National Report on Medicines use in Italy

Year 2021

THE MEDICINES UTILISATION MONITORING CENTRE

AIFA
AGENZIA ITALIANA DEL FARMACO

National Report on Medicines use in Italy Year 2021

December, 2022

Dear Readers,
this is an extract/adaptation of 2021 OsMed Report.
The original numeration of tables and figures was left unchanged in order to allow easy data consultation.

The English version of the document was edited by:
Mariarita Cafulli, Giuseppina Camposarcuno, Marco De Martino, Linda Pierattini, Marta Toma, Giorgia Viceconte.

Please quote the Report as follows:
The Medicines Utilisation Monitoring Centre. National Report on Medicines use in Italy. Year 2021. Rome: Italian Medicines Agency, 2022.

ISBN: 979-12-80335-26-5

The Report is available at the following website:
www.aifa.gov.it

Italian Medicines Agency (AIFA)
Director General: *Nicola Magrini*

Working group:
Coordination:
Agnese Cangini, Filomena Fortinguerra, Andrea Pierantozzi
Francesco Trotta, Giuseppe Traversa - Italian Medicines Agency (AIFA), Rome
Roberto Da Cas - National Institute of Health (ISS)

Italian Medicines Agency (AIFA)
HTA & Pharmaceutical Economy Division:
Eva Alessi, Domenico Caiazza, Antonietta Colatrella, Eleonora Capannini, Antonio La Greca,
Annalisa Milano, Luciana Mucci, Giovanni Polimeni
Health Budget Monitoring and Regional Relations Office:
Agnese Cangini, Aurora Di Filippo, Vincenzo Drago, Filomena Fortinguerra, Francesca Gallinella,
Maria Alessandra Guerrizio, Mariarosaria Italiano, Marco Marinelli, Roberto Marini, Maria Lucia Marino,
Federica Milozzi, Serena Perna, Alessandro Petrella, Andrea Pierantozzi, Linda Pierattini, Emanuela Pieroni,
Matteo Sacconi, Daniela Settesoldi, Francesco Trotta, Simona Zito
Information Communication Technology (ICT) Department:
Andrea Fabrizi, Marco Fontanella, Maurizio Trapanese
Monitoring Registers Office:
Valeria Angelini, Giorgia Bartoccioni, Simone Celant, Pier Paolo Olimpieri, Daniele Ricagni,
Valentina Summa, Luca Tomassini, Pierluigi Russo
Press & Communication Office:
layout and graphic design: *Ivano Comessatti*
editing: *Filippo Pomponi*

National Institute of Health (ISS) - National Center for Drug Research and Evaluation
Roberto Da Cas, Ilaria Ippoliti, Paola Ruggeri

Ministry of Health – Directorate general of the Health care statistical and information system
Claudia Biffoli, Chiara Brutti

Ministry of Economy and Finance – Department of Treasury
Antonietta Cavallo, Sara Guerrini, Marco Martino

Italian National Agency for Regional Healthcare Services (AGENAS)
Marco Di Marco, Elisa Guidotti

Information Technology Company (SOGEI)
Silvio Andreoli, Stefania Chiapparino, Cinzia Frigulietti, Donato Sansone

For the analysis of the appropriateness of prescription:
Italian Society of General Medicine and Primary Care
Claudio Cricelli, Alessandro Rossi, Pierangelo Lora Aprile, Gerardo Medea, Ignazio Grattagliano, Raffaella Michieli,
Francesco Paolo Lombardo, Damiano Parretti, Francesco Lapi, Ettore Marconi, Iacopo Cricelli

For the review of therapeutic categories:
Emilio Maestri (AUSL Reggio Emilia), Pier Mannuccio Mannucci (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano), Alessandro Perrella (P.O. Domenico Cotugno - Ospedali Dei Colli Di Napoli), Francesco Perrone (Istituto Nazionale Tumori di Napoli), Nicola Vanacore (ISS), Giampiero Mazzaglia (Università di Milano Bicocca)

Acknowledgments
Special thanks go to:
Federfarma and Assofarm for providing data on reimbursed medicines subject to prescription;
Farmadati for its contribution to listing medical products;
Giovanni Affronti, Alice De Corato, Federica Cuppone, Cristiano Niccolini, Imma Pagano,
Arianna Pasquazi, Sandra Petraglia - Pre-Authorization Department (AIFA)
for data on access to drugs for rare diseases under Law 648 and Ministerial Decree Sept. 7, 2017

Filena Fortinguerra, Infinite

Introduction

National Report
on Medicines
use in Italy
Year 2021

The Medicines Utilisation Monitoring Centre (OsMed) publishes the *22nd National Report on Medicines Use in Italy (Year 2021)* with an increasingly complete and critical description of pharmaceutical care, a crucial point for the protection of health, engaging, for the public component, a share of more than 17% of health expenditure, to which further 9 billion must be added for private expenditure, paid directly by citizens.

Overall, pharmaceutical expenditure in Italy is to be considered under control, since it is growing at a slower rate than the other components of health expenditure (personnel, hospital care, etc.), even though there are many areas for improvement for prescription based on the best scientific evidence and more consistent throughout the country. However, it should be kept into account that there is a sharp increase in expenditure for vaccines, antivirals, monoclonal antibodies for COVID-19 amounting to over 2.3 billion euros for 2021, necessary to cope with the recent and unexpected health emergency. The expenditure trend in recent years should therefore be seen as a virtuous result of AIFA, the National Health System (NHS) and the Regional Health Systems, having allowed full access to all innovative therapies relatively quickly; this sustainability has been achieved thanks to AIFA's ability to govern innovation, coupled with good negotiating and planning skills also at the regional level.

The new regulatory measures approved by Parliament for 2021 have led both to an increase in the resources available for pharmaceuticals thanks to the increase in the National Healthcare Fund (FSN), but also to a reshaping of the ceilings in favour of direct purchases (from 6.89% to 7.85%); this has led to a clear reduction in overspending to be refunded by Regions and pharmaceutical companies.

A special comment should be made on the new AIFA Notes, which have undergone a major change by becoming notes by pathology (vit.D, respiratory, intravitreal and diabetes) and no longer by single medicine, thus enhancing the ability to direct prescription according to the best scientific evidence.

A critical and cautionary note must be struck on private expenditure (borne by citizens), which has been progressively increasing over the last 10 years and will exceed 9 billion in 2021: this must be considered to all intents and purposes as a health expenditure that is sometimes improper and should be kept more under the magnifying glass of the actions of prescribing appropriateness and good use of medicines.

It was decided to keep the structure of the Report unchanged from the previous edition, which was already quite voluminous; this year's edition consists of 700 pages, making the OSMED report a volume "for reference" given the amount of data made available.

Greater emphasis has been placed on time trends, in order to capture changes in prescribing trends, to intercept changes in the population health, and to analyse the impact of regulatory actions such as on certain medicines for Covid-19, and the new AIFA Notes to improve prescribing appropriateness.

In the important chapter on international comparisons, Italian prices were compared with those of other European countries, not only for the year 2021, but over a broader period, from 2014 to 2021. Medicine prices were compared also based on the first launch date in Europe and by distinguishing between the market for off-patent medicines and the market for medicines with market exclusivity. The analysis of the time trend of prices in Italy was further deepened by including insights - under the approved care regime - of the effect on prices produced by the entry of new medicines in the transparency list and, in the area of direct purchases, by the entry of new medicines on the market. In the analysis of adherence to pharmacological treatment, the trend over the three-year period 2019-2021 has been assessed, also with the aim of verifying any changes that may have occurred in the pandemic period. In addition to prevalence, the incidence of the pathology has also been assessed, through the analysis of prescription by General Practitioners.

Finally, in the light of the importance of the new therapeutic entities, both in terms of expected benefit and in terms of expenditure governance, a specific section on the evolution of expenditure was introduced to assess and monitor the impact of the new molecules on NHS pharmaceutical expenditure, also for planning purposes.

Further investigations were carried out into the regional delivery methods of medicines, in particular, with regard to direct distribution and distribution "on behalf", which show considerable, perhaps excessive, variability between the different regions.

The Report, drawing on the various information flows and with its detailed analysis, sheds light on the information potential of our NHS, which can provide the necessary elements for implementing and evaluating policies aiming at the sustainability of pharmaceutical expenditure. What is needed, however, is a cultural change that may lead to – at least – a three-year planning (2022 - 2024) that defines system policy objectives within the overall sustainability of the NHS - of which AIFA is a part - and enhances the understanding of citizens and patients of how all the most costly innovative and chronic therapies are guaranteed in Italy universally (to all) and free of charge.

Nicola Magrini

AIFA Director General

Summary

National Report
on Medicines
use in Italy
Year 2021

This Report analyses pharmaceutical prescription data in Italy in 2021 by using the various information flows available, which allow to obtain a comprehensive picture of pharmaceutical care in the local and hospital settings, both when costs are borne by the National Health Service (NHS) and when they are borne by the citizen through private purchases.
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, 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.
Finally, 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.

Section 1. General characteristics of medicines use in Italy

In 2021 the **overall pharmaceutical expenditure** (public and private) amounted to 32.2 billion euros, increasing by 3.5% compared to 2020. It represents an important component of the national health expenditure, accounting for 1.9% of gross domestic product (GDP). **Public expenditure**, worth 22.3 billion euros, accounts for 69.2% of total pharmaceutical expenditure and 17.4% of public health expenditure and has slightly increased compared to 2020 (+2.6%) (**Table 1.1.1**).
In 2021 the **overall local pharmaceutical expenditure**, both public and private, amounted to 21.2 billion euros, increasing by 3.2% over the previous year. Stability of public local expenditure and an increase in private local expenditure can be observed.
Public local expenditure, including expenditure on Class A medicines provided under approved care regime and direct and "on behalf" distribution, was equal to 12.0 billion euros, stable compared to 2020. This trend was mainly driven by stability of the expenditure under approved care regime (-0.4%), reduction in expenditure for pharmaceuticals in direct distribution (-1.1%) and the increase of expenditure for pharmaceuticals in distribution "on behalf" (+7.9%) (**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 9.2 billion euros, increasing by 6.3% compared to 2020. Almost all components show a reduction compared to 2020, in particular expenditure for self-medication (+9.5%) and for medicinal products purchased in stores (+14.9%). Citizen cost-sharing remains almost stable (-0.4%),

given the reduction of the fixed co-payment (-2.7%), while the share exceeding the reference price is unchanged compared to the previous year (+0.4%).
In 2021, **17 packs** per citizen and **1133.2 doses** per 1,000 inhabitants were consumed every day under approved care regime, resuming, after the decrease observed in 2020, the upward trend of the pre-pandemic period (+3.2% compared with 2020; **Table 1.2.2**).
Within local care, both public and private, **about 1.8 billion packs were dispensed**, with a slight reduction compared to the previous year (-1.4%). It can be noted that the number of packages dispensed by direct distribution fell by 12.0%, while those dispensed “on behalf” increased (+7.1%). Packages of self-medication medicines also fell considerably (-13.4%), despite the increase in expenditure.

The **main components of the change in gross pharmaceutical expenditure** under approved care regime in 2021 (-0.5%) compared with the previous year show an increase in consumption (+2.2% in terms of doses), a slight reduction in average prices (-0.5%) and, finally, a shift in prescription towards less 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 (199.9 euros per capita), while the lowest value was found in the A.P. of Bolzano (113.4 euros per capita), with a 76% difference between the two regions (**Table 1.2.4**). As regards **consumption**, the region with the highest levels was Campania (1334.3 DDD/1000 inhabitants per day), while the lowest consumption was found in the A.P. of Bolzano (821.4 DDD/1000 inhabitants per day).
Expenditure on **medicines purchased by public health facilities** was around 13.8 billion euros (233.5 euros per capita), up from 2020 (+4.8%), while consumption was almost stable (-0.3%; **Table 1.3.1**).
Regions with the highest expenditure were Umbria (269.3 euros per capita), Campania (266.7 euros per capita) and Puglia (260.3 euros per capita). Conversely, Valle d’Aosta (175.9 euros per capita), Lombardy (195.7 euros per capita) and the A.P. of Trento (197.9 euros per capita) showed the lowest values. An increase in expenditure, compared to 2020, was recorded, with the exception of Tuscany and Basilicata, in all the Regions, with the greatest variations in Emilia Romagna (+11.7%) and Sicily (+9.7%).

In 2021, **slightly more than 6 out of 10 citizens received at least one medicine prescription**, with a difference between men and women of 58% and 67%, respectively (**Table 1.4.1 and Figure 1.4.1**). Per capita expenditure and consumption increase with age: specifically, the population over 64 years of age accounted for about 70% of expenditure and doses. Generally, Northern Regions have a lower prevalence (59.3%) compared to Central (64.7%) and Southern (66.7%) ones (**Table 1.4.2**).

In 2021, **over 3.3 million children and adolescents** (35.1% of the overall paediatric population) received at least one pharmaceutical prescription, with pre-school children (1-5 years of age) accounting for 53.8% (**Table 1.5.1** and **Figure 1.5.2**). Compared to the year 2020, there is an increase in packages per capita in both males and females, and it is noticeable that the increase is concentrated in children in the first 5 years of life, while consumption in school-age children and adolescents is reduced (**Table 1.5.2**). **Anti-infectives for systemic use** continue to be the most consumed medicines, followed by medicines for the respiratory system. However, for the former a reduction in consumption continues to be observed (-4.2%) compared with the previous year, while for medicines for the respiratory system there is an increase in consumption (+12.9%). Central nervous system medicines rank fourth among the most prescribed medicines, accounting for 10.7% of the total consumption, confirming the growing trend of the packages dispensed (+5.9% compared to 2020; **Figure 1.5.3** and **Table 1.5.3**)

In the **elderly population**, the average expenditure per user was equal to 557.6 euros (599.4 euros for men and 525.1 euros for women) and almost all the geriatric population (97.1%) 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. In addition, each user took 7.4 different substances, with the lowest rate (5.8 substances per user) recorded in the 65-69 age group, and the highest rate (8.4 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. During 2021, 66.6% of users aged ≥65 years received prescriptions for at least 5 different substances (i.e. polypharmacy) and approximately one person in four (26.8%) took at least 10 different active ingredients (**Figure 1.6.2**).

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. Class C medicines requiring a prescription show a decreasing trend in the period 2006-2017, while in the last 4 years (2018-2021) 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 shows a reduction in the average price per dose for class A medicines under approved care regime (**Figure 1.8.1**) and an increase in outpatient class C medicines requiring prescription (**Figure 1.8.4**). The in-depth analysis of the medicines dispensed under approved care regime that entered the transparency list after 1 January 2018, shows how the expiry of the patent and consequently the entry into the market of equivalent medicines is able to affect the reduction in prices (**Figure 1.8.3**); 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 ex-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 medicines 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). There is still a low incidence of expenditure on generic medicines (**Figure 1.9.7**) compared to other European countries, although Italy ranks second and first in the incidence of spending and consumption of biosimilars, respectively (**Figures 1.9.9 and 1.9.10**). Through the Herfindhal-Hirschman index, the penetration of biosimilars and the level of market concentration for single molecules were analysed. The price comparison shows that Italy has higher prices than France, Portugal and Poland only, for medicines dispensed in the local and hospital settings (**Figure 1.9.16**). Italy, with 31.2 euros per capita, ranks 6th for expenditure on orphan medicines, after Austria (43.4 euros), Germany (41.0 euros), France (40.3 euros), Spain (36.7 euros) and Great Britain (33.9 euros). After the decrease recorded in 2020, all countries show an increase in orphan medicines expenditure compared to the previous year (**Figure 1.9.13**).

Section 2. Detailed analysis of expenditure and consumption of medicines

In 2021, **off-patent medicines** accounted for 69.8% of expenditure and 86.0% of consumption of class A medicines under approved care regime. The percentage share of generic medicines, excluding those with patent coverage, accounted for 21.0% of expenditure and 29.6% of consumption. Citizen cost-sharing for the amount exceeding the reference price of off-patent medicines (hereinafter “cost-sharing”) was equal to 18.3 euros per capita (approximately 1.1 billion euros), representing 73% of the total citizen cost-sharing and showing a higher per capita value in the South and the Islands (€23.80) compared to the Centre (€20.20) and the North (€13.60) 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.

As regards **biosimilars**, an increase in the consumption of medicinal products that have been available for a long time and a positive trend for more recent ones (anti TNF-alpha, bevacizumab, rituximab, trastuzumab and teriparatide) are confirmed, although a certain regional variability in consumption and incidence of expenditure remains (**Table 2.1.11**).

Total expenditure on class C-NN medicines amounted to approximately €180 million, corresponding to a per capita expenditure of €3.04, which overall doubled 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 €10.03 (594 million euros), increasing by 8.5% compared to the previous year.

In 2021 expenditure for **medicines dispensed via direct (DD) and "on behalf" (DPC) distribution** equalled 8.7 billion euros (€147.2 per capita), with 74.7% attributable to direct distribution and 25.3% to "on behalf" distribution (**Table 2.3.1a**). As far as direct distribution is concerned, class H medicines account for the largest share of expenditure (67.4%), while in the distribution "on behalf" all expenditure is absorbed by class A medicines (**Tables 2.3.2 and 2.3.3**).

In 2021, the total per capita expenditure for **medicines distributed in hospital and local settings** amounted to 176.19 euros per capita (10.4 billion euros), increasing by 4.8% compared to 2020. Pembrolizumab is the main active ingredient dispensed in the hospital and ambulatory setting, followed by lenalidomide and daratumumab (**Tables 2.4.1 and 2.4.4**).

Expenditure for **class C medicines** equalled approximately 6.1 billion euros in 2021, showing an increase over 2020. 56.9% (3.5 billion euros) of this amount relates to prescription medicines, whereas 43.1% (2.6 billion euros) relates to self-medication medicines (OTC), including those sold in shops. 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,** cholecalciferol, pantoprazole and amoxicillin in combination with clavulanic acid ranked in the top three places in 2021, all showing an increase in expenditure of 8.0%, 9.3% and 13.3% respectively (**Table 2.6.7**).

Among **self-medication medicines**, propionic acid derivatives account for 10.2% of total expenditure and the active ingredients with the highest expenditure are diclofenac, ibuprofen and paracetamol (**Tables 2.6.3 and 2.6.4**).

Section 3. Consumption and expenditure by therapeutic category

In 2021, the **pharmaceutical expenditure borne by the NHS**, expressed as a per capita value, was 396.81 euros, increasing by 2.8% compared to the previous year (**Table 3.1**). This trend was mainly determined by the increase in expenditure for public health facilities (233.53 euros; +4.8%), while the expenditure for class A drugs under approved care regime remained almost stable (163.28 euros; +0.2%). Consumption remained at 1,306.8 DDD/1000 inhabitants per day, increasing by 2.8%, compared to 2020 (**Table 3.2**).

Cardiovascular medicines represent the therapeutic category with the highest expenditure (49.51 euros per capita) and consumption (486.9 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** (107.59 euros per capita) and consumption (50.6 DDD) among medicines **purchased directly by public health facilities**.

Under the approved care regime, the active ingredients with the highest incidence on expenditure are atorvastatin (273.7 million), pantoprazole (260.5 million) and colecalciferol (246.9 million); this latter, after the reduction in expenditure recorded in 2020, registered a slight increase over the previous year of 1.6% (**Table 3.11**).

The molecules with the highest variation in expenditure compared to the previous year are: dulaglutide, ezetimibe/rosuvastatin, and glycopyrronium/beclomethasone/formoterol. Under the approved care regime, colecalciferol, ramipril and atorvastatin are the most consumed active ingredients (**Tables 3.14 and 3.16**).

Taking into account **medicines purchased by public health facilities**, the active ingredients with the highest incidence on expenditure are cancer drugs, such as pembrolizumab (379.8 million euros), lenalidomide (323.9 million euros) and daratumumab (240.8 million euros). Dolutegravir/lamivudine for the treatment of HIV and the adjuvanted surface antigen inactivated virus influenza vaccine are the active ingredients with the greatest variation in expenditure compared to 2020 (**Tables 3.20 and 3.22**).

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 epidemiological classification, the time trend of consumption and expenditure, national and regional data. Where possible, indicators of exposure and adherence to pharmacological treatment in the population are analysed, together with prescribing profiles in the general practice.

The assessment of adherence and persistence indicators was carried out using the flow data of the Health Card (*Tessera sanitaria*) for the following categories of pharmaceuticals: antidiabetics, anticoagulants, platelet aggregation inhibitors, 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 (67.7%) followed, for the male population alone, by medicines for benign prostatic hypertrophy (62.8%) and finally by platelet aggregation inhibitors (59.7%). 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 (42.2%) and antidiabetics (28.9%).

As regards **persistence**, the therapeutic categories reaching the highest levels of persistence at 12 months are anticoagulants (63.1%), antihypertensives (52.3%) and platelet aggregation inhibitors (52.0%).

Finally, a description is given of the prescribing profiles and the results of a set of indicators for the evaluation of the prevalence and incidence of the main chronic diseases, as well as the appropriateness of use of the main categories of medicines prescribed by General Practitioners (GPs), such as medicines for the prevention of cardiovascular risk (e.g. antihypertensives and lipid-lowering agents), medicines for obstructive respiratory tract disorders, anti-acids/antisecretors/gastroprotectors, antidepressants, sedative-hypnotics and anxiolytics and medicines for the treatment of osteoporosis.

Section 4. Monitoring registries and conditional reimbursement agreements

As of 31 December 2021, **162 registries** were available **online** (intended as single IT entities active during 2021) (**Table 4.1.1**). Specifically, during 2021 24 new registries were released online, 13 registries were modified or merged into new registers, either by adding a new indication or by extending an indication already monitored, and 25 registries were closed.
In 2021, the ATC categories D “Dermatological medicines”, N “Central Nervous System” and R “Respiratory system” recorded a relative increase of more than 50% in terms of new patients, while category B "Blood and haematopoietic organs” - still including the therapeutic plans of the new oral anticoagulants - has the highest number of patients within the platform of the Monitoring Registries (**Table 4.1.2**).
An analysis is presented of treatments initiated with PCSK-9 inhibitors in the treatment of hypercholesterolaemia, as well as an analysis of treatments with anti-neovascularising medicines for intravitreal use and CAR-T-based cell therapy.
Finally, data on reimbursements paid by companies in 2021 - 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 344.4 million euros, with a financial impact of *Managed Entry Agreements* (MEAs) on the NHS expenditure of 1.4%.

Section 5. New therapeutic entities and orphan medicines

One of the important novelties of the OsMed 2021 Report is the analysis of **new therapeutic entities**, given their impact in terms of pharmaceutical expenditure and expected benefits. The new therapeutic entities were selected from class A and H medicines marketed in the period 2014-2021 and tracked in the OsMed and Medicine Traceability flows. In the period indicated, the new therapeutic entities increased from 210 to 274 (incident and prevalent); among these, incident entities in 2021, i.e. those marketed for the first time during the year, were 35 (**Table 5.1.1 and Table 5.1.2**) with an expenditure of €131.7 million. **Expenditure of new incident and prevalent therapeutic entities increased from about €5,371 million in 2014 to about €8,291 million in 2021**; the incidence of expenditure of new therapeutic entities on total NHS expenditure also increased over the years, from a share of 27% in 2014 to 35% in 2021 (**Table 5.1.2**). ATC L category 'Antineoplastic and immunomodulatory medicines' 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 2014-2021 (from €2,709 million to €4,922 million, increasing by 92%) (**Table 5.1.3**).

Orphan medicines are medicinal products used for the diagnosis, prevention and treatment of rare diseases. During 2021, the European Medicines Agency (EMA) granted the authorisation to a total of 13 new orphan medicines: of these, 11 have entered the price and reimbursement negotiation process and 2 are already on the market, including one in class C.

As of 31 December 2021, out of a total of 130 orphan medicines authorised by EMA, 122 were available in Italy. Of the remaining 8, 4 have been marketed as of 2022, 2 are undergoing a price and reimbursement procedure and 2 were not requested for price and reimbursement by their manufacturers (**Figure 5.2.2**).

The expenditure for orphan medicines, including purchase by public health facilities and the provision under the approved care regime, showed **in 2021 an increase of 9.4% compared to 2020, reaching a value of €1.53 billion**, corresponding to 6.4% of 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 (57.8% and 56.4%, respectively) (**Figure 5.2.3**).

Section 1

General characteristics of pharmaceutical use in Italy

1.1 General data on expenditure and consumption

In 2021 the overall pharmaceutical expenditure (both public and private) amounted to 32.2 billion euros, increasing by 3.5% compared to 2020. This expenditure is a significant component of healthcare expenditure, accounting for 1.9% of the national gross domestic product at current prices. Gross public pharmaceutical expenditure, equal to 22.3 billion euros, accounts for 69.2% of total pharmaceutical expenditure and for 17.4% of public healthcare expenditure, with a slight increase compared to 2020 (+2.6%); the largest share of expenditure was made by local health authorities, hospitals, healthcare residences and prisons (43.5% of public expenditure). The private pharmaceutical expenditure, including citizens' cost-sharing, amounts to 9.2 billion euros, and mainly concern class C prescription only medicines (POM) (37.6% of private expenditure). The increase in the total pharmaceutical expenditure compared to 2020 is mainly attributable to the trend of the expenditure on medicines provided by the local health authorities, hospitals, healthcare residences and prisons (+4.4%) and of class A medicines distributed "on behalf" (+7.9%), self-medication medicines (+9.5%), the private purchase of class A medicines (+7.6%) and extra DRG expenditure (+13.2%). Conversely, a slight decrease is observed in net expenditure under approved care regime (-0.4%), in directly distributed A class medicines (-1.1%) and fixed co-payment (ticket) (-2.7%) (Table 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 (OTC medicines), class A medicines purchased privately by citizens and Class C medicines requiring a medical prescription is lower compared to Northern Regions (Table 1.1.2).
Figure 1.1.1 shows that public territorial expenditure has been decreasing over the last five years (although during 2021 there has been a slight increase); conversely, expenditure related to hospitals and to class A medicines purchased privately by citizens is constantly growing.
Figure 1.1.2 shows the comparison between National Healthcare Fund, the current healthcare public expenditure, the public pharmaceutical expenditure, the pharmaceutical expenditure borne by the NHS calculated for the purposes of monitoring compliance with pharmaceutical ceilings (hereinafter: NHS pharmaceutical expenditure) and the planned funding for pharmaceutical care, corresponding to the sum of pharmaceutical expenditure caps as defined by laws and regulations (including funds for innovative medicines) over the period 2014-2021. To respond to the emergency situation arising from 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%. The inter-temporal comparison between the National Healthcare Fund (hereinafter: NHF) and healthcare expenditure shows that the largest differences between the two figures were found in 2020, when the NHF was lower by €3,148 million. In 2021, healthcare expenditure amounted to €127,834 million[1] and the expenditure component with the largest increase was

[1] Ministero dell'Economia e delle Finanze. Documento di Economia e Finanza 2022. https://www.mef.gov.it/documenti-pubblicazioni/doc-finanza-pubblica/index.html

intermediate consumption, at €43,146 million, up 10.1% compared to 2020. This increase is attributable, to a lesser extent, to expenditure for the purchase of pharmaceuticals.
By contrast, the remainder of intermediate consumption expenditure (+13.1%), and specifically the part necessary to combat the COVID-19 health emergency, accounted for most of the increase. As a matter of fact, if we look at NHS pharmaceutical expenditure, there is no major increase in 2020 compared to 2019 (+0.8%).
Comparing, on the other hand, the financing of pharmaceutical expenditure and NHS pharmaceutical expenditure, the largest difference can be found in the year 2016; then this difference fell sharply in 2017 and increased again in 2018, remaining stable in the following years. In 2021, an excess of NHS expenditure over funding of 6% was observed, also in comparison with the average of the period 2014-2021, equal to 8%. However, it should be pointed out that this figure could deviate from the value of the overrun, especially for direct purchases, given the presence of separate ceilings for 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 medicines and Class C-non-negotiated medicines purchased by public health facilities, foreign medicines, vaccines, galenic preparations, and extra DRGs). Public pharmaceutical expenditure in 2021 was €22.3 billion compared to €20.2 billion for NHS expenditure; both show a slight increase compared to 2020, by 2.4% and 2.6% respectively. The incidence of public expenditure over GDP is higher in Southern Regions (2.3%) compared to the Centre (1.4%) and the North (1.1%) of Italy, with a national percentage of 1.4%. The incidence of public pharmaceutical expenditure over GDP in Calabria (2.62%) is more than 3 times higher than in the Autonomous Province (A.P.) of Bolzano (0.71%) (Table 1.1.3). 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 1.1.3). Analysing, on the other hand, the correlation between regional *per capita* income and private *per capita* expenditure, no real correlation appears between the two variables. Furthermore, it can be seen that Campania, among the Regions with the lowest income, has the highest private expenditure, and, on the contrary, the P.A. of Bolzano, i.e. the one with the highest income, records the lowest expenditure after the P.A. of Trento (Figure 1.1.4).
As regards consumption, an upward trend can be observed for class A-NHS pharmaceuticals dispensed under the approved care regime until 2020, when a reduction in consumption was recorded (1,098.4 DDD/1000 inhabitants *die* in 2020 compared to 1,143.9 in 2019) probably to be attributed to the effect of the pandemic, while in 2021 an increase was observed that brought consumption levels back to pre-pandemic levels (1,133.2 DDD). Medicines purchased by public health facilities show an upward trend in consumption from 2006 to 2013 and become then stable. Regarding consumption of class C medicines with prescription, no significant changes were recorded in the period 2004-2020 (Figure 1.1.5). An increase by 8.1% over 2020 is recorded in 2021.

Table 1.1.1 Composition of pharmaceutical expenditure: 2021-2020 comparison (Table and Figure)

	Expenditure *(million)*	%°	%°°	Δ % 21-20
Net expenditure under approved care regime	7,582.9	23.5	34.0	-0.4
of which oxygen and vaccines	*82.0*			*2.5*
Class A medicines - direct distribution	2,180.6	6.8	9.8	-1.1
Class A medicines - "on behalf" distribution	2,218.0	6.9	10.0	7.9
Local health authorities, Hospitals, Healthcare residences and prisons*	9,690.1	30.1	43.5	4.4
of which oxygen and vaccines	*804.1*	-	-	*0.5*
Import	47.9	0.1	0.2	-19.3
Galenicals	42.4	0.1	0.2	1.5
Extra tariff	526.7	1.6	2.4	13.2
Public expenditure	**22,288.6**	**69.2**	**100.0**	**2.6**
Fixed co-payment (ticket)	398.4	1.2	4.3	-2.7
Reference price share	1,082.7	3.4	11.7	0.4
Class A medicines paid by citizens	1,643.8	5.1	17.8	7.6
C with prescription	3,466.4	10.8	37.6	6.0
SOP - OTC	2,336.9	7.3	25.4	9.5
Shops	286.9	0.9	3.1	14.9
Private expenditure	**9,215.1**	**28.6**	**100.0**	**6.3**
Discounts approved care regime	708.5	2.2	-	**-1.2**
Total	**32,212.3**	**100.0**		**3.5**

^ Including expenditure for class C reimbursed medicines (20.0 million euros)
* not including expenditure for class A medicines under direct and "on behalf" distribution
* calculated on overall expenditure
°° calculated on overall partial expenditure (public and private expenditure)
Note: Figures do not include expenditure values for the purchase by the commissioner of anti-covid vaccines amounting to €2,163.6 million and antivirals and monoclonal antibodies amounting to €147,3 million.

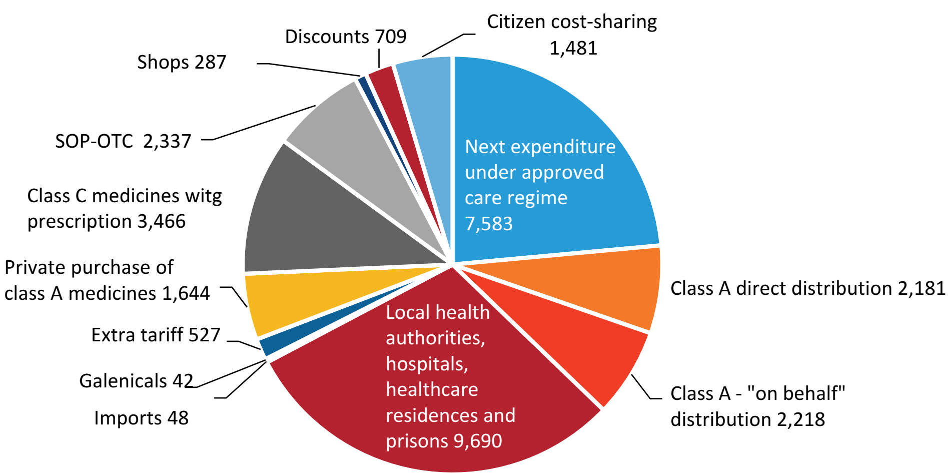
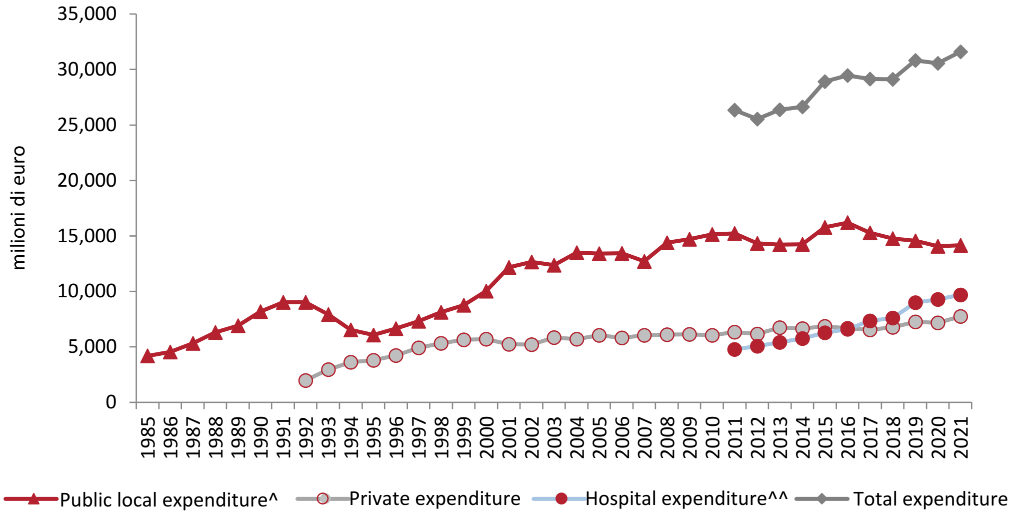


Table 1.1.2 Composition of total pharmaceutical expenditure in 2021 by Region

Region	Gross expenditure under approved care regime[1]		A Class private		C Class with prescription		Self-medication (public and private pharmacies)		Shops		Public health facilities		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°	%	€°
Piedmont	619	27.4	165	7.3	274	12.1	182	8.1	21	0.9	997	44.2	2,258
Valle d'Aosta	17	29.7	3	5.4	7	12.6	5	9.0	1	1.8	23	41.4	55.5
Lombardy	1,770	34.5	315	6.1	612	11.9	419	8.2	52	1.0	1,968	38.3	5,136
P.A. Bolzano	56	25.8	9	4.1	21	9.6	21	9.6	0	-	111	50.8	218.4
P.A. Trento	73	31.5	6	2.6	24	10.3	22	9.5	1	0.4	106	45.7	232
Veneto	645	27.7	121	5.2	252	10.8	202	8.7	19	0.8	1,092	46.9	2,331
Friuli VG	183	29.4	22	3.5	61	9.8	49	7.9	4	0.6	303	48.7	622
Liguria	240	26.4	62	6.8	117	12.9	80	8.8	9	1.0	401	44.1	909
Emilia R.	572	24.7	101	4.4	252	10.9	189	8.1	30	1.3	1,175	50.7	2,319
Tuscany	523	26.6	89	4.5	222	11.3	168	8.6	25	1.3	937	47.7	1,964
Umbria	148	30.0	15	3.0	49	9.9	32	6.5	4	0.8	246	49.8	494.4
Marche	245	29.1	40	4.8	85	10.1	60	7.1	7	0.8	404	48.1	840.6
Lazio	1,037	33.4	125	4.0	343	11.1	235	7.6	18	0.6	1,343	43.3	3,101
Abruzzo	236	33.0	21	2.9	64	9.0	45	6.3	6	0.8	342	47.9	713.8
Molise	50	32.9	5	3.3	15	9.9	9	5.9	1	0.7	72	47.4	151.9
Campania	1,060	31.6	193	5.8	425	12.7	229	6.8	32	1.0	1,415	42.2	3,354
Puglia	725	33.3	77	3.5	193	8.9	131	6.0	18	0.8	1,035	47.5	2,179
Basilicata	103	35.1	11	3.7	23	7.8	15	5.1	3	1.0	139	47.2	294.3
Calabria	350	34.0	39	3.8	99	9.6	57	5.5	9	0.9	475	46.2	1,029
Sicily	843	33.6	194	7.7	238	9.5	133	5.3	14	0.6	1,086	43.3	2,508
Sardinia	277	31.4	31	3.5	91	10.3	53	6.0	12	1.4	418	47.4	882.4
Italy	**9,772**	**30.9**	**1,644**	**5.2**	**3,466**	**11.0**	**2,337**	**7.4**	**287**	**0.9**	**14,089**	**44.6**	**31,595**
North	4,046	29.0	804	5.8	1,619	11.6	1,169	8.4	137	1.0	6,177	44.3	13,952
Centre	1,953	30.5	269	4.2	699	10.9	495	7.7	54	0.8	2,930	45.8	6400
South and Islands	3,773	33.6	571	5.1	1,148	10.2	673	6.0	95	0.8	4,982	44.3	11,242

[1] The expenditure refers to class A-NHS medicines and class C medicines (€20.0 million) reimbursed by the NHS
°Million euros
* Calculated on overall regional expenditure

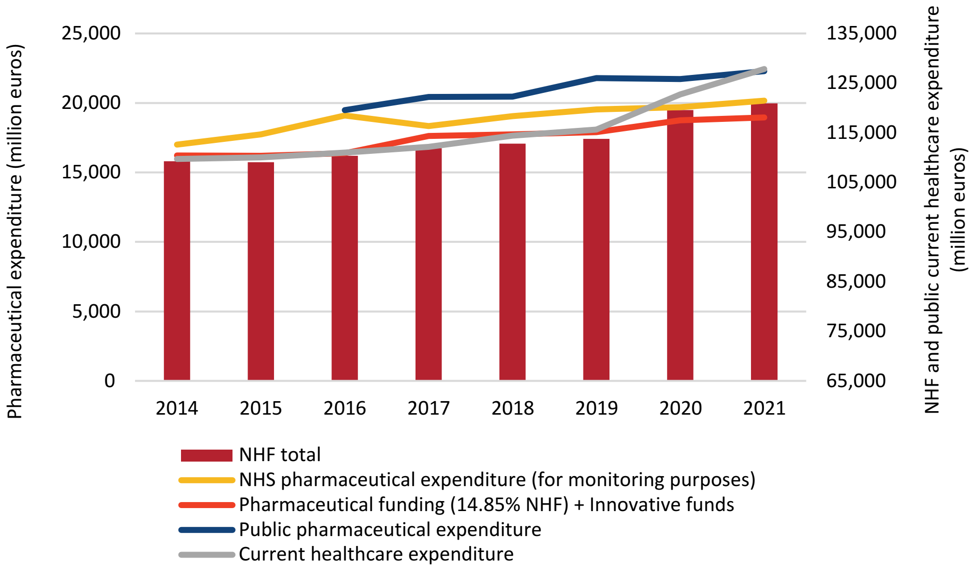
Figure 1.1.1 Pharmaceutical expenditure in the period 1985 - 2021 (Figure and Table)



Year	Gross expenditure under approved care regime	Direct and "on behalf" distribution Class A	Public^ local expenditure (1)	Private expenditure (2)	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	4,774	26,339
2012	11,488	2,837	14,325	6,152	5,055	25,532
2013	11,226	3,003	14,229	6,732	5,421	26,383
2014	10,988	3,250	14,238	6,648	5,744	26,630
2015	10,863	4,921	15,784	6,859	6,282	28,926
2016	10,638	5,556	16,194	6,681	6,587	29,461
2017	10,499	4,792	15,291	6,526	7,332	29,149
2018	10,141	4,620	14,761	6,771	7,594	29,126
2019	10,089	4,481	14,570	7,261	8,980	30,811
2020	9,820	4,259	14,080	7,180	9,284	30,544
2021	**9,772**	**4,399**	**14,171**	**7,734**	**9,690**	**31,595**

^ including the pharmaceutical expense under approved care regime (gross of pay-back and discount) and the direct and "on behalf" distribution of A Class-NHS medicines, including the share paid by citizens
^^ Expenditure by public health facilities (gross of *pay-back)* net of the direct and "on behalf" distribution of A Class-NHS medicines

Figure 1.1.2 Trend of National Healthcare Fund, health expenditure, financing of pharmaceutical expenditure and pharmaceutical expenditure borne by the NHS over the period 2014-2021



Source: For healthcare expenditure 2014-2017, AIFA processing on data from "MEF-Monitoraggio della spesa sanitaria- Rapporto N.8". For the years 2018-2021, the figure published in DEF 2022 was used.
NHS pharmaceutical expenditure for monitoring purposes includes:
- net expenditure under approved care regime, i.e. expenditure net of discounts paid by pharmacies, of the 1.83% payback paid to the regions, gross of regional co-payments;
- Expenditure for direct purchases of Class A and H medicines, net of vaccines and paybacks, including the expenditure for innovative medicines.

Public pharmaceutical expenditure includes net expenditure under approved care regime, purchases by public health facilities including oxygen and vaccines, class C and C-NN medicines, medicines imported from abroad, galenic preparations and extra DRG expenditure.

