2.6.16). In terms of expenditure, the first three medicines that are most sold in retailing pharmacies are ibuprofen (EUR 0.45 *per capita*), diclofenac (EUR 0.34) and paracetamol (EUR 0.31) representing around 20% of total spending (Table 2.6.17). As far as consumption is concerned, among the first active ingredients most frequently supplied by commercial shops, we find naphazoline, as a nasal decongestant (1.7 DDD per 1000 inhabitants per day), diclofenac (1.2 DDD per 1000 inhabitants per day) and glycerol (0.9 DDD per 1000 inhabitants per day) (Table 2.6.18).

Figure 2.6.1 Trend of local expenditure on Class C medicines with prescription in the period 2012-2022: consumption, price and mix effect

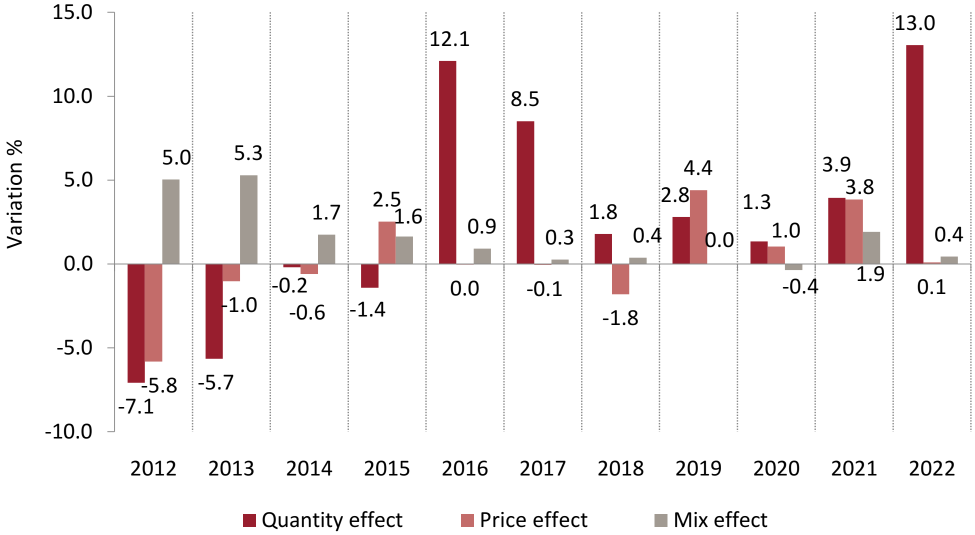
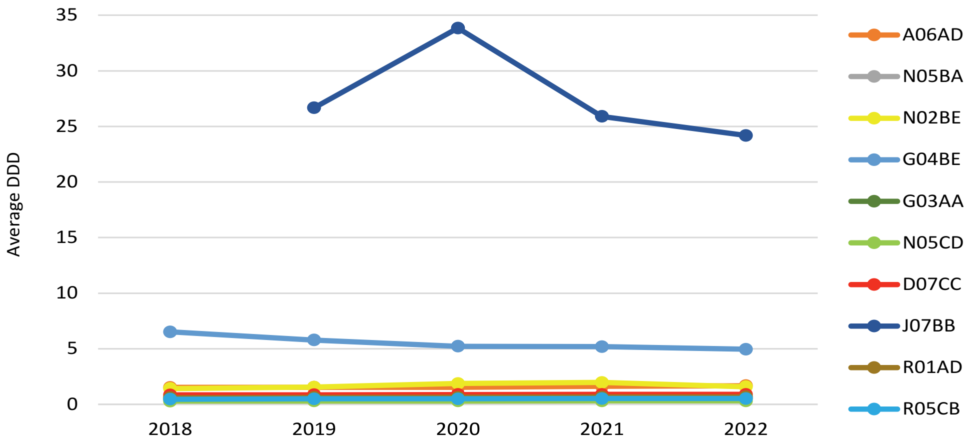


Table 2.6.1 First 20 spending class C therapeutic categories with prescription in 2022: comparison 2022-2021

ATC I	Therapeutic category	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	%*	Δ % 22-21
N	Benzodiazepine derivatives (anxiolytics)	26.1	-4.4	379.3	10.8	-5.4
N	Anilides	8.0	6.7	272.6	7.7	-14.6
G	Medications for erectile dysfunction	2.3	9.5	240.6	6.8	1.2
G	Fixed-dose oestrogen/progestogen combinations	19.8	-0.5	215.6	6.1	0.7
N	Benzodiazepine derivatives (hypnotics and sedatives)	21.6	1.9	144.3	4.1	0.4
D	Active corticosteroids, in combination with antibiotics	4.9	0.0	94.1	2.7	0.0
J	Influenza vaccines	0.2	100.0	79.6	2.3	6.3
R	Corticosteroids	5.5	14.6	79.5	2.3	15.6
R	Mucolytics	7.0	66.7	78.6	2.2	65.8
A	Osmotic laxatives	2.1	-4.5	76.9	2.2	1.2
N	Benzodiazepine analogues	6.0	3.4	74.5	2.1	1.6
S	Antibacterial-corticosteroid combinations	3.2	3.2	73.6	2.1	2.4
N	Other psychostimulants and nootropics	1.4	7.7	66.8	1.9	4.7
M	Other centrally acting muscle relaxants	1.2	0.0	66.5	1.9	-3.9
M	Other muscle relaxants with peripheral action	0.0		64.6	1.8	10.8
B	Heparins	2.3	-4.2	53.4	1.5	-4.8
N	Antivertigo preparations	2.8	-3.4	51.3	1.5	-3.2
G	Estrogen-progestogen, sequential combinations	3.6	2.9	46.8	1.3	4.7
M	Biphosphonates	0.0		43.3	1.2	-4.2
S	Antibiotics	2.5	19.0	37.8	1.1	18.9
	Total top 20	**120.5**	**3.3**	**2,239.6**	**63.5**	**-0.2**
	Total	**241.7**	**13.8**	**3,525.3**	**100.0**	**1.7**

* Calculated on overall expenditure

Figure 2.6.2 Annual trend in average DDD cost of highest-spending class C therapeutic categories with prescription - top 10 (2018-2022)



A06AD – Osmotic laxatives	N05BA – Benzodiazepine derivatives (anxiolytics)	N02BE – Anilides
G04BE – Medications used for erectile dysfunction	G03AA – Fixed-dose oestrogen/progestogen combinations	N05CD – Benzodiazepine derivatives (hypnotics and sedatives)
D07CC – Active corticosteroids, in combination with antibiotics	J07BB – Influenza vaccines	R01AD – Corticosteroids
R05CB - Mucolytics		

Table 2.6.2 Top 20 class C therapeutic categories with prescription with the highest consumption in 2022: comparison 2022-2021

ATC I	Therapeutic category	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	%*	Δ % 22-21
S	Nonsteroidal anti-inflammatory medicines	38.8	196.2	33.1	0.9	0.9
B	Vitamin B12 (cyanocobalamin and derivatives)	29.1	-4.3	6.1	0.2	-6.2
N	Benzodiazepine derivatives (anxiolytics)	26.1	-4.4	379.3	10.8	-5.4
N	Benzodiazepine derivatives (hypnotics and sedatives)	21.6	1.9	144.3	4.1	0.4
G	Fixed-dose oestrogen/progestogen combinations	19.8	-0.5	215.6	6.1	0.7
N	Anilides	8.0	6.7	272.6	7.7	-14.6
R	Mucolytics	7.0	66.7	78.6	2.2	65.8
N	Benzodiazepine analogues	6.0	3.4	74.5	2.1	1.6
R	Corticosteroids	5.5	14.6	79.5	2.3	15.6
D	Active corticosteroids, in combination with antibiotics	4.9	0.0	94.1	2.7	0.0
G	Estrogen-progestogen, sequential combinations	3.6	2.9	46.8	1.3	4.7
S	Corticosteroid and antimicrobial combinations	3.2	3.2	73.6	2.1	2.4
D	Other antibiotics for topical use	3.2	0.0	36.4	1.0	-1.4
G	Intrauterine contraceptives	3.0	-3.2	8.1	0.2	-4.7
D	Corticosteroids, active (group III)	2.9	-6.5	30.6	0.9	-7.3
N	Antivertigo preparations	2.8	-3.4	51.3	1.5	-3.2
A	Vitamin D and analogues	2.8	16.7	6.5	0.2	20.4
G	Progestinic	2.6	13.0	25.3	0.7	16.1
S	Antibiotics	2.5	19.0	37.8	1.1	18.9
G	Intrauterine contraceptives	2.4	-4.0	32.9	0.9	-2.7
	Total top 20	**195.7**	**17.0**	**1,727.0**	**49.0**	**-0.8**
	Total	**241.7**	**13.8**	**3,525.3**	**100.0**	**1.7**

* calculated on overall consumption

Table 2.6.3 Top 30 class C active ingredients with prescription with the highest expenditure in 2022: comparison 2022-2021

ATC I	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	%*	Δ % 22-21	Average DDD cost
N	paracetamol	7.6	5.6	260.0	7.4	-16.0	1.59
N	alprazolam	10.3	-1.0	132.7	3.8	-1.8	0.60
G	tadalafil	1.3	8.3	120.2	3.4	5.1	4.22
N	lorazepam	9.7	-6.7	108.8	3.1	-8.1	0.52
G	sildenafil	0.8	0.0	94.8	2.7	-1.0	5.68
D	gentamicin/betamethasone	4.2	0.0	78.6	2.2	-0.3	0.87
N	zolpidem	5.8	3.6	71.7	2.0	1.6	0.58
R	acetylcysteine	6.2	67.6	69.6	2.0	71.4	0.52
N	lormetazepam	15.6	2.6	67.9	1.9	3.2	0.20
G	drospirenone/ethinylestradiol	5.5	0.0	67.7	1.9	-1.5	0.58
M	*Clostridium botulinum* type A toxin	0.0		64.3	1.8	10.3	198.26
A	macrogol 3350/ sodium chloride/ sodiumbi carbonate/ potassium chloride	1.8	-5.3	49.7	1.4	-2.0	1.26
N	delorazepam	2.5	-3.8	47.0	1.3	-3.7	0.87
N	bromazepam	1.3	-7.1	47.0	1.3	-6.6	1.64
N	levo-acetylcarnitine	0.9	0.0	47.0	1.3	2.2	2.40
G	dienogest/ethinylestradiol	4.0	0.0	44.9	1.3	2.0	0.52
N	triazolam	3.7	0.0	44.7	1.3	-1.8	0.57
M	thiocolchicoside	0.5	0.0	41.9	1.2	-2.8	3.67
G	dienogest/estradiol	2.9	7.4	41.8	1.2	8.0	0.66
J	inactivated, split virus tetravalent influenza vaccine	0.1	0.0	39.5	1.1	25.4	19.08
N	betahistine	2.2	-4.3	36.2	1.0	-3.5	0.76
R	mometasone	2.1	23.5	33.9	1.0	24.6	0.73
J	tetravalent influenza vaccine (surface antigen, inactivated), adjuvanted	0.0	-100.0	33.9	1.0	-8.6	34.00
G	etonogestrel/ethinylestradiol	2.4	-4.0	32.9	0.9	-2.7	0.63
B	mesoglycan	1.6	0.0	32.6	0.9	-5.0	0.97
N	choline alfoscerate	0.3	0.0	30.5	0.9	2.0	4.56
J	nirmatrelvir/ritonavir	0.0		29.2	0.8		264.00
M	clodronic acid	0.0		28.9	0.8	-6.5	63.00
G	levonorgestrel/ethinylestradiol	2.7	-3.6	26.9	0.8	-6.3	0.47
A	liraglutide	0.2	0.0	26.4	0.7	38.9	5.05
	Total top 30	**96.5**	**2.6**	**1,851.1**	**52.5**	**-2.0**	**0.89**
	Total	**241.7**	**13.8**	**3,525.3**	**100.0**	**1.7**	**0.68**

* Calculated on overall expenditure

Table 2.6.4 Top 30 class C active ingredients with prescription with the highest consumption in 2022: comparison 2022-2021

ATC I	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	%*	Δ % 22-21	Average DDD cost
S	diclofenac	37.7	214.2	6.8	0.2	3.0	0.01
B	cyanocobalamin	28.8	-4.3	4.2	0.1	-4.5	0.01
N	lormetazepam	15.6	2.6	67.9	1.9	3.2	0.20
N	alprazolam	10.3	-1.0	132.7	3.8	-1.8	0.60
N	lorazepam	9.7	-6.7	108.8	3.1	-8.1	0.52
N	paracetamol	7.6	5.6	260.0	7.4	-16.0	1.59
R	acetylcysteine	6.2	67.6	69.6	2.0	71.4	0.52
N	zolpidem	5.8	3.6	71.7	2.0	1.6	0.58
G	drospirenone/ethinylestradiol	5.5	0.0	67.7	1.9	-1.5	0.58
D	gentamicin/betamethasone	4.2	0.0	78.6	2.2	-0.3	0.87
G	dienogest/ethinylestradiol	4.0	0.0	44.9	1.3	2.0	0.52
N	triazolam	3.7	0.0	44.7	1.3	-1.8	0.57
G	gestodene/ethinylestradiol	3.4	-10.5	22.9	0.6	-9.8	0.31
G	levonorgestrel/	3.0	-3.2	8.1	0.2	-4.7	0.13
G	dienogest/estradiol	2.9	7.4	41.8	1.2	8.0	0.66
A	cholecalciferol	2.8	16.7	6.5	0.2	22.6	0.11
G	levonorgestrel/ethinylestradiol	2.7	-3.6	26.9	0.8	-6.3	0.47
D	gentamicin	2.7	0.0	23.6	0.7	-0.4	0.41
N	delorazepam	2.5	-3.8	47.0	1.3	-3.7	0.87
G	etonogestrel/ethinylestradiol	2.4	-4.0	32.9	0.9	-2.7	0.63
N	betahistine	2.2	-4.3	36.2	1.0	-3.5	0.76
R	mometasone	2.1	23.5	33.9	1.0	24.6	0.73
D	clortetracyclines	1.9	-5.0	6.9	0.2	-5.5	0.17
A	macrogol 3350/sodium chloride/sodium bicarbonate/potassium chloride	1.8	-5.3	49.7	1.4	-2.0	1.26
G	desogestrel	1.8	0.0	16.7	0.5	0.6	0.43
R	budesonide	1.8	5.9	9.3	0.3	4.5	0.24
G	nomegestrol/estradiol	1.6	-5.9	23.0	0.7	-1.3	0.65
R	bilastine	1.6	14.3	19.1	0.5	9.8	0.56
B	mesoglycan	1.6	0.0	32.6	0.9	-5.0	0.97
S	tobramycin	1.5	25.0	24.5	0.7	27.6	0.74
	Total top 30	**179.4**	**17.6**	**1,419.1**	**40.3**	**-4.3**	**0.37**
	Total	**241.7**	**13.8**	**3,525.3**	**100.0**	**1.7**	**0.68**

* calculated on overall consumption

Table 2.6.5 Top 20 self-medication therapeutic categories (SOP and OTC) with the highest expenditure in 2022: comparison 2022-2021

ATC I	Therapeutic category	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	%*	Δ % 22-21
M	Propionic acid derivatives	7.6	26.7	364.0	12.3	36.5
M	Topical nonsteroidal anti-inflammatory medicines	13.6	-9.9	233.7	7.9	-7.1
N	Anilides	5.1	34.2	221.8	7.5	45.6
A	Other agents for local oral treatment	7.0	62.8	162.3	5.5	74.1
A	Antidiarrheal microorganisms	2.5	4.2	146.0	4.9	15.2
R	Mucolytics	5.6	133.3	126.2	4.3	68.0
C	Bioflavonoids	5.5	7.8	108.3	3.7	11.8
R	Sympathomimetics, non-associated	14.3	27.7	87.8	3.0	0.2
N	Salicylic acid and derivatives	1.7	30.8	79.0	2.7	33.2
R	Antiseptics	1.3	44.4	72.2	2.4	60.2
D	Imidazole and triazole derivatives	3.0	-6.3	66.0	2.2	-52.6
A	Enemas	2.2	-8.3	57.5	1.9	-1.8
R	Other cough suppressants	2.6	188.9	53.9	1.8	198.2
G	Imidazole derivatives	1.5	0.0	53.9	1.8	5.0
A	Contact laxatives	4.1	-6.8	48.8	1.6	-3.0
R	Sympathomimetics	0.4	100.0	46.6	1.6	99.0
A	Antipropulsives	0.4	0.0	41.7	1.4	21.0
C	Corticosteroids	2.2	-4.3	38.1	1.3	1.8
S	Sympathomimetics used as decongestants	6.6	-21.4	37.6	1.3	-10.7
A	Other anti-peptic ulcer and gastroesophageal reflux disease medicines (GERD)	0.6	20.0	36.8	1.2	25.9
	Total top 20	**87.8**	**14.5**	**2,082.2**	**70.3**	**19.8**
	Total	**137.6**	**8.9**	**2,962.3**	**100.0**	**14.1**

*Calculated on overall expenditure

Table 2.6.6 Top 20 self-medication therapeutic categories (SOP and OTC) with the highest consumption in 2022: comparison 2022-2021

ATC I	Therapeutic category	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	%*	Δ % 22-21
R	Sympathomimetics, non-associated	14.3	27.7	88	3.0	0.2
M	Topical nonsteroidal anti-inflammatory medicines	13.6	-9.9	234	7.9	-7.1
M	Propionic acid derivatives	7.6	26.7	364	12.3	36.5
A	Other agents for local oral treatment	7.0	62.8	162	5.5	74.1
S	Sympathomimetics used as decongestants	6.6	-21.4	38	1.3	-10.7
R	Mucolytics	5.6	133.3	126	4.3	68.0
C	Bioflavonoids	5.5	7.8	108	3.7	11.8
N	Anilides	5.1	34.2	222	7.5	45.6
A	Other medicines for constipation	4.2	-12.5	26	0.9	-9.8
A	Contact laxatives	4.1	-6.8	49	1.6	-3.0
D	Imidazole and triazole derivatives	3.0	-6.3	66	2.2	-52.6
A	Osmotic laxatives	2.8	-6.7	24	0.8	-30.4
R	Other cough suppressants	2.6	188.9	54	1.8	198.2
A	Antidiarrheal microorganisms	2.5	4.2	146	4.9	15.2
A	Enemas	2.2	-8.3	58	1.9	-1.8
C	Corticosteroids	2.2	-4.3	38	1.3	1.8
D	Iodine derivatives	1.8	5.9	28	0.9	13.1
D	Sulfonamides	1.8	-5.3	22	0.8	4.6
N	Salicylic acid and derivatives	1.7	30.8	79	2.7	33.2
D	Other antiseptics and disinfectants	1.7	0.0	14	0.5	-0.9
	Total top 20	**95.9**	**11.1**	**1,946**	**65.7**	**15.9**
	Total	**137.6**	**8.9**	**2,962.3**	**100.0**	**14.1**

* calculated on overall consumption

Table 2.6.7 Top 30 self-medication active ingredients (SOP and OTC) with the highest expenditure in 2022: comparison 2022-2021

ATC I	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	Δ % 22-21	%*	% SOP (no prescription required)	% OTC	Average DDD cost
M	Ibuprofen (M01AE01)	4.1	51.9	252.8	52.5	8.5	20.2	79.8	2.9
M	diclofenac (M02AA15)	11.0	-9.8	183.8	-4.1	6.2	9.2	90.8	0.8
N	paracetamol	3.5	20.7	153.2	31.1	5.2	74.3	25.7	2
A	flurbiprofen	5.2	85.7	122.8	97.3	4.1	0	100	1.1
A	antidiarrheal microorganisms	2.0	5.3	110.6	16.9	3.7	0	100	2.5
C	diosmin/hesperidin	4.6	12.2	92.4	13.9	3.1	100	0	0.9
M	ketoprofen	1.6	6.7	72.0	12.2	2.4	0	100	2.1
N	acetylsalicylic acid/ ascorbic acid	1.5	36.4	66.9	39.8	2.3	5.0	95.0	2.1
R	naphazoline	10.3	32.1	62.0	35.0	2.1	0	100	0.3
R	carbocisteine	2.7	170.0	49.8	176.1	1.7	23.3	76.7	0.9
A	loperamide	0.4	0.0	41.6	21.9	1.4	19.1	80.9	4.5
M	diclofenac (M01AB05)	0.7	0.0	35.6	16.3	1.2	0	100	2.3
R	acetylcysteine	1.5	114.3	34.4	123.5	1.2	17.8	82.2	1.0
N	paracetamol/ascorbic acid/ phenylephrine	0.6	100.0	34.4	132.2	1.2	0	100	2.5
R	dichlorophenyl carbinol/ amylmetacresol/ascorbic acid	0.5	66.7	33.6	62.2	1.1	0	100	3.2
A	glycerol	1.6	-11.1	30.1	-6.7	1.0	1.6	98.4	0.9
R	ibuprofen/pseudoephedrine	0.2	100.0	28.9	135.2	1.0	0	100	6.1
G	clotrimazole/metronidazole	0.9	0.0	27.9	8.5	0.9	100	0	1.4
A	glycerol	4.2	-12.5	26.4	-9.8	0.9	6.4	93.6	0.3
D	povidone iodine	1.7	6.2	26.1	12.6	0.9	0	100	0.7
R	dextromethorphan/ guaiaphenesin	0.5	150.0	26.1	158.5	0.9	0	100	2.5
M	naproxen	0.9	12.5	25.3	12.8	0.9	16.9	83.1	1.3
A	magnesium hydroxide/ /alginate/dimethicone	0.3	0.0	25.2	-1.0	0.9	0	100	3.5

continued

Table 2.6.7 – *continued*

ATC I	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	Δ % 22-21	%*	% SOP (no prescription required)	% OTC	Average DDD cost
R	levodropropyzine	1.1	266.7	25.1	257.8	0.8	4.1	95.9	1.1
M	Ibuprofen (M02AA13)	1.8	-5.3	24.6	-0.7	0.8	10.3	89.7	0.7
R	cloperastine	1.2	140.0	23.9	153.5	0.8	68.2	31.8	0.9
A	sodium citrate/potassium citrate/ vitamin complex	0.3	50.0	23.2	25.5	0.8	6.7	93.3	4.0
A	saccharomyces boulardii	0.3	50.0	23.0	21.1	0.8	48.7	51.3	3.6
A	butylscopolamine	0.5	25.0	21.5	15.7	0.7	0	100	2.2
C	fluocinolone/ketocaine	1.2	0.0	21.4	4.2	0.7	0	100	0.8
	Top 30	**66.9**	**20.3**	**1,724.5**	**32.4**	**58.2**	**20.5**	**79.5**	**1.2**
	Total	**137.6**	**8.9**	**2,962.3**	**14.1**	**100.0**	**34.3**	**65.7**	**1.0**

* Calculated on overall expenditure

Table 2.6.8 Top 30 self-medication active ingredients (SOP and OTC) with the highest consumption in 2022: comparison 2022-2021

ATC I	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	Δ % 22-21	%*	% SOP (no prescription required)	% OTC	Average DDD cost
M	diclofenac	11.00	-9.8	183.8	-4.1	6.2	9.2	90.8	0.8
R	Naphazoline (R01AA08)	10.30	32.1	62.0	35.0	2.1	0	100	0.3
A	flurbiprofen	5.20	85.7	122.8	97.3	4.1	0	100	1.1
C	diosmin/hesperidin	4.60	12.2	92.4	13.9	3.1	100	0	0.9
S	naphazoline (S01GA01)	4.40	-27.9	19.7	-17.9	0.7	0	100	0.2
A	glycerol	4.20	-12.5	26.4	-9.8	0.9	6.4	93.6	0.3
M	ibuprofen	4.10	51.9	252.8	52.5	8.5	20.2	79.8	2.9
N	paracetamol	3.50	20.7	153.2	31.1	5.2	74.3	25.7	2.0
R	carbocisteine	2.70	170.0	49.8	176.1	1.7	23.3	76.7	0.9

continued

Table 2.6.8 – *continued*

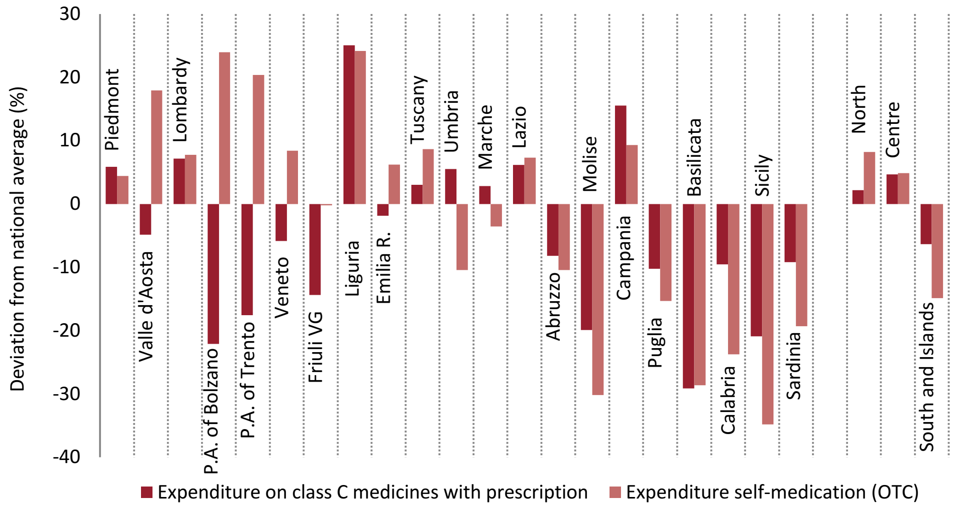
ATC I	Active ingredient	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *(million)*	Δ % 22-21	%*	% SOP (no prescription required)	% OTC	Average DDD cost
R	oxymetazoline	2.70	17.4	4.4	-82.0	0.1	0	100	0.1
A	antidiarrheal microorganisms	2.00	5.3	110.6	16.9	3.7	0	100	2.5
A	lactulose	2.00	-4.8	10.6	-47.8	0.4	38.6	61,	0.3
M	ibuprofen	1.80	-5.3	24.6	-0.7	0.8	10.3	89.7	0.7
D	povidone iodine	1.70	6.2	26.1	12.6	0.9	0	100	0.7
A	senna	1.70	-5.6	17.6	-3.2	0.6	0	100	0.5
A	ascorbic acid	1.70	-5.6	5.3	-1.9	0.2	0	100	0.1
M	ketoprofen	1.60	6.7	72.0	12.2	2.4	0	100	2.1
A	glycerol	1.60	-11.1	30.1	-6.7	1.0	1.6	98.4	0.9
A	bisacodyl	1.60	0.0	21.1	3.4	0.7	0	100	0.6
N	acetylsalicylic acid/ascorbic acid	1.50	36.4	66.9	39.8	2.3	5.0	95.0	2.1
R	acetylcysteine	1.50	114.3	34.4	123.5	1.2	17.8	82.2	1.0
D	silver sulfadiazine	1.30	0.0	10.8	7.1	0.4	100	0	0.4
A	sodium bicarbonate	1.30	8.3	2.9	8.2	0.1	100	0	0.1
R	cloperastine	1.20	140.0	23.9	153.5	0.8	68.2	31.8	0.9
C	fluocinolone/ketocaine	1.20	0.0	21.4	4.2	0.7	0	100	0.8
R	levodropropyzine	1.10	266.7	25.1	257.8	0.8	4.1	95.9	1.1
C	heparinoids	1.10	-8.3	15.4	-3.2	0.5	83.1	16.9	0.6
A	thiamine	1.10	0.0	2.2	4.9	0.1	100	0	0.1
R	xylometazoline	1.00	11.1	17.5	27.1	0.6	0	100	0.8
G	clotrimazole/metronidazole	0.90	0.0	27.9	8.5	0.9	100	0	1.4
	Total top 30	**81.60**	**11.6**	**1,533.6**	**24.4**	**51.8**	**23.4**	**76.6**	**0.9**
	Total	**137.6**	**8.9**	**2,962.3**	**14.1**	**100.0**	**34.3**	**65.7**	**1.0**

* calculated on overall consumption

Table 2.6.9 2022 local pharmaceutical prescriptions of Class C OTC medicines with prescription (Table) and deviation (%) of gross expenditure from national average (Figure): comparison 2022-2021

Region	Class C with prescription				Self-medication (SOP and OTC)			
	Expenditure *per capita*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21	Expenditure *per capita*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21
Piedmont	63.30	3.4	248.9	9.5	47.10	16.0	127.2	1.6
Valle d'Aosta	56.90	10.3	251.3	6.8	53.20	26.7	139.7	18.7
Lombardy	64.10	3.4	246.0	10.9	48.60	14.6	129.1	9.0
A.P. of Bolzano	46.60	12.6	164.6	13.0	55.90	35.4	137.8	23.5
A.P. of Trento	49.30	10.3	231.0	22.5	54.30	29.6	138.6	22.0
Veneto	56.30	9.3	264.6	28.6	48.90	18.7	129.7	11.6
Friuli V.G.	51.20	7.8	235.4	23.6	45.00	15.7	120.6	8.9
Liguria	74.80	6.9	296.1	8.8	56.00	16.2	159.2	9.2
Emilia R.	58.70	5.0	251.7	14.6	47.90	14.0	129.4	10.8
Tuscany	61.60	6.8	275.2	12.9	49.00	12.4	136.8	10.0
Umbria	63.10	16.2	391.3	100.4	40.40	14.1	108.8	12.4
Marche	61.50	11.6	263.7	18.6	43.50	12.1	119.9	9.7
Lazio	63.50	5.0	240.2	15.6	48.40	16.6	136.1	12.3
Abruzzo	54.90	12.3	178.3	10.9	40.40	16.4	110.8	12.7
Molise	47.90	0.4	157.5	0.6	31.50	11.3	88.9	6.3
Campania	69.10	-15.3	234.0	3.4	49.30	12.3	142.1	7.4
Puglia	53.70	7.8	211.8	19.6	38.20	13.0	101.2	8.6
Basilicata	42.40	0.0	222.2	24.7	32.20	14.6	86.1	10.2
Calabria	54.10	0.0	235.6	7.8	34.40	9.9	93.2	5.1
Sicily	47.30	-6.9	191.3	4.8	29.40	3.5	82.4	0.2
Sardinia	54.30	-1.3	219.9	0.5	36.40	12.7	94.2	9.2
Italy	**59.80**	**2.2**	**241.7**	**13.8**	**45.10**	**14.2**	**123.0**	**8.8**
North	61.10	5.2	251.4	14.7	48.80	16.2	130.7	9.0
Centre	62.60	7.2	265.9	20.7	47.30	14.3	132.2	11.3
South and Islands	56.00	-5.2	212.9	7.7	38.40	11.0	106.3	6.5

* Including medicines classified in Class C - Non-negotiated



Class A medicines - private purchase

Table 2.6.10 2022 expenditure and consumption of Class A out-of pocket medicines (Table) and deviation (%) of gross expenditure from national average (Figure)

Region	*Per capita* expenditure	Δ % 22-21	DDD/1000 inhabitants per day	Δ % 22-21
Piedmont	41.80	13.6	264.7	2.0
Valle d'Aosta	76.40	274.5	258.4	30.0
Lombardy	27.30	-13.9	260.8	-6.6
A.P. of Bolzano	23.80	35.2	268.3	21.2
A.P. of Trento	31.50	176.3	149.9	28.8
Veneto	26.10	7.9	327.9	1.3
Friuli V.G.	21.80	25.3	262.4	45.6
Liguria	36.90	-0.3	325.5	-5.6
Emilia R.	21.20	-5.8	185.0	-7.6
Tuscany	23.00	2.2	248.1	0.6
Umbria	30.50	87.1	178.2	27.1
Marche	30.60	18.1	219.7	15.6
Lazio	46.00	111.0	200.0	8.2
Abruzzo	70.30	334.0	171.6	20.9
Molise	13.70	-19.4	117.8	-17.1
Campania	32.80	-11.1	266.4	-10.3
Puglia	20.70	5.6	168.0	6.3
Basilicata	9.70	-51.7	84.7	-73.7
Calabria	27.50	31.0	205.3	30.0
Sicily	12.70	-25.3	111.8	-27.3
Sardinia	70.00	282.5	115.8	-1.5
Italy	**30.60**	**19.5**	**225.4**	**-1.8**
North	29.00	1.0	262.9	-1.2
Centre	35.40	60.2	216.3	7.1
South and Islands	29.80	27.4	177.0	-8.8

* Including medicines classified in Class C - Non-negotiated

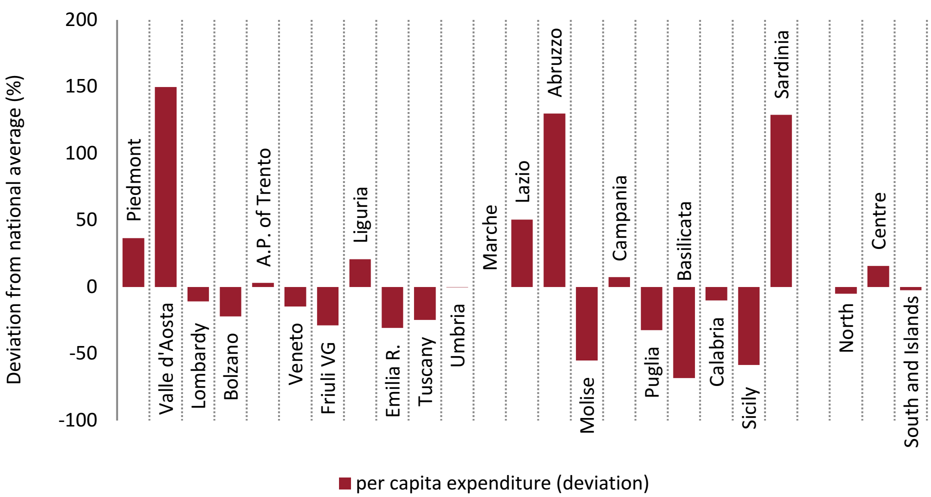


Table 2.6.11 Top 20 class A therapeutic categories purchased privately by the citizen in descending order of expenditure in 2022: comparison 2022-2021

ATC I	Therapeutic category	DDD/1000 inhab. per day	Δ% 22-21	Expenditure *(million)*	Δ% 22-21	%*	% medicines paid out of pocket**
A	Proton pump inhibitors	16.2	-4.7	145.2	-7.0	8.1	17.4
M	Propionic acid derivatives	18.0	32.4	129.1	38.8	7.2	72.3
J	Combination of penicillins, incl. beta-lactamase inhibitors	2.1	23.5	65.2	19.0	3.6	24.8
A	Vitamin D and analogues	54.1	-9.1	62.3	-16.8	3.5	18.3
B	Direct Xa factor inhibitors	0.6	500.0	56.0	617.9	3.1	9.6
C	HMG-CoA reductase inhibitors	8.2	7.9	49.6	7.1	2.8	9.4
B	Platelet aggregation inhibitors, excl. heparin	23.5	25.0	49.6	29.5	2.8	13.7
A	GLP-1 (glucagon-like peptide-1) receptor analogues	0.3	200.0	48.7	245.4	2.7	10.4
H	Glycocorticoids	6.0	11.1	44.4	8.0	2.5	28.2
B	Other antianemic preparations	0.1		37.5	886.8	2.1	17.5
R	Glycocorticoids	1.5	50.0	36.0	46.3	2.0	25.8
M	Acetic acid derivatives and related substances	3.6	9.1	33.3	7.8	1.8	40.1
B	Coagulation factors	0.0		32.9	558.0	1.8	6.8
J	Macrolides	1.1	57.1	30.0	58.7	1.7	23.9
A	Insulins and injectable analogues, long-acting	0.4		26.2	803.4	1.5	11.3
C	Other lipid modifying agents	0.7	0.0	24.7	1.6	1.4	6.3
R	Piperazine derivatives	3.8	0.0	24.0	1.3	1.3	49.3
C	Beta blockers, selective	3.1	-6.1	23.6	6.8	1.3	7.4
C	Ace inhibitors, not in combination	9.4	-9.6	22.1	-16.6	1.2	9.5
N	Diazepines, oxazepines, thiazepines and oxepins	0.4	33.3	21.3	31.5	1.2	20.9
	Top 20	**153.0**	**3.9**	**961.8**	**32.6**	**53.4**	**15.8**
	Total	**226.0**	**-1.5**	**1,802.1**	**18.8**	**100.0**	**6.7**

* Calculated on the total expenditure of Class A medicines paid out of pocket by citizens

** Calculated on total expenditure (under approved care regime, out of pocket expenses and purchases by public health facilities) of the active ingredient

Table 2.6.12 Top 20 class A therapeutic categories purchased privately by the citizen in descending order of expenditure in 2022: comparison 2022-2021

ATC I	Therapeutic category	DDD/1000 inhab. per day	Δ% 22-21	Expenditure *(million)*	Δ% 22-21	%*	% medicines paid out of pocket**
A	Vitamin D and analogues	54.1	-9.1	62.3	-16.8	3.5	18.3
B	Platelet aggregation inhibitors, excl. heparin	23.5	25.0	49.6	29.5	2.8	13.7
M	Propionic acid derivatives	18.0	32.4	129.1	38.8	7.2	72.3
A	Proton pump inhibitors	16.2	-4.7	145.2	-7.0	8.1	17.4
C	ACE inhibitors, not in combination	9.4	-9.6	22.1	-16.6	1.2	9.5
C	HMG-CoA reductase inhibitors	8.2	7.9	49.6	7.1	2.8	9.4
H	Thyroid hormones	7.2	-11.1	17.6	-8.3	1.0	17.3
H	Glycocorticoids	6.0	11.1	44.4	8.0	2.5	28.2
R	Piperazine derivatives	3.8	0.0	24.0	1.3	1.3	49.3
M	Acetic acid derivatives and related substances	3.6	9.1	33.3	7.8	1.8	40.1
C	Sulfonamides, not in combination	3.5	-14.6	7.3	-16.1	0.4	12.6
N	Selective serotonin reuptake inhibitors	3.3	-13.2	20.5	-13.9	1.1	9.3
C	Dihydropyridine derivatives	3.2	0.0	13.1	-1.5	0.7	5.1
C	Beta blockers, selective	3.1	-6.1	23.6	6.8	1.3	7.4
R	Other antihistamines for systemic use	2.6	0.0	17.7	1.7	1.0	30.8
C	Angiotensin II receptor blockers (ARBs), not in combination	2.5	-19.4	12.3	-21.2	0.7	4.1
B	Folic acid e derivatives	2.4	-14.3	9.2	-17.9	0.5	23.0
A	Biguanides	2.3	-14.8	8.8	-16.2	0.5	8.2
M	Other non-steroidal anti-inflammatory/anti-rheumatic pharmaceuticals	2.3	0.0	12.0	-4.0	0.7	56.5
J	Combination of penicillins, incl. beta-lactamase inhibitors	2.1	23.5	65.2	19.0	3.6	24.8
	Top 20	**177.2**	**0.0**	**767.1**	**3.6**	**42.6**	**17.0**
	Total	**226.0**	**-1.5**	**1,802.1**	**18.8**	**100.0**	**6.7**

* Calculated on the total expenditure of Class A medicines paid out of pocket by citizens

** Calculated on total consumption (under approved care regime, out of pocket expenses and purchases by public health facilities) of the active ingredient

Table 2.6.13 Top 30 class A active ingredients purchased privately by the citizen in descending order of expenditure in 2022: comparison 2022-2021

ATC I	Active ingredient	DDD/1000 inhab. per day	Δ% 22-21	Expenditure *(million)*	Δ% 22-21	%*	% medicines paid out of pocket**	Average DDD cost
M	ibuprofen	6.9	86.5	64.4	87.2	3.6	70.8	0.43
J	amoxicillin/clavulanic acid	2.1	23.5	62.8	22.7	3.5	28.2	1.40
A	cholecalciferol	53.9	-9.3	58.4	-16.7	3.2	19.6	0.05
A	pantoprazole	6.2	5.1	57.9	4.3	3.2	17.4	0.43
M	ketoprofen	9.9	12.5	56.6	12.1	3.1	77.8	0.26
B	acetylsalicylic acid	21.6	31.7	35.5	32.0	2.0	33.4	0.08
A	omeprazole	3.8	-13.6	29.2	-19.6	1.6	18.1	0.36
A	lansoprazole	2.9	-6.5	28.8	-7.1	1.6	18.1	0.46
M	diclofenac	3.2	6.7	27.8	7.3	1.5	42.1	0.40
C	rosuvastatin	4.4	41.9	25.5	42.5	1.4	22.5	0.27
A	esomeprazole	2.9	-6.5	25.2	-9.4	1.4	15.9	0.40
A	semaglutide	0.1	—	24.7	194.0	1.4	13.9	20.14
H	betamethasone	2.7	22.7	24.4	25.8	1.4	55.8	0.41
R	beclomethasone	1.0	42.9	23.1	46.2	1.3	37.1	1.07
B	apixaban	0.2	—	22.7	773.1	1.3	10.2	4.26
B	rivaroxaban	0.3	—	20.9	596.7	1.2	9.8	3.84
J	azithromicyn	0.7	75.0	20.6	70.2	1.1	26.7	1.43
R	cetirizine	3.2	3.2	20.2	3.1	1.1	52.5	0.29
A	dulaglutide	0.2	—	19.3	394.9	1.1	7.5	4.91
B	epoetin alfa	0.1	—	18.9	845.0	1.0	20.8	11.55
C	omega-3	0.4	0.0	18.8	-1.6	1.0	12.8	2.37
H	levothyroxine	7.2	-11.1	17.3	-8.0	1.0	17.3	0.11
C	bisoprolol	1.2	20.0	16.6	23.9	0.9	9.0	0.62
J	fosfomycin	0.1	-50.0	16.0	-1.8	0.9	24.0	4.98
B	enoxaparin	0.3	50.0	14.5	29.5	0.8	6.0	2.17
C	ramipril	7.4	-6.3	14.1	-10.8	0.8	10.9	0.09
N	quetiapine	0.2	100.0	14.0	30.8	0.8	24.2	3.45
A	rifaximin	0.3	50.0	13.7	47.3	0.8	13.0	2.14
B	edoxaban	0.1		12.4	463.6	0.7	8.6	4.46
C	atorvastatin	2.3	-14.8	12.4	-16.2	0.7	4.3	0.25
	Top 30	**146.0**	**4.4**	**816.4**	**26.4**	**45.3**	**18.4**	**0.26**
	Total	**226.0**	**-1.5**	**1,802.1**	**18.8**	**100.0**	**6.7**	**0.37**

* Calculated on the total expenditure of Class A medicines paid out of pocket by citizens

** Calculated on total expenditure (under approved care regime, out of pocket expenses and purchases by public health facilities) of the active ingredient

Table 2.6.14 Top 30 class A active ingredients purchased privately by the citizen in descending order of consumption in 2022: comparison 2022-2021

ATC I	Active ingredient	DDD/1000 inhab. per day	Δ% 22-21	Expenditure *(million)*	Δ% 22-21	%*	% medicines paid out of pocket**	Average DDD cost
A	cholecalciferol	53.9	-9.3	58.4	-16.7	3.2	19.6	0.05
B	acetylsalicylic acid	21.6	31.7	35.5	32.0	2.0	33.4	0.08
M	ketoprofen	9.9	12.5	56.6	12.1	3.1	77.8	0.26
C	ramipril	7.4	-6.3	14.1	-10.8	0.8	10.9	0.09
H	levothyroxine	7.2	-11.1	17.3	-8.0	1.0	17.3	0.11
M	ibuprofen	6.9	86.5	64.4	87.2	3.6	70.8	0.43
A	pantoprazole	6.2	5.1	57.9	4.3	3.2	17.4	0.43
C	rosuvastatin	4.4	41.9	25.5	42.5	1.4	22.5	0.27
A	omeprazole	3.8	-13.6	29.2	-19.6	1.6	18.1	0.36
C	furosemide	3.3	-15.4	6.5	-14.5	0.4	12.8	0.09
M	diclofenac	3.2	6.7	27.8	7.3	1.5	42.1	0.40
R	cetirizine	3.2	3.2	20.2	3.1	1.1	52.5	0.29
A	lansoprazole	2.9	-6.5	28.8	-7.1	1.6	18.1	0.46
A	esomeprazole	2.9	-6.5	25.2	-9.4	1.4	15.9	0.40
H	betamethasone	2.7	22.7	24.4	25.8	1.4	55.8	0.41
B	folic acid	2.4	-14.3	9.2	-17.9	0.5	23.0	0.18
C	atorvastatin	2.3	-14.8	12.4	-16.2	0.7	4.3	0.25
A	metformin	2.3	-14.8	8.8	-16.2	0.5	8.2	0.18
M	nimesulide	2.3	0.0	12.0	-3.2	0.7	57.3	0.24
J	amoxicillin/clavulanic acid	2.1	23.5	62.8	22.7	3.5	28.2	1.40
C	amlodipine	2.0	-13.0	6.4	-15.8	0.4	6.3	0.15
R	salbutamol	2.0	11.1	8.1	12.5	0.4	42.0	0.19
D	clobetasol	2.0	-9.1	7.0	-11.4	0.4	60.9	0.17
M	allopurinol	1.9	-13.6	4.7	-14.5	0.3	17.8	0.12
H	prednisone	1.8	0.0	9.7	-17.1	0.5	18.6	0.25
B	cyanocobalamin	1.6	-11.1	0.7	-12.5	0.0	11.0	0.02
C	bisoprolol	1.2	20.0	16.6	23.9	0.9	9.0	0.62
C	simvastatin	1.2	-14.3	8.8	-16.2	0.5	9.9	0.34
M	etoricoxib	1.1	10.0	10.8	5.9	0.6	23.0	0.45
C	ramipril/ hydrochlorothiazide	1.1	0.0	5.0	-3.8	0.3	13.5	0.22
	Top 30	**167.0**	**1.2**	**674.5**	**5.8**	**37.4**	**21.3**	**0.19**
	Total	**226.0**	**-1.5**	**1,802.1**	**18.8**	**100.0**	**6.7**	**0.37**

* Calculated on the total expenditure of Class A medicines paid out of pocket by citizens

** Calculated on total expenditure (under approved care regime, out of pocket expenses and purchases by public health facilities) of the active ingredient

Table 2.6.15 Breakdown of consumption by price range of Class A medicines paid out of pocket by citizens in 2022

Region	<2 € %	≥2 <3 € %	≥3 <6 € %	≥6 <10 € %	≥10 <30 € %	≥30 € %
Piedmont	7.9	13.3	30.9	29.2	14.6	4.2
Valle d'Aosta	8.9	17.5	25.5	21.8	14.6	11.6
Lombardy	12.3	21.5	30.2	23.0	12.0	1.1
A.P. of Bolzano	8.3	18.5	32.6	24.2	14.3	2.0
A.P. of Trento	11.7	10.2	29.7	25.3	15.8	7.2
Veneto	12.5	21.2	31.2	21.7	12.2	1.2
Friuli V.G.	4.9	23.7	38.3	21.0	11.0	1.1
Liguria	11.3	18.5	29.8	27.4	12.2	0.8
Emilia R.	9.5	11.0	36.3	27.2	14.7	1.3
Tuscany	10.7	14.1	35.6	24.8	13.7	1.0
Umbria	9.2	12.6	34.5	27.3	13.3	3.1
Marche	10.1	10.8	30.5	29.1	16.1	3.4
Lazio	10.6	16.2	30.9	24.1	13.3	4.9
Abruzzo	11.2	12.6	28.6	21.8	11.5	14.3
Molise	9.8	16.4	35.1	26.4	11.7	0.6
Campania	11.6	24.8	30.1	22.3	10.1	1.1
Puglia	12.8	16.7	33.2	23.3	12.7	1.4
Basilicata	12.1	20.8	34.4	21.6	10.5	0.6
Calabria	9.1	25.4	32.7	22.2	9.3	1.2
Sicily	9.8	29.3	31.6	21.3	7.7	0.3
Sardinia	10.9	10.7	21.7	16.8	12.4	27.5
Italy	**10.8**	**19.0**	**31.5**	**23.9**	**12.3**	**2.5**
North	10.8	18.5	31.5	24.6	12.8	1.8
Centre	10.5	14.6	32.6	25.2	13.8	3.4
South and Islands	11.2	22.6	30.8	22.0	10.3	3.1

Table 2.6.16 Expenditure and consumption of OTC self-medication medicines provided by retail pharmacies by Region in 2022 and deviation (%) from national average (Table and Figure)

Region	Expenditure *(million)*	Δ % 22-21	Expenditure *per capita*	DDD/1000 inhab. per day
Piedmont	24.6	17.6	5.5	15.6
Valle d'Aosta	0.7	13.9	5.8	15.9
Lombardy	59.5	15.4	6.0	16.6
A.P. of Bolzano	0.4	52.7	0.8	1.9
A.P. of Trento	2.0	30.6	3.7	9.6
Veneto	22.1	16.0	4.5	12.5
Friuli V.G.	5.0	16.8	3.9	11.1
Liguria	9.8	8.1	5.9	19.2
Emilia R.	34.6	14.6	7.7	22.8
Tuscany	27.8	10.4	7.3	20.2
Umbria	4.8	21.5	5.3	15.7
Marche	7.0	4.6	4.6	13.9
Lazio	19.9	8.4	3.5	10.5
Abruzzo	6.7	6.1	5.2	15.3
Molise	1.2	17.4	3.8	11.5
Campania	40.4	25.9	7.8	23.3
Puglia	19.4	10.6	5.0	14.8
Basilicata	3.5	6.9	6.3	17.1
Calabria	9.8	6.9	5.4	15.3
Sicily	12.8	-9.1	2.7	8.8
Sardinia	14.4	22.3	8.7	23.1
Italy	**326.3**	**13.7**	**5.5**	**15.9**
North	158.6	15.4	5.7	16.2
Centre	59.6	9.8	5.0	14.4
South and Islands	108.1	13.6	5.6	16.4

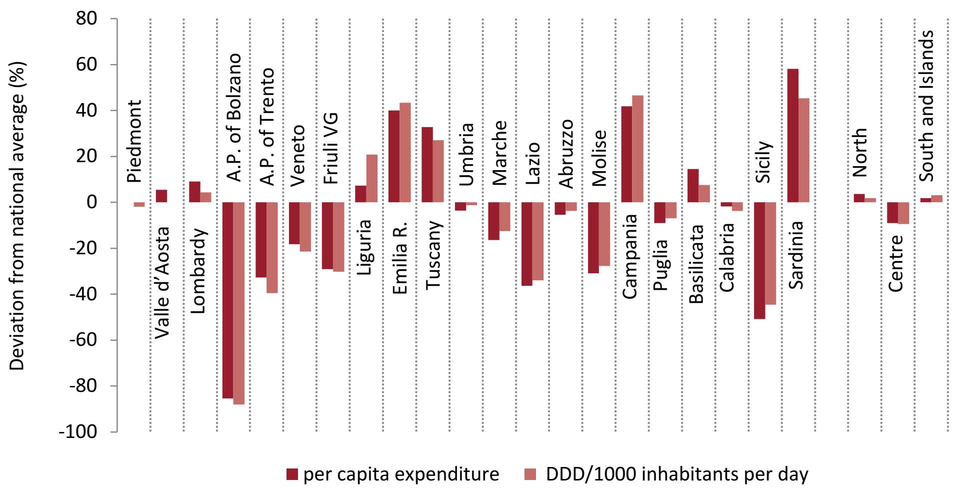


Table 2.6.17 Top 30 self-medication active ingredients supplied by commercial shops in descending order of expenditure in 2022: comparison 2022-2021

ATC	Active substances	Expenditure *per capita*	Expenditure *(million)*	Δ % 22-21	Inc. %	% cum.	DDD/1000 inhab. per day	Δ % 22-21	Average cost DDD
M	ibuprofen	0.5	26.7	36.7	8.2	8.2	0.5	35.3	2.69
M	diclofenac	0.3	20.2	-0.4	6.2	14.4	1.2	-4.7	0.77
N	paracetamol	0.3	18.3	19.8	5.6	20.0	0.5	12.5	1.57
A	flurbiprofen	0.2	13.6	68.2	4.2	24.2	0.6	62.9	1.12
A	antidiarrheal microorganisms	0.2	12.4	31.3	3.8	28.0	0.2	15.8	2.59
M	ketoprofen	0.2	11.7	16.1	3.6	31.6	0.3	12.5	2.02
C	diosmin/hesperidin	0.2	11.6	21.3	3.5	35.1	0.6	18.0	0.92
R	naphazoline	0.2	10.2	22.3	3.1	38.2	1.7	21.4	0.28
N	acetylsalicylic acid/ ascorbic acid	0.1	6.2	28.7	1.9	40.1	0.2	25.0	1.87
A	glycerol (A06AG04)	0.1	5.7	3.8	1.8	41.9	0.3	-3.1	0.86
A	glycerol (A06AX01)	0.1	4.8	-3.4	1.5	43.4	0.9	-3.4	0.26
M	diclofenac	0.1	4.3	13.7	1.3	44.7	0.1	12.5	2.26
R	carbocisteine	0.1	3.9	117.2	1.2	45.9	0.2	100.0	0.82
R	dichlorophenyl carbinol/ amylmetacresol/ascorbic acid	0.1	3.9	35.7	1.2	47.1	0.1	20.0	3.17
A	loperamide	0.1	3.8	15.3	1.2	48.3	0.0	0.0	4.32
A	bisacodyl	0.1	3.5	8.8	1.1	49.4	0.3	3.8	0.61
N	paracetamol/ /ascorbic acid/phenylephrine	0.1	3.5	57.5	1.1	50.5	0.1	50.0	2.52
A	magnesium hydroxide/ /alginate/dimethicone	0.1	3.1	-2.4	1.0	51.5	0.0	0.0	3.51
R	ibuprofen/ pseudoephedrine	0.1	3.1	71.3	0.9	52.4	0.0	100.0	6.05
R	xylometazoline	0.1	3.0	23.2	0.9	53.3	0.2	20.0	0.80
M	naproxen	0.1	2.9	15.3	0.9	54.2	0.1	10.0	1.25
R	acetylcysteine	0.1	2.9	37.8	0.9	55.1	0.2	36.4	0.90
A	sodium alginate/ sodium bicarbonate	0.1	2.7	16.5	0.8	55.9	0.1	0.0	2.49
A	sodium alginate/ sodium bicarbonate/ calcium carbonate	0.1	2.7	33.1	0.8	56.7	0.0	0.0	3.74
S	naphazoline	0.0	2.6	-8.1	0.8	57.5	0.6	-9.4	0.21
D	escin/l-thyroxine	0.0	2.6	-29.0	0.8	58.3	0.1	-25.0	2.14
C	fluocinolone/ketocaine	0.0	2.5	3.4	0.8	59.1	0.1	7.7	0.82
N	nicotine	0.0	2.5	-10.4	0.8	59.9	0.0	0.0	5.52
M	ibuprofen	0.0	2.4	5.1	0.7	60.6	0.2	0.0	0.58
R	dextromethorphan/ guaiaphenesin	0.0	2.4	95.6	0.7	61.3	0.1	150.0	2.44
	Total top 30	**3.4**	**199.9**	**21.9**	**61.3**		**9.2**	**11.7**	**1.01**
	Total	**5.5**	**326.3**	**14.2**	**100.0**		**15.9**	**8.4**	**0.95**

Table 2.6.18 Top 30 self-medication active ingredients supplied by commercial shops in descending order of consumption in 2022: comparison 2022-2021

ATC	Active substances	Expenditure *per capita*	Expenditure *(million)*	Δ % 22-21	Inc. %	% cum.	DDD/1000 inhab. per day	Δ % 22-21	Average cost DDD
R	naphazoline	0.2	10.2	22.3	3.1	3.1	1.7	21.4	0.28
M	diclofenac	0.3	20.2	-0.4	6.2	9.3	1.2	-4.7	0.77
A	glycerol	0.1	4.8	-3.4	1.5	10.8	0.9	-3.4	0.26
C	diosmin/hesperidin	0.2	11.6	21.3	3.5	14.3	0.6	18.0	0.92
S	naphazoline	0.0	2.6	-8.1	0.8	15.1	0.6	-9.4	0.21
A	flurbiprofen	0.2	13.6	68.2	4.2	19.3	0.6	62.9	1.12
N	paracetamol	0.3	18.3	19.8	5.6	24.9	0.5	12.5	1.57
M	ibuprofen	0.5	26.7	36.7	8.2	33.1	0.5	35.3	2.69
R	oxymetazoline	0.0	0.9	-86.6	0.3	33.4	0.5	9.5	0.09
A	glycerol	0.1	5.7	3.8	1.8	35.2	0.3	-3.1	0.86
A	bisacodyl	0.1	3.5	8.8	1.1	36.3	0.3	3.8	0.61
M	ketoprofen	0.2	11.7	16.1	3.6	39.9	0.3	12.5	2.02
A	antidiarrheal microorganisms	0.2	12.4	31.3	3.8	43.7	0.2	15.8	2.59
R	carbocisteine	0.1	3.9	117.2	1.2	44.9	0.2	100.0	0.82
A	senna	0.0	2.3	1.8	0.7	45.6	0.2	-4.3	0.48
A	lactulose	0.0	1.2	-35.3	0.4	46.0	0.2	0.0	0.30
M	ibuprofen	0.0	2.4	5.1	0.7	46.7	0.2	0.0	0.58
R	xylometazoline	0.1	3.0	23.2	0.9	47.6	0.2	20.0	0.80
A	ascorbic acid	0.0	0.5	17.2	0.2	47.8	0.2	0.0	0.15
N	acetylsalicylic acid/ ascorbic acid	0.1	6.2	28.7	1.9	49.7	0.2	25.0	1.87
D	silver sulfadiazine	0.0	1.0	28.9	0.3	50.0	0.2	-6.3	0.31
R	acetylcysteine	0.1	2.9	37.8	0.9	50.9	0.2	36.4	0.90
D	povidone iodine	0.0	2.0	-2.2	0.6	51.5	0.2	15.4	0.65
C	fluocinolone/ketocaine	0.0	2.5	3.4	0.8	52.3	0.1	7.7	0.82
C	phosphatidylcholine/escin	0.0	1.6	20.6	0.5	52.8	0.1	9.1	0.64
D	benzalkonium chloride	0.0	0.8	-22.8	0.2	53.0	0.1	-8.3	0.32
M	naproxen	0.1	2.9	15.3	0.9	53.9	0.1	10.0	1.25
D	minoxidil	0.0	2.1	-10.5	0.7	54.6	0.1	-8.3	0.91
S	naphazoline/tonzilamine	0.0	1.1	19.3	0.4	55.0	0.1	0.0	0.52
M	ketoprofen/sucralfate	0.0	0.8	-21.0	0.2	55.2	0.1	-9.1	0.35
	Total top 30	**3.0**	**179.6**	**16.6**	**55.0**		**10.6**	**9.5**	**0.79**
	Total	**5.5**	**326.3**	**14.2**	**100.0**		**15.9**	**8.4**	**0.95**

Benzodiazepine

- In 2022, the consumption of benzodiazepines reached 53.7 DDD/1000 inhabitants per day, a slight decrease (-1.2%) compared to the previous year, whereas the last 8 years have seen an increase of 34% with an average annual change of +4.3%. Over the same period, the average cost per therapy day has remained stable with values ranging from EUR 0.49 in 2015 to EUR 0.52 in 2022. Total expenditure was around EUR 600 million, corresponding to a *per capita* value of EUR 10.14. This indicator also showed a decrease compared to 2021 of 2.8% (Figure 2.6.19a and Table 2.6.19a).
- Anxiolytics, with 379 million euro, represent the category with the highest expenditure (6.43 euro *per capita*) and account for 63.4% of total expenditure, showing a 5% reduction compared to 2021. In terms of consumption, they are also confirmed as the first category, indeed, 26.1 doses per thousand inhabitants are used, with a reduction of 4.4%. This is followed by benzodiazepines with a hypnotic effect, which in 2022 recorded an expenditure of EUR 2.45 *per capita* and a consumption of 21.6 DDD, up 0.8% and 1.9% respectively (Table 2.6.19a). Finally, as far as sedatives are concerned, there is an increase in consumption (+2.2% compared to 2021 and a CAGR 15-22 of +9.7%) and expenditure (+1.8%, with a CAGR +10.6%), taking into account, however, that this category accounts for slightly more than 10% of the total of benzodiazepines (Table 2.6.19a).
- The average cost per day of therapy of anxiolytics is more than double that of hypnotics (0.67 vs. 0.31 Euro).
- Alprazolam and lorazepam, with EUR 2.25 and EUR 1.84 *per capita* respectively, are confirmed as the substances with the highest expenditure in 2022, occupying 40.4% of the total of benzodiazepines, with reductions of 1.4% and 7.8% respectively. The largest increases in expenditure and consumption compared to 2021 are observed for zolpidem (+2% and +2.3% respectively) and lormetazepam (+3.7% and +3.1% respectively) and a 2015-2022 expenditure CAGR of 10% for both substances (Table 2.6.10a).
- Lormetazepam is the most widely used molecule in the population with a value of 15.6 DDD, and also has the lowest cost per day of therapy of the entire category (EUR 0.20).
- At the level of geographical area, a wide variability in terms of consumption is observed, with Northern Regions showing a 73% higher consumption than Southern Regions. The southern regions show a reduction of 4.9% in consumption compared to 2021, while in the North and in the Centre consumption remains substantially stable. At regional level, Liguria records a value (83.5 DDD) three times higher than Basilicata (26.5 DDD). Friuli and Bolzano are the regions with the greatest increases (+3% and +3.5% respectively), while Sicily (-12.6%) and Basilicata (-6.1%) show the greatest decreases (Table 2.6.19b).

Figure 2.6.19a Benzodiazepine, trend 2015-2022 in local consumption and DDD average cost

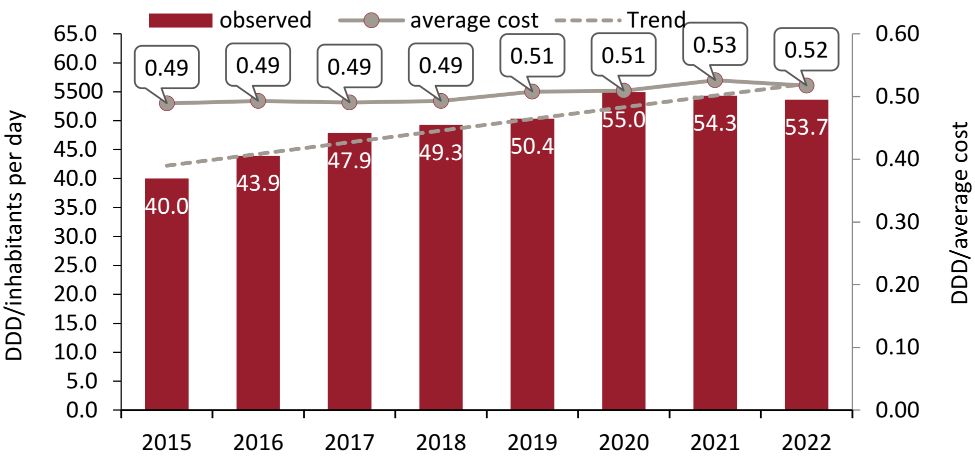


Table 2.6.19a Benzodiazepine, *per capita* expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2015-2022

Subgroups and substances	Expenditure (million)	*Per capita* expenditure	Δ % 22-21	CAGR % 15-22	DDD/1000 inhab. per day	Δ % 22-21	CAGR % 15-22	Average cost DDD	Δ % 22-21
Anxiolytics	379.3	6.43	-5.0	4.1	26.1	-4.4	3.0	0.67	-0.6
Hypnotics	144.3	2.45	0.8	5.7	21.6	1.9	4.7	0.31	-1.0
Sedatives	74.3	1.26	1.8	10.6	6.0	2.2	9.7	0.58	-0.3
Benzodiazepine	**597.9**	**10.14**	**-2.8**	**5.1**	**53.7**	**-1.2**	**4.3**	**0.52**	**-1.6**
alprazolam	132.7	2.25	-1.4	7.1	10.3	-1.3	5.7	0.60	-0.1
lorazepam	108.8	1.84	-7.8	1.7	9.7	-6.8	0.8	0.52	-1.1
zolpidem	71.7	1.22	2.0	10.9	5.8	2.3	10.0	0.58	-0.3
lormetazepam	67.9	1.15	3.7	6.2	15.6	3.1	5.0	0.20	0.6
delorazepam	47.0	0.80	-3.1	5.0	2.5	-2.6	4.3	0.87	-0.5
bromazepam	47.0	0.80	-6.0	3.1	1.3	-5.6	1.8	1.64	-0.4
triazolam	44.7	0.76	-1.4	5.9	3.7	-1.0	4.5	0.57	-0.4
diazepam	21.4	0.36	-4.7	3.9	1.3	-4.8	3.4	0.77	0.2
brotizolam	19.5	0.33	-0.3	5.3	1.4	0.7	3.8	0.63	-1.0
flurazepam	8.7	0.15	-2.9	5.1	0.7	-3.1	3.9	0.62	0.2

Table 2.6.19b Benzodiazepine, regional trend of weighted DDD/1000 inhab. per day: comparison 2015-2022

Region	2015	2016	2017	2018	2019	2020	2021	2022	Δ % 22-21
Piedmont	54.5	66.8	66.6	70.2	69.8	75.1	74.5	75.4	1.3
Valle d'Aosta	53.9	66.6	67.3	72.5	73.4	72.7	70.1	70.3	0.3
Lombardy	42.7	45.5	55.6	57.8	59.4	62.3	61.1	60.5	-1.0
A.P. of Bolzano	34.9	35.7	35.5	35.8	34.1	35.0	33.6	34.8	3.5
A.P. of Trento	59.4	59.5	59.1	60.2	58.5	58.7	57.8	58.0	0.3
Veneto	57.1	56.0	69.9	68.8	71.1	73.2	71.4	71.8	0.6
Friuli V.G.	47.6	56.5	60.9	60.7	61.3	63.6	62.1	64.0	3.0
Liguria	63.7	75.8	74.9	79.1	79.6	86.0	83.8	83.5	-0.4
Emilia R.	48.2	53.1	55.4	52.8	54.8	58.3	57.8	57.5	-0.5
Tuscany	40.6	42.3	44.8	48.3	47.0	50.0	49.4	48.0	-2.8
Umbria	28.2	31.0	31.3	31.4	29.7	46.8	54.1	55.0	1.6
Marche	26.8	29.7	29.9	28.1	31.4	52.5	60.3	59.5	-1.4
Lazio	33.4	36.2	41.0	45.1	49.4	52.6	51.6	52.0	0.7
Abruzzo	36.1	37.8	37.5	36.6	39.2	41.4	41.4	42.3	2.1
Molise	24.9	29.7	29.7	30.7	29.9	30.8	30.8	29.7	-3.3
Campania	31.8	33.8	35.0	35.8	35.6	41.7	41.1	39.1	-5.0
Puglia	25.0	27.0	27.0	28.7	30.6	32.8	32.3	32.0	-0.9
Basilicata	20.7	26.3	26.5	27.2	27.5	28.7	28.2	26.5	-6.1
Calabria	25.4	31.2	32.1	33.3	33.4	39.0	41.3	40.3	-2.6
Sicily	24.4	28.0	30.1	30.8	29.5	38.4	35.7	31.2	-12.6
Sardinia	50.6	61.5	60.7	62.7	63.9	66.6	66.7	65.1	-2.4
Italy	**40.0**	**43.9**	**47.9**	**49.3**	**50.4**	**55.0**	**54.3**	**53.7**	**-1.2**
North	49.8	54.6	61.0	62.1	63.3	66.6	65.4	65.4	0.0
Centre	34.5	36.9	40.0	42.9	44.8	51.3	52.2	51.9	-0.6
South and Islands	29.5	33.1	33.9	35.0	35.3	40.5	39.7	37.8	-4.9

Contraceptive medicines

- During 2015-2022, there was a gradual but steady increase in the consumption of contraceptive medicines, with a value of DDD/1000 inhabitants per day rising from 98.2 in 2015 to 141.8 corresponding to an increase of 44% and a CAGR of +5.4%. Over the same period, the average cost per DDD increased by 13.1% to EUR 0.51 in 2022 (Figure 2.6.20a). In 2022, the total expenditure was approximately EUR 350 million or EUR 26.49 *per capita* (female population 12-50 years) with an average annual growth since 2015 of 7.3%, and an increase over 2021 of 4% (Table 2.6.20a).
- Fourth-generation estroprogestin oral contraceptives account for 47.1% of consumption, up 4.4% from 2021, and 54% of expenditure in the entire category (€14.31), up 5.2% from 2021 (Table 2.6.20a). All subgroups show average annual increases in terms of expenditure and consumption (CAGR 2015-2021) except for third-generation oestrogen oral contraceptives (-0.6% expenditure and -3.3% consumption). Systemic contraceptives with subcutaneous implant, emergency oral and progestin oral contraceptives register important increases in expenditure (around 20%) and consumption (between 14 and 22%) compared to the previous year, while transdermal oestrogen, second and third generation oral contraceptives register the highest decreases in consumption (-5.6%, -3.8% and -4.1% respectively).
- Analysing in more detail the active ingredients, the combination drospirenone/ethinylestradiol maintains the highest values in terms of expenditure and consumption at 5.17 euro *per capita* and 24.5 DDD/1000 inhabitants per day, stable compared to the previous year. Dienogest, in combination with ethinylestradiol or oestradiol, ranks second and third in terms of expenditure with € 3.42 and € 3.19 respectively; both combinations show increases compared with 2021. Ulipristal (emergency contraceptive to be taken within 5 days of unprotected sexual intercourse or failure of another contraceptive method) is the active ingredient with the largest increases in use and expenditure of the whole category (+26%), while the combination gestodene/ethinylestradiol has the largest decrease (-10%) (Table 2.6.20a).
- Confirming the national data, the consumption of these medicines increased in the geographical macro-areas of the North (+2.2%) and the Centre (+6.8%), while in the South and the Islands it decreased by 4% (Table 2.6.20b). In detail, the consumption of the Northern regions is more than double that of the Southern ones (187.0 vs. 82.7 DDD); however, analysing the regional variability, differences between the different regions of 5 times are noted, with Sardinia reaching the highest value with 270 DDD and Basilicata, Campania and Molise registering instead the lowest levels of consumption (about 60 DDD). Latium and Sicily are the Regions with the greatest changes in consumption compared to 2021 (+9.8% and -13.7% respectively).

All indicators presented in this section are calculated on the female population (12-50 years)

Figure 2.6.20a Contraceptive medicines, 2015-2022 time trend in consumption and average DDD cost

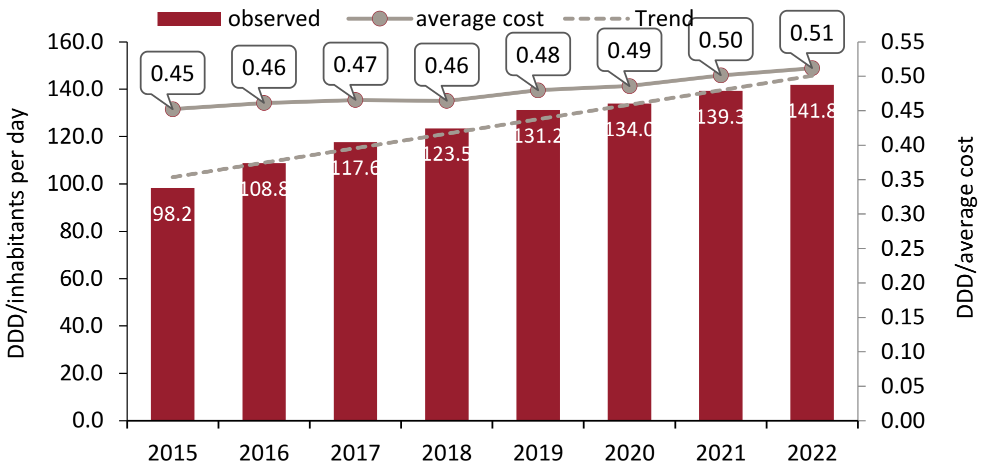


Table 2.6.20a Contraceptive medicines, *per capita* expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2015-2022

Subgroups and substances	Expenditure million	Expenditure *per capita*	Δ % 22-21	CAGR % 15-22	DDD/1000 inhab. per day	Δ % 22-21	CAGR % 15-22	Average cost DDD	Δ % 22-21
Estroprogestinic oral contraceptives of fourth generation	187.5	14.31	5.2	8.0	66.8	4.4	7.2	0.59	0.7
Estroprogestinic oral contraceptives of third generation	39.7	3.03	-0.8	-0.6	23.9	-4.1	-3.3	0.35	3.4
Intravaginal contraceptive medicines	32.9	2.51	-1.3	5.4	10.9	0.0	6.9	0.63	-1.3
Estroprogestinic oral contraceptives of second generation	26.9	2.05	-4.9	7.4	12.0	-3.8	6.4	0.47	-1.2
Estroprogestinic oral contraceptives	24.6	1.88	17.8	18.9	10.8	14.4	18.3	0.48	2.9
Oral emergency contraceptives	18.4	1.41	19.4	21.1	0.2	18.0	18.2	24.06	1.2
Transdermal estroprogestin contraceptives	8.3	0.63	-5.6	3.8	2.9	-5.6	3.2	0.60	-0.1
Intrauterine contraceptives	8.1	0.62	-2.6	10.7	13.5	-1.3	11.4	0.13	-1.3
Systemic subcutaneous implant contraceptives	0.8	0.06	21.9	17.2	0.8	21.9	17.2	0.20	0.0
Contraceptive medicines	**347.1**	**26.49**	**4.0**	**7.3**	**141.8**	**1.8**	**5.4**	**0.51**	**2.1**
drospirenone/ ethinylestradiol	67.7	5.17	-0.2	-0.1	24.5	-0.8	-0.7	0.58	0.6
dienogest/ ethinylestradiol	44.9	3.42	3.2	21.6	18.2	3.2	21.0	0.52	0.0
dienogest/ estradiol	41.8	3.19	9.5	15.4	13.2	9.7	14.2	0.66	-0.2
ethonogestrel/ ethinylestradiol	32.9	2.51	-1.3	5.4	10.9	0.0	6.9	0.63	-1.3
levonorgestrel/ ethinylestradiol	26.9	2.05	-4.9	7.4	12.0	-3.8	6.4	0.47	-1.2
gestodene/ ethinylestradiol	25.3	1.93	-10.8	-3.4	17.7	-10.3	-5.0	0.30	-0.6
nomegestrol/ estradiol	23.0	1.75	-0.2	14.4	7.4	0.0	12.8	0.65	-0.2
desogestrel	16.7	1.28	1.7	12.5	8.1	2.1	13.4	0.43	-0.3
levonorgestrel/	14.2	1.08	1.7	12.1	13.5	-1.2	11.4	0.22	2.9
ulipristal	12.4	0.94	26.0	26.0	0.1	25.8	26.0	26.85	0.1

Table 2.6.20b Contraceptive medicines, regional trend of weighted DDD/1000 inhab. per day: comparison 2015-2022

Region	2015	2016	2017	2018	2019	2020	2021	2022	Δ % 22-21
Piedmont	133.6	166.2	169.6	181.0	188.5	189.4	195.8	200.1	2.2
Valle d'Aosta	158.4	206.4	217.6	216.1	212.4	220.5	221.9	232.9	5.0
Lombardy	119.2	130.4	161.2	178.3	189.1	186.9	194.3	198.9	2.4
A.P. of Bolzano	221.5	212.0	202.3	201.8	194.3	184.8	184.4	185.3	0.5
A.P. of Trento	153.9	150.4	155.6	165.1	172.9	167.1	177.1	187.3	5.8
Veneto	118.0	114.1	145.1	151.7	159.6	156.0	160.8	165.3	2.8
Friuli V.G.	107.5	128.0	142.2	148.6	151.1	154.1	160.2	162.9	1.7
Liguria	143.2	181.3	185.0	193.4	206.1	208.5	208.0	210.4	1.2
Emilia R.	134.5	148.0	159.0	152.1	161.5	159.7	166.4	169.1	1.7
Tuscany	121.6	125.0	136.1	150.3	156.3	157.3	164.3	172.4	4.9
Umbria	61.6	65.2	63.7	64.6	66.8	104.5	124.3	129.5	4.2
Marche	53.0	53.0	48.8	46.1	57.8	90.6	110.6	113.5	2.6
Lazio	73.8	76.5	89.5	102.4	117.5	117.8	120.5	132.3	9.8
Abruzzo	88.6	89.7	87.4	83.5	93.2	93.0	94.8	98.9	4.4
Molise	53.1	61.9	60.5	58.4	58.9	60.1	59.8	58.9	-1.5
Campania	52.5	69.1	51.7	48.6	51.4	55.5	60.0	58.8	-2.1
Puglia	67.9	68.3	67.4	70.8	77.8	77.9	78.2	79.6	1.8
Basilicata	44.2	56.4	55.8	56.0	58.1	56.9	59.8	55.8	-6.8
Calabria	44.4	57.5	55.4	56.0	58.5	61.8	66.6	65.4	-1.9
Sicily	52.6	58.7	60.6	59.6	59.5	75.3	74.5	64.3	-13.7
Sardinia	223.2	266.7	265.6	267.3	274.3	274.2	281.4	270.0	-4.1
Italy	**98.2**	**108.8**	**117.6**	**123.5**	**131.2**	**134.0**	**139.3**	**141.8**	**1.8**
North	127.3	140.8	160.7	169.6	178.4	176.8	182.9	187.0	2.2
Centre	84.6	87.3	96.6	107.0	118.2	125.4	132.9	142.0	6.8
South and Islands	69.6	80.9	75.6	75.0	78.5	83.8	86.1	82.7	-4.0

Medicines for erectile dysfunction

- Expenditure on medicines for erectile dysfunction stands at €240 million in 2022 with €9.88 *per capita* (figure calculated on the male population aged 18+ years), an increase of 1.1% compared to 2021. Consumption shows an increasing trend since 2015 with an increase of 90% and an average annual variation of +9.6% and an increase of 5.7% compared to the previous year; from 2015 to 2022 the average cost of the category has almost halved (from €8.11 to €4.97) due to the patent expiry of the main molecules (Figure 2.6.21a and Table 2.6.21a).
- Tadalafil and sildenafil remained the substances with the highest expenditure (EUR 4.98 and EUR 3.95 *per capita* respectively) and consumption (3.2 and 1.9 DDD respectively) and accounted for about 90% of the expenditure and doses in this category. For all molecules, except for tadalafil (+4.7 %) there was a decrease in expenditure in 2022. In particular, alprostadil, a medicine administered by intracavernous injection, recorded a contraction of 12.7 %, while still maintaining the highest cost per DDD in the category (28.44 euro), albeit with reduced consumption.
- In the Central regions, consumption is 22% higher than the average (6.7 vs. 5.5 DDD), while the values in the South are in line with the national value; those in the North are 11% lower. Campania registers the highest consumption with 7.7 DDD, followed by Latium 7.1 DDD and Tuscany with 6.6 DDD; Latium, Trento and Abruzzi register the highest increases, exceeding 10% (Table 2.6.21b).

All indicators presented in this section are calculated on the male population over the age of 18

Figure 2.6.21a Erectile dysfunction medicines, 2015-2022 time trends in consumption and average DDD cost

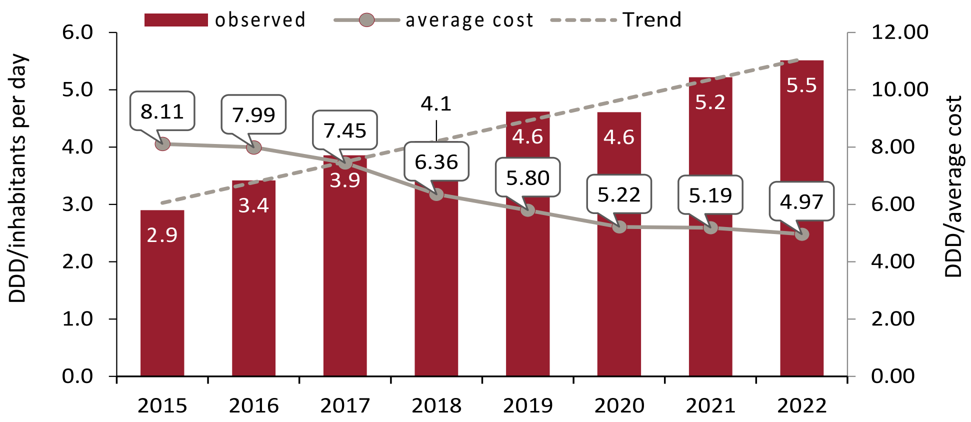


Table 2.6.21a Medicines for erectile dysfunction, *per capita* expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2015-2022

Subgroups and substances	Expenditure million	Expenditure *per capita*	Δ % 22-21	CAGR % 15-22	DDD/1000 inhab. per day	Δ % 22-21	CAGR % 15-22	Average cost DDD	Δ % 22-21
Medicines for erectile dysfunction	**240.0**	**10.00**	**1.1**	**2.2**	**5.5**	**5.7**	**9.6**	**4.97**	**-4.3**
tadalafil	119.7	4.98	4.7	3.2	3.2	10.8	16.0	4.23	-5.5
sildenafil	94.8	3.95	-0.9	6.0	1.9	0.2	7.4	5.68	-1.1
vardenafil	16.6	0.69	-5.0	-10.3	0.3	-4.4	-6.3	7.13	-0.7
avanafil	4.8	0.20	-7.8	-7.7	0.1	-7.1	-7.0	5.49	-0.7
alprostadil	4.2	0.17	-12.7	1.7	0.0	-13.9	-0.8	28.85	1.4

Table 2.6.21b Medicines for erectile dysfunction, regional trend of weighted DDD/1000 inhab. per day: comparison 2015-2022

Region	2015	2016	2017	2018	2019	2020	2021	2022	Δ % 22-21
Piedmont	3.1	3.9	4.0	4.3	4.7	4.5	5.1	5.3	3.9
Valle d'Aosta	2.5	3.6	3.6	4.0	4.2	4.1	4.4	4.4	-1.2
Lombardy	2.6	3.0	3.8	4.1	4.3	4.0	4.4	4.6	5.2
A.P. of Bolzano	3.0	3.1	3.0	3.2	3.3	3.2	3.2	3.5	6.8
A.P. of Trento	2.5	2.6	2.6	2.8	2.9	2.7	3.0	3.3	10.7
Veneto	2.6	2.7	3.5	3.6	4.1	3.8	4.1	4.3	6.0
Friuli V.G.	2.2	2.7	3.1	3.1	3.5	3.3	3.7	3.9	6.2
Liguria	3.9	4.9	5.2	5.7	5.9	5.8	6.4	6.5	1.3
Emilia R.	4.0	4.6	5.0	4.9	5.4	5.1	5.6	5.9	6.1
Tuscany	4.1	4.7	5.3	5.7	6.0	5.8	6.4	6.6	3.2
Umbria	2.3	2.9	3.1	3.1	3.4	4.3	5.7	6.0	5.2
Marche	2.3	2.6	2.8	2.5	3.5	4.4	5.7	6.1	6.5
Lazio	3.1	3.6	4.2	4.8	5.7	5.6	6.2	7.1	13.3
Abruzzo	3.5	3.8	4.1	4.0	4.9	4.6	5.3	5.9	10.2
Molise	2.5	2.8	3.0	3.2	3.8	3.5	4.3	4.5	5.7
Campania	3.5	4.2	4.4	4.7	5.6	6.0	7.3	7.7	5.6
Puglia	2.7	3.0	3.3	3.6	4.3	4.2	4.7	5.1	9.2
Basilicata	1.6	2.1	2.1	2.3	2.6	2.7	3.3	3.5	8.7
Calabria	1.7	2.3	2.5	2.6	3.1	3.3	4.1	4.3	5.7
Sicily	1.9	2.5	3.0	3.2	3.8	4.5	5.0	4.9	-2.7
Sardinia	2.3	3.1	3.1	3.3	3.8	3.6	4.2	4.2	0.0
Italy	**2.9**	**3.4**	**3.9**	**4.1**	**4.6**	**4.6**	**5.2**	**5.5**	**5.7**
North	2.9	3.4	4.0	4.2	4.5	4.3	4.7	4.9	5.1
Centre	3.3	3.8	4.3	4.7	5.3	5.4	6.2	6.7	8.6
South and Islands	2.6	3.2	3.5	3.7	4.3	4.6	5.4	5.6	4.4

NSAIDs and antipyretics

- In the last seven years, the consumption of antipyretic medicines has progressively increased from 16.2 to 25 DDD/1000 inhabitants per day (Figure 2.6.22a) with an average annual variation of 6.4%, but with an increase of 20% in the last year alone.
- Expenditure in 2022 amounted to more than EUR 1 billion or EUR 17.45 *per capita* with an increase of about 18% over the previous year (Table 2.6.22a).
- Paracetamol alone or in combination and traditional NSAIDs, which according to the main recommendations can be used as symptomatic therapy in patients with COVID-19 at home in case of fever or muscle pain, account for 90% of the consumption and expenditure of the whole category. For these reasons, an important increase in the use of these categories had already been observed in 2020 and was maintained in 2021 and 2022; for traditional NSAIDs (+23.7%) and for paracetamol alone or in combination (+16.2%).
- Paracetamol is the substance with the highest expenditure with €7.01 *per capita* and consumption with 11.1 DDD/1000 inhabitants per day, followed by ibuprofen (€4.30 and 4.1 DDD/1000 inhabitants per day, both up by about 50%), which alone accounts for more than 50% of all NSAIDs and is the medicine with the highest cost per day of therapy with €2.89.
- The variation in the consumption of paracetamol (alone or in combination) could depend on the high incidence of influenza-like syndromes in the paediatric segment during the 2022-2023 season, while for ibuprofen the increases could be more related to the home treatment of COVID-19.
- Instead, considering consumption at the regional level, it may be noted that in the macro-areas of the North there is greater consumption than the national average (27.6 DDD), while the Centre and in particular the South and the Islands record lower consumption than the average (Table 2.6.13b). Compared to the previous year, variations are observed ranging from +15.8 in the South and Islands to +22.3% in the Centre. In detail, it goes from 15.8 DDD in Sicily, a value more than half smaller than the maximum in Valle d'Aosta (33.1 DDD); the two Autonomous Provinces of Trento and Bolzano have increases in consumption of more than 30%.

Figure 2.6.22a NSAIDs and antipyretics, 2015-2022 time trend in consumption and average DDD cost

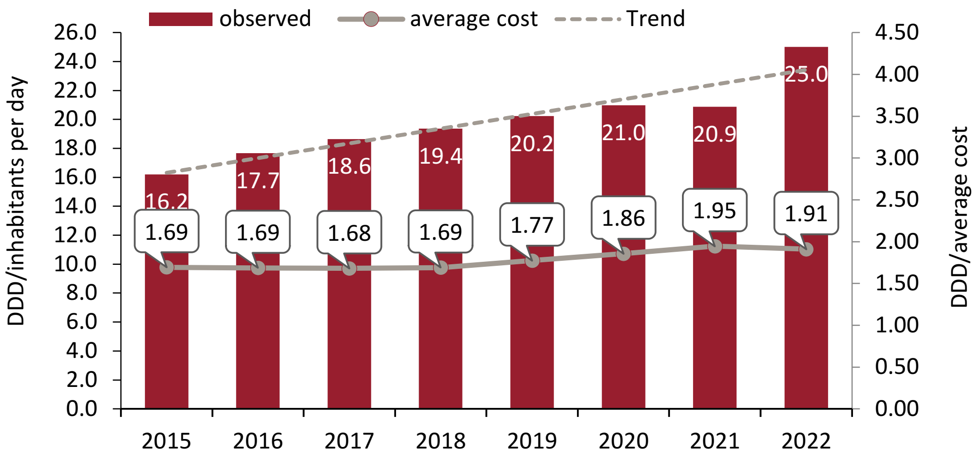


Table 2.6.22a NSAIDs and antipyretics, *per capita* expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2015-2022

Subgroups and substances	Expenditure million	Expenditure *per capita*	Δ % 22-21	CAGR % 15-22	DDD/1000 inhab. per day	Δ % 22-21	CAGR % 15-22	DDD average cost	Δ % 22-21
Paracetamol plain and in combination	494.8	8.39	5.2	8.5	13.2	16.2	7.5	1.75	-9.4
Traditional NSAIDs	429.8	7.29	33.6	9.8	9.3	23.7	6.5	2.15	8.0
Other antipiretics - salicylic acid and derivatives	80.3	1.36	32.4	2.5	1.7	26.8	0.3	2.15	4.3
Other antipiretics - Pyrazolones	12.8	0.22	-10.1	-1.8	0.3	-10.3	-4.1	2.33	0.3
Other nonsteroidal anti-inflammatory/ anti-rheumatic medicines	10.8	0.18	54.9	11.2	0.6	59.5	15.6	0.89	-2.9
Coxib	0.5	0.01	4.7	10.8	0.0	5.2	8.4	1.22	-0.5
Oxicam	0.0	0.00	-70.9	-23.8	0.0	-79.3	-27.0	1.24	40.6
NSAIDs and antipyretics	**1,029.0**	**17.45**	**17.7**	**8.2**	**25.0**	**19.9**	**6.4**	**1.91**	**-1.8**
paracetamol	413.3	7.01	-2.7	9.6	11.1	9.6	8.9	1.73	-11.2
ibuprofen	253.8	4.30	52.8	10.3	4.1	47.6	9.2	2.89	3.5
ketoprofen	73.6	1.25	12.3	13.6	1.7	9.3	12.4	2.00	2.8
acetylsalicylic acid/ ascorbic acid	66.9	1.13	40.2	3.6	1.5	33.0	1.3	2.07	5.4
diclofenac	38.0	0.64	14.8	9.8	0.8	8.7	7.3	2.13	5.6
paracetamol/ascorbic acid/phenylephrine	34.4	0.58	132.7	3.5	0.6	127.0	1.8	2.53	2.5
naproxen	25.5	0.43	12.6	10.0	0.9	7.6	7.5	1.30	4.6
acetylsalicylic acid	13.0	0.22	3.9	-1.9	0.2	-1.5	-4.6	2.66	5.5
ketorolac	12.9	0.22	8.2	7.7	0.2	8.3	7.1	2.43	-0.1
paracetamol /chlorphenamine	10.7	0.18	72.8	0.8	0.5	76.1	-1.0	1.10	-1.9

Table 2.6.22b NSAIDs and antipyretics, regional trend of weighted DDD/1000 inhab. per day: comparison 2015-2022

Region	2015	2016	2017	2018	2019	2020	2021	2022	Δ % 22-21
Piedmont	18.8	21.8	22.4	23.3	22.7	24.3	22.4	28.0	24.8
Valle d'Aosta	23.5	27.6	28.8	29.4	28.5	30.0	26.0	33.1	27.3
Lombardy	17.1	19.1	21.7	22.2	22.7	23.6	22.6	27.2	20.5
A.P. of Bolzano	20.5	20.4	20.8	21.3	21.3	20.1	20.1	26.4	31.2
A.P. of Trento	21.0	21.2	21.7	22.7	22.2	21.5	20.6	27.5	33.5
Veneto	19.7	20.6	23.3	23.6	24.0	23.5	23.2	27.9	20.3
Friuli V.G.	18.3	20.1	21.7	22.3	22.2	22.8	22.6	26.7	17.8
Liguria	18.3	21.6	22.0	23.0	23.6	23.4	23.2	27.5	18.7
Emilia R.	20.1	20.8	21.5	21.3	22.6	22.7	23.1	27.8	20.4
Tuscany	15.2	16.0	16.6	17.4	18.1	19.2	19.8	24.3	23.0
Umbria	15.3	15.7	15.5	15.6	15.8	20.5	22.4	26.4	17.6
Marche	11.8	12.7	12.2	12.6	13.3	16.5	18.4	22.5	22.3
Lazio	15.1	16.0	17.5	19.1	21.2	20.6	20.4	25.0	22.5
Abruzzo	15.4	15.9	15.8	16.6	18.4	17.8	17.7	21.5	21.6
Molise	11.8	13.4	13.5	14.3	15.0	14.8	14.7	17.5	19.3
Campania	16.2	17.4	16.8	17.7	19.3	23.1	24.6	27.2	10.7
Puglia	14.9	16.2	15.9	16.7	18.7	18.7	18.6	22.5	21.0
Basilicata	13.8	16.0	16.0	16.4	18.0	17.0	17.4	21.4	22.9
Calabria	11.8	13.6	14.1	14.9	15.5	16.0	17.3	20.1	16.0
Sicily	10.1	11.4	12.1	12.9	13.4	14.2	13.8	15.8	14.6
Sardinia	14.6	17.4	18.0	18.9	19.7	18.0	17.8	21.4	20.4
Italy	**16.2**	**17.7**	**18.6**	**19.4**	**20.2**	**21.0**	**20.9**	**25.0**	**19.9**
North	18.6	20.4	22.1	22.6	22.9	23.4	22.7	27.6	21.3
Centre	14.7	15.6	16.3	17.4	18.8	19.6	20.1	24.6	22.3
South and Islands	13.7	15.1	15.2	16.0	17.3	18.3	18.7	21.6	15.8

Section 3

Consumption and expenditure by therapeutic class

General data on expenditure and consumption by ATC group

This section presents the trend in pharmaceutical expenditure and consumption, including the prescription under approved care and the supply of medicines purchased directly from public health facilities. National and regional data are analysed by ATC level I, by therapeutic category and by active ingredient.

In 2022, the NHS pharmaceutical expenditure, expressed as a per capita value, was 419.37 euro, with a 5.7% increase compared to the previous year (Table 3.1). This trend was mainly determined by an 8.6% increase in expenditure for public health facilities (253.59 euro, equal to 60% of total expenditure), while the expenditure for class A drugs under approved care regime showed a more moderate increase (+1.5%; 165.78 euro).

Within the approved care regime, antimicrobials for systemic use are the category with the highest increase (+16.1%), followed by musculoskeletal system drugs and systemic hormonal preparations (+4.2% and +4.1% respectively). Reductions of slightly less than 2% are seen for sensory organs, respiratory drugs and dermatologicals. As already highlighted in previous years, once again in 2022 cardiovascular system drugs are the category with the highest per capita expenditure (50.29 euro, equal to 87% of the total in the category) stable in the 2017-2022 period. These are followed by medicines for the gastrointestinal system (32.64 euro) and those for the central nervous system (23.81 euro). As regards the medicines dispensed by public health facilities, antineoplastic and immunomodulators reached 113.04 euro per capita in 2022 (96% of total expenditure), an increase of 5.1% compared to 2021 and with a constant trend increase in the last 6 years and an average cost per DDD that goes from 15.78 euro in 2017 to 17.21 in 2022 (Figures 3.1 and 3.3). Among the categories with the highest expenditure, there were significant increases for gastrointestinal medicines (+16.5%; 22.58 euro), respiratory drugs (+66.2%; 10.37 euro) and central nervous system drugs (+18.7 %; 9.77 euro).

In terms of total consumption (1325.21 DDD/1000 inhabitants per day), there is an increase of 1.6% over the previous year (Table 3.2), with consumption in approved care regime accounting for 86% of the total doses. Cardiovascular drugs account for 38.1% of the total DDDs consumed, with the highest number of doses (505.32 DDD/1000 inhabitants per day, almost entirely represented by the prescription under approved care regime) and stable compared to the previous year. These are followed by medicines acting on the gastrointestinal system and metabolism (316.7 DDD), stable compared to 2021, as well as in the last 6 years (Figure 3.2), on blood and blood forming organs (143.6 DDD/1000 inhabitants per day; +2.2%) and on the central nervous system (98.2 DDD; +2.8%).

Public and private expenditure by ATC 1st level (Table 3.3) show that antineoplastic and immunomodulating agents have the highest expenditure, with a value of 7.0 billion, an incidence of 21.1% on total pharmaceutical expenditure and a per capita value of 118.83 euro. As expected for this category, the largest share of expenditure (95.1%) refers to purchases by public health facilities. Gastrointestinal drugs account for 14.2% of total expenditure and represent, in absolute values, the most privately purchased category in the case of both class A medicines (403 million euro), class C medicines (276 million), and self-medication drugs (782 million euro). Medicines acting on the central nervous system have the highest absolute expenditure value of class C drugs sold upon prescription (1.20 billion euro) and in fact represent 34.1% of the total expenditure in this reimbursement range. As for purchases by public health facilities, 44.6% (equal to 6.7 billion euro) refers to antineoplastics and immunomodulators; as for class A drugs, 30.3% relates to cardiovascular drugs, for a total expenditure of 2.97 billion euro.

The most consumed privately purchased class A drugs (Table 3.4) are gastrointestinal system drugs (78.0 DDD/1000 inhabitants per day), while drugs acting on the central nervous system are the most used within class C drugs with prescription (70.3 DDD/1000 inhabitants per day); gastrointestinal drugs rank first for consumption within self-medication drugs (35.7 DDD/1000 inhabitants per day), followed by drugs for the respiratory system (39.9 DDD). Blood and blood-forming organs drugs (53 DDD, equal to 28.8%) show the highest consumption within public health facilities, while cardiovascular drugs are the most used in class A, with 487.4 DDD (42.7% of the total).

Table 3.5 shows the distribution of gross per capita expenditure under approved care regime of class A drugs, classified by Region and geographical area. Overall, compared to the national value of 165.8 euro, the Northern and Central Regions report lower values, respectively 153.8 and 162.5 euro, while the Southern Regions show a higher value, equal to 185.1 euro (+13% compared to the national average). The greatest variability, highlighted by the variation coefficient (VC), is observed for the ATC “Various” (VC: 123%). A large variability is also observed for ATC “Blood and blood forming organs” drugs (VC: 54%), as the expenditure values range from 2.2 euro in Liguria to 12.4 euro in Lazio. These differences are probably due to the different use of alternative drug dispensing methods (e.g. direct and “on-behalf” distribution). Cardiovascular system drugs report the largest proportion of expenditure under approved care regime in all regions, followed by drugs for the gastrointestinal tract and metabolism, those for the central nervous system and, to a lesser extent, by respiratory drugs.

The trend in drug consumption (Table 3.6) shows a greater use in the South (1,238.2 DDD/1000 inhabitants per day, 8.6% higher than the national average) and in the Centre (1,148.5 DDD) compared to the North (1069.2 DDD, 6.3% below the average). For ATC “Antineoplastics and immunomodulators” (VC 26%) the highest consumption is observed in Campania (22.2 DDD/1000 inhab. per day) and the lowest in the Province of Bolzano (8.1 DDD). The first three categories with the highest consumption (ATC A, B and C) account for over 75% of the doses in all regions.

Table 3.7 shows the regional trend of per capita expenditure of drugs purchased by public health facilities by ATC 1st level. In general, the Central and Southern Regions show a higher per capita expenditure, respectively of 255.0 euro and 267.3 euro, compared to the Northern Regions (243.4 euro). Drugs in the “Various” category, musculoskeletal and cardiovascular system drugs and the genitourinary drugs report the largest regional variability (VC: 31-24%). The per capita expenditure values of drugs for the musculoskeletal system vary in particular from 1.5 euro in the Aosta Valley to 7.2 euro in the Province of Bolzano. The antineoplastics and immunomodulators category represents, in almost all the Regions, about half of the expenditure of public health facilities.

However, when analysing consumption (Table 3.8), the greatest heterogeneity in the Regions is observed for genitourinary drugs (VC: 92%), with a difference between the maximum value (10.8 DDD/1000 inhabitants per day in Emilia Romagna) and the minimum value (0.8 DDD/1000 inhabitants per day in Molise) up to 10 DDD. The category with the highest consumption in all Regions is ATC B with values ranging between 16.9% and 41.9%,

which (together with ATC A and N) accounts for over 65% of the consumption of drugs purchased by public health facilities in all the Regions.
Table 3.9 shows, for each ATC 1st level category, the therapeutic subgroups in descending order of expenditure, sorted by per capita expenditure, up to the value of 0.10 euro of per capita expenditure. Information relating to expenditure, prescribed doses and average cost per day of therapy is provided, the variation with respect to the previous year and the mix effect is calculated (Table 3.9 and Figure 3.4). For class A drugs dispensed under approved care regime, it should be noted that the change in expenditure of +1.1% compared to 2021 was determined by an increase in the quantities prescribed (+0.4%) and by a shift towards specialties more expensive (mix effect: +1.7%), with an average cost per DDD slightly up by 0.7%, on the contrary prices decreased by 1.1%. However, there are many differences between the therapeutic categories. As regards cardiovascular system drugs, the increase in expenditure was due almost exclusively to a positive mix effect (+1.3%) and to an increase in the average DDD cost (+0.9%), offset by stable consumption (+0.2%) and by a reduction in prices (-0.4%). Also for drugs acting on the gastrointestinal tract there is an increase in expenditure (+0.6%) entirely due to the mix effect (+3.2%) despite a reduction in the quantities prescribed and in prices (-2.1 % and -0.4% respectively). For respiratory drugs, a reduction in expenditure was observed (-1.9%) deriving from a contraction in prices (-3.8%) partly offset by an increase in quantities (+2.1%). For antimicrobials, however, expenditure increased by 15.6% originating exclusively from a 22.7% increase in quantities despite a mix effect of -5.5%.
When analysing the individual therapeutic categories, acid pump inhibitors show the highest value of per capita expenditure (11.40 euro), with a mix effect of -2.3% (determined by competition on the market for generic medicines) and a consumption increased by 1.3%, followed by statins (HMG-CoA reductase inhibitors) with 8.15 euro, with all indicators stable compared to 2021. Adrenergic drugs combined with corticosteroids or others, excluding anticholinergics (7.20 euro) belonging to respiratory system drugs, show a reduction in all indicators (expenditure: -8.2%, DDD: -2.7%, prices: -5.9%, mix effect: 0.2%).
The higher consumptions, in addition to vitamin D and analogues (139.2 DDD), are mostly due to cardiovascular drugs, in particular for HMG-CoA reductase inhibitors (82.3 DDD/1000 inhabitants per day) and ACE inhibitors not in combination (80.4 DDD/1000 inhabitants per day), followed by acid pump inhibitors (77.5 DDD/1000 inhabitants per day) and platelet aggregation inhibitors (61.1 DDD/1000 inhabitants per day). The trend in vitamin D expenditure (-2.8%) is entirely due to the reduction in consumption (-2.7%), while for ACE inhibitors, expenditure decreased by 4.5% compared to 2021 with all the other indicators declining. The expenditure for GLP-1 receptor analogues increases by 66.3% due to a combination of increased consumption (+57.2%) and a mix effect (+5.8%).
Considering the percentage of expenditure for 1st level ATC (Table 3.10), we can see that as for cardiovascular drugs, atorvastatin accounts for 9.3% of expenditure and 10.4% of doses, ramipril on the other hand, although accounting for 12.6% of doses, accounts for only 3.9% of expenditure. Cholecalciferol alone accounts for about half of the consumption of gastrointestinal drugs (49%). As regards the central nervous system, three SSRI antidepressants (sertaline, paroxetine and escitalopram) individually represent more than 10% of the doses. Finally, the formoterol/beclomethasone and vilanterol/fluticasone furoate associations account for one third of the expenditure of respiratory drugs, just as

the amoxicillin/clavulanic acid association represents 34% of the consumption and 23.7% of the expenditure of antimicrobial drugs.
The first thirty active ingredients for class A approved care expenditure (Table 3.11) represent 37.7% of the total class A-NHS expenditure, equal to an absolute value of 3687.1 million euro. Overall, twelve molecules belong to the category of meidicines acting on the cardiovascular system and are mainly represented by atorvastatin (276 million), bisoprolol (166.5 million), omega-3 (127.1 million) and ramipril (115 million); the combination ezetimibe/rosuvastatin rose from 42nd rank in 2021 to 21st in 2022, reaching 91.2 million in expenditure, this being among other things the substance that had the greatest change in rank. Another nine belong to the category of drugs acting on the gastrointestinal system and metabolism, including: pantoprazole (266.3 million), cholecalciferol (239.0 million), esomeprazole (132.2 million), lansoprazole (128.2 million) and omeprazole (127.5 million).
The average cost of direct purchases is an indicator that provides an estimate of the effect of regional purchasing procedures for individual active ingredients and, as expected, there are large differences that indicate different drug dispensing methods, for example for pantoprazole the average cost of direct purchases is half that of purchases under approved care regime. For cholecalciferol it goes from 0.01 euro in direct purchases to 0.08 euro under approved care regime (+70%), while for amoxicillin/clavulanic acid there are smaller differences (+36%) as well as for the combination formoterol/beclometasone (+33%). A case worth mentioning concerns rifaximin, the average cost of which in direct purchases is higher than that under approved care regime (2.19 vs 2.08 euro). Table 3.12 shows the regional trend of the ranks for the first 30 active ingredients by expenditure, showing that cholecalciferol ranks 12th in Tuscany and is among the top 3 drugs in almost all the other Regions. Enoxaparin, the 13th most expensive active ingredient, ranks over 200th in eight Regions including Marche, Piedmont and Emilia Romagna (Regions where it is mainly supplied by direct distribution) while it ranks 2nd in Lazio and 3rd in the Province of Bolzano and 5th in Lombardy, where it is mainly supplied by approved care regime. Finally, it should be noted that insulin lispro and letrozole rank over 100th in Emilia Romagna while in the other Regions they rank between 10th and 60th.
In 2022, the drugs supplied under approved care regime with the highest average cost per day of therapy were teriparatide (14.15 euro; a 9.5% decrease compared to 2021), ceftriaxone (11.93 euro), semaglutide (7.90 euro, an increase of 3.2% compared to 2021), followed by the valsartan/sacubitril combination (7.21 euro) (Table 3.13). Among the top 30 active ingredients with the lowest average cost per day of therapy, there are acetylsalicylic acid (0.07 euro), cholecalciferol and furosemide (0.08 euro), more than half of the substances listed belong to the category of cardiovascular drugs (18 out of 30) (Table 3.14).
Among the first 30 active ingredients with the greatest change in expenditure, two antidiabetics (semaglutide and dulaglutide; +112.3% and +51.1% respectively) rank 1st and 2nd (Table 3.15), followed by ezetimibe/rosuvastative (+50.2%), clarithromycin and cefixime (+48.8% and +43.1%). Among the first 30 active ingredients with the smallest reduction in expenditure is a drug for pain therapy (naloxone/oxycodone: -29.1%), followed by four respiratory drugs indicated for the treatment of asthma and COPD (salmeterol/fluticasone, aclidinium, tiotropium and umeclidinium) with variations between -28.2% and -15.4% (Table 3.16).

Table 3.17 shows the top 30 most consumed active ingredients; cholecalciferol with 136.8 DDD ranks 1st and accounts for 12% of the total consumption in class A-NHS approved care regime, followed by ramipril with less than half of DDD (61.5), atorvastatin (50.9 DDD) and acetylsalicylic acid (45 DDD). The first thirty substances represent more than 58.5% of the total expenditure. As expected, there are large differences in the average cost for DDD between purchase under approved care regime and direct purchases, for example for atorvastatin, amlodipine and valsartan.
Table 3.18 shows the regional ranks of the first 30 active ingredients by consumption relating to approved care pharmaceutical expenditure. The first 5 molecules (cholecalciferol, ramipril, atorvastatin, acetylsalicylic acid and pantoprazole) show no particular differences in rank within the Regions. Exceptions are molecules such as omeprazole which ranks 40th rank in the Province of Bolzano and in the Marches, as well as the combination of olmesartan/hydrochlorothiazide in Emilia Romagna and Tuscany and sertraline in the southern Regions.
Table 3.19 shows, with regard to purchases by health facilities, for each ATC 1st level category, the therapeutic subgroups in descending order of expenditure, up to 0.10 euro of per capita expenditure. Information relating to expenditure, prescribed doses and average cost per day of therapy is provided, the variation with respect to the previous year and the mix effect is calculated (Table 3.19 and Figure 3.5). In 2022, per capita expenditure for drugs purchased directly by public health facilities was 253.59 euro, an increase of 8.1% over the previous year. This trend is produced by an increase in consumption (+6.1%) and by a shift towards more expensive medicines (mix effect: +5.6%) offset by a 3.5% drop in prices. The expenditure for immunomodulatory and immunostimulant drugs (ATC L) increased by 4.6% due to an increase in consumption (+9.2%), a positive mix effect (+1.4%) and a price reduction of 5.6%. Only two categories show a negative mix effect: other immunosuppressants and CD-38 inhibitors (around 30%). For the latter category, the mix effect was caused by a marked increase in consumption for the daratumumab pack which has the lowest average cost per DDD in the category. Among antiandrogens, the mix effect is instead +40%, to be attributed to the introduction on the market of two new active ingredients apalutamide and darolutamide which have the highest average cost per DDD in their category. Among the antimicrobial drugs for systemic use, it should be noted that expenditure on the Herpes Zooster vaccine increased by 300% due to the recent marketing of two packs of adjuvanted recombinant vaccines which have an average cost per DDD of around 180 euro.
Table 3.20 shows the most prescribed active ingredients by ATC 1st level in public health facilities. The drugs with the greatest expenditure impact by category include the following: dupilumab, which accounts for about 85% of dermatologicals, atovaquone (60.6% of antiparasitic drugs), aflibercept (45.1% of sensory organs drugs), nusinersen (30.7% of musculoskeletal system drugs).
With reference to the first thirty most expensive active ingredients, which represent 32% of the total expenditure by healthcare facilities, 18 molecules belong to the category of antineoplastic and immunomodulatory drugs and 4 to blood and blood-forming organs drugs. Pembrolizumab and daratumumab recorded the highest values of per capita expenditure, equal to 7.54 and 6.62 euro respectively (Table 3.21), with a total expenditure of 445 and 391 million respectively. Followed by the association elexacaftor/tezacaftor/ivacaftor with 3.50 euro per capita (which shows a rapid growth

moving from rank 89th in 2021 to rank 3rd in 2022), ibrutinib with 3.42 euro and nivolumab with 3.30 euro. Dulaglutide and semaglutide, antidiabetics administered weekly, move to rank 10th and 27th in 2022 starting from rank 18th and rank 85th in 2021; the same for dupilumab, a monoclonal antibody indicated for the treatment of atopic dermatitis, which goes from rank 28th to rank 11th. Among the first four most expensive medicines there are no particular differences in the regional ranks with the exception of Valle d'Aosta which records lower spending positions of some molecules compared to the other Regions, while in Lombardy dulaglutide and semaglutide occupy respectively the 788th and the 252nd position, probably due to the dispensing of these drugs under approved care regime (Table 3.22). In this context, they are in fact the first and third most expensive substance in this Region. Analysing the first 30 active ingredients with the greatest increase in expenditure (Table 3.23), eleven belong to the category of oncologicals and immunosuppressants, although the greatest increases refer to the varicella vaccine Zooster (>1000%), tafamidis (>500%) recently approved and indicated for the treatment of cardiomyopathy due to transthyretin-mediated amyloidosis (ATTR-CM) in adults, to the combination of elexacaftor/tezacaftor/ivacaftor (>300%) and ivacaftor alone (>130%), both used in the treatment of cystic fibrosis. The drugs with the greatest expenditure reduction (Table 3.24) are lenalidomide (-55.7%), deferasirox (-32.2%), octocog-alfa (-30.7%), trastuzumab (-27.1%) and the combination dolutegravir/abacavir/lamivudine (-26.6%). Agalsidase alfa and imiglucerase, used as enzyme therapy for Fabry disease and Gaucher disease respectively, algucosidase alfa indicated in Pompe disease, and albutrepenonacog alfa, indicated in the treatment and prophylaxis of bleeding in patients with haemophilia B, are the first four active ingredients with an average cost per DDD greater than 1,000 euro (Table 3.25). As many as fourteen molecules belong to the category of antineoplastic and immunomodulatory drugs, four to the category of blood and blood-forming organs drugs and another four to the category of gastrointestinal drugs. For all molecules, there is no significant change in the average cost per DDD compared with the previous year, with the exception of normal human immunoglobulin for extravascular administration, which increased by 30%. Table 3.26 shows the drugs with the lowest average cost per day of therapy and among these can be found electrolytes for intravenous solution (0.40 euros), followed by denosumab (0.85 euro) and enoxaparin (0.87 euros); important reductions of this indicator are found for semaglutide, trastuzumab, adalimumab and etanercept. Within the most consumed drugs, the first six active ingredients, with more than 5 DDD, belong to the blood and blood-forming organs category: electrolytes for intravenous solution (6.6 DDD), rivaroxaban and enoxaparin (5.7 DDD), clopidogrel (5.5 DDD) and cyanocobalamin (5.3 DDD) and apixaban (5.1 DDD) (Table 3.27). Dapaglifozin is among the drugs that have gained positions and moved from rank 39th to 18th. Tables 3.28 and 3.29 show the top 30 active ingredients by expenditure and consumption in relation to the approved care regime and purchases by public health facilities. In detail, two antineoplastic drugs (pembrolizumab and daratumumab) rank 1st and 2nd in terms of expenditure (444.5 and 390.6 million euro respectively) and an average cost per DDD higher than 90 euro, followed by atorvastatin, pantoprazole and cholecalciferol with a cost ranging between 240 and 280 million euro (average cost per DDD less than 0.5 euro). The latter three substances are also among the most consumed (cholecalciferol: 139.8 DDD; atorvastatin 52.4 DDD e pantoprazole 30.7 DDD).

Table 3.1 NHS expenditure in approved care regime (A-NHS) and public health facilities by ATC 1st level in descending order of total NHS expenditure: comparison 2022-2021 (Table and Figure)

ATC 1st level	Per capita expenditure Approved care regime (a)	Δ% 22-21	Per capita expenditure Public health facilities (b)	Δ% 22-21	NHS Expenditure (a+b)	Δ% 22-21
L	4.48	2.3	113.04	5.1	117.53	5.0
C	50.29	1.6	7.34	13.3	57.63	2.9
A	32.64	1.0	22.58	16.5	55.22	6.8
J	10.98	16.1	33.34	1.7	44.32	4.9
B	7.43	-2.3	34.19	6.7	41.62	5.0
N	23.81	-0.7	9.77	18.7	33.58	4.3
R	15.88	-1.5	10.37	66.2	26.25	17.4
M	5.39	4.2	4.54	18.9	9.93	10.4
H	3.98	4.1	4.30	1.5	8.28	2.7
S	3.65	-1.6	3.28	8.3	6.93	2.9
G	5.58	0.9	1.29	-5.0	6.88	-0.3
V	0.14	-0.2	6.38	1.9	6.52	1.8
D	1.30	-1.5	3.13	54.0	4.42	32.2
P	0.23	2.1	0.03	7.1	0.26	2.6
Total	**165.78**	**1.5**	**253.59**	**8.6**	**419.37**	**5.7**

A Gastrointestinal system and metabolism
B Blood and blood-forming organs
C Cardiovascular system
D Dermatologicals
G Genito-urinary system and sex hormones
H Systemic hormonal preparations, excluding sex hormones
J Antimicrobials for systemic use
L Antineoplastic and immunomodulatory pharmaceuticals
M Musculo-skeletal system
N Central nervous system
P Antiparasitic products
R Respiratory system
S Sensory organs
V Various

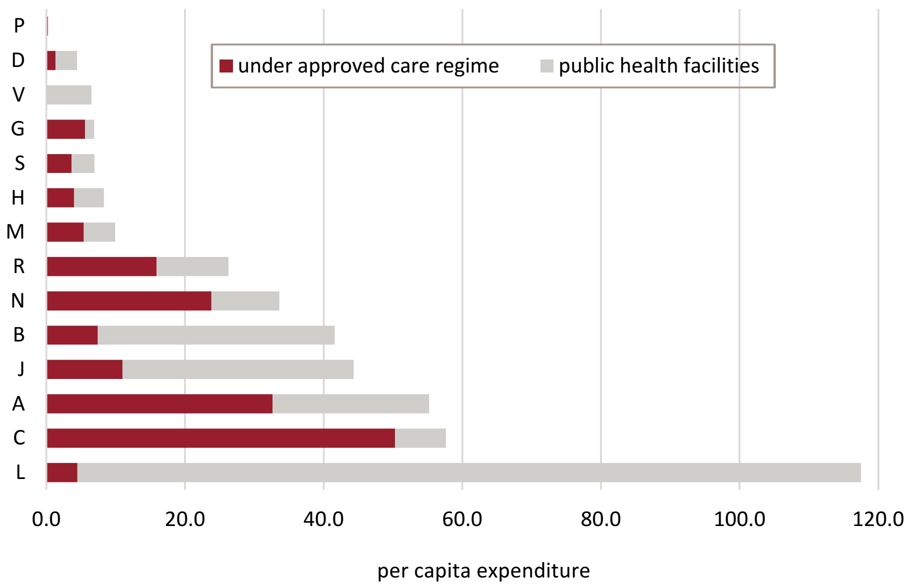


Table 3.2 NHS Consumption (DDD/1000 inhab. per day) in approved care regime (A-NHS) and public health facilities by ATC 1st level in descending order of total NHS consumption: comparison 2022-2021 (Table and Figure)

ATC 1st level	DDD/1000 inhab. per day Approved care regime (a)	Δ% 22-21	DDD/1000 inhab. per day Public health facilities (b)	Δ% 22-21	DDD/1000 inhab. per day NHS (a+b)	Δ% 22-21
C	487.39	0.6	17.93	7.8	505.32	0.8
A	279.52	-1.7	37.18	11.7	316.70	-0.3
B	90.65	1.2	52.97	3.9	143.62	2.2
N	70.27	2.0	27.88	5.1	98.16	2.8
G	44.76	2.5	2.77	10.6	47.54	2.9
M	39.12	4.0	6.31	13.5	45.43	5.2
H	38.86	5.6	5.17	10.3	44.03	6.2
R	40.85	2.5	2.26	14.8	43.11	3.1
S	21.31	2.1	2.16	5.0	23.47	2.4
J	15.29	23.3	5.81	1.1	21.10	16.2
L	6.48	2.8	12.22	9.7	18.70	7.2
D	4.95	-0.5	8.79	-1.4	13.74	-1.1
V	0.10	-4.5	3.16	-0.3	3.26	-0.4
P	1.02	2.0	0.01	62.8	1.03	2.4
Total	**1140.57**	**0.9**	**184.64**	**6.6**	**1325.21**	**1.6**

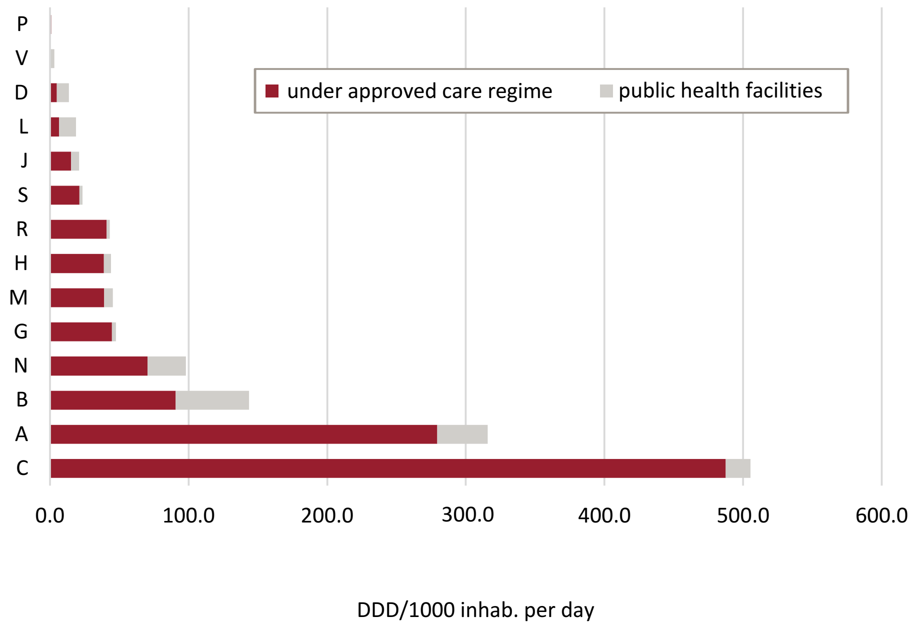


Table 3.3 Composition of 2022 pharmaceutical expenditure by ATC 1st level and reimbursement class (descending order for total expenditure)

1st level ATC	Class A-NHS^		Private purchase of class A		Class C with prescription		Self-medication SOP and OTC		Public health Facilities§		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°
L	265	2.7	53	2.8	24	0.7	-	-	6,668	44.6	7,009
A	1,925	19.7	403	21.1	276	7.8	782	26.2	1,332	8.9	4,719
C	2,966	30.3	223	11.7	35	1.0	187	6.3	433	2.9	3,844
N	1,404	14.4	160	8.4	1,202	34.1	335	11.2	576	3.9	3,679
J	648	6.6	182	9.5	199	5.7	-	-	1,966	13.1	2,995
B	438	4.5	243	12.7	88	2.5	4	0.1	2,016	13.5	2,790
R	937	9.6	146	7.6	201	5.7	511	17.1	612	4.1	2,406
M	318	3.3	211	11.1	231	6.6	658	22.1	268	1.8	1,687
G	329	3.4	48	2.5	676	19.2	96	3.2	76	0.5	1,225
D	76	0.8	27	1.4	276	7.8	314	10.5	184	1.2	878
S	215	2.2	13	0.7	222	6.3	90	3.0	194	1.3	734
H	235	2.4	79	4.1	47	1.3	-	-	254	1.7	614
V	8	0.1	116	6.1	45	1.3	1	0.0	376	2.5	547
P	14	0.1	4	0.2	3	0.1	6	0.2	2	0.0	29
Total	**9,778**	**100.0**	**1,908**	**100.0**	**3,526**	**100.0**	**2,984**	**100.0**	**14,958**	**100.0**	**33,154**

^ Expenditure for Class A net of Class C reimbursed (32.4 million); § Not including oxygen; ° Gross in million euro

* calculated on the category

Source: OsMed, Traceability of medicinal products

Table 3.4 Composition of 2022 consumption (in terms of DDD/1000 inhabitants per day), by ATC 1st level and reimbursement class (descending order of consumption)

1st level ATC	Class A-NHS^		Private purchase of class A		Class C with prescription		Self-medication SOP and OTC		Public health Facilities		Total
	No.	%*	No.	%*	No.	%*	No.	%*	No.	%*	No.
C	487.4	42.7	39.0	17.3	1.1	0.4	10.4	7.5	17.9	9.7	555.8
A	279.5	24.5	78.0	34.5	11.0	4.6	35.7	25.7	37.2	20.1	441.4
B	90.7	7.9	30.0	13.3	32.1	13.3	0.1	0.1	53.0	28.7	205.8
N	70.3	6.2	8.1	3.6	70.3	29.1	8.1	5.8	27.9	15.1	184.6
M	39.1	3.4	28.5	12.6	3.3	1.3	23.2	16.7	6.3	3.4	100.4
R	40.8	3.6	12.1	5.3	15.0	6.2	29.9	21.5	2.3	1.2	100.1
G	44.8	3.9	4.7	2.1	37.5	15.5	2.4	1.8	2.8	1.5	92.1
S	21.3	1.9	1.7	0.8	48.4	20.0	10.0	7.2	2.2	1.2	83.6
H	38.9	3.4	13.4	5.9	2.3	0.9	-	-	5.2	2.8	59.7
D	4.9	0.4	4.4	1.9	17.7	7.3	19.0	13.7	8.8	4.8	54.7
J	15.3	1.3	5.3	2.4	2.0	0.8	-	-	5.8	3.1	28.4
L	6.5	0.6	0.5	0.2	0.2	0.1	-	-	12.2	6.6	19.3
V	0.1	0.0	0.1	0.0	1.0	0.4	-	-	3.2	1.7	4.4
P	1.0	0.1	0.2	0.1	-	-	-	-	-	-	1.3
Total	**1,140.6**	**100.0**	**226.0**	**100.0**	**241.7**	**100.0**	**138.9**	**100.0**	**184.6**	**100.0**	**1,931.8**

* calculated on the category

Source: OsMed, Traceability of medicinal products

Figure 3.1 Trend of per capita expenditure in approved care regime (A-NHS) and public health facilities in the period 2017-2022 by ATC 1st level (*first 8 ATC with highest expenditure in 2022*)

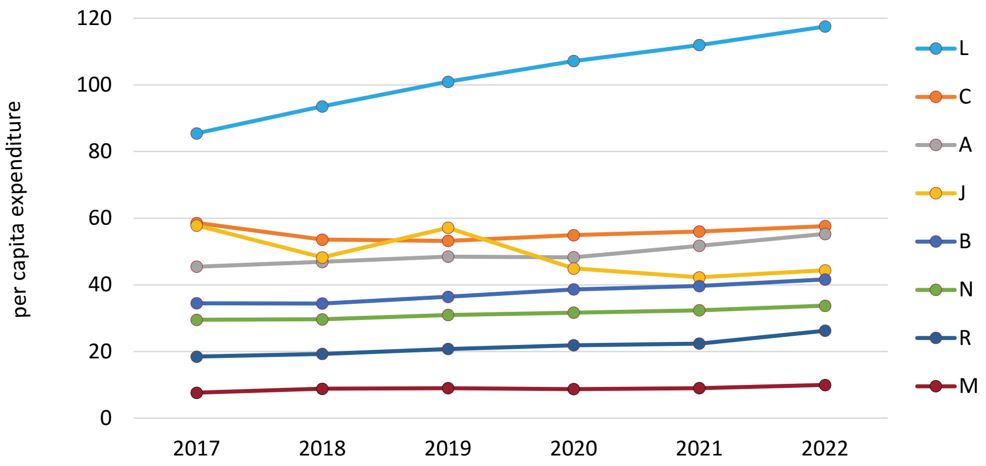


Figure 3.2 Trend of consumption in approved care regime (A-NHS) and public health facilities in the period 2017-2022 by ATC 1st level (*first 8 ATC with highest consumption in 2022*)

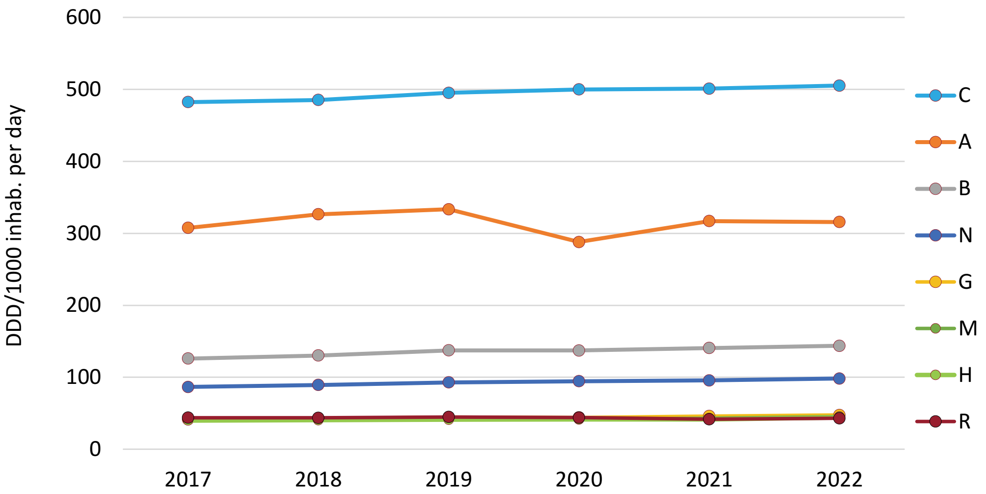


Figure 3.3 Trend of the average DDD cost of medicines in approved care regime (A-NHS) and public health facilities in the period 2017-2022 by ATC 1st level (*first 8 ATC with highest average cost in 2022*)

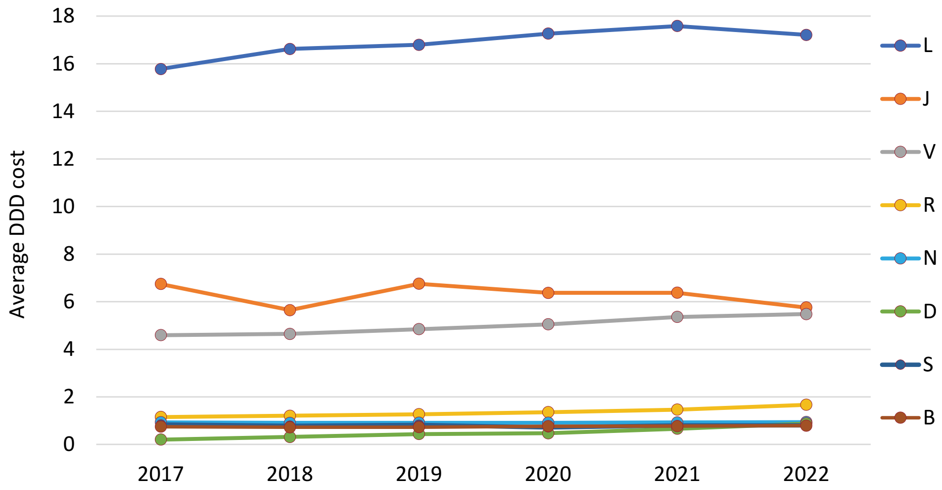


Table 3.5 Regional distribution by ATC 1st level of gross per capita approved care expenditure (on weighted population) for class A-NHS medicines: year 2022 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	24.9	2.9	43.7	1.2	5.0	3.8	8.3	4.4	4.3	23.4	0.2	13.9	4.0	0.0	140.1
Valle d'Aosta	24.7	2.6	38.1	1.1	5.3	3.3	7.2	3.8	4.4	23.2	0.2	14.1	3.4	0.1	131.5
Lombardy	48.3	12.2	48.1	1.1	5.9	3.6	9.0	6.7	4.1	28.1	0.3	15.3	3.1	0.5	186.2
P.A. of Bolzano	17.2	6.0	33.2	1.0	3.7	3.1	5.1	3.5	3.3	24.5	0.2	11.9	2.6	0.0	115.3
P.A. of Trento	26.4	5.3	39.7	1.4	5.1	4.1	8.3	4.7	4.6	23.6	0.3	15.6	2.9	0.0	141.9
Veneto	22.1	2.7	45.0	1.2	4.8	3.6	7.0	4.4	3.9	21.5	0.3	13.2	3.2	0.0	132.9
Friuli VG	26.4	5.3	46.2	1.4	4.6	3.7	6.4	4.9	4.7	23.4	0.3	13.2	4.0	0.1	144.7
Liguria	28.7	2.2	43.3	1.2	5.4	2.9	8.2	4.4	4.3	24.9	0.1	16.0	3.9	0.0	145.5
Emilia Romagna	21.7	3.4	47.8	1.2	5.5	2.9	7.4	1.1	4.2	16.7	0.3	13.8	4.7	0.0	130.7
Tuscany	21.9	5.2	43.1	1.2	5.1	4.2	8.5	1.1	4.1	22.5	0.3	15.7	4.6	0.0	137.3
Umbria	24.0	3.6	53.3	1.1	6.0	4.6	10.7	4.5	4.6	23.9	0.3	14.0	4.4	0.1	155.0
Marche	26.1	3.1	53.5	1.1	6.3	4.4	11.9	4.5	5.5	23.5	0.2	14.0	5.2	0.0	159.5
Lazio	31.7	12.4	54.2	1.3	5.7	4.9	12.9	4.6	6.6	25.0	0.2	18.1	3.8	0.1	181.5
Abruzzo	32.7	10.7	53.2	1.2	5.8	5.1	14.2	4.8	7.0	29.5	0.2	15.1	4.5	0.1	184.2
Molise	32.1	5.8	53.8	1.2	5.6	4.4	13.0	5.3	6.8	22.6	0.1	13.4	3.0	0.1	167.2
Campania	41.0	7.8	60.0	1.8	6.1	4.3	17.7	5.0	7.0	21.9	0.2	21.8	3.3	0.1	197.9
Puglia	34.4	10.7	56.1	1.3	6.1	4.5	14.8	4.9	7.7	25.3	0.1	17.1	3.3	0.1	186.3
Basilicata	40.2	10.1	56.1	1.4	6.6	4.6	13.4	4.7	7.8	24.6	0.2	17.5	3.7	0.1	190.8
Calabria	36.5	10.9	56.4	1.5	5.8	4.3	17.3	5.1	7.6	23.0	0.2	15.5	3.3	0.5	187.8
Sicily	34.6	7.1	56.3	1.4	5.6	4.0	13.7	4.3	6.6	22.1	0.2	15.8	3.0	0.1	174.7
Sardinia	33.8	4.3	49.0	1.5	5.5	4.0	11.4	5.3	7.0	27.5	0.2	17.3	3.3	0.2	170.3
Italy	**32.6**	**7.4**	**50.3**	**1.3**	**5.6**	**4.0**	**11.0**	**4.5**	**5.4**	**23.8**	**0.2**	**15.9**	**3.6**	**0.1**	**165.8**
North	32.4	6.4	46.0	1.2	5.4	3.5	8.0	4.7	4.2	23.8	0.3	14.3	3.6	0.2	153.8
Centre	27.3	8.2	50.5	1.2	5.6	4.6	11.2	3.5	5.5	23.9	0.3	16.5	4.3	0.1	162.5
South and Islands	36.4	8.4	56.4	1.5	5.9	4.3	15.1	4.8	7.1	23.8	0.2	17.7	3.3	0.1	185.1

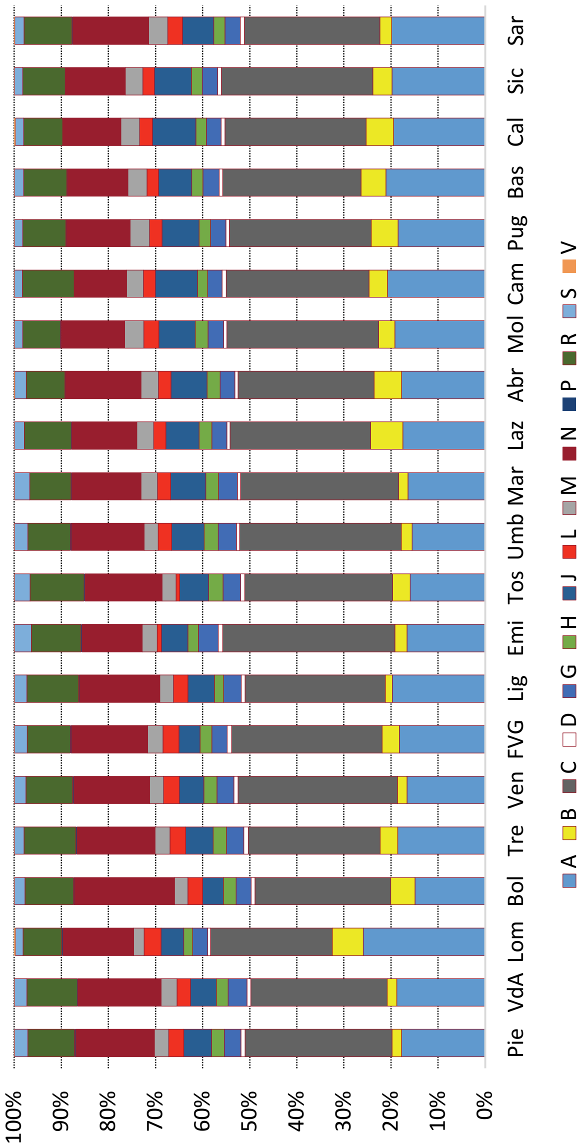

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Table 3.6 Regional distribution by ATC 1st level of DDD/1000 inhabitants per day (on weighted population) for class A-NHS medicines under approved care regime: year 2022 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	244.1	84.7	453.0	4.1	41.7	37.2	12.1	6.7	33.3	75.5	1.0	34.1	23.8	0.0	1051.3
Valle d'Aosta	239.6	65.8	376.6	3.7	39.9	31.6	11.0	5.7	33.2	66.6	1.1	35.2	19.8	0.0	929.9
Lombardy	308.6	79.3	457.9	3.6	41.6	28.3	12.7	8.7	28.4	73.7	1.2	37.4	17.7	0.3	1099.3
P.A. of Bolzano	206.0	56.1	357.9	3.6	30.6	30.0	8.1	5.7	23.7	76.8	0.8	28.5	16.0	0.0	843.8
P.A. of Trento	269.2	100.5	423.4	5.4	42.7	44.4	13.1	7.3	33.3	67.9	1.1	44.1	17.0	0.0	1069.4
Veneto	242.9	53.5	468.3	4.5	39.0	33.1	10.9	6.9	28.1	63.9	1.1	33.1	19.2	0.0	1004.5
Friuli VG	276.5	82.6	489.0	5.0	38.3	39.3	11.0	7.8	36.3	60.5	1.3	33.8	23.4	0.1	1104.7
Liguria	266.4	56.0	417.0	4.0	44.3	23.5	11.7	6.5	29.9	80.9	0.6	40.2	21.2	0.0	1002.2
Emilia Romagna	243.0	107.5	510.0	4.6	45.5	43.2	12.4	2.7	32.8	66.6	1.1	37.1	27.9	0.0	1134.3
Tuscany	210.2	105.7	482.1	4.4	43.3	46.6	13.2	1.8	33.6	86.2	1.3	38.8	26.7	0.0	1094.0
Umbria	211.7	89.9	583.2	4.0	49.1	48.9	16.7	7.0	37.3	78.4	1.3	34.7	24.8	0.1	1187.0
Marche	227.1	87.8	507.7	3.7	52.3	43.9	16.6	6.6	43.5	72.3	1.0	33.0	30.8	0.1	1126.5
Lazio	271.8	114.0	493.3	5.1	47.0	45.8	17.4	6.9	46.2	68.2	1.1	46.2	22.2	0.1	1185.1
Abruzzo	293.5	119.0	480.9	4.8	46.8	46.4	20.2	6.7	52.4	77.7	0.9	38.7	26.7	0.1	1214.8
Molise	296.0	101.4	483.9	4.8	43.5	48.0	17.4	6.7	51.0	64.6	0.7	34.9	16.4	0.1	1169.4
Campania	355.3	85.6	538.9	8.1	49.5	37.4	22.2	6.5	49.4	61.2	0.9	59.8	18.6	0.1	1293.4
Puglia	315.3	113.4	510.0	5.2	50.0	47.7	19.6	7.0	55.9	67.2	0.6	46.6	19.5	0.1	1258.1
Basilicata	335.8	116.9	505.4	6.1	52.2	48.9	18.8	6.6	56.5	68.4	0.6	44.1	21.6	0.1	1282.1
Calabria	298.1	113.8	503.2	6.2	45.4	41.4	20.5	7.0	53.5	68.4	0.9	39.0	19.8	0.2	1217.6
Sicily	287.6	89.0	526.8	6.1	46.5	38.6	18.6	6.2	45.4	62.6	0.9	42.2	17.9	0.1	1188.4
Sardinia	327.6	85.8	466.2	5.5	47.0	47.1	14.0	8.2	49.2	79.8	1.1	45.9	20.2	0.1	1197.8
Italy	**279.5**	**90.7**	**487.4**	**4.9**	**44.8**	**38.9**	**15.3**	**6.5**	**39.1**	**70.3**	**1.0**	**40.8**	**21.3**	**0.1**	**1140.6**
North	269.2	78.9	463.5	4.1	41.6	33.5	12.0	6.8	30.3	70.9	1.1	36.0	21.0	0.1	1069.2
Centre	241.7	106.1	498.3	4.6	46.7	46.0	15.9	5.3	41.1	75.3	1.1	41.3	25.0	0.1	1148.5
South and Islands	317.6	98.0	514.9	6.3	48.1	42.1	19.6	6.7	50.5	66.3	0.9	47.5	19.5	0.1	1238.2

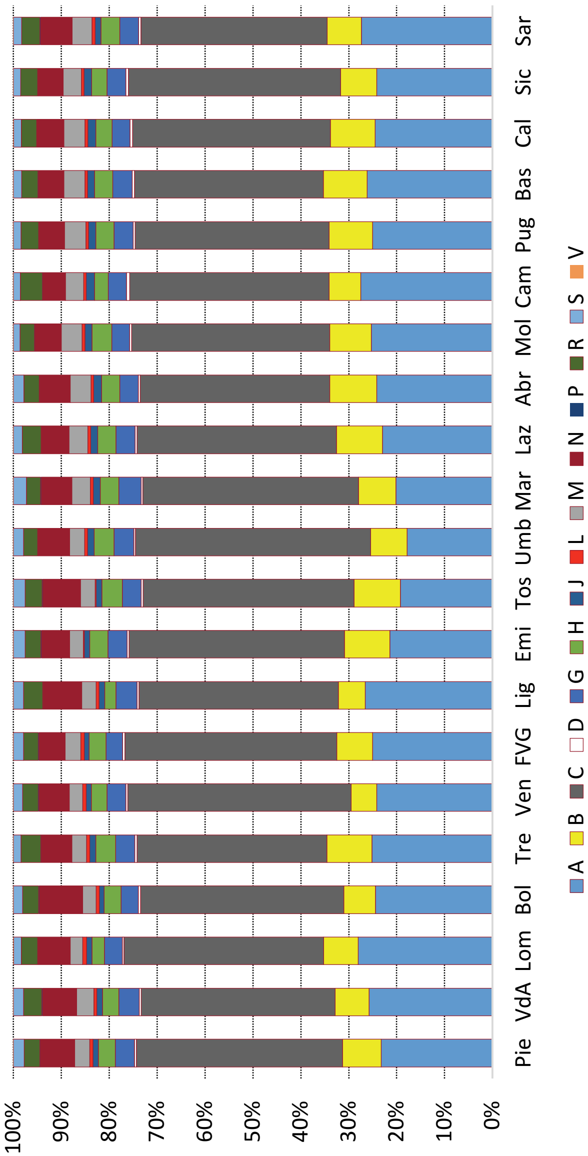
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Table 3.7 Regional distribution by ATC 1st level of per capita expenditure (on weighted population) for medicines purchased by public health facilities: year 2022 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	21.8	34.9	7.8	3.7	1.2	4.0	32.5	106.4	4.0	8.9	0.0	9.6	3.8	5.6	244.3
Valle d'Aosta	12.3	37.8	6.5	2.2	1.3	3.0	27.9	72.2	1.5	8.6	0.1	6.3	3.4	6.4	189.3
Lombardy	13.7	28.6	4.4	2.5	1.1	4.2	39.6	94.0	5.1	7.0	0.0	10.2	3.2	5.6	219.2
P.A. of Bolzano	15.6	26.0	5.9	2.8	1.4	4.6	27.6	117.9	7.2	11.5	0.0	12.6	4.5	5.9	243.5
P.A. of Trento	25.5	29.3	5.1	2.8	1.9	3.8	30.8	86.9	4.1	8.7	0.0	9.8	4.1	4.1	217.1
Veneto	23.1	31.5	6.0	2.9	1.2	4.4	36.9	110.1	4.7	10.4	0.0	9.8	3.9	6.6	251.4
Friuli VG	21.5	29.2	6.8	2.6	1.2	3.8	30.5	122.4	6.4	9.7	0.1	8.7	4.9	6.1	254.0
Liguria	19.1	38.1	9.1	2.4	0.8	4.5	38.0	120.1	3.9	10.8	0.0	11.3	4.8	5.0	268.0
Emilia Romagna	25.0	38.3	6.7	3.1	1.8	4.6	39.4	123.4	4.1	13.4	0.1	10.0	2.7	7.3	279.9
Tuscany	20.1	34.5	7.5	3.1	1.5	4.5	33.6	111.1	3.9	11.6	0.0	9.6	2.3	7.0	250.3
Umbria	24.8	38.5	7.8	2.8	1.0	4.3	36.9	128.0	3.3	10.9	0.0	8.8	3.3	6.0	276.5
Marche	20.7	38.9	9.0	4.3	1.1	4.9	31.8	137.7	6.0	13.2	0.0	11.0	3.0	6.7	288.3
Lazio	23.8	33.2	7.2	2.8	1.6	4.2	36.0	104.4	5.5	10.0	0.0	9.7	2.3	5.1	245.6
Abruzzo	24.9	42.3	7.8	3.0	1.0	5.1	29.6	131.2	4.4	11.4	0.1	10.9	3.9	6.7	282.4
Molise	20.8	31.4	7.0	4.6	0.9	3.5	17.4	135.9	3.5	9.5	0.0	7.9	5.2	4.0	251.6
Campania	31.1	40.6	13.1	4.4	1.8	5.1	27.7	134.7	4.6	8.8	0.0	9.6	3.6	5.3	290.3
Puglia	28.5	36.8	8.8	3.7	1.3	4.2	28.8	122.6	4.7	11.0	0.0	12.5	4.2	8.0	275.1
Basilicata	25.6	34.8	10.8	4.0	1.1	4.1	25.2	121.6	2.1	8.9	0.0	17.6	3.8	10.2	269.6
Calabria	31.9	38.8	9.6	3.7	1.3	4.8	24.3	123.9	3.7	8.9	0.0	13.1	2.7	8.6	275.5
Sicily	23.2	30.4	5.8	2.7	1.0	3.5	26.6	102.6	3.3	9.4	0.0	12.3	2.7	6.0	229.4
Sardinia	22.9	35.7	6.5	2.8	0.9	3.3	26.9	129.8	4.4	8.7	0.0	7.2	3.4	12.4	265.0
Italy	**22.6**	**34.2**	**7.3**	**3.1**	**1.3**	**4.3**	**33.3**	**113.0**	**4.5**	**9.8**	**0.0**	**10.4**	**3.3**	**6.4**	**253.6**
North	19.4	32.3	6.0	2.9	1.2	4.3	37.0	106.6	4.7	9.4	0.0	10.0	3.5	6.0	243.4
Centre	22.3	34.7	7.6	3.1	1.4	4.4	34.8	112.6	4.9	11.0	0.0	9.8	2.5	6.0	255.0
South and Islands	27.3	36.6	9.1	3.5	1.3	4.3	27.2	122.5	4.1	9.6	0.0	11.2	3.4	7.1	267.3

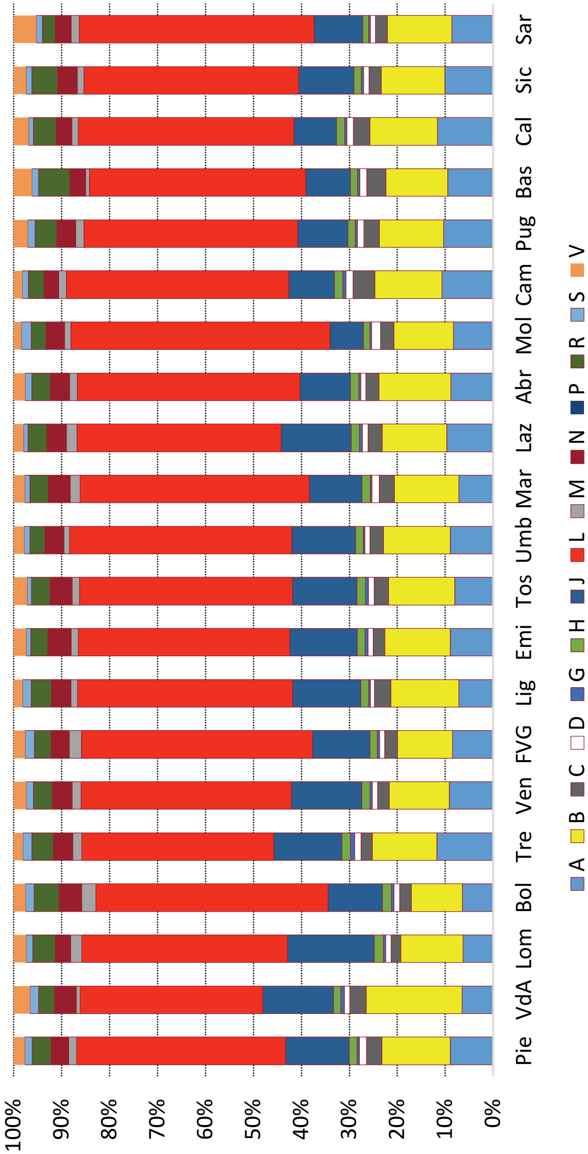
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Table 3.8 Regional distribution by ATC 1st level of DDD/1000 inhabitants per day (on weighted population) of medicines purchased by public health facilities: year 2022 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	44.7	60.8	27.9	8.0	2.4	5.9	6.0	11.8	6.6	34.4	0.0	2.9	2.2	4.6	218.3
Valle d'Aosta	30.6	58.0	19.7	9.8	5.1	6.3	5.8	8.8	5.4	38.5	0.0	4.8	1.9	5.4	200.1
Lombardy	20.6	31.8	9.6	5.1	2.4	3.5	6.6	9.1	6.3	15.5	0.0	2.0	2.1	3.2	117.9
P.A. of Bolzano	57.8	36.6	23.8	9.0	1.9	7.8	5.0	13.6	10.5	39.8	0.0	3.3	3.0	5.4	217.3
P.A. of Trento	50.0	50.3	21.1	8.1	3.5	6.5	5.4	10.9	5.9	29.8	0.0	2.6	2.5	6.9	203.4
Veneto	51.6	55.6	23.1	14.6	2.1	5.5	6.4	12.0	5.7	40.5	0.0	3.2	3.2	4.2	227.7
Friuli VG	42.0	48.6	21.2	22.0	2.0	4.7	5.8	12.1	5.9	34.2	0.0	2.9	2.3	1.1	204.9
Liguria	41.8	70.4	23.0	6.6	1.9	6.6	5.9	11.7	7.0	40.8	0.0	2.7	3.0	4.0	225.6
Emilia Romagna	61.5	82.8	40.1	10.3	10.8	8.4	9.2	16.0	7.5	55.6	0.0	5.2	3.8	6.5	317.5
Tuscany	32.7	66.0	18.9	6.9	6.3	7.1	6.1	16.7	5.0	35.1	0.0	3.2	2.6	2.9	209.4
Umbria	39.7	71.3	24.1	16.5	1.9	5.1	6.1	12.4	4.5	43.6	0.0	2.2	2.7	3.7	234.0
Marche	35.9	97.2	16.6	11.1	2.6	6.5	5.6	14.0	8.0	26.5	0.0	1.8	2.3	4.5	232.5
Lazio	31.5	39.3	13.4	5.2	1.3	3.8	5.4	11.1	6.7	22.1	0.0	1.1	1.3	1.8	144.0
Abruzzo	37.8	37.7	13.2	6.7	0.7	9.9	5.0	13.6	8.0	21.1	0.0	1.5	2.1	2.0	159.2
Molise	33.9	53.0	12.0	4.7	0.8	3.5	3.4	12.4	6.4	18.8	0.0	0.9	2.2	2.0	154.1
Campania	37.6	61.6	15.1	8.0	1.1	4.4	4.5	13.2	6.2	21.5	0.0	1.5	1.5	1.6	177.9
Puglia	37.5	42.3	12.1	11.4	1.7	4.8	4.8	12.6	6.1	16.7	0.0	1.5	2.4	2.2	156.3
Basilicata	36.4	47.4	10.8	14.9	1.2	4.5	4.1	12.2	5.2	21.4	0.0	2.0	2.0	2.7	164.7
Calabria	40.0	49.8	12.7	10.7	1.1	4.5	3.4	11.4	5.8	19.1	0.0	1.2	0.9	1.8	162.2
Sicily	28.7	46.4	13.9	7.7	1.2	4.3	4.5	11.4	4.9	20.8	0.0	1.3	0.9	1.4	147.5
Sardinia	38.1	60.0	12.6	11.8	1.2	3.5	5.2	13.1	8.6	29.8	0.0	1.5	1.8	4.2	191.3
Italy	**37.2**	**53.0**	**17.9**	**8.8**	**2.8**	**5.2**	**5.8**	**12.2**	**6.3**	**27.9**	**0.0**	**2.3**	**2.2**	**3.2**	**184.6**
North	40.0	52.5	21.7	9.1	3.7	5.4	6.8	11.6	6.5	32.6	0.0	3.0	2.7	4.2	199.7
Centre	33.1	57.8	16.4	7.4	3.1	5.3	5.7	13.4	6.1	28.4	0.0	1.9	2.0	2.6	183.2
South and Islands	35.6	50.7	13.5	9.2	1.2	4.7	4.5	12.5	6.1	20.8	0.0	1.4	1.6	2.0	163.9

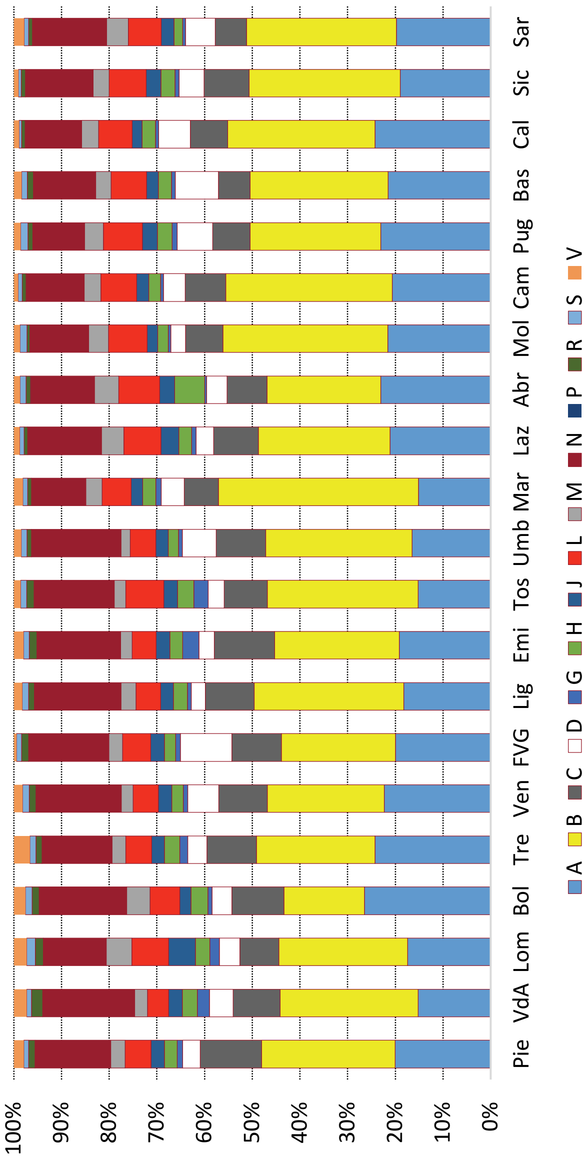
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Figure 3.4 Consumption, price and mix effect on variation of class A-NHS approved care pharmaceutical expenditure by ATC 1st level: comparison 2022-2021

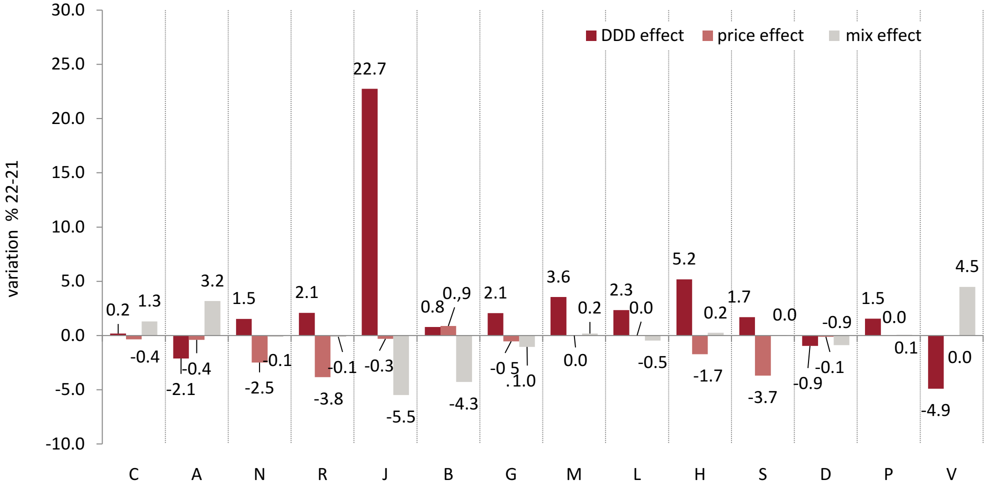


Table 3.9 Consumption, price and mix effect on variation of class A-NHS approved care pharmaceutical expenditure: comparison 2022-2021

(any ATC category includes the therapeutic subgroups in decreasing order of per capita expenditure, up to the value of 0.10 euro)

ATC 4th level Subgroups	Gross expenditure per capita	DDD/ 1000 inhab. per day	Δ % 22-21				Δ % average DDD cost
			Expen diture	DDD cost	Prices	Mix	
Italy	**165.78**	**1140.6**	**1.1**	**0.4**	**-1.1**	**1.7**	**0.7**
C - Cardiovascular system	**50.29**	**487.4**	**1.1**	**0.2**	**-0.4**	**1.3**	**0.9**
HMG-CoA reductase inhibitors	8.15	82.3	-0.3	0.3	0.0	-0.6	-0.6
Beta blockers, selective	4.98	41.2	2.2	1.2	0.0	1.0	1.0
Angiotensin II receptor blockers, not in combination	4.91	58.0	0.3	-0.3	-0.2	0.8	0.6
Dihydropyridine derivatives	4.07	49.5	-2.6	-1.6	-0.5	-0.4	-1.0
Other lipid modifying agents	3.87	8.9	5.6	8.0	0.0	-2.3	-2.3
Angiotensin II receptor blockers, and diuretics	3.78	31.8	-3.3	-2.6	-0.2	-0.5	-0.7
ACE inhibitors, not in combination	3.56	80.4	-4.5	-2.8	-0.7	-1.1	-1.8
Lipid modifying agents in combination	2.91	16.7	29.4	46.8	-2.8	-9.3	-11.8
ACE inhibitors and diuretics	2.37	18.6	-5.4	-4.7	-0.2	-0.5	-0.7
ACE inhibitors and calcium channel blockers	1.64	12.2	-1.7	-0.5	0.0	-1.2	-1.2
Angiotensin II receptor blockers and calcium channel blockers	1.53	10.5	11.3	11.7	0.0	-0.4	-0.4
Alpha-adrenoreceptor blockers	1.23	7.5	-1.7	-1.5	0.0	-0.3	-0.3
Antiarrhythmic agents, class IC	1.10	4.7	1.2	-0.4	0.0	1.6	1.6
Sulfonamides, not in combination (C03CA)	0.82	24.5	-4.3	-3.6	0.0	-0.8	-0.7
ACE inhibitors, other combinations	0.77	5.8	4.8	11.4	-3.6	-2.4	-5.9
Selective beta-blockers and thiazides	0.59	6.0	0.9	1.0	0.0	-0.1	-0.1
Aldosterone antagonists	0.56	3.4	2.7	1.9	-1.5	2.4	0.8
Angiotensin II receptor blockers, other combinations	0.51	0.2	36.8	43.4	0.0	-4.6	-4.6
Organic nitrates	0.49	4.7	-13.6	-13.8	0.0	0.2	0.2
Alpha and beta adrenoreceptor blockers	0.46	2.6	-7.1	-6.5	0.0	-0.6	-0.6
Fibrates	0.41	2.9	0.3	0.5	0.0	-0.2	-0.2
Antiarrhythmic agents, class III	0.26	2.8	-0.2	-1.1	0.0	0.9	0.9
Imidazoline receptor agonists	0.18	1.2	-7.8	-7.8	0.0	0.0	0.0
Other cardiac preparations	0.18	0.5	32.5	11.9	-4.2	23.6	18.3
Benzothiazepine derivatives	0.15	0.9	-9.1	-8.8	0.0	-0.4	-0.4
Beta blockers, not selective	0.14	1.5	-1.6	-1.7	0.0	0.1	0.1
High-ceiling diuretics in combination with potassium-sparing agents	0.11	0.6	-2.6	-2.7	0.0	0.1	0.1
Phenylalkylamine derivatives	0.11	0.9	-8.5	-8.7	0.1	0.1	0.2
Sulfonamides, not in combination (C03BA)	0.11	1.6	-7.0	-7.1	0.1	0.1	0.2

ATC 4th level Subgroups	Gross expenditure per capita	DDD/ 1000 inhab. per day	Δ % 22-21				Δ % average DDD cost
			Expen diture	DDD cost	Prices	Mix	
Selective beta-blockers and other diuretics	0.11	1.5	-6.7	-6.8	0.0	0.1	0.1
A - Gastrointestinal system and metabolism	**32.64**	**279.5**	**0.6**	**-2.1**	**-0.4**	**3.2**	**2.8**
Proton pump inhibitors	11.40	77.5	-1.1	1.3	0.0	-2.3	-2.4
Vitamin D and analogues	4.70	139.2	-2.8	-2.7	0.0	-0.1	-0.1
Insulins and injectable analogues, fast-acting	3.23	7.0	-6.2	-3.1	-3.2	0.0	-3.2
Insulins and injectable analogues, fast-acting	3.23	7.0	-6.2	-3.1	-3.2	0.0	-3.2
Aminosalicylic acid and analogues	2.20	5.7	2.3	2.2	0.0	0.1	0.1
GLP-1 receptor analogues *(Glucagon-Like Peptide*-1)	2.19	1.0	66.3	57.2	0.0	5.8	5.8
Biguanides	1.66	23.1	1.4	0.1	0.0	1.4	1.4
Antibiotics	1.48	2.0	0.0	-0.1	0.0	0.0	0.0
Bile acids and derivatives	0.93	2.8	3.3	3.4	0.0	0.0	0.0
Oral hypoglycemic agents, in combination	0.61	1.5	8.0	-12.4	-0.2	23.5	23.2
Aluminium, calcium and magnesium compounds in combination	0.56	2.5	36.0	35.1	-0.3	0.9	0.6
Insulins and injectable analogues, long-acting	0.46	0.2	13.5	4.2	-0.1	9.0	8.9
Sulfonylureas	0.42	6.0	-13.8	-15.9	-0.1	2.5	2.5
Other anti-peptic antiulcer and gastroesophageal reflux disease	0.40	1.9	-56.1	-55.7	0.0	-0.8	-0.8
Calcium, combinations with vitamin D and/or other medicines	0.30	3.2	-4.7	-5.1	0.0	0.4	0.4
Corticosteroids for topical use	0.29	0.4	-2.0	-1.7	-1.3	1.0	-0.3
Enzyme preparations	0.25	0.6	4.1	4.0	0.0	0.0	0.0
Dipeptidyl Peptidase-4 inhibitors (DPP-4)	0.22	0.3	7.2	8.9	-0.5	-1.1	-1.6
Serotonin antagonists (5HT3)	0.20	0.0	5.8	4.1	0.0	1.7	1.7
Other hypoglycaemic agents, excluding insulins	0.19	1.3	-19.3	-20.4	0.0	1.4	1.4
SGLT2 cotransporter inhibitors (sodium-glucose type 2)	0.12	0.1	34.4	39.2	0.0	-3.4	-3.4
Alpha Glucosidase Inhibitors	0.12	0.5	-10.9	-10.8	0.0	-0.1	-0.1
Thiazolidinediones	0.12	0.5	9.3	11.3	0.0	-1.8	-1.8
Osmotic laxatives	0.10	1.0	-6.0	-6.3	0.0	0.3	0.3
N- Central nervous system	**23.81**	**70.3**	**-1.1**	**1.5**	**-2.5**	**-0.1**	**-2.6**
Other antidepressants	3.41	12.3	4.4	4.2	0.0	0.2	0.2
Selective serotonin reuptake inhibitors	3.39	30.5	-0.4	1.2	0.0	-1.5	-1.5
Other antiepileptics	3.21	3.8	2.1	4.2	-2.5	0.5	-2.1
Gabapentinoids	1.71	2.9	4.3	5.3	0.0	-0.9	-0.9
Phenylpiperidine derivatives	1.29	0.6	-4.6	-2.5	-2.0	-0.2	-2.2
Other opioids	1.28	1.0	-13.2	-0.8	-14.5	2.3	-12.5

ATC 4th level Subgroups	Gross expenditure per capita	DDD/ 1000 inhab. per day	Δ % 22-21				Δ % average DDD cost
			Expen diture	DDD cost	Prices	Mix	
Dopamine agonists	1.06	1.0	-5.3	-4.3	-1.4	0.4	-1.0
Diazepines, oxazepines, thiazepines and oxepins	1.02	1.3	-0.2	2.8	0.0	-3.0	-3.0
Fatty acid derivatives	1.00	2.3	0.8	1.0	0.0	-0.2	-0.2
5HT1 selective receptor agonists	1.00	0.8	-1.3	-1.1	0.0	-0.2	-0.2
Natural opium alkaloids	0.86	0.6	-24.7	-3.0	-22.4	0.1	-22.4
Type B monoamine oxidase inhibitors	0.78	1.6	0.3	0.5	0.0	-0.1	-0.1
DOPA and derivatives	0.72	2.1	0.5	0.5	0.0	0.0	0.0
Opioids in combination with non-opioid analgesics	0.53	1.4	-0.7	0.0	-1.2	0.5	-0.7
Carboxamide derivatives	0.47	1.8	-2.1	-2.1	-0.1	0.2	0.0
Amides	0.36	0.3	-1.5	-1.5	0.0	0.0	0.0
Oripavine derivatives	0.33	0.2	16.2	12.3	-1.5	5.1	3.5
Other antipsychotics	0.27	0.5	3.0	11.3	-5.0	-2.6	-7.4
Non-selective monoamine reuptake inhibitors	0.16	1.0	-0.3	-0.2	0.2	-0.3	-0.1
Anticholinesterases	0.13	0.4	-6.3	1.2	0.0	-7.4	-7.4
R- Respiratory system	**15.88**	**40.8**	**-1.9**	**2.1**	**-3.8**	**-0.1**	**-4.0**
Adrenergics in combination with corticosteroids or others excluding anticholinergics	7.20	12.4	-8.2	-2.7	-5.9	0.2	-5.7
Anticholinergics	2.54	4.9	-17.5	-13.6	-2.7	-1.9	-4.5
Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	2.34	3.1	23.4	26.6	-2.6	0.0	-2.6
Glycocorticoids	1.73	4.6	36.8	34.4	-1.8	3.7	1.8
Other antihistamines for systemic use	0.67	6.1	0.9	1.0	0.0	0.0	0.0
Leukotriene receptor antagonists	0.46	2.0	-0.7	-1.1	0.0	0.4	0.4
Selective agonists of beta2-adrenergic receptors	0.46	3.1	-10.8	-0.1	-1.1	-9.7	-10.7
Piperazine derivatives	0.42	4.2	2.9	3.0	0.0	-0.2	-0.2
J- General antimicrobials for systemic use	**10.98**	**15.3**	**15.6**	**22.7**	**-0.3**	**-5.5**	**-5.8**
Penicillin combinations, including betalactamase inhibitors	2.72	5.2	23.9	24.8	0.0	-0.7	-0.7
Third generation cephalosporins	2.46	1.7	24.3	32.8	0.0	-6.4	-6.4
Macrolides	1.58	3.6	34.9	38.7	-0.1	-2.6	-2.7
Fluoroquinolones	1.14	1.5	5.6	7.9	-0.3	-1.9	-2.2
Triazole and tetrazole derivatives	0.83	0.5	-3.2	-2.9	0.0	-0.3	-0.3
Other antibacterials	0.64	0.4	0.7	0.9	0.0	-0.2	-0.2
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.56	0.3	1.1	5.3	-4.3	0.3	-4.0
Specific immunoglobulins	0.36	0.0	-6.2	-4.4	0.0	-1.9	-1.9