Table 1.1.3 Regional incidence of public pharmaceutical expenditure over GDP: period 2017- 2021

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

Figure 1.1.3 Relationship between *per capita* public pharmaceutical expenditure and *per capita* regional income in 2021

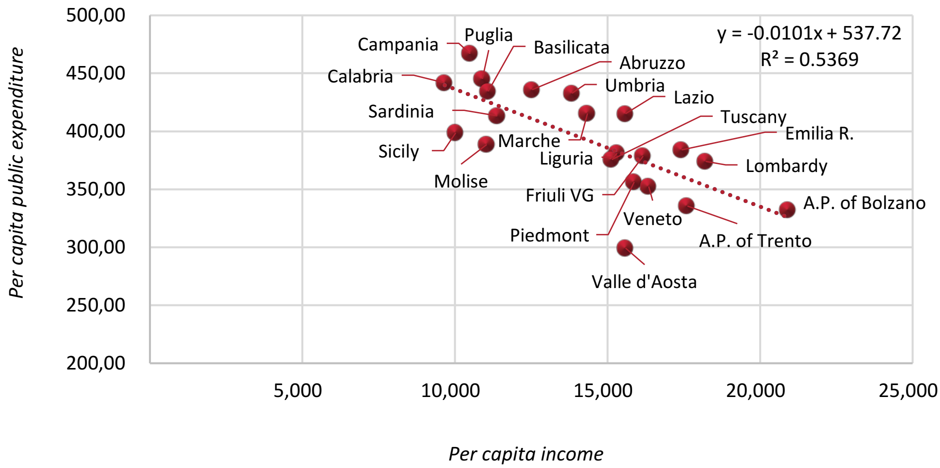


Figure 1.1.4 Relationship between *per capita* private pharmaceutical expenditure and *per capita* regional income in 2021

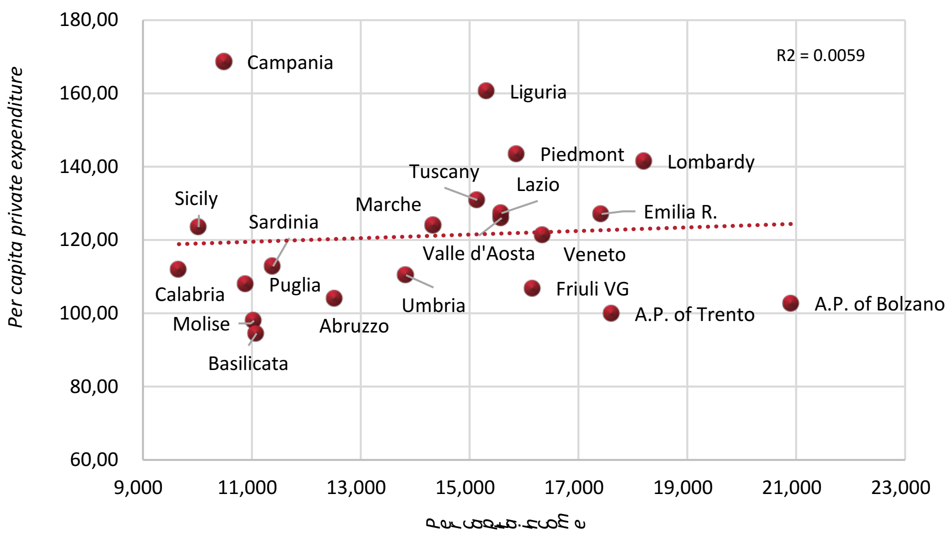
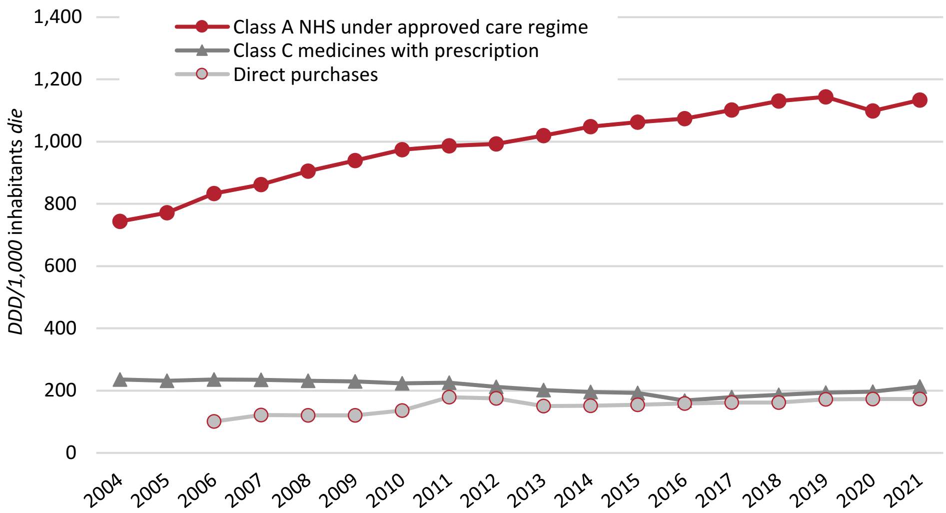


Figure 1.1.5 Consumption (DDD/1,000 inhabitants *die*) in the period 2004-2021 (Figure and Table)



Year	DDD/1,000 inhab. *die*		
	Class A-NHS medicines under approved care regime	Class C with prescription	Direct purchases
2004	743.6	235.9	
2005	771.9	231.7	
2006	833.0	235.4	100.6
2007	861.6	235.0	121.7
2008	904.9	231.9	120.4
2009	939.4	229.6	120.9
2010	973.9	223.8	136.5
2011	987.0	225.7	178.8
2012	992.3	212.2	175.1
2013	1019.2	202.4	150.9
2014	1047.9	195.8	151.2
2015	1062.4	193.0	154.3
2016	1074.3	168.2	159.1
2017	1101.6	178.8	162.1
2018	1130.8	186.0	161.5
2019	1143.9	193.2	171.8
2020	1098.4	196.7	173.1
2021	**1133.2**	**212.8**	**173.5**

1.2 Local pharmaceutical expenditure and consumption

In 2021 the overall local pharmaceutical expenditure, both public and private, amounted to €21,196 million, increasing by 3.2% compared to the previous year (Table 1.2.1). The NHS local pharmaceutical expenditure includes net expenditure for medicines supplied under the approved care regime (€7,583 million) as well as class A medicines supplied through direct (€2.181 million) and "on behalf" (€2.218 million) distribution channels (Table 1.2.1). Public local expenditure amounted to €11,981 million (€202.3 *per capita*) - compared to 2020, this latter shows a stable trend, with a slight reduction in expenditure for class A medicines supplied by direct distribution (-1.1%) and an increase in expenditure for class A medicines supplied "on behalf" (+7.9%). Net expenditure under the approved care regime remains stable (-0.4%).

In 2021 public local expenditure accounted for 56.5% of the total local pharmaceutical expenditure - this incidence in the last 5 years has shown a decreasing trend due, on one hand, to the reduction in public expenditure and, on the other, to the increase in private expenditure.

Citizens pharmaceutical expenditure (Table 1.2.1 and Figure 1.2.1), including citizen cost-sharing (regional tickets and difference between the off-patent price and the corresponding reference price), expenditure on privately purchased class A medicines and for class C medicines amounted to € 9,215 million euros, with an increase of 6.3% compared to 2020. This trend was influenced by the increase in private expenditure on class A medicines (+7.6%), the increase in expenditure on class C prescription-only medicines (+6.0%), OTC medicines (+9.5%) and medicines supplied in shops (+14.9%). Instead, a stable trend was recorded in expenditure for citizens' co-payment (-0.4%) with a value of €1,481 million (approximately €25.00 *per capita*) and an incidence on gross pharmaceutical expenditure under the approved care regime of 15.2%. Compared to 2020, expenditure change (-0.4%) was mainly determined by the reduction in expenditure for the per prescription/package citizen co-payment (-2.7%), while the co-payment for the share exceeding the reference price of off-patent medicines remains stable (+0.4%).

On the consumption side, stability in the number of packages supplied under approved care regime (+0.4%) was recorded (Table 1.2.2). During 2021, an average of 1,3332.1 daily doses per 1,000 inhabitants (hereinafter DDD) of NHS reimbursed class A medicines were consumed, with an increase of 3.2% compared to 2020 (in the previous year, 1098.4 DDD were recorded), corresponding to more than 1 billion packages supplied (17.4 packages per inhabitant). The average cost per day of therapy was €0.39 in 2021, decreasing by 2.6% compared to the previous year, and confirming the downward trend of the previous 4 years. With regard to the purchase of class C medicines, the number of packages of prescription-only medicines remains stable, while the number of packages of OTC medicines decreases sharply (-13.2%), against an increase in expenditure of 9.5% (Tables 1.2.1 and 1.2.2).

At national level, net expenditure amounted to €7,583 million (Table 1.2.3), with the highest values - in absolute terms - recorded in Lombardy (€1,367.9 million), Lazio (€795.0 million) and Campania (€778.0 million). The Regions with the highest expenditure in absolute terms for fixed co-payments (ticket) are Lombardy (€118.9 million), Campania (€72.1 million) and Veneto (€55.7 million). The greatest reductions with respect to the year 2020 were found in Tuscany (-97.8%), Basilicata (-97.1%), Umbria (-89.4%), and Emilia Romagna (-85.7%); these regions abolished the fixed co-payment (ticket) in 2020. With regard to citizen cost-sharing for the portion exceeding the reference price, Lazio (€ 141.6 million), Lombardy (€

137.3 million), Campania (€ 131.7 million) and Sicily (€ 111.8 million) show the highest expenditure in absolute terms. The largest reduction compared to 2020 was recorded in Molise (-2.3%), while the largest increase was observed in Basilicata (+3.2%).

The region with the highest *per capita* gross expenditure for A-NHS medicines was Campania with 199.9 euros *per capita*, while the lowest value was found in the A.P. of Bolzano (113.4 euros *per capita*), with a 76% difference between the two regions (Table 1.2.4). Regarding consumption, the region with the highest levels was again Campania with 1,334.3 DDD/1000 inhabitants per day, while the lowest consumption was found in the A.P. of Bolzano (821.4 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. At national level, citizen expenditure for self-medication pharmaceuticals, class C medicines with prescription and class A medicines amounted to €130.6 *per capita*. Some variability across Italian Regions emerges, with Campania registering the highest value with €168.7 *per capita* and Molise registering the minimum value with €96.4 (Table 1.2.4). Contrary to what was found for class A medicines reimbursed by the NHS, Northern Regions showed higher private expenditure than Central and Southern Regions.

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 the regions with the lowest consumption and average cost compared to the national average.

Gross expenditure in 2021 decreased slightly compared to the previous year - by 0.5% at national level. The greatest reductions were found in Molise (-2.9%) and Valle d'Aosta (-2.7%), while Emilia Romagna (+1.5%), Basilicata (+1.9%) and Campania (+0.4%) were the only Regions that presented increases 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 1.2.2 and Table 1.2.6) show, with respect to the previous year, an increase in the consumption of prescribed pharmaceuticals (+2.2% in terms of DDD), a slight reduction in average prices (-0.5%), linked in part to an increasing use of off-patent products, and finally an increase in the prescription of less expensive products (mix effect: -2.1%). Similar to 2020, also in 2021 the average DDD cost decreased by 2.6% due to the expiry of the patent for widely used molecules. Against these national average values, regional variability is very broad: change in prices compared to the previous year ranges between -4.1% in Valle d'Aosta and -0.6% in Campania; the mix effect varies between -2.3% in Campania and Piedmont and +1.7% in Valle d'Aosta. The change in consumption fluctuates between +5.2% in Basilicata and -0.3% in Valle d'Aosta, the only Region that recorded a reduction in consumption compared to 2020.

Table 1.2.7 shows data on class A local expenditure (approved care regime and direct and "on behalf" distribution) and private expenditure (A class, C class, self-medication). The A.P. of Bolzano has the lowest local public expenditure (€176.3 *per capita*), while Campania, Puglia and Basilicata are the regions with the highest local public expenditure (287.4, 279.9 and 272.8 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 (277.2 and 456.1 euros *per capita*, respectively) (Table and Figure 1.2.7).

Table 1.2.1 Public and private local pharmaceutical expenditure: comparison 2017-2021

		2017 *(million)*	2018 *(million)*	2019 *(million)*	2020 *(million)*	2021 *(million)*	Δ % 18-17	Δ % 19-18	Δ % 20-19	Δ % 21-20
1	**Gross expenditure under approved care regime**	**10,499**	**10,141**	**10,089**	**9,820**	**9,772**	**-3.4**	**-0.5**	**-2.7**	**-0.5**
2	Citizen cost-sharing	1,549	1,608	1,582	1,487	1,481	3.8	-1.6	-6.0	-0.4
3	Fixed co-payment (ticket)	499	482	459	409	398	-3.4	-4.7	-10.9	-2.7
4	Reference price share	1,050	1,126	1,123	1,078	1,083	7.2	-0.3	-4.0	0.4
5	Discount^	830	751	743	717	709	-9.5	-1.1	-3.4	-1.2
6=1-2-5	**Net expenditure under approved care regime**	**8,120**	**7,781**	**7,764**	**7,616**	**7,583**	**-4.2**	**-0.2**	**-1.9**	**-0.4**
7	Class A direct distribution°	3,171	2,829	2,541	2,205	2,181	-10.8	-10.2	-13.2	-1.1
8	Class A - distribution “on behalf”	1,622	1,794	1,939	2,055	2,218	10.6	8.1	6.0	7.9
9=6+7+8	**Public local expenditure**	**12,913**	**12,404**	**12,244**	**11,875**	**11,981**	**-3.9**	**-1.3**	**-3.0**	**0.9**
10	Citizen cost-sharing	1,549	1,608	1,582	1,487	1,481	3.8	-1.6	-6.0	-0.4
11	Private purchase of class A medicines	1,317	1,360	1,544	1,528	1,644	3.3	13.5	-1.1	7.6
12	Class C medicines with prescription	2,813	2,875	3,066	3,269	3,466	2.2	6.6	6.6	6.0
13	Self-medication pharmaceuticals	2,109	2,270	2,392	2,134	2,337	7.6	5.4	-10.8	9.5
14	Shops	286	266	259	250	287	-7	-2.5	-3.7	14.9
15=10+11 +12+13+ 14	**Total private expenditure**	**8,074**	**8,379**	**8,843**	**8,668**	**9,215**	**3.8**	**5.5**	**-2.0**	**6.3**
16=9+15	**Total pharmaceutical expenditure**	**20,987**	**20,783**	**21,087**	**20,543**	**21,196**	**-1.0**	**1.5**	**-2.6**	**3.2**
9/16	Share borne by the NHS (%)	**61.5**	**59.7**	**58.1**	**57.8**	**56.5**				

^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 manufacturers- 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

° 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 2021 this condition was not applied to any Region.

Source: OsMed analysis on NSIS data

Figure 1.2.1 Composition of local pharmaceutical expenditure: comparison 2014-2021

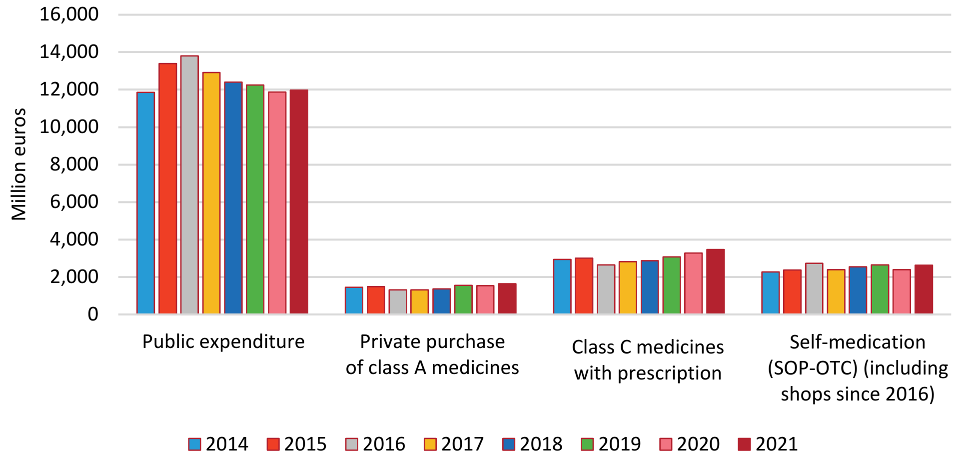


Table 1.2.2 Consumption for public and private local pharmaceutical care: comparison 2017-2021

		2017 *(million)^*	2018 *(million)^*	2019 *(million)^*	2020 *(million)^*	2021 *(million)^*	Δ % 18-17	Δ % 19-18	Δ % 20-19	Δ % 21-20
1	Approved care regime	1,110	1,102	1,083	1,034	1,029	-0.7	-1.7	-4.6	-0.4
2	Class A - Private*	216	162	190	215	227	-25.0	17.4	13.3	5.3
3	Class A - direct distribution	66	175	64	50	44	164.7	-63.2	-22.9	-12.0
4	Class A - "on behalf" distribution	38	44	47	52	55	15.2	7.3	8.7	7.1
5=1+2+3+4	**Total class A packages**	**1,431**	**1,484**	**1,385**	**1,350**	**1,355**	**3.7**	**-6.6**	**-2.5**	**0.4**
6	Class C with prescription	222	229	234	243	244	3.2	2.1	4.1	0.4
7	Self-medication pharmaceuticals (OTC)	231	241	242	248	215	4.3	0.6	2.2	-13.4
8	Shops	30	29	28	27	28	-3.3	-4.0	-1.9	2.0
9=6+7+8	**Total class C packages**	**484**	**498**	**504**	**519**	**487**	**2.9**	**1.2**	**2.9**	**-6.1**
10=5+9	**Total packages**	**1,915**	**1,982**	**1,889**	**1,869**	**1,842**	**3.5**	**-4.6**	**-1.1**	**-1.4**
	DDD/1000 inhab. per day#	1101.6	1130.8	1143.9	1098.4	1133.2	2.7	1.2	-4.0	3.2
	Average DDD cost#	0.43	0.41	0.40	0.41	0.39	-5.7	-1.5	0.9	-2.6
	Prescriptions#	581	576	570	541	552	-0.9	-1.0	-5.2	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 2021

Region	Gross expenditure *(million)*	Citizen cost-sharing				Discount^ *(million)*	Net expenditure^^ *(million)*
		Fixed co-payment (ticket) *(million)*	Δ % 21-20	Reference price *(million)*	Δ % 21-20		
Piedmont	619.1	0.4	0.0	62.1	-1.1	40.3	516.2
Valle d'Aosta	16.5	1.4	-0.9	1.6	-1.7	0.9	12.6
Lombardy	1,770.4	118.9	0.7	137.3	0.0	146.3	1,367.9
A.P. of Bolzano	56.4	4.3	3.8	5.9	0.5	4.0	42.2
A.P. of Trento	73.0	0.1	10.1	6.8	1.0	4.9	61.2
Veneto	644.6	55.7	2.5	68.5	0.9	41.9	478.6
Friuli VG	183.0	0.0	-	18.4	-1.8	12.1	152.6
Liguria	240.0	17.9	3.0	24.7	-1.5	15.5	181.9
Emilia R.	572.4	0.3	-85.7	65.6	2.7	34.2	472.3
Tuscany	523.2	0.3	-97.8	52.8	2.1	35.4	434.7
Umbria	148.4	0.0	-89.4	18.0	-0.3	10.0	120.4
Marche	244.6	0.0	-	29.3	0.3	17.0	198.4
Lazio	1,036.8	20.7	1.6	141.6	1.2	79.8	795.0
Abruzzo	235.8	6.9	-0.5	27.2	0.3	15.7	185.9
Molise	49.9	2.6	3.3	6.5	-2.3	2.9	37.8
Campania	1,059.5	72.1	1.2	131.7	0.5	77.8	778.0
Puglia	724.7	43.7	2.2	85.0	0.8	53.8	542.2
Basilicata	103.3	0.1	-97.1	12.9	3.2	6.8	83.5
Calabria	350.2	9.3	0.4	46.1	0.9	22.1	272.7
Sicily	843.0	44.0	2.8	111.8	-1.1	68.1	619.2
Sardinia	277.4	0.0	-	28.8	-0.4	19.0	229.6
Italy	**9,772.3**	**398.4**	**-2.7**	**1,082.7**	**0.4**	**708.5**	**7,582.9**
North	4,046.0	194.6	0.5	378.3	0.3	224.3	3,285.4
Centre	1,953.1	21.0	-35.9	241.8	1.2	109.8	1,548.4
South and Islands	3,773.2	182.9	-0.1	462.7	0.2	212.6	2,749.0

^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 manufacturers- 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 Summary Accounting Statement (DCR Distinte Contabili Riepilogative)

The data in the following tables are calculated net of oxygen

Table 1.2.4 Regional variability of pharmaceutical consumption through local, public and private pharmacies: year 2021 (Table and Figure)

Region	Class A medicines reimbursed by the NHS					Private purchase of class A, class C and SOP-OTC medicines	
	Gross expenditure A-NHS^	Weighted gross per capita expenditure	Δ % 21-20	DDD 1000 inhab. *die*	Δ % 21-20	*Per capita* expenditure	Δ % 21-10
Piedmont	618	138.1	-1.2	1,031.4	3.3	143.3	6.1
Valle d'Aosta	16	129.6	-2.7	917.0	1.0	122.2	-16.6
Lombardy	1,753	177.4	-0.3	1,077.7	3.6	141.5	7.8
A.P. of Bolzano	56	113.4	-1.1	821.4	2.3	100.9	3.0
A.P. of Trento	73	136.8	-0.2	1,043.8	3.6	101.0	4.1
Veneto	640	130.8	-0.5	1,003.1	1.6	121.4	4.8
Friuli VG	182	143.1	-1.8	1,080.4	2.3	107.2	-2.3
Liguria	239	143.2	-1.7	983.5	2.5	160.7	6.2
Emilia R.	571	126.8	1.5	1,103.3	6.1	127.1	11.6
Tuscany	518	134.7	-0.4	1,091.7	3.3	130.9	7.6
Umbria	148	163.7	-0.7	1,234.5	2.2	110.5	34.1
Marche	244	157.8	-0.9	1,115.6	3.8	124.3	36.1
Lazio	1,028	181.6	-0.6	1,185.2	2.0	127.4	5.1
Abruzzo	234	179.2	0.0	1,186.0	3.8	104.7	-5.2
Molise	49	160.8	-2.9	1,150.0	4.3	96.4	10.6
Campania	1,042	199.9	0.4	1,334.3	4.6	168.7	14.8
Puglia	718	184.9	-0.1	1,255.6	2.6	107.9	5.6
Basilicata	103	186.8	1.9	1,249.1	6.6	96.5	10.4
Calabria	342	187.8	-1.6	1,214.3	2.0	111.7	13.4
Sicily	820	175.0	-1.9	1,182.9	1.5	123.5	7.1
Sardinia	277	167.0	-0.9	1,183.4	2.6	112.8	12.8
Italy	**9,672**	**163.3**	**-0.5**	**1,133.2**	**3.2**	**130.6**	**8.5**
North	4,148	149.0	-0.4	1,049.8	3.5	133.9	6.8
Centre	1,939	162.1	-0.6	1,149.9	2.6	126.8	10.7
South and Islands	3,585	184.6	-0.6	1,242.6	3.1	128.0	9.6

Amounts in million euros
^Expenditure for class A medicines net of class C reimbursed medicines (20 million euros) and oxygen including expenditure for vaccines

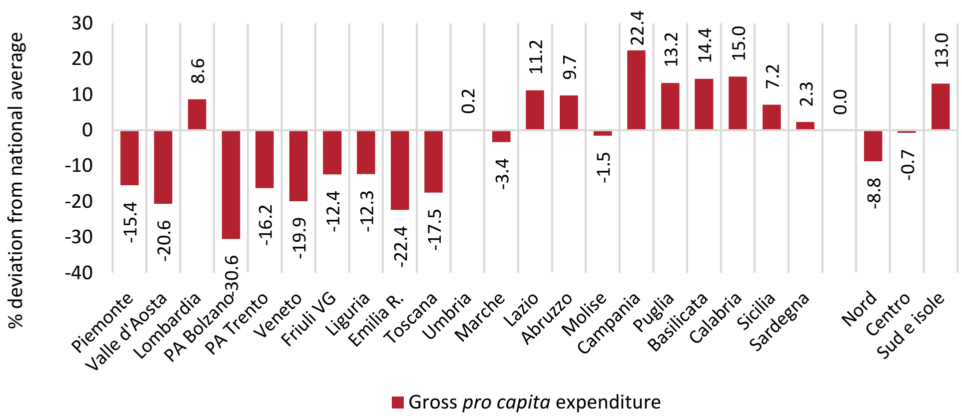


Table 1.2.5 Regional variability of 2021 pharmaceutical consumption under approved care regime by quantity, average cost per day of therapy and expenditure (% deviations from national average) (Table and Figure)

Region	**% deviation from national average**			**Expenditure rank**
	DDD/1000 inhab. *die*	**Average DDD cost**	**Gross expenditure *per capita***	
Campania	18	4	22	1
Calabria	7	7	15	2
Basilicata	10	4	14	3
Puglia	11	2	13	4
Lazio	5	6	11	5
Abruzzo	5	5	10	6
Lombardy	-5	15	9	7
Sicily	4	3	7	8
Sardinia	4	-2	2	9
Umbria	9	-8	0	10
Molise	1	-3	-2	11
Marche	-2	-2	-3	12
Liguria	-13	1	-12	13
Friuli VG	-5	-8	-13	14
Piedmont	-9	-7	-16	15
A.P. of Trento	-8	-9	-16	16
Tuscany	-4	-14	-18	17
Veneto	-11	-9	-20	18
Valle d'Aosta	-19	-2	-21	19
Emilia R.	-3	-20	-22	20
A.P. of Bolzano	-28	-4	-31	21
North	-7	-1	-9	
Centre	1	-2	-1	
South and Islands	10	3	13	

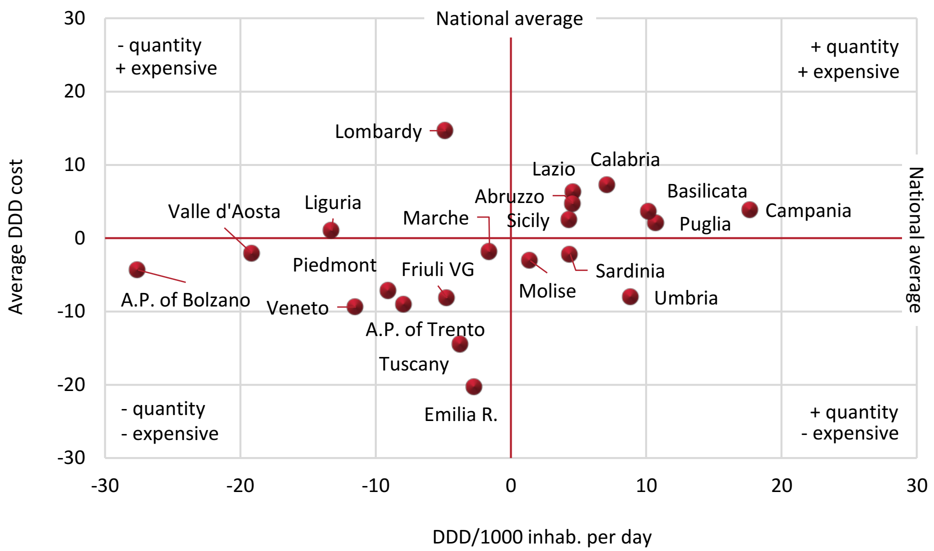


Figure 1.2.2 Trend of class A-NHS pharmaceutical expenditure under approved care regime in the period 2010-2021: consumption, price and mix effect

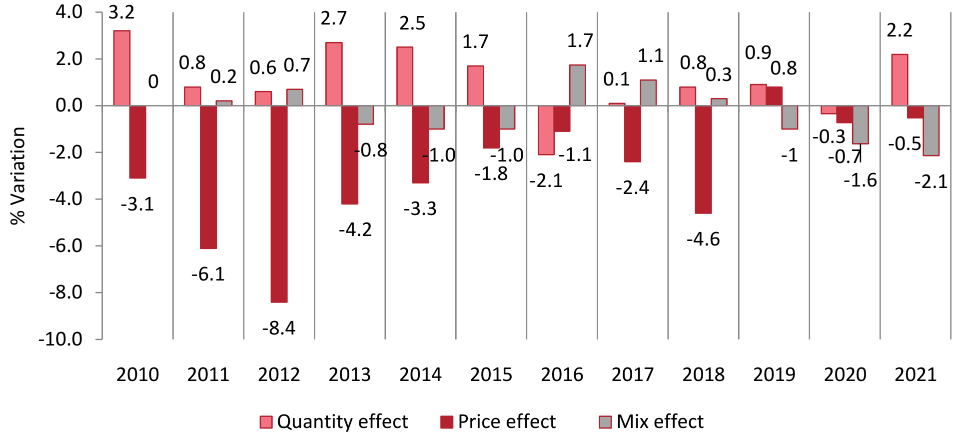


Table 1.2.6 Consumption, price and mix effect on the variation in class A-NHS pharmaceutical expenditure under approved care regime: comparison 2021-2020

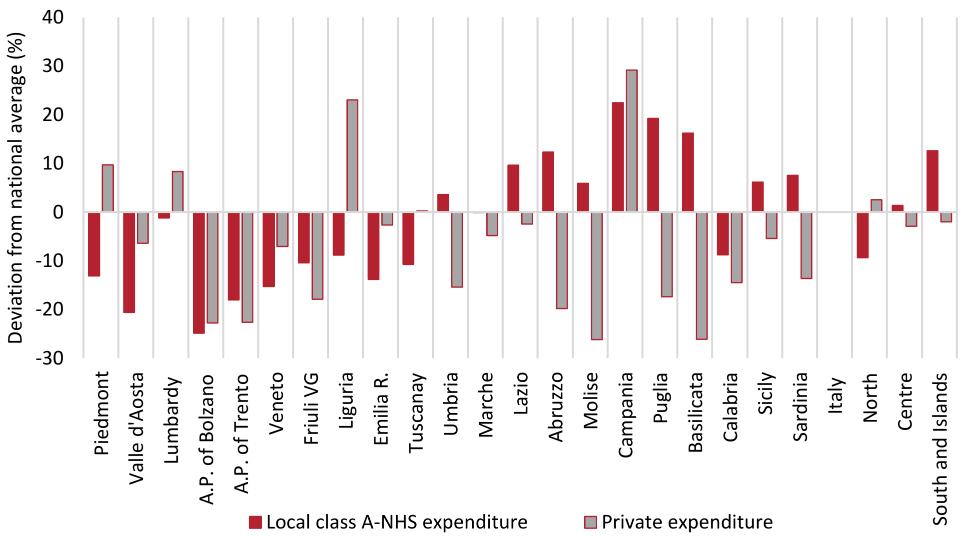
Region	Gross expenditure 2021 *(million)*	Δ % 2021-2020 expenditure	Δ % 2021-2020 DDD	Δ % 2021-2020 prices	Δ % 2021-2020 mix	Average cost DDD 2021	Δ % average cost DDD
Piedmont	617.8	-1.2	1.8	-0.8	-2.3	0.4	-3.0
Valle d'Aosta	16.4	-2.7	-0.3	-4.1	1.7	0.4	-2.4
Lombardy	1,753.0	-0.3	2.4	-0.7	-2.0	0.5	-2.7
A.P. of Bolzano	56.3	-1.1	1.8	-2.4	-0.5	0.4	-2.9
A.P. of Trento	72.6	-0.2	2.2	-1.8	-0.6	0.4	-2.4
Veneto	640.4	-0.5	1.0	-0.8	-0.7	0.4	-1.5
Friuli VG	182.2	-1.8	1.2	-1.3	-1.7	0.4	-3.0
Liguria	239.0	-1.7	1.2	-1.0	-1.8	0.4	-2.8
Emilia R.	570.5	1.5	4.7	-0.9	-2.1	0.3	-3.0
Tuscany	518.5	-0.4	2.6	-0.8	-2.1	0.3	-2.9
Umbria	148.3	-0.7	1.4	-1.2	-0.9	0.4	-2.1
Marche	244.3	-0.9	2.5	-1.2	-2.2	0.4	-3.3
Lazio	1,028.4	-0.6	1.4	-1.0	-1.0	0.4	-2.0
Abruzzo	234.3	-0.0	2.7	-0.9	-1.7	0.4	-2.6
Molise	49.3	-2.9	2.4	-3.1	-2.2	0.4	-5.2
Campania	1,041.8	0.4	3.3	-0.6	-2.3	0.4	-2.9
Puglia	717.6	-0.1	2.3	-0.7	-1.6	0.4	-2.3
Basilicata	102.8	1.9	5.2	-1.9	-1.2	0.4	-3.1
Calabria	342.2	-1.6	0.7	-0.9	-1.4	0.4	-2.3
Sicily	820.3	-1.9	1.0	-1.5	-1.5	0.4	-2.9
Sardinia	276.7	-0.9	1.9	-1.1	-1.7	0.4	-2.8
Italy	**9,672.4**	**-0.5**	**2.2**	**-0.5**	**-2.1**	**0.4**	**-2.6**
North	4,148.2	-0.4	2.3	-0.6	-2.1	0.4	-2.7
Centre	1,939.4	-0.6	1.9	-0.7	-1.7	0.4	-2.4
South and Islands	3,584.8	-0.6	2.2	-0.5	-2.2	0.4	-2.7

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 2021 (weighted population) (Table). % deviation from national average (Figure)

Region	*Per capita* local^ expenditure for class A-NHS medicines	Per capita private expenditure (A, C, SOP and OTC)	Per capita local pharmaceutical expenditure
Piedmont	204.0	143.3	347.3
Valle d'Aosta	186.4	122.2	308.6
Lombardy	231.9	141.5	373.3
A.P. of Bolzano	176.3	100.9	277.2
A.P. of Trento	192.4	101.0	293.4
Veneto	198.9	121.4	320.4
Friuli VG	210.3	107.2	317.5
Liguria	213.9	160.7	374.6
Emilia R.	202.3	127.1	329.4
Tuscany	209.5	130.9	340.4
Umbria	243.2	110.5	353.6
Marche	234.5	124.3	358.8
Lazio	257.3	127.4	384.6
Abruzzo	263.6	104.7	368.3
Molise	248.5	96.4	344.9
Campania	287.4	168.7	456.1
Puglia	279.9	107.9	387.9
Basilicata	272.8	96.5	369.3
Calabria	214.1	111.7	325.8
Sicily	249.2	123.5	372.7
Sardinia	252.4	112.8	365.3
Italy	**234.7**	**130.6**	**365.3**
North	212.8	133.9	346.7
Centre	237.9	126.8	364.7
South and Islands	264.2	128.0	392.2

^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 €13.8 billion (€233.5 *per capita*) (Table 1.3.1) and registered an increase of 4.8% compared to 2020, against a substantial stability in consumption (-0.3%; 173.0 DDD/1000 inhab.*die*) and an increase in the average cost per DDD of 4.8%. 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. While this assumption is 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 can vary depending on the patient's care needs. Regions with the highest expenditure were Umbria (269.3 *per capita*), Campania (266.7 euros *per capita*) and Puglia (260.3 euros *per capita*). Conversely, Valle d'Aosta (175.9 euros *per capita*), Lombardy (195.7 euros *per capita*) and the A.P. of Trento (197.9 euros *per capita*) showed the lowest values. An increase in expenditure, compared to 2020, was recorded, except for Tuscany and Basilicata, in all the Regions, with the greatest variations in Emilia Romagna (+11.7%) and Sicily (+9.7%).

In terms of consumption, Emilia Romagna (300.1 DDD) and Lombardy (111.7 DDD) represent the regions with the highest and lowest levels of consumption, respectively. The Regions with the largest increases in consumption compared to the year 2020 are Sicily (+12.8%), Molise (+9.4%) and Friuli Venezia Giulia (+8.2%), while the largest decreases were in Valle d'Aosta (-7.8%), Abruzzo (-7.5%), Tuscany (-4.8%) and Liguria (-4.5%).

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 only Valle d'Aosta consumes fewer quantities at a lower cost than the national average. Lombardy, Lazio, Abruzzo, Basilicata, Molise, Calabria, Campania, Puglia and Sicily registered lower consumption, but with an average cost per DDD higher than the national average. Emilia Romagna, Friuli Venezia Giulia, Marche, Veneto, Tuscany, Umbria, Liguria, Piedmont, A.P. of Bolzano and A.P. of Trento consume 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. Expenditure in 2021 recorded, at a national level, an increase by 3.6%, driven mainly by a shift towards more expensive molecules (mix effect: +11.9%), while consumption remained more or less stable (-0.8%) and a reduction in prices is observed of 6.7%. However, the average cost per DDD increased by 4.4%, with the greatest changes recorded in Emilia Romagna (+12.5%) and Abruzzo (+11.2%).

Table 1.3.1 Expenditure and consumption for medicines purchased by public health facilities: comparison 2021-2020 (weighted population) (Table and Figure)

Region	NHS Expenditure (million)	NHS Expenditure *per capita*		DDD/1000 inhab. *die*		Average cost DDD	
		€	Δ % 21/20	No.	Δ % 21/20	€	Δ % 21/20
Piedmont	975.5	218.1	1.9	189.4	-3.9	3.1	5.7
Valle d'Aosta	22.3	175.9	7.9	169.3	-7.8	2.8	16.7
Lombardy	1,934.1	195.7	4.7	111.7	1.2	4.8	3.2
A.P. of Bolzano	109.3	220.2	3.2	195.9	-2.2	3.1	5.2
A.P. of Trento	105.0	197.9	7.1	198.1	4.3	2.7	2.3
Veneto	1,082.5	221.2	4.4	210.2	-4.3	2.9	8.8
Friuli VG	300.1	235.8	2.2	193.5	8.2	3.3	-5.9
Liguria	397.5	238.2	4.4	207.1	-4.5	3.1	9.0
Emilia R.	1,157.1	257.1	11.7	300.1	-2.1	2.3	13.8
Tuscany	926.9	240.8	-0.7	204.0	-4.8	3.2	4.0
Umbria	243.9	269.3	7.0	222.3	0.5	3.3	6.2
Marche	398.1	257.2	3.7	223.4	-1.1	3.1	4.7
Lazio	1,321.1	233.3	4.3	131.8	-2.3	4.8	6.5
Abruzzo	335.6	256.6	3.4	138.5	-7.5	5.1	11.5
Molise	70.2	229.4	2.3	144.0	9.4	4.4	-6.8
Campania	1,389.9	266.7	4.0	157.6	3.0	4.6	0.7
Puglia	1,010.3	260.3	4.6	152.8	-0.6	4.7	5.0
Basilicata	136.0	247.3	0.0	147.7	0.7	4.6	-1.0
Calabria	461.9	253.5	6.9	150.9	6.6	4.6	0.0
Sicily	1,047.8	223.5	9.7	155.4	12.8	3.9	-3.0
Sardinia	408.1	246.2	3.3	181.4	6.0	3.7	-2.7
Italy	**13,833.2**	**233.5**	**4.8**	**173.0**	**-0.3**	**3.7**	**4.8**
North	6,083.3	218.5	5.3	184.8	-1.8	3.2	6.9
Centre	2,890.0	241.5	2.8	173.7	-2.8	3.8	5.5
South and Islands	4,859.9	250.2	5.3	155.7	4.4	4.4	0.6

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

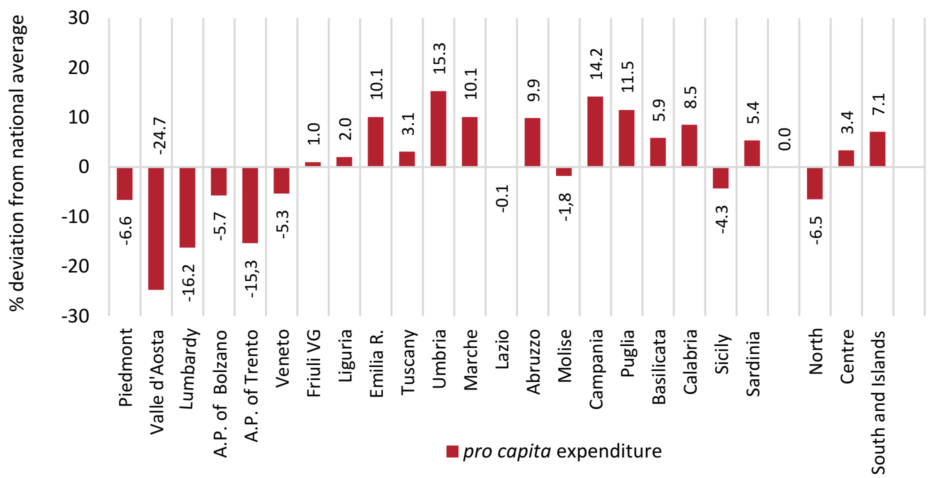
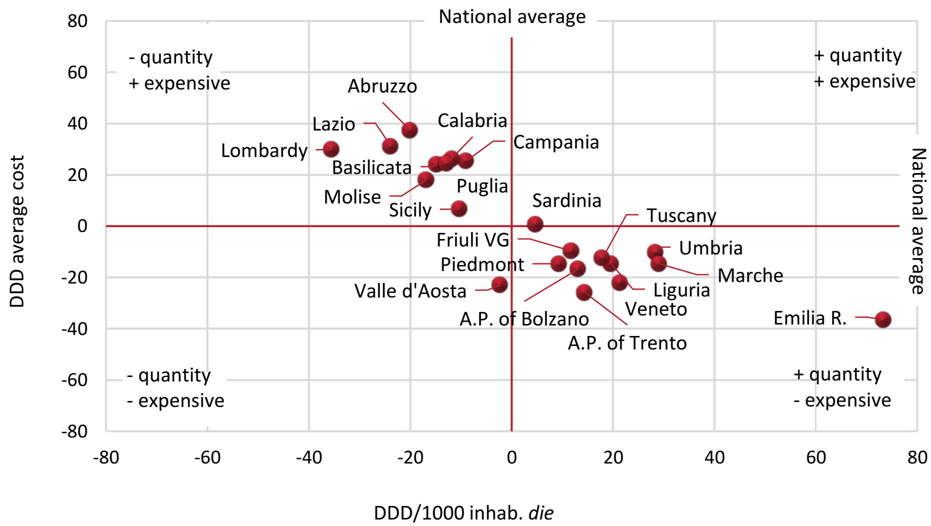


Table 1.3.2 Regional variability of consumption of medicines purchased by public health facilities in 2021 by quantity, average cost per day of therapy and expenditure (% deviations from national average) (Table and Figure)

Region	% deviation from national average			Expenditure rank
	DDD/1000 inhab. *die*	Average cost DDD	*Per capita* gross expenditure	
Umbria	28	-10	15	1
Campania	-9	25	14	2
Puglia	-12	26	11	3
Marche	29	-15	10	4
Emilia R.	73	-37	10	5
Abruzzo	-20	37	10	6
Calabria	-13	24	9	7
Basilicata	-15	24	6	8
Sardinia	5	1	5	9
Tuscany	18	-13	3	10
Liguria	20	-15	2	11
Friuli VG	12	-10	1	12
Lazio	-24	31	0	13
Molise	-17	18	-2	14
Sicily	-10	7	-4	15
Veneto	21	-22	-5	16
A.P. of Bolzano	13	-17	-6	17
Piedmont	9	-15	-7	18
A.P. of Trento	14	-26	-15	19
Lombardy	-35	30	-16	20
Valle d'Aosta	-2	-23	-25	21
North	7	-12	-6	
Centre	0	3	3	
South and Islands	-10	19	7	



BACK

Table 1.3.3 Consumption, price and mix effect on the variation of expenditure for medicines purchased by public health facilities: comparison 2021-2020

Region	Gross expenditure 2021 *(million)*	Δ % 2021-2020				2021 DDD average cost	Δ % 21-20
		expenditure	DDD	prices	mix		
Piedmont	943	0.5	-4.8	-10.1	17.5	3.1	5.6
Valle d'Aosta	21	5.7	-2.9	-29.6	54.5	2.5	8.8
Lombardy	1,831	2.9	0.0	-8.2	12.1	4.6	2.8
A.P. of Bolzano	104	2.5	-2.5	-28.6	47.1	2.9	5.1
A.P. of Trento	99	5.8	3.6	-26.2	38.4	2.6	2.1
Veneto	1,028	3.8	-4.4	-9.3	19.8	2.7	8.6
Friuli VG	286	-0.3	7.3	-31.2	35.2	3.2	-7.0
Liguria	382	2.5	-5.0	-13.3	24.5	3.0	7.9
Emilia R.	1,101	9.5	-2.6	-9.9	24.9	2.2	12.5
Tuscany	894	-0.7	-4.9	-13.8	21.2	3.1	4.4
Umbria	233	4.9	0.1	-12.1	19.2	3.2	4.8
Marche	384	2.4	-1.9	-10.1	16.1	3.0	4.4
Lazio	1,259	4.4	-2.6	-10.2	19.3	4.6	7.1
Abruzzo	323	1.6	-8.6	-11.3	25.4	4.9	11.2
Molise	67	-0.8	7.0	-21.2	17.7	4.2	-7.3
Campania	1,330	2.3	2.2	-9.9	11.2	4.5	0.2
Puglia	965	4.4	-0.6	-10.3	17.1	4.5	5.1
Basilicata	131	-1.7	-0.2	-23.0	27.9	4.4	-1.5
Calabria	443	5.0	5.3	-13.4	15.2	4.4	-0.3
Sicily	991	8.9	13.0	-8.8	5.7	3.7	-3.6
Sardinia	395	2.4	5.8	-15.4	14.5	3.6	-3.2
Italy	**13,212**	**3.6**	**-0.8**	**-6.7**	**11.9**	**3.5**	**4.4**
North	5,795	3.7	-2.4	-7.2	14.5	3.1	6.3
Centre	2,771	2.4	-3.1	-7.7	14.5	3.7	5.7
South and Islands	4,645	4.1	3.9	-6.8	7.5	4.2	0.2

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 the distribution of consumption and expenditure, as well as of the prevalence of use of medicines by age and gender 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 2021, 62.8% of the population received at least one pharmaceutical prescription, with a *per capita* expenditure of €201 and a consumption of 1,184 DDD/1000 inhabitants *die* (this suggests that on average every Italian citizen received slightly more than one dose of a medicine each day of the year) (Tables 1.4.1 and 1.4.2).