ATC 4th level Subgroups	Gross expenditure per capita	DDD/ 1000 inhab. per day	Δ % 22-21 Expen diture	DDD cost	Prices	Mix	Δ % average DDD cost
Broad-spectrum penicillins	0.18	0.9	22.3	24.3	0.0	-1.6	-1.6
B - Blood and blood-forming organs	**7.43**	**90.7**	**-2.7**	**0.8**	**0.9**	**-4.3**	**-3.5**
Platelet aggregation inhibitors, excl. heparin	2.98	61.1	0.2	-0.1	0.0	0.3	0.3
Heparins	2.25	2.7	-9.6	-9.3	1.1	-1.4	-0.4
Folic acid e derivatives	0.52	6.8	1.6	2.0	0.0	-0.4	-0.4
Bivalent iron, oral preparations	0.37	3.0	1.2	1.9	-0.5	-0.2	-0.7
Direct Xa factor inhibitors	0.33	0.2	12.9	13.2	0.0	-0.2	-0.2
Blood substitutes and plasma protein fractions	0.24	0.0	-5.1	-5.8	0.0	0.7	0.7
Vitamin K antagonists	0.15	2.5	27.1	-13.5	47.1	-0.1	47.0
Solutions affecting the electrolyte balance	0.15	0.2	-10.4	-3.7	-7.3	0.3	-7.0
Vitamina B12 (cyanocobalamin and derivatives)	0.11	13.6	5.3	10.0	0.0	-4.3	-4.3
G - Genito-urinary system and sex hormones	**5.58**	**44.8**	**0.5**	**2.1**	**-0.5**	**-1.0**	**-1.6**
Alpha adrenergic receptor antagonists	2.95	28.6	1.8	2.8	0.0	-1.0	-1.0
Testosterone-5-alpha reductase inhibitors	1.58	11.0	-0.8	0.7	-0.4	-1.1	-1.5
Gonadotropins	0.16	0.0	-0.5	4.7	-1.6	-3.3	-4.9
Other estrogens	0.13	0.8	1.8	2.2	0.0	-0.4	-0.4
Pregnene derivatives (4)	0.12	1.0	0.2	4.9	-0.3	-4.2	-4.5
M - Musculo-skeletal system	**5.39**	**39.1**	**3.7**	**3.6**	**0.0**	**0.2**	**0.2**
Biphosphonates	1.36	7.1	1.8	2.3	0.0	-0.5	-0.5
Preparations inhibiting formation of uric acid	0.92	10.8	4.7	2.2	0.0	2.4	2.4
Acetic acid derivatives and related substances	0.82	5.1	3.6	4.5	-0.1	-0.7	-0.8
Propionic acid derivatives	0.80	6.2	20.0	15.8	0.0	3.6	3.6
Coxib	0.72	4.3	2.1	2.8	0.0	-0.7	-0.7
Biphosphonates, combinations	0.40	1.9	-5.0	-4.9	0.0	-0.1	-0.1
Other anti-inflammatory/ nonsteroidal antirheumatics	0.16	1.8	-1.7	-1.7	-0.1	0.1	0.0
L- Antineoplastic and immunomodulating agents	**4.48**	**6.5**	**1.9**	**2.3**	**0.0**	**-0.5**	**-0.4**
Aromatase inhibitors	2.35	3.2	5.1	4.6	0.0	0.5	0.5
Other immunosuppressants	0.83	1.7	5.2	4.0	0.0	1.2	1.1
Calcineurin inhibitors	0.53	0.2	-4.3	-5.4	0.0	1.1	1.1
Other antineoplastics	0.18	0.3	4.8	2.6	2.0	0.1	2.1
Colony stimulating factors	0.13	0.0	-29.2	-8.3	-0.4	-22.5	-22.8
Antiandrogens	0.11	0.2	-4.0	-3.9	0.0	-0.1	-0.1
H - Systemic hormonal preparations, excluding sex hormones	**3.98**	**38.9**	**3.6**	**5.2**	**-1.7**	**0.2**	**-1.5**
Glycocorticoids	1.53	14.6	5.8	7.1	-0.2	-1.0	-1.3
Thyroid hormones	1.43	22.7	13.1	4.5	0.0	8.3	8.3

ATC 4th level Subgroups	Gross expenditure per capita	DDD/ 1000 inhab. per day	Δ % 22-21				Δ % average DDD cost
			Expen diture	DDD cost	Prices	Mix	
Parathyroid hormones and analogues	0.67	0.1	-14.2	-5.2	-8.0	-1.7	-9.5
Vasopressin and analogues	0.13	0.1	1.7	1.3	0.0	0.4	0.4
S - Sensory organs	**3.65**	**21.3**	**-2.0**	**1.7**	**-3.7**	**0.0**	**-3.6**
Beta-blockers	2.06	11.9	-3.6	2.2	-6.4	0.8	-5.6
Prostaglandins analogues	1.19	5.6	-0.5	0.0	0.0	-0.4	-0.4
Carbonic anhydrase inhibitors	0.27	1.8	2.2	3.7	0.0	-1.5	-1.4
Sympathomimetics for treatment of glaucoma	0.10	1.5	2.2	3.1	-1.1	0.1	-0.9
D - Dermatologicals	**1.30**	**4.9**	**-1.9**	**-0.9**	**-0.1**	**-0.9**	**-1.0**
Other antipsoriatic agents for topical use	0.88	2.5	-1.4	-0.8	0.0	-0.6	-0.6
Retinoids for acne treatment	0.11	0.2	-2.2	-1.7	0.0	-0.6	-0.6
P - Antiparasitic drugs, insecticides and repellents	**0.23**	**1.0**	**1.6**	**1.5**	**0.0**	**0.1**	**0.1**
Aminoquinolines	0.17	0.9	2.3	2.3	0.0	0.0	0.0
V - Miscellaneous	**0.14**	**0.1**	**-0.6**	**-4.9**	**0.0**	**4.5**	**4.5**
Drugs for the treatment of hyperkalemia and hyperphosphatemia	0.12	0.1	-1.5	-4.2	0.0	2.8	2.8

Table 3.10 2022 expenditure, consumption and average cost per day of therapy under approved care regime (class A-NHS): most prescribed active ingredients by ATC 1st level (up to 75% of the category expenditure)

Therapeutic category	Gross expenditure *per capita*	%*	Δ % 22-21	DDD/ 1000 inhab. per day	%*	Δ % 22-21	Average DDD cost	Δ % 22-21
C - Cardiovascular system	**50.29**		**1.6**	**487.4**		**0.6**	**0.28**	**0.9**
atorvastatin	4.68	9.3	1.3	50.9	10.4	1.3	0.25	0.0
bisoprolol	2.82	5.6	3.9	12.8	2.6	3.8	0.60	0.1
omega 3	2.15	4.3	3.4	2.5	0.5	4.4	2.32	-1.0
ramipril	1.95	3.9	-3.4	61.5	12.6	-1.5	0.09	-2.0
olmesartan	1.92	3.8	7.7	16.7	3.4	7.7	0.31	0.0
ezetimibe	1.71	3.4	9.5	6.4	1.3	10.1	0.73	-0.6
amlodipine	1.60	3.2	-1.2	28.0	5.7	-0.3	0.16	-0.9
nebivolol	1.56	3.1	1.8	16.9	3.5	2.0	0.25	-0.2
ezetimibe/rosuvastatin	1.55	3.1	50.2	10.6	2.2	69.0	0.40	-11.2
rosuvastatin	1.49	3.0	5.2	15.8	3.2	6.1	0.26	-0.9
olmesartan/amlodipine	1.45	2.9	10.9	9.9	2.0	11.2	0.40	-0.2
simvastatin	1.36	2.7	-6.4	11.4	2.3	-6.1	0.33	-0.3
olmesartan/hydrochlorothiazide	1.26	2.5	3.6	10.4	2.1	3.8	0.33	-0.3
doxazosin	1.23	2.4	-1.4	7.5	1.5	-1.1	0.45	-0.3
ezetimibe/simvastatin	1.23	2.4	2.1	5.1	1.0	2.3	0.66	-0.3
flecainide	0.92	1.8	3.4	3.1	0.6	4.2	0.81	-0.7
barnidipine	0.87	1.7	-1.6	4.9	1.0	0.7	0.49	-2.2
perindopril/amlodipine	0.82	1.6	-1.7	5.3	1.1	-0.8	0.42	-0.9
lercanidipine	0.77	1.5	-1.2	9.4	1.9	-1.1	0.22	-0.1
losartan	0.71	1.4	-4.5	6.7	1.4	-4.6	0.29	0.2
furosemide	0.70	1.4	-3.4	23.3	4.8	-3.0	0.08	-0.4
valsartan	0.68	1.4	1.9	10.0	2.1	1.5	0.19	0.5
zofenopril	0.67	1.3	-0.9	4.5	0.9	-1.1	0.41	0.3
valsartan/hydrochlorothiazide	0.65	1.3	-3.7	5.9	1.2	-3.4	0.30	-0.2
irbesartan	0.64	1.3	-4.2	7.8	1.6	-4.2	0.22	0.1
perindopril/indapamide/ amlodipine	0.64	1.3	3.8	4.7	1.0	11.5	0.37	-6.9
zofenopril/hydrochlorothiazide	0.62	1.2	-2.5	4.0	0.8	-2.4	0.43	-0.1
irbesartan/hydrochlorothiazide	0.56	1.1	-5.4	4.8	1.0	-5.1	0.32	-0.3
ramipril/hydrochlorothiazide	0.55	1.1	-3.5	6.4	1.3	-2.3	0.23	-1.3
A - Gastrointestinal and metabolism	**32.64**		**1.0**	**279.5**		**-1.7**	**0.32**	**2.8**
pantoprazole	4.51	13.8	2.7	29.0	10.4	5.3	0.43	-2.5
cholecalciferol	4.05	12.4	-2.8	136.8	49.0	-2.3	0.08	-0.5
esomeprazole	2.24	6.9	0.5	15.8	5.7	3.1	0.39	-2.6
lansoprazole	2.17	6.7	-5.1	13.3	4.8	-3.4	0.45	-1.7
omeprazole	2.16	6.6	-2.9	17.6	6.3	-0.2	0.34	-2.7
mesalazine	2.13	6.5	2.7	5.4	1.9	2.6	1.09	0.2
metformin	1.66	5.1	1.9	23.1	8.3	0.5	0.20	1.4
insulin lispro	1.40	4.3	-5.6	3.2	1.1	-3.0	1.22	-2.7
rifaximin	1.38	4.2	0.3	1.8	0.7	0.3	2.08	0.0
insulin aspart	1.31	4.0	-6.9	2.8	1.0	-1.9	1.30	-5.1
dulaglutide	1.31	4.0	51.1	0.7	0.3	48.1	4.94	2.0

Therapeutic category	Gross expenditure *per capita*	%*	Δ % 22-21	DDD/ 1000 inhab. per day	%*	Δ % 22-21	Average DDD cost	Δ % 22-21
ursodeoxycholic acid	0.91	2.8	3.9	2.7	1.0	3.9	0.92	0.0
N- Central nervous system	**23.81**		**-0.7**	**70.3**		**2.0**	**0.93**	**-2.6**
fentanyl	1.29	5.4	-4.2	0.6	0.9	-2.1	5.64	-2.2
tapentadol	1.05	4.4	-14.4	0.6	0.8	3.3	5.18	-17.1
paroxetine	1.00	4.2	-1.7	7.9	11.3	0.0	0.34	-1.6
valproic acid	0.97	4.1	1.3	2.3	3.3	1.5	1.16	-0.2
escitalopram	0.97	4.1	0.2	7.6	10.9	0.6	0.35	-0.5
sertraline	0.82	3.5	2.5	9.1	13.0	5.0	0.25	-2.4
vortioxetine	0.82	3.4	13.6	2.0	2.8	13.5	1.14	0.1
venlafaxine	0.82	3.4	1.6	3.7	5.3	2.9	0.60	-1.2
duloxetine	0.82	3.4	3.2	3.3	4.7	3.8	0.67	-0.6
lacosamide	0.66	2.8	-3.0	0.4	0.5	11.8	4.67	-13.2
naloxone/oxycodone	0.63	2.6	-29.1	0.4	0.5	-1.7	4.69	-27.8
rotigotine	0.60	2.5	-6.9	0.3	0.4	-5.1	5.31	-1.9
quetiapine	0.59	2.5	-2.3	0.5	0.7	-1.8	3.45	-0.5
lamotrigin	0.47	2.0	4.9	0.7	1.0	5.0	1.77	-0.2
trazodone	0.42	1.7	2.8	1.2	1.7	2.8	0.98	0.0
safinamide	0.40	1.7	1.9	0.3	0.4	3.3	4.30	-1.4
citalopram	0.40	1.7	-1.3	3.9	5.5	-0.9	0.28	-0.4
pramipexole	0.36	1.5	-0.7	0.4	0.6	-1.2	2.32	0.5
lidocaine	0.36	1.5	-1.1	0.3	0.4	-1.1	3.61	0.0
levodopa/benserazide	0.35	1.5	2.6	1.0	1.5	0.4	0.94	2.1
gabapentin	0.35	1.5	3.8	0.5	0.6	3.9	2.15	-0.1
mirtazapine	0.35	1.5	0.2	1.7	2.5	2.1	0.56	-1.9
buprenorphine	0.33	1.4	16.7	0.2	0.3	12.8	4.61	3.5
topiramate	0.28	1.2	1.4	0.3	0.5	1.4	2.41	0.0
paracetamol/codeine	0.27	1.1	0.3	1.0	1.5	0.3	0.71	0.0
rasagiline	0.26	1.1	-0.8	0.3	0.5	-0.5	2.13	-0.3
olanzapine	0.26	1.1	11.1	0.5	0.7	11.3	1.39	-0.2
paracetamol/oxycodone	0.24	1.0	-0.5	0.3	0.5	2.1	2.08	-2.5
rizatriptan	0.24	1.0	7.6	0.2	0.3	7.2	2.87	0.3
carbamazepine	0.24	1.0	-1.9	1.2	1.7	-1.8	0.56	-0.1
tramadol	0.23	1.0	-5.1	0.5	0.7	-4.3	1.27	-0.8
sumatriptan	0.22	0.9	1.8	0.2	0.2	0.8	3.66	1.0
levodopa/carbidopa	0.20	0.8	2.8	0.8	1.2	2.9	0.64	-0.1
almotriptan	0.20	0.8	6.7	0.2	0.2	6.7	3.21	0.0
eletriptan	0.18	0.8	7.9	0.1	0.2	8.0	3.50	0.0
bupropione	0.18	0.8	4.7	0.3	0.4	5.1	1.70	-0.3
oxcarbazepine	0.18	0.7	-1.4	0.6	0.8	-1.6	0.84	0.2
R - Respiratory system	**15.88**		**-1.5**	**40.8**		**2.5**	**1.07**	**-4.0**
formoterol/beclomethasone	2.53	15.9	2.5	4.0	9.9	3.4	1.72	-0.8
vilanterol/fluticasone furoate	2.11	13.3	-10.1	3.6	8.8	-2.8	1.61	-7.5
formoterol/budesonide	1.33	8.4	-6.0	2.0	4.9	-1.0	1.80	-5.0
tiotropium	0.98	6.2	-16.3	1.8	4.4	-14.7	1.50	-1.9
salmeterol/fluticasone	0.88	5.6	-28.2	2.0	4.9	-12.6	1.20	-17.8
umeclidinium	0.71	4.5	-15.4	1.3	3.2	-10.9	1.51	-5.0

Therapeutic category	Gross expenditure *per capita*	%*	Δ % 22-21	DDD/ 1000 inhab. per day	%*	Δ % 22-21	Average DDD cost	Δ % 22-21
formoterol/glycopyrronium /beclomethasone	0.66	4.1	30.2	0.6	1.5	31.7	3.02	-1.1
R - Respiratory system	**15.88**		**-1.5**	**40.8**		**2.5**	**1.07**	**-4.0**
beclomethasone	0.64	4.1	38.4	1.7	4.2	35.3	1.02	2.3
vilanterol/umeclidinium /fluticasone furoate	0.54	3.4	15.2	0.5	1.3	19.5	2.73	-3.6
aclidinium	0.49	3.1	-18.7	0.9	2.2	-14.3	1.51	-5.1
montelukast	0.46	2.9	-0.3	2.0	5.0	-0.7	0.62	0.4
budesonide	0.45	2.8	68.2	0.8	1.9	56.4	1.56	7.6
vilanterol/umeclidinium	0.41	2.6	56.3	0.6	1.4	64.6	1.97	-5.1
J - Antimicrobials	**10.98**		**16.1**	**15.3**		**23.3**	**1.97**	**-5.8**
amoxicillin/clavulanic acid	2.60	23.7	25.7	5.2	34.2	25.4	1.36	0.3
cefixime	0.99	9.1	43.1	1.2	7.6	42.8	2.33	0.2
azithromicyn	0.94	8.6	30.5	1.8	11.8	35.0	1.43	-3.3
ceftriaxone	0.94	8.5	14.5	0.2	1.4	15.1	11.93	-0.5
fluconazole	0.66	6.0	-2.5	0.3	2.1	-2.1	5.53	-0.4
fosfomycin	0.64	5.8	1.1	0.4	2.5	1.3	4.62	-0.2
ciprofloxacin	0.63	5.7	7.1	0.7	4.4	7.5	2.56	-0.4
clarithromycin	0.58	5.3	48.8	1.8	11.6	45.5	0.90	2.2
levofloxacin	0.39	3.5	10.1	0.7	4.8	11.8	1.47	-1.5
B - Blood and blood-forming organs	**7.43**		**-2.3**	**90.7**		**1.2**	**0.22**	**-3.5**
enoxaparin	2.04	27.4	-7.6	2.5	2.8	-7.5	2.20	-0.1
clopidogrel	1.21	16.3	4.5	6.0	6.6	6.1	0.56	-1.5
acetylsalicylic acid	1.19	16.1	1.4	45.6	50.4	1.5	0.07	-0.1
folic acid	0.52	7.0	2.0	6.8	7.5	2.4	0.21	-0.4
ferrous sulfate	0.27	3.6	2.4	2.4	2.6	2.4	0.31	0.0
apixaban	0.27	3.6	22.3	0.2	0.2	22.7	3.83	-0.3
human albumin	0.24	3.2	-4.7	0.0	0.0	-5.4	52.16	0.7
G - Genito-urinary system and sex hormones	**5.58**		**0.9**	**44.8**		**2.5**	**0.34**	**-1.6**
tamsulosin	1.14	20.5	2.1	11.2	25.0	3.0	0.28	-0.9
dutasteride	1.03	18.5	-0.6	8.4	18.7	0.6	0.34	-1.1
alfuzosin	0.92	16.4	3.3	9.8	21.8	4.3	0.26	-0.9
silodosin	0.73	13.1	3.5	6.5	14.4	4.3	0.31	-0.8
finasteride	0.55	9.8	-0.1	2.6	5.9	2.9	0.57	-2.8
M - Musculo-skeletal system	**5.39**		**4.2**	**39.1**		**4.0**	**0.38**	**0.2**
alendronic acid	0.81	15.1	4.2	4.3	11.1	5.3	0.51	-1.1
diclofenac	0.64	11.9	6.3	4.4	11.1	6.4	0.40	-0.1
etoricoxib	0.61	11.3	3.7	3.6	9.3	4.5	0.46	-0.8
febuxostat	0.55	10.2	7.5	2.3	5.8	8.0	0.67	-0.4
ibuprofen	0.42	7.9	49.4	2.8	7.1	48.2	0.42	0.8
alendronic acid/ cholecalciferol	0.40	7.4	-4.6	1.9	4.8	-4.5	0.58	-0.1
allopurinol	0.37	6.8	1.7	8.6	22.0	1.3	0.12	0.3
risendronic acid	0.36	6.8	-1.0	2.1	5.4	-0.2	0.48	-0.8

Therapeutic category	Gross expenditure *per capita*	%*	Δ % 22-21	DDD/ 1000 inhab. per day	%*	Δ % 22-21	Average DDD cost	Δ % 22-21
L - Antineoplastic and immunomodulating agents	**4.48**		**2.3**	**6.5**		**2.8**	**1.90**	**-0.4**
letrozole	1.51	33.6	6.9	1.8	28.3	7.1	2.25	-0.3
methotrexate	0.73	16.3	6.6	1.4	21.7	5.7	1.43	0.8
exemestane	0.48	10.7	8.8	0.6	9.1	9.2	2.22	-0.4
ciclosporin	0.45	10.0	-5.8	0.2	2.3	-5.6	8.11	-0.2
anastrozole	0.36	8.1	-3.2	0.7	11.3	-2.8	1.36	-0.5
H - Systemic hormones	**3.98**		**4.1**	**38.9**		**5.6**	**0.28**	**-1.5**
levothyroxine	1.39	35.0	14.0	22.7	58.3	4.9	0.17	8.7
prednisone	0.71	17.8	3.8	7.2	18.4	5.9	0.27	-2.0
teriparatide	0.67	16.9	-13.8	0.1	0.3	-4.8	14.15	-9.5
betamethasone	0.32	7.9	21.9	2.1	5.3	22.5	0.42	-0.5
methylprednisolone	0.20	5.1	2.9	3.2	8.2	6.2	0.17	-3.1
S - Sensory organs	**3.65**		**-1.6**	**21.3**		**2.1**	**0.47**	**-3.6**
tafluprost	0.52	14.2	4.7	1.7	7.8	5.5	0.86	-0.8
dorzolamide/timolol	0.48	13.1	20.1	3.2	15.0	17.3	0.41	2.4
timolol	0.38	10.3	4.0	3.1	14.7	1.8	0.33	2.2
bimatoprost	0.32	8.7	0.1	1.8	8.4	0.6	0.49	-0.5
timolol/bimatoprost	0.31	8.5	-28.7	1.4	6.6	0.7	0.60	-29.2
tafluprost/timolol	0.28	7.7	9.7	0.8	3.7	9.7	0.96	0.0
timolol/brinzolamide	0.21	5.7	-12.1	1.1	5.1	-12.1	0.53	0.0
travoprost	0.18	4.9	-12.2	0.9	4.2	-8.4	0.54	-4.2
latanoprost	0.17	4.7	0.3	1.3	6.1	0.5	0.37	-0.2
D - Dermatologicals	**1.30**		**-1.5**	**4.9**		**-0.5**	**0.72**	**-1.0**
calcipotriol/betamethasone	0.84	64.4	0.0	2.4	48.2	0.8	0.96	-0.8
isotretinoin	0.11	8.3	-1.8	0.2	4.3	-1.2	1.38	-0.6
clobetasol	0.07	5.7	-3.7	1.0	19.9	-1.5	0.21	-2.1
diclofenac	0.06	5.0	1.8	0.1	1.2	4.0	2.89	-2.1
terbinafine	0.05	3.9	0.3	0.1	2.0	-0.1	1.42	0.4
P - Antiparasitic products	**0.23**		**2.1**	**1.0**		**2.0**	**0.62**	**0.1**
hydroxychloroquine	0.17	73.7	2.8	0.9	88.1	2.8	0.52	0.0
mefloquine	0.02	9.0	11.6	0.0	0.4	11.6	13.27	0.0
mebendazole	0.02	7.8	-2.1	0.1	7.2	-4.9	0.67	2.9
metronidazole	0.01	5.4	5.1	0.0	3.2	5.2	1.03	0.0
tinidazole	<0.005	2.0	-4.3	0.0	0.5	-4.3	2.71	0.0
V - Miscellaneous	**0.14**		**-0.2**	**0.1**		**-4.5**	**3.95**	**4.5**
sevelamer	0.06	41.7	6.1	<0.05	30.6	6.4	5.38	-0.3
polystyrene sulfonate	0.04	29.3	-7.5	<0.05	41.6	-7.5	2.79	0.0
sucroferric oxyhydroxide	0.01	10.5	-12.4	<0.05	4.9	-12.4	8.44	0.0
calcium acetate/ magnesium carbonate	0.01	4.0	-9.5	<0.05	15.5	-9.5	1.02	0.0
deferoxamine	<0.005	3.5	-9.7	<0.05	0.7	-9.7	19.62	0.0

* The expenditure and DDD percentages are calculated on the total of ATC 1st level category

Table 3.11 First thirty active ingredients by expenditure under approved care regime (A-NHS): comparison 2022-2021

ATC	Active substance	Expenditure *(million)*	%*	Gross expenditure *per capita*	Rank 2022	Rank 2021	Average DDD cost	Δ % 22-21	Average DDD cost direct purchases
C	atorvastatin	276.0	2.8	4.68	1	1	0.25	0.0	<0.005
A	pantoprazole	266.3	2.7	4.51	2	2	0.43	-2.5	0.21
A	cholecalciferol	239.0	2.4	4.05	3	3	0.08	-0.5	0.01
C	bisoprolol	166.5	1.7	2.82	4	4	0.60	0.1	0.09
J	amoxicillin/ clavulanic acid	153.4	1.6	2.60	5	13	1.36	0.3	0.86
R	formoterol/ beclomethasone	149.3	1.5	2.53	6	5	1.72	-0.8	1.15
A	esomeprazole	132.2	1.4	2.24	7	8	0.39	-2.6	0.27
A	lansoprazole	128.2	1.3	2.17	8	7	0.45	-1.7	0.07
A	omeprazole	127.5	1.3	2.16	9	9	0.34	-2.7	0.24
C	omega 3	127.1	1.3	2.15	10	11	2.32	-1.0	0.41
A	mesalazine	125.6	1.3	2.13	11	12	1.09	0.2	0.19
R	vilanterol/ fluticasone furoate	124.7	1.3	2.11	12	6	1.61	-7.5	0.83
B	enoxaparin	120.3	1.2	2.04	13	10	2.20	-0.1	0.87
C	ramipril	115.0	1.2	1.95	14	14	0.09	-2.0	0.01
C	olmesartan	113.0	1.2	1.92	15	15	0.31	0.0	0.10
C	ezetimibe	101.0	1.0	1.71	16	19	0.73	-0.6	0.12
N	levetiracetam	98.9	1.0	1.68	17	18	2.02	-0.1	0.76
A	metformin	98.0	1.0	1.66	18	16	0.20	1.4	0.05
C	amlodipine	94.4	1.0	1.60	19	17	0.16	-0.9	<0.005
C	nebivolol	91.8	0.9	1.56	20	20	0.25	-0.2	0.05
C	ezetimibe/ rosuvastatin	91.2	0.9	1.55	21	42	0.40	-11.2	0.03
L	letrozole	89.0	0.9	1.51	22	26	2.25	-0.3	0.14
C	rosuvastatin	87.6	0.9	1.49	23	24	0.26	-0.9	0.04
C	olmesartan/ amlodipine	85.8	0.9	1.45	24	29	0.40	-0.2	0.25
A	insulin lispro	82.8	0.8	1.40	25	21	1.22	-2.7	0.35
H	levothyroxine	82.1	0.8	1.39	26	34	0.17	8.7	0.05
A	rifaximin	81.6	0.8	1.38	27	27	2.08	0.0	2.19
N	pregabalin	80.3	0.8	1.36	28	30	1.53	-1.0	0.10
C	simvastatin	80.2	0.8	1.36	29	22	0.33	-0.3	0.03
R	formoterol/ budesonide	78.5	0.8	1.33	30	23	1.80	-5.0	0.15
	Total	**3,687.1**	**37.7**						
	Total expenditure class A-NHS	**9,778.4**							

* Calculated on overall expenditure under approved care regime

Table 3.12 2022 regional ranks of the first 30 active ingredients by expenditure under approved care regime (class A-NHS)

Rank	Active ingredient	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Sicily	Sardinia
1	atorvastatin	2	5	6	2	3	1	2	3	1	1	1	1	3	3	3	3	1	3	1	1
2	pantoprazole	1	1	4	1	7	6	3	1	2	2	2	2	1	2	4	1	2	2	2	4
3	cholecalciferol	3	2	2	4	2	3	1	2	5	12	3	3	4	1	1	2	3	1	3	2
4	bisoprolol	6	9	10	7	8	4	4	6	3	5	7	4	5	5	5	8	5	4	5	5
5	amoxicillin/ clavulanic acid	5	8	11	8	6	9	10	7	8	8	4	5	8	4	6	5	4	6	8	6
6	formoterol /beclomethasone	4	4	9	5	5	5	9	5	7	3	6	11	9	20	28	9	14	10	19	13
7	esomeprazole	7	3	8	10	4	13	11	11	12	26	33	23	14	7	14	6	12	5	9	16
8	lansoprazole	28	11	35	69	1	2	7	4	4	13	47	10	11	11	2	16	9	12	24	14
9	omeprazole	19	29	14	83	30	22	28	18	29	20	9	63	17	14	7	4	21	9	4	3
10	omega 3	25	6	23	58	18	18	17	16	19	30	11	8	6	8	9	7	6	14	6	9
11	mesalazine	9	20	19	14	15	8	14	10	9	7	13	7	10	15	23	15	8	8	12	10
12	vilanterol/ fluticasone furoate	8	10	13	34	13	11	18	8	13	4	12	6	13	10	15	12	16	16	14	12
13	enoxaparin	407	252	5	3	299	245	8	265	306	117	282	565	2	12	120	14	7	167	15	7
14	ramipril	12	14	25	9	12	7	5	19	6	6	5	26	12	25	25	22	28	22	21	19
15	olmesartan	27	12	22	12	17	20	13	9	27	34	10	16	15	13	10	10	10	13	10	8
16	ezetimibe	14	28	21	33	23	14	16	14	10	16	20	12	16	19	20	26	43	38	34	21
17	levetiracetam	11	22	17	6	14	10	12	13	234	86	15	9	21	9	26	13	20	19	16	17
18	metformin	17	16	32	40	28	23	21	32	20	10	21	25	20	21	18	27	15	17	17	11
19	amlodipine	16	27	24	26	22	17	19	27	11	9	8	13	25	34	27	28	30	40	36	27
20	nebivolol	18	26	33	53	42	25	24	20	24	19	14	15	30	23	16	18	18	20	25	18
21	ezetimibe/ rosuvastatin	15	19	30	25	19	16	25	15	21	17	25	20	22	27	33	20	46	27	33	29
22	letrozole	10	17	15	11	10	12	15	12	271	118	29	14	28	26	12	25	26	21	32	23
23	rosuvastatin	22	41	20	17	21	24	22	31	14	21	27	19	27	30	34	38	27	24	30	43

continued

Table 3.12 - *continued*

Rank	Active ingredient	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Sicily	Sardinia
24	olmesartan/ amlodipine	38	18	31	16	26	28	29	17	32	38	26	21	29	18	21	19	13	23	23	24
25	insulin lispro	30	25	34	45	38	21	33	53	400	11	18	47	57	33	22	23	24	11	13	15
26	levothyroxine	26	34	46	27	11	19	23	50	18	24	16	31	18	32	13	44	23	26	35	30
27	rifaximin	21	21	40	154	53	34	53	30	17	31	38	18	23	38	47	24	19	15	26	44
28	pregabalin	13	7	28	20	24	31	26	22	31	60	17	28	19	35	36	37	33	31	42	35
29	simvastatin	31	38	37	21	29	27	31	49	15	18	28	24	32	42	24	36	22	29	39	26
30	formoterol/ budesonide	37	35	29	13	20	15	27	25	16	28	57	45	42	45	42	30	38	34	47	36

Table 3.13 First thirty active ingredients* with highest average cost per day of therapy under approved care regime (A-NHS): comparison 2022-2021

ATC	Active ingredient	Average DDD cost	Δ % 22-21	Gross expenditure *per capita*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21
H	teriparatide	14.15	-9.5	0.67	-13.8	0.1	-4.8
J	ceftriaxone	11.93	-0.5	0.94	14.5	0.2	15.1
A	semaglutide	7.90	3.2	0.87	112.3	0.3	105.7
C	valsartan/sacubitril	7.21	0.0	0.51	37.1	0.2	37.1
N	fentanyl	5.64	-2.2	1.29	-4.2	0.6	-2.1
J	fluconazole	5.53	-0.4	0.66	-2.5	0.3	-2.1
N	rotigotine	5.31	-1.9	0.60	-6.9	0.3	-5.1
N	tapentadol	5.18	-17.1	1.05	-14.4	0.6	3.3
A	dulaglutide	4.94	2.0	1.31	51.1	0.7	48.1
N	naloxone/oxycodone	4.69	-27.8	0.63	-29.1	0.4	-1.7
N	lacosamide	4.67	-13.2	0.66	-3.0	0.4	11.8
J	fosfomycin	4.62	-0.2	0.64	1.1	0.4	1.3
N	quetiapine	3.45	-0.5	0.59	-2.3	0.5	-1.8
R	formoterol/glycopyrronium/ beclomethasone	3.02	-1.1	0.66	30.2	0.6	31.7
R	vilanterol/umeclidinium/ fluticasone furoate	2.73	-3.6	0.54	15.2	0.5	19.5
J	ciprofloxacin	2.56	-0.4	0.63	7.1	0.7	7.5
J	cefixime	2.33	0.2	0.99	43.1	1.2	42.8
C	omega 3	2.32	-1.0	2.15	3.4	2.5	4.4
L	letrozole	2.25	-0.3	1.51	6.9	1.8	7.1
B	enoxaparin	2.20	-0.1	2.04	-7.6	2.5	-7.5
A	rifaximin	2.08	0.0	1.38	0.3	1.8	0.3
N	levetiracetam	2.02	-0.1	1.68	3.8	2.3	3.9
R	formoterol/budesonide	1.80	-5.0	1.33	-6.0	2.0	-1.0
R	formoterol/beclomethasone	1.72	-0.8	2.53	2.5	4.0	3.4
R	vilanterol/fluticasone furoate	1.61	-7.5	2.11	-10.1	3.6	-2.8
N	pregabalin	1.53	-1.0	1.36	5.0	2.4	6.1
R	umeclidinium	1.51	-5.0	0.71	-15.4	1.3	-10.9
R	aclidinium	1.51	-5.1	0.49	-18.7	0.9	-14.3
R	tiotropium	1.50	-1.9	0.98	-16.3	1.8	-14.7
J	azithromicyn	1.43	-3.3	0.94	30.5	1.8	35.0

* selected among the top 100 active ingredients with highest per capita expenditure

Table 3.14 First thirty active ingredients* with the lowest average cost per day of therapy under approved care regime (A-NHS): comparison 2022-2021

ATC	Active ingredient	Average DDD cost	Δ % 22-21	Gross expenditure *(in million)*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21
B	acetylsalicylic acid	0.07	-0.1	70.4	1.4	45.6	1.5
A	cholecalciferol	0.08	-0.5	239.0	-2.8	136.8	-2.3
C	furosemide	0.08	-0.4	41.1	-3.4	23.3	-3.0
C	ramipril	0.09	-2.0	115.0	-3.4	61.5	-1.5
C	amlodipine	0.16	-0.9	94.4	-1.2	28.0	-0.3
C	telmisartan	0.17	-1.6	29.7	-4.9	8.3	-3.4
H	levothyroxine	0.17	8.7	82.1	14.0	22.7	4.9
C	valsartan	0.19	0.5	40.1	1.9	10.0	1.5
A	metformin	0.20	1.4	98.0	1.9	23.1	0.5
B	folic acid	0.21	-0.4	30.7	2.0	6.8	2.4
C	lercanidipine	0.22	-0.1	45.3	-1.2	9.4	-1.1
C	irbesartan	0.22	0.1	37.7	-4.2	7.8	-4.2
C	ramipril/hydrochlorothiazide	0.23	-1.3	32.2	-3.5	6.4	-2.3
N	sertraline	0.25	-2.4	48.6	2.5	9.1	5.0
C	atorvastatin	0.25	0.0	276.0	1.3	50.9	1.3
C	nebivolol	0.25	-0.2	91.8	1.8	16.9	2.0
G	alfuzosin	0.26	-0.9	54.1	3.3	9.8	4.3
C	rosuvastatin	0.26	-0.9	87.6	5.2	15.8	6.1
H	prednisone	0.27	-2.0	41.7	3.8	7.2	5.9
G	tamsulosin	0.28	-0.9	67.3	2.1	11.2	3.0
C	nebivolol/hydrochlorothiazide	0.28	-0.2	28.7	2.2	4.7	2.5
C	losartan	0.29	0.2	41.8	-4.5	6.7	-4.6
C	valsartan/hydrochlorothiazide	0.30	-0.2	38.3	-3.7	5.9	-3.4
G	silodosin	0.31	-0.8	43.3	3.5	6.5	4.3
C	olmesartan	0.31	0.0	113.0	7.7	16.7	7.7
C	irbesartan/hydrochlorothiazide	0.32	-0.3	32.9	-5.4	4.8	-5.1
C	simvastatin	0.33	-0.3	80.2	-6.4	11.4	-6.1
C	olmesartan/hydrochlorothiazide	0.33	-0.3	74.5	3.6	10.4	3.8
A	omeprazole	0.34	-2.7	127.5	-2.9	17.6	-0.2
G	dutasteride	0.34	-1.1	60.9	-0.6	8.4	0.6

* selected among the top 100 active ingredients with highest per capita expenditure

Table 3.15 First thirty active ingredients* with highest variation in expenditure under approved care regime (A-NHS) compared to the previous year: comparison 2022-2021

ATC	Active ingredient	Gross expenditure *per capita*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21	Average DDD cost	Δ % 22-21
A	semaglutide	0.87	112.3	0.3	105.7	7.90	3.2
A	dulaglutide	1.31	51.1	0.7	48.1	4.94	2.0
C	ezetimibe/rosuvastatin	1.55	50.2	10.6	69.0	0.40	-11.2
J	clarithromycin	0.58	48.8	1.8	45.5	0.90	2.2
J	cefixime	0.99	43.1	1.2	42.8	2.33	0.2
R	beclomethasone	0.64	38.4	1.7	35.3	1.02	2.3
C	valsartan/sacubitril	0.51	37.1	0.2	37.1	7.21	0.0
A	magaldrate	0.56	36.6	2.5	35.7	0.62	0.6
J	azithromicyn	0.94	30.5	1.8	35.0	1.43	-3.3
R	formoterol/glycopyrronium/ beclomethasone	0.66	30.2	0.6	31.7	3.02	-1.1
J	amoxicillin/clavulanic acid	2.60	25.7	5.2	25.4	1.36	0.3
R	vilanterol/umeclidinium/ fluticasone furoate	0.54	15.2	0.5	19.5	2.73	-3.6
J	ceftriaxone	0.94	14.5	0.2	15.1	11.93	-0.5
H	levothyroxine	1.39	14.0	22.7	4.9	0.17	8.7
N	vortioxetine	0.82	13.6	2.0	13.5	1.14	0.1
C	olmesartan/amlodipine	1.45	10.9	9.9	11.2	0.40	-0.2
C	ezetimibe	1.71	9.5	6.4	10.1	0.73	-0.6
C	olmesartan	1.92	7.7	16.7	7.7	0.31	0.0
M	febuxostat	0.55	7.5	2.3	8.0	0.67	-0.4
J	ciprofloxacin	0.63	7.1	0.7	7.5	2.56	-0.4
L	letrozole	1.51	6.9	1.8	7.1	2.25	-0.3
L	methotrexate	0.73	6.6	1.4	5.7	1.43	0.8
M	diclofenac	0.64	6.3	4.4	6.4	0.40	-0.1
C	rosuvastatin	1.49	5.2	15.8	6.1	0.26	-0.9
N	pregabalin	1.36	5.0	2.4	6.1	1.53	-1.0
S	tafluprost	0.52	4.7	1.7	5.5	0.86	-0.8
B	clopidogrel	1.21	4.5	6.0	6.1	0.56	-1.5
M	alendronic acid	0.81	4.2	4.3	5.3	0.51	-1.1
A	ursodeoxycholic acid	0.91	3.9	2.7	3.9	0.92	0.0
C	bisoprolol	2.82	3.9	12.8	3.8	0.60	0.1

* selected among the top 100 active ingredients with highest per capita expenditure

Table 3.16 First thirty active ingredients* with highest variation in expenditure under approved care regime (A-NHS) compared to the previous year: comparison 2022-2021

ATC	Active ingredient	Gross expenditure *per capita*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21	Average DDD cost	Δ % 22-21
N	naloxone/oxycodone	0.63	-29.1	0.4	-1.7	4.69	-27.8
R	salmeterol/fluticasone	0.88	-28.2	2.0	-12.6	1.20	-17.8
R	aclidinium	0.49	-18.7	0.9	-14.3	1.51	-5.1
R	tiotropium	0.98	-16.3	1.8	-14.7	1.50	-1.9
R	umeclidinium	0.71	-15.4	1.3	-10.9	1.51	-5.0
N	tapentadol	1.05	-14.4	0.6	3.3	5.18	-17.1
H	teriparatide	0.67	-13.8	0.1	-4.8	14.15	-9.5
R	vilanterol/fluticasone furoate	2.11	-10.1	3.6	-2.8	1.61	-7.5
B	enoxaparin	2.04	-7.6	2.5	-7.5	2.20	-0.1
A	insulin aspart	1.31	-6.9	2.8	-1.9	1.30	-5.1
N	rotigotine	0.60	-6.9	0.3	-5.1	5.31	-1.9
C	simvastatin	1.36	-6.4	11.4	-6.1	0.33	-0.3
R	formoterol/budesonide	1.33	-6.0	2.0	-1.0	1.80	-5.0
A	insulin lispro	1.40	-5.6	3.2	-3.0	1.22	-2.7
C	irbesartan/hydrochlorothiazide	0.56	-5.4	4.8	-5.1	0.32	-0.3
A	lansoprazole	2.17	-5.1	13.3	-3.4	0.45	-1.7
C	telmisartan	0.50	-4.9	8.3	-3.4	0.17	-1.6
C	losartan	0.71	-4.5	6.7	-4.6	0.29	0.2
N	fentanyl	1.29	-4.2	0.6	-2.1	5.64	-2.2
C	irbesartan	0.64	-4.2	7.8	-4.2	0.22	0.1
C	valsartan/hydrochlorothiazide	0.65	-3.7	5.9	-3.4	0.30	-0.2
C	ramipril/hydrochlorothiazide	0.55	-3.5	6.4	-2.3	0.23	-1.3
C	ramipril	1.95	-3.4	61.5	-1.5	0.09	-2.0
C	furosemide	0.70	-3.4	23.3	-3.0	0.08	-0.4
A	insulin glulisine	0.49	-3.0	1.0	-3.0	1.32	0.0
N	lacosamide	0.66	-3.0	0.4	11.8	4.67	-13.2
A	omeprazole	2.16	-2.9	17.6	-0.2	0.34	-2.7
A	cholecalciferol	4.05	-2.8	136.8	-2.3	0.08	-0.5
C	zofenopril/hydrochlorothiazide	0.62	-2.5	4.0	-2.4	0.43	-0.1
J	fluconazole	0.66	-2.5	0.3	-2.1	5.53	-0.4

* selected among the top 100 active ingredients with highest per capita expenditure

Table 3.17 First thirty active ingredients by consumption under approved care regime (A-NHS): comparison 2022-2021

ATC	Active ingredient	DDD/1000 inhab. per day	%*	Rank 2022	Rank 2021	Average DDD cost	Δ % 22-21	Average DDD cost direct purchases
A	cholecalciferol	136.8	12.0	1	1	0.08	-0.5	0.01
C	ramipril	61.5	5.4	2	2	0.09	-2.0	0.01
C	atorvastatin	50.9	4.5	3	3	0.25	0.0	<0.005
B	acetylsalicylic acid	45.6	4.0	4	4	0.07	-0.1	0.02
A	pantoprazole	29.0	2.5	5	6	0.43	-2.5	0.21
C	amlodipine	28.0	2.5	6	5	0.16	-0.9	<0.005
C	furosemide	23.3	2.0	7	7	0.08	-0.4	0.03
A	metformin	23.1	2.0	8	8	0.20	1.4	0.05
H	levothyroxine	22.7	2.0	9	9	0.17	8.7	0.05
A	omeprazole	17.6	1.5	10	10	0.34	-2.7	0.24
C	nebivolol	16.9	1.5	11	11	0.25	-0.2	0.05
C	olmesartan	16.7	1.5	12	12	0.31	0.0	0.10
A	esomeprazole	15.8	1.4	13	13	0.39	-2.6	0.27
C	rosuvastatin	15.8	1.4	14	14	0.26	-0.9	0.04
A	lansoprazole	13.3	1.2	15	15	0.45	-1.7	0.07
C	bisoprolol	12.8	1.1	16	16	0.60	0.1	0.09
B	cyanocobalamin	12.2	1.1	17	18	0.02	-4.9	<0.005
C	simvastatin	11.4	1.0	18	17	0.33	-0.3	0.03
G	tamsulosin	11.2	1.0	19	19	0.28	-0.9	0.03
C	ezetimibe/ rosuvastatin	10.6	0.9	20	41	0.40	-11.2	0.03
C	olmesartan/ hydrochlorothiazide	10.4	0.9	21	20	0.33	-0.3	0.18
C	valsartan	10.0	0.9	22	21	0.19	0.5	<0.005
C	olmesartan/ amlodipine	9.9	0.9	23	24	0.40	-0.2	0.25
G	alfuzosin	9.8	0.9	24	23	0.26	-0.9	0.05
C	lercanidipine	9.4	0.8	25	22	0.22	-0.1	0.06
N	sertraline	9.1	0.8	26	25	0.25	-2.4	0.01
M	allopurinol	8.6	0.8	27	28	0.12	0.3	0.03
C	candesartan	8.4	0.7	28	27	0.15	0.3	0.02
G	dutasteride	8.4	0.7	29	29	0.34	-1.1	0.09
C	telmisartan	8.3	0.7	30	26	0.17	-1.6	0.01
	Total	**667.4**	**58.5**					
	Total DDD class A-NHS	**1140.4**						

* calculated on overall expenditure under approved care regime

Table 3.18 2022 regional ranks of the first 30 active ingredients by consumption under approved care regime (class A-NHS)

Rank	Active ingredient	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Sicily	Sardinia
1	cholecalciferol	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	ramipril	2	2	2	3	2	2	2	3	2	2	2	4	2	3	3	3	4	4	3	3
3	atorvastatin	4	4	3	2	4	3	3	2	4	3	4	3	4	4	4	2	3	3	4	2
4	acetylsalicylic acid	3	3	6	4	3	5	4	5	3	4	3	2	3	2	2	5	2	2	2	4
5	pantoprazole	6	5	4	5	11	10	7	4	10	10	8	6	5	5	8	4	5	5	7	10
6	amlodipine	5	8	5	7	8	4	5	6	5	5	5	5	7	6	9	7	10	9	10	8
7	furosemide	7	10	7	8	6	6	9	13	8	7	6	7	9	9	6	14	8	8	8	7
8	metformin	9	7	8	11	10	8	8	9	9	9	9	9	8	8	10	10	6	7	6	6
9	levothyroxine	8	9	12	6	7	9	6	22	6	8	7	8	6	7	5	12	7	6	9	11
10	omeprazole	15	18	11	70	22	17	20	16	28	19	13	42	13	12	11	6	16	10	5	5
11	nebivolol	10	13	13	24	19	11	13	10	15	11	10	10	11	13	12	11	11	11	13	12
12	olmesartan	17	11	14	12	14	15	10	7	23	22	12	12	10	11	13	9	9	12	11	9
13	esomeprazole	13	6	9	15	9	16	14	11	19	28	33	22	15	10	15	8	15	13	12	14
14	rosuvastatin	11	19	10	9	12	12	11	15	12	12	15	11	12	15	19	15	13	14	15	20
15	lansoprazole	33	16	28	65	5	7	15	8	11	24	48	16	16	17	7	20	14	17	22	17
16	bisoprolol	21	22	15	13	13	14	12	12	13	18	21	15	19	18	17	19	21	20	17	15
17	cyanocobalamin	12	24	16	66	37	44	22	23	7	6	11	33	23	25	39	35	25	19	18	39
18	simvastatin	24	25	17	16	16	21	18	33	16	17	20	14	24	27	18	21	18	26	25	16
19	tamsulosin	14	14	18	14	20	22	16	14	17	16	14	17	27	23	20	23	27	24	28	27
20	ezetimibe/rosuvastatin	20	20	20	22	18	19	19	18	22	23	26	20	21	22	33	16	34	29	24	23
21	olmesartan/hydrochlorothiazide	30	15	26	21	24	24	17	17	42	50	35	25	26	20	24	13	12	16	14	21
22	valsartan	28	26	24	32	30	30	25	29	14	13	17	18	29	24	31	24	26	15	23	19
23	olmesartan/amlodipine	38	17	22	18	23	25	23	19	36	38	31	23	25	19	22	17	19	23	19	22
24	alfuzosin	42	41	32	87	34	27	53	27	30	34	52	21	20	21	29	18	20	21	21	13
25	lercanidipine	18	12	25	10	33	13	21	30	20	33	24	24	28	32	27	26	41	51	37	28
26	sertraline	16	29	21	19	17	20	33	20	18	14	22	29	40	28	42	56	45	50	32	43
27	allopurinol	25	23	46	34	36	37	26	37	21	20	18	13	31	16	16	36	22	22	27	35
28	candesartan	31	75	40	20	45	40	32	24	34	29	27	26	30	26	14	27	17	31	33	24
29	dutasteride	36	37	27	33	26	26	27	26	35	32	19	19	33	29	35	38	24	27	31	33
30	telmisartan	23	38	30	29	21	42	31	36	37	39	16	37	17	30	25	31	33	38	20	29

Figure 3.5 Consumption, price and mix effect on variation in expenditure for medicines dispensed by public health facilities by ATC 1st level: comparison 2022-2021

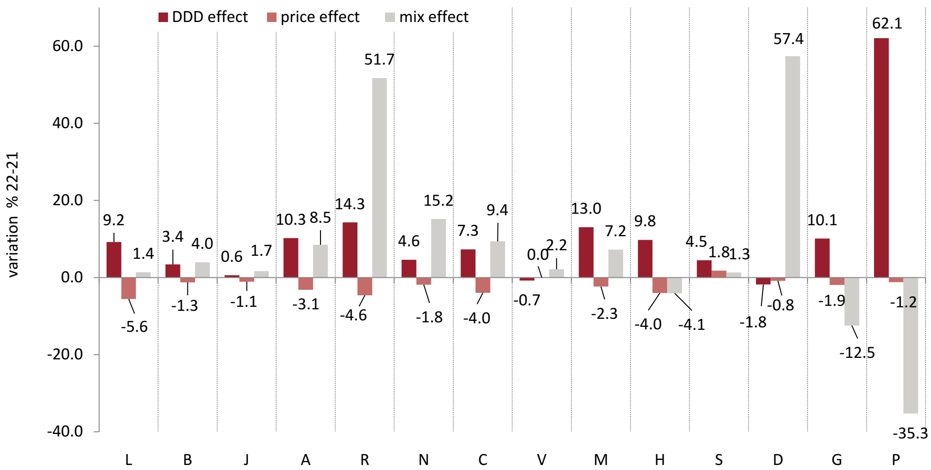


Figure 3.19 Consumption, price and mix effect on variation in expenditure for medicines dispensed by public health facilities: comparison 2022-2021
(any ATC category includes the therapeutic subgroups in decreasing order of per capita expenditure, up to the value of 0.10 euro)

ATC 1st level Subgroups	Expenditure expenditure *per capita*	DDD/ 1000 inhab. per day	Δ % 22-21 Expen diture	DDD cost	Prices	Mix	Δ % Average DDD cost
Italy	**253.59**	**184.6**	**8.1**	**6.1**	**-3.5**	**5.6**	**1.9**
L- Antineoplastic and immunomodulating agents	**113.04**	**12.2**	**4.6**	**9.2**	**-5.6**	**1.4**	**-4.2**
Selective immunosuppressants	16.97	1.6	13.1	14.1	-2.5	1.6	-0.9
PD-1/PDL-1 inhibitors (prog. 1/LIG1 cell death protection)	13.25	0.4	9.5	16.3	-5.6	-0.3	-5.8
Interleukin inhibitors	9.86	1.1	15.0	27.4	-6.0	-3.9	-9.7
Other immunosuppressants	7.04	0.5	-29.9	4.7	-5.0	-29.6	-33.1
CD38 inhibitors (clusters of differentiation 38)	6.90	0.2	68.6	160.9	-11.9	-26.6	-35.4
HER2 inhibitors (human epid. growth factor 2 receptor)	4.73	0.3	1.8	4.1	-10.9	9.7	-2.2
Tumor necrosis factor alpha inhibitors (TNF-alpha)	4.66	1.7	-7.8	11.5	-6.9	-11.2	-17.3
Other kinase protein inhibitors	4.34	0.1	1.0	11.0	-4.4	-4.9	-9.0
Cyclin-dependent kinase inhibitors (CDK)	3.81	0.2	10.4	14.9	-3.2	-0.7	-3.9
Bruton tyrosine kinase (BTK) inhibitors	3.80	0.1	11.4	16.2	-4.6	0.5	-4.1
BCR-ABL tyrosine kinase inhibitors	3.15	0.2	-8.1	0.5	-0.9	-7.8	-8.6
Inhib. epidermal growth factor receptor tyrosine kinase (EGFR)	2.94	0.1	11.6	13.0	-4.1	3.0	-1.3
Antiandrogens	2.59	0.6	13.0	-1.9	-18.2	40.8	15.2
Other monoclonal antibodies and antibody-drug conjugates	2.56	0.0	110.5	124.7	2.1	-8.3	-6.3
Janus-associated kinase (JAK) inhibitors	2.13	0.1	13.2	14.1	0.0	-0.8	-0.7
Gonadotropin-releasing hormone analogues	2.07	1.2	8.9	14.6	-0.7	-4.3	-4.9
Poly (ADP-RIBOSE) polymerase (PARP) inhibitors	1.89	0.0	24.6	34.7	-8.9	1.6	-7.5
Other hormone antagonists and related substances	1.58	0.1	-20.6	-5.7	-11.3	-5.0	-15.7
Other antineoplastics	1.56	0.1	6.6	5.2	-2.6	4.1	1.4
Interferons	1.52	0.3	-13.9	-17.2	-0.2	4.2	3.9
Serine-threonine kinase B-RAF inhibitors	1.50	0.0	10.7	9.7	-1.2	2.2	0.9
Anaplastic lymphoma kinase inhibitors (ALK)	1.44	0.0	11.6	19.0	-1.6	-4.7	-6.2
VEGF/VEGFR inhibitors (angiogenic growth factor)	1.28	0.1	-17.6	21.3	-6.8	-27.1	-32.1
Antineoplastic cell and gene therapy	1.19	0.0	45.2	36.2	8.6	-1.8	6.6
EGFR inhibitors (epidermal growth factor receptor)	1.05	0.0	-6.5	3.1	-9.3	0.0	-9.3

ATC 1st level Subgroups	Expenditure expenditure *per capita*	DDD/ 1000 inhab. per day	Δ % 22-21 Expen diture	DDD cost	Prices	Mix	Δ % Average DDD cost
CD20 inhibitors (clusters of differentiation 20)	1.04	0.5	-23.4	-1.0	-10.0	-14.0	-22.6
Pyrimidine analogues	0.98	0.5	-16.0	11.0	-4.3	-20.9	-24.3
Antineoplastic cell and gene therapy	0.95	0.0	16.4	14.6	8.6	-6.5	1.5
Calcineurin inhibitors	0.89	0.4	3.4	5.5	-0.1	-1.9	-2.0
Proteasome inhibitors	0.85	0.0	-2.2	0.6	-4.9	2.2	-2.8
Mitogen-activated protein kinase (MEK) inhibitors	0.71	0.0	6.0	9.7	0.0	-3.4	-3.4
Other immunostimulating agents	0.59	0.1	-3.2	-16.9	-10.8	30.5	16.4
Taxanes	0.45	0.2	-34.2	-0.5	-22.6	-14.5	-33.9
Tyrosine kinase receptor inhibitors endovascular growth factor (VEGFR)	0.44	0.0	33.5	46.5	-8.8	0.0	-8.9
Anthracyclines and related substances	0.44	0.1	-15.2	-9.5	1.0	-7.2	-6.3
Rapamycin and mammalian target of rapamycin (MTOR) inhibitors	0.37	0.0	-24.0	5.8	-20.2	-10.0	-28.1
Colony stimulating factors	0.35	0.1	-12.4	9.0	-11.7	-9.0	-19.7
Hedgehog pathway inhibitors	0.30	0.0	-24.1	23.9	-36.6	-3.4	-38.7
Folic acid analogues	0.26	0.1	-69.5	-13.4	-12.5	-59.8	-64.8
Other antineoplastics	0.24	0.0	0.0	0.0	0.0	0.0	0.0
Other alkaloids derived from plants and other natural products	0.22	0.0	-24.6	-1.4	-23.0	-0.6	-23.5
Antineoplastics in combination	0.17	0.0	8.1	19.0	-0.3	-8.9	-9.1
Antiestrogens	0.13	0.1	-59.3	-39.9	-6.2	-27.9	-32.4
Vinca alkaloids and analogues	0.12	0.0	-30.7	-4.9	-22.4	-6.1	-27.1
CD22 inhibitors (clusters of differentiation 22)	0.11	0.0	35.6	34.4	0.9	0.0	0.9
Nitrogen mustard analogues	0.10	0.1	-9.3	-3.2	-5.4	-1.0	-6.3
B - Blood and blood-forming organs	**34.19**	**53.0**	**6.2**	**3.4**	**-1.3**	**4.0**	**2.7**
Direct Xa factor inhibitors	8.58	14.2	14.2	12.4	-0.2	1.7	1.5
Blood coagulation factors	7.61	0.1	-3.1	1.0	-1.1	-3.1	-4.1
Other hemostatics for systemic use	3.05	0.1	21.8	18.7	-4.8	7.8	2.6
Other antianemic preparations	2.90	3.9	15.3	5.2	-3.0	12.9	9.5
Platelet aggregation inhibitors, excl. heparin	2.33	9.7	-1.5	-1.2	-5.4	5.5	-0.2
Heparins	2.22	6.4	4.6	-1.2	6.4	-0.6	5.8
Direct thrombin inhibitors	1.27	2.4	-3.2	-0.8	-2.0	-0.4	-2.4
Solutions affecting the electrolyte balance	1.02	6.8	6.8	0.0	3.8	2.8	6.8
Other antithrombotics	0.92	0.5	26.6	-7.3	1.3	34.9	36.7
Parenteral nutritional solutions	0.75	0.7	-8.1	1.9	-4.9	-5.2	-9.8
Medicines used in hereditary angioedema	0.68	0.0	12.0	35.5	-1.9	-15.8	-17.4

ATC 1st level / Subgroups	Expenditure expenditure *per capita*	DDD/ 1000 inhab. per day	Δ % 22-21 Expen diture	DDD cost	Prices	Mix	Δ % Average DDD cost
Hypertonic solutions	0.44	0.1	-16.5	-10.4	-7.2	0.4	-6.8
Local hemostatics	0.44	0.0	13.6	17.3	0.1	-3.3	-3.2
Iron, parenteral preparations	0.38	0.1	-7.8	-8.3	0.3	0.2	0.5
Protease inhibitors	0.29	0.0	9.8	-2.4	-0.1	12.6	12.5
Fibrinogen	0.29	0.0	15.9	19.1	-33.0	45.1	-2.7
Blood substitutes and plasma protein fractions	0.28	0.0	-14.3	-15.7	2.3	-0.6	1.7
Enzymes	0.21	0.0	-15.4	-15.6	-8.0	8.9	0.2
Isotonic solutions	0.19	0.1	-1.3	-11.0	4.7	6.0	10.9
J- General antimicrobials for systemic use	**33.34**	**5.8**	**1.3**	**0.6**	**-1.1**	**1.7**	**0.7**
Antivirals for treatment of HCV infections, combinations	8.57	1.4	3.0	0.9	-0.8	2.9	2.0
Influenza vaccines	2.64	0.7	-14.3	-15.0	-10.3	12.4	0.9
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	2.11	0.1	-10.7	8.2	1.1	-18.3	-17.4
Human normal immunoglobulin	1.94	0.0	-2.7	-19.5	12.9	6.8	20.9
Meningococcal vaccines	1.74	0.1	-10.2	-7.2	-1.6	-1.7	-3.3
Varicella Zoster vaccines	1.60	0.0	355.5	97.0	-0.9	133.2	131.2
Human papillomavirus vaccines	1.44	0.1	21.0	20.9	0.0	0.0	0.1
Pneumococcal vaccines	1.30	0.1	-33.1	-30.7	-0.2	-3.7	-3.4
Antivirals for treatment of HCV infections	1.29	0.0	-10.7	-9.3	-0.2	-1.4	-1.5
Integrase inhibitors	1.20	0.2	-16.6	-16.5	0.1	-0.3	-0.2
Bacterial and viral vaccines in combination	0.84	0.1	-5.5	1.6	-7.6	0.7	-6.9
Antibiotics	0.83	0.0	15.7	14.3	0.1	1.0	1.2
Other cephalosporins and penems	0.74	0.0	208.0	219.1	0.3	-4.0	-3.5
Measles vaccines	0.64	0.0	4.2	-2.7	-2.0	9.1	7.0
Penicillin combinations, including betalactamase inhibitors	0.63	0.5	3.0	15.9	-8.5	-2.8	-11.1
Triazole and tetrazole derivatives	0.53	0.1	-0.6	0.9	0.9	-2.4	-1.5
Third-generation cephalosporins	0.53	0.3	-10.4	15.5	-1.8	-21.4	-22.5
Other antibacterials	0.50	0.1	-5.4	35.5	9.5	-36.3	-30.2
Antiviral monoclonal antibodies	0.46	0.0	12.4	67.2	0.0	-32.8	-32.8
Carbapenems	0.43	0.1	38.6	16.1	-0.9	20.4	19.4
Other antivirals	0.41	0.0	-2.3	-7.5	-0.9	6.5	5.5
Specific immunoglobulins	0.31	0.0	1.6	0.5	-0.6	1.8	1.1
Nucleosides and nucleotides inhibitors of reverse transcriptase	0.28	0.7	-2.3	-5.6	-8.6	13.2	3.5
Other antifungals for systemic use	0.28	0.0	-23.3	-4.8	-17.1	-2.8	-19.5
Glycopeptide antibacterials	0.27	0.0	4.2	11.5	-10.0	3.9	-6.5
Rotavirus diarrhea vaccines	0.25	0.0	-13.3	-1.6	-9.7	-2.5	-11.9

ATC 1st level Subgroups	Expenditure expenditure *per capita*	DDD/ 1000 inhab. per day	Δ % 22-21 Expen diture	DDD cost	Prices	Mix	Δ % Average DDD cost
Non-nucleosides inhibitors of reverse transcriptase	0.19	0.1	4.1	-5.2	-1.2	11.1	9.8
Polymyxins	0.17	0.0	-12.8	-19.3	0.9	7.1	8.0
Pertussis vaccines	0.13	0.0	18.4	30.4	-9.0	-0.2	-9.2
A - Gastrointestinal system and metabolism	**22.58**	**37.2**	**16.0**	**11.2**	**-3.1**	**7.6**	**4.3**
Enzymes	5.62	0.0	5.8	11.2	-0.3	-4.8	-4.8
GLP-1 receptor analogues (Glucagon-Like Peptide-1)	4.93	5.5	39.0	42.5	-7.1	5.0	-2.4
Insulins and injectable analogues, long-acting	3.03	5.3	0.4	-3.2	-3.3	7.3	3.7
Oral hypoglycemic agents, in combination	2.35	6.0	8.1	9.3	-4.4	3.5	-1.1
SGLT2 cotransporter inhibitors (sodium-glucose type 2)	1.78	3.8	77.1	84.3	-4.9	1.0	-3.9
Various products for gastrointestinal system and metabolism	1.56	0.0	26.3	18.6	-1.8	8.4	6.5
Dipeptil Peptidase 4 Inhibitors (DPP-4)	1.25	3.2	-6.0	3.3	-8.5	-0.6	-9.0
Bile acids and derivatives	0.40	0.1	22.5	103.0	0.0	-39.7	-39.7
Proton pump inhibitors	0.25	3.8	6.2	4.0	7.7	-6.1	2.1
Antibiotics	0.24	0.3	27.1	11.3	-0.1	14.3	14.2
Serotonin antagonists (5HT3)	0.19	0.1	11.2	26.7	1.1	-13.2	-12.3
Insulins and injectable analogues, fast acting	0.16	0.9	-4.0	3.9	-4.5	-3.3	-7.6
Amino acids and derivatives	0.15	0.1	8.9	2.2	-4.0	10.9	6.5
Polyvitamins, not in combination	0.14	0.1	2.2	-3.1	5.5	0.0	5.5
R- Respiratory system	**10.37**	**2.3**	**65.4**	**14.3**	**-4.6**	**51.7**	**44.8**
Other preparations for the respiratory system	7.14	0.1	102.4	133.3	-7.5	-6.2	-13.3
Other systemic drugs for obstructive airway disorders	2.66	0.3	24.9	23.5	-0.7	1.8	1.1
Mucolytics	0.23	0.2	-9.7	13.5	0.6	-20.9	-20.5
N- Central nervous system	**9.77**	**27.9**	**18.2**	**4.6**	**-1.8**	**15.2**	**13.0**
Other antipsychotics	3.07	2.8	4.0	5.6	-0.4	-1.0	-1.5
Other medicines for the nervous system	2.01	0.1	140.2	55.8	-5.3	62.8	54.2
Other antiepileptics	0.71	0.9	21.9	9.1	-4.5	16.9	11.7
DOPA and derivatives	0.53	0.2	2.3	0.8	0.3	1.2	1.5
Calcitonin gene-related peptide antagonists	0.47	0.2	43.6	37.8	0.8	3.3	4.2
Medicines used in opioid addiction	0.45	3.2	-0.8	-2.7	-2.7	4.9	2.0
Diazepines, oxazepines, thiazepines and oxepins	0.35	3.6	3.3	2.2	2.1	-1.0	1.1
Halogenated hydrocarbons	0.20	0.0	4.1	5.5	-2.0	0.7	-1.3
Amides	0.17	2.1	6.7	6.6	0.2	-0.1	0.0

ATC 1st level Subgroups	Expenditure expenditure *per capita*	DDD/ 1000 inhab. per day	Δ % 22-21 Expen diture	DDD cost	Prices	Mix	Δ % Average DDD cost
Other dopaminergic substances	0.15	0.1	17.8	19.5	-1.2	-0.2	-1.4
Other general anesthetics	0.15	0.2	-36.3	-32.1	-9.4	-7.9	-6.2
Anilides	0.11	4.2	20.3	22.2	3.3	-4.7	-1.5
Indole derivatives	0.11	0.1	12.5	11.0	-0.6	2.0	1.4
Anticholinesterases	0.11	0.9	-9.5	-4.7	-30.3	36.5	-5.0
C - Cardiovascular system	**7.34**	**17.9**	**12.8**	**7.3**	**-4.0**	**9.4**	**5.1**
Other lipid modifying agents	2.35	0.8	40.8	50.8	-6.7	0.1	-6.6
Angiotensin II receptor blockers (ARBS), other combinations	1.54	1.0	35.3	35.2	0.0	0.0	0.0
Antihypertensives for pulmonary arterial hypertension	1.37	0.1	3.9	9.6	0.0	-5.2	-5.2
Other cardiac preparations	1.26	2.2	-16.1	-9.7	-4.5	-2.6	-7.1
Vasopressin antagonists	0.17	0.0	-15.4	9.0	-24.1	2.2	-22.4
Adrenergics and dopaminergics	0.14	1.0	5.7	2.4	4.3	-1.0	3.2
Other inotropic substances	0.11	0.0	-12.9	7.1	-19.3	0.7	-18.7
V - Miscellaneous	**6.38**	**3.2**	**1.4**	**-0.7**	**0.0**	**2.2**	**2.2**
Hydrosol., nephrotropic, low osmolar radiological contrast media	1.33	0.1	5.1	3.6	0.7	0.7	1.5
Antidotes	1.17	0.2	25.8	8.5	-0.8	16.9	15.9
Iron chelating agents	1.05	0.1	-31.6	-2.6	-7.7	-23.9	-29.8
Other diagnostic radiopharmaceuticals for tumour detection	0.47	0.0	9.4	2.6	6.5	0.1	6.6
Paramagnetic contrast agents	0.45	0.0	6.0	7.1	-2.1	1.1	-1.0
Detoxifying substances for cytostatic treatments	0.30	0.2	12.9	-1.7	8.0	6.4	14.9
Various therapeutic radiopharmaceuticals	0.28	0.0	5.0	-10.4	14.6	2.3	17.3
Drugs for the treatment of hyperkalemia and hyperphosphatemia	0.27	0.2	32.5	7.8	3.6	18.7	23.0
Iodine-123I compounds	0.17	0.0	3.2	6.0	-2.7	0.0	-2.6
Allergenic extracts	0.13	0.2	22.4	5.1	-0.4	16.9	16.4
Various thyroid diagnostic radiopharmaceuticals	0.12	0.0	-13.5	-19.1	5.8	1.0	6.9
Solvents and thinners, including cleaning solutions	0.11	2.1	-9.2	-2.7	5.1	-11.2	-6.7
Other diagnostics	0.11	0.0	40.6	18.8	11.2	6.5	18.4
M - Musculo-skeletal system	**4.54**	**6.3**	**18.4**	**13.0**	**-2.3**	**7.2**	**4.8**
Other drugs for musculoskeletal system disorders	2.31	0.0	23.2	15.0	-5.2	13.0	7.1
Other drugs acting on bone structure and mineralization	1.70	4.5	22.0	16.3	0.0	4.9	4.9
Other muscle relaxants with peripheral action	0.25	0.0	9.6	6.6	1.0	1.8	2.8
H - Systemic hormonal preparations, excluding sex hormones	**4.30**	**5.2**	**1.1**	**9.8**	**-4.0**	**-4.1**	**-7.9**
Somatostatin and analogues	1.62	0.2	4.4	7.9	-3.2	-0.1	-3.3

ATC 1st level Subgroups	Expenditure expenditure *per capita*	DDD/ 1000 inhab. per day	Δ % 22-21 Expen diture	DDD cost	Prices	Mix	Δ % Average DDD cost
Somatropin and somatropin agonists	1.16	0.3	-4.5	2.0	-7.5	1.4	-6.4
Other antiparathyroid substances	0.56	0.4	-3.8	1.4	-4.1	-1.1	-5.1
Other hormones of the anterior pituitary lobe and analogues	0.41	0.0	-2.0	-0.3	-1.7	0.0	-1.7
Glycocorticoids	0.39	3.8	17.2	12.3	3.0	1.3	4.3
S - Sensory organs	**3.28**	**2.2**	**7.9**	**4.5**	**1.8**	**1.3**	**3.2**
Antineovascularization substances	2.45	0.1	12.0	-4.1	1.1	15.5	16.8
Corticosteroids, not in combination	0.47	0.3	9.1	8.2	2.3	-1.4	0.9
Other ophthalmological drugs	0.21	0.1	-23.2	0.4	8.7	-29.6	-23.5
D - Dermatologicals	**3.13**	**8.8**	**53.3**	**-1.8**	**-0.8**	**57.4**	**56.1**
Substances for dermatitis, excluding corticosteroids	2.69	0.3	65.8	69.6	-3.7	1.6	-2.2
Biguanides and amidines	0.11	1.3	9.5	-21.6	6.7	31.0	39.8
G - Genito-urinary system and sex hormones	**1.29**	**2.8**	**-5.4**	**10.1**	**-1.9**	**-12.5**	**-14.1**
Gonadotropins	0.91	0.1	-3.9	-11.5	-1.0	9.7	8.6
Prostaglandins	0.10	0.0	-2.9	-10.0	-0.1	7.9	7.9
P - Antiparasitic drugs, insecticides and repellents	**0.03**	**<0.05**	**6.7**	**62.1**	**-1.2**	**-35.3**	**-34.2**

Table 3.20 2022 expenditure, consumption and average cost per day of therapy for medicines supplied by public health facilities: most prescribed active ingredients by ATC 1st level (up to 75% of the category expenditure)

ATC 1st level / Subgroups	Expenditure NHS *per capita*	%	Δ % 22-21	DDD/ 1000 inhab. per day	%	Δ % 22-21	Average DDD cost	Δ % 22-21
L- Antineoplastic and immunomodulating agents	**113.04**		**5.1**	**12.2**		**9.7**	**25.34**	**-4.2**
pembrolizumab	7.54	6.7	17.5	0.2	1.8	18.6	92.20	-0.9
daratumumab	6.62	5.9	62.9	0.2	1.6	>100	94.35	-36.9
ibrutinib	3.42	3.0	0.9	0.1	0.6	6.1	123.57	-4.9
nivolumab	3.30	2.9	-10.7	0.1	0.8	0.3	98.58	-11.0
osimertinib	2.84	2.5	14.3	0.1	0.5	20.4	140.78	-5.1
pertuzumab	2.62	2.3	7.6	0.1	0.6	14.5	105.55	-6.1
dimethyl fumarate	2.58	2.3	-2.3	0.2	1.8	1.4	31.67	-3.7
lenalidomide	2.42	2.1	-55.7	0.1	1.2	18.9	45.72	-62.8
ustekinumab	2.29	2.0	11.7	0.4	3.6	38.5	14.42	-19.3
ocrelizumab	2.24	2.0	30.0	0.1	1.1	38.8	45.24	-6.4
ruxolitinib	2.10	1.9	12.2	0.1	0.4	12.6	110.52	-0.3
fingolimod	2.09	1.8	-10.0	0.1	0.9	-9.4	53.53	-0.7
secukinumab	2.03	1.8	7.2	0.2	1.5	11.7	29.37	-4.0
enzalutamide	2.01	1.8	-0.2	0.1	0.7	20.4	69.20	-17.1
eculizumab	2.01	1.8	-6.7	<0.05	0.1	-1.8	728.78	-5.0
natalizumab	1.89	1.7	8.4	0.1	0.8	8.4	50.04	0.0
palbociclib	1.65	1.5	-11.2	0.1	0.6	-7.7	65.78	-3.8
nintedanib	1.59	1.4	20.6	<0.05	0.4	27.0	91.84	-5.0
abiraterone	1.50	1.3	-20.9	0.1	0.5	-4.6	70.74	-17.1
adalimumab	1.45	1.3	-7.0	0.8	6.4	20.2	5.11	-22.6
ribociclib	1.41	1.2	32.9	0.1	0.5	32.7	68.09	0.1
vedolizumab	1.34	1.2	11.1	0.1	1.0	16.8	30.92	-4.9
trastuzumab emtansine	1.29	1.1	20.3	<0.05	0.2	52.5	152.79	-21.1
ixekizumab	1.23	1.1	28.5	0.1	0.9	28.6	30.29	0.0
etanercept	1.21	1.1	-19.5	0.3	2.5	4.0	10.94	-22.6
abatacept	1.19	1.0	3.7	0.1	0.5	3.4	49.48	0.3
dabrafenib	1.17	1.0	4.7	<0.05	0.2	4.8	105.68	0.0
olaparib	1.13	1.0	17.6	<0.05	0.2	20.5	129.06	-2.4
nilotinib	1.13	1.0	-3.9	<0.05	0.2	-3.8	131.22	-0.1
canakinumab	1.07	0.9	8.7	<0.05	0.2	15.6	147.79	-5.9
alectinib	1.06	0.9	4.5	<0.05	0.2	7.2	158.45	-2.4
leuprorelin	1.05	0.9	3.9	0.2	1.5	3.8	15.97	0.1
venetoclax	1.04	0.9	19.3	<0.05	0.1	19.0	158.77	0.2
pomalidomide	1.03	0.9	21.0	<0.05	0.1	22.8	242.57	-1.4
teriflunomide	1.03	0.9	0.6	0.1	0.9	4.1	26.23	-3.4
triptorelin	1.01	0.9	15.8	1.0	8.4	17.4	2.70	-1.4
atezolizumab	1.01	0.9	1.0	<0.05	0.3	22.4	89.08	-17.5
interferon beta 1a	1.00	0.9	-17.9	0.3	2.1	-18.9	10.77	1.3
pirfenidone	0.94	0.8	-3.1	<0.05	0.3	-2.2	63.84	-0.9
tocilizumab	0.90	0.8	-11.9	0.1	0.8	-7.2	24.18	-5.0
dasatinib	0.89	0.8	-3.4	<0.05	0.2	4.1	94.22	-7.2
golimumab	0.88	0.8	0.8	0.1	1.0	1.1	19.56	-0.3

ATC 1st level Subgroups	Expenditure NHS *per capita*	%	Δ % 22-21	DDD/ 1000 inhab. per day	%	Δ % 22-21	Average DDD cost	Δ % 22-21
tacrolimus	0.83	0.7	4.5	0.4	3.1	6.7	6.01	-2.1
trastuzumab	0.81	0.7	-27.1	0.2	1.4	-3.4	13.28	-24.5
cladribine	0.80	0.7	36.7	<0.05	0.4	41.4	46.81	-3.3
abemaciclib	0.76	0.7	44.7	<0.05	0.3	62.7	61.60	-11.0
brentuximab vedotin	0.75	0.7	>100	<0.05	0.1	56.1	293.19	37.0
rituximab	0.74	0.7	-32.5	0.4	3.6	-1.0	4.56	-31.8
bevacizumab	0.73	0.6	-26.6	0.1	0.9	23.2	17.57	-40.4
trametinib	0.69	0.6	6.9	<0.05	0.2	7.0	64.29	-0.1
guselkumab	0.69	0.6	40.4	0.1	0.6	75.3	24.39	-19.9
B - Blood and blood-forming organs	**34.19**		**6.7**	**53.0**		**3.0**	**1.77**	**2.7**
rivaroxaban	3.25	9.5	7.3	5.7	10.8	4.8	1.56	2.4
apixaban	3.13	9.2	15.8	5.1	9.6	15.9	1.69	-0.1
edoxaban	2.20	6.4	25.5	3.4	6.4	24.2	1.78	1.1
enoxaparin	1.80	5.3	5.9	5.7	10.7	0.6	0.87	5.3
emicizumab	1.58	4.6	24.8	<0.05	0.0	37.7	683.30	-9.3
dabigatran	1.26	3.7	-2.2	2.4	4.6	-0.4	1.43	-1.8
epoetin alfa	1.17	3.4	10.2	2.5	4.7	20.0	1.28	-8.2
octocog alfa	1.15	3.4	-30.7	<0.05	0.0	-29.4	325.96	-2.0
efmorocotog alfa	1.07	3.1	3.6	<0.05	0.0	3.7	357.01	0.0
electrolytes for intravenous solutions	0.97	2.8	7.9	6.6	12.5	1.3	0.40	6.5
ticagrelor	0.96	2.8	-0.8	1.1	2.1	4.1	2.33	-4.7
eltrombopag	0.94	2.7	16.4	0.1	0.1	16.4	49.36	0.0
albutrepenonacog alfa	0.90	2.6	12.7	<0.05	0.0	15.7	1058.45	-2.6
darbepoetin alfa	0.89	2.6	-2.1	0.4	0.8	-1.8	5.87	-0.3
damoctocog alfa pegol	0.66	1.9	51.0	<0.05	0.0	51.0	329.94	0.0
parenteral nutrition solutions	0.60	1.7	-9.3	0.2	0.3	-0.2	9.79	-9.1
treprostinil	0.56	1.6	-5.9	<0.05	0.0	6.3	485.26	-11.5
caplacizumab	0.55	1.6	89.8	<0.05	0.0	86.3	3395.13	1.8
pegylated turoctocog alfa	0.48	1.4	>100	<0.05	0.0	>100	257.33	0.0
activated heptacog alfa (recombinant DNA coagulation factor VII)	0.46	1.3	-23.0	<0.05	0.0	-22.4	4049.19	-0.8
romiplostim	0.45	1.3	10.0	<0.05	0.0	10.3	50.27	-0.3
moroctocog alfa	0.44	1.3	-25.0	<0.05	0.0	-22.7	323.55	-3.0
hypertonic solutions for peritoneal dialysis	0.44	1.3	-16.1	0.1	0.3	-9.9	9.05	-6.8
J - General ntimicrobials for systemic use	**33.34**		**1.7**	**5.8**		**1.1**	**15.73**	**0.7**
emtricitabine/ tenofovir alafenamide/ bictegravir	2.28	6.8	26.0	0.3	5.4	26.0	19.96	0.0

ATC 1st level Subgroups	Expenditure NHS *per capita*	%	Δ % 22-21	DDD/ 1000 inhab. per day	%	Δ % 22-21	Average DDD cost	Δ % 22-21
remdesivir	2.01	6.0	-10.7	<0.05	0.2	-11.8	379.50	1.3
dolutegravir/lamivudine	1.57	4.7	44.9	0.3	4.5	44.9	16.60	0.0
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.44	4.3	21.4	0.1	1.0	21.4	69.31	0.0
meningococcal vaccines group B	1.34	4.0	-10.8	0.1	1.0	-10.6	62.14	-0.2
emtricitabine/rilpivirine/ tenofovir alafenamide	1.33	4.0	-12.7	0.2	3.2	-10.3	19.43	-2.7
adjuvanted recombinant varicella zoster vaccine	1.26	3.8	>100	<0.05	0.2	>100	271.97	-5.6
human normal immunoglobulin for extravascular administration	1.20	3.6	0.1	<0.05	0.1	-22.3	454.25	28.9
influenza vaccine tetravalent (split virion, inactivated)	0.99	3.0	-17.2	0.3	5.5	-18.1	8.50	1.1
amphotericin B	0.83	2.5	16.2	<0.05	0.4	14.8	101.59	1.2
emtricitabine/tenofo viralafenamide/ darunavir/obicistat	0.80	2.4	-2.9	0.1	1.7	-2.9	21.85	0.0
dolutegravir/abacavir /lamivudine	0.77	2.3	-26.6	0.1	1.7	-26.6	21.48	0.0
dolutegravir	0.77	2.3	-18.6	0.1	2.2	-18.6	16.42	0.0
human normal immunoglobulin for intravascular administration	0.74	2.2	-6.0	<0.05	0.1	-14.8	352.81	10.4
thirteen-valent pneumococcal vaccine	0.71	2.1	-59.1	<0.05	0.7	-59.0	48.70	-0.3
measles, mumps, rubella and chicken pox vaccine	0.61	1.8	6.3	<0.05	0.6	4.5	47.61	1.7
glecaprevir/pibrentasvir	0.61	1.8	-14.3	<0.05	0.3	-14.3	107.91	0.0
sofosbuvir/velpatasvir	0.61	1.8	-3.2	<0.05	0.4	-2.5	71.13	-0.7
dolutegravir/rilpivirine	0.54	1.6	22.8	0.1	1.4	22.8	18.31	0.0
hexavalent vaccine	0.53	1.6	-5.0	0.1	0.9	5.4	26.53	-9.8
piperacillin/tazobactam	0.49	1.5	-1.7	0.2	2.6	11.7	8.89	-12.0
palivizumab	0.46	1.4	12.8	0.0	0.0	12.6	808.81	0.2
emtricitabine/tenofovir alafenamide	0.41	1.2	-19.5	0.1	1.7	-19.5	11.29	0.0
raltegravir	0.40	1.2	-15.7	0.1	2.0	-16.4	9.60	0.9
Ventivalent pneumococcal vaccine	0.39	1.2	0.0	<0.05	0.4	0.0	48.45	-
ceftazidime/avibactam	0.39	1.2	-16.0	<0.05	0.1	-14.3	190.50	-2.0

ATC 1st level Subgroups	Expenditure NHS *per capita*	%	Δ % 22-21	DDD/ 1000 inhab. per day	%	Δ % 22-21	Average DDD cost	Δ % 22-21
cefiderocol	0.36	1.1	>100	<0.05	0.0	>100	549.90	0.1
A - Gastrointestinal system and metabolism	**22.58**		**16.5**	**37.2**		**11.7**	**1.66**	**4.3**
dulaglutide	2.74	12.1	46.0	3.4	9.5	49.4	2.18	-2.3
semaglutide	1.71	7.6	96.0	1.4	3.9	104.8	3.24	-4.3
insulin glargine	1.50	6.6	-3.7	3.1	8.5	-7.9	1.34	4.6
agalsidase alfa	1.42	6.3	9.8	0.0	0.0	9.8	1062.25	0.0
dapagliflozin	0.93	4.1	>100	2.0	5.6	>100	1.26	-5.4
agalsidase beta	0.91	4.0	17.8	0.0	0.0	17.8	483.63	0.0
agalsidase alfa	0.81	3.6	-8.7	0.0	0.0	-7.8	1676.64	-0.9
imiglucerase	0.79	3.5	2.5	0.0	0.0	2.5	1096.50	0.0
insulin egludec/liraglutide	0.70	3.1	23.2	0.5	1.4	31.5	3.73	-6.3
insulin degludec	0.69	3.0	-4.2	1.5	4.0	2.7	1.28	-6.8
empagliflozin	0.61	2.7	67.4	1.3	3.6	67.5	1.30	-0.1
linagliptin	0.58	2.6	7.9	1.4	4.0	11.2	1.11	-3.0
dapagliflozin/metformin	0.57	2.5	26.0	1.2	3.4	32.9	1.26	-5.2
sitagliptin	0.53	2.3	-12.1	1.4	3.9	4.1	1.02	-15.5
sitagliptin/metformin	0.49	2.2	-8.4	1.4	3.8	-0.7	0.98	-7.8
idursulfase	0.49	2.2	-6.4	0.0	0.0	-2.6	2762.70	-4.0
migalastat	0.39	1.7	5.5	0.0	0.0	5.5	465.68	0.0
eliglustat	0.38	1.7	23.7	0.0	0.0	23.7	622.68	0.0
dapagliflozin/metformin	0.36	1.6	33.9	0.9	2.5	37.4	1.10	-2.6
obeticholic acid	0.31	1.4	24.2	0.0	0.0	26.8	81.23	-2.1
elosulfase alfa	0.29	1.3	7.0	0.0	0.0	7.0	2992.00	0.0
R- Respiratory system	**10.37**		**66.2**	**2.3**		**14.8**	**12.57**	**44.8**
elexacaftor/tezacaftor/ ivacaftor	3.50	33.7	>100	0.0	1.5	>100	289.31	-1.1
ivacaftor	3.04	29.3	>100	0.0	0.9	>100	429.02	-13.4
omalizumab	1.08	10.4	11.3	0.1	5.2	12.6	25.36	-1.2
mepolizumab	0.88	8.5	39.9	0.1	3.6	40.7	29.96	-0.6
benralizumab	0.70	6.7	34.8	0.1	2.9	34.8	28.98	0.0
N- Central nervous system	**9.77**		**18.7**	**27.9**		**5.1**	**0.96**	**13.0**
paliperidone	1.59	16.3	4.2	0.9	3.1	5.2	5.05	-1.0
aripiprazole	1.16	11.9	7.2	1.2	4.2	4.9	2.69	2.2
tafamidis	1.13	11.6	>100	0.0	0.2	>100	64.67	-71.4
patisiran	0.67	6.8	48.0	0.0	0.0	48.0	516.03	0.0
levodopa/carbidopa	0.50	5.2	3.1	0.1	0.4	5.1	12.67	-1.9
methadone	0.29	3.0	-3.4	2.3	8.3	-3.0	0.35	-0.3
risperidone	0.29	2.9	-8.1	0.7	2.5	3.8	1.12	-11.5
lacosamide	0.20	2.1	10.5	0.1	0.4	22.2	5.59	-9.6
erenumab	0.18	1.8	9.4	0.1	0.5	16.1	3.77	-5.7
galcanezumab	0.18	1.8	74.4	0.1	0.3	70.8	6.82	2.1
quetiapine	0.16	1.6	-3.8	1.5	5.4	0.7	0.28	-4.5
opicapone	0.14	1.4	21.2	0.1	0.4	22.1	3.23	-0.7
sevoflurane	0.13	1.3	3.6	0.0	0.0	4.5	58.90	-0.9
cannabidiol	0.13	1.3	>100	0.0	0.0	>100	47.56	0.3

ATC 1st level Subgroups	Expenditure NHS *per capita*	%	Δ % 22-21	DDD/ 1000 inhab. per day	%	Δ % 22-21	Average DDD cost	Δ % 22-21
levetiracetam	0.12	1.2	-21.5	0.4	1.6	2.8	0.76	-23.7
olanzapine	0.12	1.2	16.3	1.7	6.0	5.1	0.19	10.7
fremanezumab	0.12	1.2	86.7	0.0	0.2	86.5	7.01	0.1
perampanel	0.11	1.1	11.5	0.1	0.2	11.9	4.59	-0.4
paracetamol	0.11	1.1	20.9	4.2	14.9	22.7	0.07	-1.5
lurasidone	0.11	1.1	15.8	0.1	0.5	16.3	2.08	-0.4
C - Cardiovascular system	**7.34**		**13.3**	**17.9**		**7.8**	**1.12**	**5.1**
valsartan/sacubitril	1.54	21.0	35.8	1.0	5.8	35.8	4.08	0.0
evolocumab	1.19	16.2	37.4	0.3	1.5	50.3	11.97	-8.6
ranolazine	1.16	15.9	-16.7	1.2	6.5	-12.4	2.72	-4.9
macitentan	1.00	13.7	6.8	<0.05	0.2	6.8	87.71	0.0
alirocumab	0.98	13.3	48.9	0.3	1.9	60.3	7.84	-7.1
V - Miscellaneous	**6.38**		**1.9**	**3.2**		**-0.3**	**5.53**	**2.2**
sugammadex	0.96	15.1	20.3	<0.05	1.0	20.4	81.33	-0.1
deferasirox	0.95	14.9	-32.2	<0.05	1.1	-0.9	75.13	-31.6
iomeprol	0.55	8.6	7.1	<0.05	0.6	2.8	75.49	4.1
fluoride deoxyglucose (18F)	0.35	5.6	9.6	<0.05	0.1	3.1	426.30	6.3
lutetium oxodotreotide (177Lu)	0.24	3.8	9.4	<0.05	0.0	-7.0	16632.93	17.6
iodinaxol	0.24	3.7	4.5	<0.05	0.3	2.1	77.66	2.3
gadobutrol	0.22	3.4	8.1	<0.05	0.2	8.0	77.79	0.1
iopromide	0.19	2.9	1.7	<0.05	0.3	4.7	54.93	-2.8
iodine ioflupane (123I)	0.17	2.7	3.7	<0.05	0.0	6.5	817.30	-2.6
rasburicase	0.15	2.4	8.5	<0.05	0.0	4.3	839.24	4.1
iobitridol	0.12	1.9	2.4	<0.05	0.2	5.7	47.13	-3.2
iopamidol	0.12	1.9	6.9	<0.05	0.4	3.4	27.26	3.3
andexanet alfa	0.11	1.7	>100	<0.05	0.0	>100	3520.00	0.0
tecnetium pertecnetate (99 Tc)	0.11	1.7	-13.4	<0.05	0.0	-25.9	387.57	16.7
calcium levofolinate	0.09	1.4	10.9	0.1	4.1	-0.3	1.93	11.2
ioexol	0.09	1.4	15.0	<0.05	0.2	10.3	32.78	4.2
lanthanum	0.09	1.4	0.9	<0.05	1.2	-6.9	6.59	8.3
gadoxetic acid	0.09	1.4	9.5	<0.05	0.0	9.4	175.79	0.1
M - Musculo-skeletal system	**4.54**		**18.9**	**6.3**		**13.5**	**1.97**	**4.8**
denosumab	1.39	30.7	17.3	4.5	71.2	16.8	0.85	0.5
nusinersen	1.12	24.6	-15.8	<0.05	0.1	-15.0	401.90	-0.9
risdiplam	0.72	15.8	>100	<0.05	0.1	>100	382.85	>100
ataluren	0.33	7.3	6.1	<0.05	0.0	7.7	1557.36	-1.5
burosumab	0.29	6.4	49.2	<0.05	0.1	48.8	188.68	0.3
H - Systemic hormonal preparations, excl. sex hormones	**4.30**		**1.5**	**5.2**		**10.3**	**2.28**	**-7.9**
somatropin	1.15	26.8	-4.0	0.3	5.3	2.5	11.42	-6.3
lanreotide	0.74	17.2	10.0	0.1	2.2	19.6	17.57	-8.1

ATC 1st level Subgroups	Expenditure NHS *per capita*	%	Δ % 22-21	DDD/ 1000 inhab. per day	%	Δ % 22-21	Average DDD cost	Δ % 22-21
octreotide	0.73	16.9	-3.4	0.1	2.1	-2.5	18.54	-0.9
etelcalcetide	0.43	10.0	14.1	0.1	2.3	13.9	10.03	0.1
pegvisomant	0.41	9.6	-1.6	<0.05	0.3	0.1	68.33	-1.7
S - Sensory organs	**3.28**		**8.3**	**2.2**		**5.0**	**4.15**	**3.2**
aflibercept	1.48	45.1	12.7	<0.05	0.4	12.5	493.19	0.1
ranibizumab	0.80	24.2	-3.0	0.1	4.5	-5.7	22.42	2.8
dexamethasone	0.44	13.5	12.6	0.3	12.3	9.5	4.55	2.9
brolucizumab	0.15	4.7	>100	<0.05	0.0	>100	401.04	0.7
voretigene neparvovec	0.13	4.0	-36.5	<0.05	0.0	-36.3	297000.0	-0.3
D - Dermatologicals	**3.13**		**54.0**	**8.8**		**-1.4**	**0.97**	**56.1**
dupilumab	2.67	85.4	66.1	0.3	3.0	72.0	28.02	-3.4
chlorhexidine/ isopropyl alcohol	0.07	2.3	26.2	0.1	0.8	14.5	2.94	10.2
povidone iodine	0.06	2.0	12.0	0.9	10.2	2.8	0.19	8.9
silver sulfadiazine	0.06	1.9	2.1	0.7	7.7	-3.6	0.25	5.9
sodium hypochlorite	0.04	1.2	5.0	2.6	29.4	7.3	0.04	-2.1
G - Genito-urinary system and sex hormones	**1.29**		**-5.0**	**2.8**		**10.6**	**1.28**	**-14.1**
follitropin alfa from recombinant DNA	0.28	22.0	-22.4	<0.05	1.6	-17.4	17.19	-6.1
follitropin alfa/lutropin alfa	0.22	17.0	36.5	<0.05	0.1	0.3	291.61	36.1
menotropin	0.20	15.1	-16.4	<0.05	1.4	-16.9	13.55	0.6
follitropin beta	0.09	6.7	5.8	<0.05	0.3	6.0	27.16	-0.2
dinoprostone	0.08	6.3	-12.7	<0.05	1.5	-12.6	5.34	-0.1
testosterone	0.07	5.1	-3.9	0.1	4.9	-3.7	1.33	-0.2
urofollitropin	0.05	3.7	24.9	<0.05	0.4	9.1	12.10	14.5
P - Antiparasitic drugs, insecticides and repellents	**0.03**		**7.1**	**<0.05**		**62.8**	**7.54**	**-34.2**
atovaquone	0.02	60.6	-12.6	<0.05	39.1	0.2	11.68	-12.7
permethrin	0.01	21.9	29.5	<0.05	16.5	33.2	10.00	-2.8
atovaquone/proguanil	<0.005	5.2	>100	<0.05	8.8	>100	4.39	8.0
ivermectin	<0.005	2.9	>100	<0.05	1.0	>100	20.85	2.4
metronidazole	<0.005	2.8	17.1	<0.05	58.7	10.5	0.36	6.0

Table 3.21 First thirty active ingredients purchased by public health facilities in terms of expenditure: comparison 2022-2021

ATC	Active ingredient	Expenditure *(million)*	%*	Expenditure *per capita*	Rank 2022	Rank 2021	Average DDD cost	Δ % 22-21	Average DDD cost under approved care regime
L	pembrolizumab	444.5	3.0	7.54	1	1	92.20	-0.9	-
L	daratumumab	390.6	2.6	6.62	2	3	94.35	-36.9	-
R	elexacaftor/ tezacaftor/ ivacaftor	206.2	1.4	3.50	3	89	289.31	-1.1	-
L	ibrutinib	202.0	1.4	3.42	4	5	123.57	-4.9	-
L	nivolumab	194.7	1.3	3.30	5	4	98.58	-11.0	-
B	rivaroxaban	191.7	1.3	3.25	6	6	1.56	2.4	4.09
B	apixaban	184.5	1.2	3.13	7	7	1.69	-0.1	3.83
R	ivacaftor	179.4	1.2	3.04	8	41	429.02	-13.4	-
L	osimertinib	167.5	1.1	2.84	9	9	140.78	-5.1	-
A	dulaglutide	161.6	1.1	2.74	10	18	2.18	-2.3	4.94
D	dupilumab	157.5	1.1	2.67	11	28	28.02	-3.4	89.70
L	pertuzumab	154.6	1.0	2.62	12	10	105.55	-6.1	-
L	dimethyl fumarate	152.3	1.0	2.58	13	8	31.67	-3.7	25.02
L	lenalidomide	142.8	1.0	2.42	14	2	45.72	-62.8	-
L	ustekinumab	135.0	0.9	2.29	15	14	14.42	-19.3	-
J	emtricitabine/ tenofovir alafenamide/ bictegravir	134.7	0.9	2.28	16	21	19.96	0.0	-
L	ocrelizumab	132.4	0.9	2.24	17	25	45.24	-6.4	-
B	edoxaban	129.7	0.9	2.20	18	22	1.78	1.1	4.77
L	ruxolitinib	123.8	0.8	2.10	19	19	110.52	-0.3	-
L	fingolimod	123.3	0.8	2.09	20	11	53.53	-0.7	95.75
L	secukinumab	119.5	0.8	2.03	21	17	29.37	-4.0	-
L	enzalutamide	118.8	0.8	2.01	22	15	69.20	-17.1	-
J	remdesivir	118.6	0.8	2.01	23	12	379.50	1.3	-
L	eculizumab	118.5	0.8	2.01	24	13	728.78	-5.0	-
L	natalizumab	111.5	0.7	1.89	25	24	50.04	0.0	-
B	enoxaparin	106.3	0.7	1.80	26	26	0.87	5.3	2.20
A	semaglutide	101.0	0.7	1.71	27	85	8.37	-37.2	17.83
L	palbociclib	97.3	0.7	1.65	28	20	65.78	-3.8	-
L	nintedanib	93.8	0.6	1.59	29	39	91.84	-5.0	-
N	paliperidone	93.8	0.6	1.59	30	31	5.05	-1.0	2.94
	Total	**4,787.7**	**32.0**						
	Total expenditure public health facilities	**14,957.6**							

* Calculated on the total expenditure for medicines purchased by public health facilities

Table 3.22 2022 regional ranks by expenditure relating to the first thirty active ingredients purchased by public health facilities

Rank	Active ingredient	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Sicily	Sardinia
1	pembrolizumab	1	1	2	1	3	2	1	1	1	1	1	1	1	1	5	1	1	1	2	1
2	daratumumab	2	37	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	3	3	2
3	elexacaftor/tezacaftor/ivacaftor	11	21	3	4	4	7	8	8	10	6	16	4	5	4	13	13	7	2	7	5
4	ibrutinib	3	17	4	3	8	6	10	3	5	3	5	6	7	11	8	14	4	7	28	10
5	nivolumab	10	58	9	7	53	11	9	6	3	5	14	11	4	9	16	3	14	9	16	7
6	rivaroxaban	5	6	11	8	18	4	4	7	8	7	4	5	9	5	4	8	10	5	10	8
7	apixaban	4	2	10	31	2	33	3	5	4	4	3	10	3	10	25	12	12	18	24	12
8	ivacaftor	15	46	6	5	9	13	14	11	14	12	17	12	8	14	20	17	8	4	5	6
9	osimertinib	14	88	8	16	22	8	6	12	9	9	8	8	6	21	33	24	18	53	40	13
10	dulaglutide	9	71	788	32	7	5	11	21	11	11	13	18	12	13	26	16	3	17	4	3
11	dupilumab	6	23	13	21	13	17	24	29	21	13	22	9	15	17	6	6	11	10	9	16
12	pertuzumab	23	4	21	6	24	15	12	18	12	18	9	15	18	3	19	4	13	8	17	30
13	dimethyl fumarate	21	16	22	12	27	10	7	26	13	17	7	13	13	8	10	37	17	13	19	14
14	lenalidomide	31	60	14	62	15	12	21	17	53	62	15	3	36	12	57	5	28	6	1	33
15	ustekinumab	28	62	24	9	26	26	17	25	27	21	26	23	28	30	31	9	9	15	35	4
16	emtricitabine/tenofovir alafenamide/bictegravir	13	40	5	29	37	43	31	13	24	8	12	27	10	67	123	32	35	87	143	35
17	ocrelizumab	18	11	28	18	11	18	20	9	20	19	53	38	31	6	1	19	23	98	23	24
18	edoxaban	30	25	12	24	19	9	18	19	16	16	20	20	30	34	71	38	24	28	38	32
19	ruxolitinib	29	72	25	59	57	27	33	14	25	31	11	26	25	24	12	15	6	20	26	11
20	fingolimod	17	7	19	23	20	22	27	20	41	39	30	24	21	7	24	25	15	34	27	25
21	secukinumab	12	32	44	13	54	29	25	42	28	25	42	16	41	15	7	11	16	19	8	21
22	enzalutamide	27	53	38	25	5	19	5	34	15	20	10	19	45	20	18	18	20	24	29	29
23	remdesivir	26	3	16	60	42	21	15	4	19	14	19	31	11	18	222	82	49	41	80	64
24	eculizumab	7	29	23	10	38	45	52	35	7	22	46	14	76	23	23	21	31	25	42	50
25	natalizumab	24	61	39	17	16	16	19	16	23	34	44	52	35	32	3	41	44	140	30	9
26	enoxaparin	25	19	118	53	6	14	35	40	6	10	6	7	73	31	21	48	71	21	55	65
27	semaglutide	19	111	252	87	34	24	22	39	52	29	25	63	14	16	34	22	5	22	60	22
28	palbociclib	52	39	41	14	71	37	23	37	26	47	29	21	19	33	60	28	56	106	56	23
29	nintedanib	47	73	40	51	55	65	78	41	33	23	24	17	29	19	28	30	26	30	34	53
30	paliperidone	41	41	31	41	107	50	97	24	42	37	48	29	34	38	69	34	19	29	47	26

Table 3.23 First thirty active ingredients* with highest increase in expenditure relating to medicines purchased by public health facilities compared to the previous year: comparison 2022-2021

ATC	Active ingredient	Expenditure *per capita*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21	Average DDD cost	Δ % 22-21
J	adjuvanted recombinant varicella zostervaccine	1.26	1556.2	<0.05	1654.7	271.97	-5.6
N	tafamidis	1.13	534.7	<0.05	2121.8	64.67	-71.4
R	elexacaftor/tezacaftor/ivacaftor	3.50	308.6	<0.05	313.2	289.31	-1.1
R	ivacaftor	3.04	132.5	<0.05	168.5	429.02	-13.4
A	dapagliflozin	0.93	104.1	2.0	115.7	1.26	-5.4
A	semaglutide	1.71	96.0	1.4	104.8	3.24	-4.3
D	dupilumab	2.67	66.1	0.3	72.0	28.02	-3.4
L	daratumumab	6.62	62.9	0.2	158.0	94.35	-36.9
C	alirocumab	0.98	48.9	0.3	60.3	7.84	-7.1
A	dulaglutide	2.74	46.0	3.4	49.4	2.18	-2.3
J	dolutegravir/lamivudine	1.57	44.9	0.3	44.9	16.60	0.0
R	mepolizumab	0.88	39.9	0.1	40.7	29.96	-0.6
C	evolocumab	1.19	37.4	0.3	50.3	11.97	-8.6
L	cladribine	0.80	36.7	<0.05	41.4	46.81	-3.3
C	valsartan/sacubitril	1.54	35.8	1.0	35.8	4.08	0.0
L	ribociclib	1.41	32.9	0.1	32.7	68.09	0.1
L	ocrelizumab	2.24	30.0	0.1	38.8	45.24	-6.4
L	ixekizumab	1.23	28.5	0.1	28.6	30.29	0.0
J	emtricitabine/tenofovir alafenamide/bictegravir	2.28	26.0	0.3	26.0	19.96	0.0
B	edoxaban	2.20	25.5	3.4	24.2	1.78	1.1
B	emicizumab	1.58	24.8	<0.05	37.7	683.30	-9.3
J	human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.44	21.4	0.1	21.4	69.31	0.0
L	pomalidomide	1.03	21.0	<0.05	22.8	242.57	-1.4
L	nintedanib	1.59	20.6	<0.05	27.0	91.84	-5.0
V	sugammadex	0.96	20.3	<0.05	20.4	81.33	-0.1
L	trastuzumab emtansine	1.29	20.3	<0.05	52.5	152.79	-21.1
L	venetoclax	1.04	19.3	<0.05	19.0	158.77	0.2
A	agalsidase beta	0.91	17.8	<0.05	17.8	483.63	0.0
L	olaparib	1.13	17.6	<0.05	20.5	129.06	-2.4
L	pembrolizumab	7.54	17.5	0.2	18.6	92.20	-0.9

* selected among the top 100 active ingredients with highest per capita expenditure

Table 3.24 First thirty active ingredients* with highest reduction in expenditure relating to medicines purchased by public health facilities compared to the previous year: comparison 2022-2021

ATC	Active ingredient	Expenditure *per capita*	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21	Average DDD cost	Δ % 22-21
L	lenalidomide	2.42	-55.7	0.1	18.9	45.72	-62.8
V	deferasirox	0.95	-32.2	<0.05	-0.9	75.13	-31.6
B	octocog alfa	1.15	-30.7	<0.05	-29.4	325.96	-2.0
L	trastuzumab	0.81	-27.1	0.2	-3.4	13.28	-24.5
J	dolutegravir/abacavir/lamivudine	0.77	-26.6	0.1	-26.6	21.48	0.0
L	abiraterone	1.50	-20.9	0.1	-4.6	70.74	-17.1
L	etanercept	1.21	-19.5	0.3	4.0	10.94	-22.6
L	interferon beta 1a	1.00	-17.9	0.3	-18.9	10.77	1.3
J	inactivated, split virus tetravalent influenza vaccine	0.99	-17.2	0.3	-18.1	8.50	1.1
C	ranolazine	1.16	-16.7	1.2	-12.4	2.72	-4.9
M	nusinersen	1.12	-15.8	<0.05	-15.0	401.90	-0.9
J	emtricitabine/rilpivirine/tenofovir alafenamide	1.33	-12.7	0.2	-10.3	19.43	-2.7
L	tocilizumab	0.90	-11.9	0.1	-7.2	24.18	-5.0
J	tetravalent influenza vaccine (surface antigen, adjuvated)	1.33	-11.5	0.2	-10.7	14.87	-0.9
L	palbociclib	1.65	-11.2	0.1	-7.7	65.78	-3.8
J	group B meningococcal vaccine	1.34	-10.8	0.1	-10.6	62.14	-0.2
L	nivolumab	3.30	-10.7	0.1	0.3	98.58	-11.0
J	remdesivir	2.01	-10.7	<0.05	-11.8	379.50	1.3
L	fingolimod	2.09	-10.0	0.1	-9.4	53.53	-0.7
A	agalsidase alfa	0.81	-8.7	<0.05	-7.8	1676.64	-0.9
L	adalimumab	1.45	-7.0	0.8	20.2	5.11	-22.6
L	eculizumab	2.01	-6.7	<0.05	-1.8	728.78	-5.0
H	somatropin	1.15	-4.0	0.3	2.5	11.42	-6.3
L	nilotinib	1.13	-3.9	0.0	-3.8	131.22	-0.1
A	insulin glargine	1.50	-3.7	3.1	-7.9	1.34	4.6
L	dasatinib	0.89	-3.4	<0.05	4.1	94.22	-7.2
L	pirfenidone	0.94	-3.1	<0.05	-2.2	63.84	-0.9
S	ranibizumab	0.80	-3.0	0.1	-5.7	22.42	2.8
J	emtricitabine/tenofovir alafenamide/ darunavir/cobicistat	0.80	-2.9	0.1	-2.9	21.85	0.0
L	dimethyl fumarate	2.58	-2.3	0.2	1.4	31.67	-3.7

* selected among the top 100 active ingredients with highest per capita expenditure

Table 3.25 First thirty active ingredients by average cost per day of therapy for medicines purchased by public health facilities^: comparison 2022-2021

ATC	Active ingredient	Average DDD cost	Δ % 22-21	Expenditure per capita	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21
A	agalsidase alfa	1676.6	-0.9	0.81	-8.7	<0.05	-7.8
A	imiglucerase	1096.5	0.0	0.79	2.5	<0.05	2.5
A	agalsidase alfa	1062.3	0.0	1.42	9.8	<0.05	9.8
B	albutrepenonacog alfa	1058.5	-2.6	0.90	12.7	<0.05	15.7
L	eculizumab	728.8	-5.0	2.01	-6.7	<0.05	-1.8
B	emicizumab	683.3	-9.3	1.58	24.8	<0.05	37.7
S	aflibercept	493.2	0.1	1.48	12.7	<0.05	12.5
A	agalsidase beta	483.6	0.0	0.91	17.8	<0.05	17.8
J	human normal immunoglobulin for extravascular administration	454.3	28.9	1.20	0.1	<0.05	-22.3
R	ivacaftor	429.0	-13.4	3.04	132.5	<0.05	168.5
M	nusinersen	401.9	-0.9	1.12	-15.8	<0.05	-15.0
J	remdesivir	379.5	1.3	2.01	-10.7	<0.05	-11.8
B	efmorocotog alfa	357.0	0.0	1.07	3.6	<0.05	3.7
B	octocog alfa	326.0	-2.0	1.15	-30.7	<0.05	-29.4
R	elexacaftor/tezacaftor/ivacaftor	289.3	-1.1	3.50	308.6	<0.05	313.2
J	adjuvanted recombinant varicella zostervaccine	272.0	-5.6	1.26	1556.2	<0.05	1654.7
L	pomalidomide	242.6	-1.4	1.03	21.0	<0.05	22.8
L	venetoclax	158.8	0.2	1.04	19.3	<0.05	19.0
L	alectinib	158.5	-2.4	1.06	4.5	<0.05	7.2
L	trastuzumab emtansine	152.8	-21.1	1.29	20.3	<0.05	52.5
L	canakinumab	147.8	-5.9	1.07	8.7	<0.05	15.6
L	osimertinib	140.8	-5.1	2.84	14.3	0.1	20.4
L	nilotinib	131.2	-0.1	1.13	-3.9	<0.05	-3.8
L	olaparib	129.1	-2.4	1.13	17.6	<0.05	20.5
L	ibrutinib	123.6	-4.9	3.42	0.9	0.1	6.1
L	ruxolitinib	110.5	-0.3	2.10	12.2	0.1	12.6
L	dabrafenib	105.7	0.0	1.17	4.7	<0.05	4.8
L	pertuzumab	105.6	-6.1	2.62	7.6	0.1	14.5
J	amphotericin B	101.6	1.2	0.83	16.2	<0.05	14.8
L	nivolumab	98.6	-11.0	3.30	-10.7	0.1	0.3

^ selected among the top 100 active ingredients with highest per capita expenditure

Table 3.26 First thirty active ingredients by average cost per day of therapy for medicines purchased by public health facilities^: comparison 2022-2021

ATC	Active ingredient	Average DDD cost	Δ % 22-210	Expenditure per capita	Δ % 22-21	DDD/1000 inhab. per day	Δ % 22-21
B	electrolytes for intravenous solutions	0.40	6.5	0.97	7.9	6.6	1.3
M	denosumab	0.85	0.5	1.39	17.3	4.5	16.8
B	enoxaparin	0.87	5.3	1.80	5.9	5.7	0.6
A	dapagliflozin	1.26	-5.4	0.93	104.1	2.0	115.7
B	epoetin alfa	1.28	-8.2	1.17	10.2	2.5	20.0
A	insulin glargine	1.34	4.6	1.50	-3.7	3.1	-7.9
B	dabigatran	1.43	-1.8	1.26	-2.2	2.4	-0.4
B	rivaroxaban	1.56	2.4	3.25	7.3	5.7	4.8
B	apixaban	1.69	-0.1	3.13	15.8	5.1	15.9
B	edoxaban	1.78	1.1	2.20	25.5	3.4	24.2
A	dulaglutide	2.18	-2.3	2.74	46.0	3.4	49.4
B	ticagrelor	2.33	-4.7	0.96	-0.8	1.1	4.1
N	aripiprazole	2.69	2.2	1.16	7.2	1.2	4.9
L	triptorelin	2.70	-1.4	1.01	15.8	1.0	17.4
C	ranolazine	2.72	-4.9	1.16	-16.7	1.2	-12.4
A	semaglutide	3.24	-4.3	1.71	96.0	1.4	104.8
C	valsartan/sacubitril	4.08	0.0	1.54	35.8	1.0	35.8
N	paliperidone	5.05	-1.0	1.59	4.2	0.9	5.2
L	adalimumab	5.11	-22.6	1.45	-7.0	0.8	20.2
B	darbepoetin alfa	5.87	-0.3	0.89	-2.1	0.4	-1.8
L	tacrolimus	6.01	-2.1	0.83	4.5	0.4	6.7
C	alirocumab	7.84	-7.1	0.98	48.9	0.3	60.3
J	tetravalent influenza vaccin (split virion, inactivated)	8.50	1.1	0.99	-17.2	0.3	-18.1
L	interferon beta 1a	10.77	1.3	1.00	-17.9	0.3	-18.9
L	etanercept	10.94	-22.6	1.21	-19.5	0.3	4.0
H	somatropin	11.42	-6.3	1.15	-4.0	0.3	2.5
C	evolocumab	11.97	-8.6	1.19	37.4	0.3	50.3
L	trastuzumab	13.28	-24.5	0.81	-27.1	0.2	-3.4
L	ustekinumab	14.42	-19.3	2.29	11.7	0.4	38.5
J	tetravalent influenza vaccine inactivated, surface antigen, adjuvanted	14.87	-0.9	1.33	-11.5	0.2	-10.7

^ selected among the top 100 active ingredients with highest per capita expenditure

Table 3.27 First thirty active ingredients purchased by public health facilities in terms of consumption: comparison 2022-2021

ATC	Active substance	DDD/ 1000 inhab. per day	Δ % 22-21	Rank 2022	Rank 2021	Expenditure per capita	Δ % 22-21	Average DDD cost	Δ % 22-21	Average DDD cost under approved care regime
B	electrolytes for intravenous solutions	6.6	1.3	1	1	0.97	7.86	0.40	6.5	1.78
B	rivaroxaban	5.7	4.8	2	4	3.25	7.34	1.56	2.4	4.09
B	enoxaparin	5.7	0.6	3	3	1.80	5.93	0.87	5.3	2.20
B	clopidogrel	5.5	-4.5	4	2	0.11	-9.62	0.05	-5.3	0.56
B	cyanocobalamin	5.3	5.5	5	5	0.01	6.55	0.00	1.0	0.02
B	apixaban	5.1	15.9	6	6	3.13	15.84	1.69	-0.1	3.83
M	denosumab	4.5	16.8	7	8	1.39	17.33	0.85	0.5	1.76
C	furosemide	4.4	8.7	8	7	0.05	-4.68	0.03	-12.3	0.08
N	paracetamol	4.2	22.7	9	9	0.11	20.90	0.07	-1.5	-
A	dulaglutide	3.4	49.4	10	16	2.74	45.97	2.18	-2.3	4.94
B	edoxaban	3.4	24.2	11	12	2.20	25.53	1.78	1.1	4.77
A	insulin glargine	3.1	-7.9	12	10	1.50	-3.67	1.34	4.6	2.06
A	cholecalciferol	3.0	4.2	13	11	0.01	1.04	0.01	-3.0	0.08
D	sodium hypochlorite	2.6	7.3	14	14	0.04	5.05	0.04	-2.1	-
B	epoetin alfa	2.5	20.0	15	17	1.17	10.20	1.28	-8.2	13.12
B	dabigatran	2.4	-0.4	16	13	1.26	-2.22	1.43	-1.8	4.16
N	methadone	2.3	-3.0	17	15	0.29	-3.35	0.35	-0.3	1.25
A	dapagliflozin	2.0	>100	18	39	0.93	>100	1.26	-5.4	2.00
V	sodium chloride	1.8	-1.1	19	18	0.05	3.15	0.08	4.4	0.26
A	semaglutide	1.8	104.9	20	215	2.58	101.24	4.04	-1.8	7.90
A	pantoprazole	1.7	10.6	20	21	0.13	5.90	0.21	-4.3	0.43
N	olanzapine	1.7	5.1	21	20	0.12	16.26	0.19	10.7	1.39
C	ramipril	1.6	-2.3	22	19	0.00	>100	0.01	278.1	0.09
C	atorvastatin	1.6	8.5	23	24	0.00	20.49	0.00	11.0	0.25
N	quetiapine	1.5	0.7	24	22	0.16	-3.75	0.28	-4.5	3.45
N	lidocaine	1.5	8.7	25	26	0.09	5.80	0.16	-2.7	3.61
A	insulin degludec	1.5	2.7	26	23	0.69	-4.25	1.28	-6.8	3.66
A	linagliptin	1.4	11.2	27	30	0.58	7.85	1.11	-3.0	2.21
A	sitagliptin	1.4	4.1	28	28	0.53	-12.06	1.02	-15.5	1.89
A	sitagliptin/ metformin	1.4	-0.7	29	25	0.49	-8.41	0.98	-7.8	2.12

Table 3.28 Top thirty active ingredients with the highest expenditure for medicines under approved care regime (A-NHS) and purchased by public health facilities: comparison 2022-2021

ATC	Active ingredient	Expenditure *(million)*	%*	Expenditure *per capita*	Rank 2022	Rank 2021	Average DDD cost	Δ % 22-21
L	pembrolizumab	444.5	3.0	7.54	1	1	92.20	-0.9
L	daratumumab	390.6	2.6	6.62	2	6	94.35	-36.9
C	atorvastatin	276.1	1.8	4.68	3	3	0.24	-0.2
A	pantoprazole	274.0	1.8	4.65	4	4	0.42	-2.7
A	cholecalciferol	239.5	1.6	4.06	5	5	0.08	-0.6
A	dulaglutide	238.8	1.6	4.05	6	12	2.66	-1.1
B	enoxaparin	226.6	1.5	3.84	7	7	1.28	0.4
R	elexacaftor/tezacaftor/ ivacaftor	206.2	1.4	3.50	8	144	289.31	-1.1
L	ibrutinib	202.0	1.4	3.42	9	9	123.57	-4.9
B	apixaban	200.2	1.3	3.39	10	11	1.76	0.1
L	nivolumab	194.7	1.3	3.30	11	8	98.58	-11.0
B	rivaroxaban	193.6	1.3	3.28	12	10	1.57	2.4
R	ivacaftor	179.4	1.2	3.04	13	70	429.02	-13.4
L	osimertinib	167.5	1.1	2.84	14	16	140.78	-5.1
C	bisoprolol	167.1	1.1	2.83	15	13	0.59	0.1
J	amoxicillin/clavulanic acid	159.8	1.1	2.71	16	25	1.33	0.7
D	dupilumab	157.5	1.1	2.67	17	46	28.03	-3.4
L	pertuzumab	154.6	1.0	2.62	18	17	105.55	-6.1
A	semaglutide	152.4	1.0	2.58	19	75	4.04	-1.8
L	dimethyl fumarate	152.3	1.0	2.58	20	14	31.67	-3.7
R	formoterol/beclomethasone	151.6	1.0	2.57	21	15	1.70	-0.9
L	lenalidomide	142.8	1.0	2.42	22	2	45.72	-62.8
L	ustekinumab	135.0	0.9	2.29	23	28	14.42	-19.3
J	emtricitabine/tenofovir alafenamide/bictegravir	134.7	0.9	2.28	24	35	19.96	0.0
A	esomeprazole	132.8	0.9	2.25	25	23	0.39	-2.8
L	ocrelizumab	132.4	0.9	2.24	26	41	45.24	-6.4
A	omeprazole	132.3	0.9	2.24	27	20	0.33	-2.9
B	edoxaban	131.8	0.9	2.23	28	36	1.80	0.5
A	lansoprazole	129.8	0.9	2.20	29	21	0.42	-0.8
C	omega 3	127.5	0.9	2.16	30	26	2.28	-0.9
	Total	**5,728.4**	**38.3**					
	Total expenditure by public health facilities	**24,736.0**						

Table 3.29 Top thirty most consumed active ingredients for medicines under approved care regime and purchased by public health facilities: comparison 2022-2021

ATC	Active ingredient	DDD/ 1000 inhab. per day	Δ % 22-21	Rank 2022	Rank 2021	Expenditure per capita	Δ % 22-21	Average DDD cost	Δ % 22-21
A	cholecalciferol	139.8	-2.2	1	1	4.06	-2.8	0.08	-0.6
C	ramipril	63.1	-1.5	2	2	1.95	-3.3	0.08	-1.8
C	atorvastatin	52.4	1.5	3	3	4.68	1.3	0.24	-0.2
B	acetylsalicylic acid	46.9	1.8	4	4	1.20	1.5	0.07	-0.2
A	pantoprazole	30.7	5.6	5	5	4.65	2.7	0.42	-2.7
C	amlodipine	29.0	-0.1	6	6	1.60	-1.2	0.15	-1.1
C	furosemide	27.7	-1.4	7	7	0.75	-3.5	0.07	-2.2
A	metformin	23.4	0.4	8	8	1.67	1.9	0.19	1.5
H	levothyroxine	23.0	4.9	9	9	1.40	14.1	0.17	8.8
A	omeprazole	18.5	-0.1	10	10	2.24	-3.0	0.33	-2.9
B	cyanocobalamin	17.6	9.2	11	12	0.10	5.6	0.02	-3.3
C	nebivolol	17.0	2.1	12	11	1.56	1.8	0.25	-0.3
C	olmesartan	16.7	7.7	13	13	1.92	7.7	0.31	0.0
A	esomeprazole	15.9	3.2	14	14	2.25	0.3	0.39	-2.8
C	rosuvastatin	15.9	6.2	15	15	1.49	5.2	0.26	-1.0
A	lansoprazole	14.4	-3.5	16	16	2.20	-4.3	0.42	-0.8
C	bisoprolol	13.1	3.8	17	17	2.83	3.9	0.59	0.1
C	simvastatin	11.6	-6.0	18	18	1.36	-6.4	0.32	-0.3
B	clopidogrel	11.5	0.7	19	19	1.32	3.2	0.32	2.4
G	tamsulosin	11.4	3.2	20	20	1.14	2.1	0.27	-1.1
C	ezetimibe/ rosuvastatin	10.7	69.1	21	44	1.55	50.1	0.40	-11.2
C	olmesartan/ hydrochlorothiazide	10.4	3.8	22	22	1.26	3.3	0.33	-0.5
C	valsartan	10.2	1.5	23	21	0.68	1.9	0.18	0.4
C	olmesartan/ amlodipine	9.9	11.1	24	26	1.45	10.9	0.40	-0.2
G	alfuzosin	9.8	4.3	25	24	0.92	3.4	0.26	-0.9
N	sertraline	9.8	5.4	26	25	0.82	2.7	0.23	-2.6
C	lercanidipine	9.4	-1.0	27	23	0.77	-1.2	0.22	-0.2
M	allopurinol	8.9	1.4	28	27	0.37	1.7	0.11	0.3
G	dutasteride	8.4	0.8	29	31	1.04	-0.6	0.34	-1.3
C	candesartan	8.4	-2.6	30	29	0.46	-2.2	0.15	0.4

Table 3.30 Expenditure and consumption by group and sub-group of medicines supplied under approved care regime and purchased by public facilities

ATC 1st level / Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Antineoplastic medicines	**2.90**	**4.5**	**1.75**	**71.16**	**6.4**	**30.49**	**4368.0**	**235.6**	**46.1**	**2.6**
Monoclonal antibodies inhibiting immune check points				13.82	0.4	98.83	815.2	8.2	7.6	
Monoclonal antibodies acting on specific targets				8.66	0.7	36.10	511.1	14.2	7.2	
Monoclonal antibodies blocking growth factors				5.77	0.4	40.92	340.1	8.3	3.6	
Associated multitarget tyrosin kinase inhibitors				4.15	0.1	99.17	245.0	2.5	97.0	
Endocrine therapy - aromatase inhibitors	2.35	3.2	2.04	1.60	0.7	6.63	233.3	82.3	40.0	2.3
CDK protein kinase inhibitors				3.81	0.2	65.71	225.0	3.4	95.0	
Bruton tyrosine kinase (BTK) inhibitors				3.80	0.1	124.61	224.1	1.8	96.0	
BRC-ABL tyrosin kinase inhibitors	<0.005	<0.05	10.80	3.15	0.2	46.80	186.0	4.0	95.5	2.5
EGFR tyrosin kinase inhibitors				2.94	0.1	127.46	173.4	1.4	96.3	
Endocrine therapy – antiandrogens	0.11	0.2	1.38	2.59	0.6	12.45	159.7	17.2	94.2	0.7
Monoclonal antibodies conjugated with drugs				2.67	<0.05	211.82	157.7	0.7	2.9	
Endocrine therapy - hormones and GnRH analogues	0.07	0.1	3.18	2.07	1.2	4.65	126.5	27.6	7.4	81.5
JAK tyrosin kinase inhibitors				2.13	0.1	110.02	125.4	1.1	93.7	
Cytostatic antineoplastics - PARP inhibitors				1.89	<0.05	135.40	111.2	0.8	94.8	
Cytostatic antineoplastics - other cytostatics	0.19	0.3	1.72	1.63	0.1	74.51	107.2	7.8	55.7	0.4
BRAF tyrosin kinase inhibitors				1.50	<0.05	112.10	88.5	0.8	95.7	
ALK tyrosin kinase inhibitors				1.44	<0.05	141.57	85.0	0.6	95.4	
Cytostatic antineoplastics – antimetabolites	0.09	0.1	2.37	1.27	0.5	6.43	79.9	13.8	25.4	0.4
CAR-T				1.19	<0.05	209748.35	70.3	0.0	26.0	
Cytostatic antineoplastics - proteasome inhibitors				0.85	<0.05	60.20	50.0	0.8	18.4	

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
MEK tyrosin kinase inhibitors				0.71	<0.05	56.43	42.0	0.7	96.4	
Other protein kinase inhibitors				0.55	<0.05	445.46	32.3	0.1	83.7	
Cytotoxic antineoplastics - products of natural derivation – others				0.45	0.2	6.78	26.5	3.9	3.4	
Cytotoxic antineoplastics – antibiotics cytotoxic anthracyclines and related substances				0.44	0.1	12.61	25.9	2.1	2.9	
MTOR protein kinase inhibitors	<0.005	<0.05	269.79	0.37	<0.05	67.11	21.6	0.3	101.3	2.0
Cytotoxic antineoplastics - products of natural derivation – others	0.01	<0.05	56.90	0.35	0.1	17.38	21.0	1.2	27.8	1.0
Cytostatic antineoplastics - alkylating agents	0.01	<0.05	1.31	0.34	0.2	5.82	20.3	3.8	8.5	0.5
Hedgehog pathway inhibitors				0.30	<0.05	117.73	17.7	0.2	108.8	
Endocrine therapy - antiestrogens	0.07	0.7	0.28	0.13	0.1	2.39	11.7	17.8	68.4	0.1
Combination of antineoplastic agents				0.15	<0.05	3809.3 0	8.9	<0.05	3.2	
Cytostatic antineoplastics - PI3K inhibitors				0.08	<0.05	102.73	4.6	<0.05	99.1	
Cytostatic antineoplastics – platinum compounds				0.08	0.2	1.00	4.6	4.6	1.8	
HER2 tyrosine kinase inhibitors				0.08	<0.05	70.36	4.6	0.1	99.8	
Cytotoxic antineoplastics – cytotoxic antibiotics – others				0.07	0.1	1.48	4.2	2.8	1.7	
TRK protein kinase inhibitors				0.06	<0.05	180.73	3.8	<0.05	76.5	
Cytostatic antineoplastics - top1 inhibitors				0.03	<0.05	2.29	1.5	0.6	9.4	0.9
Antineoplastics in combination				0.02	<0.05	1897.2 5	1.0	<0.05	0.8	
RET protein kinase inhibitors				0.01	<0.05	40.55	0.7	<0.05	52.8	
FGFR tyrosine kinase inhibitors				0.01	<0.05	197.38	0.5	<0.05	69.1	
Bispecific fusion protein (immtac)				<0.005	<0.05	0.11	<0.05	<0.05		
Medicines for hypertension and heart failure	**32.81**	**362.4**	**0.25**	**1.83**	**11.1**	**0.45**	**2043.1**	**8040.6**	**1.3**	**3.0**
Beta blockers	5.58	45.4	0.34	0.11	1.2	0.24	335.3	1002.5	0.5	0.1
Angiotensin II antagonists	4.91	58.0	0.23	<0.005	0.5	0.02	290.0	1260.3	0.0	0.0

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Calcium channel blockers (dihydropyridines)	4.07	49.5	0.23	0.03	1.2	0.07	241.7	1089.8	0.1	0.0
Angiotensin II receptor blockers and diuretics (combinations)	3.78	31.8	0.33	<0.005	0.1	0.05	223.1	684.7	0.0	0.0
ACE inhibitors	3.56	80.4	0.12	0.01	1.8	0.01	210.3	1770.7	0.1	0.0
ACE inhibitors and diuretics (combinations)	2.37	18.6	0.35	<0.005	0.1	0.03	139.6	401.4	0.1	0.0
Angiotensin II receptor blockers and neprilysin inhibitor	0.51	0.2	7.21	1.54	1.0	4.08	121.3	26.5	18.0	49.8
ACE inhibitors and calcium channel blockers (combinations)	1.64	12.2	0.37	<0.005	<0.05	0.22	96.8	262.3	0.0	0.0
Angiotensin II receptor blockers and calcium channel blockers (combinations)	1.53	10.5	0.40	<0.005	<0.05	0.25	90.0	225.3	0.0	0.0
Alpha-blockers	1.23	7.5	0.45	0.02	0.2	0.19	73.6	167.1	0.0	0.0
Diuretics with greater diuretic action alone or in combination with potassium-sparing diuretics	0.93	25.1	0.10	0.06	4.4	0.04	58.5	635.8	1.1	0.0
Beta blockers and diuretics (combinations)	0.70	7.6	0.25	<0.005	<0.05	0.11	41.3	163.2	0.0	0.0
ACE inhibitors, calcium channel blockers and diuretics (triple combination)	0.64	4.7	0.37	<0.005	<0.05	0.25	37.6	101.5	0.0	0.0
Potassium-sparing diuretics	0.56	3.4	0.46	0.03	0.3	0.33	35.3	79.2	1.9	0.0
Calcium channel blockers (not dihydropyridines)	0.26	1.8	0.40	<0.005	<0.05	0.27	15.3	38.9	0.5	0.0
Thiazides and similars (including combinations)	0.21	3.5	0.16	<0.005	0.1	0.06	12.5	77.1	0.5	0.0
Imidazoline receptor agonists	0.18	1.2	0.39	0.01	0.1	0.33	11.2	28.8	1.8	0.0
ACE inhibitors, other combinations	0.13	1.0	0.33	<0.005	<0.05	0.21	7.5	22.5	0.0	0.0
Aliskiren plain or in combination	0.03	0.1	0.85	<0.005	<0.05	0.52	1.6	1.9	0.3	
Alpha-2 adrenergic receptor agonists	0.01	<0.05	0.37	<0.005	<0.05	0.23	0.3	0.9	0.8	
Angiotensin II receptor blockers, calcium channel blockers and diuretics (triple combination)	<0.005	<0.05	0.31	<0.005	<0.05	0.22	0.1	0.2		
Immunosuppressants and immunomodulating agents	**0.71**	**0.2**	**8.75**	**29.16**	**4.6**	**17.35**	**1761.4**	**103.9**	**75.1**	**5.5**
Interleukin inhibitors				9.86	1.1	25.27	581.4	23.0	89.1	

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Tumor necrosis factor alpha inhibitors (TNF-alpha)				4.66	1.7	7.54	275.1	36.5	93.5	
Other immunosuppressants				4.44	0.2	59.12	261.8	4.4	104.9	
Selective immunosuppressants (monoclonal antibodies)				3.86	0.2	66.52	227.5	3.4	24.8	
JAK tyrosin kinase inhibitors				1.45	0.2	21.99	85.4	3.9	93.1	
Calcineurin inhibitors	0.53	0.2	8.42	0.89	0.4	5.90	83.7	12.6	18.3	39.9
Selective immunosuppressants	0.03	<0.05	2.12	1.24	0.6	5.90	75.2	13.3	53.7	30.4
Selective T cell co-stimulation modulators				1.20	0.1	48.71	70.8	1.5	89.1	
MTOR protein kinase inhibitors	<0.005	<0.05	21.41	0.70	0.1	17.47	41.7	2.4	22.5	63.1
Growth factors	0.13	<0.05	58.54	0.35	0.1	8.65	28.5	2.5	15.4	50.8
Other immunomodulators	0.00	<0.05	6.98	0.41	<0.05	173.43	24.2	0.1	2.1	
Interferons	0.01	<0.05	44.45	0.10	<0.05	25.30	6.1	0.2	66.5	9.3
Antidiabetics	**9.40**	**41.5**	**0.62**	**13.52**	**25.3**	**1.46**	**1352.4**	**1439.5**	**2.2**	**52.9**
GLP-1 (glucagon-like one) analogues	2.19	1.0	5.81	4.93	5.5	2.48	419.7	139.6	2.3	62.1
Fast acting insulins	3.23	7.0	1.26	0.16	0.9	0.49	200.1	170.6	2.0	2.0
Long acting insulins	0.06	0.1	2.24	2.26	4.7	1.31	136.7	102.8	3.6	87.1
Glifozins (SGLT2 inhibitors) plain	0.12	0.1	2.73	1.78	3.8	1.29	112.0	84.0	4.1	79.5
Metformin	1.66	23.1	0.20	0.01	0.3	0.05	98.3	504.8	0.3	0.0
Gliptins (DPP-4 inhibitors) plain	0.22	0.3	2.19	1.25	3.2	1.07	86.8	75.0	2.5	81.5
Glifozins (SGLT2 inhibitors), combination with metformin	0.20	0.2	2.33	1.07	2.5	1.19	74.9	58.2	1.7	75.7
Insulins combined with GLP-1 (glucagon-like one) analogues	0.40	0.1	9.20	0.77	0.6	3.70	69.2	14.9	2.2	61.3
Gliptins (DPP-4 inhibitors) in combination with metformin	0.04	0.1	2.05	0.86	2.3	1.00	52.7	51.4	1.6	92.7
Gliptins (DPP-4 inhibitors) in combination with glifozins (SGLT2 inhibitors)	0.20	0.1	3.64	0.29	0.6	1.37	29.1	15.9	2.3	54.8
Sulfonylureas plain	0.42	6.0	0.19	<0.005	0.1	0.01	25.0	129.9	0.0	0.0

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Repaglinide	0.19	1.3	0.40	<0.005	<0.05	0.09	11.0	27.7	0.3	0.0
Glitazones in combination with metformin	0.10	0.3	0.96	0.05	0.4	0.36	8.9	14.3	0.4	32.9
Glitazones plain	0.12	0.5	0.68	0.02	0.3	0.18	8.2	17.0	0.5	14.7
Acarbose	0.12	0.5	0.72	<0.005	<0.05	0.37	7.0	9.8	0.2	0.0
Gliptins (DPP-4 inhibitors) in combination with pioglitazone	0.02	<0.05	2.00	0.06	0.2	1.02	4.6	3.9	1.1	68.1
Combined insulins (long/intermediate with fast)	0.06	0.1	1.25	<0.005	<0.05	0.77	4.0	3.3	1.7	4.7
Sulfonylureas in combination with metformin	0.05	0.7	0.21	<0.005	<0.05	0.07	3.1	15.2	0.2	
Sulfonylureas in combination a pioglitazone	<0.005	<0.05	1.83	0.02	<0.05	0.98	1.1	1.0	0.2	83.8
Intermediate acting insulins	<0.005	<0.05	0.59	<0.005	<0.05	0.10	0.2	0.3	0.9	
Antidiabetics							<0.05	<0.05		
Rosiglitazone plain and in combination							<0.05	<0.05		
Lipid-lowering medicines	**15.37**	**111.0**	**0.38**	**2.36**	**2.7**	**2.35**	**1045.4**	**2449.8**	**12.8**	**0.0**
Statins, plain	8.15	82.3	0.27	<0.005	1.8	0.01	480.9	1811.4	0.0	0.0
Ezetimibe and statins (association)	2.91	16.7	0.48	<0.005	0.1	0.08	171.8	361.1	0.1	0.0
PCSK9 inhibitors	<0.005	<0.05	23.19	2.17	0.6	9.67	127.7	13.2	97.4	0.0
Omega 3	2.15	2.5	2.32	0.01	0.1	0.41	127.5	56.0	0.3	0.0
Ezetimibe	1.71	6.4	0.73	0.00	0.1	0.12	101.3	140.2	0.1	0.0
Fibrates	0.41	2.9	0.38	0.00	<0.05	0.17	24.1	62.8	0.2	0.0
MTP inhibitor				0.12	<0.05	800.65	6.9	<0.05	98.2	
Drugs for the alteration of lipid metabolism of genetic origin				0.05	<0.05	8190.1 9	2.9	<0.05	70.7	
Statins, calcium channel blockers and ACE inhibitors (triple combination)	0.03	0.2	0.45	<0.005	<0.05	0.30	1.6	3.7		
Statins in combination	0.01	0.1	0.24	<0.005	<0.05	0.19	0.4	1.5	0.0	
PCSK9 inhibitors (sirnas)				<0.005	<0.05	8.84	0.2	<0.05	17.0	
Acetylsalicylic acid/atorvastatin/ramipril							<0.05	<0.05		
Asthma and COPD	**14.77**	**30.4**	**1.33**	**2.87**	**1.5**	**5.11**	**1040.5**	**687.6**	**9.6**	**4.3**
LABAs+ICS	7.09	12.2	1.60	0.07	0.3	0.79	422.6	267.0	0.5	0.0

ATC 1st level / Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Monoclonal antibodies	<0.005	<0.05	62.08	2.66	0.3	27.67	156.8	5.7	59.9	27.8
LAMAs	2.50	4.5	1.51	0.04	0.1	0.73	149.4	100.5	0.8	0.0
ICSs	1.73	4.6	1.04	0.03	0.2	0.33	103.6	102.9	0.3	0.0
LABAs+LAMAs+ICS	1.25	1.2	2.87	0.04	0.1	1.89	75.9	26.9	1.3	0.4
LABAs+LAMAs	0.94	1.3	1.97	0.01	<0.05	1.05	56.5	29.0	0.8	0.5
Antileukotrienes (LTRAs)	0.46	2.0	0.62	<0.005	<0.05	0.09	27.1	44.0	0.1	0.0
LABAs	0.27	0.8	0.99	<0.005	<0.05	0.55	16.3	16.6	0.7	
SABAs	0.18	2.3	0.22	0.01	0.3	0.12	11.5	56.5	1.1	0.0
SABAs+SAMAs	0.14	0.6	0.68	<0.005	<0.05	0.17	8.6	13.1	0.2	0.0
SABAs+ICSs	0.11	0.2	1.21	<0.005	<0.05	0.72	6.4	5.3	0.1	
SAMAs	0.04	0.4	0.29	0.01	0.2	0.12	2.9	12.4	2.5	0.0
Theophylline-based bronchodilators	0.04	0.3	0.36	<0.005	<0.05	0.24	2.7	7.6	0.7	0.0
PDE-4 inhibitors	<0.005	<0.05	2.20	<0.005	<0.05	1.46	0.2	0.2	4.1	74.6
Chromones	<0.005	<0.05	0.67				<0.05	<0.05		
Anticoagulants	**2.77**	**5.5**	**1.38**	**13.20**	**23.6**	**1.53**	**942.2**	**627.4**	**6.3**	**65.1**
NOAs	0.35	0.2	3.95	9.84	16.6	1.63	600.9	362.3	2.8	91.9
LMWH	2.23	2.7	2.25	2.00	6.1	0.90	249.4	189.5	10.4	20.0
Monoclonal antibodies for episodes of acquired TTP				0.55	<0.05	3395.13	32.4	<0.05	43.3	
Fondaparinux	0.02	<0.05	6.62	0.27	0.5	1.53	17.3	10.7	10.5	62.8
Heparin and heparinoids	0.02	<0.05	2.59	0.22	0.3	1.71	13.9	7.9	2.4	1.0
Antithrombotic enzymes				0.21	<0.05	786.43	12.4	<0.05	2.8	
Vitamin K antagonists	0.15	2.5	0.17	<0.005	0.1	0.05	9.3	57.0	1.0	0.0
Other antithrombotics				0.10	<0.05	4094.72	6.1	<0.05		
Antithrombotics - direct thrombin inhibitors				0.01	<0.05	216.82	0.6	<0.05		
Multiple sclerosis	**0.83**	**1.7**	**1.34**	**12.73**	**1.2**	**28.46**	**799.8**	**62.9**	**59.0**	**6.5**
Monoclonal antibodies				4.29	0.2	49.08	253.2	5.2	15.4	
Immunosuppressants	0.83	1.7	1.33	3.40	0.4	25.33	249.3	44.4	72.8	4.9
Fingolimod (S1P receptor modulators)	<0.005	<0.05	95.75	2.09	0.1	53.53	123.3	2.3	95.3	1.4

ATC 1st level / Subgroups	Approved care regime: Expenditure *per capita*	Approved care regime: DDD/1000 inhab. per day	Approved care regime: Average DDD average	Direct purchases: Expenditure *per capita*	Direct purchases: DDD/1000 inhab. per day	Direct purchases: Average DDD cost	Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
Interferons	<0.005	<0.05	21.25	1.42	0.3	12.89	84.1	6.5	68.1	30.8
Pyrimidine synthesis inhibitors	<0.005	<0.05	54.67	1.03	0.1	26.23	60.5	2.3	86.6	15.6
Other S1P receptor modulators				0.31	<0.05	31.13	18.4	0.6	82.7	0.2
Glatiramer (AA copolymers)	<0.005	<0.05	45.45	0.18	0.1	6.85	10.9	1.6	84.2	25.3
Antibiotics	**9.24**	**14.4**	**1.75**	**3.98**	**1.7**	**6.38**	**779.5**	**347.4**	**3.0**	**0.0**
Combinations of penicillins (including beta lactamase inhibitors)	2.72	5.2	1.42	0.63	0.5	3.41	197.6	123.5	0.6	0.0
Third-generation cephalosporins	2.46	1.7	3.90	0.53	0.3	5.02	176.4	43.5	0.6	0.0
Macrolides and lincosamides	1.61	3.7	1.20	0.04	0.2	0.74	97.5	82.3	0.2	0.0
Fluroquinolones	1.14	1.5	2.07	0.11	0.2	1.76	73.9	36.2	6.1	0.0
Other antibacterials	0.64	0.4	4.62	0.50	0.1	10.31	67.0	11.0	2.2	0.3
Other cephalosporins and penems				0.74	<0.05	220.48	43.8	0.2	0.4	
Carbapenems				0.43	0.1	17.08	25.3	1.5	4.0	
Glycopeptides	0.07	<0.05	67.49	0.27	<0.05	15.51	19.8	1.1	3.2	0.0
Broad-spectrum penicillins	0.18	0.9	0.57	0.09	<0.05	7.28	15.7	19.5	1.6	0.0
Polymyxin				0.17	<0.05	36.82	10.2	0.3	63.7	
Tetracyclines	0.08	0.3	0.66	0.08	<0.05	7.21	9.3	8.0	0.9	0.0
Aminoglycosides	0.04	<0.05	8.72	0.09	<0.05	8.54	7.9	0.9	51.3	0.0
First-generation cephalosporins	0.02	<0.05	2.06	0.09	0.1	3.05	6.5	2.3	0.7	0.0
Second-generation cephalosporins	0.08	0.1	1.55	0.01	<0.05	7.46	5.4	3.0	0.5	0.0
Sulphonamides (plain or in combination)	0.06	0.3	0.48	0.02	0.1	0.85	4.5	8.6	2.8	0.0
Beta-lactamase resistant penicillins	0.01	<0.05	1.83	0.07	<0.05	8.30	4.5	0.7	1.4	
Fourth-generation cephalosporins	0.03	<0.05	34.23	0.05	<0.05	16.65	4.2	0.2	1.5	0.0
Other combinations	0.06	<0.05	6.74	<0.005	<0.05	4.17	3.4	0.5	0.9	
Nitrofuran derivatives	0.05	0.1	0.94	<0.005	<0.05	0.18	3.0	3.3	0.2	0.0
Monobactams				0.03	<0.05	88.12	2.1	<0.05	89.8	
Imidazole derivatives	<0.005	<0.05	16.82	0.01	<0.05	0.97	0.9	0.9	0.5	
Beta-lactamase sensitive penicillins	<0.005	<0.05	81.25	0.01	<0.05	47.37	0.5	<0.05	24.7	1.6
Amphenicols	<0.005	<0.05	3.86	<0.005	<0.05	6.05	0.1	<0.05	33.5	0.7
Other quinolones							<0.05	<0.05		

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	**12.44**	**82.2**	**0.41**	**0.26**	**4.0**	**0.18**	**749.2**	**1855.7**	**0.3**	**0.0**
Proton pump inhibitors	11.40	77.5	0.40	0.25	3.8	0.18	687.5	1750.8	0.3	0.0
Antacids	0.56	2.5	0.62	0.01	0.1	0.18	33.8	57.1	0.6	0.0
Other medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	0.41	2.0	0.58	<0.005	<0.05	0.27	24.4	42.4	0.2	0.0
H2 receptor antagonists	0.05	0.2	0.64	<0.005	<0.05	0.43	3.2	5.1	0.5	0.0
Prostaglandins	0.01	<0.05	1.12	<0.005	<0.05	0.56	0.3	0.3	0.2	
Vaccines	**0.04**	**<0.05**	**19.41**	**10.80**	**1.2**	**25.41**	**639.2**	**25.2**	**0.7**	**0.1**
Papillomavirus vaccine				1.44	0.1	69.31	85.2	1.2	0.8	
Meningococcal B vaccine	<0.005	<0.05	146.67	1.34	0.1	62.14	79.0	1.3	0.0	0.0
Inactivated, split virus tetravalent influenza vaccine	<0.005	<0.05	34.00	1.33	0.2	14.87	78.8	5.3	0.1	
Adjuvanted recombinant varicella zoster virus vaccine	<0.005	<0.05	365.42	1.26	<0.05	271.97	74.3	0.3	1.9	0.0
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	<0.005	<0.05	110.00	1.16	0.1	47.53	68.3	1.4	0.6	0.1
MMRV vaccine (measles/mumps/rubella/ varicella)				0.61	<0.05	47.61	36.0	0.8	0.0	
Hexavalent vaccine (diphtheria/tetanus/pertussis/ haemophilus influenzae B/ poliomyelitis/hepatitis b)				0.53	0.1	26.53	31.2	1.2	0.0	
Tetravalent meningococcal conjugate vaccine	<0.005	<0.05	92.00	0.38	<0.05	27.13	22.5	0.8	0.0	0.0
Tetravalent vaccine (diphtheria /tetanus/ pertussis/poliomyelitis)	<0.005	<0.05	45.10	0.32	<0.05	18.03	18.6	1.0	0.0	

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Live attenuated varicella zoster vaccine	<0.005	<0.05	192.40	0.26	<0.05	96.19	15.4	0.2	2.8	0.0
Rotavirus attenuated vaccine	<0.005	<0.05		0.25	<0.05	20.18	14.8	0.7	0.0	
Influenza vaccine - nasal tetravalent	<0.005	<0.05	33.50	0.15	<0.05	19.64	8.7	0.4	0.0	
Pneumococcal 23 vaccine	<0.005	<0.05	42.53	0.14	<0.05	22.36	8.5	0.4	1.4	0.8
DTP vaccine (diphtheria /tetanus/pertussis)	<0.005	<0.05	29.72	0.13	<0.05	11.84	7.8	0.7	1.5	0.0
Live attenuated varicella vaccine				0.08	<0.05	31.12	4.6	0.1	0.0	
Encephalitis vaccine				0.07	<0.05	35.04	3.8	0.1		
Hepatitis A vaccine				0.04	<0.05	17.13	2.6	0.2	0.1	
Hepatitis B vaccine	<0.005	<0.05	28.04	0.04	<0.05	17.10	2.5	0.1	0.5	
MMR vaccine (measles/mumps/rubella)				0.03	<0.05	9.07	1.6	0.2	0.3	
Meningococcal C conjugate vaccine				0.02	<0.05	11.93	1.4	0.1		
Yellow fever vaccine				0.01	<0.05	20.25	0.6	<0.05	0.1	
Typhus vaccine	<0.005	<0.05	28.56	0.01	<0.05	11.06	0.6	0.1		
Rabies vaccine				0.01	<0.05	50.19	0.5	0.0	0.0	
Tetanus vaccine	<0.005	<0.05	9.03	0.01	<0.05	4.45	0.3	0.1	0.1	
Haemophilus influenzae B vaccine				0.01	<0.05	14.03	0.3	<0.05	0.0	
Hepatitis A and B vaccine				0.01	<0.05	30.78	0.3	<0.05	0.3	
DT vaccine (diphtheria/tetanus)	<0.005	<0.05	11.56	<0.005	<0.05	4.71	0.3	0.1	0.5	
Poliomyelitis inactivated vaccine				<0.005	<0.05	7.67	0.2	<0.05		
Cholera vaccine				<0.005	<0.05	27.49	0.1	<0.05		
Pentavalent vaccine (diphtheria/tetanus/ pertussis/haemophilus influenzae B/ poliomyelitis)							<0.05	<0.05		
Herpes simplex vaccine							<0.05	<0.05		
Adjuvanted trivalent influenza vaccine							<0.05	<0.05		
Non-adjuvanted trivalent influenza vaccine							<0.05	<0.05		
Tetravalent meningococcal vaccine							<0.05	<0.05		
Trivalent vaccine (diphtheria/tetanus/poliomyelitis)							<0.05	<0.05		

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Smallpox vaccine							<0.05	<0.05		
Anti-HIV antivirals	**0.03**	**<0.05**	**6.19**	**10.38**	**2.5**	**11.34**	**613.6**	**54.2**	**96.4**	**0.7**
Co-formulated regimens - 2 nucleoside/nucleotide reverse transcriptase inhibitors + 1 protease inhibitor (2 NRTIs + 1 PI)				3.21	0.4	20.50	189.0	9.2	95.9	
Co-formulated regimens - 2 nucleoside/nucleotide reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor (2 NRTIs + 1 NNRTI)				1.62	0.3	17.48	95.6	5.5	96.6	
Co-formulated regimens - 1 nucleoside/nucleotide reverse transcriptase inhibitors + 1 integrase Inhibitor (1 NRTI + 1 INSTI)				1.57	0.3	16.60	92.5	5.6	99.2	
Integrase inhibitors (INSTI)				1.20	0.2	13.17	70.5	5.4	98.3	
Co-formulated regimens - 2 nucleoside/nucleotide reverse transcriptase inhibitors + 1 protease inhibitor (2 NRTIs + 1 IP)				0.80	0.1	21.85	47.2	2.2	96.0	
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	0.03	<0.05	6.19	0.71	0.9	2.20	43.8	19.4	84.2	10.2
Co-formulated regimens - 1 non nucleoside reverse transcriptase inhibitors + 1 integrase inhibitor (1 NNRTI + 1 INSTI)				0.54	0.1	18.31	31.9	1.7	101.4	
Protease inhibitors (PIs)	<0.005	<0.05	9.97	0.45	0.1	8.90	26.5	3.0	100.6	
Non-nucleoside reverse transcriptase inhibitors (NRTIs)				0.19	0.1	5.29	11.4	2.1	93.9	
Other anti-HIV antivirals				0.09	<0.05	38.28	5.2	0.1	91.3	
Medicines for osteoporosis	**7.51**	**152.0**	**0.14**	**1.89**	**7.8**	**0.66**	**554.0**	**3440.6**	**6.3**	**10.0**
Vitamin D and analogues	4.70	139.2	0.09	0.02	3.0	0.02	278.5	3062.0	0.2	0.0

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Bisphosphonates alone	1.32	7.1	0.51	0.08	0.1	3.61	82.7	154.2	0.4	0.0
Monoclonal antibodies-denosumab	<0.005	<0.05	1.76	1.39	4.5	0.85	82.5	96.9	21.3	66.8
Teriparatide	0.67	0.1	14.15	0.09	<0.05	6.38	44.9	3.6	9.1	0.2
Biphosphonates in combination	0.40	1.9	0.58	<0.005	<0.05	0.29	23.7	40.8	0.0	
Calcium and vitamin D	0.30	3.2	0.26	<0.005	0.1	0.06	18.0	70.0	0.3	0.0
Monoclonal antibodies-burosumab				0.29	<0.05	188.68	17.3	0.1	71.3	
Calcium	0.09	0.5	0.51	0.01	0.1	0.28	5.7	12.0	1.8	0.0
SERM – selective estrogen receptor modulators	0.01	<0.05	0.76	<0.005	<0.05	0.78	0.8	1.0	0.1	
Monoclonal antibodies-romosozumab				<0.005	<0.05	14.00	0.1	<0.05	16.3	17.8
Other medicines for osteoporosis							<0.05	<0.05		
Double-acting medicines							<0.05	<0.05		
Coagulation factors	**0.06**	**0.0**	**402.16**	**9.19**	**0.1**	**405.20**	**545.5**	**1.3**	**74.0**	**12.7**
Haemophilia A (long acting-recombinant)	0.01	<0.05	591.81	2.53	<0.05	320.02	149.5	0.5	75.6	17.1
Haemophilia A (short acting-recombinant)	0.01	<0.05	553.74	2.50	<0.05	335.60	148.0	0.4	70.7	19.9
Haemophilia A (monoclonal antibodies)				1.58	<0.05	683.30	93.4	0.1	94.7	0.3
Haemophilia B (long acting-recombinant)	0.01	<0.05	.425.88	1.20	<0.05	922.52	70.9	0.1	80.3	10.2
Factor VII deficiency (short acting-recombinant)				0.46	<0.05	4049.19	26.9	<0.05	26.9	
Haemophilia A (plasma derivatives)	0.02	<0.05	376.42	0.31	<0.05	244.69	19.0	0.1	78.9	18.4
Haemophilia B (short acting-recombinant)	<0.005	<0.05	568.96	0.24	<0.05	377.08	14.1	<0.05	75.2	14.1
Antihemophilic prothrombin complex activated human				0.12	<0.05	8383.04	6.9	<0.05	40.0	0.4
Combination of coagulation factors (plasma derivatives)	<0.005	<0.05	208.13	0.08	<0.05	104.52	4.6	<0.05	1.0	
Factor VIII deficiency (plasma products)	<0.005	<0.05	376.39	0.08	<0.05	361.21	4.5	<0.05	28.6	27.3
Von Willebrand's disease (plasma derivatives)				0.05	<0.05	71.71	3.1	<0.05	69.2	
Other deficiencies of coagulation factors (long-acting, recombinant)				0.05	<0.05	15524. 20	2.8	<0.05	30.0	
Haemophilia B (plasma derivatives)	0.01	<0.05	236.68	<0.005	<0.05	173.48	1.0	<0.05	31.9	

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Other deficiencies of coagulation factors (plasma derivatives)				0.01	<0.05	5490.88	0.6	<0.05	16.6	
Cystic fibrosis				**7.30**	**0.1**	**237.33**	**430.8**	**1.8**	**91.8**	**0.0**
CFTR modulator therapies				7.09	0.1	341.35	418.2	1.2	91.9	
Mucolytics with specific action				0.21	<0.05	21.32	12.6	0.6	88.1	0.3
Antidepressants	**6.96**	**43.7**	**0.44**	**0.09**	**2.0**	**0.12**	**415.9**	**985.3**	**0.8**	**0.0**
SSRI antidepressants	3.39	30.5	0.30	0.01	1.3	0.03	200.7	683.5	0.3	0.0
SNRI antidepressants	1.63	7.1	0.63	0.01	0.3	0.06	96.7	157.7	0.2	0.0
Other antidepressants	0.96	3.2	0.82	0.04	0.4	0.29	59.3	78.2	3.3	0.0
Vortioxetine	0.82	2.0	1.14	0.01	<0.05	0.70	49.0	43.4	0.7	0.0
1st generation antidepressants, plain or in combination	0.16	1.0	0.43	<0.005	0.1	0.22	9.4	22.5	2.2	0.0
Esketamine				0.01	<0.05	12.66	0.8	0.1	18.7	
Medicines for eye disorders	**3.62**	**20.9**	**0.47**	**3.14**	**0.5**	**15.97**	**398.4**	**462.4**	**7.3**	**0.0**
Antiglaucoma preparations - beta blocking agents plain or in combination	2.12	12.4	0.47	0.00	0.1	0.16	125.3	268.0	0.1	0.0
Recombinant anti-VEGF fusion proteins				1.48	<0.05	493.19	87.3	0.2	13.1	
Antiglaucoma preparations - prostaglandin analogues	1.19	5.6	0.58	<0.005	<0.05	0.21	70.2	121.8	0.1	0.0
Monoclonal antibodies anti-VEGF - ranibizumab				0.80	0.1	22.42	46.9	2.1	15.4	
Corticosteroids (intravitreal implants)				0.46	0.3	4.79	26.9	5.6	13.4	
Antiglaucoma preparations - carbonic anhydrase inhibitors plain or in combination	0.21	1.4	0.41	<0.005	<0.05	0.28	12.5	30.3	0.4	0.0
Monoclonal anti-VEGF antibodies—brolucizumab				0.15	<0.05	401.04	9.1	<0.05	17.3	
Other ophthalmological medicines (gene therapy)				0.13	<0.05	297000.00	7.7	<0.05	15.4	
Antiglaucoma preparations – sympathomimetic drugs	0.10	1.5	0.18	<0.005	<0.05	0.06	5.9	33.3	0.1	0.0
Other ophthalmological drugs	<0.005	<0.05	6.87	0.07	<0.05	11.88	4.1	0.3	87.3	0.6

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Antineovascularising agents (photodynamic therapy)				0.02	<0.05	790.72	0.9	<0.05	3.2	
Corticosteroids	<0.005	<0.05	0.79	0.01	<0.05	3.24	0.7	0.2	2.7	0.0
Antiglaucoma preparations parasympathomimetics	<0.005	<0.05	0.10	0.01	<0.05	1.73	0.6	0.6	0.3	0.0
Other ophthalmological medicines (cell therapy)				<0.005	<0.05	94310.54	0.2	<0.05		
Antiglaucoma preparations - others	<0.005	<0.05	0.77	<0.005	<0.05	0.35	<0.05	<0.05	14.9	
Anti-VEGF oligonucleotides							<0.05	<0.05		
Antiglaucoma preparations - carbonic anhydrase inhibitors							<0.05	<0.05		
Pain therapy	**6.10**	**6.9**	**2.43**	**0.19**	**1.0**	**0.50**	**370.5**	**169.8**	**1.4**	**0.4**
Major opioids, plain or in combination - oral	2.59	1.5	4.76	0.07	0.1	1.77	156.5	34.3	1.4	0.4
Medications for neuropathic pain	1.72	2.9	1.62	0.02	0.4	0.14	102.4	71.0	0.4	0.7
Major opioids, plain or in combination - transdermal	0.85	0.7	3.27	0.04	0.1	0.79	52.7	18.3	2.5	0.0
Minor opioids, plain or in combination	0.61	1.7	0.98	0.02	0.2	0.24	37.0	41.0	0.7	0.0
Major opioids, plain or in combination - nasal	0.30	<0.05	27.80	0.02	<0.05	17.85	18.9	0.7	4.1	
Major opioids, plain or in combination - parenteral	0.02	<0.05	2.53	0.03	0.2	0.40	3.0	4.5	7.1	0.0
Major opioids and antispasmodics in combination							<0.05	<0.05		
Anti-epileptics	**4.83**	**9.6**	**1.39**	**0.83**	**1.5**	**1.55**	**334.0**	**237.3**	**4.9**	**6.1**
Second-generation antiepileptics	2.69	4.0	1.83	0.16	0.7	0.65	168.2	101.2	1.3	3.3
Fisrt-generation antiepileptics	1.36	5.1	0.73	0.08	0.5	0.43	84.8	120.3	2.2	0.0
Third-generation antiepileptics	0.78	0.4	4.98	0.46	0.3	4.21	72.6	15.6	6.3	20.3
Cannabidiol				0.13	<0.05	47.56	7.5	0.2	97.5	
Other antiepileptics	<0.005	<0.05	13.83	0.01	<0.05	8.16	0.9	0.1	43.8	8.6
Platelet aggregation inhibitors	**2.98**	**61.1**	**0.13**	**2.33**	**9.7**	**0.66**	**313.3**	**1523.8**	**16.9**	**20.5**
P2Y12 platelet receptor inhibitors	1.36	7.3	0.51	1.15	6.8	0.46	147.7	304.3	1.6	38.2
Acetylsalicylic acid plain and in combination	1.43	52.9	0.07	0.01	1.5	0.02	85.0	1171.2	0.5	0.0
Other platelet aggregation inhibitors	<0.005	<0.05	3.36	1.03	<0.05	135.79	60.8	0.5	82.7	0.7
Acetylsalicylic acid/clopidogrel	0.19	0.9	0.60	0.13	1.4	0.25	18.5	47.8	0.3	40.5

ATC 1st level / Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Glycoprotein IIb/IIIa inhibitors				0.02	<0.05	64.49	1.2	<0.05	0.0	
Antipsychotics	**1.53**	**2.9**	**1.45**	**3.66**	**7.6**	**1.33**	**305.8**	**224.8**	**31.4**	**9.0**
Atypical and other antipsychotics	1.31	1.7	2.10	3.40	6.3	1.48	278.0	172.4	32.8	7.8
Typical antipsychotics	0.18	1.1	0.42	0.13	1.1	0.32	17.8	47.5	20.1	0.0
Atypical and other antipsychotics - lurasidone	0.03	<0.05	3.17	0.11	0.1	2.08	8.0	3.6	9.9	64.5
Atypical and other antipsychotics - brexpiprazole	0.01	<0.05	4.15	0.02	0.1	1.12	2.0	1.3	13.6	35.5
Medicines for genitourinary disorders	**4.62**	**40.1**	**0.32**	**0.01**	**0.5**	**0.07**	**273.1**	**873.7**	**0.2**	**0.0**
Medicines for benign prostatic hypertrophy (alpha blockers)	2.95	28.6	0.28	0.01	0.4	0.05	174.3	624.3	0.1	0.0
Medicines for benign prostatic hypertrophy (5-alpha reductase inhibitors)	1.58	11.0	0.39	<0.005	0.1	0.07	93.3	239.5	0.2	0.0
Medicines for incontinence and urination disorders (anticholinergics)	0.09	0.4	0.55	<0.005	<0.05	0.39	5.3	9.8	1.7	0.0
Other medicines for benign prostatic hypertrophy	<0.005	<0.05	1.35	<0.005	<0.05	0.78	0.1	0.1	16.4	0.0
Medicines for incontinence and urination disorders (beta-3 adrenergic antagonists)	<0.005	<0.05	2.44	<0.005	<0.05	1.18	0.1	<0.05	37.8	3.2
Medicines for benign prostatic hypertrophy (alpha-blockers in combination)	<0.005	<0.05	1.33	<0.005	<0.05	0.98	<0.05	<0.05	5.5	3.2
Antiparkinson medicines	**2.67**	**5.1**	**1.43**	**0.75**	**0.6**	**3.43**	**201.5**	**123.3**	**15.9**	**5.1**
DOPA-derivatives agonists, plain or in combination	0.72	2.1	0.94	0.53	0.2	5.90	73.9	50.8	39.1	1.0
Dopamine-agonists	1.06	1.0	2.97	0.04	0.1	1.29	65.0	23.0	2.0	1.7
MAO inhibitors	0.78	1.6	1.32	0.02	<0.05	0.98	47.0	36.0	1.2	1.1
COMT inhibitors	0.07	<0.05	6.92	0.15	0.1	3.30	13.0	3.3	8.7	61.7
Anticholinergics	0.04	0.4	0.28	<0.005	0.1	0.14	2.6	10.2	6.5	0.0
Amantadine	<0.005	<0.05	0.98	<0.005	<0.05	0.71	<0.05	0.1	126.1	1.9
NSAIDs	**2.59**	**18.1**	**0.39**	**0.07**	**0.9**	**0.19**	**156.6**	**410.6**	**0.3**	**0.0**
Traditional NSAIDs	1.77	13.1	0.37	0.06	0.9	0.19	108.1	302.3	0.4	0.0
Coxib	0.72	4.3	0.46	<0.005	<0.05	0.57	42.6	92.3	0.1	0.0

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Oxicam	0.09	0.7	0.36	<0.005	<0.05	0.13	5.5	15.5	0.0	
Other non-steroidal anti-inflammatory/ antirheumatic medicines	0.01	<0.05	0.66	<0.005	<0.05	0.63	0.3	0.5	0.3	
Antifungals for systemic use	**0.83**	**0.5**	**4.52**	**1.66**	**0.1**	**31.92**	**147.0**	**13.9**	**10.2**	**1.9**
Triazole derivatives	0.83	0.5	4.52	0.53	0.1	14.70	80.4	13.0	17.4	3.3
Polyenes				0.83	<0.05	101.59	48.8	0.5	0.4	
Echinocandins				0.28	<0.05	54.06	16.3	0.3	1.0	
Imidazole derivatives	<0.005	<0.05	13.60	0.02	<0.05	9.43	1.4	0.1	40.7	8.2
Pyrimidine analogues							<0.05	<0.05		
Contrast agents				**1.87**	**0.1**	**52.13**	**110.6**	**2.1**	**0.0**	
Radiocontrast agents				1.34	0.1	51.65	79.0	1.5	0.0	
MRI contrast agents				0.45	<0.05	48.30	26.2	0.5		
Contrast agents for ultrasound				0.09	<0.05	111.93	5.3	<0.05		
MRI contrast agents							<0.05	<0.05		
Thyroid medicines	**1.48**	**24.0**	**0.17**	**0.01**	**0.4**	**0.05**	**88.0**	**526.0**	**0.3**	**0.0**
Thyroid hormones	1.43	22.7	0.17	0.01	0.4	0.05	84.5	496.6	0.2	0.0
Antithyroid preparations	0.06	1.3	0.12	<0.005	0.1	0.07	3.4	29.3	1.7	0.0
Other preparations							<0.05	<0.05		
Antimigraine medicines	**1.00**	**0.8**	**3.22**	**0.47**	**0.2**	**5.21**	**86.8**	**23.7**	**30.3**	**0.0**
Triptans	1.00	0.8	3.22	<0.005	<0.05	3.38	59.0	18.3	0.4	0.0
Calcitonin gene-related peptide antagonists (monoclonal antibodies)	<0.005	<0.05	22.21	0.47	0.2	5.24	27.8	5.3	93.9	
Other antimigraine medicines	<0.005	<0.05	1.21	<0.005	<0.05	0.84	<0.05	<0.05	14.6	
Ergot alkaloids	<0.005	<0.05	0.69	<0.005	<0.05	0.19	<0.05	<0.05	46.0	5.2
Radiopharmaceuticals				**1.20**	**<0.05**	**521.01**	**71.0**	**0.1**	**3.6**	
Radiopharmaceuticals for cancer detection				0.47	<0.05	536.24	28.0	0.1		
Other radiopharmaceuticals for therapeutic use				0.31	<0.05	2466.7 3	18.1	<0.05	14.1	
CNS diagnostic radiopharmaceuticals				0.21	<0.05	704.43	12.3	<0.05	0.0	
Thyroid diagnostic radiopharmaceuticals				0.12	<0.05	237.91	7.3	<0.05	0.0	

ATC 1st level Subgroups	Approved care regime			Direct purchases			Total expenditure (million)	Total DDD (million)	% expenditure DD	% expenditure DPC
	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD average	Expenditure *per capita*	DDD/ 1000 inhab. per day	Average DDD cost				
Other diagnostic radiopharmaceuticals				0.04	<0.05	26162.34	2.6	<0.05		
Cardiovascular system diagnostic radiopharmaceuticals				0.03	<0.05	92.43	1.7	<0.05		
Skeletal system diagnostic radiopharmaceuticals				0.01	<0.05	79.14	0.5	<0.05		
Renal system diagnostic radiopharmaceuticals				<0.005	<0.05	127.58	0.3	<0.05		
Respiratory system diagnostic radiopharmaceuticals				<0.005	<0.05	150.00	0.2	<0.05		
Radiodiagnostics of the hepatic and reticuloendothelial system				<0.005	<0.05	450.87	<0.05	<0.05		
Radiopharmaceuticals for the detection of inflammation and infections				<0.005	<0.05	575.19	<0.05	<0.05		
Radiopharmaceuticals with analgesic/ anti-inflammatory action				<0.005	<0.05	784.88	<0.05	<0.05		
Antidementia medicines	**0.21**	**0.7**	**0.85**	**0.14**	**1.7**	**0.23**	**20.6**	**51.1**	**2.9**	**36.5**
Anticholinesterases	0.13	0.4	0.95	0.11	0.9	0.31	14.0	28.2	3.2	39.2
Other antidementia medicines	0.08	0.3	0.71	0.04	0.8	0.13	6.6	22.9	2.1	30.9

Most frequently prescribed therapeutic classes

For each ATC 1st level, after showing the overall data on expenditure, consumption and exposure, we provide in-depth analyses, mainly for the most prescribed therapeutic categories, reporting the temporal trend of consumption and expenditure along with national and regional data; where possible, indicators of exposure and adherence to drug treatment in the population are analysed. The national data on expenditure and consumption include both drugs supplied under approved care regime, including co-payments and discounts, and drugs purchased directly by public health facilities. The exposure data and the adherence and persistence indicators were processed through the administrative flow of prescriptions for class A-NHS drugs dispensed through local pharmacies, including “on-behalf” distribution (so-called Art.50 flow/Health Card).
The categories that will be examined in depth are the following:

- **ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**
  - Antineoplastic medicines
  - Immunosuppressants and immunomodulating agents
- **CARDIOVASCULAR SYSTEM**
  - Medicines for hypertension and heart failure
  - Lipid-lowering medicines
  - Acute Coronary Syndrome
- **GASTROINTESTINAL SYSTEM AND METABOLISM**
  - Antidiabetics
  - Medicines for peptic ulcer and GERD
  - Metabolic disorders
- **GENERAL ANTIMICROBIALS FOR SYSTEMIC USE**
  - Antibiotics
  - Anti-HIV antivirals
  - Vaccines
  - Antifungals for systemic use
- **BLOOD AND BLOOD-FORMING ORGANS**
  - Anticoagulants
  - Coagulation factors
- **CENTRAL NERVOUS SYSTEM**
  - Medicines for multiple sclerosis
  - Antidepressants
  - Medicines for pain therapy
  - Anti-epileptics
  - Antipsychotics
  - Antiparkinsonians
  - Antimigraine medicines
  - Antidementia medicines
- **RESPIRATORY SYSTEM**
  - Medicines for asthma and COPD
  - Medicines for cystic fibrosis
- **MUSCULO-SKELETAL SYSTEM**
  - Medicines for osteoporosis
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
- **SYSTEMIC HORMONAL PREPARATIONS, EXCLUDING SEX HORMONES AND INSULINS**
  - Thyroid medicines
- **GENITO-URINARY SYSTEM AND SEX HORMONES**
  - Medicines for genitourinary disorders
- **SENSORY ORGANS**
  - Medicines for eye disorders
- **VARIOUS**
  - Contrast agents
  - Radiopharmaceuticals
- **DERMATOLOGICALS**

For categorization, please refer to Appendix 3.