There is a slight difference in the level of exposure to medication between the two genders, with a prevalence of 58% in men and of 67% in women. As far as consumption is concerned, the number of doses registered are 1,107 DDD in men and 1,257 in women, whereas pharmaceutical expenditure reported €197 *per capita* in men and €204 in women (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 325 and 496 DDD/1000 inhabitants per day in the 40-49 age group and reaches over 3,000 in the population over 70 years of age (Figure 1.4.1 and 1.4.2, Table 1.4.1). This value shows that each person in this age group has taken at least 3 doses of medicine every day of the year. The population over 64 years of age accounts for more than 70% of expenditure and DDD (Table 1.4.1).

Gender differences can be seen especially in the 20-64 age group, where women show a higher prevalence of use than men (Figure 1.4.1). Compared to a prevalence of use of 62.8% at a national level in 2021, the values of the different Regions vary between 48.2% in the P.A. of Bolzano and 69.9% in Abruzzo (Table 1.4.2). Generally, Northern Regions have a lower prevalence (59.3%) compared to Central (64.7%) and Southern (66.7%) ones. An expenditure of €339.0 per user was incurred in the South (+6.1% compared to the national average of €319.4), compared to €300.4 in the North and €324.1 in the Centre. These differences are mainly due to increased consumption and 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 (696.6 DDD) than in the Centre (692.2 DDD) and in the North (676.8 DDD). This could reflect a different epidemiological trend of the pathologies, both in terms of severity and the presence of comorbidity. Compared to 2020, both prevalence of use and doses per user show an increase of 1.0% and 2.0% respectively, with the greatest increases in the South. In these Regions, even though the doses per user increased (+2.2%), there is a stability in expenditure per user (+0.5%), probably due to a greater recourse to medicines with a lower average cost compared to the previous year (Table 1.4.2). In relation to the two genders (Table 1.4.3), there are no differences in the average age of the users, which is equal to 53 and 55 years in men and women respectively, while there are differences in consumption, which is higher in men in terms of DDD per user (692.8 in men and 683.8 in women) and in terms of packages per user (29.8 in men and 28.2 in women). This consumption trend is also reflected in the expenditure sustained per user, which is equal to 337.9 euros in men and 304.1 euros in women (Table 1.4.3).

Table 1.4.1 Breakdown of local expenditure and consumption by age group in 2021

Age group	*Per capita* gross expenditure			Total expenditure		DDD/1000 inhab. per day			Total DDD	
	men	women	total	%	cum. %	men	women	total	%	cum. %
0-4	18.9	16.4	17.7	0.3	0.3	103	95	100	0.3	0.3
5-9	17.5	15.6	16.6	0.4	0.7	51	45	48	0.2	0.5
10-14	27.8	20.8	24.4	0.6	1.3	58	52	55	0.2	0.7
15-19	37.0	25.3	31.3	0.8	2.0	81	91	86	0.3	1.1
20-24	32.9	34.6	33.7	0.8	2.9	100	134	116	0.5	1.6
25-29	39.7	42.0	40.8	1.0	3.9	119	165	141	0.6	2.2
30-34	43.5	54.9	49.1	1.3	5.2	145	213	179	0.8	3.0
35-39	54.5	71.8	63.1	1.9	7.1	197	271	234	1.2	4.1
40-44	70.4	86.3	78.4	2.6	9.7	293	358	325	1.9	6.0
45-49	96.7	105.3	101.1	4.0	13.7	465	526	496	3.3	9.3
50-54	137.6	143.2	140.4	5.7	19.4	741	824	783	5.4	14.7
55-59	204.2	194.6	199.3	7.8	27.2	1,171	1,220	1,196	7.9	22.6
60-64	299.6	264.7	281.6	9.3	36.5	1,765	1,721	1,742	9.8	32.4
65-69	414.7	354.9	383.4	11.2	47.7	2,485	2,351	2,414	12.0	44.4
70-74	519.2	445.5	480.0	13.9	61.6	3,137	2,959	3,042	14.9	59.3
75-79	666.6	570.4	613.5	13.1	74.8	4,006	3,755	3,867	14.0	73.3
80-84	719.3	613.6	657.8	12.6	87.4	4,290	4,002	4,122	13.4	86.7
85+	783.8	630.5	681.8	12.6	100.0	4,611	4,041	4,232	13.3	100.0
Total	**197.0**	**204.0**	**201.0**	**100.0**		**1,107**	**1,257**	**1,184**	**100.0**	

Figure 1.4.1 Trend in prevalence of use of local pharmaceuticals by age and gender in 2021

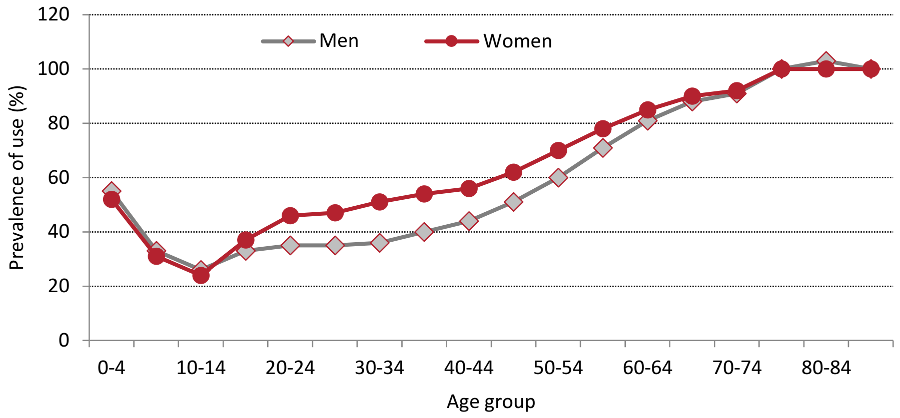


Figure 1.4.2 Trend in local DDD/1000 inhabitants per day in 2021 by age and gender

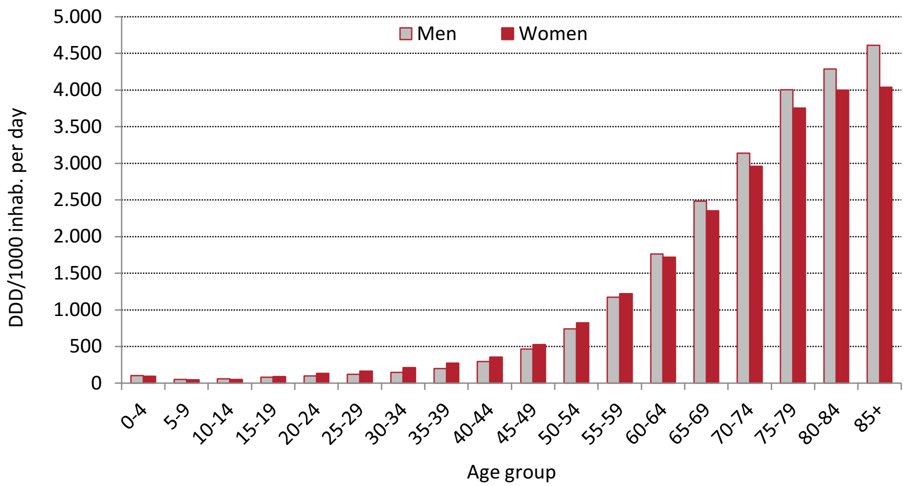


Table 1.4.2 Prevalence and intensity of use at local level by Region (2019-21)

Region	Prevalence of use (%)				Expenditure per user				DDD per user			
	2019	2020	2021	Δ % 20-21	2019	2020	2021	Δ % 20-21	2019	2020	2021	Δ % 20-21
Piedmont	65.7	60.9	61.7	1.3	272.4	292.5	291.8	-0.2	639.6	666.5	675.7	1.4
Valle d'Aosta	62.8	58.2	57.9	-0.4	259.0	275.4	274.1	-0.5	582.0	607.0	615.2	1.3
Lombardy	63.0	57.5	58.0	0.9	314.4	348.1	347.3	-0.2	637.5	673.2	686.0	1.9
A.P. of Bolzano	53.0	47.7	48.2	0.9	240.3	265.7	267.8	0.8	579.4	595.5	604.9	1.6
A.P. of Trento	66.5	61.7	62.3	0.9	238.2	259.1	263.4	1.7	590.1	605.8	617.2	1.9
Veneto	62.6	57.3	57.4	0.3	251.2	277.2	280.4	1.1	658.5	666.1	673.1	1.1
Friuli VG	65.1	60.7	61.2	0.8	292.5	315.0	311.8	-1.0	678.0	706.4	716.4	1.4
Liguria	65.1	60.6	61.0	0.7	303.9	321.8	316.5	-1.7	662.4	685.9	691.0	0.7
Emilia R.	67.2	62.2	62.6	0.7	209.7	224.1	229.0	2.2	604.8	639.3	659.3	3.1
Tuscany	66.7	62.3	62.9	1.0	249.1	273.0	277.1	1.5	655.5	681.3	695.2	2.0
Umbria	71.2	67.1	67.2	0.0	313.7	336.4	338.2	0.5	689.7	731.5	746.8	2.1
Marche	72.1	66.5	67.1	0.9	284.2	304.1	306.1	0.7	626.8	652.1	668.0	2.4
Lazio	68.1	64.8	64.9	0.2	337.5	352.6	355.8	0.9	645.8	673.9	687.8	2.1
Abruzzo	74.1	69.4	69.9	0.7	283.7	317.2	319.7	0.8	604.8	640.1	658.2	2.8
Molise	72.6	68.3	69.2	1.4	309.6	327.6	331.2	1.1	605.9	652.8	682.5	4.6
Campania	69.3	65.4	67.0	2.5	324.1	350.2	353.0	0.8	646.3	694.1	712.7	2.7
Puglia	73.2	68.9	69.5	0.8	307.8	330.4	341.0	3.2	640.0	661.6	677.0	2.3
Basilicata	71.8	67.6	69.6	3.0	307.8	330.4	334.9	1.4	637.0	673.0	696.0	3.4
Calabria	65.0	61.7	63.4	2.6	359.9	381.3	365.6	-4.1	663.5	706.7	720.9	2.0
Sicily	66.5	63.1	64.1	1.7	303.7	323.6	323.9	0.1	641.3	685.4	692.4	1.0
Sardinia	69.5	66.1	67.2	1.6	298.7	321.5	316.8	-1.4	659.4	694.2	706.8	1.8
Italy	**66.6**	**62.2**	**62.8**	**1.0**	**294.6**	**317.8**	**319.4**	**0.5**	**642.9**	**674.3**	**687.9**	**2.0**
North	64.0	58.9	59.3	0.8	274.8	299.6	300.4	0.2	637.6	665.0	676.8	1.8
Centre	68.4	64.3	64.7	0.5	301.9	321.1	324.1	0.9	649.9	677.9	692.2	2.1
South and Islands	69.4	65.6	66.7	1.8	313.8	337.3	339.0	0.5	643.0	681.8	696.6	2.2

Table 1.4.3 Prevalence and intensity of use at local level by Region and age (year 2021)

Region	Average age		Expenditure per user		DDD per user		Packages per user	
	M	W	M	W	M	W	M	W
Piedmont	55	57	309.4	277.4	695.5	659.6	29.5	27.0
Valle d'Aosta	54	56	293.9	258.3	638.9	596.2	27.6	24.9
Lombardy	53	55	373.7	325.4	697.0	676.9	28.9	26.6
A.P. of Bolzano	52	54	288.3	251.3	616.1	595.8	25.0	22.6
A.P. of Trento	51	53	276.7	252.3	632.9	604.1	27.3	25.3
Veneto	54	56	300.8	263.2	695.0	654.7	28.2	25.1
Friuli VG	56	57	337.4	291.3	749.5	689.8	31.2	28.0
Liguria	57	59	331.3	304.6	692.5	689.8	29.4	28.3
Emilia R.	53	55	238.8	221.0	664.7	654.8	27.8	26.5
Tuscany	55	57	291.8	265.1	702.1	689.5	29.1	27.7
Umbria	54	56	358.9	321.2	768.0	729.5	32.8	30.8
Marche	53	55	326.1	289.4	694.4	645.8	30.0	27.6
Lazio	52	54	384.9	332.1	692.7	683.8	30.7	29.7
Abruzzo	52	54	331.7	309.6	661.8	655.2	29.1	28.2
Molise	54	56	354.3	311.7	676.3	687.8	30.3	29.3
Campania	50	52	361.7	345.7	690.9	731.0	30.7	30.4
Puglia	52	53	354.7	329.5	669.4	683.4	30.1	29.4
Basilicata	53	55	349.4	322.6	683.3	706.7	31.1	30.4
Calabria	53	54	399.3	337.3	730.5	712.9	33.6	32.1
Sicily	52	54	336.2	313.8	692.1	692.7	30.4	29.7
Sardinia	54	56	331.2	305.0	689.3	721.2	29.8	28.8
Italy	**53**	**55**	**337.9**	**304.1**	**692.8**	**683.8**	**29.8**	**28.2**
North	54	56	320.5	283.8	690.8	665.4	28.7	26.5
Centre	53	55	346.9	305.5	701.9	684.4	30.3	28.9
South and Islands	52	53	352.9	327.4	688.0	703.7	30.6	29.9

1.5 Pharmaceutical use in the paediatric age

This section presents an analysis of the pharmaceutical use in the paediatric age taking into consideration data from all Italian regions, with a resident paediatric population (age <18 years) of 9.3 million individuals in 2021.

In 2021 almost 3.3 million children and adolescents received at least one pharmaceutical prescription, corresponding to 35.1% of the general paediatric population, with a slightly higher prevalence in males than females (35.9% *vs.* 34.3%). Furthermore, in the same year, 13.3 million prescriptions were issued, for a total of 13.6 million packages (approximately 1.5 packages per user) and a total expenditure of €207.6 million (€22.20 *per capita* and €63.30 per user). In contrast to the year 2020, an increase in consumption is observed in 2021, both in terms of prescriptions (+6.5%) and packages (+5.3%) and in terms of expenditure *per capita* (+2.1%) and expenditure per user (+5.1%). On average, during the year, each child received 1.4 prescriptions and 1.5 packages of pharmaceuticals, with a slight difference between males and females: 1.5 *versus* 1.3 prescriptions and 1.5 *versus* 1.4 packages, respectively (Table 1.5.1).

At regional level, a marked variability was recorded in the use of pharmaceuticals in the paediatric age, with a prevalence of use ranging from 27% in the A.P. of Bolzano to 43% in Abruzzo (Figure 1.5.1).

The prevalence of use peaks in the pre-school age group (1-5 years) (53.8%), and then gradually decreases in the following years to reach a value of 28.7% in the 12-17 age group (Figure 1.5.2).

A similar trend by age regards consumption, with the number of packages *per capita* going from 2.1 in pre-school age children (1-5 years) to 1.1 in school-age children (6-11 years) to 1.4 in adolescents (12-17 years), with a negligible difference by gender: 1.5 packages for males *versus* 1.3 packages for females. Compared to the year 2020, there is an increase in packages *per capita* in both males and females, and it is noticeable that, considering age groups, the increase is concentrated in children in the first 5 years of life, while consumption in school-age children and adolescents is limited (Table 1.5.2).

As expected, antimicrobials for systemic use are the medicines with the highest consumption (33.6% of the total number of packages prescribed in the Italian paediatric population), followed by respiratory system medicines (26.7%); antimicrobials for systemic use also show in 2021 a reduction in prescriptions compared to the previous year, although less than that observed in 2020 (2021-2020: -4.2% and 2020-2019: -46.0%). On the contrary, as regards medicines of the respiratory system, after the significant reduction in packages observed in 2020 (-30.3%), there was a recovery in consumption in 2021 with an increase of 12.9% compared to 2020. Among the most widely used pharmaceutical categories, central nervous system medicines are in fourth place, with consumption accounting for 10.7% of the total, continuing to record an increase in packages compared to the previous year, even greater than that recorded in 2020 (2021-2020: +5.9% and 2020-2019: +3.0%) (Figure 1.5.3, Table 1.5.3).

The analysis of distribution of consumption by gender 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 67% *vs.* males 33%), anti-neoplastic and immunomodulatory medicines (females 63% *vs.* males 37%), anti-parasitics, insecticides

and repellents (females 52% *vs.* males 48%) and medicines belonging to the blood and haemopoietic organs category (females 51% *vs.* males 49%) (Figure 1.5.4).
As already highlighted, antimicrobials for systemic use are confirmed as the therapeutic category with the highest consumption in the paediatric age group (490.8 packages per 1,000 patients), despite the downward trend of the last two years, with the combination amoxicillin/clavulanic acid proving to be the most prescribed medicine in the category (179.1 prescriptions per 1,000 patients), although lower than 2020 (-5.8%; Table 1.5.3). Despite the strong reduction in consumption, the prescribing pattern of antibiotics in the Italian paediatric population is confirmed: the amoxicillin/clavulanic acid association ranks first among the 20 active ingredients with the highest consumption also in 2021, while amoxicillin alone, 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 association with clavulanic acid) ranks third in terms of consumption in the category and sixth in the ranking of the top 20 active ingredients by consumption (70.0 packages per 1,000 patients) with a reduction compared to 2020 of 7.5% (Tables 1.5.3 and 1.5.4). The second most important antibiotic by number of packages is azithromycin (71.5 packages per 1,000 patients), with a strong increase over 2020 (+19.4%).
In the ranking of the most prescribed categories, respiratory system medicines come next with a prevalence of 257.2 per 1,000 patients and 389.3 packages per 1,000 patients. The medicines authorised for the treatment of bronchial asthma, such as the inhaled corticosteroids, budesonide and beclomethasone, and salbutamol - a selective beta-2 adrenergic receptor agonist - record the highest prevalence of use values within the category, with strong increases in prescriptions compared to 2020 (from +15.7% for salbutamol to +48.9% for budesonide), after the strong decreases recorded in 2020 (Table 1.5.3). The antihistamine cetirizine ranks third in terms of prevalence of use (107.6 per 1,000 children) and number of packages per 1,000 patients (57.0 with an increase of 3.7%) (Tables 1.5.3 and 1.5.4). The third category by consumption is represented by medicines of the gastrointestinal and metabolic system, which registered a significant increase over 2020 (+13.3%), recording in 2021 159.8 packages per 1,000 patients. Cholecalciferol is the most prescribed medicine (84.2 packages per 1,000 patients), followed by lansoprazole and insulin lispro, both with 8.3 packages, and insulin aspart with 6.9 packages per 1,000 patients.
The fourth most prescribed category is central nervous system medicines (156.7 packages per 1,000 patients, increasing by 5.9% compared to 2020); in this category, valproic acid is the most prescribed active ingredient (51.5 packages per 1,000 patients), followed by two other antiepileptic medicines (carbamazepine and levetiracetam). Considering also lamotrigine and etosuccimide, other anti-epileptic medicines in fifth and ninth position by consumption, these active ingredients cover more than half of the consumption of the nervous system pharmaceutical category. Although it shows a low consumption (8.2 packages per 1,000 patients), aripiprazole, indicated for the treatment of schizophrenia from the age of 15 and bipolar disorder from the age of 13, is the second substance with the largest increase in both 2021 and 2020, with changes of +32.9% and +16.8% respectively, compared to the previous year. The active substance with the largest increase (+49.8%) is sertraline, a serotonin reuptake inhibitor antidepressant (SSRI) authorised for

the treatment of obsessive-compulsive disorder (OCD) in children and adolescents aged 6-17 years (Table 1.5.3).

Among the first 20 active ingredients with the highest consumption (Table 1.5.4) in the paediatric population for the year 2021, there are 7 belonging to the category of respiratory system medicines, 6 antibiotics, 3 in the category of hormones (excluding sexual hormones), 2 of the central nervous system (antiepileptics), one belonging to the category of medicines of the gastrointestinal tract and one belonging to the category of pesticides, insecticides and repellents. After the combination amoxicillin/clavulanic acid, cholecalciferol, betamethasone and azithromycin are in the top positions in terms of consumption with, respectively, 84.2, 81.1 and 71.5 packages per 1,000 patients. All these active ingredients, with the exception of the combination amoxicillin/clavulanic acid, show an increase over 2020, ranging from 30.6% for betamethasone to 19.4% for azithromycin. Among the active ingredients with the highest consumption, only levothyroxine (a medicine indicated in forms of hypothyroidism), cholecalciferol and mebendazole show higher consumption in females than in males (Table 1.5.4).

Table 1.5.1 General prescription data in the paediatric population in 2021

	Males	Females	Total
Users	**1,727,741**	**1,554,440**	**3,282,181**
Prevalence (%)	35.9	34.3	35.1
Prescriptions	**7,267,825**	**6,033,683**	**13,301,508**
Per capita	1.5	1.3	1.4
Δ % 20-19	-31.3	-32.8	-32.0
Δ % 21-20	5.7	7.4	6.5
Packaging	**7,460,039**	**6,187,434**	**13,647,473**
Per capita	1.5	1.4	1.5
Δ % 20-19	-31.5	-33.0	-32.2
Δ % 21-20	4.5	6.3	5.3
Expenditure	**121,934,344**	**85,670,300**	**207,604,644**
Per capita	25.3	18.9	22.2
Δ % 20-19	-19.9	-22.4	-20.9
Δ % 21-20	0.6	4.3	2.1
Per user	70.6	55.1	63.3
Δ % 20-19	4.8	3.5	4.4
Δ % 21-20	4.0	6.9	5.1

Figure 1.5.1 Regional trend in prescription in the paediatric population in 2021

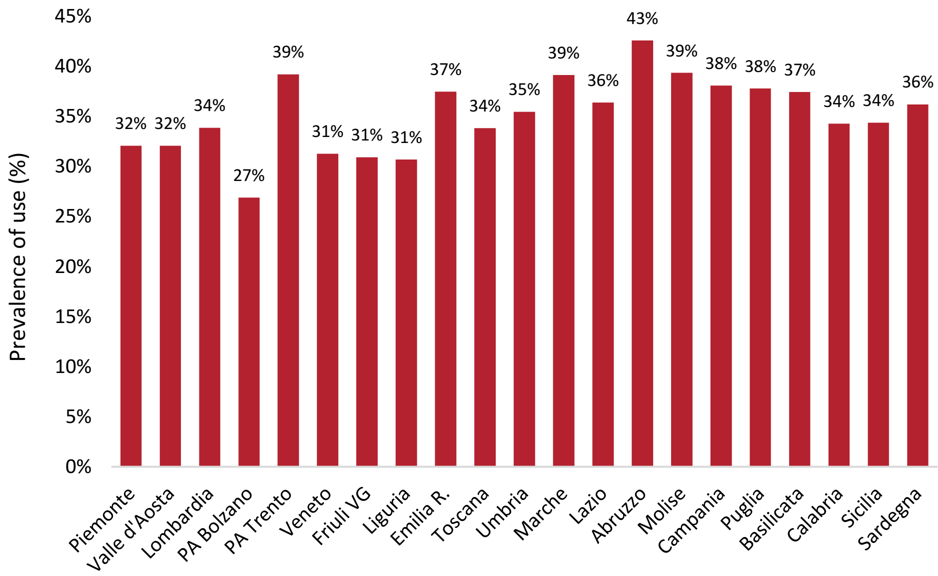


Figure 1.5.2 Trend in the prevalence of use and prescription in the paediatric population by age in 2021

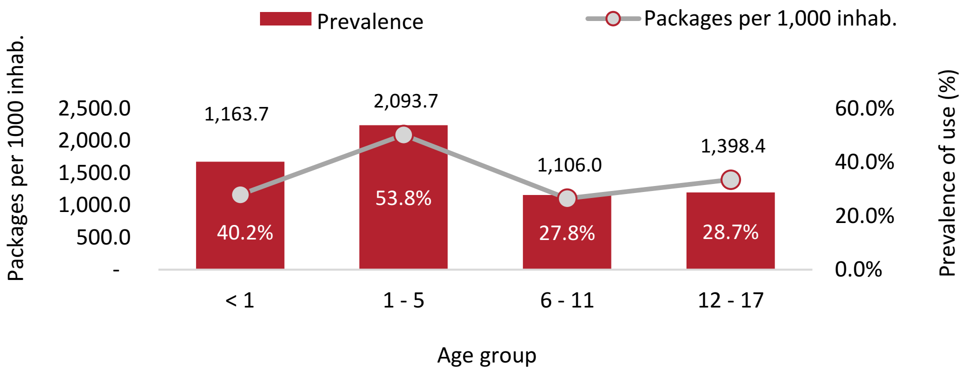


Table 1.5.2 Distribution of consumption (packages) by age and gender in the paediatric population in 2021

Age group	*Per capita* packages					
	males	Δ % 21-20	females	Δ % 21-20	total	Δ % 21-20
< 1	1.3	89.2	1.1	91.6	1.2	90.3
1 - 5	2.2	35.1	2.0	35.9	2.1	35.5
6 - 11	1.2	-13.9	1.0	-15.5	1.1	-14.6
12 - 17	1.5	-6.0	1.3	-1.5	1.4	-4.0
Total	**1.5**	**4.5**	**1.4**	**6.3**	**1.5**	**5.3**

Figure 1.5.3 Percentage distribution of consumption (packages) in the paediatric age by ATC I level in 2021

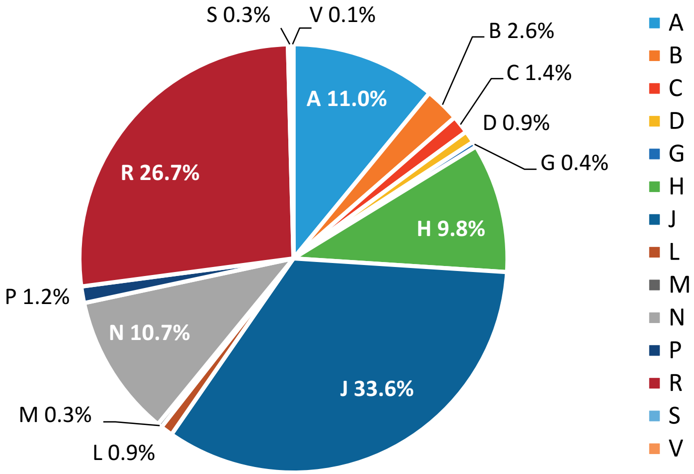
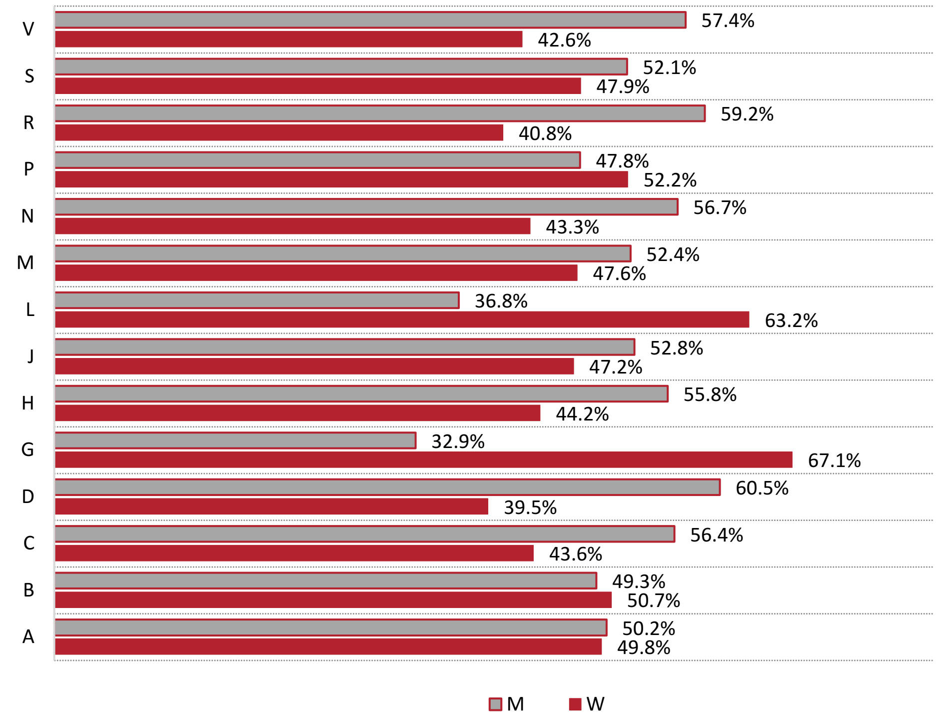


Figure 1.5.4 Percentage distribution of consumption (packages) in the paediatric age by ATC I level and gender in 2021



A	Gastrointestinal tract and metabolism
B	Blood and blood-forming organs
C	Cardiovascular system
D	Dermatological
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	Central 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 2021

Therapeutic category/ substance	Packages (per 1,000 inhab.)	Δ % 21-20	Δ % 20-19	Prevalence (per 1,000 inhab.)	Ratio M/F
J - Anti-infectives for systemic use	**490.8**	**-4.2**	**-46.0**	**475.8**	**1.1**
amoxicillin/clavulanic acid	179.1	-5.8	-46.6	367.2	1.1
azithromycin	71.5	19.4	-35.5	163.2	1.2
amoxicillin	70.0	-7.5	-53.1	131.0	1.1
cefixime	53.4	2.8	-44.7	126.2	1.0
R - Respiratory system	**389.3**	**12.9**	**-30.3**	**257.2**	**1.3**
beclomethasone	70.5	30.5	-38.3	221.8	1.2
salbutamol	60.7	15.7	-39.6	178.9	1.5
cetirizine	57.0	3.7	-5.0	107.6	1.5
budesonide	56.9	48.9	-42.8	169.9	1.2
fluticasone	26.5	-0.9	-27.4	62.7	1.7
salbutamol/hypratropium	25.8	40.2	-47.9	92.3	1.2
A - Gastrointestinal and metabolism	**159.8**	**13.3**	**-5.5**	**82.8**	**1.0**
cholecalciferol	84.2	22.0	-5.7	649.6	1.0
lansoprazole	8.3	1.8	-1.6	31.0	1.0
insulin lispro	8.3	12.2	12.3	16.7	1.1
insulin aspart	6.9	3.8	2.7	10.5	1.1
esomeprazole	6.1	5.8	-0.5	30.9	1.0
ursodesoxycholic acid	5.0	8.0	7.5	6.8	1.0
omeprazole	4.3	1.5	-13.6	24.5	0.9
N - Nervous system	**156.7**	**5.9**	**3.0**	**15.8**	**1.3**
valproic acid	51.5	-1.3	0.2	167.8	2.0
carbamazepine	14.9	4.1	3.4	56.1	1.3
levetiracetam	13.4	-0.1	1.0	81.6	0.8
aripiprazole	8.2	32.9	16.8	69.0	1.0
lamotrigine	7.1	4.3	1.3	27.7	0.6
sertraline	6.4	49.8	7.6	69.4	0.5
methylphenidate	6.2	24.2	3.2	50.9	6.2
phenobarbital	4.9	-7.3	-0.3	16.6	1.2
risperidone	4.4	5.1	5.1	70.6	2.7
ethosuximide	4.3	1.2	5.2	22.3	0.7
H - Hormones, excluding sex hormones	**142.4**	**16.1**	**-28.8**	**104.9**	**1.3**
betamethasone	81.1	30.6	-42.3	811.7	1.3
somatropin	21.0	-5.3	3.9	11.8	1.4
levothyroxine	15.5	1.9	-0.4	33.6	0.6
B - Blood and haemopoietic organs	**38.1**	**25.1**	**-20.0**	**19.8**	**0.9**
enoxaparin	6.7	30.8	-21.4	149.8	1.7
ferrous sulphate	4.9	32.1	-16.3	182.6	0.3
sodium chloride	4.9	-16.5	-28.6	58.1	1.2
folic acid	4.6	25.8	-16.7	181.9	0.5
polymerised iron	4.2			138.5	1.1
tranexamic acid	2.2	3.8	-34.1	90.6	1.0
sodium ferrigluconate	1.4	13.7	-26.0	48.2	1.2

Therapeutic category/ substance	Packages (per 1,000 inhab.)	Δ % 21-20	Δ % 20-19	Prevalence (per 1,000 inhab.)	Ratio M/F
C - Cardiovascular system	**19.9**	**-0.4**	**9.7**	**4.5**	**1.2**
enalapril	2.0	-1.4	-1.2	76.7	1.4
ramipril	1.9	-1.7	-6.4	80.4	1.6
flecainide	1.6	4.6		48.2	1.1
furosemide	1.5	-0.8	-2.8	86.6	1.1
bisoprolol	1.4	4.8	13.0	75.4	1.2
carvedilol	1.3	1.9	7.0	35.8	1.3
losartan	1.3	-0.5	0.6	35.2	1.9
spironolactone	1.0	8.6	7.4	30.4	0.7
amlodipine	1.0	-5.4	2.8	54.5	1.4
propranolol	0.9	9.8	9.1	47.5	0.6
omega 3	0.5	21.2	17.5	23.9	1.4
pravastatin	0.4	5.0	3.7	10.4	1.1
atorvastatin	0.4	-5.6	4.3	30.1	1.2
P - Pesticides, insecticides and repellents	**18.2**	**-4.8**	**-14.1**	**21.0**	**0.9**
mebendazole	14.1	-6.1	-9.8	780.5	0.9
L - Antineoplastics and immunomodulators	**13.5**	**8.9**	**7.4**	**2.3**	**0.5**
triptorelin	3.6	39.5	17.2	290.7	0.1
methotrexate	3.0	-0.6	3.6	266.2	0.5
tacrolimus	2.2	0.3	11.1	69.2	1.2
azathioprine	1.1	8.4	-4.0	95.7	1.0
cyclosporine	0.8	-11.8	-11.1	70.2	1.1
D - Dermatological	**13.4**	**17.6**	**2.2**	**7.2**	**1.3**
isotretinoin	7.6	29.0	10.8	338.1	2.0
calcipotriol/betamethasone	1.1	-8.3	-11.2	118.4	0.9
methylprednisolone	1.0	8.1	-4.1	141.3	1.1
clobetasol	0.9	14.9	13.3	88.8	0.9
G - Genito-urinary system and sex hormones	**6.0**	**8.6**	**-5.0**	**2.5**	**0.3**
oxybutynin	2.0	7.6	-3.2	195.8	1.6
cyproterone/ethinylestradiol	0.8	1.2	-15.1	88.2	0.0
dydrogesterone	0.5	14.2	-1.5	120.5	0.0
estradiol	0.5	4.7	-1.5	43.1	0.0
cabergoline	0.3	9.8	-4.6	61.2	0.1
nomegestrol	0.3	29.9	54.6	96.8	0.0
progesterone	0.2	7.5	-13.1	82.2	0.0
M - Musculoskeletal system	**5.0**	**9.8**	**-14.9**	**4.5**	**1.0**
ketoprofen	1.0	11.1	-30.2	265.8	1.0
ibuprofen	0.9	51.2	-23.0	238.2	1.0
baclofen	0.7	-3.8	1.8	27.6	1.5
allopurinol	0.4	3.2	12.9	41.5	1.7
diclofenac	0.4	4.4	-18.9	100.5	1.0
colchicine	0.2	11.6	10.6	28.5	1.3
nimesulide	0.2	13.1	-21.5	61.0	1.0
S - Sense organs	**4.1**	**-3.7**	**-1.1**	**1.1**	**0.9**
acetazolamide	1.2	1.9	9.1	121.1	0.9
timolol	0.7	13.1	0.4	321.5	0.7
dorzolamide/timolol	0.5	-0.1	7.5	123.1	1.3

Therapeutic category/ substance	Packages (per 1,000 inhab.)	Δ % 21-20	Δ % 20-19	Prevalence (per 1,000 inhab.)	Ratio M/F
thymolol/brinzolamide	0.2	-12.1		45.0	1.4
brinzolamide	0.2	-1.7	11.7	35.1	1.8
dorzolamide	0.2	5.2	4.1	49.4	1.0
bimatoprost	0.2	-4.2	-1.2	39.2	1.2
V - Various	**2.0**	**-7.7**	**23.3**	**0.7**	**1.4**
oxygen	0.6	-5.2	14.9	440.7	1.1
deferasirox	0.3	4.2	7.8	52.6	1.3
grass pollen phleum pratense/dactylis glomerata/ anthoxanthum odoratum/lolium perenne/poa pratensis	0.2	-12.2	-16.0	214.8	2.4
grass pollen (phleum pratense)	0.2	-6.9	93.9	150.2	2.0
calcium levofolinate	0.2	-27.9	50.6	20.5	1.0

Table 1.5.4 Top 20 active ingredients by paediatric consumption in 2021

ATC I	Active ingredient	Packages (per 1000 inh.)	Δ % 21-20	Δ % 20-19	Consumption (%)*		Inc. cum**%
					males	females	
J	amoxicillin/clavulanic acid	179.1	-5.8	-46.6	53.7	46.3	17.4
A	cholecalciferol	84.2	22.0	-5.7	49.3	50.7	25.6
H	betamethasone	81.1	30.6	-42.3	57.5	42.5	33.5
J	azithromycin	71.5	19.4	-35.5	54.0	46.0	40.4
R	beclomethasone	70.5	30.5	-38.3	55.3	44.7	47.3
J	amoxicillin	70.0	-7.5	-53.1	53.0	47.0	54.1
R	salbutamol	60.7	15.7	-39.6	60.5	39.5	60.0
R	cetirizine	57.0	3.7	-5.0	61.8	38.2	65.5
R	budesonide	56.9	48.9	-42.8	56.2	43.8	71.1
J	cefixime	53.4	2.8	-44.7	50.2	49.8	76.3
N	valproic acid	51.5	-1.3	0.2	66.8	33.2	81.3
J	clarithromycin	29.8	-23.5	-49.7	54.5	45.5	84.2
R	fluticasone	26.5	-0.9	-27.4	63.6	36.4	86.7
R	salbutamol/hypratropium	25.8	40.2	-47.9	55.2	44.8	89.3
R	montelukast	24.0	-19.9	-14.1	63.9	36.1	91.6
J	cefpodoxima	21.1	-10.8	-51.9	53.2	46.8	93.6
H	somatropin	21.0	-5.3	3.9	60.6	39.4	95.7
H	levothyroxine	15.5	1.9	-0.4	38.7	61.3	97.2
N	carbamazepine	14.9	4.1	3.4	56.1	43.9	98.6
P	mebendazole	14.1	-6.1	-9.8	48.1	51.9	100.0
	Total	**1028.4**	**6.6**	**-37.2**	**55.6**	**44.4**	**100.0**

* calculated in relation to the total consumption of the molecule in paediatric age

** calculated on total paediatric consumption

1.6 Pharmaceutical use in the geriatric age

In Italy, the population aged 65 and over reached about 13.9 million people in 2021, or 24% of the Italian population. Women are about 7.8 million, representing 56.3% of this age group.
As expected, drug use increases with age up to the 80-84 years 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 (4087.4 and 3853.8 DDD/1000 users per day, respectively), with a per user expenditure equal to 652.3 euros and 620.9 euros, respectively (Table 1.6.1). In all age groups, there was a difference between the two genders, with men consuming and spending more than women. In particular, the largest difference is in the 65-69 years group, where men have 8% more doses than women (Figure 1.6.1). Overall, the average expenditure per user was 557.6 euros (599.4 in men and 525.1 in women), stable compared with 2020 (-0.7%). Analysis of drug consumption in those who received at least one prescription in 2021 showed that the number of DDD/1000 users per day was higher in men than in women (3,586.8 vs. 3,438.8) and a stable dose delivery per user in 2021 compared to 2020 (+0.8 %).
When analysing prevalence of use, almost the entire population (97%) received at least one prescription during the year, with no particular differences between genders and a stable trend compared to 2020. In contrast, incidence of use recorded a 35.4 % increase compared to 2020, with a higher increase in the population up to 79 years and then declining in older people. It is noteworthy that in 2020 there was a reduction in the incidence of use for several drug categories used in the treatment of chronic conditions (drugs for diabetes, osteoporosis, hypertension, depression, anticoagulants) compared with 2019, and this reduction was mainly observed in younger age groups (specifically 65-69 years). This can be explained by the lack of new diagnoses due to reduced access to outpatient care during the first phase of the pandemic (lockdown), and by the fact that younger age groups are indeed the most commonly diagnosed with new chronic diseases and new pharmacological treatments *(Medicines Utilisation Monitoring Centre. L'uso dei farmaci nella popolazione anziana in Italia. Rapporto Nazionale 2019*).
Politherapy in this population group was studied using as proxy the median number of substances prescribed per user.
In 2021, each user used 7.4 different substances, with a lower value (5.8 substances per user) recorded in the 65-69 years age group and the highest figure (8.4 substances per user) in people aged 85 and over. Both genders registered a progressive growth in the number of different active ingredients taken, which increased with age. In men, a shift was reported from 5.8 substances taken in the 65-69 age group to 8.6 in people aged 85 years and over. A similar trend was also found in women, with 5.9 different substances taken in the 65-69 age group and 8.3 different active ingredients taken by women aged 85 years or over (Table 1.6.2).
Additionally, the distribution of users by number of different active ingredients (Figure 1.6.2) showed that around 66.6% of elderly users received prescriptions for at least 5 different substances (i.e. polypharmacy) during the reference year and that approximately one subject in 4 (26.8%) aged 65 years or over 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. In addition, when looking at the 3

combinations of the most common therapeutic categories in patients taking 5 substances, those people are reported to take at least two antihypertensives, one lipid-lowering agent and one antiplatelet agent. Anti-diabetics, peptic ulcer and antigout drugs are added to the above categories for people taking 8 substances (Table 1.6.3).