Figure 3.6 Variation in consumption 2022-2021 for the most frequently prescribed therapeutic categories

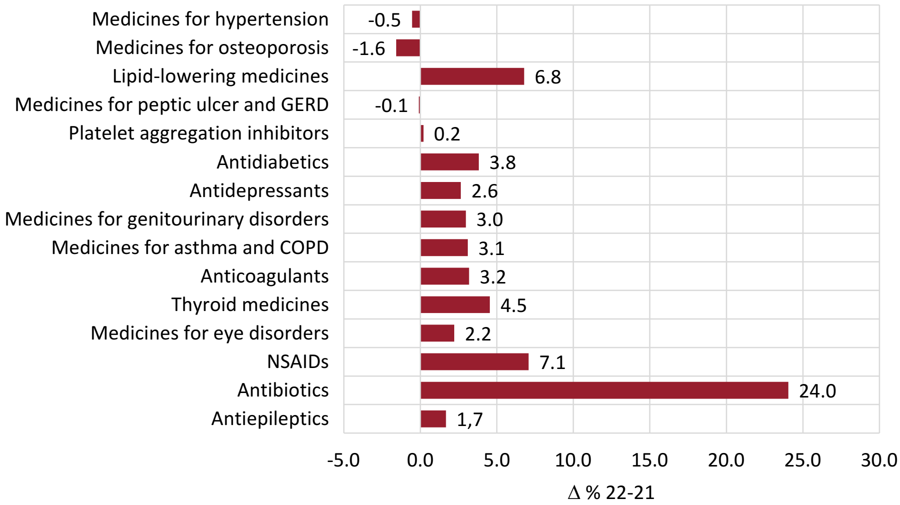


Figure 3.7 % Variation 2022-2021 in high adherence by therapeutic category

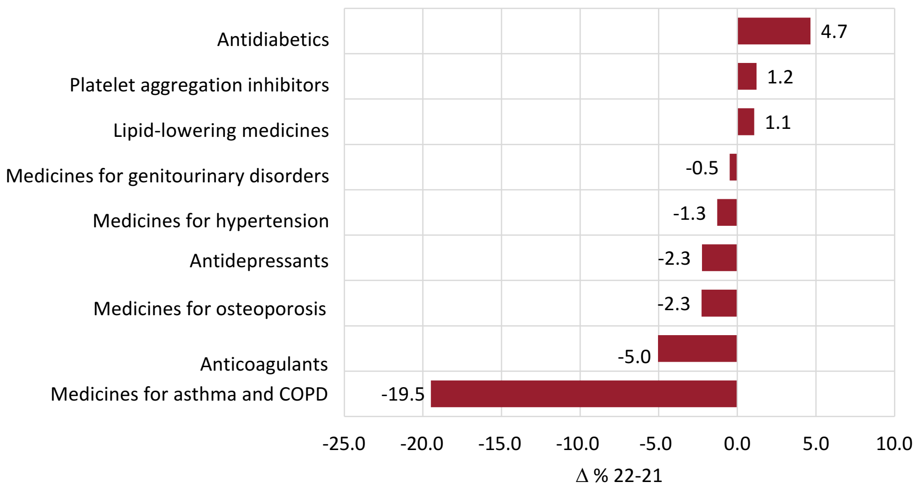
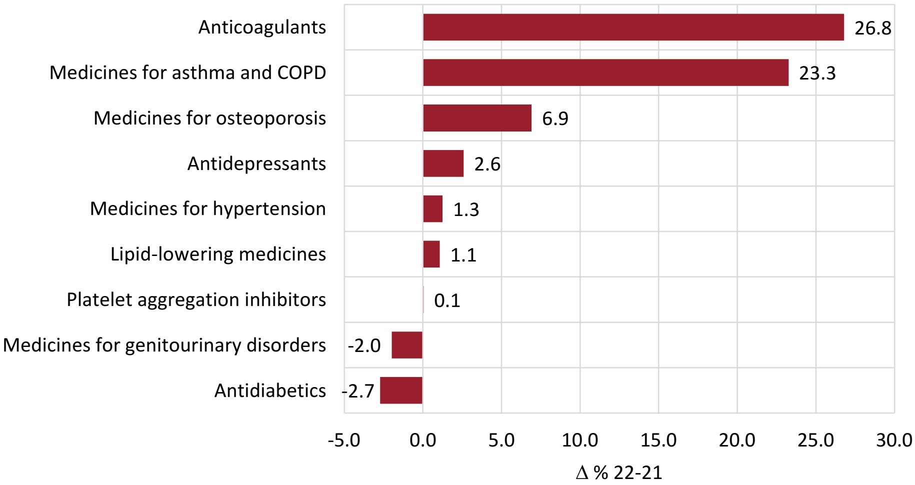


Figure 3.8 % Variation 2022-2021 in low adherence by therapeutic category



3.1 Antineoplastic and immunomodulating agents

Antineoplastic and immunomodulating agents are the therapeutic category with the highest public expenditure in 2022, amounting to 6,932 million euros (28.0% of overall expenditure), with a 5.0% increase compared to the previous year (Box. Main expenditure, consumption and exposure indices). The overall per capita expenditure for such medicines was 117.53 euro, mainly due to the purchase by public health facilities (113.04 euro per capita), thus recording a sharp increase compared to the previous year (+5.0%). On the contrary, the contribution by the approved care regime was lower (4.48 euro per capita) (Table 3.1). Consumption for this category of drugs was 18.7 DDD/1000 inhabitants per day, with a 7.2% increase compared to 2021 (Table 3.2), which confirms the trend of the last nine years.
The analysis of the medicine utilisation profile by age group and gender (including approved care regime and “on-behalf” distribution) confirms a higher use of antineoplastic and immunomodulating drugs with increasing age, with a marked increase in the prevalence of use in women compared to men starting from the age of 35, which is probably attributable to the prescription of medicines for breast cancer therapy and to the different prevalence of autoimmune diseases. However, a turnaround is recorded in the population over 75 years of age, with a greater prevalence of use in the male population (5.3% compared to 4.0% in women), probably due to the increase in the incidence of prostate cancer in this population. The value of per capita expenditure on antineoplastic drugs is higher in women than in men and increases with age up to the range 65-74 years, reaching a greater value in men aged over 75 (26.1 euro per capita compared to 14.3 euro in women).
Analysing the trends over the last six years (2017-2022) of the per capita expenditure, consumption and average cost per DDD of class A medicines and medicines purchased by public facilities (Figures 3.1-3.3), it is evident that the category of antineoplastics and immunosuppressants ranks first in terms of expenditure and average cost per DDD. In particular, per capita expenditure shows an evident upward trend, driven both by an increase in consumption and in the average cost per DDD. For the latter, however, there was a slight decrease in the last year. As regards approved care regime, the regional distribution (Table 3.5) shows a high variability (CV 28.9%) of gross per capita expenditure with maximum values in Lombardy (6.7 euro), Molise and Sardinia (5.3 euro) and minimums in Emilia Romagna and Tuscany (1.1 euro). The regional variability of consumption (Table 3.6) (CV 24.3%) shows the same trends, with a greater use in Lombardy and Sardinia (8.7 and 8.2 DDD/1000 inhabitants per day) and a lower one in Tuscany (1.8 DDD) and in Emilia Romagna (2.7 DDD). As for approved care regime, per capita expenditure was 4.5 euro, up 1.9% compared to 2021; this trend was determined exclusively by an increase in consumption (+2.3%), in fact there was no shift towards more expensive medicinal products (mix effect: -0.5%) and the average cost remained stable (-0. 4%) (Table 3.9). Under this supply regime, aromatase inhibitors are the first category both in terms of expenditure (2.35 euros per capita) and consumption (3.2 DDD), followed by other substances with immunosuppressive action and calcineurin inhibitors (belonging to the class of immunosuppressants), with a per capita expenditure respectively of 0.83 euro and 0.53 euro and 1.7 and 0.2 DDD (Table 3.9). Letrozole, an aromatase inhibitor used for the treatment of breast cancer in menopausal women, is the first active ingredient in the

category by per capita expenditure (1.51 euro) and by consumption (1.8 DDD/1000 inhabitants per day) (Table 3.10). It is the only antineoplastic and immunosuppressant drug within the first 30 active ingredients for expenditure under approved care regime (Table 3.11), and it is the only oncological drug that appears among the top thirty active ingredients with the highest average cost DDD with a value equal to 2.25 euro (Table 3.13). Letrozole, together with methotrexate, is listed among the top 30 active ingredients with the greatest variation in expenditure for the previous year, with a difference of 6.9% and 6.6% respectively (Table 3.15).
As for purchases by public healthcare facilities, the regional distribution (Table 3.7) shows a moderate variability (CV 18.3%) of gross per capita expenditure with maximum values in the Marche (137.7 euro) and in Molise (135.9 euro) and minimum values in Valle d'Aosta (72.2 euro) and in the Province of Trento (86.9 euro). The distribution of consumption (CV 22.8%) shows high values of use in Tuscany (16.7 DDD) and Emilia Romagna (16.0 DDD) and lower values for Valle d'Aosta (8.8 DDD) and Lombardy (9.1 DDD) (Table 3.8). Overall, an increase in expenditure (+4.6%) and consumption (+9.2%) was recorded, as well as a shift towards more expensive medicinal products (mix effect: +1.4%). Compared to 2021, on the other hand, there was a reduction in prices (-5.6%) and in the DDD average cost (-4.2%) (Table 3.19).
Selective immunosuppressants are the first category in terms of per capita expenditure (16.97 euro), with a 13.1% increase compared to the previous year; they also record an increase in consumption (+14.1%) and a shift towards more expensive drugs (mix effect: +1.6%), while reporting a reduction in prices (-2.5%) and in the DDD average cost (-0.9%). PD-1/PDL-1 inhibitors, which include among others nivolumab and pembrolizumab, rank second (13.25 euro per capita), while interleukin inhibitors (9.86 euro per capita) rank third by expenditure. For these two categories there were increases both in terms of expenditure (respectively +9.5% and +15%) and consumption (respectively +16.3% and +27.4%) compared to the previous year, as well as a reduction of prices (-5.6% and -6.0%) and of the average DDD cost (-5.8% and -9.7%). The shift towards less expensive medicinal products (mix effect: -3.9%) is instead recorded for interleukin inhibitors. The increase in expenditure for CD38 inhibitors (+68.6%) is particularly important and is attributable to an increase in consumption (+160.9%) and driven by the active ingredient daratumumab, which was reimbursable at the end of 2021, in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. The category "Other monoclonal antibodies and antibody drug conjugates" also shows, compared to the previous year, an increase in both expenditure and consumption of more than 100%. On the other hand, expenditure for the category of other immunosuppressants decreased, mainly driven by the shift towards less expensive medicinal products (mix effect: -29.6%) and by the reduction in the average DDD cost (-33.1%). As observed the previous year, there was a reduction in the expenditure of anti-TNF-alpha drugs, despite an increase in consumption, mainly due to a reduction in prices and the shift towards less expensive medicinal products. The expenditure trend in this category is attributable to the reduction in prices (-6.9%) due to the presence on the market of biosimilars of some molecules. HER2 inhibitors, on the other hand, show an increase in expenditure (+1.8%) and consumption (+4.1%), a reduction in prices (-10.9%), but a shift towards higher cost medicines (mix effect:

+9.7%), attributable to a greater use of trastuzumab emtansine and pertuzumab (Table 3.20).

In 2022, pembrolizumab and daratumumab are the drugs with the highest value of expenditure per capita (7.54 euro and 6.62 euro) and account for 6.7% and 5.9% of expenditure in this category, respectively (Table 3.20). For pembrolizumab there was an increase in consumption of +18.6% and a slight reduction in the average DDD cost (-0.9%). In the case of daratumumab, on the other hand, there was a considerable increase in consumption (>100%), while the average DDD cost fell by 36.9%. Ibrutinib, a Bruton's tyrosine kinase inhibitor, is the third active ingredient by per capita expenditure and shows a 6.1% increase in consumption and a 4.9% reduction in the average DDD cost, presumably connected with a reclassification and renegotiation of the drug. On the other hand, for the active ingredient lenalidomide, there was a reduction in expenditure (-55.7%) and in the average DDD cost (-62.8%), probably attributable to negotiated discounts. Pembrolizumab and daratumumab also rank within the top two most expensive drugs purchased by public health facilities (Table 3.21). The list of the most expensive medicines purchased by public health facilities includes 18 active ingredients belonging to the category of antineoplastics and immunomodulators. On the other hand, 11 active ingredients of the ATC L group are included in the list of the top thirty with the greatest variation in expenditure compared to the previous year (Table 3.23). The first active principle with the greatest reduction in expenditure is represented by lenalidomide (Table 3.24). Eculizumab, a drug used in the treatment of adults and children with paroxysmal nocturnal hemoglobinuria (PNH), together with 13 other active ingredients belonging to the category of antineoplastics and immunomodulators, ranks among the top thirty drugs purchased by public health facilities for average cost per day of therapy, with a value of 728.8 euro, a reduction of 5.0% compared to 2021. The other 13 active ingredients have an average cost that varies between a maximum of 242.6 euro for pomalidomide and a minimum of 98.6 euro for nivolumab (Table 3.25) There are 7 active ingredients in the list of the top 30 active ingredients with the lowest average cost per day of therapy for drugs purchased from public health facilities (Table 3.26), including triptorelin with an average DDD cost of 2.7 euro, adalimumab with a value of 5.11 euro and tacrolimus (6.01 euro). No drug belonging to the antineoplastic and immunomodulatory category is listed within the first thirty drugs purchased by public health facilities by consumption, calculated as DDD per 1000 inhabitants per day (Table 3.27).

Table 3.30 shows the different trend in terms of expenditure, consumption and average DDD cost between the approved care regime and direct purchases for antineoplastic medicines, immunosuppressants and immunomodulating agents.

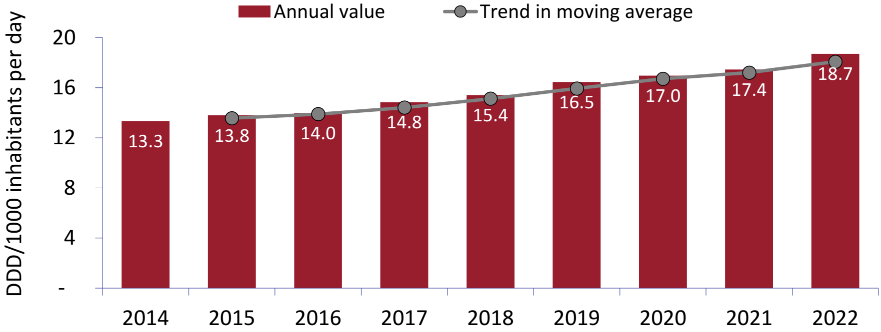
For further information on the use of medicines related to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region. These analyses concerned antineoplastic medicines, immunosuppressants and immunomodulating agents (Tables 3.1.1a and following).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

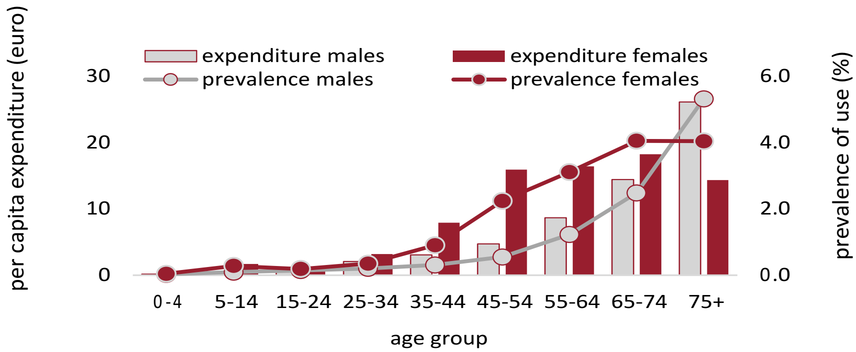
Antineoplastic and immunomodulating agents

Public expenditure* in EUR million (% over total)	**6,932.3**	**(28.0)**
Δ % 2022-2021		5.0
Regional range gross expenditure per capita:	75.9	142.2
DDD/1000 inhabitants per day* (% over total)	**18.7**	**(1.4)**
Δ % 2022-2021		7.2
Regional range DDD/1000 inhabitants per day	14.5	21.3

** includes prescriptions under approved care regime and purchases by public health facilities*



Breakdown of prevalence of use and consumption under approved care regime and distribution on behalf by age and gender in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.2	0.2	0.2	0.1	0.1	0.1
5-14	0.6	1.7	1.1	0.4	1.5	1.0
15-24	1.1	1.2	1.1	0.6	0.7	0.7
25-34	2.1	3.2	2.6	0.9	1.7	1.3
35-44	3.1	7.9	5.5	1.4	6.2	3.8
45-54	4.7	15.9	10.4	2.5	16.9	9.8
55-64	8.7	16.4	12.6	5.3	19.5	12.6
65-74	14.4	18.3	16.4	10.4	24.4	17.8
75+	26.1	14.3	19.1	26.9	22.0	24.0

3.1.1 Antineoplastic medicines

- In the period 2014-2022, expenditure on antineoplastic medicines more than doubled (+113%), going from a value of 34.8 euro to one of 74.1 euro, recording a 9.9% average annual increase. At the same time, the average DDD cost increased by 70%, moving from 10.9 to 18.5 euro (Figure 3.1.1a). Consumption shows a 2.8% average annual increase, with 10.9 DDD/1000 inhabitants per day in 2022 (Table 3.1.1a).
- In 2022, the first three categories with the highest expenditure are monoclonal antibodies (mAbs) (Table 3.1.1a). Immune check-point inhibitors rank first (13.82 euro), with a significant increase in expenditure (+12.1%) and consumption (+17.7%), despite a reduction in the average DDD cost (-4.8%) compared to 2021. This category shows the most marked increase in the last 8 years (Figure 3.1.1b). The reasons for this trend are due to the numerous extensions of indication of use for these molecules, in combination with other drugs in various solid tumors, all of which have reported results of therapeutic improvement. Monoclonal antibodies acting on specific targets (8.66 euro) rank second with an increase (+47.2%) compared to 2021 and monoclonal antibodies blocking the action of growth factors (5.77 euro) rank third and show an increase in consumption (+7%), a decrease in expenditure (-7.3%) and average DDD cost (-15.4%) compared to 2021, attributable to the presence of biosimilars for some drugs of this class. Monoclonal antibodies conjugated with drugs represent the category with the greatest variation in expenditure (+64.8%) and consumption (+70.5%), while CAR-T present the highest average DDD cost (about 210 thousand euro), increasing by 6.2% compared to 2021 (Table 3.1.1a).
- The trend of the individual active ingredients follows the trend of the categories; in fact, pembrolizumab (7.54 euro) and daratumumab (6.62 euro) are at the top of the list, both with an increase in expenditure and consumption compared to the previous year. In particular, daratumumab showed a substantial increase in expenditure (+62.8%) and consumption (+158%) and a reduction in average cost per DDD of about 37% (Table 3.1.1a). On the other hand, the active ingredient with the lowest cost per DDD is palbociclib with 65.78 euro, a 3.8% reduction.
- Analysing the regional per capita expenditure (national average value 74.05 euro), the Regions of the Centre and of the South tend to spend more (76.84 and 76.41 euro respectively) than the Regions of the North (71.22 euros) and the North (Table 3.1.1b). The profound variability is evident from the difference between Umbria's highest expenditure value (89.78 euro) and Valle d'Aosta's lowest (43.69 euro), the only Region to record in 2022 a reduction in per capita expenditure compared to the previous year (-8.3%). Valle d'Aosta also presents the highest increase in consumption compared to 2021 (+23%), and at the same time the lowest average cost per DDD (13.65 euro), a 25% reduction compared to the previous year. Conversely, the highest average cost per DDD is recorded for the Province of Bolzano (21.88 euro). The Marche Region shows the highest consumption (12.6 DDD/1000 inhabitants per day). The average DDD cost for this category of drugs in 2022 was 18.54 euro, with a 2.7% increase compared to the previous year. The greatest increases in this value were observed in Friuli Venezia-Giulia (+11.1%) and Sicily (+8.6%).

Figure 3.1.1a Antineoplastic medicines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

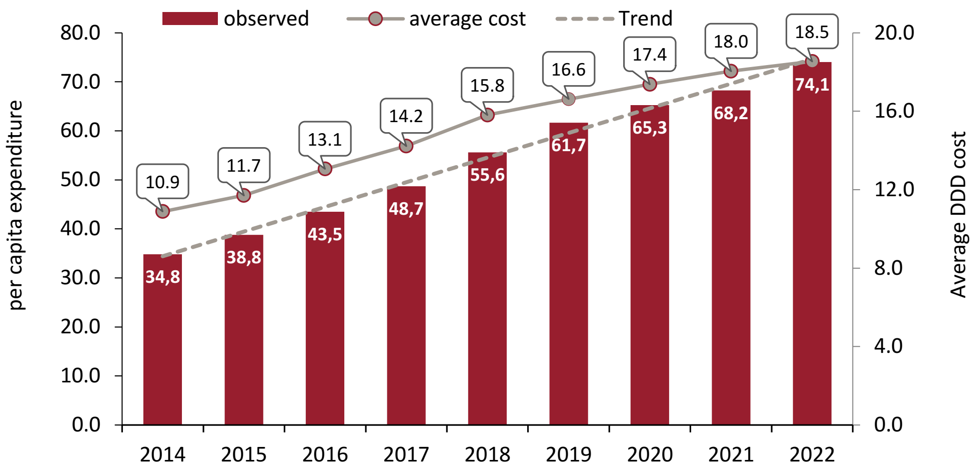


Table 3.1.1a Antineoplastic medicines, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Expen diture per capita	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Monoclonal antibodies inhibiting immune check points	13.82	12.1	45.0	0.4	17.7	82.4	98.83	-4.8
Monoclonal antibodies active on specific targets	8.66	47.2	13.5	0.7	22.8	6.5	36.10	19.9
Monoclonal antibodies blocking growth factors	5.77	-7.3	-4.4	0.4	7.0	5.2	40.92	-13.3
VEGFR-associated multitarget tyrosine kinase inhibitors	4.15	0.0	9.3	0.1	12.7	12.5	99.17	-11.3
Endocrine therapy - aromatase inhibitors	3.95	-7.1	5.7	3.8	4.3	5.6	2.84	-10.9
CDK protein kinase inhibitors	3.81	10.9	-	0.2	15.4	-	65.71	-3.9
Bruton tyrosine kinase (BTK) inhibitors	3.80	11.9	-	0.1	16.7	-	124.61	-4.1
BRC-ABL tyrosin kinase inhibitors	3.15	-7.7	-5.2	0.2	1.0	2.7	46.77	-8.6
EGFR tyrosin kinase inhibitors	2.94	12.0	14.1	0.1	13.5	6.9	127.46	-1.3
Endocrine therapy – antiandrogens	2.71	12.7	34.3	0.8	-2.1	-4.6	9.31	15.1
Monoclonal antibodies conjugated with drugs	2.67	64.8	31.4	<0.05	70.5	37.5	211.82	-3.4
Endocrine therapy - hormones and GnRH analogues	2.14	9.2	1.2	1.3	15.1	3.0	4.58	-5.1
JAK tyrosin kinase inhibitors	2.13	13.7	88.4	0.1	14.6	92.7	110.02	-0.7
Cytostatic antineoplastics – PARP inhibitors	1.89	25.2	-	<0.05	35.3	-	135.40	-7.5
Cytostatic antineoplastics – other cytostatics	1.82	6.5	14.8	0.4	3.3	3.9	13.77	3.1
BRAF tyrosin kinase inhibitors	1.50	11.2	14.8	<0.05	10.2	31.1	112.10	0.9
ALK tyrosin kinase inhibitors	1.44	12.1	-	<0.05	19.5	-	141.57	-6.2
Cytostatic antineoplastics – antimetabolites	1.35	-36.4	-8.6	0.6	3.8	-4.0	5.78	-38.7
CAR-T	1.19	45.8	-	<0.05	36.8	-	209748.35	6.6
Cytostatic antineoplastics – proteasome inhibitors	0.85	-1.8	-6.6	<0.05	1.0	3.3	60.20	-2.8
MEK tyrosin kinase inhibitors	0.71	6.4	-	<0.05	10.2	-	56.43	-3.4
Other protein kinase inhibitors	0.55	22.8	-	<0.05	13.9	-	445.46	7.8
Naturally derived cytotoxic antineoplastics-taxanes	0.45	-34.0	-2.1	0.2	-0.1	2.7	6.78	-33.9
Cytotoxic antineoplastics-cytotoxic antibiotics -anthracyclines and related substances	0.44	-14.8	-2.0	0.1	-9.1	-2.3	12.61	-6.3
MTOR protein kinase inhibitors	0.37	-23.5	-12.6	0.0	6.3	-4.1	67.27	-28.0
Naturally derived cytotoxic antineoplastics – others	0.36	-25.6	-4.3	0.1	-0.5	-1.0	17.59	-25.2
Cytostatic antineoplastics – alkylating agents	0.34	-7.1	-9.2	0.2	-2.7	-3.8	5.37	-4.6
Hedgehog pathway inhibitors	0.30	-23.8	61.7	<0.05	24.4	81.0	117.73	-38.7
Endocrine therapy - antiestrogens	0.20	-49.1	-11.7	0.8	-14.4	-4.2	0.65	-40.5

continued

Table 3.1.1a – *continued*

Subgroups and substances	Expenditure per capita	Δ % 22-21	CAGR % 14-22	DDD/1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Antineoplastic medicines	**74.05**	**8.5**	**9.9**	**10.9**	**5.6**	**2.8**	**18.54**	**-1.3**
pembrolizumab	7.54	17.5	-	0.2	18.6	-	92.20	-0.9
daratumumab	6.62	62.9	-	0.2	158.0	-	94.35	-36.9
ibrutinib	3.42	0.9	-	0.1	6.1	-	123.57	-4.9
nivolumab	3.30	-10.7	-	0.1	0.3	-	98.58	-11.0
osimertinib	2.84	14.3	-	0.1	20.4	-	140.78	-5.1
pertuzumab	2.62	7.6	33.8	0.1	14.5	37.9	105.55	-6.1
ruxolitinib	2.10	12.2	88.1	0.1	12.6	92.3	110.52	-0.3
enzalutamide	2.01	-0.2	87.4	0.1	20.4	103.5	69.20	-17.1
palbociclib	1.65	-11.2	-	0.1	-7.7	-	65.78	-3.8
nintedanib	1.59	20.6	-	<0.05	27.0	-	91.84	-5.0

Figure 3.1.1b Antineoplastic medicines, temporal trend 2014-2022 of per capita expenditure for most expensive subgroups

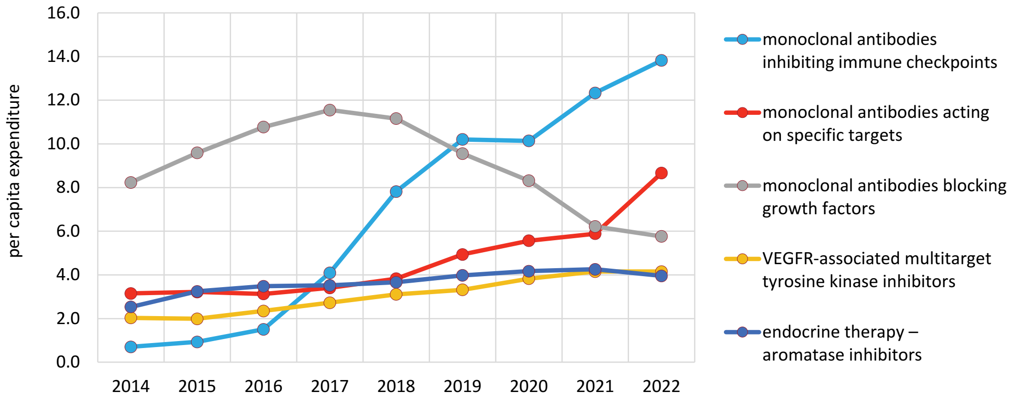


Table 3.1.1b Antineoplastic medicines, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	60.07	10.0	16.45	65.60	10.8	16.68	9.2	7.7	1.4	8.6	2.8	5.7
Valle d'Aosta	47.63	7.1	18.30	43.69	8.8	13.65	-8.3	23.0	-25.4	6.7	2.0	4.5
Lombardy	59.82	10.2	16.02	65.37	11.1	16.21	9.3	8.0	1.2	10.7	2.2	8.3
Province of Bolzano	72.13	8.9	22.22	74.37	9.3	21.88	3.1	4.7	-1.5	9.0	4.1	4.8
Province of Trento	51.54	9.7	14.52	56.99	10.3	15.19	10.6	5.7	4.6	9.8	3.7	5.9
Veneto	64.38	10.3	17.19	73.23	11.0	18.31	13.7	6.8	6.5	10.3	2.9	7.1
Friuli VG	75.58	11.0	18.82	82.65	10.8	20.92	9.3	-1.6	11.1	8.9	1.2	7.6
Liguria	73.93	10.8	18.71	82.82	11.3	20.05	12.0	4.6	7.1	11.1	2.7	8.2
Emilia Romagna	73.08	10.5	19.04	82.09	11.0	20.44	12.3	4.6	7.3	11.1	3.2	7.7
Tuscany	68.28	10.1	18.58	73.78	11.0	18.37	8.1	9.3	-1.1	7.4	2.7	4.6
Umbria	86.05	11.2	20.99	89.78	11.6	21.17	4.3	3.4	0.9	11.5	3.7	7.5
Marche	77.26	11.8	17.97	87.21	12.6	18.99	12.9	6.8	5.7	10.1	3.3	6.6
Lazio	73.60	10.5	19.12	74.03	11.1	18.30	0.6	5.1	-4.3	10.4	2.4	7.8
Abruzzo	75.33	10.9	18.86	80.51	11.8	18.77	6.9	7.4	-0.5	8.3	2.7	5.4
Molise	66.30	10.2	17.76	73.62	10.7	18.87	11.0	4.5	6.2	11.6	4.4	6.8
Campania	80.04	10.7	20.40	86.26	11.4	20.72	7.8	6.1	1.6	9.9	3.9	5.7
Puglia	72.75	10.5	18.99	80.32	11.0	19.98	10.4	4.9	5.2	9.2	2.4	6.7
Basilicata	74.21	9.7	20.86	77.10	10.8	19.61	3.9	10.5	-6.0	8.5	4.1	4.2
Calabria	67.41	10.0	18.40	70.81	10.3	18.80	5.0	2.8	2.2	10.6	3.6	6.7
Sicily	59.40	9.5	17.05	64.42	9.5	18.51	8.4	-0.1	8.5	10.8	2.7	7.8
Sardinia	67.44	11.0	16.82	73.35	11.1	18.03	8.8	1.5	7.2	8.6	3.3	5.1
Italy	**68.23**	**10.4**	**18.05**	**74.05**	**10.9**	**18.54**	**8.5**	**5.6**	**2.7**	**9.9**	**2.8**	**6.9**
North	64.38	10.3	17.18	71.22	10.9	17.85	10.6	6.5	3.9	10.2	2.6	7.4
Centre	73.30	10.6	18.94	76.84	11.3	18.65	4.8	6.5	-1.5	9.4	2.7	6.5
South and Islands	70.65	10.3	18.72	76.41	10.7	19.48	8.2	3.9	4.1	9.7	3.2	6.4

In the field of oncological pathologies, the most important clinical development concerns the implementation and diffusion of genetic tests for tumor profiling (next generation sequencing, NGS), with the development of therapies aimed at specific biomarkers. This new model of mutational oncology makes it possible to personalize oncological treatments. In fact, the molecular alterations present in a single patient can be used to identify targeted, precise molecular treatments with fewer adverse effects compared to traditional cytotoxic therapies. However, this type of approach requires the development of specific clinical skills. For this reason, Molecular Tumor Boards (MTBs), i.e. multidisciplinary working groups, involving different healthcare professionals (oncologists, geneticists, pharmacologists, radiologists, surgeons, oncologists, pathologists, etc.), are spreading with the aim of discussing the clinical cases, define the best strategies for genomic profiling, interpret the results and identify personalized therapy. The indication for a treatment by MTB is based on the probability that the patient can respond more to a drug already on the market, used for different therapeutic indications, or available in clinical trials. This type of approach certainly leads to an increase in the number of therapeutic options available for the individual patient and to an improvement in prognosis, however, from a regulatory point of view, it implies a lower level of evidence in the clinical trials that lead to the registration of a drug. In fact, in the case of patients who present specific relatively rare mutations, the registration trials are Phase I or II without a comparison with the therapeutic options currently available. To this we must add the lack of targeted guidelines, the possible territorial heterogeneity of MTBs, whose organization is a regional responsibility, as well as the economic impact that sequencing tests could have in current clinical practice; instead, the development of immunotherapies has led to 4 different types of approaches to the treatment of oncological pathology: monoclonal antibodies, immune checkpoint inhibitors, vaccines, adoptive cell transfer. Among these, immune checkpoint inhibitors have undergone a great acceleration, bringing forward very important clinical developments in multiple indications, with progressive replacement of chemotherapies, greater efficacy and better tolerability profile. More recently introduced is the approach based on the transfer of adoptive T cells, i.e. T lymphocytes engineered with chimeric antigen receptors (CAR). Overall, oncology research is constantly developing. Therefore, if on the one hand the therapeutic options for patients are increasing, on the other the choice of the most appropriate treatment is becoming increasingly complex for clinicians. From a regulatory point of view, however, the decision for admission to reimbursement for payers is often complicated by registration studies that prevent the real valorization of new drugs and the related therapeutic indications.

3.1.2 Immunosuppressants and immunomodulating agents

- In the period 2014-2022, expenditure on immunosuppressants and immunomodulating agents has increased by about 39%, shifting from 21.5 euro to 29.86 euro per capita, with an average annual increase equal to 4.2%. However, the average DDD cost decreased by 30% from 24.4 to 17.0 euro (Figure 3.1.2a). Consumption shows a 9% average annual increase, with 4.8 DDD/1000 inhabitants per day in 2022 (Table 3.1.2a).
- In 2022, the two categories with the greatest expenditure are interleukin inhibitors (9.86 euro), up 15.5% compared to 2021, and TNF-α
- inhibitors (4.66 euro), whose values decreased compared to the previous year (-7.4%). The subgroup "Other immunosuppressants" recorded the most significant reduction in per capita expenditure (-39.4%), due to the marked reduction in the average DDD cost (-47%) compared to the previous year, maybe due to greater use of biosimilar drugs. The subgroup of growth factors also showed a reduction in the indicators mentioned above, with an increase in consumption (+8.4%). Conversely, interleukin inhibitors, immunosuppressive monoclonal antibodies, JAK tyrosine kinase inhibitors, and calcineurin inhibitors show increases in both expenditure and consumption, despite a reduction in the average DDD cost (Table 3.1.2a). Interleukin inhibitors, immunosuppressive monoclonal antibodies and JAK tyrosine kinase inhibitors show a constantly increasing trend, especially in the last five years (Figure 3.1.2b).
- Analysing the performance of the individual active ingredients, lenalidomide records the highest expenditure value (2.42 euro), confirming the growing trend in consumption in recent years (CAGR 2014-2022: +16.8%), despite a 55.7% reduction in per capita expenditure and a 62.8% reduction in the average DDD cost over the past year, attributable to patent expiration. The largest expenditure increases were observed for ixekizumab (+28.5%), ustekinumab (+11.7%) and vedolizumab (+11.1%). After lenalidomide (-55.7%), the molecule with the greatest cost reduction is etanercept (-19.5%), also showing a 22.6% decrease in the average DDD cost, similarly to adalimumab, probably thanks to the presence of biosimilars on the market (Table 3.1.2a).
- Analysing the regional variability of per capita expenditure, the Southern regions show a higher value (34.93 euro) compared to the national average (29.86 euro), while the Northern regions (27.62 euro) and the Central ones (26.86 euro) show lower values (Table 3.1.2b). The marked regional variability is evident considering the minimum value in Valle d'Aosta (20.85 euro) and the maximum value in Calabria (44.42 euro). Similarly, the Southern Regions show a higher value of DDD/1000 inhabitants per day (5.2 DDD) compared to the national average (4.8 DDD), while the Central Regions (4.7 DDD) and the Northern Regions (4.6 DDD) present values in line with the average. Calabria records the highest average DDD cost (23.78 euro) while Lazio shows the lowest (14.03 euro). Compared to a national figure equal to 16.95 euro, the Southern Regions show a higher value (18.26 euro), while the Northern Regions (16.50 euro) and the Central Regions (15.62 euro) show lower values. Compared to the previous year, Campania in 2022 shows the greatest increase in both per capita expenditure (+9.9%) and consumption (+19.3%). All Regions show a reduction in the DDD cost, with values ranging between -2.6% in Calabria and 25.8% in Umbria.

Figure 3.1.2a Immunosuppressants and immunomodulating agents, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

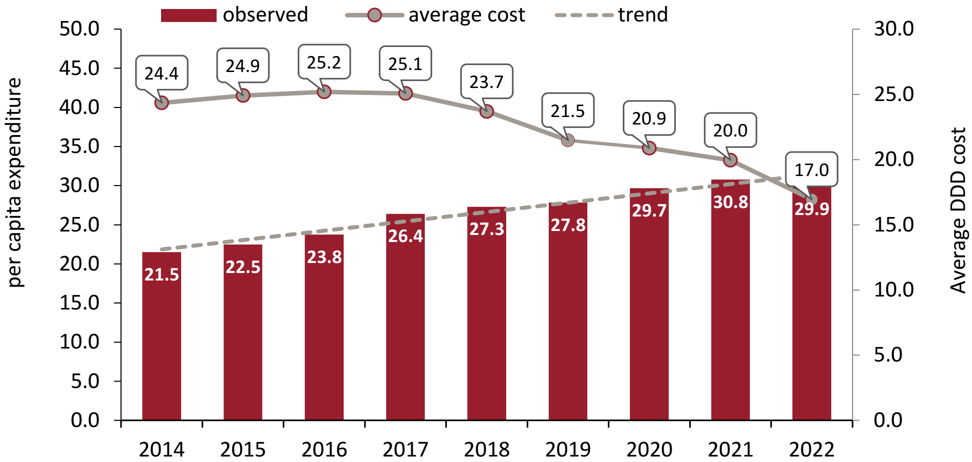


Table 3.1.2a Immunosuppressants and immunomodulating agents, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Expenditure per capita	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Interleukin inhibitors	9.86	15.5	28.0	1.1	27.9	33.4	25.27	-9.7
Tumor necrosis factor alpha inhibitors (TNF-alpha)	4.66	-7.4	-9.3	1.7	12.0	8.0	7.54	-17.3
Other immunosuppressants	4.44	-39.5	5.9	0.2	14.1	15.6	59.12	-47.0
Selective mmunosuppressants (monoclonal antibodies)	3.86	8.4	15.7	0.2	18.4	49.7	66.52	-8.4
JAK tyrosin kinase inhibitors	1.45	38.0	-	0.2	54.6	-	21.99	-10.8
Calcineurin inhibitors	1.42	0.8	-2.5	0.6	2.5	0.5	6.64	-1.6
Selective immunosuppressants	1.27	20.6	11.0	0.6	5.8	5.7	5.65	14.0
Selective T cell co-stimulation modulators	1.20	3.9	11.2	0.1	3.8	9.6	48.71	0.1
MTOR protein kinase inhibitors	0.71	4.6	4.0	0.1	4.2	5.8	17.48	0.4
Growth factors	0.48	-17.5	-12.4	0.1	8.4	1.9	11.33	-23.9
Other immunomodulators	0.41	26.3	9.5	<0.05	27.3	8.6	168.73	-0.7
Interferons	0.10	37.1	-25.0	<0.05	28.6	-28.3	26.13	6.6
Immunosuppressants and immunomodulating agents	**29.86**	**-3.0**	**4.2**	**4.8**	**14.1**	**9.0**	**16.95**	**-15.0**
lenalidomide	2.42	-55.7	0.1	0.1	18.9	16.8	45.72	-62.8
ustekinumab	2.29	11.7	16.7	0.4	38.5	26.4	14.42	-19.3
secukinumab	2.03	7.2	-	0.2	11.7	-	29.37	-4.0
eculizumab	2.01	-6.7	7.0	<0.05	-1.8	10.4	728.78	-5.0
adalimumab	1.45	-7.0	-12.3	0.8	20.2	12.4	5.11	-22.6
vedolizumab	1.34	11.1	-	0.1	16.8	-	30.92	-4.9
ixekizumab	1.23	28.5	-	0.1	28.6	-	30.29	0.0

Subgroups and substances	Expenditure per capita	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
etanercept	1.21	-19.5	-12.6	0.3	4.0	1.4	10.94	-22.6
abatacept	1.19	3.7	11.1	0.1	3.4	9.3	49.48	0.3
canakinumab	1.07	8.7	33.9	<0.05	15.6	39.1	147.79	-5.9

Figure 3.1.2b Immunosuppressants and immunomodulating agents, temporal trend 2014-2022 in per capita expenditure for most expensive subgroups

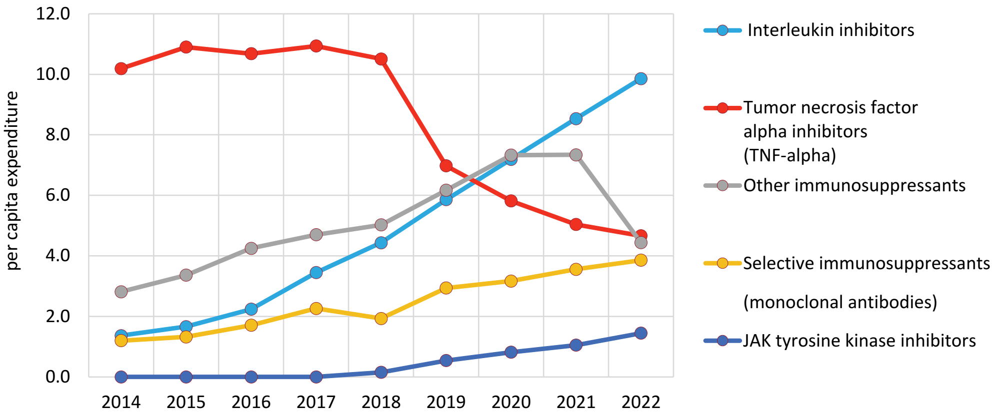


Table 3.1.2b Immunosuppressants and immunomodulating agents, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	30.82	4.0	20.87	30.80	4.7	17.81	-0.1	17.1	-14.7	6.4	10.7	-3.9
Valle d'Aosta	23.17	2.7	23.19	20.85	3.2	17.59	-10.0	18.6	-24.1	7.0	6.8	0.1
Lombardy	25.72	3.4	20.43	25.27	4.0	17.22	-1.8	16.6	-15.7	3.9	8.1	-3.9
Province of Bolzano	35.23	5.6	17.26	32.69	6.2	14.35	-7.2	11.6	-16.9	3.7	10.3	-5.9
Province of Trento	25.00	4.0	17.15	21.75	4.2	14.05	-13.0	6.2	-18.1	4.6	9.6	-4.5
Veneto	28.67	4.3	18.22	27.27	5.1	14.67	-4.9	18.1	-19.5	3.9	10.4	-5.9
Friuli VG	35.14	5.2	18.65	31.18	5.4	15.95	-11.3	3.7	-14.5	4.6	8.1	-3.2
Liguria	26.35	3.6	20.05	26.81	4.1	17.89	1.7	14.0	-10.8	6.3	8.6	-2.2
Emilia Romagna	33.58	4.5	20.30	29.66	5.0	16.30	-11.7	10.1	-19.7	6.1	10.2	-3.7
Tuscany	31.97	4.4	19.75	27.42	5.0	14.89	-14.2	13.8	-24.6	1.2	8.0	-6.4
Umbria	35.49	4.3	22.71	29.30	4.8	16.85	-17.4	11.3	-25.8	3.7	9.2	-5.0
Marche	37.47	4.5	22.91	41.51	5.3	21.44	10.8	18.3	-6.4	7.2	10.0	-2.6
Lazio	24.86	3.9	17.45	22.11	4.3	14.03	-11.1	10.6	-19.6	0.9	8.5	-7.0
Abruzzo	38.43	4.4	23.75	37.12	5.2	19.44	-3.4	18.0	-18.2	6.0	10.1	-3.7
Molise	36.02	3.8	25.79	35.79	4.5	21.60	-0.6	18.6	-16.3	4.4	9.0	-4.2
Campania	36.12	4.7	21.12	39.71	5.6	19.46	9.9	19.3	-7.8	6.4	9.8	-3.0
Puglia	34.45	4.7	20.06	32.11	5.3	16.67	-6.8	12.1	-16.9	1.2	7.5	-5.9
Basilicata	34.46	4.5	20.91	35.69	5.0	19.52	3.6	10.9	-6.6	5.0	8.6	-3.3
Calabria	40.87	4.6	24.42	44.42	5.1	23.78	8.7	11.6	-2.6	6.5	8.5	-1.9
Sicily	28.33	4.5	17.21	28.27	5.1	15.11	-0.2	13.6	-12.2	4.3	9.3	-4.6
Sardinia	33.23	4.5	20.41	32.76	4.7	19.02	-1.4	5.8	-6.8	2.6	6.6	-3.7
Italy	**30.80**	**4.2**	**19.95**	**29.86**	**4.8**	**16.95**	**-3.0**	**14.1**	**-15.0**	**4.2**	**9.0**	**-4.4**
North	28.94	4.0	19.80	27.62	4.6	16.50	-4.6	14.5	-16.7	4.8	9.4	-4.1
Centre	29.58	4.2	19.40	26.86	4.7	15.62	-9.2	12.8	-19.5	2.2	8.6	-5.9
South and Islands	34.21	4.6	20.45	34.93	5.2	18.26	2.1	14.3	-10.7	4.5	8.8	-4.0

The data highlights, for pathologies that require the use of immunosuppressants and/or immunomodulating agents, a growing use of biotechnological medicines compared to chemically synthesized ones. Analysing the categories and active ingredients with the greatest impact in terms of both expenditure and consumption, it is clear that chronic inflammatory bowel diseases (IBD) and chronic inflammatory rheumatic diseases are those on which the most widely used drug therapies are focused. In the context of IBD, the increase in the consumption of ustekinumab and vedolizumab highlights how, in clinical practice, TNF-α inhibitors have been joined by interleukin inhibitors and anti-integrin drugs, although they are indicated in patients with inadequate response or intolerance to anti-TNF-α. These therapeutic options, however, may not be sufficient, especially in the latency phases of the pathologies and cause side effects, including the establishment of opportunistic infections due to interference in the immune response. Research is therefore focusing on the identification of new therapeutic strategies, ranging from the identification of new therapeutic targets (e.g. inhibition of lymphocyte migration in inflamed areas) to strategies for repairing the mucosa or modulating the intestinal microbiome, with the aim of restoring the integrity of the epithelial barrier and determining an improvement in the pathological condition. Even in the case of chronic inflammatory rheumatic diseases it is possible to highlight more recent therapeutic strategies aimed at reducing inflammation, which include the use of interleukin or Janus kinase inhibitors. In the case of this last category, however, it is important to remember that EMA has recommended a series of measures to minimise the risk of side effects linked to the use of the relevant drugs in chronic inflammatory disorders. Finally, from a technological point of view, there is a progressive increase in biobetter medicines, for which it will be necessary to evaluate the economic impact, against the advantages in terms of compliance and improvement in therapy management.

3.2 Cardiovascular system

Cardiovascular diseases are the main cause of death in the world, with about 18 million deaths every year, accounting for about 30% of the total, 85% of which are due to heart attack and stroke. The prevalence of these conditions is increasing in several countries, including Italy; this is partly attributable to the progressive increase in life expectancy, with an increasingly "elderly" and therefore "fragile" population, and to the prevalence of cardiovascular risk factors such as obesity, sedentary lifestyle, excessive stress, arterial hypertension, hypercholesterolemia, diabetes, smoking, alcohol.
In 2022, cardiovascular drugs represent the second therapeutic category with the highest public expenditure, accounting for 3,400 million euro and 13.7% of total public expenditure (Box. Main expenditure, consumption and exposure indices). The total per capita expenditure on these drugs was equal to 57.63 euro, of which 87.3% refers to the approved care regime (50.29 euro per capita). They are therefore the most widely dispensed drugs under approved care regime, with a slight increase in expenditure compared to the previous year (+1.6%); the purchase by public health facilities is significantly lower (7.34 euro per capita) despite a marked increase compared to the previous year (+13.3%) (Table 3.1).
Cardiovascular drugs are confirmed to be the most used: the consumption for this therapeutic category was equal to 505.32 DDD/1000 inhabitants per day, remaining substantially unchanged compared to the previous year (+0.8%), of which 96.5% of the total doses refers to the approved care regime (487.39 DDD/1000 inhabitants per day) (Table 3.2).
The analysis of the exposure profile by age group and gender confirms the constant increase in the use of cardiovascular drugs with increasing age for both genders, with a maximum prevalence recorded in people aged 75 years or older (90%). At the same time, the NHS per capita expenditure also increases with age, reaching 199.9 euro in males and 172.9 euro in females aged 75 or over.
With regard to the approved care regime (Table 3.9), the change in expenditure (+1.1%) was driven by the shift of prescription towards higher-cost specialties (mix effect: +1.3%), while both consumption and prices remain stable compared to the previous year (respectively +0.2% and -0.4%); the average DDD cost increased slightly by 0.9% compared to 2021. In 2022, HMG-CoA reductase inhibitors (statins) are confirmed as the active ingredients with the greatest use (82.3 DDD/1000 inhabitants per day) and expenditure per capita (8.15 euro), whose indicators remain unchanged compared to the previous year. The second most used category for this ATC is that of "unassociated" ACE inhibitors with a value equal to 80.4 DDD/1000 inhabitants per day, although there is a reduction in almost all the indicators considered (expenditure -4.5%, DDD -2.8%, prices -0.7%); while selective beta-blockers represent the second category with the highest per capita expenditure for this ATC (4.98 euro), showing an increase in expenditure and consumption equal to 2.2% and 1.2% respectively. The major changes in expenditure compared to 2021 are instead attributable to other combinations of angiotensin II receptor blockers (+36.8%) and to the combinations of various lipid-lowering drugs (+29.4%), which recorded an increase in consumption equal to 43.4% and 46.8% respectively. However, a trend in prescriptions towards lower cost specialties is observed (mix effect: -4.6% and -9.3%). Also in 2022, atorvastatin confirms as the molecule with the highest per capita expenditure (4.68 euro), increasing by 1.3% compared to the previous year, and also recording a 1.3% increase in consumption (Table

3.10). Atorvastatin represents 9.3% of approved care pharmaceutical expenditure for this category, followed by bisoprolol and omega 3, with per capita expenditure values equal to 2.82 and 2.15 euro respectively. Regarding consumption, the most used active ingredient is ramipril (61.5 DDD/1000 inhabitants per day), slightly decreasing compared to 2021 (-1.5%), while there was an increase in the ezetimibe/rosuvastatin combination (+69.0%) and the olmesartan/amlodipine combination (+11.2%).

Among the top 30 active ingredients for expenditure under approved care regime, atorvastatin records the highest figure (276.0 million), confirming the 1st rank for per capita expenditure (Table 3.11), remaining in second rank by consumption immediately after ramipril, with a value of 50.9 DDD (Table 3.17) and showing a reduced regional variability in terms of consumption (Table 3.18). The ezetimibe/rosuvastatin combination shows the greatest variation in per capita expenditure (+50.2%) due to the increase in its use, although there is a 11.2% reduction in the average cost per day of therapy, attributable to entry onto the market of equivalent medicines in recent years (Table 3.15). Compared to the previous year, among the first thirty active ingredients with the greatest reduction in expenditure under approved care regime, a third belongs to the cardiovascular system category and the first is represented by simvastatin which, with an expenditure equal to 1.36 euro per capita, records a reduction by 6.4% compared to 2021 (Table 3.16).

As regards cardiovascular medicines purchased directly by public health facilities (Table 3.19), per capita expenditure is equal to 7.34 euro, with a 12.8% increase compared to the previous year, due to the growth in consumption (+7.3%) despite the reduction in prices (-4.0%). The increase in expenditure compared to 2021 was therefore driven by a shift towards more expensive medicines (mix effect +9.4%). The average DDD cost consequently recorded a sharp increase by 5.1% compared to 2021.

Also in 2022, "Other lipid modifying substances", including PCSK-9 inhibitors, are the category with the highest expenditure per capita (2.35 euro) with a 40.8% increase; followed by the other combinations of angiotensin II receptor blockers (1.54 euro) and medicines used in the treatment of pulmonary arterial hypertension (1.37 euro), both with increases of 35.3% and 3.9% respectively (Table 3.19).

80% of the expenditure incurred by public health facilities for cardiovascular drugs relates five active ingredients: the sacubitril/valsartan combination, evolocumab, ranolazine, macitentan and alirocumab. The sacubitril/valsartan combination, used in the treatment of chronic symptomatic heart failure with reduced ejection fraction, represents the specialty with the highest per capita expenditure (1.54 euro), and records a significant increase of approximately 36% in consumption and expenditure; followed by the PCSK9 inhibitor monoclonal antibody, evolocumab, which records a 16.2% increase in expenditure (1.19 euro), which is explained by the significant increase in consumption (+50.3%) and the 8.6% reduction in the average DDD cost (Table 3.20). Alirocumab, together with evolocumab and sacubitril/valsartan, are among the top thirty active ingredients with the greatest variation in expenditure among the medicines purchased by public health facilities (Table 3.23), while ranolazine is among the top thirty active ingredients with the greatest reduction in expenditure (Table 3.24). Four active ingredients belonging to the cardiovascular system category are in the list of the first 30 medicines purchased by public health facilities with the lowest average cost per day of therapy: ranolazine (2.72 euro), valsartan/sacubitril (4.08 euro), alirocumab (7.84 euro) and evolocumab (11.97 euro) (Table 3.26). As for

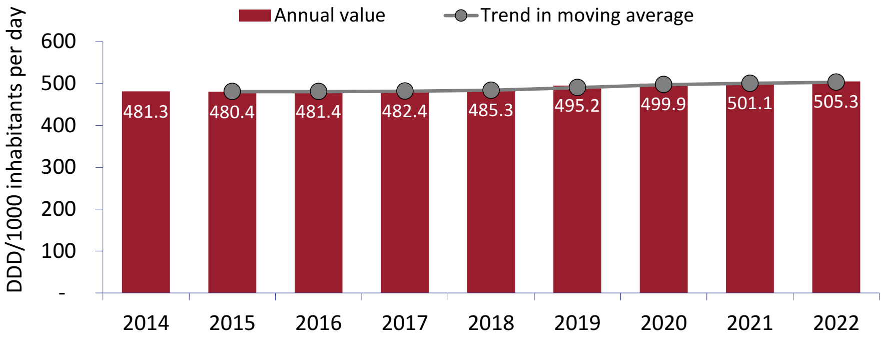
consumption, three active ingredients of the cardiovascular system category are in the list of the first 30 most consumed drugs purchased by public health facilities: furosemide 4.4 DDD, ramipril 1.6 DDD and atorvastatin 1.6 DDD (Table 3.27). The latter confirms itself as the third active ingredient with the highest expenditure and consumption for medicines dispensed under approved care regime and purchased by public health facilities in 2022, with expenditure amounting to 276.1 million euro (-0.2%, stable compared to 2021) (Table 3.28) and consumption equal to 52.4 DDD/1000 inhabitants per day (Table 3.29). Table 3.30 shows the different trend in terms of expenditure, consumption and average DDD cost between the approved care regime and direct purchases for drugs for hypertension and heart failure and for lipid-lowering drugs.
Analyses of the historical series of consumption and expenditure by active ingredient and by Region have been carried out for more information on the use of medicines belonging to the same therapeutic area. Such analyses focused on medicines for hypertension and heart failure and on lipid-lowering drugs (Tables 3.2.1a and following).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

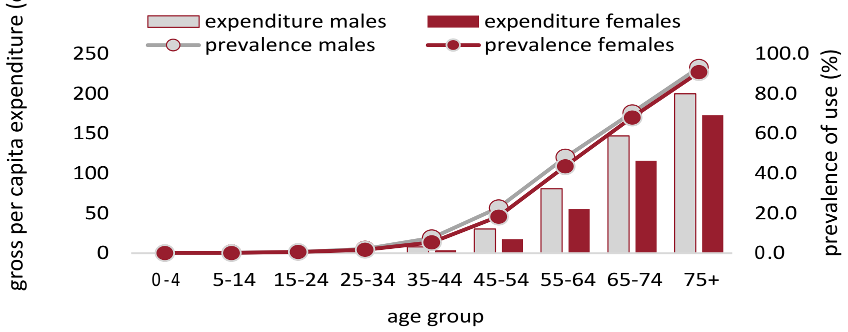
Cardiovascular system

Public expenditure* in EUR million (% over total)	**3,400.0**	**(13.7)**
Δ % 2022-2021		2.9
Regional range gross expenditure per capita:	39.1	73.1
DDD/1000 inhabitants per day* (% over total)	**505.3**	**(38.1)**
Δ % 2022-2021		0.8
Regional range DDD/1000 inhabitants per day	381.7	607.3

* *includes prescriptions under approved care regime and purchases by public health facilities*



Breakdown of prevalence of use and consumption under approved care regime and distribution on behalf by age and gender in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.1	0.3	0.2	0.4	0.4	0.4
5-14	0.1	0.1	0.1	0.9	0.7	0.8
15-24	0.4	0.3	0.4	3.8	2.5	3.2
25-34	1.6	0.9	1.3	14.3	7.7	11.0
35-44	8.0	3.9	6.0	71.2	35.9	53.5
45-54	30.2	17.5	23.8	278.0	166.4	221.6
55-64	80.8	55.6	67.8	743.5	515.1	625.9
65-74	147.1	116.0	130.6	1,339.6	1,054.4	1,188.9
75+	199.9	172.9	183.8	1,892.2	1,653.6	1,749.7

3.2.1 Medicines for hypertension and heart failure

- Consumption of medicines for hypertension and heart failure has been basically stable over the last nine years (CAGR -0.1%), recording a value of 373.5 DDD in 2022 and an average cost per day of therapy of 0.25 euros, with a 1.3% increase compared to the previous year (Figure 3.2.1a). The per capita expenditure for these drugs, equal to 34.64 euros, remains unchanged compared to 2021 (0.8%), although recording an average annual reduction rate of 0.8%, calculated from 2014 (Figure 3.2.1a and Table 3.2.1a).
- Beta blockers are the therapeutic category with the highest per capita expenditure (5.69 euros), showing a 1.4% increase compared to the previous year and an average cost per day of therapy of 0.33 euros, slightly higher than the value observed for the entire therapeutic class (0.25 euros). DDD/1000 inhabitants per day were 46.6, increasing by 2% compared to 2021. Analysing the trend of expenditure and consumption for this subgroup over time, an annual increase can be noted, over the period 2014-2022, by respectively 2.5% and 1.4% (Figure 3.2.1b). ACE inhibitors remain the category with the highest consumption (82.2 DDD/1000 inhabitants per day) and with the lowest average DDD cost (0.12 euros). The per capita expenditure for this class of drugs was instead 3.57 euros, albeit with a tendential reduction over time in all the values considered (CAGR expenditure -2.8%, CAGR consumption -1.2%).
- Bisoprolol is the substance with the highest per capita expenditure, recording a value of 2.83 euros, increasing by 3.9% compared to the previous year, while ramipril recorded the highest value of DDD/1000 inhabitants per day (63.1). Particularly interesting is the increase in both expenditure and consumption (+36%) of the sacubitril/valsartan combination, the only drug belonging to the category of angiotensin II receptor blockers in combination with inhibitors of neprilysin, approved for the treatment of chronic symptomatic heart failure with reduced ejection fraction. The olmesartan/amplodipine combination increases by more than 10% in terms of expenditure and consumption, in line with what was observed in 2021.
- The analysis of regional consumption (Table 3.2.1b) shows that in 2022 Umbria is the Region reporting the highest value (481.8 DDD/1000 inhabitants per day), while the Province of Bolzano is confirmed to have the lowest value (277.2 DDD/1000 inhabitants per day). Campania, Calabria and Basilicata, although with lower consumption than other regions (380-400 DDD), show the highest average cost per DDD (0.29 and 0.30 euros). Compared to the national average, the Northern Regions showed a lower consumption (359.0 compared to 373.5 DDD/1000 inhabitants per day), while those of the Centre and the South have higher values, equal to 384.0 and 387.7 DDD/1000 inhabitants per day, respectively. There is no particular change from 2021 for all other indicators (Table 3.2.1b).

Figure 3.2.1a Medicines for hypertension and heart failure, temporal trend (2014-2021) of consumption and average cost per day of therapy

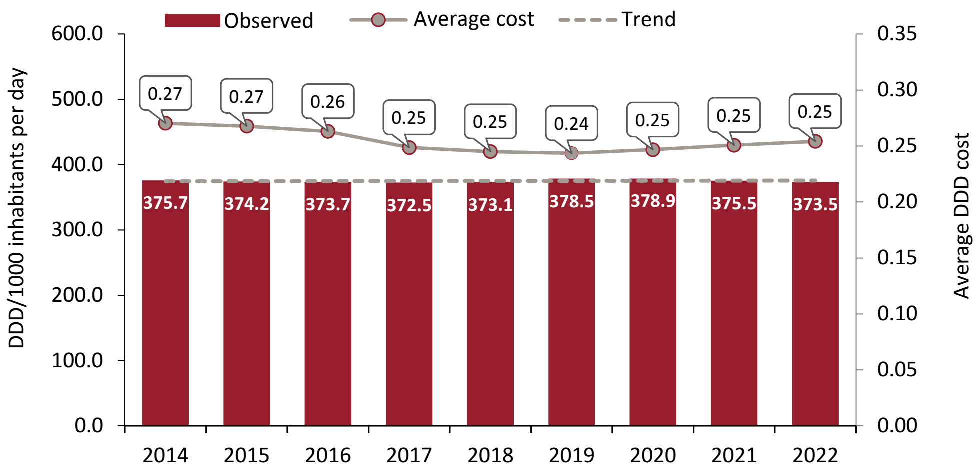


Table 3.2.1a Medicines for hypertension and heart failure, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average cost DDD	Δ % 22-21
Beta blockers	5.69	1.4	2.5	46.6	1.8	1.4	0.33	-0.4
Angiotensin II antagonists	4.92	0.8	-2.4	58.5	0.2	0.5	0.23	0.6
Calcium channel blockers (dihydropyridines)	4.10	-2.0	-1.7	50.6	-1.1	-0.8	0.22	-1.0
Angiotensin II antagonists and diuretics (combinations)	3.78	-3.0	-6.7	31.8	-2.2	-2.7	0.33	-0.8
ACE inhibitors	3.57	-4.0	-2.8	82.2	-2.4	-1.2	0.12	-1.7
ACE inhibitors and diuretics (combinations)	2.37	-4.9	-5.1	18.6	-4.4	-3.6	0.35	-0.6
Angiotensin II antagonists and neprilysin inhibitors	2.06	36.2	-	1.2	36.0	-	4.58	0.1
ACE inhibitors and calcium channel blockers (combinations)	1.64	-1.3	3.5	12.2	-0.1	7.9	0.37	-1.2
Angiotensin II antagonists and and calcium channel blockers (combinations)	1.53	11.7	6.1	10.5	12.2	18.1	0.40	-0.4
Alpha blockers	1.25	-1.3	-0.1	7.8	-0.8	-0.1	0.44	-0.5
Diuretics with greater diuretic action alone or in combination with potassium-sparing diuretics	0.99	-3.6	-0.9	29.5	-1.6	-0.1	0.09	-2.0
Beta blockers and diuretics (combinations)	0.70	0.1	0.9	7.6	-0.3	2.2	0.25	0.4
ACE inhibitors, calcium channel blockers and diuretics	0.64	4.2	-	4.7	12.1	-	0.37	-7.1
Potassium-sparing diuretics	0.60	3.5	1.4	3.7	2.8	0.6	0.45	0.7
Calcium channel blockers (not dihydropyridines)	0.26	-8.4	-8.6	1.8	-8.2	-8.1	0.39	-0.2
Thiazides and similars (including combinations)	0.21	-5.1	-3.9	3.6	-4.6	-5.2	0.16	-0.5
Imidazoline receptor agonists	0.19	-6.9	-7.2	1.3	-6.9	-5.8	0.39	0.0
ACE inhibitors, other combinations	0.13	10.9	-	1.0	10.8	-	0.33	0.0
Aliskiren plain or in combination	0.03	-34.8	-19.6	0.1	-31.4	-18.9	0.85	-4.9
Alpha-2 adrenergic receptor agonists	0.01	19.4	-3.8	<0.05	20.4	-3.8	0.35	-0.8
Medicines for hypertension and heart failure	**34.64**	**0.8**	**-0.8**	**373.5**	**-0.5**	**-0.1**	**0.25**	**1.3**
bisoprolol	2.83	3.9	6.3	13.1	3.8	6.0	0.59	0.1
valsartan/sacubitril	2.06	36.2	-	1.2	36.0	-	4.58	0.1
ramipril	1.95	-3.3	-0.7	63.1	-1.5	0.2	0.08	-1.8
olmesartan	1.92	7.7	-2.0	16.7	7.7	10.9	0.31	0.0
amlodipine	1.60	-1.2	0.0	29.0	-0.1	0.3	0.15	-1.1
nebivolol	1.56	1.8	2.4	17.0	2.1	3.0	0.25	-0.3
olmesartan/amlodipine	1.45	10.9	5.5	9.9	11.1	17.3	0.40	-0.2
olmesartan/hydrochlorothiazide	1.26	3.3	-5.9	10.4	3.8	5.9	0.33	-0.5
doxazosin	1.23	-1.3	-0.1	7.7	-0.9	-0.1	0.44	-0.5
barnidipine	0.87	-1.6	0.5	4.9	0.7	1.0	0.49	-2.3

Figure 3.2.1b Medicines for hypertension and heart failure, temporal trend (2014-2022) of consumption and average cost per day of therapy

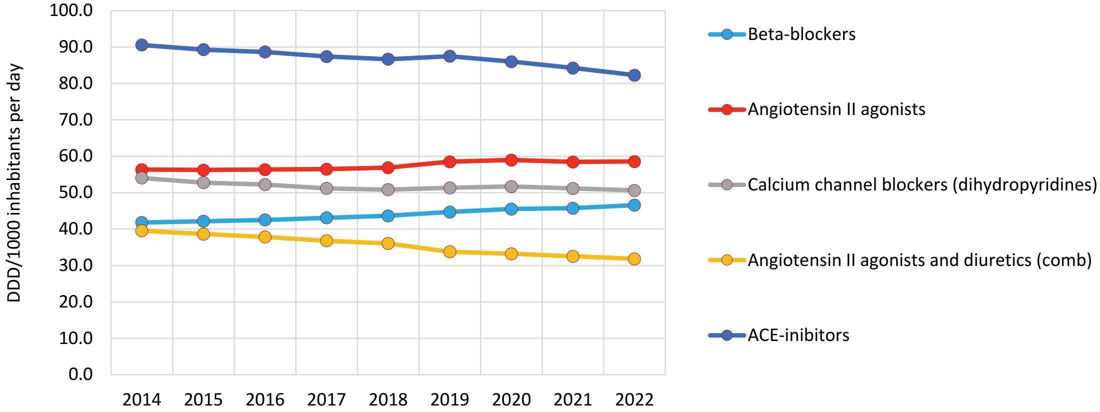


Table 3.2.1b Medicines for hypertension and heart failure, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost DDD
Piedmont	30.94	361.7	0.23	31.00	365.7	0.23	0.2	1.1	-0.9	-1.5	0.0	-1.5
Valle d'Aosta	27.71	307.5	0.25	28.66	307.0	0.26	3.4	-0.1	3.6	-1.7	-1.4	-0.3
Lombardy	31.24	342.9	0.25	31.87	341.2	0.26	2.0	-0.5	2.5	-0.8	-0.6	-0.3
A.P. of Bolzano	23.81	277.2	0.24	23.97	277.2	0.24	0.7	0.0	0.7	-2.0	-1.0	-1.0
A.P. of of Trento	26.52	326.0	0.22	26.75	325.5	0.23	0.9	-0.2	1.0	-1.5	-0.3	-1.1
Veneto	30.54	362.0	0.23	30.65	360.1	0.23	0.4	-0.5	0.9	-1.7	-0.9	-0.8
Friuli V.G.	31.07	373.7	0.23	31.22	372.5	0.23	0.5	-0.3	0.8	-1.7	-0.4	-1.3
Liguria	30.50	328.0	0.25	30.88	326.5	0.26	1.3	-0.5	1.7	-1.8	-0.8	-1.0
Emilia R.	32.82	412.1	0.22	33.29	413.2	0.22	1.4	0.3	1.1	-0.2	0.0	-0.2
Tuscany	30.22	380.5	0.22	30.46	377.3	0.22	0.8	-0.8	1.6	-0.6	0.1	-0.7
Umbria	39.49	488.2	0.22	39.39	481.8	0.22	-0.3	-1.3	1.1	0.2	0.5	-0.2
Marche	36.11	377.6	0.26	36.55	376.8	0.27	1.2	-0.2	1.4	-0.6	0.1	-0.7
Lazio	36.50	380.3	0.26	36.73	375.0	0.27	0.6	-1.4	2.1	-0.6	0.0	-0.6
Abruzzo	36.35	366.2	0.27	37.00	366.7	0.28	1.8	0.1	1.7	-0.2	0.3	-0.6
Molise	37.33	374.1	0.27	38.05	375.5	0.28	1.9	0.4	1.6	-1.0	0.3	-1.3
Campania	41.64	406.3	0.28	42.11	404.3	0.29	1.1	-0.5	1.6	-0.1	0.8	-1.0
Puglia	38.63	386.4	0.27	38.54	381.3	0.28	-0.2	-1.3	1.1	-1.2	-0.2	-1.0
Basilicata	40.45	381.3	0.29	41.45	383.4	0.30	2.5	0.5	1.9	0.5	1.0	-0.5
Calabria	40.26	390.9	0.28	40.29	383.8	0.29	0.1	-1.8	1.9	-0.7	0.0	-0.6
Sicily	39.06	404.9	0.26	38.92	401.6	0.27	-0.3	-0.8	0.5	-0.5	0.6	-1.1
Sardinia	31.59	339.0	0.26	31.51	335.8	0.26	-0.3	-0.9	0.7	-2.4	-0.6	-1.8
Italy	**34.37**	**375.5**	**0.25**	**34.64**	**373.5**	**0.25**	**0.8**	**-0.5**	**1.3**	**-0.8**	**-0.1**	**-0.8**
North	31.03	359.3	0.24	31.40	359.0	0.24	1.2	-0.1	1.3	-1.1	-0.4	-0.7
Centre	34.65	388.2	0.24	34.89	384.0	0.25	0.7	-1.1	1.8	-0.5	0.1	-0.6
South and Islands	38.97	390.9	0.27	39.13	387.7	0.28	0.4	-0.8	1.2	-0.7	0.3	-1.0

Exposure and adherence in population

- Health Card data were collected to perform an analysis aimed at estimating exposure to medication for the treatment of hypertension and heart failure in the general population, as well as adherence and persistence to treatment. In 2022, high exposure is observed in the over-75 age group, with higher prevalence and consumption in males (Figure 3.2.1b).
- In 2022, about a quarter of the Italian population (26.6%) used these drugs, with a higher prevalence in the South and the Islands (28.3%) and in the Centre (27.2%), than in the North (25.1%) (Table 3.2.1c). There are no major differences in median age, and overall, there is a higher prevalence of use in women.
- Umbria appears to be the region with the highest prevalence of use (30.9%), which is about 13 percentage points higher than the Province of Bolzano, which has the lowest prevalence (18.2%). Each individual uses about 489 doses per year, indicating the simultaneous intake of several molecules throughout the year. Half of the exposed population is treated with a number of DDDs greater than 364, while only 3% of users received a single prescription.
- The highest-exposure category is beta-blockers (11%), which, however, show a median duration of therapy of only 3.5 months (98 days), probably explained by the indication for the treatment of heart failure rather than hypertension. Sartans, dihydropyridine calcium channel blockers, and ACE inhibitors are the categories having a prevalence higher than 5%. The average cost per user of sacubitril/valsartan is the highest in the category (1,124 euros) (Table 3.2.1d). Interestingly, ACE inhibitors have a 30% lower average cost per user than sartans, whereas when considering the combination of these two categories with diuretics or calcium channel blockers, the costs become overlapping.
- As for adherence and persistence analyses, exposure data refer to a cohort of new users over 45 years old, who were followed-up for one year. The study population includes a total of 273,179 new users, with a median age of 63 years (IQR 55-72) and a greater proportion of women than men (52.4% vs 47.6%).
- The percentage of people with high and low adherence to treatment with drugs for hypertension was 52.4% and 18.2%, respectively (Table 3.2.1e). Low adherence tends to increase with age, recording the highest value in people aged over 85 (25.2%) and in women compared to men (21.2% and 14.8% respectively). Stratifying by age and geographical area, the highest percentage of low adherence was observed in users aged over 85 living in Southern Italy (29.5%). High adherence, on the other hand, tends to decrease with increasing age, showing a greater value in the 55-64 age group (54.1%) - until it decreases to 40.9% in the over-80s - and being higher in men than women (57.3% and 47.9%, respectively). Users living in Northern Italy and aged between 45 and 54 years showed the greatest percentage value of high adherence (56.1%).
- Analysing the persistence to medicines for hypertension and heart failure (Table 3.2.1f. and Figure 3.2.1d), it can be highlighted that about half of the new users are found to be persistent to treatment after one year (52%). This trend is quite similar by geographic area (North 51.7%, Centre 53.6% and South 51.8%), but it drops to 41.4% in users over 85 and is lower in women (47.9%) than in men (56.4%). By evaluating the persistence

for different time intervals, the percentage of persistent patients decreases as the observation time increases, passing from 52.3% at 12 months from the beginning of the treatment to 33.3% at 36 months from the beginning of the treatment (Table 3.2.1g and Figure 3.2.1e). There are no differences between geographic areas, but stratifying by age it is apparent that in the 75+ age groups there is a sharp reduction in persistence, particularly at 36 months, where only 29.4% of those aged 75-84 remain persistent. This percentage drops to 23.4% in those over the age of 85. In addition, at 36 months, men are more persistent than women, probably due to the presence of caregivers who are more attentive to therapy maintenance.

Figure 3.2.1c Distribution of prevalence of use and consumption of medicines for hypertension and heart failure under approved care regime and "on behalf" distribution (year 2022)

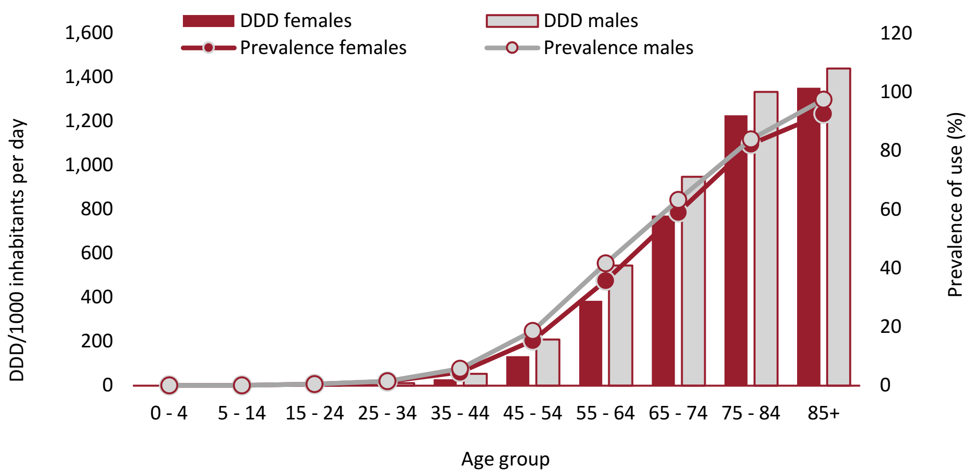


Table 3.2.1c Exposure and duration of therapy with medicines for hypertension and heart failure by Region under approved care regime and "on behalf" distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Piedmont	26.3	28.1	27.2	72	116.50	481.2	364.0	2.9
Valle d'Aosta	22.7	24.1	23.4	71	120.55	458.0	352.9	2.5
Lombardy	23.3	24.1	23.8	71	125.58	485.9	360.0	2.3
A.P. of Bolzano	17.8	18.5	18.2	72	120.39	487.2	360.5	2.6
A.P. of Trento	22.2	22.6	22.4	71	112.03	485.5	364.0	2.5
Veneto	24.7	24.8	24.8	71	120.97	508.4	378.5	2.4
Friuli V.G.	25.9	26.6	26.3	72	124.11	525.2	392.0	2.5
Liguria	26.5	28.3	27.5	73	119.35	449.1	339.5	3.4
Emilia R.	25.4	27.0	26.2	71	117.75	530.2	392.0	2.7
Tuscany	25.8	27.4	26.6	72	114.65	514.8	385.0	4.3
Umbria	29.9	31.8	30.9	71	130.79	571.3	409.5	3.3
Marche	27.2	28.8	28.0	72	130.43	487.9	372.3	3.0
Lazio	26.1	27.5	26.8	70	132.37	491.7	378.0	3.0
Abruzzo	27.6	29.9	28.8	70	121.06	447.3	360.0	3.4
Molise	29.0	32.1	30.6	70	124.54	447.7	360.0	3.0
Campania	27.0	28.7	27.9	67	136.24	477.3	364.0	2.7
Puglia	28.0	30.4	29.2	70	120.81	451.5	360.0	2.9
Basilicata	28.3	31.7	30.0	69	136.15	460.0	364.0	3.6
Calabria	27.9	30.4	29.2	69	132.31	458.9	364.0	3.3
Sicily	26.4	29.4	27.9	70	128.05	495.9	374.5	3.3
Sardinia	25.6	27.5	26.5	71	119.70	461.9	360.0	3.1
Italy	**25.8**	**27.4**	**26.6**	**71**	**124.85**	**488.7**	**364.0**	**2.9**
North	24.5	25.6	25.1	71	121.13	496.0	364.0	2.6
Centre	26.4	27.9	27.2	71	126.57	504.9	384.0	3.4
South and Islands	27.1	29.5	28.3	69	128.38	470.7	364.0	3.1

Table 3.2.1d Exposure and duration of therapy with medicines for hypertension and heart failure by subgroup under approved care regime and "on behalf" distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Beta blockers	10.3	12.0	11.2	72	49.10	145.4	98.0	4.6
Angiotensin II antagonists	5.7	6.0	5.8	71	82.45	355.1	308.0	5.6
Calcium channel blockers (dihydropyridines)	5.7	5.5	5.6	74	71.09	315.4	308.0	8.3
Angiotensin II antagonists and diuretics (combinations)	3.6	4.7	4.2	73	88.85	272.2	308.0	4.1
ACE inhibitors	6.7	5.6	6.1	71	56.90	469.2	336.0	5.7
ACE inhibitors and diuretics (combinations)	2.4	2.8	2.6	72	89.33	256.2	280.0	3.8
Angiotensin II antagonists and neprilysin inhibitors	0.2	0.1	0.1	72	1,124.51	236.7	252.0	4.0
ACE inhibitors and calcium channel blockers (combinations)	1.9	1.3	1.6	68	99.77	270.2	300.0	5.4
Angiotensin II antagonists and calcium channel blockers	1.7	1.2	1.4	67	103.51	259.0	280.0	6.5
Alpha blockers	1.5	1.2	1.4	74	88.35	197.1	180.0	8.2
High-ceiling diuretics, alone or in combination with potassium-sparing agents	4.1	5.3	4.7	80	19.22	189.1	112.5	18.8
Beta blockers and diuretics	0.7	1.4	1.1	67	64.42	254.3	280.0	4.8
ACE inhibitors, calcium channel blockers and diuretics	0.8	0.6	0.7	69	95.15	256.5	300.0	7.1
Potassium-sparing diuretics	1.4	1.3	1.3	78	41.19	90.3	64.0	12.4
Calcium channel blockers (not dihydropyridines)	0.3	0.4	0.3	76	72.30	182.6	168.0	4.9
Thiazides and similars (including combinations)	0.6	1.0	0.8	74	25.50	155.0	120.0	17.5
Imidazoline receptor agonists	0.2	0.2	0.2	76	107.52	272.7	244.4	6.8
ACE inhibitors, other combinations	0.2	0.2	0.2	65	78.74	235.8	240.0	7.2
Aliskiren plain or in combination	0.01	0.01	0.01	72	286.61	337.3	336.0	7.5
Alpha-2 adrenergic agonists	<0,05	0.02	0.01	40	35.31	95.9	45.0	28.3
Medicines for hypertension and heart failure	**25.8**	**27.4**	**26.6**	**71**	**124.85**	**488.7**	**364.0**	**2.9**

Table 3.2.1e Indicators of adherence to treatment with drugs for hypertension and heart failure in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Low adherence*											
	2019	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**	**2019**	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**
	Total N=273.179						**North N=127.331**					
45-54 years	16.4	16.3	16.9	17.1	1	4	15.1	14.9	15.5	15.9	3	5
55-64 years	16.1	16.5	16.9	16.9	0	5	15.0	15.6	15.9	15.6	-2	4
65-74 years	17.7	18.2	17.9	18.2	2	3	16.7	16.7	16.7	16.8	0	1
75-84 years	20.2	21.1	20.2	20.5	1	2	18.8	19.7	18.5	18.9	2	1
≥ 85 years	25.0	25.8	23.7	25.2	6	1	22.8	23.3	21.8	22.3	2	-2
Women	20.5	20.9	20.8	21.2	2	4	19.1	19.4	19.4	19.6	1	3
Men	14.7	15.1	14.8	14.9	1	1	13.9	14.2	13.8	13.9	1	0
Total	**17.7**	**18.1**	**18.0**	**18.2**	**1**	**3**	**16.6**	**16.9**	**16.8**	**16.9**	**1**	**2**
	Centre N=56.128						**South N=89.720**					
45-54 years	16.6	16.9	17.3	17.1	-1	3	17.6	17.6	18.3	18.4	1	5
55-64 years	16.0	16.7	17.0	17.1	1	7	17.4	17.6	18.0	18.5	3	6
65-74 years	17.5	19.2	18.4	18.7	2	7	19.2	19.7	19.3	20.0	4	4
75-84 years	20.8	21.5	21.3	21.4	0	3	22.2	23.4	22.6	23.1	2	4
≥ 85 years	25.7	27.3	24.3	26.4	9	3	28.2	28.8	26.5	29.5	11	5
Women	20.8	22.2	21.5	22.1	3	6	22.1	22.2	22.3	23.0	3	4
Men	14.7	15.1	15.1	14.8	-2	1	15.8	16.3	16.0	16.4	3	4
Total	**18.0**	**18.8**	**18.5**	**18.6**	**1**	**4**	**19.1**	**19.4**	**19.3**	**19.9**	**3**	**4**

continued

Table 3.2.1e – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=273.179						North N=127.331					
45-54 years	54.8	54.9	54.0	54.0	-1	-1	56.7	56.8	55.6	55.1	-3	-1
55-64 years	55.4	54.6	54.7	54.1	-2	-2	56.5	56.0	55.9	55.2	-2	-1
65-74 years	53.9	53.0	53.9	53.0	-2	-2	54.6	54.3	54.5	54.0	-1	-1
75-84 years	49.5	48.2	49.7	49.1	-1	-1	50.6	49.5	51.1	50.4	0	-1
≥ 85 years	41.0	40.9	42.7	40.9	0	0	42.1	43.0	44.6	43.8	4	-2
Women	48.7	48.1	48.6	47.9	-2	-2	49.9	49.5	49.9	49.4	-1	-1
Men	58.0	57.3	57.8	57.3	-1	-1	58.7	58.5	58.6	58.0	-1	-1
Total	**53.1**	**52.5**	**53.0**	**52.4**	**-1**	**-1**	**54.1**	**53.8**	**54.0**	**53.5**	**-1**	**-1**
	Centre N=56.128						South N=89.720					
45-54 years	55.8	55.9	55.5	56.1	1	1	52.3	52.2	51.3	51.4	-2	-2
55-64 years	56.7	55.7	56.4	55.8	-2	-2	53.5	52.2	52.1	51.6	-3	-3
65-74 years	55.9	53.5	54.9	55.0	-2	-2	51.8	51.1	52.2	50.1	-3	-3
75-84 years	50.0	48.7	50.2	50.0	0	0	47.3	45.6	46.5	46.1	-2	-2
≥ 85 years	41.2	39.5	42.5	40.2	-2	-2	39.0	38.8	39.6	36.2	-7	-7
Women	49.5	48.4	49.4	49.4	0	0	46.7	46.1	46.3	45.0	-4	-4
Men	59.5	58.2	59.4	59.1	-1	-1	56.2	55.2	55.6	55.2	-2	-2
Total	**54.1**	**53.0**	**54.1**	**53.9**	**0**	**0**	**51.2**	**50.5**	**50.8**	**49.9**	**-3**	**-3**

*Adherence to treatment was assessed during the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to the statistical methods).
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of subjects with low/high adherence related to the specified category.
Median follow-up time (IQR): 327 (277-348).

Table 3.2.1f Persistence after one year of treatment with medicines for hypertension and heart failure in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Persistence after 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=273,179						North N=127,331					
45-54 years	55.0	54.6	54.3	53.7	-1	-2	55.2	55.4	54.9	53.5	-3	-3
55-64 years	55.4	54.7	55.1	54.1	-2	-2	55.4	54.9	55.5	53.8	-3	-3
65-74 years	53.5	53.0	53.9	52.2	-3	-3	53.1	53.1	53.8	51.8	-4	-2
75-84 years	49.0	47.5	48.8	47.9	-2	-2	49.0	48.0	49.6	48.0	-3	-2
≥ 85 years	41.1	40.5	42.8	41.4	-3	1	41.0	41.4	44.2	42.9	-3	4
Women	48.9	48.2	49.1	47.9	-2	-2	48.7	48.4	49.4	47.7	-3	-2
Men	57.5	56.9	57.5	56.4	-2	-2	57.1	57.0	57.8	56.1	-3	-2
Total	**53.0**	**52.3**	**53.1**	**52.0**	**-2**	**-2**	**52.7**	**52.5**	**53.4**	**51.7**	**-3**	**-2**
	Centre N=56.128						South N=89.720					
45-54 years	55.4	54.6	55.7	55.7	0	0	54.6	53.7	52.9	52.9	0	-3
55-64 years	56.4	54.9	56.6	55.6	-2	-1	55.0	54.3	53.8	53.5	-1	-3
65-74 years	54.7	52.8	55.6	54.4	-2	-1	53.5	52.9	52.9	51.3	-3	-4
75-84 years	49.4	47.8	50.1	48.9	-2	-1	48.6	46.4	46.2	46.8	1	-4
≥ 85 years	40.9	40.0	42.9	41.4	-4	1	41.4	39.5	40.1	38.8	-3	-6
Women	49.3	47.7	50.3	49.5	-2	0	48.9	48.1	47.9	47.3	-1	-3
Men	58.4	57.3	59.0	58.2	-1	0	57.6	56.4	56.2	55.8	-1	-3
Total	**53.5**	**52.2**	**54.4**	**53.6**	**-2**	**0**	**53.0**	**52.1**	**51.9**	**51.4**	**-1**	**-3**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to statistical methods)

Figure 3.2.1d Time (in days) to discontinuation of treatment with medicines for hypertension and heart failure in the population aged ≥45 years stratified by geographic area; the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)

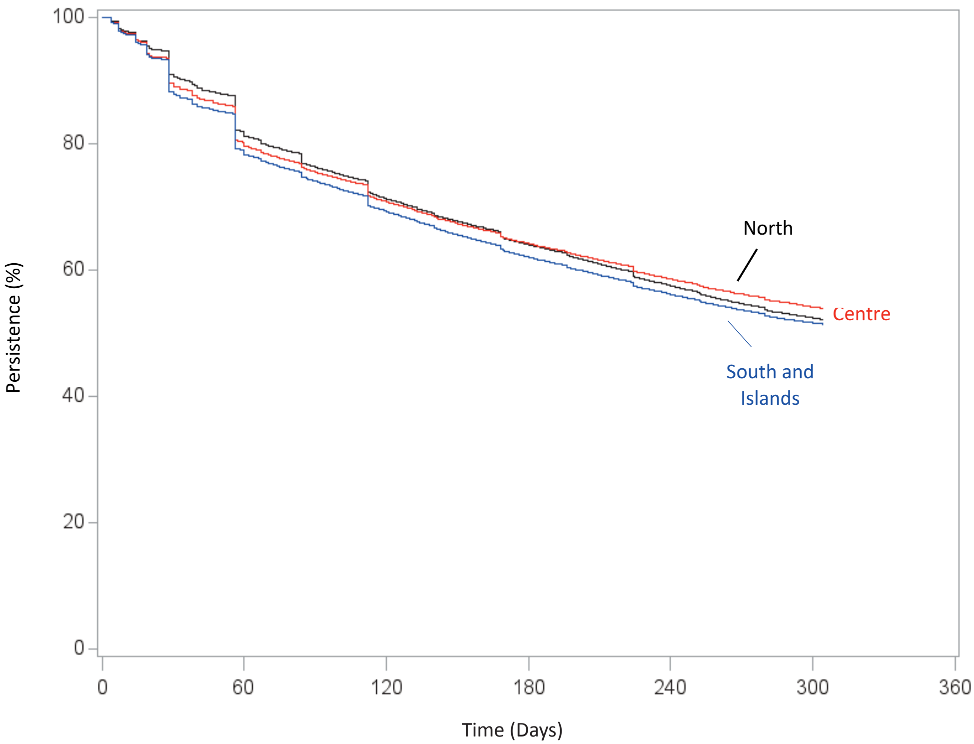
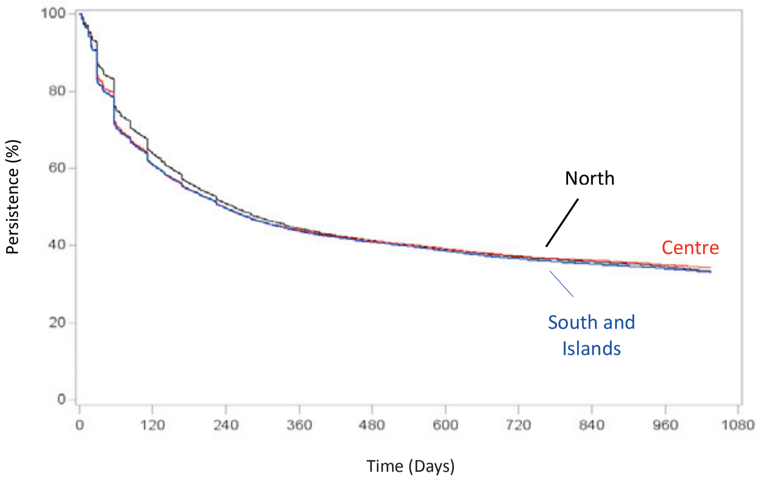


Table 3.2.1g Persistence to treatment with medicines for hypertension and heart failure in the population aged ≥45 years with 3 years of follow-up

Persistence (%)	Total N=276.708			North N=124.032			Centre N=57.588			South N=95.088		
	12 months	24 months	36 months	12 months	24 months	36 months	12 months	24 months	36 months	12 months	24 months	36 months
45-54 years	55.4	48.5	34.5	56.7	49.6	34.5	55.4	49.1	35.2	54.0	47.0	34.1
55-64 years	54.8	48.0	35.1	55.2	48.2	34.8	55.0	48.7	36.2	54.3	47.4	34.8
65-74 years	52.2	45.3	33.9	52.3	45.3	33.7	52.0	45.8	34.4	52.1	45.1	33.9
75-84 years	46.5	39.7	29.4	47.1	40.0	29.8	47.2	40.4	30.0	45.1	38.4	28.1
≥ 85 years	40.2	32.9	23.4	41.1	33.6	23.6	39.6	32.0	23.7	39.1	32.6	22.7
Women	47.9	40.8	29.3	48.2	40.9	29.1	47.6	41.0	29.9	47.8	40.6	29.2
Men	57.1	50.4	37.8	57.4	50.6	37.6	57.5	51.2	38.6	56.4	49.8	37.7
Total	**52.3**	**45.4**	**33.3**	**52.6**	**45.6**	**33.1**	**52.2**	**45.8**	**34.0**	**51.9**	**45.0**	**33.2**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions during the first year of treatment. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to the statistical methods).
N: refers to new users, who received a first prescription in the period 01/10/2019-31/12/2019, not treated in the previous months starting from 01/01/2019 and followed up for 3 years

Figure 3.2.1e Time (in days) to discontinuation of treatment with medicines for hypetension after 3 years of follow-up in the population aged ≥45 years with at least 2 prescriptions in the first year of treatment, stratified by geographical area. Curves are adjusted by gender and age (the Cox model was used to estimate persistence curves)



Consumption of drugs for hypertension and heart failure appears stable over the last nine years. Almost all the most used categories recorded a stable or slightly reduced consumption compared to 2021, with the exception of the combination of angiotensin II receptor antagonists and neprilysin inhibitors, and the combination of antagonists of the angiotensin II receptor and calcium channel blockers, both of which recorded an increase.

ACE inhibitors, and ramipril in particular, are confirmed as the drugs with the highest consumption and the lowest average cost per day of therapy, while the sacubitril/valsartan combination, used for symptomatic chronic heart failure with reduced ejection fraction, has seen a significant increase in spending and consumption, and the highest average cost per day of therapy and per user in the entire category, as the only drug in the category to be placed on the market in recent years, in a clinical setting characterized by unmet therapeutic need. Beta-blockers, although registering lower consumption than ACE inhibitors, represent the class with the highest prevalence of use and per capita expenditure; bisoprolol represents the most widely used drug in the class, a phenomenon likely attributable to the greater tolerability of the active ingredient, the wide possibility of titrating the dose, and the possibility of administration in a single daily dose, all factors that may promote greater patient compliance with therapy.

The data relating to DDD per user confirms the tendency by the Italian doctors to use combinations of different drugs to achieve the therapeutic target. Since antihypertensive drugs, as well as heart failure drugs, interfere with various synergistic pathophysiological mechanisms, the combined strategy is associated with greater efficacy in reducing cardiovascular events, while allowing the dosage of individual active ingredients to be reduced, minimizing potential adverse events.

The prevalence of use increases with increasing age, reaching nearly 100% in males older than 85 years. This trend could be partially explained by the greater fragility of the elderly population, generally undergoing polytherapy which makes them more frequently at risk of adverse drug reactions.

Wide regional variability in consumption is confirmed, which cannot be fully explained by geographic differences in the prevalence of hypertension and heart failure, but rather by a different prescriptive attitude at the regional level. This variability is also confirmed, albeit to a lesser extent, in treatment adherence, which tends to decrease as age increases, registering the lowest values in the over-85s living in the South. Moreover, only half of new users nationwide are found to be persistent on treatment one year later, with no significant differences between geographic areas. Older age, frailty status, comorbidities as well as the number of medications taken, and suboptimal medical follow-up probably contribute to the poor adherence and persistence to therapies observed with this drug category.

3.2.2 Lipid-lowering medicines

- Consumption of lipid-lowering drugs has shown a 47% increase over the years, moving from 77.2 DDD/1000 inhabitants per day in 2014 to 113.8 in 2022 (CAGR +5%). The average DDD cost, on the other hand, recorded a 27% decrease, moving from 0.59 euros in 2014 to 0.43 in 2022 (Figure 3.2.2a). The per capita expenditure value for these drugs was 17.72 euros, with a 9.9% increase compared to the previous year, the value of CAGR shows a 0.8% increase in the last 9 years (Table 3.2.2a).
- Statins not in combination with other molecules are the therapeutic category with the highest per capita expenditure and consumption (8.15 euros and 84,1 DDD), stable compared to the previous year, and an average DDD cost lower than the value calculated for the entire class of lipid-lowering drugs (0.27 euros). The trend in expenditure and consumption values for this subgroup over the last nine years shows an annual increase of 2.7% (Figure 3.3.2b). Ezetimibe in combination, on the other hand, represents the second category with the highest expenditure, recording a value of 2.91 euros, up 29.7% compared to the previous year. For this class, an equally important increase was observed in terms of consumption (+47%), which stands at 16.8 DDD/1000 inhabitants per day. Particularly interesting is the reduction in the average cost per day of ezetimibe therapy, especially in combination (-13.3%), probably attributable to patent expiries in recent years. PCSK-9 inhibitors, which have been on the market since 2015 and have a good efficacy and safety profile, continue to increase in terms of both expenditure (€ 42.3) and consumption (55.7 DDD), ranking third in terms of average cost per DDD. Since several studies in Italy have estimated an important proportion of subjects potentially eligible for treatment, it is appropriate to continue monitoring activities to assess prescriptive appropriateness and the impact on pharmaceutical spending.
- Atorvastatin is the active ingredient with the highest per capita expenditure (4.68 euros), up 1.3% compared to 2021, and 5.4% in the last nine years; however, it recorded the lowest average DDD cost, equal to 0.24 euros. The consumption value was 52.4 DDD/1000 inhabitants per day, a 1.5% increase compared to the previous year. The monoclonal antibodies evolocumab and alirocumab, which bind to proprotein convertase subtilisin/kexin type 9 (PCSK9), recorded the highest average DDD values of respectively 11.97 euros and 7.84 euros; they are among the top ten active ingredients per annual expenditure. The ezetimibe/rosuvastatin combination has the largest increase in consumption (+69%) (Table 3.2.2a).
- In 2022 Campania recorded the highest value in terms of consumption, with 130 DDD/1000 inhabitants per day, while Valle d'Aosta recorded the lowest value, equal to 71 DDD (Table 3.2.2b). In general, the consumption data of the Regions of the Centre is aligned with the national value, with 112.1 DDD/1000 inhabitants per day. The North showed a lower dose consumption (108.6 DDD/1000 inhabitants per day), while the South showed a higher value (122.3 DDD). Marche, Friuli Venezia Giulia and Emilia Romagna consumed the greatest quantities and at the lowest cost; Sicily and Sardinia, on the other hand, recorded an average DDD cost in line with the national value, but a higher consumption.

Figure 3.2.2a Lipid-lowering medicines, temporal trend 2014-2022 of consumption and average cost per day of therapy

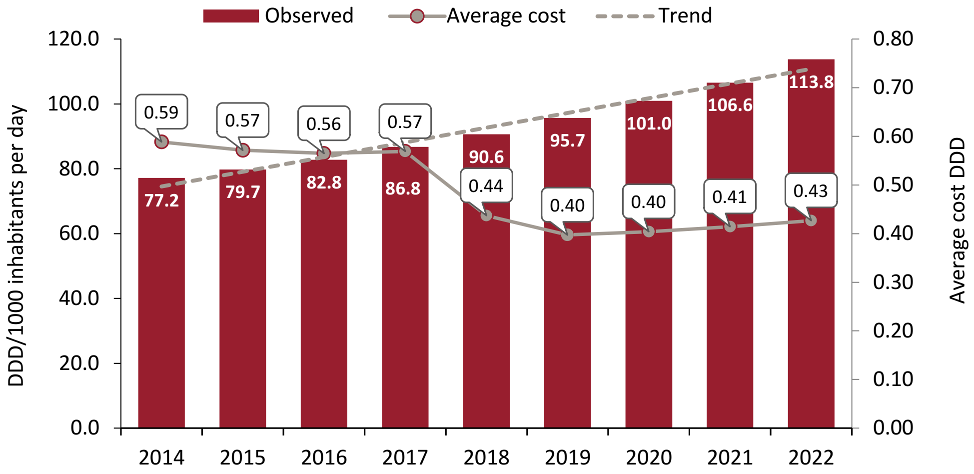


Table 3.2.2a Lipid-lowering medicines, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhabit.	Δ % 22-21 per day	CAGR % 14-22	Cost cost DDD	Δ % 22-21
Statins, plain	8.15	0.2	-3.3	84.1	0.9	2.7	0.27	-0.8
Ezetimibe and statins (association)	2.91	29.7	1.2	16.8	47.0	21.5	0.48	-11.8
PCSK9 inhibitors	2.17	42.3	-	0.6	55.7	-	9.67	-8.6
Omega 3	2.16	3.6	0.8	2.6	4.5	4.7	2.28	-0.9
Ezetimibe	1.72	9.5	8.5	6.5	10.7	21.1	0.72	-1.0
Fibrates	0.41	0.8	1.3	2.9	1.0	1.8	0.38	-0.3
MTP inhibitor	0.12	1.6	-	<0.05	2.9	-	800.65	-1.3
Treatments for disorders of lipid metabolism	0.05	194.6	-	<0.05	194.6	-	8190.19	0.0
Statins, calcium channel blockers and ace inhibitors (triple combination)	0.03	41.5	-	0.2	41.7	-	0.45	-0.1
Statins in combination	0.01	469.2	-	0.1	437.0	-	0.24	6.0
Lipid-lowering medicines	**17.72**	**9.9**	**0.8**	**113.8**	**6.8**	**5.0**	**0.43**	**3.0**
atorvastatin	4.68	1.3	5.4	52.4	1.5	6.0	0.24	-0.2
omega 3	2.16	3.6	0.8	2.6	4.5	4.7	2.28	-0.9
ezetimibe	1.72	9.5	8.5	6.5	10.7	21.1	0.72	-1.0
ezetimibe/rosuvastatin	1.55	50.1	-	10.7	69.1	-	0.40	-11.2
rosuvastatin	1.49	5.2	-13.5	15.9	6.2	1.6	0.26	-1.0
simvastatin	1.36	-6.4	-3.8	11.6	-6.0	-3.7	0.32	-0.3
ezetimibe/simvastatin	1.23	1.7	-9.1	5.2	2.0	4.9	0.65	-0.3
evolocumab	1.19	37.3	-	0.3	50.3	-	11.97	-8.6
alirocumab	0.98	48.9	-	0.3	60.3	-	7.84	-7.1
fenofibrate	0.38	1.4	1.9	2.7	1.7	2.4	0.38	-0.2

Figure 3.2.2b Lipid-lowering medicines, temporal trend 2014-2022 in consumption (DDD/1000 inhabitants per day) of the subgroups with the highest expenditure

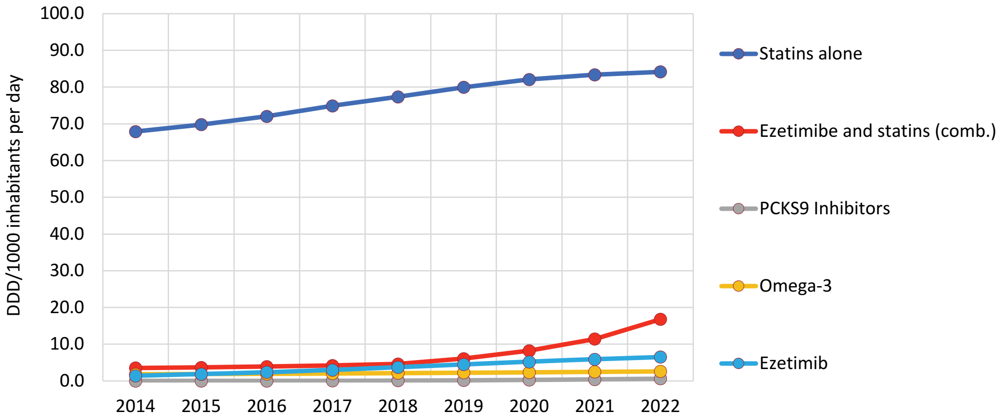


Table 3.2.2b Lipid-lowering medicines, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD
Piedmont	13.36	88.3	0.41	15.38	96.4	0.44	15.1	9.1	5.5	0.8	5.0	-4.0
Valle d'Aosta	10.48	67.0	0.43	12.19	71.3	0.47	16.3	6.4	9.3	-0.3	3.1	-3.2
Lombardy	13.87	99.5	0.38	15.27	107.1	0.39	10.1	7.6	2.3	0.1	5.2	-4.8
Province of Bolzano	10.19	88.1	0.32	10.96	94.4	0.32	7.6	7.1	0.5	0.5	6.1	-5.3
Province of Trento	12.72	95.1	0.37	13.90	103.7	0.37	9.3	9.1	0.2	0.4	6.3	-5.5
Veneto	14.26	105.6	0.37	15.60	113.8	0.38	9.4	7.7	1.6	-0.2	4.9	-4.9
Friuli V.G.	14.38	108.3	0.36	15.86	116.4	0.37	10.3	7.5	2.7	-0.4	4.8	-5.0
Liguria	14.70	91.4	0.44	16.72	98.7	0.46	13.8	7.9	5.4	1.7	5.1	-3.2
Emilia R.	15.10	113.1	0.37	16.75	123.1	0.37	10.9	8.8	2.0	2.3	5.4	-2.9
Tuscany	13.64	98.7	0.38	14.92	106.1	0.39	9.4	7.5	1.8	2.0	5.2	-3.0
Umbria	16.19	103.6	0.43	16.72	106.9	0.43	3.3	3.2	0.1	3.2	5.3	-2.0
Marche	17.79	121.4	0.40	19.56	129.5	0.41	10.0	6.7	3.1	0.8	5.0	-4.1
Lazio	18.16	106.8	0.47	19.58	112.3	0.48	7.8	5.1	2.6	-0.8	3.3	-4.0
Abruzzo	16.53	101.2	0.45	18.37	109.2	0.46	11.1	8.0	2.9	2.1	5.8	-3.5
Molise	15.27	91.1	0.46	17.03	98.7	0.47	11.5	8.4	2.9	-0.3	5.1	-5.1
Campania	22.56	124.1	0.50	25.27	130.2	0.53	12.0	4.9	6.8	4.2	6.0	-1.7
Puglia	17.99	114.2	0.43	19.61	121.3	0.44	9.0	6.2	2.6	-0.1	4.8	-4.7
Basilicata	18.13	109.3	0.45	20.38	118.4	0.47	12.4	8.3	3.8	4.2	6.1	-1.9
Calabria	18.37	108.5	0.46	20.16	114.6	0.48	9.8	5.6	3.9	0.2	4.2	-3.9
Sicily	17.04	115.0	0.41	18.25	120.8	0.41	7.1	5.1	2.0	0.8	5.1	-4.0
Sardinia	18.02	121.6	0.41	19.13	128.2	0.41	6.1	5.5	0.6	-2.5	3.9	-6.2
Italy	**16.12**	**106.6**	**0.41**	**17.72**	**113.8**	**0.43**	**9.9**	**6.8**	**3.0**	**0.8**	**5.0**	**-3.9**
North	14.03	100.5	0.38	15.58	108.6	0.39	11.1	8.1	2.8	0.6	5.2	-4.3
Centre	16.51	105.8	0.43	17.87	112.1	0.44	8.2	5.9	2.2	0.4	4.3	-3.7
South and Islands	18.89	115.8	0.45	20.71	122.3	0.46	9.7	5.6	3.8	1.4	5.2	-3.6

Exposure and adherence in population

- Health Card data were collected to perform an analysis aimed at estimating exposure to lipid-lowering medicines in the general population, as well as adherence and persistence to treatment. Exposure shows a growing trend starting from the 45-54 age group, it reaches a maximum value of both prevalence of use and consumption (350-450 DDD/1000 inhabitants per day) in the 75-84 age group, then decreases in people over 85 (Figure 3.2.2b). Analyzing the exposure by sex, it is evident that men are more exposed, especially in terms of consumption, than women, regardless of the age considered. Furthermore, prevalence of use tends to be higher in the Southern regions (16%), compared to Central (14.6%) and Northern regions (13.2%) (Table 3.2.2c).
- The prevalence of use of lipid-lowering medicines in the population is 14.4%, up 13.5% from 2021. The median age of users is 71 years and, on average, each user was treated for 276 days (just over nine months), and half of them were treated for a period longer than seven months (median DDD 224). Only 3.8% received a single prescription, however, this percentage reaches about 36% for PCSK-9 inhibitors.
- Statins alone reach 11% prevalence of use, with a mean age of 72 years. This was followed by the combination of statins and ezetimibe (2.6%), with sex differences (2.9% men and 2.3% women). Omega-3s and ezetimibe alone are the categories with a prevalence around 1%. The annual cost per user ranges from a maximum of 1,500 euros for PCSK-9s to a minimum of 70 euros for statins alone (Table 3.2.2d).
- Adequate levels of adherence and persistence to lipid-lowering therapy are associated with a reduction in the risk of cardiovascular events within patients in both primary and secondary prevention. Failure to adhere to lipid-lowering treatment leads to negative repercussions both in terms of public health and health costs. For this reason, an analysis was performed to estimate adherence and persistence of chronic lipid-lowering treatments, focusing attention on new users of at least 45 years, and considering a one-year follow-up. The study population included a total of 290,263 new users, with a median age of 67 years (IQR 58-73), and a greater proportion of women than men (54% vs 46%).
- The percentage of people with high and low adherence to treatment was 43.3% and 15.3%, respectively; values similar to those observed in 2021 (Table 3.2.2e). Low adherence tends to increase with age, recording the highest value in subjects over 85 (18.2%) and in women (16.8%) compared to men (13.5%). Users living in Northern Italy and aged between 55 and 64 years have a higher percentage value of high adherence, equal to 46.5%.
- Analyzing persistence, overall there is no substantial change from the previous year (Table 3.2.2f); less than half of new users were found to be persistent to treatment (48.7%), with higher values in the Central Regions (50.5%), lower values in the North (50.1%) and especially in the South (45.9%) (Figure 3.2.2d). Men recorded higher persistence rates (52.3%) than women (45.6%). By assessing persistence for different time intervals, it is observed that the percentage of persistent patients decreases as the observation period increases, moving from 45.4% at 12 months from the start of treatment to 36.4% at 24 months and 26.1% at 36 months from the beginning of treatment (Table 3.2.2f). Three years after starting treatment, about one-third (27.8%) of those in the North are still in treatment, compared with 26.6% in the Center and 24.1% in the South (Figure 3.2.2e).

Figure 3.2.2c Distribution of prevalence of use and consumption of medicines for lipid-lowering drugs under approved care regime and “on-behalf” distribution in 2022

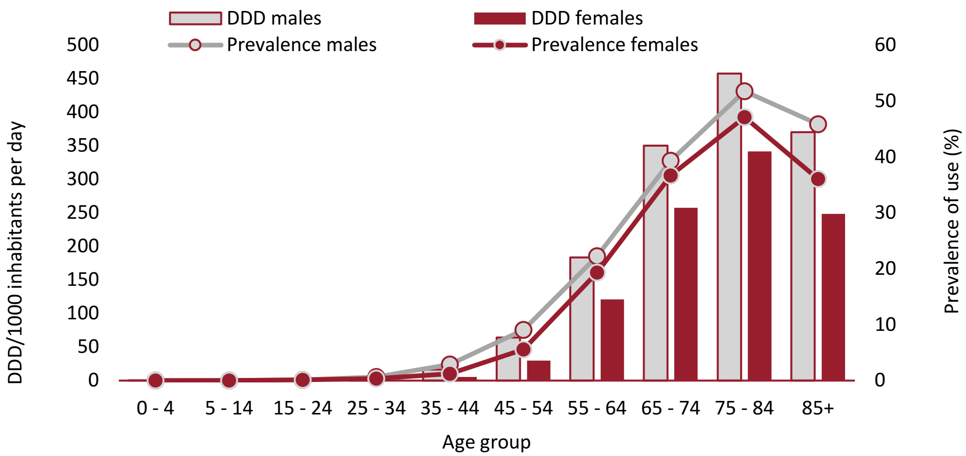


Table 3.2.2c Exposure and duration of therapy with lipid-lowering medicines by Region under approved care regime and "on-behalf" distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Piedmont	13.5	12.5	13.0	72	100.01	272.4	224.0	3.0
Valle d'Aosta	10.4	9.1	9.7	72	104.06	255.6	210.0	2.7
Lombardy	13.4	12.3	12.9	71	102.04	283.2	224.0	2.4
A. P. of Bolzano	9.9	8.9	9.4	73	99.71	329.0	261.3	2.1
A. P. of Trento	12.4	11.5	11.9	72	105.10	297.8	240.0	2.3
Veneto	13.9	12.4	13.2	72	107.49	306.4	246.7	2.5
Friuli V.G.	14.1	13.1	13.6	73	109.93	320.0	261.3	2.1
Liguria	13.7	13.2	13.5	73	104.70	276.9	240.0	4.1
Emilia R.	14.6	14.5	14.5	71	100.83	277.5	224.0	2.8
Tuscany	14.1	13.5	13.8	73	95.00	280.5	224.0	5.9
Umbria	14.6	14.1	14.3	72	104.03	274.6	234.0	5.0
Marche	16.4	16.2	16.3	72	108.88	289.5	240.0	3.6
Lazio	14.6	14.9	14.7	71	115.87	269.4	224.0	3.6
Abruzzo	14.7	14.6	14.6	70	107.79	263.4	224.0	4.9
Molise	14.3	14.4	14.4	71	108.20	251.4	224.0	4.2
Campania	15.9	16.5	16.2	68	107.58	262.0	224.0	4.6
Puglia	16.0	16.6	16.3	70	100.68	259.4	224.0	3.4
Basilicata	15.5	16.1	15.8	70	101.44	267.1	224.0	5.5
Calabria	15.5	15.8	15.7	69	104.06	254.3	210.0	6.3
Sicily	15.6	16.5	16.1	70	102.36	261.6	224.0	5.3
Sardinia	14.8	16.4	15.6	71	112.35	303.0	240.0	3.8
Italy	**14.5**	**14.3**	**14.4**	**71**	**104.67**	**276.0**	**224.0**	**3.8**
North	13.7	12.7	13.2	72	103.01	286.7	240.0	2.7
Centre	14.7	14.6	14.6	72	107.88	275.9	232.0	4.4
South and Islands	15.6	16.3	16.0	70	104.83	264.0	224.0	4.7

Table 3.2.2d Exposure and duration of therapy with lipid-lowering medicines by subgroup under approved care regime and "on-behalf" distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Statins, plain	11.1	11.5	11.3	72	70.63	260.2	210.0	4.2
Ezetimibe and statins (association)	2.9	2.3	2.6	69	109.27	228.4	240.0	6.9
PCSK9 inhibitors	0.0	0.0	0.0	64	1,493.34	76.8	69.4	35.7
Omega 3	1.5	0.9	1.2	67	178.32	77.0	70.0	3.9
Ezetimibe	1.1	1.0	1.0	69	164.58	224.6	240.0	8.3
Fibrates	0.8	0.5	0.6	65	63.70	165.7	174.0	7.7
Statins, calcium channel blockers and ACE inhibitors (triple combination)	0.03	0.02	0.02	68	111.03	247.7	300.0	7.7
Statins in combination	0.02	0.02	0.02	70	28.74	120.7	90.0	17.3
Lipid-lowering medicines	**14.5**	**14.3**	**14.4**	**71**	**104.67**	**276.0**	**224.0**	**3.8**

Table 3.2.2e Indicators of adherence to treatment with lipid-lowering drugs in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=290.263						North N=127.468					
45-54 years	16.1	15.7	14.3	15.5	8	-4	13.4	12.9	12.2	13.3	9	-1
55-64 years	15.4	15.1	14.1	14.4	2	-7	12.9	13.1	11.7	12.1	3	-6
65-74 years	16.6	16.1	15.2	15.2	0	-8	14.5	14.1	13.0	13.3	2	-8
75-84 years	17.4	16.8	16.7	16.1	-3	-8	15.6	15.0	14.5	14.0	-3	-10
≥ 85 years	18.8	19.1	19.0	18.2	-4	-3	16.8	17.3	16.1	15.9	-1	-5
Women	18.4	18.0	17.0	16.8	-1	-9	16.1	16.1	40.5	14.8	-63	-8
Men	14.4	13.9	13.0	13.5	4	-6	12.4	11.9	51.2	11.4	-78	-8
Total	**16.5**	**16.0**	**15.1**	**15.3**	**1**	**-7**	**14.3**	**14.0**	**12.9**	**13.2**	**2**	**-8**
	Centre N=58.627						South N=104.168					
45-54 years	15.9	16.3	14.6	16.0	10	1	18.5	17.7	16.3	17.7	8	-4
55-64 years	15.5	15.2	14.2	14.7	4	-5	17.9	16.9	16.6	16.7	1	-7
65-74 years	16.5	16.2	15.5	14.9	-4	-10	18.8	18.0	17.7	17.8	1	-5
75-84 years	17.2	17.7	17.4	16.9	-3	-2	20.0	18.8	19.5	18.9	-3	-5
≥ 85 years	18.9	19.1	20.2	18.3	-9	-3	21.1	21.1	22.1	21.1	-4	0
Women	18.5	18.4	38.1	17.1	-55	-8	20.6	19.6	35.3	19.0	-46	-8
Men	14.0	14.1	48.2	13.6	-72	-3	16.7	15.8	45.0	16.1	-64	-3
Total	**16.4**	**16.4**	**15.5**	**15.5**	**0**	**-6**	**18.8**	**17.9**	**17.5**	**17.7**	**1**	**-6**

continued

Table 3.2.2e – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=290.263						North N=127.468					
45-54 years	40.2	41.7	42.7	42.3	-1	5	43.1	45.9	46.2	45.3	-2	5
55-64 years	41.5	42.2	43.8	43.7	0	5	44.6	45.1	46.8	46.5	-1	4
65-74 years	40.3	41.8	42.6	43.4	2	8	42.7	44.7	45.3	45.8	1	7
75-84 years	40.6	41.9	42.2	43.7	4	8	43.1	43.9	44.5	46.1	4	7
≥ 85 years	40.7	41.6	40.9	42.0	3	3	43.0	44.4	43.5	44.6	2	4
Women	35.7	37.2	38.1	39.1	3	10	38.2	39.5	40.5	41.6	3	9
Men	46.3	47.2	48.4	48.3	0	4	48.8	50.2	51.2	50.9	-1	4
Total	**40.7**	**41.9**	**42.8**	**43.3**	**1**	**6**	**43.4**	**44.8**	**45.6**	**46.0**	**1**	**6**
	Centre N=58,627						South N=104,168					
45-54 years	41.7	40.8	42.8	43.0	0	3	37.2	38.6	39.3	38.9	-1	5
55-64 years	42.1	42.8	44.2	44.0	0	5	38.2	39.4	40.5	40.3	-1	5
65-74 years	40.9	41.8	42.2	44.1	5	8	37.5	38.8	39.5	40.0	1	7
75-84 years	40.9	42.0	41.5	42.9	3	5	37.2	39.2	39.1	40.4	3	9
≥ 85 years	42.5	42.2	41.4	43.8	6	3	36.8	38.1	37.0	37.2	1	1
Women	36.4	37.0	38.1	39.5	4	8	32.9	35.0	35.3	35.9	2	9
Men	47.1	47.7	48.2	48.6	1	3	43.1	43.8	45.0	44.7	-1	4
Total	**41.4**	**42.0**	**42.7**	**43.6**	**2**	**5**	**37.6**	**39.0**	**39.7**	**39.9**	**1**	**6**

*Adherence to treatment was evaluated only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to the statistical methods).
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of subjects with low/high adherence related to the specified category.
Median follow-up time (IQR): 322 (261-345).

Table 3.2.2f Persistence after one year of treatment with lipid-lowering drugs in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Persistence after 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=290,263						North N=127,468					
45-54 years	46.1	46.5	48.2	47.2	-2	2	48.6	49.7	51.2	49.1	-4	1
55-64 years	48.3	48.7	50.3	50.3	0	3	51.0	51.2	53.1	51.7	-3	1
65-74 years	47.8	48.0	49.1	49.6	1	2	49.5	50.1	51.0	50.8	0	3
75-84 years	45.9	45.6	45.9	46.7	2	1	47.6	47.1	48.1	48.2	0	1
≥ 85 years	43.0	42.7	42.5	43.3	2	0	44.8	45.8	45.4	45.1	-1	1
Women	43.1	43.6	45.1	45.6	1	3	44.5	45.1	46.8	46.5	-1	5
Men	51.5	51.3	52.5	52.3	0	2	53.9	53.9	55.2	54.1	-2	0
Total	**47.1**	**47.2**	**48.5**	**48.7**	**0**	**3**	**49.1**	**49.4**	**50.8**	**50.1**	**-2**	**2**
	Centre N=58,627						South N=104,168					
45-54 years	47.7	46.4	48.7	49.2	1	3	43.3	44.0	45.0	44.2	-2	2
55-64 years	49.6	48.6	51.6	52.3	1	5	45.2	46.5	46.7	47.8	3	6
65-74 years	47.9	48.2	50.3	52.1	4	9	46.0	45.9	46.2	46.7	1	1
75-84 years	45.6	45.5	45.4	47.5	5	4	43.9	43.7	42.8	43.7	2	-1
≥ 85 years	43.9	43.0	42.8	44.9	5	2	40.4	39.1	38.5	39.8	3	-1
Women	43.6	43.3	45.7	47.4	4	9	41.5	42.3	42.7	43.5	2	5
Men	52.1	51.6	53.4	54.3	2	4	48.5	48.4	48.5	48.9	1	1
Total	**47.6**	**47.2**	**49.2**	**50.5**	**3**	**6**	**44.7**	**45.1**	**45.3**	**45.9**	**1**	**3**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to statistical methods)

Figure 3.2.2d Time (in days) to discontinuation of treatment with lipid-lowering drugs in the population aged ≥45 years stratified by geographic area; the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)

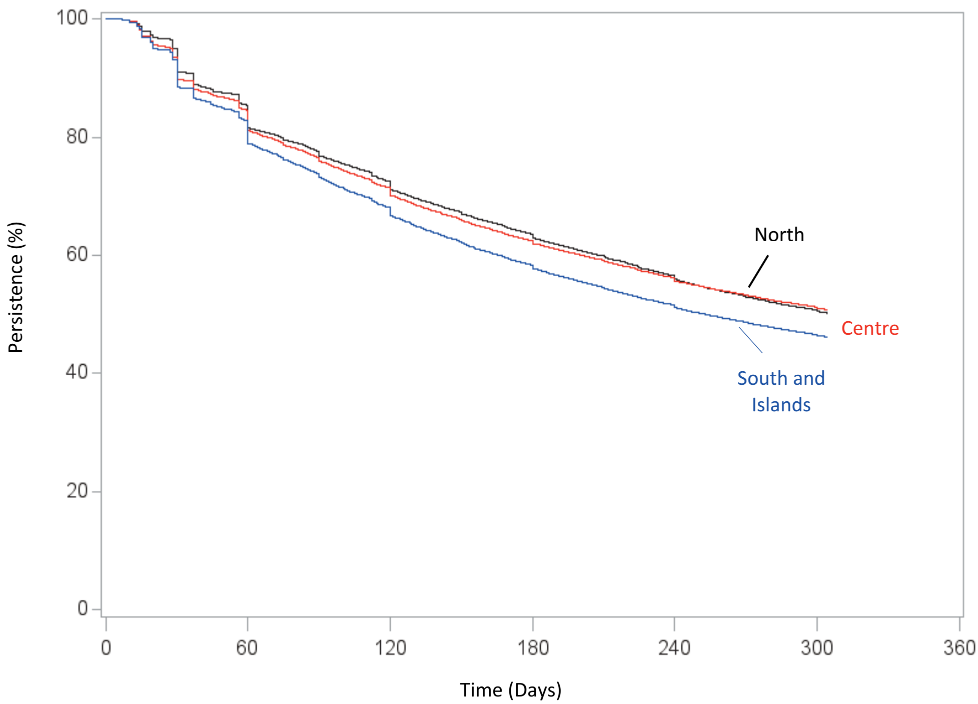


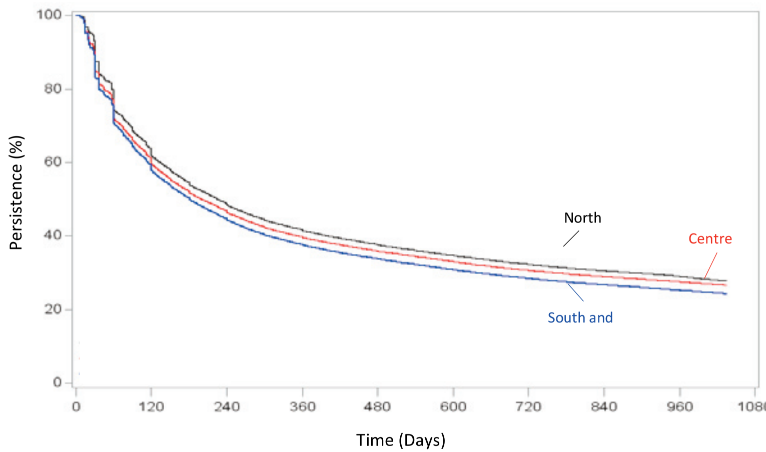
Table 3.2.2g Persistence to treatment with lipid-lowering drugs in the population aged ≥45 years in 2021 with 3 years of follow-up

Persistence (%)	Total N=244,429			North N=97,383			Centre N= 49,399			Sud N= 97,647		
	12 months	24 months	36 months	12 months	24 months	36 months	12 months	24 months	36 months	12 months	24 months	36 months
45-54 years	45.5	36.3	24.6	48.8	39.9	26.9	45.4	36.0	25.0	42.9	33.6	22.4
55-64 years	47.1	38.0	27.0	50.0	40.7	29.1	46.9	38.4	27.5	44.6	35.5	24.8
65-74 years	46.0	37.2	27.1	48.4	39.4	28.6	46.3	37.7	27.6	43.5	34.7	25.3
75-84 years	43.1	34.3	25.1	44.5	35.7	26.2	43.0	34.4	25.6	41.2	32.5	23.3
≥ 85 years	40.2	31.0	22.1	43.6	34.3	24.5	40.4	30.4	22.5	36.5	27.8	19.2
Women	41.5	32.2	22.2	43.3	33.7	23.3	41.2	32.1	22.5	40.0	30.8	21.1
Men	49.8	41.3	30.6	52.5	44.0	32.7	50.1	41.7	31.3	46.7	38.2	27.9
Total	**45.4**	**36.4**	**26.1**	**47.8**	**38.8**	**27.8**	**45.4**	**36.6**	**26.6**	**43.0**	**34.1**	**24.1**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions during the first year of treatment. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to the statistical methods).

N: refers to new users, who received a first prescription in the period 01/10/2019-31/12/2019, not treated in the previous months starting from 01/01/2019 and followed up for 3 years

Figure 3.2.2e Time (in days) to discontinuation of treatment with lipid-lowering drugs after 3 years of follow-up in the population aged ≥45 years with at least 2 prescriptions in the first year of treatment, stratified by geographical area. Curves are adjusted by gender and age (the Cox model was used to estimate persistence curves)



Over the past nine years, the consumption of lipid-lowering drugs has steadily increased. Statins not combined with other molecules represent the class with the highest per capita expenditure and consumption, but they are associated with the lowest average cost per day of therapy of the entire category. Atorvastatin is the highest-consumption and highest-spending active ingredient, likely because of the wide availability of dosages that allow titration and containment of dose-dependent side effects of this treatment, thus facilitating its prescription. The combination of rosuvastatin and ezetimibe registers the largest increase in consumption in 2022, probably because the use of two molecules with two different mechanisms of action that interfere with cholesterol metabolism by reducing its exogenous absorption and endogenous synthesis, respectively, result in an overall synergistic effect while improving drug tolerance by reduction of dose-related side effects.

PCSK9 inhibitors confirm the increasing trend, both in terms of expenditure and consumption. These drugs, approved by the EMA in 2015 and indicated in patients with familial hypercholesterolemia resistant to conventional therapy, have a good efficacy profile and an acceptable safety profile. In light of the efficacy of this class of drugs in patients at high/very high cardiovascular risk and/or in secondary prevention, in June 2022 AIFA changed the threshold values of C-LDL in the eligibility form from 100 mg/dl to 70 mg/dl for patients aged ≤80 years in secondary prevention; this change widely expands the possible use of these drugs and makes it even more necessary to constantly monitor their prescriptive appropriateness, also in order to avoid an unjustified increase in pharmaceutical spending for this class of lipid lowering drugs.

Consumption and exposure to lipid lowering agents are higher in the elderly population, with maximum values observed in patients aged 75-84 years, while they decrease slightly in very elderly patients (≥85 years). Several studies suggest a beneficial effect of lipid lowering agents in reducing cardiovascular risk even in very elderly patients; however, since the effectiveness of using lipid lowering agents in primary prevention in this population group is unproven, some of these prescriptions may be inappropriate.

Although the elderly population, as is the case for most drugs, is characterized by cognitive deterioration, comorbidities, multiple treatments, and often changing socioeconomic conditions that affect their compliance with therapy, the limited treatment adherence and persistence observed for this category of drugs can likely be attributed to the perceived low tolerability of the population at-risk. At the same time, the absence of immediate adverse clinical symptoms or outcomes following discontinuation of treatment, as is otherwise the case with antihypertensive medication and heart failure, favors discontinuation.

3.3 Gastrointestinal system and metabolism

Medicines for gastrointestinal system and metabolism were the third therapeutic category with the highest public expenditure in 2022, equal to 3.260 million euros and 13.2% of overall public expenditure (See Main expenditure, consumption and exposure indices). Total per capita expenditure for these pharmaceuticals was 55.22 euros (+6.8% compared to the previous year), mainly due to the NHS outpatient care (32.64 euros per capita). Conversely, expenditure due to purchases by public health facilities is lower (22.58 euros per capita), with a 16.5% increase compared to 2021 (Table 3.1). In 2022 consumption for this pharmaceutical category was equal to 316.70 DDD/1000 inhabitants per day, increasing by -0.3% compared to 2021 (Table 3.2).
The analysis of the drug use profile by age group and gender, including NHS outpatient care and per conto distribution, shows a progressive increase in the use of pharmaceuticals belonging to this category with increasing age for both genders, with a more marked trend in the over 45 age group. At the same time, the per capita NHS expenditure also increases with the age of patients, reaching a maximum value of EUR 143.2 in males over 75 years of age.
In 2022, expenditure under approved care regime related to this category of drugs remained almost stable (+0.6%) compared to the previous year (Table 3.9). This trend was determined by a reduction in consumption (-2.1%) and a shift in prescription towards higher-cost specialties (mix effect: +3.2%), also evidenced by the increase in average cost per DDD (+2.8%), while prices remain stable (-0.4%).
Proton pump inhibitors rank first in terms of expenditure (11.40 euros per capita) and second in terms of consumption (77.5 DDD/1000 inhabitants per day), recording an increase in use (+1.3%), a slight decrease in expenditure (-1.1%) and a use of less expensive medicinal products (mix effect: -2.3%). Vitamin D and analogues rank second by gross per capita expenditure (4.70 euros), registering a decrease in both expenditure (-2.8%) and consumption (-2.7%) in 2022. Similar reductions are also observed for the category of calcium in combination with vitamin D and/or other drugs, with decreases of 4.7% in spending and 5.1% in consumption
Also in 2022, there is a further increase in spending and consumption for GLP-1 analogs (+66.3% and +57.2%, respectively), associated with a 5.8% increase in average cost per DDD. Glyphozines, or Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors, also show substantial increases in both spending (+34.4%) and consumption (+39.2%), although a shift in prescriptions to lower-cost specialties is observed for this class of drugs (mix effect: -3.4%). Oral hypoglycemizers in combination show growth in spending (+8.0%), despite a contraction in consumption (-12.4%), a shift in prescriptions toward more expensive specialties (mix effect: +23.5%), and an increase in the average cost per day of therapy (+23.2%), probably due to an increase in prescriptions of fixed combinations of glyphozines with dipeptidyl-peptidase IV inhibitors.
Pantoprazole and cholecalciferol are the molecules with the highest per capita expenditure (4.51 euros and 4.05 euros, respectively). Together, they constitute the main cost item of the NHS outpatient pharmaceutical expenditure relating to medicines for the gastrointestinal system (26.2%) (Table 3.10). These two molecules also rank in the first places among the first 30 active ingredients by NHS outpatient expenditure (266.3 and 239.0 million euros, respectively) (Tables 3.11 and 3.12).

Three active ingredients belonging to this category of drugs rank in the list of the highest cost drugs per day of therapy under approved care regime: semaglutide (€7.90), dulaglutide (€4.94) and rifamixin (€2.08) (Table 3.13). In contrast, cholecalciferol, metformin and omeprazole ranked among the top 30 active ingredients with the lowest cost per day of therapy, costing 0.08, 0.20 and 0.34 euros per DDD, respectively (Table 3.14).
Semaglutide appears in the list of the top 30 active ingredients with the greatest increase in expenditure under approved care regime over the previous year (+112.3%) due to a marked increase in consumption (+105.7%) and in average cost per DDD (+3.2%) compared to 2021; followed by dulaglutide, with a 51.1% increase in per capita spending and 48.1% increase in consumption, and magaldrate, with a 36.6% increase in spending and 35.7% increase in consumption (Table 3.15).
Insulins aspart, lispro and glulisine (fast-acting insulin) rank among the top 30 active ingredients with the greatest reduction in the NHS outpatient expenditure compared to 2021, with -6.9%, -5.6%, -3.0%, respectively, which are accompanied by equal reductions in consumption: -3.0% for insulin glulisine and lispro, -1.9% for insulin aspart (Table 3.16). Other items in the list include lasoprazole, omeprazole, and cholecalciferol, with reductions in spending of 5.1%, 2.9%, and 2.8%, for which there are equal reductions in consumption of 3.4%, 0.2%, and 2.3%, respectively.
Six out of thirty most consumed active ingredients under the approved care regime (Table 3.17 and 3.18) belong to the category of medicinal products for gastrointestinal system and metabolism. Cholecalciferol ranks first with 136.8 DDD/1000 inhabitants per day, and becomes the most prescribed active ingredient within this category also in 2022, both nationally and at the level of individual regions. It is followed by pantoprazole (29.0 DDD/1000 inhabitants per day) and metformin (23.1 DDD/1000 inhabitants per day). The remaining active ingredients are proton pump inhibitors, omeprazole, esomeprazole and lansoprazole.
With regard to purchases by public health facilities, expenditure increased by 16.0% compared to 2021, consumption increased by 11.1% (Table 3.19), prices decreased by 3.1%, with prescriptions moving towards more expensive specialties (mix effect: +7.6%). The highest expenditure increases were recorded for SGLT2 inhibitors (+77.1%), and for GLP-1 receptor analogues (+39.0%). Enzymes such as recombinant human acid alglucosidase, agalsidase alfa, agalsidase beta, imiglucerase, idursulfase, velaglucerase alfa and elosulfase alfa account for 25% of expenditure, despite a very low average consumption, considering that they include medicines used in the treatment of rare diseases and have a high average cost per DDD. Bile acids and derivatives were the drugs that experienced the largest increase in consumption (+103.0%) and the most significant shift to less expensive specialties (mix effect: -39.7%), confirmed by a similar reduction in average cost per DDD. In contrast, intestinal antibiotics show a 27.1% increase in spending, attributable to an 11.3% increase in consumption, but mainly to a shift toward more expensive specialties (mix effect: +14.3%), confirmed by the increase in average cost per DDD.
Dulaglutide (GLP-1 analogue) is the active ingredient with the highest per capita expenditure (2.74 euros) in 2022, with a steady increase compared with the previous year (+46.0%). It accounts for 12.1% of expenditure by public health facilities for medicinal products in this category. This active ingredient is also associated with the highest consumption in the category (3.4 DDD/1000 inhabitants per day), up 49.4% from the

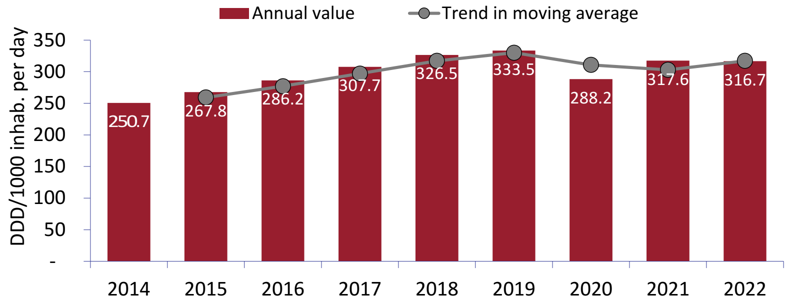
previous year. Semaglutide (analogue of GLP-1) is the second active ingredient by per capita expenditure (€1.71), up 96.0% from 2021, although lower consumption is observed for this active ingredient (1.4 DDD/1000 inhabitants per day) than for dulaglutide, which is up sharply from the previous year (+104.8%). Dulaglutide and semaglutide are the only two active ingredients in the category included in the top 30 highest spending active ingredients for drugs purchased by healthcare facilities (Tables 3.21 and 3.22).
Three antidiabetics, dapaglifozin (an SGLT2-contraceptor inhibitor), semaglutide and dulaglutide (both GLP-1 analogs), along with algazidase beta enzyme (indicated in Fabry's disease) appear in the list of the top 30 highest-spending active ingredients among drugs purchased by public health facilities (Table 3.23).
Although dapaglifozin has a lower per capita expenditure than the other two antidiabetics (€0.93 vs. €1.71 for semaglutide and €2.74 for dulaglutide), it is the active ingredient with the largest increase in per capita expenditure over the previous year (+104.1%), which is associated with a similar increase in consumption (+115.7%). Semaglutide shows a 96.0% increase in per capita spending compared with the previous year. Dulaglutide had the highest per capita spending, a 46% increase in expenditure, and a 49.4% increase in consumption. Finally, algasidase beta shows a 17.8% increase in spending despite negligible consumption, a value driven by a high average cost per DDD (€483.63) of the molecule (Table 3.23).
Algasidase alfa, another enzyme indicated in Fabry's disease, and insulin glargine are the only active ingredients that rank among the top 30 active ingredients with the greatest reduction in expenditure among drugs purchased by public health facilities, compared with the previous year, at -8.7% and -3.7%, respectively (Table 3.24).
The enzymes algasidase alpha imiglycerase and alglucosidase alpha rank in the top three places on the list of the top 30 active ingredients by average cost per day of therapy, with values of 1676.6 euros, 1096.5 euros, and 1062.3 euros, respectively; this is followed by a fourth enzyme, agalsidase beta, in eighth place, with a cost of 483.6 euros per day of therapy (Table 3.25). In contrast, as for drugs purchased by public health facilities, four antidiabetics ranked among the top 30 active ingredients with the lowest cost per therapy day: dapaglifozin, insulin glargine, dulaglutide and semaglutide (Table 3.26).
In total, ten molecules rank in the list of the top 30 active ingredients by consumption among those purchased by public health facilities in 2022 (Table 3.27). Dulaglutide registers the highest value (3.4 DDD/1000 inhabitants per day), moving from 16th to 10th place, followed by insulin glargine, which instead moves from 10th to 12th place, with a consumption of 3.1 DDD/1000 inhabitants per day, and cholecalciferol, which ranks 13th with a consumption of 3.0 DDD/1000 inhabitants per day (in 2021 it occupied 11th place). Dapaglifozin, for which there is a marked increase, with consumption of 2.0 DDD/1000 inhabitants per day, ranks 18th in 2022 (in 2021 it was 39th). As for the other active ingredients that follow the ranking position, sitagliptin (29th place) remains stable from the previous year, pantoprazole (from 21st to 20th) and linagliptin (from 30th to 27th) rise a few places, insulin degludec (from 23rd to 26th place) and sitagliptin/metformin (from 25th to 29th place) fall a few places. The greatest gain in positions is noted for semaglutide, which rises from 215th to 20th place.
When looking at drugs under approved care regime purchased by public health facilities, cholecalciferol, pantoprazole, esomeprazole, omeprazole and lansoprazole rank in both

the list of the top 30 active ingredients with the highest expenditure (Table 3.28) and the list of the top 30 with the highest consumption (Table 3.29). Dulaglutide and semaglutide also rank among the highest-expenditure active ingredients, while metformin ranks among the highest-consumption active ingredients. Finally, Table 3.30 shows different trends in terms of spending, consumption and average cost per DDD between NHS outpatient care and direct purchasing for antidiabetics, peptic ulcer drugs and gastroesophageal reflux disease (GERD).
Analyses of the historical series of consumption and expenditure by active ingredient and by Region have been carried out for more information on the use of medicines belonging to the same therapeutic area. These analyses focused on medicines for the treatment of diabetes mellitus, peptic ulcer and GERD as well as on medicines for the treatment of metabolic disorders (Table 3.3.1a and following).

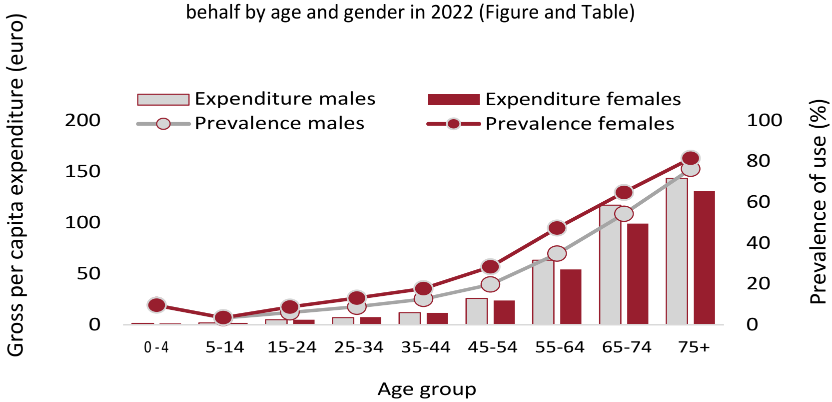
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Gastrointestinal system and metabolism

Public expenditure* in EUR million (% over total)		**3,260.0**	**(13.2)**
	Δ % 2022-2021		6.9
	Regional range of gross per capita expenditure:	32.7	72.1
DDD/1000 inhabitants per day* (% over total)		**316.7**	**(23.9)**
	Δ % 2022-2021		-0.3
	Regional range DDD/1000 inhabitants per day	243.0	393.0

** includes prescriptions under approved care regime and purchases by public health facilities*



Breakdown of prevalence of use and consumption under approved care regime and distribution on behalf by age and gender in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	1.3	1.3	1.3	60.4	59.0	59.7
5-14	1.8	1.9	1.9	18.7	20.1	19.4
15-24	4.9	4.9	4.9	23.9	35.1	29.3
25-34	7.1	7.5	7.3	32.7	53.7	43.0
35-44	11.9	11.8	11.9	54.1	90.6	72.3
45-54	25.8	23.7	24.8	113.5	206.6	160.6
55-64	63.3	54.1	58.6	270.1	470.2	373.1
65-74	117.0	98.9	107.5	529.5	816.3	681.0
75+	143.2	130.6	135.7	787.3	1,097.0	972.3

3.3.1 Antidiabetics

- The consumption of medicines for diabetes increased slightly over the period 2014-2022, from 61.8 to 66.9 DDD/1000 inhabitants per day, with an average annual change (CAGR) of 1.0% (Figure and Table 3.3.1a). Conversely, the cost per day of therapy increased by an average of 6.0% per year, reaching 0.94 euros in 2022, indicating an increasing use of high-cost drugs, such as GLP-1 analogs, glyptins, and glyphozines. In 2022 per capita expenditure was 22.93 euros, an increase of 15.3% from the previous year, while the average cost per DDD increased by 11.7%.
- The most used antidiabetics are metformin (about 30 DDD/1000 inhabitants per day when used alone or in combination with other medicines, accounting for 45.4% of the total) and insulins alone or in combination with GLP-1 analogs (about 14 DDD/1000 inhabitants per day, accounting for 21% of the total). Secretagogues (sulfonylureas alone or in combination, and glinides) still represent the third most widely used category (with a consumption of 7 DDD), albeit in sharp decrease compared with previous years, as evidenced by the CAGR.
- Among the three most recently introduced categories, glyptins are the most widely used (about 7 DDD, considering also combinations with metformin, glitazone, or glyfozines) albeit with varying trends from 2021 (down 10% in those associated with metformin or glitazone, up 63% in association with glyphozines and up 4.2% alone). Compared to 2021, there is a sharp increase in consumption of glyphozines alone (+83.2%) and in combination with metformin (+32.5%), as well as GLP1 analogs alone (+45.2%; CAGR 14-22: +35.1%) and in combination with insulins (+26.1%) (Figure 3.3.1b). The gliflozin/gliptin and GLP1 analogue/basal insulin combinations are currently characterised by marginal consumption shares (0.7 DDD each). GLP-1 analogs are the category with the highest average cost both alone (€3.01) and in combination with insulins (€4.64).
- GLP-1 analogs overall constitute the highest spending category for diabetes treatment (8.29 euros). In second place in terms of expenditure are insulins, and although rapid and slow insulin analogs represent the second and third drug classes with the highest per capita expenditure, they show a slight contraction in consumption (-1.9% and 5.6%) compared with the previous year, accompanied by a greater reduction in expenditure (-5.7% and 4.8%), likely due to the reduction in costs and consumption of some insulins (especially basal, insulin degludec and glargine, respectively).
- The active ingredient with the highest per capita expenditure is dulaglutide, an long-acting GLP-1 analogue (4.05 euros and +47.6% compared with 2021, due to a 49.2% increase in consumption and an average DDD cost of 2.66 euros, stable from 2021). In second place in terms of expenditure is semaglutide (2.58 euros; +101.2%), which also has the highest cost per day of therapy (4.04 euros; -1.8%). Metformin ranks second in terms of expenditure with 1.67 euros, showing a stable trend in terms of consumption and expenditure and an average DDD cost of 0.19 euros, the lowest of all. Dapaglifozin has the largest increase in expenditure (+104%). The insulin degludec/liraglutide combination continues to record significant increases in expenditure and consumption (>20%). Insulin aspart is the active ingredient with the largest decline in per capita

spending compared to the previous year (-7.3%), driven by a 5.4% reduction in average cost per DDD and a 2% reduction in consumption.

- In line with the prevalence of diabetes, in 2022 Southern Regions recorded a 31% higher consumption than the Northern Regions (78.7 vs 60.2 DDD) and a 18% higher consumption compared with the national average (66.9 DDD) (Table 3.3.1b). The North has the largest increases in spending (+21.8%) and consumption (+5.9%) as well as an increase in average cost per DDD (+15.0%) from the previous year. An even more marked variability is observed between the different regions: the Autonomous Province of Bolzano (41.1 DDD) consumes less than half of the doses of Calabria (89.2 DDD). Valle d'Aosta (+17.3%) and Abruzzo (+8.3%) are the regions with the highest increase in consumption compared to the previous year, while Sicily is the only one that shows a contraction in consumption (-4.6%). Consistent with consumption, southern regions have the highest per capita expenditure (€24.95) compared to other geographic areas, and up 9.2 percent in comparison with the previous year, although both the average cost per DDD (€0.87) and the average annual change (CAGR) over the 2014-2022 period (+4.0%) are lower than the national average (+6.0%). In contrast, the North shows a change of +8.1%, and among the regions, Lombardy shows the highest increase (+11.5%).

Figure 3.3.1a Antidiabetics, temporal trend in per capita expenditure and average cost per day of therapy (2014-2022)

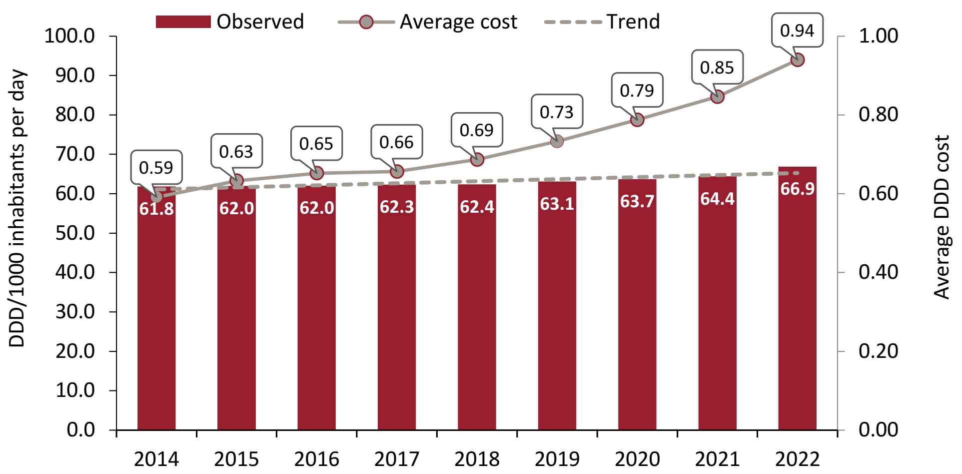


Table 3.3.1a Antidiabetics, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Expen diture *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Cost cost DDD	Δ % 22-21
GLP-1 (glucagon-like one) analogues	7.12	47.0	32.3	6.5	45.2	35.1	3.01	1.2
Fast acting insulins	3.39	-5.7	-1.8	7.9	-1.9	-0.5	1.17	-3.8
Long acting insulins	2.32	-4.8	-0.8	4.8	-5.6	-1.0	1.33	0.9
Glifozins (SGLT2 inhibitors) plain	1.90	74.3	-	3.9	83.2	-	1.33	-4.9
Metformin	1.67	1.9	2.7	23.4	0.4	1.8	0.19	1.5
Gliptins (DPP-4 inhibitors) plain	1.47	-3.8	7.7	3.5	4.2	12.1	1.16	-7.7
Glifozins (SGLT2 inhibitors) in combination with metformin	1.27	27.7	-	2.7	32.5	-	1.29	-3.6
Insulins combined with GLP-1 (glucagon-like one) analogues	1.17	20.3	-	0.7	26.1	-	4.64	-4.5
Gliptins (DPP-4 inhibitors) in combination with metformin	0.89	-16.1	-2.5	2.4	-9.6	2.2	1.03	-7.1
Gliptins (DPP-4 inhibitors) in combination with glifozins (SGLT2 inhibitors)	0.49	56.2	-	0.7	62.9	-	1.83	-4.1
Sulfonylureas plain	0.42	-13.4	-3.6	6.0	-15.5	-7.5	0.19	2.5
Repaglinide	0.19	-19.1	-12.1	1.3	-20.3	-13.0	0.40	1.4
Glitaziones in combination metformin	0.15	-9.5	-13.6	0.7	-11.7	-7.0	0.62	2.5
Glitazones plain	0.14	6.7	-2.3	0.8	-8.3	-1.2	0.48	16.4
Acarbose	0.12	-10.5	-5.4	0.5	-10.3	-4.5	0.72	-0.2
Gliptins (DPP-4 inhibitors) in combination with pioglitazone	0.08	-10.3	60.2	0.2	-9.8	65.7	1.18	-0.6
Combined insulins (long/intermediate with fast)	0.07	-21.9	-21.2	0.2	-21.3	-20.4	1.21	-0.8
Sulfonylureas in combination with metformin	0.05	-25.3	-21.1	0.7	-25.3	-21.2	0.21	0.0
Sulfonylureas in combination with pioglitazone	0.02	-23.0	-12.3	<0,05	-21.7	-10.9	1.05	-1.7
Antidiabetics	**22.93**	**15.3**	**7.0**	**66.9**	**3.8**	**1.0**	**0.94**	**11.0**
dulaglutide	4.05	47.6	-	4.2	49.2	-	2.66	-1.1
semaglutide	2.58	101.2	-	1.8	104.9	-	4.04	-1.8
metformin	1.67	1.9	2.7	23.4	0.4	1.8	0.19	1.5
insulin glargine	1.55	-3.9	-2.7	3.1	-8.0	-3.1	1.35	4.5
insulin lispro	1.49	-5.7	-3.4	3.7	-1.9	-1.1	1.11	-3.8
insulin aspart	1.43	-7.3	-3.1	3.1	-2.0	-2.1	1.26	-5.4
insulin degludec/liraglutide	1.07	22.7	-	0.6	29.7	-	4.70	-5.4
dapagliflozin	0.93	104.3	-	2.0	115.8	-	1.26	-5.3
linagliptin	0.79	7.8	30.6	1.7	10.7	34.3	1.27	-2.6
insulin degludec	0.70	-4.6	75.2	1.5	2.5	90.2	1.30	-7.0

Figure 3.3.1b Antidiabetics, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) by subgroups with the highest expenditure

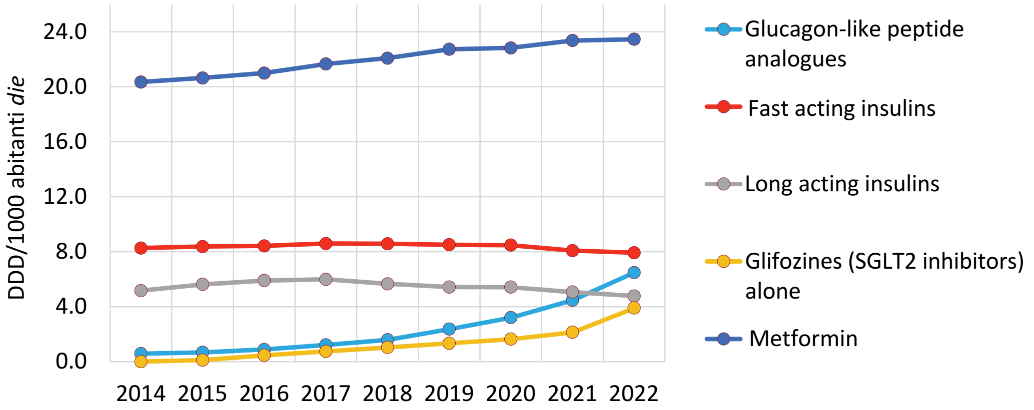


Table 3.3.1b Antidiabetics, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD
Piedmont	17.00	59.3	0.79	19.97	63.2	0.87	17.5	6.6	10.2	6.2	0.8	5.4
Valle d'Aosta	10.63	50.4	0.58	12.87	59.1	0.60	21.1	17.3	3.2	3.1	-0.2	3.3
Lombardy	24.66	57.1	1.18	31.58	60.9	1.42	28.0	6.8	19.9	12.8	1.2	11.5
Province of Bolzano	11.72	38.7	0.83	13.08	41.1	0.87	11.6	6.3	4.9	3.7	-0.6	4.3
Province of Trento	16.41	52.2	0.86	18.76	55.8	0.92	14.3	6.9	6.9	7.9	1.8	6.0
Veneto	16.52	54.7	0.83	18.78	57.0	0.90	13.7	4.2	9.1	6.6	1.1	5.4
Friuli V.G.	17.68	60.5	0.80	18.97	61.4	0.85	7.3	1.4	5.8	6.3	0.9	5.4
Liguria	13.92	49.1	0.78	16.88	52.9	0.87	21.3	7.7	12.6	6.4	0.4	6.0
Emilia R.	13.51	61.0	0.61	16.27	64.3	0.69	20.4	5.5	14.1	7.0	1.3	5.6
Tuscany	14.96	55.8	0.73	17.11	58.2	0.81	14.4	4.3	9.6	4.8	0.0	4.8
Umbria	20.47	60.2	0.93	22.24	62.1	0.98	8.6	3.1	5.4	6.0	1.0	4.9
Marche	17.22	59.5	0.79	19.19	61.8	0.85	11.5	3.9	7.3	8.5	2.6	5.8
Lazio	19.23	65.0	0.81	21.30	67.0	0.87	10.8	3.1	7.5	6.2	0.8	5.4
Abruzzo	19.47	64.0	0.83	23.85	69.3	0.94	22.5	8.3	13.0	5.0	1.1	3.9
Molise	20.13	67.8	0.81	23.17	71.1	0.89	15.1	4.9	9.7	6.0	1.2	4.7
Campania	22.68	74.8	0.83	25.63	77.8	0.90	13.0	4.0	8.7	5.4	1.7	3.7
Puglia	23.47	77.8	0.83	26.80	80.1	0.92	14.2	2.9	11.0	7.5	1.1	6.4
Basilicata	22.96	78.4	0.80	25.70	81.2	0.87	11.9	3.7	8.0	6.8	1.9	4.8
Calabria	24.51	85.9	0.78	27.72	89.2	0.85	13.1	3.8	8.9	5.8	1.6	4.2
Sicily	23.38	83.6	0.77	22.38	79.7	0.77	-4.3	-4.6	0.4	2.8	0.1	2.6
Sardinia	21.66	69.1	0.86	23.65	72.0	0.90	9.2	4.1	4.9	3.4	0.9	2.4
Italy	**19.89**	**64.4**	**0.85**	**22.93**	**66.9**	**0.94**	**15.3**	**3.8**	**11.0**	**7.0**	**1.0**	**6.0**
North	18.78	56.9	0.91	22.88	60.2	1.04	21.8	5.9	15.0	9.2	1.0	8.1
Centre	17.69	60.9	0.80	19.76	63.1	0.86	11.7	3.6	7.8	6.0	0.8	5.2
South and Islands	22.84	77.3	0.81	24.95	78.7	0.87	9.2	1.8	7.3	5.1	1.1	4.0

Exposure and adherence in population

- The Health Card (tessera sanitaria) data allowed to describe the trend in prevalence and consumption of antidiabetics by age, gender and Region, as well as to calculate some indicators of intensity of use. Adherence and persistence of chronic treatments with antidiabetics was also estimated. A deeper understanding of the population shows an increasing use of diabetes drugs with increasing age, with higher prevalence (25%) and consumption (253.2 DDD) values in men aged 75 to 84 years, in agreement with the epidemiology of the condition (Figure 3.3.1c). This difference between men and women is found in all age groups with a more marked trend from 55 to 84 years.
- On average, prevalence is equal to 6.3%, ranging from a minimum of 5.3% in the North to a maximum of 7.4% in the South (Table 3.3.1c). Calabria is the Region with the greatest use of medicines for diabetes (8.5%), whereas the Autonomous Province of Bolzano shows a prevalence of use slightly over 3.6%. As already highlighted, prevalence is higher among men than women (6.9% and 5.7%, respectively). The median age of users is 71, with no specific differences at regional level (with the exception of Liguria). The cost per user was 337.17 euros. Lombardy has three times higher values than Emilia Romagna (562 vs 201 euros).
- In line with the therapeutic regimen for a chronic condition, each user receives, on average, at least one dose of medicinal product per day (DDD per user: 357.6) and half of them are treated for at least 10 months a year (9 months in Central regions). The percentage of subjects receiving only one prescription is 3.4 percent.
- Metformin alone has the highest prevalence of use (4.3%) and a cost per user of 38.18 euros. Fifty percent of users remain on therapy for less than 6 months, probably indicating a tendency to switch to other categories after initial metformin treatment (Table 3.3.1d). High prevalence levels are also present for fast and long insulins, 1.0% and 1.3% respectively, with an average cost per user twice as high for the former as for the latter (315.35 vs. 163.98 euros).
- As for adherence and persistence analyses, exposure data refer to a cohort of new users over 45 years old, who were followed-up for one year. In detail, the study population comprises a total of 72.469 new users with a median age of 66 years (IQR 58-75), with a higher proportion of females than males (46.3% vs 53.7%).
- The percentage of subjects with high and low adherence to antidiabetic treatment was equal to 30.9% and 27.1%, respectively (Table 3.3.1e). In particular, the highest percentages of high adherence were observed in subjects aged between 45 and 54 years (38.1% in total: 46.1% in the North, 34.3% in the Centre and 33.5% in the South). Then, they decrease with increasing age. In general, males have a higher percentage of subjects with high adherence than females (34.2% vs 27.1%). The highest percentage of subjects with low adherence is recorded in subjects living in the Centre and aged at least 85 years (38.9%). Compared with 2021, a decrease in subjects with low adherence (-3%) and an increase in subject with high adherence (+5%) are found at national level. The South registers the greatest reduction in subjects with low adherence (-4%), while high adherence increases mainly in the Centre (+9%).
- In 2021, the overall percentage of those persisting on treatment at 12 months was less than half (43.1%), but it was higher in northern regions (45.1%) than in central (41.8%)

and southern (42.1%) regions. Women have a lower percentage of persistence to treatment at 12 months than men (39.9% vs 45.9%) (Table 3.3.1f). The probability of being persistent decreases with increasing age: in 2022 persistent subjects at 12 months vary from 48.3% to 30.4%, starting from the 45-54 age group up to subjects aged at least 85. Across the population as a whole, the median time to discontinuation of antidiabetic treatment was 219 days, with values ranging from 242 days in the northern regions to 202 days for the Center and South (Figure 3.3.1d).

- Based on the trend over the three-year period 2019-2022, a slight overall improvement in the indicators of high adherence and persistence can be observed. It is important to highlight that the Central regions have the greatest increase in persistent subjects at 12 months (+11%) and those with high adherence (+10%) (Tables 3.3.1e and 3.3.1f).

Figure 3.3.1c Breakdown of prevalence of use and consumption of antidiabetics under approved care regime and per conto distribution in 2022

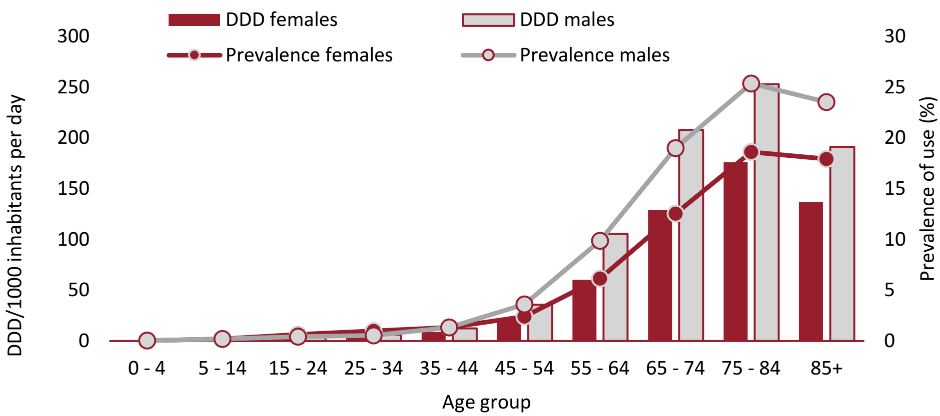


Table 3.3.1c Exposure and duration of therapy with antidiabetics by Region under approved care regime and per conto distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Piedmont	6.7	5.2	5.9	72	335.58	379.2	308.0	2.5
Valle d'Aosta	5.5	4.1	4.8	72	260.75	428.2	308.0	2.1
Lombardy	6.0	4.5	5.2	72	562.81	386.0	312.5	2.4
A.P. of Bolzano	4.1	3.1	3.6	72	379.02	409.4	336.0	2.2
A.P. of Trento	5.2	4.1	4.7	72	291.66	339.3	272.0	2.4
Veneto	5.8	4.2	5.0	72	340.08	382.2	320.0	2.4
Friuli V.G.	6.8	4.9	5.8	73	337.16	387.0	315.0	2.3
Liguria	6.1	4.9	5.5	74	297.06	347.5	280.5	3.9
Emilia R.	6.0	4.7	5.3	72	201.17	332.8	264.0	3.1
Tuscany	6.9	5.8	6.3	73	251.35	321.4	255.0	4.8
Umbria	7.2	5.8	6.5	73	347.90	346.8	300.0	3.7
Marche	6.6	5.2	5.9	72	319.43	376.7	306.0	3.5
Lazio	7.2	6.5	6.8	70	296.48	334.8	262.5	4.4
Abruzzo	7.3	6.3	6.8	72	339.64	354.4	300.0	3.9
Molise	8.0	6.6	7.3	71	294.35	333.4	280.5	3.4
Campania	7.6	6.4	7.0	70	318.67	356.1	303.0	3.6
Puglia	8.1	7.4	7.7	71	324.37	349.0	285.0	3.5
Basilicata	8.3	7.5	7.9	71	324.89	367.4	305.0	3.9
Calabria	8.9	8.0	8.5	70	292.24	348.8	280.5	4.5
Sicily	8.4	7.4	7.9	71	272.73	349.5	280.0	3.7
Sardinia	7.2	5.9	6.5	71	326.92	374.4	316.6	3.7
Italy	**6.9**	**5.7**	**6.3**	**71**	**337.17**	**357.6**	**296.5**	**3.4**
North	6.1	4.6	5.3	72	393.34	373.1	300.0	2.6
Centre	7.0	6.0	6.5	72	289.23	336.5	270.0	4.4
South and Islands	8.0	6.9	7.4	71	306.93	353.4	300.0	3.7

Table 3.3.1d Exposure and duration of therapy with antidiabetics by Region under approved care regime and per conto distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Average cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
GLP-1 (glucagon-like one) analogues	1.0	0.6	0.8	67	808.42	222.6	187.5	6.2
Fast acting insulins	1.1	0.9	1.0	70	315.35	256.9	225.0	10.8
Long acting insulins	1.4	1.1	1.3	71	163.98	121.1	78.8	14.5
Glifozins (SGLT2 inhibitors) plain	0.8	0.4	0.6	70	265.55	197.2	168.0	8.6
Metformin	4.7	3.9	4.3	70	38.18	193.8	175.0	4.6
Gliptins (DPP-4 inhibitors) plain	0.5	0.5	0.5	79	280.80	238.1	252.0	5.5
Glifozins (SGLT2 inhibitors) in combination with metformin	0.5	0.2	0.4	66	321.82	246.3	280.0	5.7
Insulins combined with GLP-1 (glucagon-like one) analogues	0.2	0.1	0.1	71	762.72	161.8	150.0	14.6
Gliptins (DPP-4 inhibitors) in combination with metformin	0.4	0.3	0.3	73	273.16	260.3	300.0	4.0
Gliptins (DPP-4 inhibitors) in combination with glifozins (SGLT2 inhibitors)	0.1	0.1	0.1	71	428.83	229.0	240.0	7.6
Sulfonylureas plain	0.8	0.7	0.8	75	54.17	278.5	240.0	5.5
Repaglinide	0.3	0.2	0.3	78	68.76	170.6	112.5	9.6
Glifozins in combination with metformin	0.1	0.1	0.1	71	151.06	242.2	224.0	4.7
Glitazones plain	0.2	0.1	0.1	72	107.34	227.0	196.0	5.4
Acarbose	0.2	0.1	0.1	76	78.53	109.3	93.3	6.7
Gliptins (DPP-4 inhibitors) in combination with pioglitazone	0.03	0.02	0.02	72	312.86	263.7	308.0	4.3
Combined insulins (long/intermediate with fast)	<0.05	<0.05	<0.05	76	228.27	185.8	150.0	14.6
Sulfonylureas in combination with metformin	0.1	0.1	0.1	77	50.81	246.7	210.0	4.3
Sulfonylureas in combination with pioglitazone	0.01	<0.05	0.01	72	289.18	268.1	280.0	4.2
Antidiabetics	**6.9**	**5.7**	**6.3**	**71**	**337.17**	**357.6**	**296.5**	**3.4**

Table 3.3.1e Indicators of adherence to treatment with antidiabetics in the population aged ≥45 years during 2019-2022 and 2022-2021 change

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=72.469						North N=27.460					
45-54 years	21.6	22.3	21.7	21.6	0	0	16.4	17.2	16.0	15.9	0	-3
55-64 years	23.8	25.4	24.3	23.0	-5	-3	18.3	20.4	18.6	18.0	-3	-2
65-74 years	28.6	30.0	29.5	28.9	-2	1	22.3	24.6	24.1	24.8	3	11
75-84 years	34.5	34.0	33.5	32.4	-3	-6	29.5	30.7	29.5	28.6	-3	-3
≥ 85 years	34.6	36.9	37.1	34.6	-7	0	29.8	32.5	32.1	30.5	-5	2
Women	31.1	32.3	31.7	30.2	-5	-3	25.5	27.8	26.7	25.9	-3	1
Men	25.2	25.9	24.6	24.3	-1	-3	20.6	22.0	20.1	20.5	2	0
Total	**27.9**	**28.9**	**27.9**	**27.1**	**-3**	**-3**	**22.8**	**24.6**	**23.0**	**22.8**	**-1**	**0**
	Centre N=16.827						South N=28.182					
45-54 years	25.0	25.7	25.1	24.1	-4	-4	23.5	24.5	24.3	24.9	3	6
55-64 years	27.0	27.5	26.9	26.0	-3	-4	26.4	28.2	27.1	25.5	-6	-4
65-74 years	32.8	32.0	31.3	31.6	1	-4	32.0	33.6	33.3	31.4	-6	-2
75-84 years	36.8	35.3	35.1	35.0	0	-5	38.4	37.0	36.8	35.5	-4	-8
≥ 85 years	38.7	37.6	39.9	38.9	-2	0	36.8	41.3	40.5	36.4	-10	-1
Women	34.4	34.0	34.0	33.2	-2	-4	33.8	35.1	34.3	32.3	-6	-5
Men	28.5	28.0	26.9	26.8	0	-6	27.6	28.5	27.5	26.9	-2	-3
Total	**31.4**	**30.9**	**30.3**	**29.9**	**-1**	**-5**	**30.6**	**31.6**	**30.7**	**29.5**	**-4**	**-3**

continued

Table 3.3.1e – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=72.469						North N=27.460					
45-54 years	37.8	36.8	37.1	38.1	3	1	45.5	42.8	45.0	46.1	2	1
55-64 years	32.6	32.4	33.5	35.3	5	8	40.0	38.9	41.3	42.3	3	6
65-74 years	27.1	26.3	26.5	28.1	6	4	31.7	31.0	32.4	33.6	4	6
75-84 years	23.5	24.1	23.8	24.9	5	6	27.2	27.2	27.0	28.7	6	5
≥ 85 years	23.6	23.9	21.5	24.0	11	2	27.5	26.7	25.2	27.9	11	1
Women	26.3	25.9	25.7	27.1	6	3	31.7	30.3	31.1	32.8	5	3
Men	31.7	31.6	32.8	34.2	4	8	36.3	35.8	38.3	39.1	2	8
Total	**29.2**	**28.9**	**29.5**	**30.9**	**5**	**6**	**34.3**	**33.4**	**35.15**	**36.3**	**3**	**6**
	Centre N=16.827						South N=28.182					
45-54 years	32.7	33.4	32.0	34.3	7	5	35.0	33.9	33.7	33.5	-1	-4
55-64 years	27.7	28.7	28.7	31.7	10	14	29.3	29.3	30.4	31.2	3	6
65-74 years	22.9	24.3	21.9	24.8	13	8	25.3	23.2	24.3	24.7	2	-2
75-84 years	20.2	22.4	20.3	21.4	6	6	21.3	21.5	22.8	22.4	-2	5
≥ 85 years	19.7	27.1	20.5	20.9	2	6	22.1	18.8	18.3	21.7	18	-2
Women	22.2	24.2	21.8	23.3	7	5	24.0	23.0	23.7	24.2	2	1
Men	27.4	29.2	28.0	31.3	12	14	29.8	28.9	30.6	30.7	0	3
Total	**24.9**	**26.7**	**25.1**	**27.4**	**9**	**10**	**27.1**	**26.1**	**27.4**	**27.7**	**1**	**2**

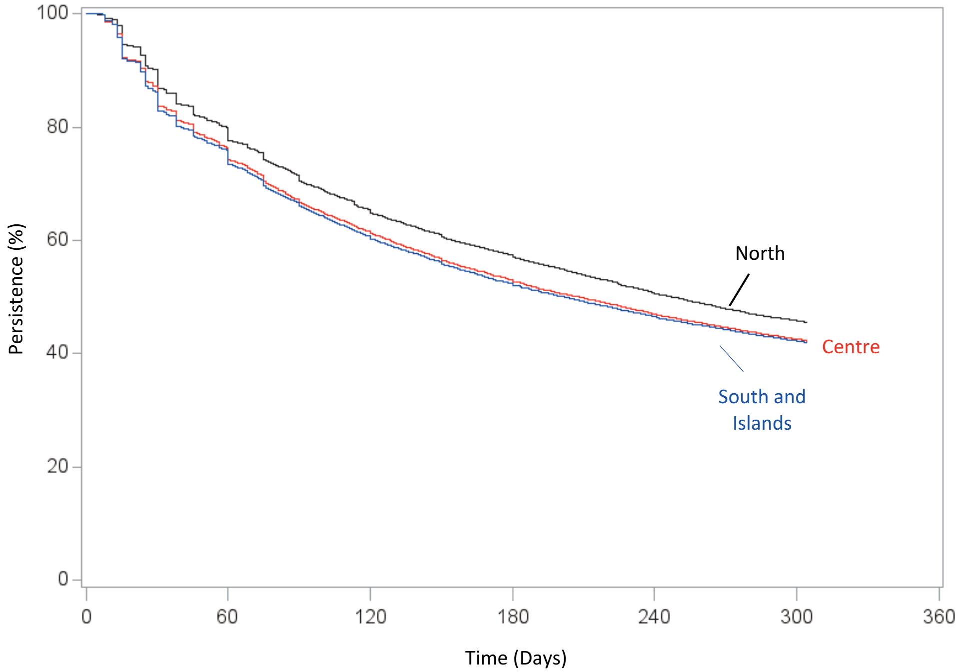
*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of people with low/high adherence relating to the specific category.
Median follow-up time (IQR): 328 (281-348)
‡ Excluding Emilia Romagna.

Table 3.3.1f Persistence to treatment with antidiabetics after one year in the population aged ≥45 years during 2019-2022 and 2022-2021 change

	Persistence after 12 months											
	2019	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**	**2019**	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**
	Total N=72.469						**North N=27.460**					
45-54 years	46.8	44.6	48.8	48.3	-1	3	49.7	48.8	52.7	52.2	-1	5
55-64 years	45.4	44.4	47.3	48.1	2	6	49.2	46.7	51.2	50.4	-2	2
65-74 years	41.2	39.5	42.5	42.4	0	3	42.4	41.4	43.8	44.3	1	5
75-84 years	34.0	32.5	35.5	36.6	3	8	35.2	34.1	36.6	37.9	4	8
≥ 85 years	28.8	26.9	29.1	30.4	5	5	31.5	29.4	32.9	34.6	5	10
Women	37.7	36.1	39.2	39.9	2	6	39.4	38.4	41.5	42.0	1	7
Men	43.4	42.0	46.1	45.9	0	6	45.1	43.3	47.7	47.5	0	5
Total	**40.8**	**39.2**	**42.9**	**43.1**	**1**	**6**	**42.6**	**41.1**	**45.0**	**45.1**	**0**	**6**
	Centre N=16.827						**South N=28.182**					
45-54 years	43.9	39.7	46.0	45.3	-1	3	46.2	44.1	47.4	46.6	-2	1
55-64 years	41.4	42.0	44.7	47.3	6	14	44.6	43.8	45.9	46.5	1	4
65-74 years	38.5	37.6	43.1	41.3	-4	7	41.7	39.0	41.0	41.3	1	-1
75-84 years	32.2	29.7	35.8	36.2	1	13	33.7	32.3	34.0	35.3	4	4
≥ 85 years	25.5	24.7	28.8	28.5	-1	11	28.3	25.7	25.1	26.9	7	-5
Women	34.8	32.9	37.8	38.0	0	9	37.9	36.0	38.1	39.3	3	4
Men	40.5	39.7	45.4	45.5	0	12	43.5	42.0	44.9	44.6	-1	2
Total	**37.7**	**36.4**	**41.8**	**41.8**	**0**	**11**	**40.9**	**39.1**	**41.8**	**42.1**	**1**	**3**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to the statistical methods).
^ Excluding Emilia Romagna

Figure 3.3.1d Time (in days) to discontinuation of treatment with antidiabetics in the population aged ≥45 years stratified by geographical area. Curves are adjusted by gender and age (the Cox model was used to estimate persistence curves). The North does not include Emilia Romagna



Year 2022 saw a further increase in the use of drugs for the treatment of type 2 diabetes mellitus belonging to the classes of GLP1 receptor agonists, SGLT2 inhibitors, and DPP4 inhibitors. The main reason for this increase can be attributed to the establishment of AIFA Note 100, which expanded the prescribing of these three classes from diabetologists only to General Practitioners and other SSN specialists (e.g. cardiologists or nephrologists) identified by the regions, as part of the National Diabetic Disease Plan aimed at making the diagnostic-therapeutic pathway more homogeneous. In addition, for only a few SGLT2 inhibitors, dapagliflozin and empagliflozin, a new therapeutic indication in chronic heart failure with reduced ejection fraction has been accepted for reimbursability. Although they are no longer recommended by national and international guidelines, drugs with secretagogue action (sulfanilureas and glinides) are still the third highest-use category, after metformin and insulins. Among all, the highest expenditure category (about 1/3 of the total) is GLP1 receptor agonists. This share can be explained by both the much higher cost per DDD than in the other categories, the increasing use (motivated by the effects of reducing HbA1c but also body weight, in an average overweight/obese population) and the switch within the category from short-acting active ingredients to longer-acting, higher-cost active ingredients (dulaglutide, semaglutide). This situation calls for the identification of diversified strategies, some of which have already been initiated, in order to ensure sustainability.

The gradual shift in therapy toward newer, higher-cost drugs is taking place throughout the country, with differences between regions and a greater increase in the North. The reduction in consumption and prevalence of use in the over 85 age group appears in line with the need in this age group to simplify therapeutic regimens towards for a more feasible home management and for a less intensive care objective. In this context, simplification aims mainly at reducing the risk of hypoglycaemia, which is more frequent in this age group and which can lead to serious consequences (cognitive deficiencies, trauma, fractures). In parallel, reducing long-term complications becomes secondary. The analysis on antidiabetic treatment adherence, although slightly improved from previous years, still shows a significant proportion of suboptimal treatment. This data is in line with previous studies promoted by AIFA in which non-adherence was observed in elderly patients and ranged between 13% and 64% for oral hypoglycaemic agents and between 19% and 46% for insulin therapy. Factors contributing to reduce adherence include both clinical aspects (comorbidities, cognitive and/or sensory deficiencies, depression) and aspects related to the medicinal product (polytherapy, complexity of the therapeutic regimen, adverse events) and the relationship with the general practitioner (poor interaction and/or information).

3.3.2 Medicines for peptic ulcer and GERD

- In 2022, on average, the consumption of medicines for peptic ulcer and GERD was 86.2 DDD/1000 inhabitants per day, with a 3% decrease compared to 2014 and a 0.4% average annual change rate in the 2014-2022 period (Figure 3.3.2a). Over the last 9 years, the average DDD cost has decreased from 0.54 to 0.40 euros. The per capita expenditure value for these drugs was 12.70 euros, a 2.8% reduction compared to the previous year and a 3.9% average annual reduction in the period 2014-2022 (Table 3.3.2a).
- With 81.3 DDD, proton pump inhibitors account for over 90% of the consumption of medicines for peptic ulcer and GERD, up by 1.9% compared to 2021 but stable over the 2014-2022 period (Figure 3.3.2b). They are also confirmed as the highest spending category, with a per capita value of 11.66 euros, despite the average DDD cost being the lowest (0.39 euros) in the category. Antacids follow with a per capita expenditure of 0.57 euros, registering an increase of more than 30% over 2021, mainly attributable to the trend of magaldrate.
- Pantoprazole is the agent with the highest per capita expenditure (€4.65) and consumption (29.0 DDD/1000 inhabitants per day), accounting for about 40% of the whole category. Omeprazole, esomeprazole and lansoprazole followed, with consumption values of 18.5, 15.9 and 14.4 DDD, respectively. Il lansoprazolo registra una contrazione del 3,5% con un aumento speculare dell'esomeprazolo (+3,2%). With the exception of sucralfate and magaldrate, the average cost per day of therapy is decreasing from 2021 for all molecules in this category.
- Analyzing the regional variability (Table 3.2.2b), it can be seen that the Southern regions have a higher drug consumption of 104.2 DDD/1000 inhabitants per day compared to 78 DDD in the North and 76.4 DDD in the Center. Consumption in Campania (126 DDD/1000 inhabitants per day) is more than double than the Autonomous Province of Bolzano (49.8 DDD). Compared with the previous year, in 2022 all regions recorded an increase in consumption, with the exception of a few including Umbria, which shows a 23% contraction, while Abruzzo shows the sharpest increase (+3.1%). All regions report a reduction in the average cost per DDD with values ranging from -1.7% in Valle d'Aosta and Trento PA to -5.7% in Umbria. Consistently with the observed consumption, the South of Italy shows higher per capita expenditure (15.72 euros) compared with the Centre (11.42 euros) and the North (11.15 euros).

Figure 3.3.2a Medicines for peptic ulcer and GERD, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

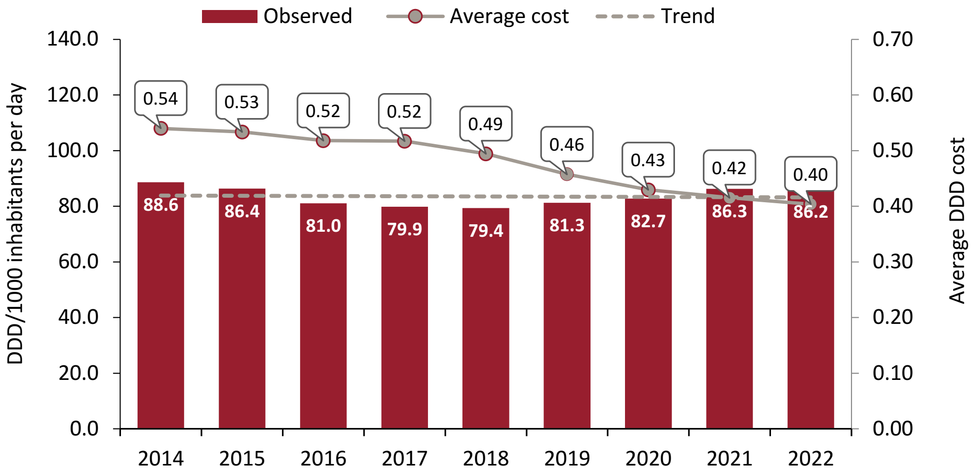


Table 3.3.2a Medicines for peptic ulcer and GERD, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Cost cost DDD	Δ % 22-21
Proton pump inhibitors	11.66	-0.5	-3.7	81.3	1.9	0.2	0.39	-2.3
Antacids	0.57	35.7	4.6	2.7	30.8	4.0	0.59	3.7
Other medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	0.41	-54.3	-8.2	2.0	-53.7	-8.4	0.57	-1.1
H2 receptor antagonists	0.05	45.0	-22.2	0.2	60.9	-25.7	0.63	-9.9
Prostaglandins	0.01	-13.5	-12.1	<0.05	-11.9	-11.1	0.99	-1.9
Medicines for peptic ulcer and GERD	**12.70**	**-2.9**	**-3.9**	**86.2**	**-0.1**	**-0.3**	**0.40**	**-2.8**
pantoprazole	4.65	2.7	-0.8	30.7	5.6	4.4	0.42	-2.7
esomeprazole	2.25	0.3	-2.3	15.9	3.2	2.2	0.39	-2.8
omeprazole	2.24	-3.0	-5.2	18.5	-0.1	-1.3	0.33	-2.9
lansoprazole	2.20	-4.3	-7.7	14.4	-3.5	-5.1	0.42	-0.8
magaldrate	0.57	36.8	4.7	2.5	35.2	4.3	0.62	1.2
sodium alginate/potassium bicarbonate	0.38	-56.5	-8.6	1.8	-56.3	-8.7	0.58	-0.4
rabeprazole	0.31	-5.9	-5.6	1.8	-3.5	-4.6	0.47	-2.4
famotidine	0.05	44.3	39.1	0.2	60.9	42.6	0.63	-10.3
sucralfate	0.03	1.6	-3.4	0.2	-0.6	-4.3	0.49	2.2
misoprostole	0.01	-13.5	-12.1	<0.05	-11.9	-11.1	0.99	-1.9

Figure 3.3.2b Medicines for peptic ulcer and GERD, temporal trends 2014-2022 in consumption (DDD/1000 population days) of the highest-spending subgroups

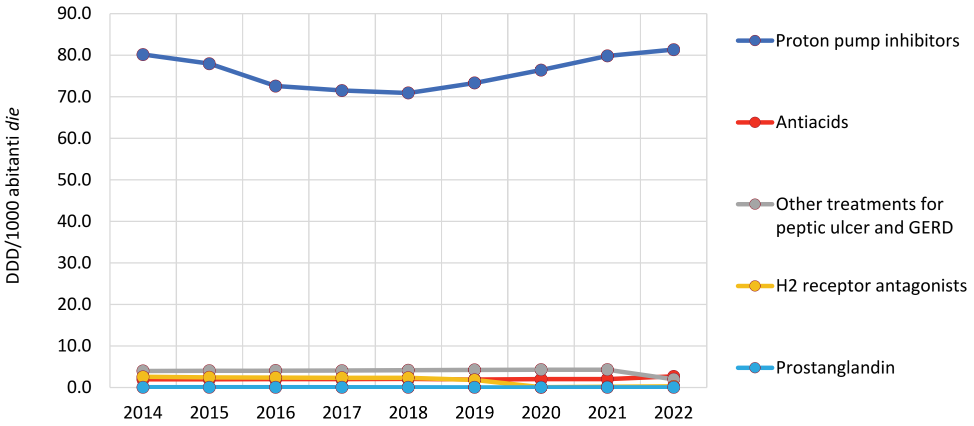


Table 3.3.2b Medicines for peptic ulcer and GERD, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD
Piedmont	10.53	72.4	0.40	10.36	73.1	0.39	-1.6	0.9	-2.5	-5.6	-1.6	-4.0
Valle d'Aosta	10.88	74.4	0.40	10.83	75.4	0.39	-0.4	1.4	-1.7	-3.9	-0.5	-3.4
Lombardy	12.18	83.2	0.40	12.12	84.6	0.39	-0.5	1.7	-2.1	-1.6	2.3	-3.7
Province of Bolzano	7.25	48.7	0.41	7.06	49.8	0.39	-2.6	2.3	-4.8	-1.4	1.8	-3.1
Province of Trento	12.93	87.6	0.40	12.90	88.9	0.40	-0.2	1.5	-1.7	-0.9	2.8	-3.6
Veneto	9.82	68.8	0.39	9.81	69.9	0.38	-0.1	1.6	-1.6	-5.2	-1.8	-3.5
Friuli V.G.	10.76	70.7	0.42	10.63	71.4	0.41	-1.3	1.0	-2.2	-4.2	-0.6	-3.6
Liguria	14.66	98.8	0.41	14.43	99.6	0.40	-1.6	0.8	-2.3	-2.8	0.5	-3.3
Emilia R.	10.53	71.3	0.40	10.45	72.9	0.39	-0.8	2.2	-2.9	-3.4	-0.7	-2.7
Tuscany	9.35	63.3	0.40	8.95	62.0	0.40	-4.3	-2.0	-2.3	-5.3	-1.7	-3.7
Umbria	13.07	85.3	0.42	9.41	65.1	0.40	-28.1	-23.7	-5.7	-7.4	-3.7	-3.8
Marche	10.43	66.6	0.43	10.04	65.9	0.42	-3.8	-1.0	-2.9	-6.4	-2.7	-3.8
Lazio	14.47	92.4	0.43	13.78	90.8	0.42	-4.8	-1.7	-3.1	-5.1	-1.6	-3.6
Abruzzo	14.23	89.4	0.44	14.19	92.2	0.42	-0.3	3.1	-3.3	-1.9	1.3	-3.2
Molise	14.22	91.3	0.43	14.32	93.9	0.42	0.7	2.8	-2.1	-3.0	0.5	-3.4
Campania	20.03	127.2	0.43	19.26	126.2	0.42	-3.8	-0.8	-3.1	-0.8	3.0	-3.7
Puglia	14.48	91.2	0.43	13.97	90.8	0.42	-3.5	-0.4	-3.1	-5.9	-2.3	-3.7
Basilicata	16.19	98.6	0.45	15.53	98.0	0.43	-4.1	-0.5	-3.6	-1.2	2.0	-3.2
Calabria	16.23	101.0	0.44	15.54	100.6	0.42	-4.3	-0.4	-3.8	-5.0	-2.0	-3.1
Sicily	15.09	100.1	0.41	14.46	99.2	0.40	-4.2	-0.9	-3.3	-5.0	-1.3	-3.7
Sardinia	14.12	93.7	0.41	13.99	95.7	0.40	-1.0	2.2	-3.0	-4.8	-1.6	-3.3
Italy	**13.08**	**86.3**	**0.42**	12.70	**86.2**	**0.40**	**-2.9**	**-0.1**	**-2.8**	**-3.9**	**-0.3**	**-3.6**
North	11.24	76.8	0.40	11.15	78.0	0.39	-0.8	1.5	-2.3	-3.4	0.2	-3.5
Centre	12.20	79.2	0.42	11.42	76.4	0.41	-6.4	-3.5	-3.0	-5.5	-1.9	-3.7
South and Islands	16.27	104.2	0.43	15.72	104.0	0.41	-3.4	-0.2	-3.2	-3.7	-0.1	-3.5

Exposure in population

- Health Card data were collected to perform an analysis aimed at estimating the general population exposure to medicines for peptic ulcer and GERD provided under approved care regime and *per conto* distribution. An analysis of prescription in the population shows an increasing use with increasing age but no meaningful differences between men and women (Figure 3.3.2c). The prevalence reaches over 50% in the ≥75 age group and 19.8% in the general population (Table 3.3.2c).
- The use tends to be higher in women than in men (21.7% v 17.7%) and the median age of users is 68 year. Analysing the regional variability, the prevalence of use is reportedly higher in the South (24.2%), compared with the Centre (19.3%) and the North (16.7%), it ranges from a low of 10.1% in the Province of Bolzano to a high of 27.5% in Campania.
- Over the year, each user consumed about 150 doses of the drug, corresponding to 5 months of treatment, and half of the users remain on treatment for less than 4 months, consistent with AIFA notes 1 and 48, while one in 5 received only one prescription during the year. Overall, the average cost per user was 61.64 euros, varying among macroareas (North: 64.03 - Centre: 58.11, South: 61.04 euros) and among individual regions, ranging from 50.64 euros in Umbria to 71.93 euros in the Province of Trento (Table 3.3.2c).
- 18.1% of the Italian population received at least one prescription for proton pump inhibitors during the year with slight differences between men and women (16.3% and 19.8% respectively) and an average cost per user of 61.78 euros. Utilization patterns for antacids involve shorter periods of therapy (median DDD 20 days), and about half of the users only one prescription (Table 3.3.2d).

Figure 3.3.2c Distribution of 2022 prevalence of use and consumption of medicines for peptic ulcer and GERD under approved care regime and per conto distribution

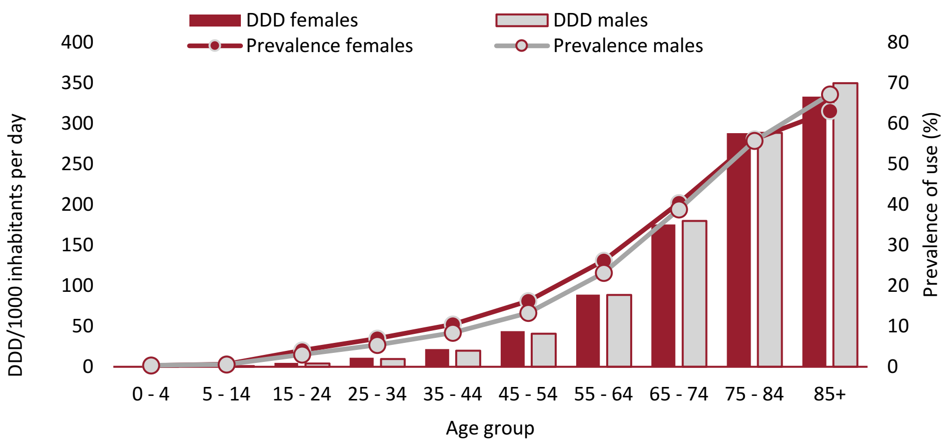


Table 3.3.2c Exposure and duration of therapy with medicines for peptic ulcer and GERD by region under approved care regime and per conto distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Piedmont	16.2	20.1	18.2	70	57.57	139.3	112.0	16.8
Valle d'Aosta	15.0	18.5	16.8	70	62.81	151.0	112.0	16.6
Lombardy	15.3	18.7	17.0	69	65.97	165.0	130.7	14.8
A.P. of Bolzano	9.3	10.9	10.1	70	62.88	141.6	93.3	19.7
A.P. of Trento	15.1	18.4	16.8	68	71.93	172.5	133.0	17.1
Veneto	12.6	15.2	13.9	70	67.38	164.6	112.0	17.5
Friuli V.G.	15.0	18.7	16.9	70	65.03	151.6	112.0	15.0
Liguria	19.7	24.6	22.2	72	68.96	165.4	140.0	14.6
Emilia R.	14.6	18.4	16.5	69	59.90	139.7	93.3	18.2
Tuscany	14.5	17.6	16.1	72	55.32	133.8	90.0	22.3
Umbria	16.9	20.2	18.6	71	50.64	123.6	84.0	20.6
Marche	16.1	18.6	17.4	71	57.07	133.2	105.0	19.3
Lazio	19.4	24.4	22.0	68	60.60	144.2	102.0	18.3
Abruzzo	20.9	25.5	23.3	68	58.60	138.0	98.0	19.8
Molise	20.7	24.6	22.7	70	62.23	149.2	112.0	16.7
Campania	24.8	30.0	27.5	64	62.94	150.0	112.0	17.3
Puglia	20.0	23.6	21.8	68	60.90	143.9	112.0	17.2
Basilicata	22.9	27.7	25.3	67	59.12	135.9	99.7	19.6
Calabria	22.3	26.3	24.4	68	60.48	144.0	112.0	17.6
Sicily	20.6	25.7	23.2	69	59.19	146.9	112.0	19.4
Sardinia	19.6	25.2	22.5	67	62.15	154.3	112.0	19.8
Italy	**17.7**	**21.7**	**19.8**	**68**	**61.64**	**148.7**	**112.0**	**17.7**
North	14.9	18.4	16.7	69	64.03	155.8	112.0	16.2
Centre	17.3	21.3	19.3	69	58.11	138.7	98.0	19.6
South and Islands	21.8	26.5	24.2	67	61.04	146.8	112.0	18.2

Table 3.3.2d Exposure and duration of therapy with medicines for peptic ulcer and GERD by region under approved care regime and per conto distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Proton pump inhibitors	16.3	19.8	18.1	69	61.78	153.3	112.0	17.4
Antacids	2.6	4.1	3.4	65	16.47	26.7	20.0	46.1
Other medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	1.9	2.6	2.2	66	18.03	31.2	16.0	30.2
H2 receptor antagonists	0.1	0.1	0.1	63	50.83	79.7	40.0	36.0
Prostaglandins	<0.05	<0.05	<0.05	72	61.96	55.4	37.5	32.5
Medicines for peptic ulcer and GERD	**17.7**	**21.7**	**19.8**	**68**	**61.64**	**148.7**	**112.0**	**17.7**

After the slight increase observed in previous years, consumption of drugs for peptic ulcer and MRGE remained stable in 2022, while per capita expenditure and average cost per day of therapy decreased slightly.The observed trends can basically be attributed to proton pump inhibitors (PPIs), which account for more than 90% of spending and consumption in the whole category. It is also important to point out that a large share of the use of the other main categories of drugs, such as antacids and H2-receptor antagonists, is not taken into account, as most of them are non-prescription drugs (OTC and SOP) and therefore purchased privately by the citizen. The wide regional variability in terms of consumption and prevalence of use that is observed for these drugs (a finding in line with what is observed for many therapeutic categories) can be attributed in part to differences in prescribing behavior by physicians and in part to the different share of private purchasing, both of OTC and SOP drugs and of class A drugs, which is quite significant for this category of drugs.
Consumption and prevalence of use increase with increasing age but, unlike many therapeutic categories, values do not decline in those over the age of 85. This finding confirms both the increased use of potentially gastrolesive drugs in this segment of the population and the possible high prevalence of gastrointestinal symptoms such as dyspepsia, reflux symptoms, and epigastric burning, which require their treatment.

The number of doses per user should reassure the appropriateness of the duration of therapy with PPIs, recommended in the first-line treatment of gastroduodenal ulcers and MRGE, diseases for which therapies of at least 4-8 weeks are required. The percentage of users with a single prescription, coupled with the prevalent use of PPIs, confirm the use of these drugs even in the treatment of upper digestive tract disorders for which there is no indication for inhibition of stomach acid secretion. It is useful to remember that these medicines do not lead to an immediate relief of burning symptoms and may require 2-3 consecutive days of treatment for symptoms to improve. Furthermore, their continued use is linked with a short-term increased risk of intestinal and lung infections, in addition to bone fracture after one year of use.

The use of antacids and other drugs for peptic ulcer and MRGE still appears to be high and has no valid counterparts in the pathophysiology of upper digestive tract disorders except in a small number of patients. A potentially improper use of these medicines can expose the patient to a reduced absorption of nutrients and other pharmaceuticals.

3.3.3 Metabolic disorders

- Over the last few years, medicines for the treatment of diseases resulting from impaired cellular metabolism has recorded negligible consumption (less than 0.05 DDD), but with an increase in per capita expenditure, due to the marketing of medicines for the treatment of diseases which, in many cases, were orphan. In 2022, the expenditure of these medicines reached a total of 9.04 euros per capita, up by 25.3% compared with the previous year, and an average DDD cost of 253.39 euros, down by 43.8% compared with the previous year due to renegotiation, at the end of 2021, of the price of tafamidis used in the treatment of hereditary amyloidosis (Table and Figure 3.3.a).
- The highest per capita expenditure is for Fabry disease, with 1.61 euros for enzyme replacement therapy (average DDD cost of 727.30 euros) and 0.39 euros for chaperone therapy (average DDD cost of 331.76 euros). In second place in descending order of expenditure is hereditary transthyretin amyloidosis (1.86; +171.6% over the previous year and an average annual increase of 37.6% since 2014) (Figure 3.3.3b) and an average cost per DDD of €97.86. This was followed by Pompe disease, for which only an enzyme therapy represented by alglucosidase alfa is available, which recorded a per capita expenditure of 1.42 euros in 2022 (+9.8% compared to 2021) and an average cost per DDD of 1062.25, which remains stable compared to the previous year.
- Algucosidase alpha also turns out to be the first active ingredient among those with the highest expenditure within the category, followed by tafamidis (1.13 euros per capita, +500% compared with 2021 as a result of the extension of indications that took place at the end of 2021) and agalsidase beta (0.91 euros, +17.8% compared with 2021). Both are used in the treatment of Fabry disease, as well as agalsidase alpha, which ranks fourth in spending (0.81 euros per capita), down by 8.7%. Patisiran is among the drugs with the largest increase in spending (+48%) over 2021 also indicated for transthyretin hereditary amyloidosis (Table 3.3.3a).
- There is a high variability in expenditure at regional level, ranging from a minimum value found in Valle d’Aosta (4.55 euros per capita) to a maximum value found in Campania (12.18 euros per capita) (Table 3.3.3b). At the macro area level, the South has more than 20% higher spending than the North (10.10 vs. 8.26). The lowest average cost per DDD of 146.32 euros was observed in Marche, while the highest value is more than three times higher (492 euros) and was observed in Calabria, this indicator decreases in all regions while spending increases from a low of +9% in Basilicata to a high of +61.8% in Valle d'Aosta.

Figure 3.3.3a Metabolic disorders, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

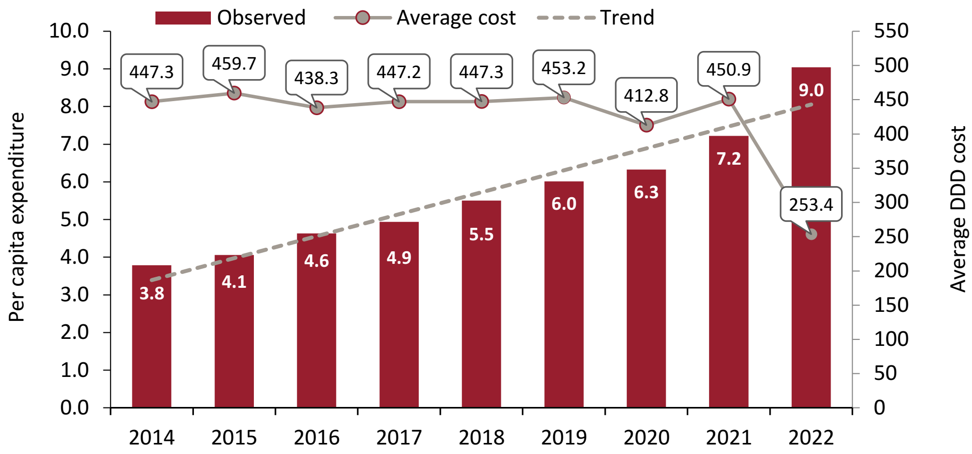


Table 3.3.3a Metabolic disorders, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Cost cost DDD	Δ % 22-21
Hereditary transthyretin-mediated amyloidosis	1.86	171.6	37.6	0.1	943.7	65.5	97.86	-74.0
Lysosomal storage diseases - Fabry disease - enzyme replacement therapy	1.71	3.7	7.5	<0.05	11.5	11.7	727.30	-7.0
Lysosomal storage diseases - Pompe disease - enzyme replacement therapy	1.42	9.8	6.8	<0.05	9.8	7.5	1062.25	0.0
Lysosomal storage diseases - type 1 Gaucher disease - enzyme replacement therapy	1.06	0.8	2.3	<0.05	0.9	2.1	1096.50	0.0
Lysosomal storage diseases - mucopolysaccharidosis II - enzyme replacement therapy	0.49	-6.4	1.2	<0.05	-2.6	1.5	2762.70	-4.0
Lysosomal storage diseases - type 1 Gaucher disease - chaperone therapy	0.42	17.2	17.9	<0.05	12.3	13.3	331.76	4.4
Lysosomal storage diseases - Fabry disease - chaperone therapy	0.39	5.5	-	<0.05	5.5	-	465.68	0.0
Lysosomal storage diseases - mucopolysaccharidosis IV-A (Morquio's syndrome) - enzyme replacement therapy	0.29	7.0	-	<0.05	7.0	-	2992.00	0.0
Congenital amino-acid transport and metabolism defects - phenylketonuria	0.22	15.1	9.2	<0.05	18.9	10.7	150.58	-3.3
Lysosomal storage diseases - mucopolysaccharidosis II - enzyme replacement therapy	0.19	4.3	6.3	<0.05	4.3	6.3	1433.74	0.0
Juvenile neuronal	0.17	132.7	-	<0.05	276.3	-	686.42	-38.2
Acute hepatic porphyria	0.15	96.6	-	<0.05	96.6	-	854.52	0.0
Lysosomal storage diseases - mucopolysaccharidosis VI - enzyme replacement therapy	0.14	-1.1	8.0	<0.05	-1.1	6.7	2869.64	0.0
Wilson's disease	0.11	23.9	40.5	<0.05	22.7	5.2	41.26	1.0
Primary hyperoxaluria (siRNA)	0.10	-	-	<0.05	-	-	1036.83	-
Lysosomal storage diseases - Liposomal acid lipase deficiency - enzyme replacement therapy	0.09	1.0	-	<0.05	9.5	-	1181.17	-7.8
Urea cycle disorders	0.08	3.6	10.1	<0.05	22.8	16.6	51.30	-15.6
Hypophosphatasia-enzyme replacement	0.04	-	-	<0.05	43.4	-	2555.74	-563.5
Lipodystrophy	0.03	22.8	-	<0.05	2.0	-	917.78	20.3

contiunued

Table 3.3.3a – *continued*

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Cost cost DDD	Δ % 22-21
Congenital amino-acid transport and metabolism defects - homocystinuria	0.03	25.8	4.9	<0.05	26.9	6.4	13.21	-0.9
Congenital amino-acid transport and metabolism defects - type 1 hereditary tyrosinemia	0.02	-25.5	-6.1	<0.05	-4.0	3.9	49.46	-22.4
Lysosomal storage diseases - alpha-mannosidosis - enzyme replacement therapy	0.01	19.2	-	<0.05	19.2	-	665.54	0.0
Congenital defects of amino acid metabolism and transport- cystinosis nephropathy manifested	0.01	25.6	7.2	<0.05	24.8	4.1	26.02	0.7
Medicines for impaired cellular metabolic function disease	**9.04**	**25.3**	**11.5**	**0.1**	**122.9**	**19.7**	**253.39**	**-43.8**
agalsidase alfa	1.42	9.8	6.8	<0.05	9.8	7.5	1062.25	0.0
tafamidis	1.13	534.7	29.4	<0.05	2121.8	63.9	64.67	-71.4
agalsidase beta	0.91	17.8	16.3	<0.05	17.8	16.3	483.63	0.0
agalsidase alfa	0.81	-8.7	2.0	<0.05	-7.8	2.0	1676.64	-0.9
imiglucerase	0.79	2.5	1.3	<0.05	2.5	1.3	1096.50	0.0
patisiran	0.67	48.0	-	<0.05	48.0	-	516.03	0.0
idursulfase	0.49	-6.4	1.2	<0.05	-2.6	1.5	2762.70	-4.0
migalastat	0.39	5.5	-	<0.05	5.5	-	465.68	0.0
eliglustat	0.38	23.7	-	<0.05	23.7	-	622.68	0.0
elosulfase alfa	0.29	7.0	-	<0.05	7.0	-	2992.00	0.0

Figure 3.3.3b Metabolic disorders, temporal trend 2014-2022 in per capita expenditure of most expensive subgroups

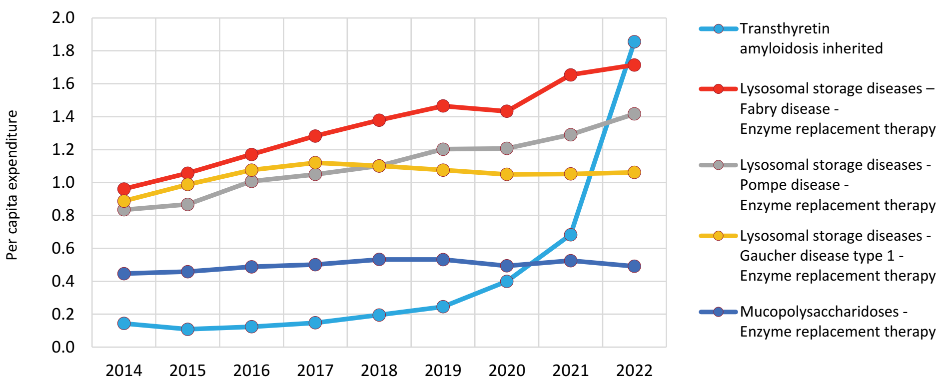


Table 3.3.3b Metabolic disorders, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: 2014-2022 comparison

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD
Piedmont	5.66	<0,05	503.34	6.59	0.1	253.11	16	131.6	-49.7	8.4	20.0	-9.7
Valle d'Aosta	2.82	<0,05	298.84	4.55	0.1	150.22	61.8	221.9	-49.7	101.3	38.2	45.7
Lombardy	6.03	<0,05	432.84	7.99	0.1	213.79	32.6	168.4	-50.6	11.0	24.3	-10.7
A.P. of Bolzano	4.83	<0,05	896.98	6.72	0.1	151.29	39.0	724.2	-83.1	14.7	41.7	-19.0
A.P. of Trento	8.16	0.1	351.77	9.83	0.1	187.59	20.5	126.0	-46.7	10.0	22.7	-10.3
Veneto	6.34	<0,05	378.68	8.33	0.1	206.19	31.4	141.3	-45.5	11.5	21.1	-7.9
Friuli V.G.	6.13	<0,05	520.83	8.15	0.1	189.20	33.0	266.0	-63.7	15.3	29.3	-10.8
Liguria	4.57	<0,05	374.91	5.67	0.1	192.84	23.9	140.9	-48.6	9.9	23.3	-10.9
Emilia R.	8.53	<0,05	523.53	11.51	0.1	262.88	34.9	168.7	-49.8	12.7	24.5	-9.4
Tuscany	6.45	<0,05	377.40	9.05	0.1	191.19	40.3	176.9	-49.3	14.0	23.5	-7.7
Umbria	6.63	<0,05	444.79	8.54	0.1	200.73	28.7	185.2	-54.9	9.5	19.8	-8.6
Marche	5.90	<0,05	516.34	8.01	0.1	146.32	35.7	379.0	-71.7	6.5	24.6	-14.5
Lazio	7.61	<0,05	465.66	9.62	0.1	286.96	26.4	105.1	-38.4	16.3	23.2	-5.6
Abruzzo	6.60	<0,05	443.81	8.01	0.1	211.15	21.5	155.3	-52.4	8.3	19.4	-9.3
Molise	4.69	<0,05	301.86	6.01	0.1	224.05	28.0	72.5	-25.8	13.1	19.8	-5.5
Campania	10.79	0.1	534.09	12.18	0.1	387.95	12.9	55.4	-27.4	10.1	14.4	-3.8
Puglia	7.31	<0,05	421.53	9.04	0.1	312.33	23.7	66.9	-25.9	14.3	13.7	0.5
Basilicata	7.29	<0,05	441.04	7.95	0.1	368.02	9.0	30.6	-16.6	11.1	13.5	-2.1
Calabria	10.02	<0,05	604.09	11.65	0.1	492.14	16.3	42.8	-18.5	10.0	8.7	1.2
Sicily	8.77	0.1	428.87	10.27	0.1	346.25	17.0	44.9	-19.3	9.7	11.7	-1.7
Sardinia	5.84	0.1	300.75	6.97	0.1	220.63	19.3	62.6	-26.6	13.5	11.3	2.0
Italy	**7.22**	**<0,05**	**450.89**	**9.04**	**0.1**	**253.39**	**25.3**	**122.9**	**-43.8**	**11.5**	**19.7**	**-6.9**
North	6.35	<0,05	448.01	8.26	0.1	221.51	30.1	163.1	-50.6	11.3	23.5	-9.9
Centre	6.94	<0,05	438.27	9.15	0.1	221.10	31.8	161.2	-49.6	13.5	23.2	-7.9
South and Islands	8.64	0.1	460.58	10.10	0.1	338.10	16.9	59.3	-26.6	10.8	13.1	-2.1

Although the category of drugs for the treatment of metabolic disorders registers negligible consumption over the years, there is a progressive increase in both per capita expenditure and consumption, justified by the market entry of new high-cost drugs for the treatment of diseases that in many cases are orphaned by therapies.
Drugs for the treatment of lysosomal storage diseases account for 70% of the expenditure of the entire category, with drugs for Fabry's disease ranking first for expenditure; recombinant human acid alglucosidase, enzyme replacement therapy for the treatment of Pompe’s disease, is instead the active ingredient with the highest per capita expenditure, also in 2022.
Tafamidis, indicated in the treatment of transthyretin, wild type, or hereditary amyloidosis in adult patients with cardiomyopathy, is the drug with the largest increase in consumption and per capita expenditure in 2022 (>100%), despite the fact that the average cost per day of therapy has been significantly reduced (-71%) due to the price renegotiation that took place at the end of 2021.

3.4 General antimicrobials for systemic use

General antimicrobials for systemic use are the fourth therapeutic category with the highest public expenditure for 2022, equal to 2616.4 million euros and 10.6% of overall public expenditure (Box. Main expenditure, consumption and exposure indices).
The overall per capita expenditure for such medicines was 44.32 euros, mainly due to the purchase by public health facilities (33.34 euros per capita). On the contrary, the contribution by the approved care regime was lower (10.98 euro per capita).
In 2022 there was an increase in spending on antimicrobials (+4.9%) with a reversal of the trend, which has been decreasing for the past two years. The increase in spending is found in both direct purchase from public health facilities (+1.7%) and approved care regime (+16.1%) (Table 3.1).
Consumption for this pharmaceutical category was equal to 21.1 DDD/1000 inhabitants per day, up 16.2% compared to 2021 (Table 3.2). Contrary to expenditure, approved care accounts for the highest quota of consumption, since almost 70% of doses are dispensed through this distribution channel.
The analysis of the drug use profile by age group and gender, including expenditure under approved care regime and on behalf distribution, indicates that the consumption of antimicrobials for systemic use increases with increasing age, and reaches the maximum value after 75 years of age, being higher in men (27.5 DDD/1000 inhabitants per day) than in women (21.8 DDD/1000 inhabitants per day). In the intermediate age groups, on the other hand, a more frequent use is confirmed in women than in men. At the same time, NHS per capita expenditure also increases with increasing age, reaching the maximum value of 23.7 euros and 20.5 euros per capita in men and women respectively, in subjects over 75 years of age.
Analysing the trends over the last six years (2017-2022) of the per capita expenditure, consumption and average cost per DDD of class A medicines and medicines purchased by public facilities (Figures 3.1-3.3), a fluctuating trend in both expenditure and average DDD cost appears evident, with maximum values in 2019 showing a slight decline in the following years. Per capita spending shows a slight increase in the last year attributable to an increase in consumptio
As regards approved care regime, the regional distribution (Table 3.5) shows a high variability (CV 30.1%) of gross per capita expenditure with maximum values in Campania (17.7 euros) and Calabria (17.3 euros) and minimums in the Province of Bolzano (5.1 euros) and Friuli VG (6.4 euro). The distribution of consumption (Table 3.6) shows similar trends (CV 26.0%). Overall, spending in this delivery channel increased by 15.6%, due solely to an increase in consumption (+22.7%). It can be seen that prices remain essentially stable, while there is a reduction in the average DDD cost (-5.8%) and a shift to lower-cost medicinal products (mix effect: -5.5%) (Table 3.9). Within this dispensing channel, penicillin combinations, including beta-lactamase inhibitors, are the category with the highest expenditure (2.72 euros), registering an increase of +23.9% related exclusively to an increase in consumption (+24.8%), followed by third-generation cephalosporins with a value of 2.46 euros per capita and an increase in both expenditure and consumption of +24.3% and 32.8%, respectively, and macrolides (1.58 euros per capita) up +34.9% and +38.7%, respectively. Among antimicrobial drugs, there is a worrisome increase in

fluoroquinolones both in terms of expenditure (+5.6%) and consumption (+7.9%), in the face of a reduction in average DDD cost (-2.2%) and a shift toward less expensive medicinal products (mix effect: -1.9%).
Amoxicillin in combination with clavulanic acid is the first active ingredient in the category by per capita expenditure (2.60 euros) and consumption (5.2 DDD) (Table 3.10), as well as being the only active ingredient in this category listed within the top +34.2 molecules with the greatest impact on outpatient expenditure (Table 3.10). In 2022, the active ingredients most commonly dispensed under approved care regime show major increases in consumption, with the only exception of fluconazole (-2.1%). In particular, clarithromycin (45.5%), cefixime (42.8%) and azithromycin (35.0%) show the largest increases.
The combination of amoxicillin/clavulanic acid is the only active ingredient in this category to be among the top 30 molecules with greater impact on approved care regime, with a total expenditure value of 153.4 million (Table 3.11). Ceftriaxone (11.99 euros), fluconazole (5.53 euros) phosphomycin (4.62 euros), ciprofloxacin (2,56 euro), cefixime (2.33 euros) and azithromycin (1.43 euros) are among the top thirty active ingredients with the highest average cost per day of therapy under approved care regime (Table 3.13). No systemic use antimicrobials are on the list of the top 30 active ingredients with the lowest DDD cost (Table 3.14). Clarithromycin (+48.8%), cefixime (+43.1%), azithromycin (+30.5%), amoxicillin in combination with clavulanic acid (+25.7%), ceftriaxone (+14.5%), and ciprofloxacin (+7.1%) are included among the top thirty active ingredients with the greatest change in spending over the previous year in this delivery channel (Table 3.15). For all active ingredients, the increase in spending is associated with a relative increase in consumption, while the average DDD cost remains almost stable, with only a slight increase for clarithromycin (+2.2%) and a decrease for azithromycin (-3.3%). Fluconazole is the only molecule in this ATC to be on the list of the top 30 active ingredients with the largest reduction in spending in contracted care (-2.5%) (Table 3.16). In contrast, no active ingredients are included in the list of those with the highest consumption in this delivery channel (Table 3.17).
As for purchases by public healthcare facilities, the regional distribution (Table 3.7) shows a moderate variability (CV 18.3%) of gross per capita expenditure with maximum values in Lombardia (39.6 euro) and in Emilia Romagna (39.4 euro) and minimum values in Molise (17.4 euro) and Calabria (24.3 euro). The distribution of consumption (CV 22.8%) (Table 3.8) shows higher values of use in Emilia Romagna (9.2 DDD) and in Veneto (6.6 DDD) and lower in Calabria and Sicily (3.4 DDD). Overall, there was a 1.3% increase in spending compared to 2021, linked to an increase in consumption (+0.6%), average DDD cost (+0.7%) and especially a shift to more expensive medicinal products (mix effect +1.7%; Table 3.19). Antiviral combinations for the treatment of HIV infections are the highest spending category (8.57 euros per capita), followed by flu vaccines (2.64 euros per capita). The latter group experienced a sharp decrease in spending (-14.3%) mainly due to a decrease in consumption (-15.0%) and a reduction in prices (-10.3%), although there was a shift toward more expensive medicinal products (mix effect: +12.4%). The varicellosis zoster vaccines category records a more than threefold increase in expenditure value compared to last year (+355.5%), correlated with an increase in consumption (+97%) and a shift to more expensive medicinal specialties (mix effect: +133.2%).

The active ingredients with the highest expenditure are represented by the combination of emtricitabine/tenofovir alafenamide/bictegravir (2.28 euros per capita), remdesivir (2.01 euros), the combination of dolutegravir/lamivudine (1.57 euros) and the human papilloma virus vaccine (1.44 euros) (Table 3.20). Overall, there is a sustained increase in spending and consumption for the two HIV drugs and papilloma virus vaccine and a 10.7% decrease in spending and 11.8% decrease in consumption for remdesivir. The latter, along with the combination of emtricitabine/tenofovir alafenamide/bictegravir is on the list of the top thirty active ingredients by expenditure of drugs purchased by public facilities, with a total value of 118.6 and 134.7 million, respectively (Table 3.21). Among the molecules with the greatest change in spending in 2022 are the adjuvanted recombinant zoster vaccine (>100%), the dolutegravir/lamivudine combination (+44.9%), the emtricitabine/ tenofovir alafenamide/bictegravir combination (+26.0%), and the human papilloma virus vaccine (+21.4%) (Table 3.23). Seven active ingredients belonging to antimicrobials are included among the molecules with the greatest reduction in spending (Table 3. 24) and they are: the combination dolutegravir/abacavir/lamivudine (-26.6%), the inactivated trivalent split influenza virus vaccine (-17.2%), the combination emtricitabine/rilpivirine/tenofovir alafenamide (-12.7%), the adjuvanted tetravalent influenza vaccine from inactivated virus, surface antigen (-11.5%), the meningococcal B vaccine (-10.8%), remdesivir (-10.7%), and the combination emtricitabine/tenofovir alafenamide/darunavir/cobicistat (-2.9%). Human immunoglobulin for extravascular administration (€454.3), remdesivir (€379.5), adjuvanted recombinant zoster vaccine (€272), and amphotericin B (€101.6) are the antimicrobials that rank among the highest DDD cost active ingredients (Table 3.25). The lowest-cost active ingredients (Table 3.26), on the other hand, include tetravalent influenza vaccines, one of which is the split inactivated (€8.50) and the other is the one consisting of the adjuvanted surface antigen (€14.87). In contrast, no systemic use antimicrobials are among the highest consumed antimicrobials (Table 3.27). Overall, considering both approved care regime and direct purchases, the top 30 active ingredients by expenditure include: the combination amoxicillin/clavulanic acid (159.8 million and emtricitabine/tenofovir alafenamide/bictegravir (134.7 million) (Table 3.28). In contrast, no active ingredient of this ATC is on the list of the highest consumed molecules (Table 3.29).

Table 3.30 shows the different trend in terms of expenditure, consumption and average DDD cost between the approved care regime and direct purchases for antibiotics, HIV antivirals, vaccines, and antifungals.

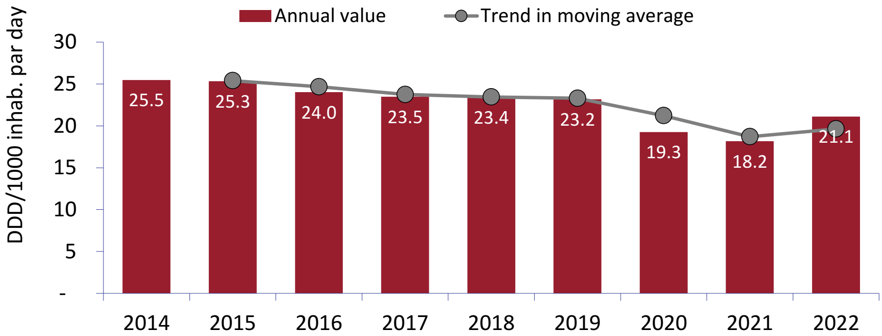
Analyses of the historical series of consumption and expenditure by active ingredient and by Region have been carried out for more information on the use of medicines belonging to the same therapeutic area. These analyses focused on antibiotics, antifungals, anti-HIV antivirals and vaccines (Table 3.4.1 and following).

Main indices of expenditure, consumption and exposure

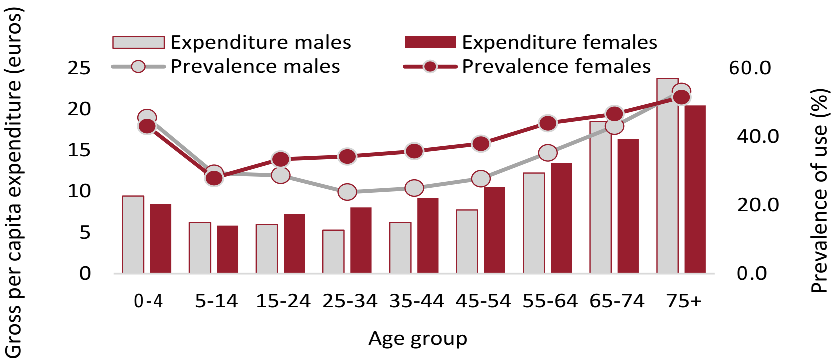
Antimicrobials for systemic use

Public expenditure* in EUR million (% over total)	**2,616.4**	**(10.6)**
Δ % 2022-2021		4.9
Regional range of gross per capita expenditure:	30.4	48.8
DDD/1000 inhabitants per day* (% over total)	**21.1**	**(1.6)**
Δ % 2022-2021		16.2
Regional range DDD/1000 inhabitants per day	13.1	26.7

* *includes prescriptions under approved care regime and purchases by public health facilities*



Breakdown of prevalence of use and consumption under approved care regime and distribution on behalf by age and gender in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	9.4	8.5	9.0	13.8	12.4	13.1
5-14	6.2	5.8	6.0	9.6	8.9	9.3
15-24	6.0	7.2	6.6	10.5	11.8	11.1
25-34	5.3	8.1	6.6	8.5	12.3	10.4
35-44	6.2	9.2	7.7,	9.6	13.9	11.7
45-54	7.7	10.5	9.1	11.4	15.4	13.4
55-64	12.2	13.5	12.9	16.1	19.0	17.6
65-74	18.5	16.4	17.4	22.2	21.6	21.9
75+	23.7	20.5	21.8	27.5	23.7	25.2

3.4.1 Antibiotics

- In 2022, there is a recovery in the consumption of systemic antibiotics, standing at 16.1 DDD/1000 inhabitants per day (+24.0% compared to 2021), corresponding to a per capita expenditure of 13.22 euros (+19.2% compared to the previous year; Figure 3.4.1a and Table 3.4.1a), while the average cost per DDD, after an increase in 2021, shows a decrease in 2022 of 3.9% and is 2.24 euros.
- Penicillin combinations, almost entirely represented by amoxicillin+clavulanic acid, remain the category of antibiotics with the highest prescription (5.7 DDD), with an expenditure of 3.35 euros per capita in 2022 (+24.5% and +19.9% compared to 2021 for consumption and expenditure, respectively). They are followed in consumption by macrolides and lincosamides (3.8 DDD). For these two categories, although there is an increase in consumption in the last year, the average annual change is negative (-1.5% and -1.4% respectively) (Figure 3.4.1b). Similar to 2021, the second largest category in terms of spending is 3rd generation cephalosporins (2.99 euros per capita). Most subgroups of antibiotics showed an increase in consumption compared to the previous year, except for polymyxin (-18.9%) and monobactams (-10.8%). Important variations were observed among the highest-consumption subgroups, such as for macrolides and lincosamides (+39.2%) and 3rd generation cephalosporins (+30.6%) (Table 3.4.1a). The subgroup that has seen the greatest increase, both in terms of expenditure and consumption, is the other cephalosporins and penemes (>200%); while the cost per DDD of this subgroup has remained stable and is the highest in the entire category (220.48 euros). The second subgroup by expenditure change is carbapenems (+39.2%), which also note increases in consumption (+16%) and average cost per DDD (+19.4%). This trend is attributable to the entry into the market of two new combinations: imipenem/cylastatin/relebactam and meropenem/vaborbactam. Both are indicated in the treatment of infections due to gram-negative aerobic organisms in adults with limited therapeutic options.
- Amoxicillin+clavulanic acid, a broad spectrum medicines widely used in paediatrics, confirms as the most widely used molecule with 5.6 DDD, followed by azithromycin and clarithromycin. All these molecules recorded a decrease in consumption compared to 2021: 24.9%, 36.3% and 44.3%, respectively. In contrast, a decline in spending and consumption is noted for the ceftazidime/avibactam combination (-16% and -14.3% respectively) compared to 2022. This association has one of the highest average costs in the category (190.50 euros). Ceftriaxone and cefixime, the second and third substances by expenditure, are the 3rd generation cephalosporins that increase the most (+14.6% and +43%).
- Despite a decreasing trend in consumption in all Regions, a wide variability is still observed, although smaller in magnitude than in the previous year, with values ranging from 9.7 DDD in the Province of Bolzano to 22.3 DDD in Campania (Table 3.4.1b). Regional variability in consumption is also reflected in per capita expenditure, with a maximum value recorded in Campania (18.92 euros) and a minimum value recorded in the Province of Bolzano (7.14 euros). The average cost per DDD decreases in all regions except Friuli VG (+0.2%), and the largest changes from 2021 are observed in the Province of Bolzano (-9%), Tuscany (-8.2%) and the Province of Trento (-8.1%). Comparing the

consumption and the average cost of dispensed doses, it should be noted that most Regions in the Centre and the South have a number of doses and average cost per day of therapy higher than the national average while, on the contrary, Northern Regions show lower consumption and average cost (Table 3.4.1.b).

Figure 3.4.1a Antibiotics, temporal trend in per capita expenditure and average cost per day of therapy (2014-2022)

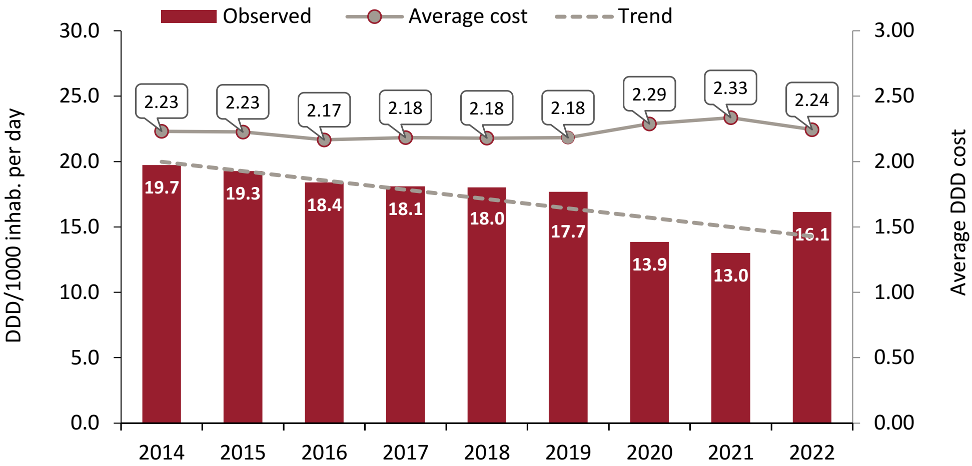


Table 3.4.1a Antibiotics, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Cost cost DDD	Δ % 22-21
Penicillin combinations (including beta lactamase inhibitors)	3.35	19.9	-0.7	5.7	24.5	-1.5	1.60	-3.7
Third-generation cephalosporins	2.99	16.8	-1.7	2.0	30.6	-0.3	4.06	-10.6
Macrolides and lincosamides	1.65	34.0	-1.9	3.8	39.2	-1.4	1.18	-3.7
Fluroquinolones	1.25	4.7	-8.6	1.7	8.6	-8.8	2.04	-3.6
Other antibacterials	1.14	-1.7	-3.7	0.5	8.5	3.5	6.10	-9.4
Other cephalosporins and penems	0.74	209.4	112.1	<0.05	220.5	91.9	220.48	-3.5
Carbapenems	0.43	39.2	-1.8	0.1	16.6	-0.4	17.08	19.4
Glycopeptides	0.34	0.7	-10.6	0.1	10.3	-3.5	18.26	-8.7
Broad-spectrum penicillins	0.27	20.3	-3.2	0.9	24.4	-6.8	0.81	-3.3
Polymyxin	0.17	-12.4	-1.7	<0.05	-18.9	-1.7	36.82	8.0
Tetracyclines	0.16	-5.2	-12.2	0.4	-0.2	0.8	1.17	-5.0
Aminoglycosides	0.13	-3.3	-5.7	<0.05	-7.5	-7.2	8.60	4.6
First-generation cephalosporins	0.11	3.4	-0.6	0.1	7.9	-0.6	2.82	-4.2
Second-generation cephalosporins	0.09	31.8	-9.5	0.1	34.4	-8.5	1.76	-1.9
Sulphonamides (plain and in combination)	0.08	5.9	1.9	0.4	7.3	2.1	0.53	-1.3
Beta-lactamase resistant penicillins	0.08	13.7	21.6	<0.05	16.2	8.5	6.65	-2.1
Fourth-generation cephalosporins	0.07	2.4	-0.4	<0.05	8.7	2.9	20.54	-5.8
Other combinations	0.06	16.3	-	<0.05	16.4	-	6.70	0.0
Nitrofuran derivatives	0.05	3.0	74.9	0.2	3.3	51.2	0.92	-0.3
Monobactams	0.03	-10.8	-2.7	<0.05	-10.8	-2.7	88.12	0.0
Imidazole derivatives	0.02	4.9	-0.3	<0.05	8.4	1.0	1.01	-3.2
Beta-lactamase sensitive penicillins	0.01	789.1	-4.8	<0.05	-83.5	-25.7	50.05	5294.7
Amphenicols	0.00	25.9	-2.2	<0.05	56.2	-1.3	5.26	-19.4
Antibiotics	**13.22**	**19.2**	**-2.4**	**16.1**	**24.0**	**-2.5**	**2.24**	**-3.9**
amoxicillin/clavulanic acid	2.71	25.9	-1.6	5.6	24.9	-1.6	1.33	0.7
ceftriaxone	1.02	14.6	-5.5	0.4	15.0	-2.5	6.37	-0.3
cefixime	1.00	43.0	1.7	1.2	42.7	1.9	2.28	0.2
azithromicyn	0.96	30.2	3.7	1.9	36.3	4.3	1.38	-4.5
fosfomycin	0.86	5.1	4.6	0.4	1.6	1.3	5.85	3.5
ciprofloxacin	0.65	7.1	-6.6	0.7	7.6	-6.0	2.40	-0.4
piperacillin/tazobactam	0.61	-0.9	6.8	0.2	11.3	7.5	10.57	-11.0
clarithromycin	0.60	46.6	-6.1	1.8	44.3	-4.7	0.90	1.6
levofloxacin	0.48	6.0	-8.5	0.8	11.8	-9.8	1.59	-5.1
ceftazidime/avibactam	0.39	-16.0	-	<0.05	-14.3	-	190.50	-2.0

Figure 3.4.1b Antibiotics, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) by subgroups with the highest expenditure

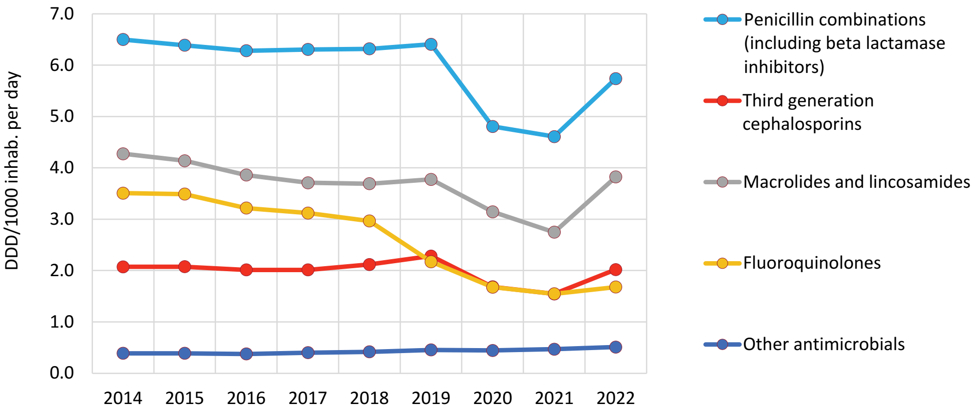


Table 3.4.1b Antibiotics, temporal trend of per capita regional expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD
Piedmont	8.67	10.5	2.26	10.78	13.6	2.18	24.3	29.4	-3.9	-2.4	-2.3	-0.1
Valle d'Aosta	8.26	10.5	2.15	9.66	12.9	2.05	16.9	22.5	-4.6	-4.1	-3.3	-0.8
Lombardy	8.16	10.3	2.17	10.06	13.2	2.09	23.3	28.5	-4.0	-1.6	-2.4	0.9
Province of Bolzano	6.10	7.6	2.21	7.14	9.7	2.01	17.0	28.6	-9.0	-3.9	-2.9	-1.1
Province of Trento	8.49	11.1	2.09	9.87	14.1	1.92	16.3	26.6	-8.1	-3.1	-1.9	-1.2
Veneto	9.04	9.9	2.50	10.51	12.4	2.32	16.2	25.3	-7.3	-2.0	-3.0	1.0
Friuli V.G.	8.34	10.2	2.24	10.04	12.3	2.24	20.3	20.1	0.2	-0.9	-2.4	1.5
Liguria	10.04	9.8	2.82	12.54	12.9	2.66	24.9	32.2	-5.5	0.0	-1.3	1.3
Emilia R.	9.01	11.5	2.15	11.09	15.0	2.03	23.0	30.7	-5.9	-1.7	-2.1	0.3
Tuscany	9.98	11.8	2.31	11.48	14.8	2.12	15.0	25.3	-8.2	-3.4	-3.0	-0.4
Umbria	14.56	14.7	2.71	16.87	18.2	2.55	15.9	23.3	-6.0	-1.2	-2.5	1.4
Marche	13.11	14.0	2.58	15.13	17.5	2.37	15.3	25.2	-7.8	-2.5	-2.5	-0.1
Lazio	12.46	14.2	2.40	15.20	17.7	2.36	22.0	24.3	-1.8	-2.1	-2.3	0.3
Abruzzo	14.12	15.8	2.44	18.66	20.9	2.44	32.2	32.4	-0.2	0.2	-1.0	1.3
Molise	11.23	14.1	2.18	13.08	17.5	2.05	16.5	23.8	-5.9	-4.5	-2.9	-1.6
Campania	16.72	19.1	2.40	18.92	22.3	2.33	13.1	16.5	-2.9	-3.0	-2.5	-0.5
Puglia	14.39	16.7	2.37	16.30	19.7	2.26	13.3	18.4	-4.3	-4.3	-3.4	-0.9
Basilicata	13.57	15.7	2.36	15.77	19.5	2.22	16.2	24.1	-6.3	-2.0	-2.1	0.1
Calabria	14.85	16.4	2.48	18.22	20.2	2.47	22.6	23.2	-0.5	-2.1	-2.3	0.1
Sicily	12.82	15.8	2.22	15.23	18.9	2.20	18.8	19.8	-0.8	-2.8	-2.2	-0.6
Sardinia	8.83	11.4	2.12	10.74	14.1	2.09	21.7	23.3	-1.4	-3.5	-3.1	-0.5
Italy	**11.09**	**13.0**	**2.33**	**13.22**	**16.1**	**2.24**	**19.2**	**24.0**	**-3.9**	-2.4	**-2.5**	**0.1**
North	8.62	10.4	2.28	10.51	13.3	2.16	21.9	28.3	-5.0	-1.8	-2.4	0.6
Centre	11.91	13.4	2.43	14.12	16.8	2.31	18.6	24.6	-4.8	-2.4	-2.6	0.2
South and Islands	14.11	16.5	2.34	16.54	19.8	2.29	17.2	20.0	-2.3	-2.9	-2.5	-0.4

Exposure in population

- Health Card data were collected to perform an analysis aimed at estimating exposure to antibiotics in the general population in 2022. About three out of ten people received at least one antibiotic prescription during the year, with higher levels of use in children up to 4 years of age and in people over 75 years old. There is a higher prevalence in women than men (38.7% vs. 32.2%), with more marked differences between 35 and 54 years of age, probably driven by the use of antibiotics in the treatment of urinary tract infections in women. The median age of users is 53 years and each subject is treated on average for 2 weeks, costing EUR 25.45. Moreover, 40.7% receives only one prescription during the year (Table 3.4.1c).
- Prevalence of use tends are higher in the Southern regions (43.3%), compared to Central (37.9%) and Northern regions (28.9%). The South also has a higher number of DDDs per user (South: 15 DDD *vs* Centre: 14.5 DDD and North: 14 DDD) and a higher cost per user than the Centre and the North (28.38 euros in the South and 26.86 euros in the Centre compared to 22.02 euros in the North; Table 3.4.1c). Abruzzo, Apulia and Campania are the regions with the highest levels of prevalence of use (around 45%), more than twice as high as the Province of Bolzano, which notes the lowest values (20.6%). Campania and Calabria have the highest average cost per DDD, exceeding 30 euros, while the Province of Bolzano has a cost of less than 20 euros.
- Penicillin combinations including beta-lactamase inhibitors and macrolides and lincosamides have the highest exposure in the population, with values of 16% and 11.2% respectively. Third-generation cephalosporins follow (7.9%) and fluroquinolones (5,9%). There is wide variability in the median age of antibiotic users, ranging from 37 years for beta-lactamase-sensitive penicillins to more than 70 years for aminoglycosides, glycopeptides, and 4th generation cephalosporins. For the latter two categories we note low levels of exposure and lower levels of sporadic prescribing (7.1% and 3.4% respectively), but high costs per user of 589 euros and 110 euros respectively. On average, each user receiving tetracyclines was treated for 3 weeks (3.4.1d).

Figure 3.4.1c Distribution of prevalence of use and consumption of antibiotics for systemic use under approved care regime and on behalf distribution in 2022

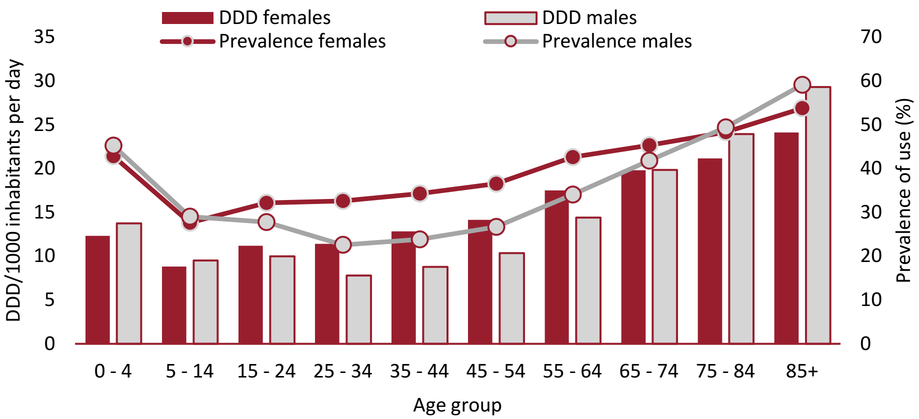


Table 3.4.1c Exposure and duration of therapy with antibiotics for systemic use by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Piedmont	28.2	34.8	31.6	54	21.95	13.7	10.0	42.3
Valle d'Aosta	23.0	29.6	26.4	54	21.65	13.9	10.0	41.2
Lombardy	25.6	30.9	28.3	50	22.77	14.3	10.0	39.1
A. P. of Bolzano	18.3	22.9	20.6	46	18.79	12.1	8.0	50.4
A. P. of Trento	26.6	32.7	29.7	49	21.78	14.2	10.0	40.6
Veneto	24.1	29.7	27.0	52	21.59	13.8	10.0	42.2
Friuli V.G.	22.1	28.2	25.2	53	22.50	15.7	14.0	32.1
Liguria	28.3	33.8	31.2	56	23.98	13.8	10.0	40.5
Emilia R.	27.7	34.0	30.9	51	20.48	13.6	10.0	43.0
Tuscany	30.8	37.2	34.1	54	22.07	13.7	9.0	48.6
Umbria	36.9	44.2	40.7	54	24.18	14.7	10.0	40.5
Marche	37.9	44.1	41.1	52	25.52	14.1	10.0	41.7
Lazio	34.9	42.8	39.0	53	28.35	15.1	10.0	38.4
Abruzzo	42.1	49.6	45.9	53	26.38	14.8	10.0	41.5
Molise	39.1	46.3	42.7	55	26.90	14.4	10.0	40.9
Campania	40.9	48.2	44.7	52	32.11	15.8	10.0	35.9
Puglia	41.0	48.5	44.8	52	27.32	14.7	10.0	41.3
Basilicata	40.2	48.0	44.2	54	26.14	14.8	10.0	40.3
Calabria	39.4	45.7	42.7	55	31.54	15.8	10.0	37.6
Sicily	39.3	46.2	42.8	54	25.60	14.4	10.0	43.4
Sardinia	29.9	38.0	34.0	53	23.91	13.9	10.0	44.6
Italy	**32.2**	**38.7**	**35.5**	**53**	**25.45**	**14.5**	**10.0**	**40.7**
North	26.0	31.7	28.9	51	22.02	14.0	10.0	40.8
Centre	34.2	41.3	37.9	54	25.86	14.5	10.0	41.9
South and Islands	39.5	46.8	43.3	53	28.38	15.0	10.0	40.0

Table 3.4.1d Exposure and duration of therapy with antibiotics by subgroup under approved care regime and per conto distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Combinations of penicillins (including	15.2	16.8	16.0	51	16.61	11.7	7.0	57.5
Third-generation cephalosporins	7.3	8.4	7.9	55	30.56	7.8	5.0	48.0
Macrolides and lincosamides	10.1	12.3	11.2	51	14.04	11.7	10.0	58.0
Fluroquinolones	5.4	6.4	5.9	65	18.89	9.1	6.0	39.0
Other antibacterials	1.4	6.1	3.8	63	16.56	3.6	2.0	64.3
Glycopeptides	0.0	0.0	0.0	71	589.28	8.8	5.5	7.1
Broad-spectrum penicillins	2.7	3.2	2.9	42	6.04	10.7	8.0	60.9
Tetracyclines	0.5	0.5	0.5	42	15.74	23.9	20.0	39.7
Aminoglycosides	0.1	0.1	0.1	72	59.98	6.9	5.1	5.3
First-generation cephalosporins	0.1	0.1	0.1	60	15.12	7.4	4.0	37.0
Second-generation cephalosporins	0.4	0.5	0.5	41	15.72	10.2	10.0	41.8
Sulphonamides (plain and in combination)	0.8	0.7	0.8	66	7.51	15.8	8.0	66.1
Beta-lactamase resistant penicillins	<0.05	<0.05	<0.05	57	16.75	9.2	6.0	72.9
Fourth-generation cephalosporins	<0.05	<0.05	<0.05	76	109.67	3.2	3.0	3.4
Other combinations	0.1	0.1	0.1	56	71.33	10.6	10.0	95.6
Nitrofuran derivatives	0.2	0.6	0.4	69	13.45	14.4	10.0	70.9
Imidazole derivatives	<0.05	<0.05	<0.05	68	51.72	3.1	2.0	20.5
Beta-lactamase sensitive penicillins	<0.05	<0.05	<0.05	37	70.91	0.9	0.8	44.8
Amphenicols	<0.05	<0.05	<0.05	61	31.79	8.2	6.0	51.9
Antibiotics	**32.2**	**38.7**	**35.5**	**53**	**25.45**	**14.5**	**10.0**	**40.7**

In 2022, there is a resurgence in the consumption of systemic antibiotics after the sharp reduction observed during the COVID-19 pandemic. The largest increases were in penicillin combinations (including beta-lactamase inbitors), covering one-third of consumption, macrolides and lincosamides, and third-generation cephalosporins. These data, also in the light of what has recently been experienced with the COVID-19 pandemic, suggest on the one hand the need for antibiotic therapy guidelines for the territory, with related awareness campaigns to stem the observed increases, and on the other hand the need to initiate audits and more in-depth analyses. For example, a cross-match of data could be conducted on platforms such as Premal or with microbiological/epidemiological DataBase, in order to correlate increased consumption trends in relation to data from microbiologies, infectious disease reports and possibly even hospitalization, so as to highlight any increases in the spread of pathogenic bacteria. This last reflection also stems from the observed increase in the consumption of amoxicillin/clavulanic acid and amoxicillin alone, which could find its partial explanation in the increase of group A streptococcal infections recorded throughout Europe and also in Italy, as a possible post-COVID-19 effect for reduced antigenic exposure.

References

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3.4.2 Antiretroviral agents for the treatment of HIV

- In 2022, per capita expenditure for antiretroviral agents purchased directly by public facilities was € 10.40, substantially stable compared to the previous year. This was driven by a reduction in consumption (-3.3%) offset by an increase in average cost per DDD (+3.8%) (Table and Figure 3.4.2a). In general, compared to 2014, the expenditure for this category of medicines recorded a reduction of 13.7% and an average annual decrease rate (CAGR) of 1.8%. The average cost per DDD showed a decreasing trend in the period 2018-2020, and then increased in the last two years to reach 11.32 euros in 2022. The total consumption for this category of medicines was 2.5 DDD per 1000 inhabitants per day, down 10.4% compared to the previous year, with an average annual growth rate (CAGR) of 0.2% over the period 2014-2022.
- Combination antiretroviral therapy comprising 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and 1 integrase strand transfer inhibitors (INSTI) account for 30.8% of the expenditure for this category of pharmaceuticals, with a 1.7% increase compared to 2021 and an average annual growth rate (CAGR) of 69.6% compared to 2014. Consumption increases by 3.8% compared to 2021, while the average DDD cost decreases by 2%. Despite this it remains among the highest in the entire category (20.50 euros).
- Considering the trend in consumption, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) show the highest value, equal to 0.9 DDD per 1000 inhabitants per day, despite a decrease (9.3%) compared to the previous year. This corresponds to a per capita expenditure of 0.74 euros, down 13.5% from 2021. Among combination antiretroviral therapies, those with a non-nucleoside reverse transcriptase inhibitor (NNRTI) and an integrase strand transfer inhibitor (INSTI) are the category with the largest increase in both expenditure and consumption (+45%), registering a per capita expenditure of 1.57 euros.
- The bictegravir/emtricitabine/tenofovir alafenamide combination ranks first among the active substances with the highest expenditure (2.28 euros per capita) (Table 3.4.2a). This combination (+26%) is the only one, along with dolutegravir/lamivudine (+44.9%) and dolutegravir/rilpivirine (+22.8%) to show an increase in spending over 2021. In fact, all active ingredients, with the exception of the combination emtricitabine/ rilpivirine/tenofovir alafenamide (-2.7%), show a stable trend.
- Regional per capita expenditure (Table 3.5.2b) varies widely, ranging from a minimum value of 3.03 euros in Molise (+7.8% compared to 2021) to a maximum of 17.37 euros in Lombardy (+1.7% compared to 2021). The latter, along with Lazio, is the region with the highest number of doses and cost above the national average. Conversely, all Regions of the South, with the exception of Abruzzo, register consumption and average DDD cost below the national average. Overall, both spending and consumption in the South are about half of those in the North. There is a wide variability among regions in variations both in consumption and in spending with respect to the previous year, with Puglia showing the largest decrease in terms of spending (-10.8%) and the Province of Bolzano the highest increase in both spending (+9.6%) and consumption (+12.4 %). In contrast, Tuscany shows the largest reduction in consumption (-15.3%). Over the period 2014-2022, spending decreased in all regions except for Val d'Aosta (CAGR: +4.3%) and Friuli VG (CAGR: +0.6%).

Figure 3.4.2a Antiretroviral therapies, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

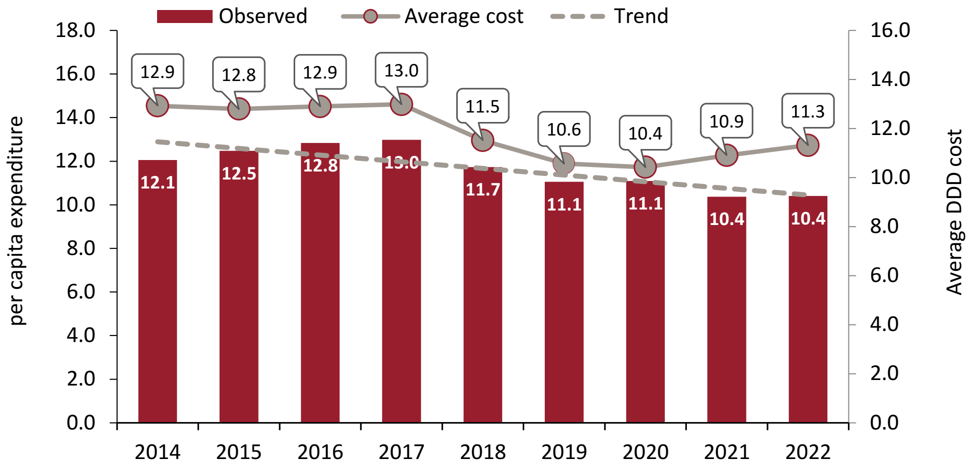


Table 3.4.2a Antiretroviral therapies, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhabitants per day	Δ % 22-21	CAGR % 14-22	Cost cost DDD	Δ % 22-21
Coformulated regimens (2 NRTIs + 1 INSTI)	3.21	1.7	69.6	0.4	3.8	75.3	20.50	-2.0
Coformulated regimens (2 NRTIs + 1NNRTI)	1.62	-7.3	-2.6	0.3	-4.1	-0.1	17.48	-3.4
Coformulated regimens (1 NNRTI + 1 INSTI)	1.57	44.9	-	0.3	44.9	-	16.60	0.0
INSTI	1.20	-16.3	3.3	0.2	-16.1	5.5	13.17	-0.2
Coformulated regimens (2 NRTI + 1 IP)	0.80	-2.9	-	0.1	-2.9	-	21.85	0.0
NRTI	0.74	-13.5	-21.9	0.9	-9.3	-4.2	2.25	-4.6
Coformulated regimens (1 NRTI + 1 INSTI)	0.54	22.8	-	0.1	22.8	-	18.31	0.0
IP	0.45	-20.3	-20.7	0.1	-21.1	-16.8	8.90	1.0
NNRTI	0.19	4.5	-12.9	0.1	-4.8	-10.4	5.29	9.8
Other antiretroviral agents	3.21	1.7	69.6	0.4	3.8	75.3	20.50	12.0
Antiretroviral therapies	**10.40**	**0.3**	**-1.8**	**2.5**	**-3.3**	**-0.2**	**11.32**	**3.8**
emtricitabine/tenofovir alafenamide/bictegravir	2.28	26.0	-	0.3	26.0	-	19.96	0.0
dolutegravir/lamivudine	1.57	44.9	-	0.3	44.9	-	16.60	0.0
emtricitabine/rilpivirine/ tenofovir alafenamide	1.33	-12.7	-	0.2	-10.3	-	19.43	-2.7
emtricitabine/tenofovir alafenamide/darunavir/ cobicistat	0.80	-2.9	-	0.1	-2.9	-	21.85	0.0
dolutegravir/abacavir/ lamivudine	0.77	-26.6	-	0.1	-26.6	-	21.48	0.0
dolutegravir	0.77	-18.6	74.9	0.1	-18.6	75.0	16.42	0.0
dolutegravir/rilpivirine	0.54	22.8	-	0.1	22.8	-	18.31	0.0
emtricitabine/tenofovir alafenamide	0.41	-19.5	-	0.1	-19.5	-	11.29	0.0
raltegravir	0.40	-15.7	-9.7	0.1	-16.4	-4.0	9.60	0.9
darunavir/cobicistat	0.35	-14.7	-	0.1	-14.7	-	12.25	0.0

Figure 3.4.2b Antiretroviral therapies, temporal trend 2014-2022 in per capita expenditure of most expensive subgroups

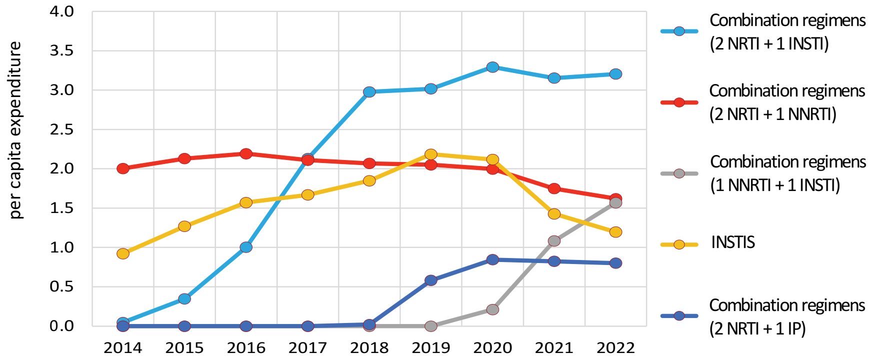


Table 3.4.2b Antiretroviral therapies, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Cost cost DDD
Piedmont	10.08	2.3	12.09	10.41	2.3	12.16	3.3	2.7	0.6	-0.8	0.5	-1.3
Valle d'Aosta	7.41	1.8	11.07	7.71	1.9	10.92	4.1	5.5	-1.3	4.3	6.3	-1.9
Lombardy	17.07	3.8	12.31	17.37	3.6	13.06	1.7	-4.1	6.1	-1.6	-1.5	-0.1
Province of Bolzano	5.92	1.3	12.86	6.49	1.4	12.54	9.6	12.4	-2.5	-1.9	-2.3	0.4
Province of Trento	8.02	1.8	12.31	7.98	1.9	11.81	-0.5	3.7	-4.1	0.0	1.5	-1.5
Veneto	8.89	2.5	9.65	9.47	2.4	10.60	6.6	-3.0	9.9	-1.3	-0.3	-1.0
Friuli V.G.	7.35	2.1	9.59	7.72	2.1	10.08	5.1	0.0	5.1	0.6	3.0	-2.3
Liguria	10.63	2.2	13.48	11.07	2.2	13.62	4.1	3.1	1.0	-0.8	-0.5	-0.2
Emilia R.	12.67	4.2	8.30	13.13	4.0	9.05	3.6	-4.9	9.0	-2.7	0.5	-3.1
Tuscany	12.08	2.5	13.05	11.10	2.1	14.16	-8.1	-15.3	8.5	-1.6	-1.8	0.2
Umbria	10.20	2.0	13.72	9.27	2.0	12.73	-9.1	-2.0	-7.3	-1.2	-0.5	-0.8
Marche	9.69	2.3	11.42	9.46	2.3	11.39	-2.4	-2.2	-0.3	-1.7	0.3	-2.1
Lazio	12.55	2.9	11.92	12.92	2.7	13.00	3.0	-5.6	9.1	-2.0	-1.6	-0.4
Abruzzo	7.23	1.8	11.04	6.80	1.8	10.41	-5.9	-0.2	-5.7	-0.3	2.9	-3.1
Molise	2.81	1.0	8.02	3.03	1.0	8.61	7.8	0.4	7.4	-1.0	3.7	-4.5
Campania	6.08	1.9	8.56	5.66	1.9	8.00	-6.9	-0.4	-6.5	-3.2	2.4	-5.5
Puglia	7.10	2.2	8.88	6.33	2.1	8.24	-10.8	-3.8	-7.2	-4.5	1.0	-5.4
Basilicata	3.52	1.1	8.79	3.42	1.1	8.85	-2.6	-3.2	0.6	-2.5	1.9	-4.3
Calabria	3.53	1.0	10.17	3.35	0.9	10.52	-5.1	-8.3	3.5	-3.4	-0.8	-2.6
Sicily	6.32	1.6	10.61	6.27	1.6	10.55	-0.7	-0.1	-0.6	-0.9	1.7	-2.6
Sardinia	9.33	2.7	9.40	9.23	2.8	8.91	-1.0	4.4	-5.2	-4.7	0.3	-5.1
Italy	**10.37**	**2.6**	**10.91**	**10.40**	**2.5**	**11.32**	**0.3**	**-3.3**	**3.8**	**-1.8**	**-0.2**	**-1.6**
North	12.55	3.1	11.01	12.95	3.0	11.66	3.2	-2.6	5.9	-1.5	-0.4	-1.0
Centre	11.85	2.6	12.32	11.62	2.4	13.12	-2.0	-8.0	6.5	-1.8	-1.3	-0.4
South and Islands	6.33	1.8	9.42	6.00	1.8	9.02	-5.2	-0.9	-4.3	-2.9	1.6	-4.4

In 2022, per capita spending on antiretroviral agents for the treatment of HIV remained stable from the previous year, although consumption decreased by 3.3%. Among coformulated regimens, there is increased use of those based on an integrase strand transfer inhibitor (INSTI) in combination with one or two nucleoside reverse transcriptase inhibitors (NRTIs) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Coformulated regimens based on an integrase strand transfer inhibitor (INSTI) and two nucleoside reverse transcriptase inhibitors (NRTIs) have seen the most marked increases in spending since their entry onto the market. The increased use of "other antiretroviral medications" is also reported. It includes fostemsavir, eligible for reimbursement in 2022, and indicated in combination with other antiretrovirals in the treatment of patients with resistant HIV infection. New developments of major interest in 2022 also include the availability of long-acting rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) which reduces the frequency of drug administration. However, such therapy is reserved for patients in virological suppression, with a stable antiretroviral regimen and without present or past evidence of viral resistance or previous virologic failure to NNRTIs and INSTIs Utilization trend of antiretroviral agents reflects use in line with national and international guidelines, indicating the excellent performance of the HIV infection management strategy.

3.4.3 Vaccines

- Expenditure for vaccines more than doubled from 2014 to 2022, from 4.79 euros to 10.84 euros per capita. An increase in spending on vaccines is confirmed in 2022, as already observed in 2021, with a change of 2.8%. Similarly, the average DDD cost (€25.38), after decreasing in 2020, increased by 6.6% in 2021 and further increased by 13.1% in 2022 (Figure 3.4.3a and Table 3.4.3a).
- The human papillomavirus (HPV) vaccine represents the first expenditure item in this category, accounting for nearly 13% of the total and standing at €1.44 per capita in 2022, an increase of 21.5% from the previous year and an average annual growth rate (CAGR) of 18.2% over the period 2014-2022 (Figure 3.4.3b). However, the flu vaccine (divided into three subcategories) has the highest overall expenditure (2.69 euros), registering a decrease for both adjuvanted (-11.8%) and non-adjuvanted (-15.3%), as well as nasal (-10.2%) formulations. This is followed by the meningococcal B vaccine at €1.34, which showed a decrease of 10.8% in 2022, and the recently marketed zoster vaccine (recombinant, adjuvanted) at €1.26, with an increase of more than 100% and the highest average cost per DDD in the category (€271.97). There are increases of more than 40% also for the live attenuated varicella vaccine, and for vaccines against encephalitis, yellow fever, typhoid and rabies reporting increases in excess of 100% (Table 3.4.3a). Almost all of expenditure for pneumococcal polysaccharide conjugate vaccine (1.16 euros per capita) is attributable to the 13-valent pneumococcal conjugate vaccine (PCV13) with 0.71 euros, which shows a 60% reduction in both expenditure and consumption. It should be noted that a new 20-valent pneumococcal polysaccharide conjugate pneumococcal vaccine administered from the age of 18 years was first marketed in 2022, and it has already reached an expenditure of 0.39 euros per capita and an average cost per DDD of 48.45 euros.
- Northern Regions, with an expenditure of 11.81 euros per capita and an increase of 13.5% over the previous year, are the geographical area with the highest spending, while Southern and Central Regions have fairly similar values (10.20 and 9.59 euros per capita respectively), both decreasing by 8% and 3.7% respectively (Table 3.4.3b). The Province of Trento is the region with the highest expenditure (15.26 euros per capita), up by 28.4%, followed by Veneto with 14.20 euros (+28.7%) and the Province of Bolzano with 12.53 euros (+15.9%). Piedmont recorded the largest increase (+37.7%) despite spending less than the national average (9.90 euros). The Province of Trento shows consumption and average cost per DDD above the national average, while Valle d'Aosta, Marche, Lazio, Abruzzo, Campania, Calabria and Sardinia show values below the national average for both indicators. All regions show a positive change during 2014-2022, with a peak of +15% in Tuscany and a low of +4.5% in Apulia.

Figure 3.4.3a Vaccines, 2014-2022 temporal trend of per capita expenditure and average cost per day of therapy

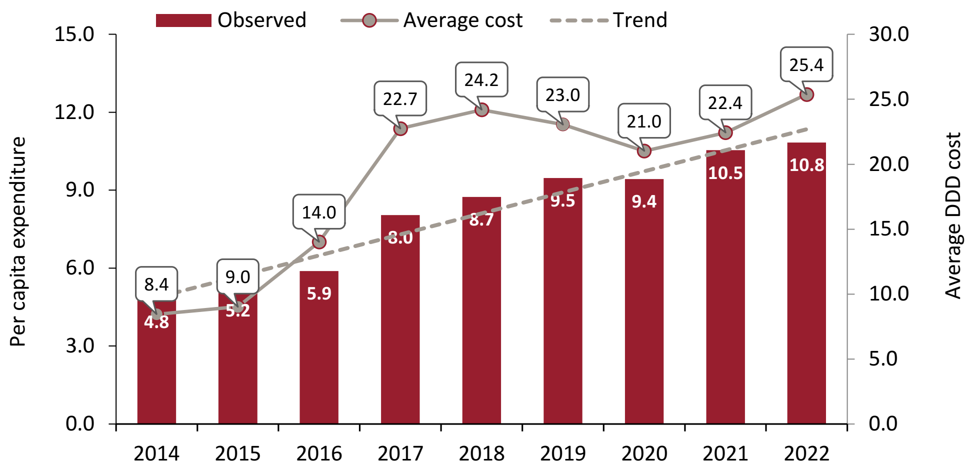


Table 3.4.3a Vaccines, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/1000 inhabitants per day	Δ % 22-21	CAGR % 14-22	Average cost of DDD	Δ % 22-21
Human papillomavirus (HPV) vaccine	1.44	21.5	18.2	0.1	21.4	11.2	69.31	0.1
Meningococcal B vaccine	1.34	-10.8	44.3	0.1	-10.6	44.4	62.14	-0.2
Inactivated quadrivalent split-virus influenza vaccine	1.34	-11.8	-	0.2	-10.9	-	14.89	-1.1
Adjuvanted recombinant varicella zoster vaccine	1.26	>100	-	<0.05	>100	-	271.97	-5.6
Inactivated quadrivalent split-virus influenza vaccine	1.20	-15.3	99.5	0.4	-16.5	100.5	8.40	1.4
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	1.16	-35.2	-2.0	0.1	-34.3	-2.3	47.55	-1.4
MMRV vaccine (measles/mumps/rubella/varicella)	0.61	6.3	16.4	<0.05	4.5	18.0	47.61	1.7
Hexavalent vaccine (diphtheria/tetanus/pertussis/ haemophilus Influenzae B/poliomyelitis/hepatitis B)	0.53	-5.0	-10.1	0.1	5.4	-1.8	26.53	-9.8
Quadrivalent meningococcal conjugate vaccine	0.38	-5.1	27.5	<0.05	4.2	32.6	27.13	-8.9
Quadrivalent vaccine (diphtheria/tetanus/pertussis/ poliomyelitis)	0.32	-5.1	9.5	<0.05	-1.5	9.6	18.03	-3.6
Live attenuated varicella-zoster vaccine	0.26	43.2	144.9	<0.05	43.9	142.0	96.19	-0.5
Attenuated rotavirus vaccine	0.25	-12.9	21.2	<0.05	-1.2	30.6	20.18	-11.9
Intranasal quadrivalent influenza vaccine	0.15	-10.2	-	<0.05	-7.1	-	19.65	-3.3
Pneumococcal polysaccharide vaccine (PPSV23)	0.14	-6.8	31.2	<0.05	-11.0	25.8	22.37	4.7
DTaP vaccine (diphtheria /tetanus/pertussis)	0.13	18.9	3.5	<0.05	30.9	5.7	11.84	-9.2
Live attenuated varicella vaccine	0.08	-15.1	-4.9	<0.05	-11.7	-3.2	31.12	-3.8
Encephalitis vaccine	0.07	>100	31.1	<0.05	>100	32.8	35.04	-4.7
Hepatitis A vaccine	0.04	54.5	-2.5	<0.05	50.0	-0.4	17.13	3.0
Hepatitis B vaccine	0.04	11.5	-0.7	<0.05	7.9	-1.4	17.10	3.4
MMR vaccine (measles/mumps/rubella)	0.03	-24.1	-18.6	<0.05	-24.1	-17.6	9.07	-0.1
Meningococcal C conjugate vaccine	0.02	-24.2	-16.3	<0.05	-27.2	-18.2	11.93	4.2
Yellow fever vaccine	0.01	>100	2.4	<0.05	>100	-3.2	20.25	10.4
Typhus vaccine	0.01	>100	0.9	<0.05	>100	-12.0	11.06	8.5
Rabies vaccine	0.01	>100	11.3	<0.05	>100	2.3	50.19	1.4
Tetanus vaccine	0.01	-2.9	-9.0	<0.05	-5.6	-16.1	4.46	2.9
Haemophilus influenzae B vaccine	0.01	24.4	13.8	<0.05	30.5	11.3	14.03	-4.7
Hepatitis A and B vaccine	0.01	88.5	-4.0	<0.05	88.7	11.7	30.78	-0.1
DT vaccine (diphtheria/tetanus)	0.00	-41.7	-12.9	<0.05	-41.8	-19.6	4.71	0.3

continued

Table 3.4.3a – *continued*

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/1000 inhabitants per day	Δ % 22-21	CAGR % 14-22	Average cost of DDD	Δ % 22-21
Inactivated polio vaccine (IPV)	0.00	3.6	-8.0	<0.05	4.1	-10.5	7.67	-0.5
Cholera vaccine	0.00	-5.7	-18.1	<0.05	-12.5	-21.3	27.49	7.8
Vaccines	**10.84**	**2.8**	**10.8**	**1.2**	**-9.1**	**-3.5**	**25.38**	**13.1**
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.44	21.4	-	0.1	21.4	-	69.31	0.0
Meningococcal group B (MenB) vaccine	1.34	-10.8	44.3	0.1	-10.6	44.4	62.14	-0.2
quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted)	1.34	-11.8	-	0.2	-10.9	-	14.89	-1.1
adjuvanted recombinant varicella zoster vaccine	1.26	>100	-	<0.05	>100	-	271.97	-5.6
quadrivalent influenza vaccine (split virion, inactivated)	1.02	-14.6	95.6	0.3	-16.9	95.9	8.65	2.7
13-valent pneumococcal vaccine	0.71	-59.2	-7.8	<0.05	-59.1	-8.3	48.73	-0.4
measles, mumps, rubella and varicella vaccine	0.61	6.3	16.4	<0.05	4.5	18.0	47.61	1.7
diphtheria/hepatitis B (recombinant)/ haemophilus influenzae type B conjugate (adjuvanted)/ acellular pertussis/inactivated poliomyelitis/ tetanus vaccine	0.53	-5.0	-10.1	0.1	5.4	-1.8	26.53	-9.8
20-valent pneumococcal vaccine	0.39	-	-	<0.05	-	-	48.45	-
diphtheria/pertussis/polio/ tetanus vaccine	0.32	-5.1	9.5	<0.05	-1.5	9.6	18.03	-3.6

Figure 3.4.3b Vaccines, temporal trend 2014-2022 of per capita expenditure of the highest-spending subgroups

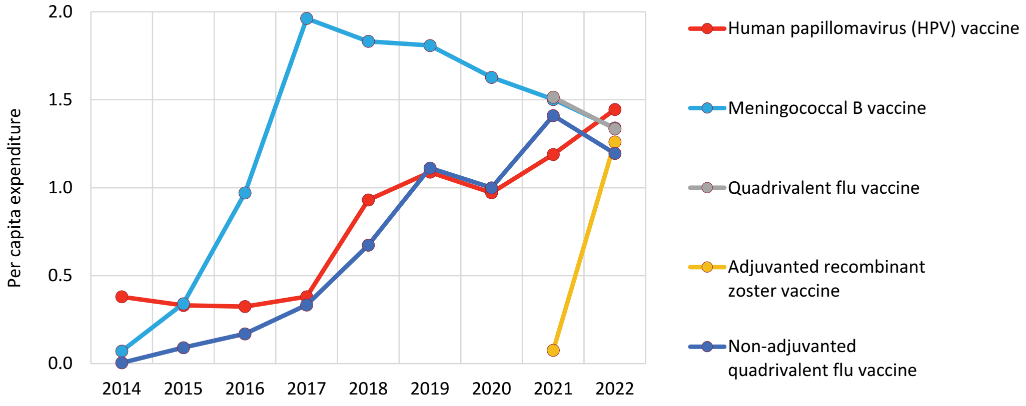


Table 3.4.3b Vaccines, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD
Piedmont	7.19	1.0	20.46	9.90	1.0	27.09	37.7	4.0	32.4	12.9	4.0	8.6
Valle d'Aosta	8.50	1.1	21.91	8.04	0.9	23.62	-5.5	-12.3	7.8	8.5	2.9	5.5
Lombardy	10.68	1.3	23.17	11.59	1.3	25.22	8.6	-0.2	8.8	14.0	-9.9	26.5
Province of Bolzano	10.81	1.2	25.34	12.53	1.2	29.10	15.9	1.0	14.8	11.3	-9.6	23.2
Province of Trento	11.89	1.4	23.96	15.26	1.4	28.94	28.4	6.3	20.8	14.4	6.8	7.1
Veneto	11.03	1.3	23.52	14.20	1.2	32.96	28.7	-8.1	40.1	13.3	-1.9	15.5
Friuli V.G.	11.77	1.6	20.45	10.68	1.1	25.50	-9.2	-27.2	24.7	8.8	-3.8	13.0
Liguria	8.84	1.2	19.70	10.41	1.1	27.15	17.8	-14.5	37.8	12.4	2.6	9.5
Emilia R.	12.38	1.5	22.86	12.06	1.3	25.50	-2.6	-12.7	11.6	12.9	-3.3	16.7
Tuscany	8.84	1.2	19.88	9.89	1.2	22.19	11.8	0.2	11.6	15.0	-6.7	23.3
Umbria	10.20	1.2	23.04	9.82	1.4	19.92	-3.7	11.4	-13.5	10.1	5.0	4.9
Marche	9.18	1.2	20.82	8.88	1.1	22.76	-3.3	-11.5	9.3	10.2	3.5	6.5
Lazio	10.89	1.3	22.75	9.54	1.1	23.94	-12.4	-16.8	5.3	10.0	0.9	9.0
Abruzzo	9.66	1.2	22.94	9.03	1.1	23.01	-6.5	-6.8	0.3	9.8	2.4	7.2
Molise	10.75	1.4	21.09	10.50	1.3	22.02	-2.3	-6.4	4.4	9.5	3.7	5.6
Campania	11.32	1.3	23.27	10.06	1.1	24.02	-11.1	-13.9	3.2	9.9	-0.1	10.0
Puglia	12.05	1.6	20.83	10.93	1.3	23.57	-9.3	-19.8	13.1	4.5	-1.0	5.5
Basilicata	9.12	1.2	21.06	11.15	1.2	25.43	22.3	1.2	20.8	8.6	-0.1	8.7
Calabria	10.43	1.2	23.33	10.22	1.1	24.91	-2.0	-8.2	6.8	10.1	-1.2	11.5
Sicily	12.07	1.3	24.82	10.75	1.2	25.40	-10.9	-12.9	2.3	5.8	-3.6	9.7
Sardinia	7.86	1.1	20.27	7.93	0.9	24.85	0.9	-17.7	22.6	8.0	-1.6	9.8
Italy	**10.54**	**1.3**	**22.43**	**10.84**	**1.2**	**25.38**	**2.8**	**-9.1**	**13.1**	**10.8**	**-3.5**	**14.7**
North	10.41	1.3	22.53	11.81	1.2	27.13	13.5	-5.7	20.4	13.1	-5.3	19.4
Centre	9.96	1.3	21.64	9.59	1.1	22.85	-3.7	-8.8	5.6	11.5	-1.9	13.7
South and Islands	11.08	1.3	22.76	10.20	1.1	24.33	-8.0	-13.9	6.9	7.3	-1.3	8.7

The use of seasonal vaccines, such as flu vaccines, decreased in 2022. It would be useful to improve awareness of the importance of vaccines with information campaigns and population survey analysis through GPs or territorial pharmacies in order to implement the use of seasonal vaccines. Information campaigns have shown their effectiveness in the clear evidence of increased vaccine use for the reactivation of varicella zoster virus (VZV) and human papillomavirus (HPV). The latter is also a result of the extension of age-based reimbursability. The uneven utilization data of vaccines at regional level suggests the need, in addition to nationwide prevention and information campaigns, of a more comprehensive approach in terms of information on vaccination.

3.4.4 Antifungals for systemic use

- Over the last nine years, an average annual decrease (CAGR -3.7%) in expenditure for antifungals was recorded, with values shifting from 3.37 euros in 2014 to 2.49 euros per capita in 2022. This indicator also showed a decrease compared to 2021 of 0.7% (Figure 3.4.4a and Table 3.4.4a). Consumption recorded a reduction of 1% compared to 2021, while in the period 2014-2022 the average annual change was -4%. The average DDD cost showed variations in the different years considered, with an increase until 2017, followed by a subsequent decrease and a slight increase in the last 3 years (reaching 10.50 euros in 2022).
- Triazole derivatives, mainly represented by fluconazole, constitute the category with the highest consumption (0.6 DDD) and expenditure, registering a value of 1.36 euros per capita in 2022, down 1.8% from the previous year and 3.7% over the period 2014-2022 (Figure 3.4.4b). This is followed by polyenes (0.83 euros per capita), represented exclusively by amphotericin B, partly confirming the increase already seen in 2021 (+30.2%) or 16.2%. The subgroup with the largest reduction in expenditure and average cost per DDD are echinocandins (-22.7% and -19.3% respectively).
- Fluconazole represents the highest consumed drug (0.4 DDD), followed by itraconazole (0.2 DDD) with a change from 2021 of -1.8% and -3.6%, respectively. The four triazole derivatives, namely fluconazole, isavuconazole, itraconazole, and posaconazole, rank first in terms of expenditure after amphotericin B; all show a decrease from 2021 with the exception of isavuconazole (+13.3%) (Table 3.4.4a). Micafungin, an echinocandin, is the substance with the highest average cost per DDD (€238.71)
- There is higher spending in the southern regions (2.62 euros per capita) in comparison with the North (2.46 euros) and the Center (2.35 euros); the latter is increasing by 6% compared to 2021, whereas in the South there is a decrease of 2.4% and in the North it remains stable (Table 3.4.5b). Over the past nine years, all geographic areas show decreases ranging from 2.6% in the North to 4.2% in the South and 5.2% in the Centre. The average cost per DDD in the South is about 30% lower than in the North (8.78 vs. 12.31 euros). There are more than 4-fold differences in per capita spending between regions, ranging from a low of 1.01 in the Province of Bolzano PA to 4.07 in Calabria. Changes from 2021 range from -41.6% in the Province of Bolzano to +22% in Val d'Aosta. The lowest average cost per DDD is found in Molise (5.77 euros) 60% lower than in Veneto (14.58 euros).

Figure 3.4.4a Antifungals for systemic use, 2014-2022 temporal trend of per capita expenditure and average cost per day of therapy

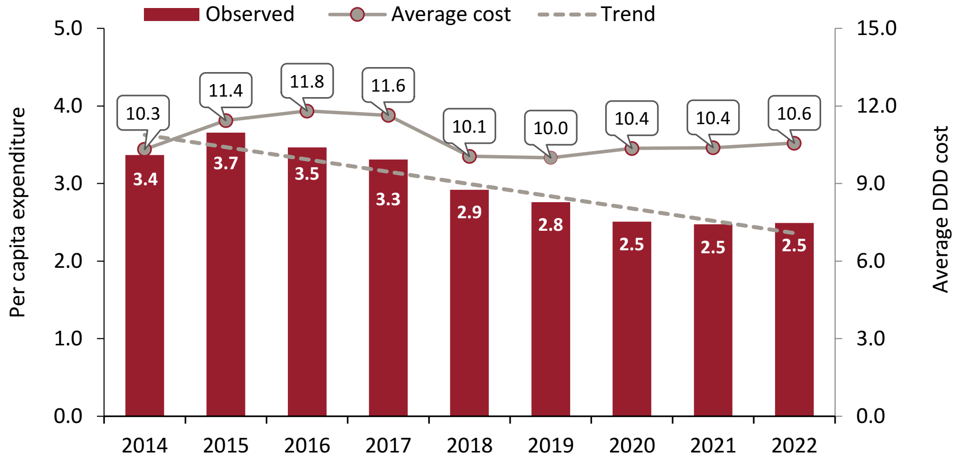


Table 3.4.4a Antifungals for systemic use, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average cost cost DDD	Δ % 22-21
Triazole derivatives	1.36	-1.8	-3.7	0.6	-1.8	-4.5	6.19	0.1
Polyenes	0.83	16.2	7.6	<0.05	14.8	6.0	101.59	1.2
Echinocandins	0.28	-22.7	-15.4	<0.05	-4.2	8.0	54.06	-19.3
Imidazole derivatives	0.02	56.2	78.8	<0.05	56.6	58.7	9.45	-0.3
Antifungals	**2.49**	**0.7**	**-3.7**	**0.6**	**-1.0**	**-4.0**	**10.56**	**1.7**
amphotericin B	0.83	16.2	7.6	<0.05	14.8	6.0	101.59	1.2
fluconazole	0.68	-2.4	-4.3	0.4	-1.8	-3.8	4.81	-0.6
isavuconazole	0.33	13.1	-	<0.05	19.3	-	105.50	-5.2
itraconazole	0.17	-3.8	-7.3	0.2	-3.6	-7.1	2.55	-0.3
posaconazole	0.16	-15.6	-2.3	<0.05	16.1	4.1	23.82	-27.3
caspofungin	0.14	-16.4	-18.3	<0.05	-3.8	11.1	34.15	-13.1
micafungin	0.11	-26.7	-3.6	<0.05	0.7	1.4	238.71	-27.2
anidulafungin	0.03	-32.0	-20.8	<0.05	-9.3	0.7	51.66	-25.0
voriconazole	0.03	-23.6	-27.6	<0.05	-12.9	1.5	7.83	-12.2
ketoconazole	0.02	56.2	-	<0.05	56.6	-	9.45	-0.3

Figure 3.4.4b Antifungals, temporal trend 2014-2022 of per capita expenditure of the highest-spending subgroups

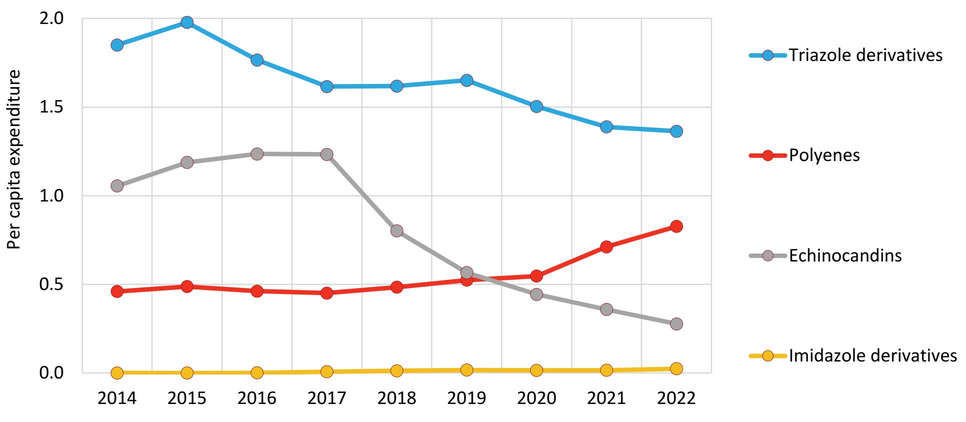


Table 3.4.4b Antifungals for systemic use, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD
Piedmont	2.10	0.6	9.81	2.30	0.6	10.25	9.5	4.8	4.5	-4.1	-2.4	-1.7
Valle d'Aosta	0.97	0.4	5.96	1.18	0.5	7.02	22.0	3.6	17.8	-2.2	-3.0	0.9
Lombardy	2.25	0.5	12.45	2.22	0.5	12.41	-1.4	-1.1	-0.3	-2.2	-3.6	1.4
Province of Bolzano	1.72	0.3	16.47	1.01	0.3	10.09	-41.6	-4.6	-38.7	-11.9	-4.6	-7.7
Province of Trento	1.44	0.5	7.45	1.40	0.5	6.99	-2.9	3.6	-6.2	-5.3	-2.3	-3.1
Veneto	2.72	0.5	13.63	2.91	0.5	14.58	6.9	-0.1	7.0	-2.3	-4.4	2.2
Friuli V.G.	2.15	0.6	10.44	2.20	0.6	10.64	2.2	0.3	1.9	-3.9	-3.7	-0.2
Liguria	3.59	0.7	14.70	3.17	0.6	13.65	-11.7	-4.9	-7.1	-3.8	-3.1	-0.7
Emilia R.	2.78	0.6	13.36	2.81	0.6	13.11	1.1	3.0	-1.9	-0.2	-3.1	3.1
Tuscany	1.83	0.5	9.35	2.06	0.5	10.81	12.3	-2.9	15.6	-5.5	-4.3	-1.2
Umbria	3.21	0.6	14.33	2.83	0.6	13.03	-11.8	-3.0	-9.0	-8.1	-5.0	-3.2
Marche	2.24	0.7	8.69	2.40	0.7	9.14	7.3	2.0	5.2	-2.3	-3.8	1.5
Lazio	2.30	0.6	9.88	2.45	0.6	10.67	6.2	-1.6	8.0	-5.1	-5.4	0.4
Abruzzo	2.94	0.7	11.25	3.01	0.7	11.19	2.4	3.0	-0.6	0.2	-3.1	3.4
Molise	1.21	0.6	5.93	1.16	0.5	5.77	-4.2	-1.5	-2.7	-10.6	-5.8	-5.1
Campania	2.83	0.8	9.29	2.67	0.8	8.99	-5.7	-2.6	-3.3	-3.7	-3.0	-0.7
Puglia	2.60	0.8	9.35	2.36	0.7	8.68	-9.4	-2.5	-7.1	-6.8	-5.0	-2.0
Basilicata	1.65	0.7	6.81	1.59	0.6	6.82	-3.6	-3.8	0.2	-8.1	-3.8	-4.4
Calabria	3.77	1.1	9.35	4.07	1.1	10.25	8.1	-1.4	9.7	-0.8	-2.8	2.1
Sicily	2.34	0.9	7.26	2.39	0.9	7.68	2.1	-3.4	5.7	-5.0	-4.9	-0.1
Sardinia	2.68	0.8	8.99	2.50	0.8	8.59	-6.4	-2.0	-4.5	-4.5	-4.4	-0.2
Italy	**2.48**	**0.7**	**10.38**	**2.49**	**0.6**	**10.56**	**0.7**	**-1.0**	**1.7**	**-3.7**	**-4.0**	**0.3**
North	2.44	0.5	12.34	2.46	0.5	12.38	0.9	0.7	0.3	-2.6	-3.4	0.9
Centre	2.21	0.6	9.89	2.35	0.6	10.65	6.0	-1.5	7.7	-5.2	-4.9	-0.4
South and Islands	2.69	0.8	8.79	2.62	0.8	8.78	-2.4	-2.3	-0.1	-4.2	-4.0	-0.2

During 2022, the consumption of systemic antifungals decreases slightly while per capita spending increases moderately. Triazole derivatives cover almost all consumption and have the lowest average cost per day of therapy in the category. In contrast, the polyene antifungal amphotericin B, although with negligible consumption values, accounts for about one-third of the category's per capita expenditure, with values increasing over the past 3 years.
There is evidence of increased antifungal resistance in recent years, especially for the triazole class of antifungals, which are more widely used. As with antibiotics, it is important to abstain from using these medications without medical supervision and to avoid do-it-yourself therapies that could result in a loss of activity as well as in an increased risk of side effects. Strategies for the implementation of antifungal stewardship in the context of antimicrobial stewardship are desirable in the whole country.

3.5 Blood and blood-forming organs

Medicines for blood and blood-forming organs represent the fifth therapeutic category with high public expenditure in 2022 (2.455 million euros), accounting for 10% of total public expenditure (Box Main expenditure, consumption and exposure indexes). Overall, per capita expenditure for these medicines was equal to 41.62 euros, mainly driven by the purchase by public health facilities (34.19 euros per capita), up from the previous year (+5.0%). On the contrary, the contribution provided through the NHS outpatient care was lower (7.43 euros per capita), a 2.3% decrease compared to the previous year (Table 3.1). In terms of consumption, overall there are values of 143.62 DDDs per 1,000 inhabitants per day, with a percentage increase of 2.2% over the previous year. It confirms the upward trend in both NHS outpatient care and direct purchases in 2022 as well (Table 3.2).
The analysis of the drug use profile by age group and gender, including pharmaceutical expenditure under approved care regime and on behalf distribution, shows a progressive increase in the use of these medicines with increasing age. A more marked increase is found in men aged 55-64 years, probably due to the different prevalence of cardio-cerebrovascular diseases. The highest prevalence is reached in patients over 75, with values of 60.4% and 69.4% for females and males, respectively. In the younger age groups, prevalence is higher in women than in men, probably due to a greater use of anti-anemic preparations. At the same time, the per capita NHS expenditure shows a similar trend, reaching the maximum value of 98.7 euros per capita in the +75 age group (112.80 euros in men and 89.19 euros in women).
By analyzing trends over the last six years (2017-2022) of class A drugs purchased by public facilities and belonging to this category (Figures 3.1-3.3), it can be seen that they are the fifth largest category by expenditure and the third largest by consumption, with values rather constant over time.
As regards approved care regime, the regional distribution (Table 3.5) shows a high variability (CV: 39.6%) of gross per capita expenditure with maximum values in Lazio (12.4 euro) and Lombardia (12.2 euro) and minimums in Liguria (2.2 euros) and Valle d'Aosta (2.6 euro). The distribution of consumption (CV: 22,7%) appears to be slightly different with maximum values in Abruzzo (119.0 DDD) and Basilicata (116.9 DDD) and minimums in Veneto (53.5 DDD) and Liguria (56.0 DDD). Concerning the approved care regime, expenditure recorded a reduction in 2022 compared to the previous year (-2.7%), together with an increase in consumption (+0.8%). For this year, however, there is a shift in prescribing toward less expensive medicinal products (mix effect: -4.3%) and a reduction in average DDD cost (-3.5%) (Table 3.9). The therapeutic categories that have the greatest impact on expenditure are platelet aggregation inhibitors (2.98 euros per capita) and heparins (2.25 euros per capita). Compared to the previous year, coagulation factor Xa inhibitors (10a), including apixaban, rivaroxaban and edoxaban, recorded a marked increase in expenditure (+12.9%) and consumption (+13.2%), with a mix effect, i.e., the shift to medicines with different cost, rather stable (-0.2%). In 2022, vitamin K antagonists (AVKs) show a 27.1% growth in spending, against a decrease in consumption (-13.5%). It is due to a 47% price increase resulting from renegotiation of warfarin (Determination No. 299, April 21, 2022, G.U. 101, May 2, 2022). Enoxaparin (€2.04), clopidogrel (€1.21) and acetylsalicylic acid (€1.19) represent the highest per capita spending compounds and together constitute

the main cost item of the NHS outpatient pharmaceutical expenditure for blood and hematopoietic organs drugs (59.8%) (Table 3.10). In 2022, there is evidence of an increase in consumption of all active ingredients, with the only exceptions being enoxaparin (-7.5%) and human albumin (-5.4%). Overall, the average DDD cost remained fairly stable compared to the previous year, with the only exception of clopidogrel recording a 1.5 % decrease.
Enoxaparin, which alone accounts for 27.4% of spending for the entire category, is the only drug in the ATC to be included in the list of the top 30 active ingredients with the greatest impact on contracted pharmaceuticals (Table 3.11). It also ranks among the active ingredients with the highest average cost per day of therapy with a value of 2.20 euros (Table 3.13) and among drugs with the greatest reduction in spending (-7.6%) (Table 3.16). Acetylsalicylic acid and folic acid, on the other hand, appear in the list of drugs with the lowest average cost per day of therapy, with values of 0.07 and 0.21 euros, respectively (Table 3.14). Clopidogrel is included in the list of the top 30 active ingredients with the greatest change in spending compared to 2021, registering an increase of 4.5% (Table 3.15). Finally, acetylsalicylic acid and cyanocobalamin are on the list of the highest consumed drugs, with values of 45.6 and 12.2 DDD/1000 inhabitants per day, respectively (Table 3.17).
As for purchases by public healthcare facilities, the regional distribution (Table 3.7) shows a moderate variability (CV 12.8%) with maximum values in Abruzzo (42.3 euro) and Campania (40.6 euro) and minimum values in the Province of Bolzano (26 euro) and Lombardy (28.6 euro). On the other hand, greater variability in consumption is recorded (CV 28.7%), with highest values in Marche (97.2 DDD) and Emilia Romagna (82.8 DDD) and lowest in Lombardy (31.8 DDD) and the Province of Bolzano (36.6 DDD).PA Overall, compared to 2022, there was an increase in both expenditure (+6.2%) and consumption (+3.4%) and a shift towards more expensive specialties (mix effect +4.0%) (Table 3.19). The therapeutic category with the highest impact on expenditure is represented by factor Xa inhibitors, with a per capita expenditure of 8.58 euros, followed by coagulation factors and other systemic hemostatics (3.05 euros per capita). The most frequently used therapeutic categories include direct factor Xa inhibitors (14.2 DDD), followed by platelet aggregation inhibitors, excluding heparin (9.7 DDD). Rivaroxaban is the active ingredient ranking first in terms of per capita expenditure (3.25 euros) in 2022 as well, with an increase of 7.3% in expenditure and 4.8% in consumption compared to the previous year (Table 3.20). This is followed by apixaban (€3.13), edoxaban (€2.20) and enoxaparin (€1.80). These active ingredients also rank among the top 30 highest-spending active ingredients among drugs purchased by healthcare facilities (Table 3.21).
The oral anticoagulant edoxaban and the monoclonal antibody emicizumab rank 20th (+25.5%) and 21st (+24.8%), respectively, among the top active ingredients with greater variation in expenditure compared to the previous year purchased by public health facilities (Table 3.23). Octocog alfa, a drug used for the prophylaxis and treatment of hemophilia A, is the only active ingredient in the blood category to be on the list of the top 30 active ingredients with the greatest reduction in drug expenditure purchased by healthcare facilities, registering a decrease of 30.7%, compared to the previous year (Table 3.24).
The top 30 active ingredients for DDD average cost purchased by public health facilities include four coagulation factors, with values ranging from a maximum of 1058,5 euros for albutrepenonacog alfa to a minimum of 357 euros for efmoroctocog alfa and of 326 euros for octocog alfa (Table 3.25). Among the compounds with the lowest average cost per day

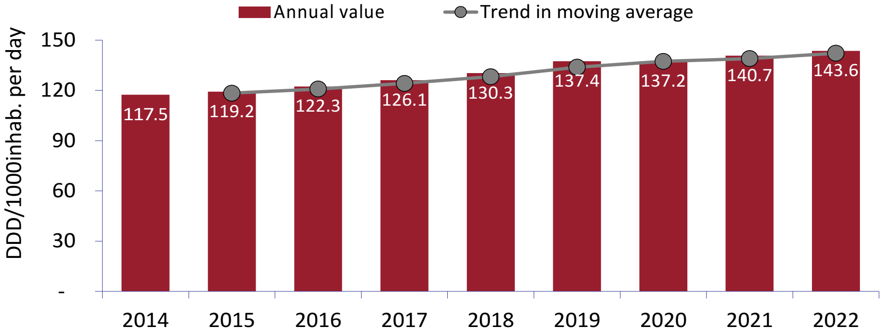
of therapy (Table 3.26) we find in first place electrolytes for intravenous solutions with an average value of 0.40 euros. These drugs also show the highest consumption (6.6 DDD/1000 population days) (Table 3.27). Considering the active ingredients with the highest consumption in public health facilities, there are 10 active ingredients belonging to the blood and hematopoietic organs category, including rivaroxaban, enoxaparin (5.7 DDD) and clopidogrel alone (5.5 DDD). Evaluating the trend in total spending, considering both NHS outpatient care and the share purchased directly from public facilities, enoxaparin ranks 7th with a total spending value of 226.6 million, 1.5% of the total (Table 3.28). Within this ranking we also find three NOACs with total expenditure values of 200.2 million for apixaban, 193.6 million for rivaroxaban, and 131.8 million for edoxaban. Analyzing the trend in total consumption, referring to both NHS outpatient care and public facility care, acetylsalicylic acid is the third active ingredient with a value of 46.9 DDD, cyanocobalamin the eleventh, with a value of 17.6 DDD, and clopidogrel the nineteenth with a value of 11.5 DDD/1000 inhabitants per day (Table 3.29). Table 3.30 shows the different trend in terms of expenditure, consumption and average DDD cost between the approved care regime and direct purchases foranticoagulants, coagulation factors, and antiplatelet agents.
For further information on the use of medicines belonging to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region. These analyses covered anticoagulants, coagulation factors and platelet aggregation inhibitors (Table 3.5.1a and following).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

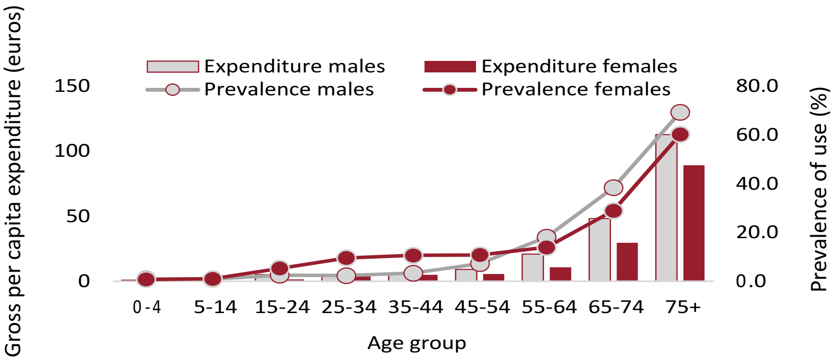
Blood and blood-forming organs

Public expenditure* in EUR million (% over total)		**2,455.1**	**(9.9)**
	Δ % 2022-2021		5.0
	Regional range of gross per capita expenditure:	32.0	53.0
DDD/1000 inhabitants per day* (% over total)		**143.6**	**(10.9)**
	Δ % 2022-2021		2.2
	Regional range DDD/1000 inhabitants per day	92.7	190.3

* *includes prescriptions under approved care regime and purchases by public health facilities*



Breakdown of prevalence of use and consumption under approved care regime and distribution on behalf by age and gender in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.8	0.1	0.5	3.0	2.1	2.5
5-14	2.2	0.4	1.3	1.7	1.6	1.6
15-24	5.2	1.5	3.4	4.7	10.0	7.3
25-34	4.9	3.7	4.3	5.7	23.9	14.6
35-44	5.6	4.9	5.2	11.9	29.0	20.4
45-54	9.2	5.6	7.4	38.7	35.2	36.9
55-64	20.9	10.7	15.7	124.8	73.2	98.3
65-74	48.3	29.5	38.4	309.3	200.9	252.1
75+	112.8	89.2	98.7	591.4	473.2	520.8

3.5.1 Anticoagulants

- As of 2014, Italy has seen a significant increase in the consumption of anticoagulants (CAGR: +5.7%), reaching 29.1 DDD/1000 inhabitants per day in 2022 and increasing by 3.2% compared to the previous year. At the same time, per capita spending shows an increase since 2014 (CAGR: +8.4%) with a difference between 2022 and the previous year of +7.8% standing at about 16 euros. This result is probably due to the fact that drugs with the highest consumption and expenditure, represented by NOAs, are still covered by patents (Figure 3.5.1a and Table 3.5.1a). The average cost per DDD reaches 1.50 euros in 2022, confirming the upward trend of recent years (Figure 3.5.1a).
- In 2022, the NOA class registers the highest consumption of 16.8 DDD/1000 inhabitants per day increasing by 10.8% compared to 2021 with an average annual change 2014-2022 of +34.3% while vitamin K antagonists (AVKs) register a consumption of 2.6 DDD/1000 inhabitants per day showing a 12.6% reduction in consumption compared to the previous year (Figure 3.5.1b). These trends can be explained by the possible use of NOAs for prophylaxis or treatment of thromboembolic conditions as an alternative to AVKs. NOAs, in fact, are preferred in clinical use because they do not require periodic monitoring of hemocoagulative status and are burdened with lower hemorrhagic risk, especially cerebral (Table 3.5.1a). Monoclonal antibodies for the treatment of acquired Thrombotic Thrombocytopenic Purpura (PTT) episodes, represented by caplacizumab, show a per capita expenditure increase of about 90% over the previous year with an average cost per DDD among the highest in the category of 3395.13 euros. NOAs show more marked increases in consumption of the more recently introduced edoxaban (+23.7%) and apixaban (+16.2%) compared to rivaroxaban, which shows a smaller increase (+4.8%), despite higher consumption (5.7 DDD), compared to 2021. Dabigatran, however, shows a slight decrease in consumption (-0.5%).
- In 2022, the difference between the highest consuming region (Province of Trento with 36.9 DDDs) and the lowest consuming region (Sicily with 22.7 DDD/1000 inhabitants per day) is 14.2 DDD/1000 inhabitants per day with a delta of about -18% compared to 2021 (Table 3.5.1b). The Province of Bolzano has the largest increase in per capita expenditure (+45.9%) with a 22% increase in consumption and a 19.6% increase in average cost per DDD; this scenario is likely due to the increased use of NOAs, which are characterized by a higher average cost. As in the previous year, interregional variability in the consumption of anticoagulant drugs is confirmed, probably not solely ascribed to geographic differences in the prevalence of clinical conditions, but rather to the different prescriptive attitude of physicians towards prophylaxis of thromboembolism in fibrillation (AF), which is a prevalent clinical condition compared with venous thromboembolism (VTE).
- From 2020, the publication of AIFA Note 97 extended the prescription of NOAs for patients with FANV to general practitioners in addition to specialists. In the context of assessing trends in the consumption of anticoagulants (particularly NOAs) and interregional variability, the usefulness of conducting analyses and studies to assess the potential effect of AIFA Note 97 is seen.

Figure 3.5.1a Anticoagulants, 2014-2022 temporal trend of consumption and average cost per day of therapy

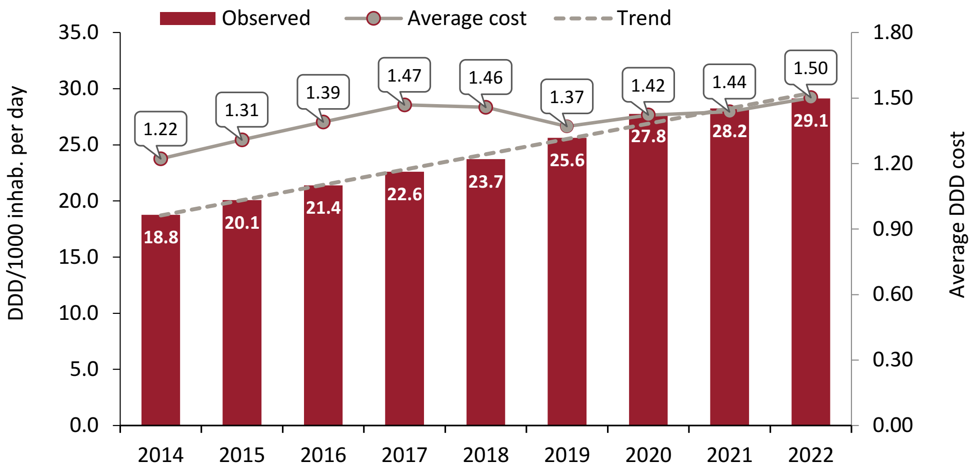


Table 3.5.1a Anticoagulants, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhabitants per day	Δ % 22-21	CAGR % 14-22	Average cost cost DDD	Δ % 22-21
NOAs	10.19	12.2	27.1	16.8	10.8	34.3	1.66	1.3
LMWH	4.23	-3.2	-3.6	8.8	-3.6	-1.2	1.32	0.4
Monoclonal antibodies for episodes of acquired TTP	0.55	89.8	-	<0.05	86.3	-	3395.13	1.8
Fondaparinux	0.29	-10.9	1.7	0.5	-7.6	5.7	1.62	-3.5
Heparin and heparinoids	0.24	8.0	-6.5	0.4	2.9	-5.9	1.76	5.0
Antithrombotic enzymes	0.21	-15.1	-1.5	<0.05	-15.3	0.2	786.43	0.2
Vitamin K antagonists	0.16	27.1	-6.6	2.6	-12.6	-10.7	0.16	45.4
Other antithrombotics	0.10	-26.2	-	<0.05	-29.8	-	4094.72	5.2
Antithrombotics - direct thrombin inhibitors	0.01	-45.0	-18.1	<0.05	-38.9	-14.9	216.82	-10.0
Anticoagulants	**15.97**	**7.8**	**8.4**	**29.1**	**3.2**	**5.7**	**1.50**	**4.5**
enoxaparin	3.84	-1.7	-0.4	8.2	-2.1	1.2	1.28	0.4
apixaban	3.39	16.3	40.5	5.3	16.2	49.4	1.76	0.1
rivaroxaban	3.28	7.3	25.3	5.7	4.8	32.0	1.57	2.4
edoxaban	2.23	24.2	-	3.4	23.7	-	1.80	0.5
dabigatran	1.28	-2.4	7.1	2.4	-0.5	15.6	1.44	-1.9
caplacizumab	0.55	89.8	-	<0.05	86.3	-	3395.13	1.8
nadroparin	0.29	-15.6	-15.2	0.4	-17.3	-13.5	1.89	2.1
fondaparinux	0.29	-10.9	1.7	0.5	-7.6	5.7	1.62	-3.5
heparin	0.18	15.4	-4.8	0.4	3.0	-5.9	1.38	12.0
alteplase	0.16	-10.2	9.3	<0.05	-10.7	9.2	828.13	0.5

Figure 3.5.1b Anticoagulants, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) by subgroups with the highest expenditure

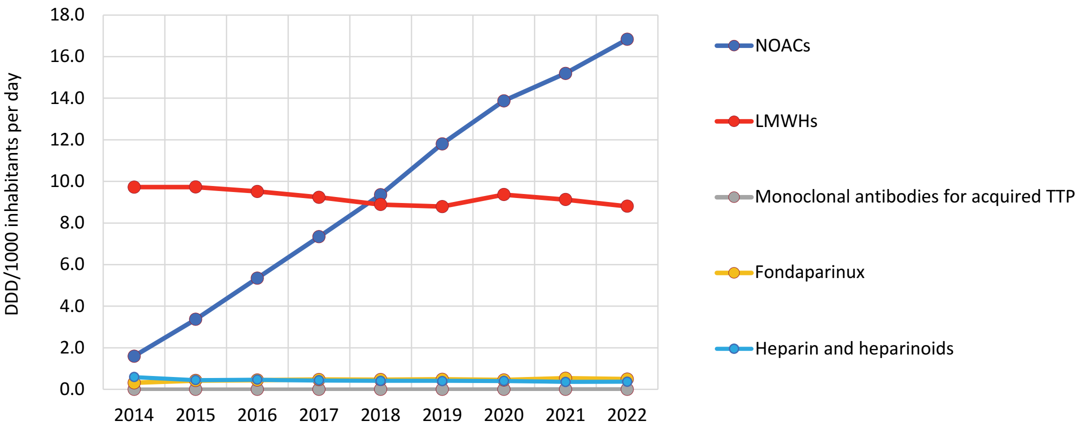


Table 3.5.1b Anticoagulants, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			CAGR % 14-22		
	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD	Expenditure *per capita*	DDD/ 1000 inhabitants per day	Average cost cost DDD
Piedmont	12.54	26.7	1.29	14.52	28.9	1.38	15.8	8.3	6.9	10.1	7.0	2.9
Valle d'Aosta	13.90	21.2	1.80	16.28	29.3	1.52	17.1	38.3	-15.3	15.4	5.8	9.1
Lombardy	16.20	27.2	1.63	17.53	28.1	1.71	8.2	3.1	4.9	9.8	6.5	3.1
Province of Bolzano	9.69	20.5	1.30	14.14	25.0	1.55	45.9	22.0	19.6	8.6	2.5	5.9
Province of Trento	17.07	37.8	1.24	17.49	36.9	1.30	2.5	-2.5	5.2	16.0	6.1	9.3
Veneto	11.95	27.5	1.19	14.23	30.2	1.29	19.0	9.9	8.3	7.6	3.1	4.4
Friuli V.G.	17.22	34.3	1.38	18.25	34.0	1.47	6.0	-0.9	6.9	10.0	5.1	4.6
Liguria	15.22	28.0	1.49	16.05	28.8	1.53	5.4	2.7	2.7	9.1	3.0	5.9
Emilia R.	15.61	34.8	1.23	17.11	36.1	1.30	9.7	3.6	5.8	13.6	5.2	8.1
Tuscany	14.13	29.6	1.31	15.77	32.2	1.34	11.6	8.7	2.7	8.7	3.6	5.0
Umbria	18.62	36.8	1.39	18.76	36.0	1.43	0.7	-2.2	3.0	13.2	5.4	7.3
Marche	15.90	35.5	1.23	16.83	35.5	1.30	5.8	0.2	5.6	17.0	10.5	5.9
Lazio	16.17	27.8	1.59	16.60	28.2	1.61	2.7	1.2	1.5	6.7	6.5	0.3
Abruzzo	15.15	27.5	1.51	17.49	30.5	1.57	15.4	10.9	4.1	9.7	7.2	2.3
Molise	12.26	26.1	1.29	13.73	28.1	1.34	12.0	7.8	3.9	10.1	7.2	2.7
Campania	14.22	24.8	1.57	15.03	25.1	1.64	5.7	1.1	4.6	4.7	7.2	-2.3
Puglia	14.76	27.6	1.46	15.91	28.3	1.54	7.8	2.6	5.0	6.0	5.9	0.0
Basilicata	13.81	26.8	1.41	16.85	29.4	1.57	22.0	9.9	11.0	9.1	6.3	2.7
Calabria	14.29	25.5	1.54	15.22	26.1	1.60	6.5	2.4	4.0	3.0	4.8	-1.7
Sicily	14.41	24.8	1.59	13.35	22.7	1.61	-7.3	-8.6	1.4	5.9	5.7	0.2
Sardinia	15.77	31.4	1.38	17.15	31.4	1.49	8.8	0.2	8.6	9.8	5.3	4.3
Italy	**14.82**	**28.2**	**1.44**	**15.97**	**29.1**	**1.50**	**7.8**	**3.2**	**4.5**	**8.4**	**5.7**	**2.6**
North	14.65	28.8	1.39	16.28	30.3	1.47	11.1	5.1	5.7	10.1	5.3	4.6
Centre	15.66	30.1	1.43	16.53	31.0	1.46	5.5	3.1	2.4	8.8	5.8	2.9
South and Islands	14.53	26.3	1.52	15.20	26.3	1.58	4.6	0.3	4.3	6.0	6.2	-0.1

Exposure and adherence in population

- Health Card data allowed to describe the trend in prevalence and consumption of anticoagulants by age group, gender and region and to calculate some indicators of intensity of use. Adherence and persistence to treatment were also estimated.
- In 2022, exposure to anticoagulants in the general population tends to increase with the age of patients for both genders, reaching a prevalence of use of 36.4% in men over 85, with greater use in men than in women for all age groups, with the exception of patients between the ages of 25 and 54 years old (Figure 3.5.1b).
- The prevalence of use at national level was 5.8%, with values more or less overlapping in the Centre (6.6%), the South (5.6%) and the North (5.7%) (Table 3.5.1c). Veneto has the lowest prevalence (5%), while Marche has the highest prevalence (7.7%). The median age of users is 74 years and each user receives on average about 147.2 DDD of medicine per year with a cost per user of 220.38 euros. Half of the exposed population was treated with 91 DDDs (equivalent to nearly 3 months of therapy), while 17.8% of users received only one with a value ranging from a low of 10.4% in Friuli Venezia-Giulia to a high of 22.7% in Sicily. The apparently different distribution of DDD and therefore of prescriptions in the user population partly reflects the different duration of anticoagulant therapy depending on different clinical indications. Indeed, in most cases, this turns out to be indefinite for prophylaxis of AF thromboembolism, and more time-limited for VTE prophylaxis and treatment of DVT in surgical and nonsurgical patients.
- Analysis by exposure and duration of anticoagulant therapy shows substantially overlapping prevalence of use rates between males and females in all subgroups and a higher median age for AVKs and NOAs than for LMWHs, heparin/heparin and fondaparinux (Table 3.5.1d). The percentage of users who received only one prescription ranged from 3.6% of NOACs to 39.2% of heparin and heparinoids. It should be noted that these data are in line with the clinical indications and treatment duration of the different categories of anticoagulants.
- Adherence and persistence analyses to treatment with anticoagulants were conducted on a cohort of new users of at least 45 years of age, followed over a period of one year.
- The study population included 70,561 individuals on anticoagulant therapy, of a median age of 75 years (IQR 67-82), and consisted of 53% of men. The percentage of individuals with high and low adherence to treatment was 51.6% and 10.4%, respectively (Table 3.5.1e). Low adherence increases with age, with a greater percentage increase among individuals in the 75-84 age group and those aged 85 years or older (10.3% and 14.5%, respectively). Similarly, the percentage of individuals with high adherence, i.e. therapeutic coverage of more than 80% of the considered period, increases up to 74 years of age, reaching 64.8%, and then decreases in the subsequent age groups, to 24.5% in individuals aged 85 or over. These data reflect the reduced compliance of users, which tends to worsen with age due to the deterioration in cognitive functions, the likely worsening of the health status and the change in socio-economic conditions. In general, the percentage of individuals with high adherence is slightly higher in men than in women (55.1% and 47.6%, respectively), with a more marked difference between genders in the North.

- A comparison between 2022 and 2021 at national level shows that the percentage of users with low adherence increaesed by 27%. On the contrary, the percentage of users with high adherence increased by 5%. The largest increases in low adherence rates are observed in the South and, in particular, in individuals aged 55-64 years. The largest reductions in high adherence were observed in the Southern Regions and particularly in individuals aged 55 to 64 years while slight increases were observed in individuals over 85 years of age in the Northern and Southern Regions with a percentage of high adherence being suboptimal on the whole.
- Taking into account the persistence to anticoagulant treatment (Table 3.5.1f), 65.1% of new users are still treated 12 months after the start of therapy. This means that within one year of treatment, approximately 35% of individuals experience an interruption of at least 60 days. Higher probability of persistence at one year of treatment is observed for individuals aged 65 to 74 years, in all geographical areas considered. Minor and non-significant differences are found by gender, with men slightly more persistent than women (65.2% vs 64.9%, respectively). If the average time to treatment discontinuation is taken into account, 35% of users discontinue anticoagulants after 1 day.
- In general, a comparison of persistence data between 2021 and 2022 shows substantial stability (with some cases of slight decrease) in the percentage of persistent subjects at 12 months in all geographic areas, with more pronounced changes in the Southern Regions (-3%) than in the Northern and Central Regions (-1%) (Table 3.5.1f). At the national level, the exception is the slight increase (+1%) in one-year persistence to treatment in the age group of those over 85 compared to the previous year, while, at the level of geographic macro-area, positive variations compared to 2021 are found in the Northern and Southern Regions (+4% and +1%, respectively) in those over 85 years old. Finally, in the North (63.3%) persistent individuals at 12 months are slightly fewer than in the Centre (66.4%) and in the South (67.1%) (Figure 3.5.1d). Even in this case, although there is an increase in the percentage of persistence for all regions, this appears to be suboptimal. In particular, even if we want to consider the influence of the different duration of therapy according to the approved indications, basically of indefinite duration for AF prophylaxis and more time-limited for VTE, and considering the different prevalence in the general population of the main clinical indications the suboptimal values of adherence and persistence are mainly attributable to prophylaxis for the first clinical indication, which shows a lower tolerance to chronic treatment by patients than that found for more time-limited treatment.
- It should be noted that, to some extent, the observed data of reduced adherence and persistence could be affected, albeit to a small extent, by a relative increase in the older population in the use of anticoagulants for indications other than thromboembolic prevention in atrial fibrillation, such as the treatment and prophylaxis of VTE, whose recommended duration of treatment in the data sheet is no more than six months in the prophylaxis of nonsurgical patients at increased risk of venous thromboembolism and 28 days in post-surgical prophylaxis.
- Reduced compliance with chronic treatment by patients on AF thromboembolism prophylaxis, justifiable by lower treatment tolerance compared with a more time-limited duration of therapy, could also influence the observed suboptimal values of adherence and persistence. Such reduced compliance together with individual

socioeconomic conditions may be the preeminent factors for poor adherence and persistence in the older population (especially in those over 85 years old). Conversely, suboptimal therapeutic coverage in the younger population can be ascribed mainly to differences in medical care, diagnosis, clinical follow-up, and prescriptive attitude toward younger people, who are more often asymptomatic or have episodic/occasional atrial fibrillation.

Figure 3.5.1c Distribution of prevalence of use and 2022 consumption of anticoagulant drugs under approved care regime

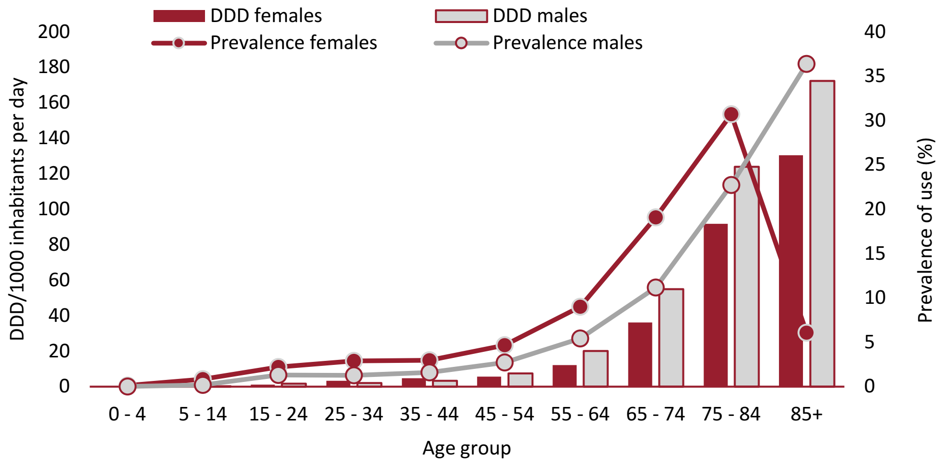


Table 3.5.1c Exposure and duration of anticoagulant therapy by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Average cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
Piedmont	5.4	5.5	5.5	76	210.50	157.5	120.0	16.0
Valle d'Aosta	5.7	5.4	5.5	74	224.89	154.6	120.0	11.6
Lombardy	5.6	6.0	5.8	73	261.50	147.4	90.0	17.4
A.P. of Bolzano	5.5	5.2	5.4	74	223.55	153.5	120.0	13.5
A.P. of Trento	6.0	5.8	5.9	73	173.67	141.7	84.0	15.3
Veneto	5.2	4.8	5.0	76	237.37	177.7	160.0	11.4
Friuli V.G.	5.9	5.7	5.8	77	265.96	180.1	165.0	10.4
Liguria	6.8	7.4	7.1	76	201.90	146.3	90.0	12.4
Emilia R.	5.6	5.7	5.6	75	199.52	155.3	120.0	20.5
Tuscany	6.7	7.3	7.1	76	173.17	130.8	75.0	20.1
Umbria	7.0	7.5	7.3	76	223.80	161.6	120.0	10.3
Marche	7.2	8.1	7.7	75	189.30	147.8	84.0	19.9
Lazio	5.6	6.3	6.0	74	237.33	146.3	84.0	19.8
Abruzzo	6.3	7.2	6.8	74	206.22	137.5	75.0	20.6
Molise	5.5	6.4	5.9	75	194.37	138.5	84.0	15.8
Campania	5.1	6.4	5.7	71	197.34	128.2	60.0	19.2
Puglia	5.1	5.9	5.5	75	243.32	155.1	112.0	14.8
Basilicata	5.8	7.4	6.6	73	208.13	143.9	80.0	17.0
Calabria	5.3	6.4	5.9	73	196.41	129.5	63.0	22.2
Sicily	4.7	5.6	5.2	74	215.15	132.8	60.0	22.7
Sardinia	5.5	6.1	5.8	75	202.60	155.6	110.0	20.5
Italy	**5.6**	**6.1**	**5.8**	**74**	**220.38**	**147.2**	**91.0**	**17.8**
North	5.6	5.7	5.6	75	233.39	156.3	120.0	15.9
Centre	6.3	7.0	6.6	75	207.82	142.6	84.0	19.1
South and Islands	5.2	6.2	5.7	73	211.32	138.1	80.0	19.5

Table 3.5.1d Exposure and duration of anticoagulant therapy by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Average cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	males	females	total					
NOAs	2.6	2.3	2.4	80	388.68	232.8	242.0	3.6
LMWH	2.7	3.5	3.1	67	97.90	61.4	36.0	34.8
Fondaparinux	0.1	0.2	0.2	71	128.56	76.3	40.0	28.4
Heparin and heparinoids	0.02	0.02	0.02	77	95.28	37.9	15.0	39.2
Vitamin K antagonists	0.7	0.6	0.7	79	23.11	137.6	120.0	4.8
Anticoagulants	**5.6**	**6.1**	**5.8**	**74**	**220.38**	**147.2**	**91.0**	**17.8**

Table 3.5.1e Indicators of adherence to treatment with anticoagulant medicines in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=70.561						North N=35.059					
45-54 years	6.7	5.1	6.6	7.9	19	18	4.1	4.0	4.7	5.5	18	35
55-64 years	6.2	5.5	5.5	9.5	73	52	5.1	4.3	4.3	6.4	50	26
65-74 years	6.6	5.4	5.7	8.9	57	35	6.1	4.2	4.6	6.2	34	2
75-84 years	9.2	8.2	8.6	10.3	20	12	9.2	7.6	7.6	8.5	12	-7
≥ 85 years	15.8	14.2	14.5	14.5	0	-8	15.5	13.5	13.5	13.6	1	-12
Women	10.6	9.1	9.2	10.0	9	-6	10.3	8.3	8.3	8.6	3	-17
Men	8.3	7.5	7.3	10.7	47	29	7.9	6.6	6.2	8.0	30	1
Total	**9.4**	**8.3**	**8.2**	**10.4**	**27**	**10**	**9.1**	**7.4**	**7.2**	**8.3**	**16**	**-8**
	Centre N=14.324						South N=21.178					
45-54 years	10.7	7.4	8.6	7.6	10.7	7.4	7.6	5.2	8.1	12.1	49	59
55-64 years	8.8	6.4	6.4	10.7	8.8	6.4	6.1	6.6	6.5	13.1	102	113
65-74 years	7.9	6.2	6.5	11.5	7.9	6.2	6.5	6.2	6.5	11.4	74	75
75-84 years	10.3	8.6	8.7	11.8	10.3	8.6	8.5	9.1	10.3	12.5	22	47
≥ 85 years	18.1	15.5	15.4	14.8	18.1	15.5	14.5	14.3	15.2	16.0	5	11
Women	13.3	10.5	10.3	11.2	13.3	10.5	9.3	9.3	9.7	11.4	18	22
Men	9.4	8.1	8.0	12.6	9.4	8.1	8.2	8.3	8.6	14.1	64	72
Total	**11.3**	**9.3**	**9.1**	**11.9**	**11.3**	**9.3**	**8.8**	**8.8**	**9.2**	**12.8**	**40**	**46**

continued

Table 3.5.1e – *continued*

	High adherence*											
	2019	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**	**2019**	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**
	Total N=70.561						**North N=35.059**					
45-54 years	62.8	62.7	64.0	62.1	-3	-1	66.5	63.5	65.5	64.3	-2	-3
55-64 years	64.9	66.1	69.8	64.5	-8	-1	65.3	66.1	70.1	67.3	-4	3
65-74 years	64.0	67.2	68.8	64.8	-6	1	63.5	68.3	70.5	67.3	-5	6
75-84 years	47.0	50.1	49.5	47.5	-4	1	47.1	51.9	51.8	49.9	-4	6
≥ 85 years	25.5	25.9	24.2	24.5	1	-4	26.2	27.9	25.3	25.7	2	-2
Women	46.0	47.9	49.4	47.6	-4	4	45.3	48.4	49.8	48.7	-2	8
Men	53.1	55.8	58.8	55.1	-6	4	53.4	57.5	60.8	57.8	-5	8
Total	**49.6**	**52.0**	**54.3**	**51.6**	**-5**	**4**	**49.6**	**53.2**	**55.7**	**53.6**	**-4**	**8**
	Centre N=14.324						**South N=14.324**					
45-54 years	56.1	60.8	59.3	60.3	2	8	62.1	62.6	65.0	59.7	-8	-4
55-64 years	61.0	64.2	68.8	62.7	-9	3	66.5	67.2	69.9	61.5	-12	-8
65-74 years	60.0	65.4	67.0	61.7	-8	3	66.9	66.9	67.7	62.8	-7	-6
75-84 years	45.3	48.8	48.8	46.4	-5	2	47.8	48.1	46.3	43.7	-6	-9
≥ 85 years	22.9	25.4	24.3	23.7	-2	3	26.3	23.3	22.2	22.8	3	-13
Women	42.3	46.1	47.0	44.7	-5	6	48.9	48.6	50.7	47.9	-6	-2
Men	49.6	53.4	56.6	53.1	-6	7	54.8	55.0	57.3	51.8	-10	-5
Total	**46.0**	**49.8**	**52.0**	**49.1**	**-6**	**7**	**51.8**	**51.8**	**54.0**	**49.9**	**-8**	**-4**

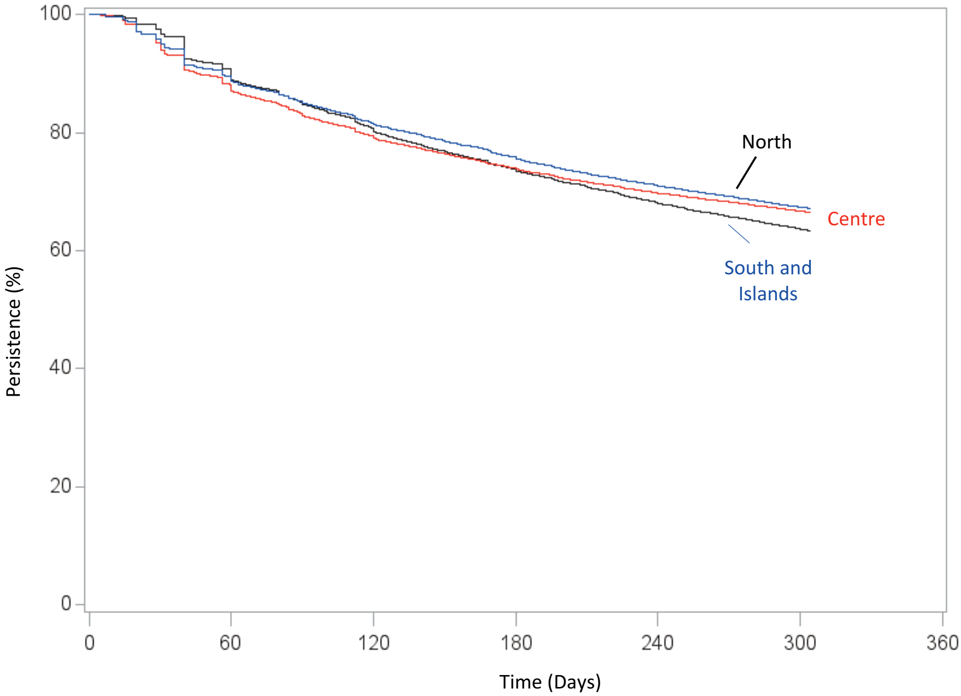
*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to the statistical methods).
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of subjects with low/high adherence related to the specified category.
Median follow-up time (IQR): 334 (300-350)

Table 3.5.1f Persistence after one year of treatment with anticoagulant medicines in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Persistence after 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=70.561						North N=35.059					
45-54 years	55.9	56.1	57.7	56.4	-2	1	56.0	54.7	54.9	54.0	-2	-3
55-64 years	61.8	62.6	65.6	63.4	-3	3	58.5	60.8	62.0	61.6	-1	5
65-74 years	67.2	68.8	71.3	70.0	-2	4	64.6	68.6	70.3	69.2	-2	7
75-84 years	63.5	64.9	67.5	66.3	-2	4	59.4	64.0	65.7	64.9	-1	9
≥ 85 years	53.7	53.8	57.5	58.1	1	8	49.0	52.3	52.5	54.5	4	11
Women	61.1	62.3	65.6	64.9	-1	6	57.1	60.7	62.4	62.8	1	10
Men	62.8	63.8	66.7	65.2	-2	4	59.5	63.2	65.0	63.7	-2	7
Total	**62.0**	**63.1**	**66.2**	**65.1**	**-2**	**5**	**58.4**	**62.0**	**63.8**	**63.3**	**-1**	**8**
	Centre N=14.324						South N=21.178					
45-54 years	47.2	56.7	58.1	59.3	2	26	60.6	57.8	61.4	58.5	-5	-3
55-64 years	57.4	59.9	66.4	62.3	-6	9	67.6	66.4	69.7	66.6	-4	-1
65-74 years	61.8	64.6	70.5	69.4	-1	12	73.2	71.7	73.1	71.6	-2	-2
75-84 years	60.3	61.2	69.3	68.4	-1	13	71.2	68.9	69.2	67.3	-3	-5
≥ 85 years	50.3	51.8	62.1	62.5	1	24	62.5	57.6	61.7	61.3	-1	-2
Women	56.1	58.6	66.8	66.3	-1	18	68.9	66.7	69.2	67.3	-3	-2
Men	59.1	60.7	67.9	66.5	-2	13	69.5	66.9	68.7	67.0	-2	-4
Total	**57.6**	**59.7**	**67.3**	**66.4**	**-1**	**15**	**69.2**	**66.8**	**69.0**	**67.1**	**-3**	**-3**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to the statistical methods).

Figure 3.5.1d Time (in days) to discontinuation of treatment with anticoagulants in the population aged ≥45 years stratified by geographical area. Curves are adjusted by gender and age (the Cox model was used to estimate persistence curves). The North does not include Emilia Romagna



Management of the patient with chronicity is increasingly one of the major areas of activity especially in the continuity of care setting. In this context, anticoagulation is of increasing importance, for which shared and integrated management of patients undergoing treatment among the health care professionals involved (GPs, specialists, nurses) is essential to offer the anticoagulated patient the best possible care.

Whereas in the past, the lack of specific antidotes made it possible to manage bleeding associated with the use of New Oral Anticoagulants (NOACs) through the use of prothrombin complex concentrates (PCCs) or activated prothrombin complex concentrates (aPCCs), today specific antidotes are also available (idarucizumab to antagonize the anticoagulant effect of dabigatran and andexanet alfa for apixaban and rivaroxaban). Other heparin- and NOA-specific antidotes, however, are in pre-clinical trials.

In order to reduce the hemorrhagic risk from anticoagulant treatments, research has directed its attention to molecules that can act further upstream in the coagulation cascade at the level of factor XI, which, although it plays a key role in contributing to thrombus growth, has a less prominent function in hemostatic processes. Currently, they are not yet available in clinical practice, and studies are under way to evaluate their efficacy and safety.

3.5.2 Coagulation factors

- In 2022, coagulation factors recorded an increase in overall per capita expenditure (+1.2%), corresponding to an increase in consumption (+4.3%). Per capita expenditure has shown an increasing trend since 2014 (CAGR: +2.8%). Conversely, the average DDD cost has continued to decrease over the last three years, reaching EUR 405.2 in 2022 (Figure 3.5.2a).
- Short-acting recombinant factors for the treatment of haemophilia A showed a reduction in consumption also in 2022 (-23%). By contrast, long-acting recombinant factors recorded an increase in use, although less significant than the previous year (2022: +31% vs 2021: +47.2%) and continued to be the category with the highest per capita expenditure (EUR 2.53) (Table 3.5.2a).
- Short-acting recombinant factors for the treatment of haemophilia B showed a reduction in consumption (-6.1%). By contrast, long-acting recombinant factors recorded an increase in in consumption (+11.9%) and continued to be the category with the highest per capita expenditure for factor IX deficiency, equal to EUR 1.20 (Table 3.5.2a).
- Concerning recombinant factors, long-acting factors show a better pharmacokinetic profile compared to short-acting formulations. This allows to increase the interval between infusions, and have greater safety margins against haemorrhagic episodes. This has various benefits, including improving adherence to prophylaxis and the quality of life of patients. These aspects have led to a greater use of active substances with longer half-life over the last three years, as shown by the increasing spending trend of long-acting factors compared to short-acting factors (Figure 3.5.2b).
- For the treatment of haemophilia A, in 2022 monoclonal antibody emicizumab recorded an increase in consumption (+37.7%) compared to the previous year (Table 3.5.2a). This medicine, that should be administered subcutaneously on a weekly basis, was initially authorised for routine prophylaxis in patients with haemophilia A with factor VIII inhibitors. Now such medicine can be used in patients with severe (coagulating factor activity <1%) and moderate (coagulating factor activity 1-5%) condition, even in the absence of inhibitors. In view of the trend so far and the recent extension of the indications to patients with moderate condition (with or without inhibitors), it seems plausible that emicizumab has not yet reached the maximum possible use in Italy and that it can record a further increase in the near future.
- Just like in the previous year, a high regional variability is observed with higher expenditure in the South compared to the North (North: 8.64 - Centre: 9.50 - South: 9.97 EUR) (Table 3.5.2b). Campania and Calabria are the Regions with the highest expenditure on these medicines, with values above EUR 11. Significant regional differences are also found in the average DDD cost, which goes from EUR 324.41 in Sardinia to a practically double value in Valle d’Aosta (EUR 662.28).