Table 1.6.1 Distribution by age and gender of pharmaceutical prescription in the population aged ≥65 years (2021)

Age group	Expenditure per user				DDD/1000 users per day				Prevalence of use (%)				Incidence of use (%)			
	M	W	T	Δ % 21-20	M	W	T	Δ % 21-20	M	W	T	Δ % 21-20	M	W	T	Δ % 21-20
65-69	470.5	394.7	430.4	-0.4	2,818.9	2,613.7	2,710.3	0.7	88.1	89.9	89.1	1.6	6.3	5.8	6.0	38.7
70-74	568.5	486.6	524.9	-0.6	3,435.0	3,231.4	3,326.5	0.5	91.3	91.6	91.5	-5.2	3.9	3.6	3.7	33.0
75-79	652.6	568.5	606.5	-1.1	3,922.0	3,742.1	3,823.4	0.5	102.1	100.3	101.1	8.0	2.9	2.6	2.7	51.8
80-84	701.0	616.1	652.3	-1.0	4,180.7	4,018.2	4,087.4	0.8	102.6	99.6	100.9	-2.1	2.0	1.9	1.9	29.9
85 +	684.4	586.9	620.9	-0.3	4,026.4	3,761.2	3,853.8	1.5	114.5	107.4	109.8	-0.4	2.2	2.2	2.2	14.9
Total	**599.4**	**525.1**	**557.6**	**-0.7**	**3,586.8**	**3,438.8**	**3,503.5**	**0.8**	**97.1**	**97.1**	**97.1**	**0.1**	**3.8**	**3.4**	**3.6**	**35.4**

Figure 1.6.1 Prescription trend in the population aged ≥65 years (DDD/1000 users per day and gross expenditure per user) (2021)

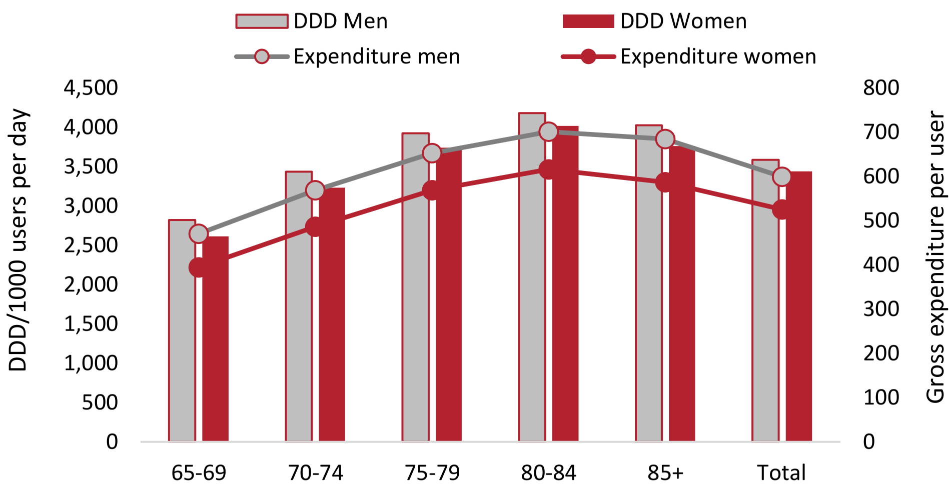


Table 1.6.2 Average number of substances by age and gender in 2021

Age group	Average number of substances			Average last 5 years
	Men	Women	Total	
65-69	5.8	5.9	5.8	6.0
70-74	6.8	6.8	6.8	7.0
75-79	7.6	7.7	7.6	7.9
80-84	8.2	8.2	8.2	8.5
≥85 years	8.6	8.3	8.4	8.6
Total	**7.4**	**7.4**	**7.4**	**7.6**

Figure 1.6.2 Percentage distribution of users in the population ≥ 65 years by number of different substances in 2021

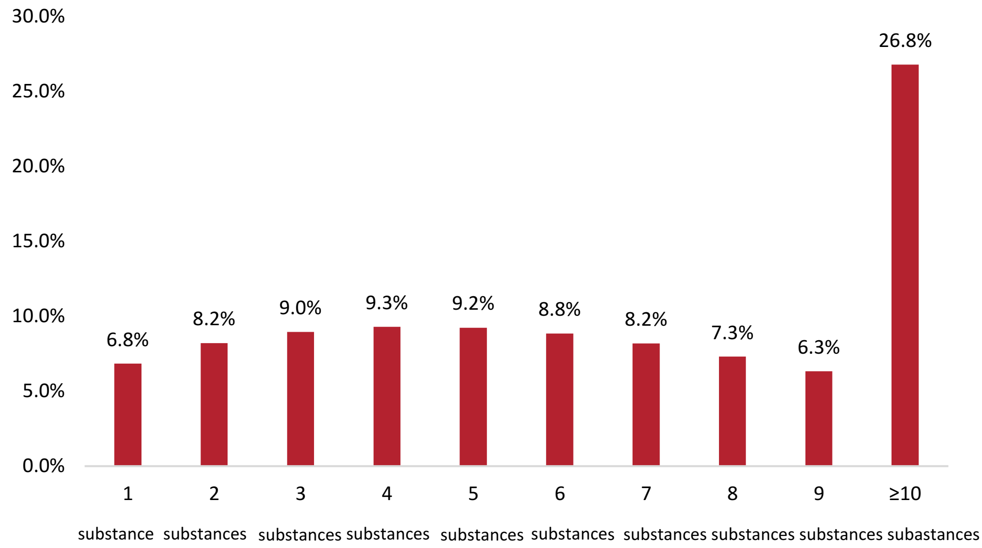


Table 1.6.3 Frequency of the main combinations of therapeutic categories by number of substances received in 2021

Number of substances received	Combinations of therapeutic categories	Number of users	% of users
2	Antihypertensives (2 categories)	122,442	11.0
	Antihypertensives — Lipid lowering agents	58,811	5.3
	Antibiotics — Antihypertensives	49,512	4.5
3	Antihypertensives (2 categories) — Lipid-lowering agents	33,684	2.8
	Antihypertensives (3 categories)	30,059	2.5
	Antibiotics — Antihypertensives (2 categories)	22,904	1.9
4	Antiplatelets — Antihypertensives (2 categories) — Lipid lowering agents	19,084	1.5
	Antiplatelets — Antihypertensives — Drugs for peptic ulcer and gastroesophageal reflux disease (GERD) — Lipid-lowering agents	15,108	1.2
	Antihypertensives (3 categories) — Lipid-lowering agents	10,279	0.8
5	Antiplatelets — Antihypertensives (2 categories) — Drugs for peptic ulcer — Lipid-lowering agents	19,268	1.5
	Antiplatelets — Antihypertensives (3 categories) — Lipid-lowering agents	7,337	0.6
	Antiplatelets — Antidiabetics — Antihypertensives (2 categories) — Lipid-lowering agents	4,583	0.4
6	Anti-platelets — Antihypertensives (3 categories) — Drugs for peptic ulcer — Lipid-lowering agents	9,229	0.8
	Antiplatelets — Antibiotics — Antihypertensives (2 categories) — Drugs for peptic ulcer — Lipid-lowering agents	4,709	0.4
	Antiplatelets — Antidiabetic agents — Antihypertensives (2 categories) — Drugs for peptic ulcer — Lipid-lowering agents	4,003	0.3
7	Anti-platelets — Antihypertensives (4 categories) — Drugs for peptic ulcer — Lipid-lowering agents	2,997	0.3
	Antiplatelets — Antidiabetic agents (2 categories) — Antihypertensives (2 categories) — Drugs for peptic ulcer and GERD — Lipid-lowering agents	2,492	0.2
	Antiplatelets — Antibiotics — Antihypertensives (3 categories) - Lipid-lowering medicines	2,305	0.2
8	Antiplatelets — Antidiabetic agents (2 categories) — Antihypertensives (3 categories) — Drugs for peptic ulcer — Lipid-lowering agents	1,429	0.1
	Antiplatelets — Antidiabetic agents (3 categories) — Antihypertensives (2 categories) — Drugs for peptic ulcer — Lipid-lowering agents	1,096	0.1
	Antiplatelets — Antihypertensives (4 categories) — Antigout medicines — Drugs for peptic ulcer — Lipid-lowering agents	769	0.1

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

1.7 Temporal trend of monthly drug consumption

Approved care regime - Class A-NHS

Figure 1.7.1 shows the trend in consumption of class A-NHS medicines in DDD/1000 inhabitants per day during the period 2002-2021.
In this period, pharmaceutical consumption has registered a growing trend, increasing from 743.6 DDD/1000 inhabitants per day in 2004 to 1133.2 DDD/1000 inhabitants per day in 2021.
Drug consumption, as well as a growing trend, also shows a seasonal trend. This is reflected in the regular monthly consumption peaks reported in Figure 1.7.1. Generally, systemic antimicrobials and respiratory medicines are the therapeutic categories on which consumption seasonality has the highest impact.
If we analyse the trend over four years, we can observe how consumption increased more in the period 2006-2009 (CAGR: +0.3%), how this is stable over the period 2013-2017 (CAGR: +0.0%), while slightly decreasing in the last period 2018-2021 (CAGR: —0.1%). Trends over the last period have been influenced by the reduced consumption in 2020 following the SARS-CoV-2 pandemic, which led to a decrease in consumption of certain categories of drugs prevalently 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 2006. Trends in consumption might be influenced by regulatory decisions that over time have resulted in the inclusion or exclusion of medicines from reimbursement and price updating every two years. In the periods 2006-2009, 2010-2013 and 2014-2017, consumption decreased with an average annual variation of -0.3%, -0.4% and -0.6%, respectively; in the last 4 years consumption has increased from an annual average of 186.0 DDD in 2018 to an average of 212.8 DDD in 2021, with a 14.4% increase and a 0.3% average annual change (see Section 2.6 for further details). In 2021, the months with the highest average consumption were October (249.2 DDD) and November (249.0 DDD).By contrast, August showed the lowest consumption figure (176.1 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 2006-2021. Consumption shows an increasing trend from an average of 100.6 DDD in 2006 to an average of 173.5 DDD in 2021 (+72.5%). The chart shows that the largest increase in consumption was recorded in the period 2006-2009; consumption was fairly stable over subsequent periods. In 2021 the lowest consumption rates were observed in August with 104.2 DDD and in December with 154.2 DDD, while July (with 216.4 DDD) and November (with 203.6 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 procedure 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 2002-2021 of total DDD/1000 inhabitants per day of class A-NHS medicines under approved care regime

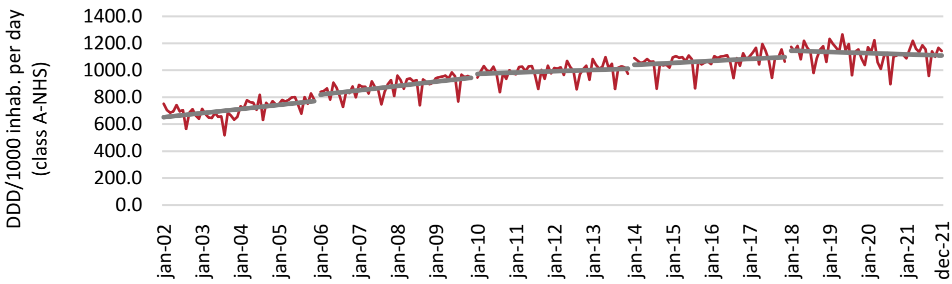


Figure 1.7.2 Time series 2006-2021 of total DDD/1000 inhabitants per day of class C medicines with prescription

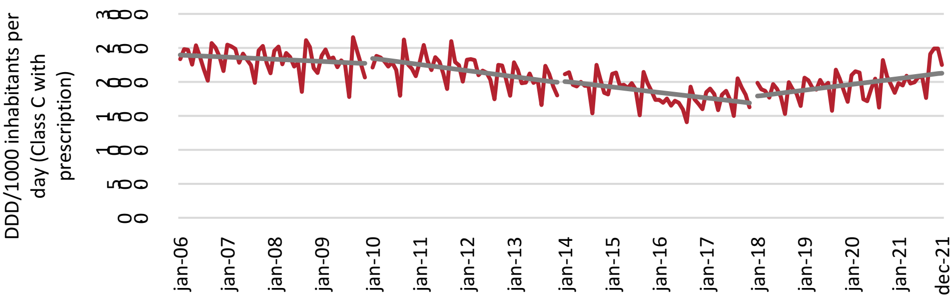
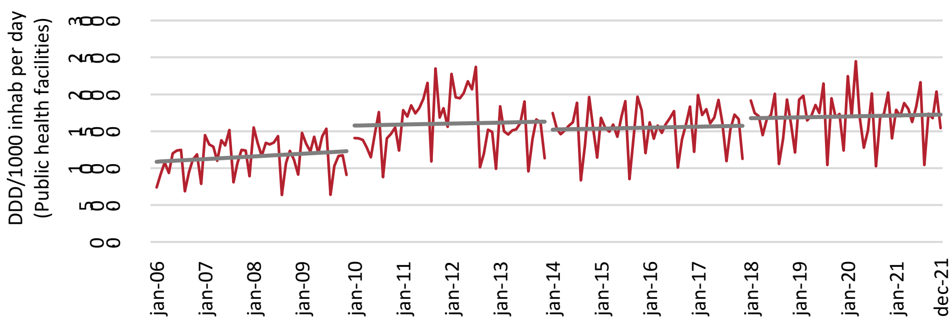


Figure 1.7.3 Time series 2006-2021 of DDD/1000 inhabitants per day of medicines purchased by public health facilities



1.8 Temporal trend of drug prices

Approved care regime - Class A-NHS

Figure 1.8.1 shows the trend in the DDD-weighted average price for class A-NHS drugs in the period January 2002 - December 2021. The time series shows a decreasing trend, especially starting from 2006-2009 (CAGR: -0.6%) and in the period 2010-2013 (CAGR: -0.5%). This decrease was mainly due to the patent expiries of important molecules during that period (e.g. valsartan and atorvastatin), to the price reductions implemented at national level since 2006 and to the economic effects of AIFA Resolution of 8 April 2011. These measures led to a reduction in reference prices of medicinal products included in the transparency lists on the basis of a comparison of prices of equivalent products in Italy with those of the same package sizes marketed in Germany, UK, France and Spain. Average prices were also reduced in 2018 due to the entry into the market of equivalent drugs of high consumption molecules under approved care regime like rosuvastatin, the simvastatin/ezetimibe combination and dutasteride resulting in an annual reduction in the average cost of 5.7% compared to 2017.
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 and of those not included in the list in the period 2017-2021. Both listed and non-listed drugs show a substantial stability in average prices (by DDD and by package) over the analysed period, although the average price of medicinal products on the transparency list is well below those not listed, as expected. In 2021, the price per DDD of the listed medicinal products, amounting to 0.32 euros, was almost half the price of the non-listed medicinal products (0.72 euros).
Figure 1.8.3 shows average price trends over the period January 2017 - December 2021 for drugs included in the transparency list as of 1 January 2018. There is a clear effect on price reduction due to the inclusion in the transparency list, since prices decreased significantly as compared to 2018 and 2019 (-28.3% and -21.6%, respectively), when high consumption molecules were listed, such as rosuvastatin and the simvastatin/ezetimibe combination, whereas price reduction was lower in 2020 and 2021 (-8.4% and -10.2%, respectively).

Class C medicines with prescription

Figure 1.8.4 shows the trend in average weighted price per package and per DDD of class C medicines with prescription in the period 2004-2021. Looking at the monthly data of the time series, trends between these two indexes show regular growth from 10.13 euros per package (and 0.6 euros per DDD) in 2004 to 14.15 euros per package (and 0.76 euros per DDD) in 2021, up by respectively 39.7% and 26.7%, compared to 2004. In 2021, an odd year when pharmaceutical companies could change the price of these medicines[1] a 3.8% increase was recorded compared to 2020, slightly lower than in 2019 (+4.4 %) (See Section 2.6 for further details).

[1]Article 1, paragraph 3, of Law Decree no. 87 of 27 May 2005

Medicines purchased by public health facilities

Figure 1.8.5 shows the trend of average cost per package and DDD of medicines purchased by public health facilities in the period 2006-2021. The price trend increased from 2006 to 2009, then stabilised in the period 2010-2013 and increased again from 2014 to 2017. Starting from 2018, a reduction is likely to be associated with the marketing of biosimilars and generics of widely used molecules (e.g. trastuzumab, bevacizumab, pegfilgrastim, gefitinib, erlotinib, and dasatinib).To investigate this effect, an analysis was carried out of medicines that have lost market exclusivity since January 2017. As a proxy for the loss of exclusivity, the marketization was used of at least one other specialty based on the same active ingredient. Figure 1.8.6 shows with evidence the effect on the price due to entry into the market of the competitors. In fact, comparing the average price per DDD and per package at the beginning of the period with the 2021 period, there was a reduction by over 50%. The average price per package goes from 304.57 euros in 2016 to 151.60 euros in 2021, while the price for DDD shifts from 27.02 euros to 13.44 euros. During this period, various generics and biosimilars of molecules entered the market, mainly purchased by public health facilities.

If we consider the drugs that have only one specialty on the market each year (Figure 1.8.7), we can see that both the price per DDD and per package has decreased in the period 2016-2021. In detail, the price per pack goes from 221.60 euros in 2016 to 196.38 euros in 2021 while the price for DDD goes from 15.37 euros in 2016 to 9.18 euros in 2021. These values are well above the prices of all medicines purchased by public health facilities (Figure 1.8.5), since the effects of competition do not apply to these medicines.

Figure 1.8.1 2002-2021 trend of average price of class A-NHS drugs under approved care regime

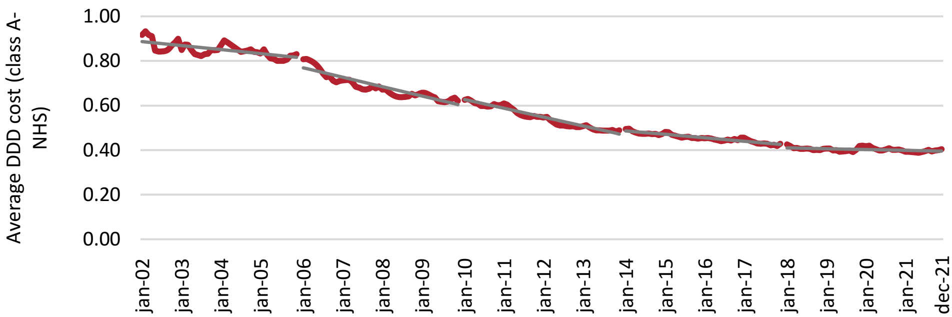


Figure 1.8.2 2017-2021 trend of average price for drugs included in the transparency list and not included in the list (approved care regime)

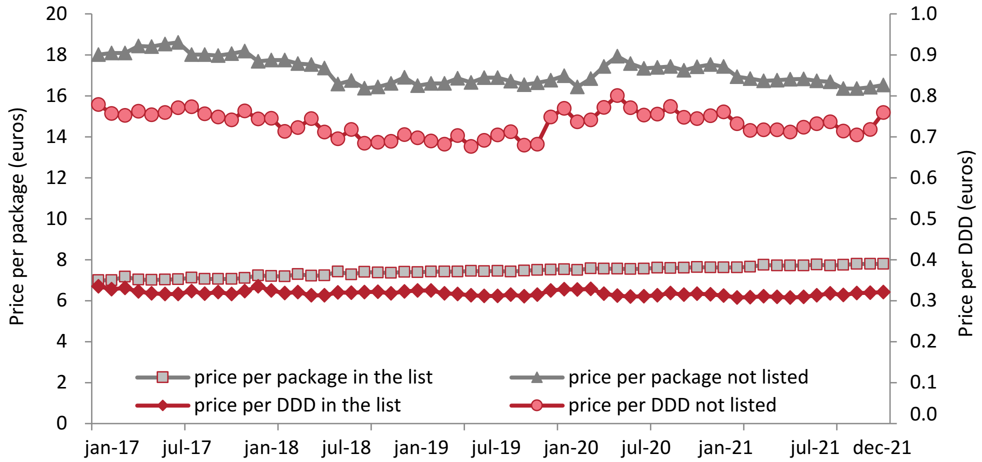


Figure 1.8.3 2017-2021 trend of average price for drugs included in the transparency list as of 1 January 2018 (approved care regime)

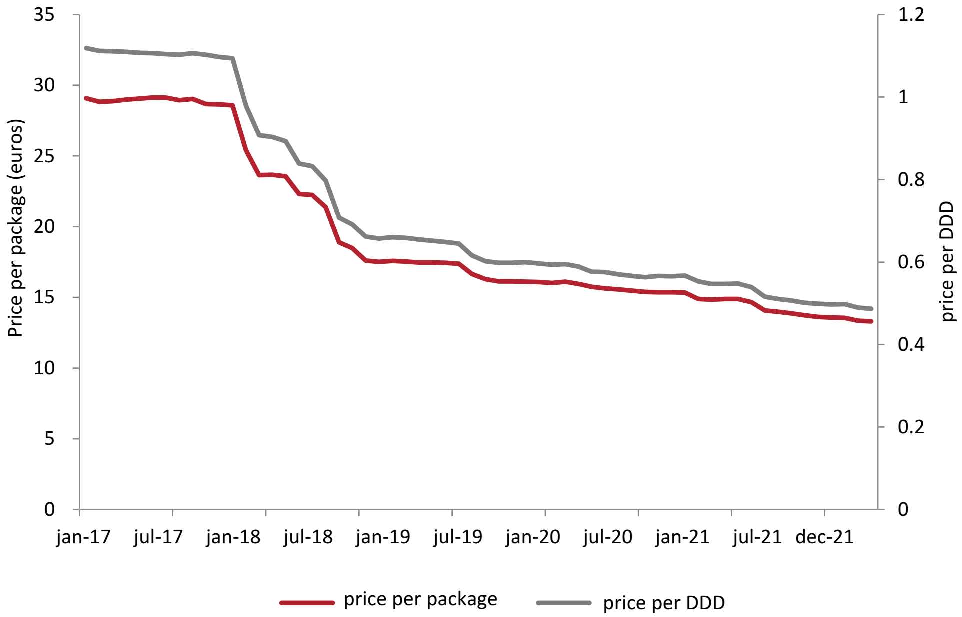


Figure 1.8.4 2016-2021 trend of average price for class C drugs with prescription (local pharmacies)

Figure 1.8.5 2006-2021 trend of average price for drugs purchased by public health facilities

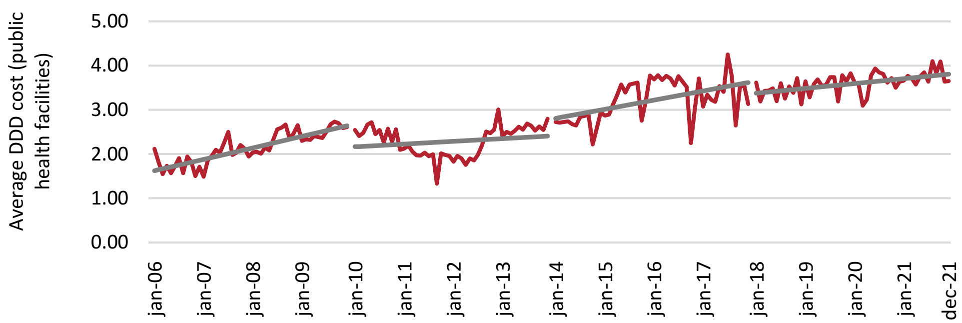


Figure 1.8.6 2016-2021 trend of average price for drugs having lost market exclusivity as of 1 January 2017 (public health facilities)

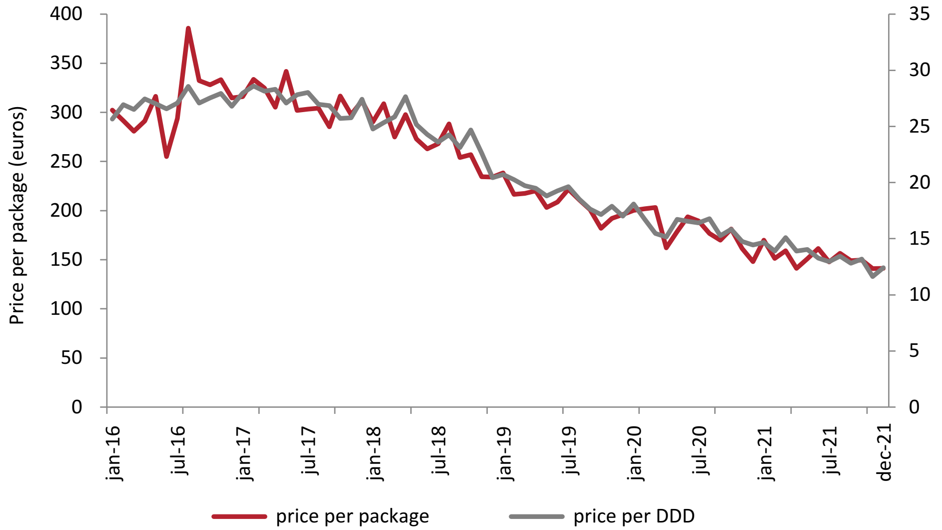
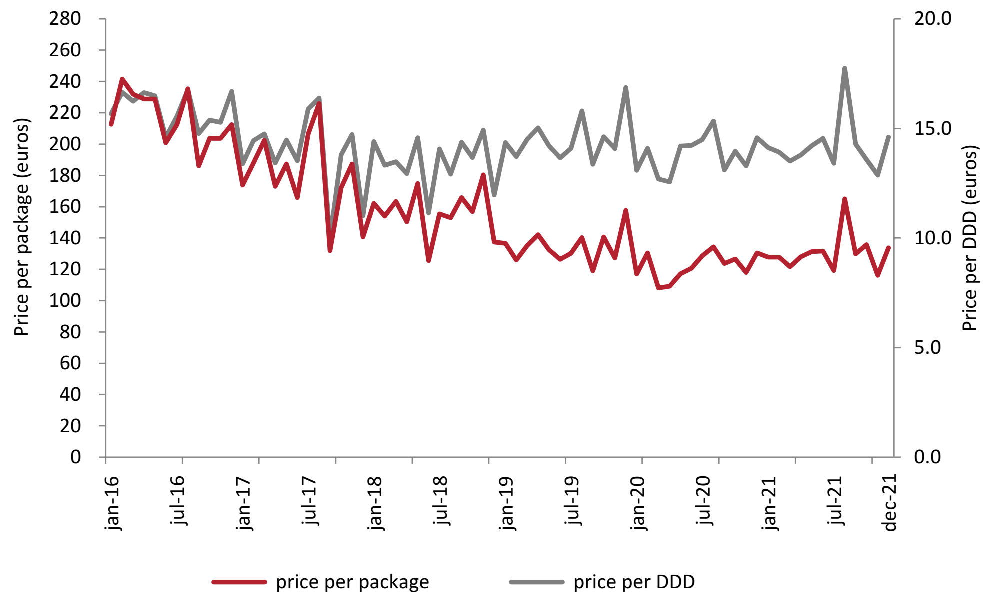


Figure 1.8.7 2016-2021 trend of average price for drugs with only one specialty in the market (public health facilities)



1.9 International comparison

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

- impact of pharmaceutical expenditure on Gross Domestic Product (GDP);
- 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 and the comparison with the previous year regarding:
  - penetration of equivalent and biosimilar drugs;
  - level of market concentration in relation to off-patent biological medicines;
  - expenditure on orphan medicinal products
- a price comparison analysis in 2021;
- a time analysis (2014-2021) comparing ex-factory prices against the European average for products covered and not covered by patents;
- a comparison analysis of ex-factory prices or industry in Italy during 2014-2021 against the European average for drug payers, defined on the basis of their launch date.

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 and is net of direct and "on-behalf" distribution. In addition to 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)[2].

Comparison of expenditure and consumption

In Italy in 2021 the incidence of total pharmaceutical expenditure on GDP was 1.7%, lower only if compared to Spain (2.0%) and Portugal (1.8%). Significantly lower percentages were recorded in Sweden (0.9%) and UK (1.1%) (Figure 1.9.1). All countries showed an increase from 2019 to 2020 in GDP percentage related to pharmaceutical expenditure. This trend is essentially due to a decrease in GDP recorded in all countries, against an increase in pharmaceutical expenditure. In 2021, on the other hand, compared to 2020, there is a substantial stability in the incidence of total pharmaceutical expenditure on GDP.
The total Italian pharmaceutical expenditure, including local public and private expenditure and hospital expenditure, was equal to 507 euros per capita, lower than that Germany (610

[2] Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, UK, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, Hungary.

euros), Austria (572 euros), Belgium (563 euros) and Spain (520 euros), while it is well above the values of Poland (197 euros), Portugal (377 euros), UK (428 euros), Sweden (444 euros) and the average of the European countries, which is equal to 328 euros (Figure 1.9.2). Important differences exist in the breakdown of pharmaceutical expenditure in the two delivery channels: hospital expenditure on the total ranges between 67% in Italy and 23% (in Germany) and 29% (in Poland) (Figure 1.9.2). These differences may be due to heterogeneity in the way medicines are delivered and to the fact that, for Italy, the drugs distributed directly and "on behalf" are included in the hospital expenditure budget.

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 838 SU in Italy, lower than all countries considered (average countries analysed (EU 10) 1,097 SU per capita and average Europe 1,093). This ranking mainly depends on the local distribution channel, lower than all countries, while as regards hospitals, Italy ranks second in per capita consumption with 65 SU, lower only than UK (72 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. With the same treatment adherence, a country that has on average a smaller number of dose units per package will find 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 in the local area contain on average a lower number of SU and DDD than the European average.

When looking at the average cost per dose unit, Italy with 0.21 euros has a 19% lower value in the area than the average (0.26 euros) of the 10 countries analysed (Figure 1.9.4). In Italy, the average cost is fairly stable compared with 2020 (+ 1.0%), with the largest variation found in Austria (+10.3%) and Germany (+ 9.3%). In hospital settings, Italy has an average cost for Standard Unit (5.25 euros) higher than the average of the countries analysed (3.84 euros), with a 36.6% percentage difference. It is important to underline that the comparison is not carried out on a common basket of drugs 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. All countries analysed, except Poland and Portugal, show an increase compared to 2020 (Figure 1.9.5).

As for community care, in Italy a larger share of expenditure (20.4%) is due to cardiovascular system drugs, higher than in other countries. For example, in Sweden, only 5.2% of such expenditure is due to this drug category. In UK and Spain, both with a value of 23%, central nervous system drugs record the highest incidence on expenditure. Poland (13.5%) and UK (12.3%) are the countries with the highest incidence of expenditure due to respiratory system drugs. Finally, gastro-intestinal drugs account for a larger share of expenditure in Portugal (22.7%), UK (21.1%) and Spain (21.1%). Sweden (9.8%) and France (9.1%) report a considerably higher proportion of antimicrobial expenditure than Italy (4.2%) (Table 1.9.1). Italy ranks first in incidence of community consumption of cardiovascular system drugs (26.2%; Table 1.9.2), followed by Portugal (22.6%). The percentage of SU consumed for central nervous system drugs (14.2%) is lower than nearly all countries considered except Germany (14.0%) and Poland (14.2%): Spain 26.5%, Sweden 24.6%, France 23.1%, Portugal 22.6%, Belgium 21.9%, UK 21.9% and Austria 16.2%. The percentage of consumption of respiratory system drugs also shows a low value in Italy (10.7%), lower than all the other countries analysed, with the exception of Portugal (9.3%). 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 Poland, France and UK.

As regards hospital care (Table 1.9.3), in Italy the first item of expenditure is antineoplastic drugs (42.8%), although higher percentages are observed in almost all the countries considered, with the exception of Germany (37.8%) and Sweden (41.3%). For antimicrobials, Germany (21.8%), Portugal (18.8%), Spain (17.0%) and Italy (15.6%) have the highest incidence of expenditure compared to other countries. This incidence in Italy has gradually been decreasing, in fact it was 22.6% in 2019 and 17.6% in 2020. Italy shows the highest incidence, after Sweden (12.8%), of expenditure on haematological drugs (12.7%), compared to the countries considered in the analysis (average 9.0%) and to the EU average (9.1%) (Table 1.9.3).

Central nervous system drugs rank first in incidence on hospital consumption (25.1%), higher than the average of the countries considered in the analysis (24.1%) and the EU average (19.1%). Similarly to expenditure, Italy shows the highest incidence of consumption for haematological drugs, with a much higher percentage (24.0%) than recorded in other countries (EU10 average: 7.4% and European average: 6.1%). Also for gastrointestinal drugs, Italy has the highest incidence on hospital consumption (17.6% vs EU10 average: 13.8% and European average: 12.2%). On the other hand, the percentage of SU consumed in hospital for respiratory system drugs is low (2.8%) compared to the consumption percentages of all the countries analysed (EU 10 average: 11.2% and Europe average: 9.6%) (Table 1.9.4).

Wide differences are found in the ranks of the most expensive active ingredients, in both community and hospital settings. For example, paracetamol ranks first in Italy, while in Germany it ranks 254th; cholecalciferol in Italy ranks 2nd (in 2020 it ranked 4th), while in France it ranks 87th. As for consumption, the top 4 molecules in Italy also feature in the ranking of the top 30 molecules in all countries. It should be noted that pantoprazole, 5th active ingredient for consumption in Italy, ranks over the 100th position in Sweden and UK. These differences, in addition to the different prescription profiles, may also be attributed to different modalities of medicine reimbursement (Tables 1.9.5 and 1.9.6). For hospital care, pembrolizumab, which ranks 1st in Italy, holds the first 2 positions in all countries (except the UK where it ranks 5th). Nivolumab, 3rd in Italy for expenditure, is also in the top 10 positions in all countries analysed except Great Britain (19th rank), while for lenalidomide there is a high heterogeneity within the countries analysed: 2nd rank in Italy, 202nd in Germany, 156th in Austria and 144th in Sweden. The sofosbuvir/velpatasvir combination, indicated in the treatment of HCV infection, ranks 8th (in 2020 it was 4th) in Italy in terms of expenditure, while it ranks over 600th in Austria and over 350th in Germany. These differences may also be attributed to the different methods of drug distribution, together with the different epidemiology of the disease in the various countries. In fact, in Italy, as anti-HCV drugs are distributed directly and "on behalf", they are included in the hospital channel, while in other countries these drugs are included in the community delivery channel (Table 1.9.7). Wide variability is found in the ranks of the active ingredients with the highest hospital consumption: apixaban, ranking 1st in Italy for hospital consumption, ranks over 200th in Portugal. Similarly to what has been discussed for anti-HCV drugs, these differences may be attributed to the different delivery methods of the new oral anticoagulants (Table 1.9.8).

Figure 1.9.1 International comparison: incidence of total pharmaceutical expenditure on GDP in the period 2016-2021

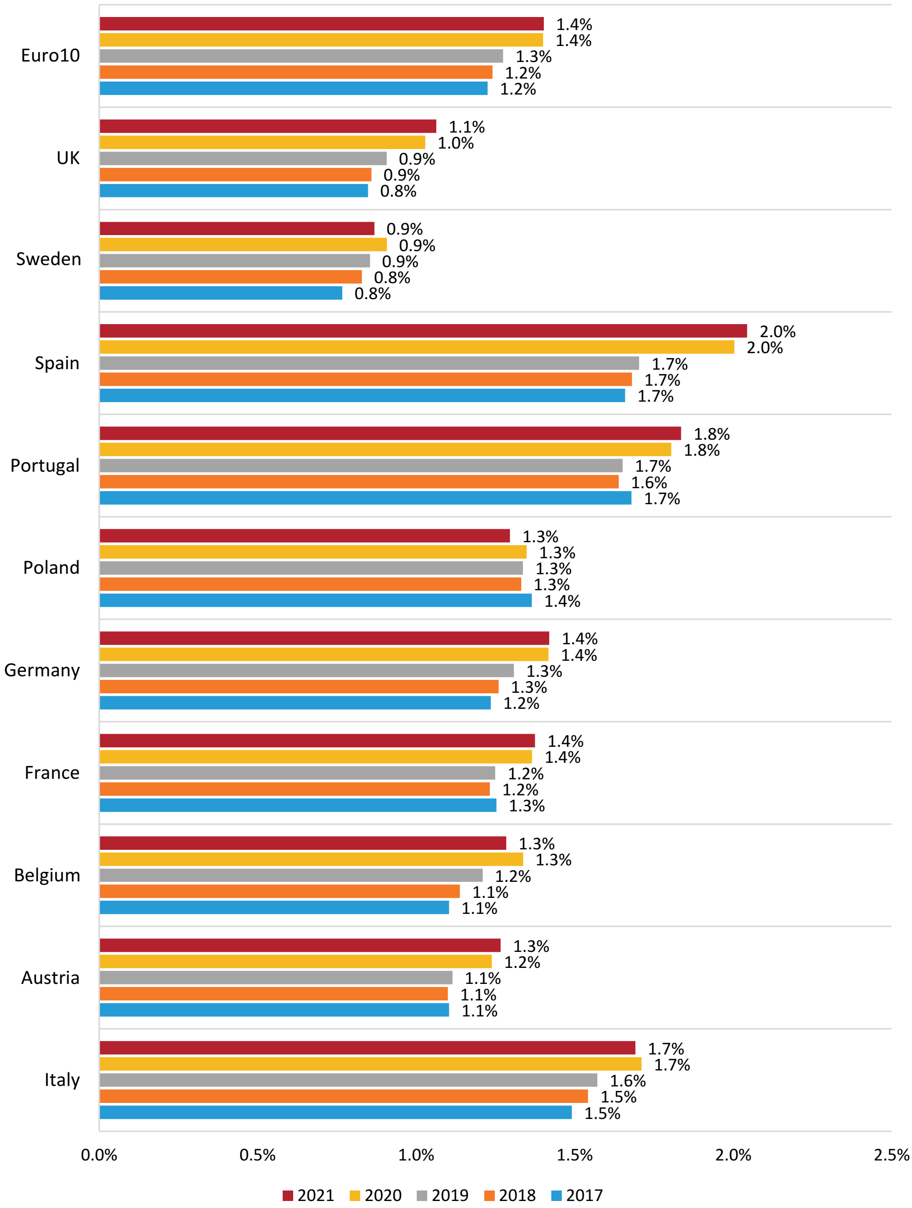


Figure 1.9.2 International comparison of overall per capita pharmaceutical expenditure by distribution channel (Year 2021)

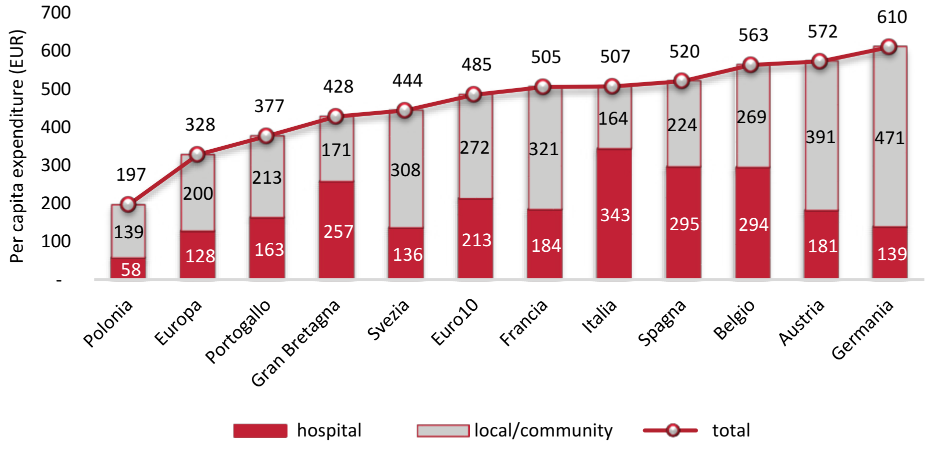


Figure 1.9.3 International comparison of total per capita consumption (Standard Unit per inhabitant) by distribution channel (Year 2021)

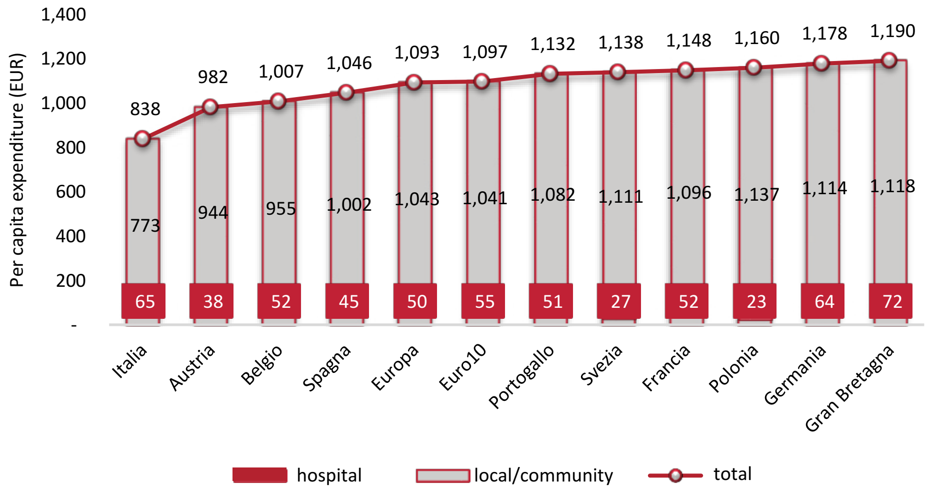


Figure 1.9.4 International comparison of the average cost by Standard Unit in the 2021 community area and 2021-2020 variation

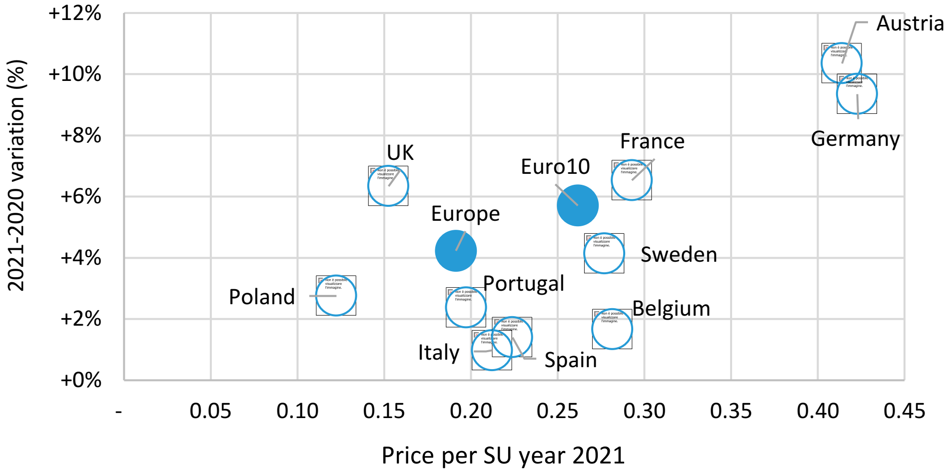


Figure 1.9.5 International comparison of average cost by Standard Unit in hospital setting in 2021 and 2021-2020 variation

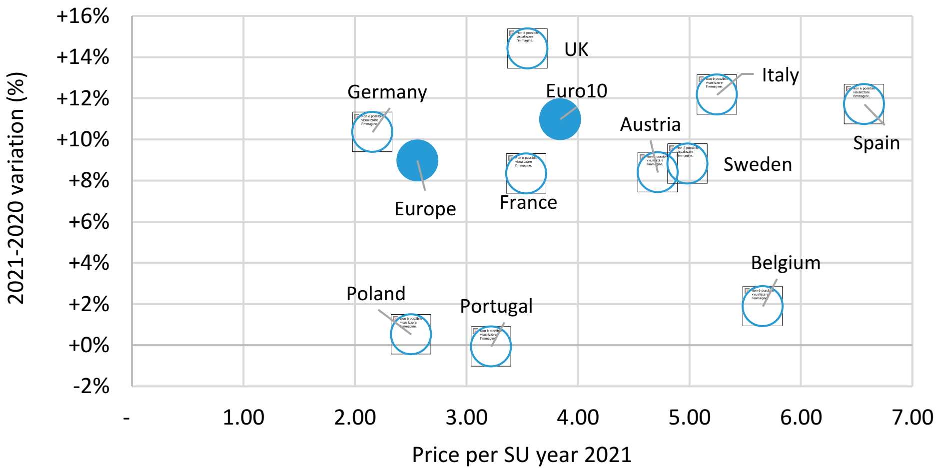


Figure 1.9.6 International comparison of average cost by Standard Unit in local/community care and in hospital setting in 2021 and 2021-2020 variation

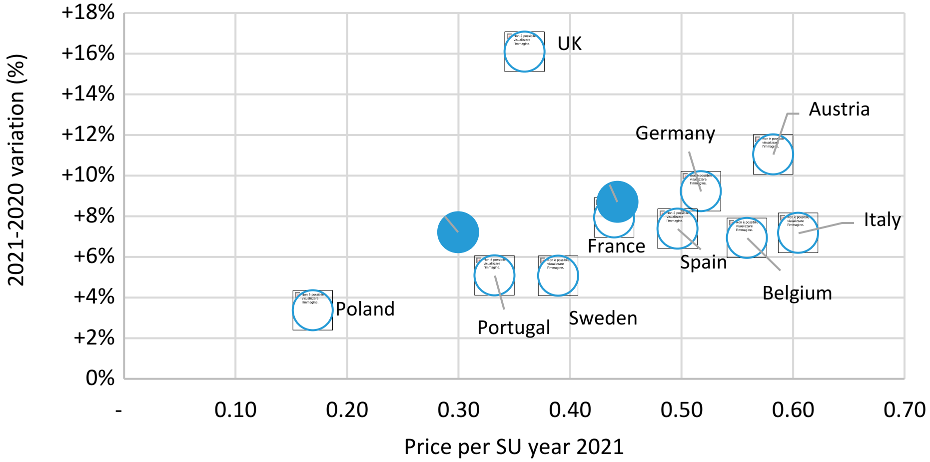


Table 1.9.1 International comparison of percent distribution of local pharmaceutical expenditure* in 2021 by ATC 1st level

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
C - Cardiovascular system	20.4	10.1	10.8	8.6	7.7	16.4	18.9	14.8	5.2	12.3	11.5	10.9
N - CNS	19.3	15.4	17.8	13.8	14.2	14.9	19.0	23.3	16.8	23.4	15.7	16.8
A - Gastrointestinal tract and metabolism	18.2	10.2	14.6	11.4	12.0	19.2	22.7	21.1	13.6	21.1	15.8	14.9
R - Respiratory system	10.0	8.7	9.7	8.9	7.8	13.5	7.8	9.1	8.4	12.3	9.3	9.2
G - Genito-urinary and sex hormones	7.2	2.1	4.7	3.4	2.5	6.1	5.5	6.0	3.9	5.1	4.2	4.0
M - Musculo-skeletal system	5.9	4.7	4.0	2.8	3.8	5.0	5.5	4.2	3.2	2.1	4.2	3.7
J - Antimicrobials for systemic use	4.2	5.7	8.6	9.1	8.0	4.1	3.4	2.7	9.8	3.1	6.6	6.6
D - Dermatologicals	4.0	2.4	3.2	1.9	3.2	3.2	2.8	2.7	2.0	2.9	2.9	2.9
S - Sensory organs	3.4	0.7	1.3	5.4	2.9	1.8	1.8	2.0	1.8	2.4	2.8	3.1
B - Blood and blood forming organs	3.3	8.1	10.6	8.7	9.2	12.2	9.8	8.0	8.9	9.9	8.7	8.7
H - Systemic hormones	2.1	1.7	2.2	2.5	2.0	1.3	0.9	2.1	2.8	2.2	2.0	2.1
L - Antineoplastic and immunomodulating agents	1.5	28.6	12.1	22.6	24.5	1.6	0.5	3.5	22.8	2.7	14.9	16.0
V - Various	0.4	1.5	0.3	0.6	2.2	0.6	1.2	0.5	0.6	0.2	1.3	1.1
P - Antiparasitic products	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.2	0.2

*drugs dispensed by licensed pharmacies, excluding distribution "on behalf"

Table 1.9.2 International comparison of the percentage distribution of local/community consumption* by ATC 1st level

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
C - Cardiovascular system	26.2	19.9	18.3	16.1	23.0	21.3	22.6	17.8	17.4	16.5	18.0	19.9
A - Gastrointestinal tract and metabolism	17.5	15.0	15.9	17.8	13.7	22.6	14.5	15.2	17.2	17.0	16.7	16.7
N - Nervous system	14.2	16.2	21.9	23.1	14.0	14.2	22.6	26.5	24.6	21.9	16.1	19.2
R - Respiratory system	10.7	20.1	17.5	14.9	15.4	15.5	9.3	13.2	16.0	19.1	18.9	15.2
S - Sensory organs	8.1	4.9	5.3	7.1	7.2	4.9	4.8	6.6	5.6	5.6	7.9	6.5
M - Musculo-skeletal system	6.4	7.7	5.0	4.8	6.0	6.8	7.7	5.8	3.6	3.1	5.5	5.4
B - Blood and blood forming organs	5.4	4.9	5.9	4.5	5.3	4.7	4.5	4.6	4.9	4.3	4.5	4.8
H - Systemic hormones	3.8	3.3	2.5	2.7	4.1	2.5	2.1	2.7	2.8	2.7	2.4	3.1
D - Dermatologicals	3.0	4.0	3.0	3.8	4.0	2.8	3.8	3.3	4.3	5.6	4.4	3.9
G - Genito-urinary system and sex hormones	2.8	2.0	2.6	2.2	2.5	2.6	2.6	2.1	2.0	2.2	2.2	2.4
J - Antimicrobials for systemic use	1.3	0.8	1.3	1.8	0.7	1.4	1.0	1.3	0.8	1.4	1.5	1.2
L - Antineoplastic and immunomodulating agents	0.4	0.6	0.7	0.5	0.5	0.3	0.2	0.6	0.7	0.4	0.7	0.5
V - Various	0.2	0.5	0.1	0.5	3.4	0.4	4.2	0.1	0.1	0.1	0.9	1.0
P - Antiparasitic products	0.0	0.1	0.1	0.1	0.3	0.1	0.2	0.1	0.1	0.1	0.1	0.1

*drugs dispensed by licensed pharmacies, excluding distribution "on behalf"

Table 1.9.3 International comparison of percentage distribution of 2021 hospital pharmaceutical expenditure by Level I ATC

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
L - Antineoplastic and immunomodulating agents	42.8	55.7	59.6	50.5	37.8	52.2	42.9	49.9	41.3	45.5	45.7	46.1
J - Antimicrobials for systemic use	15.6	15.4	7.8	10.4	21.8	10.2	18.8	17.0	12.8	14.3	16.1	15.2
B - Blood and blood forming organs	12.7	8.6	9.6	9.9	10.0	4.9	5.7	6.3	12.8	6.4	9.0	9.1
N - Nervous system	9.7	7.7	6.4	13.8	15.6	18.7	13.8	9.2	9.6	7.7	10.7	10.8
A - Gastrointestinal tract and metabolism	7.3	4.1	5.9	6.2	4.8	2.1	6.6	4.1	5.3	4.5	5.3	5.4
R - Respiratory system	3.0	0.9	2.3	0.9	1.1	2.2	3.4	4.5	1.2	9.0	3.5	3.8
C - Cardiovascular system	2.5	2.3	1.8	2.5	2.1	3.2	1.4	1.9	1.7	1.5	2.0	2.1
M — Musculo-skeletal system	1.7	1.5	1.3	2.1	2.0	1.4	1.7	1.8	4.4	2.9	2.3	2.1
H - Systemic hormones	1.5	0.8	0.7	1.0	0.9	1.8	1.3	1.2	0.7	1.1	1.2	1.2
S - Sensory organs	1.2	1.6	3.3	0.5	1.6	2.6	2.2	2.9	8.8	5.5	2.6	2.6
V - Various	0.7	0.6	0.6	0.5	1.2	0.3	0.6	0.2	0.8	0.5	0.6	0.6
D - Dermatologicals	0.7	0.2	0.1	1.0	0.8	0.3	1.2	0.9	0.1	0.6	0.7	0.7
G - Genito-urinary system and sex hormones	0.5	0.6	0.5	0.6	0.3	0.3	0.2	0.2	0.3	0.5	0.4	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 1.9.4 International comparison of percentage distribution of 2021 hospital consumption by Level I ATC

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK	Europe	EU10
N - Nervous system	25.1	25.5	37.2	33.3	20.0	27.0	13.1	22.9	38.2	19.7	19.1	24.1
B - Blood and blood forming organs	24.0	4.7	4.3	4.2	3.3	6.3	1.9	2.8	5.0	4.5	6.1	7.4
A - Gastrointestinal tract and metabolism	17.6	13.2	11.2	14.4	14.2	17.2	6.6	7.5	17.0	13.2	12.2	13.8
C - Cardiovascular system	10.5	12.1	8.1	7.9	9.7	13.3	5.1	6.2	8.4	5.7	8.7	8.4
L - Antineoplastic and immunomodulating agents	4.9	0.6	3.2	0.7	0.3	2.9	8.8	3.4	1.1	4.5	3.7	2.8
J - Antimicrobials for systemic use	4.7	3.9	4.6	3.5	2.9	6.2	7.4	6.7	6.4	7.1	8.3	4.9
S - Sensory organs	3.4	9.8	11.1	8.3	9.9	7.9	9.4	19.4	5.4	17.3	8.4	10.9
R - Respiratory system	2.8	13.4	11.1	12.4	11.8	6.4	28.8	15.9	6.3	13.4	9.6	11.2
D - Dermatologicals	2.6	5.6	3.6	8.4	10.9	3.7	13.5	10.2	2.6	7.1	14.7	7.6
H - Systemic hormones	1.5	2.0	1.4	1.9	1.7	2.8	1.8	2.0	5.4	3.0	2.2	2.1
M - Musculo-skeletal system	1.1	6.3	2.6	1.8	4.4	4.6	1.3	2.2	2.1	1.7	2.2	2.5
V - Various	1.0	1.8	0.6	2.4	10.2	0.3	1.5	0.2	0.8	1.1	4.0	3.3
G - Genito-urinary system and sex hormones	0.6	1.0	0.9	0.9	0.6	1.2	0.8	0.5	1.1	1.5	0.8	0.9
P - Antiparasitic products	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.1

Table 1.9.5 International comparison of the first 20 active substances in Italy: rank by community/local expenditure* in 2021

Active substance	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe
paracetamol	1	152	3	254	4	28	14	10	15	24	5
cholecalciferol	2	92	87	77	24	11	56	62	86	51	23
pantoprazole	3	41	60	59	7	19	30	28	462	344	20
atorvastatin	4	36	35	120	18	9	6	1	81	1	4
diclofenac	5	27	62	38	23	6	22	67	73	90	11
ibuprofen	6	43	89	35	27	5	9	25	48	106	8
bisoprolol	7	75	49	207	74	7	33	88	196	73	43
amoxicillin/clavulanic acid	8	133	82	149	89	45	37	80	605	338	57
esomeprazole	9	140	24	293	122	117	21	19	125	100	52
ketoprofen	10	914	219	1,808	442	33	360	602	417	574	153
beclomethasone/formoterol	11	60	66	34	20	32		26	93	4	12
omeprazole	12	307	98	186	17	26	35	13	69	19	33
lansoprazole	13	281	155	1,257	414	682	134	86	464	43	123
enoxaparin	14	46	26	58	30	4	38	6	356	120	18
fluticasone furoate/vilanterol	15	319	103	162	21		44	47	287	52	71
alprazolam	16	478	260	1,146	38	154	45	132	545	978	179
ramipril	17	167	114	169	173	14	96	139	353	44	79
mesalazine	18	109	132	88	98	38	42	42	34	17	40
acetylsalicylic acid	19	162	67	156	76	12	27	93	239	80	51
lorazepam	20	503	533	607	121	282	92	133	870	217	263

*Medicines dispensed by local pharmacies, net of direct and “on behalf” distribution

Table 1.9.6 International comparison of the first 20 active substances in Italy: rank by community/local expenditure* in 2021

Active substance	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe
acetylsalicylic acid	1	5	4	3	2	2	8	7	14	19	5
metformin	2	10	3	11	5	1	3	8	2	3	4
levothyroxine	3	4	5	2	6	6	10	5	12	8	6
bisoprolol	4	8	8	7	7	7	11	13	27	15	8
pantoprazole	5	6	18	8	4	14	9	38	129	159	13
diclofenac	6	2	6	6	9	4	7	15	31	54	7
atorvastatin	7	13	7	16	10	11	4	9	7	6	10
paracetamol	8	12	1	28	1	17	2	1	1	2	2
furosemide	9	35	15	111	101	56	15	23	32	39	25
ramipril	10	36	20	4	99	12	41	52	55	11	15
naphazoline	11	46		1,235	419	634		265	233	129	11
ketoprofen	12	446	72	934	206	30	548	187	181	300	51
salbutamol	13	15	2	9	12	27	13	3	13	1	3
ibuprofen	14	11	9	5	8	10	5	4	10	24	9
omeprazole	15	186	17	34	14	35	14	2	5	7	12
amlodipine	16	18	29	14	23	23	36	26	9	9	14
lansoprazole	17	169	73	561	285	514	75	103	269	13	46
esomeprazole	18	60	12	97	36	41	16	45	48	100	33
simvastatin	19	29	59	19	13	72	12	10	33	21	21
alprazolam	20	91	13	497	16	122	6	17	198	683	42

* Drugs dispensed by licensed pharmacies, excluding “on behalf” distribution

Table 1.9.7 International comparison of the first 20 active substances in Italy: rank by community/local expenditure* in 2021

Active substance	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe
pembrolizumab	1	1	1	1	1	2	2	1	2	5	1
lenalidomide	2	156	5	202	3	7	6	4	144	8	5
nivolumab	3	4	3	6	2	3	5	10	6	19	2
adalimumab	4	163	412	120	245	59	21	2	327	1	6
epoetin alfa	5	220	113	150	57	147	263	90	1,008	125	50
ibrutinib	6	288	304	293	6	11	7	3	326	13	14
immunoglobulin base	7	8	4	2	7	30	1	9	3	7	3
sofosbuvir/velpatasvir	8	600	226	354	56	14	93	11	77	18	21
daratumumab	9	3	2	8	8	25	13	7	4	17	4
rivaroxaban	10	164	189	140	237	141	695	418	293	211	56
apixaban	11	151	103	106	204	279	553	376	126	133	54
palbociclib	12	414	351	321	9	20	32	17	424	14	24
trastuzumab	13	7	13	29	11	13	8	14	9	24	10
dimethyl fumarate	14	760	920	667	834	6	31	35	984	16	37
enzalutamide	15	214	345	299	18	4	17	29	300	10	18
pertuzumab	16	11	14	16	14	5	9	15	19	36	12
glecaprevir/pibrentasvir	17	720	199	409	59	9	80	33	562	90	45
enoxaparin sodium	18	14	16	12	51	16	60	84	172	42	20
epoetin zeta	19	128	165	887			358	429	102	421	125
bictegravir/emtricitabine/ tenofovir alafenamide	20	589	151	513	190		34	5	256	55	27

Table 1.9.8 International comparison of the first 20 active substances in Italy: rank by hospital expenditure* in 2021

Active substance	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK	Europe
apixaban	1	48	25	56	82	168	260	152	31	37	9
quetiapine	2	14	121	49	30	11	59	25	70	122	22
rivaroxaban	3	148	153	160	167	97	439	282	194	110	29
dabigatran	4	221	293	390	200	161	649	334	286	474	43
clopidogrel	5	123	147	124	114	133	253	162	142	79	35
ranolazine	6	381		327		1,462	991	592		311	79
edoxaban	7	186		265	203		598	392	360	244	104
lidocaine	8	7	5	14	1	8	12	88	1	90	8
metformine/sitagliptin	9	207	361	319	813	1,115		603	569	1,358	127
enoxaparin	10	9	15	62	22	7	29	27	173	41	24
pantoprazole	11	5	11	10	7	1	27	50	146	335	14
furosemide	12	18	12	46	79	4	24	18	13	44	19
ticagrelor	13	288	333	275	266	216	334	372	205	196	118
olanzapine	14	146	127	132	73	55	123	75	60	162	77
methadone	15	1,087	124	572	574	39	151	57	63	172	91
carbidopa/levodopa	16	299	41	150	4	61	82	9	180	53	41
sevoflurane	17	4	3	13	2	12	17	8	8	17	7
ivabradine	18	376	379	380	469	527	544	384	674	383	165
dapagliflozin/metformin	19	430	1,420	794	1,307	885	1,035	873	1,159	1,704	191
paracetamol	20	6	2	20	3	3	7	2	2	2	3

Off-patent medicines and biosimilars

In Italy there is still a low incidence of expenditure on equivalent drugs (41.1%) compared to other European countries, resulting in the third lowest in the ranking of the 10 countries. The average percentage of community/local expenditure for equivalent drugs in the countries analysed is 48.5% (European average: 48.1%) and varies between 33.8% in Belgium and 67.9% in Poland (Figure 1.9.7). While the percentage of consumption ranges between 49.7% in Belgium and 82.7% in Germany (Figure 1.9.8) with Italy ranking, similarly to expenditure, in third last position with a 52.7% incidence of equivalent drugs.
The penetration of biosimilar drugs in terms of expenditure and consumption was also investigated (Figures 1.9.9 and 1.9.10). Italy ranks 2nd and 1st in the incidence, respectively, of expenditure and consumption of biosimilars. Figure 1.9.11 illustrates the penetration of biosimilars in terms of expenditure and consumption by single molecule. Within the countries analysed, the highest percentage of biosimilar drug use was recorded for infliximab, rituximab, trastuzumab, filgrastim and pegfilgrastim. Low biosimilar penetration rates are observed for insulins and teriparatide in all countries.
Figure 1.9.12 represents, through the Herfindhal-Hirschman index (HHI), the market concentration and market shares of the competitors of the single off-patent 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 assumes 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. Insulin lispro and insulin aspart have a high concentration index in most countries, since in addition to the reference product, a single biosimilar is present with still minimal market shares. Teriparatide also shows generally high concentration indexes due to its recent entry into the market. Infliximab is generally characterized by a low concentration index as a plurality of competitors with a similar distribution of market shares are present on the market. Even trastuzumab has a low concentration rate in most countries analysed, although its first biosimilar was authorised in Europe in 2018.

Figure 1.9.7 International comparison of the percentage distribution of 2021 community pharmaceutical expenditure on off-patent medicines

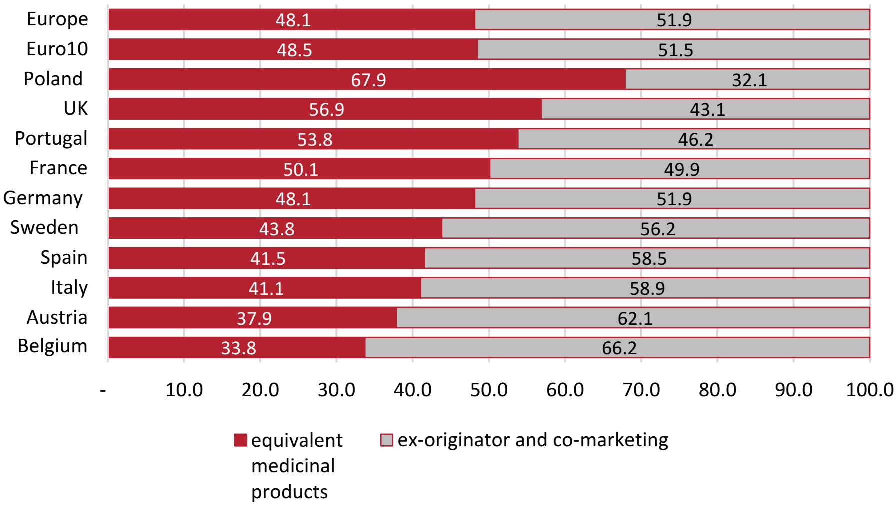


Figure 1.9.8 International comparison of the percentage distribution of 2021 community pharmaceutical expenditure on off-patent medicines

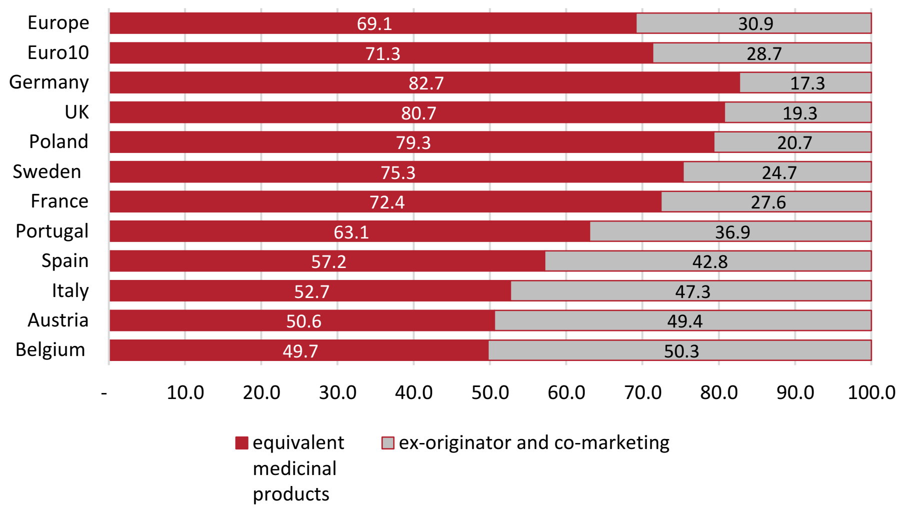


Figure 1.9.9 International comparison of the percentage distribution of 2021 expenditure on biosimilars

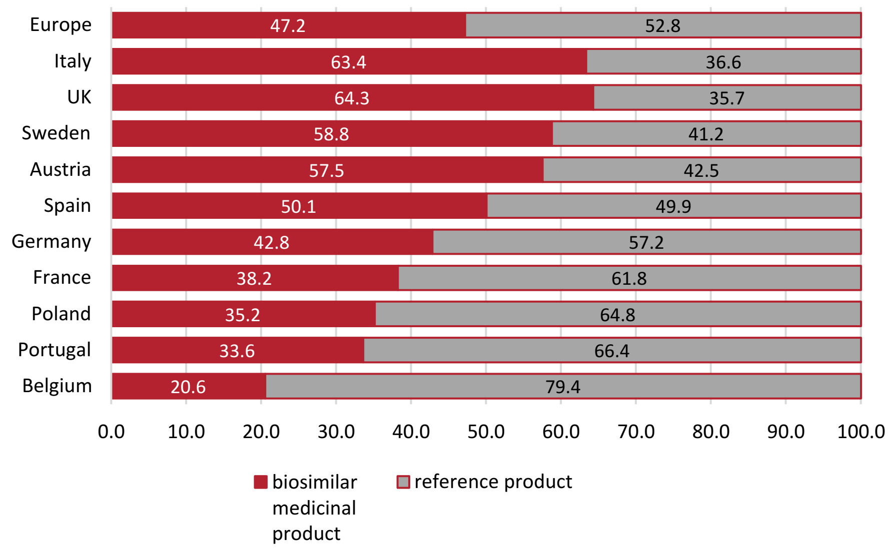


Figure 1.9.10 International comparison of the percentage distribution of 2021 consumption of biosimilar medicinal products

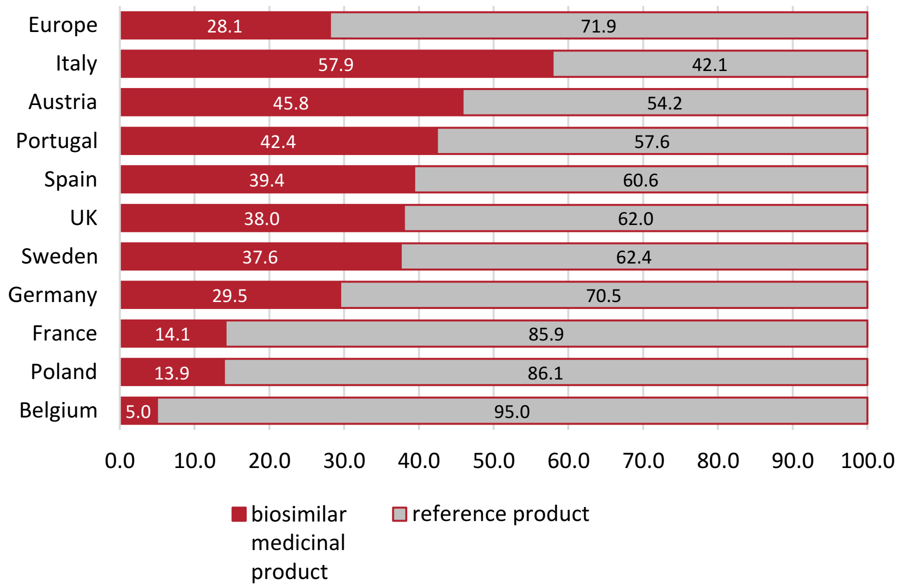


Figure 1.9.11
Percentage distribution of biosimilar consumption (Standard Unit) by country and molecules (year 2021)

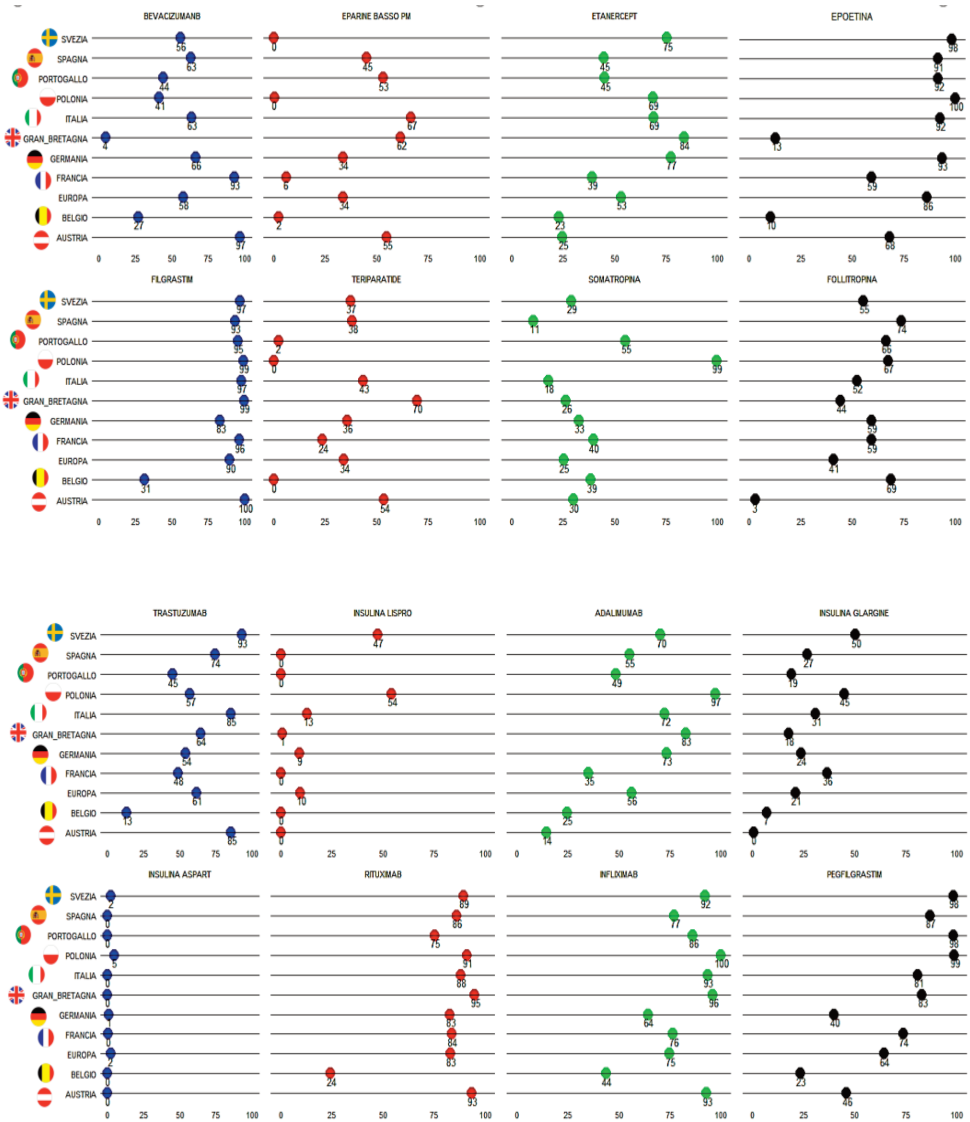
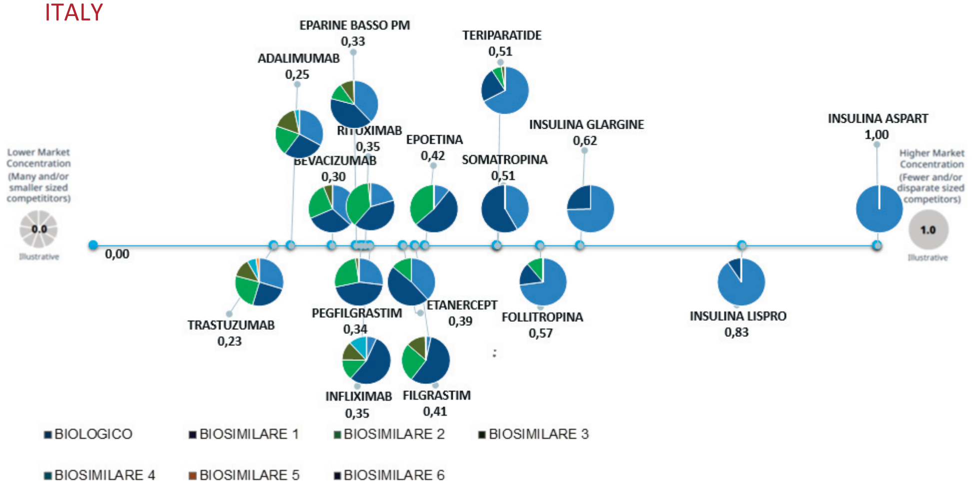
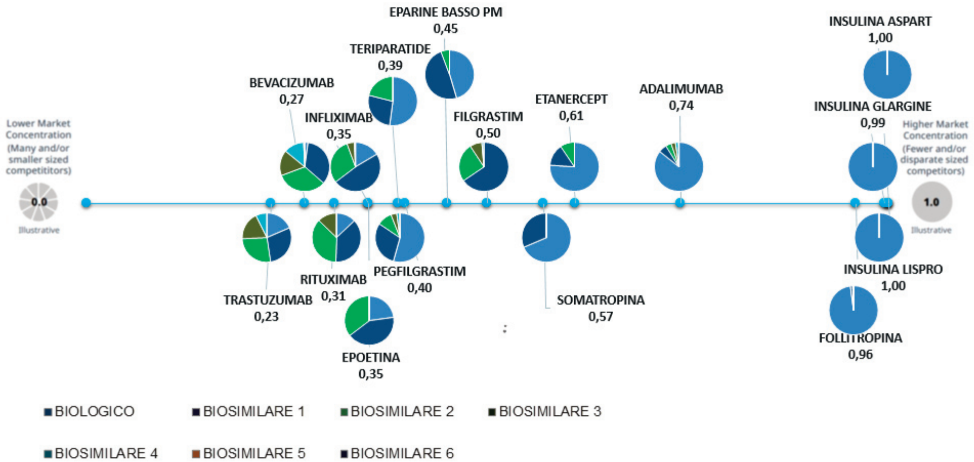


Figure 1.9.12 Off-patent biological medicinal products: Herfindahl-Hirschman index (HHI) and market shares by competitor by country (year 2021)

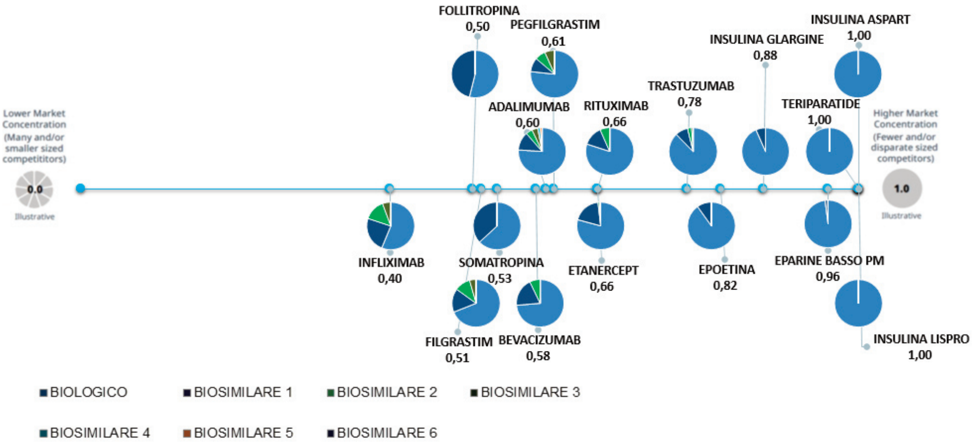
ITALY



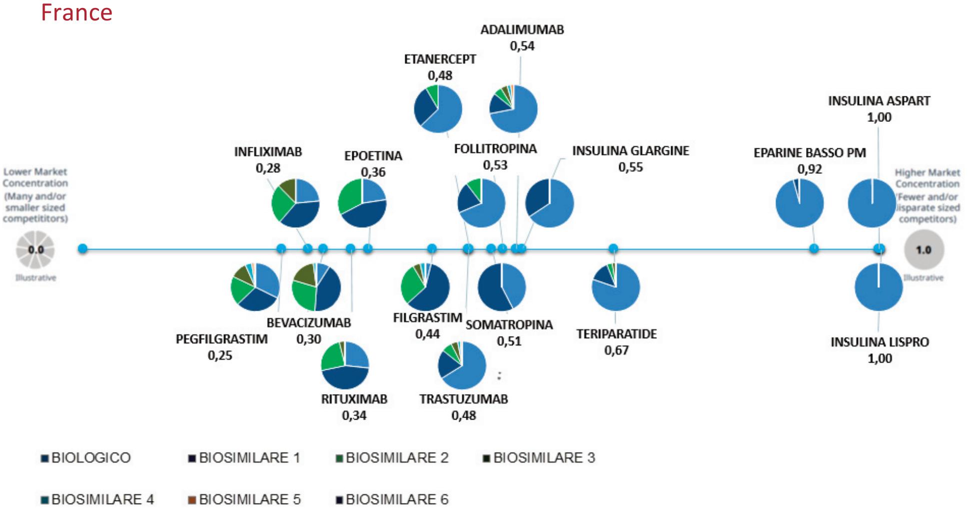
Austria



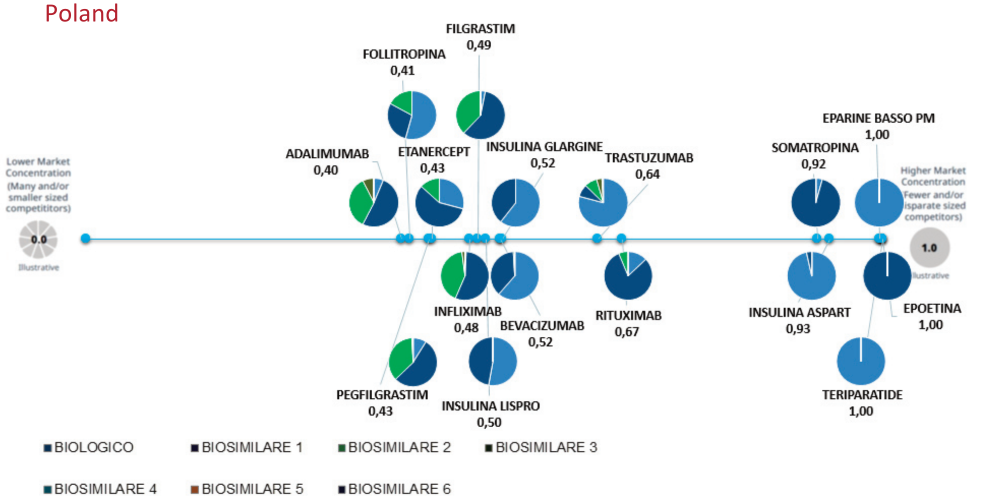
Belgium



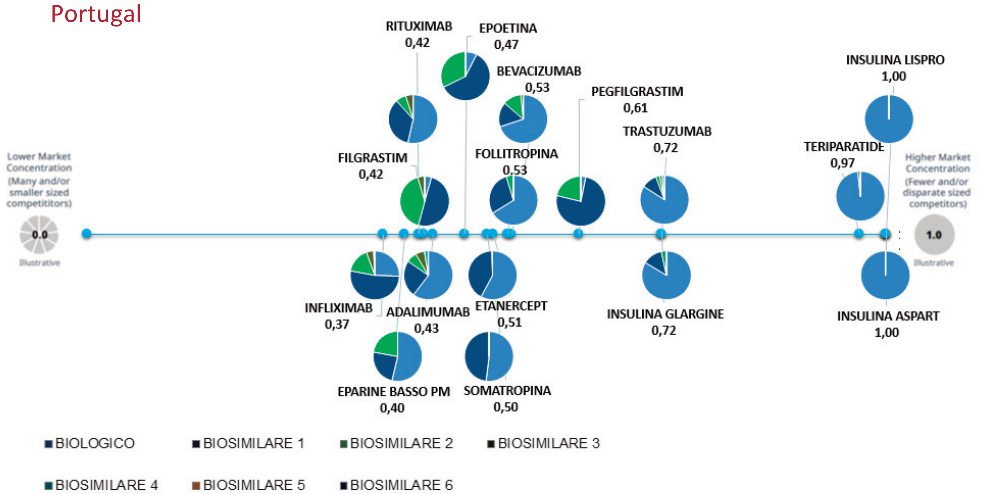
France



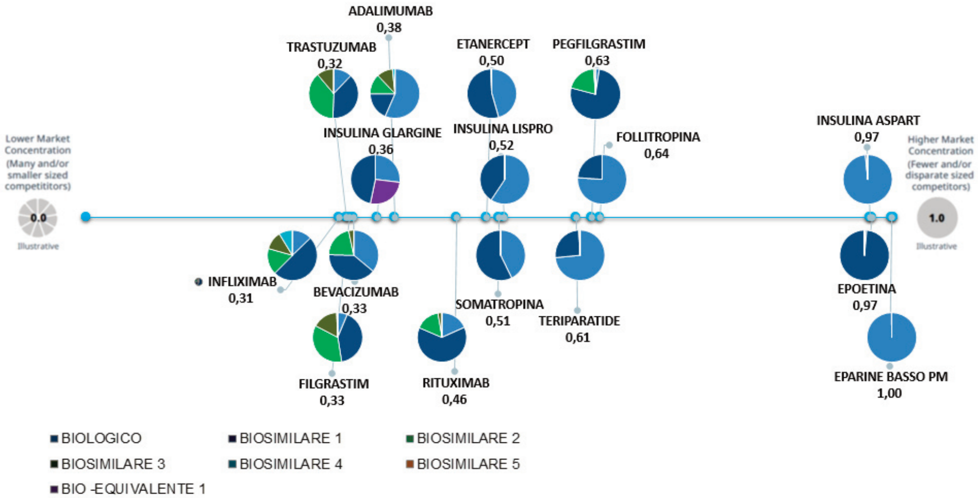
Poland



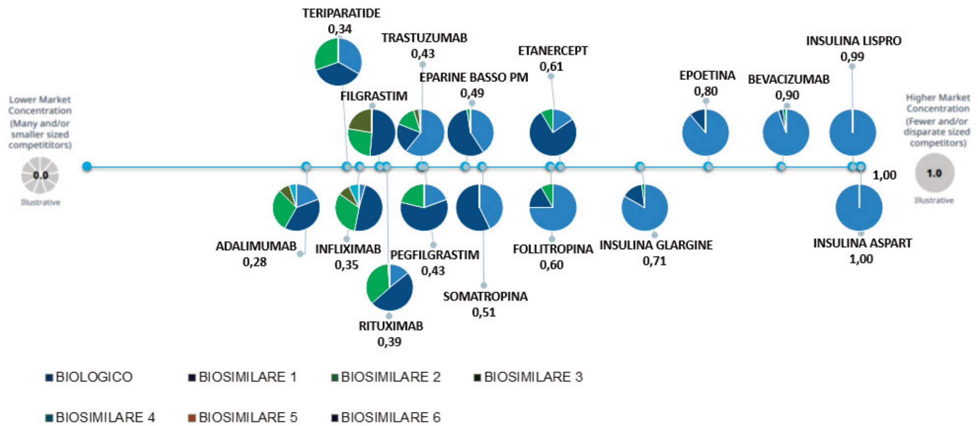
Portugal



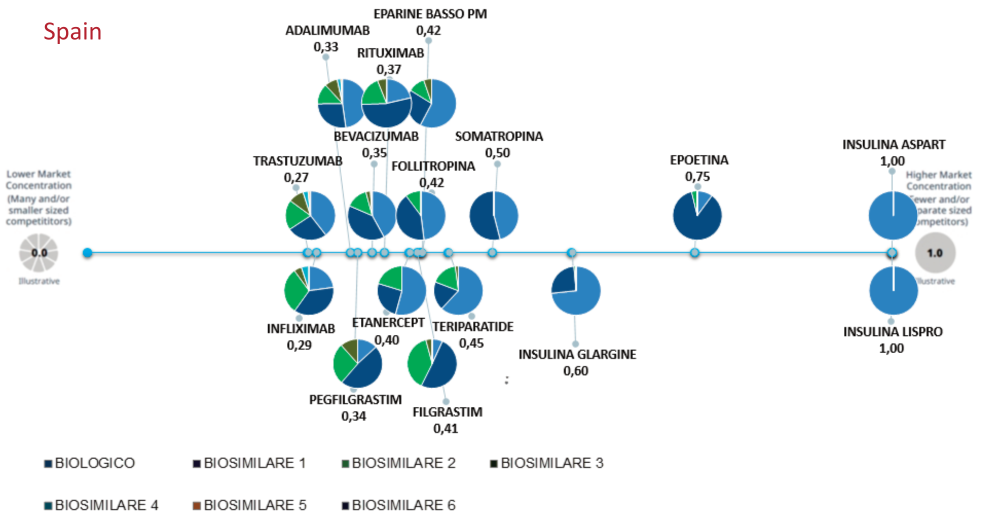
Sweden


ADALIMUMAB
0,38
TRASTUZUMAB
0,32
ETANERCEPT
0,50
PEGFILGRASTIM
0,63
INSULINA GLARGINE
0,36
INSULINA LISPRO
0,52
FOLLITROPINA
0,64
INSULINA ASPART
0,97
Lower Market Concentration (Many and/or smaller sized competititors)
0.0
Illustrative
Higher Market Concentration (Fewer and/or disparate sized competitors)
1.0
Illustrative
INFLIXIMAB
0,31
BEVACIZUMAB
0,33
SOMATROPINA
0,51
TERIPARATIDE
0,61
EPOETINA
0,97
FILGRASTIM
0,33
RITUXIMAB
0,46
EPARINE BASSO PM
1,00
BIOLOGICO
BIOSIMILARE 1
BIOSIMILARE 2
BIOSIMILARE 3
BIOSIMILARE 4
BIOSIMILARE 5
BIO -EQUIVALENTE 1