Figure 3.5.2a Coagulation factors, temporal trend in per capita expenditure and average cost per day of therapy (2014-2022)

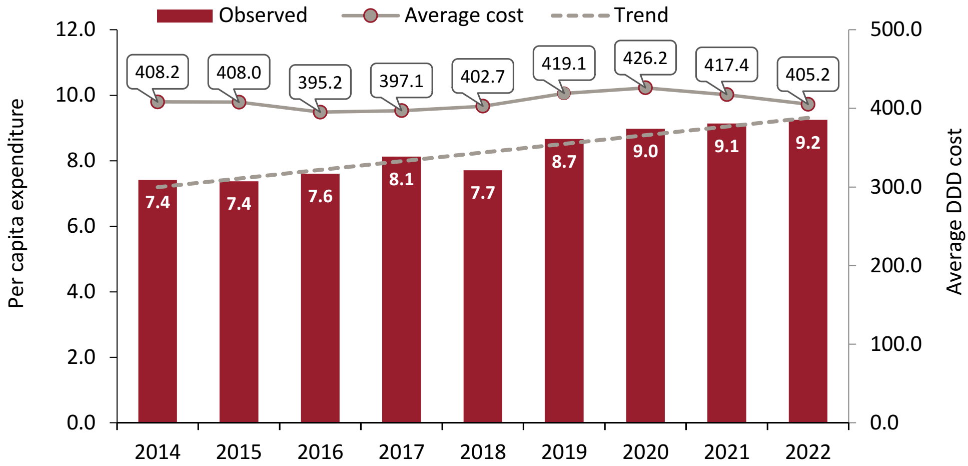


Table 3.5.2a Coagulation factors, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Haemophilia A (long-acting recombinant factors)	2.53	31.0	-	<0.05	34.5	-	320.39	-2.6
Haemophilia A (short-acting recombinant factors)	2.51	-23.7	-7.5	<0.05	-23.0	-6.6	336.25	-0.8
Haemophilia A (monoclonal antibodies)	1.58	24.8	-	<0.05	37.7	-	683.30	-9.3
Haemophilia B (long-acting recombinant factors)	1.20	11.0	-	<0.05	11.9	-	924.16	-0.8
Factor VII deficiency (short-acting recombinant factors)	0.46	-23.0	-9.2	<0.05	-22.4	-8.0	4049.19	-0.8
Haemophilia A (plasma derivatives)	0.32	-11.1	-7.3	<0.05	-9.4	-6.5	249.44	-1.9
Haemophilia B (short-acting recombinant factors)	0.24	-5.0	-10.8	<0.05	-6.1	-10.9	377.47	1.2
Activated human antihemophilic prothrombin complex	0.12	-9.2	-14.7	<0.05	-12.0	-15.6	8383.04	3.1
Combination of coagulation factors (plasma derivatives)	0.08	16.6	13.4	<0.05	18.5	13.2	104.55	-1.6
Factor VII deficiency (plasma derivatives)	0.08	31.3	7.3	<0.05	30.7	7.3	361.53	0.5
Von Willebrand's disease (plasma derivatives)	0.05	137.9	1.2	<0.05	138.6	1.2	71.71	-0.3
Other deficiencies of coagulation factors (long acting recombinant factors)	0.05	-5.4	33.5	<0.05	-5.4	30.5	15524.20	0.0
Haemophilia B (plasma derivatives)	0.02	-9.0	-4.1	<0.05	-16.0	-5.5	216.09	8.3
Other deficiencies of coagulation factors (plasma derivatives)	0.01	21.1	-	<0.05	21.1	-	5490.88	0.0
Coagulation factors	**9.25**	**1.2**	**2.8**	**0.1**	**4.3**	**2.9**	**405.18**	**-2.9**
emicizumab	1.58	24.8	-	<0.05	37.7	-	683.30	-9.3
octocog alfa	1.16	-30.5	-13.3	<0.05	-29.2	-12.2	326.68	-1.8
efmorocotog alfa	1.07	3.5	-	<0.05	3.6	-	357.07	-0.1
albutrepenonacog alfa	0.90	12.9	-	<0.05	15.9	-	1060.05	-2.5
damoctocog alfa pegol	0.66	51.2	-	<0.05	51.1	-	330.13	0.1
turoctocog alfa pegol	0.49	103.7	-	<0.05	102.8	-	258.63	0.5
heptacog alfa activated (recombinant DNA coagulation factor VII)	0.46	-23.0	-9.2	<0.05	-22.4	-8.0	4049.19	-0.8
moroctocog alfa	0.45	-24.8	-10.0	<0.05	-22.6	-8.6	325.05	-2.8
lonoctogoc alfa	0.38	-4.9	-	<0.05	-3.6	-	315.97	-1.4
factor VIII/ von Willebrand's factor	0.32	-10.8	-6.7	<0.05	-9.1	-5.8	250.66	-1.8

Figure 3.5.2b Coagulation factors, temporal trend 2014-2022 in per capita expenditure of most expensive subgroups

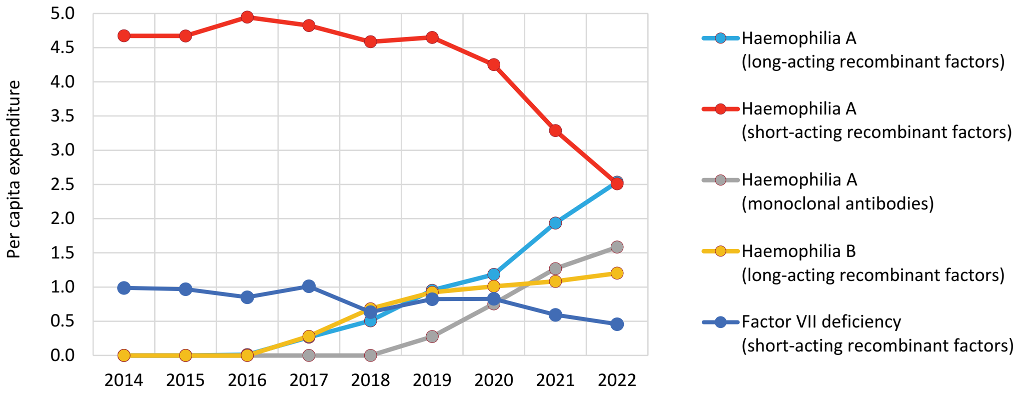


Table 3.5.2b Coagulation factors, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	8.49	0.1	450.12	9.11	0.1	463.12	7.3	4.3	2.9	1.9	0.3	1.6
Valle d'Aosta	4.45	0.0	284.18	10.71	<0.05	662.28	140.8	3.3	133.0	16.1	9.0	6.4
Lombardy	8.21	0.0	454.16	8.42	0.1	418.72	2.5	11.2	-7.8	5.4	4.9	0.4
A.P. of Bolzano	4.33	0.0	289.83	6.17	0.1	334.97	42.5	23.3	15.6	0.9	0.9	0.0
A.P. of Trento	5.06	0.0	359.59	5.52	<0.05	346.49	9.0	13.1	-3.6	2.6	3.2	-0.5
Veneto	7.17	0.0	396.71	8.15	0.1	396.37	13.6	13.7	-0.1	7.1	5.6	1.3
Friuli VG	4.25	0.0	552.88	5.41	<0.05	587.15	27.3	19.8	6.2	-6.2	-4.7	-1.5
Liguria	8.33	0.0	509.20	8.54	0.1	462.80	2.6	12.9	-9.1	7.2	4.4	2.7
Emilia Romagna	9.55	0.1	405.17	10.71	0.1	423.03	12.1	7.4	4.4	7.4	8.0	-0.5
Tuscany	9.27	0.0	513.85	9.00	0.1	485.75	-2.8	2.8	-5.5	2.9	3.4	-0.5
Umbria	6.77	0.0	400.02	6.94	<0.05	395.36	2.6	3.9	-1.2	8.8	8.9	-0.1
Marche	6.09	0.0	466.76	7.42	<0.05	417.72	21.9	36.2	-10.5	1.7	4.3	-2.5
Lazio	10.84	0.1	342.41	10.81	0.1	347.73	-0.3	-1.8	1.6	1.7	2.4	-0.7
Abruzzo	11.66	0.1	435.22	14.32	0.1	429.81	22.8	24.4	-1.2	7.3	6.4	0.9
Molise	6.95	0.1	358.45	6.77	<0.05	378.05	-2.6	-7.7	5.5	2.4	1.7	0.7
Campania	12.33	0.1	389.76	11.48	0.1	387.22	-6.9	-6.2	-0.7	0.0	1.3	-1.3
Puglia	12.12	0.1	457.18	9.74	0.1	391.48	-19.6	-6.2	-14.4	-0.1	0.3	-0.4
Basilicata	5.86	0.0	413.13	6.04	<0.05	400.69	3.1	6.3	-3.0	-0.1	-1.9	1.9
Calabria	12.08	0.1	461.13	11.46	0.1	431.27	-5.1	1.5	-6.5	2.9	1.7	1.2
Sicily	9.22	0.1	400.66	8.96	0.1	371.44	-2.8	4.9	-7.3	0.8	1.9	-1.0
Sardinia	5.76	0.0	333.84	5.39	<0.05	324.41	-6.5	-3.8	-2.8	-0.6	-1.0	0.4
Italy	**9.14**	**0.1**	**417.43**	**9.25**	**0.1**	**405.18**	**1.2**	**4.3**	**-2.9**	**2.8**	**2.9**	**-0.1**
North	7.97	0.1	433.80	8.64	0.1	426.83	8.4	10.1	-1.6	4.8	4.3	0.5
Centre	9.41	0.1	396.23	9.50	0.1	390.69	1.0	2.4	-1.4	2.4	3.2	-0.8
South and Islands	10.64	0.1	412.75	9.97	0.1	389.11	-6.3	-0.6	-5.7	1.0	1.4	-0.4

One of the most significant problems in the treatment of haemophilia is the risk of developing inhibitor antibodies against FVIII and FIX, especially in paediatric subjects. In this context, the role of the different types of molecules in the development of inhibitors in patients previously treated and *naïve* remains to be defined. Comparative studies appear necessary to reduce the use of bypassing agents and for the adoption of a common conduct in clinical practice.

In haemophilia B, a condition in which inhibitors develop much less frequently than haemophilia A, data published on prophylaxis with the use of bypassing agents and their efficacy remain limited.

A new class of FVIII with a markedly extended half-life is currently being studied for the prophylaxis of adult and paediatric patients with haemophilia A to allow weekly administration of the medicine, while ensuring an adequate efficacy and safety profile.

Currently, scientific research is aimed at identifying a curative therapeutic strategy for congenital haemorrhagic diseases. Gene therapies for haemophilia A and B have recently been authorised by European and international competent authorities. However, the type of subjects receiving such therapies will need to be identified, also to assess the impact on health expenditure.

3.5.3 Platelet aggregation inhibitors

- The consumption of platelet aggregation inhibitors appears generally stable over the period 2014-2020 (CAGR: +0.5%), with 70.8 DDD/1000 inhabitants per day in 2022. As in 2021, within this category, a stable trend in expenditure is observed (per capita expenditure equal to EUR 1.44). A minimum increase is recorded in the consumption of acetylsalicylic acid alone or in combination (+0.5% and stable over the past nine years, Figure 3.5.3b) and of ticagrelor (consumption: +1.1%). For the latter a slight reduction in expenditure was observed (-0.9%), counterbalanced by a minimum increase in the expenditure of other active ingredients belonging to the class of P2Y12 platelet receptor inhibitors (+0.7%). As in the previous year, clopidogrel registers an increase in expenditure and stability in consumption (expenditure: +3.2%; consumption: +0.7%) (Table 3.5.3a and Figure 3.5.3a).
- Despite the trend over the past two years, ticagrelor is the platelet aggregation inhibitor with the greatest increase in expenditure (CAGR: +8.2%) and consumption (CAGR: +10.4%) in the 2014-2022 period. It is used in combination with acetylsalicylic acid in the prevention of atherothrombotic events in adult patients with acute coronary syndrome or with a history of myocardial infarction at high risk of developing events. Ticagrelor requires two daily administrations and has a higher cost compared with other medicines of the same class, with the exception of cangrelor (EUR 222.52) (Table 3.5.3a and Figure 3.5.3a).
- Regional data show a wide variability in consumption and expenditure of platelet aggregation inhibitors. In 2022, the Region with the highest consumption recorded a value twice as large as the Region with the lowest consumption (Molise: 94.9 DDD/1000 inhabitants per day vs A.P. of Bolzano: 43.8 DDD/1000 inhabitants per day). In terms of per capita expenditure, the largest change compared to 2021 shows a positive sign for Tuscany (+14.5%) and a negative sign for Umbria (-14.4%) (Table 3.5.3b). It should be pointed out that Emilia-Romagna, despite consumption levels similar to those of Lazio and Puglia, has a 50% lower expenditure. This difference could be attributable to the use of medicines with a lower price (average cost: EUR 0.13 vs. EUR 0.25/EUR 0.27) (Table 3.5.3b).
- The analysis of the consumption of platelet aggregation inhibitors shows a preferential use of monotherapy or concomitant therapy based on clopidogrel and acetylsalicylic acid, compared to the fixed combination. Dual antiplatelet therapy reduces short- and long-term ischemic risk, although it exposes to a bleeding risk directly proportional to the duration of treatment, generally equal to 12 months.

Figure 3.5.3a Platelet aggregation inhibitors, temporal trend in per capita expenditure and average cost per day of therapy 2014-2022

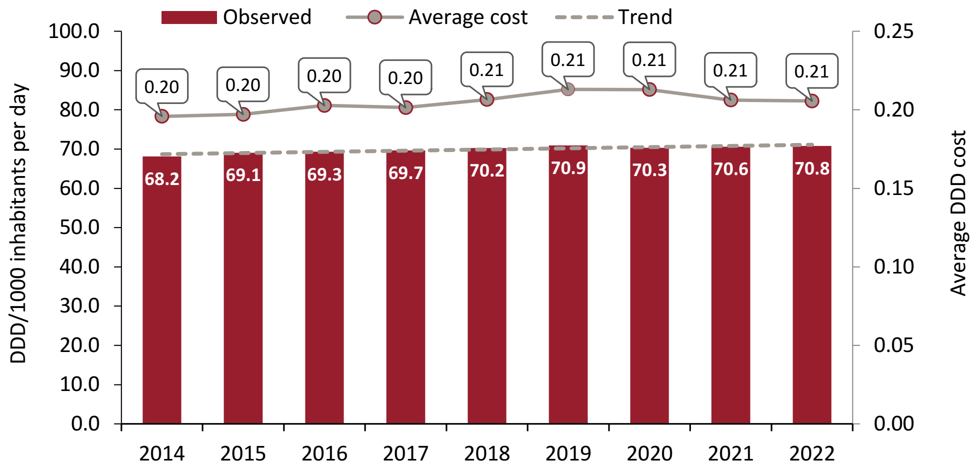


Table 3.5.3a Platelet aggregation inhibitors, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
P2Y12 platelet receptor inhibitors	2.50	0.7	2.2	14.1	-0.9	1.5	0.49	1.7
Acetylsalicylic acid alone and in combination	1.44	0.0	-0.4	54.4	0.5	0.0	0.07	-0.5
Other platelet aggregation inhibitors	1.03	-0.2	3.0	<0.05	8.9	0.9	127.90	-8.3
Acetylsalicylic acid/clopidogrel	0.31	-5.3	0.4	2.2	0.5	7.1	0.39	-5.7
Glycoprotein IIb/IIIa inhibitors	0.02	-15.8	-22.3	<0.05	5.9	-4.6	64.49	-20.5
Platelet aggregation inhibitors	**5.31**	**-0.1**	**1.1**	**70.8**	**0.2**	**0.5**	**0.21**	**-0.3**
clopidogrel	1.32	3.2	3.5	11.5	0.7	6.3	0.32	2.4
acetylsalicylic acid	1.20	1.5	1.4	46.9	1.8	0.9	0.07	-0.2
ticagrelor	0.97	-0.9	8.2	1.1	4.0	10.4	2.34	-4.7
treprostinil	0.56	-5.9	1.8	<0.05	6.3	5.0	485.26	-11.5
clopidogrel/acetylsalicylic acid	0.31	-5.3	0.4	2.2	0.5	7.1	0.39	-5.7
selexipag	0.29	30.6	-	<0.05	29.4	-	109.66	0.9
lysine acetylsalicylate	0.19	-6.6	-3.3	6.3	-6.3	-2.8	0.08	-0.3
iloprost	0.14	-21.0	-7.4	<0.05	-8.0	-3.3	75.29	-14.1
ticlopidine	0.12	-16.0	-14.2	1.4	-16.0	-14.4	0.25	0.0
cangrelor	0.05	27.7	-	<0.05	24.2	-	222.52	2.8

Figure 3.5.3b Platelet aggregation inhibitors, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) of subgroups with the highest expenditure

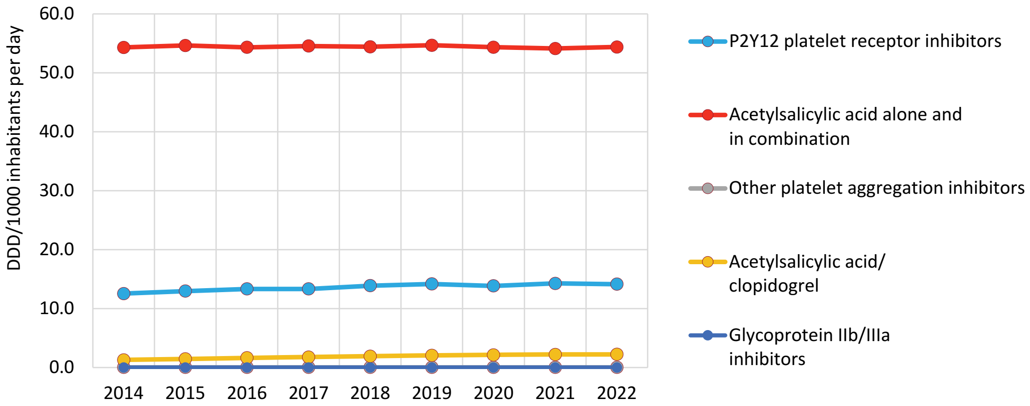


Table 3.5.3b Platelet aggregation inhibitors, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	3.92	71.1	0.15	4.08	72.4	0.15	3.9	1.8	2.0	-0.8	-0.1	-0.7
Valle d'Aosta	3.12	60.8	0.14	3.25	62.2	0.14	4.0	2.3	1.6	-2.5	-2.4	-0.1
Lombardy	4.79	48.1	0.27	4.88	48.5	0.28	1.9	0.8	1.2	2.0	0.0	2.0
A.P. of Bolzano	2.99	44.0	0.19	3.30	43.8	0.21	10.1	-0.3	10.4	2.1	-1.7	3.9
A.P. of Trento	4.44	75.1	0.16	4.20	74.8	0.15	-5.3	-0.5	-4.9	-1.0	-0.2	-0.9
Veneto	2.99	46.8	0.17	3.01	46.5	0.18	0.6	-0.6	1.3	-0.8	0.7	-1.5
Friuli VG	3.80	69.8	0.15	3.48	68.7	0.14	-8.4	-1.7	-6.8	-1.8	-1.4	-0.3
Liguria	3.81	55.6	0.19	3.61	56.6	0.17	-5.2	1.8	-6.9	-0.6	-1.0	0.5
Emilia Romagna	3.88	82.0	0.13	4.06	83.6	0.13	4.7	1.9	2.7	-0.5	-0.5	0.0
Tuscany	4.54	75.3	0.17	5.20	76.2	0.19	14.5	1.1	13.2	1.4	-0.5	2.0
Umbria	6.31	76.1	0.23	5.40	74.6	0.20	-14.4	-2.0	-12.7	1.7	-0.3	2.0
Marche	4.67	84.6	0.15	4.71	85.0	0.15	0.7	0.5	0.2	2.9	0.9	1.9
Lazio	8.12	80.3	0.28	8.04	80.3	0.27	-1.1	0.0	-1.1	2.2	1.1	1.0
Abruzzo	7.92	91.2	0.24	7.95	92.4	0.24	0.3	1.3	-1.0	2.6	1.0	1.6
Molise	5.25	94.3	0.15	4.66	94.9	0.13	-11.4	0.7	-11.9	-3.8	1.0	-4.8
Campania	6.49	74.4	0.24	6.52	76.5	0.23	0.4	2.8	-2.3	1.0	2.8	-1.8
Puglia	8.16	87.7	0.25	8.06	87.7	0.25	-1.3	0.0	-1.2	2.8	0.9	1.8
Basilicata	8.73	88.3	0.27	8.92	91.3	0.27	2.2	3.5	-1.2	4.6	2.1	2.5
Calabria	8.07	88.9	0.25	8.10	89.3	0.25	0.3	0.5	-0.2	6.4	1.2	5.2
Sicily	4.85	82.9	0.16	4.18	78.2	0.15	-13.9	-5.7	-8.7	-2.7	1.1	-3.8
Sardinia	3.89	72.9	0.15	3.92	72.2	0.15	0.6	-0.9	1.6	-1.6	-0.9	-0.7
Italy	**5.32**	**70.6**	**0.21**	**5.31**	**70.8**	**0.21**	**-0.1**	**0.2**	**-0.3**	**1.1**	**0.5**	**0.6**
North	4.03	59.0	0.19	4.10	59.5	0.19	1.6	0.9	0.7	0.3	-0.3	0.6
Centre	6.39	78.9	0.22	6.50	79.2	0.22	1.7	0.3	1.4	2.0	0.4	1.6
South and Islands	6.50	82.2	0.22	6.32	81.7	0.21	-2.7	-0.5	-2.2	1.3	1.3	-0.1

Exposure and adherence in population

- The data of the Health Card flow allowed to describe the trend in the prevalence and consumption of platelet aggregation inhibitors by age, gender and region and calculate some indicators of the intensity of use. Adherence and persistence to treatment were also estimated.
- In 2022, exposure to platelet aggregation inhibitors in the general population tends to increase with age for patients of both genders, reaching a higher prevalence of use in men aged 85 years or older (49.7%). In all age groups, except for 15-34 years, men consume more doses than women (Figure 3.5.3c). Women show double consumption compared to men in the 25-34 age group.
- The prevalence of use at national level was 9.1%, with values more or less overlapping in the Centre (10.4%), the South (10.8%), that show higher percentages compared to the North (7.4%) (Table 3.5.3c). The Autonomous Province of Bolzano has the lowest prevalence (5%), while Molise has the highest (12.8%). The median age of users is 75 years and each individual receives an average of 268 DDD of product during the year, with a cost per user equal to EUR 43.65. Half of the nationally exposed population is treated for at least 10 months in one year (median DDD: 300). 4% of users at national level receives only one prescription in the year, with a value ranging from a minimum of 2% in Valle d'Aosta to a maximum of 6.6% in Campania.
- The analysis by exposure and duration of anticoagulant therapy shows substantially overlapping prevalence rates between men and women in all subgroups, with a percentage of users receiving only one prescription ranging from 3.6% of acetylsalicylic acid alone and in combination to 27.5% of other platelet aggregation inhibitors (Table 3.5.3d).
- As regards adherence and persistence, exposure refers to a cohort of new users aged at least 45 years, followed during one year. The study population included 163,545 new users, with a median age of 70 years (IQR 62-78), made up of 50.8% of men.
- In 2022, the proportion of subjects with high and low adherence to platelet aggregation inhibitors treatment was 61.1% and 7%, respectively (Table 3.5.3e). The percentage of individuals with low adherence tends to increase with age, recording the highest value in the over 85 age group (8%) and in women compared to men (7.7% and 6.4%, respectively). Stratified by age and geographical area, the largest proportion of individuals with low adherence is observed in the over 75 age group and in the Regions of Southern Italy (9.5%). As expected, high adherence tends to decrease with increasing age, with a higher value in the age group between 45 and 54 years (64.4%), and to a slightly greater extent in men than in women (64% and 58.1%). Users in Northern Italy and aged between 45 and 54 years have the highest percentage of adherence (70%). The reduced adherence with increasing age is due to the poor compliance that characterises the elderly population, affected by cognitive impairment, numerous comorbidities requiring numerous pharmacological therapy and socio-economic conditions.
- A comparison of 2021-2022 adherence data shows a general stable trend (a slight increase in some cases) in the percentage of subjects with high adherence, except for subject over 75 years in Central Regions (-4%) and in subject over 85 years of age. In Central Regions an increase is also observed in the percentage of individuals with low adherence (+14%) as opposed to the regions of the North and South, where a decrease

is recorded (-1% in the North and -7% in the South) (Table 3.5.3e). This trend in adherence rates at national level and for the geographical areas concerned may be attributable to inadequate awareness of the importance of cardiovascular prevention by the general population.

- Analysing the persistence of treatment with platelet aggregation inhibitors (Table 3.5.3f), it is evident that more than half of new users are persistent to treatment after one year (52.9%), with slightly lower percentages in the South (50%) compared to the Centre (54.4%) and the North (55%). One year after the start of treatment, the percentage of users who discontinue treatment for at least 60 days increases with increasing age. In general, men show slightly higher persistence rates than women (55.8% and 49.9%, respectively). For the North and the Centre, the data observed in 2022 are broadly similar to those of 2021, while the South shows a slight increase (+3%) of persistent individuals 12 months from the start of treatment compared to the previous year.
- Finally, comparing persistence data among geographical areas (Figure 3.5.3d), platelet aggregation inhibitors show a median time to treatment discontinuation greater than 365 days.
- In general, both adherence and persistence to treatment with platelet aggregation inhibitors are suboptimal in the population at cardiovascular risk and further efforts should be supported to improve use in cardiovascular prevention.

Figure 3.5.3c Breakdown of the prevalence of use and consumption of platelet aggregation inhibitors under approved care regime and on behalf distribution (year 2022)

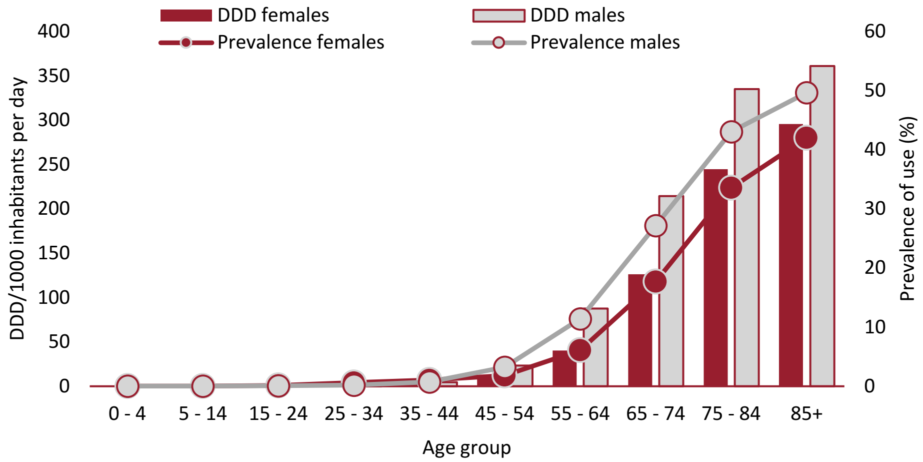


Table 3.5.3c Exposure and duration of therapy with platelet aggregation inhibitors by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	10.4	8.5	9.5	75	32.11	273.5	300.0	2.7
Valle d'Aosta	8.2	7.4	7.8	76	29.78	267.8	296.0	2.0
Lombardy	6.9	5.4	6.1	76	61.69	266.0	270.0	2.9
A.P. of Bolzano	5.4	4.6	5.0	77	45.61	269.6	300.0	2.3
A.P. of Trento	9.1	8.1	8.6	75	41.27	288.9	300.0	2.4
Veneto	6.6	4.5	5.6	75	40.68	281.2	300.0	2.3
Friuli VG	9.6	8.2	8.9	76	30.77	282.7	300.0	2.3
Liguria	8.2	8.1	8.2	78	35.12	246.7	270.0	4.6
Emilia Romagna	10.6	9.3	9.9	75	25.85	276.9	300.0	2.6
Tuscany	10.9	9.6	10.2	76	41.99	268.6	300.0	5.6
Umbria	10.7	8.9	9.8	76	35.06	278.5	300.0	4.6
Marche	12.0	10.2	11.1	76	33.41	277.1	300.0	3.4
Lazio	10.9	10.0	10.4	75	58.68	271.8	300.0	3.6
Abruzzo	12.8	11.7	12.2	75	54.48	268.0	300.0	4.0
Molise	13.4	12.3	12.8	74	27.73	266.7	300.0	3.6
Campania	10.6	9.7	10.1	73	43.32	244.6	261.3	6.6
Puglia	12.0	10.5	11.3	74	52.16	272.6	300.0	3.7
Basilicata	12.6	11.7	12.2	74	58.93	269.9	300.0	5.9
Calabria	12.1	11.6	11.8	74	53.06	263.1	288.0	5.7
Sicily	10.6	10.3	10.4	75	29.54	262.7	280.0	4.8
Sardinia	9.6	9.1	9.3	75	32.78	279.9	300.0	3.9
Italy	**9.8**	**8.6**	**9.1**	**75**	**43.65**	**268.0**	**300.0**	**4.0**
North	8.2	6.7	7.4	76	41.23	272.2	300.0	2.7
Centre	11.0	9.8	10.4	75	48.47	272.0	300.0	4.2
South and Islands	11.2	10.4	10.8	74	43.20	261.8	300.0	5.0

Table 3.5.3d Exposure and duration of therapy with platelet aggregation inhibitors by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
P2Y12 platelet receptor inhibitors	2.3	1.7	2.0	76	112.37	235.8	252.0	5.3
Acetylsalicylic acid alone and in combination	8.0	7.1	7.5	75	18.61	251.3	280.0	4.7
Other platelet aggregation inhibitors	<0.05	<0.05	<0.05	79	2,029.68	119.3	70.0	27.5
Acetylsalicylic acid/clopidogrel	0.5	0.2	0.3	73	97.74	248.4	280.0	6.4
Platelet aggregation inhibitors	**9.8**	**8.6**	**9.1**	**75**	**43.65**	**268.0**	**300.0**	**4.0**

Table 3.5.3e Indicators of adherence to treatment with platelet aggregation inhibitors in the population aged ≥45 years in the period 2019-2022 and 2022-2021 change

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N= 163,545						North N= 62,704					
45-54	7.6	7.3	6.6	6.5	-2	-15	4.2	4.5	4.5	4.4	-3	5
55-64	7.3	7.4	6.6	6.6	1	-9	4.5	4.7	4.1	4.3	4	-5
65-74	7.8	7.4	6.7	6.9	2	-12	5.5	5.0	4.6	4.7	2	-14
75-84	8.1	8.0	7.4	7.4	0	-8	5.7	6.0	5.7	5.7	0	0
≥85	9.1	8.3	8.4	8.0	-4	-12	6.7	5.9	6.8	6.2	-9	-7
Females	8.8	8.4	7.8	7.7	-2	-12	6.2	6.0	5.7	5.7	1	-8
Males	7.1	6.9	6.2	6.4	3	-9	4.7	4.7	4.5	4.4	-3	-6
Total	**7.9**	**7.7**	**7.0**	**7.0**	**0**	**-12**	**5.4**	**5.3**	**5.1**	**5.0**	**-1**	**-8**
	Centre N= 35,088						South N=65,753					
45-54	7.2	7.3	5.7	6.5	14	-10	10.6	9.5	8.9	8.2	-8	-22
55-64	6.6	6.9	5.2	6.0	16	-9	9.8	9.9	9.5	8.7	-8	-12
65-74	7.6	7.5	5.6	6.4	15	-16	9.8	9.3	9.5	9.0	-5	-8
75-84	7.8	8.3	6.6	7.3	11	-7	10.9	10.3	10.1	9.5	-6	-13
≥85	9.7	9.5	8.0	8.8	10	-9	11.6	10.6	10.6	9.5	-11	-18
Females	8.5	8.4	6.8	7.3	7	-14	11.2	10.7	10.5	9.6	-9	-14
Males	6.9	7.3	5.2	6.3	22	-9	9.4	9.0	8.8	8.4	-4	-11
Total	**7.7**	**7.8**	**6.0**	**6.8**	**14**	**-12**	**10.3**	**9.8**	**9.7**	**9.0**	**-7**	**-13**

continued

Table 3.5.3e – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N= 163,545						North N= 62,704					
45-54	62.4	62.8	63.3	64.4	2	3	69.9	69.9	69.8	70.0	0	0
55-64	61.5	61.8	62.3	63.6	2	3	68.4	68.9	68.1	68.7	1	0
65-74	59.7	60.1	60.9	61.7	1	3	65.6	65.5	65.6	66.1	1	1
75-84	58.0	58.2	58.4	58.7	0	1	63.0	62.3	61.6	62.1	1	-1
≥85	55.4	56.4	55.9	56.1	0	1	60.2	60.8	58.8	59.8	2	-1
Females	56.2	56.8	57.3	58.1	1	3	61.7	61.8	61.5	61.8	1	0
Males	62.4	62.5	63.2	64.0	1	3	68.0	67.7	67.4	68.2	1	0
Total	**59.3**	**59.7**	**60.4**	**61.1**	**1**	**3**	**65.0**	**64.9**	**64.6**	**65.1**	**1**	**0**
	Centre N= 35,088						South N=65,753					
45-54	64.1	61.3	63.8	64.9	2	1	55.6	57.7	57.6	59.5	3	7
55-64	62.0	61.3	63.6	65.5	3	6	55.6	56.2	56.7	58.8	4	6
65-74	59.2	60.1	62.0	63.1	2	7	55.3	55.6	56.1	57.1	2	3
75-84	56.9	56.9	59.6	58.9	-1	4	53.0	54.1	53.5	54.5	2	3
≥85	53.9	54.3	56.2	53.8	-4	0	50.8	52.0	51.8	53.1	2	5
Females	56.5	56.2	58.4	59.3	2	5	51.2	52.5	52.8	54.0	2	5
Males	61.3	61.6	64.1	64.3	0	5	57.6	57.9	58.2	59.7	3	4
Total	**58.8**	**58.9**	**61.4**	**61.8**	**1**	**5**	**54.4**	**55.2**	**55.5**	**56.8**	**2**	**5**

*Adherence to treatment was assessed within 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions provided. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods).

N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.

Percentages of subjects with low/high adherence related to the specified category.

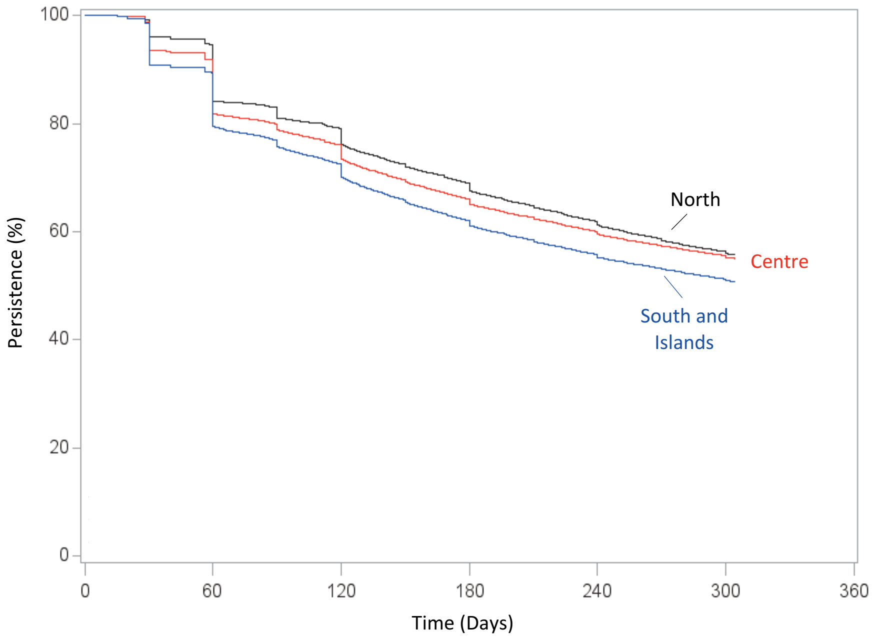
Median follow-up time (IQR): 321 (258-345)

Table 3.5.3f Persistence after one year on treatment with platelet aggregation inhibitors in the population aged ≥ 45 years in the period 2019-2022 and 2022-2021 change

	Persistence at 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N= 163,545						North N= 62,704					
45-54	53.0	54.0	55.0	55.8	1	5	59.7	60.4	59.9	59.9	0	0
55-64	53.6	54.7	55.8	55.9	0	4	59.5	60.5	60.2	58.9	-2	-1
65-74	52.6	52.8	54.1	54.1	0	3	56.5	56.7	56.6	56.4	0	0
75-84	49.9	49.5	49.9	50.1	0	0	53.2	52.1	51.8	51.6	0	-3
≥85	46.7	47.2	47.1	46.6	-1	0	49.6	50.4	48.2	48.3	0	-2
Females	48.2	48.5	49.6	49.9	1	4	51.9	52.0	51.8	51.3	-1	-1
Males	54.5	54.9	55.9	55.8	0	2	58.6	58.6	58.6	58.3	0	-1
Total	**51.4**	**51.7**	**52.8**	**52.9**	**0**	**3**	**55.4**	**55.4**	**55.4**	**55.0**	**-1**	**-1**
	Centre N= 35,088						South N=65,753					
45-54	53.2	51.8	54.9	56.8	4	7	47.7	49.9	50.9	51.8	2	8
55-64	53.5	53.9	58.0	57.7	-1	8	48.9	50.4	50.6	52.7	4	8
65-74	52.6	52.3	56.9	56.6	-1	8	49.5	49.9	49.9	50.9	2	3
75-84	49.1	48.6	51.3	51.1	0	4	46.6	46.9	46.5	47.6	2	2
≥85	45.5	44.5	49.1	45.5	-7	0	44.0	44.7	44.1	45.2	3	3
Females	48.0	47.4	51.2	51.9	1	8	45.1	45.8	46.4	47.6	3	6
Males	54.0	53.8	58.2	56.8	-2	5	50.9	51.8	51.5	52.8	3	4
Total	**50.9**	**50.6**	**54.9**	**54.4**	**-1**	**7**	**48.0**	**48.8**	**48.9**	**50.2**	**3**	**5**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to statistical methods)

Figure 3.5.3d Time (in days) to discontinuation of treatment with platelet aggregation inhibitors in the population aged ≥45 years stratified by geographical area; curves are adjusted by gender and age (the Cox model was used to estimate persistence curves)



In the context of long-term antithrombotic strategies, a prominent role has been played by the possible implementation of an approach customising therapies to individual patients based on the assessment of the risk-benefit ratio and its variation in relation to increasing age, as well as, where appropriate, to comorbidity or other factors capable of modifying the ischemic and haemorrhagic risks.

In recent years, significant progress has been made in characterising the main determinants of inter-individual variability in response to platelet aggregation inhibitors, and in developing of biochemical and genetic tools to investigate prevalence in various stages of the condition. In parallel, *in silico* pharmacodynamic/pharmacokinetic models were developed to test different approaches for optimising the inactivation of the target medicinal product in specific clinical settings or in individual patients with comorbidities.

The ideal platelet aggregation inhibitor should selectively inhibit thrombosis, leaving the essential haemostatic mechanisms unaltered. In this regard, signaling molecules downstream of receptor-mediated platelet activation have aroused considerable interest in the research. Experimental studies are underway to investigate several potential new targets for the development of a new generation of platelet aggregation inhibitors.

3.6 Central Nervous System

Also in 2022, Central Nervous System (CNS) medicines ranked sixth among the categories with the highest public expenditure (EUR 1,989.9 million), accounting for 8.0% of the total (Box: Main indices of expenditure, consumption and exposure). Overall per capita expenditure was equal to EUR 33.58, up 4.3% compared to the previous year and mainly related to expenditure under approved care regime (EUR 23.81 per capita), slightly down from the previous year (-0.7%). The expenditure relating to the purchase by public health facilities is less significant (EUR 9.77 per capita). However, a +18.7% increase was recorded compared to the previous year (Table 3.1).
Analysing consumption under approved care regime, this category still ranks fourth with 98.16 DDD/1000 inhabitants per day, up 2.8% compared to 2021. Also in this case, the higher consumption is recorded in the approved care regime setting, with 70.3 DDD/1000 inhabitants per day, whereas purchasing by public health facilities accounts for about one-third of the total (27.9 DDD) (Table 3.2). During the period 2014-2022, total consumption of CNS medicines increased by an average of 1.8% each year.
The analysis of the drug use profile by age group and gender in the context of community assistance (including approved care regime and on behalf distribution) confirms the constant increase in the use of central nervous system medicines with increasing age, for both genders, with a higher prevalence of use in women from 15 years of age, consistent with epidemiological data on the frequency of neurological and psychiatric diseases. Men and women in the over 75 years age group reach the highest level of prevalence (45.0% and 33.5%, respectively) and expenditure (EUR 76.13 and EUR 59.96 per capita, respectively). In the 5-14 years age group, in one year about one in 100 children receives at least one prescription of central nervous system medicines, mainly antidepressants, antipsychotics, and antiepileptics.
As for the approved care regime, per capita expenditure for central nervous system medicines was equal to EUR 23.81. The change in expenditure compared to 2021 (-1.1%) was determined solely by a reduction in prices (-2.5%), also confirmed by the 2.6% reduction in the average cost per day of therapy, while the consumption of these medicines increased by 1.5%, with a mix effect (-0.1%) which remained stable in 2022 (Table 3.9). Analysing the individual sub-categories, “other antidepressants”, “selective serotonin reuptake inhibitors (SSRIs)” and “other antiepileptics” have the greatest impact on expenditure, with EUR 3.41, EUR 3.39 and EUR 3.21, respectively. SSRIs also show the greatest levels of consumption with 30.5 DDD/1000 inhabitants per day, accounting for almost half of the entire category. They are followed by “other antidepressants” (12.3 DDD/1000 inhabitants per day) and “other antiepileptics” (3.8 DDD/1000 inhabitants per day) (Table 3.9). All three mentioned sub-categories show increases compared to 2021 in terms of consumption. Concerning expenditure, only SSRIs report a 0.4% decrease and a trend towards purchasing less expensive pharmaceuticals (mix effect -1.5%). This results in a decrease in the average cost per day of therapy for these medicines (-1.5%). Oripavine derivatives show a significant increase in expenditure (+16.2%) and consumption (+12.3%), due to a shift towards more expensive medicines (mix effect: +5.1%). However, expenditure and consumption levels are lower (EUR 0.33 per capita and 0.2 DDD, respectively). Conversely, natural opium alkaloids,

together with other opioids, are the pharmaceuticals with the smallest impact on expenditure (-24.7% and -13.2%, respectively), as a result of lower prices (-22.4% and -14.5%, respectively) and average cost per day of therapy (-22.4% and -12.5%, respectively). Fentanyl, tapentadol and paroxetine are the molecules with the greatest impact on the expenditure of the category with values of EUR 1.29, EUR 1.05 and EUR 1.00 per capita respectively, although they are decreasing compared to the previous year (Table 3.10). Levetiracetam and pregabalin are included in the first thirty active ingredients with the highest impact on the 2022 expenditure under approved care regime. They rank 17th (EUR 98.9 million) and 28th (EUR 80.3 million), respectively, gaining one or two positions compared to the previous year (Table 3.11). However, a high variability is found in the regional ranking (Table 3.12). As many as 8 molecules (fentanyl, rotigotine, tapentadol, naloxone/oxycodone, lacosamide, quetiapine, levetiracetam and pregabalin) are among the most expensive active substances per day of therapy (Table 3.13). Values range from a maximum of EUR 5.64 per DDD of fentanyl to a minimum of EUR 1.53 per DDD of pregabalin. Sertraline is the only active ingredient in the category that ranks among the first thirty active ingredients with lowest average cost per day of therapy (14th place with EUR 0.25 for DDD) (Table 3.14).
Vortioxetine and pregabalin, on the other hand, are the active ingredients belonging with the largest increase in expenditure under approved care regime compared to 2021 (+13.6% and +5.0%, respectively) (Table 3.15). Naloxone/oxycodone, tapentadol, rotigotine, fentanyl and lacosamide are among those with the largest reduction in expenditure under approved care regime between 2021 and 2022 (Table 3.16). With the highest consumption in the category (9.1 DDD/1000 inhabitants per day), sertraline is the only molecule falling within the first thirty most consumed active ingredients under approved care regime (26yh place in 2022). However, this active ingredient shows a high variability in terms of regional consumption (Tables 3.17 and 3.18).
As regards purchases by public health facilities, an increase is observed in both expenditure (+18.2%) and consumption (+4.6%), with a shift towards more expensive medicines (mix effect: +15.2% and average cost per DDD: +13.0%), despite a 1.8% reduction in prices compared with the previous year (Table 3.19). The subgroup of “other antipsychotics” has the highest value of expenditure (EUR 3.07 per capita), up 4% compared to 2021. Anilides (4.2 DDD/1000 inhabitants per day) and “diazepines, oxazepines, thiazepines and oxepines” (3.6 DDD/1000 inhabitants per day) are the most consumed categories. They also record increases both in terms of consumption (+22.2% and +2.2%, respectively) and spending (+20.3% and +3.3%, respectively) compared to the previous year, despite the propensity to use cheaper pharmaceuticals (mix effect: -4.7% and -1.0%). “Other central nervous system medicines” rank second in terms of expenditure (EUR 2.01) and register a 140.2% increase compared to 2021 due to an increase in consumption (+55.8%) and a greater use of more expensive medicines (mix effect: +62.8% and average cost per DDD: +54.2%) (Table 3.19). The “calcitonin gene-related peptide receptor antagonists” show the greatest increases in expenditure and consumption (+43.6% and +37.8%) compared to the previous year, following the “other medicines for the nervous system”. Paliperidone and aripiprazole, two antipsychotics, are the molecules with the highest per capita expenditure in 2022 (EUR 1.59 and EUR 1.16), up by 4.2% and 7.2%, respectively, compared to the previous year. They account for 28% of the expenditure of the entire category (Table 3.20).

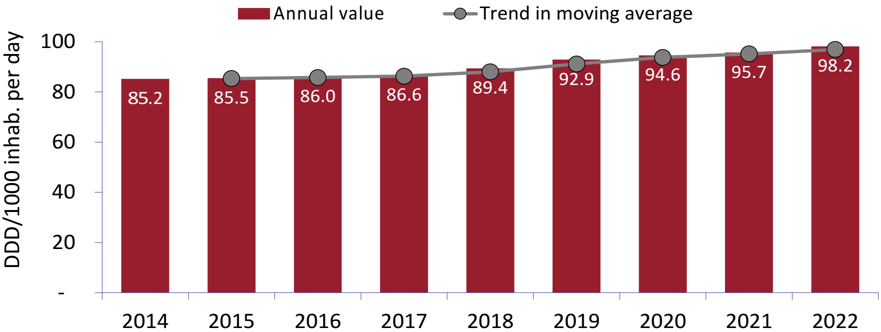
Paliperidone ranks 30th among the active ingredients with the highest expenditure purchased by public health facilities (total expenditure of EUR 93.8 million and average cost per day of therapy of EUR 5.05), accounting for 0.6% of the total expenditure recorded by public health facilities (Tables 3.21 and 3.22). Despite its low consumption, tafamidis is the only medicine in the category among the top 30 active ingredients with the greatest increase in expenditure in 2022 (+534.7% compared to the previous year) among those purchased by public health facilities (Table 3.23). No active ingredient in the category is included in the list of the first 30 active ingredients with the greatest reduction in expenditure (Table 3.24) and among the top 30 with the highest average cost per day of therapy (Table 3.25). Finally, aripiprazole and paliperidone are included among the top 30 active ingredients with lowest average cost (EUR 2.69 and EUR 5.05 per DDD respectively), although the first one increased by 2.2% compared to the previous year and the second decreased by 1% (Table 3.26). Paracetamol, methadone, olanzapine, quetiapine and lidocaine, on the other hand, are among the 30 highest consumed molecules among those purchased by public health facilities (Table 3.27). Finally, no active ingredient in this category appears to be listed in the top 30 active ingredients with highest expenditure and consumption of medicines under approved care regime and purchased by public health facilities (Tables 3.28 and 3.29). Table 3.30 shows the different trend in terms of expenditure, consumption and average DDD cost between the approved care regime and direct purchases of nervous system medicines.

Analyses of the historical series of consumption and expenditure by active ingredient and by Region have been carried out for more information on the use of medicines belonging to the same therapeutic area. These analyses focused on medicines for multiple sclerosis, antidepressants, medicines for pain therapy, antiepileptics, antipsychotics, antiparkinsonian medicines, anti-migraine and, anti-dementia medicines (Table 3.6.1a and following).

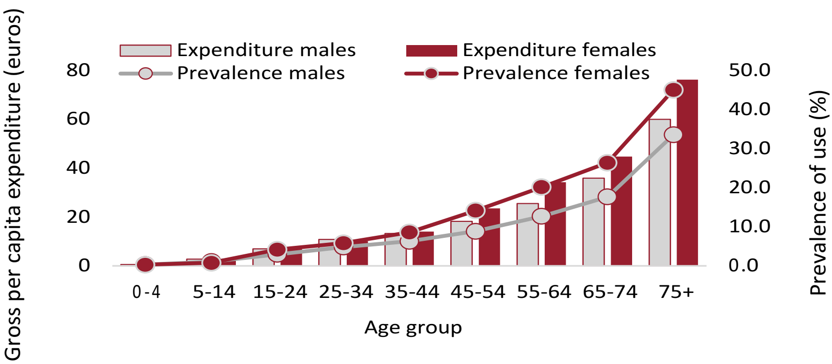
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Central Nervous System

Public expenditure* in EUR million (% over total)	**1,989.9**	**(8.0)**
Δ % 2022-2021		4.2
Regional range of gross per capita expenditure:	30.2	40.9
DDD/1000 inhabitants per day* (% over total)	**98.2**	**(7.4)**
Δ % 2022-2021		2.8
Regional range DDD/1000 inhabitants per day:	82.8	122.3

* *includes prescriptions under approved care regime and purchases by public health facilities*



Breakdown of prevalence of use and consumption under approved care regime and on behalf distribution by age and gender in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.5	0.5	0.5	0.6	0.5	0.6
5-14	2.7	2.1	2.4	4.5	3.4	4.0
15-24	6.9	7.7	7.3	18.0	23.0	20.4
25-34	10.8	10.1	10.4	31.9	30.4	31.2
35-44	13.2	14.0	13.6	40.1	44.1	42.1
45-54	18.2	23.5	20.9	55.5	76.5	66.1
55-64	25.5	34.1	29.9	74.1	117.2	96.3
65-74	35.9	44.7	40.5	96.8	150.2	125.0
75+	60.0	76.1	69.6	167.3	237.9	209.5

3.6.1 Medicines for multiple sclerosis

- Over the last nine years the consumption of medicines for multiple sclerosis has increased (CAGR: +3.9%), reaching 2.9 DDD in 2022, a 2.4% increase compared to 2021 (Figure 3.6.1a and Table 3.6.1a). The average cost per day of therapy has gradually increased up to EUR 12.7 in 2022, probably due to the introduction of monoclonal antibodies on the market.
- Immunosuppressants account for about 70% of consumption of the entire category (2.1 DDD/1000 inhabitants per day) and, despite the average DDD cost being the lowest in the category (EUR 5.61), account for one third of the category expenditure (EUR 4.23 out of EUR 13.56). From 2014 to 2022 their consumption has doubled (Figure 3.6.1b) Monoclonal antibodies also have a significant impact on per capita expenditure (EUR 4.29), mainly due to a high average cost per day of therapy (EUR 49.08; -1.8% compared to 2021), as against low levels of consumption (0.2 DDD/1000 inhabitants per day), up more than 20% compared to 2021.
- The three categories that register a decrease compared to 2021 are fingolimod, interferons and glatiramer (from -9.4% to -19% in consumption), while siponimod, a sphingosine 1-phosphate receptor modulator (S1PR) reimbursed since April 2021, shows a per capita expenditure of EUR 0.31, up 600%.
- Analysing the active ingredients individually, methotrexate is reportedly the most used pharmaceutical (1.5 DDD, accounting for 50% of the entire category), but with a relatively low impact on per capita expenditure (EUR 0.75) due to the average cost per day of therapy, which is the lowest in the category (EUR 1.38). The most expensive medicines in terms of day of therapy are fingolimod (EUR 53.54), monoclonal antibodies, including natalizumab (EUR 50.04) and ocrelizumab (EUR 45.24) and cladribine (EUR 46.81).
- In Central Italy, the consumption of medicines for multiple sclerosis is lower than the national average, while in the North and South it is similar and stable compared to 2021. In any case, the South has the highest average DDD cost (EUR 13.22) and therefore shows the highest expenditure (EUR 14.43 per capita) (Table 3.6.1b).
- At regional level, in line with evidence in literature on the prevalence of the condition, the highest level of consumption has been observed in Sardinia (5.4 DDD), stable compared with the previous year (+2.8%). In Tuscany, the lowest level of consumption (2.4 DDD) is recorded, equal to less than half compared to those in Sardinia and down 2.9% compared to 2021. Molise is the region with the highest per capita expenditure (EUR 31.76), but with consumption levels that are slightly higher than the national average (3.9 DDD/1000 inhabitants per day; +16.8% of DDD and expenditure). Such consumption levels are similar to those of the Autonomous Province of Trento (3.6 DDD), which, by contrast, records a 60% lower average expenditure and cost per day of therapy.

Figure 3.6.1a Medicines for multiple sclerosis, temporal trend in per capita expenditure and average cost per day of therapy (2014-2022)

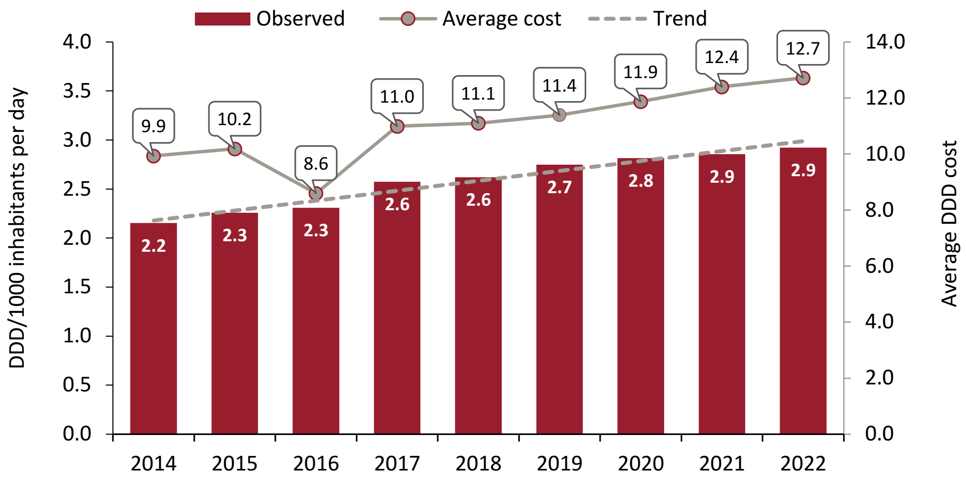


Table 3.6.1a Medicines for multiple sclerosis, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Monoclonal antibodies	4.29	21.7	17.5	0.2	23.9	19.8	49.08	-1.8
Immunosuppressants	4.23	4.9	31.5	2.1	4.4	7.6	5.61	0.5
Fingolimod (S1P receptor modulators)	2.09	-10.0	3.4	0.1	-9.4	5.3	53.54	-0.7
Interferons	1.43	-15.6	-10.4	0.3	-17.8	-10.8	12.89	2.7
Pyrimidine synthesis inhibitors	1.03	0.7	69.0	0.1	4.2	70.3	26.25	-3.3
Other S1P receptor modulators	0.31	660.4	-	<0.05	636.9	-	31.13	3.2
Glatiramer (AA copolymers)	0.19	-35.6	-19.9	0.1	-19.0	-5.4	6.88	-20.5
Medicines for multiple sclerosis	**13.56**	**5.0**	**7.2**	**2.9**	**2.4**	**3.9**	**12.71**	**2.6**
dimethyl fumarate	2.58	-2.3	-	0.2	1.4	-	31.67	-3.7
ocrelizumab	2.24	30.0	-	0.1	38.8	-	45.24	-6.4
fingolimod	2.09	-10.0	3.4	0.1	-9.4	5.3	53.54	-0.7
natalizumab	1.89	8.4	6.0	0.1	8.4	7.9	50.04	0.0
teriflunomide	1.03	0.7	69.0	0.1	4.2	70.3	26.25	-3.3
interferon beta 1a	1.00	-17.9	-13.1	0.3	-18.9	-11.8	10.77	1.3
cladribine	0.80	36.7	-	<0.05	41.4	-	46.81	-3.3
methotrexate	0.75	6.4	9.7	1.5	5.7	8.6	1.38	0.7
interferon beta 1a pegylated	0.36	-7.5	-	<0.05	-6.9	-	29.51	-0.7
siponimod	0.31	649.1	-	<0.05	629.0	-	31.00	2.8

Figure 3.6.1b Medicines for multiple sclerosis, temporal trend in consumption (DDD/1000 inhab. per day) of most expensive subgroups (2014-2022)

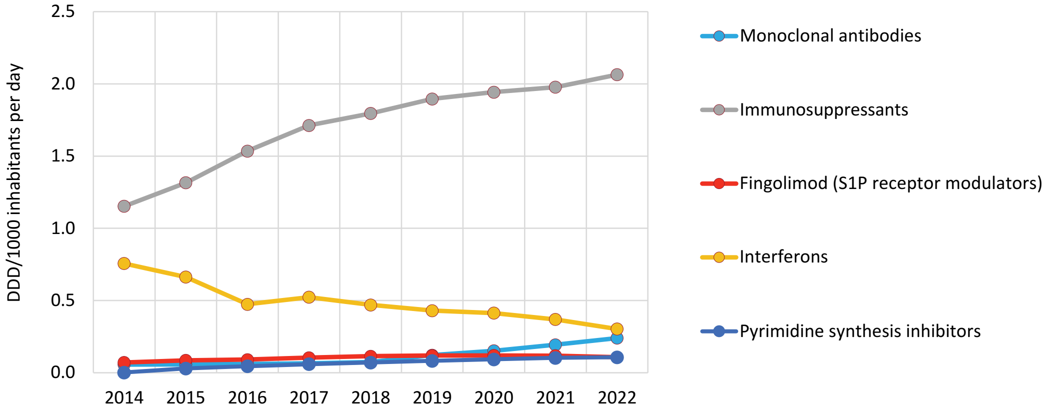


Table 3.6.1b Medicines for multiple sclerosis, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	13.32	2.9	12.75	14.43	3.0	13.22	8.3	4.5	3.7	8.1	4.6	3.3
Valle d'Aosta	11.54	2.4	13.38	11.21	2.5	12.37	-2.9	5.0	-7.5	5.9	3.8	2.1
Lombardy	9.11	2.6	9.54	9.98	2.7	10.08	9.5	3.6	5.7	8.1	4.0	3.9
A.P. of Bolzano	14.20	3.7	10.58	14.32	3.7	10.50	0.9	1.6	-0.7	6.8	3.1	3.6
A.P. of Trento	10.95	3.4	8.70	12.76	3.6	9.61	16.5	5.5	10.4	8.6	5.0	3.5
Veneto	12.93	2.8	12.55	13.92	2.9	13.09	7.6	3.2	4.3	9.5	3.9	5.4
Friuli VG	13.36	3.7	9.90	13.48	3.7	10.07	0.9	-0.8	1.7	6.0	2.1	3.8
Liguria	13.01	2.6	13.87	14.87	2.7	15.03	14.4	5.6	8.3	9.3	4.2	4.8
Emilia Romagna	11.69	2.5	12.70	12.73	2.6	13.25	8.9	4.3	4.3	9.5	4.6	4.6
Tuscany	11.88	2.5	12.95	10.95	2.4	12.30	-7.8	-2.9	-5.1	5.2	3.5	1.6
Umbria	12.80	2.9	11.92	13.28	3.0	12.13	3.7	1.9	1.8	7.2	3.0	4.1
Marche	12.28	2.7	12.50	13.43	2.7	13.44	9.4	1.8	7.5	6.4	2.6	3.7
Lazio	12.58	2.6	13.35	12.81	2.6	13.45	1.8	1.1	0.7	5.7	3.6	2.1
Abruzzo	18.18	3.1	15.85	18.36	3.3	15.24	1.0	5.0	-3.8	7.3	4.8	2.4
Molise	27.19	3.3	22.45	31.76	3.9	22.45	16.8	16.8	0.0	18.7	8.9	8.9
Campania	13.24	2.6	13.75	13.63	2.7	13.67	3.0	3.6	-0.6	6.6	4.3	2.2
Puglia	14.42	3.2	12.22	15.01	3.3	12.53	4.0	1.5	2.5	5.7	3.4	2.2
Basilicata	13.42	3.0	12.31	13.46	3.1	12.02	0.3	2.7	-2.3	6.6	4.6	1.9
Calabria	13.14	2.9	12.35	13.70	2.9	12.86	4.2	0.1	4.1	8.8	4.2	4.4
Sicily	14.05	3.0	12.83	14.23	3.0	13.10	1.3	-0.8	2.1	5.9	4.0	1.9
Sardinia	26.89	5.3	13.98	28.90	5.4	14.62	7.5	2.8	4.6	5.1	2.9	2.1
Italy	**12.91**	**2.9**	**12.40**	13.56	**2.9**	**12.71**	**5.0**	**2.4**	**2.6**	**7.2**	**3.9**	**3.1**
North	11.44	2.8	11.37	12.42	2.9	11.91	8.5	3.6	4.7	8.5	4.1	4.2
Centre	12.33	2.6	12.99	12.33	2.6	12.99	0.0	0.0	0.0	5.8	3.4	2.3
South and Islands	13.32	2.9	12.75	14.43	3.0	13.22	8.3	4.5	3.7	8.1	4.6	3.3

The trend in the consumption of medicines for multiple sclerosis shows an increase over the period 2014-2022 for those medicines predominantly used as second line, such as monoclonal antibodies, immunosuppressants (e.g. methotrexate), fingolimod and pyrimidine synthesis inhibitors, against a decrease in the category of interferons and glatiramer.

The marked increase in the use of siponimod, as observed in the last year, may be due to the specific indication for patients with secondary progressive multiple sclerosis (MS), a clinical stage that was little studied with the previous MS pharmaceuticals.

The wide availability of medicines in the treatment of MS has led to a high level of therapy customisation based on the risk-benefit profile of the medicine and the in-depth knowledge of the mechanisms of action of the molecules as recalled by the recent Italian guidelines promoted by the Italian Society of Neurology and approved by the National Guidelines System (*Sistema Nazionale Linee Guida*, SNLG). In this specific context, it would be desirable, from a public health perspective, to promote and conduct a greater number of studies on the use of medicines for MS in the real world, in order to characterise the different prescribing patterns in relation to the numerous clinical phenotypes of the disease. Recently, some studies have documented a reduction in mortality of patients exposed to disease-modifying pharmaceuticals compared with those not exposed to them, as well as a better survival in relation to the level of adherence.

References

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3.6.2 Antidepressants

- In 2022, daily consumption of antidepressants was equal to 45.8 DDD per 1,000 inhabitants, up 2.6% over the previous year and with an average annual change of 2% since 2014. The average DDD cost in 2022 was EUR 0.42, which has remained stable since 2016 (Figure 3.6.2a).
- In 2022, consumption of antidepressants was 3.5% of the total consumption of medicines in Italy, with a per capita expenditure of 1.7%, up 2.6% compared with 2021 (EUR 7.05) (Table 3.6.2a).
- SSRIs account for 70% (31.7 DDD) of consumption (up 1.8% compared to 2021 and stable since 2014, Figure 3.6.2b) and 50% (EUR 3.40 per capita) of expenditure for the entire category. Major changes in these indicators are observed for other antidepressants (DDD: +3.1%, expenditure: +2.5%) and for SNRIs (DDD: +3.5%, expenditure: +3.4%).
- With EUR 1.00 per capita and down 1.6% compared to 2021, paroxetine remains the most expensive molecule, while sertraline is the most consumed one (9.8 DDD, up 5.4% compared to 2021 and with an average annual change of +3.9% since 2014). Bupropion records the highest average DD cost (EUR 1.69) against limited levels of consumption and per capita expenditure. It should be noted that this medicine is also indicated as a treatment for smoking cessation. Vortioxetine is the active ingredient with the largest increases in both expenditure and consumption in 2022 (+13.8%). It should be highlighted that its cost per day of therapy is almost three times higher than the category average (EUR 1.13 vs 0.42) (Table 3.6.2a). Esketamine is indicated for the treatment of major depression resistant to other therapies but has not been recognised as innovative. It registers the largest increase in expenditure (above 100%) although with a reduced value (EUR 0.01 per capita).
- Central Regions show a level of use (51.3 DDD) about 6% higher than the North (48.5 DDD) and 33% higher than the South (38.5 DDD) (Table 3.6.2b). Tuscany is actually the Italian Region with the highest use of antidepressants, with 67.6 DDD/1000 inhabitants per day in 2022, a value almost double that of Campania and Basilicata (about 36 DDD). All regions show increases in expenditure and consumption compared with the previous year, particularly Piedmont and Emilia Romagna. For antidepressants, limited regional variability is observed in the average cost per day of therapy (CV 8%). Marche and Sardinia are the regions with consumption and cost per day of therapy higher than the national average.

Figure 3.6.2a Antidepressants, temporal trend in per capita expenditure and average cost per day of therapy (2014-2022)

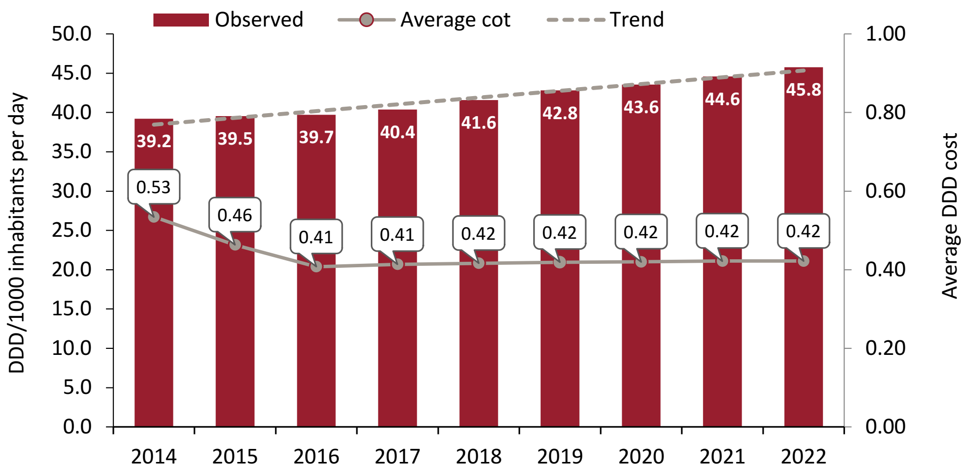


Table 3.6.2a Antidepressants, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
SSRI antidepressants	3.40	0.1	-2.3	31.7	1.8	1.1	0.29	-1.7
SNRI antidepressants	1.64	2.4	-5.3	7.3	3.5	2.3	0.61	-1.0
Other antidepressants	1.01	2.5	2.8	3.6	3.1	3.5	0.76	-0.6
Vortioxetine	0.83	13.8	-	2.0	13.8	-	1.13	0.0
First-generation antidepressants plain or in combination	0.16	0.1	-2.0	1.0	0.2	-1.3	0.42	-0.1
Esketamine	0.01	>100	-	<0.05	2.6	-	12.66	6103.1
Antidepressants	**7.05**	**2.6**	**-1.0**	**45.8**	**2.6**	**2.0**	**0.42**	**0.0**
paroxetine	1.00	-1.6	-2.5	8.2	0.1	0.2	0.34	-1.7
escitalopram	0.97	0.2	-5.6	7.7	0.6	0.8	0.34	-0.5
vortioxetine	0.83	13.8	-	2.0	13.8	-	1.13	0.0
sertraline	0.82	2.7	3.2	9.8	5.4	3.9	0.23	-2.6
duloxetine	0.82	3.3	-9.3	3.4	4.0	3.2	0.66	-0.7
venlafaxine	0.82	1.6	1.0	3.9	3.1	1.6	0.58	-1.4
trazodone	0.45	3.4	5.7	1.4	3.8	6.4	0.91	-0.3
citalopram	0.40	-1.3	-2.3	4.1	-0.5	-1.9	0.27	-0.8
mirtazapine	0.35	0.2	2.1	1.9	2.3	2.7	0.50	-2.1
bupropione	0.18	4.9	0.0	0.3	5.4	1.8	1.69	-0.5

Figure 3.6.2b Antidepressants, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) of subgroups with the highest expenditure

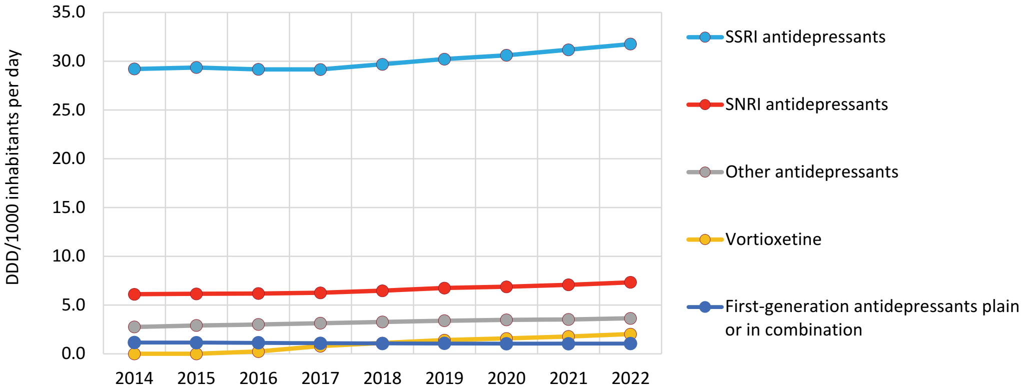


Table 3.6.2b Antidepressants, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	7.33	50.4	0.40	7.57	52.5	0.40	3.4	4.1	-0.7	-2.0	2.1	-4.1
Valle d'Aosta	6.60	43.6	0.41	7.03	44.9	0.43	6.5	3.1	3.3	-1.5	1.8	-3.3
Lombardy	6.31	42.3	0.41	6.53	43.6	0.41	3.5	3.2	0.3	-1.1	2.2	-3.2
A.P. of Bolzano	8.66	57.1	0.42	8.97	59.0	0.42	3.6	3.2	0.4	-1.8	1.6	-3.4
A.P. of Trento	6.72	45.1	0.41	6.92	46.0	0.41	3.1	2.0	1.1	-0.2	2.4	-2.5
Veneto	6.45	43.1	0.41	6.65	44.4	0.41	3.0	3.1	-0.1	-1.0	2.2	-3.1
Friuli VG	5.48	37.8	0.40	5.63	39.1	0.39	2.7	3.4	-0.7	-2.0	1.7	-3.7
Liguria	9.00	58.7	0.42	9.23	60.3	0.42	2.6	2.7	-0.1	-1.2	1.5	-2.7
Emilia Romagna	7.42	55.1	0.37	7.65	57.1	0.37	3.1	3.7	-0.5	-0.7	1.7	-2.3
Tuscany	9.42	66.3	0.39	9.57	67.6	0.39	1.6	1.9	-0.3	-0.7	1.3	-2.0
Umbria	8.31	57.6	0.40	8.29	57.8	0.39	-0.3	0.3	-0.6	-1.3	1.7	-2.9
Marche	7.57	46.7	0.44	7.66	47.5	0.44	1.3	1.6	-0.3	-0.7	1.7	-2.5
Lazio	6.57	39.5	0.46	6.69	40.4	0.45	1.9	2.2	-0.3	-1.3	2.0	-3.2
Abruzzo	7.53	43.6	0.47	7.82	45.0	0.48	3.8	3.1	0.6	0.5	2.6	-2.0
Molise	6.23	37.5	0.45	6.38	38.3	0.46	2.4	2.0	0.5	-1.4	1.8	-3.1
Campania	6.02	35.1	0.47	6.18	35.8	0.47	2.6	2.2	0.4	-0.1	2.5	-2.5
Puglia	5.94	35.8	0.45	6.10	36.5	0.46	2.7	2.0	0.7	-1.0	2.1	-3.1
Basilicata	5.86	34.9	0.46	6.04	35.8	0.46	3.1	2.5	0.5	-0.2	2.0	-2.2
Calabria	6.93	41.4	0.46	6.98	41.8	0.46	0.7	0.9	-0.2	-1.1	1.7	-2.7
Sicily	6.10	35.7	0.47	6.25	36.4	0.47	2.5	1.9	0.5	-0.8	2.1	-2.8
Sardinia	7.81	48.2	0.44	8.03	49.4	0.45	2.7	2.3	0.4	-1.8	1.5	-3.2
Italy	**6.87**	**44.6**	**0.42**	**7.05**	**45.8**	**0.42**	**2.6**	**2.6**	**0.0**	**-1.0**	**2.0**	**-2.9**
North	6.85	46.9	0.40	7.07	48.5	0.40	3.2	3.4	-0.1	-1.2	2.0	-3.2
Centre	7.75	50.4	0.42	7.86	51.3	0.42	1.5	1.8	-0.3	-1.0	1.6	-2.6
South and Islands	6.36	37.7	0.46	6.52	38.5	0.46	2.5	2.1	0.5	-0.7	2.1	-2.7

Exposure and adherence in population

- Health Card data allowed to describe the trend in prevalence and consumption by age group, gender and region and to calculate some indicators of intensity of use. Moreover, adherence and persistence were also estimated of chronic treatments with antidepressants.
- Around 6.7% of the Italian population used antidepressants in 2022, with Tuscany and Liguria reaching 10%, while Campania registering a drop to 5.3%. In the South of Italy, prevalence is reduced to 5.9% compared to 7.8% in the Centre and 6.9% in the North (Table 3.6.c). As expected, consumption increases with age, reaching a prevalence of 27.7% in women aged +85. The difference in terms of consumption between genders persists in all age groups, with levels that are more than double in women than in men aged ≥45 years (Figure 3.6.2b).
- Half of users are over 67 years of age with no particular regional differences, and each subject remains on treatment for an average of 8 months. Half of subjects use antidepressants for less than 6 months and one in ten receives only one prescription (11.8%). This shows that these medicines are often prescribed for clinical conditions unrelated to a depressive pathology, which could be treated with non-pharmacological approaches (Table 3.6.2c) The average cost per user is EUR 101 with slight differences between Regions, with a minimum of EUR 94.0 in Emilia Romagna and a maximum of EUR 118 in the Autonomous Province of Bolzano.
- Among the categories, the prevalence of use is 4.4% in SSRIs, with women recording twice as high as men (5.9% vs 2.9%), followed by SNRIs and other antidepressants both with 1.2%. For each vortioxetine user, EUR 207.91 is spent on average in one year compared to EUR 135.15 for SNRIs and EUR 75.85 for SSRIs (Table 3.6.2d). The average treatment days for users go from a minimum of 63 for first generation antidepressants to about 250 for SSRIs. Half of SNRI users remain in treatment for less than 6 months. This value reaches 7.5 months for SSRIs. One in five patients treated with other antidepressants or vortioxetine receives only one prescription in one year.
- The assessment relating to adherence and persistence to treatment was conducted on a cohort of 124,025 new users of antidepressants, aged at least 45 years, considering a one-year follow-up. The median age of the cohort is 69 years (interquartile range [IQR]: 57-79), with women accounting for about 67 percent of the total, and more than a third (35.2%) are over 75 years old.
- In 2022 the percentage of subjects with high and low adherence to antidepressant treatment was 37.6% and 27.7%, respectively. High adherence shows a 2% increase, while low adherence decreases by 3% compared to 2021. In particular, the percentages of high adherence decrease with age (from 42.4% in subjects aged between 45 and 54 years to 24.4% in subjects aged +85 years), and by geographical area (with a maximum of 38.9% in the North and minimum of 36% in the South), despite a median age of subjects included in the study 1 year lower than the median of the other geographical areas. Concerning the low adherence indicator, there are differences between geographical areas, ranging from 26.8% in the North, to 27.9% in the Centre and 29% in the South, with a gradient by age with a maximum value of about 46.9% in the South in the 85+ age group (Table 3.6.2e).

- Men show higher percentage adherence compared to women (39.3% vs 36.8%), while women have a low adherence percentage of 28.1%. Compared with 2021, a 2% decrease in high adherence is recorded in both genders. Among the different geographical areas, the highest value of high adherence among men is 40.9% in the North, while low adherence reaches a value of 29.4% in women in the South.
- Analysing the persistence to treatment at 12 months (calculated on new users with at least two antidepressants prescriptions and considering an interruption of at least 60 days) only one in three subjects (32.6%) remained persistent, there were no marked differences in gender and between geographical areas. Also in 2022 a reduction in persistence with increasing age is confirmed, shifting from 35.8% in the 45-54 age group up to 25.9% in subjects aged ≥85 years. This gradient is found in every geographical area, even if the percentage variation is less marked in the Centre (Δ%=-7.2%) compared with the North (Δ %=-11.5%) and the South (Δ %=-9.3%) (Table 3.6.2f).
- Considering the median time to discontinuation of antidepressants treatment, a 50% probability of discontinuing treatment is achieved at approximately 148 days, similar to the figure observed in 2021 (143 days). In addition, values differ from geographical areas, ranging from 148 days in the North, to 140 days in the Centre and 126 days in the South and Islands (Figure 3.6.2d). Men are slightly more persistent (145 days), especially in the North (156) and in general persistence decreases with increasing age, from 168 days (45-54 years) to 93 days (85+ years).

Figure 3.6.2c Breakdown of prevalence of use and consumption of antidepressants under approved care regime and on behalf distribution (year 2022)

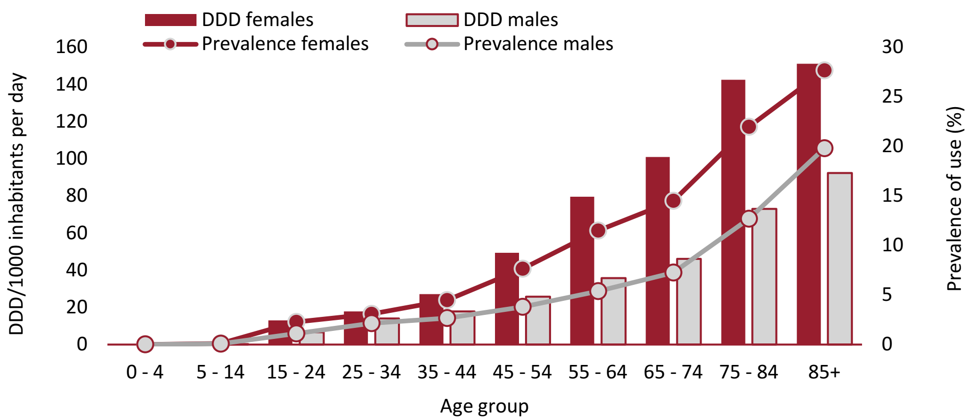


Table 3.6.2c Exposure and duration of therapy with antidepressants by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	5.2	10.6	8.0	68	96.47	233.2	182.0	10.8
Valle d'Aosta	4.0	9.0	6.6	69	102.59	226.3	180.0	10.2
Lombardy	4.0	8.4	6.2	66	98.07	237.2	189.0	9.2
A.P. of Bolzano	4.6	9.1	6.8	67	118.16	260.8	220.0	10.0
A.P. of Trento	3.9	8.4	6.2	65	104.39	243.1	180.0	10.9
Veneto	4.0	8.4	6.2	67	103.72	239.7	183.7	11.2
Friuli VG	3.5	8.2	5.9	67	97.96	223.4	180.0	10.4
Liguria	6.2	13.2	9.8	71	98.42	222.2	180.0	12.8
Emilia Romagna	4.8	10.3	7.6	68	96.10	233.8	183.7	10.6
Tuscany	6.5	13.7	10.2	69	94.50	234.4	182.0	13.7
Umbria	5.3	11.6	8.5	70	97.34	229.7	196.0	12.6
Marche	5.0	9.8	7.4	69	103.86	230.2	180.0	11.3
Lazio	4.0	8.3	6.2	66	104.91	229.3	180.0	11.3
Abruzzo	4.5	9.2	6.9	67	110.87	231.9	182.0	12.9
Molise	3.9	7.9	5.9	68	108.74	237.5	189.0	10.7
Campania	3.6	6.9	5.3	65	105.54	223.5	168.0	14.0
Puglia	3.9	7.4	5.7	66	103.36	223.6	172.0	12.8
Basilicata	3.9	7.7	5.8	67	102.97	222.6	180.0	14.3
Calabria	4.5	8.6	6.6	66	102.21	223.4	170.5	14.9
Sicily	3.8	7.6	5.8	67	103.63	219.5	168.0	14.8
Sardinia	4.1	10.0	7.1	66	115.28	257.0	224.0	10.5
Italy	**4.4**	**9.0**	**6.7**	**67**	**101.11**	**231.8**	**180.0**	**11.8**
North	4.4	9.3	6.9	67	98.87	235.1	182.0	10.4
Centre	5.0	10.4	7.8	68	99.92	231.5	180.0	12.4
South and Islands	3.9	7.8	5.9	66	105.64	226.6	180.0	13.6

Table 3.6.2d Exposure and duration of therapy with antidepressants by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
SSRI antidepressants	2.8	5.9	4.4	66	75.87	248.9	224.0	10.9
SNRI antidepressants	0.7	1.6	1.2	66	135.16	213.2	178.5	8.6
Other antidepressants	0.9	1.5	1.2	77	76.00	92.9	50.0	20.2
Vortioxetine	0.3	0.5	0.4	70	207.91	182.7	120.0	19.0
1st generation antidepressants, plain or in combination	0.3	0.8	0.6	61	27.27	63.4	30.0	30.7
Esketamine	2.8	5.9	4.4	66	75.87	248.9	224.0	10.9
Antidepressants	**4.4**	**9.0**	**6.7**	**67**	**101.11**	**231.8**	**180.0**	**11.8**

Table 3.6.2e Indicators of adherence to treatment with antidepressants in the population aged ≥45 years in the period 2019-2022 and 2022-2021 change

	Low adherence*											
	2019	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**	**2019**	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**
	Total N= 124,025						**North N= 58,368**					
45-54	22.3	21.9	22.3	22.4	1	1	21.1	20.5	21.6	20.9	-3	-1
55-64	22.1	22.2	22.0	23.2	6	5	20.3	21.3	20.7	21.6	5	6
65-74	24.3	24.6	23.7	24.7	4	2	22.5	23.3	22.6	23.1	2	3
75-84	29.5	30.4	30.5	30.9	1	5	28.3	29.6	30.3	30.9	2	9
≥85	43.2	44.6	45.6	45.7	0	6	42.7	45.5	45.6	45.4	0	6
Females	27.6	28.0	27.2	28.1	3	2	26.5	27.5	26.9	27.2	1	3
Males	26.4	26.9	26.5	27.0	2	2	24.8	25.8	25.6	26.1	2	5
Total	**27.2**	**27.6**	**27.0**	**27.7**	**3**	**2**	**26.0**	**27.0**	**26.5**	**26.8**	**1**	**3**
	Centre N=28,284						**South N=37,373**					
45-54	21.8	22.1	21.8	23.6	8	8	24.4	23.8	23.7	24.0	1	-2
55-64	22.1	22.1	22.2	23.7	7	7	24.6	23.6	23.5	25.1	7	2
65-74	24.6	23.9	23.3	24.5	5	0	26.6	26.7	25.4	27.1	7	2
75-84	29.2	29.9	29.0	29.8	3	2	31.9	32.3	32.3	31.7	-2	-1
≥85	43.5	43.4	47.0	45.0	-4	3	43.8	44.2	44.3	46.9	6	7
Females	27.7	27.5	26.8	28.2	5	2	29.1	29.3	28.1	29.4	5	1
Males	26.6	27.4	26.9	27.3	1	3	28.5	28.0	27.6	28.1	2	-1
Total	**27.3**	**27.4**	**26.9**	**27.9**	**4**	**2**	**28.9**	**28.9**	**27.9**	**29.0**	**4**	**0**

continued

Table 3.6.2e – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N= 124,025						North N= 58,368					
45-54	42.2	42.6	43.4	42.4	-2	1	44.0	45.1	44.6	44.6	0	1
55-64	42.1	41.6	42.7	41.9	-2	-1	44.1	44.1	45.1	44.2	-2	0
65-74	39.4	39.3	40.6	39.8	-2	1	41.5	41.0	42.5	41.6	-2	0
75-84	34.8	34.3	34.8	33.6	-3	-3	36.3	35.8	36.0	34.0	-6	-6
≥85	25.8	25.0	24.4	24.4	0	-5	26.6	25.2	25.1	24.4	-3	-8
Females	36.5	36.4	37.7	36.8	-2	1	37.8	38.0	39.0	37.9	-3	0
Males	39.7	39.0	40.0	39.3	-2	-1	42.0	40.7	41.5	40.9	-1	-3
Total	**37.6**	**37.2**	**38.5**	**37.6**	**-2**	**0**	**39.2**	**38.9**	**39.9**	**38.9**	**-2**	**-1**
	Centre N=28,284						South N=37,373					
45-54	42.0	40.9	42.5	39.8	-6	-5	39.3	39.8	42.1	40.9	-3	4
55-64	42.2	39.6	41.9	40.5	-3	-4	39.5	39.5	40.1	39.7	-1	1
65-74	39.5	39.2	40.1	39.8	-1	1	36.4	37.1	38.4	37.3	-3	2
75-84	35.3	34.6	34.6	34.6	0	-2	31.7	31.6	32.6	32.2	-1	2
≥85	25.5	25.2	22.6	25.7	14	1	24.7	24.4	24.8	23.1	-7	-6
Females	36.6	35.7	36.6	36.2	-1	-1	34.5	34.4	36.5	35.3	-3	2
Males	39.3	38.0	39.7	38.5	-3	-2	36.6	37.1	37.9	37.4	-1	2
Total	**37.5**	**36.5**	**37.6**	**37.0**	**-2**	**-1**	**35.2**	**35.3**	**37.0**	**36.0**	**-3**	**2**

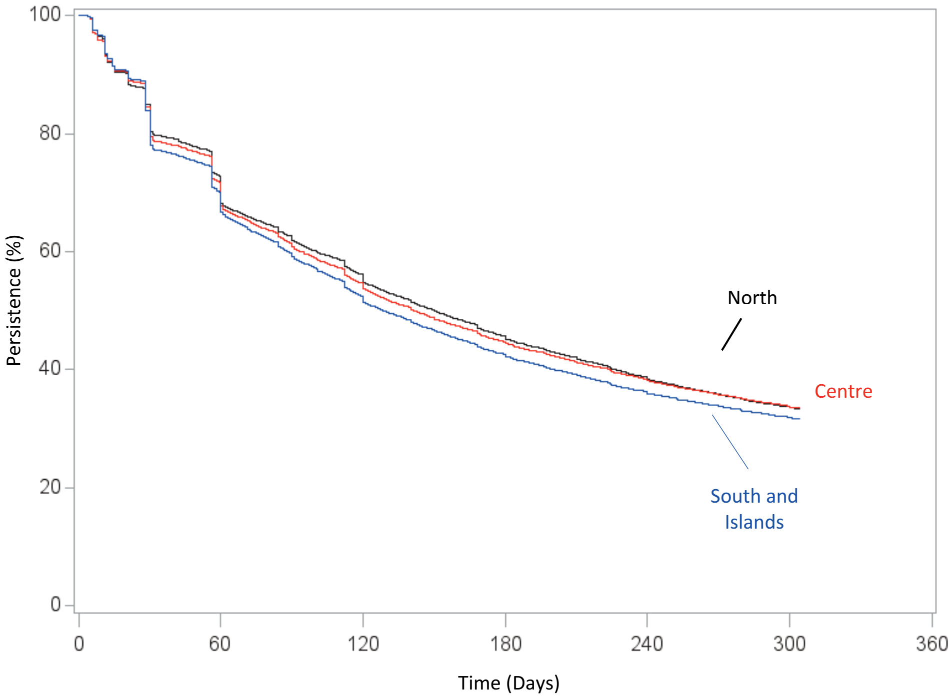
*Adherence to treatment was assessed within 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions provided. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to the statistical methods).
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of subjects with low/high adherence related to the specified category.
Median follow-up time (IQR): 307 (191-342).

Table 3.6.2f Persistence at 1 year to treatment with antidepressants in the population aged ≥45 years the period 2019-2022 and 2022-2021 change

	Persistence at 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N= 124,025						North N= 58,368					
45-54	34.5	35.6	36.1	35.8	-1	4	36.7	37.2	37.1	37.0	0	1
55-64	33.7	33.9	34.9	34.5	-1	2	35.7	35.9	36.7	35.8	-3	0
65-74	32.7	32.4	33.7	33.1	-2	1	33.7	33.3	34.7	34.0	-2	1
75-84	31.3	31.1	31.6	30.9	-2	-1	32.1	31.5	32.0	30.3	-5	-5
≥85	26.9	26.2	26.0	25.9	0	-3	27.8	25.5	26.0	25.5	-2	-8
Females	31.9	32.1	32.9	32.4	-2	2	32.8	32.7	33.4	32.5	-2	-1
Males	32.8	32.4	33.5	33.1	-1	1	34.8	33.9	35.0	34.2	-2	-2
Total	**32.2**	**32.2**	**33.1**	**32.6**	**-1**	**1**	**33.5**	**33.1**	**33.9**	**33.1**	**-2**	**-1**
	Centre N=28,284						South N=37,373					
45-54	33.4	34.7	36.2	34.6	-4	4	32.1	33.9	34.5	34.7	0	8
55-64	33.2	32.8	35.0	34.6	-1	4	31.3	32.0	32.3	32.5	1	4
65-74	33.1	33.0	34.5	34.8	1	5	31.2	30.8	31.6	30.8	-3	-1
75-84	30.8	31.5	32.6	31.9	-2	3	30.4	29.9	30.3	31.1	3	3
≥85	25.5	27.2	24.7	27.4	11	8	26.5	26.3	27.3	25.4	-7	-4
Females	31.3	32.4	33.2	33.1	0	6	30.8	30.9	31.9	31.5	-2	2
Males	32.1	31.5	33.7	33.1	-1	3	30.3	30.7	31.1	31.6	1	4
Total	**31.6**	**32.1**	**33.4**	**33.1**	**-1**	**5**	**30.6**	**30.9**	**31.7**	**31.5**	**-1**	**3**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to the statistical methods).

Figure 3.6.2d Time (in days) to discontinuation of treatment with antidepressants in the population aged ≥45 years stratified by geographical area. Curves are adjusted by gender and age (the Cox model was used to estimate persistence curves)



The increase in the use of antidepressants in 2022 is in line with the trend recorded in previous years. The phenomenon appears complex, given that against a 2.6% national increase, there are significant regional and macro-area differences (e.g. prevalence of use of about 2% in the South compared to the Centre). This could be due to the combination of factors, such as the different regional variability and the reduced accessibility to services, documented by the reduction of new diagnoses, which falls within a "historical" prescriptive pattern of antidepressants in the different territories as well as to a possible different role of GPs in different areas of the country.

Data on exposure and adherence to treatment in the population show a high level of inadequacy of these medicines against their under-use, when considering the indicators on the disease frequency. For many years now, this framework has been a great challenge for public health, which, in pursuing appropriateness, must necessarily outline a new relationship between specialist medicine and general medicine. In this context, conducting real-world studies is essential to better characterize the risk-benefit profile of these pharmaceuticals than conducting RCTs on selected populations over a short period of time. In this direction of public health, the recent publication of some systematic reviews on the risk-benefit profile in the current clinical practice of vortioxetine and ketamine are extremely useful.

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3.6.3 Medicines for pain therapy

(Includes pregabalin and gabapentin prescription for all authorized indications)

- The use of medicines for pain therapy has slightly increased over the years with a 1.7% average annual variation (CAGR), moving from 6.9 DDD/1000 inhabitants per day in 2014 to 7.9 DDD/1000 inhabitants per day in 2022 (Figure 3.6.3a). The average cost per day of therapy decreased in 2018 and remained stable until 2021. It then decreased again (-7.8%), reaching a value of EUR 2.18 in 2022.
- Major opioids plain or in combination (oral, parenteral, transdermal, and nasal) account for 62% of the expenditure of the entire category, with EUR 3.91 per capita. Oral opioids do not show significant changes in consumption, while transdermal opioids increase by 2.4%. Nasal and parenteral preparations decrease by 4.2% and 7.0%, respectively (Table 3.6.2a).
- The most widely used medicines are those for neuropathic pain, accounting for more than 41% of total DDD. This means a 4.8% increase compared to 2021, with a 5.2% average annual change compared to 2014 (Figure 3.6.2d). However, these medicines record a cost per day of therapy 3 times lower than major oral opioids, which explains the lower per capita expenditure (EUR 1.74 vs 2.65) (Table 3.6.3a).
- By analysing the individual active ingredients in detail, pregabalin, fentanyl, tapentadol are the medicines with the greatest impact on expenditure (EUR 1.37, 1.34 and 1.07 per capita, respectively). Concerning fentanyl and tapentadol this is due to the high costs per day of therapy (EUR 4.83 and 5.11, respectively). Concerning pregabalin, this is due to the high levels of consumption (2.7 DDD/1000 inhabitants per day). Regarding the other molecules, it is worth mentioning the year-on-year decrease for oxycodone (-6.2%) and the increase for pregabalin (+4.9%) and an even more marked increase for buprenorphine (+12.4%). It should be noted that this molecule is also used as a maintenance treatment within the activity of drug addiction services (Table 3.6.3a).
- At the macro-area level, consumption tends to decrease from North to South, with the latter having the lowest levels of consumption (6.2 DDD), about 22% lower than the national average. By contrast, the North shows a 14% higher level of consumption (Table 3.6.3b). Consumption in the South increases by 3.5%, while the average cost per DDD goes down in all macro-areas by about 8%.
- In details, the highest levels of consumption are found in Valle d'Aosta (10.2 DDD), Piedmont and Liguria (9.7 DDD), while Calabria is the Region with the lowest level of consumption (5.4 DDD). Overall, a clear variability in consumption is found compared to 2021, ranging from a 6.4% reduction in Emilia Romagna to a 9.2% increase in Basilicata. Regarding the average DDD cost, it should be noted that Emilia Romagna records EUR 1.73, 38% lower than that of Molise (EUR 2.80). These Regions with the highest per capita expenditure are Friuli (EUR 8.73), Lombardy (EUR 7.81) and Valle d'Aosta (EUR 7.64).

Figure 3.6.3a Pain therapy, temporal trend in per capita expenditure and average cost per day of therapy (2014-2022)

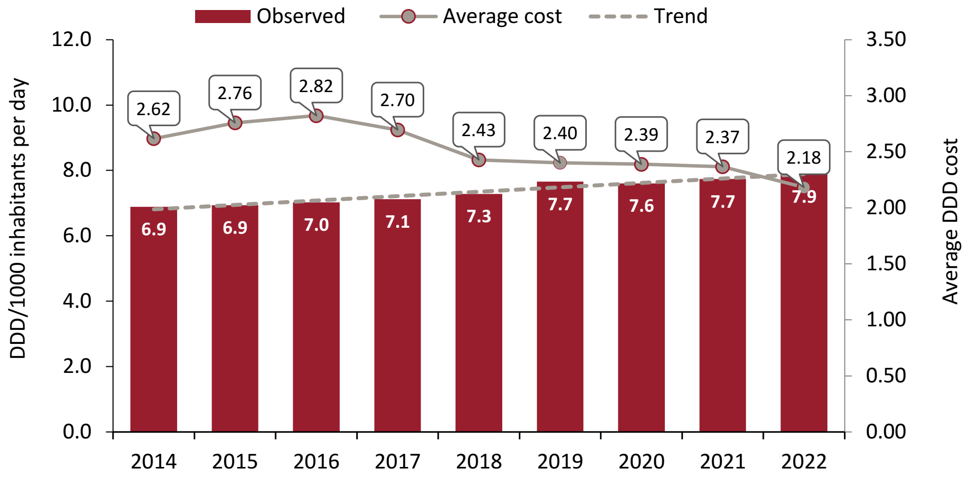

Table 3.6.3a Pain therapy, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD Cost	Δ % 22-21
Major opioids plain or in combination - oral	2.65	-15.7	2.0	1.6	0.4	3.8	4.57	-16.1
Medicines for neuropathic pain	1.74	4.8	-4.5	3.3	4.8	5.2	1.44	0.0
Major opioids plain or in combination - transdermal	0.89	4.7	4.3	0.9	2.4	2.3	2.88	2.3
Minor opioid plain or in combination	0.63	-1.8	-4.1	1.9	-0.4	-3.3	0.90	-1.4
Major opioids plain or in combination - nasal	0.32	-2.3	3.9	<0.05	-4.2	4.0	26.94	2.0
Major opioids plain or in combination - parenteral	0.05	-7.9	1.2	0.2	-7.0	-4.3	0.67	-0.9
Pain therapy	6.28	**-6.0**	**-0.6**	**7.9**	**2.0**	**1.7**	**2.18**	**-7.8**
pregabalin	1.37	5.1	-5.7	2.7	4.9	6.1	1.38	0.2
fentanyl	1.34	-3.0	2.1	0.8	-0.7	1.5	4.83	-2.4
tapentadol	1.07	-15.3	8.0	0.6	1.5	10.7	5.11	-16.6
naloxone/oxycodone	0.64	-28.7	-1.2	0.4	-0.7	4.8	4.43	-28.3
gabapentin	0.36	3.6	1.6	0.6	4.0	1.9	1.72	-0.4
buprenorphine	0.34	16.8	11.5	0.2	12.4	5.6	4.46	3.9
paracetamol/codeine	0.31	-0.1	-5.1	1.2	0.2	-4.1	0.73	-0.3
paracetamol/oxycodone	0.25	-0.3	0.0	0.3	2.5	0.7	2.03	-2.7
tramadol	0.24	-4.2	-4.6	0.6	-1.2	-3.3	1.08	-3.0
oxycodone	0.14	-8.4	-4.0	0.1	-6.2	-1.6	2.95	-2.3

Figure 3.6.3b Pain therapy, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) of subgroups with the highest expenditure

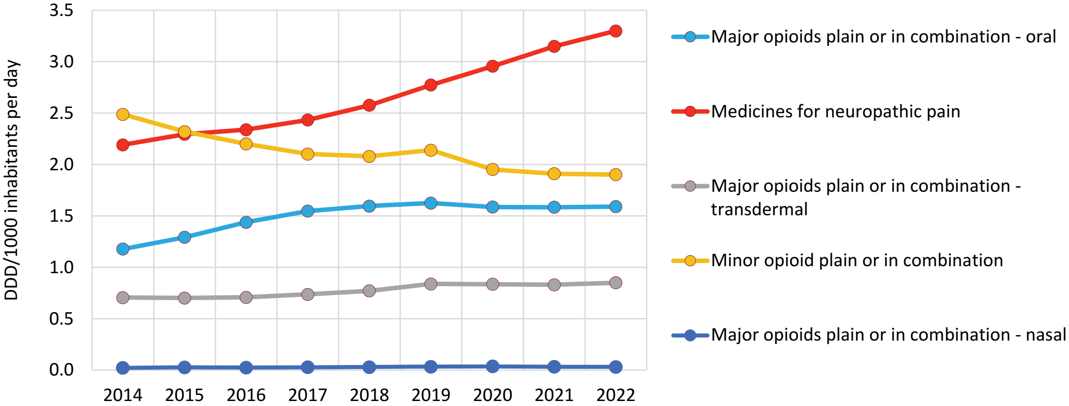

Table 3.6.3b Pain therapy, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost
Piedmont	7.49	9.3	2.20	7.03	9.7	1.98	-6.2	4.5	-10.2	-1.5	1.7	-3.1
Valle d'Aosta	8.40	10.3	2.24	7.64	10.2	2.04	-9.0	-0.2	-8.8	-2.9	1.0	-3.9
Lombardy	8.37	8.9	2.57	7.81	9.2	2.33	-6.7	2.5	-9.0	-0.1	2.2	-2.3
A.P. of Bolzano	6.58	7.9	2.28	6.06	8.0	2.08	-7.9	1.0	-8.8	-0.8	1.3	-2.1
A.P. of Trento	7.03	8.4	2.30	7.15	8.6	2.28	1.7	2.8	-1.1	2.6	2.3	0.3
Veneto	6.38	7.7	2.27	6.04	7.9	2.10	-5.4	2.5	-7.7	-0.3	1.6	-1.9
Friuli VG	9.57	9.6	2.74	8.73	9.6	2.48	-8.8	0.7	-9.3	0.4	0.5	-0.1
Liguria	7.80	9.5	2.24	7.14	9.7	2.01	-8.4	2.3	-10.4	-0.6	1.9	-2.4
Emilia Romagna	6.09	9.5	1.76	5.60	8.9	1.73	-8.0	-6.4	-1.7	-1.2	0.4	-1.6
Tuscany	6.21	8.7	1.94	5.79	9.1	1.75	-6.7	3.8	-10.1	-2.6	-0.2	-2.5
Umbria	6.33	8.1	2.15	5.69	7.9	1.97	-10.0	-2.1	-8.0	-1.6	2.4	-3.9
Marche	5.44	6.6	2.26	5.16	6.6	2.14	-5.1	0.6	-5.6	-1.6	0.4	-2.0
Lazio	6.58	7.6	2.38	6.24	7.7	2.21	-5.2	2.1	-7.1	-0.9	2.5	-3.3
Abruzzo	6.24	6.2	2.75	6.20	6.5	2.60	-0.7	5.1	-5.5	1.8	2.3	-0.5
Molise	5.92	5.4	2.98	5.76	5.6	2.80	-2.8	3.7	-6.3	1.5	2.0	-0.5
Campania	4.85	5.3	2.52	4.68	5.6	2.31	-3.4	5.4	-8.4	-0.9	2.9	-3.7
Puglia	6.51	6.6	2.71	6.13	6.8	2.48	-5.8	2.7	-8.3	0.6	2.3	-1.7
Basilicata	5.05	6.3	2.18	4.97	6.9	1.97	-1.5	9.2	-9.8	1.0	4.1	-3.0
Calabria	5.06	5.2	2.64	4.89	5.4	2.46	-3.4	3.6	-6.8	-0.5	1.7	-2.1
Sicily	5.61	5.7	2.69	5.34	5.8	2.50	-4.9	2.5	-7.2	-0.6	1.8	-2.4
Sardinia	8.16	8.1	2.76	7.49	8.1	2.53	-8.2	0.1	-8.3	0.7	2.3	-1.6
Italy	**6.68**	**7.7**	**2.37**	**6.28**	**7.9**	**2.18**	**-6.0**	**2.0**	**-7.8**	**-0.6**	**1.7**	**-2.2**
North	7.48	8.9	2.30	6.97	9.0	2.12	-6.7	1.1	-7.8	-0.5	1.6	-2.1
Centre	6.29	7.9	2.19	5.91	8.0	2.02	-6.0	2.2	-8.0	-1.6	1.2	-2.8
South and Islands	5.78	6.0	2.65	5.52	6.2	2.44	-4.6	3.5	-7.8	0.0	2.4	-2.3

Exposure in population

- Health Card data were collected to perform an analysis aimed at estimating exposure to medicines used for pain therapy in the general population. Exposure data indicate a prevalence of use that progressively increases with increasing age, reaching the highest values in the 85+ age group (23.7% in women and 18.3% in men) (Figure 3.6.3b).
- There are significant differences in terms of consumption in the 65-74 age group, reaching a 50% difference in the 85+ age group (34.1 DDDs in women versus 22.5 DDDs in men). The prevalence of use at national level is 5.4%. Piedmont is the Region with the highest level of prevalence (6.8%), while the Autonomous Province of Bolzano registers the lowest level (3.7%). Prevalence data do not show marked differences between the Centre (registering the highest percentages, compared to the national average; 5.7% vs. 5.4%), and the South, that shows a lower prevalence (5.1%) (Table 3.6.3c).
- The median age of patients using pain medication is 71 years, with a higher proportion of women. In addition, each prevalent user has received at least one dose of medication per day for about 1.5 months of therapy, with a cost per user of EUR 110 with wide differences between Regions (EUR 80.15 in Basilicata to EUR 157.45 in Friuli Venezia Giulia). Northern Regions have an average annual coverage that is slightly higher than 7 days compared with Central and Southern Regions. However, when analysing the DDD indicator by user, it must be taken into account that the results can be influenced by extreme values, relating both to the share of subjects who start treatment at the end of the observation period (incident cases), and to those who have interrupted therapy in the first months of the year (e.g. side effects, death and hospitalisation).
- For a more complete and detailed analysis, the "median DDD" indicator was also considered, which is not influenced by extreme values: the result obtained (median DDD equal to 12 days) indicates that half of the users have been treated for less than two weeks. In addition, more than one third of subjects (34.0%) received only one prescription during the year, with Southern Regions reporting the highest levels of sporadic users (37.8%). Among these, Calabria is the Region with the highest percentage of sporadic users (39.7%), while Valle d'Aosta shows the lowest share (26.5%) (Table 3.6.3c).
- The prevalence of use is higher for the category of minor opioids plain or in combination (2.9%), followed by medicines for neuropathic pain (1.8%) and major oral opioids plain or in combination (1.5%). In all categories, women have a higher prevalence of use (Table 3.6.3d). The median age of users of major parenteral or transdermal opioids is close to 80 years.
- The annual cost for each neuropathic pain medicine user is half that of major oral or transdermal opioids (EUR 93 vs 180). For neuropathic pain, half of the users are treated for less than a month. Conversely, major opioids are used as needed and have a median use time of less than two weeks, as confirmed by the number of subjects receiving only one prescription (4 out of 10).

Figure 3.6.3c Breakdown of prevalence of use and consumption of medicines for pain therapy under approved care regime and on behalf distribution (year 2022)

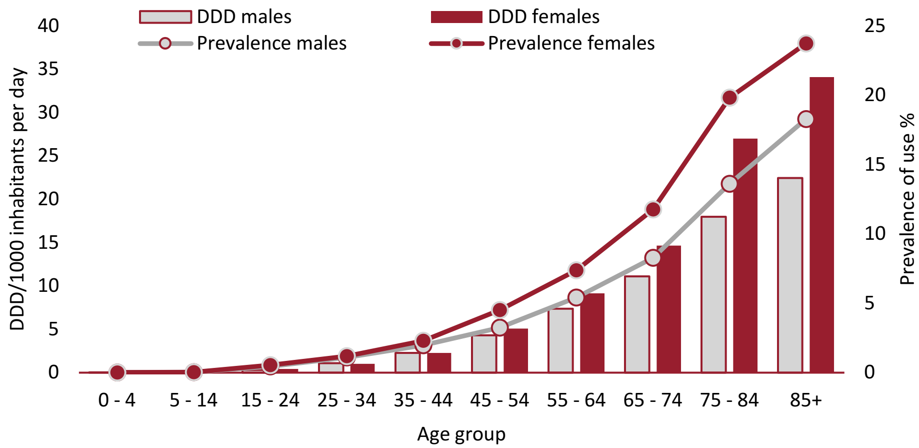

Table 3.6.3c Exposure and duration of medicines for pain therapy by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	5.4	8.3	6.9	70	102.20	46.5	10.7	33.6
Valle d'Aosta	4.4	6.7	5.5	72	130.57	57.4	15.8	26.5
Lombardy	4.0	6.2	5.1	71	139.75	55.6	15.0	29.0
A.P. of Bolzano	2.9	4.4	3.7	73	144.95	58.8	14.5	29.7
A.P. of Trento	4.3	6.5	5.4	70	120.98	47.8	10.7	32.3
Veneto	3.1	5.1	4.1	73	138.33	57.7	14.5	32.2
Friuli VG	4.3	6.9	5.6	72	157.45	58.0	14.9	27.6
Liguria	5.3	8.2	6.8	73	110.43	47.1	13.3	32.9
Emilia Romagna	4.6	7.3	6.0	70	86.29	45.6	10.7	34.8
Tuscany	5.1	8.3	6.8	72	82.16	41.6	10.7	37.0
Umbria	4.2	6.8	5.6	73	102.31	46.3	11.3	32.5
Marche	4.0	6.2	5.2	72	98.80	43.6	10.7	37.4
Lazio	3.9	6.4	5.2	70	116.12	50.0	14.0	29.8
Abruzzo	3.7	5.9	4.9	71	122.11	45.3	10.7	37.2
Molise	3.7	5.8	4.8	71	118.78	41.3	10.7	37.7
Campania	3.6	6.0	4.8	68	89.01	36.3	10.7	39.1
Puglia	4.7	7.5	6.2	70	95.76	37.3	10.7	38.4
Basilicata	4.5	7.6	6.1	70	80.15	36.9	10.7	38.7
Calabria	3.7	5.8	4.8	71	93.21	38.1	10.7	39.7
Sicily	3.6	5.8	4.7	71	108.39	41.9	10.7	37.1
Sardinia	4.0	6.5	5.3	70	144.10	54.4	14.0	31.6
Italy	**4.1**	**6.6**	**5.4**	**71**	**110.59**	**46.7**	**12.0**	**34.0**
North	4.2	6.6	5.5	71	121.07	51.7	14.0	31.6
Centre	4.3	7.0	5.7	71	100.53	45.9	12.0	33.6
South and Islands	3.9	6.3	5.1	70	101.91	40.1	10.7	37.8

Table 3.6.3d Exposure and duration of therapy with medicines for pain therapy by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Major opioids plain or in combination - oral	1.1	1.8	1.5	73	174.10	36.6	7.5	38.9
Medicines for neuropathic pain	1.4	2.2	1.8	70	92.75	60.7	25.7	20.1
Major opioids plain or in combination - transdermal	0.3	0.6	0.5	78	178.80	54.7	13.5	30.6
Minor opioids plain or in combination	2.2	3.5	2.9	71	20.59	21.2	8.7	49.1
Major opioids plain or in combination - nasal	0.0	0.0	0.0	70	2,011.96	74.3	6.7	43.7
Major opioids plain or in combination - parenteral	0.0	0.0	0.0	79	53.49	21.1	3.3	47.0
Pain therapy	**4.1**	**6.6**	**5.4**	**71**	**110.59**	**46.7**	**12.0**	**34.0**

The combination of a decrease in consumption of minor opioids and major opioids plain or in combination - parenteral, with an increase in a marked regional variability in the consumption of major opioids plain or in combination - oral/transdermal/nasal, implies, on the one hand, a focus on prescribing these medicines only for the treatment of chronic pain and, on the other hand, the urgent need to ensure access to palliative care and pain therapy in all territories in accordance with Law No. 38 of 15 March 2010. This is also in consideration of a marked regional variability in the prevalence of use of these pharmaceuticals.
The data on the percentages of users with a single prescription at national and regional level indicate the need to disseminate and implement recommendations on the use of these medicines with the usual training tools, both face-to-face and remote, as well as with specific audits in the various care settings.
It should be noted that neuropathic pain medicines include prescriptions for pregabalin and gabapentin which have indications in other areas of medicine as well (epilepsy). This makes it difficult to comment on the prescribing pattern in the general population, without specific drug use studies by diagnostic area. This should be done by stimulating the creation of ad hoc clinical practice registries as was recently documented in Greece, or conducting a higher number of pragmatic clinical trials.

References

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3.6.4 Anti-epileptics

(Do not include pregabalin and gabapentin prescription)

- In 2022, the consumption of anti-epileptics stood at 11.0 DDD/1000 inhabitants per day, with a slight increase (1.7%) compared to the previous year, while an increase was recorded for expenditure (+4.3%), equal to a value of EUR 5.34 per capita (Table 3.6.4a). Since 2014 there has been an average annual increase of 1.3% in terms of consumption and 4.3% in terms of expenditure. The average cost per day of therapy has shown a steady growth from EUR 1.11 in 2014 to EUR 1.41 in 2022 (+27%) (Figure 3.6.4a).
- With EUR 2.85 per capita, second generation anti-epileptics are the category with the highest expenditure, up 1.7% from 2021. They account for 50.4% of the whole category (Table 3.6.4.a). These medicines have recorded the highest increases since 2014 (CAGR: 3.5%) (Figure 3.6.4b). First generation anti-epileptics are the most used category in the population (5.6 DDD) even if they record a 1.1% decrease compared to 2021. They also show a median annual change equal to -1.4%. Third-generation anti-epileptics, on the other hand, show an increase in consumption and expenditure (+15% and +3.6%, respectively).
- Cannabidiol records an expenditure of EUR 0.13 per capita (up 300%, equal to consumption), and average cost per DDD of EUR 47.56, the highest in the category. This medicine was marketed in 2021 as an adjunctive therapy for seizures associated with tuberous sclerosis complex (TSC) and for the treatment of Dravet syndrome (DS) and Lennox-Gasteaux syndrome (LGS), in combination with clobazam, in patients aged 2 years and older. Levetiracetam and valproic acid (2.7 and 2.6 DDD, respectively) are confirmed as the most used molecules with an increase of 3.8% and 1.7%, respectively, compared to 2021. A similar trend is observed for lacosamide and perampanel, showing increases in consumption of around 13% (Table 3.6.4a). These new generation pharmaceuticals are indicated for the adjunctive treatment of partial seizures with or without secondary generalization in patients with epilepsy aged 16 and 12 years or older, respectively. Brivaracetam, indicated for or as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy, shows 28% increases in consumption and expenditure compared to 2021.
- By analysing regional variability, it appears that there is a greater use of these medicines in the Centre-South. The Regions with the highest consumption are Tuscany (12.7 DDD) and Calabria 12.6 DDD), whereas the two Regions with the lowest consumption are Lombardy and Valle d'Aosta (below 10 DDD) (Table 3.6.4b). Compared to 2021, Tuscany has the largest changes in consumption (+5.4%), but has the lowest average cost (EUR 0.96). Conversely, Marche shows the highest increases in expenditure (7.4%) and average cost per DDD (+5.7%). Compared to 2014, there is an average annual increase for all Regions in both expenditure and consumption (with the exception of Valle d'Aosta).

Figure 3.6.4a Anti-epileptics, temporal trend in consumption and average cost per day of therapy (2014-2022)

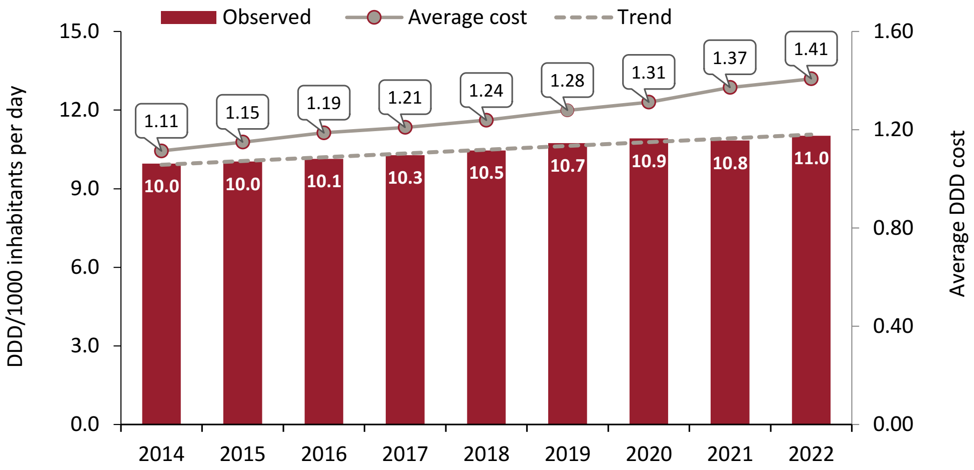

Table 3.6.4a Anti-epileptics, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD Cost	Δ % 22-21
Second-generation anti-epileptics	2.85	1.7	2.2	4.7	3.1	3.5	1.66	-1.4
First-generation anti-epileptics	1.44	2.1	1.1	5.6	-1.1	-1.4	0.70	3.3
Third-generation anti-epileptics	1.23	3.6	17.6	0.7	15.0	21.7	4.67	-9.9
Cannabidiol	0.13	353.5	-	<0.05	352.6	-	47.56	0.2
Other antiepileptics	0.02	-	-	<0.05	-	-	8.33	-
Anti-epileptics	**5.66**	**4.3**	**4.3**	**11.0**	**1.7**	**1.3**	**1.41**	**2.6**
levetiracetam	1.80	1.6	3.8	2.7	3.8	5.7	1.82	-2.1
valproic acid	1.03	1.4	1.7	2.6	1.7	1.3	1.08	-0.3
lacosamide	0.86	-0.1	15.4	0.5	13.8	17.8	4.86	-12.2
lamotrigin	0.48	4.8	3.8	0.9	6.0	5.0	1.50	-1.1
topiramate	0.30	-0.3	-0.9	0.4	0.0	-0.5	2.25	-0.2
carbamazepine	0.24	-1.9	-1.2	1.2	-1.8	-1.7	0.55	-0.1
oxcarbazepine	0.18	-1.2	-3.3	0.6	-1.3	-2.0	0.82	0.1
perampanel	0.15	13.3	-	0.1	12.7	-	5.27	0.5
cannabidiol	0.13	353.5	-	<0.05	352.6	-	47.56	0.2
brivaracetam	0.12	28.0	-	0.1	28.6	-	2.92	-0.5

Figure 3.6.4b Anti-epileptics, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) of subgroups with the highest expenditure

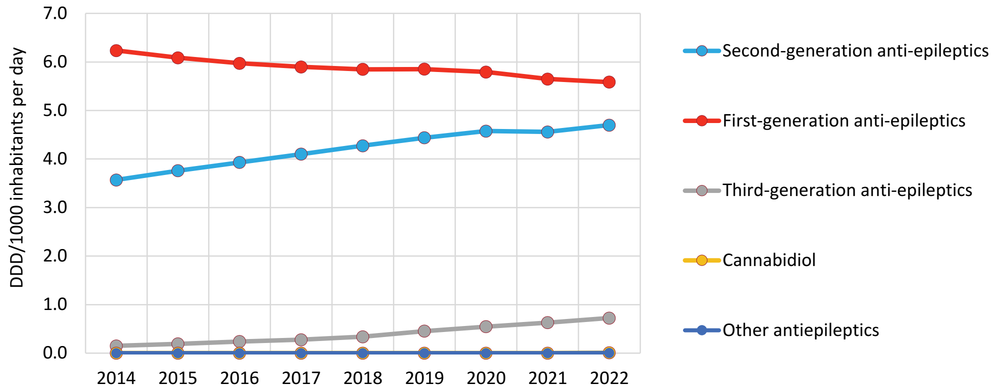

Table 3.6.4b Anti-epileptics, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost
Piedmont	5.35	10.6	1.38	5.55	10.9	1.40	3.9	2.8	1.0	4.3	1.5	2.7
Valle d'Aosta	4.46	9.0	1.36	4.36	9.1	1.31	-2.2	1.6	-3.8	3.9	-0.2	4.2
Lombardy	4.87	8.7	1.53	5.17	8.9	1.59	6.3	2.1	4.1	4.9	1.2	3.6
A.P. of Bolzano	5.76	10.0	1.59	5.93	10.4	1.56	2.8	4.6	-1.7	2.7	1.4	1.2
A.P. of Trento	5.30	10.6	1.37	5.61	10.7	1.44	5.8	0.6	5.2	4.3	0.0	4.3
Veneto	5.08	9.9	1.41	5.39	10.1	1.47	6.1	2.1	3.9	5.1	1.1	4.0
Friuli VG	5.20	10.1	1.41	5.36	10.3	1.43	3.0	1.7	1.4	5.1	1.1	4.0
Liguria	5.36	11.1	1.33	5.67	11.4	1.36	5.8	2.8	3.0	4.2	1.1	3.1
Emilia Romagna	3.72	10.4	0.98	3.88	10.6	1.01	4.5	1.8	2.7	2.9	0.9	2.0
Tuscany	4.32	12.0	0.98	4.46	12.7	0.96	3.3	5.4	-2.0	4.3	1.7	2.6
Umbria	5.56	12.3	1.24	5.80	12.4	1.28	4.4	1.3	3.1	5.4	1.0	4.4
Marche	6.30	12.0	1.44	6.77	12.2	1.53	7.4	1.6	5.7	4.9	0.8	4.0
Lazio	6.06	11.5	1.44	6.34	11.6	1.49	4.6	1.0	3.5	4.4	1.4	2.9
Abruzzo	6.66	12.2	1.49	7.05	12.4	1.55	5.8	1.6	4.1	3.6	1.0	2.6
Molise	5.44	11.4	1.31	5.58	11.6	1.32	2.6	1.7	0.8	4.2	1.2	3.0
Campania	6.38	12.0	1.46	6.62	12.0	1.52	3.9	0.1	3.8	4.4	1.4	3.0
Puglia	5.97	11.4	1.44	6.09	11.4	1.46	2.0	0.4	1.6	3.5	1.3	2.2
Basilicata	6.13	12.2	1.37	6.38	12.4	1.41	4.1	1.3	2.7	3.8	1.3	2.4
Calabria	6.75	12.5	1.48	6.97	12.6	1.51	3.2	0.8	2.4	4.6	1.6	3.0
Sicily	6.16	11.6	1.46	6.24	11.7	1.47	1.3	0.6	0.7	4.1	1.9	2.2
Sardinia	5.51	11.8	1.27	5.78	11.9	1.33	5.0	0.6	4.4	3.1	0.8	2.2
Italy	**5.43**	**10.8**	**1.37**	**5.66**	**11.0**	**1.41**	**4.3**	**1.7**	**2.6**	**4.3**	**1.3**	**3.0**
North	4.86	9.7	1.37	5.12	10.0	1.41	5.3	2.2	3.0	4.4	1.1	3.3
Centre	5.49	11.8	1.27	5.75	12.1	1.30	4.7	2.6	2.1	4.5	1.4	3.1
South and Islands	6.20	11.8	1.44	6.39	11.9	1.47	3.0	0.5	2.5	4.0	1.4	2.6

Exposure in population

- Health Card data allowed to estimate exposure and intensity of use of antipsychotics in the Italian population. As expected based on the epidemiology of the condition, consumption increases with age and reaches a prevalence of use of 5% in the over 85 population, both genders, and 2% in the general population.
- There are no marked gender differences, with the exception of the 25-44 age group, in which men use about 30% more anti-epileptics than women, with a slightly higher prevalence level (Figure 3.6.4b).
- All Central and Southern Regions have a prevalence of more than 2%, with values ranging from a minimum of 1.3% in the Autonomous Province of Bolzano to a maximum of 2.6% in Tuscany. The median age of users is 60 years and each subject is treated on average for 6 months, costing EUR 253.53. Marked differences between macro-areas can be seen for this indicator, with the Centre recording a value of 17% lower than the national average and the North a value that is 8% higher. Regions show a minimum of EUR 141.83 in Tuscany and a maximum of EUR 374.17 in the Autonomous Province of Bolzano (with a difference of 61%). One in ten users receive only one prescription in a year, and half of the users are on treatment for less than 4 months, indicating that the prescription is not in line with the main national and international guidelines on treatment of epilepsy (Table 3.6.4c).
- Second generation anti-epileptics are the most prescribed category with 1.3% prevalence of use without gender differences, and a slightly lower value is recorded for first-generation pharmaceuticals (0.8%). Each user treated with first-generation anti-epileptics has a cost 3.5 times higher than those who are treated with second-generation pharmaceuticals (EUR 345 vs 100). The former remains in treatment on average for about 7 months, whereas the latter remain in treatment for 4 and a half months (Table 3.6.4d).

Figure 3.6.4c Breakdown of prevalence of use and consumption of anti-epileptics under approved care regime and on behalf distribution in 2022

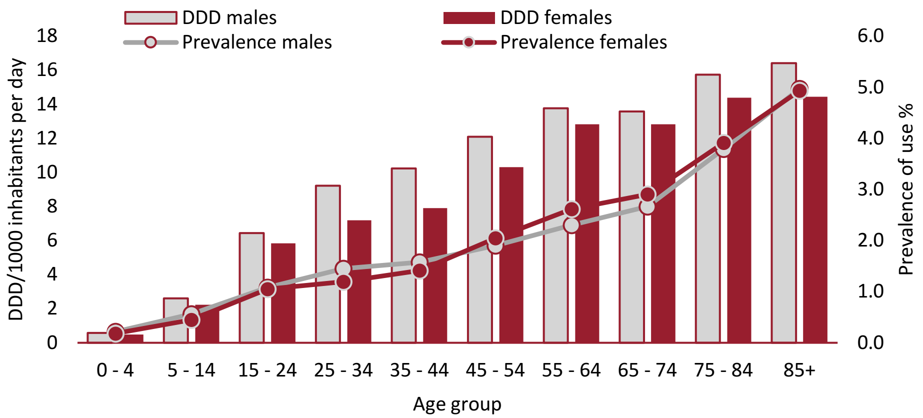

Table 3.6.4c Exposure and duration of therapy with anti-epileptics by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	1.7	1.9	1.8	61	283.75	200.7	130.0	7.7
Valle d'Aosta	1.5	1.5	1.5	59	273.03	201.2	130.7	5.8
Lombardy	1.4	1.6	1.5	59	299.12	192.3	120.0	6.9
A.P. of Bolzano	1.3	1.3	1.3	58	374.17	229.6	150.0	6.9
A.P. of Trento	1.6	1.8	1.7	61	272.22	192.7	120.0	9.4
Veneto	1.3	1.4	1.4	58	345.62	230.0	160.0	5.8
Friuli VG	1.3	1.5	1.4	61	356.01	241.0	165.0	6.7
Liguria	2.1	2.5	2.3	62	230.91	164.6	100.0	9.4
Emilia Romagna	1.6	1.8	1.7	61	147.77	162.9	94.7	11.1
Tuscany	2.5	2.8	2.6	61	141.83	150.8	84.0	11.1
Umbria	1.9	2.1	2.0	63	269.01	197.9	120.0	8.6
Marche	2.1	2.2	2.2	61	283.97	194.5	120.0	8.1
Lazio	2.3	2.6	2.5	59	235.91	163.4	90.0	8.9
Abruzzo	2.2	2.4	2.3	61	278.89	186.7	115.0	10.3
Molise	2.2	2.4	2.3	61	240.54	180.2	109.7	8.9
Campania	2.0	2.1	2.1	57	279.54	190.5	115.0	9.5
Puglia	2.1	2.2	2.1	59	265.91	186.0	114.0	8.6
Basilicata	2.4	2.4	2.4	60	245.18	177.0	112.0	11.0
Calabria	2.3	2.6	2.5	60	252.44	174.8	100.0	11.4
Sicily	2.3	2.4	2.3	60	250.34	172.9	102.0	10.2
Sardinia	2.3	2.8	2.6	59	215.78	167.2	102.0	9.4
Italy	**1.9**	**2.1**	**2.0**	**60**	**253.53**	**182.1**	**112.0**	**9.0**
North	1.5	1.7	1.6	60	274.71	194.7	120.0	7.8
Centre	2.3	2.6	2.4	60	211.64	164.7	93.3	9.5
South and Islands	2.2	2.3	2.2	59	259.49	180.7	110.0	9.8

Table 3.6.4d Exposure and duration of therapy with anti-epileptics by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Second-generation anti-epileptics	1.4	1.3	1.3	60	100.21	137.0	81.3	9.8
First-generation anti-epileptics	0.7	0.9	0.8	58	345.31	199.2	140.0	8.5
Third-generation anti-epileptics	0.1	0.1	0.1	56	1,147.83	265.7	224.0	5.4
Other anti-epileptics	<0.05	<0.05	<0.05	37	500.58	69.9	55.1	12.5
Anti-epileptics	**1.9**	**2.1**	**2.0**	**60**	**253.53**	**182.1**	**112.0**	**9.0**

From a public health perspective, there is the need to conduct more studies on the use of anti-epileptics in the real world, in order to characterise their prescribing patterns, especially on the effectiveness of third generation molecules, such as lacosamide, perampanel and brivacetam, which have recorded a remarkable increase in the last year. Recently, a meta-analysis and a pooled analysis were published on the use of lacosamide and perampanel in the real world, respectively. The results essentially document a risk-benefit profile similar to that observed in RCTs, although the safety profile should be further investigated.
The same indications emerge from an Australian study on the use of brivacetam in clinical practice in patients with drug-resistant epilepsy.
In general, the change in the prescribing pattern observed over the last seven years (decrease in the use of first-generation pharmaceuticals and increase in second and third generation pharmaceuticals) requires an in-depth study on the clinical outcomes that have the greatest impact on the quality of life of patients.

References

- Halliday AJ, Vogrin S, Ignatiadis S, et al. The efficacy and tolerability of adjunctive brivaracetam for the treatment of adult epilepsy: An Australian multi-center retrospective real- world observational cohort study. *Epilepsy Behav* 2023;145:109287.

3.6.5 Antipsychotics

- From 2014 to 2022, the consumption of antipsychotics has increased by more than 25%, from 8.3 to 10.4 DDD. Over the same period, the average annual change in the average cost per DDD has remained stable (CAGR: +0.3%), reaching EUR 1.36 in 2022 (Figure 3.6.5a). On average, for each citizen, the expenditure was equal to EUR 5.18 with a 3.4% increase compared to 2021 and a 2.7% average annual change from 2014 to 2021. The change in expenditure in 2022 was mainly due to a 3.1% increase in doses (Table 3.6.5a).
- Atypical and other antipsychotics remain the category with the highest expenditure (EUR 4.71 per capita, equal to 91% of the total) and the highest consumption (8.0 DDD equal to 77% of the total), with an increase of 2.9% and 3.9%, respectively, compared to 2021 (Table 3.6.5b). These medicines have a cost per day of therapy 4 times higher than typical antipsychotics (EUR 1.61 vs 0.37), with a 2.1% reduction in consumption and a 0.8% increase in expenditure (Table 3.6.5a).
- Again in 2021, paliperidone and aripiprazole are at the first places in terms of expenditure (EUR 1.63 and 1.29, respectively), with an increase of 4.2% and 6.3%, respectively, compared to the previous year. Despite a reduced consumption in terms of prescribed doses (from 0.9 to 1.4 DDD), the high cost of both pharmaceuticals is determined by a high average cost per day of therapy. Haloperidol and lithium are the only typical antipsychotics in the top ten with the highest cost, with a similar decrease in consumption (-2.8% and -1.9%, respectively). The only molecule registered in the last few years is lurasidone, a second generation antipsychotic indicated for the treatment of schizophrenia in adults from 18 years of age, and of bipolar disorder, plain or in combination with lithium and/or valproic acid. Despite its efficacy and safety profile comparable to other atypical antipsychotics, this molecule has shown an increase of 17% in terms of doses and expenditure in the last year, with a cost per day of therapy equal to EUR 2.23 compared to an average of EUR 1.61 for atypical antipsychotics.
- Important differences can be seen among Regions, with Sardinia (14.2 DDDs) registering a consumption that is 65% higher than Lombardy (8.6). In general, in almost all Central and Southern Regions (except for Campania), there is a more pronounced use of these medicines than the North (Table 3.6.5b). Despite a consumption that is slightly higher than the national average (10.7 vs. 10.4 DDDs), Abruzzo is the Region with the highest per capita expenditure (EUR 7.95) due to a higher use of high-cost medicines per day of therapy (EUR 2.03). The largest increases in consumption over the previous year are found in Valle d’Aosta and Molies (+34.4% and +13.1%, respectively). Sicily is the Region with the sharpest contraction (-7%).

Figure 3.6.5a Antipsychotics, temporal trend in consumption and average cost per day of therapy (2014-2022)

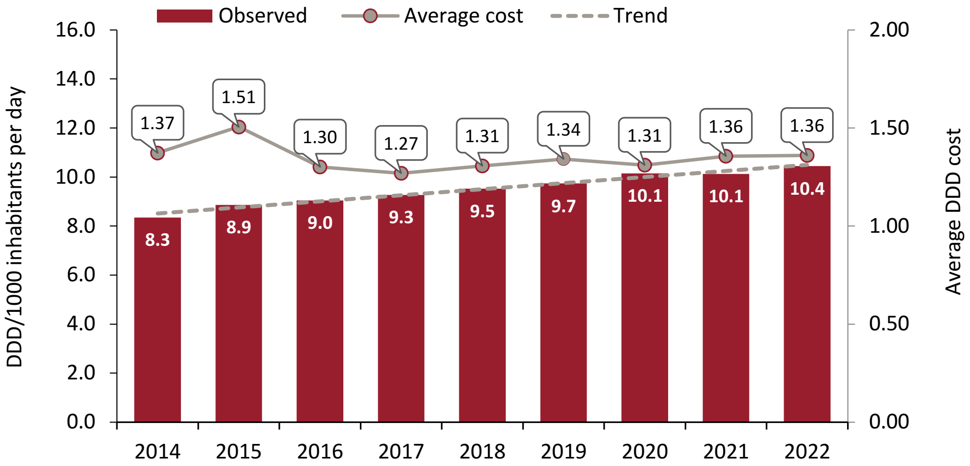

Table3.6.5a Antipsychotics, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Median DDD Cost	Δ % 22-21
Atypical and other antipsychotics	4.71	2.9	2.5	8.0	3.9	4.3	1.61	-1.0
Typical antipsychotics	0.30	0.8	-0.4	2.2	-2.1	-2.2	0.37	2.9
Atypical and other antipsychotics - lurasidone	0.14	16.5	-	0.2	16.9	-	2.23	-0.3
Atypical and other antipsychotics - brexpiprazole	0.03	139.7	-	0.1	156.6	-	1.55	-6.6
Antipsychotics	**5.18**	**3.4**	**2.7**	**10.4**	**3.1**	**2.8**	**1.36**	**0.3**
paliperidone	1.63	4.2	9.3	0.9	5.3	10.3	4.95	-1.0
aripiprazole	1.29	6.3	12.0	1.4	7.2	23.2	2.45	-0.8
quetiapine	0.75	-2.6	-3.6	2.0	0.1	2.1	1.04	-2.7
olanzapine	0.38	12.7	-0.5	2.2	6.5	2.0	0.48	5.8
risperidone	0.37	-5.9	-7.4	0.9	3.3	-0.2	1.17	-8.9
clozapine	0.16	-0.5	1.6	0.5	0.1	1.7	0.98	-0.6
lurasidone	0.14	16.5	-	0.2	16.9	-	2.23	-0.3
haloperidol	0.08	-2.3	-0.2	1.1	-2.8	-0.2	0.19	0.5
lithium	0.07	0.4	0.9	0.4	-1.9	0.6	0.54	2.4
amisulpride	0.06	-2.1	-2.9	0.1	-1.7	-2.7	1.63	-0.5

Figure 3.6.5b Antipsychotics, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) of subgroups with the highest expenditure

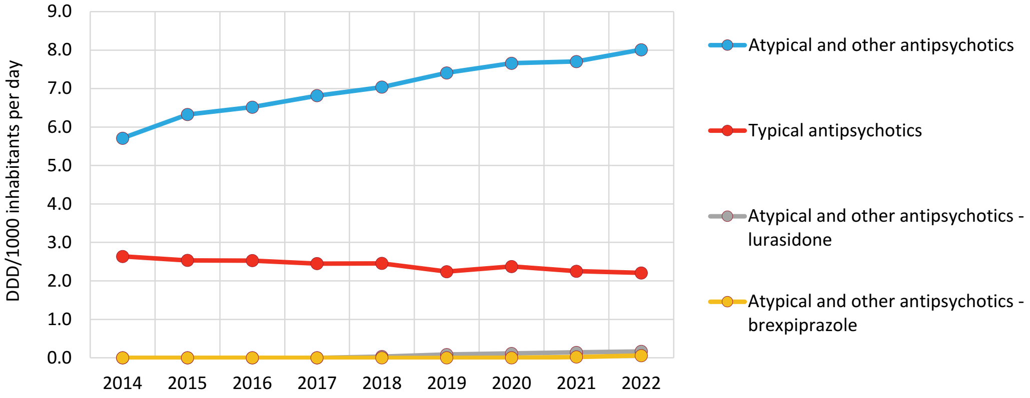

Table 3.6.5b Antipsychotics, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Median DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Median DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Median DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Median DDD Cost
Piedmont	3.49	9.7	0.98	3.63	10.3	0.97	4.0	5.8	-1.7	0.0	2.2	2.1
Valle d'Aosta	3.27	6.6	1.35	3.99	9.0	1.21	22.2	36.4	-10.4	5.7	4.3	1.3
Lombardy	6.63	8.4	2.17	6.91	8.6	2.21	4.2	2.5	1.7	6.2	3.5	2.6
A.P. of Bolzano	5.14	9.7	1.45	5.45	9.8	1.53	6.0	0.9	5.1	4.4	1.5	2.8
A.P. of Trento	3.18	10.0	0.88	3.35	9.9	0.93	5.2	-0.6	5.8	5.0	4.5	0.4
Veneto	3.80	9.7	1.08	4.05	10.0	1.11	6.5	3.5	2.9	0.8	1.4	-0.7
Friuli VG	3.14	9.9	0.87	3.26	9.9	0.90	3.7	0.2	3.5	1.0	1.6	-0.6
Liguria	4.14	10.0	1.14	4.13	10.4	1.09	-0.3	4.4	-4.6	-0.1	3.4	-3.4
Emilia Romagna	3.61	10.2	0.97	3.80	10.9	0.96	5.2	6.6	-1.3	-0.2	2.0	-2.1
Tuscany	4.60	10.3	1.23	4.72	10.6	1.22	2.5	2.8	-0.3	7.4	3.4	3.8
Umbria	4.40	11.3	1.07	4.45	11.7	1.04	1.0	3.3	-2.3	3.1	4.4	-1.3
Marche	5.97	11.3	1.45	6.09	11.7	1.42	2.0	3.7	-1.6	3.2	4.8	-1.5
Lazio	4.55	10.1	1.24	4.72	10.8	1.20	3.8	7.2	-3.2	2.9	4.1	-1.2
Abruzzo	7.74	10.4	2.04	7.95	10.7	2.03	2.7	3.3	-0.5	0.7	2.1	-1.4
Molise	3.29	9.1	0.99	4.21	10.3	1.12	28.0	13.1	13.1	-3.2	1.4	-4.5
Campania	5.19	9.3	1.53	5.35	9.7	1.51	3.1	4.1	-0.9	3.5	2.4	1.1
Puglia	7.39	11.6	1.74	7.69	12.0	1.75	4.0	3.3	0.6	6.0	3.4	2.5
Basilicata	6.73	11.4	1.62	7.27	11.9	1.67	8.0	4.7	3.1	4.8	3.8	0.9
Calabria	4.89	11.4	1.17	4.69	11.4	1.13	-4.1	-0.2	-3.9	-1.3	2.9	-4.1
Sicily	4.37	12.1	0.99	4.19	11.3	1.02	-4.1	-7.0	3.1	-1.9	2.1	-4.0
Sardinia	5.18	13.2	1.07	5.79	14.2	1.11	11.7	7.8	3.6	-1.0	2.9	-3.8
Italy	**5.01**	**10.1**	**1.36**	**5.18**	**10.4**	**1.36**	**3.4**	**3.1**	**0.3**	**2.7**	**2.8**	**-0.1**
North	4.73	9.3	1.39	4.94	9.7	1.40	4.5	4.0	0.5	3.0	2.5	0.5
Centre	4.74	10.4	1.25	4.88	10.9	1.22	2.9	5.0	-2.0	4.2	4.0	0.2
South and Islands	5.59	11.1	1.38	5.72	11.2	1.40	2.4	1.1	1.4	1.7	2.6	-0.9

Exposure in population

- Health Card data allowed to estimate exposure and intensity of use of antipsychotics in the Italian population. Consistent with the epidemiology of the clinical conditions in which antipsychotics are used, the prevalence of use increases with age to 11% in women and 9% in men in the 85+ age group. Conversely, in the ≤64 age group, men appear to use more doses than women on average, despite an overlapping prevalence of use (Figure 3.6.5b). In Italy, the prevalence of use of antipsychotic medicines reached 1.8% in 2022, with a minimum value of 1.2% in Veneto and a maximum value of 2.9% in Sardinia. The Regions of the Centre and South show greater exposure compared to the North (2.0% vs 1.6%). The median age of antipsychotic users is 66 years (North: 67 years, Centre: 68 years and South: 65 years).
- On average, every user is treated for slightly more than 4 months (128 days) and the average annual cost for each is EUR 104.71, with wide differences among Regions. Lombardy's expenditure is almost 6 times higher than that of Liguria (EUR 222 vs 38.39). In addition, several Regions show an expenditure above the national average, indicating savings margins possibly resulting from a different drug distribution method. Half of the users remain on treatment for less than two months and 12.2% receives one prescription (Table 3.6.5c). These data indicate that a significant proportion of patients may experience significant side effects, particularly related to ideation and extrapyramidal disorders (e.g. dystonia, tremor, tardive dyskinesia), or that patients with schizophrenia do not respond to conventional antipsychotics.
- Atypical and typical antipsychotics show a prevalence of 1.5% and 0.4%, respectively, with a difference of 6 years in median age (67 vs 61) and a cost per user ranging from EUR 103 for atypical antipsychotics and 38 for typical antipsychotics (Table 3.6.5d). Between the two categories there is also an average difference of one month of treatment by users (atypical: 4 months vs 3 months) and in the percentage of sporadic users (12% vs 18%).

Figure 3.6.5c Breakdown of prevalence of use and consumption of antipsychotics under approved care regime and on behalf distribution in 2022

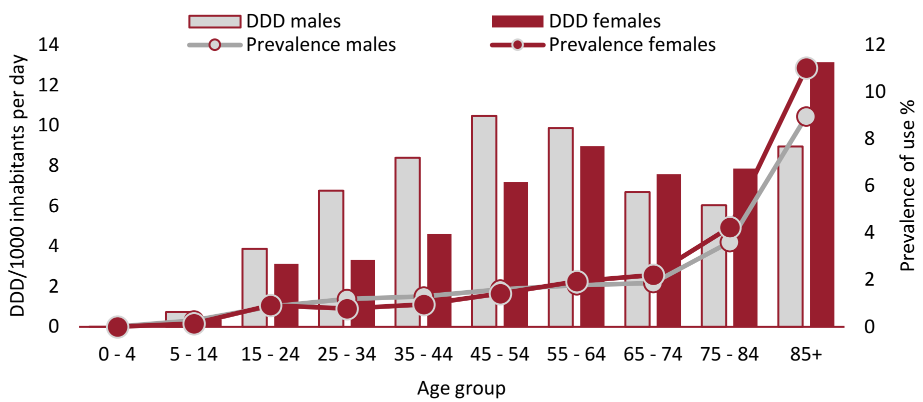

Table 3.6.5c Exposure and duration of therapy with antipsychotics by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	1.5	1.8	1.6	68	51.44	121.4	48.0	11.5
Valle d'Aosta	1.2	1.7	1.5	65	50.83	126.4	56.0	10.4
Lombardy	1.6	2.0	1.8	66	222.56	120.4	51.8	10.0
A.P. of Bolzano	1.2	1.5	1.3	65	100.36	101.3	45.0	13.5
A.P. of Trento	1.4	1.6	1.5	62	95.20	131.6	58.1	10.9
Veneto	1.1	1.3	1.2	62	86.28	129.9	60.0	13.8
Friuli VG	1.1	1.6	1.4	77	61.39	79.9	33.3	13.1
Liguria	1.7	2.3	2.0	72	38.39	97.8	40.0	13.9
Emilia Romagna	1.1	1.5	1.3	66	45.69	107.5	45.0	15.7
Tuscany	1.8	2.4	2.1	69	77.97	100.6	43.1	15.4
Umbria	1.7	2.4	2.0	79	48.25	81.9	37.5	13.5
Marche	1.8	2.2	2.0	68	59.53	125.2	56.0	12.1
Lazio	1.9	2.4	2.2	65	72.31	131.5	56.0	12.3
Abruzzo	2.1	2.5	2.3	69	173.14	125.4	53.0	12.8
Molise	1.9	2.3	2.1	69	75.85	132.9	57.6	11.9
Campania	1.6	1.7	1.6	64	86.69	147.2	60.0	11.7
Puglia	1.9	2.1	2.0	65	167.63	155.6	70.0	11.1
Basilicata	2.0	2.3	2.2	65	167.24	147.7	70.0	12.3
Calabria	1.9	2.0	2.0	63	83.51	154.0	70.0	12.6
Sicily	1.9	2.1	2.0	65	50.21	154.5	67.0	11.1
Sardinia	2.5	3.2	2.9	66	86.25	136.5	56.1	12.2
Italy	**1.6**	**2.0**	**1.8**	**66**	**104.71**	**128.7**	**56.0**	**12.2**
North	1.4	1.7	1.6	67	127.28	116.8	48.8	12.0
Centre	1.9	2.4	2.1	68	70.83	117.7	48.8	13.3
South and Islands	1.9	2.1	2.0	65	101.79	148.2	61.9	11.7

Table 3.6.5d Exposure and duration of therapy with antipsychotics by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Atypical and other antipsychotics	1.4	1.7	1.5	67	103.29	120.7	52.5	11.9
Typical antipsychotics	0.4	0.5	0.4	61	38.41	91.5	45.0	18.0
Atypical and other antipsychotics - lurasidone	0.02	0.03	0.03	47	422.53	184.4	103.6	16.0
Atypical and other antipsychotics - brexpiprazole	0.01	0.01	0.01	45	220.07	119.9	74.7	12.9
Antipsychotics	**1.6**	**2.0**	**1.8**	**66**	**104.71**	**128.7**	**56.0**	**12.2**

The 2022 data confirm a considerable regional variability in antipsychotic use that cannot be attributed to a different prevalence of mental illnesses. Furthermore, it should be reiterated that the impossibility of distinguishing between the use of antipsychotics in patients with dementia and in those with other mental disorders does not adequately assess the increase in doses recorded in 2022 compared to the previous year.
In terms of appropriateness, the prescribing patterns for users of the two categories of antipsychotics should be characterised in such a way as to define the outcomes on the course of different mental disorders. In general, a greater integration of prevalence of use and adherence data produced by OsMed with those of the Mental Health Information System (SISM) is suggested.
In a recent meta-analysis on the use of antipsychotics in schizophrenia, a good level of agreement was documented between available evidence in RCTs and real-world evidence. In a study conducted in six countries, including Italy, there was an increase in the use of antipsychotics in people with dementia during the COVID-19 pandemic that did not return to pre-pandemic levels after the acute phase.

References

- Luo H, Lau WCY, Chai Y, et al. Rates of Antipsychotic Drug Prescribing Among People Living With Dementia During the COVID-19 Pandemic. *JAMA Psychiatry* 2023;80(3):211-219.

3.6.6 Antiparkinson medicines

- In 2022, the consumption of antiparkinson medicines reached 5.7 DDD/1000 inhabitants per day, stable (+0.3%) compared with 2021. The average annual increase was equal to 0.8% between 2014 and 2022 (Figure 3.6.6a). On average, each day of therapy costs EUR 1.63, (-8.3% compared to 2014), with values among the therapeutic categories ranging between EUR 0.26 for anticholinergics and EUR 3.92 for COMTs (Table 3.6.6a).
- Among the categories of medicines for the control of the symptoms of the disease, dopa-derived agonists, plain or in combination, continue to be the most widely used in 2022, with 2.4 DDD (equal to 42% of the total antiparkinsonians) and an expenditure of EUR 1.25 per capita (+0.9% and +1.7%, respectively, compared to 2021), followed by dopamine agonists, down 3.8% in terms of doses and 4.9% in terms of expenditure. Despite accounting for a small share of consumption (0.2 DDD), COMT inhibitors continue to register an increase in consumption (+16.7%) and expenditure (++13.2%). For both indicators, the average annual change between 2014 and 2022 has exceeded 20% (Table 3.6.6a). MAO inhibitors saw a 48% increase in doses compared to 2014 (from 1.1 to 1.7 DDD), while dopamine agonists decreased by 27% in the same period (Figure 3.6.6b).
- From an in-depth analysis by active ingredient, the highest consumed medicines appear to be levodopa and benserazide in combination (1.1 DDD), selegiline and levodopa/carbidopa (both with 1.0 DDD). These three medicines have registered an increase compared to 2021. As already observed in 2021, the increase in opicapone consumption continues (+18.4%). This substance is the latest molecule to be marketed in the COMT inhibitor class and, due to its prolonged action, allows for single daily administration. The molecules with the highest cost per day of therapy (as they are still covered by patent) are rotigotine (EUR 5.19, found in the transdermal patch pharmaceutical form), safinamide (EUR 4.20) and opicapone (EUR 3.90) (Table 3.6.6a).
- Among the different macroareas, the highest consumption is found in the Centre (6.2 DDD), in the South and Islands (6 DDD), and in the North (5.3 DDD). Central Regions also have a higher average cost per DDD (EUR 1.75) and higher expenditure (EUR 3.97 per capita), compared to the South (EUR 1.63 and 3.56, respectively), and the North (EUR 1.58 and 3.08, respectively).
- The variability in terms of consumption among Regions ranges from 4.1 DDD in the Autonomous Province of Bolzano to a maximum at 6.7 DDD in Marche. Liguria and Valle d'Aosta are the only Regions showing an increase in expenditure above 3%. Sardinia has an average cost per DDD almost double than that of Emilia Romagna (EUR 1.97 vs. 1.06). This Region also shows the lowest per capita expenditure (EUR 1.99), whereas Abruzzo has the highest expenditure (EUR 4.71).

Figure 3.6.6a Antiparkinson medicines, temporal trend in consumption and average cost per day of therapy (2014-2022)

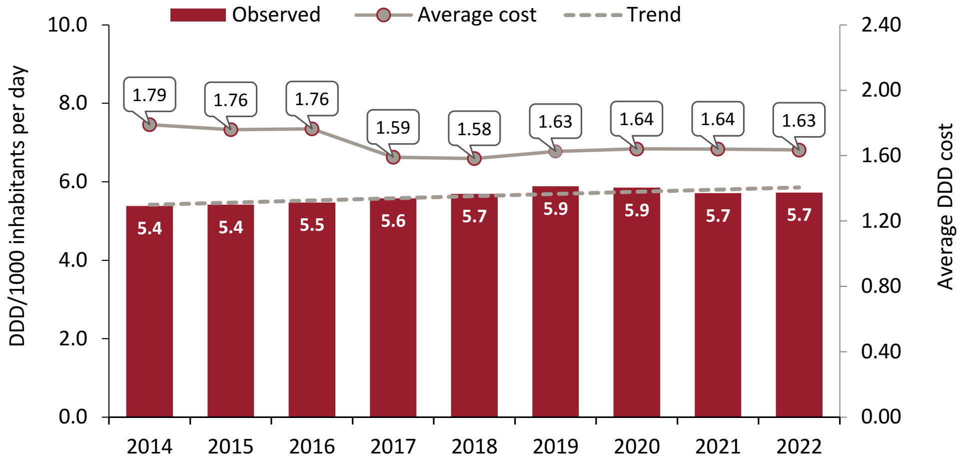

Table 3.6.6a Antiparkinson medicines, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD Cost	Δ % 22-21
DOPA-derived agonists plain or in combination	1.25	1.7	0.5	2.4	0.9	0.7	1.45	0.7
Dopamine-agonists	1.10	-4.9	-2.7	1.1	-3.8	-3.8	2.82	-1.1
MAO inhibitors	0.80	0.8	-0.8	1.7	1.0	5.0	1.31	-0.1
COMT inhibitors	0.22	13.2	21.4	0.2	16.7	23.4	3.92	-3.0
Anticholinergics	0.04	-1.2	-1.4	0.5	-0.6	-1.4	0.26	-0.6
Amantadine	<0.005	114.7	-3.4	<0.05	93.0	-10.7	0.74	11.3
Antiparkinson medicines	**3.42**	**-0.1**	**-0.4**	**5.7**	**0.3**	**0.8**	**1.63**	**-0.4**
levodopa/carbidopa	0.70	3.0	4.5	1.0	3.1	1.3	2.02	-0.1
rotigotine	0.63	-6.8	-0.4	0.3	-5.0	-0.1	5.19	-1.9
safinamide	0.41	1.9	-	0.3	2.7	-	4.20	-0.9
pramipexole	0.37	-0.8	-3.8	0.5	-1.2	-2.7	2.17	0.4
levodopa/benserazide	0.36	2.8	3.1	1.1	0.9	2.6	0.92	1.9
rasagiline	0.27	-0.7	-12.3	0.4	-0.6	-2.1	2.03	-0.1
opicapone	0.21	15.1	-	0.1	18.4	-	3.90	-2.8
melevodopa/carbidopa	0.15	-1.5	1.6	0.2	-1.4	0.6	1.82	-0.2
selegiline	0.12	0.8	3.6	1.0	1.1	5.1	0.31	-0.3
ropinirole	0.09	-7.1	-9.0	0.3	-6.8	-8.5	0.96	-0.3

Figure 3.6.6b Antiparkinson medicines, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) by subgroups with the highest expenditure

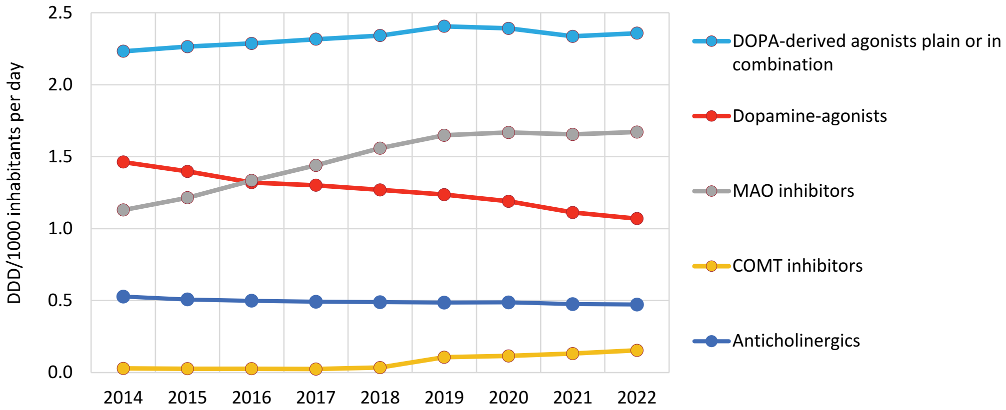

Table 3.6.6b Antiparkinson medicines, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost
Piedmont	3.52	6.0	1.61	3.55	6.1	1.59	0.9	1.8	-0.8	-2.1	0.5	-2.6
Valle d'Aosta	3.45	6.0	1.57	3.64	6.2	1.60	5.4	3.5	1.8	3.1	2.6	0.5
Lombardy	3.16	4.8	1.81	3.19	4.8	1.83	0.8	-0.1	0.9	0.4	0.8	-0.4
A.P. of Bolzano	1.99	3.9	1.39	1.98	4.1	1.33	-0.4	3.4	-3.7	-1.0	-1.0	0.0
A.P. of Trento	3.13	4.7	1.84	3.01	4.7	1.74	-4.0	1.7	-5.7	-0.9	-0.7	-0.2
Veneto	3.42	5.7	1.65	3.47	5.8	1.65	1.7	1.5	0.2	0.3	0.6	-0.3
Friuli VG	2.80	5.3	1.45	2.84	5.3	1.46	1.3	0.6	0.7	-0.9	0.7	-1.6
Liguria	3.39	6.4	1.46	3.43	6.6	1.43	1.1	3.2	-2.1	0.0	0.5	-0.5
Emilia Romagna	1.94	5.1	1.04	1.99	5.1	1.06	2.8	0.7	2.1	-3.1	-0.5	-2.7
Tuscany	3.45	5.7	1.66	3.42	5.7	1.65	-0.9	-0.6	-0.3	-0.2	0.1	-0.3
Umbria	4.43	6.5	1.86	4.39	6.5	1.85	-0.8	-0.2	-0.6	-0.3	1.1	-1.4
Marche	3.76	6.7	1.55	3.78	6.7	1.54	0.7	1.1	-0.4	-1.2	0.2	-1.4
Lazio	4.34	6.4	1.84	4.33	6.4	1.85	-0.3	-0.7	0.4	0.6	1.5	-0.9
Abruzzo	4.76	6.9	1.89	4.71	6.9	1.87	-0.9	0.5	-1.4	-0.6	2.2	-2.7
Molise	3.62	5.8	1.70	3.56	5.8	1.67	-1.7	-0.3	-1.4	-1.8	1.0	-2.8
Campania	3.13	5.6	1.52	3.08	5.6	1.51	-1.6	-0.7	-0.9	-1.0	1.7	-2.7
Puglia	4.01	6.0	1.84	3.95	6.0	1.82	-1.4	-0.4	-0.9	0.2	0.3	-0.1
Basilicata	3.81	6.1	1.71	3.93	6.1	1.75	3.1	0.8	2.3	0.9	1.5	-0.6
Calabria	3.48	5.9	1.62	3.50	5.9	1.64	0.6	-0.5	1.2	1.6	0.6	1.0
Sicily	3.43	6.4	1.47	3.33	6.4	1.42	-2.8	0.5	-3.3	-0.2	1.5	-1.6
Sardinia	3.91	5.4	1.98	3.83	5.3	1.97	-2.1	-1.4	-0.7	-1.2	1.0	-2.2
Italy	**3.42**	**5.7**	**1.64**	**3.42**	**5.7**	**1.63**	**-0.1**	**0.3**	**-0.4**	**-0.4**	**0.8**	**-1.1**
North	3.04	5.3	1.58	3.08	5.3	1.58	1.2	1.0	0.1	-0.7	0.4	-1.1
Centre	3.99	6.2	1.75	3.97	6.2	1.75	-0.4	-0.4	0.0	0.1	0.9	-0.8
South and Islands	3.61	6.0	1.65	3.56	6.0	1.63	-1.5	-0.2	-1.2	-0.3	1.2	-1.5

Exposure in population

- Using Health Card data, an analysis was conducted to estimate the exposure and intensity of use of antiparkinson medicines in the general population. Epidemiological data on Parkinson's disease indicate that, in general, the disease occurs after the age of 60, although about 10% of patients are around 40 years of age. Parkinson’s disease is a neurodegenerative and progressive disease. The prevalence data of medicine use and consumption show a sharp increase with age, up to a value of 5.6% in the 85+ age group. Men show a greater use in the 65+ age group, with differences in consumption ranging from 60% to 70% compared to women (Figure 3.6.6b).
- Approximately one in 100 people was treated with antiparkinson medicines in 2022, with a regional variability going from 0.5% to 1%. Half of the users are older than 77 years and, on average, each subject has been treated for slightly more than 8 months, with an expenditure of EUR 359.69. For this last indicator, there is wide regional variability, with Emilia-Romagna having a cost per user 60% lower than Lombardy (EUR 186 vs 454) (Table 3.6.6c). This difference may depend on both the dispensing mode (direct vs agreed distribution) and the effect of different competitive biddings, when the distribution channel is the same. It should be noted that half of the subjects were treated for less than 4 months and 8.6% received only one prescription during the year with great variability among Regions (A.P. of Bolzano: 2.5 months).
- Dopa-derived medicines plain or in combination have a prevalence of use of 0.5%, whereas that of dopamine agonists is lower (0.3%). For these two categories, there is a difference of 5 years in the median age of users (80 vs 75), of one month in treatment days (6 vs 5 months), of EUR 244 in the average cost per user (EUR 157 vs 402) and of 3.7% for users with a single prescription (5.8% vs 9.5%).

Figure 3.6.6c Breakdown of prevalence of use and consumption of antiparkinson medicines under approved are regime and on behalf distribution in 2022

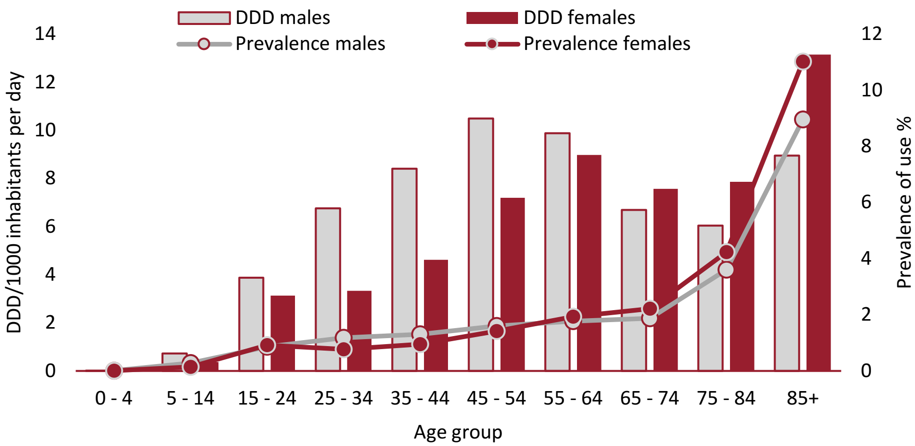

Table 3.6.6c Exposure and duration of therapy with antiparkinson medicines by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	0.8	0.8	0.8	78	352.98	252.4	120.0	7.5
Valle d'Aosta	0.7	0.8	0.8	77	441.70	278.2	133.3	8.0
Lombardy	0.6	0.6	0.6	77	453.56	263.3	133.3	6.3
A.P. of Bolzano	0.6	0.7	0.6	77	252.87	181.7	76.0	8.2
A.P. of Trento	0.6	0.5	0.5	75	382.45	258.5	133.9	6.7
Veneto	0.7	0.7	0.7	76	386.98	273.7	133.3	7.1
Friuli VG	0.6	0.6	0.6	78	392.82	280.7	133.3	6.7
Liguria	1.0	1.0	1.0	80	308.44	235.2	116.7	9.7
Emilia Romagna	0.7	0.7	0.7	78	186.44	208.6	110.0	8.0
Tuscany	0.8	0.9	0.8	79	333.21	225.6	102.0	10.7
Umbria	0.9	1.0	1.0	80	371.61	233.6	120.0	8.3
Marche	0.9	1.0	0.9	78	370.76	250.1	120.0	8.6
Lazio	0.8	0.8	0.8	78	450.09	279.5	140.0	8.1
Abruzzo	1.0	1.0	1.0	78	389.21	243.1	120.0	9.3
Molise	0.8	0.8	0.8	76	354.31	252.7	150.0	8.0
Campania	0.8	0.7	0.8	77	335.07	243.9	120.0	10.5
Puglia	0.9	0.8	0.9	77	364.78	238.8	120.0	7.9
Basilicata	0.9	0.8	0.8	76	348.56	260.7	140.0	8.9
Calabria	0.9	0.8	0.8	74	309.05	241.9	120.0	10.8
Sicily	0.9	0.9	0.9	76	300.18	243.0	130.0	9.6
Sardinia	0.8	0.8	0.8	73	362.16	248.9	140.0	9.5
Italy	**0.8**	**0.8**	**0.8**	**77**	**359.69**	**249.1**	**123.1**	**8.5**
North	0.7	0.7	0.7	78	361.75	251.3	122.7	7.3
Centre	0.8	0.8	0.8	78	395.68	254.6	122.8	9.0
South and Islands	0.9	0.8	0.8	76	336.06	243.3	123.6	9.5

Table 3.6.6d Exposure and duration of therapy with antiparkinson medicines by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
DOPA-derived agonists plain or in combination	0.5	0.4	0.5	80	157.37	170.4	133.3	5.8
Dopamine-agonists	0.2	0.3	0.3	75	401.98	140.0	58.5	9.5
MAO inhibitors	0.2	0.1	0.2	76	466.64	355.0	336.0	7.5
COMT inhibitors	<0.05	<0.05	<0.05	72	951.51	234.5	253.3	8.9
Anticholinergics	<0.05	<0.05	<0.05	73	161.95	165.3	140.0	27.5
Amantadine	0.1	0.1	0.1	58	29.11	103.1	80.0	14.7
Antiparkinson medicines	**0.8**	**0.8**	**0.8**	**77**	**359.69**	**249.1**	**123.1**	**8.5**

The wide regional variability in the use of antiparkinson medicines and some specific categories (MAO inhibitors and dopa-derived agonists plain or in combination) together with the fact that half of the subjects are treated for less than 4 months and 8.7% have received only one prescription during the year highlight the need to further disseminate and implement the recommendations contained in the guidelines on the diagnosis and treatment of Parkinson's disease, in order to pursue diagnostic and prescriptive appropriateness.
In this regard, a recent Chinese study has documented that people with Parkinson's disease have a high level of inappropriate prescriptions according to the Beers criteria updated by the American Society of Geriatrics.
The need to define complex therapeutic schemes, especially in the moderate and advanced forms of the disease, with constant use of medicines with multiple active ingredients, calls for a rational spreading in the territories of centres with experience in the diagnosis and treatment of this pathology and the drafting of a greater number of PDTAs, which define competences and activities for all stages of the disease. There is an urgent need to characterise prescribing patterns for this disease also for non-motor symptoms, which have a considerable influence on the quality of life of patients and their families, with rigorous and reliable evaluation tools in current clinical practice.

References

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3.6.7 Antimigraine medicines

- Over the past eight years, the DDD/1000-inhabitants-per-day consumption of medicines for the treatment of migraine has been almost stable, with slight average annual changes (CAGR +3.2%), and a 6.1% increase in 2022. Similarly, the total per capita expenditure remained almost stable (CAGR +1.3%). Conversely, compared to 2021, the average cost per day of therapy (EUR 3.67) has increased by 3.7%, entirely due to the marketing of monoclonal antibodies (EUR 5.24) (Figure 3.6.7a and Table 3.6.7a).
- Triptans account for almost all expenditure (68%; EUR 1.0 out of 1.47 per capita) and consumption (81%, with 0.9 DDD/1000 inhabitants per day) for the entire category. They have remained stable over the period 2014-2022 (CAGR: +0.5%) (Figure 3.6.7b).
- Monoclonal antibodies were authorised in February 2019 through a centralised procedure, and have recorded a 44.2% increase in expenditure compared to 2021. This has led to an increase in the total expenditure of the category (+10%). The single active ingredients show a significant increase over 2021, although still small in absolute values: erenumab (+9.4%), galcanezumab (+74.4%) and fremanezumab (+86.7%) (Table 3.6.7a). Consequently, when interpreting indicators of expenditure and consumption in the different subgroups, particularly monoclonal antibodies and triptans, the different modes of use for prophylaxis and acute treatment, respectively, must be taken into account. Among triptans, the one with the highest levels of consumption is eletriptan (+8%). This triptan is among those with the lowest consumption value (0.1 DDD).
- At regional level, there are no major changes in consumption and expenditure: North (+9.3% in expenditure and +5.5% in consumption), Centre (+10.3% and +6.4%), and South and Islands (+11.5% and +6.8%). The Region with the highest expenditure is Sardinia (EUR 1.92), with a value almost double than that of Umbria (EUR 1.06). This difference is determined by a higher usage (EUR 1.4 vs 0.8), while the average cost per DDD is similar. Among Regions, increases in consumption range from a minimum of 2.7% in Sicily to 16.1% in Abruzzo, whereas expenditure goes from +0.1% in the Autonomous Province of Bolzano to +22.7% in Molise (Table 3.6.7b). Molise is also the Region with the highest DDD cost (EUR 3.96).

Figure 3.6.7a Antimigraine medicines, temporal trend in consumption and average cost per day of therapy (2014-2022)

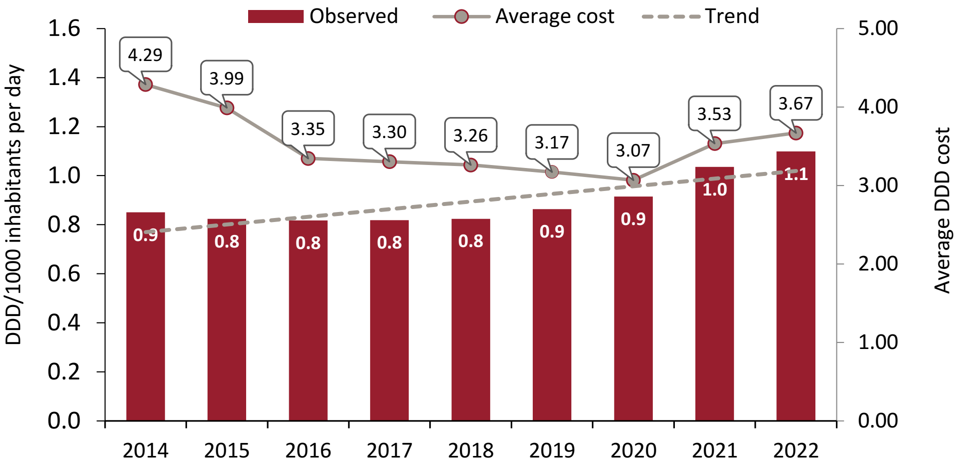


Table 3.6.7a Antimigraine medicines, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD Cost	Δ % 22-21
Triptans	1.00	-0.9	-3.5	0.9	-0.7	0.5	3.22	-0.2
Calcitonin gene-related peptide antagonists (monoclonal antibodies)	0.47	44.2	-	0.2	38.4	-	5.24	4.2
Other antimigraine medicines	0.00	10.0	-22.4	<0.05	9.2	-32.8	1.10	0.8
Ergot alkaloids	0.00	30.4	-42.5	<0.05	54.8	-40.6	0.24	-15.8
Antimigraine medicines	**1.47**	10.2	**1.3**	**1.1**	**6.1**	**3.2**	**3.67**	**3.9**
rizatriptan	0.24	7.6	1.8	0.2	7.2	2.5	2.87	0.4
sumatriptan	0.22	1.7	-1.5	0.2	0.7	-1.0	3.66	1.0
almotriptan	0.20	6.7	-5.7	0.2	6.8	1.0	3.21	-0.1
eletriptan	0.18	7.9	-2.3	0.1	8.0	4.8	3.50	0.0
erenumab	0.18	9.4	-	0.1	16.1	-	3.77	-5.7
galcanezumab	0.18	74.4	-	0.1	70.8	-	6.82	2.1
fremanezumab	0.12	86.7	-	<0.05	86.5	-	7.01	0.1
frovatriptan	0.08	-41.1	-13.0	0.1	-38.5	-6.5	3.06	-4.2
zolmitriptan	0.07	4.4	-0.5	0.1	5.2	0.8	2.92	-0.8
indomethacin/ caffeine/ prochlorperazine	0.00	10.1	1.5	<0.05	9.5	2.8	1.10	0.6

Figure 3.6.7b Antimigraine medicines, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) by subgroups with the highest expenditure

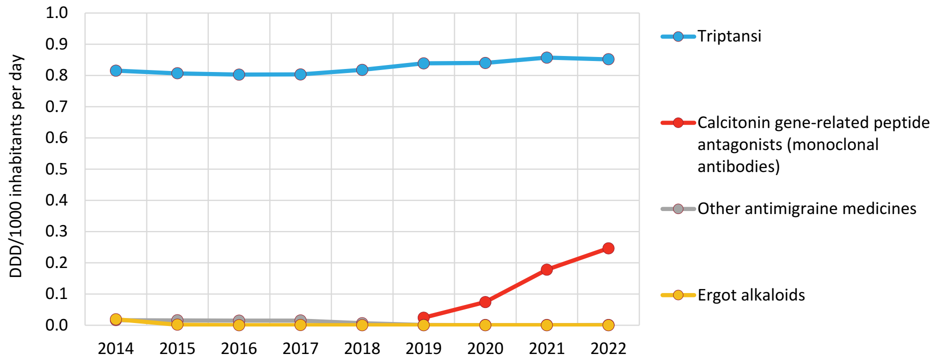


Table 3.6.7b Antimigraine medicines, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost
Piedmont	1.38	1.1	3.31	1.57	1.2	3.48	14.0	8.2	5.4	0.0	2.3	-2.2
Valle d'Aosta	1.62	1.3	3.43	1.69	1.3	3.57	3.9	-0.1	4.0	-0.7	1.3	-2.0
Lombardy	1.26	1.0	3.50	1.31	1.0	3.54	4.3	3.0	1.2	-0.7	2.0	-2.7
A.P. of Bolzano	1.60	1.1	3.83	1.60	1.1	3.86	0.1	-0.8	0.9	3.5	4.0	-0.5
A.P. of Trento	1.33	1.1	3.23	1.48	1.2	3.42	11.4	5.0	6.0	-0.4	1.3	-1.7
Veneto	1.51	1.2	3.49	1.71	1.3	3.67	13.2	7.5	5.3	0.8	2.9	-2.1
Friuli VG	1.69	1.3	3.64	1.84	1.3	3.82	8.5	3.6	4.8	1.2	3.3	-2.0
Liguria	1.16	0.9	3.38	1.41	1.1	3.66	21.5	11.9	8.6	1.9	3.4	-1.4
Emilia Romagna	1.76	1.4	3.56	1.90	1.4	3.66	8.1	5.1	2.9	2.5	4.1	-1.6
Tuscany	1.07	0.8	3.59	1.25	0.9	3.74	16.5	11.8	4.2	2.4	3.4	-1.0
Umbria	0.97	0.7	3.70	1.06	0.8	3.82	9.6	6.1	3.3	2.4	3.8	-1.4
Marche	1.37	1.0	3.60	1.47	1.1	3.69	7.5	4.9	2.4	2.0	4.1	-2.0
Lazio	1.53	1.1	3.67	1.65	1.2	3.81	8.1	4.0	3.9	2.7	4.6	-1.9
Abruzzo	1.37	1.0	3.57	1.68	1.2	3.77	22.4	16.1	5.4	4.6	5.7	-1.0
Molise	1.01	0.8	3.64	1.24	0.9	3.96	22.7	12.9	8.7	2.7	4.7	-2.0
Campania	1.07	0.8	3.70	1.21	0.9	3.86	12.3	7.5	4.5	4.0	5.0	-1.0
Puglia	1.35	1.1	3.51	1.48	1.1	3.65	9.6	5.4	3.9	1.4	3.3	-1.9
Basilicata	0.91	0.7	3.44	1.03	0.8	3.66	13.8	6.8	6.5	2.4	2.8	-0.4
Calabria	1.16	0.9	3.65	1.29	0.9	3.78	11.5	7.5	3.7	1.9	3.7	-1.7
Sicily	1.14	0.9	3.42	1.20	0.9	3.52	5.8	2.7	3.1	-0.6	2.0	-2.6
Sardinia	1.67	1.3	3.60	1.92	1.4	3.81	15.4	9.2	5.7	0.4	2.7	-2.2
Italy	**1.34**	**1.0**	3.53	**1.47**	1.1	**3.67**	**10.2**	**6.1**	**3.9**	1.3	3.2	-1.9
North	1.43	1.1	3.48	1.56	1.2	3.60	9.3	5.5	3.6	0.6	2.8	-2.1
Centre	1.32	1.0	3.64	1.45	1.1	3.77	10.3	6.4	3.7	2.5	4.2	-1.6
South and Islands	1.22	0.9	3.56	1.36	1.0	3.71	11.5	6.8	4.4	1.7	3.5	-1.8

Exposure in population

- Health Card data were collected to perform an analysis aimed at estimating exposure and intensity of use of antimigraine medicines in the general population. In 2022, a 0.6% prevalence of use is registered with a median age of users of 51 years, with no variability between regions (Table 3.6.7c). In line with prevalence data relating to migraine disorders available in the literature, clear differences are observed between men and women, which are consequently also reflected in the levels of consumption (Figure 3.6.7b). In detail, starting from the 15-24 age group, there is a progressive increase in the prevalence of use in women, which reaches about 2% between the ages of 45 and 54, and then decreases after 65 years of age. Consumption levels also follow the same trend, with a maximum value of 4.8 DDD reached in the same age group as prevalence. A similar, but significantly less pronounced trend is seen in men, with higher prevalence (0.5%) and consumption (0.7 DDD) values in the 45-54 age group.
- Each user received, on average during the year, at least one dose of medicine for about 50 days, with an expenditure of EUR 155 (Table 3.6.7c). The cost goes from EUR 126 in Calabria to EUR 198 in Sardinia, which also has the highest intensity of use with 58 days per user. For this indicator, too, the Northern Regions appear to have the highest levels of intensity of use with 50 days per user. This indicator could be affected by extreme values due, for example, to the inclusion of individuals who receive a prescription toward the end of the year or those who discontinue treatment early. Therefore, the median DDD indicator was also considered so as to detect, where present, any bias that could lead to an overestimation or underestimation of the average days of therapy calculated for each user. The results show that the median duration of treatment at national level falls to 24 days. This difference is also observed to a greater or lesser extent in single Regions. Slightly more than 22% of individuals received a single prescription in 2021, with Southern Regions recording the highest proportion (26.1%). Almost all prescriptions for antimigraine medicines are attributable to the category of triptans (Table 3.6.7d).

Figure 3.6.7c Breakdown of prevalence of use and consumption of antimigraine medicines under approved care regime and on behalf distribution in 2022

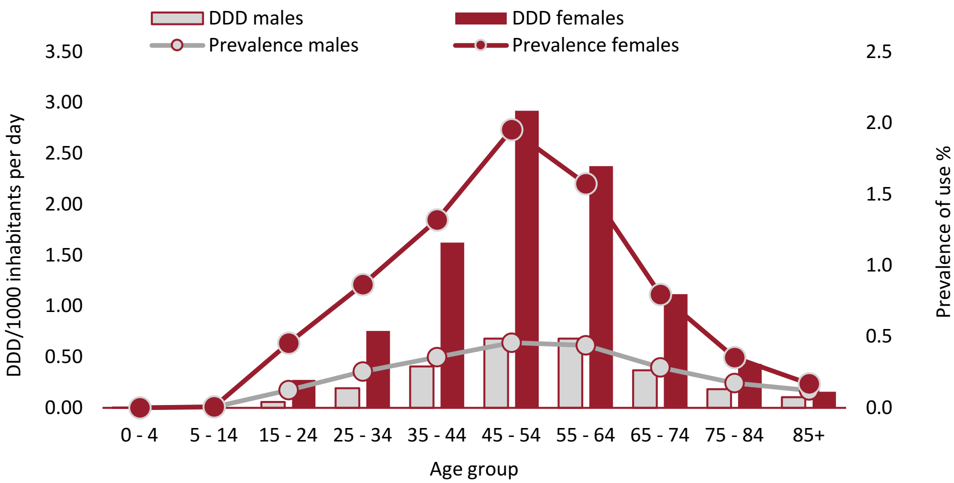


Table 3.6.7c Exposure and duration of therapy with antimigraine medicines by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	0.3	1.2	0.8	51	157.83	50.6	24.0	19.8
Valle d'Aosta	0.2	1.1	0.7	50	168.07	50.8	30.0	16.1
Lombardy	0.2	0.9	0.6	50	155.35	48.0	24.0	18.6
A.P. of Bolzano	0.2	1.0	0.6	50	136.89	41.9	24.0	19.6
A.P. of Trento	0.3	1.1	0.7	51	153.88	50.7	24.0	19.0
Veneto	0.3	1.1	0.7	51	167.34	52.5	24.0	19.7
Friuli VG	0.3	1.2	0.8	51	172.65	52.1	24.0	17.4
Liguria	0.3	0.9	0.6	52	147.60	47.0	24.0	22.6
Emilia Romagna	0.3	1.2	0.7	50	167.89	53.0	24.0	20.4
Tuscany	0.2	0.8	0.5	51	144.87	45.8	24.0	27.1
Umbria	0.2	0.7	0.4	51	150.35	46.4	24.0	24.1
Marche	0.3	1.0	0.7	51	144.70	45.7	24.0	23.0
Lazio	0.3	1.0	0.6	52	159.91	48.4	24.0	20.4
Abruzzo	0.2	0.9	0.6	51	147.04	46.7	21.0	26.6
Molise	0.2	0.7	0.5	51	155.64	46.5	22.0	23.7
Campania	0.2	0.7	0.5	51	134.95	41.4	18.0	25.9
Puglia	0.3	1.0	0.6	50	156.43	48.8	24.0	24.0
Basilicata	0.2	0.8	0.5	51	131.70	41.6	16.0	29.7
Calabria	0.3	0.9	0.6	52	126.13	38.7	12.0	30.3
Sicily	0.3	0.9	0.6	52	144.35	45.0	18.0	26.7
Sardinia	0.3	1.2	0.7	51	197.56	58.1	30.0	19.6
Italy	**0.3**	**1.0**	**0.6**	**51**	**155.07**	**48.2**	**24.0**	**22.1**
North	0.3	1.1	0.7	50	160.35	50.3	24.0	19.5
Centre	0.3	0.9	0.6	51	152.94	47.2	24.0	22.9
South and Islands	0.3	0.9	0.6	51	148.09	45.7	20.0	25.6

Table 3.6.7d Exposure and duration of therapy with antimigraine medicines by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Triptans	0.3	1.0	0.6	51	155.08	48.2	24.0	22.1
Calcitonin gene-related peptide antagonists (monoclonal antibodies)	-	<0.05	<0.05	39	1,332.70	60.0	60.0	
Other antimigraine medicines	<0.05	<0.05	<0.05	60	116.00	96.3	36.0	47.1
Ergot alkaloids	<0.05	<0.05	<0.05	74	37.16	51.9	20.0	54.5
Antimigraine medicines	**0.3**	**1.0**	**0.6**	**51**	**155.07**	**48.2**	**24.0**	**22.1**

In 2022 there was a slight increase in the consumption of migraine medicines. Triptans accounted for more than 80% of these pharmaceuticals. In this category, a marked gender difference in the prevalence of use is observed, with a peak in the 45-54 age group. In addition, a wide regional variability is observed, which cannot be explained by a marked difference in the frequency of the disease.

The marketing of monoclonal antibodies (erenumab, galcanezumab e fremanezumab) raises the question of evaluating the appropriateness of these active ingredients in the current clinical practice, in order to characterise a risk-benefit profile with respect to drug trials. In a recent 12-month observational study, conversion from chronic to episodic migraine was documented for about half of the patients treated with a monoclonal antibody.

It is desirable to increase the number of these types of studies in the different clinical subtypes of patients with episodic and chronic migraine. In this regard, studies are needed that characterise, on a population basis, the evolution of episodic to chronic clinical forms in order to characterise factors, such as chronic use of analgesics and/or monoclonal antibodies, allowing to define the appropriateness of treatments.

Recently, a systematic review of the methodology of real-world evidence-based observational studies has documented high heterogeneity and/or lack of predefined primary outcomes/objectives, definitions of outcome measures, and the use of longitudinal monitoring (e.g. headache diaries) in the evaluation of migraine medicines used in both episodic and chronic forms.

References

- Vandenbussche N, Pisarek K, Paemeleire K. Methodological considerations on real-world evidence studies of monoclonal antibodies against the CGRP-pathway for migraine: a systematic review. *J Headache Pain* 2023;24(1):75.

3.6.8 Antidementia medicines

- In 2022 the medicines used in dementia recorded a slight reduction in consumption compared to 2019 (+1.0%). Consumption stood at 2.4 DDD/1000 inhabitants per day, with a +0.6% average annual variation (CAGR) in the 2014-2022 period. Expenditure continued to decrease (-5.3%) compared to 2021, standing at EUR 0.35 per capita. In the same period, the average cost per day of therapy reduced by 70% (from EUR 1.19 to EUR 0.40) due to the patent expiry of all molecules belonging to the category (Figure 3.6.8a and Table 3.6.8a).
- In detail, all medicines, with the exception of donepezil (+6.6%) show reductions in expenditure (from -0.7% of memantine to -12% of rivastigmine) compared to 2021. Rivastigmine is the active ingredient that accounts for half of the entire category expenditure (EUR 0.16 per capita), and with a higher average cost per day of therapy (EUR 0.94; four times higher than that of donepezil). Galantamine is the molecule with the smallest impact on expenditure (EUR 0.01 per capita), due to low consumption (Table 3.6.8a). Memantine accounts for almost half of consumption (1.1 DDD/1000 inhabitants per day), up 5.1% compared to 2021. In the period 2014-2022, this medicines has registered an increase equal to 37% (Figure 3.6.8b).
- At macro-area level, the Centre shows higher consumption (3.0 DDD, +5.3%) compared to 2.2 DDD in the North and the South (+0.4% and -1.6%, respectively). Despite the low levels of consumption, the North registers the highest per capita expenditure (EUR 0.39) as a result of increased use of medicines with a higher average cost per DDD (EUR 0.49). At the level of the individual Regions, there is a minimum expenditure of EUR 0.11 in Piedmont and a maximum of EUR 0.72 in Lombardy. In terms of DDD, there is a decrease from 1.1 in the Autonomous Province of Trento to 4.3 in Lombardy. Finally, the average cost ranges from a minimum value of EUR 0.16 in Piedmont to EUR 0.94 in Lombardy. There is wide regional variability in all indicators compared 2021. The range of expenditure goes from -34.9% in Sicily to +56.3% in Valle d'Aosta. The range of consumption goes from -19% in Sicily to +38.3% in Valle d'Aosta. The range of average cost goes from -30.4% in Umbria to +28.5% in Molise.

Figure 3.6.8a Antidementia medicines, temporal trend in consumption and average cost per day of therapy (2014-2022)

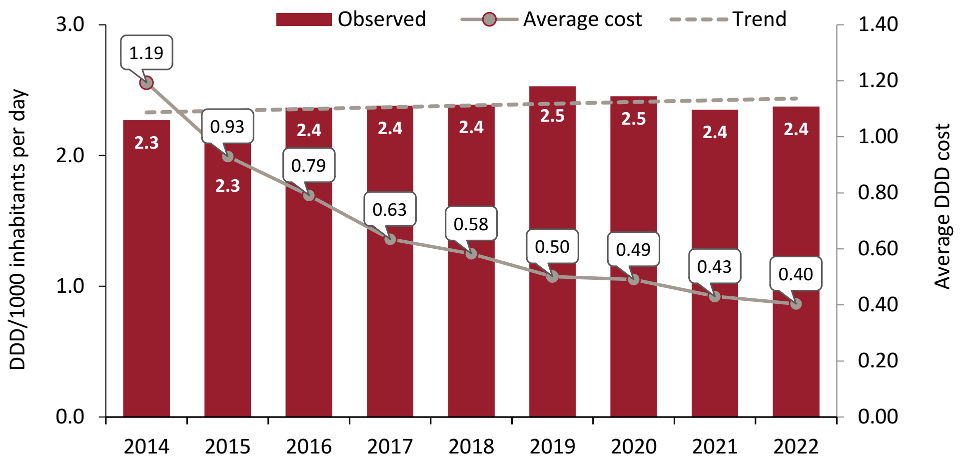


Table 3.6.8a Antidementia medicines, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD Cost	Δ % 22-21
Anticholinesterases	0.24	-7.4	-12.5	1.3	-2.7	-1.6	0.50	-4.8
Other antidementia medicines	0.11	-0.7	-11.5	1.1	5.9	4.0	0.29	-6.3
Antidementia medicines	**0.35**	**-5.3**	**-12.2**	**2.4**	**1.0**	**0.6**	**0.40**	**-6.2**
rivastigmine	0.16	-12.0	-14.7	0.5	-3.3	-4.1	0.94	-8.9
memantine	0.11	-0.7	-11.5	1.1	5.9	4.0	0.29	-6.3
donepezil	0.07	6.6	-3.9	0.8	-2.4	0.8	0.22	9.3
galantamine	0.01	-10.5	-11.9	<0.05	-0.1	-11.2	0.93	-10.4

Figure 3.6.8b Antidementia medicines, 2014-2022 temporal trend in consumption (DDD/1000 inhabitants per day) of the subgroups with the highest expenditure

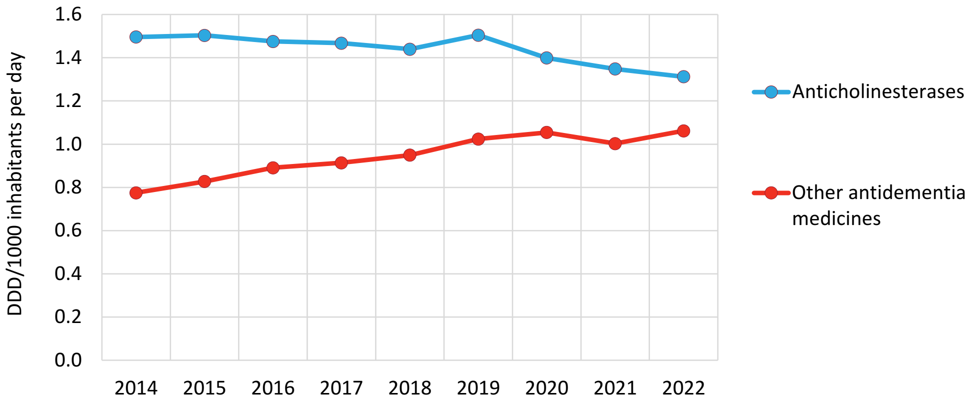


Table 3.6.8b Antidementia medicines, regional trend in per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD Cost
Piedmont	0.11	1.8	0.17	0.11	2.0	0.16	2.1	8.1	-5.6	-21.3	-1.4	-20.3
Valle d'Aosta	0.19	1.6	0.33	0.30	2.2	0.37	56.3	38.3	13.0	-11.9	1.1	-12.8
Lombardy	0.75	2.1	0.98	0.72	2.1	0.94	-4.1	-0.2	-3.9	-5.1	0.5	-5.5
A.P. of Bolzano	0.88	4.3	0.56	0.67	4.0	0.47	-23.7	-7.7	-17.4	-7.7	1.6	-9.1
A.P. of Trento	0.14	1.1	0.36	0.14	1.1	0.36	-3.0	-0.4	-2.6	-15.0	-2.4	-12.9
Veneto	0.20	2.4	0.22	0.21	2.4	0.24	5.4	-2.3	7.9	-17.2	0.1	-17.2
Friuli VG	0.44	2.0	0.59	0.43	2.0	0.58	-1.6	0.4	-2.1	-9.6	0.4	-9.9
Liguria	0.33	3.7	0.24	0.33	3.6	0.25	1.9	-1.9	3.9	-15.0	0.1	-15.1
Emilia Romagna	0.16	2.0	0.22	0.17	2.0	0.24	10.2	1.0	9.1	-14.3	0.6	-14.8
Tuscany	0.28	3.2	0.24	0.29	3.3	0.24	1.4	3.6	-2.1	-17.3	0.9	-18.0
Umbria	0.94	4.1	0.63	0.68	4.3	0.44	-27.3	4.4	-30.4	-11.3	3.2	-14.0
Marche	0.27	2.5	0.30	0.27	2.4	0.31	-1.0	-3.6	2.6	-14.8	-0.8	-14.2
Lazio	0.31	2.6	0.33	0.28	2.8	0.27	-9.6	9.3	-17.3	-15.1	2.4	-17.0
Abruzzo	0.54	3.7	0.40	0.58	3.9	0.40	6.8	6.5	0.3	-15.6	0.9	-16.3
Molise	0.18	2.8	0.18	0.23	2.7	0.23	23.5	-3.9	28.5	-12.3	6.0	-17.3
Campania	0.26	2.4	0.30	0.23	2.5	0.25	-12.5	3.1	-15.2	-14.0	2.2	-15.8
Puglia	0.59	2.2	0.72	0.58	2.3	0.70	-1.6	1.9	-3.5	-5.6	1.2	-6.8
Basilicata	0.62	2.3	0.75	0.62	2.4	0.70	0.6	7.3	-6.2	-3.5	4.4	-7.6
Calabria	0.31	2.1	0.40	0.29	2.0	0.40	-8.4	-7.2	-1.2	-17.4	-1.2	-16.4
Sicily	0.20	1.7	0.34	0.13	1.3	0.27	-34.9	-19.0	-19.6	-18.4	-3.3	-15.6
Sardinia	0.17	2.1	0.22	0.17	2.2	0.21	-1.3	3.7	-4.8	-22.4	-0.5	-22.0
Italy	**0.37**	**2.4**	**0.43**	**0.35**	**2.4**	**0.40**	**-5.3**	**1.0**	**-6.2**	**-12.2**	**0.6**	**-12.7**
North	0.40	2.2	0.50	0.39	2.2	0.49	-2.2	0.4	-2.6	-10.1	0.1	-10.2
Centre	0.34	2.9	0.33	0.31	3.0	0.28	-9.5	5.3	-14.0	-15.3	1.5	-16.6
South and Islands	0.34	2.2	0.42	0.31	2.2	0.39	-8.0	-1.6	-6.5	-13.3	0.4	-13.6

Exposure in population

- Health Card data were collected to perform an analysis aimed at estimating exposure to and intensity of use of antidementia medicines in the general population. Exposure data of antidementia medicines are in line with data on the prevalence of the disease that tends to occur mainly in the 75+ age group. In detail, the prevalence of use of these medicines goes from 0.4% in the 65-74 age group, up to 2.5% in the 85+ age group. Women have a higher level of exposure and consumption in all age groups, particularly in the 85+ (2.9% vs 2.5% and 18.5 vs 15.9 DDD) (Figure 3.6.8d).
- In the overall population, the prevalence of use is 0.3% with some differences between Regions (Table 3.6.8c). Value range from 0.1% in the Autonomous Province of Trento to 0.6% in Abruzzo and Umbria. As expected, the median age of users is 82 years and there are no differences among the individual Regions.
- On average, each user has remained in treatment for 8 months, with an expenditure of EUR 102.04 and a wide variability between Regions: from EUR 47.57 in Piedmont to EUR 231.66 in Lombardy (approx. 400% difference). Half of users remain in treatment for less than 7 months, with no substantial differences between geographical areas. In detail, values range from 6 months in Valle d'Aosta to approx. 10 in the Autonomous Province of Bolzano. Nationwide, 7.8% of users received only one prescription during the year. The Regions with the highest proportion of users with only one prescription are Sardinia, Lazio (13.3% and 11%, respectively). By contrast, Friuli Venezia Giulia shows the lowest proportion (less than 4%).
- The prevalence of use at the level of individual categories is similar (0.2%), while the cost per user of anticholinesterases is about twice as much as other antidementia medicines (115 vs 64). Similarly, DDDs per user are 10% higher (223 vs 202 days) (Table 3.6.8d).

Figure 3.6.8c Breakdown of 2022 prevalence of use and consumption of antidementia medicines under approved care regime and on behalf distribution

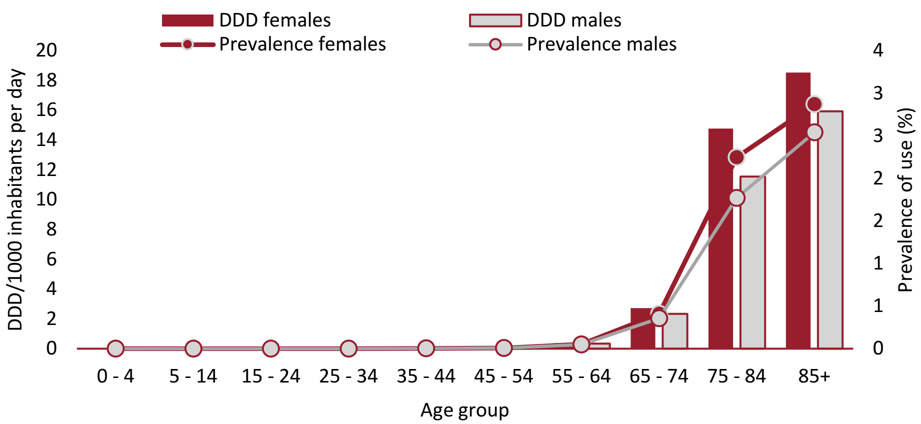


Table 3.6.8c Exposure and duration of therapy with antidementia medicines by Region under approved care regime and on behalf distribution (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	0.2	0.4	0.3	82	47.57	237.8	209.1	5.8
Valle d'Aosta	0.3	0.4	0.3	82	92.84	213.3	180.0	4.2
Lombardy	0.2	0.4	0.3	82	231.66	246.9	224.0	4.0
A.P. of Bolzano	0.3	0.4	0.3	83	178.62	297.1	290.5	7.8
A.P. of Trento	0.1	0.1	0.1	81	87.62	244.1	224.0	6.3
Veneto	0.2	0.4	0.3	82	60.24	253.4	224.0	5.0
Friuli VG	0.2	0.3	0.3	82	160.63	259.3	224.0	3.6
Liguria	0.4	0.7	0.5	83	58.17	243.8	205.3	8.2
Emilia Romagna	0.2	0.3	0.2	82	57.94	212.4	196.0	8.5
Tuscany	0.3	0.5	0.4	83	59.62	230.8	190.7	10.1
Umbria	0.4	0.7	0.6	83	118.59	246.5	224.0	7.8
Marche	0.2	0.5	0.4	83	73.59	235.9	224.0	7.6
Lazio	0.3	0.5	0.4	82	71.27	232.1	196.0	11.0
Abruzzo	0.4	0.7	0.6	82	96.97	240.7	203.4	8.3
Molise	0.3	0.5	0.4	82	64.73	228.0	185.1	10.1
Campania	0.3	0.4	0.4	80	55.91	222.9	205.3	9.6
Puglia	0.3	0.4	0.3	81	161.75	232.4	196.0	8.7
Basilicata	0.3	0.4	0.4	82	180.37	254.7	233.3	9.3
Calabria	0.2	0.3	0.3	81	85.62	227.2	196.0	10.7
Sicily	0.1	0.2	0.2	80	73.31	253.4	224.0	4.3
Sardinia	0.2	0.4	0.3	82	59.38	229.2	196.0	13.3
Italy	**0.2**	**0.4**	**0.3**	**82**	**102.04**	**237.7**	**205.3**	**7.8**
North	0.2	0.4	0.3	82	127.67	243.78	224.00	5.51
Centre	0.3	0.5	0.4	82	72.69	233.59	196.00	10.02
South and Islands	0.2	0.4	0.3	81	92.55	233.13	205.34	8.89

Table 3.6.8d Exposure and duration of therapy with antidementia medicines by subgroup under approved care regime and on behalf distribution (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Anticholinesterases	0.1	0.2	0.2	81	115.75	223.0	192.9	7.3
Other antidementia medicines	0.1	0.2	0.2	82	64.34	202.4	196.0	9.8
Antidementia medicines	**0.2**	**0.4**	**0.3**	**82**	**102.04**	**237.7**	**205.3**	**7.8**

The slight increase in the consumption of antidementia medicines in 2022 compared to 2021 is due to the significant increase in memantine against a reduction in the three cholinesterase inhibitors (dopenepzil, rivstigmine, galantamine). This phenomenon is probably linked to a greater use of memantine not only in treating cognitive disorders in the moderate to severe phase of the disease but also for the good tolerability in treating frequent behavioural disorders.
The regional variability in the use of memantine is probably affected by the different territorial application of Note 85, in particular in relation to the possibility of a concomitant use of cholinesterase inhibitors and memantine in the moderate forms of the disease, requiring a more in-depth study, and in the off-label use of memantine to treat behavioural disorders as well.
There is a need to further characterise the use of cholinesterase inhibitors in very early stages of the disease, between mild cognitive impairment (MCI) and early dementia. Between off-label and indicated use of these medicines, this subgroup of patients represents the target category of the new antidementia medicines currently being tested and authorised.

3.7 Respiratory system

In 2022 medicines for respiratory system are the seventh therapeutic category with the highest public expenditure, amounting to EUR 1,549.1 million and 6.3% of total public expenditure (+17.4% compared to 2021) (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these medicines is equal to EUR 26.25, mainly due to the pharmaceutical expenditure under approved care regime (EUR 15.88 per capita), down 1.5% compared to the previous year. Purchases by public health facilities account for a lower proportion (EUR 10.37 per capita), despite a +66.2% increase compared to 2021 (Table 3.1).
Consumption for this pharmaceutical category was equal to 43.11 DDD/1000 inhabitants per day, up 3.1% compared to 2021 (Table 3.2).
Analysis of the drug use profile by age and gender, including approved care regime and on behalf distribution, shows that children under the age of 5 and subjects over 75 years of age are those with the highest prevalence of use. The analysis of consumption shows that DDDs tend to increase with age and the highest value is reached in the 75+ age group (98.88 DDD/1000 inhabitants per day), probably due to the treatment of chronic obstructive pulmonary disease (COPD). With regard to gender differences, there is a higher prevalence of use in men up to the age of 24 and over 75 years. At the same time, per capita expenditure borne by the NHS also varies with patient age, reaching a maximum value of EUR 47.04 per capita in the 75+ age group, with a different contribution from the two genders (EUR 61.16 in men and EUR 37.51 in women).
As regards the approved care regime, per capita expenditure was equal to EUR 15.88, with a 1.9% decrease in absolute values compared to 2021. This trend was determined by a decrease in prices (-3.8%), average DDD cost (-4%) and a slight shift towards less expensive medicines (mix effect: -0.1%) (Table 3.9). On the other hand, consumption is increasing, which stands at 40.8 DDD per 1000 inhabitants die (+2.1% compared to 2021). Within this category, beta-adrenergics in combination with corticosteroids or other medicines, excluding anticholinergics, represent the most expensive and consumed category, with EUR 7.2 per capita and 12.4 DDD/1000 inhabitants per day, respectively. The beclomethasone/formoterol combination represents the medicine with the highest impact on expenditure (15.9%), followed by vilanterol/fluticasone furoate (13.3%) (Table 3.10). These active substances belong to the LABA+ICS group (long-acting beta2-agonists and inhaled corticosteroids). They are used for the treatment of asthma and COPD and fall within the top 30 active substances for expenditure, with values equal to EUR 149.3 and 124.7 million, respectively. The formoterol/budesonide combination ranks last with EUR 78.5 million (Table 3.11). Medicines with the most significant changes in expenditure and consumption in 2022 compared 2021 were budesonide (expenditure: +68.2%, consumption: +56.4%) and the vilanterol/umeclidinium combination (expenditure: +56.3%, consumption: +64.6%) (Table 3.10).
Among the top 30 active ingredients with the highest average cost per day of therapy, three medicines in this category can be found: glycpyrronium/beclomethasone/formoterol, vilanterol/umeclidinium/fluticasone furoate (LABA+LAMA+ICS), formoterol/budesonide, formoterol/beclomethasone, vilanterol/fluticasone furoate (LABA/ICS), umeclidinium, aclidinium and thiotropium (LAMA) and, with an average cost per DDD of EUR 3.02, EUR

2.73, EUR 1.80, EUR 1.72, EUR 1.61, EUR 1.51, EUR 1.51 and EUR 1.50, respectively (Table 3.13). The triple combinations of glycopyrrolate/beclomethasone/formoterol and vilanterol/umeclidinium/fluticasone furoate are in the top 30 active ingredients with the greatest change in pharmaceutical expenditure under approved care regime compared to 2021, registering an increase of 30.2% and 15.2%, respectively (Table 3.15). This list also includes beclomethasone, an inhaled cortisonic that shows a +38.4% change in expenditure, mainly due to an increase in consumption (+35.3%) (Table 3.15). The top 30 active ingredients with the greatest reduction in expenditure include salmeterol/fluticasone (-28.2%), aclidinium (-18.7%), tiotropium (-16.3%), umeclidinium (-15.4%), vilanterol/fluticasone furoate (-10.1%) and beclometasone/formeterol (-6.0%) (Table 3.16). No medicines in the respiratory system category are included in the top thirty most used active ingredients dispensed under approved care regime (Table 3.17).
In terms of purchases by public health facilities, compared to 2021, there was an increase in expenditure (+65.4%) and in consumption (+14.3%), against a reduction in prices (-4.6%) and a shift towards the purchase of more expensive pharmaceuticals (mix effect: +51.7%) (Table 3.19). The medicines with the greatest impact on expenditure for this category are the elexacaftor/tezacaftor/ivacaftor combination (33.7%) and ivacaftor (29.3%), used to treat cystic fibrosis, followed by omalizumab (10.4%), used in allergic asthma due to IgE hyperproduction (Table 3.20). The elexacaftor/tezacaftor/ivacaftor combination is included in the list of the first 30 active ingredients for expenditure by public health facilities, with a total expenditure of EUR 206.2 million, followed by ivacaftor with EUR 179.4 million. Both are also included in the first 30 active ingredients purchased by public health facilities which have registered a change in expenditure compared to 2021: the elexacaftor/tezacaftor/ivacftor combination shows a 308.6% increase in per capita expenditure, whereas ivacaftor shows a 132.5% increase in per capita expenditure. They are followed by mepolizumab, with +39.9% increase (Table 3.23). The first two are also among the top 30 active ingredients by average cost per day of therapy purchased by public health facilities: ivacaftor has an average DDD cost of EUR 429 EUR and a per capita expenditure of EUR 3.04; the elexacaftor/tezacaftor/ivacaftor combination has an average DDD cost of 289.3 EUR and a per capita expenditure of EUR 3.50 (Table 3.25). The top 30 active ingredients with the highest expenditure in terms of medicines under approved care regime and purchased by public health facilities include the ivacaftor/elexacaftor/tezacaftor combination (expenditure: EUR 206.2 million), accounting for 1.4% of total expenditure; ivacaftor (expenditure: EUR 179.4 million), accounting for 1.2% of total expenditure, and the formoterol/beclometasone combination (expenditure: EUR 151.6 million), accounting for 1% of total expenditure (Table 3.28). As regards expenditure and consumption by group and subgroup, medicines for asthma and COPD and for cystic fibrosis are the most significant in the category (Table 3.30). The former have a total expenditure of EUR 1,040.5 million, and a consumption of 687.6 DDD. They are mainly dispensed under approved care regime, where they register a per capita expenditure of EUR 14.77 and a consumption of 30.4 DDD/1000 inhabitants per day. The share of asthma and COPD medicines dispensed under the direct purchasing channel is minimal, with a per capita expenditure of EUR 2.87 and 1.5 DDD/1000 inhabitants. The subgroup of monoclonal antibodies for asthma therapy (EUR 2.66 per capita) is the most relevant. The therapeutic subgroups with the highest expenditure are LABA+ICS (EUR 422.6 million), followed by

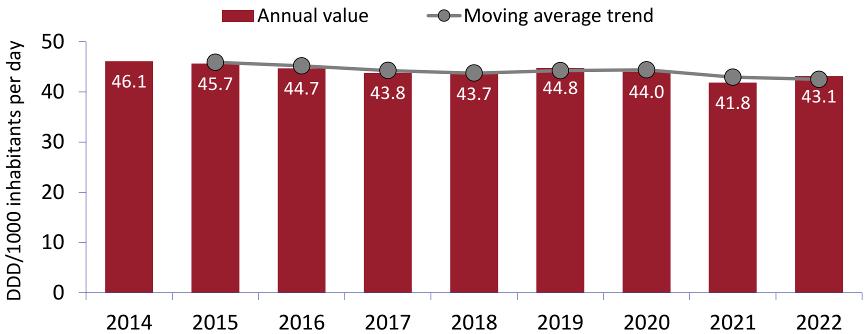
monoclonal antibodies (EUR 156.8 million), LAMA (EUR 149.4 million) and inhaled cortisonics (ICS, EUR 103.6 million) (Table 3.30). Medicines for cystic fibrosis show a total expenditure of EUR 430.8 million, and 1.8 million daily doses dispensed. They are dispensed exclusively through the direct distribution channel, with a per capita expenditure of EUR 7.30. The subgroups with the highest expenditure and consumption is represented by CFTR modulators (EUR 418.2 million in expenditure and 1.2 million DDD).
For further information on the use of medicines related to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region. These analyses focused on medicines for asthma and COPD and on medicines for the treatment of cystic fibrosis (Table 3.7.1a and following).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

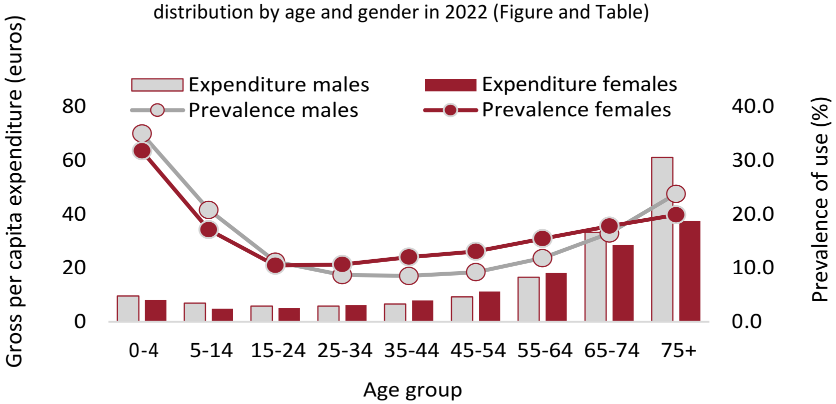
Respiratory system

Public expenditure* in EUR million (% over total)	**1,549.1**	**(6.3)**
Δ % 2022-2021		17.4
Regional range of gross per capita expenditure:	17.4	20.4
DDD/1000 inhabitants per day* (% over total)	**43.1**	**(3.3)**
Δ % 2022-2021		3.1
Regional range DDD/1000 inhabitants per day:	31.8	61.3

** includes prescriptions under approved care regime and purchases by public health facilities*



Breakdown of prevalence of use and consumption under approved care regime and on behalf distribution by age and gender in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	9.7	8.1	8.9	27.5	22.5	25.1
5-14	7.0	4.9	6.0	24.3	16.7	20.6
15-24	5.9	5.1	5.5	22.6	19.1	20.9
25-34	5.9	6.1	6.0	20.0	20.9	20.5
35-44	6.7	8.0	7.4	20.2	24.8	22.5
45-54	9.3	11.3	10.3	25.3	33.1	29.3
55-64	16.6	18.1	17.4	38.8	46.1	42.6
65-74	33.2	28.6	30.8	67.7	64.8	66.1
75+	61.2	37.5	47.0	121.3	83.8	98.9

3.7.1 Medicines for asthma and COPD

- In the last nine years there has been a decrease in the consumption of medicines for asthma and COPD, about 7.9% in 2022 compared to 2014 and with an average annual change of -1.0%. In 2022, consumption was 31.9 DDD, up 3.1% compared to 2021. Expenditure stands at EUR 17.64 per capita, an increase of 1.5% compared to the previous year, and an average annual change in the period 2014-2022 of +0.8%. A day of therapy with these drugs has a cost of EUR 1.51, a reduction of 1.6% compared to the previous year (Figure and Table 3.7.1a).
- The association between long-acting beta2 agonists and inhaled corticosteroids (LABA+ICS) remains the highest-prescription category in 2022 (12.4 DDD/1000 inhabitants per day) with a per capita expenditure of EUR 7.16, although both values have decreased compared to 2021 by 2.5% and 8% respectively; moreover consumption has increased by 2.1% since 2014 (Figure 3.7.1b). In terms of expenditure, monoclonal antibodies are second (used in uncontrolled severe asthma with other therapies) and show an increase in expenditure by more than 25% (EUR 7.16) and an average DDD cost of EUR 27.68. They are followed by long-acting anticholinergic/antimuscarinic (LAMA), with EUR 2.53 per capita and 4.7 DDD (both indicators are reduced compared to 2021), and by ICS with EUR 1.76 and 4.8 DDD, with 35% higher increases for both indicators. The growing trend is confirmed as regards consumption for the triple association LAMA+LABA+ICS (+31%), and for expenditure (+27.9%), probably as a result of the amendment of the AIFA Note 99, which extended the possibility of prescribing also the triple association (for further details see Appendix 1). Significant increases in expenditure and consumption also affected the associations LABA+LAMA (expenditure: +16%, consumption: +20%), while LABAs have decreased the most compared to 2021 (expenditure: -22%, consumption: -20%).
- The first two major substances are confirmed to be beclomethasone+formoterol and vilanterol+fluticasone with an increase of the former (+3.6%) and a reduction by 2.9% of the latter compared to 2022. Mepolizumab and benralizumab increased by 40.7% and 34.7%, respectively, while omalizumab increased by only 12%.
- In terms of consumption, there is a North-South gradient. In fact, the Southern Regions show higher consumption (34.6 DDD) and average cost per day of therapy (EUR 1.56) than the national average;in contrast, the Northern Regions show lower consumption (29.9 DDD) and average cost per day of therapy (1.48 DDD). Compared to 2021, there is an increase in consumption in all regions except Umbria, Puglia, Basilicata, and Calabria (with variations ranging from -1.9% for Umbria and -0.8% in Puglia); the PA Trento recorded the largest increases (+11.8 %) and Campania remained the region with highest consumption (41.9 DDD, about 70% higher than the PA Bolzano with 24.8 DDD). The average cost per DDD is reduced in all regions except Puglia and Calabria, ranging from a minimum of EUR 1.37 of the PA Trento to a maximum of 1.75 in Basilicata (Table 3.7.1b).

Figure 3.7.1a Therapies for asthma and COPD, temporal trend of consumption and average cost per day of therapy (2014-2022)

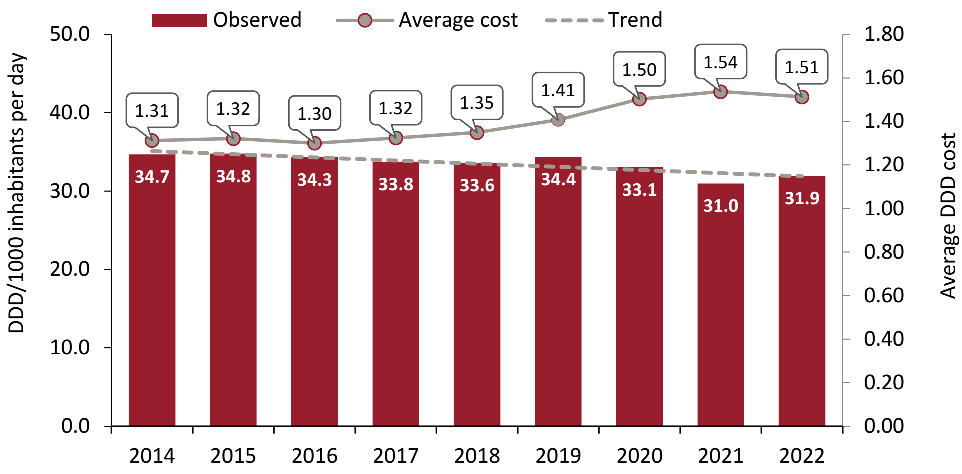


Table 3.7.1a Therapies for asthma and COPD, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	*Per capita* expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
LABAs+ICS	7.16	-8.0	-1.2	12.4	-2.5	2.1	1.58	-5.6
Monoclonal antibodies	2.66	25.4	28.7	0.3	25.4	31.2	27.68	0.0
LAMAs	2.53	-17.5	-3.4	4.7	-14.8	-2.2	1.49	-3.2
ICSs	1.76	37.5	-4.9	4.8	35.6	-5.0	1.01	1.4
LAMAS+LABAS+ICSs	1.29	27.9	-	1.2	31.0	-	2.83	-2.3
LABAs+LAMAs	0.96	16.0	259.1	1.3	20.0	154.0	1.94	-3.3
Antileukotrienes (LTRAs)	0.46	-0.3	-2.0	2.0	-0.7	-0.6	0.62	0.4
LABAs	0.28	-22.4	-14.0	0.8	-20.4	-13.7	0.98	-2.6
SABAs	0.20	16.6	-4.8	2.6	10.4	-3.7	0.20	5.6
SABAs+SAMAs	0.15	32.0	-4.2	0.6	31.1	-4.4	0.66	0.7
SABAs+ICSs	0.11	6.3	-6.5	0.2	6.8	-6.3	1.20	-0.4
SAMAs	0.05	16.2	-9.7	0.6	22.9	-3.8	0.23	-5.5
Theophylline-based bronchodilators	0.05	-5.6	-9.7	0.4	-9.0	-11.7	0.35	3.7
PDE-4 inhibitors	<0.005	-16.7	-14.1	<0.05	-15.7	-13.6	1.54	-1.2
Medicines for asthma and COPD	**17.64**	**1.5**	**0.8**	**31.9**	**3.1**	**-1.0**	**1.51**	**-1.6**
formoterol/ beclomethasone	2.57	2.7	4.7	4.1	3.6	5.3	1.70	-0.9
vilanterol/ fluticasone furoate	2.13	-10.1	-	3.7	-2.9	-	1.60	-7.4
formoterol/ budesonide	1.33	-6.0	1.5	2.1	-1.0	4.0	1.78	-5.0
omalizumab	1.08	11.1	15.0	0.1	12.5	18.5	25.36	-1.3
tiotropium	1.01	-16.2	-10.8	1.9	-14.4	-9.3	1.46	-2.1
salmeterol/ fluticasone	0.90	-28.2	-18.8	2.1	-12.7	-12.2	1.18	-17.7
mepolizumab	0.88	39.8	-	0.1	40.7	-	29.96	-0.6
umeclidinium	0.72	-15.4	-	1.3	-11.0	-	1.51	-5.0
benralizumab	0.70	34.7	-	0.1	34.7	-	28.99	-0.1
formoterol/ glycopyrronium/ beclomethasone	0.68	29.1	-	0.6	30.2	-	2.96	-0.9

Figure 3.7.1b Therapies for asthma and COPD, temporal trend of consumption (DDD/1000 inhab. per day) of most expensive subgroups (2014-2022)

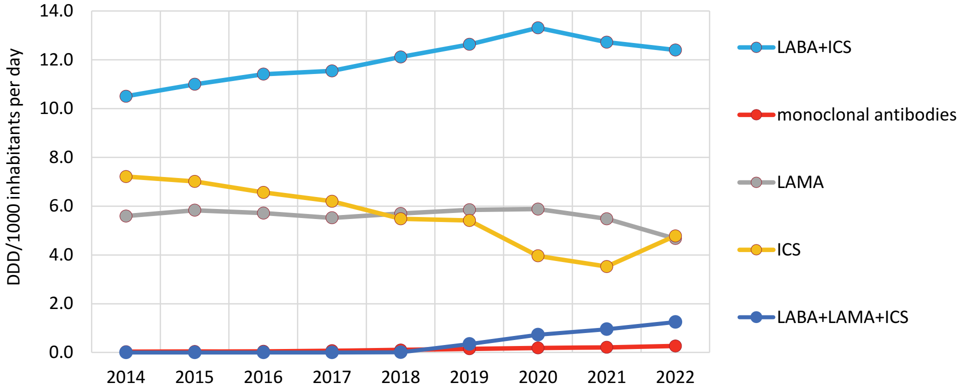


Table 3.7.1b Medicines for COPD, temporal trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	16.33	28.0	1.60	16.49	28.5	1.59	1.0	1.9	-0.9	0.6	-1.3	1.9
Valle d'Aosta	16.13	29.6	1.49	16.01	30.5	1.44	-0.7	3.0	-3.6	-2.7	-3.3	0.6
Lombardy	16.09	28.8	1.53	16.77	30.4	1.51	4.2	5.4	-1.2	0.9	-0.3	1.2
PA Bolzano	12.89	23.7	1.49	13.10	24.8	1.45	1.6	4.5	-2.8	0.3	-0.9	1.1
PA Trento	14.64	28.8	1.39	16.07	32.2	1.37	9.8	11.8	-1.8	1.1	0.2	0.9
Veneto	14.29	26.2	1.50	14.93	27.9	1.47	4.5	6.6	-2.0	1.1	-0.6	1.8
Friuli VG	14.33	27.5	1.42	14.68	28.9	1.39	2.5	4.9	-2.4	0.5	-0.6	1.1
Liguria	17.59	31.2	1.54	17.99	32.3	1.53	2.3	3.5	-1.2	1.6	-0.4	1.9
Emilia R.	15.23	29.4	1.42	15.96	31.8	1.38	4.8	8.0	-3.0	0.8	-0.6	1.5
Tuscany	17.74	31.8	1.53	17.45	32.2	1.49	-1.6	1.1	-2.7	0.9	-0.9	1.8
Umbria	16.17	28.9	1.53	15.41	28.3	1.49	-4.7	-1.9	-2.9	0.3	-1.5	1.8
Marche	15.95	27.1	1.61	15.69	27.7	1.55	-1.6	2.3	-3.8	-0.5	-1.5	1.0
Lazio	19.00	33.9	1.54	19.06	34.6	1.51	0.4	2.2	-1.8	0.2	-1.6	1.8
Abruzzo	16.51	27.9	1.62	16.70	29.5	1.55	1.2	5.8	-4.4	1.5	-0.1	1.6
Molise	14.26	24.1	1.62	14.18	25.0	1.55	-0.6	3.8	-4.2	-0.1	-1.5	1.4
Campania	22.35	41.4	1.48	22.37	41.9	1.46	0.1	1.3	-1.2	1.1	-0.5	1.7
Puglia	19.90	33.1	1.65	19.84	32.9	1.65	-0.3	-0.8	0.5	0.3	-2.7	3.0
Basilicata	21.79	34.0	1.75	21.49	33.7	1.75	-1.4	-0.9	-0.5	1.9	-1.7	3.7
Calabria	18.76	30.4	1.69	18.66	30.1	1.70	-0.5	-1.2	0.6	1.2	-1.7	2.9
Sicily	17.90	31.1	1.58	18.18	31.5	1.58	1.5	1.5	0.1	1.3	-1.2	2.5
Sardinia	18.28	33.8	1.48	18.55	35.2	1.44	1.5	4.1	-2.5	-0.6	-1.7	1.1
Italy	**17.38**	**31.0**	**1.54**	**17.64**	**31.9**	**1.51**	**1.5**	**3.1**	**-1.6**	**0.8**	**-1.0**	**1.8**
North	15.60	28.3	1.51	16.16	29.9	1.48	3.6	5.4	-1.7	0.9	-0.6	1.5
Centre	17.98	31.9	1.54	17.83	32.5	1.51	-0.8	1.6	-2.4	0.3	-1.4	1.7
South and Islands	19.57	34.2	1.57	19.65	34.6	1.56	0.4	1.2	-0.8	0.9	-1.3	2.2

Exposure and adherence in population

- In 2022, the national prevalence of medicines for asthma and COPD was 11.1%, up compared to 8.9% in 2021, probably due to the effect of AIFA Note 100, which extended the possibility by GPs of prescribing these drugs. Prevalence, similar to consumption, shows higher levels in extreme age groups; in particular in the paediatric population 0-4 years, with 33.8% and 30.7% in males and females respectively, and in the 85-year-old (and over) age group with 23.8% and 16.6% respectively in males and females (Figure 3.7.1c). The differences between males and females are more marked in terms of consumption; in particular, in the over 85-year-old group, males show a consumption level by 82% higher than females. These differences, albeit to a lesser extent, remain in the paediatric age group. In preschool children, high use is likely associated with acute infectious episodes affecting the upper respiratory tract, while in older adults consumption may be associated with chronic treatment of COPD, the most prevalent clinical condition in males over 65.
- Comparing the various geographical areas, there are higher prevalence levels of use in the South (12.4%), compared to Central (11.3%) and Northern Italy (9.9%). The median age of users decreased by three years compared to 2021 (50 years), and for each user, on average, around 99 DDD were dispensed, compared with a cost per user of EUR 137.67. Around 43% of users received only one prescription in the year, without substantial differences between geographical areas (Table 3.7.1c). Half of the users remain in treatment for less than 30 days. The prevalence of use in Campania is about twice than Piedmont (15.3% vs 8.4%). Piedmont shows the lowest prevalence of use but the highest average cost per DDD (EUR 191.39), 76% higher than Emilia Romagna (EUR 108.79).
- As regards the therapeutic categories, ICS have the highest exposure values (6.6%); however, these drugs are used as needed and in particular in asthma the median age of users is 38 years, half of the users receive less than 13 doses in one year and 71% receive only one prescription. Another high-exposure category is the combination LABA+ICS (3.1%), used predominantly for COPD; in fact, the median age of users is 61 years and the median duration of treatment is 3 months. They are folloed by SABAs (2.2%) with a median age of 32 years and an average cost per user of EUR 8.22, the lowest in the category. In contrast, monoclonal antibodies have an average annual cost per user of EUR 5,690 although with low prevalence levels (0.01%), but 50% of users are on treatment for at least 6 months.
- An in-depth analysis to estimate adherence and persistence with drugs for obstructive respiratory disorders through health card data, focused on new users, aged at least 45 years, considering a follow-up of one year; the cohort was then selected from exposure. The study population includes 184,211 new users of treatments for obstructive airway diseases aged 45 years and over. The median age is 67 years (interquartile IQR range: 57-76), with a higher proportion of females than males (58.3% vs 41.7%). The percentage of subjects with high and low adherence to treatment was 19.5% and 53.6% respectively, with a reduction in subjects with high adherence (-19%), in both males (-20%) and females (-18%) compared to 2021, and a 23% increase in low adherence, especially in males (+26%). In general, males have a higher percentage of subjects with

high adherence than females (21.3% vs 18.2%). The proportion of subjects with high adherence to treatment was higher in the North (21.5%) and the Centre (20.0%) compared to the South and the Islands (17.7%) (Table 3.7.1e), while for low adherence the trend is reversed, with the Southern regions showing the highest values (56.9%). Considering the persistence of treatment at 12 months (7.9 %), persistent subjects range from 5% (45-54 years) to 8.9% (subjects aged at least 85 years). Males show higher percentages than females (10.1% vs 6.3%), with the highest values in the North (9.6% vs 6.4% in the South) (Table 3.7.1f). There is a 50% chance of stopping treatment at 34 days, and the risk of discontinuity increases in the South and Islands compared to the North (30 vs 46 days) and in females (30 vs 43 days) (Figure 3.7.1d).

- Focusing the analysis on the ≥ 65-year-old, high adherence increases (21.4%) in both males (22.8%) and females (20.3%) and low adherence decreases to 50.8% (Table 3.7.1 g). 9.4% of subjects remain persistent after one year with ever higher values in males (11.7 vs 7.6%) and ranging from 7.5% in the South to 11.6 % in the North (Table 3.7.1h). The median time to discontinuation is 76 days and the probability of stopping is greater in females and in the South (70 days) (Figure 3.7.1.e).

Figure 3.7.1c Distribution of prevalence of use and consumption of medicines for asthma and COPD under approved care regime and distribution "on-behalf" in 2022

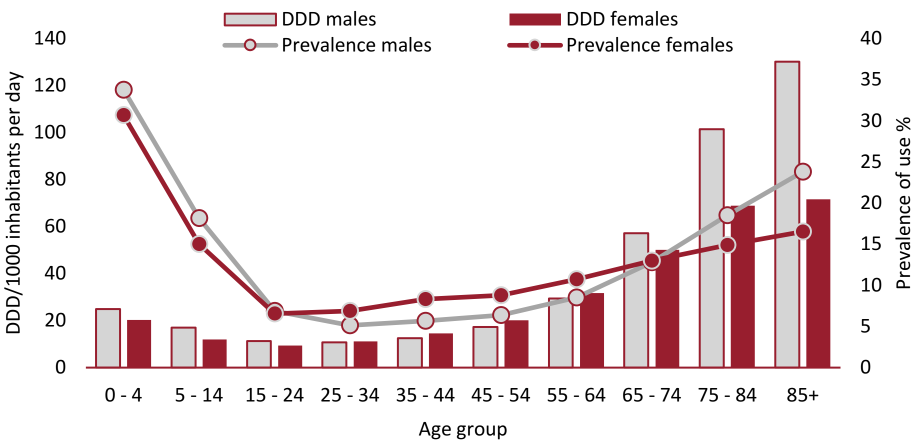


Table 3.7.1c Exposure and duration of therapy with medicines for asthma and COPD by Region under approved care regime and distribution "on-behalf" (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	8.3	8.5	8.4	53	191.39	119.8	33.3	38.1
Valle d'Aosta	9.3	9.9	9.6	49	137.46	103.6	30.0	41.9
Lombardy	9.7	10.1	9.9	46	141.79	101.5	30.0	41.5
PA Bolzano	8.8	8.8	8.8	41	118.36	88.1	26.7	45.9
PA Trento	12.5	12.8	12.6	42	112.35	84.5	28.8	44.3
Veneto	9.4	9.4	9.4	45	131.45	100.6	30.0	43.4
Friuli VG	8.9	9.2	9.1	53	149.21	114.3	30.0	41.5
Liguria	10.8	11.3	11.0	54	146.77	109.3	31.3	37.9
Emilia R.	11.3	12.0	11.7	46	108.79	85.8	30.0	45.2
Tuscany	9.0	9.3	9.2	53	165.62	121.4	40.8	40.7
Umbria	9.7	9.9	9.8	54	139.55	103.2	30.0	45.6
Marche	9.4	9.4	9.4	50	151.21	105.1	30.0	45.3
Lazio	12.6	14.2	13.5	50	134.69	90.5	30.0	42.8
Abruzzo	11.0	11.7	11.4	48	138.56	90.4	30.0	49.2
Molise	9.9	10.4	10.1	55	131.00	90.0	30.0	47.9
Campania	14.6	16.0	15.3	48	130.37	89.6	30.0	40.7
Puglia	10.6	10.4	10.5	54	143.09	107.4	31.3	41.4
Basilicata	10.8	11.2	11.0	56	146.61	106.8	30.0	43.2
Calabria	10.8	11.4	11.1	55	138.47	92.9	30.0	45.1
Sicily	11.1	11.8	11.5	55	121.89	93.8	30.0	44.6
Sardinia	12.2	14.2	13.2	52	125.22	97.5	30.0	45.6
Italy	**10.8**	**11.3**	**11.1**	**50**	**137.67**	**98.6**	**30.0**	**42.6**
North	9.8	10.1	9.9	48	139.76	101.1	30.0	42.0
Centre	10.9	11.8	11.3	51	144.56	100.6	30.0	42.7
South and Islands	12.0	12.8	12.4	52	131.70	94.9	30.0	43.1

Table 3.7.1d Exposure and duration of therapy of medicines for asthma and COPD per subgroup under approved care regime and distribution “on behalf” (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
LABAs+ICS	3.0	3.3	3.1	61	221.19	138.5	90.0	28.4
Monoclonal antibodies	0.01	0.02	0.01	56	5,690.42	207.7	168.8	3.5
LAMAs	1.0	0.8	0.9	75	279.32	185.1	180.0	17.3
ICSs	6.2	6.9	6.6	38	25.90	24.9	13.3	71.3
LAMAS+LABAS+ICSs	0.3	0.1	0.2	75	602.49	210.6	210.0	12.2
LABAs+LAMAs	0.3	0.2	0.3	75	367.16	187.5	180.0	18.2
Antileukotrienes (LTRAs)	0.5	0.6	0.5	48	85.12	137.3	84.0	23.8
LABAs	0.1	0.1	0.1	73	204.88	207.4	150.0	20.3
SABAs	2.3	2.1	2.2	31	8.22	38.0	25.0	66.7
SABAs+SAMAs	1.1	1.2	1.2	44	11.96	17.5	10.0	82.4
SABAs+ICSs	0.2	0.2	0.2	58	46.41	38.3	25.0	66.9
SAMAs	0.3	0.3	0.3	69	14.57	50.9	16.7	54.7
Theophylline-based bronchodilators	0.2	0.2	0.2	74	19.55	54.2	10.0	45.4
PDE-4 inhibitors	<0.05	<0.05	<0.05	74	357.71	232.1	240.0	9.2
Medicines for asthma and COPD	**10.8**	**11.3**	**11.1**	**50**	**137.67**	**98.6**	**30.0**	**42.6**

Table 3.7.1e Indicators of adherence to treatment with medicines for asthma and COPD in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=184,211						Nord N=63,053					
45-54 years	55.0	49.7	48.6	59.4	22	8	51.6	45.5	41.8	55.6	33	8
55-64 years	51.8	44.7	44.8	55.3	24	7	49.6	40.7	38.8	51.5	33	4
65-74 years	48.8	42.8	42.3	52.6	24	8	46.3	39.4	37.4	47.7	28	3
75-84 years	46.1	41.1	39.8	48.3	21	5	44.5	38.2	34.3	43.6	27	-2
≥ 85 years	48.9	43.2	42.5	50.5	19	3	48.6	41.2	39.5	47.9	21	-1
Females	51.9	45.4	46.1	55.6	21	7	50.0	42.1	40.4	51.9	29	4
Males	47.2	42.2	40.2	50.7	26	7	44.6	38.7	35.1	45.9	31	3
Total	**49.9**	**44.0**	**43.5**	**53.6**	**23**	**7**	**47.7**	**40.6**	**38.0**	**49.4**	**30**	**4**
	Centre N=38,420						South N=82,738					
45-54 years	54.8	49.7	48.7	60.3	24	10	57.3	52.4	52.7	62.1	18	8
55-64 years	52.2	44.3	44.6	56.0	25	7	52.9	47.2	48.0	57.8	20	9
65-74 years	47.9	40.9	40.3	52.3	30	9	50.7	45.7	45.9	56.1	22	11
75-84 years	44.6	39.9	36.9	46.2	25	4	48.2	43.8	44.9	53.1	18	10
≥ 85 years	46.5	41.2	39.3	48.8	24	5	50.5	45.9	46.2	53.5	16	6
Females	50.5	43.7	44.7	55.1	23	9	53.9	48.5	50.2	58.7	17	9
Males	47.0	41.8	38.0	50.6	33	8	48.9	44.7	44.1	54.4	23	11
Total	**49.1**	**42.9**	**41.8**	**53.3**	**27**	**9**	**51.8**	**46.8**	**47.5**	**56.9**	**20**	**10**

continued

Table 3.7.1e – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=184,211						Nord N=63,053					
45-54 years	15.8	18.0	20.4	15.5	-24	-2	17.3	19.1	22.9	17.1	-25	-1
55-64 years	18.6	22.1	23.1	18.3	-21	-2	20.4	25.1	25.6	19.7	-23	-3
65-74 years	20.9	24.2	25.2	20.3	-19	-3	22.7	26.9	27.8	22.9	-17	1
75-84 years	22.3	25.9	27.0	22.9	-15	3	24.3	28.2	29.5	25.7	-13	6
≥ 85 years	21.4	25.3	25.2	21.8	-14	2	22.7	27.5	27.9	23.4	-16	3
Females	18.6	22.0	22.2	18.2	-18	-2	19.8	24.2	24.3	19.9	-18	0
Males	21.7	24.7	26.8	21.3	-20	-2	24.1	27.3	29.8	23.8	-20	-1
Total	**19.9**	**23.2**	**24.2**	**19.5**	**-19**	**-2**	**21.7**	**25.6**	**26.8**	**21.5**	**-20**	**-1**
	Centre N=38,420						South N=82,738					
45-54 years	16.3	18.9	20.3	14.5	-29	-11	14.6	16.9	19.0	14.7	-22	1
55-64 years	18.9	22.5	24.3	18.7	-23	-1	17.4	20.0	21.2	17.0	-20	-2
65-74 years	22.0	25.7	26.6	20.9	-21	-5	19.3	21.9	23.2	18.2	-22	-5
75-84 years	22.9	27.6	28.8	24.5	-15	7	20.6	23.4	24.5	19.9	-19	-3
≥ 85 years	23.8	26.4	26.5	23.3	-12	-2	19.1	23.1	22.8	19.7	-14	3
Females	19.9	23.4	23.2	19.0	-18	-5	16.9	19.9	20.5	16.6	-19	-2
Males	22.0	25.8	28.6	21.6	-24	-2	20.1	22.5	24.2	19.2	-21	-4
Total	**20.8**	**24.4**	**25.5**	**20.0**	**-22**	**-4**	**18.3**	**21.0**	**22.2**	**17.7**	**-20**	**-3**

*Adherence to treatment was assessed within 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions provided. Low adherence to treatment was defined as therapeutic coverage (assessed by DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥ 80% of the observation period (see statistical methods for further details).
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of subjects with low/high adherence related to the specified category.
^ Excluding Emilia Romagna.
Median follow-up time (IQR): 244 (106-330)

Table 3.7.1f Persistence after one year of treatment with medicines for asthma and COPDin the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Persistence after 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=184,211						Nord N=63,053					
45-54 years	5.2	6.5	8.1	5.0	-39	-5	6.6	8.0	10.3	5.9	-43	-10
55-64 years	6.9	9.2	9.9	6.8	-31	-1	8.7	11.3	11.8	8.1	-31	-7
65-74 years	8.9	11.0	12.3	8.5	-31	-5	11.0	13.3	14.9	10.8	-27	-1
75-84 years	10.2	12.3	13.5	10.8	-20	6	11.9	14.3	15.2	13.1	-13	10
≥ 85 years	9.5	10.8	12.9	8.9	-31	-6	9.8	11.3	14.6	10.3	-29	5
Females	6.5	8.2	9.4	6.3	-33	-4	7.9	9.8	11.4	7.6	-33	-4
Males	10.4	12.6	13.7	10.1	-26	-3	12.5	14.9	15.9	12.3	-22	-1
Total	**8.2**	**10.1**	**11.3**	**7.9**	**-30**	**-4**	**9.9**	**12.0**	**13.4**	**9.6**	**-28**	**-3**
	Centre N=38,420						South N=82,738					
45-54 years	5.5	6.2	8.5	4.7	-44	-14	4.2	5.6	6.6	4.3	-35	3
55-64 years	6.2	9.1	10.8	7.2	-34	15	6.1	8.0	8.5	5.7	-34	-7
65-74 years	8.9	11.8	13.7	8.6	-37	-3	7.7	9.2	10.3	6.8	-34	-12
75-84 years	9.8	12.6	15.2	11.7	-23	19	9.1	10.7	11.6	8.4	-27	-7
≥ 85 years	10.0	10.7	12.8	9.4	-27	-7	9.0	10.5	11.8	7.5	-36	-16
Females	6.7	8.6	10.3	6.7	-35	0	5.5	7.0	7.8	5.0	-36	-9
Males	10.0	12.8	15.2	10.3	-32	3	9.4	10.9	11.8	8.4	-29	-10
Total	**8.1**	**10.3**	**12.4**	**8.2**	**-34**	**1**	**7.2**	**8.7**	**9.6**	**6.4**	**-33**	**-10**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to statistical methods)

^ Excluding Emilia Romagna

Figure 3.7.1d Time (in days) to discontinuation of treatment with medicines for asthma and COPD in the population aged ≥45 years stratified by geographical area; curves are adjusted by gender and age (the Cox model was used to estimate persistence curves). The North does not include Emilia Romagna

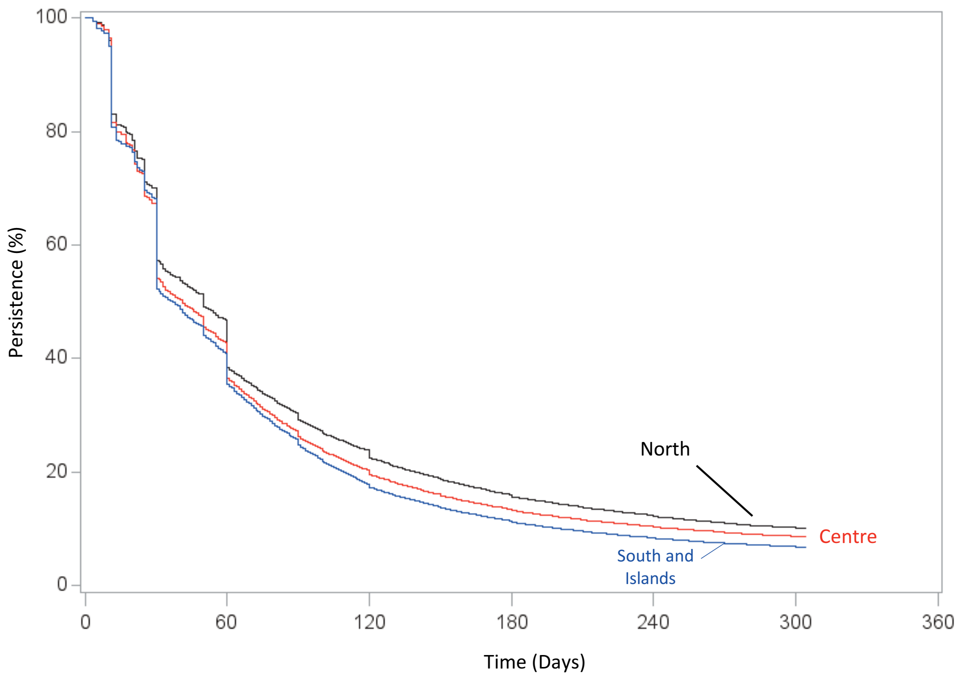


Table 3.7.1g Indicators of adherence to treatment with medicines for asthma and COPD in the population aged ≥65 years in the period 2019-2022 and variation 2022-2021

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=103,100						North N=34,983					
65-74 years	48.8	42.8	42.3	52.6	24	8	46.3	39.4	37.4	47.7	28	3
75-84 years	46.1	41.1	39.8	48.3	21	5	44.5	38.2	34.3	43.6	27	-2
≥ 85 years	48.9	43.2	42.5	50.5	19	3	48.6	41.2	39.5	47.9	21	-1
Females	49.6	43.5	43.6	52.4	20	6	48.2	40.6	38.6	48.0	25	0
Males	45.6	40.6	38.8	48.7	26	7	43.2	37.6	34.0	43.9	29	2
Total	**47.8**	**42.2**	**41.4**	**50.8**	**23**	**6**	**46.0**	**39.3**	**36.5**	**46.2**	**27**	**1**
	Centre N=21,468						South N=46,649					
65-74 years	47.9	40.9	40.3	52.3	30	9	50.7	45.7	45.9	56.1	22	11
75-84 years	44.6	39.9	36.9	46.2	25	4	48.2	43.8	44.9	53.1	18	10
≥ 85 years	46.5	41.2	39.3	48.8	24	5	50.5	45.9	46.2	53.5	16	6
Females	47.3	41.3	41.0	50.8	24	7	51.9	46.8	47.9	56.3	18	9
Males	45.1	39.6	36.0	48.0	33	6	47.3	43.1	42.9	52.7	23	12
Total	**46.4**	**40.6**	**38.8**	**49.6**	**28**	**7**	**49.8**	**45.1**	**45.6**	**54.7**	**20**	**10**

continued

Table 3.7.1g – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=103,100						North N=34,983					
65-74 years	20.9	24.2	25.2	20.3	-19	-3	22.7	26.9	27.8	22.9	-17	1
75-84 years	22.3	25.9	27.0	22.9	-15	3	24.3	28.2	29.5	25.7	-13	6
≥ 85 years	21.4	25.3	25.2	21.8	-14	2	22.7	27.5	27.9	23.4	-16	3
Females	20.2	23.9	23.9	20.3	-15	0	21.3	26.1	25.8	22.5	-13	5
Males	23.1	26.5	28.2	22.8	-19	-1	25.8	29.2	31.6	25.9	-18	1
Total	**21.5**	**25.0**	**25.9**	**21.4**	**-17**	**0**	**23.3**	**27.5**	**28.4**	**24.0**	**-16**	**3**
	N=21,468						South N=46,649					
65-74 years	22.0	25.7	26.6	20.9	-21	-5	19.3	21.9	23.2	18.2	-22	-5
75-84 years	22.9	27.6	28.8	24.5	-15	7	20.6	23.4	24.5	19.9	-19	-3
≥ 85 years	23.8	26.4	26.5	23.3	-12	-2	19.1	23.1	22.8	19.7	-14	3
Females	21.9	25.6	25.4	21.7	-15	-1	18.5	21.4	22.0	18.0	-18	-3
Males	23.7	27.8	30.0	23.8	-21	1	21.2	24.1	25.4	20.2	-21	-5
Total	**22.7**	**26.5**	**27.4**	**22.6**	**-17**	**0**	**19.7**	**22.6**	**23.6**	**19.0**	**-19**	**-4**

*Adherence to treatment was assessed within 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions provided. Low adherence to treatment was defined as therapeutic coverage (assessed by DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥ 80% of the observation period (see statistical methods for further details).

N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.

Percentages of subjects with low/high adherence related to the specified category.

^ Excluding Emilia Romagna.

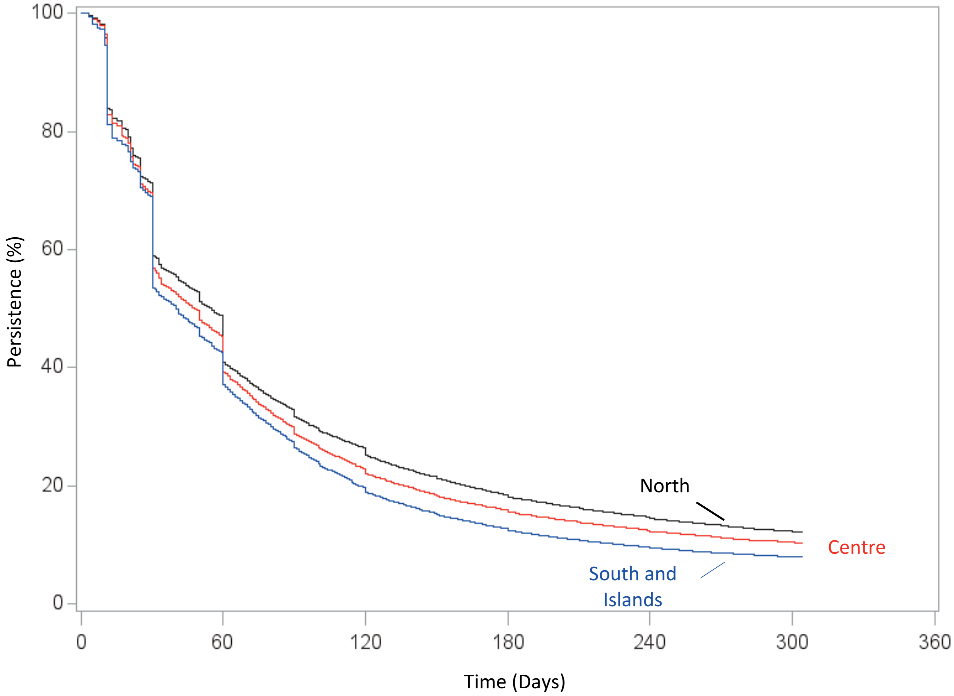
Median follow-up time (IQR): 244 (114-330)

Table 3.7.1h Persistence after one year of treatment with medicines for asthma and COPDin the population aged ≥65 years in the period 2019-2022 and variation 2022-2021

	Persistence after 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=103,100						North N=34,983					
65-74 years	8.9	11.0	12.3	8.5	-31	-5	11.0	13.3	14.9	10.8	-27	-1
75-84 years	10.2	12.3	13.5	10.8	-20	6	11.9	14.3	15.2	13.1	-13	10
≥ 85 years	9.5	10.8	12.9	8.9	-31	-6	9.8	11.3	14.6	10.3	-29	5
Females	7.6	9.4	10.9	7.6	-30	-1	9.0	11.0	13.0	9.4	-28	5
Males	11.8	13.9	15.3	11.7	-24	-1	13.9	16.2	17.3	14.4	-16	4
Total	**9.5**	**11.4**	**12.9**	**9.4**	**-27**	**-1**	**11.1**	**13.4**	**15.0**	**11.6**	**-22**	**4**
	Centre N=21,468						South N=46,649					
65-74 years	8.9	11.8	13.7	8.6	-37	-3	7.7	9.2	10.3	6.8	-34	-12
75-84 years	9.8	12.6	15.2	11.7	-23	19	9.1	10.7	11.6	8.4	-27	-7
≥ 85 years	10.0	10.7	12.8	9.4	-27	-7	9.0	10.5	11.8	7.5	-36	-16
Females	8.1	10.0	12.0	8.3	-31	2	6.5	8.1	9.0	5.9	-35	-9
Males	11.3	14.4	16.9	11.9	-29	6	10.7	12.1	13.3	9.5	-29	-12
Total	**9.4**	**11.9**	**14.1**	**9.8**	**-31**	**4**	**8.4**	**9.9**	**11.0**	**7.5**	**-32**	**-11**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to statistical methods)
^ Excluding Emilia Romagna

Figure 3.7.1e Time (in days) to discontinuation of treatment with drugs for obstructive respiratory disorders in the population aged ≥ 65 years stratified by geographical area; the curves are adjusted by gender and age (the Cox model was used for estimation of persistence curves).



The consumption of asthma and COPD drugs increased slightly in 2022, following the slow and progressive decrease observed in previous years, while the average cost per day of therapy decreased slightly.

The dual association LABA+ICS, mainly used in the treatment of COPD, covers about 40% of the total expenditure and consumption of the category, although the values decreased compared to the previous year. The expenditure and consumption values are also reduced for LABA and LAMA, probably to the advantage of the triple fixed combination LAMA+LABA+ICS, which continues to show an increasing trend in use, probably due to the amendment of the AIFA Note 99, which extended the possibility by general practitioners of also prescribing the triple fixed association.

Monoclonal antibodies (omalizumap, mepolizumab, benralizumab), recently marketed drugs referred to as adjunctive therapy in the treatment of severe allergic asthma in adults and adolescents with symptoms that are not effectively controlled with other inhalers (corticosteroids and beta2-agonists with long-acting duration) show low consumption, but have increased compared to the previous year.

Significant increases in expenditure and consumption also affected inhaled corticosteroids (ICS), with the highest prevalence of use within the category, with more than 70% of users receiving only one prescription during the year, indicating that these drugs are used as needed, and most likely associated with the treatment of asthma or upper respiratory tract infections. This hypothesis also seems to be confirmed by the trend in the prevalence of use, which shows two peaks in consumption in the most extreme age groups, in line with the epidemiology of respiratory diseases affecting different population groups: in preschool children, high use is probably associated with acute infectious episodes affecting the upper respiratory tract, while in the elderly, consumption is more associated with chronic treatment of COPD.

Data on adherence and persistence to treatment show a worsening of the indicators compared to the previous year, confirming the decreasing trend from North to South already shown in previous years. Males are more adherent and persistent to therapy than females, probably because the use of these drugs is more linked to chronic COPD therapy, a condition more prevalent in males than in females. A more accurate selection of patients with COPD, e.g. thorugh record-linkage with other information streams (e.g. Hospital dismission records) could allow a more careful monitoring, also in terms of clinical outcomes, of the pharmacological therapy of patients with COPD; indeed this is a chronic and irreversible disease that evolves towards stages of greater severity if adequate and continuous drug therapy is not established over time, taking into account all the main risk factors (e.g. age and comorbidity) of treatment discontinuation.

3.7.2 Medicines for cystic fibrosis

- Per capita expenditure on medicines for cystic fibrosis has increased significantly in the last nine years, reaching EUR 7.30 in 2022, twice compared to 2021 and with a CAGR of +65.1% in the period 2014-2022. The cost for DDD also showed a significant increase of 22.5%, reaching a value of EUR 237.33 (Figure and Table 3.7.2a).
- The trend in expenditure in the category is determined exclusively by CFTR modulators, which account for 97% of the total. These drugs shifted from EUR 0.22 per capita in 2015 to EUR 7.09 in 2022 (CAGR: +63.8%) (Figure 3.7.2b). The category 'Specific action mucolitics' includes only the active substance deoxyribonuclease, indicated to improve lung function in patients with cystic fibrosis. This drug showed a limited impact on the total expenditure of the category and in 2022 it recorded a reduction in both expenditure and consumption (-10.2% for both indicators).
- The triple combination elexacaftor/tezacaftor/ivacaftor, recently placed on the market (2021), is the highest-spending substance with EUR 3.50 per capita (+ 308.6% compared to 2021). This is followed by ivacaftor plain, with an expenditure of EUR 3.04 per capita, also increasing compared to 2021 (+132.5%). The combination lumacaftor/ivacaftor recorded a decrease by 61% and shows the highest average cost per DDD (EUR 437.25). Despite a reduced overall expenditure, the combination ivacaftor/tezacaftor continues to increase in terms of per capita expenditure (+10.8%) and consumption (+36.7%) (Table 3.7.2a).
- An increased variability is confirmed between the different regions, with the South and the Islands having a per capita expenditure higher than the rest of Italy (EUR 7.61; + 4% than the national average). However, the Centre recorded the highest increased in expenditure (+118%) compared to 2021 (Table 3.7.2b). To confirm this, the expenditure of Basilicata is about 4 times higher than Valle d'Aosta (12.20 vs 3.23), as well as the average cost (269.74 vs 130.68). All regions recorded higher increases than the previous year (nine regions doubled expenditure).

Figure 3.7.2a Medicines for cystic fibrosis, temporal trend 2014-2022 of per capita expenditure and average cost per day of therapy

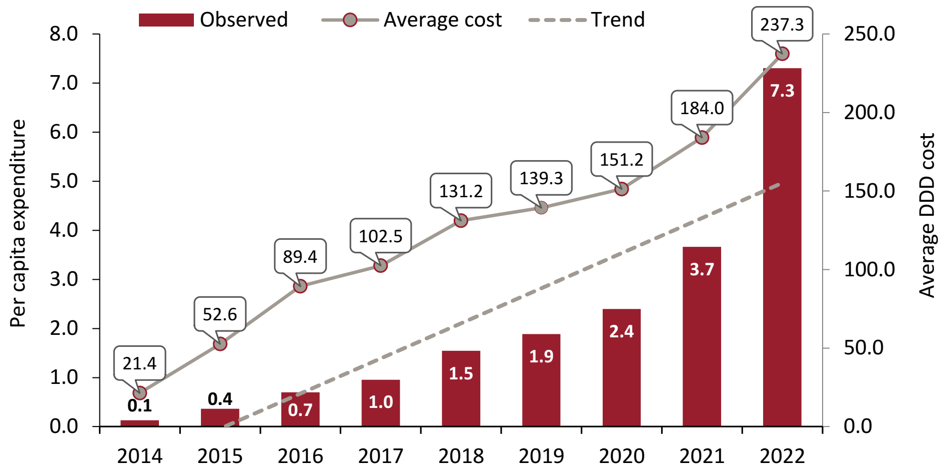


Table 3.7.2a Medicines for cystic fibrosis, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	*Per capita* expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
CFTR Modulators	7.09	106.8	-	0.1	136.5	-	341.35	-12.5
Specific action mucolytics	0.21	-10.2	6.3	<0.05	-10.2	6.4	21.32	0.0
Medicines for cystic fibrosis	**7.30**	**99.3**	**65.3**	**0.1**	**54.5**	**22.4**	**237.33**	**29.0**
elexacaftor/tezacaftor/ ivacaftor	3.50	308.6	-	<0.05	313.2	-	289.31	-1.1
ivacaftor	3.04	132.5	-	<0.05	168.5	-	429.02	-13.4
lumacaftor/ivacaftor	0.46	-61.0	-	<0.05	-62.7	-	437.25	4.5
deoxyribonuclease	0.21	-10.2	6.3	<0.05	-10.2	6.4	21.32	0.0
ivacaftor/tezacaftor	0.09	10.8	-	<0.05	36.7	-	169.29	-18.9

Figure 3.7.2b Medicines for cystic fibrosis, temporal trend 2014-2022 of per capita expenditure of subgroups with higher expenditure

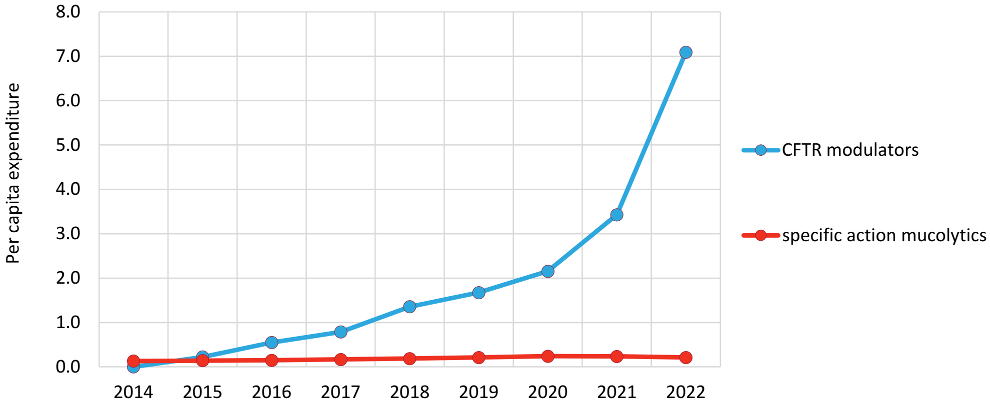


Table 3.7.2b Medicines for cystic fibrosis, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	2.72	0.1	132.37	6.05	0.1	190.84	122.4	54.3	44.2	56.6	19.0	31.6
Valle d'Aosta	1.62	0.1	79.32	3.23	0.1	130.68	100.1	21.4	64.8	49.3	19.3	25.2
Lombardy	3.40	0.1	174.65	7.71	0.1	240.67	127.2	64.8	37.8	69.6	25.4	35.2
PA Bolzano	5.70	0.1	133.40	10.56	0.2	186.32	85.5	32.8	39.7	48.8	13.8	30.8
PA Trento	5.42	0.1	190.59	7.59	0.1	206.80	40.0	29.0	8.5	58.3	19.4	32.6
Veneto	2.80	0.1	127.15	7.00	0.1	212.05	149.8	49.8	66.8	60.4	20.6	33.0
Friuli VG	3.57	0.0	257.32	6.27	0.1	274.90	75.6	64.4	6.8	78.7	30.0	37.5
Liguria	3.21	0.1	158.11	8.11	0.1	232.54	152.4	71.6	47.1	61.2	19.8	34.5
Emilia R.	3.70	0.0	271.07	6.71	0.1	291.69	81.2	68.4	7.6	82.6	31.7	38.7
Tuscany	3.45	0.1	178.38	6.77	0.1	232.69	96.3	50.5	30.4	62.8	21.0	34.5
Umbria	3.33	0.1	168.30	6.44	0.1	218.37	93.0	48.8	29.7	54.6	15.6	33.7
Marche	3.79	0.1	174.28	8.24	0.1	229.87	117.3	64.8	31.9	62.8	21.2	34.3
Lazio	3.03	0.1	165.25	7.27	0.1	244.15	139.8	62.3	47.7	58.3	16.7	35.6
Abruzzo	3.48	0.1	165.53	7.96	0.1	230.08	128.9	64.7	39.0	69.9	26.5	34.3
Molise	2.12	0.0	125.32	5.78	0.1	224.51	172.5	52.1	79.1	54.3	15.2	33.9
Campania	3.58	0.1	195.88	6.70	0.1	241.83	87.5	51.8	23.5	66.2	23.0	35.2
Puglia	5.30	0.1	238.49	7.96	0.1	256.48	50.4	39.8	7.5	75.6	28.8	36.3
Basilicata	6.85	0.1	225.09	12.20	0.1	269.74	77.9	48.5	19.8	51.4	10.5	37.0
Calabria	4.84	0.1	196.99	8.61	0.1	232.05	77.7	50.9	17.8	67.8	24.5	34.8
Sicily	5.27	0.1	234.45	8.49	0.1	266.35	61.2	41.9	13.6	79.6	29.2	38.9
Sardinia	2.54	0.0	165.35	4.64	0.1	198.96	82.5	51.7	20.3	66.7	26.4	31.9
Italy	**3.67**	**0.1**	**184.00**	**7.30**	**0.1**	**237.33**	**99.3**	**54.5**	**29.0**	**65.3**	**22.4**	**35.1**
North	3.30	0.1	169.01	7.14	0.1	230.91	116.5	58.4	36.6	65.1	22.7	34.5
Centre	3.29	0.1	171.06	7.17	0.1	236.55	118.2	57.8	38.3	59.9	18.5	35.0
South and Islands	4.42	0.1	211.38	7.61	0.1	247.07	72.2	47.3	16.9	69.8	24.9	36.0

In recent years, the pharmacological treatment scenario of cystic fibrosis has undergone major improvements, thanks to innovative therapeutic options acting on the genetic mutations underlying the disease development, the so-called CFTR protein modulators, which directly correct the function of the defective CFTR protein.

In fact, in the last nine years there has been a marked increase in the per capita expenditure of these drugs (in 2022 it doubled compared to the previous year), associated with a marked increase in the average cost per day of therapy, which increased from EUR 21.4 in 2014 to 273.3 in 2022.

In 2022, the increases recorded were mainly due to the triple combination elexacaftor/tezacaftor/ivacaftor (two correctors and one enhancer), recently approved for reimbursement, indicated in patients with at least one CFTR gene F508del mutation, and ivacaftor plain, which also confirms in 2022 the upward trend recorded in previous years. Conversely, the combination lumacaftor/ivacaftor, indicated in homozygous patients for F508del mutation in the CFTR gene, shows a reduction in expenditure and consumption.

Access to therapies with innovative high-cost drugs, combined with increasingly early neonatal screenings, on the one hand has allowed an improvement in the quality of life of patients with cystic fibrosis, resulting in an increase in their life expectancy; on the other hand, it has significantly increased the impact of expenditure for this category of drugs in recent years.

3.8 Musculo-skeletal system

Medicines for the musculoskeletal system represent the eighth category for public expenditure in 2022, with EUR 586.6 million, and 2.4% of public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was EUR 9.93, mainly due to the approved care pharmaceutical expenditure (EUR 5.39 per capita), reporting a +4.2% increase compared to the previous year; similarly, there was an increase in expenditure related to the purchase by public health facilities, with a marked increase of 18.9%, setting at EUR 4.54 per capita (Table 3.1).
Consumption for this category of drugs was 45.43 DDD/1000 inhabitants per day, a 5.2% increase compared to 2021. There is a bog difference between approved care regime (39.12 DDD/1000 inhabitants per day) and public health facilities (6.31 DDD/1000 inhabitants per day) (Table 3.2).
The analysis of the use profile, including approved care regime and distribution on behalf, confirms the steady increase, both in terms of expenditure and prevalence of use, with increasing age and for both sexes, reaching the maximum values in the subjects aged over 75 (prevalence: 48.1% in females and 44.4% in males; expenditure: EUR 27.24 in females and 13.35 in males); females show greater use than males from 25 years of age. Even the highest consumption values are reached in the over 75 age group (females 158.9 and males 111.0 DDD/1000 inhabitants per day). This difference is probably attributable to the increased use by females of drugs against osteoporosis or other osteorticular diseases.
As regards approved care regime, per capita expenditure was EUR 5.39, with a 3.7% increase compared to 2021 (Table 3.9). This development was driven solely by an increase in consumption (+3.6%), while prices, average cost per DDD and the mix effect remain stable. Within this distribution channel, bisphosphonates have the largest impact on expenditure (EUR 1.36 per capita), slightly higher than in 2021. These are followed by preparations inhibiting uric acid production, with a per capita expenditure of 0.92 euros, up 4.7% due to the combined effect of a 2.2% increase in consumption and a shift towards more expensive molecules (mix effect: +2.4%). Propionic acid derivatives show largest variation in expenditure and consumption (+20.0% and +15.8% respectively). The category with the greatest decrease is bisphosphonates in combination (-5.0% of expenditure and -4.9% of DDDs). Within bisphosphonates, alendronic acid is the active substance with the greatest impact on expenditure (EUR 0.81 per capita, equal to 15.1% in the category), with an increase of 4.2% compared to 2021 (Table 3.10), while allopurinol shows the highest consumption (8.6 DDD/inhabitants per day and +1.3%) (Table 3.17). Diclofenac is the second active ingredient with the highest per capita expenditure (EUR 0.64) accounting for 11.9% of expenditure for the category, followed by etoricoxib (EUR 0.61) with an increase of 3.7% compared to 2021 (Table 3.10). It should be noted that for febuxostat, after a reduction in expenditure and consumption in 2020 as a result of the patent expiry, both indicators increased in 2022, by 7.5% and 8% respectively. In 2022 ibuprofen recorded marked increases in expenditure and consumption, by 49.4% and 48.2% respectively.
No drug in this category is among the top 30 active ingredients with the highest expenditure under approved care regime, with higher average cost per DDD and with greater reduction in expenditure. Febuxostat, diclofenac and alendronic acid are among the top 30 active

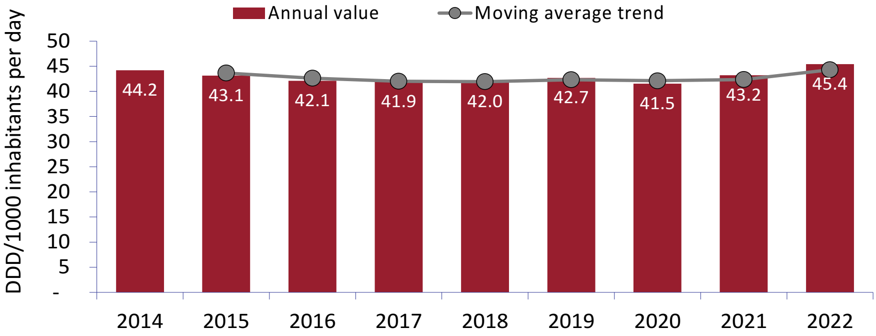
substances with greater variation under approved care regime (Table 3.15). Allopurinol ranks twenty-seventh for consumption under approved care regime (Table 3.17 and 3.18).
As for public health facilities, in 2022 there was an increase in expenditure (+18.4%) due to both an increase in consumption (+13.0%) and to a shift towards more expensive medicines (mix effect: +7.2%), offset by a price reduction of 2.3% (Table 3.19). The subgroups “other drugs for diseases of the musculoskeletal system” and “other drugs acting on bone structure and mineralisation” account for 93.3% of the total expenditure for this category; both recorded increases in expenditure (+23.2% and +22.0%), consumption (+15.0% and +16.3%), and mix effect (+13.0% and +4.9%).
Considering the most expensive active ingredients, denosumab, authorised for osteoporosis/bone loss, ranks first for per capita expenditure (EUR 1.39), followed by nusinersen (EUR 1.12), indicated in the treatment of spinal muscular atrophy (SMA); together they account for more than 55% of the expenditure in the category (Table 3.20). Nusinersen is also present in the top 30 drugs with the highest reduction in expenditure and higher average cost per DDD (Tables 3.24 and 3.25); denosumab is second in the top 30 active ingredients with the least average cost per day of therapy (Table 3.26) and seventh among the top 30 most consumed active ingredients (Table 3.27).
For further information on the use of medicinal products belonging to the same therapeutic area, analyses have been developed on the historical consumption series by active substance and by Region. These analyses concerned drugs for the treatment of osteoporosis and nonsteroidal anti-inflammatory drugs (Sections 3.8.1 and 3.8.2). Although vitamin D does not belong to the ATC M category according to the WHO classification, it has been included, by therapeutic analogy, within the drugs used for the treatment of osteoporosis. See section 3.8.1 for further information.

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

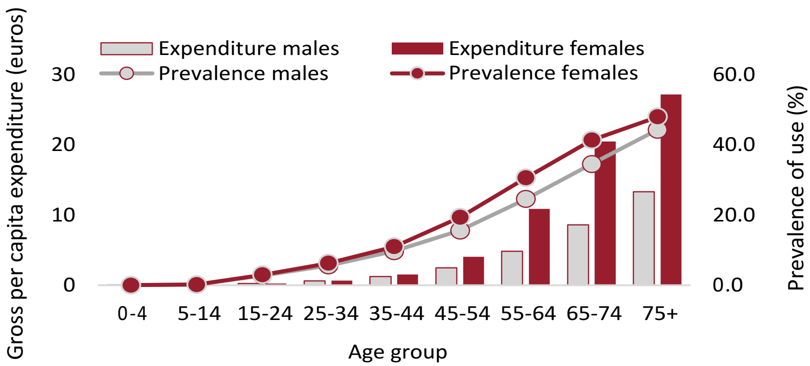
Musculo-skeletal system

Public expenditure* in million euros (% over total)	**586.6**	**(2.4)**
Δ % 2022-2021		10.4
Regional range of gross per capita expenditure:	5.9	12.4
DDD/1000 inhabitants per day* (% over total)	**45.4**	**(3.4)**
Δ % 2022-2021		5.2
Regional range DDD/1000 inhabitants per day	33.8	62.0

** includes prescriptions under approved care regime and purchases by public health facilities*



Age and gender distribution of expenditure, prevalence of use and consumption under approved care regime and distribution "on behalf" in 2022 (Figure and Table)

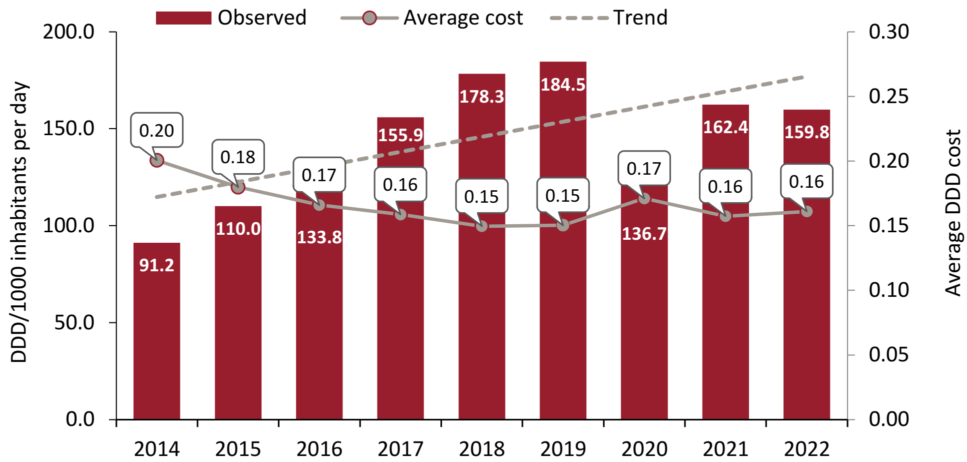


Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.0	0.0	0.0	0.0	0.0	0.0
5-14	0.0	0.0	0.0	0.2	0.2	0.2
15-24	0.3	0.3	0.3	2.1	2.0	2.0
25-34	0.6	0.7	0.6	4.5	4.7	4.6
35-44	1.3	1.5	1.4	9.4	10.4	9.9
45-54	2.5	4.1	3.3	19.3	25.6	22.5
55-64	4.9	10.9	8.0	39.6	62.7	51.5
65-74	8.6	20.5	14.9	74.1	115.3	95.9
75+	13.4	27.2	21.6	116.0	158.9	141.6

3.8.1 Medicines for osteoporosis

- The consumption trend of osteoporosis drugs (including vitamin D and metabolites) shows a marked increase between 2014 and 2019, followed by a 26% decrease in 2020, due to the entry into force of the AIFA Note 96. Subsequently, a further increase of 20.7% was recorded in 2021 (Figure and Table 3.8.1a) and a slight decrease in 2022 (-1.6%). Over the same period, the average cost per day of therapy has remained stable over the last 6 years, reaching a value of EUR 0.16 in 2022. Per capita expenditure on these drugs is EUR 9.39, stable (+0.7%) compared to the previous year.
- Expenditure on vitamin D and analogues (EUR 4.72 per capita) accounts for around 50% of the entire category, a 2.4% reduction compared to 2021. This data highlights the extensive use of cholecalciferol and metabolites for extra-skeletal indications, for which RCTs did not provide evidence of efficacy. This is confirmed by an average annual increase in consumption of 8.9% over the period 2014-2022 (Figure 3.8.1b). Monoclonal antibodies, mainly represented by the antiresorptive drug denosumab, rank second in terms of expenditure with EUR 1.69 (EUR 1.40 for denosumab and EUR 0.29 for burosumab), up from the previous year, although they represent a reduced share of consumption (4.5 DDD/1000 inhabitants per day). On the contrary, teriparatide, a biologic off-patent drug, authorised for use in postmenopausal women at high risk of fracture or in adults with osteoporosis caused by prolonged therapy with systemic glucocorticoids, shows a reduction in expenditure (-12.8%) and a stable consumption (+0.1%). Bisphosphonates plain show an increase in consumption (+2.8%) while those in combination decreased by 4.5%.
- Analysing the individual active ingredients, cholecalciferol is the molecule with the highest per capita expenditure (EUR 4.06) and consumption (139.8 DDD/1000 inhabitants per day), both of which decreased compared to 2021. This is followed by denosumab (EUR 1.40 and 4.5 DDD), increasing by about 17%, and alendronic acid (EUR 0.81 and 4.4 DDD). The drug with the highest average cost (EUR 188.68) is burosumab.
- The macro-areas of South and Islands (167.9 DDD/1000 inhabitants per day) show a consumption similar to the North (165.9 DDD) and 27% higher than the Central regions (133.5 DDD/1000 inhabitants per day), with reductions for Centre and South (-3.4% and -5.6%) and an increase in the North (+ 2.2 %), compared to 2021. Similarly, expenditure decreased by 3.4% in the South, while the Centre and the North showed an increase by 0.7% and 4.7% respectively. Within the individual regions, Sardinia recorded the highest consumption (200.3 DDD), while Tuscany the lowest consumption (117.4 DDD), with a difference between the two of almost 70%. As for the variations compared to 2021, there is a wide variability between the individual regions, with a maximum reduction of 18.8% in Campania and a maximum increase in Friuli VG (+8.9%).

Figure 3.8.1a Medicines for osteoporosis*, 2014-2022 temporal trend of consumption and average cost per day of therapy



** excluding raloxifene*

Table 3.8.1a Medicines for osteoporosis, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	*Per capita* expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Vitamin D and analogues	4.72	-2.4	11.1	142.2	-2.2	8.9	0.09	-12.5
Bisphosphonates plain	1.40	2.1	-1.7	7.2	2.8	0.4	0.54	0.0
Monoclonal antibodies-denosumab	1.40	17.2	19.8	4.5	16.7	20.3	0.85	-12.5
Teriparatide	0.76	-12.8	-1.6	0.2	0.1	0.8	12.40	0.0
Bisphosphonates in combination	0.40	-4.6	-12.3	1.9	-4.5	-7.3	0.58	-12.5
Calcium and vitamin D	0.30	-4.3	-6.4	3.2	-4.0	-6.9	0.26	0.0
Monoclonal antibodies-burosumab	0.29	49.2	-	<0.05	48.8	-	188.68	-12.5
Calcium	0.10	-6.3	-3.2	0.6	-7.2	-12.4	0.47	0.0
SERM (selective estrogen-eceptor modulators)	0.01	-0.2	-4.7	<0.05	-0.4	-4.7	0.76	-12.5
Monoclonal antibodies-romosozumab	0.00	-	-	<0.05	-	-	14.00	-
Medicines for osteoporosis	**9.39**	**0.7**	**4.4**	**159.8**	**-1.6**	**7.3**	**0.16**	**2.3**
cholecalciferol	4.06	-2.8	11.9	139.8	-2.2	8.9	0.08	-0.6
denosumab	1.40	17.2	19.8	4.5	16.7	20.3	0.85	0.4
alendronic acid	0.81	4.2	3.6	4.4	5.5	5.3	0.51	-1.2
teriparatide	0.76	-12.8	-1.6	0.2	0.1	0.8	12.40	-12.9
alendronic acid/ cholecalciferol	0.40	-4.6	-12.3	1.9	-4.5	-7.3	0.58	0.0
riseronic acid	0.36	-1.0	-5.2	2.1	-0.2	-3.5	0.48	-0.8
calcium/cholecalciferol	0.30	-4.3	-6.4	3.2	-4.0	-6.9	0.26	-0.3
burosumab	0.29	49.2	-	<0.05	48.8	-	188.68	0.3
calcifediol	0.24	4.3	14.3	0.2	4.3	14.2	3.63	0.0
calcitriol	0.22	-0.2	0.1	1.0	0.3	-0.3	0.60	-0.5

Figure 3.8.1b Medicines for osteoporosis, 2014-2022 temporal trend of consumption (DDD/1000 inhabitants per day) of the subgroups with the highest expenditure

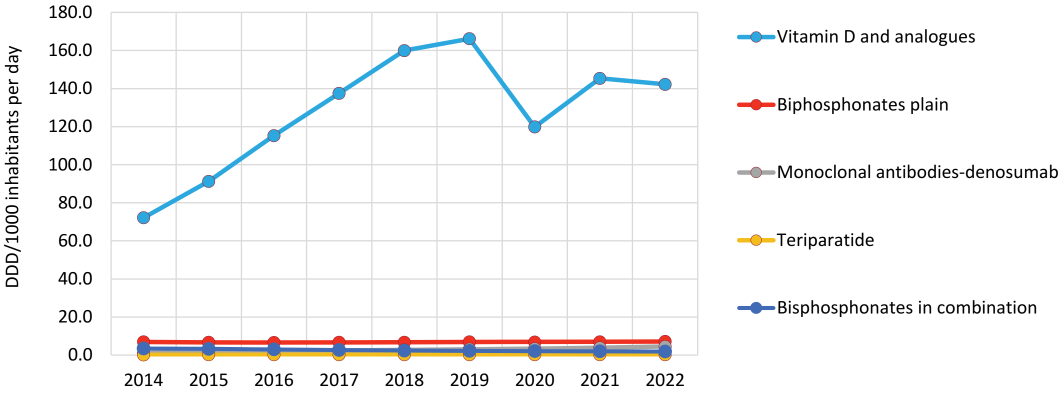


Table 3.8.1b Medicines for osteoporosis temporal trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	7.34	138.8	0.14	7.73	146.8	0.14	5.4	5.7	-0.3	4.3	8.3	-3.7
Valle d'Aosta	6.84	127.7	0.15	6.94	130.1	0.15	1.4	1.8	-0.5	3.7	10.5	-6.1
Lombardy	9.80	179.1	0.15	10.22	183.4	0.15	4.2	2.4	1.8	6.8	9.9	-2.9
PA Bolzano	7.85	158.8	0.14	8.85	170.7	0.14	12.7	7.5	4.8	5.9	3.2	2.6
PA Trento	7.76	161.9	0.13	8.17	166.4	0.13	5.2	2.8	2.4	6.4	8.2	-1.6
Veneto	6.68	164.6	0.11	7.02	157.8	0.12	5.1	-4.2	9.7	1.2	-2.8	4.2
Friuli VG	8.61	164.3	0.14	9.38	178.9	0.14	9.0	8.9	0.1	7.0	9.6	-2.3
Liguria	8.34	143.3	0.16	8.70	151.8	0.16	4.3	5.9	-1.5	4.5	8.5	-3.6
Emilia R.	6.79	154.0	0.12	6.94	156.8	0.12	2.2	1.9	0.4	2.3	4.7	-2.3
Tuscany	6.63	130.8	0.14	6.61	117.4	0.15	-0.3	-10.2	11.1	1.0	1.3	-0.3
Umbria	7.97	137.7	0.16	7.12	119.6	0.16	-10.7	-13.2	2.9	5.2	7.9	-2.5
Marche	9.44	128.5	0.20	9.56	133.2	0.20	1.3	3.6	-2.3	4.5	7.3	-2.6
Lazio	10.52	143.8	0.20	10.77	144.6	0.20	2.3	0.6	1.7	3.9	9.5	-5.2
Abruzzo	11.78	166.5	0.19	12.21	170.2	0.20	3.7	2.2	1.4	4.1	7.0	-2.7
Molise	10.11	171.5	0.16	10.12	167.3	0.17	0.0	-2.5	2.6	6.2	11.2	-4.5
Campania	13.45	226.6	0.16	11.55	184.0	0.17	-14.1	-18.8	5.8	9.2	16.3	-6.1
Puglia	10.87	181.2	0.16	10.94	179.0	0.17	0.7	-1.2	1.9	2.5	7.2	-4.4
Basilicata	11.48	181.7	0.17	11.72	188.4	0.17	2.1	3.7	-1.6	7.1	13.1	-5.3
Calabria	10.16	138.2	0.20	10.39	144.7	0.20	2.2	4.7	-2.3	5.3	12.4	-6.4
Sicily	10.15	133.3	0.21	9.95	135.5	0.20	-2.0	1.6	-3.6	3.4	11.0	-6.9
Sardinia	9.42	196.5	0.13	10.64	200.3	0.15	12.9	1.9	10.8	0.2	8.8	-7.9
Italy	**9.33**	**162.4**	**0.16**	**9.39**	**159.8**	**0.16**	**0.7**	**-1.6**	**2.3**	**4.4**	**7.3**	**-2.7**
North	8.14	162.3	0.14	8.52	165.9	0.14	4.7	2.2	2.4	4.7	5.5	-0.8
Centre	8.94	137.2	0.18	9.00	132.5	0.19	0.7	-3.4	4.3	3.3	6.2	-2.7
South and Islands	11.27	178.0	0.17	10.88	167.9	0.18	-3.4	-5.6	2.4	4.6	11.0	-5.7

Exposure and adherence in population

- Health Card data were collected to perform an analysis aimed at estimating exposure and duration of treatment to osteoporosis medicines in the general population, as well as adherence and persistence to treatment. As expected based on the prevalence of osteoporosis in the population, exposure is significantly higher in females than in males (19.7% vs 5.4%). This difference persists in all age groups and reaches a maximum of 50% for females in the 75-84 age group and 24.4% for males over eighty-five (Figure 3.8.1c).
- Looking at the trend in the prevalence of use by geographical area (Table 3.8.1d), the Southern Regions show a higher figure (14.7%) than both the Centre (11.5%) and the North (11.8%); Abruzzo is the region with the highest exposure in the general population (17.1%), both in females (25.5%) and in males (8.3%). Only three regions have values of prevalence of use below 10%.
- The median age of the patients was 68 years and the annual expenditure for each user was EUR 65.49, with a regional range between EUR 43.44 in Emilia Romagna and EUR 77.78 in Lazio. On average, each user received 435 doses of osteoporosis drugs, half were treated for more than eight months, and 14.6% received only one prescription.
- The highest exposure category among osteoporosis drugs was vitamin D and analogues (11.8%), the average cost per user in this category is EUR 39, while teriparatide has the highest cost of all osteoporosis drugs (EUR 2567). The second category by prevalence of use is bisphosphonates plain, covering 1.1%. The median age of users is higher than the entire category (73 years), and half of the users received a dose of the drug for at least 7 months. Among monoclonal antibodies, the average cost per user of denosumab is lower by half than romosozumab (339 vs 711) (Table 3.8.1d).
- As regards adherence and persistence analyses, the exposure data refer to a cohort of new users over 45 years old, who were monitored considering a one-year follow-up. The study population comprises 45,937 new users, with a median age of 69 years (IQR 61-76), and the ratio of females is significantly higher than males (91.8% vs 8.2%). The ratio of subjects with high and low adherence to treatment with medicines for osteoporosis was 67.3% and 7.5% respectively, with values comparable to those observed in 2021 (68.8% and 7% respectively) (Table 3.8.1e). Adherence is highest in people aged 55-64 and in living in the North (72.5%), while it is lower in people aged over 85 living in the Centre (59.3%). Low adherence tends to increase with age, from 6.9% in the 45-54 age group to 9.6% in the over-85. There are differences between males and females in terms of adherence to therapy, with the former having the lowest level of adherence (11.5% vs 7.2%). Patients over 85 years of age and living in Central Italy have the lowest adherence value of 13.1%. The percentages of low adherence have all increased compared to both the previous year and 2019, with the exception of the over 85 age group, which instead shows a decrease.
- Analysing the persistence of osteoporosis drugs (Table 3.8.1f), just over half of new users are persistent on treatment even after one year (51%). The trend is better in the North (54.7%) and the Centre (53.4%), compared to the South, where less than half of patients do not stop treatment for a period of more than 60 days (45.6%). Females show greater

persistence than males (51.7% and 42.5%), and overall persistence tends to decrease with age, rising from 54.8% in the 45-54 age group to 43% in the over 85.

- Comparing persistence data by geographical area (Figure 3.8.1d), no particular differences are found; it can be noted that for these drugs the median time to discontinuity exceeds 365 days, except in the South, where it reaches 245 days. This time of discontinuation decreases progressively with age: in the population over 85 years it is 242 days. In addition, there are differences in sex, with males showing less persistence on treatment than females (226 vs 365 days).

Figure 3.8.1c Distribution of prevalence of use and consumption of medicines for osteoporosis under approved care regime and distribution "on behalf" in 2022

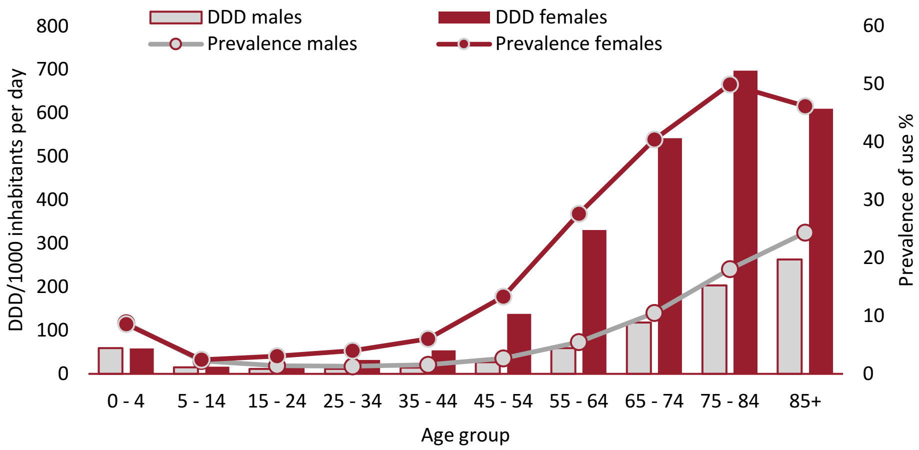


Table 3.8.1c Exposure and duration of therapy with medicines for osteoporosis by Region under approved care regime and distribution on behalf (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	4.9	18.2	11.7	70	61.70	447.9	330.0	13.4
Valle d'Aosta	4.7	15.9	10.5	70	56.52	428.3	312.5	6.3
Lombardy	5.7	19.5	12.7	68	72.38	488.1	375.0	8.5
PA Bolzano	4.2	13.2	8.7	69	61.67	548.8	375.0	12.0
PA Trento	5.9	17.8	12.0	66	59.85	458.9	321.0	8.9
Veneto	4.5	14.7	9.7	69	60.85	558.0	375.0	15.8
Friuli VG	6.5	20.4	13.6	69	69.57	488.2	375.0	11.3
Liguria	4.8	19.5	12.4	73	69.79	456.6	364.0	12.2
Emilia R.	4.9	18.0	11.6	68	43.44	443.6	260.0	15.3
Tuscany	3.9	14.8	9.5	70	56.86	445.0	250.0	27.2
Umbria	4.3	18.9	11.9	70	59.85	370.1	250.0	21.8
Marche	4.7	18.3	11.7	70	76.42	404.5	250.0	15.8
Lazio	4.9	20.0	12.7	68	77.78	402.7	250.0	14.3
Abruzzo	8.3	25.5	17.1	67	66.05	353.0	250.0	20.4
Molise	6.9	25.0	16.1	68	61.95	382.8	250.0	13.4
Campania	6.5	22.4	14.6	66	64.78	411.9	250.0	11.5
Puglia	6.9	24.6	16.0	68	61.21	394.5	250.0	17.8
Basilicata	6.5	25.9	16.4	67	70.74	416.4	280.0	13.7
Calabria	6.4	22.4	14.6	68	62.91	346.3	250.0	17.6
Sicily	5.3	20.9	13.3	69	67.05	354.2	250.0	17.2
Sardinia	4.9	22.2	13.7	69	71.05	534.7	375.0	19.3
Italy	**5.4**	**19.7**	**12.7**	**68**	**65.49**	435.3	252.7	14.6
North	5.2	18.1	11.8	69	63.66	483.2	368.1	11.8
Centre	4.5	18.1	11.5	69	70.84	411.4	250.0	18.4
South and Islands	6.2	22.8	14.7	68	65.04	394.0	250.0	16.0

Table 3.8.1d Exposure and duration of therapy with osteoporosis drugs by Region under approved care regime and distribution on behalf (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Vitamin D and analogues	5.1	18.1	11.8	68	39.16	423.3	250.0	15.8
Bisphosphonates plain	0.2	2.0	1.1	73	114.10	223.9	226.0	9.4
Monoclonal antibodies-denosumab	0.04	0.52	0.29	74	339.13	333.8	363.6	33.0
Teriparatide	0.01	0.05	0.03	74	2,567.46	186.3	180.0	11.5
Bisphosphonates in combination	<0.05	0.6	0.3	74	130.87	225.8	252.0	7.3
Calcium and vitamin D	0.2	1.5	0.9	73	32.74	125.3	90.0	21.6
Calcium	0.2	0.5	0.3	71	24.82	48.6	30.0	26.1
SERM – selective estrogen receptor modulators	<0.05	<0.05	<0.05	67	180.87	237.8	280.0	6.6
Monoclonal antibodies-romosozumab	-	<0.05	<0.05	70	711.84	50.9	60.2	38.5
Medicines for osteoporosis	**5.4**	**19.7**	**12.7**	**68**	**65.49**	**435.3**	**252.7**	**14.6**

Table 3.8.1e Indicators of adherence to treatment with osteoporosis medicines in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=45,937						North N=18,732					
45-54 years	7.2	7.0	6.8	6.9	2	-4	4.7	4.9	5.2	4.7	-9	1
55-64 years	6.2	6.1	6.4	6.8	6	10	4.9	5.3	4.9	5.2	5	6
65-74 years	6.8	6.5	6.5	7.6	16	13	5.3	5.1	5.4	6.2	15	16
75-84 years	7.4	7.2	7.8	8.0	2	8	5.8	5.9	6.4	6.9	7	20
≥ 85 years	9.8	8.1	9.9	9.6	-3	-2	8.7	6.8	7.3	8.5	16	-2
Females	6.7	6.5	6.6	7.2	9	7	5.5	5.3	5.4	5.8	8	6
Males	10.7	9.4	11.4	11.5	1	8	6.6	6.7	7.9	8.6	8	30
Total	**7.1**	**6.8**	**7.0**	**7.5**	**7**	**7**	**5.6**	**5.5**	**5.6**	**6.1**	**8**	**9**
	Centre N=9,647						South N=17,558					
45-54 years	6.8	6.6	4.8	5.8	21	-14	8.6	9.1	9.8	9.5	-3	10
55-64 years	6.4	6.5	6.5	6.1	-6	-5	6.6	6.8	7.9	8.8	12	33
65-74 years	6.2	6.5	6.7	8.0	20	28	7.7	7.9	7.7	8.7	14	13
75-84 years	7.2	7.5	9.1	8.2	-9	15	8.5	8.6	8.8	9.4	7	10
≥ 85 years	8.8	9.2	12.2	13.1	8	49	11.0	9.0	11.3	8.8	-22	-20
Females	6.5	6.7	6.9	7.3	5	12	7.5	7.6	7.8	8.5	9	14
Males	9.4	10.5	12.0	11.0	-8	17	14.2	12.6	15.7	15.4	-2	8
Total	**6.8**	**7.0**	**7.3**	**7.6**	**4**	**12**	**7.9**	**7.9**	**7.3**	**9.0**	**23**	**13**

continued

Table 3.8.1e – *continued*

	High adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=45,937						North N=18,732					
45-54 years	64.8	68.5	71.1	68.1	-4	5	72.6	73.2	75.9	71.0	-6	-2
55-64 years	67.8	68.7	70.6	68.6	-3	1	71.4	71.5	74.2	72.5	-2	2
65-74 years	68.0	68.0	69.5	67.5	-3	-1	72.8	72.0	73.3	70.3	-4	-3
75-84 years	67.5	67.2	66.5	66.0	-1	-2	70.2	70.6	68.8	67.8	-1	-3
≥ 85 years	62.5	64.7	62.7	63.1	1	1	64.6	67.4	65.6	65.5	0	1
Females	67.3	67.7	69.1	67.4	-2	0	70.8	71.1	72.3	70.1	-3	-1
Males	66.1	67.8	65.8	65.3	-1	-1	73.1	71.9	70.5	68.9	-2	-6
Total	**67.2**	**67.7**	**68.8**	**67.3**	**-2**	**0**	**71.0**	**71.2**	**72.15**	**70.0**	**-3**	**-1**
	Centre N=9,647						South N=17,558					
45-54 years	66.4	69.2	74.3	71.1	-4	7	60.2	63.7	64.1	63.5	-1	6
55-64 years	68.5	69.6	71.3	70.8	-1	3	65.9	65.6	66.6	63.8	-4	-3
65-74 years	68.0	68.2	68.9	67.7	-2	0	65.8	64.4	66.0	64.6	-2	-2
75-84 years	69.0	66.9	66.4	66.8	1	-3	64.9	63.4	63.4	63.2	0	-3
≥ 85 years	65.4	63.0	62.9	59.3	-6	-9	59.4	62.5	59.6	62.3	5	5
Females	68.3	67.9	69.6	68.1	-2	0	65.0	64.4	65.4	64.3	-2	-1
Males	66.2	67.6	64.1	69.2	8	5	61.2	62.5	60.2	58.4	-3	-5
Total	**68.1**	**67.9**	**69.2**	**68.2**	**-1**	**0**	**64.7**	**64.2**	**65.1**	**63.9**	**-2**	**-1**

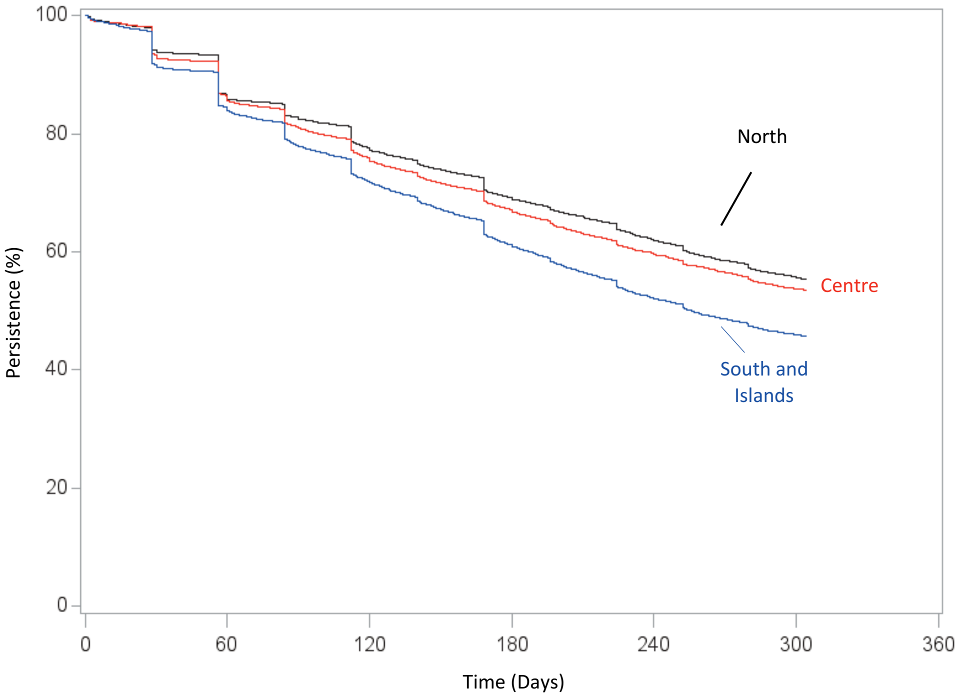
*Adherence to treatment was assessed within 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions provided. Low adherence to treatment was defined as therapeutic coverage (assessed based on DDD) <40% of the observation period, whereas high adherence was defined as therapeutic coverage ≥ 80% of the observation period (for further details please refer to the statistical methods).
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of subjects with low/high adherence related to the specified category.
Median follow-up time (in days) (IQR): 314 (192-343)

Table 3.8.1f Persistence after one year of treatment with medicines for osteoporosis in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Persistence after 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=45,937						North N=18,732					
45-54 years	51.1	54.7	55.4	54.8	-1	7	58.8	59.6	60.6	58.7	-3	0
55-64 years	51.8	54.1	55.1	54.1	-2	5	58.0	59.0	60.4	58.2	-4	0
65-74 years	49.9	51.3	51.8	50.6	-2	1	57.6	57.3	57.2	54.7	-4	-5
75-84 years	47.9	48.7	48.0	48.3	0	1	54.0	53.2	52.1	51.7	-1	-4
≥ 85 years	41.4	43.7	41.8	43.0	3	4	44.5	48.9	48.6	48.1	-1	8
Females	49.8	51.2	52.3	51.7	-1	4	55.9	56.2	57.1	55.5	-3	-1
Males	43.5	47.1	42.8	42.5	-1	-2	53.0	53.8	50.4	47.6	-6	-10
Total	**49.3**	**50.9**	**51.5**	**51.0**	**-1**	**3**	**55.6**	**55.9**	**56.5**	**54.7**	**-3**	**-2**
	Centre N=9,647						South N=17,558					
45-54 years	54.1	58.9	62.4	60.6	-3	12	45.9	47.8	45.5	47.7	5	4
55-64 years	55.6	56.4	58.6	57.6	-2	4	47.2	48.3	47.7	48.2	1	2
65-74 years	50.5	53.0	52.9	52.6	0	4	46.0	44.9	45.6	45.4	0	-1
75-84 years	48.8	46.9	47.7	50.0	5	2	43.7	44.3	42.9	43.0	0	-2
≥ 85 years	44.4	41.1	37.1	39.3	6	-11	37.8	39.1	37.4	39.2	5	4
Females	51.7	52.4	54.2	54.0	0	5	45.7	45.8	46.1	46.5	1	2
Males	42.9	44.0	42.6	45.6	7	6	37.3	39.7	32.6	34.1	4	-9
Total	**50.9**	**51.7**	**53.3**	**53.4**	**0**	**5**	**45.1**	**45.4**	**45.1**	**45.6**	**1**	**1**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to the statistical methods).

Figure 3.8.1d Time (in days) to discontinuation of treatment with medicines for osteoporosis in the population aged ≥45 years stratified by geographical area; curves are adjusted by gender and age (the Cox model was used to estimate persistence curves)



In 2022 there was a slight reduction in the use of osteoporosis drugs, but at lower levels than before the pandemic. Almost 90% of consumption in the category refers to cholecalciferol, which records the highest prevalence of use in the category. This active ingredient also ranks first in terms of consumption and third in per capita expenditure among the medicines provided under approved care regime. After the recovery in consumption observed in 2021, to be attributed to the dilution of the effects of the application of Note 96 and to the inappropriate prescription of vitamin D as an anti-COVID-19 protective, in 2022 the consumption of cholecalciferol decreased slightly.

Among the remaining classes of drugs, an increase is recorded in the consumption of bisphosphonates and monoclonal antibodies, in particular denosumab, probably due to a greater confidence in handling the drug, together with the unavailability of strontium ranelate as an alternative to bisphosphonates; the prevalence of these classes of drugs is significantly lower (at least 10 times) than vitamin D and analogues.

It is estimated that most of the real-life population is exposed to the sun for adequate periods to ensure sufficient serum levels of vitamin D (≥ 20ng/mL in countries at UK latitudes). The high level of vitamin D consumption and prescription observed in Italy, as well as the universal screening to establish circulating vitamin D levels, therefore appears unjustified and could constitute an overtreatment of the healthy population; this could expose a significant ratio of individuals to potential health risks, without any benefit in terms of reducing the incidence of bone fractures. Vitamin D supplementation should only be practiced in patients with documented osteoporosis or with previous pathological fractures and in particular risk groups, such as elderly people in nursing homes, pursuant to AIFA Note 96. The inappropriate use of vitamin D is laso confirmed by the increased consumption observed in the Southern Regions, contrary to what can be assumed given the higher exposure based on latitude.

The analysis of adherence and persistence to treatment continues to show low levels, with half of the patients discontinuing therapy in the first year after initiation; this data could also be explained by an excessive and inappropriate prescription of vitamin D preparations. Adherence to treatment is one of the key points of therapy for osteoporosis, and in cases where it is indicated, the prescriber is required to carefully evaluate the preferences and lifestyle of the patient, in order to devise a therapeutic strategy that is appropriate and effective from a clinical point of view, but also well tolerated by the patient, in order to avoid most of the therapeutic failures in this care setting.

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3.8.2 Nonsteroidal anti-inflammatory drugs (NSAIDs)

- As already observed in 2021, NSAID consumption increased in 2022 (Figure and Table 3.8.2a). In detail, in the last year there was a 7.1% increase in consumption (19.1 DDD), while the cost per day of therapy remained stable at EUR 0.38. Extending the analysis to the last nine years, however, an average annual variation decreasing by 2.2% is observed. Per capita expenditure on these drugs was EUR 2.65, up 7.2% compared to 2021.
- The main therapeutic categories (traditional NSAIDs and Coxib) show expenditure increases of 11.2% and 2.5% respectively. Traditional NSAIDs represent the category with the highest per capita expenditure (1.83 euros) and consumption (14.0 DDD, a 9.8% increase), both accounting for about 70% of the entire category. From 2014 to 2020, there has been a gradual reduction in consumption for this category, while in the last two years there has been an increase, reaching in 2022 a value similar to 2017 (Figure 3.8.2b). The second category with the highest expenditure (0.72 euros) and consumption (4.3 DDD/1000 inhabitants per day, a 3.3% increase), is represented by Coxibs, which show a stability in the average DDD cost (-0.7%), equal to EUR 0.46.
- The analysis of the individual molecules shows a pattern similar to that observed for the categories. In particular, the most expensive active ingredient is diclofenac (EUR 0.65), followed by etoricoxib (EUR 0.61) and ibuprofen (EUR 0.45), all three with increases of 6.3%, 3.7% and 50.7% respectively. The increase of ibuprofen is attributable to a high incidence of influenza in the 2022-2023 season, especially in the paediatric age, which led to a wide use of this drug for fever symptoms. Ketorolac, approved only for the short-term treatment (maximum five days) of moderate-to-severe post-operative pain, is among the molecules with the highest average cost per DDD (EUR 0.48); it decreased by 8.9% compared to 2021, whereas consumption increased by 12.6% (Table 3.8.2a). Significant reductions in consumption (-22.6%) are observed for piroxicam, a molecule with significant side effects, including an important risk of gastrolesivity.
- Analysing the regional variability of NSAID consumption (Table 3.8.2b), the Southern Regions (27.5 DDD/1000 inhabitants per day) have more than double consumption compared to the North (13.3 DDD/1000 inhabitants per day) and about 50% higher than the Centre (18.7 DDD/1000 inhabitants per day). For all three geographical areas, there was an increase in consumption between 6.3% in the Centre, 6.9% in the South and 7.9% in the North. Calabria, Campania and Puglia are the regions with the highest values, respectively 30.2 for the first two and 28.4 DDD respectively; PA of Bolzano, Veneto and Lombardy show the lowest values (12 DDD for the first two and 12.1 DDD respectively). The highest increases were in Emilia Romagna, Molise and Abruzzo, respectively 13.8%, 13.2% and 12.3% compared to 2021, while the only region with a reduction in consumption is Umbria (-5.6%). Since the average cost per DDD is quite similar in the various Italian regions, those with higher consumption, such as Calabria, Campania and Puglia, are also the ones with the highest expenditure, with EUR 4.22, 4,19 and 4.03 per capita respectively.

Figure 3.8.2a Nonsteroidal anti-inflammatory drugs (NSAIDs), 2014-2022 temporal trend of consumption and average cost per day of therapy

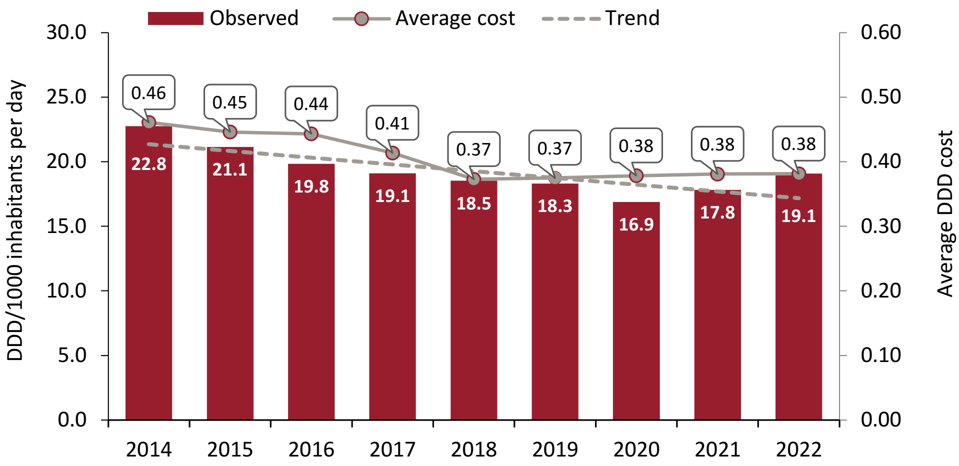


Table 3.8.2a Nonsteroidal anti-inflammatory drugs (NSAIDs), per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Traditional NSAIDs	1.83	11.2	-1.8	14.0	9.8	-2.1	0.36	1.3
Coxib	0.72	2.5	-8.8	4.3	3.3	-1.3	0.46	-0.7
Oxicam	0.09	-19.7	-7.5	0.7	-14.4	-7.4	0.36	-6.2
Other nonsteroidal anti-inflammatory/ anti-rheumatic medicines	0.01	-11.7	-13.7	<0.05	-12.8	-16.3	0.66	1.2
Nonsteroidal anti-inflammatory drugs (NSAIDs)	**2.65**	**7.2**	**-4.5**	**19.1**	**7.1**	**-2.2**	**0.38**	**0.1**
diclofenac	0.65	6.3	0.9	4.5	6.4	0.8	0.40	0.0
etoricoxib	0.61	3.7	-8.1	3.6	4.5	-0.4	0.46	-0.8
ibuprofen	0.45	50.7	3.6	3.0	47.5	3.8	0.41	2.2
ketoprofen	0.27	-0.6	-6.1	2.7	-0.4	-5.6	0.28	-0.2
nimesulide	0.15	-0.6	-4.8	1.9	-0.8	-5.2	0.22	0.2
celecoxib	0.11	-3.6	-11.6	0.6	-3.4	-5.0	0.47	-0.2
ketorolac	0.10	2.6	-3.5	0.6	12.6	-1.5	0.48	-8.9
aceclofenac	0.07	-3.5	-10.0	0.4	-2.7	-8.8	0.49	-0.8
piroxicam	0.06	-27.5	-7.0	0.4	-22.6	-6.7	0.42	-6.3
dexibuprofen	0.06	0.4	-1.5	0.3	0.4	-1.5	0.49	0.0

Figure 3.8.2b Nonsteroidal anti-inflammatory drugs (NSAIDs), temporal trend of consumption (DDD/1000 inhab. per day) of the most expensive subgroups (2014-2022)

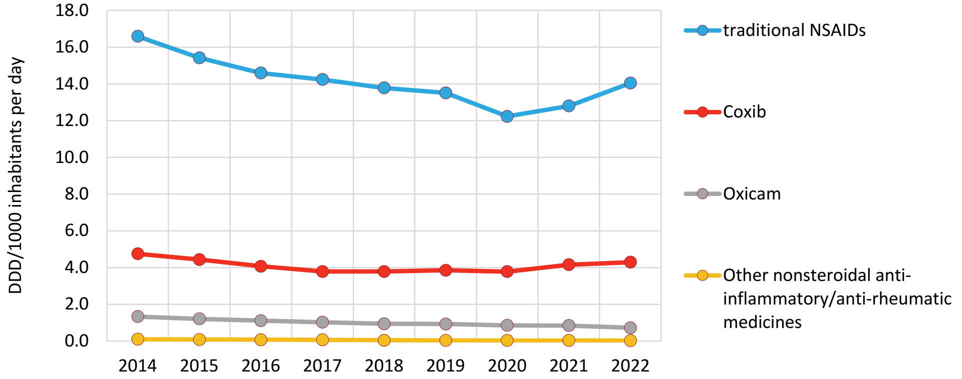


Table 3.8.2b Nonsteroidal anti-inflammatory drugs (NSAIDs), temporal trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	2.01	14.4	0.38	2.14	15.4	0.38	6.3	6.8	-0.4	-4.2	-2.2	-2.1
Valle d'Aosta	2.23	15.8	0.39	2.36	16.8	0.39	6.1	6.4	-0.3	-5.5	-3.5	-2.1
Lombardy	1.55	11.2	0.38	1.67	12.1	0.38	7.4	7.5	-0.2	-4.0	-1.3	-2.8
PA Bolzano	1.53	11.4	0.37	1.64	12.0	0.37	7.1	4.9	2.1	-6.5	-3.5	-3.2
PA Trento	2.19	16.3	0.37	2.38	17.6	0.37	8.6	8.2	0.4	-2.0	0.7	-2.7
Veneto	1.58	11.5	0.38	1.67	12.0	0.38	5.3	4.3	0.9	-6.0	-3.4	-2.7
Friuli VG	2.38	18.1	0.36	2.59	19.5	0.36	8.8	7.7	1.0	-3.7	-0.9	-2.9
Liguria	1.80	12.4	0.40	1.97	13.6	0.40	9.9	9.4	0.4	-4.8	-2.0	-2.8
Emilia R.	1.56	11.7	0.36	1.72	13.4	0.35	10.3	13.8	-3.1	-3.0	-0.5	-2.5
Tuscany	1.81	13.2	0.38	1.85	13.4	0.38	2.0	1.3	0.7	-5.5	-3.8	-1.8
Umbria	1.87	13.7	0.37	1.76	12.9	0.37	-5.7	-5.6	-0.2	-5.2	-3.3	-2.0
Marche	1.91	13.3	0.39	2.00	14.0	0.39	4.8	5.1	-0.2	-5.8	-3.3	-2.5
Lazio	3.10	22.4	0.38	3.41	24.5	0.38	10.0	9.6	0.4	-5.0	-2.1	-3.0
Abruzzo	2.76	19.6	0.39	3.11	22.0	0.39	12.6	12.3	0.2	-2.6	-0.5	-2.1
Molise	3.36	22.9	0.40	3.78	25.9	0.40	12.6	13.2	-0.6	-3.8	-1.1	-2.8
Campania	3.86	27.9	0.38	4.19	30.2	0.38	8.6	8.1	0.4	-2.8	-1.0	-1.9
Puglia	3.85	27.1	0.39	4.03	28.4	0.39	4.6	4.7	0.0	-5.6	-3.9	-1.7
Basilicata	3.43	24.4	0.39	3.84	27.3	0.39	11.8	11.8	-0.1	-2.2	-0.4	-1.8
Calabria	3.92	28.2	0.38	4.22	30.2	0.38	7.4	6.9	0.5	-4.2	-2.2	-2.0
Sicily	3.28	23.2	0.39	3.47	24.3	0.39	5.6	4.7	0.9	-5.0	-2.6	-2.4
Sardinia	3.67	26.1	0.38	3.94	28.1	0.38	7.4	7.7	-0.2	-4.9	-2.8	-2.1
Italy	**2.48**	**17.8**	**0.38**	**2.65**	**19.1**	**0.38**	**7.2**	**7.1**	**0.1**	**-4.5**	**-2.2**	**-2.3**
North	1.70	12.4	0.38	1.83	13.3	0.38	7.5	7.9	-0.4	-4.3	-1.7	-2.6
Centre	2.44	17.6	0.38	2.60	18.7	0.38	6.7	6.3	0.4	-5.2	-2.7	-2.6
South and Islands	3.61	25.8	0.38	3.88	27.5	0.39	7.2	6.9	0.3	-4.2	-2.2	-2.0

Exposure in population

- Health Card data were collected to perform an analysis aimed at estimating exposure and intentsity of use of NSAIDs in the general population. In 2022, around 16 out of 100 citizens received at least one NSAID prescription, with a higher level of exposure in females (18.1%) than males (13.7%). As expected, on the basis of the epidemiology of some clinical conditions such as arthritis and osteoarthritis in which these drugs are used, consumption increases with age until it reaches a maximum value of 53.3 in females and 37.6 DDD/1000 inhabitants per day in males in the 75-84 age group. In this same group, the prevalence of use is between 37.5% in women and 30.8% in males (Figure 3.8.2c), while up to the age of 34 it does not reach 10%, and in any case in all groups females show higher values than males.
- The analysis of the prescribing profile in the population and by Region shows that the median age of users is 63 years, with regional fluctuations between 61 and 67 years (Table 3.8.2c). The regional variability is highlighted by the higher prevalence values found in the South (22.0%), compared to the Centre (17.4%) and especially the North (10.9%), with a maximum value of 24.0% in Puglia and a minimum of 6.6% in the Province of Bolzano. In assessing these territorial differences, it should be considered the possible greater use of private purchase of Class A or self-medication drugs in the Northern Regions. As expected, this category of drugs is used as needed and for short periods. In fact, half of users take NSAIDs for one month per year and 50.9 % receive only one prescription. The cost per user is EUR 15.95.
- 13.7% of the Italian population received at least one prescription for traditional NSAIDs and 3.2% of Coxib, whose cost per user (EUR 21.80) is about 40% higher than the average (Table 3.8.2d) and the median age of users in the latter category is 67 years. The median of use does not differ between the two categories (20 vs 30).

Figure 3.8.2c Distribution of prevalence of use and consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) under approved care regime and distribution "on behalf" (year 2022)

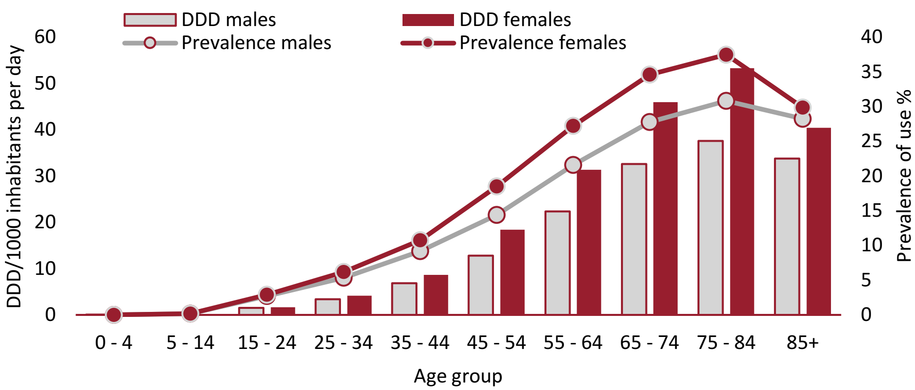


Table 3.8.2c Exposure and duration of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) by Region under approved care regime and distribution "on behalf" (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	11.2	15.4	13.4	65	16.06	40.9	23.8	53.9
Valle d'Aosta	10.6	14.9	12.8	63	17.41	44.5	30.0	53.9
Lombardy	7.7	11.1	9.4	64	15.78	40.7	30.0	54.9
PA Bolzano	5.5	7.6	6.6	67	20.41	51.4	30.0	51.2
PA Trento	11.9	15.8	13.9	61	15.74	41.5	26.0	51.2
Veneto	7.6	11.0	9.3	64	17.07	43.2	30.0	55.4
Friuli VG	12.8	17.8	15.4	63	17.03	45.4	30.0	48.8
Liguria	11.3	15.1	13.3	66	15.25	37.4	20.0	57.5
Emilia R.	9.9	13.2	11.6	62	13.52	33.7	20.0	56.2
Tuscany	11.4	14.8	13.2	64	13.67	35.1	20.0	56.9
Umbria	12.0	15.1	13.6	64	13.04	33.6	20.0	57.1
Marche	12.8	15.8	14.3	65	13.89	34.1	20.0	57.5
Lazio	18.7	24.2	21.5	62	15.39	39.8	23.8	49.7
Abruzzo	19.1	23.8	21.5	63	13.94	35.4	20.0	54.1
Molise	20.7	25.6	23.2	65	16.31	40.2	24.0	48.8
Campania	19.4	25.8	22.7	61	16.65	43.1	30.0	47.8
Puglia	21.2	26.6	24.0	63	16.05	40.7	30.0	46.3
Basilicata	20.9	26.8	23.9	62	15.62	39.9	25.0	49.9
Calabria	18.7	24.3	21.6	66	18.70	48.3	30.0	44.2
Sicily	16.4	21.4	19.0	66	17.33	43.7	30.0	47.4
Sardinia	20.3	26.4	23.4	63	17.00	43.7	30.0	46.2
Italy	**13.7**	**18.1**	**15.9**	**63**	**15.95**	**40.8**	**28.3**	**50.9**
North	9.1	12.6	10.9	64	15.74	40.1	24.0	54.7
Centre	15.1	19.5	17.4	63	14.69	37.8	21.0	52.7
South and Islands	19.1	24.7	22.0	63	16.67	42.6	30.0	47.4

Table 3.8.2d Exposure and duration of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) by subgroup under approved care regime and distribution "on behalf" (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Traditional NSAIDs	11.9	15.4	13.7	63	12.69	34.3	19.8	54.1
Coxib	2.3	4.1	3.2	67	21.80	47.3	30.0	61.2
Oxicam	0.6	1.0	0.8	67	11.08	31.1	20.0	70.3
Other nonsteroidal anti-inflammatory/ anti-rheumatic medicines	0.01	0.02	0.02	68	28.71	43.8	30.0	78.7
Nonsteroidal anti-inflammatory drugs (NSAIDs)	**13.7**	**18.1**	**15.9**	**63**	**15.95**	**40.8**	**28.3**	**50.9**

In 2022, the increasing trend in consumption of non-steroidal anti-inflammatory drugs is confirmed, reaching pre-pandemic levels. This increase is attributable to the class of traditional NSAIDs, which covers more than 70% of consumption in the category; diclofenac is the most prescribed active ingredient.

For this category, there is a high level of private purchase, which limits the possibility of adequately monitoring the prescribing appropriateness of these drugs, with a consequent difficult assessment of user compliance and the consequent potential occurrence of adverse events. For this reason, it is desirable to conduct ad hoc analyses on the impact of the private purchase of NSAIDs by citizens.

In the therapeutic choice of using an NSAID, account should be taken of both the overall benefit/risk profile of the drug and the characteristics of populations that may present contraindications or risk factors predisposing the occurrence of side effects.

3.9 Systemic hormonal preparations, excluding sex hormones and insulins

In 2022, the therapeutic category of systemic hormone preparations, excluding sex hormones and insulins (ATC H), ranks ninth in terms of public expenditure, accounting for EUR 488.4 million and 2.0% of total public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure for these drugs was EUR 8.28, mainly resulting from the purchase by public health facilities, with EUR 4.30 per capita, up 1.5%. Expenditure due to approved care regime is lower (EUR 3.98 per capita), despite recording an increase of 4.1% compared to the previous year (Table 3.1).
Consumption for this category of drugs reached 44.03 DDD/1000 inhabitants per day in 2022, up 6.2% compared to 2021, so confirming the increasing trend in the last nine years (CAGR 2014-2022: +0.9%), whereby this category ranks seventh in terms of consumption (Table 3.2).
The analysis of the drug use profile, including approved care regime and distribution “on behalf”, shows an increasing use of this category of medicinal products with increeasing age, for both females and males, with a higher increase from 35 years onwards. However, use remains consistently higher in females than in males, with the exception of the age group 0-14 years, probably justifiable with the tendency of early use of corticosteroids and treatment of subclinical hypothyroidism in paediatric age. About one in three females in the age group over 75 received at least one prescription during the year. At the same time, NHS per capita expenditure also increases with the age of patients, reaching the maximum value of EUR 12.3 per capita in patients over 75 years (EUR 14.1 in females and 9.6 in males).
As regards approved care regime, per capita expenditure was EUR 3.98, up 3.6% compared to the previous year, due to an increase in consumption (+5.2 %); a slight reduction was recorded for prices (-1.7%) and for average cost per day of therapy (-1.5%) compared to 2021 (Table 3.9).
The categories with the greatest impact on pharmaceutical expenditure are glycocorticoids (EUR 1.53 per capita, 38% of the total category), followed by thyroid hormones (EUR 1.43 per capita). Glycocorticoids show an increase in both expenditure and consumption (+5.8% and +7.1% respectively) compared to the previous year, with a shift towards less expensive specialties (mix effect -1.0%). Thyroid hormones, which show the highest consumption in the whole group of systemic hormonal preparations (22.7 DDD/1000 inhabitants per day), also recorded increases in both expenditure and consumption compared to 2021 (+13.1% and +4.5% respectively), with a higher tendency to use more expensive drugs (mix effect: +8.3%). Parathyroid hormones also recorded a decrease in expenditure and consumption in 2022 (-14.2% and -5.2% respectively) and an average cost reduction per DDD of 9.5%, due to the entry into market of generic medicines. The most expensive active ingredient is levothyroxine (EUR 1.39), followed by prednisone (EUR 0.71) and teriparatide (EUR 0.67) (Table 3.10). As for consumption, levothyroxine with 22.7 DDD accounts for 58.4% of systemic hormonal preparations (38.9 DDD). This substance ranks 14th among the 30 active substances with the largest variation in approved care expenditure compared to 2021, with an increase of +14% (Table 3.15)

and ninth within the most consumed active ingredients (Table 3.17). Prednisone ranks 19th within the drugs with the highest cost per day of therapy (Table 3.14) while teriparatide ranks 7th among the active ingredients recording higher reductions in expenditure (Table 3.16).

As for purchases by public health facilities, compared to 2021, there was a slight increase in expenditure (+1.1%) followed by a marked increase in consumption (+9.8%), a reduction in prices (-4.0%) and a shift towards cheaper medicines (mix effect: -4.1%) with a corresponding decrease in the average cost per day of therapy (-7.9%) (Table 3.19).

The category with the greatest impact on expenditure is represented by somatostatin and analogues (EUR 1.62 per capita), up by 4.4% compared to 2021, accounting for 37.7% of expenditure of the entire class, followed by somatotropin and analogues (EUR 1.16 per capita). Compared to 2021, there was an increase in consumption for both sub-categories (+7.9% and +2.0% respectively); however, for somatotropin and analogues there was a higher reduction in prices (-7.5% vs -3.2%) and in the average cost per day of therapy (-6.4% vs -3.3%) (Table 3.19).

Somatropin is the active ingredient ranking first in this category of drugs both in terms of consumption (0.3 DDD/1000 inhabitants per day) and per capita expenditure (EUR 1.15, -4.0% compared to 2021), while etelcalcetide, indicated for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease undergoing haemodialysis, is the active ingredient recordiong the greatest increase in per capita expenditure compared to 2021 (+14.1%); pegvisomant, a genetically modified human growth hormone analogue acting as a growth hormone receptor antagonist, indicated for the treatment of hyperparathyroidism in adult patients with acromegaly, is the active ingredient with the highest average cost per day of therapy in this category (EUR 68.33), despite a slight decrease by 1.7% compared to 2021 (Table 3.20). In addition, compared to 2021, somatropin is among the top 30 active ingredients purchased by public health facilities recording a greater reduction in expenditure and alower average cost per day of treatment (Table 3.24 and 3.26), while levothyroxine ranks ninth among the top 30 active ingredients with the highest consumption as for medicines in approved care regime and purchased by public health facilities (Table 3.29).

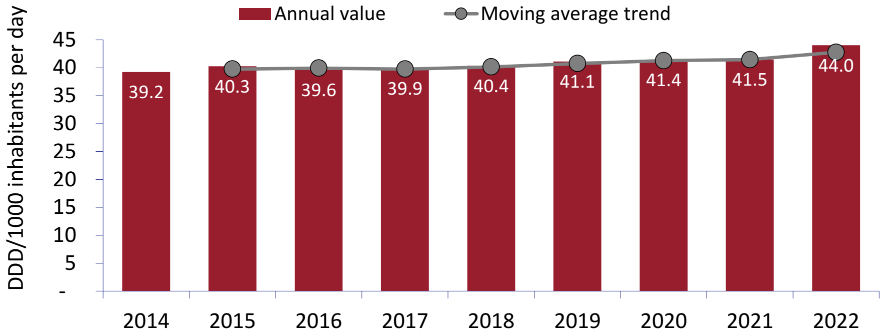
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by Region and on the efficiency in the absorption of resources according to the presence of off-patent medicines and on a regional basis. These analyses focused on thyroid drugs (Section 3.9.1).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

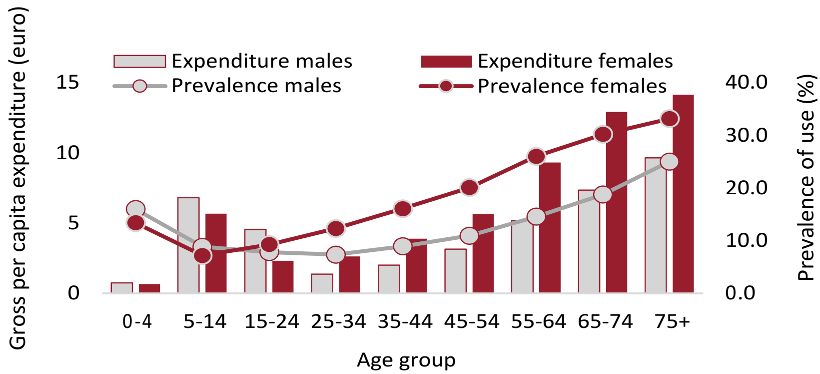
Systemic hormonal preparations, excluding sex hormones

Public expenditure* in million euros (% over total)	**488.4**	**(2.0)**
Δ % 2022-2021		2.7
Regional range of gross per capita expenditure:	6.3	10.1
DDD/1000 inhabitants per day* (% over total)	**44.0**	**(3.3)**
Δ % 2022-2021		6.2
Regional range DDD/1000 inhabitants per day	30.2	56.2

* *includes prescriptions under approved care regime and purchases by public health facilities*



Age and gender distribution of expenditure, prevalence of use and consumption under approved care regime and distribution "on behalf" in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.7	0.7	0.7	3.9	3.2	3.5
5-14	6.8	5.7	6.3	5.1	4.3	4.7
15-24	4.5	2.3	3.5	7.2	9.6	8.3
25-34	1.4	2.6	2.0	8.8	20.7	14.6
35-44	2.0	3.9	2.9	12.8	34.1	23.4
45-54	3.1	5.7	4.4	19.2	51.4	35.5
55-64	5.2	9.3	7.3	31.3	77.3	55.0
65-74	7.3	12.9	10.3	45.8	98.0	73.4
75+	9.6	14.1	12.3	63.4	104.5	87.9

3.9.1 Thyroid medicines

- Over the past 8 years, consumption of thyroid medicines has remained stable, with slight average annual variations (CAGR: +1.9%) (Figure 3.9.1.a). A slightly higher increase has been recorded since 2018 (22.1 DDD/1000 inhab. per day), reaching 24.4 DDD/1000 inhabitants per day in2 022, an increase of 4.5% compared to 2021. In recent years, there is also a greater variation in the average cost per day of therapy, which has grown overall by 53%, from EUR 0.11 in 2014 to EUR 0.17 in 2021, probably due to more expensive specialties.
- Thyroid hormones account for almost all expenditure and consumption in the entire category (EUR 1.43 per capita and 23.1 DDD/1000 inhabitants per day) (approximately 95%). In particular, in the last nine years, despite a moderate increase in consumption (CAGR: +2.1%), more significant changes have been recorded in terms of expenditure (CAGR: +7.9%), with an increase of 13.7% compared to 2021 (Table 3.9.1a and Figure 3.9.1b).
- Findings related to thyroid hormones are also observed in the analysis of the individual active substances. In fact, levothyroxine, a drug authorised for hypothyroidism and non-toxic thyroid hyperplasia or in the prevention of recurrence after partial removal of thyroid tissue, represents almost the entire prescription of the subgroup, recording in 2021 an expenditure of EUR 1.40 per capita, with an increase of 14.1% and gradually increasing over the years (CAGR: + 8.1%), and consumption levels of 23 DDD/1000 inhabitants per day. On the contrary, the use of antithyroid preparations (thiamazole) has decreased slightly over the years (CAGR: -0.8%). It should be noted that the average cost per DDD of levothyroxine increased by 8.8% due to an increased use of more expensive specialties.
- According to the prevalence data in the literature, the regions of the Centre show the highest levels of thyroid drug consumption in the last two years, reaching the value of 29.6 DDD/1000 inhabitants per day in 2022, an increase of 3.8% compared to 2021 (Table 3.9.1b), although the largest variation is recorded in the North (+5.2%). Molise is the region with the highest consumption (33.2 DDD; +6.6 % compared to 2021), followed by Basilicata (32.5 DDD). All regions, with the exception of Abruzzo, show expenditure increases of more than 10%, with per capita expenditure variability ranging from a minimum of EUR 0.80 in Liguria to EUR 2.15 in Molise (2.5 times). The average cost per DDD also increases in all regions, reaching a maximum of 12.6% in Molise.

Figure 3.9.1a Thyroid medicines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

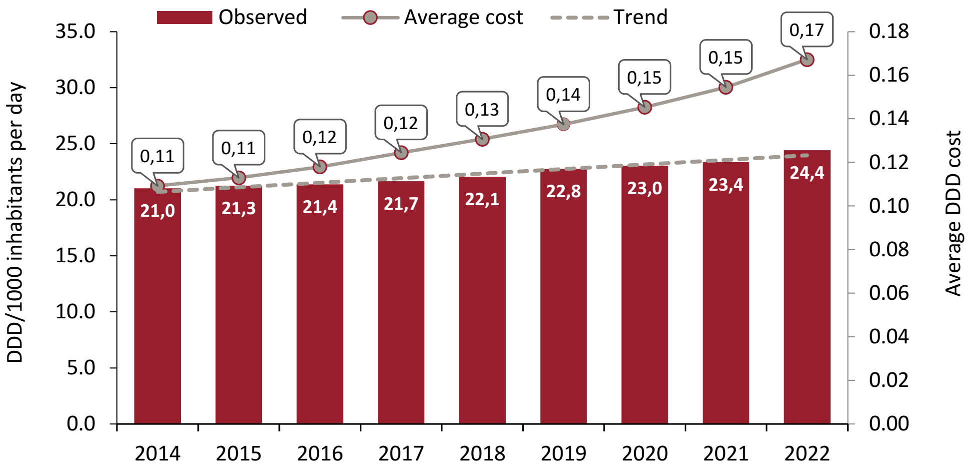


Table 3.9.1a Thyroid medicines, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Thyroid hormones	1.43	13.7	7.9	23.1	4.9	2.1	0.17	8.4
Antithyroid preparations	0.06	1.4	0.6	1.4	-0.5	-0.8	0.12	1.9
Thyroid medicines	**1.49**	**13.1**	**7.5**	**24.4**	**4.5**	**1.9**	**0.17**	**8.2**
levothyroxine	1.40	14.1	8.1	23.0	4.9	2.1	0.17	8.8
tiamazole	0.06	1.4	0.6	1.4	-0.5	-0.8	0.12	1.9
liothyronine	0.03	-0.8	1.8	<0.05	-0.8	1.8	2.07	0.0

Figure 3.9.1b Thyroid medicines, temporal trend of consumption (DDD/1000 inhab. per day) of most expensive subgroups (2014-2022)

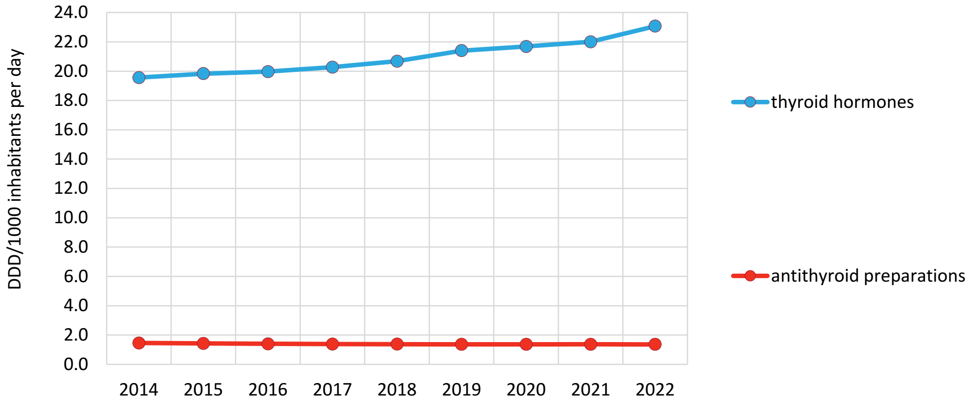


Table 3.9.1b Thyroid medicines, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	1.18	22.7	0.14	1.37	23.9	0.16	16.1	5.4	10.2	7.7	2.5	5.1
Valle d'Aosta	1.04	20.2	0.14	1.16	20.8	0.15	11.5	3.1	8.1	1.5	-2.1	3.7
Lombardy	0.96	16.2	0.16	1.10	17.1	0.18	15.1	5.7	8.9	9.3	2.8	6.3
PA Bolzano	0.99	22.0	0.12	1.10	22.6	0.13	11.1	2.8	8.0	4.7	0.8	3.9
PA Trento	1.67	29.6	0.15	1.89	31.0	0.17	12.8	4.6	7.8	7.9	2.6	5.2
Veneto	1.40	20.4	0.19	1.62	21.5	0.21	16.1	5.4	10.1	10.6	2.5	8.0
Friuli VG	1.42	26.0	0.15	1.58	27.4	0.16	11.1	5.4	5.4	7.6	2.5	5.0
Liguria	0.68	11.3	0.16	0.80	11.9	0.18	18.9	6.1	12.1	7.1	0.2	6.9
Emilia R.	1.43	30.2	0.13	1.58	31.5	0.14	10.9	4.3	6.3	5.7	1.6	4.0
Tuscany	1.21	25.4	0.13	1.35	26.8	0.14	11.2	5.8	5.1	6.3	2.3	3.8
Umbria	1.69	30.6	0.15	1.89	32.0	0.16	11.5	4.5	6.7	8.0	3.1	4.8
Marche	1.27	26.4	0.13	1.41	27.4	0.14	10.5	3.7	6.5	5.8	2.0	3.8
Lazio	1.88	31.0	0.17	2.07	31.8	0.18	10.2	2.6	7.4	6.8	0.7	6.0
Abruzzo	1.46	25.2	0.16	1.60	26.7	0.16	9.8	5.9	3.7	8.1	2.8	5.1
Molise	1.79	31.1	0.16	2.15	33.2	0.18	19.9	6.6	12.6	6.9	1.3	5.6
Campania	1.15	19.1	0.16	1.31	19.8	0.18	14.1	4.1	9.6	7.0	1.6	5.3
Puglia	1.64	28.5	0.16	1.86	29.9	0.17	13.3	4.7	8.2	7.5	2.5	4.9
Basilicata	1.51	30.6	0.13	1.69	32.5	0.14	12.1	5.9	5.8	6.9	2.8	3.9
Calabria	1.28	23.7	0.15	1.49	24.7	0.17	16.6	4.1	12.0	6.2	1.0	5.2
Sicily	1.34	22.2	0.17	1.52	23.1	0.18	13.1	4.1	8.6	8.0	2.0	6.0
Sardinia	1.56	28.9	0.15	1.74	29.5	0.16	11.3	2.2	8.9	5.9	0.1	5.8
Italy	**1.32**	**23.4**	0.15	**1.49**	24.4	0.17	**13.1**	4.5	8.2	**7.5**	1.9	**5.5**
North	1.16	20.8	0.15	1.33	21.8	0.17	14.4	5.2	8.8	8.2	2.2	5.8
Centre	1.57	28.6	0.15	1.74	29.6	0.16	10.6	3.8	6.5	6.7	1.5	5.1
South and Islands	1.38	23.9	0.16	1.57	24.9	0.17	13.4	4.3	8.7	7.2	1.8	5.3

Exposure in population

- Health Card data were collected to estimate exposure and intensity of use of thyroid medicines. As expected, according to epidemiological evidence, females use more drugs than males. Consumption increases progressively with age to reach higher values in the 75-84 age group: 75.3 DDD in females and 26.7 DDD in males. The prevalence is in line with consumption; in the age groups 65-74 and 75-84 years, females show percentage values of 17% and 15% respectively, about 6 times higher than males. However, the largest differences are observed in the 25-34 age group (F: 5.6% vs M: 1%) (Figure 3.9.1c).
- The prevalence of use is 5.2%, with a median age of 64 years and an M/F ratio of 1:4 (1.9%/8.4%). Liguria, despite having a higher median age (75 years), has the lowest prevalence of use (3.0%), while Molise -whose treated population is younger than the national average (64 years) - has a prevalence of use of 7.3%, reaching 11.6% in females. On average, each user is on treatment for about 5 and a half months, although half remain in therapy for less than 5 months, with no difference between geographical areas.
- To confirm the non-chronic use of these drugs and the not high cost per DDD, it should be emphasised that the average expenditure per user is just over EUR 27.76, but reaches EUR 36.37 in Veneto (Table 3.9.1c). Around 6% of users received in 2022 only one prescription with wide variability between regions, going from 2.7% in the PA Trento to 9.6% in Liguria.
- Almost all prescriptions are related to thyroid hormones (4.9%) while a residual share is related to anti-thyroid preparations (0.3%), predominantly used by males (0.5% vs 0.2%). For the latter category, patients are older (72 years) with a lower cost per user than thyroid hormones (EUR 16.17 vs EUR 28.5). Half of the users of these drugs are on treatment for less than 3 months and one in 3 received only one prescription, compared to 4.2% of thyroid hormone users.