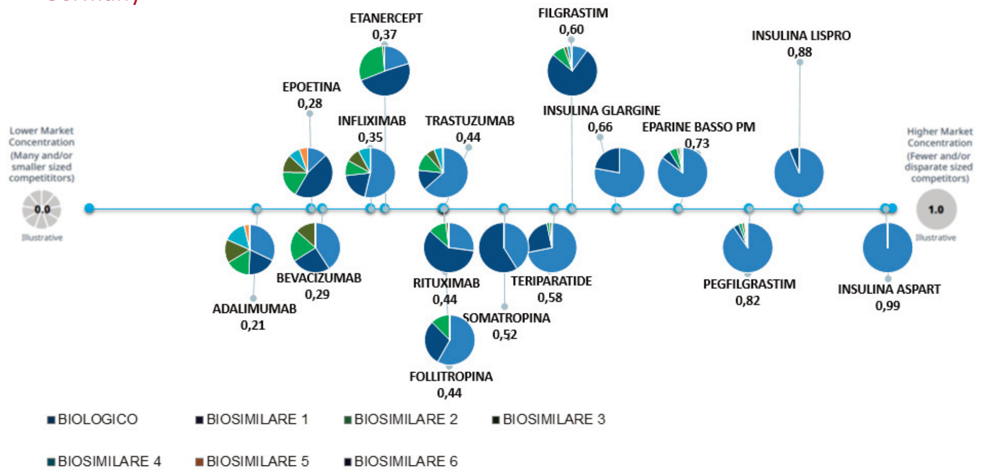
UK


TERIPARATIDE
0,34
TRASTUZUMAB
0,43
ETANERCEPT
0,61
EPARINE BASSO PM
0,49
FILGRASTIM
EPOETINA
0,80
BEVACIZUMAB
0,90
INSULINA LISPRO
0,99
Lower Market Concentration (Many and/or smaller sized competititors)
0.0
Illustrative
Higher Market Concentration (Fewer and/or disparate sized competitors)
1.0
Illustrative
1,00
ADALIMUMAB
0,28
INFLIXIMAB
0,35
PEGFILGRASTIM
0,43
FOLLITROPINA
0,60
INSULINA GLARGINE
0,71
INSULINA ASPART
1,00
SOMATROPINA
0,51
RITUXIMAB
0,39
BIOLOGICO
BIOSIMILARE 1
BIOSIMILARE 2
BIOSIMILARE 3
BIOSIMILARE 4
BIOSIMILARE 5
BIOSIMILARE 6

Spain



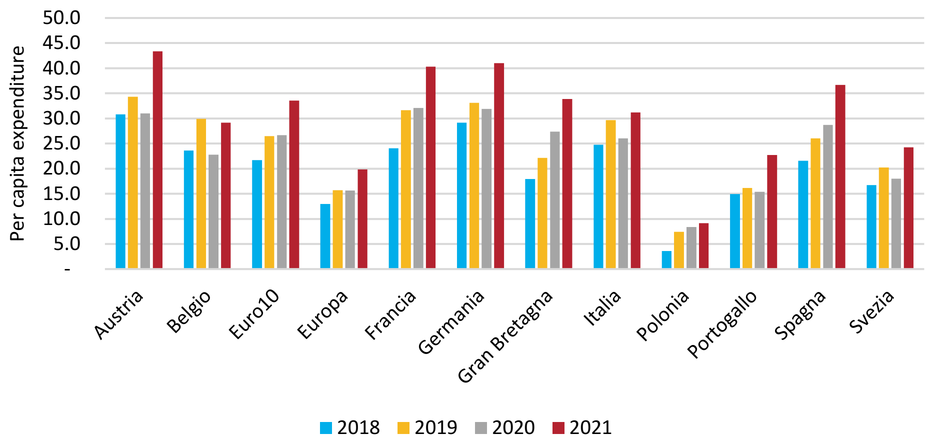
Germany



Orphan medicinal products

Italy, with 31.2 euros per capita, ranks 6th for expenditure on orphan drugs, after Austria (43.4 euros), Germany (41.0 euros), France (40.3 euros), Spain (36.7 euros) and Great Britain (33.9 euros). All countries, following the decrease recorded in 2020, show an increase in orphan drug expenditure compared to the previous year, which is more marked for Portugal and Austria with a variation of 40% or more (Figure 1.9.13).

Figure 1.9.13 Trend in per capita expenditure for orphan drugs in the period 2018-2021

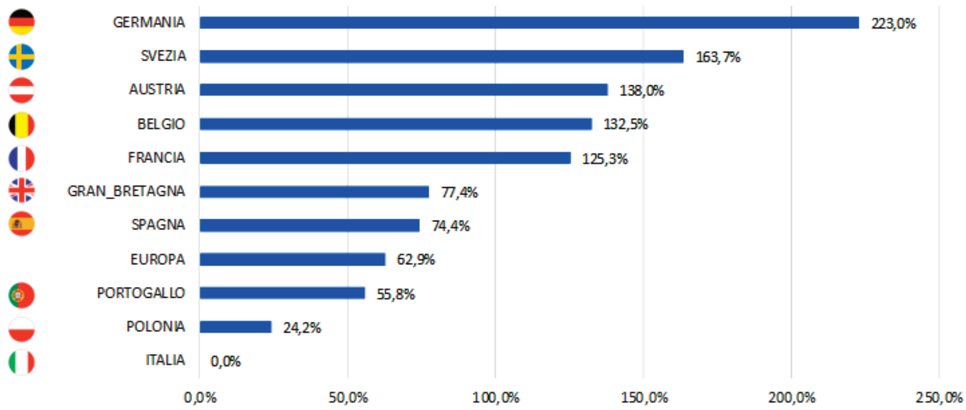


Price comparison

Figures 1.9.14 and 1.9.15 show the comparison of the weighted average ex-factory price for 2021 consumption, relating separately to medicines dispensed by local pharmacies and medicines dispensed by hospitals. Figure 1.9.16 shows a comparison of prices in the overall market, including both community 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 drugs in the various countries. The Italian 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 community channel does not include new oral anticoagulants and more recently marketed antidiabetics (e.g. glyphozine), which are included in the hospital channel. The comparison should be made only between Italy (reference country) and the other countries considered. The basket analysis changes each time according to the

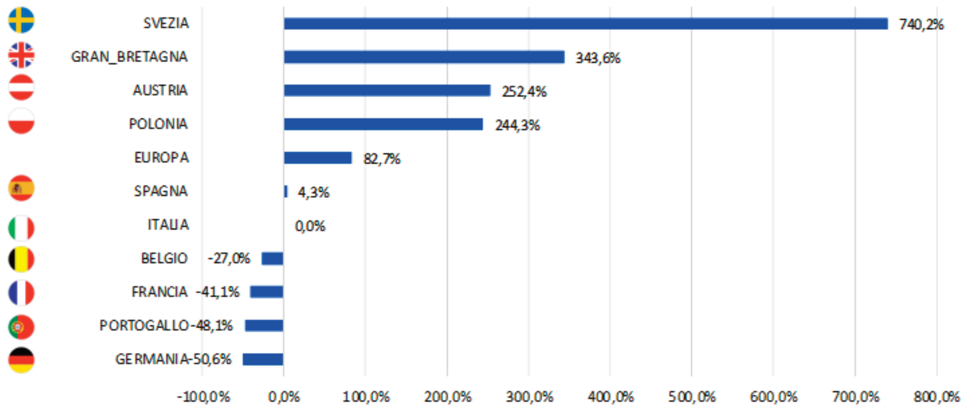
country selected. Taking the community-delivered drugs into account, Figure 1.9.14 shows that all countries considered show average prices higher than the Italian ones, with a variable range between the minimum difference of +24.2% with Poland, to the maximum of +223.0% with Germany. On average in Europe, prices are 62.9% higher than in Italy. As for hospital drugs, the situation is different, since Belgium, France, Portugal and Germany have lower prices than Italy, with differences ranging from -50.6% in Germany to -27.0% in Belgium. Italy has lower prices than Sweden (+740.2%), UK (+343.6%), Austria (+252.4%), Poland (+ 244.3%) and Spain (+4.3%) (Figure 1.9.15). Looking at the European average, as for the shared basket, hospital prices are 82.7% higher than Italy. Considering the overall market, covering both medicines delivered at a local level and in hospital settings, Italy reports lower prices than Germany (+113.4%), Belgium (+83.8%), Sweden (+53,8%), Austria (+28.5%), UK (+13.7%) and Spain (+6.6%); prices lower than Italy are reported in: France (-20.8%), Portugal (-35.6%) and Poland (-37.5 %) (Figure 1.9.16). Considering the European average, both community and hospital prices are 54.4% higher than in Italy. When interpreting the results, it is important to consider the corresponding drugs 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 (69%) and the lowest in Germany (25%). 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.
An analysis was conducted of the trends in the period 2014 - 2021 of prices in Italy compared to the other countries, separately in the patented medicines market and in the off-patent medicines market (Figure 1.9.17). Information was collected relating to the 10 countries (EU 10) 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 EU10 average prices for patented medicines and off-patent medicines. It can be noted that in Italy the price of off-patent medicines is 30.6% lower than the EU10 average in 2014 and 36.1% lower than 2021, noting that in the period considered, the price of off-patent medicines has further decreased compared to the EU10 average. By contrast, if we consider the market of patented medicines, up to 2018, prices in Italy were below the EU10 average, while since 2019 prices in Italy have been slightly above the EU10 average (+8.4 % in 2021).
Finally, a comparison of prices was conducted in Italy compared to the EU10 average based on the launch date of the products. After pooling data from 10 countries (EU10) 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 2014 to 2021. 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, the average price recorded in Italy is lower than in the 9 countries for each year of launch considered (Figure 1.9.18a). 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 1.9.18b).

Figure 1.9.14 International comparison of pharmaceutical prices (ex-factory prices) in 2021: community care



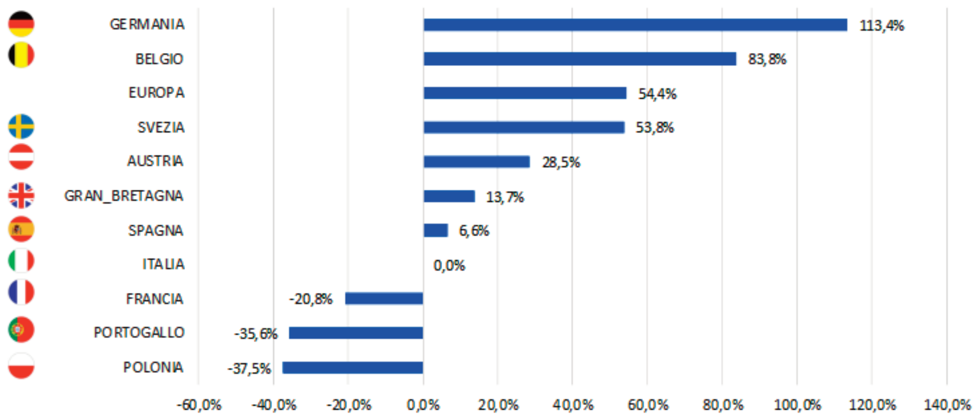
Coverage by values (%) of the country's expenditure	**Germany**	**Sweden**	**Austria**	**Belgium**	**France**	**UK**	**Spain**	**Europe**	**Portugal**	**Poland**	**Italy**
Coverage by values (%) of the country's expenditure	6	15	27	19	29	32	44	26	39	20	100
Coverage by values (%) of Italy's expenditure	26	15	23	22	23	18	30	100	24	20	100

Figure 1.9.15 International comparison of pharmaceutical prices (ex-factory prices) in 2021: hospital care*



Coverage by values (%) of the country's expenditure	Sweden	UK	Austria	Poland	Europe	Spain	Belgium	France	Portugal	Germany	Italy
Coverage by values (%) of the country's expenditure	62	32	62	50	67	86	85	75	80	61	100
Coverage by values (%) of Italy's expenditure	38	44	42	32	100	70	67	70	63	73	100

Figure 1.9.16 International comparison of pharmaceutical prices (ex-factory prices) in 2021: community and hospital care



Coverage by values (%) of the country's expenditure	Germany	Belgium	Europe	Sweden	Austria	UK	Spain	France	Portugal	Poland	Italy
Coverage by values (%) of the country's expenditure	25	57	45	33	44	34	69	50	57	30	100
Coverage by values (%) of Italy's expenditure	65	58	100	32	38	37	64	60	56	29	100

Figure 1.9.17 International comparison of patent-covered and off-patent medicines between 2014 and 2021 (ex-factory prices): community and hospital care

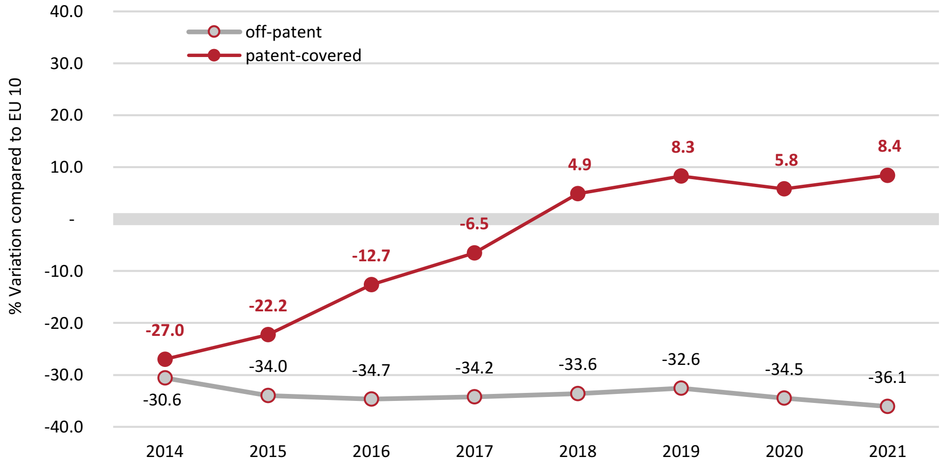
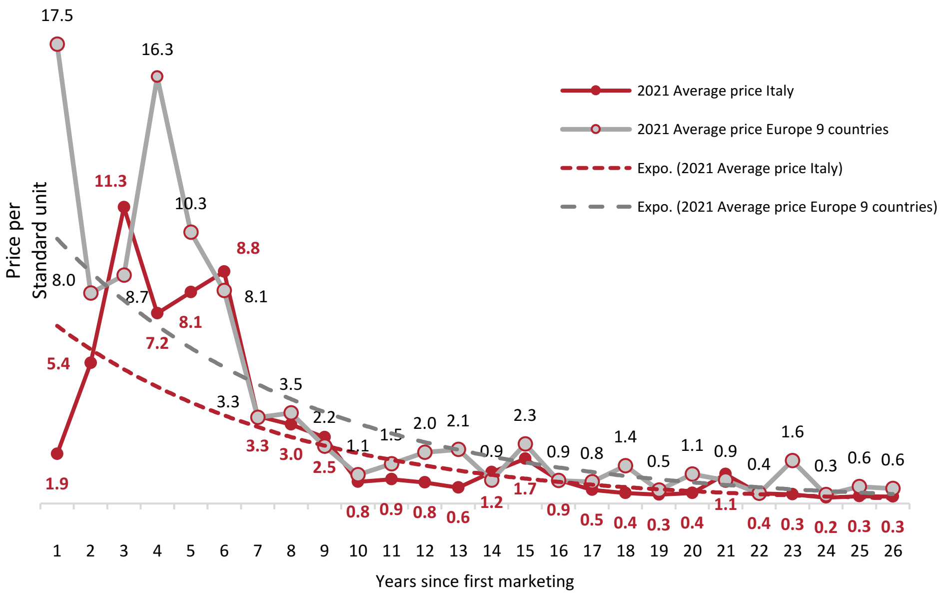
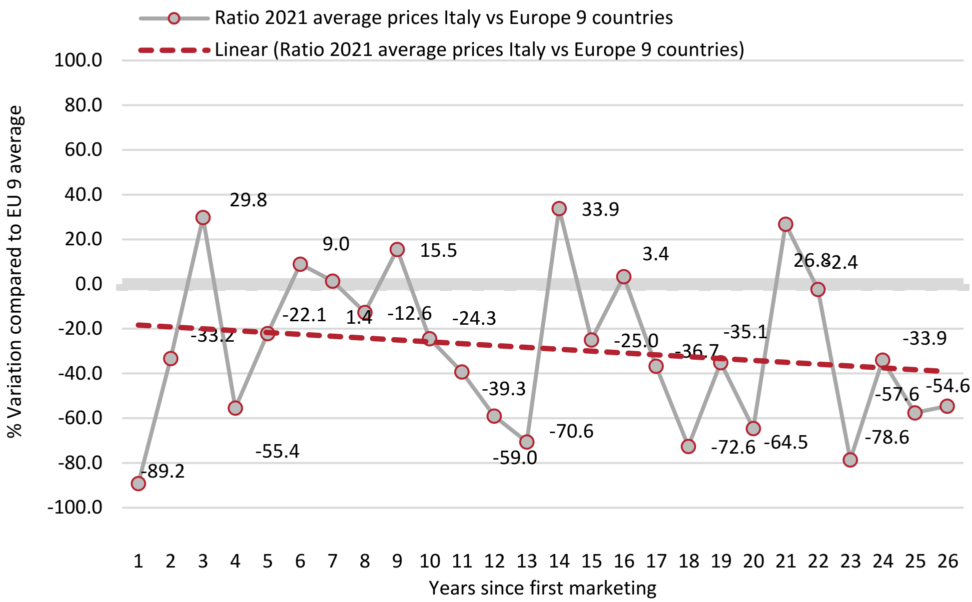


Figure 1.9.18 International comparison of the average price calculated over 8 years (2014-2021), for drugs marketed on the same year (ex-factory prices): community and hospital care

a) comparison on unit price



b) ratio between price in Italy and in Europe 9



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

2.1 Off-patent medicines and biosimilars

Off-patent medicines under approved care regime

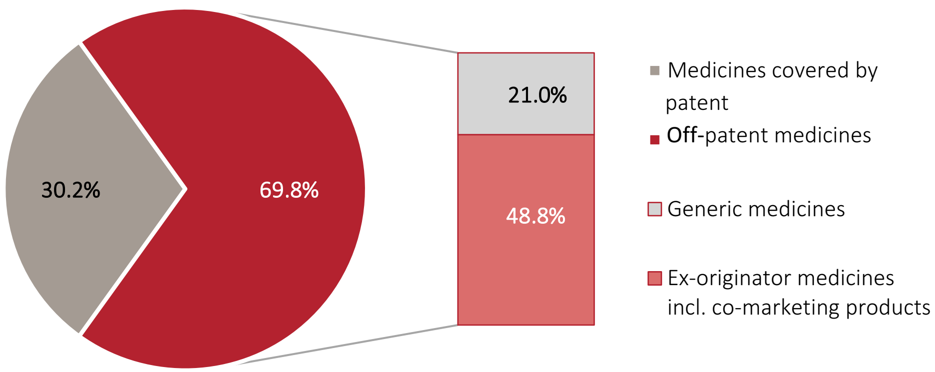
In 2021, off-patent medicines accounted for 69.8% of expenditure and 84.8% of consumption under class A approved care regime. The percentage share of equivalent medicines, i.e. medicines based on off-patent active ingredients, excluding those with patent coverage, accounted for 21.0% of expenditure and 29.6% 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 subdued over the past two years (Figure 2.1.3 and 2.1.4).
At national level, per capita expenditure on off-patent medicines amounted to EUR 114.98 in 2021, up by 3.4% from 2020, and with an increase in the percentage share of total spending switching from 67.8% in 2020 to 69.8% in 2021. Taking into account the last two years, the percentage of expenditure on equivalent medicines has remained nearly stable switching from 30.2% to 30.1% (Table 2.1.1). The Southern regions (71.2%) and the Centre (70.9%) have the highest share of expenditure on off-patent medicines, both in comparison with the Northern Regions (68.2%) and the Italian average (69.8%). In fact, the lowest value was recorded in the Province of Bolzano (EUR 79.46), while the highest in Campania (EUR 146.30). An opposite trend is observed when considering the percentage of expenditure on equivalent medicines: the Northern Regions show higher values (38.9%) compared to the Southern (27.6%) and Central Regions (21.8%).
In 2021, 974.2 daily doses per 1000 inhabitants were consumed for off-patent medicines, an increase of more than 4% compared to the previous year, corresponding to 84.8% of total DDD. On the other hand, the percentage of use of equivalent medicines, which was 34.4% in 2021, remains stable (Table 2.1.2). The Northern Regions consume a greater percentage of equivalent medicines (43.8%), compared to the Central (32.4%) and Southern Regions (24.3%), in fact the highest value was recorded in the Province of Trento (48.8%), while the lowest in Basilicata (20.8%).
In the use of off-patent 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 equivalent medicines is lower in Calabria, Basilicata and Campania (19-20%), whereas the highest values are recorded in the Province of Trento (44%), Lombardy (43%) and Friuli Venezia Giulia (42 %).
The three therapeutic categories with a higher incidence of expenditure on off-patent medicines (Table 2.1.3) are cardiovascular medications (93.8%), as well as medications acting on the genitourinary system (92.1%) and antiinfectives for systemic use (88.1%). For the ATC codes V (Various), N (Central nervous system medicines), A (Alimentary tract and metabolism), and L (Antineoplastic and immunomodulating agents), the highest percentages of expenditure on equivalent medicines were 86.7%, 40.8%, 39.3% and 34.3% respectively.
When looking at consumption, medicines acting on the cardiovascular system (96.2%) and on the genitourinary system (94.2%) as well as antiinfectives for systemic use (93.2%) 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 (84.2%) compared to that of expenditure (46.7%). Categories with the highest incidence of consumption of equivalent medicines are: ATC code V (93.5%), N (47.5%), L (44.6%), C

(37.1%) as well as the ATC code A (35.7%).

As for expenditure on the top 20 off-patent active ingredients of class A-NHS (private purchase), more than half belong to cardiovascular medications, followed by medications acting on the gastrointestinal system and metabolism (Table 2.1.4). In 2021, atorvastatin is the most expensive active substance, with an absolute value of 273.7 million, up by 2.1% compared to the previous year, and a percentage of equivalents equal to 37.7%, followed by pantoprazole (EUR 260.5 million) and cholecalciferol (EUR 242.6 million). The active substances with the highest incidence of expenditure on equivalent medicines are lansoprazole (70.9%) and pantoprazole (56.4%). In contrast, the incidence of spending on equivalents for the olmesartan/amlodipine combination (16.2%), amoxicillin/clavulanic acid (17.8%), and cholecalciferol (19.9%) is very low; the latter, together with the olmesartan/amlodipine combination, shows the greatest increase in spending in 2021, +20.5% and +11.6% respectively, amounting to an expenditure of 242.6 and 77.7 million euros.

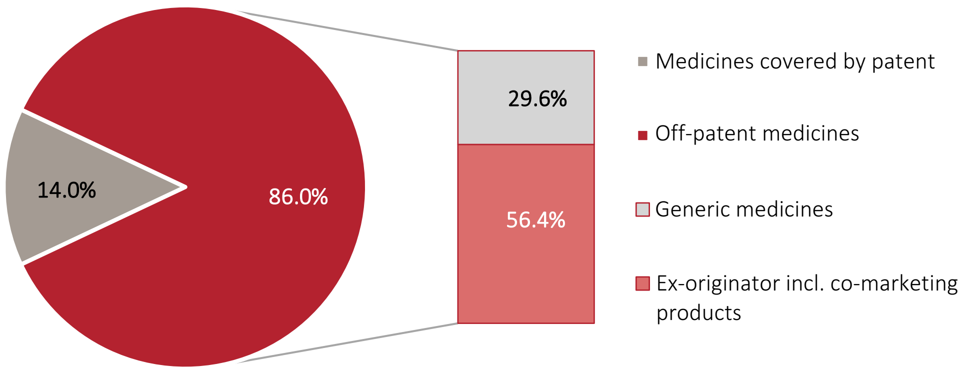
Among the active substances with higher consumption, cholecalciferol records the highest values (114.9 DDD/1000 inhabitants per day), followed by three substances acting on the cardiovascular system and three on the gastrointestinal system and metabolism: ramipril (62.4 DDD/1000 inhabitants per day), atorvastatin (50.2 DDD/1000 inhabitants per day), amlodipine (28.1 DDD/1000 inhabitants per day) acting on the cardiovascular system; pantoprazole (27.5 DDD/1000 inhabitants per day), metformin (23.0 DDD/1000 inhabitants per day), and omeprazole (17.6 DDD/1000 inhabitants per day) on the gastrointestinal system.

Figure 2.1.1 Expenditure on medicines supplied under approved care regime (class A-NHS) and broken down by patent coverage in 2021



Equivalent medicinal products are medicinal products containing off-patent active substances, 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 2021



Equivalent medicinal products are medicinal products containing off-patent active substances, 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 equivalent and off-patent medicines on the total spending on medicines under approved care regime (class A-NHS): comparison 2011-2021

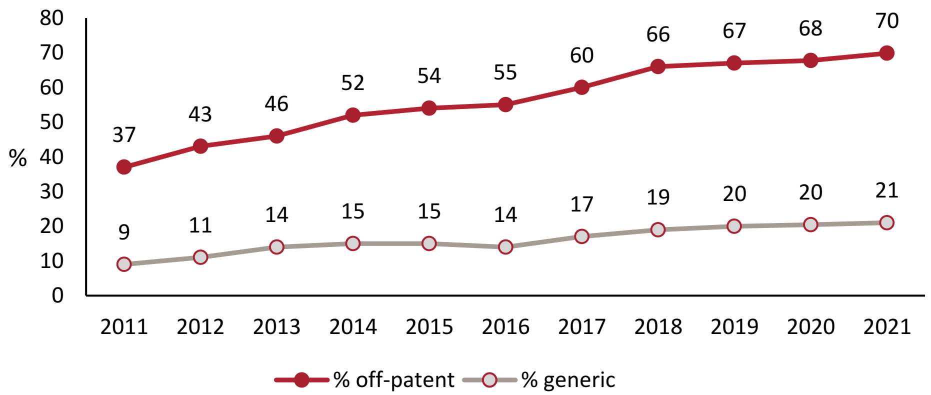


Table 2.1.1 Regional expenditure under approved care regime of off-patent medicinal products* (class A-NHS): comparison 2021-2020

Region	Per capita expenditure (euro)		% on overall expenditure		% of expenditure on generics**	
	2020	2021	2020	2021	2020	2021
Piedmont	94.75	98.02	68.5	70.9	37.1	37.4
Valle d'Aosta	88.77	90.51	67.1	69.7	36.3	36.5
Lombardy	106.55	110.43	60.2	62.1	42.3	42.5
Province of Bolzano	77.08	79.46	67.3	70.0	36.6	36.5
Province of Trento	96.97	101.34	71.3	73.8	43.4	43.4
Veneto	91.98	95.09	70.0	72.4	35.9	35.6
Friuli VG	98.02	101.85	67.5	70.9	41.5	38.2
Liguria	100.06	102.91	69.2	71.6	34.7	34.3
Emilia Romagna	90.97	96.62	73.4	76.0	36.6	36.3
Tuscany	90.29	93.77	66.5	69.0	36.9	37.0
Umbria	118.27	120.66	72.1	73.7	27.5	27.4
Marche	111.18	115.42	70.5	73.1	25.3	25.4
Lazio	126.11	129.57	68.9	70.9	23.6	23.6
Abruzzo	124.90	129.34	69.8	71.8	26.9	27.0
Molise	117.46	119.66	71.3	73.5	24.2	23.1
Campania	140.52	146.30	70.3	72.0	19.2	18.7
Puglia	130.29	133.30	69.9	71.4	24.1	24.3
Basilicata	125.69	134.62	69.0	71.7	18.9	20.2
Calabria	134.84	136.92	71.0	71.3	19.1	19.0
Sicily	123.18	125.47	67.5	69.8	20.8	20.7
Sardinia	113.88	117.67	67.8	70.3	30.5	30.2
Italy	**111.21**	**114.98**	**67.8**	**69.8**	**30.2**	**30.1**
North	98.01	101.85	65.9	68.2	39.0	38.9
Centre	112.06	115.55	68.7	70.9	27.6	27.6
South and Islands	129.67	133.46	69.4	71.2	21.9	21.8

* transparency lists published by AIFA over the years 2020-2021 have been used
** calculated on the expenditure of off-patent medicines

Figure 2.1.4 Trend in the incidence of consumption (doses) of off-patent medicines and generic medicines on total consumption of medicines under approved care regime (class A-NHS): comparison 2011-2020

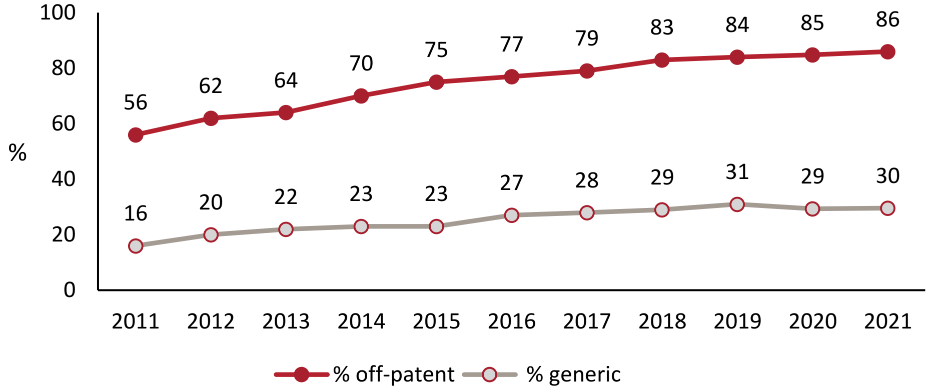


Table 2.1.2 Regional expenditure under approved care regime of off-patent medicinal products* (class A-NHS): comparison 2021-2020

Region	DDD/1000 inhabitants per day		% of total DDDs		% of expenditure on generics**	
	2020	2021	2020	2021	2020	2021
Piedmont	845.5	882.0	84.5	85.5	43.1	43.3
Valle d'Aosta	772.9	796.7	84.9	86.9	42.0	42.2
Lombardy	875.9	920.4	84.0	85.4	46.4	46.5
Province of Bolzano	669.0	691.1	83.1	84.1	41.7	41.2
Province of Trento	874.2	918.0	86.5	87.9	48.9	48.8
Veneto	807.4	831.8	81.6	82.9	41.5	41.1
Friuli VG	900.5	938.2	85.1	86.8	47.8	44.0
Liguria	815.3	845.4	84.7	86.0	39.8	39.4
Emilia Romagna	895.8	958.8	85.9	86.9	42.7	42.3
Tuscany	850.8	892.2	80.3	81.7	44.2	44.0
Umbria	1050.1	1080.3	86.7	87.5	31.6	31.1
Marche	925.6	972.6	85.9	87.2	29.3	29.1
Lazio	1003.3	1033.8	86.1	87.2	27.0	26.7
Abruzzo	977.4	1026.6	85.3	86.6	29.3	29.1
Molise	946.7	1002.7	85.6	87.2	25.2	24.9
Campania	1112.0	1174.3	86.9	88.0	22.2	21.7
Puglia	1047.8	1085.0	85.4	86.4	26.0	25.7
Basilicata	1009.5	1089.0	85.9	87.2	20.7	20.8
Calabria	1024.0	1054.4	85.8	86.8	21.3	21.1
Sicily	1009.7	1035.7	86.4	87.6	23.7	23.5
Sardinia	933.5	975.1	80.7	82.4	34.7	34.5
Italy	**933.4**	**974.2**	**84.7**	**86.0**	**34.7**	**34.4**
North	855.5	896.5	84.1	85.4	44.1	43.8
Centre	947.7	983.9	84.4	85.6	32.6	32.4
South and Islands	1036.5	1079.7	85.7	86.9	24.6	24.3

* transparency lists published by AIFA over the years 2020-2021 have been used
** calculated on the expenditure of off-patent medicines

Figure 2.1.5 Composition by Region of 2021 expenditure on off-patent medicines under approved care regime (class A-NHS)

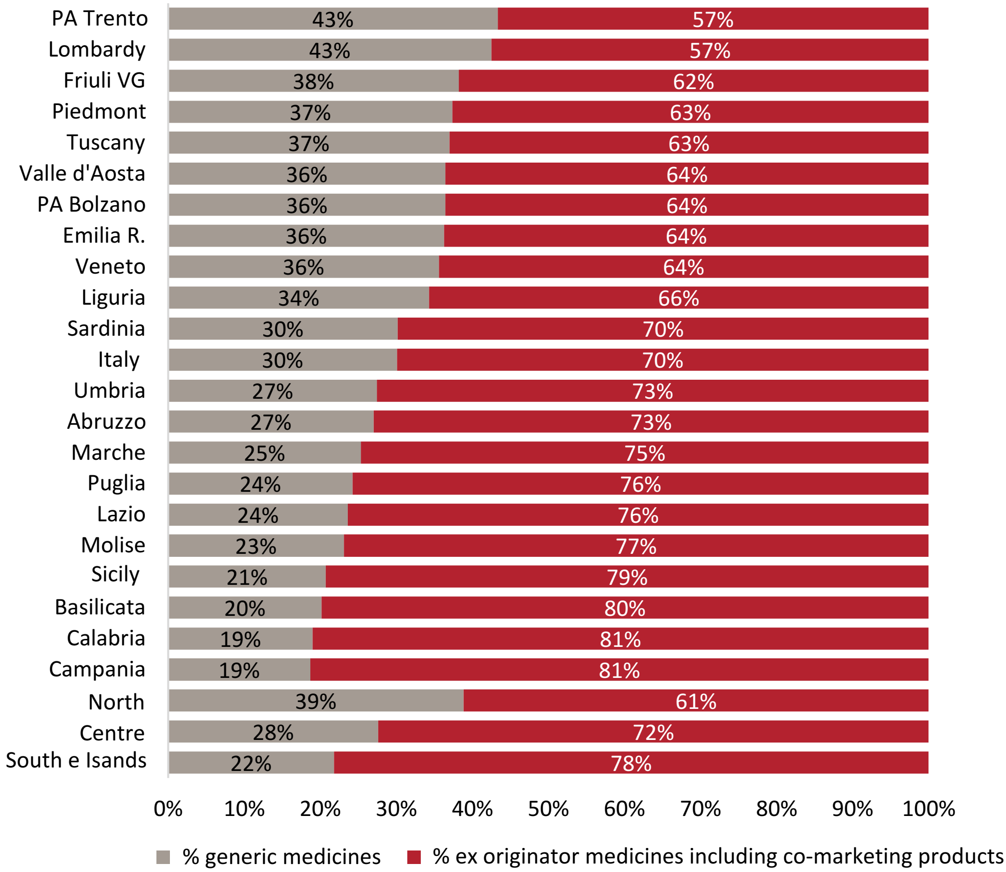


Table 2.1.3 Incidence of 2021 expenditure and consumption of off-patent medicines under approved care regime (class A-NHS) by ATC 1st level

ATC 1st level	Expenditure under approved care regime		Consumption (DDDs) under approved care regime	
	% off-patent	% generic**	%off- patent	% generic**
A	65.5	39.3	82.6	35.7
B	45.6	26.2	67.1	23.9
C	93.8	28.3	96.2	37.1
D	38.9	14.5	34.7	9.6
G	92.1	28.5	94.2	33.4
H	46.7	6.5	84.2	5.3
J	88.1	23.9	93.2	25.1
L	84.1	34.3	87.4	44.6
M	87.4	21.3	89.9	30.8
N	57.6	40.8	77.8	47.5
P	78.4	3.2	90.6	4.2
R	26.0	11.5	49.4	22.6
S	47.8	12.9	56.9	18.9
V	4.0	86.7	28.3	93.5

* transparency lists published by AIFA over the years 2020-2021 have been used
** calculated on overall expenditure and consumption of off-patent medicines

Table 2.1.4 Expenditure and consumption of the top 20 off-patent active substances* under approved care regime (class A-NHS): comparison 2021-2020

ATC	Active substance	Expenditure *(million)*	Inc.%^	Δ% 21-20	% generic**	DDD/1000 inhabitants per day	Average cost DDD
C	atorvastatin	273.7	4.0	2.1	37.7	50.2	0.3
A	pantoprazole	260.5	3.8	2.6	56.4	27.5	0.4
A	cholecalciferol	242.6	3.6	20.5	19.9	114.9	0.1
C	bisoprolol	160.9	2.4	3.7	32.1	12.3	0.6
A	lansoprazole	135.6	2.0	-5.2	70.9	13.8	0.5
A	omeprazole	131.9	1.9	-2.3	40.7	17.6	0.3
A	esomeprazole	130.9	1.9	0.1	35.9	15.3	0.4
C	omega-3	123.4	1.8	7.1	39.5	4.9	1.2
J	amoxicillin/clavulanic acid	122.2	1.8	-4.5	17.8	4.2	1.4
C	ramipril	119.6	1.8	-0.7	40.0	62.4	0.1
C	olmesartan	105.4	1.5	6.9	20.9	15.5	0.3
A	metformin	96.6	1.4	3.2	32.7	23.0	0.2
C	amlodipine	96.0	1.4	-1.0	33.1	28.1	0.2
N	levetiracetam	93.6	1.4	-1.9	39.5	2.1	2.0
C	ezetimibe	91.9	1.3	10.7	39.6	5.7	0.7
C	nebivolol	90.6	1.3	1.3	23.4	16.5	0.3
C	simvastatin	86.1	1.3	-5.6	52.6	12.2	0.3
C	rosuvastatin	83.7	1.2	4.2	29.3	14.9	0.3
L	letrozole	83.6	1.2	2.5	45.7	1.7	2.3
C	olmesartan/amlodipine	77.7	1.1	11.6	16.2	8.9	0.4
	Total of the first 20	**2,606.3**	**38.3**	**3.0**	**37.0**	**451.8**	**0.3**
	Total	**6,811.1**	**61.7**	**-7.1**	**30.1**	**974.2**	**0.3**

* transparency lists published by AIFA over the years 2020-2021 have been used
^ calculated on overall expenditure under approved care regime
** calculated on overall expenditure of the active substance

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

In 2021, spending on cost-sharing for the share exceeding the reference price of off-patent medicines (hereafter cost-sharing) was 18.3 euros per capita (about 1.1 billion euros). This value represents 73.1% of the total citizen's cost-sharing (including the ticket per prescription and/or packaging) and has shown a reduction of 0.4% compared to the previous year (Table 2.1.5) and a CAGR of 1.3% since 2017.
Expenditure per capita on cost-sharing is highest in the South and the Islands (EUR 23.8), while the lowest is in the North with EUR 13.6 (Figure and Table 2.1.5), deviating from the national average of +30.2% and -25.7% respectively. Calabria, Campania and Lazio are the regions with the highest spending values (EUR 25.2, EUR 25.1 and EUR 25.0 respectively), while Bolzano, Trento and Valle d'Aosta have the lowest values of EUR 11.8, EUR 12.7 and EUR 12.9 respectively.
An analysis of the correlation between expenditure on cost-sharing and regional per capita income shows that Regions with the lowest income are those with the highest cost-share. In particular, for Calabria, Campania, Sicily and Puglia which have a low per capita income, slightly above EUR 10.000, there is a higher share compared to the national average (>20 euros) (Figure 2.1.6). The top 5 therapeutic categories at the highest level of shared spending concern cardiovascular medications, in particular lipid modifying substances, not in combination (8.9%), beta-blockers (7.4%), angiotensin II receptor antagonists, in combination and alone (6.0% and 5.1%), ACE-inhibitors in combination (5.8%) These categories make up about one third of total expenditure (Table 2.1.6).
Compared with 2020, the value of cost-sharing spending on lipid modifying agents in combination (>100%), ACE inhibitors in combination (+16.3%), and vitamin A and D products including their combinations (+15.1%) increases This trend is mainly driven, for the former, by an increase in cost-sharing expenditure for olmesartan combinations with amlodipine or hydrochlorothiazide (+18,8%) and an increase in consumption of 12.1% and 5.8%, respectively (Table 2.1.8); as for ACE inhibitors, the increase in cost-sharing expenditure could be due to the entry of the perindopril/indapamide/amlodipine association on the transparency list; for the latter, it is due to the increase in cholecalciferol cost-sharing (+17.1%), changes that could be related to the increase in consumption in 2021 compared to 2020 (+21.8%; Tables 2.1.6 and 2.1.8). In contrast, spending on peptic ulcer treatments continues to decrease (-23.3%), and cost-sharing spending on nonsteroidal anti-inflammatory and antirheumatic drugs also declines in 2021 (-13.8%), probably due to a lower impact of the COVID-19 pandemic than in the previous year on the consumption of these medications.
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 shared expenditure. (Table 2.1.7).
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 2.1.8), with the largest difference for the category of beta blockers (C07A). Men tend to rely more on generic medicines than women 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.
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 2.1.9), it is noted that the majority of products with an average difference of less than 3 euros are dispensed through the channel under approved care regime (71.4%), accounting for more than half (64.4%) of total cost-sharing expenditure. Only 0.7% of products with a difference of more than 20 euros are distributed under approved care regime.
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 cost-sharing in the reference price of off-patent medicines, the regional differences are essentially due to the different use of generic medicines. This highlights the need for further information and training policies at both national and regional level in order to promote wider use of generics.