Figure 3.9.1c Distribution of prevalence of use and consumption of thyroid medicines under approved care regime and distribution "on behalf" in 2022

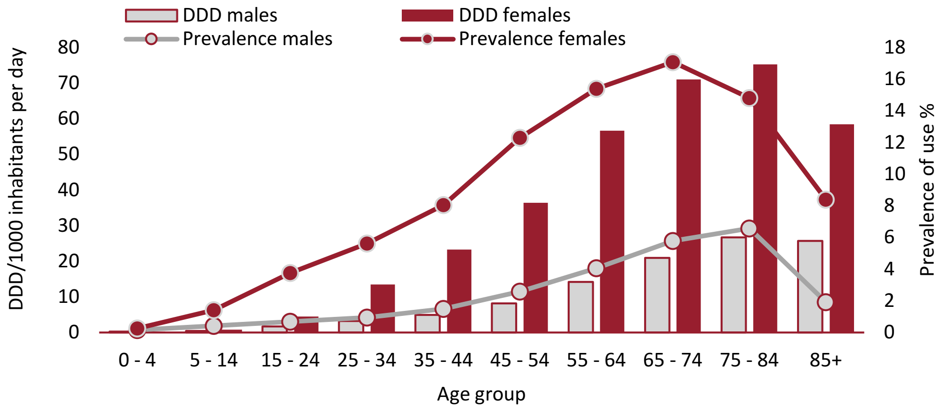


Table 3.9.1c Exposure and duration of therapy with thyroid medicines by Region under approved care regime and distribution "on behalf" (year 2022)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Piedmont	2.0	9.1	5.7	66	24.72	154.0	140.0	5.6
Valle d'Aosta	1.6	7.8	4.8	68	23.81	152.8	133.3	3.9
Lombardy	1.4	5.9	3.7	64	28.13	158.4	141.7	4.8
PA Bolzano	1.7	7.2	4.5	67	22.45	161.2	150.0	3.5
PA Trento	2.4	10.3	6.4	61	28.05	165.3	150.0	2.7
Veneto	1.6	7.1	4.4	62	36.37	172.4	153.3	4.7
Friuli VG	2.2	10.0	6.2	65	26.51	164.6	150.0	3.8
Liguria	1.1	4.8	3.0	75	28.25	144.5	133.3	9.6
Emilia R.	2.4	10.4	6.5	64	23.55	166.8	150.0	4.0
Tuscany	2.3	9.8	6.2	66	22.13	159.2	150.0	7.4
Umbria	2.8	11.4	7.2	64	26.90	164.9	150.0	6.0
Marche	2.4	9.8	6.2	65	22.92	162.6	150.0	6.0
Lazio	2.4	10.6	6.6	64	30.76	170.9	150.0	4.4
Abruzzo	2.2	9.0	5.7	64	27.63	167.5	150.0	6.2
Molise	2.7	11.6	7.3	64	30.25	168.6	150.0	4.8
Campania	1.7	6.9	4.3	62	27.64	152.4	133.3	8.3
Puglia	2.3	10.3	6.4	63	28.05	164.0	150.0	4.7
Basilicata	2.6	10.6	6.7	63	25.45	176.7	166.7	6.5
Calabria	2.1	8.3	5.2	65	27.63	166.0	150.0	8.2
Sicily	1.7	7.7	4.8	65	30.65	169.4	150.0	6.9
Sardinia	2.0	9.8	6.0	65	29.76	184.0	175.0	4.7
Italy	**1.9**	**8.4**	**5.2**	**64**	**27.76**	**164.0**	**150.0**	**5.6**
North	1.7	7.6	4.7	65	27.61	161.8	150.0	4.8
Centre	2.4	10.3	6.5	65	26.91	165.9	150.0	5.6
South and Islands	1.9	8.4	5.3	64	28.57	165.3	150.0	6.5

Table 3.9.2d Exposure and duration of therapy with thyroid medicines by subgroup under approved care regime and distribution “on behalf” (year 2022)

Subgroup	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	males	females	total					
Thyroid hormones	7.9	1.7	4.9	64	28.50	165.5	150.0	4.2
Antithyroid preparations	0.5	0.2	0.3	72	16.17	136.5	100.0	27.1
Thyroid medicines	**1.9**	**8.4**	**5.2**	**64**	**27.76**	**164.0**	**150.0**	**5.6**

In the last 9 years, the consumption of thyroid drugs has undergone a slow and progressive increase, almost exclusively due to levothyroxine, a hormone indicated for the treatment of acquired or congenital hypothyroidism, which covers more than 90% of consumption in the entire category. As expected, women have higher levels of use than men do, with a ratio of 4:1, and the Central Regions show the highest levels of consumption and prevalence compared to the South and North, according to the prevalence data in the literature.
Levothyroxine, in addition to being the highest-spending active ingredient in the category, ranks 26th among the drugs with the highest per capita expenditure provided under the approved care regime, ranked 14th among those with the highest expenditure (+14.0%), probably due to the increase in the average cost per day of therapy (+8.7%), given that consumption (22.7 DDD/1000 inhabitants per day) has only slightly increased compared to the previous year (+2.2%). On average, each user is on treatment for about 5.5 months, although half of the patients remain on therapy for less than 5 months without marked differences between geographical areas.

3.10 Sensory organs

In 2022, medicines for sensory organs are the tenth category for public expenditure, amounting to around EUR 409.1 million (1.7% of total expenditure; Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was 6.93 euros, mainly due to the approved care expenditure (EUR 3.65 per capita), reporting a -1.6% decrease compared to the previous year. Expenditure due to purchases of these medicines by public health facilities is slightly lower (EUR 3.28 per capita), but it shows an increase by 8.3% compared to 2021 (Table 3.1). Consumption for this category of drugs was 23.5 DDD/1000 inhabitants per day, an increase of 2.4% compared to the previous year (Table 3.2). This is mainly due to the approved care regime, with a consumption value of 21.3 DDD.

The analysis of the drug use profile by age group and gender, including approved care and distribution on behalf, confirms a limited use of these drugs up to 55 years, with an increase in later age groups, up to about 10 % in males over seventy-five years. The consumption remains slightly higher in males than in females, in all age groups, with the values differing more in the 75+ years (99.8 DDD in males vs 86.0 in females). At the same time, per capita expenditure also increases with age, reaching the maximum value of EUR 15.6 in the group over 75 years old and with a higher level of expenditure in males (EUR 17.0) compared to females (EUR 14.7).

As regards approved care regime, the regional distribution (Table 3.5) shows a modest variability (CV 18.8%) of gross per capita expenditure with maximum values in Marche (EUR 5.2) and Emilia Romagna (EUR 4.7) and minimum in the Provinces of Bolzano (EUR 2.6) and Trento (EUR 2.9). The distribution of consumption (Table 3.6) shows similar trends (CV 18.9%). Overall, expenditure in this distribution channel shows a reduction of 2.0%, mainly linked to a reduction in prices (-3.7%) and in the average DDD cost (-3.6%) (Table 3.9). Within this distribution channel, beta-blocking substances show the highest expenditure (EUR 2.06) and consumption (11.9 DDD). They are followed by prostaglandin analogues, with values of EUR 1.19 and 5.6 DDD respectively. The only category to record an increase in consumption in 2022 (+3.7%) is carbonic anhydrase inhibitors, medicines capable of decreasing the formation of aqueous humour, thus reducing intraocular pressure. The increase observed for this category is supported mainly by the association dorzolamide/timolol, which shows an increase in consumption of 17.3%. Timolol plain or in combination with other active ingredients accounts for about 45% of expenditure of the entire category (Table 3.10).

No active substance in this category ranks within the first thirty active ingredients for expenditure (Table 3.11), the first thirty with highest or lowest average cost per day of therapy (Table 3.13 and 3.14). The active ingredient tafluprost, used in the reduction of intraocular pressure in open-angle glaucoma and ocular hypertension, is present in the group of molecules with highest variation in the expenditure on approved care regime (Table 3.15), an increase of 4.7% compared to the previous year. In the approved care distribution channel, no molecule in the category ranks in the first thirty active ingredients with the greatest reduction in expenditure (Table 3.16) or among the first thirty for consumption (Table 3.17).

As for purchases by public health facilities, the regional distribution (Table 3.7) shows a variability (CV 23.1%) of gross per capita expenditure with maximum values in Molise (EUR 5.2) and Friuli VG (EUR 4.9) and lower values in Lazio and Tuscany (EUR 2.3). The distribution of consumption (CV 32.4%) (Table 3.8) shows higher values of use in Emilia Romagna (3.8 DDD) and in Veneto (3.2 DDD) and lower in Calabria and Sicily (0.9 DDD).

Overall, purchases by public health facilities showed an increase in expenditure of 7.9%, driven by an increase in consumption (+4.5%) and prices (+1.8%) and by the shift towards the purchase of more expensive substances (mix effect: +1.3%) (Table 3.19). The therapeutic category with the highest incidence on expenditure is antineovascularisation substances (accounting for 75% of expenditure), such as drugs for the treatment of age-related neovascular macular degeneration (AMD) and for the treatment of visual decrease caused by diabetic macular edema (DME). This category shows an increase in expenditure of 12%, mainly related to a shift towards more expensive medicinal products (mix effect: +15.5%). Within this subgroup, aflibercept is the active ingredient with the highest expenditure (EUR 1.48), with an impact on expenditure in the category of 45.1%, followed by ranibizumab (EUR 0.80 and an incidence of 24.2%) (Table 3.20). No active substance is included in the list of the first thirty active ingredients for expenditure (Table 3.21) or in the first thirty with greater variation in expenditure (Table 3.23). Ranibizumab ranks within the molecules with the greatest reduction in expenditure (Table 3.24), which, compared to the previous year recorded a reduction of 3.0%. Aflibercept is the only active ingredient in this ATC to be included in the list of molecules with the highest average cost per day of therapy (Table 3.25), with a value of EUR 493.2. On the other hand, none is present in the ranking of the active ingredients at lowest cost per DDD (Table 3.26) or in the list of the most consumed drugs (Table 3.27).

Table 3.30 shows the different trend in terms of expenditure, consumption and average DDD cost between the approved care regime and direct purchases for drugs for eye disorders.

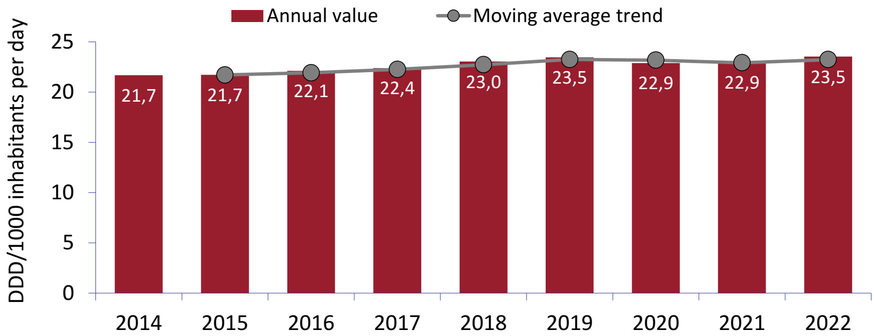
For further information on the use of medicines belonging to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region. These analyses focused on medicines for eye disorders (Section 3.10.1a).

Main indices of expenditure, consumption and exposure

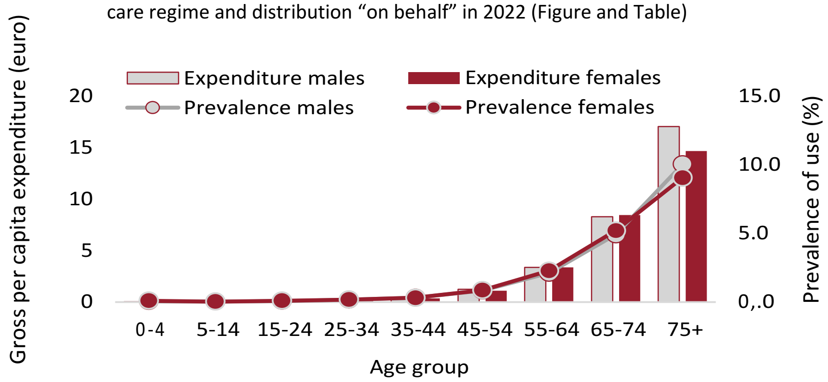
Sensory organs

Public expenditure* in million euros (% over total)	**409.1**	**(1.7)**
Δ % 2022-2021		2.9
Regional range of gross per capita expenditure:	5.7	8.9
DDD/1000 inhabitants per day* (% over total)	**23.5**	**(1.8)**
Δ % 2022-2021		2.4
Regional range DDD/1000 inhabitants per day	18.6	33.2

* *includes prescriptions under approved care regime and purchases by public health facilities*



Age and gender distribution of expenditure, prevalence of use and consumption under approved care regime and distribution “on behalf” in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.0	0.0	0.0	0.2	0.2	0.2
5-14	0.0	0.0	0.0	0.2	0.2	0.2
15-24	0.1	0.1	0.1	0.5	0.5	0.5
25-34	0.2	0.2	0.2	1.1	1.0	1.1
35-44	0.4	0.3	0.4	2.6	2.0	2.3
45-54	1.2	1.1	1.2	7.2	6.5	6.9
55-64	3.4	3.4	3.4	20.1	19.7	19.9
65-74	8.3	8.5	8.4	48.2	48.8	48.5
75+	17.0	14.7	15.6	99.8	86.0	91.6

3.10.1 Medicines for eye disorders

- In the last nine years, the consumption of drugs used for eye disorders has remained almost stable, from DDD 19.8 in 2014 to 21.5 DDD in 2022, with an average annual change of 1% (Figure and Table 3.10.1a). By analysing variation compared to the previous year, it is noted a slight 2.2% increase in consumption.
- Similarly to 2021, the highest consumption in 2022 is also represented by antiglaucoma preparations (21 DDD, or 98% of the total), which in more detail concern antiglaucoma/beta-blocking preparations plain or in combination (12.4 DDD/1000 inhabitants per day) and preparations antiglaucoma/prostanglandin analogues (5.7 DDD) (Table 3.10.1a). This trend is also partly observed for per capita expenditure, which is EUR 2.12 for the former and EUR 1.19 for the latter, both of which are down respectively 2.7% and 0.1% compared to 2021. Antiglaucoma/beta-blocking preparations alone or in combination recorded an 11% increase in DDD in 2022 compared to 2014 (Figure 3.10.1b). Anti-VEGF recombinant fusion proteins (aflibercept) increase both in terms of expenditure and consumption (+12.7%), and record values of EUR 1.48 with an average cost per day of therapy among the highest in the entire category (EUR 493.19). Monoclonal anti-VEGF antibodies (brolucizumab) and neovascularising agents (photodynamic therapy) have the highest expenditure increases (>100%).
- Timolol plain or in combination is the active ingredient with highest expenditure (EUR 2 per capita) and consumption (11.6 DDD). These are followed by aflibercept (EUR 1.48) and ranibizumab (EUR 0.80), drugs indicated in the treatment of (exudative) age-related macular degeneration (AMD) (Table 3.10.1a). As of 1 January 2021 (GU No 323 of 31 December 2020), Aifa Note 98 has entered into force, which regulates the modalities of prescribing, intravitreal administration and use of anti-VEGF medicines paid by the NHS for the treatment of maculopathy. In view of the available scientific evidence, AIFA's CTS gave its opinion on the overlapping of anti-VEGF aflibercept, bevacizumab, brolucizumab and ranibizumab as regards the indication in the treatment of AMD.
- At a regional level, there is a clear variability in consumption, with values ranging from 16.8 DDD of Molise to 31.3 DDD of Marche (a difference of 86%) (Table 3.10.1b). Friuli is the region with the highest level of per capita expenditure (EUR 8.68) while Sicily has the lowest expenditure (EUR 5.61, a difference of 55%). Valle d'Aosta is the region with the highest variation in expenditure compared to the previous year (+33.5%), while Tuscany shows the largest reduction (-9.3%). As regards consumption, all regions record an increase compared to 2021 (Table 3.10.1b). The highest average cost is found in Molise (EUR 1.31), almost double than Tuscany (EUR 0.68). The Central regions show the highest consumption (25 DDD), while the highest expenditure is observed in the North (EUR 6.92), resulting from a combination of average DDD cost of EUR 0.89 and a consumption of 21.3 DDD.

Figure 3.10.1a Medicines for eye disorders, temporal trend of consumption and average cost per day of therapy (2014-2022)

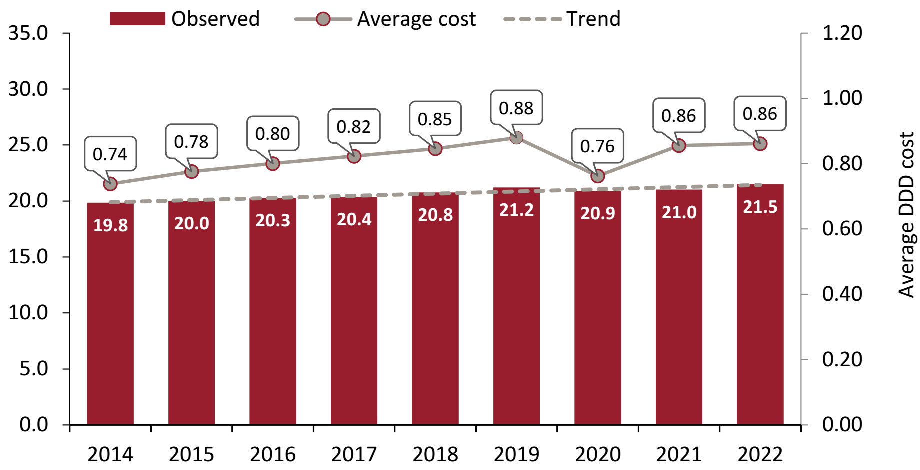


Table 3.10.1a Medicines for eye disorders, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Antiglaucoma preparations - beta blocking agents plain or in combination	2.12	-2.7	0.7	12.4	3.1	1.3	0.47	-5.6
Recombinant fusion proteins anti-VEGF	1.48	12.7	31.3	<0.05	12.5	36.7	493.19	0.1
Antiglaucoma preparations – prostanglandine analogues	1.19	-0.1	-1.1	5.7	0.3	0.1	0.58	-0.4
Monoclonal anti-VEGF antibodies— ranibizumab	0.80	-3.0	-6.0	0.1	-5.7	-5.9	22.42	2.8
Corticosteroids (intravitreal implants)	0.46	9.6	14.0	0.3	9.0	15.4	4.79	0.6
Antiglaucoma preparations – carbonic anhydrase inhibitors plain or in combination	0.21	-1.1	-3.0	1.4	0.2	-0.5	0.41	-1.2
Monoclonal anti-VEGF antibodies— brolucizumab	0.15	>100	-	<0.05	> 100	-	401.04	0.7
Other ophthalmological medicines (gene therapy)	0.13	-36.5	-	<0.05	-36.3	-	297000.00	-0.3
Antiglaucoma preparations— sympathomimetics	0.10	2.6	2.7	1.5	3.4	2.5	0.18	-0.8
Other ophthalmological medicines	0.07	24.0	37.1	<0.05	4.3	25.7	11.87	18.8
Antineovascularising agents (photodynamic therapy)	0.02	>100	-7.4	<0.05	>100	-7.3	790.72	-0.8
Corticosteroids	0.01	6.6	17.8	<0.05	-2.4	-3.4	2.82	9.2
Antiglaucoma preparations — parasympathomimetics	0.01	19.7	2.2	<0.05	8.7	-6.7	1.05	10.2
Other ophthalmological medicines (cell therapy)	0.00	0.4	-	<0.05	0.4	-	94310.54	0.0
Medicines for eye disorders	**6.75**	**2.9**	**3.0**	**21.5**	**2.2**	**1.0**	**0.86**	**0.7**
aflibercept	1.48	12.7	31.3	<0.05	12.5	36.7	493.19	0.1
ranibizumab	0.80	-3.0	-6.0	0.1	-5.7	-5.9	22.42	2.8
tafluprost	0.52	4.7	8.6	1.7	5.5	8.7	0.86	-0.8
dorzolamide/timolol	0.48	20.0	6.4	3.2	17.2	6.0	0.41	2.4
dexamethasone	0.44	12.6	13.3	0.3	9.4	13.7	4.55	2.9
timolol	0.38	4.0	3.5	3.2	1.8	-0.1	0.33	2.2
bimatoprost	0.32	0.1	-4.0	1.8	0.5	-0.3	0.49	-0.4
timolol/bimatoprost	0.31	-28.6	-1.8	1.4	0.8	2.1	0.60	-29.2
tafluprost/timolol	0.28	9.7	-	0.8	9.7	-	0.96	0.0
timolol/brinzolamide	0.27	-6.9	-1.6	1.5	-4.9	3.4	0.48	-2.0

Figure 3.10.1b Medicines for eye disorders, temporal trend of consumption (DDD/1000 inhab. per day) of the most expensive subgroups (2014-2022)

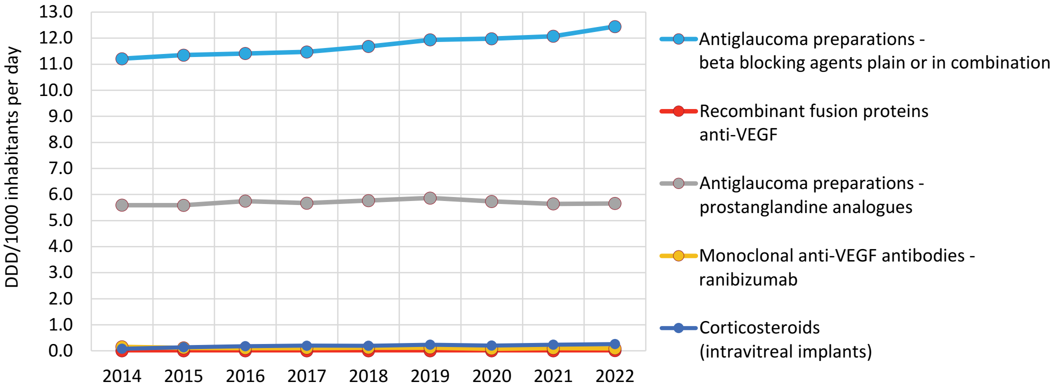


Table 3.10.1b Medicines for eye disorders, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	7.31	23.2	0.86	7.60	23.9	0.87	4.0	3.1	0.8	4.8	1.2	3.6
Valle d'Aosta	5.00	19.2	0.71	6.67	20.2	0.90	33.5	5.2	27.0	3.5	-0.2	3.7
Lombardy	5.25	17.2	0.84	6.07	17.7	0.94	15.8	3.1	12.3	1.8	1.2	0.5
PA Bolzano	6.14	16.2	1.04	6.75	16.4	1.13	9.9	1.1	8.7	4.2	1.9	2.3
PA Trento	6.27	16.8	1.02	6.68	17.3	1.06	6.4	2.7	3.6	4.6	1.7	2.8
Veneto	6.32	19.2	0.90	6.80	19.7	0.95	7.6	2.4	5.1	4.4	1.3	3.0
Friuli VG	7.96	23.2	0.94	8.68	23.7	1.00	9.0	2.2	6.7	2.7	0.6	2.0
Liguria	7.69	21.4	0.99	8.44	21.8	1.06	9.6	2.2	7.3	2.2	0.5	1.7
Emilia R.	7.05	27.9	0.69	7.22	28.5	0.69	2.5	2.3	0.2	3.6	1.6	2.0
Tuscany	7.33	26.3	0.76	6.66	26.7	0.68	-9.3	1.5	-10.6	-0.1	0.5	-0.6
Umbria	8.20	24.8	0.90	7.48	25.1	0.82	-8.7	1.1	-9.8	4.0	1.2	2.8
Marche	7.93	30.5	0.71	8.00	31.3	0.70	1.0	2.4	-1.4	1.9	1.2	0.7
Lazio	6.18	21.8	0.78	5.98	22.1	0.74	-3.3	1.1	-4.4	1.1	0.1	1.0
Abruzzo	8.02	26.2	0.84	8.33	26.7	0.86	3.9	2.0	1.9	3.4	0.7	2.7
Molise	6.97	16.0	1.19	8.02	16.8	1.31	15.1	4.5	10.2	5.2	0.7	4.4
Campania	7.19	18.2	1.08	6.77	18.7	0.99	-5.9	2.5	-8.1	6.1	1.4	4.7
Puglia	6.87	19.3	0.98	7.25	19.6	1.01	5.6	2.0	3.5	4.0	0.9	3.1
Basilicata	6.79	21.1	0.88	7.33	22.0	0.91	7.9	4.2	3.5	3.0	1.8	1.2
Calabria	5.69	19.6	0.79	5.99	19.8	0.83	5.2	1.1	4.1	3.3	0.6	2.7
Sicily	5.57	17.7	0.86	5.61	18.0	0.85	0.7	1.8	-1.1	2.9	1.4	1.5
Sardinia	7.00	19.8	0.97	6.57	20.3	0.89	-6.2	2.6	-8.6	2.5	0.5	2.0
Italy	**6.56**	**21.0**	**0.86**	**6.75**	**21.5**	**0.86**	**2.9**	**2.2**	**0.7**	**3.0**	**1.0**	**2.0**
North	6.36	20.8	0.84	6.92	21.3	0.89	8.7	2.7	5.9	3.2	1.2	1.9
Centre	6.93	24.6	0.77	6.57	25.0	0.72	-5.2	1.4	-6.5	1.0	0.5	0.5
South and Islands	6.62	19.2	0.95	6.64	19.6	0.93	0.2	2.1	-1.9	4.0	1.1	2.9

The use of drugs for eye disorders remained almost stable in the period 2014-2022, although there was an increase in per capita expenditure, mostly attributable to anti-neovascularising agents, such as aflibercept and brolucizumab, probably as a result of the entry into force in January 2021 of the AIFA Note 98, regulating the modalities of prescription, intravitreal administration and use of anti-VEGF medicines paid by th NHS for the treatment of age-related macular degeneration (AMD).

An increase in consumption and expenditure is also observed for intravitreal prolonged-release implants based on dexamethasone or fluocinolone, indicated in the treatment of chronic diabetic macular edema (DME) that does not sufficiently respond to other available therapies.

As in previous years, also in 2022 antiglaucoma preparations, especially beta-blockers plain or in combination, were the most widely used drugs.

In general, the drugs available for the treatment of eye disorders are not able to lead to a complete resolution of the pathology; however, they play a fundamental role in delaying its course, and this can have a significant impact in terms of improving the quality of life both in elderly and younger patients.

3.11 Genito-urinary system and sex hormones

In 2022, drugs for the genitourinary system and sex hormones ranked the eleventh category with highest public expenditure, accounting for EUR 406.6 million and 1.6% of total public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure for these drugs amounted to around EUR 6.88, mainly related to expenditure for the approved care regime (EUR 5.58 per capita), an increase of 0.9% compared to the year 2021. The expenditure by public health facilities is lower than approved care expenditure (EUR 1.29 per capita) and shows a reduction of 5% compared to the previous year (Table 3.1).
This category of drugs, on the other hand, ranks fifth in terms NHS consumption, with 47.54 DDD/1000 inhabitants per day, an increase of 2.9% compared to 2021.
The analysis of the drug use by age group and gender, including approved care regime and distribution "on behalf", confirms an almost exclusive use in males from 55 years, mainly due to the treatment of prostatic hypertrophy. The prevalence of such drugs in men over 75 years of age exceeds 40% of the population in this age group. At the same time, the per capita NHS expenditure also increases with the age of patients, reaching a maximum value of EUR 53.7 in males over 75 years of age. In women, however, significant consumption can be observed in the 25-64 age group, which can be justified by the use of hormonal preparations; the largest expenditure is reached in the 35-44 age group, with a value of EUR 11.7 per capita.
As for the approved care reigime, the per capita expenditure of genitourinary drugs was EUR 5.58, stable compared to 2021 (+0.5%). In fact, the 2.1% growth in consumption is accompanied by a reduction in the average cost per DDD (-1.6%), a slight reduction in prices (-0.5 %) and a negative mix effect (-1%) (Table 3.9). Within this distribution channel, alpha-adrenergic receptor antagonists are the therapeutic subcategory accounting for more than half of the expenditure and consumption of the entire category, with EUR 2.95 of per capita expenditure and 28.6 DDD/1000 inhabitants per day, followed by inhibitors of the enzyme testosterone-5-alpha reductase, with EUR 1.58 and DDD 11 (Table 3.9). While testosterone-5-alpha reductase inhibitor drugs show slight reductions in expenditure compared to 2021 (-0.8%), alpha-adrenergic receptor antagonists show higher increases in consumption (+2.8%) than expenditure (+1.8%), due to a shift towards less expensive specialties (mix effect: -1.0%). The molecules with the greatest impact on per capita expenditure in the category are tamsulosin (EUR 1.14) and dutasteride (EUR 1.03), accounting for about 40% of the entire category (Table 3.10); with alfuzosin, they are among the top 30 most consumed active ingredients (Table 3.17). In addition, alfuzosin, tamsulosin, dutasteride and silodosin are among the top 30 active substances with the lowest average cost per day of therapy (Table 3.14).
As for purchases by public health facilities, there was a reduction in expenditure (-5.4%) compared to an increase in consumption (+10.1 %). This channel also shows a reduction in prices (-1.9%), average cost per DDD (-14.1%) and a negative mix effect implying the choice of cheaper specialties (-12.5%) (Table 3.19). The subcategory of gonadotropins has the highest per capita expenditure (EUR 0.91), equal to 70% of the category. These drugs are analogues of adenopituitary hormones, used both in cases where it is necessary to restore the correct hormone levels (e.g. in the treatment of infertility), and for the treatment of

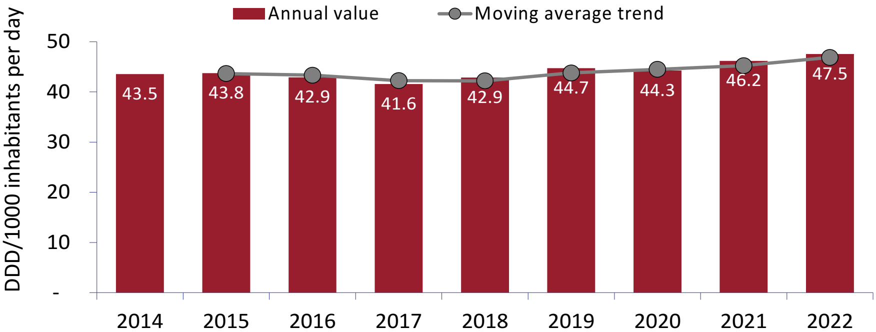
conditions that require a decrease in hormone levels (e.g. prostate cancer, surgical removal of fibroids or early menarche), as a negative feedback mechanism is exploited that leads to the suppression of adenopituitary hormone production.
The active ingredient with the highest incidence of expenditure (22%) is recombinant DNA follitropin alfa, with a cost per day of therapy of EUR 17.2 and a consumption of around 0.05 DDD, accounting for about 1.6% of the entire category, recording a decrease in both per capita expenditure (-22.4%) and consumption (-17.4%) compared to the previous year (Table 3.20). Per capita expenditure and consumption of menotropin also decreased by 16.4% and 16.9% respectively. Conversely, the combinations follitropin alfa/lutropin alfa, follitropin beta and urofollitropin have been growing in the last year in terms of both expenditure and consumption (Table 3.20). With regard to drugs under approved care regime and purchases by public health facilities, the top 30 active ingredients for consumption include tamsulosin with 11.4 DDD/1000 inhabitants per day (+3.2% compared to 2021), alfuzosin with 9.8 DDD/1000 inhabitants per day (+4.3%) and dutasteride with 8.4 DDD/1000 inhabitants per day (+0.8%) (Table 3.29).
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by region and on the efficiency in the absorption of resources according to the presence of patent-expired medicines and on a regional basis. These analyses focused on drugs for genitourinary disorders (Table 3.11.1a et seq.).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

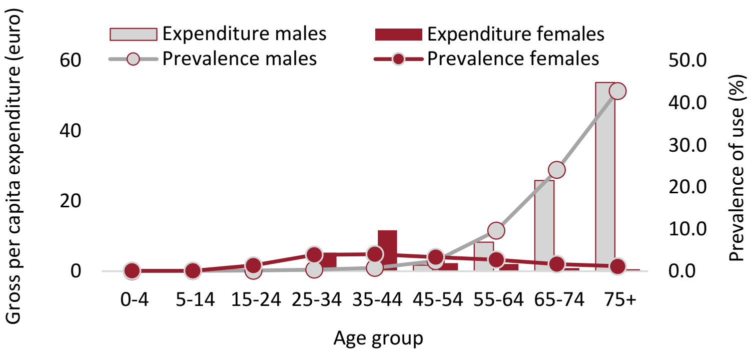
Genito-urinary system and sex hormones

Public expenditure* in million euros (% over total)	**406.6**	**(1.6)**
Δ % 2022-2021		-0.3
Regional range of gross per capita expenditure:	5.1	7.9
DDD/1000 inhabitants per day* (% over total)	**47.5**	**(3.6)**
Δ % 2022-2021		2.9
Regional range DDD/1000 inhabitants per day	32.5	56.3

* *includes prescriptions under approved care regime and purchases by public health facilities*



Age and gender distribution of expenditure, prevalence of use and consumption under approved care regime and distribution "on behalf" in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.0	0.0	0.0	0.0	0.1	0.1
5-14	0.1	0.0	0.0	0.1	0.2	0.2
15-24	0.2	0.6	0.4	0.5	3.7	2.0
25-34	0.6	5.3	2.9	1.1	10.8	5.9
35-44	1.0	11.7	6.3	2.5	14.3	8.4
45-54	1.8	2.3	2.0	11.7	14.1	12.9
55-64	8.3	2.1	5.1	69.8	15.4	41.8
65-74	25.9	0.9	12.7	221.6	8.0	108.7
75+	53.7	0.6	22.0	444.9	4.3	181.8

3.11.1 Medicines for genitourinary disorders

- Between 2014 and 2022, drug consumption for genitourinary disorders increased from 31.8 to 40.6 DDD/1000 inhabitants per day, representing an average annual increase (CAGR) of 3.1 % (Figure and Table 3.11.1a). Over the same period, the average cost per day of therapy decreased from EUR 0.48 in 2014 to EUR 0.31 in 2022 (CAGR: -5.1%). However, the highest reduction in the average cost per DDD occurred in 2018, due to the patent expiry of dutasteride, one of the most widely used drugs. Per capita expenditure (EUR 4.63) increased slightly compared to 2021 (+1.6%).
- BPH drugs (benign prostatic hypertrophy) account for almost all consumption in the category (40.1 out of 40.6 DDD). Among these, alpha-blockers account for most of the consumption (29 DDD), followed by 5-alpha-reductase inhibitors (11.1 DDD). Both categories show an increase of 3.4% and 1.2% respectively, compared to 2021. The use of urinary incontinence drugs remains marginal, although in 2022 an increase is recorded of about 27%, as well as an increase in expenditure by about 20%. The latter category has an average cost per DDD of EUR 0.54, double than alpha-blockers (EUR 0.28), which is also the category with the largest increase in consumption since 2014 (+29%) (Table 3.11.1a and Figure 3.11.1b).
- In 2022, the most prescribed molecules were tamsulosin, dutasteride, alfuzosin and silodosin, with variations compared to 2021 ranging from + 0.8% for dutasteride to + 4.4% for silodosin. Although these are the molecules with the highest consumption, they have the lowest average cost per DDD in the category, with values ranging from EUR 0.26 (alfuzosin) to EUR 0.34 (dutasteride), about half than tolterodine, a drug indicated in symptomatic treatment of urgency incontinence and/or increased urinary frequency and urgency in patients with overactive bladder syndrome, which represents the highest average cost for DDD in the whole category with EUR 0.64 (Table 3.11.1a). Solifenacin has the largest increases in expenditure and consumption (+ 80% and +84.8% respectively), while doxazosin is the drug with a 10 % reduction for both indicators. Although still limited, the use of tolterodine is up 13% compared to the previous year, with an average annual variation of 46.3% since 2014. This drug, together with oxybutynin and solifenacin, is included in AIFA Note 87, which limits its reimbursement only to Class A/RR negotiated packages, to patients with urgent urinary incontinence, in cases where the urinary disorder is related to central nervous system disorders (e.g. stroke, Parkinson’s disease, trauma, tumors, spina bifida and multiple sclerosis).
- At geographical level, there is a North-South gradient of increase both in terms of expenditure (from EUR 4.16 in the North to 5.15 in the South) and consumption (from 37.4 DDD in the North to 44 in the South), with a difference of about 20% for both indicators (Table 3.11.1b). Marche show the highest consumption (49.2 DDD), while Basilicata has the highest spending values (EUR 5.72); the lowest values are recorded in the PA Bolzano (24.9 DDD and EUR 2.66). In all regions, there are increases in consumption ranging from +1.5% in Calabria to +4.8% in Molise.

Figure 3.11.1a Medicines for genitourinary disorders, temporal trend of consumption and average cost per day of therapy (2014-2022)

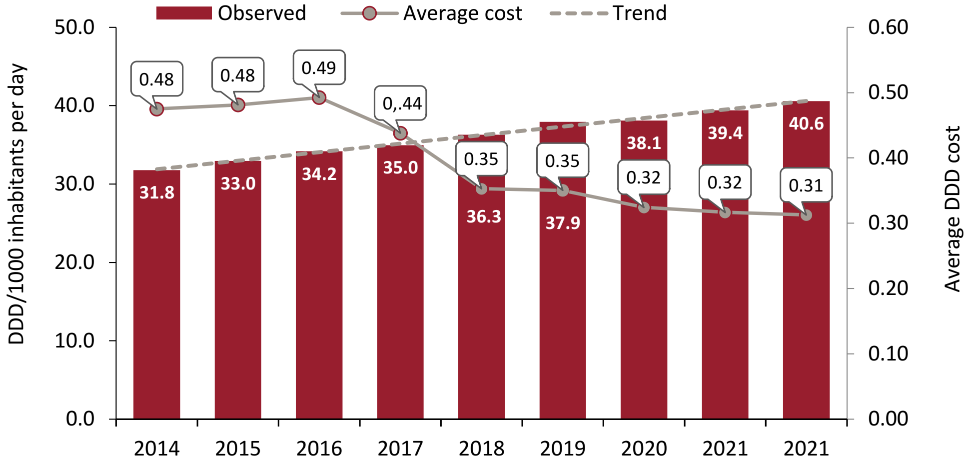


Table 3.11.1a Medicines for genitourinary disorders, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2022

Subgroups and substances	Expenditure *per capita*	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Drugs for benign prostatic hypertrophy (alpha-blockers)	2.96	2.3	1.7	29.0	3.4	3.2	0.28	-1.0
Drugs for benign prostatic hypertrophy (5-alpha reductase inhibitors)	1.58	-0.4	-7.2	11.1	1.2	2.5	0.39	-1.6
Drugs for incontinence and urinary frequency disorders (anticholinergics)	0.09	19.7	10.5	0.5	26.9	13.5	0.54	-5.7
Other drugs for benign prostatic hypertrophy	0.00	3.2	-0.5	<0.05	5.5	-1.8	1.14	-2.2
Medicines for genitourinary disorders	**4.63**	**1.6**	**-2.2**	**40.6**	**3.0**	**3.1**	**0.31**	**-1.3**
tamsulosin	1.14	2.1	1.9	11.4	3.2	2.4	0.27	-1.1
dutasteride	1.04	-0.6	-9.5	8.4	0.8	3.4	0.34	-1.3
alfuzosin	0.92	3.4	3.0	9.8	4.3	3.1	0.26	-0.9
silodosin	0.74	3.5	2.0	6.5	4.4	8.6	0.31	-0.8
finasteride	0.55	-0.1	-0.8	2.7	2.6	-0.1	0.56	-2.6
terazosine	0.14	-6.3	-5.6	1.1	-5.6	-5.2	0.33	-0.7
oxybutynin	0.05	2.5	4.2	0.2	3.0	4.4	0.61	-0.5
solifenacin	0.03	80.0	36.7	0.2	84.8	55.5	0.42	-2.6
doxazosin	0.02	-10.4	-8.0	0.1	-10.4	-8.0	0.42	0.0
tolterodine	0.01	11.5	27.7	0.1	13.0	46.3	0.64	-1.4

Figure 3.11.1b Medicines for genitourinary disorders, temporal trend of consumption (DDD/1000 inhabitants per day) of the subgroups with highest expenditure (2014-2022)

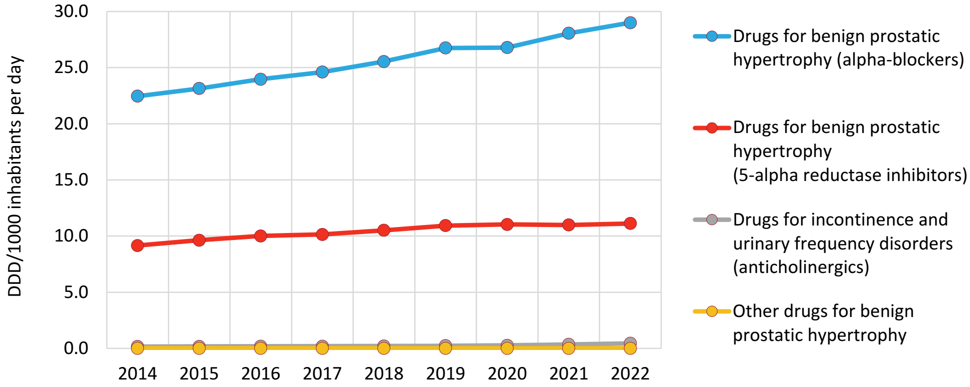


Table 3.11.1b Medicines for genitourinary disorders, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	4.16	36.6	0.31	4.20	37.8	0.30	0.8	3.1	-2.2	-3.1	2.2	-5.2
Valle d'Aosta	3.53	31.1	0.31	3.61	32.7	0.30	2.4	5.3	-2.7	-4.0	1.8	-5.6
Lombardy	3.94	35.4	0.31	4.02	36.6	0.30	1.9	3.6	-1.6	-2.7	3.2	-5.7
PA Bolzano	2.62	24.2	0.30	2.66	24.9	0.29	1.4	3.1	-1.7	-3.3	1.9	-5.1
PA Trento	4.09	36.0	0.31	4.23	37.7	0.31	3.5	4.7	-1.2	-2.5	3.4	-5.8
Veneto	3.98	34.6	0.31	4.03	35.5	0.31	1.4	2.6	-1.2	-2.3	3.1	-5.2
Friuli VG	3.86	34.1	0.31	3.93	35.2	0.31	1.8	3.4	-1.6	-3.0	2.8	-5.6
Liguria	4.59	40.3	0.31	4.63	41.3	0.31	0.9	2.4	-1.5	-3.0	2.6	-5.5
Emilia R.	4.54	40.1	0.31	4.64	41.5	0.31	2.1	3.6	-1.5	-0.9	2.8	-3.6
Tuscany	4.33	38.6	0.31	4.40	39.8	0.30	1.5	3.3	-1.7	-2.3	3.0	-5.1
Umbria	5.38	45.8	0.32	5.36	46.7	0.31	-0.4	1.9	-2.2	-2.8	3.1	-5.7
Marche	5.65	48.1	0.32	5.69	49.2	0.32	0.9	2.3	-1.4	-3.0	2.8	-5.6
Lazio	4.86	40.9	0.33	4.91	41.8	0.32	1.0	2.0	-1.0	-2.7	2.4	-5.0
Abruzzo	4.74	41.2	0.32	4.84	42.5	0.31	2.1	3.3	-1.1	-2.0	3.6	-5.4
Molise	4.66	38.5	0.33	4.79	40.3	0.33	2.9	4.8	-1.8	-1.6	3.7	-5.1
Campania	5.16	42.9	0.33	5.30	44.3	0.33	2.7	3.2	-0.5	-0.4	4.4	-4.5
Puglia	5.23	44.2	0.32	5.35	45.5	0.32	2.3	2.9	-0.7	-1.7	3.9	-5.4
Basilicata	5.69	47.2	0.33	5.79	48.4	0.33	1.8	2.5	-0.7	-1.0	4.3	-5.0
Calabria	4.96	41.2	0.33	4.99	41.9	0.33	0.6	1.5	-0.9	-2.7	2.6	-5.2
Sicily	4.99	42.6	0.32	5.07	43.7	0.32	1.7	2.7	-1.0	-2.0	3.1	-5.0
Sardinia	4.68	41.0	0.31	4.76	42.5	0.31	1.8	3.8	-1.9	-1.3	3.9	-5.0
Italy	**4.56**	**39.4**	**0.32**	**4.63**	**40.6**	**0.31**	**1.6**	**3.0**	**-1.3**	**-2.2**	**3.1**	**-5.1**
North	4.09	36.2	0.31	4.16	37.4	0.30	1.6	3.3	-1.6	-2.4	2.9	-5.1
Centre	4.83	41.5	0.32	4.88	42.5	0.31	1.0	2.4	-1.4	-2.6	2.7	-5.2
South and Islands	5.05	42.7	0.32	5.15	44.0	0.32	2.1	2.9	-0.9	-1.5	3.7	-5.0

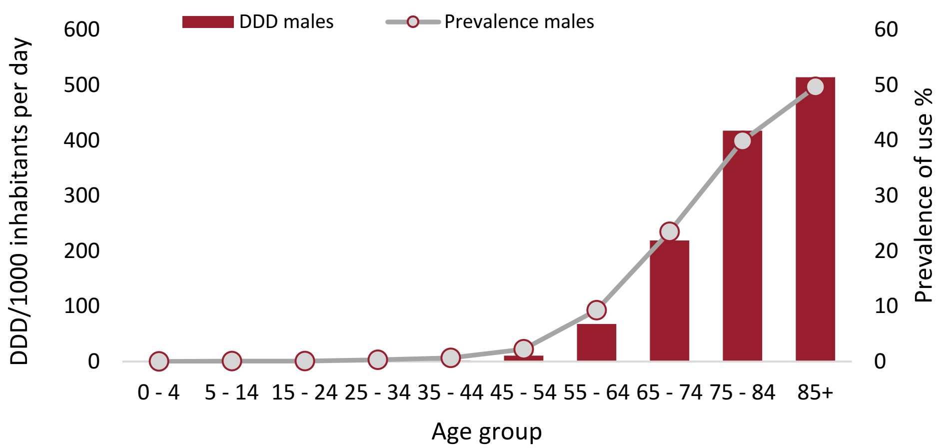
Exposure and adherence in population

- Health Card data were collected to perform an analysis aimed at estimating exposure and intensity of use of drugs for genitourinary disorders, 99% of which are due to treatment of BPH. Adherence and persistence of patients to treatment is related only to BPH drugs. From the in-depth study conducted in the male population, an increase is recorded in the use of drugs for genito-urinary disorders with increasing age, with higher values of prevalence (49.7%) and consumption (514.4 DDD) in men over 85, in accordance with the epidemiological data on the prevalence of BPH. From 65 years of age, the prevalence exceeds 20%, shifting from 23.5% in the 65-74 group to 40% in the 75-84 group, with a corresponding increase in consumption from 219 to 418 DDD (Figure 3.11.1c).
- At the national level, the prevalence in males is overall 8.7%, with a minimum of 7.9% in the North and a maximum of 9.3% in the Centre and the South. At a regional level, the highest prevalence is recorded in Marche (10.3%), Umbria (10.1%) and Basilicata (10.0%), while the PA Bolzano, with a prevalence of 5.3 %, shows the lowest level of exposure. As expected based on the prevalence of BPH, the median age of users is 74 years, without particular differences between the different regions (Table 3.11.1c).
- In line with the main guidelines for the management of BPH, a chronic condition, each user on average received at least one dose of the drug per day for about 11 months of therapy, with regional differences ranging from just under 300 days in Val d'Aosta and the PA of Bolzano to more than 350 days in the Marche region. Similar results also emerge considering median DDD. These figures are confirmed by the proportion of users with 1 prescription, which in 2022 was 7%, a lower figure than in previous years, with evident regional differences. For example, Tuscany has a percentage double than Friuli Venezia Giulia (10.2% vs 5.0%). On average, the cost per user in a year is just over EUR 100, with a range of EUR 89 in Bolzano and 114 in Basilicata (Table 3.11.1c).
- Within the therapeutic categories, alpha-blockers show a prevalence of use of 7.8%, while 5-alpha-reductase inhibitors have a 3.2% prevalence of use. Users of alpha-blockers are younger (74 vs 77 years) and, on average, a cost lower by EUR 25 (75.48 vs EUR 99.95) (Table 3.11.1d).
- Adherence and persistence analyses for BPH drugs refer to a cohort of new male users aged at least 45 years, who were followed by one-year follow-up. In detail, the study population comprises 96.886 new users with a median age of 68 years (IQR 61-75). The percentage of subjects with high adherence is 63.4%, stable compared to 2021 (63.7%) and follows a normal distribution, increasing progressively from 45 years and reaching the highest value (64.8%) in the 65-74 age group, and then decreases in later age groups (60.7% in the over 85) (Table 3.11.1e). There are no marked geographical differences, with the lowest figure in the South (62.6%) compared to the Centre (63.6%) and the North (64.1%).
- With regard to the low adherence to the treatment (9.8% in total), an opposite trend is observed. In fact, the highest percentage is recorded in the age groups between 45-54 years and in the over-85 (respectively 12.8% and 10.9%), while the 65-74 age group has the lowest share of users with low adherence (8.9%). In addition, in this case, the same trend is observed in the three macro-areas; however, the Southern regions show the

lowest adherence percentages (-10%) for all age groups. The lowest adherence value is reported in the 45-54 years in the South (14.8%) and in the >85 in the Centre (13.3%).

- Analysing the persistence data, it turns out that about half of the users (50.8%), over a period of one year, discontinued therapy for at least 60 days. These figures are identical to those in 2021 (50.7%). In the Northern Regions, there is a higher proportion of persistent users of therapy (52%), while the regions of the Centre (51%) and of the South (49.4%) show lower percentages, regardless of the age group considered. The greatest persistence is recorded in the North in the over 85, while in the Centre and South the highest values of persistence occur in the 65-74 age group (Table 3.11.1f). The median time to discontinuation of treatment is over 365 days with differences ranging from 293 in the South to over 365 in the Centre-North (Figure 3.11.1d).

Figure 3.11.1c Distribution of 2022 prevalence of use and consumption of medicines for genitourinary disorders under approved care regime and distribution "on behalf"



Note: the use of drugs for genitourinary disorders in females is negligible, so the graph shows only the data relating to the male population

Table 3.11.1c Exposure and duration of therapy with medicines for genitourinary disorders by Region under approved care regime and distribution "on behalf" (year 2022)

Region	Prevalence of use (%)	Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	8.8	75	99.68	320.0	320.0	5.7
Valle d'Aosta	7.7	74	92.48	296.7	300.0	7.5
Lombardy	7.5	74	100.23	331.5	320.0	6.4
PA Bolzano	5.3	76	89.06	291.8	300.0	8.2
PA Trento	7.2	75	109.58	347.5	340.0	8.1
Veneto	7.3	74	108.63	343.6	336.0	6.8
Friuli VG	7.7	75	107.63	345.5	336.0	5.0
Liguria	9.8	76	102.87	327.3	320.0	7.0
Emilia R.	8.5	75	106.14	336.5	320.0	6.3
Tuscany	9.3	75	97.05	316.7	320.0	10.2
Umbria	10.1	75	111.32	348.8	340.0	7.5
Marche	10.3	74	112.76	353.0	340.0	7.7
Lazio	9.0	73	106.83	331.4	320.0	6.8
Abruzzo	9.0	74	105.05	335.8	320.0	8.1
Molise	9.0	74	106.69	328.0	320.0	7.1
Campania	9.3	72	103.66	316.2	320.0	6.7
Puglia	9.3	73	111.62	346.1	334.0	6.0
Basilicata	10.0	73	113.74	345.2	336.0	7.6
Calabria	9.1	74	106.15	325.2	320.0	7.9
Sicily	9.2	73	106.87	335.5	330.0	7.7
Sardinia	9.2	73	103.81	338.0	330.0	7.8
Italy	**8.7**	**74**	**104.75**	**331.8**	**320.0**	**7.0**
North	7.9	75	103.02	332.3	320.0	6.3
Centre	9.3	74	104.98	331.3	320.0	8.1
South and Islands	9.3	73	106.66	331.5	320.0	7.1

Table 3.11.1d Exposure and duration of therapy with medicines for genitourinary disorders by subgroup under approved care regime and distribution "on behalf" (year 2022)

Subgroup	Prevalence of use (%)	Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
Drugs for benign prostatic hypertrophy (alpha-blockers)	7.8	74	75.48	267.4	300.0	7.5
Drugs for benign prostatic hypertrophy (5-alpha reductase inhibitors)	3.2	77	99.95	254.0	300.0	5.0
Drugs for incontinence and urinary frequency disorders (anticholinergics)	0.1	71	67.18	123.2	80.0	19.3
Other medicines for benign prostatic hypertrophy	0.0	73	196.43	145.3	96.0	20.3
Medicines for genitourinary disorders	**8.7**	**74**	**104.75**	**331.8**	**320.0**	**7.0**

Table 3.11.1e Indicators of adherence to treatment with medicines for genitourinary disorders in the population aged ≥45 years in the period 2019-2022 and variation 2022-2021

	Low adherence*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=96,886						Nord N=40,276					
45-54 years	14.3	13.9	12.4	12.8	3	-10	12.9	12.1	11.1	11.1	0	-14
55-64 years	10.2	10.5	9.9	9.7	-2	-5	9.3	9.4	8.8	8.7	-1	-6
65-74 years	9.4	9.4	9.3	8.9	-4	-5	8.4	8.9	8.4	7.6	-9	-10
75-84 years	10.0	10.3	10.1	10.1	0	1	9.1	9.2	9.0	8.7	-3	-4
≥ 85 years	11.6	11.0	10.7	10.9	2	-6	10.3	9.8	9.7	8.5	-12	-17
Total	**10.3**	**10.3**	**10.0**	**9.8**	**-2**	**-4**	**9.2**	**9.3**	**8.9**	**8.5**	**-4**	**-8**
	Centre N=20,425						South N=36,185					
45-54 years	13.5	12.9	12.1	11.8	-3	-12	15.8	15.7	13.6	14.8	9	-6
55-64 years	10.2	10.4	9.5	9.5	0	-7	11.2	11.6	11.3	10.7	-5	-4
65-74 years	9.8	9.1	8.7	8.9	3	-9	10.2	10.2	10.6	10.3	-3	1
75-84 years	10.1	10.7	10.7	10.7	0	6	11.2	11.5	11.5	11.7	1	4
≥ 85 years	12.6	12.4	11.0	13.3	21	6	12.7	11.8	12.2	12.7	4	0
Total	**10.4**	**10.3**	**9.8**	**9.9**	**1**	**-5**	**11.3**	**11.4**	**11.4**	**11.3**	**-1**	**0**

continued

Table 3.11.1e – *continued*

	High adherence*											
	2019	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**	**2019**	**2020**	**2021**	**2022**	**Δ % 22-21**	**Δ % 22-19**
	Total N=96,886						**Nord N=40,276**					
45-54 years	56.9	58.2	60.9	59.3	-3	4	56.9	58.0	61.6	58.8	-4	3
55-64 years	62.9	62.9	64.6	64.7	0	3	62.6	63.9	65.0	64.9	0	4
65-74 years	64.2	64.4	64.8	64.8	0	1	65.2	64.8	65.3	65.5	0	1
75-84 years	62.8	62.3	62.6	61.7	-1	-2	63.8	63.5	63.9	63.0	-1	-1
≥ 85 years	60.1	60.0	60.5	60.7	0	1	62.0	61.6	61.9	63.3	2	2
Total	**62.7**	**62.8**	**63.7**	**63.4**	**0**	**1**	**63.5**	**63.6**	**64.4**	**64.1**	**0**	**1**
	Centre N=20,425						**South N=36,185**					
45-54 years	58.3	60.8	61.8	61.8	0	6	56.0	57.0	59.9	58.4	-2	4
55-64 years	64.0	62.3	65.7	64.8	-1	1	62.6	62.3	63.7	64.4	1	3
65-74 years	64.1	65.0	65.6	65.5	0	2	63.1	63.7	63.8	63.8	0	1
75-84 years	62.9	61.7	61.9	61.4	-1	-2	61.4	61.0	61.0	60.2	-1	-2
≥ 85 years	58.7	58.9	59.7	56.7	-5	-3	58.5	58.6	59.1	59.8	1	2
Total	**63.0**	**62.8**	**64.2**	**63.6**	**-1**	**1**	**61.7**	**61.9**	**62.7**	**62.6**	**0**	**1**

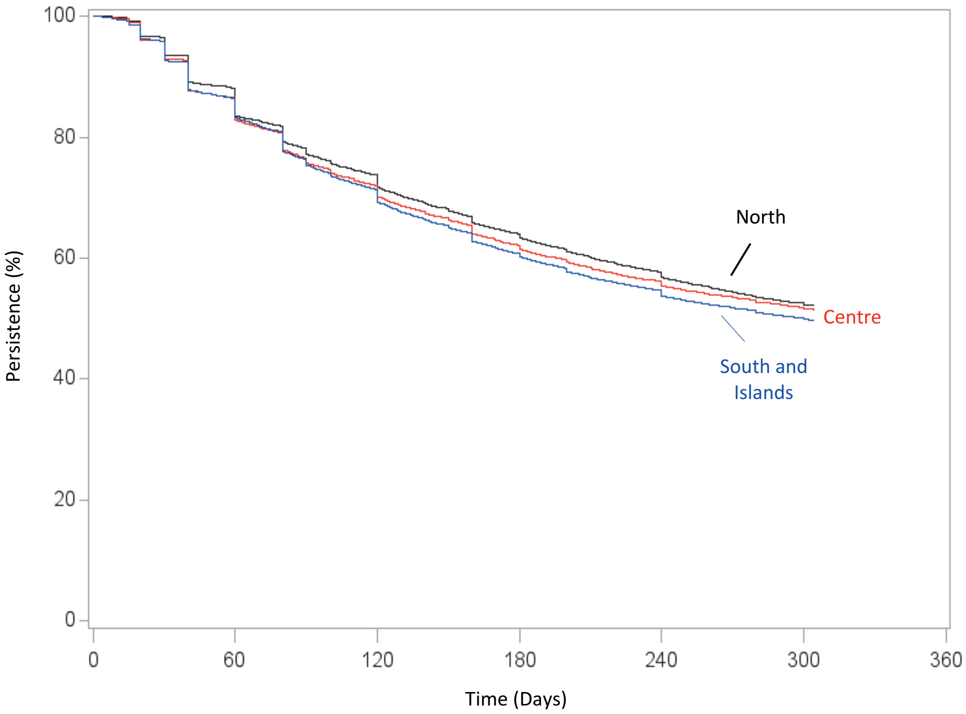
*Adherence to treatment was assessed within 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions provided.
Low adherence to treatment was defined as therapeutic coverage (assessed based on DDD) <40% of the observation period, whereas high adherence was defined as therapeutic coverage ≥ 80% of the observation period (for further details please refer to the statistical methods).
N: refers to new users, subjects who received a first prescription in the period 01/10/2021-31/12/2021, not treated in the previous months starting from 01/01/2021.
Percentages of subjects with low/high adherence related to the specified category.
Median follow-up time (IQR): 322 (220-346).

Table 3.11.1f Persistence after one year of treatment with drugs for genitourinary disorders in the population aged ≥ 45 years in the period 2019-2022 and variation 2022-2021

	Persistence after 12 months											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Total N=96,886						Nord N=40,276					
45-54 years	39.8	41.5	44.2	43.9	-1	10	40.8	42.7	46.0	44.7	-3	10
55-64 years	49.2	49.0	51.0	51.1	0	4	50.0	50.8	52.4	51.9	-1	4
65-74 years	51.5	51.6	52.1	52.4	1	2	52.8	52.8	53.0	53.3	1	1
75-84 years	51.8	50.9	51.4	50.6	-2	-2	53.2	52.7	53.0	52.1	-2	-2
≥ 85 years	50.0	49.6	49.0	51.5	5	3	52.7	51.0	51.1	54.3	6	3
Total	**50.1**	**49.9**	**50.7**	**50.8**	**0**	**2**	**51.5**	**51.6**	**52.2**	**52.0**	**0**	**1**
	Centre N=20,425						South N=36,185					
45-54 years	42.1	41.8	44.3	46.3	5	10	37.9	40.5	42.6	42.1	-1	11
55-64 years	49.3	48.3	51.8	51.6	0	5	48.5	47.5	49.2	50.0	2	3
65-74 years	52.2	52.2	52.5	53.0	1	1	49.8	50.1	50.8	51.1	0	3
75-84 years	51.3	50.3	51.3	49.8	-3	-3	50.2	48.8	49.1	49.0	0	-2
≥ 85 years	48.8	48.5	49.0	47.9	-2	-2	47.3	47.4	45.9	49.9	9	5
Total	**50.2**	**49.8**	**51.0**	**51.0**	**0**	**2**	**48.3**	**48.2**	**48.9**	**49.4**	**1**	**2**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. Treatment discontinuation occurs if the patient does not receive a prescription within 60 days (for more details please refer to the statistical methods).

Figure 3.11.1d Time (in days) to discontinuation of treatment with drugs for genitourinary disorders in the population aged ≥ 45 years stratified by geographical area; the curves are adjusted by gender and age (the Cox model was used for the estimation of persistence curves)



Drugs for genitourinary disorders are mainly used in the treatment of benign prostatic hypertrophy (BPH). In the period 2014-2022 consumption progressively increased, while per capita expenditure and the average cost per day of therapy for these drugs remained almost stable, after the reduction observed since 2018, attributable to the patent expiry of some molecules between the years 2017 and 2018.

The progressive increase in consumption is due to an increase in the prevalence of the disease, probably due to the development of new knowledge that improved diagnostic techniques, thus allowing early diagnosis and treatment of this disorder by clinicians and patients. In the male population, consumption increases progressively with age until it reaches half of the population aged over 85, which is in accordance with epidemiological data in literature.

Over 70% of consumption is represented by alpha-blockers (e.g. tamsulosin, alfuzosin, silodosin), drugs most indicated by most guidelines for the treatment of benign prostatic hypertrophy, but which are unable to act on the prostate volume or prevent its growth; 5-alpha-reductase inhibitors (e.g. dutasteride, finasteride), drugs that can act on prostate volume by reducing its size and consequently preventing further growth, cover the remaining part of consumption.

In addition, each user on average received at least one dose of the drug per day for about 11 months of therapy; this confirms the chronic use of these drugs, with slight interregional variations compared to the national average. Adherence and persistence to treatment with BPH drugs indicate a good compliance of the patient with therapy, although some critical issues are observed in Southern Italy, where more patients show lower adherence and lower persistence to therapy, regardless of the age group considered.

References

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- Società Italiana di Urologia (SIU). Low urinary tract disorders (LUTS) related to benign prostatic hyperplasia https://siu.it/salute/patologie/non-neoplastiche/trattamento-farmacologico-per-i-luts-negli-uomini-con-ipb

3.12 Various

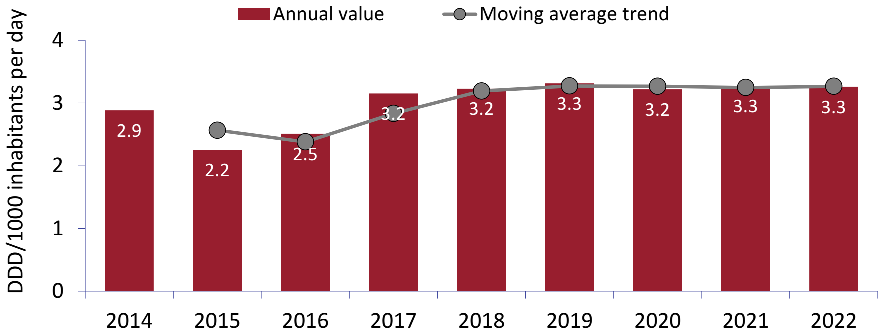
In 2022, the therapeutic category of “Various” drugs remains the twelfth for public expenditure, with EUR 384.5 million or 1.6% of the total (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure for these drugs reached EUR 6.52, an increase of 1.8% compared to the previous year, almost entirely (98%) due to purchases by public health facilities (EUR 6.38 per capita) (Table 3.1)..
Consumption for this category of drugs was 3.3 DDD/1000 inhabitants per day, with a slight decrease of 0.4% compared to 2021, with a stable trend over the last 6 years (Table 3.2).
The analysis of the drug use by age group and gender, including approved care and distribution on behalf, shows a marginal use of these drugs for both genders up to the age group between 45 and 54 years, followed by a progressive growth with increasing age. The prevalence of use is higher in over 75 years, with values of 4.1% and 3.7% for males and females, respectively. The NHS per capita expenditure also increases with patients’ age, reaching the maximum level of EUR 10.1 per capita in males and 8.2 in females over 75.
As for approved care, per capita expenditure was EUR 0.14, stable compared to 2021 (-0.6%), with a reduction in consumption (-4.9%) and a shift in prescription to more expensive medicinal products (mix effect: +4.5%), while prices remain unchanged (Table 3.9). The subgroup with the greatest impact on the approved care expenditure of this category is drugs for the treatment of hyperkalaemia and hyperphosphataemia (EUR 0.12 per capita). Also in 2022, the highest-expenditure active ingredient (EUR 0.06) was sevelamer, authorised for the control of hyperphosphataemia in patients undergoing haemodialysis or peritoneal dialysis and in patients with chronic kidney disease (CKD) not undergoing dialysis, but with a serum phosphorus concentration ≥ 1.78 mmol/L and with an incidence of 41.7% on total expenditure. This is followed by the polystyrene sulfonate, approved for the treatment of hyperkalaemia, which records an expenditure of EUR 0.04 and an incidence of 29.3% (Table 3.10).
Medicines purchased by public health facilities record an increase in expenditure (+1.4%) and in the average cost per day of therapy (+2.2%), with a shift towards higher-cost medicines (mix effect: +2.2%), while prices remain unchanged (Table 3.19). The category with the greatest impact on expenditure is radiological, water-soluble, nephrotropic and low osmolar contrast agents (EUR 1.33 per capita), followed by antidotes (EUR 1.17) and iron chelating substances (EUR 1.05); iron chelating substances record a sharp decrease in expenditure (-31.6%) corresponding to a reduction in the average DDD cost (-29.8%) and in consumption (-2.6%) (Table 3.19).
Among iron chelators, deferasirox, authorised for the treatment of chronic iron overload due to frequent hemotransfusions in patients with beta thalassemia major aged 6 years and older or in other patient groups where deferoxamine is contraindicated or inadequate, shows an impact on the category expenditure of 14.9 %, a reduction of per capita expenditure by 32.2% compared to 2021, due to a reduction in the cost per day of therapy (-31.6%) (Table 3.20). Sugammadex, antagonist of neuromuscular block from rocuronium and vecuronium, ranks first as regards impact on the category expenditure (equal to 15.1%); with a per capita expenditure of EUR 0.96, it recorded increases of about 20% both in terms of expenditure and consumption compared to the previous year. In addition, sugammadex is among the drugs with the greatest variation in expenditure (+20.3%) purchased by public

health facilities compared to 2021, while deferasirox is the second active ingredient with the greatest reduction in expenditure (-32.2%) (Tables 3.23 and 3.24).
Table 3.30 shows the different trend in terms of expenditure, consumption and average DDD cost between the approved care regime and direct purchase by public heath facilities regarding contrast agents and radiopharmaceuticals.
For further information on the use of medicines belonging to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region. These analyses focused on contrast agents and radiopharmaceuticals (Table 3.12.1a et seq.).

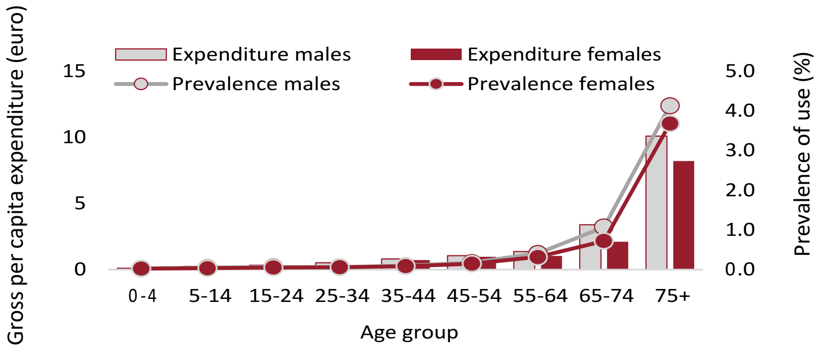
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Various

Public expenditure* in million euros (% over total)	**384.5**	**(1.6)**
Δ % 2022-2021		1.8
Regional range of gross per capita expenditure:	4.1	12.6
DDD/1000 inhabitants per day* (% over total)	**3.3**	**(0.2)**
Δ % 2022-2021		-0.4
Regional range DDD/1000 inhabitants per day	1.2	6.9

* *includes prescriptions under approved care regime and purchases by public health facilities*



Age and gender distribution of expenditure, prevalence of use and consumption under approved care regime and distribution "on behalf" in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.1	0.1	0.1	0.0	0.0	0.0
5-14	0.2	0.2	0.2	0.1	0.1	0.1
15-24	0.3	0.3	0.3	0.2	0.1	0.1
25-34	0.5	0.3	0.4	0.1	0.1	0.1
35-44	0.8	0.7	0.8	0.1	0.1	0.1
45-54	1.0	1.0	1.0	0.2	0.1	0.2
55-64	1.4	1.0	1.2	0.4	0.2	0.3
65-74	3.4	2.1	2.7	0.6	0.3	0.5
75+	10.1	8.2	9.0	0.9	0.4	0.6

3.12.1 Contrast agents

- In 2022, the use of contrast agents increased by 4.9%, confirming the increase already observed in 2021. Similarly, per capita expenditure (EUR 1.87) increased by 6.9% over the period 2022-2021, with an average annual variation of +2.7% from 2014. On the other hand, the average cost for DDD increased progressively, with a value of EUR 52.13 in 2021, up 1.9% compared to the previous year (Figure 3.12.1a).
- The therapeutic category with the highest per capita expenditure (EUR 1.34) is radiological contrast agents, up 5.6 %, covering 75% of the expenditure of the whole category. In the period 2014-2022, the average annual increase was 2.1% (Figure 3.12.1b). These are followed by contrast agents for MRI, with EUR 0.45, with an increase of 6.5%. Contrast agents for ultrasonology, albeit with a limited expenditure (EUR 0.09), increased by more than 30%; they have an average cost per DDD more than double compared to the average for the category (111.93 vs EUR 52.13) (Table 3.12.1a).
- The active ingredient with the highest expenditure is iomeprol (0.55 euros; +7.1% compared to 2021), a radiological contrast agent (iodinated, non-ionic, monomeric) with high solubility in water, low chemotoxicity, osmolality and viscosity. This is followed in second rank by iodixanol (EUR 0.24; +4.5%), another iodine radioactive agent (dimeric, non-ionic, iso-osmolal), with a diagnostic efficacy similar to other drugs of the same category (ATC V08AB). The active ingredients gadobutrol (drug containing gadolinium and the macrocyclic ligand butrol), used for the intensification of contrast in MRI, and iopromide, iodinated diagnostic agent (used for angiography, contrast enhancement in computed tomography, urography, visualisation of body cavities), have a per capita expenditure of EUR 0.22 and EUR 0.19 respectively. The active ingredient with the highest increase in expenditure in 2022 is ioexol with +15.0%; this is a low osmolality monomeric non-ion contrast agent used for myelography, angiography, urography and arthrographs. Finally, gadoxetic acid, used for the detection of focal liver lesions, has an average cost per DDD higher than category (EUR 175.79).
- Analysing the regional variability, the Central Regions show higher expenditure values (EUR 2.05), compared to the North (EUR 1.80) and the South (EUR 1.88), which show the highest increase (+9.8%) compared to 2021. A possible explanation of the difference between the North and other geographical areas is the increased use by private health facilities for carrying out diagnostic tests. To confirm this, the regions with the lowest expenditure are the PA of Trento and Lombardy (EUR 1.40 and EUR 1.50 respectively). The highest expenditure values are recorded in Valle d'Aosta and Puglia (EUR 2.54); Puglia also shows the highest average cost per DDD, about 4 times higher than PA Bolzano. Compared to the previous year, Puglia also had the largest increase in expenditure (+31.9%), followed by Emilia Romagna (+13.4%) and Piedmont (+10.2%). Molise, on the other hand, recorded the largest reduction (-13.2%).

Figure 3.12.1a Contrast agents, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

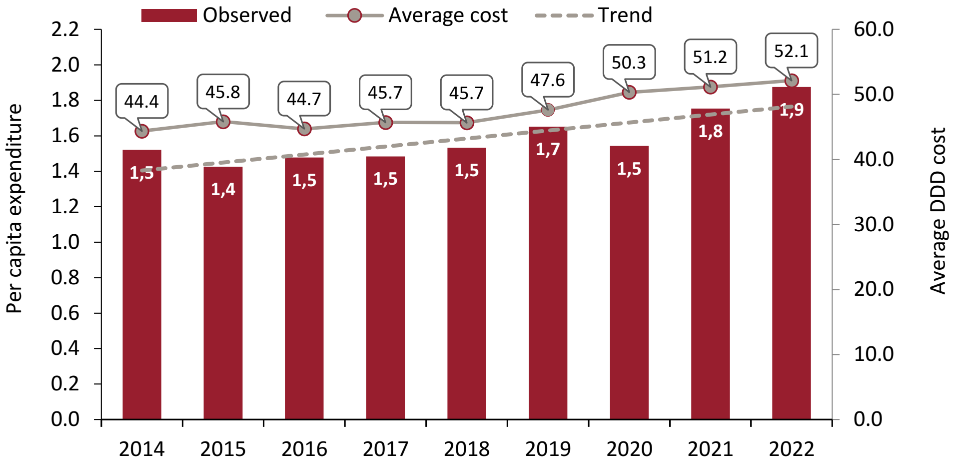


Table 3.12.1a Contrasts agents, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Radiological contrast agents	1.34	5.6	2.1	0.1	4.2	-0.2	51.65	1.4
MRI contrast agents	0.45	6.5	4.0	<0.05	7.5	4.0	48.30	-1.0
Contrast agents for ultrasonology	0.09	34.5	7.7	<0.05	1.9	1.0	111.93	31.9
Contrast agents	**1.87**	**6.9**	**2.7**	**0.1**	**4.9**	**0.6**	**52.13**	**1.9**
iomeprol	0.55	7.1	3.9	<0.05	2.8	0.0	75.49	4.1
iodixanol	0.24	4.5	1.0	<0.05	2.1	0.7	77.66	2.3
gadobutrol	0.22	8.1	6.9	<0.05	8.0	7.5	77.79	0.1
iopromide	0.19	1.7	-1.7	<0.05	4.7	-1.4	54.93	-2.8
iobitridol	0.12	2.4	0.1	<0.05	5.7	1.1	47.13	-3.2
iopamidol	0.12	6.9	6.5	<0.05	3.4	0.6	27.26	3.3
ioexol	0.09	15.0	8.2	<0.05	10.3	8.3	32.78	4.2
gadoxetic acid	0.09	9.5	9.5	<0.05	9.4	8.4	175.79	0.1
gadoteridol	0.07	8.1	27.5	<0.05	9.4	24.8	25.41	-1.2
hexafluoride sulfur	0.05	1.9	1.1	<0.05	1.9	1.0	67.50	0.0

Figure 3.12.1b Contrast agents, temporal trend in per capita expenditure of subgroups with highest expenditure (2014-2022)

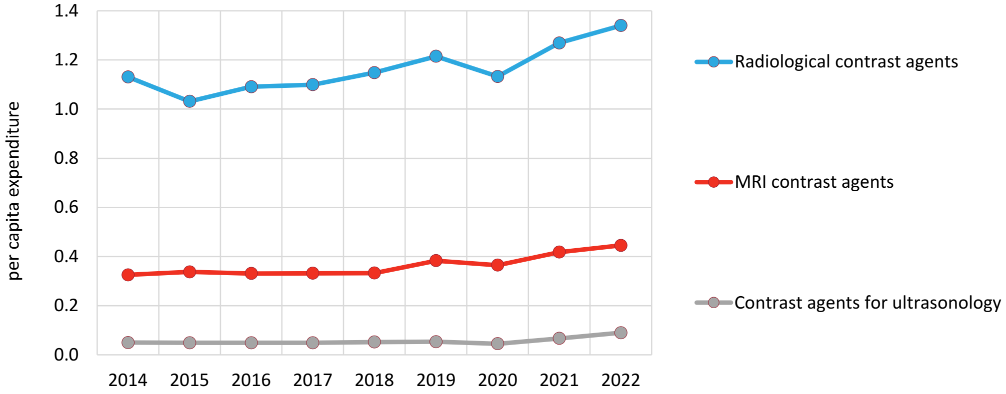


Table 3.12.1b Contrast agents, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	1.58	0.1	47.74	1.74	0.1	47.11	10.2	11.7	-1.3	1.3	1.2	0.1
Valle d'Aosta	2.63	0.1	58.92	2.71	0.1	65.33	2.9	-7.2	10.9	0.0	-3.7	3.8
Lombardy	1.39	0.1	44.94	1.50	0.1	44.40	8.1	9.4	-1.2	0.5	-0.1	0.6
PA Bolzano	1.65	0.2	27.98	1.69	0.2	28.19	2.5	1.7	0.8	2.5	-1.9	4.5
PA Trento	1.45	0.1	33.65	1.40	0.1	33.79	-3.3	-3.7	0.4	2.9	0.1	2.8
Veneto	1.91	0.1	43.05	2.01	0.1	42.28	5.3	7.3	-1.8	2.3	2.1	0.2
Friuli VG	2.43	0.1	61.49	2.31	0.1	60.99	-4.8	-4.0	-0.8	0.8	0.4	0.4
Liguria	1.45	0.1	27.95	1.55	0.2	27.94	6.7	6.7	0.0	4.4	2.4	1.9
Emilia R.	1.99	0.2	34.52	2.26	0.2	37.50	13.4	4.4	8.6	3.7	1.0	2.7
Tuscany	2.39	0.1	47.99	2.41	0.1	50.17	0.5	-3.9	4.5	3.1	0.2	2.9
Umbria	2.26	0.1	51.70	2.33	0.1	51.90	3.1	2.7	0.4	0.8	-1.1	1.9
Marche	2.21	0.1	47.34	2.26	0.1	46.20	2.2	4.8	-2.4	2.6	1.7	0.9
Lazio	1.68	0.1	66.90	1.72	0.1	67.64	2.3	1.2	1.1	1.9	-0.6	2.6
Abruzzo	2.13	0.1	59.28	2.25	0.1	60.17	5.9	4.3	1.5	3.2	0.7	2.5
Molise	1.63	0.1	52.87	1.41	0.1	55.85	-13.2	-17.8	5.6	0.3	-2.6	3.0
Campania	1.29	0.1	70.14	1.29	0.1	62.24	0.5	13.3	-11.3	6.1	4.1	1.9
Puglia	1.93	0.1	79.54	2.54	0.1	103.11	31.9	1.8	29.6	6.1	-1.0	7.2
Basilicata	2.15	0.1	72.13	2.20	0.1	69.47	2.4	6.3	-3.7	1.3	-1.6	2.9
Calabria	1.77	0.1	71.77	1.79	0.1	70.15	1.2	3.5	-2.3	4.4	0.8	3.6
Sicily	1.65	0.1	76.02	1.77	0.1	75.91	7.5	7.7	-0.1	2.9	0.1	2.8
Sardinia	2.16	0.1	70.58	2.21	0.1	71.23	2.4	1.4	0.9	1.4	-1.2	2.7
Italy	**1.75**	**0.1**	**51.17**	**1.87**	**0.1**	**52.13**	**6.9**	**4.9**	**1.9**	**2.7**	**0.6**	**2.0**
North	1.67	0.1	41.37	1.80	0.1	41.70	7.6	6.7	0.8	1.8	0.9	1.0
Centre	2.02	0.1	54.24	2.05	0.1	55.32	1.6	-0.3	2.0	2.3	0.0	2.3
South and Islands	1.71	0.1	72.18	1.88	0.1	75.04	9.8	5.6	4.0	4.1	0.5	3.6

Contrast agents, thanks to the ability to modify the absorption of X-rays of organs and tissues (similar in composition and/or thickness to the surrounding parts of the body), to date are an indispensable diagnostic tool and are essential to clinical practice.

The upward trend in per capita expenditure of contrast agents (which in 2022 exceeded the levels recorded in the pre-pandemic year 2019) confirms the gradual resumption of significantly reduced clinical activities during the COVID-19 pandemic; this increase is also associated with a progressive increase in the average cost per day of therapy, without any impact due to the outbreak of the COVID-19 pandemic.

Analysing regional variability, it emerges that the Central regions show higher expenditure values than the North and South, although the Southern regions record a higher average cost per day of therapy than other geographical areas.

3.12.2 Radiopharmaceuticals

- In 2022, per capita expenditure on radiopharmaceuticals was EUR 1.20, with an increasing trend of 4.6% compared to the previous year, and 8.9% compared to the last nine years (Figure 3.12.2a). The average cost per day of radiopharmaceutical therapy has increased by 75% in the last nine years, from a value of EUR 299.7 in 2014 to EUR 521 in 2022.
- The most expensive category is radiopharmaceuticals for cancer detection (EUR 0.37 per capita), followed by other radiopharmaceuticals for therapeutic use (EUR 0.31) and central nervous system radiodiagnostics (EUR 0.21). These three categories account for more than 80% of total expenditure in the category and have all increased compared to 2021 (+9.7%, +5.7% and +1.9% respectively). Thyroid radiodiagnostics, on the contrary, show a per capita expenditure of EUR 0.12 (down by 13.1%). Other diagnostic radiopharmaceuticals showed an increase in expenditure by 33.4% and by more than 40% in the average cost. Radiopharmaceuticals for cancer detection had an expenditure of EUR 0.20 in 2014, with an average annual increase of 11.3%, as well as for other radiopharmaceuticals for therapeutic use that recorded a 57.7% increase in CAGR (Figure 3.12.2b).
- The first active ingredient by expenditure is fluorodeoxyglucose (18F), a radiopharmaceutical for cancer detection that records a per capita expenditure of EUR 0.35, followed by lutetium (177Lu) oxodotreodite (EUR 0.24, up by 9.4% compared to 2021), indicated in adult patients for the treatment of well-differentiated, progressive, non-removable or metastatic somatostatin receptor-positive gastroenterohepatic neuroendocrine tumors (NET-GEP). Ioflupane iodine (123I) and technetium(99m CT) pertecnetate, two radiopharmaceuticals used for thyroid and central nervous system respectively, have a per capita expenditure of EUR 0.17 and EUR 0.11 (the first up by 3.7 % while the second is down by 13.4 %). For these drugs, the average cost per DDD may be affected by the presence of some medicinal products in Class C(nn).
- The wide regional variability (CV 47%), similar to 2021, is particularly evident considering the difference between the maximum value of per capita expenditure recorded in Basilicata, equal to EUR 3.06 (+6.1% compared to 2021) and the minimum observed in Sardinia (EUR 0.64, with a difference of almost 5 times), up by 10.6% compared to the previous year (Table 3.12.2b). Liguria and Valle d'Aosta are the only regions showing expenditure decreases by more than 20% compared to 2021; Abruzzo recorded increases by more than 50% and an average cost up by more than 100%. The North (EUR 1.20) and the Centre (EUR 1.31) show higher expenditure values than the South and Islands (EUR 1.15), up by 4.6%. Veneto is the region with the highest average cost (EUR 760), 3.5 times higher than Sicily (EUR 226.63).

Figure 3.12.2a Radiopharmaceuticals, temporal trend of per capita expenditure and average cost per day of therapy (2014-2022)

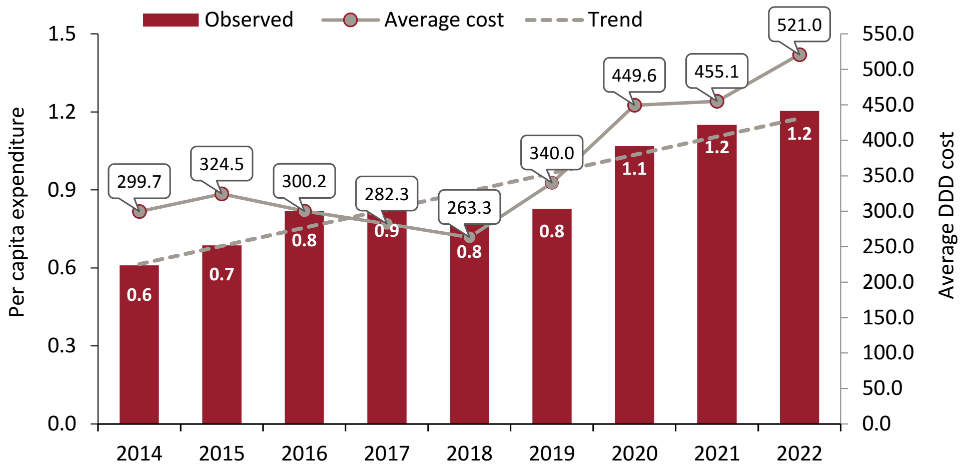


Table 3.12.2a Radiopharmaceuticals, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2022

Subgroups and substances	Per capita expenditure	Δ % 22-21	CAGR % 14-22	DDD/ 1000 inhab. per day	Δ % 22-21	CAGR % 14-22	Average DDD cost	Δ % 22-21
Radiopharmaceuticals for cancer detection	0.47	9.7	11.3	<0.05	3.0	0.3	536.24	6.5
Other radiopharmaceuticals for therapeutic use	0.31	5.7	57.7	<0.05	0.4	66.3	2466.73	5.2
CNS diagnostic radiopharmaceuticals	0.21	1.9	3.6	<0.05	0.0	1.9	704.43	1.9
Thyroid diagnostic radiopharmaceuticals	0.12	-13.1	-2.4	<0.05	-18.7	12.5	237.91	6.9
Other diagnostic radiopharmaceuticals	0.04	33.4	-	<0.05	-22.9	-	26162.34	73.1
Diagnostic radiopharmaceuticals of the cardiovascular system	0.03	-6.6	-6.7	<0.05	-21.9	0.6	92.43	19.7
Diagnostic radiopharmaceuticals of the skeletal system	0.01	8.4	-	<0.05	-17.6	-	79.14	31.5
Diagnostic radiopharmaceuticals of the renal system	0.00	11.0	2.2	<0.05	-5.0	-8.3	127.58	16.8
Diagnostic radiopharmaceuticals of the respiratory system	0.00	5.2	-4.9	<0.05	5.2	-15.0	150.00	0.0
Diagnostic radiopharmaceuticals of the hepatic and reticuloendothelial system	0.00	-31.6	-34.7	<0.05	-85.7	-46.3	450.87	379.5
Radiopharmaceuticals for detection of inflammation and infections	0.00	-39.8	-26.7	<0.05	-35.1	-31.7	575.19	-7.3
Radiopharmaceuticals with analgesic/anti-inflammatory action	0.00	45.6	-37.4	<0.05	75.8	-23.9	784.88	-17.1
Radiopharmaceuticals	**1.20**	**4.6**	**8.9**	**<0.05**	**-8.6**	**1.6**	**521.01**	**14.5**
fluoride deoxyglucose (18F)	0.35	9.6	11.2	<0.05	3.1	0.5	426.30	6.3
lutetium oxodotreotide (177Lu)	0.24	9.4	-	<0.05	-7.0	-	16632.93	17.6
ioflupane iodine (123I)	0.17	3.7	3.0	<0.05	6.5	3.4	817.30	-2.6
pertecnetate technetium (99mtc)	0.11	-13.4	-3.9	<0.05	-25.9	4.3	387.57	16.7
fluorocholine (18F)	0.07	-1.0	-	<0.05	-1.6	-	2422.77	0.6
germanium chloride/gallium chloride (68Ge/68Ga)	0.04	48.9	-	<0.05	33.9	-	86699.25	11.2
radium dichloride (223Ra)	0.04	-13.5	37.8	<0.05	-13.5	44.7	3238.89	0.0
sodium iodide (131I)	0.03	2.7	131.8	<0.05	-4.8	158.8	100.04	7.9
flutemetamol (18F)	0.03	4.0	-	<0.05	3.8	-	1220.47	0.1
gallium edotreotide (68 Ga)	0.02	22.2	-	<0.05	-2.0	-	11188.73	24.7

Figure 3.12.2b Radiopharmaceuticals, temporal trend 2014-2022 in per capita expenditure of most expensive subgroups

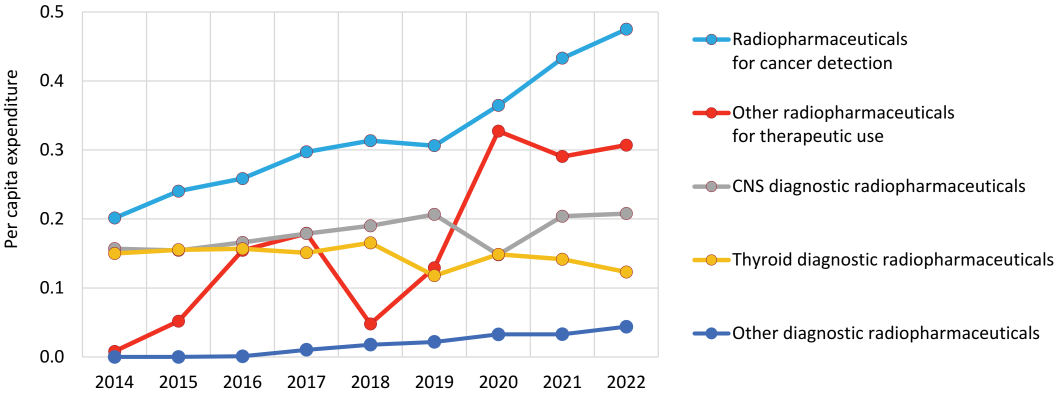


Table 3.12.2b Radiopharmaceuticals, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2022

Region	2021			2022			Δ % 22-21			% CAGR 14-22		
	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost	Per capita expenditure	DDD/ 1000 inhab. per day	Average DDD cost
Piedmont	1.00	<0.05	520.33	1.01	<0.05	511.01	1.0	2.8	-1.8	5.7	0.4	5.3
Valle d'Aosta	2.12	<0.05	593.54	1.64	<0.05	565.30	-22.6	-18.7	-4.8	-2.4	-6.7	4.7
Lombardy	1.17	<0.05	591.30	1.13	<0.05	605.02	-3.3	-5.5	2.3	9.5	-1.5	11.1
PA Bolzano	0.83	<0.05	497.86	0.88	<0.05	537.06	6.3	-1.5	7.9	5.1	-2.2	7.6
PA Trento	0.77	<0.05	450.18	0.83	<0.05	591.90	7.5	-18.2	31.5	5.7	2.9	2.8
Veneto	1.03	<0.05	603.41	1.28	<0.05	770.15	25.3	-1.9	27.6	8.4	1.2	7.1
Friuli VG	0.85	<0.05	414.13	1.06	<0.05	515.89	24.6	0.0	24.6	6.7	2.4	4.2
Liguria	1.03	<0.05	407.74	0.77	<0.05	531.63	-25.7	-43.0	30.4	-1.2	-8.7	8.2
Emilia R.	1.59	<0.05	608.54	1.69	<0.05	738.50	6.3	-12.4	21.4	9.5	-2.8	12.6
Tuscany	1.42	<0.05	359.90	1.44	<0.05	490.53	1.3	-25.7	36.3	3.3	-2.1	5.5
Umbria	0.71	<0.05	311.50	0.67	<0.05	368.44	-5.2	-19.9	18.3	0.0	2.0	-2.0
Marche	1.79	<0.05	354.29	1.79	<0.05	300.86	0.3	18.1	-15.1	2.8	-0.3	3.2
Lazio	1.04	<0.05	536.62	1.20	<0.05	700.69	15.5	-11.6	30.6	19.1	6.5	11.8
Abruzzo	0.94	<0.05	241.17	1.42	<0.05	488.56	51.2	-25.4	102.6	10.7	10.4	0.3
Molise	0.73	<0.05	391.67	0.69	<0.05	724.57	-5.5	-48.9	85.0	-1.0	-20.8	25.0
Campania	0.62	<0.05	364.93	0.62	<0.05	397.83	-0.4	-8.6	9.0	7.2	8.0	-0.8
Puglia	1.69	<0.05	552.71	1.79	<0.05	621.21	6.0	-5.7	12.4	15.6	0.4	15.1
Basilicata	2.89	<0.05	372.09	3.06	<0.05	423.08	6.1	-6.7	13.7	11.2	-1.9	13.3
Calabria	2.07	<0.05	655.09	1.98	<0.05	673.57	-4.6	-7.2	2.8	26.0	16.1	8.5
Sicily	0.80	<0.05	219.02	0.79	<0.05	226.63	-0.7	-4.1	3.5	16.1	21.9	-4.7
Sardinia	0.58	<0.05	317.40	0.64	<0.05	322.35	10.6	8.9	1.6	-4.4	1.4	-5.7
Italy	**1.15**	**<0.05**	**455.13**	**1.20**	**<0.05**	**521.01**	**4.6**	**-8.6**	**14.5**	**8.9**	**1.6**	**7.2**
North	1.15	<0.05	560.80	1.20	<0.05	631.83	3.8	-7.9	12.7	7.7	-1.4	9.3
Centre	1.23	<0.05	409.67	1.31	<0.05	493.67	6.5	-11.6	20.5	7.5	0.7	6.8
South and Islands	1.10	<0.05	377.19	1.15	<0.05	425.96	4.6	-7.4	12.9	12.0	6.6	5.1

A radiopharmaceutical is a medicine consisting of the combination of a radionucleide (radioactive isotope) responsible for diagnostic and/or therapeutic activity and a carrier molecule that determines its biological properties. Depending on the type of radionuclide, the drug may have diagnostic or therapeutic activity when it is able to destroy cells. Theorenotics, combining the ability to diagnose and therapy in the same radiopharmaceutical, represents the greatest novelty in this field.
In 2022, per capita expenditure on radiopharmaceuticals amounted to EUR 1.2, with an increasing trend in recent years. This figure is due to a higher average cost per day of therapy, which has increased by more than 50% over the past nine years. Radiopharmaceuticals for cancer detection cover almost 40% of the expenditure of the category, with significant increases in the last 3 years, mainly attributable to fluorodeoxyglucose (18F). Particularly interesting is the growth of other radiopharmaceuticals, driven by lutetium (177Lu) oxodotreodite, which confirms an increase in the use of radioligand therapy. However, a deep regional variability is confiormed in the expenditure of these drugs.

3.13 Dermatological drugs

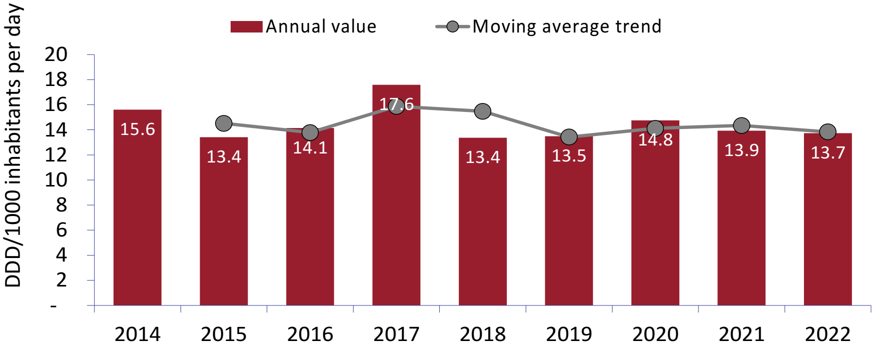
In 2022, dermatological drugs were the 13th therapeutic category with the highest public expenditure, amounting to 261.7 million euros, and corresponding to 1.1% of total public expenditure (Box Main indices of expenditure, consumption and exposure). The total per capita expenditure for these drugs is EUR 4.42, recording a sharp increase compared to the previous year (+32.2 %), mainly due to purchases by public health facilities, equal to EUR 3.13 per capita, up by 54% compared to 2021. The share of the apporoved care regime is EUR 1.30 per capita, down by 1.5% compared to the previous year (Table 3.1).
Total consumption in this category amounted to 13.7 DDD/1000 inhabitants per day, down by 1.1% compared to 2021 in both public facilities (-1.4 %) (Table 3.2) and approved care regime (-0.5%).
The analysis of the use profile by age group and gender, including approved care regime and distribution "on behalf", shows an increase in the prevalence of use and consumption of dermatological drugs, from 15 years on for both genders. In particular, males over 75 years of age record a prevalence of 3.7% and consumption of 13 DDD/1000 inhabitants per day. Females show a less evident trend with increasing age; similarly to males the prevalence of use reaches the highest level in the over 75 age group, standing at 2.3%. The NHS per capita expenditure increases with the age of the patients, reaching the maximum value of EUR 2.3 per capita in the over 75 (EUR 3.4 in males and EUR 1.6 in females).
As regards approved care, per capita expenditure (EUR 1.30) is down by 1.9%. This trend was mainly driven by a reduction in prescribed doses (-0.9%), a shift towards lower-cost specialities (mix effect: -0.9%) and reduction in average DDD cost (-1%). The category with the greatest impact on pharmaceutical expenditure is other topical antipsyoriatic drugs (EUR 0.88 per capita) (Table 3.9). The drug with the highest expenditure and consumption is the combination calcipotriol/betametasone, which accounts for almost 65% of gross expenditure in the category and 48.2% of consumption (Table 3.10), a slight increase compared to 2021 (+0.8%). Isotretinoin, a drug indicated for the treatment of severe acne in patients resistant to both systemic antibacterial and topical therapy, has decreased compared to the previous year in terms of both expenditure (-1.8%) and consumption (-1.2%).
Medicines purchased by public health facilities record a sharp increase in expenditure (+53.3%), due to the significant shift towards more expensive medicines (mix effect: +57.4%), and a decrease in consumption (-1.8%) (Table 3.19). The active ingredient with the highest expenditure is dupilumab (EUR 2.67 per capita), a monoclonal antibody that is on the list of innovative drugs and is used for the treatment of moderate to severe atopic dermatitis in adult patients, children and adolescents (aged 6-17 years) eligible for systemic therapy. This drug represents 85.4% of the total of the entire category and has increased by more than 66.1% compared to 2021 in terms of expenditure and by 72% in terms of DDD; this could be attributed to the extension of the indication of this drug for the treatment of nasal polyposis as of December 2020. The average cost per day (EUR 28.02) is the highest in the category. Sodium hypochlorite is the active ingredient with the highest consumption levels (2.6 DDD/1000 inhabitants per day) (Table 3.20). Dupilumab is among the top thirty active ingredients as for drugs purchased by public health facilities (Table 3.21) and among the top 30 for total expenditure, with a value of EUR 157.5 million (Table 3.28), as well as among the top 30 active ingredients with the greatest variation expenditure compared to

last year (+66.1%) (Table 3.23). Sodium hypochlorite is among the top 30 active ingredients for consumption as for drugs purchased by public health facilities, with 2.6 DDD per 1000 inhabitants per day, up by 7.3% compared to 2021 (Table 3.27).

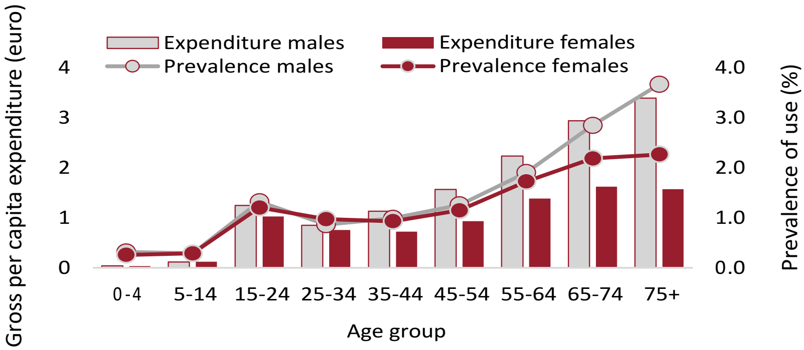
Main indices of expenditure, consumption and exposure
Dermatological drugs

Public expenditure* in million euros (% over total)	**261.7**	**(1.1)**
Δ % 2022-2021		32.0
Regional range of gross expenditure (per capita):	3.3	6.2
DDD/1000 inhabitants per day* (% over total)	**13.7**	**(1.0)**
Δ % 2022-2021		-1.1
Regional range DDD/1000 inhabitants per day	8.8	26.9

* *includes prescriptions under approved care regime and purchases by public health facilities*



Age and gender distribution of expenditure, prevalence of use and consumption under approved care regime and distribution "on behalf" in 2022 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Males	Females	Total	Males	Females	Total
0-4	0.0	0.0	0.0	0.5	0.4	0.4
5-14	0.1	0.1	0.1	0.6	0.6	0.6
15-24	1.2	1.0	1.1	3.3	2.9	3.1
25-34	0.9	0.8	0.8	2.9	2.6	2.8
35-44	1.1	0.7	0.9	4.0	2.8	3.4
45-54	1.6	0.9	1.2	5.4	3.6	4.5
55-64	2.2	1.4	1.8	7.9	5.4	6.6
65-74	2.9	1.6	2.2	10.8	6.9	8.8
75+	3.4	1.6	2.3	13.0	7.1	9.5

Section 4

Monitoring registries and conditional reimbursement agreements

4.1 Medicines Monitoring Registries

The AIFA Monitoring Registries constitute an information system that, through a web-based platform, manages the prescription and dispensing of medicines reimbursed by the NHS, in line with the indications authorised by the European Medicines Agency (EMA) and within the limits identified and set by the advisory committees of the Agency (Scientific Technical Committee [CTS] and Price and Reimbursement Committee [CPR]). Therefore, AIFA Registries ensure the monitoring of the appropriateness of use of medicines in accordance with the constraints, both regulatory, which derive from the authorisation, and related to the conditions of eligibility for reimbursement set by AIFA's advisory bodies.
Another fundamental characteristic of the AIFA Registries is that of allowing access to relevant and often high-cost therapies in a homogeneous way on the national territory, regardless of the location of the patient or the changes of residence.
Monitoring Registries also have an impact on the monitoring of national pharmaceutical expenditure, as they allow the application of specific conditions of eligibility for reimbursement of a medicine, in a specific therapeutic indication, agreed by AIFA with the pharmaceutical company in the so-called Managed Entry Agreements (MEA). In other words, the AIFA Monitoring Registries are the means by which economic agreements, some of which are based on the efficacy of the medicine in clinical practice, are made effective.
In this context, in application of the legislation introduced starting from 2015, the AIFA Registries are also used for the distribution among the Regions of the economic resources allocated by the State for the financing of innovative medicines.
Last but not least, the AIFA Registries are useful in assessing the clinical-therapeutic impact of medicines in the specific Italian healthcare context. Accordingly, the Registries are a tool to support the production of technical-scientific information useful for the decision-making processes of doctors and health professionals.

Types of monitoring

The AIFA Monitoring Registries include different types of monitoring: the **Registries in the strict sense**, which are aimed at a detailed monitoring of the use of the medicine in clinical practice, from the eligibility criteria to the outcome of the treatment, including the possible application of a MEA. Then there are the Registries that, with methods substantially similar to the Registries in the strict sense, monitor medicines reimbursed by the NHS according to Law 648/96, i.e. before their actual authorisation (**Registries of Law 648/96**). The **Web-based therapeutic plans** (Web-based TPs), instead, focus on aspects inherent to the prescription of the medicine and the eligibility criteria, as well as, less frequently, on the possible evaluation and re-evaluation of the results of the therapy. Lastly, at the end of 2019, **Simplified Monitoring Registries (single or multi- drug)** were introduced, which are a tool for prescribing and monitoring the use of multiple medicinal products within the same therapeutic indication. These particular Registries have been furtherly simplified compared to web-based TPs or Registries in the strict sense, in order to allow non-detailed monitoring and rapid compilation by doctors and pharmacists of the data required by the AIFA platform.

AIFA Registries: legal basis

Starting from 2012, the AIFA Monitoring Registries become an integral part of the National Health Service Information System (Article 15, paragraph 10 of Legislative Decree 95/2012, converted with modification into Law n. 135 of 7 August 2012). Subsequently, further legislation (Law 125/2015; Law 232/2016; Law 205/2017; Law 302/2018) assigned to the Registries further tasks related to the evaluation of the efficacy of the medicine, for the purpose of renegotiating the medicines subject to monitoring, the control of the expenditure of innovative medicines (Article 1, paragraph 578 of Law n. 145 of 30 December 2018), the allocation of resources to the Regions for the purchase of innovative medicines (Article 1, paragraph 401-404 of Law n. 232 of 11 December 2016; Ministerial Decree dated 9 October 2015 published in the Italian Official Journal n. 264 of 12 November 2015 "Costs reimbursed to Regions for the purchase of innovative medicines" and Ministerial Decree dated 16 February 2018 published in the Italian Official Journal n. 81 of 7 April 2018 "Operating procedures for the disbursement of resources allocated as a contribution to the reimbursement for the purchase of innovative and oncological medicines") and support in quantifying the so-called avoidable costs in healthcare.

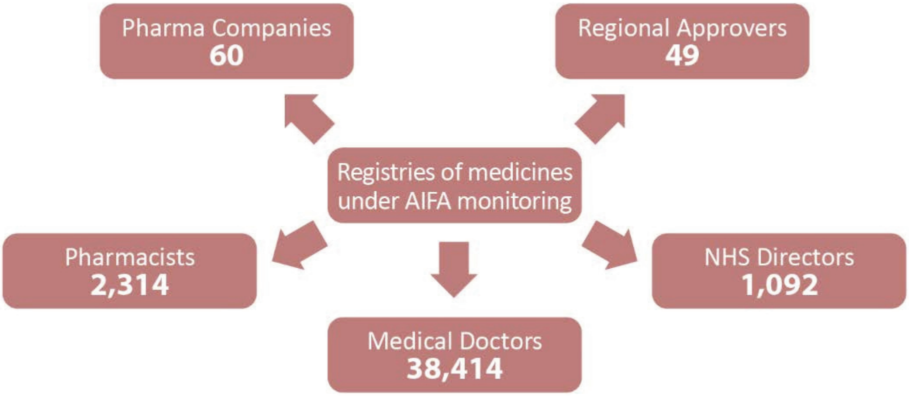
AIFA Registries and the Regions

The AIFA Monitoring Registries are a support infrastructure for the Regions. Through the functions of the AIFA Registries, the Regions exercise their responsibility in coordinating their health facilities and, consequently, in enabling their doctors to prescribe medicines subject to the Registry and the pharmacists responsible for their dispensing. The Regions, in managing the infrastructure, approve the authorisation of prescribing centers; subsequently, the health directors of the facilities that include these centers, in turn, authorise doctors and pharmacists to use the platform. Licensed doctors and pharmacists are responsible for the correct and timely entry of the data collected in the AIFA Monitoring Registries.

The collaborative network of AIFA Registries

The AIFA monitoring Registries constitute a collaborative network that allows the exchange of information between AIFA- Regions- health facilities- doctors- pharmacists- pharmaceutical companies. This network includes approximately 1,536 active health facilities (with at least one treatment started in 2022), in all 21 Italian Regions and Autonomous Provinces, 49 regional managers, 1,092 health directors, 38,414 doctors registered on the platform and 2,314 pharmacists (Figure 4.1.1). 60 pharmaceutical companies owning at least one monitoring Registry managed by the AIFA platform also contribute to this network. Pharmaceutical companies also interact with the pharmacies of the authorised health facilities, through specific profiling, in the case of Registries of medicines owned by them, admitted for reimbursement with a MEA based on the Registry. In this network, the Monitoring Registries Office is responsible for developing the monitoring form and for the process leading to its approval, for testing the production of the registries within the AIFA web platform and for interacting with all stakeholders for the management of the activities relating to the Registries and the related reporting.

Figure 4.1.1 Personnel participating in the Registries network in year 2022



Access and structure of AIFA Registries

Access to the AIFA Monitoring Registries is possible through the following web page: https://servizionline.aifa.gov.it/; the users will then have to select the link: "Registries of medicines subject to monitoring" and will thus be able to access the Registries by entering their credentials, or proceed with their registration if they are logging in for the first time. In general terms, subsequent navigation within the platform allows the doctor to select the pre-filled therapeutic indication in which he intends to prescribe the medicine being monitored, for which he has been previously enabled. Thereafter, the doctor selects the medicine he intends to prescribe, or chooses it from a list, in the event that it has been enabled and more than one monitored medicine is available in the same therapeutic indication.
At this point, the structure of the Registries provides a modular architecture, designed in order to allow a collection of both clinical-therapeutic and administrative data. This path involves the compilation of the following forms by doctors and pharmacists:

1. Patient data (unique for all Registries and/or Therapeutic Plans- AP)
2. Eligibility and clinical data (EDC)
3. Prescriptions (Medicine Request- RF)
4. Medicine dispensing (Medicine Dispensing- DF)
5. Follow-up (re-evaluations -RIV)
6. End of therapy (End of Treatment - FT)
7. Pregnancy (GV) (for medicines with Risk Management Plan)

As previously reported, in addition to the Registries in the strict sense, the web-based TPs are active, for which the participation of specialist doctors only is required, with the compilation of the following forms:

1. Patient data (unique for all Registries and/or Therapeutic Plans- AP)
2. Eligibility and clinical data (EDC)
3. Prescriptions (Medicine Request - RF)
4. Follow-up (re-evaluations - RIV)
5. End of therapy (End of Treatment - FT)

The simplified multi-drug cards share a very similar structure to those reported above, but provide for a very limited collection of data. It should be noted that, in this case, the eligibility form allows the selection of the drug used and the associated therapeutic indication.
In 2022, 283 registers were active (at least 1 day of monitoring). It is important to specify that, during the year 2023, the Monitoring Registers Office made public, on its webpage of the Agency's portal (https://www.aifa.gov.it/registri-e-piani-terapeutici1), a new definition of Monitoring Registry that goes beyond the "informatics" approach used in the past editions of this Report and takes on a more regulatory character. In fact, monitoring applied to a specific medicinal product in a specific reimbursed therapeutic indication is considered "Registry" (or Therapeutic Plan or simplified single- drug monitoring).
The pair Medicine/ indication **reimbursed** therefore becomes central in the definition of AIFA monitoring and synonym for Registry (or Therapeutic Plan or simplified single-drug monitoring) accessible through the AIFA Platform.
The numbers shown here therefore take into account this new definition and in particular consider each pair Medicine/Indication with at least 1 day of active monitoring during the year 2022. The number of Registries activated in 2022 was 80 while the registries closed in the previous year (2021) had been 38 equal to an increase of 42 new monitoring registries.

Table 4.1.1 Summary data of the Monitoring Registers present on the web platform: cumulative trend 2020-2022

	No.			Δ (%) 22-21
	2020	2021	2022	
Registries	235	241	283	17.4
Web-based TPs	15	16	20	25.0
Simplified monitoring	1	3	5	66.7
Treatments	3,220,515	3,792,875	4,441,193	17.1
Patients	2,657,977	3,094,980	3,536,714	14.3

In 2022, the ATC category A "*Alimentary tract and metabolism*" recorded a sharp increase from 165 patients initiated in 2021 to 43,317 patients initiated in 2022. This increase is due in particular to the release of two registries in 2022 for Forxiga and Jardiance in the indication for the treatment of chronic heart failure. Although these medicinal products have a main indication classifying them as active ingredients for the treatment of diabetes (ATC A), AIFA monitoring of their use is, however, related to prescription in the therapeutic indication in the field of cardiology.

The second most growing ATC category in terms of number of monitored treatments was J, related to antiinfective medicines. The increase is due to AIFA monitoring of COVID-19 drugs (antivirals: remdesivir, molnupiravir and nirmatrelvir+ritonavir; and monoclonal antibodies: bamlanivimab, bamlanivimab+etesevimab, casirivimab+imdevimab, sotrovimab and tixagevimab and cilgavimab).

Finally, it should be noted that the R class "Respiratory system" recorded for the second year in a row a relative increase of more than 50 %. The category B "Blood and blood forming organs", which includes the therapeutic plans of new oral anticoagulants, despite the recent closure of monitoring in the indication for prevention of stroke and systemic embolism in adult patients with non-valve atrial fibrillation (NVAF), is still active for the indication related to the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrence of DVT and PE. Therefore, it still remains the category that collects the highest number of patients within the platform of the Monitoring Registries (Table 4.1.2 et seq.), although, as expected given the closure of NVAF therapeutic plans, the relative increase 2022-2021 was low, around 5 %.

Table 4.1.2 Number of patients* by ATC category (I level) in the period 2020-2022

ATC Code	No. of patients			Incidence (%)			Δ%	
	2020	2021	2022	2020	2021	2022	22-21	21-20
A	127	165	43,317	0.0	0.0	1.1	2,6152.73	29.92
B	1,486,914	1,681,799	1,765,421	52.8	50.9	45.6	4.97	13.11
C	71,703	107,185	153,565	2.5	3.2	4.0	43.27	49.48
D	8,229	12,748	17,361	0.3	0.4	0.4	36.19	54.92
H	248	263	284	0.0	0.0	0.0	7.98	6.05
J	236,425	335,907	557,826	8.4	10.2	14.4	66.07	42.08
L	466,350	520,108	577,783	16.5	15.7	14.9	11.09	11.53
M	261,251	307,019	359,531	9.3	9.3	9.3	17.10	17.52
N	17,121	27,350	37,107	0.6	0.8	1.0	35.67	59.75
R	4,922	7,832	12,530	0.2	0.2	0.3	59.98	59.12
S	263,536	305,213	344,957	9.4	9.2	8.9	13.02	15.81
V	1089	1,484	1,918	0.0	0.0	0.0	29.25	36.27
Total	**2,817,915**	**3,307,073**	**3,871,600**	**100**	**100**	**100**	**17.07**	**17.36**

* The Table reports the number of naïve patients by ATC category. For each patient, only the first treatment carried out with a medicine belonging to an ATC category (level I) is counted. Given the approximation to a decimal place, the total incidences do not necessarily add up to 100%

Table 4.1.3 Number of active Registries and TPs per ATC category (Level I) in the period 2020-2022

ATC code	No. of Registers			No. of TP			Total		
	2020	2021	2022	2020	2021	2022	2020	2021	2022
A	5	5	9	0	0	2	5	5	11
B	3	2	3	8	10	11	11	12	14
C	9	8	7	1	1	1	10	9	8
D	3	3	4	0	0	0	3	3	4
H	1	1	1	0	0	0	1	1	1
J	12	10	13	0	0	0	12	10	13
L	181	183	209	0	0	0	181	183	209
M	4	4	5	4	3	4	8	7	9
N	8	8	8	1	1	1	9	9	9
R	5	12	20	1	1	1	6	13	21
S	2	3	2	0	0	0	2	3	2
V	2	2	2	0	0	0	2	2	2
Total	**235**	**241**	**283**	**15**	**16**	**20**	**250**	**257**	**303**

Table 4.1.4 Number of patients* enrolled per ICD-11 category (years 2020-2022)

ICD-11	No. of patients			Incidence (%)			Δ%	
	2020	2021	2022	2020	2021	2022	21-20	22-21
Mental and behavioural disorders	3,315	4,965	6,967	0.1	0.2	0.2	49.77	40.32
Developmental disorders	0	0	22	0.0	0.0	0.0	-	-
Diseases of the blood and blood-forming organs	6,843	7,299	8,182	0.2	0.2	0.2	6.66	12.10
Diseases of the circulatory system	1,515,392	1,726,964	1,845,512	55	53.4	49.1	13.96	6.86
Diseases of the immune system	2,077	2,605	3,232	0.1	0.1	0.1	25.42	24.07
Diseases of the musculoskeletal system and connective tissue	230,502	271,998	320,258	8.4	8.4	8.5	18.00	17.74
Diseases of the nervous system	16,080	24,676	31,548	0.6	0.8	0.8	53.46	27.85
Diseases of the digestive system	3,124	3,124	3,124	0.1	0.1	0.1	0.00	0.00
Diseases of the genitourinary system	622	777	947	0.0	0.0	0.0	24.92	21.88
Diseases of the respiratory system	14,510	17,629	21,395	0.5	0.5	0.6	21.50	21.36
Skin diseases	9,290	15,725	24,197	0.3	0.5	0.6	69.27	53.88
Eye diseases	283,157	323,778	362,923	10.3	10	9.7	14.35	12.09
Diseases of the endocrine glands of nutrition and metabolism and immune disorders	22,302	33,531	52,084	0.8	1.0	1.4	50.35	55.33
Infectious and parasitic diseases	233,033	331,324	553,280	8.5	10.2	14.7	42.18	66.99
Tumors	416,567	469,439	525,509	15.1	14.5	14	12.69	11.94
Total	**2,756,814**	**3,233,834**	**3,759,180**	**100**	**100**	**100**	**17.30**	**16.25**

* The Table reports the number of naïve patients by ICD-11 code. For each patient, only the first treatment carried out with a medicine with indication belonging to a specific ICD-11 code is counted. *ICD: International Classification of Diseases*

Demographic characteristics of patients under treatment in the Registries and TPs *web-based*

Regulatory decisions are based on information obtained considering the characteristics of the population enrolled and studied in pivotal clinical trials with the awareness that the consequences of use in real clinical practice may vary – in terms of health benefits - compared to those registered in the context of clinical trials.
In this regard, in 2015 the European Medicines Agency (EMA) began to draw up a document that aims to define how to assess the degree of fragility of the elderly population with the aim of being able to include them more adequately in the clinical trials of medicines (adopted by the CHMP in January 2018). In fact, although the elderly are among the major users of medicines, due to the concomitant (often chronic) pathologies they suffer from, they are not always enrolled in studies. Moreover, the effects, in terms of efficacy and safety, of medicines in the over 65-year-olds can vary considerably with respect to those observed in the younger adult population. Therefore, the collection and analysis of data relating to clinical practice (real world data) becomes essential, also for the purposes of any re-evaluation. For this purpose, post-marketing monitoring through the AIFA Registries constitutes an important information basis.
The percentage distribution of treatments by gender and age is shown below. As can be seen from the data, the high presence of patients over the age of 60 is evident. Specifically, in Tables 4.1.5 and 4.1.6, the distribution of treatments by age and gender is reported, separately by Registries and Therapeutic Plans. As for the Registries, the highest number of treatments was detected in the age group between 70 and 79 years, both for women and for men, while as for the TPs the highest number of treatments was observed in the same age group for men, while for women in the age groups over 80 years. The distribution by age group and ATC code shows that in the youngest patients the most populated ATCs are B, J , L and N. From the age of 50 upwards, the ATC B is the one that counts the highest number of patients entered in the Registry, while the number of patients entered in the Registries referred to ATC C and S begins to be relevant (Table 4.1.7). The latter registers up to 100,000 patients entered both in the age group 70-79 and over 80 years.

Table 4.1.5 Number of patients by age group and gender in the Registries (Year 2022)*

Class group	Females		Males	
	N° Patients	Inc %	N° Patients	Inc %
<40	35,892	5.29	38,363	5.05
40-49	57,347	8.45	68,269	8.99
50-59	113,061	16.67	141,327	18.61
60-69	151,795	22.37	184,933	24.35
70-79	192,097	28.32	216,063	28.45
≥80	128,236	18.90	110,444	14.54
Total	**678,428**	**100**	**759,399**	**100**

Table 4.1.6 Number of patients by age group and gender in the Therapeutic Plans (Year 2022)*

Class group	Females		Males	
	N° Patients	Inc %	N° Patients	Inc %
<40	14,026	1.23	19,344	2.01
40-49	28,088	2.46	30,348	3.16
50-59	74,267	6.51	83,661	8.71
60-69	181,260	15.90	189,055	19.68
70-79	372,884	32.71	330,231	34.38
≥80	469,611	41.19	308,010	32.06
Total	**1,140,136**	**100**	**960,649**	**100**

* Patients registered in a web-based TP and in Registries in the strict sense are counted in both Tables 4.1.5 and 4.1.6.

Table 4.1.7 Number of patients * by age group and gender by ATC category (level I) up to 2022

ATC	<40			40-49			50-59		
	M	W	tot	M	W	tot	M	W	tot
A	588	179	767	1509	322	1831	4743	1049	5792
B	12,112	9,676	21,788	26,137	16,069	42,206	72,113	34,358	106,471
C	2155	686	2,841	7282	1769	9,051	20769	6236	27,005
D	4506	4034	8540	1148	1091	2239	1234	1334	2568
H	23	60	83	11	69	80	15	41	56
J	20,622	13,634	34,256	42,038	21,326	63,364	74,299	41,028	115,327
L	7,244	10,382	17,626	15,125	25,352	40,477	42,734	51,872	94,606
M	1,009	3,253	4,262	1,581	13,188	14,769	5,076	42,906	47,982
N	7,143	5,270	12,413	2,346	6,444	8,790	2,483	6,884	9,367
R	2054	2661	4715	618	1101	1719	652	1111	1763
S	1,957	2,028	3,985	5,290	4,144	9,434	16,663	13,741	30,404
V	17	19	36	61	53	114	197	111	308
Total	**59,430**	**51,882**	**111,312**	**103,146**	**90,928**	**194,074**	**240,978**	**200,671**	**441,649**

ATC	60-69			70-79			≥80		
	M	W	tot	M	W	tot	M	W	tot
A	8063	2030	10093	10555	3553	14108	7295	3431	10726
B	170,472	107,606	278,078	311,366	283,620	594,986	299,829	422,063	721,892
C	31762	11342	43,104	33811	13834	47,645	16001	7918	23,919
D	997	892	1889	793	594	1387	426	312	738
H	12	28	40	2	18	20	0	5	5
J	59,806	47,463	107,269	67,270	65,519	132,789	49,295	55,526	104,821
L	86,824	73,679	160,503	108,810	80,658	189,468	39,566	35,537	75,103
M	11,536	79,376	90,912	16,295	105,858	122,153	10,500	68,953	79,453
N	1,422	2,948	4,370	908	668	1,576	487	104	591
R	1059	950	2009	1177	618	1795	361	168	529
S	36,453	31,988	68,441	57,646	65,063	122,709	44,451	65,533	109,984
V	397	153	550	535	133	668	210	32	242
Total	**408,803**	**358,455**	**767,258**	**609,168**	**620,136**	**1,229,304**	**468,421**	**659,582**	**1,128,003**

* The Table reports the number of “naïve” patients by ATC category. For each patient, only the first treatment carried out with a medicine belonging to an ATC category (level I) is counted.

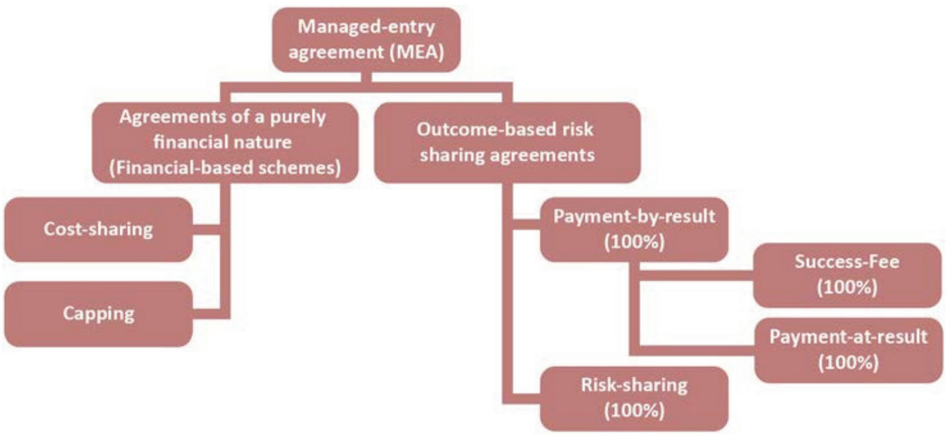
4.2 Financial impact of conditional reimbursement agreements

Italy is one of the first European countries to have adopted the so-called *Managed Entry Agreements* (MEAs), i.e. tools that allow access to new therapies which, although promising, are characterised by high costs and uncertainties related to clinical benefits and economic impact. AIFA negotiates with pharmaceutical companies various MEAs that can provide for the management of conditional reimbursement at the single *patient level* through the Monitoring Registries platform (patient- level); and at the level of the entire population (*population level*) through information flows for monitoring expenditure and consumption by the NHS (i.e. OsMed Flow and Medicine Traceability Flow).

Conditional reimbursement agreements managed through the Registries (*patient level*):

The MEAs managed through the AIFA Registries can be classified, on the basis of an international taxonomy[1] in two main categories: a) outcome-based risk sharing agreements (*Outcome –based schemes*)*;* and b) agreements of a purely financial nature (*Financial-based schemes*) (Figure 4.2.1).

Figure 4.2.1 MEA taxonomy



[1] Wenzl M, Chapman S. Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward, OECD Health Working Papers, No. 115. Paris: OECD Publishing; 2019. https://doi.org/10.1787/6e5e4c0f-en.

The first category includes two macro types of agreements, the so-called Payment by Result (PbR) and Risk Sharing (RS). In the case of PbR, the risk of failure is entirely borne by the pharmaceutical company holder of the MA. Two variants of the PBR are the Success-Fee (SF), where the entire cost of treatment is borne by the NHS only when representing a therapeutic success, and the Payment-at-Result (PaR), in which the entire cost of treatment for the NHS is broken down over time following the verification of the maintenance of therapeutic success. Finally, the second type is related to Risk-sharing (RS), in which the cost of failure is shared between the NHS and the pharmaceutical company with a variable breakdown, depending on the medicine and the pathology (N.B. in case of an early failure of treatment, the PaR in fact corresponds to a risk-sharing model).
With regard to financial-based schemes, only Cost-sharing (CS) and Capping are among those manageable through monitoring registries. In the case of CS, part of the cost of treatment is returned by the pharmaceutical company to NHS health care facilities, regardless of the outcome of the treatment (i.e.: it is applied to each patient initiating treatment), with different methods of financial compensation (credit note, pay-back, etc.).
Instead, in the case of Capping, when the patient's treatment reaches a predetermined threshold of dispensed packages – or amount of medicine – the relative cost of each additional package in continuation of treatment is returned by the pharmaceutical company to NHS health facilities.
Figure 4.2.2 shows the percentage of each agreement, as of 31 December 2022.
At the end of 2022, 13 agreements based on the clinical oucome of the treatment were active in the AIFA Monitoring Registries platform (50% of total existing agreements), mainly composed of PbR (10 agreements) and 3 PaR agreements. The financial agreements represent the remaining 50 % of the existing agreements, comprising a total of 13 agreements: 6 cost-sharing (23 % of existing agreements) and 7 capping (27 % of existing agreements).

Figure 4.2.2 Percentage distribution of the types of risk sharing agreement (as of 31 December 2022)

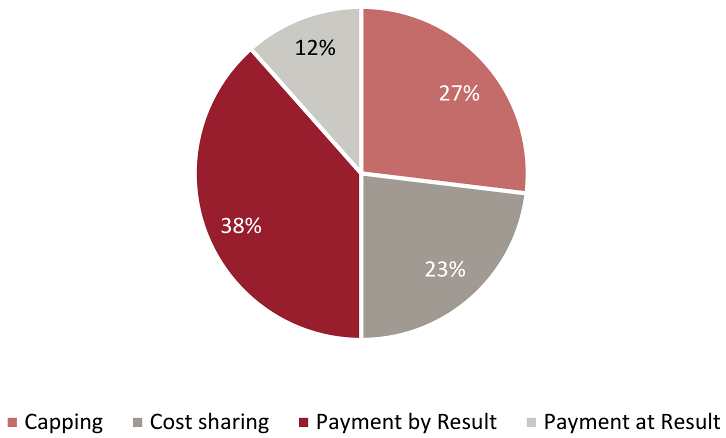


Table 4.2.1 shows the reimbursements relating to MEAs detected by the Registries platform for the three-year period 2020-2022, divided by Region.
83% of the reimbursement obtained in 2022 (approximately 67 million euros) relates to financial agreements (Figure 4.2.3), with 67% of the reimbursement for Cost Sharing agreements and 16% for Capping agreements. Payment by Result and Risk Sharing cover instead 17% of reimbursements, even though Risk Sharing represent a depleted share (> 0.01 %) resulting from the completion of treatments and related administrative procedures of Erbitux® and Vectibix® registries, now closed. It is important to note that PaR agreements provide for deferred invoicing over time and not reimbursements, so this type of agreement does not contribute to the values shown in Table 4.2.1 and Figures 4.2.3 and 4.2.4.

Table 4.2.1 Reimbursement obtained (€) for MEA online years 2020-2022*

Region	Reimbursement 2020	Reimbursement 2021	Reimbursement 2022
Abruzzo	1,909,701	1,775,971	1,404,213
Basilicata	2,601,303	1,106,373	697,721
Calabria	2,787,310	1,872,137	1,425,621
Campania	12,658,095	15,569,723	12,448,257
Emilia R.	8,403,782	9,652,272	4,401,804
Friuli VG	3,520,923	2,508,802	926,697
Lazio	14,101,607	10,750,137	6,690,372
Liguria	2,994,895	2,266,187	2,996,866
Lombardy	17,307,750	19,686,427	15,344,503
Marche	3,309,402	2,519,704	1,208,274
Molise	417,356	501,225	150,014
Piedmont	6,317,278	7,044,898	3,379,371
AP of Bolzano	1,162,700	1,015,011	628,667
AP of Trento	984,236	456,463	477,298
Puglia	9,094,019	12,288,125	7,094,415
Sardinia	3,242,559	2,319,411	1,385,282
Sicily	6,049,224	7,740,633	7,152,221
Tuscany	8,838,372	12,343,935	8,017,432
Umbria	1,317,372	966,506	1,067,861
Valle d'Aosta	89,952	423,464	295,449
Veneto	7,669,111	8,647,254	3,708,336
Total	**114,776,947**	**121,454,657**	**80,900,674**

* Reimbursement reported for 2020, 2021 and 2022 are obtained using data updated respectively to June 2021, June 2022 and June 2023.

Table 4.2.2 Reimbursements obtained by type of MEA (year 2022)

Region	Capping	Cost-sharing	Payment by result	Risk-sharing	Total
Abruzzo	252,307	958,247	193,660	-	1,404,213
Basilicata	15,611	370,426	311,684	-	697,721
Calabria	326,068	992,844	103,503	3,207	1,425,621
Campania	2,174,910	7,918,609	2,354,737	-	12,448,257
Emilia R.	887,914	2,682,747	831,142	-	4,401,804
Friuli VG	210,250	577,646	138,800	-	926,697
Lazio	836,618	5,379,404	474,350	-	6,690,372
Liguria	250,452	2,071,268	675,146	-	2,996,866
Lombardy	976,865	12,129,464	2,238,174	-	15,344,503
Marche	240,732	761,790	205,752	-	1,208,274
Molise	9,065	114,580	26,369	-	150,014
Piedmont	399,816	2,314,255	665,300	-	3,379,371
AP of Bolzano	182,199	348,703	97,766	-	628,667
AP of Trento	233,636	190,080	53,582	-	477,298
Puglia	1,321,022	5,238,764	531,898	2,729	7,094,415
Sardinia	645,002	531,659	208,621	-	1,385,282
Sicily	1,341,362	3,776,603	2,034,255	-	7,152,221
Tuscany	1,394,787	4,963,721	1,658,924	-	8,017,432
Umbria	36,405	933,255	98,201	-	1,067,861
Valle d'Aosta	-	220,266	75,182	-	295,449
Veneto	1,001,765	1,944,651	761,919	-	3,708,336
Total	**12,736,786**	**54,418,984**	**13,738,968**	**5,936**	**80,900,674**

Figure 4.2.3 Reimbursemnt 2022, percentages by type of agreement

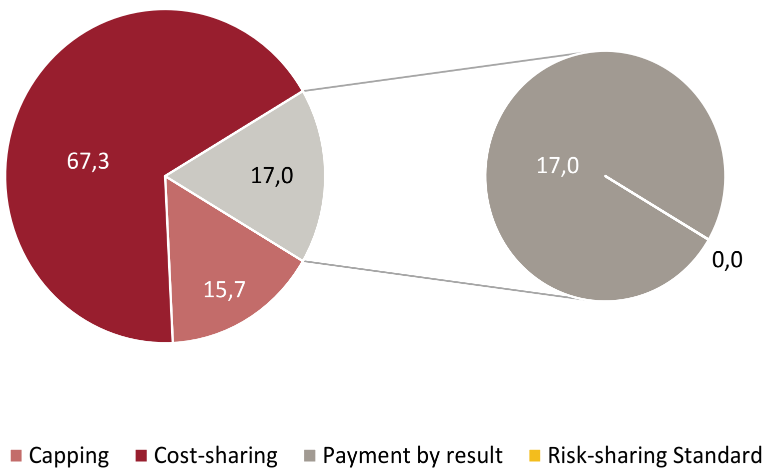
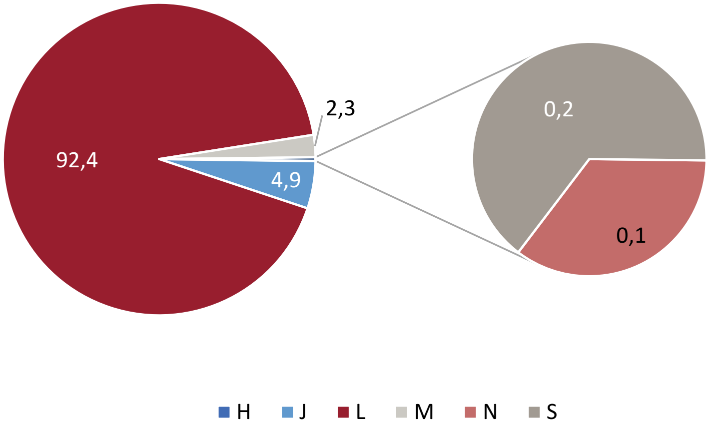


Figure 4.2.4 Reimbursement 2022, percentages for ATC level I



At ATC level (Figure 4.2.4), almost all of the reimbursement (92.4 %) are ascribable to antineoplastic and immunomodulatory medicines (L); general antimicrobials for systemic use (J) account for about 5 % of the reimbursements generated in 2022, while sensory organ drugs (S), nervous system drugs (N), endocrine system drugs (H) and muscle and skeletal (M) drugs add up to approximately 2.7 % of 2022 reimbursements.
In the overall assessment of the effectiveness of MEAs, it is necessary, first of all, to take into account the value of their management within the AIFA Registries Platform, which represents a unique experience in the European context. In this regard, it is necessary to consider the economic impact deriving from the appropriate use of medicines guaranteed through Registries, which allow to supply the medicine to selected patients in which the efficacy of the drug in the authorisation phase has been mostly demonstrated. However, in a counterfactual scenario, the non-quantifiable costs of dispensing the drug should also be considered in patients in whom it is not indicated and/or not reimbursed (inappropriateness), or where the expected efficacy would be lower (because excluded on the basis of the criteria of the Registry eligibility card). For similar reasons, it should be highlighted that when assessing the efficacy of the outcome-based MEA agreements, it is not sufficient to consider the value of the reimbursements obtained, as these are linked exclusively to the failures of the treatment and do not take into account the benefit for the NHS in terms of appropriateness. In fact, in a apparently paradoxical way, a relatively high reimbursement value from an outcome-based MEA implies relatively higher clinical-therapeutic inappropriateness with respect to the same Registry which, having been developed with more selective criteria in eligibility for reimbursement by the NHS, would lead to lower reimbursements and greater clinical-therapeutic appropriateness.

Conditional reimbursement agreements managed through information flows for monitoring expenditure and consumption (population level)

Agreements managed in a manner other than Registries are of a financial nature and can be mainly classified into "expenditure ceilings by product" and "price/volume agreements". The expenditure ceilings are used in order to promote the appropriate use of medicines. In the case of setting an expenditure ceiling, AIFA, upon the proposal of the Pricing and Reimbursement Committee, finalises the agreement with the pharmaceutical company, both in relation to the price of the medicine and in relation to the maximum expenditure sustainable by the NHS in the first 12/24 months of marketing, calculated on the basis of the estimated number of patients expected in Italy, on the basis of epidemiological data, for the reimbursed therapeutic indication. According to this logic, if the monitoring of pharmaceutical expenditure, at the end of the period defined by the contract, shows an expenditure for the product exceeding the agreed ceiling, AIFA proceeds to communicate to the pharmaceutical company the value of the *payback* for the Regions.

The price/volume agreements, on the other hand, provide for progressive discounts on the price of a medicine on the basis of the volumes reached during the contract period. These discounts can be obtained through a reduction in the price of the medicine or, if provided for in the agreement, through a *payback* in favour of the Regions.

Furthermore, AIFA, in some cases, can negotiate confidential discounts with pharmaceutical companies, which however do not result into a *payback* in favour of the Regions, but into a reduction in the price directly applied on the invoice in favour of NHS healthcare facilities. It should be noted that the aforementioned confidentiality is limited to the extent of the discounts and not to the presence or absence of this negotiation agreement.

Table 4.2.3 shows the measures that in 2022 gave rise to reimbursements by companies for the application of expenditure ceilings and price/volume agreements. The medicines involved were a total of 15 (16 *paybacks*), for a total of 114,438,117.55 euros (Tables 4.2.4, 4.2.5 and 4.2.6). In particular, 88,208,506.52 euros were paid by pharmaceutical companies for the application of the expenditure ceilings (Table 4.2.4 and 4.2.5) and the remaining 26,229,611.03 euros for the application of price/volume agreements. Considering the reimbursement class, 76,319,666.80 euros were paid for class A products and 38,118,450.75 euros for class H products.

Finally, Table 4.2.8 shows the measures that in 2022 gave rise to reimbursements by the companies in application of the “2015 Budget law” agreements. The medicines involved were a total of 30, for a total of 17,030,068.23 euros (Table 4.2.8).

Table 4.2.3 List of medicines subject to the payback mechanism for the application of expenditure ceilings and price/volume agreements

Medicine	Italian Official Journal	Type of agreement
Aimovig	GU Serie Generale n.113 del 16-05-2022	Expenditure ceiling
Benlysta	GU Serie Generale n.1 del 03-01-2022	Expenditure ceiling
Brineura	GU Serie Generale n.271 del 19-11-2022	Expenditure ceiling
Brintellix	GU Serie Generale n.113 del 16-05-2022	Price/volume
Brintellix	GU Serie Generale n.257 del 03-11-2022	Price/volume
Kaftrio	GU Serie Generale n.271 del 19-11-2022	Expenditure ceiling
Kalydeco	GU Serie Generale n.271 del 19-11-2022	Expenditure ceiling
Libtayo	GU Serie Generale n.257 del 03-11-2022	Expenditure ceiling
Novothirteen	GU Serie Generale n.257 del 03-11-2022	Expenditure ceiling
Oralair	GU Serie Generale n.72 del 26-03-2022	Expenditure ceiling
Orkambi	GU Serie Generale n.271 del 19-11-2022	Expenditure ceiling
Raxone	GU Serie Generale n.91 del 19-04-2022	Expenditure ceiling
Striverdi Respimat	GU Serie Generale n.113 del 16-05-2022	Price/volume
Symkevi	GU Serie Generale n.271 del 19-11-2022	Expenditure ceiling
Xadago	GU Serie Gnerale n.168 del 20-7-2022	Price/volume
Xtandi	GU Serie Generale n.113 del 16-05-2022	Expenditure ceiling

Table 4.2.4 Amounts paid by companies to the Regions in 2022 (class A) - Expenditure ceilings

Region	Aimovig (€)	Kaftrio (€)	Kalydeco (€)	Oralair (€)	Orkambi (€)	Raxone (€)	Symkevi (€)	Total (€)
Abruzzo	75,616.54	502,415.69	429,325.73	19,221.37	130,885.36	22,764.13	33,768.98	1,213,997.80
Basilicata	27,651.68	291,944.22	316,845.05	13,623.47	142,190.00	-	-	792,254.42
Calabria	88,402.63	565,783.39	900,908.42	30,035.85	124,654.52	-	35,755.39	1,745,540.20
Campania	172,124.26	1,440,680.13	1,665,250.87	9,287.01	604,632.57	80,980.69	30,458.30	4,003,413.83
Emilia R.	275,582.07	1,489,141.86	1,347,366.74	66,365.93	522,550.59	31,347.37	48,998.12	3,781,352.69
Friuli VG	54,425.66	408,495.56	349,038.48	1,822.66	148,240.62	23,883.70	13,670.91	999,577.60
Lazio	383,723.24	1,856,283.78	1,941,529.06	33,604.20	318,682.74	89,937.15	29,796.16	4,653,556.32
Liguria	84,581.88	553,336.13	555,977.33	3,501.77	172,841.52	20,898.24	49,660.26	1,440,797.13
Lombardy	344,380.67	3,858,642.35	3,309,291.36	184,527.48	779,688.72	53,365.15	140,372.98	8,670,268.71
Marche	107,494.31	678,940.12	577,184.06	11,754.19	69,582.34	8,210.02	21,188.38	1,474,353.43
Molise	11,898.85	84,867.52	75,216.53	2,383.30	18,151.92	-	-	192,518.12
Piedmont	104,052.87	1,067,444.69	1,107,657.39	67,458.24	404,975.47	23,510.50	79,456.43	2,854,555.59
A.P. of Bolzano	61,290.46	241,400.92	196,647.05	29,329.09	140,677.33	-	7,283.50	676,628.35
A.P. of Trento	15,030.19	242,155.26	190,154.13	4,979.15	30,253.19	2,239.10	7,283.50	492,094.52
Puglia	169,970.54	1,343,546.94	1,589,953.20	36,592.13	586,480.64	24,630.06	149,837.10	3,901,010.61
Sardinia	30,587.43	396,048.35	344,812.86	-	140,776.91	5,224.56	-	917,450.10
Sicily	99,851.05	1,589,096.86	1,848,260.75	13,878.70	897,104.15	31,720.54	122,261.34	4,602,173.39
Tuscany	140,586.75	1,286,591.44	1,145,150.40	17,386.82	361,820.59	41,796.49	62,201.12	3,055,533.62
Umbria	27,311.23	222,918.66	240,016.81	8,495.73	97,294.13	24,630.07	3,310.68	623,977.31
Valle d'Aosta	13,579.47	19,236.64	14,367.20	455.86	3,025.32	-	-	50,664.48
Veneto	175,974.64	1,726,770.82	1,486,582.73	79,498.12	334,098.59	79,861.15	65,551.54	3,948,337.59
Italy	**2,464,116.42**	**19,865,741.34**	**19,631,536.14**	**634,201.07**	**6,028,607.21**	**564,998.92**	**900,854.70**	**50,090,055.79**

Table 4.2.5 Amounts paid by companies to the Regions in 2022 (class H) - Expenditure ceilings

Region	Benlysta (€)	Brineura (€)	Libtayo (€)	Novothirteen (€)	Xtandi (€)	Total (€)
Abruzzo	27,458.23	-	476,219.14	99,146.16	515,913.71	1,118,737.24
Basilicata	16,558.19	-	208,924.28	70,445.95	172,670.12	468,598.54
Calabria	75,587.23	156,054.09	643,928.05	326,138.66	587,763.32	1,789,471.35
Campania	238,650.43	-	2,126,827.59	-	1,868,078.74	4,233,556.76
Emilia R.	135,183.66	297,245.89	809,501.44	28,700.20	1,468,730.55	2,739,361.74
Friuli VG	56,373.85	-	364,104.81	-	662,953.56	1,083,432.22
Lazio	118,669.60	2,452,278.50	1,097,724.37	-	1,719,416.04	5,388,088.51
Liguria	21,668.31	-	487,110.32	140,891.90	483,971.78	1,133,642.31
Lombardy	370,699.88	-	1,808,351.63	172,201.21	1,874,665.34	4,225,918.06
Marche	51,400.59	-	381,900.75	-	652,379.63	1,085,680.97
Molise	6,944.07	-	69,404.15	-	78,258.28	154,606.50
Piedmont	122,205.16	104,036.06	843,527.29	57,400.40	1,400,946.48	2,528,115.39
A.P. of Bolzano	12,430.83	-	190,630.03	-	136,903.24	339,964.10
A.P. of Trento	15,599.61	-	49,828.62	-	297,586.06	363,014.29
Puglia	155,346.23	-	1,325,227.57	-	1,228,898.05	2,709,471.85
Sardinia	34,475.75	-	296,266.71	-	439,873.83	770,616.29
Sicily	105,794.33	-	1,033,659.07	-	1,149,655.47	2,289,108.87
Tuscany	173,199.97	-	1,368,151.36	-	1,370,932.37	2,912,283.70
Umbria	13,985.94	-	123,717.33	-	425,303.96	563,007.23
Valle d’Aosta	-	-	5,694.69	-	22,561.39	28,256.08
Veneto	138,812.69	-	613,461.46	36,527.53	1,404,717.05	2,193,518.73
Italy	**1,891,044.55**	**3,009,614.54**	**14,324,160.66**	**931,452.01**	**17,962,178.97**	**38,118,450.73**

Table 4.2.6 Amounts paid by companies to the Regions in 2022 (class A) - Price/volume agreements (class A and H)

Region	Brintellix (€)	Striverdi Respimat (€)	Xadago (€)	Total (€)
Abruzzo	700,041.06	3,193.79	612,944.29	1,316,179.14
Basilicata	142,579.15	3,300.27	117,459.07	263,338.49
Calabria	658,062.03	7,942.46	407,682.44	1,073,686.93
Campania	1,715,178.54	43,653.40	792,780.68	2,551,612.62
Emilia R.	618,750.84	16,664.10	297,177.28	932,592.22
Friuli VG	221,262.17	14,477.35	182,636.65	418,376.17
Lazio	1,506,900.11	44,332.08	1,629,514.34	3,180,746.53
Liguria	550,362.35	12,512.98	390,733.55	953,608.88
Lombardy	1,891,008.70	37,559.68	1,839,520.92	3,768,089.30
Marche	414,203.92	5,422.48	284,241.84	703,868.24
Molise	104,547.11	855.64	74,623.37	180,026.12
Piedmont	722,800.71	28,727.59	807,337.57	1,558,865.87
A.P. of Bolzano	135,966.01	6,454.13	17,602.29	160,022.43
A.P. of Trento	143,533.78	4,095.51	72,271.06	219,900.35
Puglia	1,055,730.26	16,137.64	1,015,572.85	2,087,440.75
Sardinia	549,331.96	9,575.11	322,436.61	881,343.68
Sicily	1,315,868.55	21,420.81	758,401.44	2,095,690.80
Tuscany	1,049,446.88	23,374.72	735,456.60	1,808,278.20
Umbria	201,157.55	1,963.15	174,989.71	378,110.41
Valle d'Aosta	34,299.82	801.06	32,243.22	67,344.10
Veneto	843,153.23	18,671.35	768,665.19	1,630,489.77
Italy	**14,574,184.73**	**321,135.30**	**11,334,290.97**	**26,229,611.00**

Table 4.2.7 List of medicines subject to the payback mechanism for the application of expenditure ceilings and "Ex manovra 2015" agreements"

Medicine	Italian Official Journal
Aprovel	GU Serie Generale n.81 del 05-04-2019
Atimos	GU Serie Generale n.81 del 05-04-2019
Bonviva	GU Serie Generale n.81 del 05-04-2019
Cedravis	GU Serie Generale n.79 del 25-3-2020
Clexane	GU Serie Generale n.81 del 05-04-2019
Coaprovel	GU Serie Generale n.81 del 05-04-2019
Dumirox	GU Serie Generale n.81 del 05-04-2019
Enapren	GU Serie Generale n.81 del 05-04-2019
Fevarin	GU Serie Generale n.81 del 05-04-2019
Flutiformo	GU Serie Generale n.122 del 24-05-2021
Forzaar	GU Serie Generale n.81 del 05-04-2019
Fosamax	GU Serie Generale n.81 del 05-04-2019
Goltor	GU Serie Generale n.81 del 05-04-2019
Gopten	GU Serie Generale n.81 del 05-04-2019
Hizaar	GU Serie Generale n.81 del 05-04-2019
Karvea	GU Serie Generale n.81 del 05-04-2019
Karvezide	GU Serie Generale n.81 del 05-04-2019
Liferol	GU Serie Generale n.81 del 05-04-2019
Lortaan	GU Serie Generale n.81 del 05-04-2019
Maveral	GU Serie Generale n.81 del 05-04-2019
Medeoros	GU Serie Generale n.213 del 27-8-2020
Mepral	GU Serie Generale n.32 del 08-2-2020
Recombinate	GU Serie Generale n.81 del 05-04-2019
Sinertec	GU Serie Generale n.81 del 05-04-2019
Sinvacor	GU Serie Generale n.81 del 05-04-2019
Triatec	GU Serie Generale n.81 del 05-04-2019
Triatec Hct	GU Serie Generale n.81 del 05-04-2019
Urorec	GU Serie Generale n.81 del 05-04-2019
Vasoretic	GU Serie Generale n.81 del 05-04-2019
Zinadiur	GU Serie Generale n.38 del 15-02-2020

Table 4.2.8 Amounts paid by companies to the Regions in 2022 for the application of the "Ex manovra 2015" agreements

Region	Payback Ex manovra 2015 *(€)*
Abruzzo	369,468.54
Basilicata	171,859.94
Calabria	654,470.71
Campania	1,984,057.38
Emilia R.	949,200.23
Friuli VG	313,878.48
Lazio	2,168,980.10
Liguria	459,884.08
Lombardy	2,656,235.35
Marche	471,396.12
Molise	120,235.61
AP of Bolzano	1,267,206.38
AP of Trento	78,346.47
Piedmont	95,792.57
Puglia	1,223,203.09
Sardinia	473,856.91
Sicily	1,673,472.10
Tuscany	986,491.24
Umbria	254,437.79
Valle d'Aosta	35,196.65
Veneto	1,260,384.49
Total	**17,668,054.21**

Section 5

New therapeutic entities and orphan medicines

5.1 New therapeutic entities

Comparison between new therapeutic entities authorised by EMA and those negotiated by AIFA

This section presents a comparison between the number of new medicines authorised under the centralised procedure of the European Medicines Agency (EMA) in the period 2018-2022 and those for which the pricing and reimbursement procedure at national level has been concluded. The new medicines authorised by EMA have been identified through the list published on the European Agency's[1] website and excluding generics, biosimilars and vaccines (ATC J07).

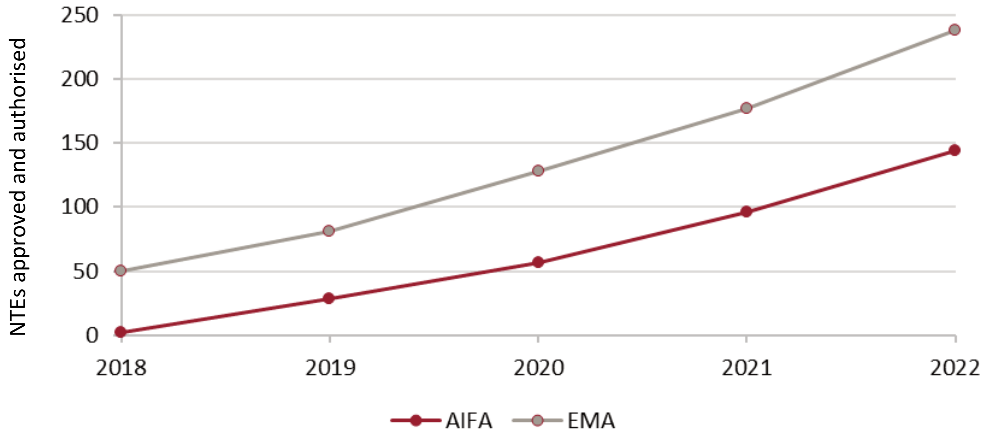
For the identification of the medicines that have concluded the pricing and reimbursement procedure in Italy, the first date of approval by the AIFA Board of Directors is considered, and if not available, the date of transmission of the Determination to the Official Journal.

The "Pricing and Reimbursement Negotiation system", known as NPR, was used to obtain this information.

Figure 5.1 shows that AIFA is in line with EMA procedures and makes available a large number of new therapeutic entities, revealing a high percentage of new negotiated therapeutic entities, as was also shown in the EFPIA Patients W.A.I.T. Indicator 2022 Survey, published in April 2023[2]. The percentage of new therapeutic entities negotiated is increasing thanks to the time gained between the conclusion of the centralised procedure and the pricing and reimbursement procedure; in fact, the percentage goes from 4 % in 2018, to 35 % in 2019, up to 61 % in 2022; considering the procedures completed until May 2023, the percentage of new therapeutic entities negotiated is 87 %.

[1] https://www.ema.europa.eu/en/medicines/download-medicine-data
[2] https://www.efpia.eu/media/s4qf1eqo/efpia-patient-wait-indicator_final-report-2023.pdf

Figure 5.1.1 Trend over time of new therapeutic entities authorised and approved by EMA and AIFA from 2018 to 2022 (Figure and Table)



Year of authorisation	EMA (1)	AIFA (2)	% (2/1)
2018	50	2	4
2019	81	28	35
2020	128	57	45
2021	177	96	54
2022*	238	144	61

* Considering the procedures completed until May 2023, the percentage of new therapeutic entities negotiated is 87 %.

Analysis of new therapeutic entities in the period 2014-2022

An analysis of the new therapeutic entities for the period 2014-2022 is presented in this section in order to monitor their impact on pharmaceutical expenditure, the sales trend and average cost per day of therapy over time. The new therapeutic entities were selected among the class A and H drugs marketed in the period 2014-2022, whose movements were detected in the OsMed flow and in the Italian Drug Traceability system. The definition of the list of new therapeutic entities provided for the following steps (Table 5.1.1):

1) **Selection of molecules with at least one movement**: only molecules moving at least one package in institutional flows (OsMed Flow or Drug Traceability) were considered in each year, from 2014 to 2022.
2) **Selection of molecules with a single specialty:** For each year, molecules with only one specialty (6-digit marketing authorisation) were considered. Such molecules are not considered even in the following years, even if only one specialty should remain on the market.
3) **Selection of molecules with patent coverage:** specialities with expired patents starting from the year of expiry and in the following years in which it is handled

have been excluded. As a proxy of patent expiry, the inclusion into the transparency list was used. For this purpose, the transparency lists published monthly by AIFA over the period 2008 to 2022 were used.

4) **Selection of molecules with time from the first authorisation ≤ 15 years:** in order to exclude molecules with time from the first authorisation above 15 years, information on the authorisation date contained in the list of authorised drugs available on the European Medicines Agency (EMA) website was used. For drugs not included in the EMA list, information on the year of first commercialisation was collected both through data flows (OsMed and Traceability) and from the Farmadati database.
5) **Selection of molecules not of known associations of active ingredients**: known associations of active ingredients have been eliminated.
6) **Selection of class A and H molecules:** only molecules with prevalence class A and H in each year were selected.
7) **Exclusion of vaccines (ATC J07)**.

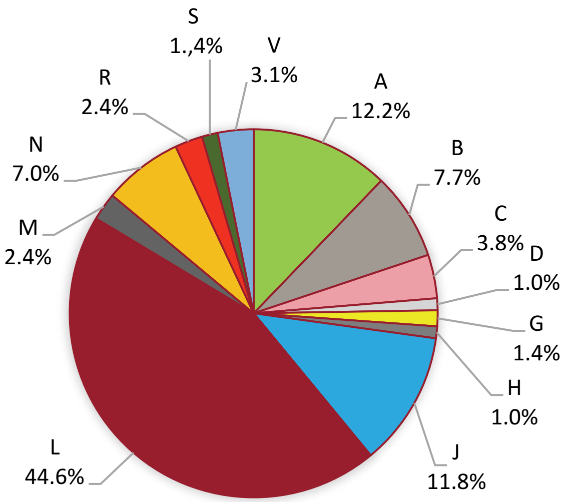
In conclusion, according to the criteria described above, the molecules analysed relating to new therapeutic entities followed from 2014 to 2022 in Italy are 449. (Table 5.1.1).
Table 5.1.1 shows for each year the number of new therapeutic entities both incident in the year and prevalent, as the respective movement over time is followed. The percentage of new therapeutic entities that have been granted the innovative status or have been designated and authorised as orphan drugs is also reported. It is observed that on average there are 27 new therapeutic entities each year, with a higher peak in 2017, in 2018, 2021 and 2022, with 33, 33, 34 and 41 new drugs, respectively. The proportion of orphan drugs increased over time from 13 % in 2014 to 28 % in 2022. Innovative medicines account for 17 % of new therapeutic entities marketed in 2022. New therapeutic entities are predominantly classified in class H, about 68 % in 2022.

Table 5.1.1 New therapeutic entities marketed in 2014-2022

	2014	2015	2016	2017	2018	2019	2020	2021	2022
No. new therapeutic entities (Incident and prevalent)	**208**	**217**	**226**	**234**	**245**	**244**	**246**	**269**	**287**
No. new therapeutic entities (Incident)	27	25	23	33	33	20	19	34	41
No. new therapeutic entities (exited: loss of requirements in the year)	15	16	14	25	22	21	17	11	23
Of which orphans	27	31	39	50	56	61	64	74	80
(%)	(13%)	(14%)	(17%)	(21%)	(23%)	(25%)	(26%)	(28%)	(28%)
Of which innovative	9	17	19	20	37	35	40	45	49
(%)	(4%)	(8%)	(8%)	(9%)	(15%)	(14%)	(16%)	(17%)	(17%)
Of which Class A	87	93	94	96	95	89	92	93	93
(%)	(42%)	(43%)	(42%)	(41%)	(39%)	(36%)	(37%)	(35%)	(32%)
Of which Class H	121	124	132	138	150	155	154	176	194
(%)	(58%)	(57%)	(58%)	(59%)	(61%)	(64%)	(63%)	(65%)	(68%)

Figure 5.1.2 represents the subdivision of incident and prevalent drugs into analysis for ATC level I. It is observed that the largest share of drugs in the period 2014-2022 is attributable to the category “L: antineoplastics and immunomodulators" which represents 44.6 % of these drugs, in second place is the category “A: alimentary tract and metabolism” with 12.2 % and third category “J: anti-infective for systemic use” with 11.8 %. In a lower share there are the categories ”B: blood and blood forming organs ", “N: Nervous system” and “C: cardiovascular system” and " that, as can be seen in the following tables, are categories of increasing economic importance.

Figure 5.1.2 New therapeutic entities incident and prevalent (N = 287) for ATC level I year 2022

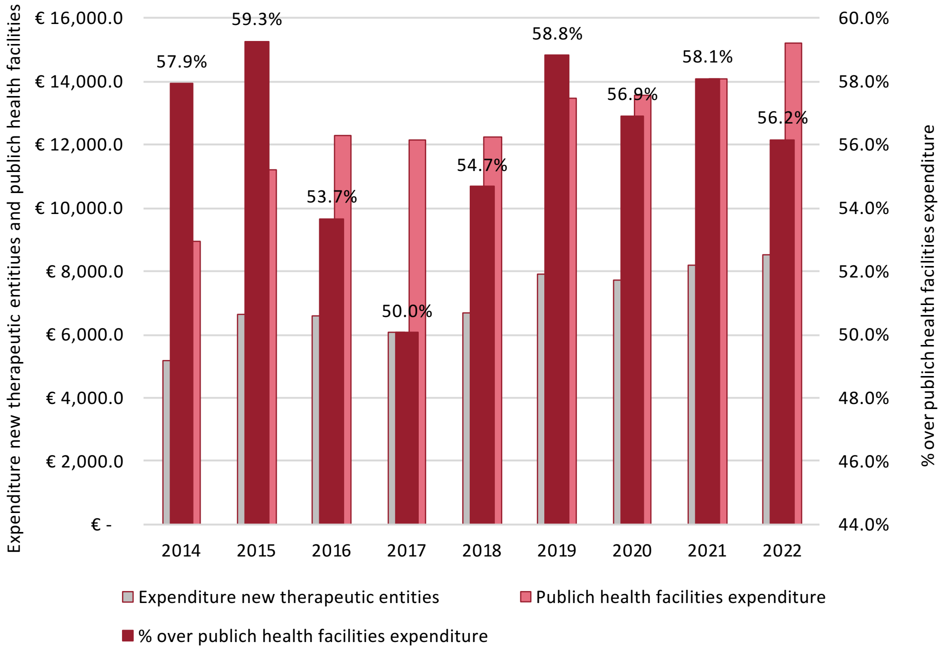


The expenditure for new incident and prevalent therapeutic entities amounted to around 5,174 million euros in 2014, up to around 8,291 million euros in 2022 (Table 5.1.2). On average, the expenditure for medicines disbursed under approved care regime from 2014 to 2022 represents a minority share (in average 5 %) of the total expenditure for new therapeutic entities, while medicines purchased by public health facilities constitute the predominant share (95 %). Over the period observed, 37 % of expenditure for medicines of incident and prevalent new therapeutic entities is represented by class A drugs, while 63 % by class H drugs. From 2014 to 2022, expenditure of new therapeutic entities increases, in correspondence with the increase in new entries that are not balanced by drugs that lose the status of new therapeutic entity, as defined above. Thus, the market for new therapeutic entities is growing steadily, with an average annual increase of about 6 % (the value of the expenditure CAGR from 2014 to 2022) (Table 5.1.3). The impact of the expenditure for new therapeutic entities on the total NHS expenditure increased over the years from 25.3 % in 2014 to 34.3 % in 2022, but, as can be seen from Figure 5.1.3, it accounts for more than half of the expenditure of public health facilities. The impact on public health facilities expenditure was higher in 2015 (59.3 %) in 2019, with an increase of 4 percentage points compared to 2018, and in 2021 (58.1 %). Although the number of orphan drugs is higher than the number of innovative medicines, the incidence of the latter on the total expenditure of new therapeutic entities is higher than that of orphan drugs. On average each year the expenditure incurred by the NHS for the new therapeutic entities marketed for the first time in the year (incident) is 191.7 million euros and the highest values were recorded in 2015 (514.2 million euros) and in 2017 (435.5 million euros; Table 5.1.2).

Table 5.1.2 NHS expenditure (in millions) for new therapeutic entities in the period 2014-2022

	2014	2015	2016	2017	2018	2019	2020	2021	2022
New therapeutic entities (Incident and prevalent) (€)	**5,173.5**	**6,647.3**	**6,600.8**	**6,068.1**	**6,680.1**	**7,916.5**	**7,707.2**	**8,184.3**	**8,540.0**
Of which incident (€)	62.2	514.2	178.0	435.5	156.0	51.7	45.3	130.9	151.1
Of which approved care regime class A (€)	485.2	341.5	339.9	401.6	403.9	308.0	308.5	284.4	251.8
Of which direct purchases class A (€)	1,312.6	2642.4	2,628.3	1,781.4	2,004.9	2,675.3	2,258.9	2,239.9	2,720.5
Total class A medicines (€)	1,797.8	2983.9	2,968.1	2,183.0	2,408.7	2,983.4	2,567.3	2,524.3	2,972.3
Of which approved care regime class H (€)	0.01	0.002	0.00	0.002	0.00	0.00	0.00	0.01	0.00
Of which direct purchases class H (€)	3,375.7	3,663.4	3,632.6	3,885.1	4,271.3	4,933.2	5,139.9	5,660.0	5,567.7
Total class H (€)	3,375.7	3,663.4	3,632.6	3,885.1	4,271.3	4,933.2	5,139.9	5,660.0	5,567.7
Of which orphans (%)	7.4	9.1	8.9	11.9	16.1	18.5	20.1	23.8	26.1
Of which innovative (%)	1.89	3.247	22.95	23.58	16.97	24.82	34.52	30.10	30.67
% on NHS total expenditure	**25.3**	**26.0**	**30.1**	**28.8**	**26.8**	**29.9**	**33.6**	**33.0**	**34.3**

Figure 5.1.3 Annual trend of NHS expenditure for new incident and prevalent therapeutic entities and total NHS expenditure



Among the incident of 2022, the most expensive molecules are risdiplam, a drug for spinal muscular atrophy, luspatercept, indicated for the treatment of anemia in myelodysplastic syndromes (MDS) and ravulizumab indicated for the treatment of adult patients with NMOSD with values of respectively, 42.4 million euros, 24.9 million euros, and 16.6 million euros.