Table 2.1.5 Distribution of share on reference price by Region (Table and Figure) (year 2021)

Region	*Per capita* expenditure weighted	Δ % 21-20	CAGR 2017-2021	Δ % national average
Piedmont	13.9	-1.1	-0.9	-24.0
Valle d'Aosta	12.9	-1.7	1.3	-29.3
Lombardy	13.9	0.0	1.2	-24.0
Province of Bolzano	11.8	0.5	1.6	-35.2
Province of Trento	12.7	1.0	2.4	-30.3
Veneto	14.0	0.9	1.2	-23.3
Friuli VG	14.4	-1.8	0.1	-21.0
Liguria	14.9	-1.5	0.5	-18.5
Emilia Romagna	14.5	2.7	1.9	-20.6
Tuscany	13.8	2.1	0.4	-24.6
Umbria	19.9	-0.3	2.3	8.9
Marche	18.9	0.3	1.6	3.5
Lazio	25.0	1.2	1.8	37.0
Abruzzo	20.8	0.3	2.1	13.8
Molise	21.2	-2.3	1.5	15.8
Campania	25.1	0.5	2.4	37.3
Puglia	22.0	0.8	0.9	20.4
Basilicata	23.3	3.2	2.8	27.7
Calabria	25.2	0.9	3.3	37.9
Sicily	23.9	-1.1	0.8	31.0
Sardinia	17.4	-0.4	1.0	-4.9
Italy	**18.3**	**0.4**	**1.3**	**-**
North	13.6	0.3	0.8	-25.7
Centre	20.2	1.2	1.5	10.7
South and Islands	23.8	0.2	1.7	30.2

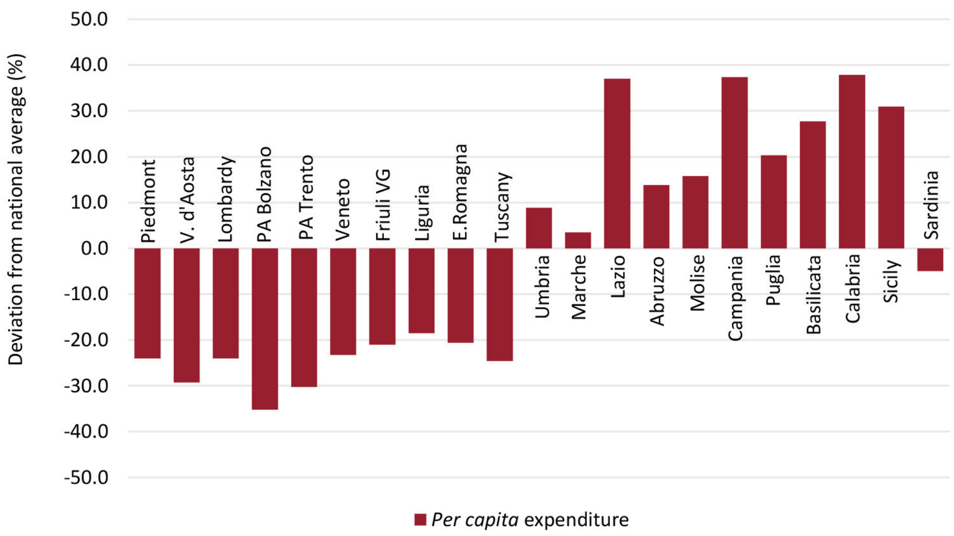


Figure 2.1.6 Correlation analysis between shared expenditure and *per capita* income (year 2021)

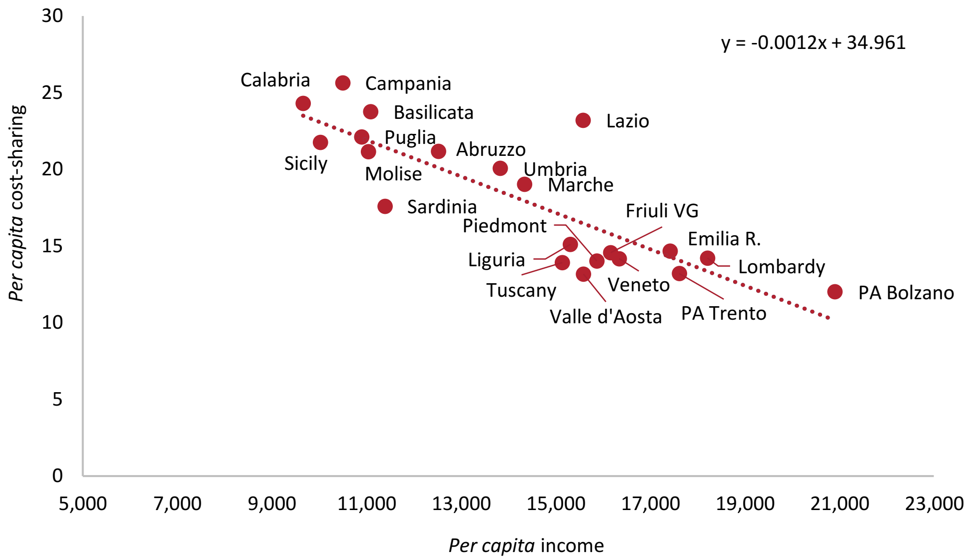


Table 2.1.6 Top 20 therapeutic categories with the largest share of expenditure on reference price (year 2021)

ATC 3rd level	Therapeutic category	Expenditure total	Δ % 21-20	%*	% cum.
C10A	Lipid modifying substances not associated	95,865,173	2.0	8.9	8.9
C07A	Beta blockers	79,177,424	1.5	7.4	16.3
C09D	Angiotensin II antagonists associated	64,805,554	0.7	6.0	22.3
C09B	Angiotensin-converting enzyme inhibitors (ACE) associated	62,642,303	16.3	5.8	28.1
C09C	Angiotensin II antagonists	54,664,559	-1.0	5.1	33.2
N06A	Antidepressants	52,038,452	-1.6	4.9	38.1
G04C	Medicines used in benign prostatic hypertrophy	47,633,721	-0.2	4.4	42.5
C09A	Angiotensin-converting enzyme inhibitors (ACE) not associated	46,984,902	-4.8	4.4	46.9
B01A	Antithrombotics	43,638,922	4.8	4.1	51.0
C08C	Selective calcium channel blockers with prevalent vascular effect	35,021,412	-2.1	3.3	54.3
A11C	Vitamins A and D, including their combinations	31,685,432	15.1	3.0	57.3
M01A	Non-steroidal anti-inflammatory and anti-rheumatic drugs	31,153,715	-13.8	2.9	60.2
A02B	Treatments for peptic ulcer	30,629,585	-23.3	2.9	63.1
N03A	Anti-epileptics	28,594,727	-4.9	2.7	65.8
A10B	Oral hypoglycemic agents	27,488,308	-6.2	2.6	68.4
S01E	Antiglaucoma and miotic preparations	26,719,743	8.4	2.5	70.9
J01C	Beta-lactam antibacterials, penicillins	18,833,908	-2.0	1.8	72.7
J01D	Other beta-lactam antibacterials	16,454,694	-4.7	1.5	74.2
C10B	Lipid modifying substances associated	16,295,917	>100	1.5	75.7
R06A	Antihistamines for systemic use	15,977,480	-2.6	1.5	77.2
	Top 20 therapeutic categories	**826,305,933**	**0.6**	**77.2**	
	Total cost-sharing	**1,082,709,857**	**0.4**	**100**	**100**

* calculated on overall shared expenditure

Table 2.1.7 Top 30 substances with the largest share of expenditure on the reference price (year 2021)

ATC 5th level	Active substance	Total expenditure	Δ % 21-20	%*	% cum.
C07AB07	bisoprolol	53.3	3.4	5.0	5.0
C10AA05	atorvastatin	41.1	8.5	3.8	8.8
A11CC05	cholecalciferol	29.0	17.1	2.7	11.5
C09AA05	ramipril	26.7	-2.4	2.5	14.0
B01AC06	acetylsalicylic acid	24.0	-0.6	2.2	16.2
C08CA01	amlodipine	20.6	-1.6	1.9	18.1
C09CA08	olmesartan	17.4	6.7	1.6	19.7
J01CR02	amoxicillin/clavulanic acid	16.7	-0.8	1.6	21.3
C10AX06	omega-3	16.1	0.8	1.5	22.8
A10BA02	metformin	15.7	-2.7	1.5	24.3
C09DA08	olmesartan/hydrochlorothiazide	15.5	4.0	1.4	25.7
B01AC04	clopidogrel	15.1	-2.1	1.4	27.1
G04CA02	tamsulosin	15.1	0.9	1.4	28.5
C09DB02	olmesartan/amlodipine	13.8	14.8	1.3	29.8
A05AA02	ursodeoxycholic acid	13.1	22.0	1.2	31.0
C09BB04	perindopril/amlodipine	13.0	-3.9	1.2	32.2
C07AB12	nebivolol	12.8	0.7	1.2	33.4
C10AA07	rosuvastatin	12.2	-3.9	1.1	34.5
G04CB02	dutasteride	12.0	-4.9	1.1	35.6
N03AX16	pregabalin	11.6	6.1	1.1	36.7
N06AB10	escitalopram	11.5	-0.8	1.1	37.8
C02CA04	doxazosin	11.5	-0.8	1.1	38.9
C09BX01	perindopril/indapamide/amlodipine	11.4	-	1.1	40.0
C10AA01	simvastatin	11.1	-6.4	1.0	41.0
J01XX01	fosfomycin	11.0	1.9	1.0	42.0
H03AA01	levothyroxine	10.7	0.0	1.0	43.0
C09CA07	telmisartan	10.2	-6.1	1.0	44.0
C01BC04	flecainide	10.0	-1.6	0.9	44.9
C09BA05	ramipril/hydrochlorothiazide	9.9	-5.2	0.9	45.8
C09DA03	valsartan/hydrochlorothiazide	9.7	-7.1	0.9	46.7
	Total of top 30	**501.8**	**4.4**	**46.7**	
	Total	**1082.7**	**0.4**	**100.0**	**100.0**

* calculated on overall shared expenditure

Table 2.1.8 Top 30 active substances by change (2021-2020) in cost-sharing for the share exceeding the reference price

ATC	Active substance	Expenditure 2021 *(million)*	Δ % 21-20	DDD 1000 inhab. per day	Δ % 21-20	Cost-sharing *(million)*	Δ % 21-20 *(million)*
C	perindopril/indapamide/ amlodipine	36.3	-2.7	4.2	16.4	11.4	11.4
C	ezetimibe/rosuvastatin	61.0	30.4	6.3	91.6	8.4	8.4
A	cholecalciferol	246.9	22.6	140.0	21.8	29.0	4.2
R	salmeterol/fluticasone	72.7	-29.7	2.3	-15.5	7.3	3.3
C	atorvastatin	273.7	2.1	50.2	3.0	41.1	3.2
B	clopidogrel/ acetylsalicylic acid	11.5	-19.9	0.8	6.6	3.3	2.7
A	ursodeoxycholic acid	51.7	10.0	2.6	7.6	13.1	2.4
S	timolol/brinzolamide	14.1	-40.7	1.2	-26.4	4.6	2.4
C	olmesartan/amlodipine	77.7	11.6	8.9	12.1	13.8	1.8
C	bisoprolol	160.9	3.7	12.3	4.2	53.3	1.7
S	timolol/brimonidine	6.4	-27.9	0.6	-10.2	2.0	1.7
J	brivudine	8.9	-25.7	0.0	1.5	1.2	1.2
C	olmesartan	105.4	6.9	15.5	7.8	17.4	1.1
R	fluticasone	15.8	-17.5	0.6	-11.4	1.0	1.0
H	methylprednisolone	11.6	0.9	3.0	2.5	0.9	0.9
M	ibuprofen	16.8	13.5	1.9	14.3	6.0	0.8
N	pregabalin	76.8	5.0	2.3	5.4	11.6	0.7
J	nitrofurantoin	2.9	100.3	0.1	104.4	0.6	0.6
C	olmesartan/hydrochlorothiazide	72.2	4.6	10.0	5.8	15.5	0.6
M	etoricoxib	34.8	9.8	3.5	11.3	6.2	0.5
S	dorzolamide	4.1	13.5	0.5	13.1	1.1	0.4
G	tibolone	7.6	4.8	0.8	6.1	1.9	0.4
R	budesonide	15.8	11.7	0.5	5.2	1.3	0.4
N	sertraline	47.6	4.0	8.7	4.8	9.1	0.4
R	tiotropium	69.2	-10.6	2.1	-10.0	2.2	0.4
D	calcipotriol/betamethasone	49.5	2.8	2.4	4.2	1.6	0.4
R	salbutamol	9.0	-8.0	2.0	-7.8	2.3	0.4
G	silodosin	42.0	0.5	6.2	15.2	9.4	0.4
B	folic acid	30.2	8.9	6.6	11.3	5.3	0.3
J	ciprofloxacin	34.9	1.0	0.6	1.9	7.6	0.3

Table 2.1.9 Distribution by geographical area, gender and age of patients using generic medicines for the top 10 therapeutic categories (ATC 3rd level) at the largest share of expenditure on the reference price (year 2021)

	C10A	C07A	C09D	C09B	C09C	N06A	G04C	C09A	B01A	C08C
Geographical Area										
North	60.4	58.9	33.7	32.7	44.3	54.0	52.8	64.4	22.7	49.2
Centre	48.8	43.2	25.6	23.4	34.2	45.3	41.3	51.0	20.4	36.0
South and Islands	40.4	33.2	19.9	17.7	24.6	34.0	31.1	38.0	17.2	25.0
Gender										
Women	48.3	43.4	25.1	24.7	32.6	45.7	38.8	51.7	17.4	36.1
Men	52.7	50.4	28.2	25.8	36.5	46.8	42.5	54.8	22.9	41.4
Age class										
<50	53.7	44.2	28.7	23.4	37.4	47.2	36.6	56.1	8.3	44.1
50-60	54.5	46.0	29.3	25.7	36.9	48.7	39.4	56.4	20.4	43.2
60-70	52.1	45.9	27.7	26.0	34.9	47.2	42.4	54.0	23.0	40.1
70-80	48.6	45.8	24.9	24.8	32.7	45.5	43.0	51.6	21.4	36.7
>80	47.2	48.9	24.8	25.3	33.1	42.6	43.5	51.4	20.3	36.6
Total	**50.5**	**46.5**	**26.5**	**25.3**	**34.4**	**46.1**	**42.4**	**53.3**	**20.1**	**38.7**

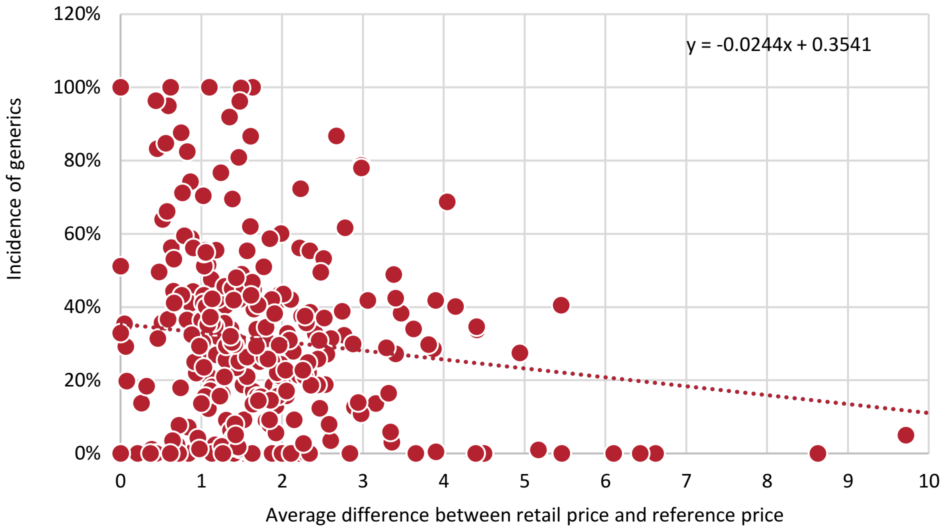
C10A: Lipid modifying substances not associated
C07A: Beta blockers
C09D: Angiotensin II antagonists associated
C09B: Angiotensin-converting enzyme inhibitors associated
C09C: Angiotensin II antagonists
N06A: Antidepressants
G04C: Medicines for benign prostatic hypertrophy
C09A: Angiotensin-converting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

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 distribution and per conto (year 2021)

Average difference between retail price and reference price (€)	% expenditure under approved care regime*	% expenditure in direct and per conto distribution**	% citizen cost-sharing on total cost-sharing
<1	9.84	1.83	7.21
≥1-<2	30.76	2.39	25.70
≥2-<3	30.83	2.80	31.46
≥3-<5	18.27	4.28	22.69
≥5-<20	9.58	14.87	11.47
≥20	0.72	73.82	1.47

** calculated on overall expenditure under approved care regime*
*** calculated on expenditure in direct distribution and per conto distribution*

Figure 2.1.7 Correlation between average difference (between retail price and reference price) and use of generics per active substance (year 2021)



Off-patent biologic medicines

By analyzing the level of competition in the biosimilars market (HHI) and market shares by competitor (Figure 2.1.8), insulin lispro and insulin glargine have a value of HHI of 0.60 and 0.59 respectively, although the largest market share belongs to the originator, which competes with only one type of biosimilar. The situation is different for somatropin (HHI=0.58), for which the largest market share is made of a single biosimilar on the market.

Follitropin alfa (HHI 0.55), teriparatide (HHI 0.48), and epoetin (HHI 0.46) have greater competitiveness, in 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=0.45), filgrastim (HHI=0.44) and pegfilgrastim (HHI=0.38) the competitiveness is even greater, in fact the ex-originator market represents a small share (minimal in the case of filgrastim) compared with that of the 3 available biosimilars. Etanercept (HHI=0,37) e infliximab (HHI=0,34) have a low market concentration, although the largest share is held by a biosimilar. Bevacizumab (HHI=0,32) and rituximab (HHI 0.33) has a fair distribution of market shares between the originator and two of the three available biosimilars. Finally, trastuzumab and adalimumab have the lowest value of HHI (0.25 and 0.22), a high-competitive index, in which there are at least 4 competitors.

Analysing the trend in expenditure and consumption of off-patent biological medicines for ATC 4th level (Table 2.1.10), 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 drugs that do not fall either within the definition of reference product or biosimilar, which reach percentages ranging between 60% and 65% (Figure 2.1.14, 2.1.15 and 2.1.19).

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, 31.98%), the highest percentage of consumption is attributable to adalimumab biosimilars (44.5%), increasing by 41.9% over 2020. Analysing the trend over the last decade it is observed a clear reduction in reference product expenditure for both adalimumab and etanercept (Figure 2.1.9). In the case of growth factors it can also be noted that, although there is a high incidence of expenditure for the originator of pegfilgrastim (Figure 2.1.13), it appears to have fallen sharply in recent years (-53.3% in 2021); as for consumption, the highest incidence is attributable to the biosimilar (39.1%) which has significantly increased compared to the previous year (+22.9%). Long-acting insulins have consumption, and consequently expenditure values, equally distributed between ex-originator (30.1%) and other insulin glargine (31.6%), although more than a third of the expenditure is attributable to the other types of long-acting insulin currently available (Figure 2.1.16). For intermediate-acting and mixed (long or intermediate acting with fast acting) insulins, the ex-originator is responsible for almost all spending and consumption.

Infliximab, rituximab and trastuzumab, which are the only three molecules to have two different formulations available (subcutaneous and intravenous) have a high incidence both for spending and consumption of the biosimilar (Figure 2.1.21 and 2.1.22); moreover, for both drugs there is a reduction in spending on the biosimilar 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 for epoetin and low molecular weight heparins, there is a higher incidence of both consumption and expenditure on biosimilars (Figures 2.1.11 and 2.1.12).

Bevacizumab, whose biosimilar was first marketed in Italy in 2020, has a high percentage of both consumption (73.6%) and expenditure (55.8%) on the biosimilar, showing a high increase (>100%) for both indicators in 2021 (Figure 2.1.10). For teriparatide, there is a similar trend, with biosimilars accounting for 58.4% in spending and 70.8% in consumption, with major increases (>100%) over the previous year (Figure 2.1.20).

Analysing the regional variability in the consumption of off-patent biological medicines (Figure 2.1.23), Lombardy, Calabria, Puglia, Molise and Campania tend to consume more former originator products, whereas Marche,Tuscany Piedmont, Basilicata and Veneto are the Italian regions with the highest consumption of biosimilars.

Analysing the regional variability in terms of biosimilar consumption and the average DDD cost of off-patent biologics in direct purchases (Figure 2.1.24), it is shown that in Emilia Romagna, the Province of Trento, Tuscany, Veneto, Piedmont, Sicily and Umbria the higher consumption of biosimilar corresponds to an average DDD cost lower than the national average. On the contrary, Basilicata and Liguria have a higher cost of off-patent biologics, despite a higher consumption of biosimilars. Sardinia consumes more biosimilars than the national average at an average cost per DDD in line with the national average. Lombardy, Calabria, Lazio, Molise, the Province of Bolzano, Abruzzo and Friuli Venezia Giulia have the highest values of cost per day of therapy compared to a lower consumption of biosimilars.

Figure 2.1.25, on the other hand, shows a linear correlation between the incidence of biosimilar consumption on the total consumption of off-patent biologics and the average cost per day of therapy of drugs purchased by public facilities. The regions with the highest biosimilar consumption that record a lower DDD cost are: Emilia Romagna, Piedmont, the Province of Trento, Veneto, Marche and Tuscany; while Lombardy and Calabria show low incidence of biosimilar and higher DDD cost.

Figure 2.1.8. Off-patent biologics: Herfindahl-Hirschman Index (HHI) and market shares by competitor (year 2021)

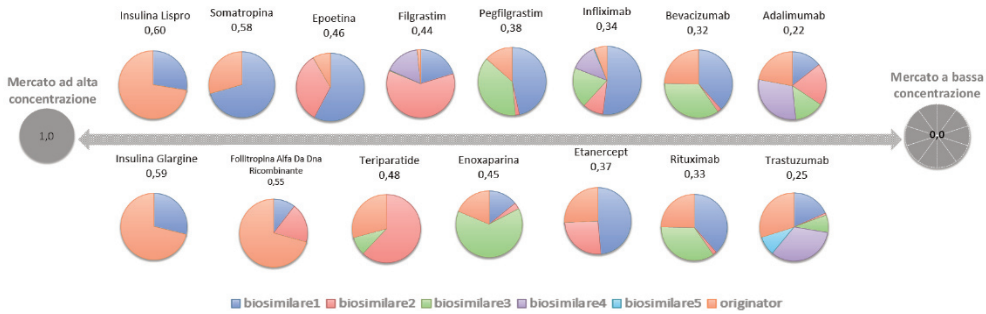


Tabella 2.1.11 Biosimilars, provision through public health facilities and NHS prescriptions (year 2021)

Group and subgroup	Expenditure *per capita*	Inc. %	Δ % 21-20	DDD/1000 inhab. per day	Inc. %	Δ % 21-20	Average cost	Δ % 21-20
Anti-TNF alpha	**4.50**	**100**	**-13.5**	**1.1**	**100.0**	**10.1**	**10.87**	**-21.4**
Biosimilar adalimumab	0.73	16.1	8.1	0.5	44.5	41.9	3.94	-23.8
Biosimilar etanercept	0.78	17.3	-7.9	0.2	19.1	12.0	9.88	-17.7
Originator adalimumab	0.83	18.5	-25.6	0.1	12.5	-26.5	16.02	1.2
Originator etanercept	0.72	16.1	-22.2	0.1	6.6	-21.1	26.43	-1.3
Other anti-TNF alpha	1.44	32.0	-12.0	0.2	17.3	1.6	20.05	-13.3
Bevacizumab	**1.00**	**100**	**-57.5**	**0.1**	**100.0**	**-8.6**	**29.48**	**-53.5**
Biosimilar	0.56	55.8	>100	0.1	76.3	>100	21.55	-19.8
Originator	0.44	44.2	-80.1	0.0	23.7	-74.9	55.04	-20.5
Low molecular weight heparins	**2.21**	**100**	**12.2**	**6.7**	**100.0**	**-7.9**	**0.91**	**21.8**
Biosimilar	1.48	66.8	34.6	4.6	69.0	15.3	0.88	16.7
Fondaparinux	0.30	13.4	27.1	0.5	7.8	17.1	1.56	8.6
Originator	0.22	10.1	-46.7	1.1	15.8	-53.0	0.58	13.5
Other low molecular weight heparin	0.21	9.7	-3.9	0.5	7.4	-12.2	1.20	9.5
Epoetins	**2.51**	**100**	**-10.2**	**3.7**	**100.0**	**1.4**	**1.88**	**-11.4**
Biosimilar	1.24	49.3	-5.3	2.9	79.2	6.8	1.17	-11.3
Originator	0.27	10.8	-34.1	0.3	7.3	-26.6	2.78	-10.3
Other epoetins	1.00	40.0	-7.0	0.5	13.6	-7.0	5.54	0.1
Growth factors	**0.40**	**100**	**-25.7**	**0.1**	**100.0**	**-2.0**	**10.77**	**-24.2**
Biosimilar filgrastim	0.10	26.1	-20.1	<0.05	44.5	-5.0	6.32	-15.9
Biosimilar pegfilgrastim	0.07	16.7	-23.7	<0.05	39.1	22.9	4.59	-38.0
Originator filgrastim	0.02	5.0	-47.5	<0.05	0.8	-43.6	71.11	-7.0
Originator pegfilgrastim	0.07	17.5	-53.3	<0.05	6.1	-52.1	30.90	-2.7
Other growth factors	0.14	34.8	5.2	<0.05	9.6	2.6	39.11	2.5

continued

Table 2.1.11 – *continued*

Group and subgroup	Expenditure *per capita*	Inc. %	Δ % 21-20	DDD/1000 inhab. per day	Inc. %	Δ % 21-20	Average cost	Δ % 21-20
Follitropins	**0.92**	**100**	**28.3**	**0.1**	**100.0**	**24.0**	**20.41**	**3.5**
Biosimilar	0.08	9.1	5.7	<0.05	13.0	13.7	14.29	-7.1
Originator	0.28	30.8	37.5	<0.05	31.5	44.0	19.95	-4.5
Other follitropin	0.55	60.1	28.0	0.1	55.5	17.2	22.10	9.2
Infliximab	**0.54**	**100**	**-12.9**	**0.4**	**100.0**	**14.2**	**3.9**	**-23.7**
Biosimilar infliximab IV	0.45	82.8	-11.5	0.4	93.6	17.2	3.45	-24.5
Biosimilar infliximab SC	0.00	0.7	>100	<0.05	0.4	>100	6.28	>100
Originator infliximab IV	0.09	16.5	-22.5	<0.05	6.0	-22.3	10.75	-0.2
Fast acting insulins	**0.17**	**100**	**-14.9**	**0.9**	**100.0**	**-9.1**	**0.53**	**-6.4**
Biosimilar	0.02	13.8	-39.3	0.1	13.9	-52.5	0.53	27.9
Originator	0.04	21.1	-11.6	0.3	35.3	38.5	0.32	-36.2
Other long acting insulins	0.11	65.1	-8.2	0.4	50.9	-8.1	0.68	-0.2
Long acting insulins	**2.36**	**100**	**0.5**	**6.3**	**100.0**	**3.7**	**1.03**	**-3.1**
Biosimilar	0.24	10.2	-13.1	0.8	12.2	-12.0	0.85	-1.3
Originator	0.68	28.8	-15.5	1.9	30.1	-11.0	0.98	-5.1
Other insulin glargine	0.63	26.8	32.4	2.0	31.6	33.6	0.87	-0.9
Other long acting insulins	0.81	34.2	2.3	1.6	26.0	3.9	1.35	-1.6
Rituximab	**1.09**	**100**	**-20.2**	**0.5**	**100.0**	**-0.1**	**6.68**	**-20.1**
Biosimilar IV	0.78	71.35	-19.9	0.3	75.3	6.8	6.34	-25.0
Originator IV	0.05	4.56	-44.7	0.0	2.4	-34.3	12.87	-15.7
Originator SC	0.26	24.09	-14.1	0.1	22.4	-14.0	7.19	0.0

continued

Table 2.1.11 – *continued*

Group and subgroup	Expenditure *per capita*	Inc. %	Δ % 21-20	DDD/1000 inhab. per day	Inc. %	Δ % 21-20	Average cost	Δ % 21-20
Somatropins	**1.20**	**100**	**-11.2**	**0.3**	**100.0**	**-4.2**	**12.19**	**-7.4**
Biosimilar	0.25	21.0	-0.9	0.1	26.6	3.9	9.62	-4.6
Originator	0.18	14.6	-17.5	<0.05	11.1	-17.1	16.09	-0.5
Other somatropin	0.77	64.4	-12.7	0.2	62.3	-4.7	12.59	-8.4
Teriparatide	**0.09**	**100**	**-37.0**	**<0.05**	**100.0**	**-22.8**	**8.06**	**-18.3**
Biosimilar	0.05	58.4	110.5	<0.05	70.8	125.4	6.64	-6.6
Originator	0.04	41.6	-68.2	<0.05	29.2	-70.3	11.51	7.0
Trastuzumab	**1.11**	**100**	**-28.4**	**0.2**	**100.0**	**-2.8**	**17.59**	**-26.4**
Biosimilar IV	0.61	54.3	-23.0	0.1	70.2	4.1	13.62	-26.0
Originator IV	0.07	6.1	-63.8	<0.05	2.1	-58.3	51.43	-13.3
Originator SC	0.44	39.6	-24.5	0.1	27.8	-8.9	25.09	-17.1
Total	**18.10**	**100**	**-14.43**	**20.3**	**100**	**-1.24**	**2.45**	**-13.4**
Biosimilar	7.43	41.1	3.1	10.2	50.28	8.74	2.00	-5.9
Originator	4.70	26.0	-40.8	4.0	19.95	-40.58	3.19	-16.8
Other	5.97	33.0	-0.6	6.0	29.77	8.27	2.71	-8.8

Figure 2.1.9 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): anti-TNF alpha

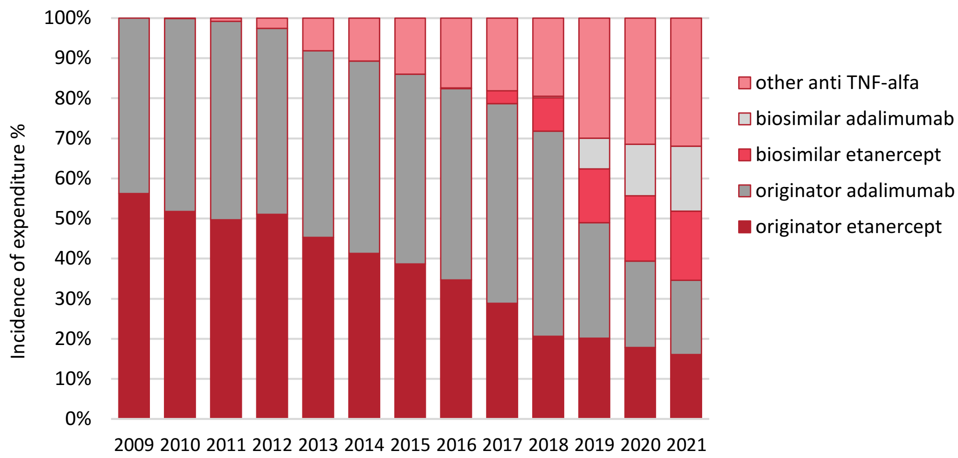


Figure 2.1.10 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: bevacizumab

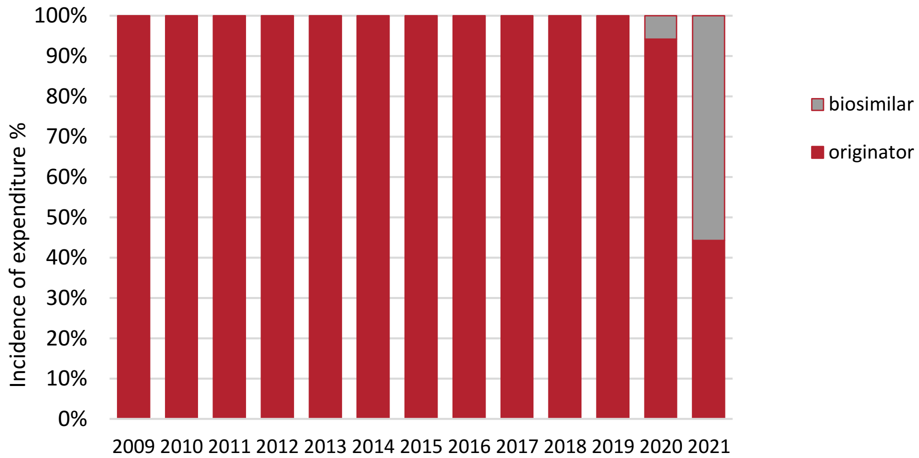


Figure 2.1.11 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): low molecular weight heparins

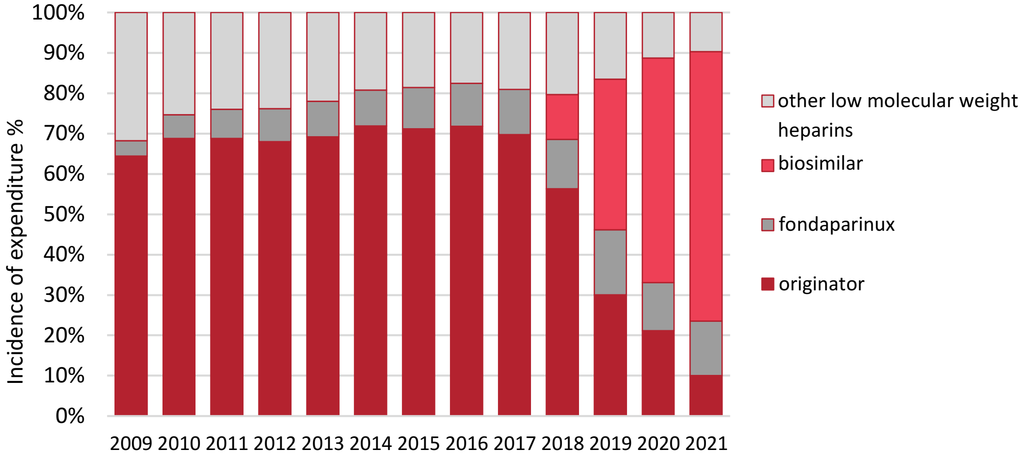


Figure 2.1.12 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): epoetin

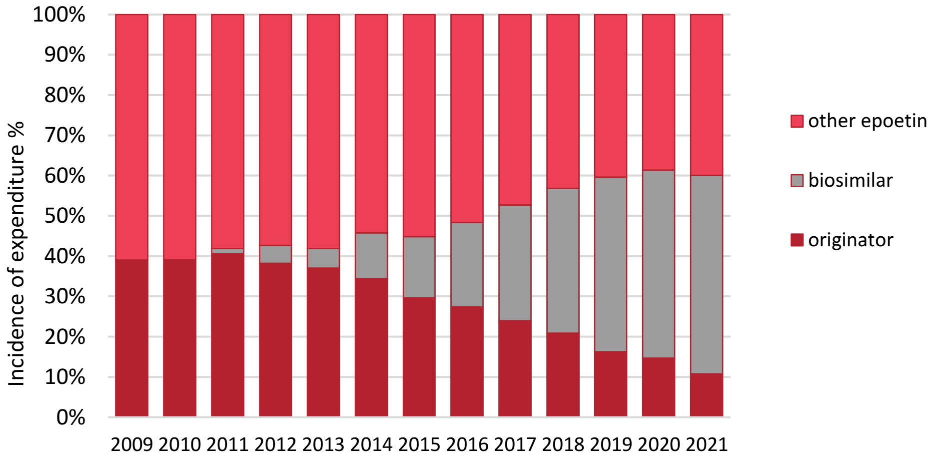


Figure 2.1.13 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): growth factors

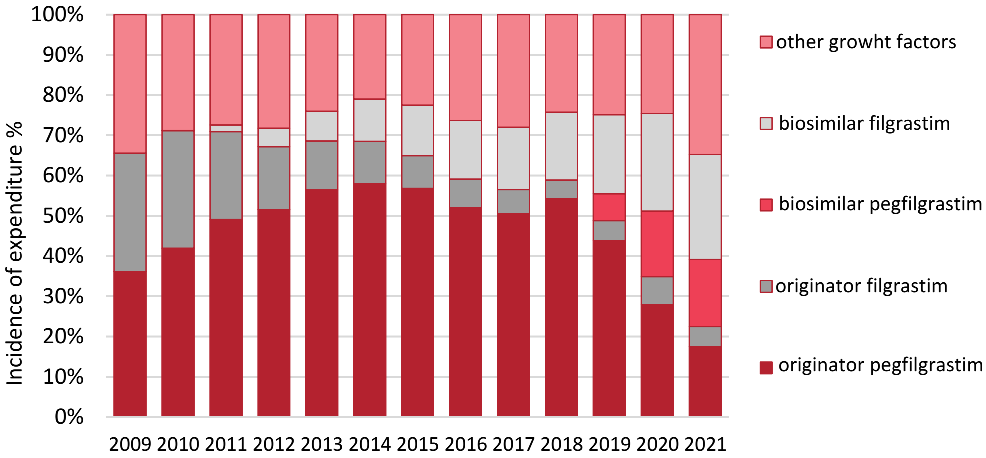


Figure 2.1.14 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): follitropin

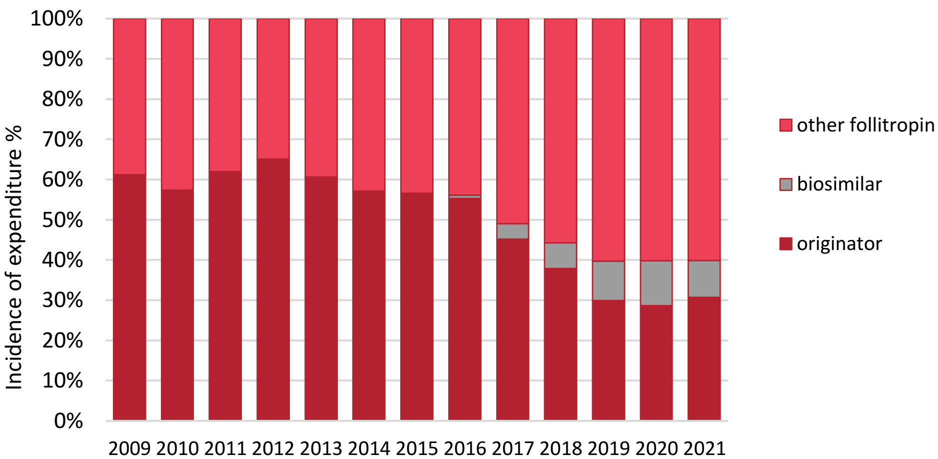


Figure 2.1.15 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): fast acting insulins

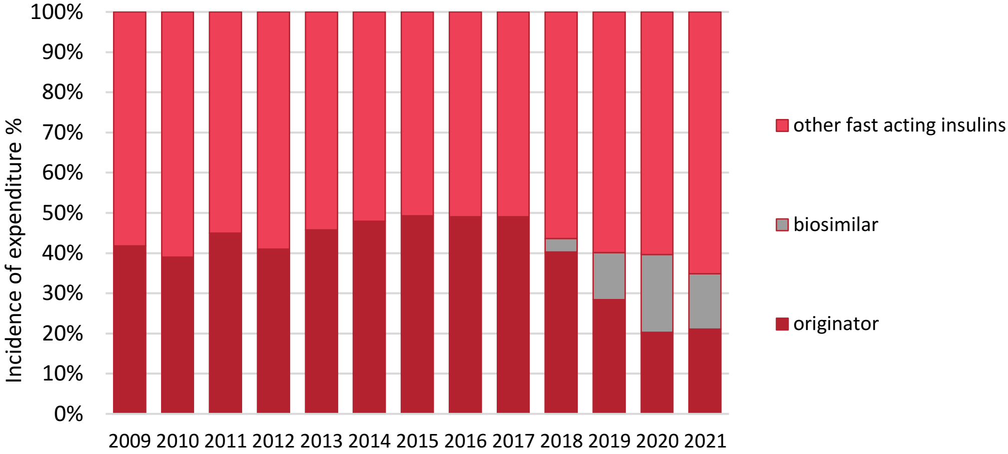


Figure 2.1.16 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): long acting insulins