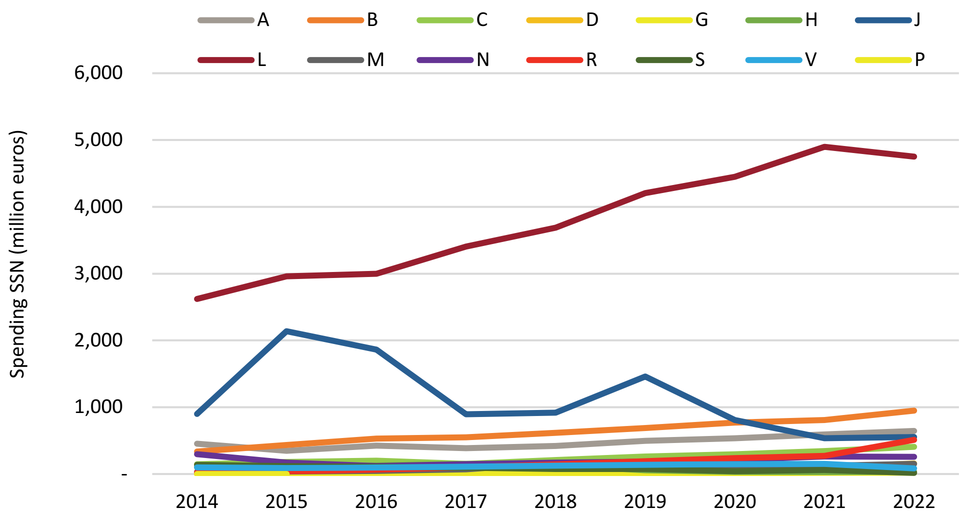
Table 5.1.3 NHS expenditure (in millions) for new incident therapeutic entities in 2022

ATC	Molecule	No. packages (consumption in thousands)		NHS Expenditure (mln euros)	
		N°	%	Values (Desc. order)	%
M09AX10	risdiplam	9	9	42.4	28
B03XA06	luspatercept	15	14	24.9	16
L04AA43	ravulizumab	3	3	16.6	11
L01XL06	brexucabtagene autoleucel (Autologous anti-CD19-transduced CD3+ cells)	0	0	13.9	9
L01FX14	polatuzumab vedotin	3	3	10.5	7
S01LA06	brolucizumab	23	21	9.1	6
L01FX17	sacituzumab govitecan	9	8	6.2	4
A16AX18	lumasiran	0	0	6.0	4
L04AA52	ofatumumab	5	4	5.8	4
L01EJ02	fedratinib	1	1	1.6	1
Total top 10 molecules per expenditure		0	0	1.4	1%
Others		40	37	14.1	9%
Total		**106**	**100**	**151.1**	**100%**

Category L, in addition to being the one with the highest number of medicines from new therapeutic entities, is also the one with the highest expenditure in the 2014-2022 observation period (from 2,621 million euros to 4,752 million euros, increasing by 81 %; Table and Figure 5.1.3). The second and third categories, A and J, have different behaviours over time: category A increased from 2014 to 2022 (CAGR 2014-2022 3.95 %)reaching in 2022 a value of 645 million euros; while category J recorded an initial increase and then decreased with a CAGR 2014-2022 of -5.30 %, as a result of the trend in drug expenditure for the treatment of hepatitis C. Categories B (CAGR 2014-2022: 12.21 %), category C (CAGR 2014-2022: 12.07 %) and category R (CAGR 2014-2022: 41.64 %; Table 5.1.4) are increasing.

Table 5.1.4 Annual trend of NHS expenditure for new incident and prevalent therapeutic entities by ATC I (Table and Figure)

I level ATC	CAGR % of expenditure 2014- 2022
A	3.95
B	12.21
C	12.07
D	54.90
G	0.92
H	-11.62
J	-5.30
L	6.83
M	18.57
N	-1.67
R	41.64
S	-20.73
V	-1.53
P	-100.00
Total	**5.67**



L Antineoplastic and immunomodulating agents	N Nervous system	G Genito urinary system and sex hormones
A Alimentary tract and metabolism	H Systemic hormonal preparations, excluding sex hormones and insulins	J Antinfective for systemic use
C Cardiovascular system	V Various	D Dermatologicals
B Blood and blood forming organs	R Respiratory system	S Sensory organs
	M Musculo-skeletal system	

Figure 5.1.4 shows the trend in the average cost per DDD of new therapeutic entities: it is noted that this trend is increasing from 8.65 euros in 2014, to 9.49 euros in 2022. A peak was reached in 2015 reaching 12.91 euros, in the following two years a decrease was observed, in 2018 and 2019 there was an increase again and in the last 4 years a decreasing trend was recorded.

Figure 5.1.4 Annual trend of average cost per DDD of new therapeutic entities over the period 2014-2022

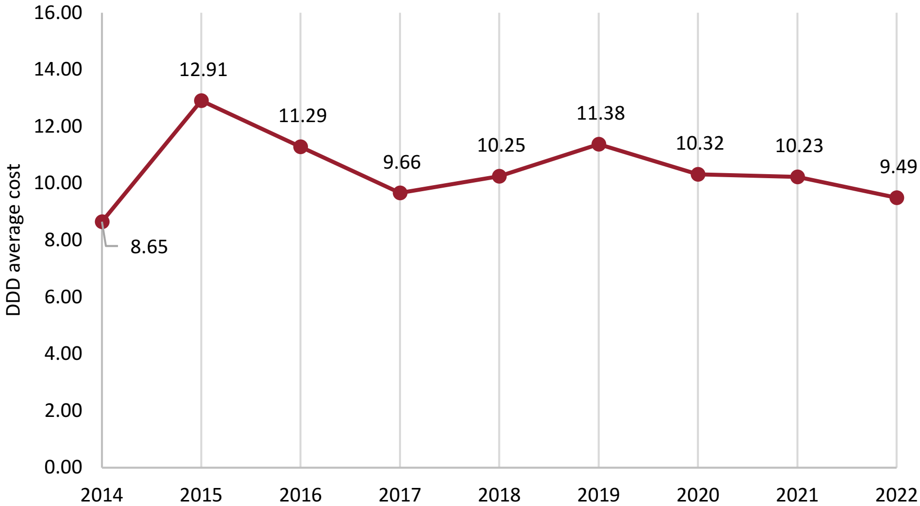


Table 5.1.5 shows the regional distribution of 2022 per capita expenditure of medicines concerning new therapeutic entities. Per capita expenditure on new therapeutic entities at national level was 145 euro, with a wide regional variability: the regions with the highest values are Campania (166.5 euro) and Marche (158.6), while the lowest values were recorded in Valle d'Aosta with 105.1 euro and in the AP of Trento with 113.1 euro. The regional expenditure trend from 2014 to 2022 is marked by a positive average annual variation in all regions, which at national level was 5.7 %. The biggest changes were recorded in Emilia Romagna (+ 7.6%), in the AP of Trento (+ 6.81 %) and in Valle d'Aosta (+ 6.63 %). The average DDD cost in 2022 was equal to 9.5 euro at national level, but fluctuates between the minimum value of 7.3 euro of the AP of Trento and a maximum of 13.0 euro of the AP of Bolzano; the latter has one of the lowest per capita expenditures, but the highest average DDD cost equal to 16.2 euro. This is attributable to a lower consumption of DDDs registered for this region, but related to higher-cost drugs.

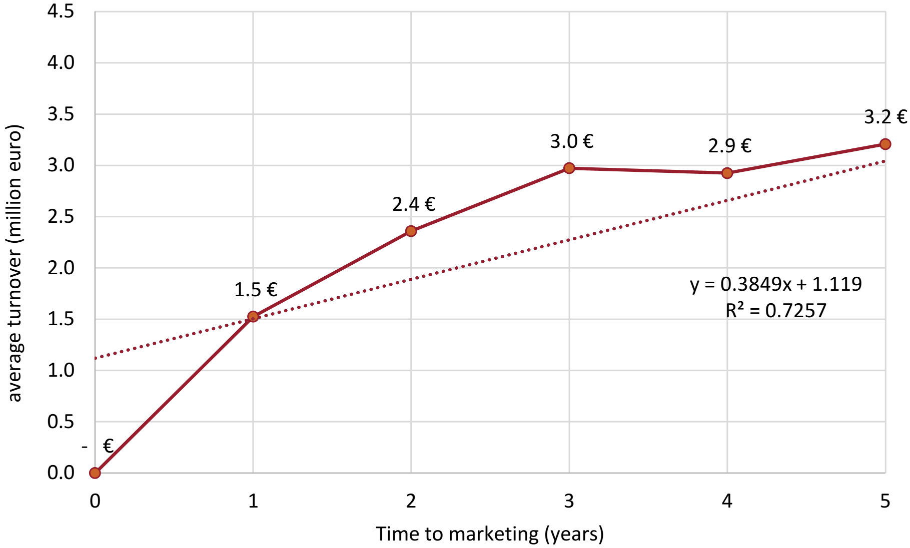
Table 5.1.5 Regional variability in expenditure and average DDD cost of new therapeutic entities. Year 2022 and comparison 2014-2022

Region	Expenditure 2022 *per capita*	Δ% compared to Italy average	CAGR 2014-2022	Average cost DDD 2022	Δ% compared to Italy average	CAGR 2014-2022
Piedmont	144.2	-0.4	6.23	9.3	-2.2	1.65
Valle d'Aosta	105.1	-27.4	6.63	7.9	-16.8	1.23
Lombardy	138.8	-4.1	6.30	9.7	1.8	0.88
AP of Bolzano	139.9	-3.4	6.36	13.0	36.9	0.49
AP of Trento	113.1	-21.9	6.81	7.3	-23.3	-1.14
Veneto	133.4	-7.8	6.28	9.6	1.4	0.67
Friuli VG	148.8	2.8	6.51	9.7	2.4	1.65
Liguria	154.0	6.4	6.41	9.4	-0.8	1.75
Emilia R.	153.8	6.2	7.16	10.5	10.7	1.57
Tuscany	145.5	0.5	4.71	9.9	4.2	0.90
Umbria	158.5	9.5	6.29	9.2	-3.3	2.16
Marche	158.6	9.6	5.86	10.0	4.9	0.33
Lazio	136.9	-5.4	4.66	8.9	-6.2	0.64
Abruzzo	152.1	5.1	4.79	9.1	-3.8	0.63
Molise	147.9	2.2	6.40	9.5	-0.3	0.88
Campania	166.5	15.0	6.28	9.8	3.5	1.27
Puglia	156.6	8.2	4.91	9.1	-3.7	0.06
Basilicata	144.6	-0.2	5.31	9.4	-1.1	1.52
Calabria	142.5	-1.6	5.03	8.6	-9.1	1.07
Sicily	130.9	-9.6	5.25	9.6	1.1	2.24
Sardinia	137.4	-5.1	2.96	8.0	-15.6	-0.68
Italy	**144.8**		**5.73**	**9.5**		**1.04**

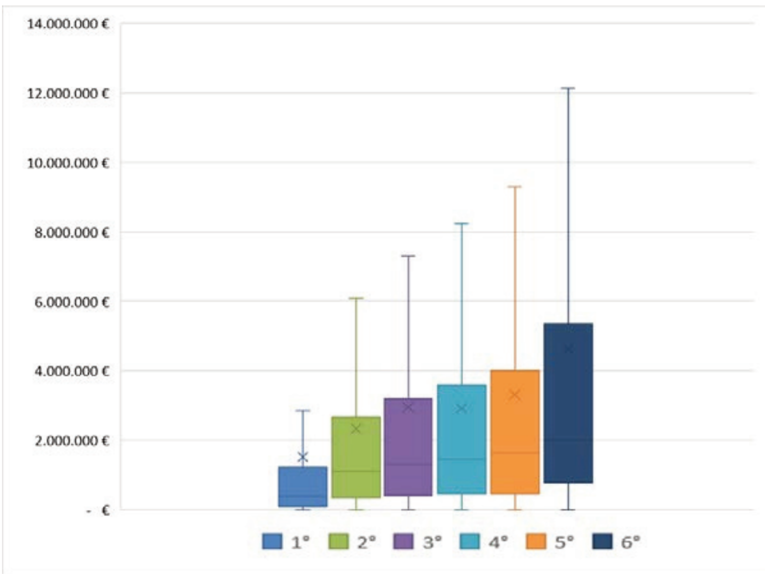
A detailed analysis of the expenditure trend and average cost of the new therapeutic entities was carried out on the basis of time from first marketing. For this purpose, only molecules with first commercialisation in year 2014 were selected: 2013 was used as a wash out period to allow the definition of first entries in 2014 and the study from that year onwards of their evolution (no. of molecules: 449). Of these molecules, only specialities with the criterion of new therapeutic entity for a period of at least 5 years have been selected and followed in order to have, for each marketing year, the same number of molecules. Figure 5.1.5a shows the average turnover from the first year of marketing up to the 5th year. It is observed that the 124 molecules, since market entry, show an upward trend in turnover, rising on average from 1.5 million in the first year of commercialisation to 3.2 million in the last year analysed. However, the box plots shows a wide variability of turnover in the various years of marketing, visible from the length of the whiskers; in particular, the upper whisker is longer and therefore the most dispersed values are the highest ones (Figure 5.1.5b). Figure 5.1.6 shows the percentage ratio of turnover per year compared to turnover in the first year. It is clear that in the third year of marketing the turnover is doubled compared to that of the first year.

Figure 5.1.5 Average turnover by time from first marketing (molecules with at least 5 observation points; N=124)

a)



b)



Note the extreme values have not been displayed

Figure 5.1.6 Percentage ratio between total expenditure at time Ti compared to expenditure at the time of first marketing (T_1) (molecules with at least 5 observation points; N= 124)

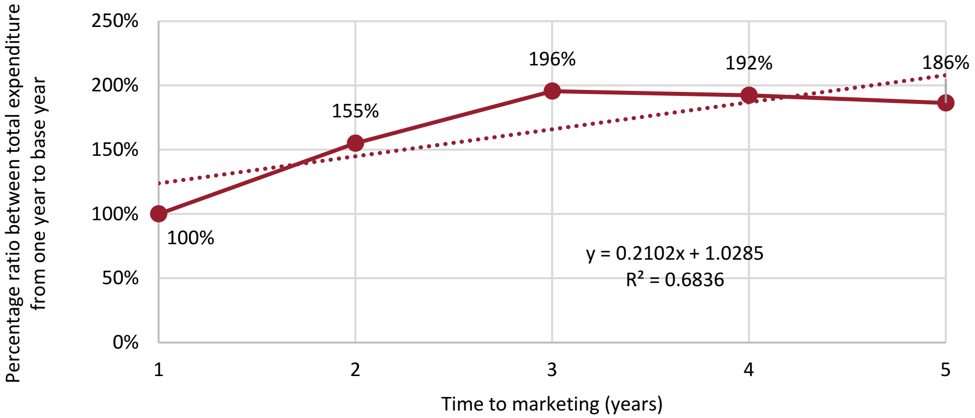
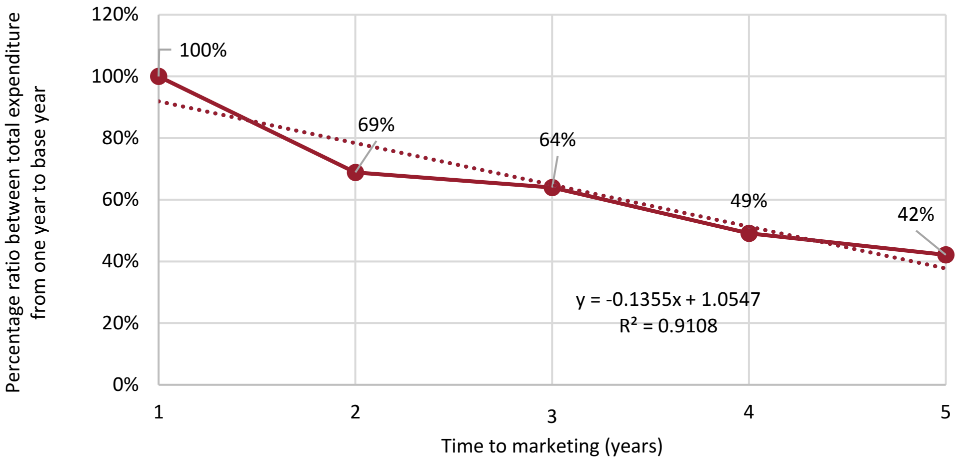


Figure 5.1.7 shows the percentage ratio between the average cost per DDD per year and the average cost in the first marketing year. A downward trend can be observed, with a shift from 69 % in the second year to 42 % in the last year. This trend could be due to the effect of renegotiations, also following extensions of indications, and to purchasing procedures at regional level.

Figure 5.1.7 Percentage ratio between average DDD cost at time Ti compared to average cost at the time of first marketing (T1) (molecules with at least 5 observation points; N=124)



5.2 Orphan medicines

Orphan medicines: authorisation through EMA centralised procedure and access in Italy

Orphan medicines are medicinal products used for the diagnosis, prevention and treatment of rare diseases. In Europe, a disease is considered rare when it affects no more than 5 people per 10,000 inhabitants. Generally, the orphan medicine, even if it meets the needs of treatment of a disease, being intended for the treatment of a few patients, may require investments in research and development that may not be profitable for the manufacturer. For this reason, orphan medicines have been excluded from the payback mechanism initiated in application of the governing discipline of hospital pharmaceutical expenditure (Article 15, paragraph 8, letters i and i-bis, of Law 135/2012, as amended by Article 1, paragraph 228, of Law 147/2013 - 2014 Stability Law - and most recently amended by Article 1, paragraph 578, of Law 145/2018 - Budget Law 2019).
Art. 1, paragraphs 575-584, of Law 145/2018 (Stability Law 2019) has modified, starting from 2019, the provisions of the Stability Law of 2014: the medicines that will benefit from the exclusion from the payback mechanism will be only the orphan medicines authorised by means of the EMA centralised procedure, excluding the so-called "Orphan Like" medicines, the medicines included in the Orphanet register and all the medicines that were authorised as orphan by the EMA but that have exhausted the period of market exclusivity. It should be noted that the EMA provides for the marketing authorisation of orphan medicines, but then it is up to the individual country to define the reimbursement class. It therefore appears clear that there is a time gap between the marketing authorisation by the EMA and the definition of the price and class of reimbursement in Italy by AIFA. However, this does not represent a limitation on access to treatment for citizens because, in Italy, a patient suffering from a rare disease can have access to the drug through various legislative instruments.
The centralised authorisation procedure represents the main access rule; alternatively, due to the lack of a marketing authorisation for an orphan medicine indicated for a rare disease, a patient can access the medicine through one of the following procedures:

- Law 648 of 1996, which allows the use of a medicine on a national basis;
- Law 326 of 2003, art. 48 (AIFA fund);
- Ministerial Decree 7 September 2017 (so-called "Compassionate use");
- Law 94 of 1998 (former Di Bella Law) which, differently from Law 648/96, regulates the prescription of the medicine for the single patient, on a nominal basis;
- non-repetitive use of advanced therapies.

In 2022, the EMA granted authorisation for a total of 24 new orphan medicines. The main therapeutic areas of medicines authorised under the centralised procedure by the EMA were metabolism (fosdenopterin [Nulibry], eladocagene exuparvovec [Upstaza], glucarpidase [Voraxaze] and olipudase alfa [Xenpozyme]), genetic diseases (vutrisiran [Amvuttra], maralixibat cloruro [Livmarli], mitapivat [Pyrukynd] and lonafarnib [Zokinvy], haematology (ciltacabtagene autoleucel [Carvykti], sutimlimab [Enjaymo], voxelotor [Oxbryta], valoctocogene roxaparvovec [Roctavian], endocrinology (octreotide [Mycapssa], somatrogon [Ngenla] and lonapegsomatropin [Skytrofa]) and oncology (tabelecleucel [Ebvallo], mosunetuzumab [Lunsumio] and asciminib [Scemblix]).

Of the 24 drugs authorised by the EMA, which are not yet available in Italy, 16 have initiated the process of negotiating the price and reimbursement and 3 were marketed in 2023. The remaining 8 medicines did not apply for price and reimbursement.

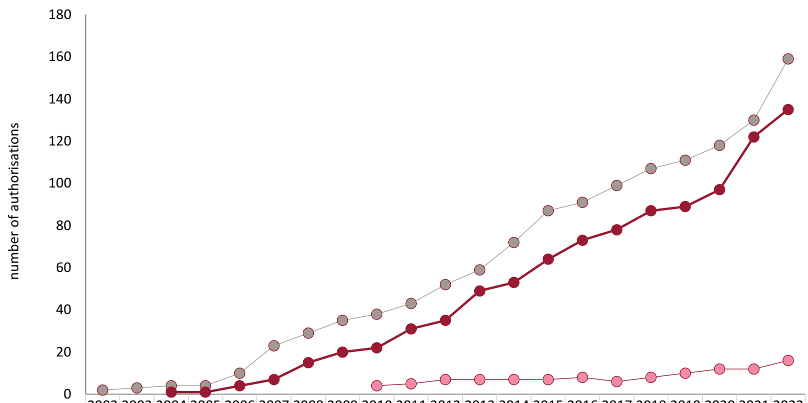
As of 31 December 2022, out of a total of 159 orphan medicines authorised by the EMA (Figure 5.2.1 and Figure 5.2.2), 135 were available in Italy of which:

- 25 (18.5%) in class A;
- 76 (56.3%) in class H;
- 16 (11.9%) in class C;
- 18 (13.3%) in class C-nn.

The 3 medicines negotiated and marketed starting from 2022 are: tebentafusp, somatrogon and asciminib.

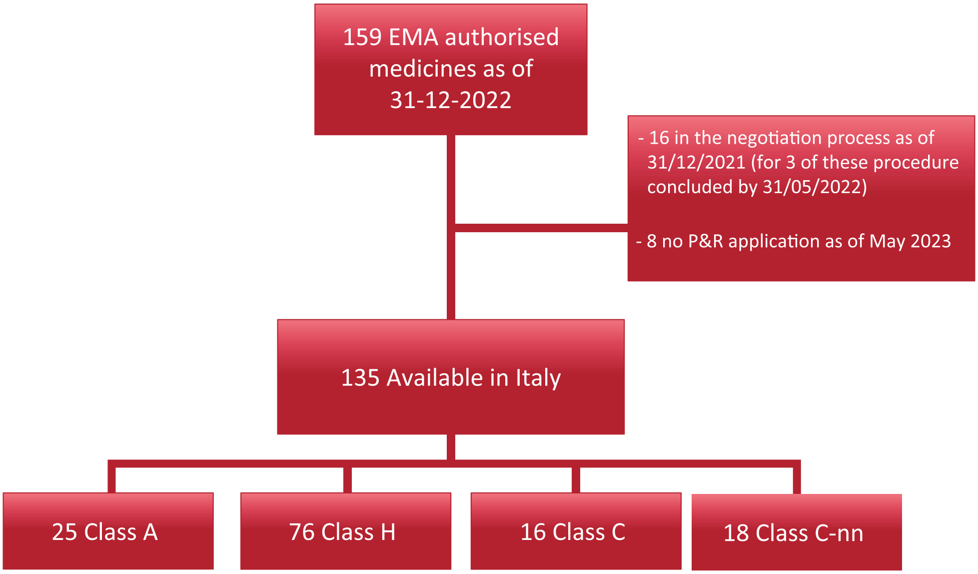
Interestingly, 41.5% of the 135 medicines included in AIFA's orphan list is subject to a Monitoring Register and 12.5% of the orphan drugs in the price and reimbursement phase have a *Managed Entry Agreement* (MEA) applied which can be either a financial agreement or an outcome-based agreement. Moreover, about 11% of medicines also obtained the innovativeness requirement (6 innovative oncological medicines and 9 innovative non-oncological medicines).

Figure 5.2.1 Comparison between medicines authorised with EMA centralised procedure and available in Italy (cumulative data 2002-2022)



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
EMA	2	3	4	4	10	23	29	35	38	43	52	59	72	87	91	99	107	111	118	130	159
AIFA			1	1	4	7	15	20	22	31	35	49	53	64	73	78	87	89	97	122	135
Availability rate (EMA/AIFA*100)	0	0	25	25	40	30	52	57	58	72	67	83	74	74	80	79	81	80	82	94	84
AIFA class C									4	5	7	7	7	7	8	6	8	10	12	12	16

Figure 5.2.2 Comparison between number of orphan medicines authorised with EMA and AIFA centralised procedure as of 31 December 2022



Expenditure and consumption of orphan medicines

The expenditure for orphan medicines, including the purchase by public health structures and the provision under the approved care regime, was approximately 1.98 billion euros in 2022 (+29.2% compared to 2021), corresponding to 6.0% of the pharmaceutical expenditure borne by the NHS. Consumption of orphan medicines amounted to 11.4 million DDD (+35.7 million compared to the previous year), corresponding to 0.04% of the total consumption of medicines. In 2022 the incidence % on the consumption of class C orphan medicines was 1.9%, showing an slight reduction compared to 2021 when an incidence of 2.2% was recorded (Table 5.2.1).

Table 5.2.1 Expenditure and consumption trend (agreed and direct purchases) for orphan medicines, years 2013-2022 in reimbursement class A-NHS, H-NHS, C, C-NN

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Expenditure orphan medicinal products (millions, traceability + OsMed)	608.9	716.2	822.2	947.6	1,022.7	1,306.9	1,554.9	1,402.7	1,535.1	1,982.7
Incidence % orphan medicinal products on pharmaceutical expenditure	6.4	7.1	6.7	4.2	4.5	5.8	6.8	6.1	6.4	6.0
Incidence % expenditure orphan direct purchase Vs orphan expenditure (traceability + OsMed)	100.0	100.0	100.0	99.7	99.6	99.7	99.9	100.0	100.0	99.9
Consumption (DDD) orphan medicinal products (millions, OsMed + traceability)	5.6	6.1	6.7	7.0	7.2	8.8	10.1	8.1	8.4	11.4
Incidence % orphan medicines on onsumption (traceability + OsMed)	0.002	0.002	0.003	0.026	0.026	0.031	0.035	0.029	0.030	0.04
Incidence % Class C orphan medicines on total orphan consumption	1.2	0.1	0.1	0.8	0.6	0.9	1.3	1.39	2.2	1.9

In terms of DDD, in 2022 as in the previous year, a greater consumption of orphan medicines in the Northern Regions can be observed, and consequently, also a greater absolute expenditure. The Regions with the highest per capita expenditure are Emilia Romagna and the AP of Bolzano, with an expenditure, respectively, of 41.2 and 38.9 euros compared to the national average of 33.6 euros. The Regions with the lowest expenditure are Valle d'Aosta and Molise (lowest expenditure also in 2021) with an expenditure of 14.1 and 25.9 euros respectively (Table 5.2.2). There are Regions that have recorded an increase in consumption of more than 100 % including, in descending order, Abruzzo, PA of Bolzano, Marche, Molise and Emilia Romagna with variations of 111 %, 106 %, 103.4 %, 103.2 % and 101.3 % respectively. The regions with the largest variations in expenditure per capita are Friuli VG (+ 66.5 %), Molise (+ 58.2 %), Marche (+ 57.3 %), Abruzzo (+ 57.3 %) and PA of Bolzano (+ 56.5 %) (Table 5.2.2).

Table 5.2.2 Consumption and expenditure (agreed and direct purchases) for orphan medicines by Region in 2022 (A-SSN, H-SSN, C, C-NN)

Region	Expenditure *(million)*	DDD *(thousand)*	Inc.% expenditure*	% purchases direct	Expenditure *per capita*	Δ % 22-21	DDD 1000 inhab. per day	Δ % 22-21
Piedmont	136.4	754.5	6.9	100.0	30.7	47.1	0.5	70.5
Valle d'Aosta	1.8	10.7	0.1	100.0	14.1	8.7	0.2	51.9
Lombardy	336.7	1,919.8	17.0	99.9	34.1	47.5	0.5	95.7
A.P. of Bolzano	19.3	123.9	1.0	100.0	38.9	56.5	0.7	106.0
A.P. of Trento	14.5	99.0	0.7	100.0	27.4	45.9	0.5	78.9
Veneto	167.8	1,023.0	8.5	100.0	34.4	53.9	0.6	92.2
Friuli VG	48.0	314.4	2.4	99.7	38.0	66.5	0.7	98.8
Liguria	59.1	346.1	3.0	100.0	35.8	48.2	0.6	71.6
Emilia R.	184.9	1,106.9	9.3	100.0	41.2	46.5	0.7	101.3
Tuscany	133.8	813.9	6.8	100.0	35.0	41.4	0.6	76.7
Umbria	34.8	200.1	1.8	100.0	38.7	34.6	0.6	91.8
Marche	59.1	383.4	3.0	99.9	38.5	57.2	0.7	103.4
Lazio	170.8	954.0	8.6	99.9	30.2	43.7	0.5	75.3
Abruzzo	45.5	285.2	2.3	100.0	35.0	56.5	0.6	111.0
Molise	7.8	48.8	0.4	100.0	25.9	58.2	0.4	103.2
Campania	168.5	895.2	8.5	100.0	32.5	42.2	0.5	78.4
Puglia	136.5	775.5	6.9	100.0	35.3	36.2	0.5	70.7
Basilicata	16.2	79.9	0.8	100.0	29.6	48.6	0.4	68.3
Calabria	53.8	279.2	2.7	99.8	29.8	28.0	0.4	52.5
Sicily	138.7	746.9	7.0	100.0	29.8	46.6	0.4	85.9
Sardinia	48.8	279.7	2.5	100.0	29.5	39.3	0.5	76.8
Italy	**1,982.7**	**11,440.0**	**100.0**	**99.9**	**33.6**	**45.6**	**0.5**	**84.8**
North	968.5	5,698.2	48.9	99.9	34.9	49.3	0.6	90.7
Centre	398.4	2,351.4	20.1	100.0	33.4	43.9	0.5	81.2
South and Islands	615.7	3,390.3	31.1	100.0	31.9	41.5	0.5	77.9

* Calculated on the total expenditure of orphan medicines nationwide

The expenditure on class C medicines in 2022 amounted to 15.5 million euro, registering a 7.6% increase (in 2021 it was 14.9 million euro). Also for class C orphan medicines, there is a higher consumption and consequently a higher expenditure in the Northern Regions. As regards per capita expenditure, northern regions have higher values than the Italian average, while the centre and southern Regions have per capita values below the national average (0.33 euro per capita in northern Regions, compared to 0,25 euro in centre Regions and 0.175 in southern Regions) (Table 5.2.3).

Table 5.2.3 Consumption and expenditure (agreed and direct purchases) for Class C* orphan medicines by Region in 2022

Region	DDD *(thousand)*	Δ % 22-21	Expenditure *(thousand)*	Δ % 22-21	Expenditure *per capita*	Incidence % on consumption ^	Incidence % on expenditure **
Piedmont	20.61	4.20	972.84	22.70	0.22	2.73	0.71
Valle d'Aosta	0.96	- 41.46	11.74	- 43.94	0.09	9.04	0.66
Lombardy	35.96	7.22	3,636.78	15.07	0.37	1.87	1.08
A.P. of Bolzano	2.60	- 20.00	429.41	- 5.66	0.86	2.10	2.22
A.P. of Trento	1.50	- 47.55	82.98	- 41.68	0.16	1.52	0.57
Veneto	20.45	5.85	1,935.65	12.92	0.40	2.00	1.15
Friuli VG	4.12	11.65	721.78	94.71	0.57	1.31	1.50
Liguria	5.19	- 10.36	142.72	- 47.75	0.09	1.50	0.24
Emilia R.	22.40	- 3.16	1,187.22	- 24.04	0.26	2.02	0.64
Tuscany	14.54	- 12.36	1,094.64	-	0.29	1.79	0.82
Umbria	5.71	16.53	235.42	- 25.55	0.26	2.85	0.68
Marche	7.46	- 33.21	780.55	0.32	0.51	1.95	1.32
Lazio	24.37	0.25	866.69	- 25.52	0.15	2.55	0.51
Abruzzo	8.67	37.84	798.96	- 3.92	0.61	3.04	1.76
Molise	0.06	-	1.59	-	0.01	0.11	0.02
Campania	11.33	- 14.88	651.51	19.42	0.13	1.27	0.39
Puglia	8.42	- 18.01	356.25	- 58.05	0.09	1.09	0.26
Basilicata	1.64	- 40.79	261.30	183.10	0.48	2.05	1.62
Calabria	4.37	56.63	368.25	- 49.23	0.20	1.56	0.68
Sicily	11.53	- 5.26	213.77	- 69.13	0.05	1.54	0.15
Sardinia	3.41	64.73	709.21	42.63	0.43	1.22	1.45
Italy	**215.34**	**- 1.96**	**15,459.25**	**7.58**	**0.26**	**1.88**	**0.78**
North	113.81	0.73	9,121.12	7.40	0.33	2.00	0.94
Centre	52.09	- 8.57	2,977.30	81.10	0.25	2.22	0.75
South and Islands	49.44	- 0.48	3,360.83	- 20.62	0.17	1.46	0.55

* excluding medicines in C-NN
^ calculated on the total consumption of orphan medicines
** calculated on the total expenditure of orphan medicines

The top 10 Class-C active ingredients in 2022 have an expenditure of approximately 15.4 million euro (99.9 %) most of which is associated with the active substance defibrotide, indicated in severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in hematopoietic stem cell transplantation (HPSCT).
The consumption of the first 10 orphan drugs in Class-C was 213,315 DDDs, representing 99.1 % of the total consumption of orphan drugs in Class-C (Table 5.2.4). The first active ingredient for consumption is pitolisant, indicated in narcolepsy.

Table 5.2.4 Top ten Class-C^ orphan medicines per expenditure 2022

Class	Active substance	Expenditure (€)	%*	Consumption (DDD)	%**
C	defibrotide	6,103,059	39.5	1,490	0.7
C	treosulfan	2,614,738	16.9	882	0.4
C	pitolisant	2,365,149	15.3	175,320	81.4
C	asfotase alfa	2,306,304	14.9	902	0.4
C	tobramycin	792,636	5.1	24,416	11.3
C	cenegermin	770,442	5.0	693	0.3
C	avapritinib	275,084	1.8	440	0.2
C	mannitol	145,942	0.9	6,801	3.2
C	telotristat	36,848	0.2	1,560	0.7
C	clormetin	35,750	0.2	810	0.4
	Total of the first 10 Class-C active substances	15,445,952	**99.9**	213,315	**99.1**
	Totale restanti Class-C active substances	13,294	**0.1**	2,023	**0.9**
	Total Class C	15,459,246	**100.0**	215,338	**100.0**

^ excluding C-NN medicines
* calculated on the total expenditure of Class C orphan medicines
** calculated on the total consumption of Class C orphan medicines

The main active ingredients with the greatest consumption in 2022 are daratumumab, tafamidis and the combination elexacaftor/tezacaftor/ivacaftor, while those with greatest expenditure are daratumumab, the combination elexacaftor/tezacaftor/ivacaftor and eculizumab, with an increase in expenditure of 62.22 % and > 100 % respectively, while for eculizumab a decrease of 7.12 % can be observed. The analysis of consumption of these active ingredients shows an increase of more than 100 %, with the exception of eculizumab, for which, in addition to a reduction in expenditure, also a decrease in consumption of 2.25 % can be observed. Ridisplam is the active ingredient that records the largest variance in expenditure together with tafamidis and the combination elexacaftor/tezacaftor/ivacaftor. The same trend can be observed in the variance in consumption (Table 5.2.5).

Table 5.2.5 Expenditure and consumption for the first 30 orphan medicines (A, H, C, C-NN) in descending order of expenditure: comparison years 2021-2022

Rank	First 30 orphan medicines (molecule)	Prevalent class in 2022	DDD *(thousand)*	Δ % 22-21	Expenditure *(million)*	Δ % 22-21	Incidence % on consumption	Incidence % on expenditure	% purchases direct
1	daratumumab	H	4,139.9	>100	390.6	62.2	36.2	19.7	100.0
2	elexacaftor/tezacaftor/ivacaftor	A	712.8	>100	206.2	>100	6.2	10.4	100.0
3	eculizumab	H	162.6	-2.3	118.5	-7.1	1.4	6.0	100.0
4	ivacaftor	A	242.3	54.9	105.6	36.2	2.1	5.3	100.0
5	tafamidis	H	1,032.8	>100	66.8	>100	9.0	3.4	100.0
6	nusinersen	H	163.7	-15.4	65.8	-16.2	1.4	3.3	100.0
7	pomalidomide	H	251.6	22.2	61.0	20.5	2.2	3.1	100.0
8	macitentan	A	674.5	6.3	59.2	6.3	5.9	3.0	100.0
9	albutrepenonacog alfa	A	50.0	15.4	53.1	12.5	0.4	2.7	99.6
10	brentuximab vedotin	H	151.1	55.5	44.3	>100	1.3	2.2	100.0
11	risdiplam	H	110.8	>100	42.4	>100	1.0	2.1	100.0
12	patisiran	H	76.2	47.3	39.3	47.3	0.7	2.0	100.0
13	carfilzomib	H	283.4	11.8	37.4	7.9	2.5	1.9	100.0
14	niraparib	H	223.2	66.6	34.3	29.6	2.0	1.7	100.0
15	caplacizumab	H	9.5	85.6	32.4	88.9	0.1	1.6	100.0
16	tisagenlecleucel	H	0.1	-13.3	30.6	-1.0	0.0	1.5	100.0
17	axicabtagene ciloleucel	H	0.2	60.0	25.7	47.4	0.0	1.3	100.0
18	luspatercept	A	231.8		24.9		2.0	1.3	100.0
19	ponatinib	H	107.9	7.3	24.7	6.6	0.9	1.3	100.0
20	migalastat	A	50.0	5.0	23.3	5.0	0.4	1.2	100.0
21	eliglustat	A	36.2	23.1	22.5	23.1	0.3	1.1	100.0
22	lanadelumab	A	37.2	55.8	20.7	56.8	0.3	1.0	100.0
23	ataluren	H	12.6	7.3	19.6	5.6	0.1	1.0	100.0
24	isavuconazole	A	182.8	18.8	19.3	12.6	1.6	1.0	99.9
25	letermovir	A	55.0	0.5	18.8	-3.1	0.5	1.0	100.0
26	obeticholic acid	H	223.8	26.3	18.2	23.7	2.0	0.9	100.0
27	obinutuzumab	H	273.4	16.1	17.8	16.2	2.4	0.9	100.0
28	eftrenonacog alfa	A	26.1	2.4	17.5	2.8	0.2	0.9	99.1
29	burosumab	H	91.4	48.2	17.3	48.5	0.8	0.9	100.0
30	elosulfase alfa	H	5.7	6.5	17.2	6.5	0.1	0.9	100.0
	Total of top 30		**9,618.5**	**104.6**	**1,674.8**	**49.6**	**84.1**	**84.5**	**100.0**
	Other orphans		1,821.5	20.1	307.8	24.6	15.9	15.5	99.8
	Total orphans		**11,440.0**	**84.0**	**1,982.7**	**45.0**	**100.0**	**100.0**	**99.9**

Among the top 20 active substances of Class A and H with the greatest variance in expenditure in 2022, the active substances with the highest values are risdiplam, belantamab mafodotin, pegvaliase, and tafamidis with increases over 100 %, although the active ingredients with higher spending values were found to be daratumumab with 390.6 million euros and a variance in expenditure of + 62.22 % and elexacaftor/tezacaftor/ivacaftor with 206.22 million euros and a variance in expenditure greater than + 306.9 % (Table 5.2.6).

Table 5.2.6 Top 20 active principles (A and H) by expenditure variance in 2022 compared to 2021

Prevalent class	Active substance	Expenditure *(million)*	Δ % 22-21	DDD *(thousand)*	Δ % 22-21
H	risdiplma	40.2	>100	110.7	>100
H	belantamab mafodotin	16.2	>100	36.5	>100
H	pegvaliase	1.9	>100	8.5	>100
H	tafamidis	66.8	>100	1,032.8	>100
H	polatuzumab vedotin	10.5	>100	34.5	>100
A	cannabidiolo	7.5	>100	157.7	>100
A	elexacaftor/tezacaftor/ivacaftor	206.2	>100	712.8	>100
H	volanesorsen	2.9	>100	0.4	>100
H	brentuximab vedotin	44.3	>100	151.1	55.5
H	cerliponase alfa	8.1	95.9	6.1	95.8
H	givosiran	8.9	95.7	10.5	95.9
H	mogamulizumab	7.3	93.3	25.1	93.5
H	caplacizumab	32.4	88.9	9.5	85.6
H	siltuximab	2.0	67.5	21.6	67.5
H	daratumumab	390.6	62.2	4,139.9	>100
A	lanadelumab	20.7	56.8	37.2	55.8
A	ketoconazole	1.4	55.6	149.5	56.0
H	burosumab	17.3	48.5	91.4	48.2
H	axicabtagene ciloleucel	25.7	47.4	0.2	60.0
H	patisiran	39.3	47.3	76.2	47.3
H	niraparib	34.3	29.6	223.2	66.6

* selected among active principles with an expenditure higher than 1 million euros

Analysing the first 30 orphan drugs per expenditure, a different behavior can be observed between Regions. Almost all molecules have different ranks in different Regions. The most significant cases concern the active substance tisagenlecleucel which ranks 47th in Marche, 49th in Campania, 52nd in Puglia compared to the 16th rank of the Italian average and the active substance axicabtagene ciloleucel which ranks 69th in Friuli V.G., 50th in Campania and 80th in Puglia compared to the 17th rank of the Italian average (Table 5.2.7).

Table 5.2.7 2021 Regional rank of the first 30 orphan medicines by expenditure in class A-NHS and H-NHS

Italy	Top 30 orphan medicines by expenditure	PIE	VDA	LOM	AP BOL	AP TRE	VEN	FRI	LIG	EMI	TUS	UMB	MAR	LAZ	ABR	MOL	CAM	PUG	BAS	CAL	SIC	SAR
1	daratumumab	1	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1
2	elexacaftor/tezacaftor/ivacaftor	3	1	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	1	2	2	4
3	eculizumab	2	3	4	3	6	6	9	4	2	3	7	3	7	3	3	3	4	4	4	5	2
4	ivacaftor	4	9	3	5	5	3	5	3	7	5	3	5	4	4	5	4	3	3	3	3	7
5	tafamidis	7	7	6	4	3	5	3	9	6	4	5	4	8	6	12	17	12	27	31	9	14
6	nusinersen	17		5	7	10	7	4	14	9	9	8	7	3	16	6	6	19	21	28	6	10
7	pomalidomide	5	10	8	6	18	4	11	10	8	6	6	8	10	11	10	11	7	9	9	7	9
8	macitentan	6	8	10	8	8	10	10	7	4	7	13	6	16	7	7	15	5	5	5	12	6
9	albutrepenonacog alfa	18		11		33	8	7	5	5	8	16	11	14	5		8	6		7	11	
10	brentuximab vedotin	10	26	13	19	24	9	8	6	10	12	19	12	9	14	21	7	15	7	11	16	12
11	risdiplam	8		7	9	4	11	6	18	14	22	29	9	13	22	15	13	10	30	15	26	13
12	patisiran	29		17	36		19	21	17	11	19		19	5	12	4	24	9		23	4	
13	carfilzomib	11	11	15	24	15	14	15	15	12	10	12	20	18	19	19	9	13	13	13	10	8
14	niraparib	16	20	22	14	11	12	14	12	15	14	18	13	12	13	8	18	11	15	8	24	15
15	caplacizumab	9	5	29	11	37	41	27	11	18	34	14	35	24	8	24	5	16	6	6	14	3
16	tisagenlecleucel	15		9			16	16	13	16	13	4	47	15	34		49	52		27	19	41
17	axicabtagene ciloleucel	30		12			31	69	8	13	17	27	14	11	21		50	80		16	17	
18	luspatercept	13		19	30	28	37	18	23	21	25	34	28	59	10	30	31	8	14	29	18	5
19	ponatinib	25	13	27	15	23	29	24	33	22	23	22	18	21	15	13	16	18	19	10	8	32
20	migalastat	14	6	20		38	21	32	44	20	18	20	55	26	45	14	10	29		22	29	16
21	eliglustat	21		23	23	9	13	28	38	17	36	17	40	17			48	39	16	30	15	11
22	lanadelumab	20	2	14	22	21	28		42	28	21	21	30	47	20		28	21		51	22	23
23	ataluren	22		32			15	17	32	19	50		10	37	18		20	25	23	14	34	
24	isavuconazole	23	23	16	27	39	23	22	29	34	15	31	26	20	17	26	35	42	28	24	43	42
25	letermovir	28		24	10		30	12	20	25	33	11	16	31	35	25	26	30	22	25	38	27
26	obeticholic acid	26	12	28	28	13	35	31	22	26	27	25	39	23	31	18	34	24	17	17	23	19
27	obinutuzumab	24	19	33	31	17	27	34	21	33	31	35	15	28	24	11	19	26	34	26	32	25
28	eftrenonacog alfa	19		26			40	37	24	41	29	57	27	25	9		27	20	20	49	25	
29	burosumab	42		57	13		18	62		42	16			22	28		14	14	44	18	20	22
30	elosulfase alfa	27	25	34		7	53			23	11	10	21	51			23	46	18	12	21	33

The first active substances for consumption are again in 2022 daratumumab, which confirms the previous year's position, tafamidis and elexacaftor/tezacaftor/ivacaftor with moderate variability in regional ranks (Table 5.2.8).

Table 5.2.8 2022 regional rank of the first 30 orphan medicines by consumption in class A-NHS and H-NHS

Italy	Top 30 orphan medicine molecules by consumption (DDD)	PIE	VDA	LOM	AP BOL	AP TRE	VEN	FRI	LIG	EMI	TuS	UMB	MAR	LAZ	ABR	MOL	CAM	PUG	BAS	CAL	SIC	SAR
1	daratumumab	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	tafamidis	2	1	2	2	2	2	2	2	2	2	2	2	2	2	5	4	4	8	14	3	6
3	elexacaftor/tezacaftor/ivacaftor	4	4	3	4	3	3	5	4	4	4	3	4	3	4	4	2	3	2	3	2	4
4	macitentan	3	3	4	3	4	4	4	3	3	3	4	3	4	3	2	6	2	3	2	4	2
5	ciclosporin	11		5	12	8	5	3	17	5	19	20	6	13	18	11	7	8		10	6	7
6	carfilzomib	8	7	8	17	12	9	10	7	6	5	7	14	15	15	18	5	7	6	7	7	5
7	obinutuzumab	7	19	12	20	6	7	15	5	10	8	12	5	9	6	3	3	6	14	8	11	12
8	pomalidomide	9	10	7	6	19	6	13	14	7	7	5	11	12	11	12	12	12	13	11	12	9
9	ivacaftor	14	14	9	7	13	10	19	12	14	11	10	10	8	9	8	8	11	4	4	5	15
10	luspatercept	6		10	23	20	19	8	15	12	12	17	17	41	5	29	19	5	5	18	8	3
11	obeticholic acid	13	5	13	18	5	15	16	6	8	9	6	20	7	13	13	17	10	7	5	10	10
12	niraparib	12	23	15	9	11	8	11	8	11	10	8	9	6	7	6	10	9	11	6	16	16
13	isavuconazole	16	24	6	16	38	12	7	18	16	6	16	15	10	8	25	21	27	23	13	26	31
14	nusinersen	21		11	8	17	13	14	21	17	18	13	12	5	24	9	18	26	26	29	18	17
15	eculizumab	10	11	16	11	15	22	23	19	9	13	22	13	23	14	10	9	16	10	16	19	8
16	cannabidiolo	20	21	18	13	7	18	24	16	13	15	18	7	11	17	31	11	22	12	9	22	11
17	brentuximab vedotin	17	26	20	22	24	14	12	9	15	17	19	16	14	20	23	13	18	9	17	20	14
18	ketoconazole	5		19	24	14	11	6	13	22	24	9	8	21	12		26	23		23	24	36
19	riociguat	15		17	5	22	24	9	10	47	16	21	23	16	19	14	15	14	34	15	17	18
20	risdiplam	18		14	10	10	21	17	25	19	25	32	19	22	30	19	24	17	29	22	25	22
21	ponatinib	24	17	21	15	21	25	21	28	18	20	23	18	20	16	15	16	15	17	12	13	27
22	pasireotide	19	15	24	34	18	16	30	11	28	21	11	22	18	10	26	20	21	18	41	14	28
23	burosumab	30		45	14		17	62		29	14			19	26		14	13	46	19	15	19
24	patisiran	37		28	44		31	27	29	20	28		28	17	22	7	31	20		28	9	
25	sorafenib	44		22	39	9	27	18	39	27	71	29	27	27	23	34	22	41	19	20	21	13
26	letermovir	31		25	21		28	20	22	25	30	35	26	29	33	28	27	29	24	24	31	30
27	ixazomib	25		33	35	26	23	46	20	35	23	34	32	31	28	22	25	25	30	55	33	23
28	albutrepenonacog alfa	38		27		42	33	26	23	21	26	33	31	32	27		28	24		25	36	
29	migalastat	23	9	26		41	32	37	44	23	27	25	60	34	47	20	23	38		26	30	25
30	everolimus	28	6	32	28	16	39	34	31	26	22	36	21	33	37		34	19	22	21	37	21

Orphan medicines also meeting the innovativeness requirement generated an expenditure in 2022 amounting to 930 million euros, a value almost doubled compared to 2021 in which the expenditure was 479 million euros, in line with the increase in consumption that instead tripled (Table 5.2.9). In 2022, medicines meeting the innovativeness requirement were 19, compared to 17 in 2021 and 11 in 2020 and 9 in 2019. Of these innovative orphan medicines, daratumumab elexacaftor/tezacaftor/ivacaftor and tafamidis are also among the top 30 most expensive orphan drugs, ranking respectively first, second and fifth.

Table 5.2.9 Orphan medicines accessing the fund for oncology and non-oncology innovative medicines: expenditure and consumption, years 2018-2022 (direct purchases)

Active substance	Expenditure *(million)*					DDD				
	2018	2019	2020	2021	2022	2018	2019	2020	2021	2022
axicabtagene ciloleucel	0.00	0.00	3.44	17.43	19.87			56	95	124
blinatumomab	0.00	0.00	0.00	0.00	3.18					1,946
brexucabtagene autoleucel (cellule cd3+ autologhe trasdotte anti-cd19)	0.00	0.00	0.00	0.00	13.94					53
cenegermin	3.64	4.04	2.79	0.20	0.00	13,104	15,232	10,976		
cerliponase alfa	0.00	0.00	0.00	4.13	8.09				3,101	6,073
citarabine/daunorubicine	0.00	2.44	8.55	9.15	4.45		608	2,249	2,396	1,170
daratumumab	58.28	156.32	211.02	240.80	390.61	312,103	838,428	1,131,465	1,611,193	4,139,895
dinutuximab beta	0.00	3.22	5.13	3.38	0.00		926	1,414	886	
eculizumab	0.00	0.00	0.00	0.00	36.18					52,084
elexacaftor/tezacaftor/ivacaftor	0.00	0.00	0.00	36.44	155.37				167,692	712,796
givosiran	0.00	0.00	0.00	4.57	8.94				5,344	10,460
ibrutinib	111.56	0.00	0.00	0.00	0.00	757,150				
ivacaftor	11.10	0.00	0.00	40.03	136.27	16,492			119,215	418,178
letermovir	0.01	10.79	18.75	15.14	0.00	1	26,653	50,020	42,417	
lumasiran	0.00	0.00	0.00	0.00	5.98					5,769
lutetium oxodotreotide (177Lu)	0.00	3.49	15.14	13.22	3.80		244	948	935	258
midostaurin	1.23	12.59	15.75	10.75	0.00	2,296	23,543	29,443	20,182	
nusinersen	92.11	102.25	70.23	0.00	0.00	242,880	242,400	166,320		
odevixibat	0.00	0.00	0.00	0.00	1.05					988
onasemnogene abeparvovec	0.00	0.00	0.00	12.48	7.54				49	42
patisiran	0.00	0.00	9.49	26.69	39.32			18,400	51,720	76,200
pomalidomide	18.63	0.00	0.00	0.00	0.00	61,859				
tafamidis	0.00	0.00	0.00	1.61	66.79				13,476	1,032,839
tisagenlecleucel	0.00	1.19	13.24	30.95	20.45		12	84	151	83
voretigene neparvovec	0.00	0.00	0.00	12.22	7.72				41	26
vosoritide	0.00	0.00	0.00	0.00	0.46					1,000
Total	**296.56**	**296.33**	**373.55**	**479.00**	**930.01**	**1,405,885**	**1,148,046**	**1,411,375**	**2,038,892**	**6,459,983**

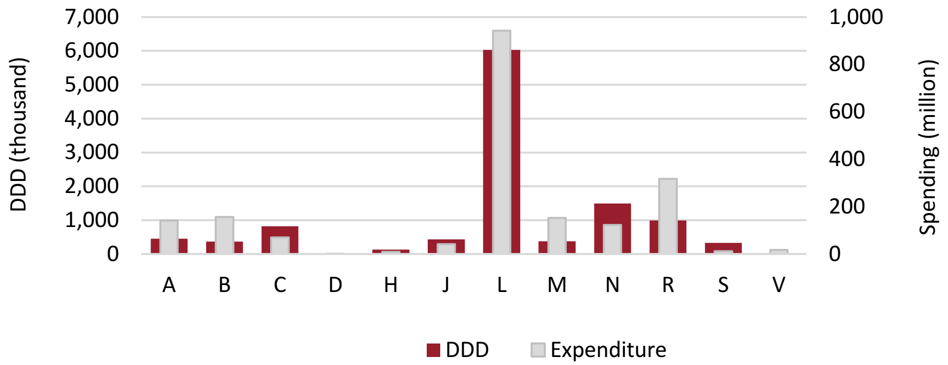
Expenditure for orphan drugs accessing funds increased in 2022 for both oncology and non-oncology innovative medicines. It should be noted that the reported expenditure values refers to the entire molecule and not to the specific indication obtaining the recognition of innovativeness. For the latter, spending has more than tripled. In 2022, the increase in expenditure on innovative non-oncological orphans compared to 2021 is equal to 209 % (Table 5.2.10).

Table 5.2.10 Orphan medicines accessing the fund for oncology and non-oncology innovative medicines: comparison expenditure and consumption, years 2021-2022

Type of medicines	Expenditure		Δ %	DDD		Δ %
	2021	2022	22-21	2021	2022	22-21
Oncology innovative medicines	326	456	40.1	1,635,838	4,143,529	153.3
Non-oncology innovative medicines	153	474	209.0	403,054	2,316,454	474.7

As regards therapeutic classes, the major expenditure was covered by antineoplastic agents and immuno-modulators (47.6%) and respiratory system medicines (16%), followed by blood and blood forming organs medicines (7.9%), musculo-skeletal system medicines (7.7%), gastrointestinal tract and metabolism medicines (7.1%) and other (13.7%) (Figure 5.2.3).
As regards consumption, the classes concerned are antineoplastics and immuno-modulators (52.75%), nervous system medicines (13%), respiratory system medicines (8.7%), cardiovascular system medicines (7.2%) and gastrointestinal tract and metabolism medicines (3.9%) while the remaining 14.5% of consumption is represented by other categories (Figure 5.2.3).

Figure 5.2.3 Expenditure and consumption of orphan medicines in Italy for ATC level I, year 2022 (Class A, H, C, C-NN)



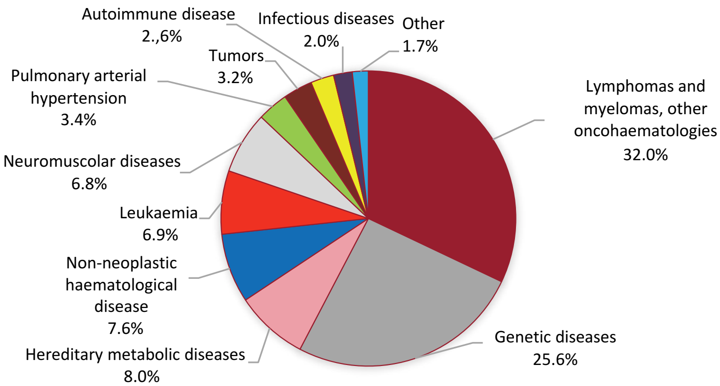
L Antineoplastic and immunomodulating agents
A Alimentary tract and metabolism
C Cardiovascular system
B Blood and blood forming organs
N Nervous system
H Systemic hormonal preparations, excluding sex hormones and insulins
V Various
R Respiratory system
M Musculo-skeletal system
G Genito urinary system and sex hormones
J Antinfective for systemic use
D Dermatologicals
S Sensory organs

A further analysis of the distribution of orphan medicines expenditure by therapeutic area reveals that the highest incidence is found for medicines intended for the treatment of lymphomas, myelomas and genetic diseases (32% and 25.6% respectively), in line with the trend of the previous year. On the consumption side, the first in the ranking are medicines used in lymphomas, myelomas and other oncohaematologic diseases, followed, with much lower values, by those for genetic diseases and inherited metabolic diseases (Table and Figure 5.2.11).

Table 5.2.11 Expenditure and consumption of orphan medicines in Italy by therapeutic area: year 2022 (Table and Figure) (Class A, H, C, C-NN)

Therapeutic Area	Spending (million)	Δ % 22-21	DDD (thousand)	Δ % 22-21	Expenditure pros understand	DDD 1000 inhab. per day	Inc.% expenditure *
Lymphomas and myelomas, other oncohaematologies	635	54.3	5,026.3	122.1	10.77	85.22	32.04
Genetic diseases	508	105.8	2,241.8	279.8	8.62	38.01	25.63
Hereditary metabolic diseases	159	24.2	328.1	30.0	2.69	5.56	8.01
Non-neoplastic haematological disease	151	11.0	411.0	143.9	2.56	6.97	7.61
Leukaemia	138	23.7	500.5	10.6	2.33	8.49	6.94
Neuromuscular diseases i	135	23.6	287.0	38.8	2.29	4.87	6.82
Pulmonary arterial hypertension	67	-2.3	820.4	-4.4	1.14	13.91	3.39
Tumors	64	2.3	296.4	9.1	1.08	5.03	3.21
Autoimmune diseases	51	59.0	233.6	28.1	0.86	3.96	2.55
Infectious diseases	41	4.6	283.6	10.2	0.69	4.81	2.05
Endocrine and metabolic diseases	12	28.3	286.2	54.1	0.21	4.85	0.61
Neurological diseases	10	170.0	344.0	81.2	0.17	5.83	0.51
Other	7	23.8	47.7	157.7	0.12	0.81	0.37
Eye diseases	4	23.8	333.5	3.8	0.07	5.65	0.21
Nephropathies	1	-	0.0	-	0.01	0.00	0.04
Total	**1,983**	**45.0**	**11,440.0**	**84.0**	**33.61**	**194.0**	**100.0**

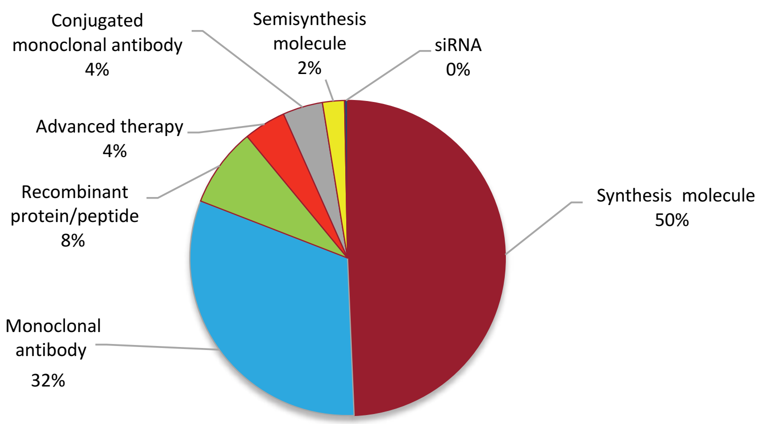
*Calculated on the total expenditure of orphan medicines nationwide



Analysis by type shows that most orphan medicines are synthesis molecules (approximately 50% of incidence on expenditure), followed by monoclonal antibodies (approximately 32% of incidence on expenditure) (Table and Figure 5.2.12). Compared to 2021, the largest increase in expenditure can be observed for the conjugated monoclonal antibody, while the largest variation in consumption is for the recombinant protein/peptide.

Table 5.2.12 Expenditure and consumption of orphan medicines in Italy by type, year 2022 (Table and Figure) (Class A, H, C, C-NN)

Type of medicines	No. Of molecules	Expenditure *(million)*	Δ % 21-20	DDD *(thousand)*	Δ % 21-20	Expenditure *per capita*	DDD 1000 inhab. per day	Inc.% expenditure *
Synthesis molecule	58	978	49.9	5,356	61.2	16.58	90.8	49.3
Monoclonal antibody	13	626	39.9	4,786	123.9	10.61	81.1	31.6
recombinant protein/peptide	18	161	32.8	477	140.7	2.73	8.1	8.1
Advanced therapy	7	86	17.0	0	20.2	1.45	0.0	4.3
Conjugated monoclonal antibody	5	81	150.7	232	110.7	1.38	3.9	4.1
Semisynthesis molecule	9	45	11.5	583	29.9	0.76	9.9	2.3
siRNA	1	6	-	6	-	0.10	0.1	0.3
Total	**111**	**1,983**	**45.0**	**11,440**	**84.0**	**33.61**	**194.0**	**100.0**



Access to medicines for rare diseases pursuant to Law 648, AIFA 5% fund and Ministerial Decree 7 September 2017

Despite notable medical advances in the diagnosis and treatment of many diseases, there are still so-called “niche” therapeutic areas which refer to unmet clinical needs and which represent a challenge and a healthcare goal for medicine.
And it is precisely in this niche position that Law n. 648/96, the National Fund and compassionate use are inserted at a regulatory level.

Law no. 648 of 1996

This rule allows the provision by the National Health Service, in the absence of a valid therapeutic alternative, of:

- innovative medicines whose marketing is authorised in other countries, but not in Italy;
- medicines not yet authorised, but undergoing clinical trials;
- medicines to be used for a therapeutic indication other than that authorszed in Italy.

In all the cases described above, the inclusion in list 648 must be supported by the results of concluded clinical studies, at least in phase II, which have demonstrated adequate efficacy with an acceptable risk profile.
With the entry into force of Law no. 79 of 2014, after AIFA's evaluation, the inclusion of medicines in the list is envisaged even in the presence of alternatives; these medicines can be used for a therapeutic indication other than that authorised, provided that this indication is known and compliant with research conducted within the national and international medical-scientific community, according to parameters of cost-effectiveness and appropriateness.
Inclusion is carried out by AIFA upon documented request by Patient Associations, Scientific Societies, Health Authorities, Universities or on the recommendation of the AIFA Scientific Technical Committee.
The list of orphan medicines and medicines for the treatment of rare diseases reimbursed pursuant to Law no. 648/96 can be downloaded from the Agency's website at the following link: https://www.aifa.gov.it/legge-648-96.

Law no. 326/2003 (AIFA 5% Fund)

Law no. 326 of 2003 provided for the establishment at AIFA of a national fund for the use of orphan medicines for the treatment of rare diseases and medicines that represent a hope of therapy, pending marketing, for particular and serious diseases.
The Fund consists of 50% of the contribution that pharmaceutical companies pay to AIFA on an annual basis. This contribution corresponds to 5% of the annual expenses that pharmaceutical companies sustain for promotional activities for healthcare professionals.

Ministerial Decree 7 September 2017

In Italy the D.M. 7 September 2017, "Discipline of the therapeutic use of medicinal products subjected to clinical trials", represents the regulatory instrument that establishes the

procedures and methods of access to experimental pharmacological therapies for the treatment of serious diseases, rare diseases, rare cancers or conditions of disease that put the patient in danger of life, when, in the opinion of the doctor, there are no further valid therapeutic alternatives or in the event that the patient cannot be included in a clinical trial or, for the purposes of therapeutic continuity, for patients already treated with clinical benefit in a completed clinical trial.
Access to the experimental medicine requires authorisation for use by the Ethics Committee within whose sphere of competence this request originated, given the prior declared availability of the pharmaceutical company to supply the medicine free of charge.
The regulatory references for this Decree of the Ministry of Health are art. 83 of Regulation (EC) no. 726/2004, as required pursuant to art. 158, paragraph 10, of the D.L. 219/2006 for aspects relating to compassionate use programs and art. 5 (1) of Directive 2001/83 for accesses on a nominal basis.
If the company is willing to provide the medicine free of charge and the conditions described in the aforementioned Decree are met, the treating physician can use this tool to provide clinical trial medicines to patients who are not part of the trials themselves, or to supply medicines with Marketing Authorisation for indications other than those approved, or for medicines authorised but not yet available on the national territory.

Access to medicines for rare diseases pursuant to Law no. 648, AIFA 5% fund and Ministerial Decree 7 September 2017

The data provided refer only to list 648 subject to clinical and expenditure monitoring; therefore, these data do not include the lists of medicines for consolidated use.
Table 5.2.13 lists the medicines included in list 648 in 2022, intended for the treatment of rare diseases, both without and without the status of orphan medicine.

Table 5.2.13 Medicines included in list 648 in 2022, intended for the treatment of rare diseases, both without the status of orphan medicine and with the status of orphan

Active substance	Therapeutic indication
Brentuximab vedotin	Treatment of paediatric patients with relapsed and/or refractory CD30+ Hodgkin lymphoma and treatment of paediatric patients with relapsed and/or refractory CD30+ anaplastic large cell lymphoma
Crizotinib	Treatment of patients with anaplastic lymphoma ALK+
Dinituximab	Treatment of relapsed or refractory neuroblastoma, with or without residual disease, and in patients who have not achieved a complete response after first line therapy, without co-administration of interleukin-2 (IL-2).
Ponatinib	First-line therapy, including induction and consolidation in combination or not with intensive chemotherapy (based on high doses of cytosin arabinoside and methotrexate) for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia and eligible for allogeneic hematopoietic cell transplantation as post-remission therapy and for patients not eligible for allogeneic stem cell transplantation but with performance status or comorbidity that make them suitable for treatment with ponatinib
Rituximab (originator and biosimilare)	Treatment of adult patients with steroid-dependent or frequently relapsing nephrotic syndrome
Rituximab (originator and biosimilare)	Treatment of frequently relapsing steroid-sensitive or-dependent idiopathic nephrotic syndrome in pediatric age
Trastuzumab (originator e biosimilare)	In combination with docetaxel, for the treatment of locally advanced salivary duct carcinoma, not eligible for surgical treatment and/or recurrent or metastatic HER2-positive
Somatostatin	Treatment of patients with stature deficit associated with altered functioning of the SHOX gene

Source: AIFA Pre-Authorisation Division

During the year 2022, 9 compassionate use programs were opened for rare diseases, 7 of which concerned medicines granted orphan designation by the COMP, for a total of 590 treated patients.
Table 5.2.14 shows the list of programmes and the number of patients included in each of them.

Table 5.2.14 Medicines intended for the treatment of rare diseases for which a program was activated in 2022 pursuant to Ministerial Decree 7 September 2017

Active substance (nome commerciale)	Therapeutic indication	No. of patients included in the program
Avacopan (Tavneos)*	In combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)	20
Glofitamab*	Treatment of patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), relapsed/refractory high grade lymphoma (R/R HGL), relapsed/refractory transformed follicular lymphoma (R/R tFL), relapsed/refractory primary mediastinal lymphoma (R/R PMBCL)	55
Mosunetuzumab (Lunsumio)*	Treatment of adult patients with relapsed/refractory follicular lymphoma	11
Odevixibat (Bylvay)*	Treatment of Alagille syndrome	6
Tafasitamab (Minjuvi)* in combination with lenalidomide	Treatment of adult patients with diffuse large B cell lymphoma (Diffuse Large B-Cell Lymphoma, DLBCL) relapsed or refractory and not eligible for autologous Stem Cell Transplant (ASCT), not eligible for authorised therapeutic alternatives.	96
Durvalumab (Imfinzi)	In combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with locally advanced or metastatic biliary tract cancer	324
Teclistamab (Tecvayli)*	Treatment of adult patients with relapsed and refractory multiple myeloma for whom no authorised therapeutic alternatives are available	60
Ivacaftor/tezacaftor/elexacaftor (Kaftrio)*	In combination with ivacaftor for the treatment of cystic fibrosis (FC) in patients aged between six and eleven years, whose cystic fibrosis is due to at least one F508del mutation in the CFTR gene.	12
Pembrolizumab (Keytruda)	In combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.	6

* medicines granted orphan designation by the COMP
Source: AIFA Pre-Authorisation Division

In addition to the new programmes mentioned above, an additional 8 programmes for rare diseases were active in 2022, activated before the year 2022 and still ongoing at the date of data processing.
Please note that the data reported are up to 30 November 2022.

Table 5.2.15 Number of requests for access to the fund and number of actual accesses obtained in the year 2022

Year	Number of patients who have submitted an application for access to the AIFA fund		Number of patients who received positive response to the request for access to the AIFA fund	
	With rare disease	With rare tumor	With rare disease	With rare tumor
2022	554	374	229	122

Source: AIFA Pre-Authorisation Division

The resources allocated in the 5 % Fund for the year 2022 were 13.153.436 euros. Compared to the last years, also for 2022, the reduction in the capacity of the Fund was affected by the decrease in promotional activities carried out by pharmaceutical companies due to the pandemic, although, compared to 2021, it is slightly increasing.
The number of requests for access to the Fund received during 2022 was 799; of these, 554 concerned patients affected by rare disease, 374 of which with rare cancer. The fund was authorised for 229 applications related to rare diseases, of which 122 related to rare cancers. Throughout the year, there was a sharp reduction in the number of requests for access to the Fund compared to the years 2019-2021 (1744 in 2019, 2215 in 2020, 2125 in 2021 vs 799 in 2022). This is linked to the adoption of the new criteria introduced at the end of 2021 to protect the sustainability of the Fund and to allow access to medicines not yet marketed in Italy and that represent a hope of cure for patients suffering from rare and serious diseases, i.e., the treatment of individual cases with an important or maximum therapeutic need.
In addition, since 1 July 2022, a new online service has been activated by the Agency, which allows the submission and monitoring of the status of requests for access and reimbursement of the 5 % fund.
Requests for the top 10 active substances make up approximately 48 % of the total requests (381 requests out of 799 total).
As can be seen from Table 5.2.16, most requests concern the active substances pembrolizumab, nivolumab and ruxolitinib.
The first 10 active substances by expenditure account for 10 030 861,54 euro of the total; among these, the first three are sebelipase alfa, followed by eculizumab and burosumab (Table 5.2.17).

Table 5.2.16 Top 10 medicines by number of requests for access to the 5% fund in year 2022

Medicine/Active substance	No. of requests
pembrolizumab	106
nivolumab	70
ruxolitinib	49
ivosidenib	28
olaparib	26
sorafenib	22
blinatumomab	21
elexacaftor/ivacaftor/tezacaftor	20
nivolumab/ipilimumab	20
eltrombopag	19

Source: AIFA Pre-Authorisation Division

Table 5.2.17 Top 10 medicines with the greatest expenditure impact on the AIFA 5% fund for year 2022

Medicine/Active substance	Authorised expenditure (€)
sebelipase alfa	2,168,089.46 €
eculizumab	2,053,891.48 €
burosumab	1,728,658.75 €
belinostat	833,072.00 €
pembrolizumab	821,810.25 €
tagraxofusp	606,180.00 €
trieptanoina	571,500.00 €
ivosidenib	524,400.00 €
ivacaftor	369,449.44 €
enfortumab vedotin	353,810.16 €

Source: AIFA Pre-Authorisation Division

Section 7

Enviromental impact of medicines

Introduction

The OsMed Reports on the use of medicines in Italy have been for years an ever increasing source of information on the use of medicines for human use in our country. Starting this year, a new section has been introduced to analyse the potential environmental impact of a range of high-use or high-toxicity active substances. The main objective of this section is to provide an informative overview and raise awareness among the public, including healthcare professionals, of the emerging problem of the impact that medicines have on the environment.

In any case, it is important to underline that therapeutic plans are and remain a choice of the treating physician considering the benefit/risk profile for the individual patient even in the case of active substances with high environmental risk. Measures to limit the impact of medicines on the environment are currently being developed and evaluated by the competent authorities[1]. As a result, clinical appropriateness in the choice of the medicinal product remains a priority.

Environmental impact of medicines

Among the many challenges that human activity poses to environmental sustainability, one is the use of medicines. After being taken, medicines are released into the environment mainly through excretion in the urine and feces, both in an unchanged form and as metabolites. In addition, expired or unused drugs, improperly disposed in the toilets, reach the drainage systems and, subsequently, the surface water, with potential negative consequences for the fauna and flora that inhabit these environments[2]. Exposure of aquatic organisms to drugs and their metabolites can result in a number of adverse reactions that pose a threat to the ecological balance. For example, the neurotoxicity of some analgesics in several animal species[3] and antimicrobial resistance in plants and animals exposed to antibiotics[4] were observed.

At European level, several measures have been taken to map the presence of pharmaceuticals in the environment and estimate their risk. In particular, these actions have been focused on the monitoring of surface water, being the first environment to be influenced by the effects of human use of drugs. Since 2006, the European Medicines Agency (EMA) has introduced an obligation for pharmaceutical companies to submit an environmental risk assessment during the marketing authorisation process for a medicine. This assessment, which is part of the European Public Assessment Report (EPAR) for each drug, should provide information on the toxicity of the active substance towards aquatic organisms, as well as information on the expected risk based on expected consumption levels[5].

In addition, in 2008 the European Commission established a mandatory surface water monitoring mechanism for chemical substances that that can cause harm to the environment called the Watch List. This monitoring campaign was launched in 2015 and the list of substances included is regularly reviewed every two to three years. Among the monitored substances, some drugs for human use are also included[6].

Calculation of environmental risk

This section of the OsMed Report includes the calculation of the environmental risk in Italy for 90 active substances selected according to three specific criteria.

- Thirty high-consumption active ingredients in Italy. This selection was carried out taking into account the consumption of the single active substance, considering separately the formulations in which it was present alone or in combination, for all the indications and formulations for which it is approved and marketed. The following were included: acetylsalicylic acid, allopurinol, amlodipine, atorvastatin, bisoprololo, cianocobalamina, clopidogrel, colecalciferolo, diclofenac, esomeprazole, ezetimibe, furosemide, ibuprofen, ketoprofen, lansoprazole, levothyroxine, lormetazepam, metformin, nafazoline, nebivolol, olmesartan, omeprazole, pantoprazole, paracetamol, ramipril, rosuvastatin, sertraline, simvastatin, tamsulosin and valsartan.
- Thirty-two active substances with high environmental toxicity, defined as the lowest PNEC (Predicted No Effect Concentration) value, i.e. the level of concentration above which aquatic organisms are likely to develop adverse reactions. The following were included: atovaquone, bedaquiline, bosentan, ceritinib, clevidipine, dabrafenib, ebastine, elbasvir, estradiol, ethinylestradiol, fedratinib, felodipine, grazoprevir, imatinib, isradipina, lacidipine, lapatinib, levonorgestrel, lomitapide, lusutrombopag, midostaurin, montelukast, nilotinib, nisoldipine, permethrin, piperaquine, proglumetacin, rifaximin, rilpivirine, toremifene, verteporfin, vinflunine.
- All active ingredients for human use included or candidates for inclusion on at least one version of the Watch List (last reference version: August 2022). The following were included: allopurinol, amoxicillin, azithromycin, cefalexin, Cyclophosphamide, ciprofloxacin, clarithromycin, clindamycin, clotrimazole, daunorubicin, diclofenac, dipyridamole, doxorubicin, erythromycin, estradiol, ethinylestradiol, fentanyl, fluconazole, fluorouracil, gabapentin, gemfibrozil, irbesartan, levonorgestrel, mebendazole, metformin, mycophenolate, miconazole, midazolam, norethisterone, ofloxacin, propranolol, sulfamethoxazole, trimethoprim, venlafaxine.

Some active substances appeared to be present in more than one category: allopurinol, diclofenac, estradiol, ethinylestradiol, levonorgestrel and metformin. Some active substances appeared to be present in more than one category: Allopurinol, diclofenac, estradiol, ethinylestradiol, levonorgestrel and metformin. For the purposes of the analysis, the last two categories (high environmental toxicity and Watch List) were considered together as the listed active were selected according to environmental criteria, while the 30 active substances analysed on the basis of high consumption, regardless of their toxicity, were analysed separately.
The environmental risk of medicinal products to the aquatic environment was assessed by calculating the ratio between the estimated concentration of the drug in surface water (PEC – *Predicted Environmental Concentration*) and a measure of the toxicity of the

substance to aquatic animals and plants, namely PNEC (see above). Based on this assessment, the environmental risk was classified as high in case of PEC/PNEC ratio greater than 10, moderate if between 1 and 10, low if between 0.1 to 1 and insignificant if less than or equal to 0.1[7].
The analysis was carried out for year 2022 at national level, broken down by geographical areas (North, Centre, South).
To calculate the PEC of each active substance, the following formula[7] was used:

$$PEC(\mu g/L) = \frac{A \times 10^9 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

Where:

- $A\ (kg)$ represents the total amount of the active substance consumed in Italy and in the geographical areas in 2022. For the calculation of this quantity, consumption for all reimbursement classes (approved, hospital and private) was considered for each active ingredient selected.
- $R\ (\%)$ represents the removal rate of the substance due to loss by volatilization, hydrolysis or biodegradation. As no specific information is available, a value of 0 % was considered.
- P represents the Italian population in 2022, calculated as the average of the resident population at 1 January 2022 and 1 January 2023[10,11].
- $V\ (L/die)$ represents the volume of waste water per capita per day and is set at 200 l according to the proposal of the European Chemicals Agency (ECHA) [9].
- D represents the dilution factor of the waste water by river flow and was set at 10 according to the ECHA [9] proposal.

The PNEC values used to assess the environmental risk have been extracted from several sources: the NORMAN ecotoxicology database [12], the website on the environmental impact of medicines developed by the Stockholm Region (Sweden) [3] and the information documents on the selection of substances for inclusion in the Watch List[14–16]. These data are derived from the study of animals or plants in natural environments or artificially exposed to concentrations of individual active ingredients. In cases where more than one PNEC value was available for a specific active substance, the lowest value[5] was selected.

Environmental risk in Italy

The environmental risk analysis carried out for the 90 selected active substances revealed a high or moderate risk for most of the therapeutic classes considered.
In particular, two nonsteroidal anti-inflammatory, diclofenac and ibuprofen, have been identified as drugs at high risk of causing adverse effects in aquatic plants and animals at Italian level.
Several high- or moderate-risk active substances have also been identified in the antibiotics class. These include two macrolides (azithromycin and clarithromycin), two

fluoroquinolones (ciprofloxacin and ofloxacin), one penicillin (amoxicillin), one lincosamide (clindamycin) and an antibiotic for intestinal infections (rifaximine). In addition, two pesticides have been identified as high-risk: atovaquone, used to treat malaria, and permethrin, used in the treatment of scabies. Antiviral for HIV rilpivirine and antimicotics clotrimazole and miconazole were classified as moderate risk.

Some antihypertensive drugs have also been associated with a high or moderate risk. These include an angiotensin II receptor antagonist (olmesartan), two dihydropyridine calcium antagonists (lacidipine and felodipine), an endothelin receptor antagonist (bosentan) and an ACE inhibitor (ramipril).

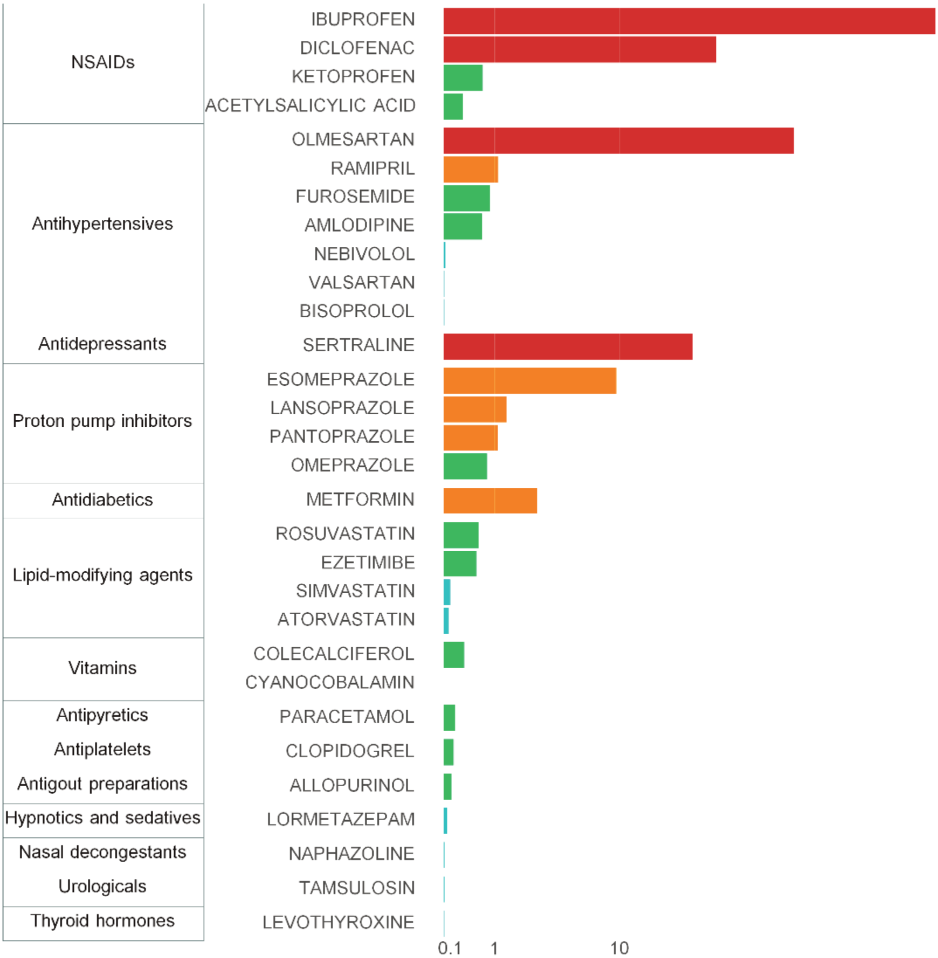
Two antidepressants, sertraline and venlafaxine, were also associated with a high environmental risk.

The active substances used as contraceptives included in this analysis, estradiol, ethinylestradiol, levonorgestrel and norethisterone, were classified as moderate risk to the environment.

Certain oncological drugs protein kinase inhibitors, dabrafenib, imatinib, lapatinib and nilotinib have been identified as moderate risk, similar to proton pump inhibitors (PPIs) esomeprazole, lansoprazole and Pantoprazol, antidiabetic metformin, antiasthmatic montelukast, antihistamine ebastine, and immunosoppressant mycophenolate mofetil.

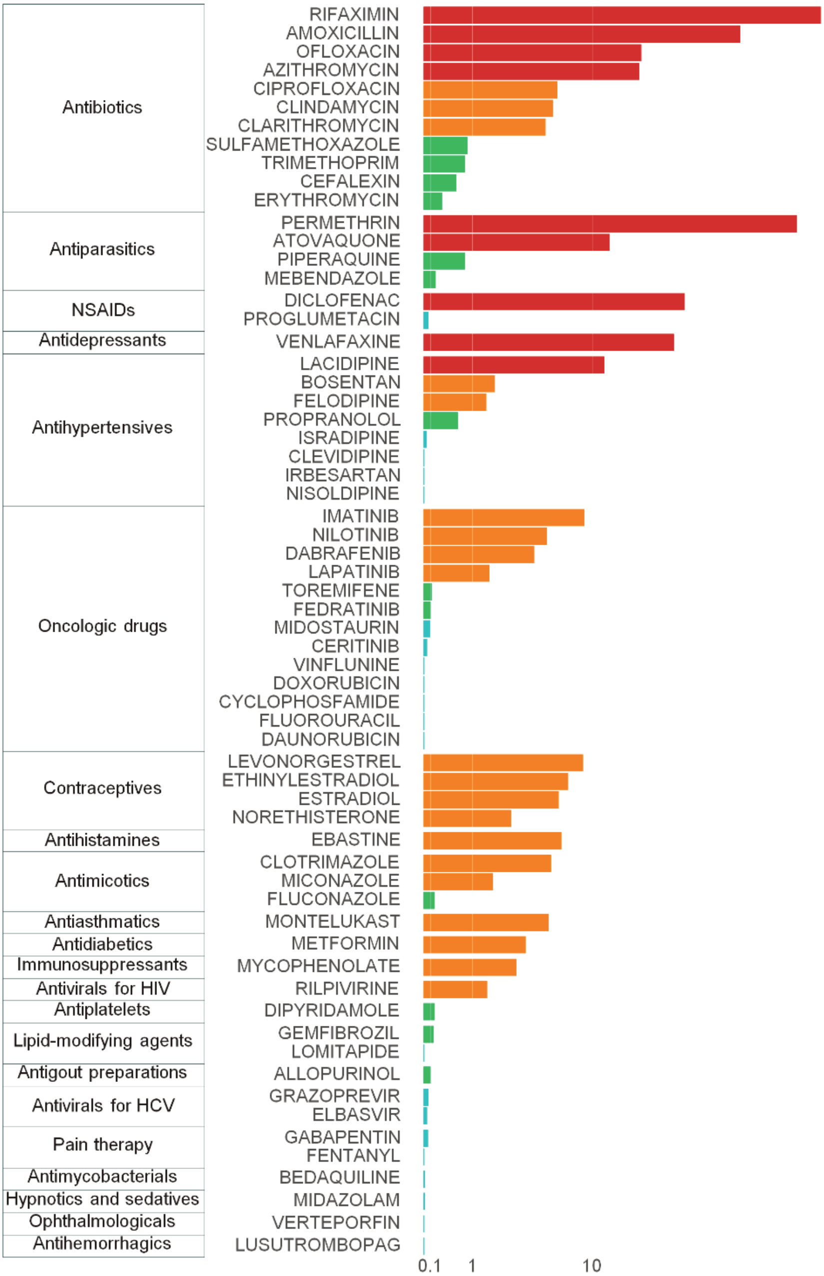
The environmental risk analysis at geographical level (North, Centre, South) reveals in general homogeneity in risk classes for most active substances, although some differences for specific drugs have been highlighted. For example, esomeprazole showed a high risk in the South, while the risk was moderate in the Northern and Centre Regions. Similarly, omeprazole showed moderate risk in the South, compared to low risk in the North and Center. A different risk class was also observed for antimalarial atovaquone, characterised by a high environmental risk in the North and the Centre, and a moderate risk in the South. A different risk category, ranging from moderate in the North and the Center to low in the South, was observed for the antihypertensives ramipril and felodipine and for the antiviral anti-HIV rilpivirine. Finally, the analysis estimated for the pesticide piperaquine a moderate environmental risk in the North, but low in the Centre and South, and for the antihypertensive propranolol a low risk in the North and Centre regions, but moderate in the South.

Figure 7.1 Environmental risk values for the top 30 pharmaceuticals by consumption in Italy in 2022



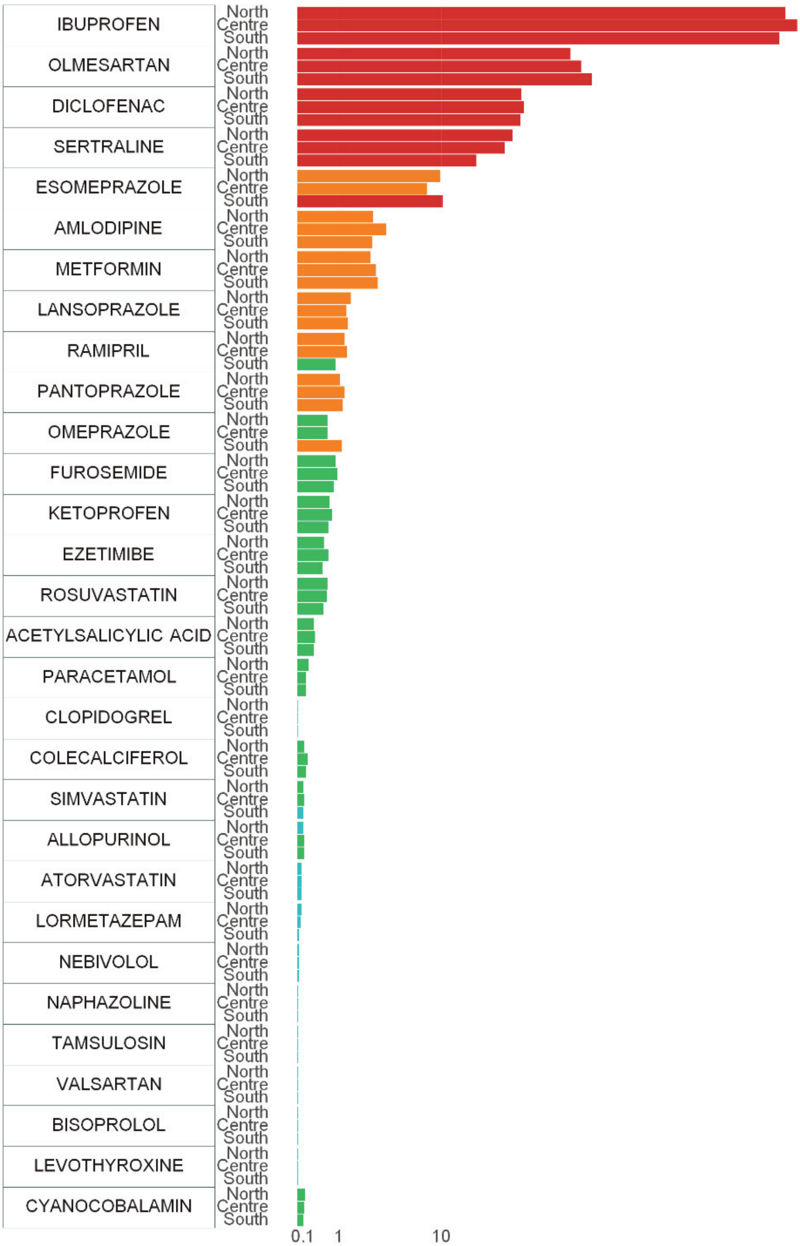
Note: the colours represents the risk categories: high risk in red (PEC/PNEC ratio >10), moderate risk in orange (PEC/PNEC ration >1), low risk in green (PEC/PNEC ration >0.1) and insignificant risk in blue (PEC/PNEC ratio ≤0.1)

Figure 7.2 Environmental risk values for medicines included in the European Watch list or with increased environmental toxicity



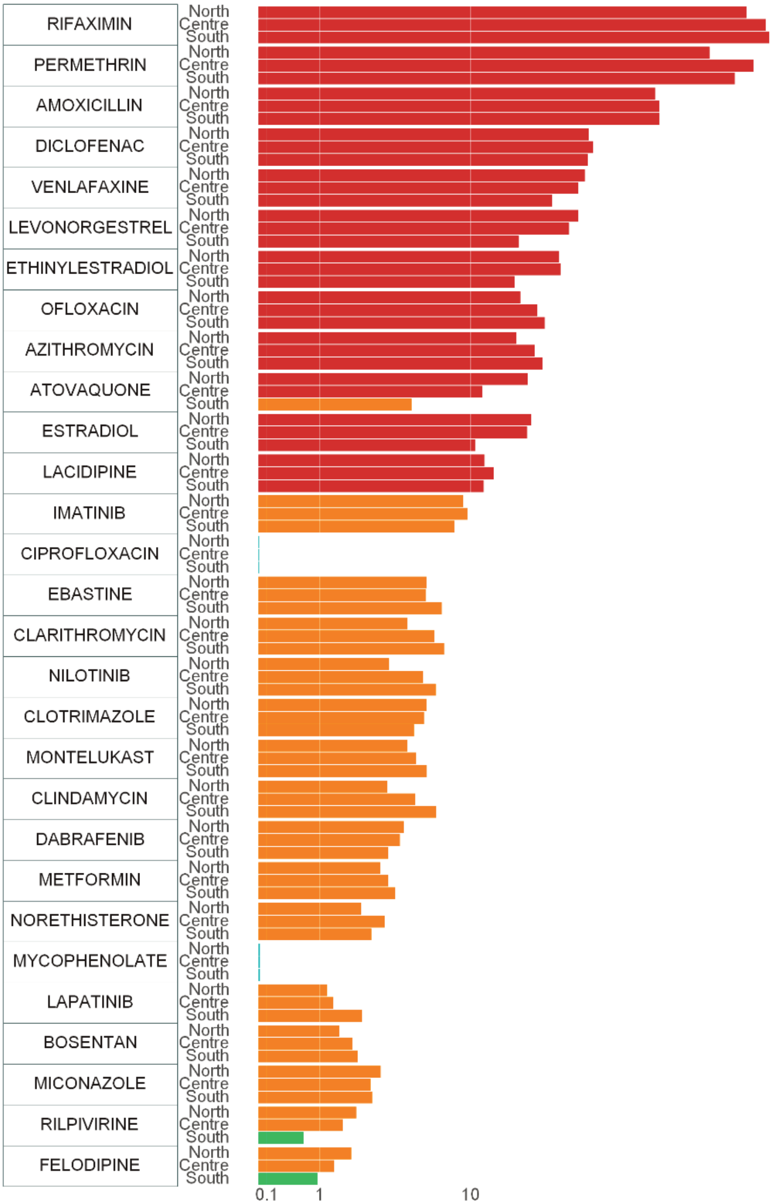
Note: the colours represents the risk categories: high risk in red (PEC/PNEC ratio >10), moderate risk in orange (PEC/PNEC ration >1), low risk in green (PEC/PNEC ration >0.1) and insignificant risk in blue (PEC/PNEC ratio ≤0.1).

Figure 7.3 Environmental risk values for the top 30 pharmaceuticals by consumption in Italy in 2022 broken down by geographical region



Note: the colours represents the risk categories: high risk in red (PEC/PNEC ratio >10), moderate risk in orange (PEC/PNEC ration >1), low risk in green (PEC/PNEC ration >0.1) and insignificant risk in blue (PEC/PNEC ratio ≤0.1).

Figure 7.4 Environmental risk values for medicines included in the European Watch list or with increased environmental toxicity that present a high or moderate environmental risk at Italian level broken down by geographical area



Note: the colours represents the risk categories: high risk in red (PEC/PNEC ratio >10), moderate risk in orange (PEC/PNEC ration >1), low risk in green (PEC/PNEC ration >0.1) and insignificant risk in blue PEC/PNEC ratio ≤0.1).

Table 7.1 Environmental risk values for medicines included in the European Watch list or with increased environmental toxicity that present a low or insignificant environmental risk at Italian level broken down by geographical area

Therapeutic class	Active ingredient	Source	North	Centre	SSouth	PIE	VDA	LOM	BOL	TRE	VEN	FVG	LIG	EMI	TOS	UMB	MAR	LAZ	ABR	MOL	CAM	PUG	BAS	CAL	SIC	SAR
Antiplatelets	dipiridamolo[1]	WL	0.2	0.2	0.1	0.2	0.4	0.2	0.1	0.1	0.1	0.2	0.2	0.1	0.3	0.3	0.3	0.1	0.1	0.2	0.1	0.1	0.2	0.1	0.1	0.2
Antibiotics	cefalexina[1]	WL	0.6	0.7	0.5	0.4	0.4	0.7	0.2	0.4	0.9	0.7	0.6	0.3	0.4	1.1	0.5	0.9	0.6	1.0	0.6	0.6	0.4	0.5	0.4	0.2
Antibiotics	eritromicina[1]	WL	0.3	0.3	0.3	0.3	0.2	0.3	0.2	0.1	0.3	0.2	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.4	0.4	0.3	0.2	0.4	0.2	0.2
Antibiotics	sulfametoxazolo[1]	WL	0.9	0.9	0.8	0.8	0.9	0.8	0.8	0.6	0.9	0.9	1.2	0.9	1.1	1.0	0.7	0.8	0.8	1.0	1.2	1.0	0.7	0,8	0.6	0.3
Antibiotics	trimetoprim[1]	WL	0.8	0.9	0.7	0.8	0.8	0.7	0.8	0.6	0.8	0.9	1.1	0.9	1.0	0.9	0.6	0.7	0.7	1.0	1.1	0.9	0.7	0.6	0.6	0.2
Antihemorrhagics	lusutrombopag[2]	PNEC	0.0	0.0	0.0	0.0		0.0			0.0	0.0	0.0	0.0	0.0		0.0	0.0	0.0		0.0	0.0		0.0	0.0	0.0
Antigout preparations	allopurinolo[1]	WL	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Antimycobacterials	bedaquilina[2]	PNEC	0.0	0.0	0.0	0.0	0.1	0.0			0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0		0.0	0.0		0.0	0.0	
Antimicotics	fluconazolo[1]	WL	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.3	0.2	0.2
Antiparasitics	piperachina[2]	PNEC	1.1	0.5	0.5	0.7		0.8	0.5	0.7	0.9	1.2	7.4	0.8	0.7	0.2	0.4	0.5	0.1	0.1	1.3	0.1		0.3	0.2	
Antiparasitics	mebendazolo[1]	WL	0.2	0.2	0.2	0.1	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2	0.1	0.2	0.1	0.1	0.2	0.2	0.1
Antihypertensives	clevidipina[2]	PNEC	0.0	0.0	0.0	0.0		0.0		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Antihypertensives	isradipina[2]	PNEC	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.0
Antihypertensives	nisoldipina[2]	PNEC	0.0		0.0	0.0															0.0					
Antihypertensives	irbesartan[1]	WL	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Antihypertensives	propranololo[1]	WL	0.7	0.5	0.5	1.3	0.5	0.6	0.5	0.5	0.7	1.0	0.6	0.7	0.5	0.6	0.4	0.5	0.4	0.7	0.6	0.4	0.4	0.7	0.4	0.7
Antivirals for HCV	elbasvir[2]	PNEC	0.0	0.0	0.1	0.1	0.1	0.0		0.0	0.0	0.1		0.1	0.0	0.1	0.1	0.0	0.0		0.1	0.1		0.1	0.1	0.0
Antivirals for HCV	grazoprevir[2]	PNEC	0.1	0.0	0.1	0.1	0.1	0.1		0.0	0.0	0.1		0.1	0.0	0.1	0.1	0.0	0.0		0.1	0.1		0.1	0.1	0.0
NSAIDs	proglumetacina[2]	PNEC	0.0	0.0	0.2	0.0		0.0		0.0	0.0	0.0	0.0	0.0	0.0		0.0	0.0	0.0	0.1	0.2	0.1	0.2	0.4	0.2	0.0
Oncologic drugs	ceritinib[2]	PNEC	0.0	0.1	0.0	0.1		0.0						0.1	0.2		0.1	0.0		0.6	0.1				0.0	
Oncologic drugs	fedratinib[2]	PNEC	0.1	0.0	0.1	0.1		0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.1		0.1	0.0	0.1	0.1	0.1	0.2	0.1	0.2	0.1	
Oncologic drugs	midostaurina[2]	PNEC	0.1	0.1	0.1	0.2		0.1	0.0	0.1	0.1	0.2	0.0	0.1	0.1	0.5	0.1	0.1	0.0	0.1	0.1	0.2	0.0	0.0	0.1	0.1
Oncologic drugs	toremifene[2]	PNEC	0.1	0.2	0.1	0.1	0.1	0.1	0.3		0.2	0.0	0.3	0.2	0.4	0.1	0.1	0.1	0.0		0.2	0.1	0.1	0.0	0.0	0.0
Oncologic drugs	vinflunina[2]	PNEC	0.0	0.0	0.0	0.0		0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		0.0	0.0		0.0	0.0	0.0
Oncologic drugs	ciclofosfamide[1]	WL	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Oncologic drugs	daunorubicina[1]	WL	0.0	0.0	0.0	0.0		0.0	0.0	0.0	0,0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0
Oncologic drugs	doxorubicina[1]	WL	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Oncologic drugs	fluorouracile[1]	WL	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ophtalmologicals	verteporfina[2]	PNEC	0.0	0.0	0.0	0.0		0.0	0,0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		0.0	0.0	0.0
Hypnotics and sedatives	midazolam[1]	WL	0.0	0.0	0.0	0.0	0.0	0.0	0,0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Lipid modifying agents	lomitapide[2]	PNEC	0.0	0.0	0.0	0.0		0.0			0.0	0.0	0.0	0.0	0.0			0.0			0.0	0.0		0.0	0.0	0.0
Lipid modifying agents	gemfibrozil[1]	WL	0.1	0.2	0.1	0.2	0.4	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.1	0.2	0.1	0.1	0.2	0.1	0.2	0.2	0.1	0.0
Pain therapy	fentanil[1]	WL	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pain therapy	gabapentin[1]	WL	0.1	0.1	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1

Note: the colours represents the risk categories: high risk in red, moderate risk in orange, low risk in green and insignificant risk in blue. The absence of data corresponds to the absence of consumption of the active substance in the Region.

Final considerations

This exploratory section on the environmental impact of drugs has taken as reference 90 active ingredients selected on the basis of criteria of environmental toxicity - included in European water monitoring programs - and highest consumption in Italy. This analysis provides an initial starting point for the assessment of the environmental impact resulting from the use of drugs in human settings. The results obtained highlight the need to pay attention to the environmental impact of drugs in different therapeutic areas. In fact, combining data on utilization with the results of major ecotoxicological studies suggests that the environmental effects of many drugs cannot be ignored. For example, the two non-steroidal anti-inflammatory drugs that have emerged as high-risk, diclofenac and ibuprofen, are emerging as global problems for ecosystem sustainability. Diclofenac was one of the first drugs to be identified as a threat when animals and plants are exposed to it through the environment. One notable case involves neurotoxicity observed in a population of vultures in Pakistan that fed on carcasses of animals previously treated with diclofenac[3]. Exposure to this active ingredient through the aquatic environment can also cause adverse effects, such as physiological alterations to the gills of fish, which can induce problems with oxygen supply and thus body's biochemical activities[17]. Ibuprofen, when present in aquatic environments, can also cause adverse effects, such as cytotoxic and genotoxic damage and effects on growth, reproduction, and behaviour of animal species[18]. The therapeutic class of antibiotics includes several high- or moderate-risk active ingredients, among those included in this analysis. The presence of antibiotics in the aquatic environment may contribute to the development and spread of bacterial resistance[19], also through bioaccumulation in fish muscle tissue and the subsequent development of bacterial resistance genes (e.g., amoxicillin)[20]. Antibiotics belonging to the class of macrolides can alter population dynamics and food webs in aquatic organisms, such as algae and cyanobacteria[21]. Finally, antibiotics belonging to the class of fluoroquinolones can cause problems in the development and reproductive capabilities of various aquatic organisms, such as fish, amphibians and algae[22]. With regard to analyses by geographic area, differences in use, and thus environmental risk, were observed between North, Central and South, suggesting that the difference in area consumption may result in different environmental risks in different geographic areas. The future extension of this preliminary analysis to all active ingredients marketed in Italy, not only for human use but also for veterinary use, will make it possible to define an overall picture of the environmental risk posed by the drugs used in our country. Inclusion of these elements, together with the consideration of territoriality, will allow in the coming years to map the environmental risk of drugs in Italy and to design interventions and actions aimed at its containment, such as recommending behaviours to direct prescribers and developing organizational and technological solutions to limit environmental reach while preserving its clinically appropriate use. Evaluating the environmental impact of drugs and designing interventions to mitigate it will involve cooperation among various players, starting from those working in the health care field, to those working in the environmental protection field, to those working in the regulatory field.

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Appendix

Regulations concerning pharmaceutical assistance in Italy

1. Main measures taken in 2022

Budget Law 2023

The Budget Law 2023 (Law No 197 of 29 December 2022) authorised an expenditure of EUR 40 million for the years 2023, 2024 and 2025 to implement the measures and interventions foreseen in the 'Antimicrobial-Resistance Plan (*Piano di Contrasto all'Antimicrobico-Resistenza*, PNCAR) 2022-2025'.

For the year 2022, an additional remuneration of EUR 150 million was granted to pharmacies for the reimbursement of medicines provided under the National Health System, pursuant to the Ministerial Decree of 11 August 2021. This measure, approved experimentally for the years 2021 and 2022, was reconfirmed by the 2023 Budget Law, which recognises, as from 1 March 2023, an additional allocation of EUR 150 million.

The National Health Fund will grow by an additional EUR 2,150 million in 2023, EUR 2,300 million in 2024 and EUR 2,600 million starting from 2025. For 2023, a portion of such increase, equal to EUR 1,400 million, is intended to contribute to the higher costs of rising energy prices. In addition, in 2023 the fund for the purchase of SARS-CoV-2 vaccines and therapeutics for COVID-19 patients is also increased by EUR 650 million.

In view of the higher costs resulting from the continuation of COVID-19 actions and the significant increase in energy costs, the revenues deriving from the 2020 and 2021 payback subject to the reserve payment can be used by the Regions and Autonomous Provinces to ensure the balance of the health sector in 2022. This is without prejudice to the possibility that such revenues are compensated from the standard national health needs of the year in which the reserve payment is defined, if they are smaller. For the 2021 payback, these provisions shall apply within the limits of what is actually paid by pharmaceutical companies on the date of entry into force of the law.

National Action Plan on Antimicrobial Resistance (PNCAR) 2022-2025

The new PNCAR 2022-2025 was approved by the State-Regions Conference at its meeting of 26 September 2022 informally and on 30 November 2022 formally. Drawn up by the Technical Group for Coordination, Monitoring and Update of the PNCAR and the National Antimicrobial Resistance Strategy (AMR), the new Plan aims at providing strategic guidelines and operational guidance to address the emergence of antimicrobial resistance in the coming years, following a multidisciplinary approach and a One Health vision. The National Antimicrobial Resistance Strategy is based on inclusive and integrated governance. It encompasses four horizontal areas of support to all themes:

- training
- information, communication and transparency
- research, innovation and bioethics
- national and international cooperation

and three vertical pillars dedicated to the main AMR prevention and control interventions in the human, animal and environmental sectors:

1. integrated surveillance and monitoring of antibiotic resistance, antibiotic use, healthcare-associated infections and environmental monitoring;

2. prevention of hospital and community acquired infections, as well as of infectious diseases and zoonoses;
3. appropriate use of antibiotics in both human and veterinary fields and proper management and disposal of antibiotics and contaminated materials.

The main innovations of the new Plan include greater integration between the human, veterinary and environmental sectors to implement the One Health approach more fully; strengthening and extending surveillance; increased attention to healthcare-associated infections and prevention, taking into account the initiatives already in place (e.g. vaccinations and National Plan for Vaccine Prevention); the development of new tools to support the prudent use of antibiotics both in the human and veterinary fields, and a greater focus on bioethical aspects, transparency and communication to foster the active participation of citizens.

Law No 118/2022 (Annual Market and Competition Act 2021)

The Market and Competition Act 2021 (Law No 118 of 5 August 2022) provided that manufacturers of generic medicines may submit to AIFA a marketing authorisation (MA) application, as well as a request for price and reimbursement before the expiry of the patent or supplementary protection certificate. These medicines may be reimbursed by the NHS from the expiry date of the patent or the supplementary protection certificate of the active ingredient, published by the Ministry of Enterprises and the Made in Italy, in accordance with the current legislation.
For medicines classified as C-NN, the possibility that the concerned company does not submit the application for the purposes of obtaining a different classification is eliminated. In addition, for orphan medicinal products or other medicinal products of exceptional therapeutic and social importance, it is established that, in case of non-submission within thirty days of granting the MA, AIFA shall urge the company to submit the request for price and reimbursement within the next thirty days. Once this term has expired, information is given on the AIFA's institutional website and the lowest price is applied within the fourth level of the Anatomic Therapeutic Chemical classification system (ATC) to which the medicine belongs. As regards the distribution of medicinal products, the holder of a wholesale distribution authorisation shall be required to hold a stock of medicinal products with a marketing authorisation, including generics and homeopathic medicinal products, to meet the needs of the geographically determined territory to which the authorisation relates. These requirements shall be assessed by the competent authority granting the distribution authorisation, on the basis of binding guidelines provided by AIFA. The obligation does not apply to medicinal products not reimbursed by the NHS.

Decree of the Ministry of Health of 21 July 2022

An update of Decree dated 4 April 2013 for the automatic negotiation of generic and biosimilar medicines ("Brackets Decree") was issued, containing the new levels of expenditure and the corresponding updates of price reductions.

Such Decree effectively contributes to the reduction of all levels of public pharmaceutical expenditure and the updating of the decree has proven necessary for the purposes of automation, efficiency and simplification of negotiations.
In particular, compared to the previous version of the Decree, the first bracket (0-19.99) has been divided into two sub-levels, as it was the largest bracket both in terms of expenditure and in terms of the number of active ingredients negotiated from January 2018 to July 2020. The aim is to increase the negotiation of new active ingredients through the simplified procedure, while ensuring the arm's length principle.

Decree of the Ministry of Health of 22 September 2022

A Decree was issued defining the procedures for implementing the provisions of the 2022 Budget Law, i.e. the re-determination of the ceilings for direct purchases equal to 8% for 2022, 8.15% for 2023 and 8.30% from 2024. This applies exclusively to pharmaceutical companies that have fully paid the payback charge for 2019 and 2020, without reserve. The measure defines the compliant pharmaceutical companies and provides that a reduction in their respective share of the payback charge is applied to them, calculated as follows:

a) for 2022, by redefining the value of the company payback, adjusting it to the payback due in relation to the application of the 8% direct purchase ceiling;
b) for 2023, by redefining the value of the company payback, adjusting it to the payback due in relation to the application of the 8.15% direct purchase ceiling;
c) starting from 2024, by redefining the value of the company payback, adjusting it to the payback due in relation to the application of the 8.30% direct purchase ceiling.

2. Main context indicators of the Italian Health System

Table 2.1 shows the main context indicators for healthcare in Italy. With regard to hospital care, a reduction in the number of hospital discharges in the period 2016-2020 can be observed, going from 9 million in 2016 to 6.8 million in 2020, down 1.7 million in the period 2019/2020. At the same time, hospital days also increased from 61.2 million in 2016 to 49.6 million in 2020, with a 9.1 million day reduction in the period 2019/2020. In that regard, the reduction of more than 2,400 beds under ordinary admission in acutes, long-term care and rehabilitation in the period 2019-2020, as well as the reduction, in the same period, of more than 180 beds for day hospital stays should be highlighted in accordance with Ministerial Decree No 70 as amended.
The trend in average stays under long-term care and rehabilitation, after the 2017 reduction compared to 2016, tends to stabilise with a slight increase both in 2018 and 2019. However, the average stay under long-term care shows a limited increase in 2020 (from 24.50 days in 2019 to 24.60 days in 2020), the average stay for rehabilitation under ordinary scheme shows a more substantial increase (from 26.20 days in 2019 to 27.50 days in 2020). The average ordinary acute stay remained broadly stable in the period from 2016 to 2019, equal to around 7 days, up to 7.5 days in 2020. A steady increase in the average weight of Diagnosis Related Groups (DRGs) was recorded, from 1.19 in 2016 to 1.31 in 2020. The

average weight of DRGs is calculated as the ratio between the sum of the DRG points produced and the total number of discharges. This is a measure of the complexity of the cases treated.

With regard to the distribution of medicines, the number of Marketing Authorisation Holders (MAHs) increased from 817 in 2018 to 875 in 2022. Unlike 2020, in 2021 and 2022, an increase in the number of pharmacies is observed, from 18,871 units in 2020 to 20,233 units in 2021 and 21,500 units in 2022. In addition, an increase in businesses is recorded, from 6,383 units in 2020 to 6,901 units in 2021 and 6,977 units in 2022. A slight increase was recorded in medicines distributors, from 2,250 units in 2020 to 2,276 units in 2021 and 2,281 units in 2021.

Regarding community assistance, a reduction in the number of General Practitioners (GPs) has continued, from 44,279 units in 2016 (7.30 GPs every 10,000 inhabitants) to 41,707 units (6.99 GPs every 10,000 inhabitants) in 2020, to 40,250 units in 2021 (6.79 GPs every 10,000 inhabitants). A reduction by more than 2,100 units was observed in the three-year period 2019-2021, compared with a decrease by more than 4,000 units in the period 2016-2021, corresponding to an overall percentage reduction of about 9%.

The number of Free Choice Paediatricians also show a steady decrease, from 7,662 units in 2016 to 7,022 units in 2021 (a more than 380 unit reduction in the three-year period 2019-2021, and a more than 640 unit reduction in the period 2016-2021, corresponding to an overall percentage reduction of more than 8%).

Considering the incidence of Free Choice Paediatricians (referring to children aged <15 years – values for every 10,000 children) in the period 2016/2021, there is a progressive increase from 9.30 in 2016 to 9.43 in 2020 and a reduction of 9.20 in 2021.

Finally, as regards the number of local health authorities on the national territory, their number has remained substantially unchanged, amounting to 99 in 2020/2021 and increasing to 106 in 2022. This increase was determined by the territorial reorganisation carried out by the Region of Sardinia.

Table 2.1 Context indicators of healthcare in Italy

	2016	2017	2018	2019	2020	2021	2022
Total hospital discharges (1)	9,061,064	8,872,090	8,691,638	8,520,801	6,803,328		
Total days paid (1) (2)	61,236,601	59,955,328	59,533,633	58,799,017	49,618,858		
Beds in ordinary acute stay (3)	158,113	155,929	155,446	153,945	151,607		
Beds in ordinary long-term stay (3)	8,767	8,332	8,373	8,198	8,056		
Beds in ordinary rehabilitation stay (3)	24,674	24,487	24,632	24,867	24,851		
Beds in day hospital stay (3)	22,067	21,278	20,886	20,562	20,374		
Beds in ordinary stay for 1,000 inhabitants (3)	3.16	3.12	3.12	3.13	3.10		
Beds in day hospital stay for 1,000 inhabitants (3)	0.36	0.35	0.35	0.34	0.34		
Average ordinary rehabilitation stay (1)	25.80	25.50	26.10	26.20	27.50		
Average long-term stay (1)	27.60	24.10	24.20	24.50	24.60		
Relationship between Dh and OR days (acute) (1)	0.12	0.11	0.11	0.10	0.09		
Average ordinary acute stay (1)	6.90	6.90	7.00	7.00	7.5		
Average weight (1) (4) (5)	1.19	1.19	1.22	1.24	1.31		
Average no. of diagnosis for ordinary stay (1) (4)	2.50	2.80	2.50	2.50	2.60		
Average no. of procedures for ordinary stay (1) (4)	2.90	2.90	3.00	3.10	3.20		
No. of MAHs (6)			817	849	844	861	875
No. of Medicine Distributors (7)			2,273	2,327	2,250	2,276	2,281
No. of Pharmacies (7)			19,782	20,375	18,871	20,233	21,500
Pharmacies per 10,000 inhabitants			3	3	3	3	4
Inhabitants per pharmacy			3,058	2,962	3,160	2,928	2,743
No. of Shops (7)			6,438	6,644	6,383	6,901	6,977
Inhabitants per shop			9,395	9,085	9,344	8,584	8,454
Shops per 10,000 inhabitants			1	1	1	1	1
No. of GPs (8)	44,279	43,731	42,987	42,428	41,707	40,250	
No. of GPs per 10,000 inhabitants (8)	7.30	7.22	7.12	7.03	6.99	6.79	
No. of Free Choice Paediatricians (8)	7,662	7,590	7,499	7,408	7,285	7,022	
No. of Free Choice Paediatricians per 10,000 inhabitants (8)	9.30	9.33	9.35	9.41	9.43	9.20	
No. of Local Health Authorities (9)	121	101	101	101	99	99	106

(1) Ministry of Health - Annual Report on hospital admission activity - Ordinary stay data 2020 (page 75);
(2) Total of hospital admissions, including nursery;
(3) “Istituti di cura” (Healthcare Facilities) dataset on ISTAT website;
(4) Ordinary acute admissions;
(5) DRG relative weight pursuant to Ministerial Decree 1997 (up to 2005), Medicare 2002 (2006-2008), pursuant to MD 18/12/2008;
(6) Medicines Database, Italian Medicines Agency;
(7) Medicines manufacturing and distribution chain dataset, "Open data” section, Ministry of Health;
(8) "Assistenza sanitaria di base” (Primary Healthcare) dataset on ISTAT website;
(9) "Aziende Sanitarie Locali” (Local Health Authorities) dataset, Open data section, Ministry of Health.

3. Analysis of health expenditure in Italy and international comparison

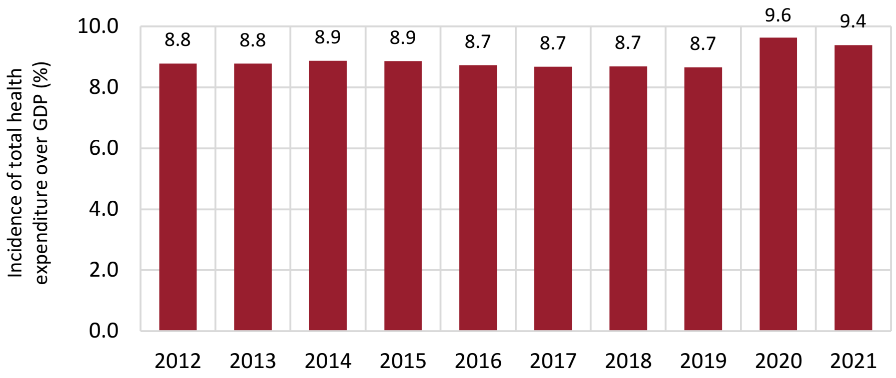
Table 3.1 presents Eurostat data on the development of total health expenditure and GDP in Italy in the years 2012 to 2021. Compared to 2012, 2013 shows a reduction in both GDP and expenditure. During the subsequent years, the total health expenditure shows an upward trend, but maintains a decreasing incidence compared to GDP over time, which is always above 8.6%. In 2020, the incidence of health expenditure over GDP reached 9.63%, equal to an increase of around one percentage point, mainly due to a 7.5% reduction in GDP and, to a greater extent, to the increase in expenditure (+2.6%). In 2021 this ratio stood at 9.4%, with an increase in expenditure equal to more than 5% and a GDP increase of 7.5% compared to 2020 (Table 3.1 and Figure 3.1).

Table 3.1 Impact of total health expenditure over GDP: 2012-2022 comparison

Years	Total health expenditure (EUR million)	GDP (EUR million)	% incidence
2012	142,676	1,624,359	8.78
2013	141,526	1,612,751	8.78
2014	144,317	1,627,406	8.87
2015	146,613	1,655,355	8.86
2016	147,963	1,695,787	8.73
2017	150,697	1,736,593	8.68
2018	153,790	1,771,391	8.68
2019	155,523	1,796,649	8.66
2020	159,628	1,661,020	9.63
2021	167,855	1,787,675	9.39
2022	na	1,909,154	--

Source: AIFA processing of Eurostat, OECD and ISTAT data

Figure 3.1 Percentage incidence of total health expenditure over GDP in Italy: 2012-2021 comparison



Source: Processing of Eurostat, OECD and ISTAT data

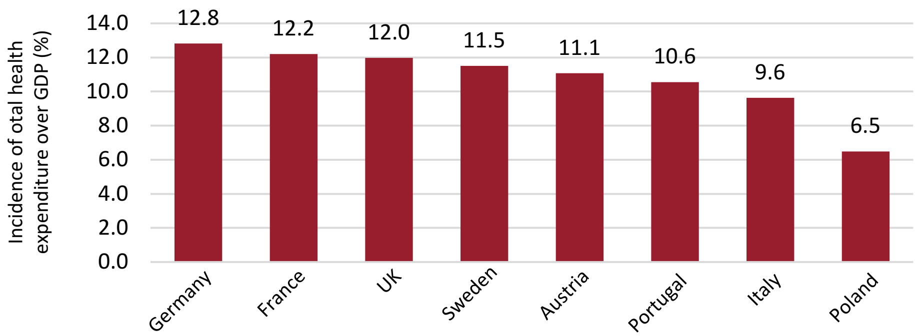
Using Eurostat data, a comparison was made of the incidence of total health expenditure over GDP in the main countries of the European Union and the United Kingdom (Table 3.2 and Figure 3.2). By analysing the data, the countries in question can be grouped into three main groups: the first consists of Germany and France, with an incidence of total health expenditure over GDP always above 11% as of 2014 and over 12% in the two-year period 2020/2021; the second consists of Austria and Sweden, with an incidence of total health expenditure over GDP between 10% and 11%, with Austria standing at 12.2% in 2021. Finally, the third group consists of Italy, Portugal and the United Kingdom with values ranging from 8% to 10%. The United Kingdom shows the highest values in each year; in 2020 the percentage is equal to 12%, while in 2021 it is slightly lower, equal to 11.9%. Among the countries considered, only Poland shows steady values over time, between 6% and 7%.

Table 3.2 International comparison in the incidence of total health expenditure over GDP: 2013-2021

	2013 %	2014 %	2015 %	2016 %	2017 %	2018 %	2019 %	2020 %	2021 %
Germany	11.0	11.0	11.2	11.2	11.3	11.5	11.7	12.8	12.8
France	11.4	11.5	11.4	11.5	11.4	11.2	11.1	12.2	12.4
Sweden	10.9	10.9	10.8	10.9	10.8	10.9	10.8	11.5	11.4
Austria	10.3	10.4	10.4	10.4	10.4	10.4	10.5	11.5	12.2
United Kingdom	9.8	9.8	9.8	9.7	9.6	9.7	9.9	12.0	11.9
Portugal	9.4	9.3	9.3	9.4	9.3	9.4	9.5	10.6	11.2
Italy	8.8	8.9	8.9	8.7	8.7	8.9	8.7	9.6	9.5
Poland	6.4	6.3	6.4	6.5	6.6	6.3	6.4	6.5	6.6
Belgium	10.6	10.6	10.8	10.8	10.8	10.8	10.7	11.1	na
Spain	9.1	9.1	9.1	9.0	9.0	9.0	9.1	10.7	na

Source: Processing of Eurostat data

Figure 3.2 International comparison of the incidence of total health expenditure over GDP in 2021

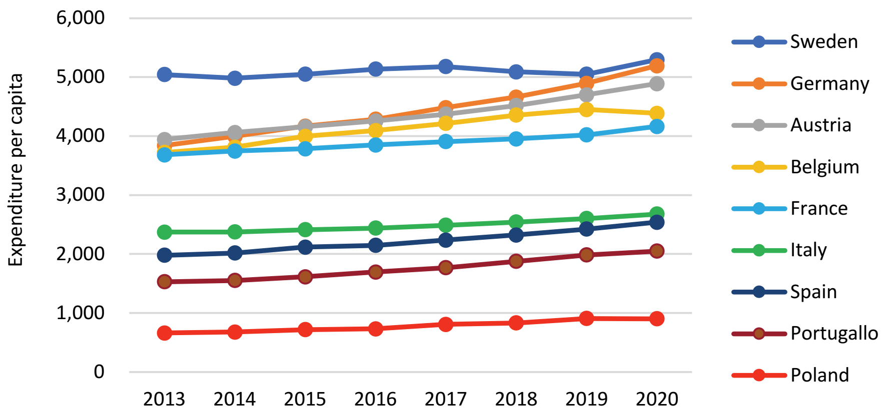


Source: Processing of Eurostat data

With regard to per capita health expenditure (Table 3.3 and Figure 3.3), countries can be grouped into three main groups. The first consists of Sweden and Germany, which show a per capita health expenditure of more than EUR 5,000 in 2020. The second group consists of Austria, Belgium and France, with an amount EUR 4,000 and EUR 5,000. The third group consists of Italy, Spain and Portugal, with a per capita expenditure between EUR 2,000 and EUR 3,000.
The comparison of the percentage change in per capita health expenditure between 2013 and 2020 shows the largest increase in Poland (+36%), followed by Germany (+35%) and Portugal (+34%), while expenditure remains broadly stable in Sweden (+5%). Italy shows a 12.9% increase, while the remaining countries register an increase in per capita expenditure between 13% (France) and 28% (Spain).
Looking at the 2019-2020 trend, the largest increases are observed in Germany, Sweden and Spain, while Belgium and Poland show slight reductions (-1.5% and -0.6%, respectively). Italy records a 2.9% increase, the lowest among the countries subject to comparison.

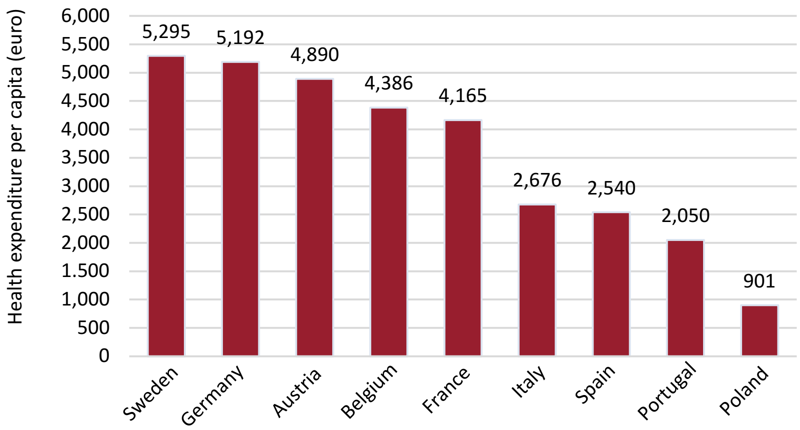
Table 3.3 International comparison – Trend in total per capita health expenditure (amounts in EUR) over the period 2013-2020 (Table and Figure)

	2013	2014	2015	2016	2017	2018	2019	2020	Δ% % 20-13	Δ% 20-19
Sweden	5,042	4,981	5,049	5,137	5,180	5,088	5,049	5,295	5.0	4.9
Germany	3,840	3,995	4,168	4,285	4,483	4,661	4,893	5,192	35.2	6.1
Austria	3,942	4,060	4,158	4,255	4,372	4,519	4,700	4,890	24.0	4.0
Belgium	3,721	3,812	3,995	4,092	4,215	4,354	4,452	4,386	17.9	-1.5
France	3,681	3,748	3,785	3,851	3,905	3,953	4,020	4,165	13.2	3.6
Italy	2,371	2,374	2,412	2,439	2,487	2,543	2,600	2,676	12.9	2.9
Spain	1,980	2,017	2,117	2,147	2,235	2,321	2,423	2,540	28.3	4.8
Portugal	1,529	1,551	1,614	1,694	1,769	1,877	1,985	2,050	34.1	3.3
Poland	661	676	718	731	808	830	906	901	36.2	-0.6



Source: AIFA processing of Eurostat data

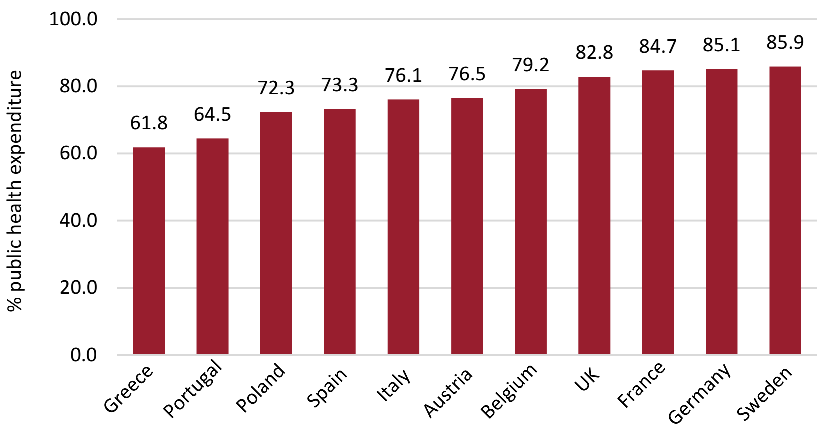
Figure 3.3 Total per capita health expenditure - 2020 (amounts in EUR)



Source: Processing of Eurostat data

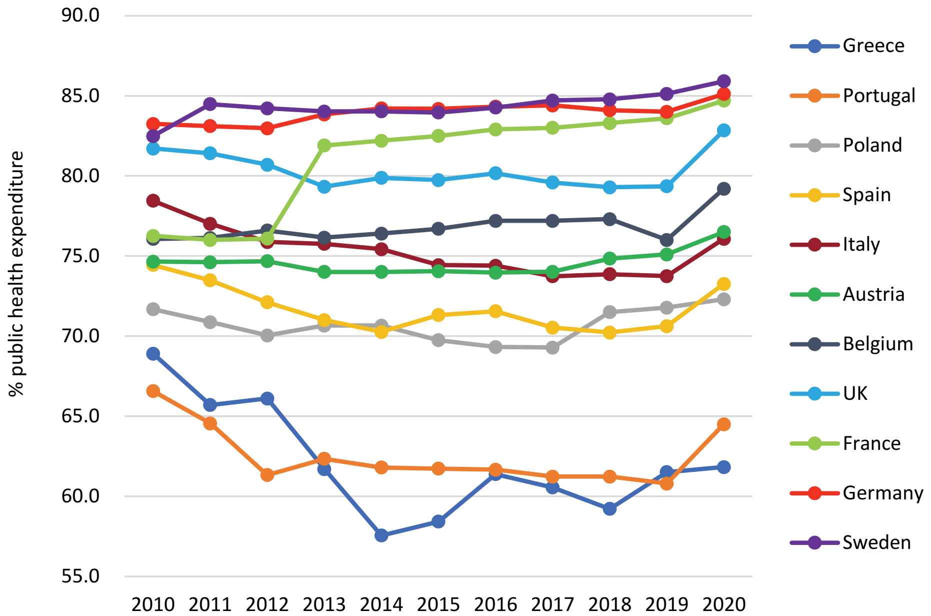
By analysing the incidence of public health expenditure, the countries with the largest share of public expenditure in 2020 were Sweden (85.9%) and Germany (85.1%). Conversely, countries showing the lowest incidence were Greece (61.8%) and Portugal (64.5%) (Figure 3.4). Looking at the trend over 2019 and 2020, it is observed that all countries show an increase in the incidence of government expenditure. In particular, Portugal, the United Kingdom and Belgium register an increase above three percentage points (Figure 3.5).

Figure 3.4 Impact of public health expenditure in 2020: international comparison



Source: Processing of Eurostat and OECD data

Figure 3.5 Time trend in the incidence of public health expenditure over the overall health expenditure in the period 2010-2020: international comparison



Source: Processing of OECD data

4. Medicines reimbursement and supply scheme

The reimbursement and supply scheme, as well as the price of the medicine, is the result of relatively complex and very differentiated decision-making processes between the different European and non-European countries. In the Italian context, these processes depend on AIFA and its advisory bodies. In Italy, the medicinal products in the National Medicines List reimbursed by the NHS are classified in Class A or Class H when they are dispensed by hospitals or similar facilities (Article 8(10)(a) of Law No 537 of 24 December 1993 as amended). Alternatively, medicinal products may be classified in Class C when they are not reimbursed by the NHS, with the exception of people entitled to a direct life war pension (Article 1 of Law No 203 of 19 July 2000) in cases where the general practitioner attests to their proven therapeutic usefulness for the patient.
Medicinal products reimbursed by the NHS include essential medicines intended for the treatment of chronic diseases, reimbursed for any authorised therapeutic indication, unless there is an AIFA Note that restricts reimbursement to only some of them. This is in order to ensure the appropriate use of the medicine in question, guiding, in some cases, the therapeutic choices in favour of more effective and tested molecules.

Consequently, Class A medicines, the therapeutic indications of which are not included in the Notes, are fully borne by the patient. Class C medicines are not considered essential medicines (compared with those reimbursed by the NHS) and can be dispensed to the citizen after the presentation of a medical prescription (C with prescription), or can be purchased directly from the citizen without a prescription.
The latter category includes both Class C-bis medicines (Article 8(10)(c-bis), Law No 537/1993 as amended), called over-the-counter (OTC) medicines, and Class C-without-prescription medicines, but that are not over the counter. By judgment No 2217 of 12 May 2017, the Italian Council of State (*Consiglio di Stato*) rejected the appeal brought by the Ministry of Health against the decision of the Lazio Regional Administrative Court No 7539/2016, confirming the full admissibility of advertising to the public of medicinal products without prescription not belonging to the category of self-medication medicinal products (OTC). By Ministerial Decree of 18 April 2012, implementing the provisions of Article 32(1) of Decree-Law No 201 of 6 December 2011, converted, with amendments, by Law No 214 of 22 December 2011, AIFA updated the supply scheme for Class C medicines with a prescription obligation, defining which medicines required the presentation of a medical prescription for being dispensed and which could be included in Class C without prescription, thus allowing them to be sold through the shops referred to in Article 32(1) of Decree-Law No 201/2011 (i.e. through large retailers and parapharmacies). Subsequently, Ministerial Decree of 18 April 2012 was updated, as it became necessary to supplement the list of medicines reclassified in Class C without prescription, on the basis of the prior opinion of the CTS (Ministerial Decree of 15 November 2012). This measure was further amended by the Decree dated 21 February 2014, thus amended by Decree dated 8 May 2014 (published in the Official Gazette No 119 of 24 May 2014).
In addition, Article 12(5) of Decree-Law No 158 of 13 September 2012, converted, with amendments, by Law No 189 of 8 November 2012 (‘Balduzzi Decree’) as amended, provided that medicinal products with a marketing authorisation granted under a centralised, decentralised, national and parallel import procedure are automatically classified in the new grouping ‘C - Non Negotiated’ (C-NN), pending submission by the MAH of a specific application for classification for the purposes of pricing and reimbursement. The MAH is required to notify AIFA, prior to marketing, the ex-factory price and the price to the public of the medicinal product classified in Class C-NN, as well as the date on which it was placed on the market. The Market and Competition Law of 2021 for classified medicines removed the possibility for the company concerned not to apply for a different classification of medicinal product.
In addition, for orphan medicinal products or other medicinal products of exceptional therapeutic and social importance, it is established that, in case of non-submission within thirty days of granting the MA, AIFA shall urge the company to submit the request for price and reimbursement within the next thirty days. Once this term has expired, information is given on the AIFA’s institutional website and the lowest price is applied within the fourth level of the Anatomic Therapeutic Chemical classification system (ATC) to which the medicine belongs.
When a pharmaceutical company submits the dossier to AIFA requesting pricing and reimbursement, AIFA competent offices and advisory bodies verify the regularity and completeness of the documentation and initiate the procedure aimed at assessing and deciding the place in therapy, as well as the reimbursement of the medicinal product. At the end of the decision-making process and the negotiation process by the Technical

Scientific Commission (CTS) and the Price and Reimbursement Committee (CPR), the decision authorising the reimbursement of the medicinal product, its supply scheme and the price borne by the NHS is ratified by the AIFA Management Board and sent to the Ministry of Justice for publication in the Official Gazette.
For the purposes of supply, within the meaning of Article 87 of Legislative Decree No 219 of 24 April 2006, as amended, medicines can be classified as follows:

a) medicines subject to medical prescription (RR)
b) medicines subject to medical prescription that can be renewed from time to time (RNR)
c) medicines subject to special medical prescription (RMS) (Consolidated Law on narcotics - Presidential Decree No 309 of 9 October 1990, as amended)
d) medicines subject to restricted medical prescription, including:
   - medicines that can be sold to the general public upon prescription by hospitals or specialists (RRL; RNRL)
   - medicines that can only be used in hospitals or in a similar environment (H);
   - medicines that can only be used by specialists identified in accordance with the provisions of the Regions or Autonomous Provinces (USPL);
e) medicines not subject to medical prescription, including:
   - over-the-counter medicines (OTC)
   - other medicines not subject to medical prescription.

The renewable prescription is the most common form of prescription. It is valid for six months and the patient is automatically authorised to present it at the pharmacy up to ten times within that period. A particular case is the prescription of psychotropic medicines (anxiolytics, sedatives, hypnotics), for which the prescription is valid for thirty days and can be renewed no more than three times.
The non-renewable prescription is necessary for all medicines with potential risks of acute or chronic toxicity, addiction and tolerance and potential for abuse by the patient. This tool is much more rigorous than the previous one, as is based on the inability of the patient to access the medicine without the intervention of the doctor, who issues the necessary prescription from time to time.
The validity of the prescription is fixed at 30 days for the number of packages indicated (otherwise it is valid for three months if it relates to galenic preparations not containing narcotic substances). A particular case is isotretinoin that can be prescribed and dispensed only within a teratogenic risk prevention program and upon presentation of a non-renewable prescription valid for seven days.
The restricted renewable and non-renewable prescriptions are tools that limit the prescription and use of certain types of medicines to certain specialists or in certain settings. These are:

- medicines that can only be used in hospitals (Article 92 of Legislative Decree No 219/2006);
- medicines that can be sold to the public upon prescription by hospitals or specialists (Article 93 of Legislative Decree No 219/2006);
- medicines that can only be used by specialists in an outpatient setting (USPL) (Article 94 of Legislative Decree No 219/2006).

Pharmacies are not allowed to sell medicines included in the USPL category to the public, but may have tem, which can also be supplied directly to the specialist by manufacturers and wholesalers.
AIFA Decision No 1522 of 13 January 2010, published in Ordinary Supplement No 21 of Official Gazette No 25 of 1 February 2010, updated the supply scheme of hospital medicines. In particular, the previous H1 and H2 classifications for supply purposes were abolished and new ones entered into force on 16 February 2010. Medicines previously classified under the H1 supply scheme were reclassified under the H scheme, without further changes to the already defined conditions and characteristics. Medicines previously classified as H2 had their supply scheme modified to RR, RNR, RRL or RNRL. Subsequently, in view of AIFA implementation of the provisions of Article 11(7)(a) of Decree-Law No 78 of 31 May 2010, converted, with amendments, by Law No 122 of 30 July 2010, as amended, most of Class H medicines with RR, RNR, RRL or RNRL supply scheme were reclassified into Class A-PHT (AIFA Decision of 2 November 2010).
In light of the national legislation regulating the reimbursement of medicinal products and their supply scheme, within the pharmaceutical assistance structure, it is possible to identify different methods for the supply of medicines reimbursed by the NHS, depending on their dispensing and use in both outpatient and inpatient settings. In particular, medicines in the outpatient setting are dispensed based on the prescription by general practitioners and free-choice paediatricians, as well as on the prescription or issuance of therapeutic plans by specialised doctors operating in public health facilities. While in the first case the prescribed medicine is dispensed to the patient by affiliated, public and private, pharmacies that can be found in the national territory (conventional dispensing scheme), in the second case the medicine taken by the patient at home is dispensed either directly by healthcare facilities (direct distribution) or, alternatively, by affiliated pharmacies as a result of specific agreements signed locally (distribution on behalf of the public health facility). Article 8 of Decree-Law No 347 of 18 September 2001, converted, with amendments, by Law No 405 of 16 November 2001, as amended, introduced the direct distribution and the on-behalf distribution as alternative methods for dispensing medicinal products, as opposed to the conventional dispensing scheme. These arrangements provide for the purchase by public facilities of high-consumption medicinal products and their dispensing through:

- direct distribution by public health facilities to the patient for the first course of therapy, following hospital discharge or after specialist outpatient visits, or to patients who need periodic controls. This dispensing scheme does not only contribute to limiting expenditure, but also helps ensuring the clinical safeguard of the patient and the therapeutic continuity from the inpatient to the outpatient setting, as well as the appropriate use of medicines;
- distribution on behalf of local health authorities, by pharmacies open to the public on the basis of specific agreements concluded by the Regions and Autonomous Provinces with the associations of the affiliated pharmacies, to allow patients suffering from chronic diseases and who, therefore, require continuous pharmaceutical assistance, to obtain supplies from local pharmacies.

Table 4.1 Number of medicines authorised and marketed in 2022 by reimbursement class

Class	MA number		Medicine		Active substances	
	No.	% over total	No.	% over total	No.	% over total
A	10716	52.7	4829	48.6	855	33.2
C	7571	37.2	4015	40.4	1180	45.8
H	2052	10.1	1092	11.0	541	21.0
Total	**20339**	**100.0**	**9936**	**100.0**	**2576**	**100.0**

5. Distribution margins and discounts for the NHS

The margins of pharmaceutical companies, wholesalers and pharmacies for medicines payable by the NHS are equal to 66.65%, 3.0% and 30.35% respectively, of the selling price to the public, excluding VAT (Law No 662 of 23 December 1996 as amended). At the same time, the NHS makes a deduction from the pharmacies quota equal to 1.82% of the price for the public exclusive of VAT (this quota does not apply to subsidised rural pharmacies in areas with resident population of less than 3000 inhabitants and with annual turnover not exceeding EUR 387,324.67 as well as to other pharmacies with an annual turnover not exceeding EUR 258,228.45). Pharmaceutical companies pay to the Regions an amount of 1.83% of the price for the public exclusive of VAT. The change in the margins of wholesalers and pharmacists, provided for in Article 11(6) of Decree-Law No 78/2010, converted with amendments by Law No 122/2010 as amended, also involves medicines with expired patent. In the case of generics, excluding medicines originally covered by a patent or which have been licensed under that patent, the share of the pharmaceutical companies remains equal to 58.65%, as provided for by Decree-Law No 39 of 28 April 2009, converted, with amendments, by Law No 77 of 24 June 2009, and the remaining 8% (66.65%) is redistributed among pharmacists and wholesalers in accordance with market rules.
Decree-Law No 95/2012, converted with amendments by Law No 135/2012 as amended, introduced some important provisions concerning the governance of pharmaceutical expenditure, including the increase in the discount for pharmacies from 1.82% to 2.25%, currently in force, and the temporary increase in the burden on pharmaceutical companies from 1.83% to 4.1% until 31 December 2012.
Table 5.1 shows the discounts paid by pharmacies in favour of the NHS, updated by Decree-Law No 148 of 16 October 2017, converted with amendments by Law No 172 of 4 December 2017 (Article 18-bis(2)). These changes have been applied as of 1 January 2018.
Decree-Law No 41 of 22 March 2021 introduced, for 2021 and 2022, an additional remuneration to pharmacies for the reimbursement of medicines dispensed by the NHS, in order to structurally strengthen the resilience, proximity and timeliness of the NHS response to emerging infectious diseases and other health emergencies, as well as the COVID-19 vaccination activity in pharmacies. The remuneration and its regional breakdown was recognised by Ministry of Health Decree dated 11 August 2021, adopted in agreement with the Ministry of Economy and Finance and published in the Official Gazette of 29 October 2021. A total of EUR 200 million was allocated, of which EUR 50 million from 1 September

to December 2021 and EUR 150 million for 2022. The 2023 Budget Law confirmed, as from 1 March 2023, the additional remuneration for pharmacies for the reimbursement of medicines dispensed by the NHS, up to EUR 150 million per year from 2023.

Table 5.1 Discounts to pharmacies on medicines dispensed by the NHS

Price range (EUR)	Rates for unsubsidised urban and rural pharmacies (%)			Rates for subsidised rural pharmacies (%)		
	NHS Turnover					
	greater than 300,000 (EUR)	less than EUR 300,000 and above EUR 150,000	less than EUR 150,000*	greater than 450,000	less than 450,000 and more than 150,000	less than 150,000*
0 to 25.82	3.75	1.50	Total exemption	3.75	fixed rate 1.5	Total exemption
from 25.83 to 51.65	6.0	2.40		6.0	fixed rate 1.5	
from 51.66 to 103.28	9.0	3.60		9.0	fixed rate 1.5	
from 103.29 to 154.94	12.50	5.0		12.50	fixed rate 1.5	
more than 154.94	19.0	7.60		19.0	fixed rate 1.5	
further deduction	2.25	-		2.25	-	

* Introduced by Law No 145 of 30 December 2018

6. Citizen cost-sharing

Law No 405/2001 as amended provided for the possibility for Regions to adopt resolutions to introduce/increase the cost shared by citizens, by introducing or modulating the cost per prescription or packs (the 'ticket'), in order to compensate for any deficits in regional pharmaceutical expenditure compared to the planned ceiling. This provision has been applied primarily in Regions subject to a repayment plan and to date in almost all other regions. However, the citizen's share in the pharmaceutical expenditure does not derive exclusively from regional tickets, but also from the quota paid on expired patent medicines. Since 1 December 2001, medicinal products without patent coverage reimbursed by the NHS, including generics, have been grouped into AIFA Transparency Lists, currently drawn up on a monthly basis, in order to identify a single reference price for all interchangeable packages. The differential between the price of the prescribed medicine and the cheapest medicine with the same composition shall be borne by the patient. Specifically, if two medicines are available with the same active ingredient, route of administration, pharmaceutical form and dosage units, but with different prices, the NHS reimburses the medicine with the lowest reference price.
Since Article 7 of Law No 405/2001, as amended, defines the level of NHS reimbursement up to the lowest price of the corresponding product available in the normal regional distribution cycle, the possibility has been granted to fix reference prices by means of regional measures. That provision played an important role, in particular, in the early 2000s, when the availability of generic on the whole national territory, generally with the lowest

price to the public, could not be guaranteed. As a matter of fact, to date, in most Italian Regions the reference prices correspond to the prices published in the AIFA Transparency Lists. A detailed analysis of the citizen cost-sharing for the reference price of generic is provided in section 2.1. Although citizen cost-sharing, given by the difference between the price to the public of the prescribed medicine and the reference price in the AIFA Transparency Lists, is substantially homogeneous in the national territory, with the exception of some Regions, the procedures for imputing the regional ticket to the citizen are, on the other hand, very diverse (Table 6.1). This condition is expressly permitted by Article 4 of Law No 405/2001 as amended, which empowers Regions to apply measures to cover possible management deficits through the introduction of various initiatives, including *the introduction of forms of accountability of the main actors contributing to the determination of expenditure (so-called 'tickets')*. That option has become a legal obligation for regional governments by virtue of Article 5(4) of Decree-Law No 159 of 1 October 2007, converted, with amendments, into Law No 222 of 29 November 2007, which expressly provided for the adoption of measures to contain expenditure, including direct distribution, for an amount equal to at least 30% of the regional pharmaceutical expenditure deficit in relation to the ceiling. These measures constitute a regional fulfilment for accessing supplementary State financing.

Three Regions did not implement a ticket in 2022 (Friuli Venezia Giulia, Marche and Sardinia).

At national level, the citizen share in the expenditure amounts to EUR 1.50 billion (of which 72.2% is attributable to the share of the reference price and the remaining 27.8% to the fixed ticket), representing 15.2% of gross reimbursed pharmaceutical expenditure and with a slight change of 1.36% compared to 2021. Concerning the citizen cost-sharing over the reference price, there is a marked variability at regional level: while the national value is equal to EUR 18.4 per capita (EUR 23.2 in the South and Islands, EUR 20.3 in the Centre and EUR 14.2 in the North), Calabria shows a value of EUR 25.6 per capita, which is more than double compared with the Autonomous Province of Bolzano (average of EUR 12.0 per capita Table 2.1.5).

Table 6.1 shows the main measures related to the ticket in the Italian Regions in 2022, with the aim of providing a summary as comprehensive as possible (Source: Federfarma, https://www.federfarma.it/Ticket-Regionali.aspx), without prejudice to the exemptions provided for by current legislation (exemptions for income, chronic diseases, rare diseases, disability and situations of particular social interest – Table 4.2 – which summarises the information published on the website of the Ministry of Health).

Table 6.1 Application of regional tickets in 2022

Region	Exemption		Ticket (EUR)			Transparency lists *	Notes	Legal basis
	Income (EUR)	Condition	Pack	Max prescription	Share on prescription			
Valle d'Aosta	0-9,999	yes	no	no	no	yes	Patients with chronic and debilitating diseases are exempt from payment	DGR No 1899 of 28/12/2017
	10,000-25,000	no	1	2	no			
	> 25,000	no	2	4	no			
Piedmont	N/A	yes	no	no	no	yes	Subject with exemption codes E92, G01 G02, V01, V01.2 are excluded from payment of difference between the public price and the reference price for medicines in the Transparency List	DGR No 57-5740 of 3/4/2002 DGR No 36-7965 of 28/12/2007 DGR No 16-3096 of 12/11/2011 DGR No 39-8425 of 15/2/2019
		no	no	no	no			
Lombardy	> 20,000	no	2	4	no	yes + ticket		DGR No 4230 of 25/10/2012
		yes	1	3	no	yes	Chronic diseases and rare diseases; certain types of invalidity limited to single-dose antibiotics, IFN for hepatitis, medicines administered via drip (L.405/2001)	
	Up to 20,000	no	no	no	no	yes		
AP of Bolzano	N/A	yes	no	no	1	yes + ticket	Chronic diseases Rare diseases, people with incapacity for work, civilian disabled, deaf people, victims of terrorism	DGR No 1862 of 27/05/2002
		no	1	2	no		Fiscally dependent children	
		no	2	4	no			

Region	Exemption		Ticket (EUR)			Transparency lists *	Notes	Legal basis
	Income (EUR)	Condition	Pack	Max prescription	Share on prescription			
AP of Trento	N/A	no	no	no	no	yes	No cost sharing	Provincial Law 14 of 23/12/2019
Veneto	> 12,000	no	2	4	no	yes + ticket		DGR 744 of 11/03/2005
	Up to 12,000	yes	no	no	no	yes	Pain Therapy, severe invalidity, chronic diseases, rare diseases	
Friuli V.G	N/A	no	no	no	no	yes	No cost sharing	
Liguria	N/A	no	2	4	no	yes + ticket	Also for single-dose antibiotics and medicines administered via drip	DGR No 163 of 20/2/2002 DGR No 1116 of 9/9/2011
		yes	no	no	no	yes	The victims of terrorism and people with disability by war are exempt from the cost sharing	
Tuscany	N/A	no	no	no	no	yes	No cost sharing	DGR No 1134 of 3/8/2020
Emilia-Romagna	N/A	no	no	no	no	yes	No cost sharing	DGR No 1044 of 24/8/2020
Umbria	N/A	no	no	no	no	yes	No cost sharing	DGR No 682 of 30/7/2020
Marche	N/A	no	no	no	no	yes	No cost sharing	
Lazio	N/A	yes	2	no	no	yes	Medicines with sale price >EUR 5, not included in AIFA Transparency List	DCA 45 of 17/11/2008
		no	4	no	no			
		yes	1	no	no		Medicines with sale price ≤EUR 5, not included in the AIFA Transparency List	
		no	2.5	no	no			
Abruzzo	N/A	no	2	6	no	yes + ticket	Medicines with sale price >EUR 5	DCA 26 of 4/7/2012
		yes	1	3	no			
		no	0.5	1.5	no		Medicines with sale price ≤EUR 5 and medicines not covered by patent with a price to the public higher than the referencenprice	
		yes	0.2	0.75	no			
		no	no	no	no	yes	Chronic and debilitating diseases Medicines not covered by a patentnwith a price to the public aligned with the reference price	

Region	Exemption		Ticket (EUR)			Transparency lists *	Notes	Legal basis
	Income (EUR)	Condition	Pack	Max prescription	Share on prescription			
Molise	N/A	no	2	6	0.5	yes + ticket	Medicines covered by patent with a sale price >EUR 5	DGR 1188 of 29/7/2002 DD.CC.AA 87 and 97/2011 Circular 4702 of 3/4/2012
			0.5	no			Expired patent medicines with a sale price >EUR 5	
			no	no		yes	Pain therapy	
Campania	N/A	no	1.5	no	2	yes + ticket	The ticket per package does not apply to medicines not covered by a patent with a price aligned with the regional reference price. The quota per prescription does not apply to oxygen prescriptions and PHT medicines	DCA 67 of 4/11/10, DC 141 of 31/10/2014, DC 147 of 24/12/2014, DC 34 of 13/3/2015
			no	no	2	yes	Medicines not covered by a patent with a price aligned with the reference price	
		yes	no	no	1	yes	Disability and chronic and debilitating diseases with income less than EUR 50,000	
Puglia	>23,000	no	2	5.5	1	yes + ticket		DGR 1718 of 19/11/2004 DGR 1198 of 6/8/2005 DGR 2789 of 14/12/2010 DGR 1389 of 21/6/2011, DGR 1391 of 21/6/2011
		yes	0.5	no	1		Single-dose antibiotics, IFN for hepatitis, medicines administered via drip (L.405/2001)	
		no	no	no	1		Medicines included in the Transparency List	
		no	no	no	1		Disability, pain therapy, victims of terrorism, chronic and debilitating diseases, rare diseases	
	<23,000	no	1	no	1	yes		
		no	no	no	no	yes	Minimum pensions	
Basilicata	N/A	no	no	no	no	yes	No cost sharing	DGR 496 of 17/7/2020
Calabria	N/A	no	2	5	1	yes		DGR No 247 of 5/5/2009
		yes	no	no	no	yes	Chronic diseases Rare diseases	
		yes	no	no	1	yes	People with incapacity for work, service and civilian disabled	

Region	Exemption		Ticket (EUR)			Transparency lists *	Notes	Legal basis
	Income (EUR)	Condition	Pack	Max prescription	Share on prescription			
		no	no	no	no	no	People with disability by war and victims of terrorism	
Sicily	N/A	no	4	no	no	yes	Medicines with sale price ≤EUR 25	Regional Law 6 of 10/1/2012
		yes	1.5					
		no	2				Generics with sale price ≤EUR 25	
		yes	1					
		no	4.5			yes	Medicines with sale price >EUR 25	
		yes	2					
		no	2.5				Generics with sale price >EUR 25	
		yes	1.5					
Sardinia	N/A	no	no	no	no	yes	No cost sharing	

* Difference between medicine price and reference price

Exemptions

(Source Ministry of Health, 2019; http://www.salute.gov.it/portale/esenzioni/homeEsenzioni.jsp)

Income exemptions

E01: Citizens under six years of age and over sixty-five years of age, belonging to a household with a total annual income not exceeding EUR 36,151.98.

E02: Unemployed and their dependent family members belonging to a household with a total annual income of less than EUR 8,263.31, increased to EUR 11,362.05 if there is a spouse and by additional EUR 516.46 for each dependent child.

E03: Holders of social pensions and their dependent family members.

E04: Holders of pensions aged over sixty and their dependent family members, belonging to a household with a total annual income of less than EUR 8,263.31, increased to EUR 11,362.05 if there is a spouse and by additional EUR 516.46 for each dependent child.

Chronic diseases

The list of chronic diseases exempt from cost sharing has been redefined and updated by Annex 8 to Decree of President of the Council of Ministers, of 12 January 2017, on the new Essential Service Levels.

Rare diseases

The list of rare diseases exempted from cost sharing has been extended by Annex 7 to Decree of President of the Council of Ministers of 12 January 2017 defining the new Essential Service Levels. The new exemptions for rare diseases entered into force on 15 September 2017, to give the Regions time to identify reference centres experienced in the treatment of new diseases.

Disability

Only people with disability by war, direct pensioners and victims of terrorism have the right to receive free of charge medicines belonging to class “C”, based on GP prescription attesting to their proven therapeutic usefulness.

Other exemptions for situations of particular social interest

Maternity protection, limited to the services defined by the Decree of the President of the Council of Ministers of 12 January 2017 (Annex 10).
Prevention of the spread of HIV infection, limited to the assessment of the state of infection, in favour of subjects belonging to categories at risk, with behaviour at risk or incidentally exposed to risk of infection.
Promotion of donations of blood, organs and tissues, limited to the services related to the donation activity.
Protection of persons damaged by irreversible complications due to mandatory vaccinations, transfusions and administration of blood products referred to in Law No 210 of 25 February 1992, limited to the services indicated therein.
Victims of terrorism and organised crime.

7. Price of medicines

Since 1 January 2004 the price of all medicines reimbursed by the NHS has been set following negotiation between AIFA and the manufacturers, based on methods and criteria that had been previously applied to centralised procedures.
In the context of the negotiations, the parameters set out in Ministerial Decree of 2 August 2019 (OJ General Series No 185 of 24-07-2020) are taken into account, according to which the following supporting documents should be included by the company in its request for negotiation:

- scientific documentation on the potential added therapeutic value of the medicine, in relation to the main treatments with which the product is compared;
- the economic assessment;
- documentation on marketing, consumption and reimbursement in other countries, and in that case, the relevant price and reimbursement conditions, including any further negotiation agreements;
- the annual market shares expected to be acquired over the next 36 months in the specific market segment;
- the certification by the company about its production capacity and management of possible unforeseen events that could put production standards at risk as well as the activities that will be put in place in order to ensure the adequate supply of the medicines to the NHS according to the needs of the population;
- the forecast and changes in expenditure for the NHS resulting from the proposed prices, in their separate components;
- self-certified quantification of any public contributions and incentives aimed at promoting research and development programmes;
- quantification of the economic and financial impact on the NHS and consumption resulting from the possible inclusion of the medicine in early access programmes.

The pricing and reimbursement process is characterised by four steps:

1. the pharmaceutical company submits the request for the price and reimbursement to AIFA;
2. the CTS assesses the dossier and gives a binding opinion on the therapeutic value of the medicine, defining its place in therapy, its supply regime and its possible innovativeness;
3. the CPR, taking into account the opinion expressed by the CTS, assesses the dossier and, where necessary, convenes the applicant for negotiation;
4. the result of the negotiation, in case of admission to reimbursement, is submitted to the final assessment of the Management Board of AIFA. The opinions of the CTS and the decisions of the CPR shall be delivered within a total of 180 days from the date of submission of a valid application, and the company's revenue price is published in the Official Gazette.

By way of derogation from those provisions, Decree-Law No 69 of 21 June 2013, converted, with amendments, by Law No 98 of 9 August 2013,amended Decree-Law No 158 of 13 September 2012, converted, with amendments, by Law No 189 of 8 November 2012, by introducing paragraph 5-bis, which provided that orphan medicines, hospital medicines or medicines of exceptional therapeutic and social importance should be assessed as a priority over the proceedings pending on the date of submission of the application, including through the establishment of extraordinary sessions of the CTS and CPR, within the period of 100 days (see also Section 5 Orphan medicines). Moreover, for these medicines, the current legislation provides for a further facilitation, i.e. the right for the company to submit to AIFA – in case of a positive opinion by the EMA – the application for price and reimbursement before the issue of their marketing authorisation by the European Commission.

With regard to Class A medicines dispensed through local pharmacies, under agreed disbursement arrangements, the price published in the Official Gazette is the same as the price to the public of the individual pack, including the quota borne by the citizen, any mandatory discounts payable by pharmacies and pharmaceutical companies and the value added tax. Consequently, the price charged to the NHS is the same as the public price net of both discounts and any quota borne by the citizen. The ex-factory price, excluding VAT, is also published in the Official Gazette.

For Class A and H medicines purchased by public health facilities, the price charged to the NHS is the same as the ex-factory price resulting from purchase tenders or determined as a result of direct negotiation by the health authority (or the Region) with the pharmaceutical company, including VAT.

In the case of Class C medicines, the price is determined independently by the pharmaceutical company. It is not published in the Official Gazette, but is communicated to AIFA. For Class C prescription medicines - with the exception of C-bis medicines - the price may be increased only in January of each odd year (Decree-Law No 87 of 27 May 2005, converted, with amendments, by Law No 149 of 26 July 2005), while reductions are always allowed.

Article 9-ter(11) of Decree-Law No 78 of 19 June 2015 (D-L. Local Authorities), converted with amendments by Law 125/2015, with regard to the definition of the price of medicinal products, supplemented Article 48 of Decree-Law No 269 of 30 September 2003, converted, with amendments, by Law No 326 of 24 November 2003 and subsequent amendments thereto. It introduced paragraph 33-bis, which provides that, upon expiry of the patent on the active substance of a biotechnological medicinal product and in the absence of a concomitant price negotiation procedure for a biosimilar or therapeutically equivalent medicinal product, AIFA shall initiate a new price negotiation procedure with the marketing authorisation holder of the same biotechnological medicinal product, in order to reduce the reimbursement price borne by the NHS. Paragraph 33-ter was also included, providing that, for medicines subject to AIFA Monitoring Registries, AIFA will start a new negotiation procedure with the marketing authorisation holder, in order to reduce the price in case the benefits found, two years after the granting of the MA, have been lower than those identified under the negotiation agreement.

8. AIFA Notes on the appropriate use of medicinal products

AIFA Notes define the therapeutic indications for which certain medicinal products are reimbursed by the NHS and represent the regulatory tool aimed at ensuring their appropriate use, guiding prescription by GPs based on the best evidence of efficacy found in literature. The Notes may be introduced if the medicine in question is authorised for several clinical indications, of which only some concern relevant diseases, or where the medicine is used to prevent a significant risk in one or more population groups, as well as where the medicine could be subject to any misuse with no proven efficacy or which may reduce its safety of use. The periodic review of the Notes also makes them more responsive to new scientific evidence and, above all, makes them flexible to the needs of daily medical practice on the national territory. Amendments are aimed at a simpler and more direct management of the patient by the GP, better correspondence between indications of proven effectiveness and those eligible for full reimbursement by the NHS, and prevention of misuse or significant risk only for one or more population groups.
During 2022, Note 100 concerning the prescription of certain classes of antidiabetic medicines was published and the following Notes were updated: Note 65 on the prescription of medicines for the treatment of multiple sclerosis, Note 95 on the prescription of topical medicines for actinic keratosis, as well as Note 99 on medicines used in inhaled COPD maintenance therapy.

Note 65

Note 65 states that the prescription of disease modifying medicines for Multiple Sclerosis (MS) reimbursed by the NHS is allowed only to doctors operating in specialised centres, universities and health authorities, in accordance with the provisions established by the Regions and Autonomous Provinces of Trento and Bolzano (Multiple Sclerosis Specialist Centres). Note 65 on MS medicines was introduced in 2007 and updated in 2018. The Note concerns first-line medicines in the treatment of MS (glatiramer acetate, interferon β-1a, interferon β-1b, teriflunomide, dimethylfumarate, peginterferon beta-1a) and refers to a paper prescription card for the use of so-called “second line” medicines or for severe rapidly evolving forms (alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, siponimod).
The latest update in Decision No 354/2018 of 2 March 2018 (DG Decision No 399/2022, published in Official Gazette, General Series, No 232 of 4 October 2022) updated the reference to the diagnostic criteria used for the diagnosis of multiple sclerosis, removing the restriction to the 2010 McDonald criteria and adding reference to the 2017 McDonald criteria. Concerning medicines indicated for relapsed or relapsed-remitting multiple sclerosis, so-called “second-line” therapy, currently included in the paper prescription form (natalizumab, fingolimod, alemtuzumab and cladribine, but also ocrelizumab, ozanimod, ofatumumab and ponesimod), the following changes have been introduced: reduction of treatment duration for the definition of failure of a first-line medicine to 6 to 12 months and simplification of NMR criteria (1 or more new lesions in T2-weighted sequences or 1 new gadolinium catching lesion). The change in the time criterion for the definition of therapeutic failure from 12 months to 6 to 12 months, may allow – if clinically necessary

and appropriate – to put forward the transition to a medicine with greater efficacy, although with a more complex safety profile.

Note 95

In 2022, Note 95 was updated twice. It was introduced with DG Decision No 1466/2016, concerning to the prescription of topical medicines for actinic keratosis reimbursed by the NHS. The first update (DG Decision No 384/2022, published in the Official Gazette, General Series, No 222 of 22 September 2022) concerned the inclusion in the Note of active substance tirbanibulin among the topical treatments for non-hypertrophic, non-hyperkeratotic actinic keratosis, reimbursed by the NHS. The second update (DG Decision No 528/2022, published in the Official Gazette, General Series, No 276 of 25 November 2022) relates to the eligibility criteria for treatment with the medicines included in the note, based on the severity of actinic keratosis assessed on the Olsen scale. In particular, it is established that treatment is reserved in the following cases:

1. Only for Olsen grade I/II lesions localised on the face and/or bold scalp in immunocompetent patients;
2. Visible or clinically palpable lesions on the face and bald scalp in immunocompetent patients when other topical treatment options are contraindicated or not appropriate;
3. Olsen grade I/II lesions localised on the face, ears and/or scalp;
4. Exclusively for Olsen grade I lesions on the face or scalp.

Note 99

By DG Decision 02/2022 of 10 January 2022 (published in Official Gazette, General Series, No 8 of 12 January 2022) the triple budesonide/glycopyrronium/formoterol combination was added in Note 99 (established by AIFA Decision No 965/2021 of 12 August 2021, published in Official Gazette No 207 of 30 August 2021 as amended). This combination is indicated for maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated with an inhaled corticosteroid combination and a long-acting beta2-agonist (LABA/ICS) or a combination of a long-acting beta2-agonist and a long-acting muscarinic receptor antagonist (LABA/LAMA). With two subsequent decisions (DG Decision 31/2022 of 28/01/2022, published in Official Gazette, General Series, No 30 of 05-02-2022 and DG Decision 92/2022 of 15/02/2022, published in Official Gazette, General Series, No 47 of 25-02-2022), Note 99 was further amended to transpose the authorised indication extension and reimbursement for the other two triple combinations (beclometasone/formoterol/glycopyrronium and fluticasone furoate/umeclidinium/vilanterol), that were indicated only in the maintenance therapy of adult patients who are not sufficiently controlled by the LABA/ICS combination. Now they are reimbursed also for adult patients not sufficiently controlled by the LABA/LAMA combination.

Note 100

Note 100, established by AIFA Decision No 19/2022 of 21 January 2022 (published in Official Gazette, General Series, No 19 of 25 January 2022) established the criteria for the prescription and reimbursement by the NHS of three classes of medicines for the treatment of adult patients with type 2 diabetes mellitus under inadequate glycaemic control (glycated hemoglobin – HbA1c – greater than 53 mmol/mol or 7.0%), i.e. SGLT2 inhibitors, GLP1 receptor agonists and DPP4 inhibitors. The main novelty introduced by Note 100 is the extension of the prescription of these medicines by GPs, with the aim of granting access to all patients, thus facilitating the integration of the treatment process between hospital and territory. Specifically, the Note provides for the prescription by GPs or NHS specialists authorised by the Regions of:

- SGLT2 inhibitors (SGLT2i) alone and in fixed or extemporaneous combination with other medicines, except for the combination with GLP1 receptor agonists or DPP4 inhibitors;
- GLP1 receptor agonists (GLP1-RA) alone and in fixed or extemporaneous combination with other medicines, except for the combination with SGLT2 inhibitors;
- DPP4 inhibitors (DPP4i) alone and in fixed or extemporaneous combination with other medicines, except for the combination with SGLT2 inhibitors.

The combinations, either fixed or extemporaneous, between medicines covered by the Note, i.e. SGLT2 inhibitors + DPP4 inhibitors and SGLT2 inhibitors + GLP1 receptor agonists (in combination with or as an alternative to other antidiabetic medicines) can be prescribed, and then reimbursed by the NHS, exclusively by specialists operating in structures identified by the Regions (diabetics centres), as part of a more complex assessment that will be carried out taking into account the characteristics of each individual patient and the general considerations set out in the Note.

The Note also provides indications on the preferential use of one or more classes of medicines under specific conditions such as established cardiovascular disease, high cardiovascular risk, heart failure and chronic kidney disease. For patients without these conditions, no indications are given to prefer a specific class of medicines over another, as insufficient evidence is available. In such patients, the therapeutic choice should therefore take into account other factors such as the individual characteristics of the subject, the tolerability profile of the medicine, the extent of HbA1c reduction to be achieved or the effect on the body weight.