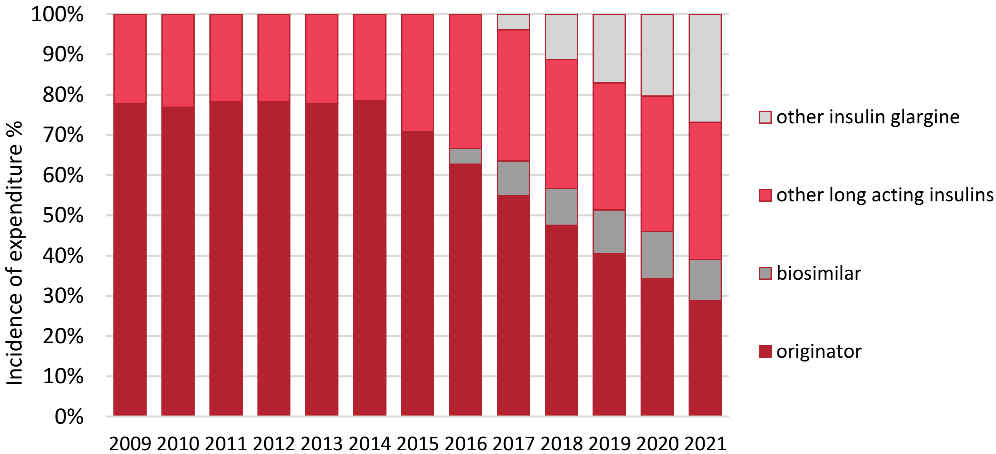


Figure 2.1.17 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): premixed (long/intermediate acting with fast acting) insulins

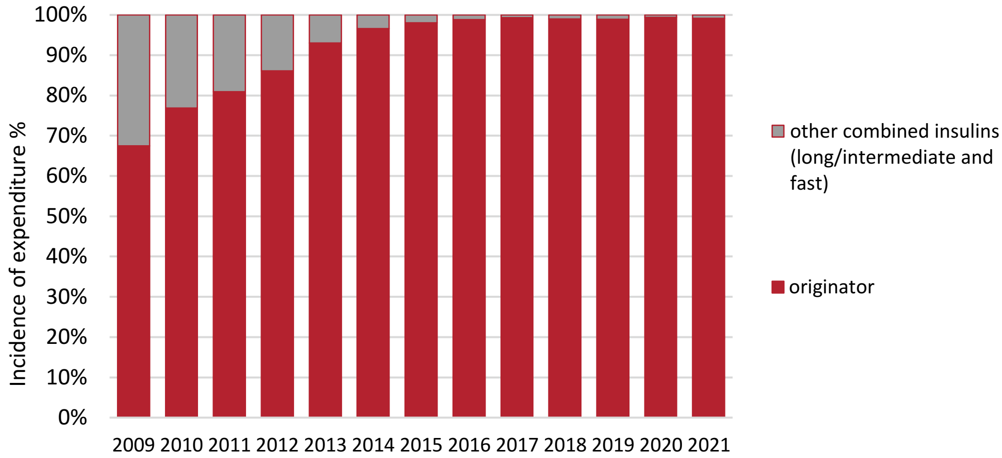


Figure 2.1.18 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: rituximab

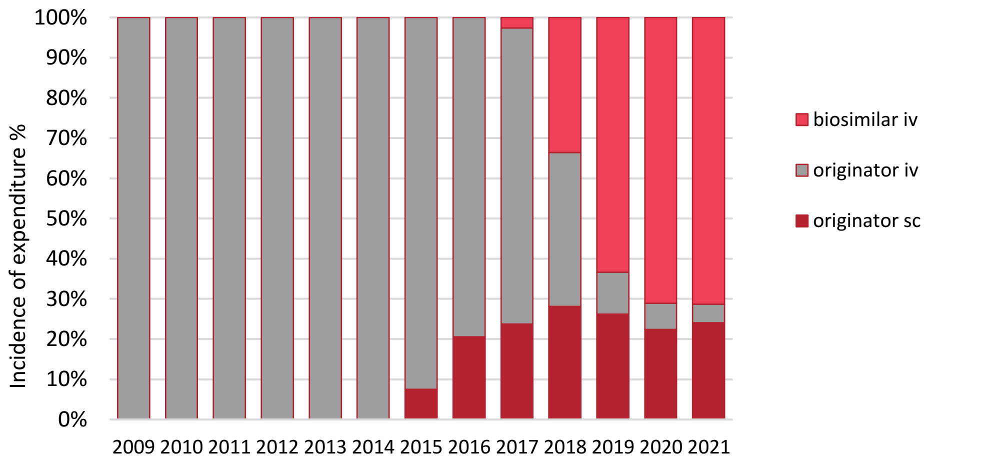


Figure 2.1.19 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: somatropin

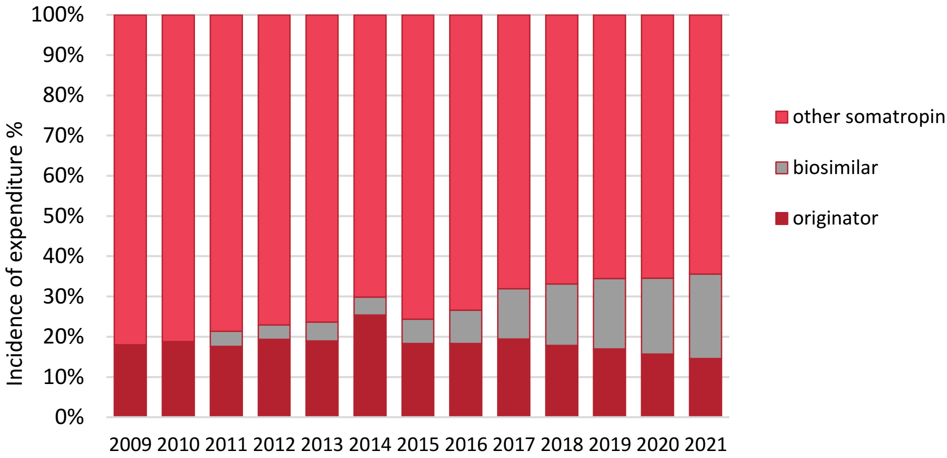


Figure 2.1.20 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: teriparatide

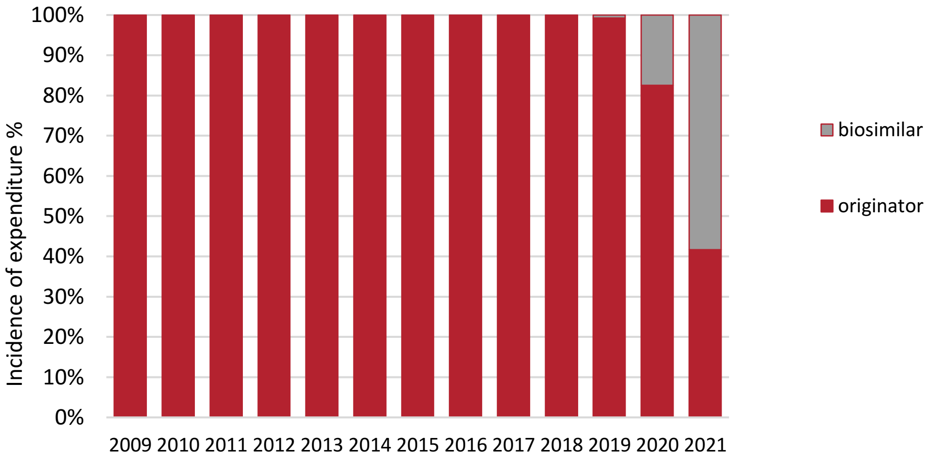


Figure 2.1.21 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: trastuzumab

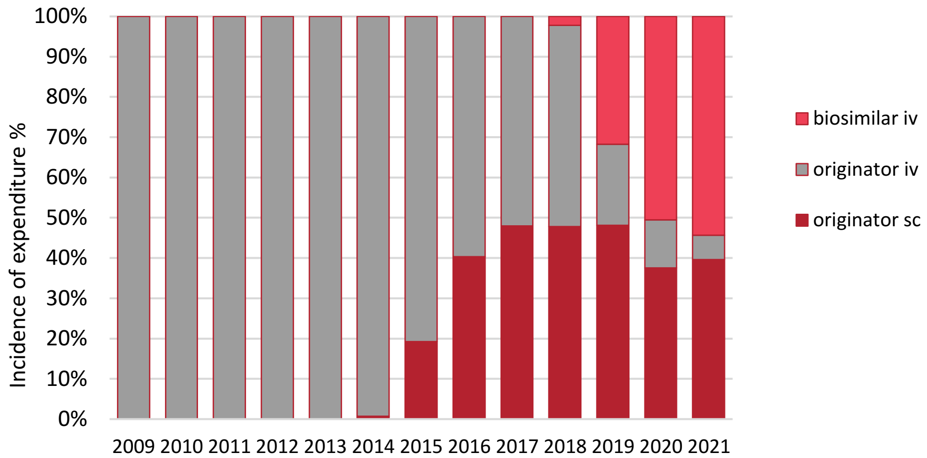
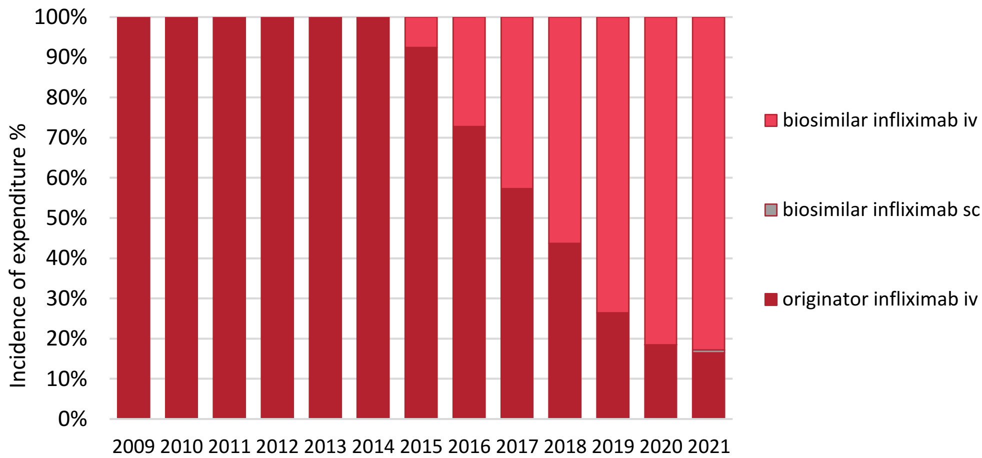


Figure 2.1.22 Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: infliximab



2.1.23 Consumption (DDD/1000 inhab. per day) of biosimilar vs originator drugs compared to the national average (year 2021)

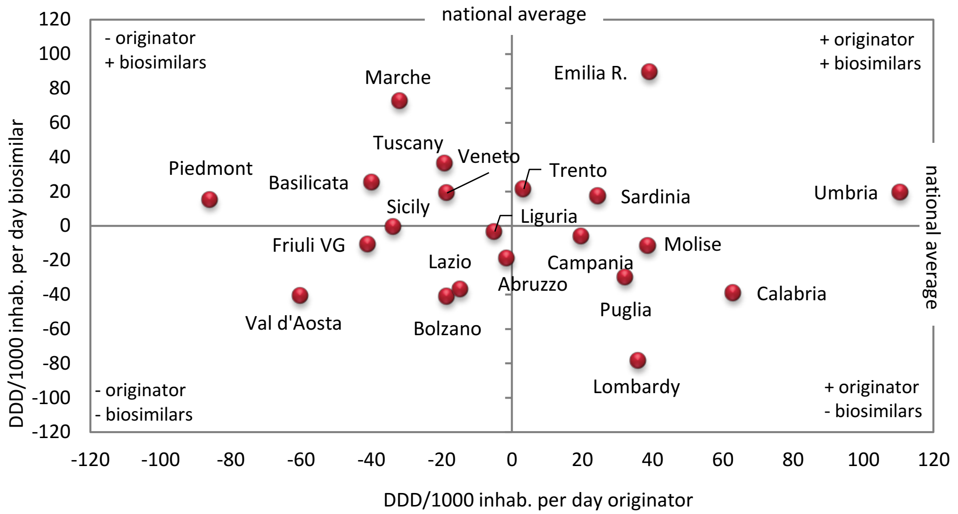


Figure 2.1.24 Regional variability in biosimilar drug consumption and average DDD cost of off-patent biologics in 2021 (% deviations from national average)

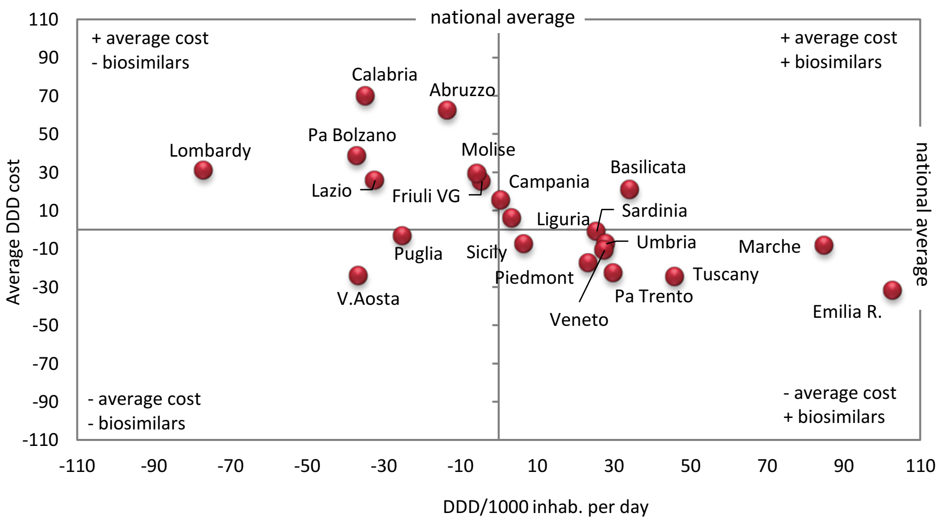
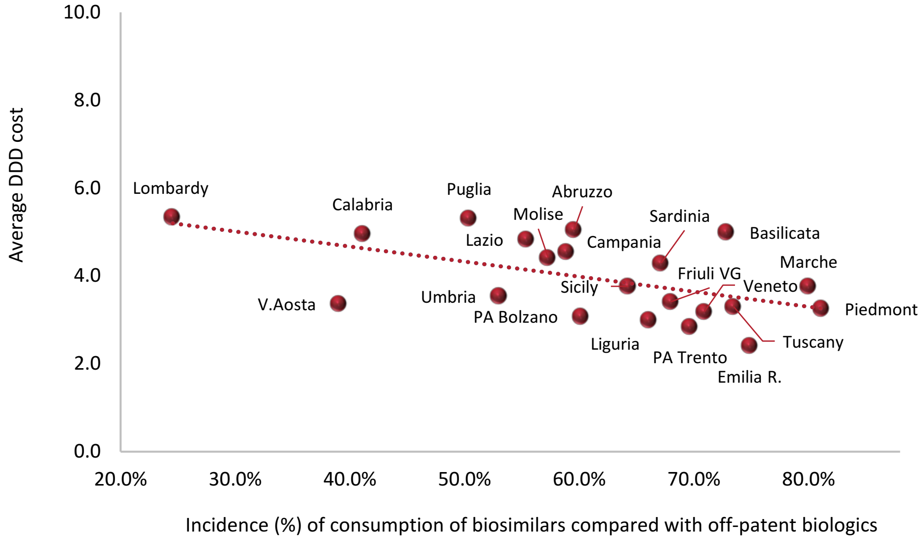


Figure 2.1.25 Correlation analysis between the incidence of biosimilar consumption on off-patent biologics and average DDD cost in direct purchases (year 2021)



2.2 Class C medicines reimbursed by the NHS

Decree Law No. 158 of 2012 (the so-called Balduzzi Decree) converted into Law No. 189/2012 (Art. 12) establishes that medicines approved by the European Medicines Agency (EMA) and awaiting price negotiation in Italy are placed in class C-Non-Negotiated (so-called C-NN). Public health facilities can purchase the medicine by negotiating the price directly with the manufacturing companies, if they have decided to market the product. In the event that the owner of the product does not submit an application for reimbursement and price within 30 days of the issue of the MA, the AIFA sends a reminder by PEC to submit such an application, assigning a deadline of 30 days for the transmission of the relative application and the necessary documentation. If the owner of the product sends what is requested within this deadline, the procedure corresponding to the specific type of negotiation is started; otherwise pursuant to Article 12, paragraph 5-ter of the aforesaid Decree-Law no. 158/2012, AIFA adopts a provision ordering the suspension of the medicine from placement in the C-NN class, with the consequence that the same - except for temporary exceptions due to public health interests and/or relevant reasons of therapeutic continuity - may not be further marketed on the national territory until the reactivation of the ordinary procedure by the Applicant or by AIFA. Table 2.2.1 describes the per capita expenditure and consumption (DDD/1000 inhabitants per day), with regional detail, of class C-NN medicines reimbursed by the NHS and purchased directly by public health facilities in 2021. Total expenditure for C-NN medicines almost doubled (+90.0%) compared with the previous year, amounting to around 180 million euros (3.04 euros per capita). The Central Regions are those with the highest per capita expenditure (3.88 euros), compared to the Northern (3.01 euros) or the Southern (2.55 euros), and they also register the greatest increase compared to 2020 (+123.9%). The Northern Regions, on the other hand, tend to consume these medicines the most, registering values of 2.6 DDD/1000 inhabitants per day. Compared to the previous year, there is a clear reduction in consumption of 24.5% at the national level, which is however more marked in the North (-34.3%) and in the Centre (-27.8%), while in the South an increase of 99.3% is recorded. The doubling of expenditure accompanied by a reduction in consumption is probably attributable to a net increase in the average DDD cost (>100%), which in the Centre (17.74 euros) is more than five times higher than in the North (3.26 euros) and shows an increase of 211.1% compared to 2020. The deep regional variability is highlighted precisely by the average DDD cost, which goes from 80.94 euros in the Marche to 0.53 euros in Sardinia. In fact, Marche ranks third in terms of per capita expenditure (4.52 euros).
Analysing the top 30 active ingredients by expenditure, purchased directly by the public health structures (Table 2.2.2), in first place, with an expenditure of 133.3 million euros, there is remdesivir, approved for the treatment of COVID-19 disease in adults and adolescents (aged 12 years or more and weighing at least 40 kg) with pneumonia requiring supplementary oxygen therapy. This expenditure was calculated using the price per package ex factory, before VAT. Similarly to 2020, the active ingredient ivacaftor associated with lumacaftor (7.3 million) and ivacaftor alone follow, and both show reductions in expenditure compared to 2020, with the lumacaftor/ivacaftor combination showing the largest reductions (-32.6%). These reductions are partly attributable to the fact that both

medicines were classified in reimbursement class A during 2021. In 7th and 8th position we find two other medicines indicated in the treatment of cystic fibrosis: ivacaftor/tezacaftor which with 2.3 million euros records a 42.7% reduction in expenditure in the C-NN class, making this drug move from 3rd position in 2020 to 7th position in 2021, due to its classification as class A medicine during the year; the triple association elexacaftor/tezacaftor/ivacaftor moves from the 152nd position in 2020 to the 8th in 2021. The most consumed active ingredient is paracetamol which, although it shows a 33.0% reduction compared to the previous year, registers a value of 0.96 DDD/1000 inhabitants per day. Over a quarter of the expenditure for medicines classified as C-NN class concerns medicines with a price higher than 10.000 euros, with a considerable regional variability which goes from 0% in the Valle d'Aosta to over half (59.5%) in Sicily (Table 2.2.3). Table 2.2.4 shows the expenditure and prices of medicines authorised by EMA in the period 2019-2021, with a stay in class C-NN for at least 6 months. The prices applied in C-NN were compared with those recorded following reclassification in class A/H. It can be seen that the price detected following reclassification to class A/H is higher in all but one case than that applied in C-NN, with variations >100% in most medicines.

Table 2.2.1 Regional per capita expenditure and consumption 2021 of medicines purchased directly from public health facilities in class C-NN

Region	Expenditure *per capita*	Δ % 21-20	Inc. %	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
Piedmont	2.78	66.3	6.9	0.5	-55.4	15.43	273.7
Valle d'Aosta	4.36	141.9	0.3	0.5	-49.6	25.52	381.0
Lombardy	2.73	62.7	15.0	3.3	-34.8	2.24	150.1
Province of Bolzano	2.34	2.1	0.6	0.7	30.0	8.92	-21.2
Province of Trento	1.50	22.3	0.4	2.2	8.7	1.83	12.8
Veneto	2.28	27.1	6.2	4.9	-43.3	1.26	124.8
Friuli VG	1.81	62.1	1.3	1.3	211.4	3.86	-47.8
Liguria	4.76	81.9	4.4	0.6	75.9	21.54	3.7
Emilia R.	4.55	116.8	11.4	1.7	-3.6	7.32	125.6
Tuscany	3.77	133.6	8.1	0.8	-3.4	13.46	142.6
Umbria	2.85	82.2	1.4	0.2	80.7	42.63	1.1
Marche	4.52	190.1	3.9	0.2	-12.7	80.94	233.1
Lazio	3.95	108.9	12.5	0.7	-41.5	16.05	258.1
Abruzzo	3.91	100.7	2.8	0.2	17.6	48.79	71.2
Molise	0.67	-12.5	0.1	0.2	172.5	7.42	-67.8
Campania	1.77	134.5	5.1	0.5	-3.5	10.58	143.5
Puglia	3.20	93.9	6.9	0.6	1.1	13.73	92.2
Basilicata	5.16	127.6	1.6	0.5	502.3	27.78	-62.1
Calabria	2.90	91.6	2.9	0.5	77.3	17.07	8.3
Sicily	2.67	154.2	7.0	0.2	1.7	39.17	150.8
Sardinia	1.24	12.2	1.1	6.4	347.0	0.53	-74.8
Italy	**3.04**	**90.0**	**100.0**	**1.6**	**-24.5**	**5.12**	**152.4**
North	3.01	67.3	46.6	2.6	-34.3	3.22	155.5
Centre	3.88	123.9	25.8	0.6	-27.8	17.74	211.1
South and Islands	2.55	108.0	27.6	0.9	99.3	7.63	4.7

Not including vaccines (ATC J07) and oxygen (V03AN01)

Table 2.2.2 Top 30 active ingredients by expenditure directly purchased by public health facilities of class C-NN: comparison 2021-2020

ATC	Active Ingredient	Rank 2021	Rank 2020	Expenditure *(million)*	Δ % 21-20	% expenditure*	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
J05AB16	remdesivir	1	1	133.3	>100	74.1	0.02	>100	374.7	-1.3
R07AX30	lumacaftor/ivacaftor	2	2	7.3	-32.6	4.1	<0.005	-33	559.1	0.9
R07AX02	ivacaftor	3	4	3.8	-4.2	2.1	<0.005	-3	707.1	0.0
V09IX07	fluoromethylcholine (18F)	4	5	2.9	-9.5	1.6	<0.005	-11	2390.3	2.4
B02BB01	human fibrinogen	5	-	2.5	-	1.4	<0.005	-	2128.5	-
B01AC11	Iloprost	6	13	2.4	>100	1.3	<0.005	>100	63.1	-0.5
R07AX31	ivacaftor/tezacaftor	7	3	2.3	-42.7	1.3	<0.005	-42	278.8	0.6
R07AX32	elexacaftor/tezacaftor/ivacaftor	8	-	2.1	-	1.2	<0.005	-	385.8	-
L01AB02	treosulfan	9	14	1.9	>100	1.0	<0.005	>100	2927.3	14.4
V09AB03	iodine ioflupane (123I)	10	38	1.6	>100	0.9	<0.005	>100	701.4	-7.2
V03AB38	andexanet alfa	11	-	1.5	-	0.8	<0.005	-	3520.0	-
L04AA04	antithymocyte immunoglobulin (rabbit)	12	6	1.5	-47.6	0.8	<0.005	-20	297.0	-33.9
J01CR02	amoxicillin/clavulanic acid	13	8	1.5	-40.3	0.8	0.02	-44	3.2	7.2
V09IX09	edotreotide	14	15	1.1	59.2	0.6	<0.005	-21	8972.9	102.5
V09HX01	gallium citrate (67Ga)	15	10	0.9	-11.1	0.5	<0.005	-33	67276.7	33.4
J01XX09	daptomycin	16	-	0.9	-	0.5	0.02	-	2.5	-
N02BE01	paracetamol	17	9	0.9	-29.7	0.5	0.96	-33	0.0	5.4
B01AE06	bivalirudin	18	17	0.8	55.8	0.4	<0.005	-62	296.0	>100
V09FX03	sodium iodide (131I)	19	11	0.8	-21.8	0.4	<0.005	-34	76.3	19.5
R07AX01	nitric oxide	20	24	0.6	>100	0.3	<0.005	51	1261.1	50.3
V10XA01	sodium iodide (131I)	21	12	0.6	-40.8	0.3	<0.005	-46	188.8	9.8
V04CL	allergy tests	22	-	0.5	-	0.3	<0.005	68	60.3	-
J01XA02	teicoplanin	23	41	0.5	>100	0.3	<0.005	>100	8.7	-8.2
L01FX15	belantamab mafodotin	24	-	0.4	-	0.2	<0.005	-	601.7	-
G02BB01	ethinyl estradiol/etonogestrel	25	20	0.4	17.5	0.2	0.05	19	0.3	0.0
M05BA08	zoledronic acid	26	-	0.4	-	0.2	<0.005	-	177.9	-
J06BA02	human normal immunoglobulin for intravascular administration	27	-	0.3	-	0.2	<0.005	-	377.0	-
M03AC09	rocuronium	28	-	0.3	-	0.2	0.01	-	2.9	-
V09EB01	oxydronate	29	22	0.3	3.1	0.2	<0.005	-31	47.3	50.8
N01BB09	ropivacaine	30	21	0.3	-8.4	0.2	0.10	-12	0.1	5.3
	Total top 30			**174.4**	**99.2**	**97.0**	**1.08**	**-29.0**	**7.48**	**183.0**
	Total			**179.8**			**1.63**	**-25.0**	**5.18**	**155.7**

Not including vaccines (ATC J07) and oxygen (V03AN01) *calculated on the total cost of the molecule

Table 2.2.3 Percentage distribution by Region of class C-NN expenditure by price range* (year 2021)

Region	Price range (€)			
	<400	401-1.000	1.001-9.999	≥10.000
Piedmont	33.5	15.6	28.5	22.4
Valle d'Aosta	81.9	4.7	13.5	0.0
Lombardy	33.7	10.9	33.8	21.7
Province of Bolzano	22.2	1.0	55.3	21.6
Province of Trento	57.8	2.4	32.9	6.9
Veneto	17.8	8.5	55.7	18.0
Friuli VG	37.8	12.1	42.3	7.9
Liguria	62.8	12.1	21.0	4.1
Emilia R.	34.8	10.1	33.9	21.2
Tuscany	32.9	27.2	14.2	25.7
Umbria	25.1	34.7	13.5	26.7
Marche	14.3	8.9	43.2	33.6
Lazio	25.0	28.7	34.0	12.2
Abruzzo	30.5	12.3	43.9	13.2
Molise	42.2	19.9	37.9	0.0
Campania	22.1	12.4	14.6	50.9
Puglia	16.7	8.0	48.9	26.3
Basilicata	19.4	17.0	21.7	41.9
Calabria	6.6	10.9	65.9	16.6
Sicily	15.4	5.5	19.5	59.5
Sardinia	42.8	15.5	6.9	34.8
Italy	**27.0**	**13.2**	**33.1**	**26.7**
North	32.6	10.3	37.8	19.3
Centre	28.4	25.4	22.3	23.8
South and Islands	18.7	9.9	33.2	38.2

* not including vaccines (ATC J07), oxygen (V03AN01) and remdesivir (J05AB16)

Table 2.2.4 Expenditure and prices by active ingredient among those authorised by EMA in the period 2019-2021

ATC	Active Ingredient	Expenditure C-NN			Price C-NN	Price SSN (A/H)	Δ% prices
		2019	2020	2021			
N06AX27	esketamine	-	333	12,047	1.07	297.15	>100
H02CA02	osilodrostat	-	-	471	1.10	8,548.10	>100
L04AA44	upadacitinib	-	486	-	1.10	552.08	>100
L01EX13	gilteritinib	-	391	164	1.13	10,338.31	>100
L04AA45	filgotinib	-	0	8,110	9.70	456.56	>100
H04AA01	glucagon	-	-	701	140.29	75.96	-46
S01LA06	brolucizumab	-	-	2,327,897	398.27	1,012.85	>100
L03AB15	ropeginterferon alfa	-	11,355	149,884	1,378.11	3,407.29	>100
L01FX14	polatuzumab	-	-	189,217	2,174.91	3,925.70	80
L01AB02	treosulfan	8,899	712,741	1,876,081	3,612.96	5,339.40	48
V03AB38	andexanet alfa	-	-	1,520,640	14,080.00	23,407.34	66

Class C medicines reimbursed by the NHS purchased directly from public health facilities

Regarding class C medicines dispensed directly by public health facilities, per capita expenditure was equal to 10.03 euros, with a 8.5% increase compared to the previous year. On the contrary, consumption, equal to 42.5 DDD/1000 inhabitants per day, is down by 2%; therefore, the trend in spending is attributable to the increase in the average DDD cost compared to the previous year which was 11.0% (Table 2.2.5). The Northern Regions show higher values of expenditure (10.60 euros) and of consumption (48.4 DDD/1000 inhabitants per day) than the Central (9.72 euros and 43.3DDD/1000 inhabitants per day) and the Southern Regions (9.40 euros and 33.7 DDD/1000 inhabitants per day). The average cost per DDD is fairly heterogeneous at the regional level, with the highest values found in the South (0.77 euro) compared to the North (0.60 euro) and the Centre (0.62 euro). The Southern Regions are also those that record the greatest increases in average cost compared to 2020 (+ 16.4%), while in the Central Regions (+ 14.3%) and in the Northern Regions (+ 6.7%). Analysing the regional variability, the per capita expenditure value turns out to be higher in the Marche (14.26 euros) and lower in Molise (6.88 euros). Analysing consumption, on the other hand, the Marche with a value of 78.4 days of therapy per 1000 inhabitants per day recorded the highest value, and Molise with 24.9 DDD/1000 inhabitants per day the lowest. Abruzzo, on the other hand, is the Region with the highest DDD cost, equal to 1.14 euros. Considering the top 30 active ingredients for class C expenditure purchased directly from public health facilities (Table 2.2.7), 11 belong to the class of medicines active on blood and haematopoietic organs (ATC B) and are mainly infusion or dialysis solutions, 5 are antimicrobials for systemic use, including amphotericin B which, with a per capita expenditure of 0.71 euros and an increase of 30.6% over the previous year, is the second molecule by expenditure, and 8 belong ATC V, including the iomeprol contrast agent which, with an expense of 0.51 euros, represents the third for expenditure, observing an increase of 17.6% compared to the year 2020. Particularly interesting is the increase in terms of expenditure and consumption of human fibrinogen (>100%), whose use is authorised in the treatment and perioperative prophylaxis of bleeding in patients with congenital hypo- or afibrinogenemia with a tendency to bleed. This active ingredient, in fact, goes from the 57th rank in 2020 to the 8th in 2021.

Table 2.2.5 Regional per capita expenditure and consumption 2021 of medicines purchased directly from public health facilities in class C-NN

Region	Expenditure *per capita*	Δ % 21-20	Inc. %	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
Piedmont	10.10	4.5	7.6	44.2	-8.4	0.63	14.4
Valle d'Aosta	10.00	7.4	0.2	55.7	1.1	0.49	6.6
Lombardy	8.47	12.1	14.1	33.1	4.2	0.70	7.8
Province of Bolzano	11.37	7.7	1.0	48.9	-4.2	0.64	12.7
Province of Trento	9.81	15.3	0.9	49.5	-1.1	0.54	17.0
Veneto	13.17	-3.8	10.8	60.7	-5.6	0.59	2.2
Friuli VG	10.27	-3.3	2.2	44.7	-1.7	0.63	-1.3
Liguria	10.20	6.2	2.9	40.7	-13.6	0.69	23.3
Emilia R.	13.28	11.2	10.1	76.1	9.0	0.48	2.3
Tuscany	10.54	5.1	6.8	47.1	-4.5	0.61	10.4
Umbria	11.25	1.5	1.7	57.4	-4.5	0.54	6.6
Marche	14.26	11.2	3.7	78.4	-2.6	0.50	14.5
Lazio	7.67	8.8	7.3	28.8	-9.8	0.73	21.0
Abruzzo	11.77	11.6	2.6	28.3	-6.1	1.14	19.2
Molise	6.88	-6.5	0.4	24.9	-12.7	0.76	7.5
Campania	8.08	10.4	7.1	27.9	-0.2	0.79	11.0
Puglia	10.53	14.7	6.9	44.6	-8.9	0.65	26.3
Basilicata	12.66	12.3	1.2	40.0	-0.3	0.87	12.9
Calabria	10.02	21.5	3.1	35.5	-1.0	0.77	23.0
Sicily	8.40	15.4	6.6	26.7	4.2	0.86	11.1
Sardinia	10.57	15.9	2.9	47.6	5.6	0.61	10.0
Italy	**10.03**	**8.5**	**100.0**	**42.5**	**-2.0**	**0.65**	**11.0**
North	10.60	5.8	49.7	48.4	-0.5	0.60	6.7
Centre	9.72	7.2	19.6	43.3	-5.9	0.62	14.3
South and Islands	9.40	13.9	30.7	33.7	-1.8	0.77	16.4

Not including vaccines (ATC J07) and oxygen (V03AN01)

Table 2.2.6 Top 20 categories (ATC IV level) by expenditure directly purchased by public health facilities of class C-NN: comparison 2021-2020

ATC	Category	Expenditure *(million)*	Δ % 21-20	% expenditure*	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
B05BB	Solutions affecting the electrolyte balance	55.9	5.7	9.4	6.7	2.0	0.39	4.5
V08AB	Water-soluble, nephrotropic, low osmotic radiological contrast media	50.0	47.2	8.4	<0,05	55.9	60.73	-4.7
B05BA	Parenteral nutritional solutions	47.8	-1.6	8.0	0.7	-7.3	3.36	7.3
J02AA	Antibiotics	42.0	29.7	7.1	<0,05	30.8	102.34	0.1
B05DB	Hypertonic solutions	31.2	0.0	5.3	0.1	7.5	9.81	-6.1
V08CA	Paramagnetic contrast agents	21.8	86.6	3.7	<0,05	47.7	46.89	27.5
B02BC	Local hemostatics	12.1	23.6	2.0	<0,05	17.6	320.29	6.1
J01CR	Water-soluble, nephrotropic, low osmotic radiological contrast media	11.7	17.0	2.0	<0,05	24.1	11.20	-4.8
J01XB	Polymyxins	11.7	-9.8	2.0	<0,05	-3.7	34.08	-5.4
B05DA	Isotonic solutions	11.4	8.2	1.9	0.1	9.5	7.55	-0.3
B02BB	Fibrinogen	11.3	350.7	1.9	<0,05	361.3	2189.94	-1.4
V03AF	Detoxifying substances for cytostatic treatments	11.2	13.9	1.9	0.1	1.4	5.94	13.4
J06BA	Human normal immunoglobulin	10.2	-8.6	1.7	<0,05	-11.6	389.47	4.4
N01BB	Amides	8.7	0.1	1.5	1.6	11.9	0.25	-9.7
B01AX	Other antithrombotics	8.3	5.9	1.4	<0,05	11.2	3893.34	-3.8
V09AB	Iodine-123I compounds	8.1	12.0	1.4	<0,05	12.6	873.72	0.4
A11BA	Polyvitamins, not in combination	7.8	-21.9	1.3	0.1	-11.9	4.27	-10.5
C01CX	Other inotropic substances	7.7	-6.0	1.3	<0,05	13.2	512.46	-16.2
V09FX	Various thyroid diagnostic radiopharmaceuticals	7.6	-3.3	1.3	<0,05	16.0	275.11	-15.8
V07AB	Solvents and thinners, including cleaning solutions	7.3	18.5	1.2	2.2	-0.1	0.15	19.7
N03AX	Other antiepileptics	7.1	31.4	1.2	<0,05	23.1	13.57	7.8
N07XX	Other medicines for the nervous system	6.6	3.6	1.1	<0,05	10.8	23.72	-5.6
B05ZB	Hemofiltrates	6.5	15.9	1.1	<0,05	15.2	7.41	1.6
B01AC	Platelet aggregation inhibitors, excl. heparin	6.1	-8.6	1.0	<0,05	1.7	42.57	-9.3
H02AB	Glycocorticoids	6.0	-18.6	1.0	1.0	-35.2	0.28	26.8
D08AC	Biguanides and amidines	6.0	8.9	1.0	1.6	-3.9	0.17	14.4
J01MA	Fluoroquinolones	5.2	-1.1	0.9	<0,05	-27.8	22.54	38.4
N01AX	Other general anesthetics	5.2	-10.1	0.9	<0,05	-33.8	43.70	37.1
G02AD	Prostaglandins	5.0	-7.3	0.8	<0,05	-2.7	5.06	-3.8
J01GB	Other aminoglycosides	4.7	-3.0	0.8	<0,05	-5.5	22.31	3.6
	Total top 30	**442.4**	**12.9**	**74.5**	**14.4**	**-2.2**	**1.42**	**16.5**
	Total	**594.1**	**8.5**		**42.5**	**-2.0**	**0.65**	**11.0**

Not including vaccines (ATC J07) and oxygen (V03AN01); *calculated on the total expenditure for medicines purchased directly from public health facilities in class C

Table 2.2.7. Top 30 active ingredients by expenditure directly purchased by public health facilities of class C-NN: comparison 2021-2020

ATC	Active Ingredient	Rank 2021	Rank 2020	Expenditure *per capita*	Δ % 21-20	% expenditure *	% cum	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
B05BB01	sodium chloride	1	1	0.77	6.5	7.6	7.6	5.7	1.7	0.37	4.9
J02AA01	amphotericin B	2	2	0.71	30.6	7.1	14.7	0.0	30.8	102.34	0.1
V08AB10	iomeprol	3	3	0.51	17.3	5.1	19.8	0.0	14.1	72.53	3.0
B05DB	glucose/sodium chloride/calcium chloride/ magnesium chloride/sodium bicarbonate /sodium lactate	4	4	0.39	-1.9	3.9	23.7	0.1	9.3	10.11	-10.0
B05BA10	glucose/amino acids/olive oil/soya oil/sodium acetate/sodium glycerophosphate/ calcium chloride/magnesium chloride/potassium chloride	5	5	0.29	-0.4	2.9	26.6	0.0	4.1	16.65	-4.1
B02BC30	human fibrinogen/human thrombin	6	10	0.20	24.3	2.0	28.6	0.0	17.2	320.58	6.3
J01XB01	colistimetate	7	7	0.20	-9.2	2.0	30.6	0.0	-3.7	34.08	-5.4
B02BB01	human fibrinogen	8	57	0.19	353.8	1.9	32.5	0.0	361.3	2189.94	-1.4
J01CR05	piperacillin/tazobactam	9	11	0.18	12.1	1.8	34.3	0.0	16.5	11.67	-3.5
J06BA02	human normal immunoglobulin for intravascular administration	10	8	0.17	-8.0	1.7	36.0	0.0	-11.6	389.47	4.4
V08CA09	gadobutrol	11	1011	0.15	-	1.5	37.5	0.0	-	77.49	-
V03AF07	rasburicase	12	17	0.14	17.5	1.4	38.9	0.0	15.0	806.55	2.5
B01AX01	defibrotide	13	13	0.14	6.7	1.4	40.3	0.0	11.2	3893.34	-3.8
B05DA	icodextrin/sodium chloride/sodium lactate/ calcium chloride/magnesium chloride	14	15	0.14	5.6	1.4	41.7	0.0	6.3	11.72	-0.4
V09AB03	iodine ioflupane (123I)	15	16	0.14	12.8	1.4	43.0	0.0	12.6	873.72	0.4
V08AB05	iopromide	16	1046	0.14	-	1.4	44.4	0.0	-	56.12	-
A11BA	vitamin complex	17	9	0.13	-21.4	1.3	45.7	0.1	-11.9	4.27	-10.5
C01CX08	levosimendan	18	12	0.13	-5.4	1.3	47.0	0.0	13.2	512.46	-16.2
V09FX01	technetium pertechnetate (99mTc)	19	14	0.13	-4.4	1.3	48.3	0.0	-5.5	331.97	1.5
V08AB11	iobitridol	20	20	0.12	8.9	1.2	49.5	0.0	6.4	48.69	2.6

B05BA10	glucose/amino acids/soya oil/medium chain triglycerides/sodium glycerophosphate/sodium acetate/potassium chloride/magnesium sulphate/ calcium chloride	21	18	0.11	-1.1	1.1	50.6	0.1	2.7	4.30	-3.4
B01AC11	Iloprost	22	19	0.10	-8.3	1.0	51.6	0.0	1.8	82.51	-9.7
J01MA12	Levofloxacin	23	21	0.09	-0.4	0.9	52.5	0.0	-27.8	22.54	38.4
B05BA10	glucose/amino acids/soya oil/olive oil/medium chain triglycerides/oil of omega-3-enriched fish/sodium glycerophosphate/sodium acetate/calcium chloride/magnesium sulphate	24	22	0.09	-0.3	0.9	53.3	0.0	-1.5	19.87	1.5
B05DB	glucose/sodium chloride/calcium chloride/ magnesium chloride/sodium lactate	25	28	0.08	15.3	0.8	54.2	0.0	7.3	7.53	7.7
N03AX18	Lacosamide	26	31	0.08	25.5	0.8	55.0	0.0	25.9	59.65	0.0
N01BB02	Lidocaine	27	25	0.08	4.1	0.8	55.8	1.3	8.0	0.16	-3.3
V08CA10	gadoxetic acid	28	30	0.08	17.3	0.8	56.6	0.0	16.3	175.64	1.1
G02AD02	Dinoprostone	29	23	0.08	-4.2	0.8	57.4	0.0	-4.6	4.96	0.6
J01GB01	Tobramycin	30	24	0.08	-1.4	0.8	58.1	0.0	4.8	33.89	-5.7
	Total top 30			**5.83**	**15.4**			**7.6**	**3.0**	**2.09**	**12.4**
	Total			**10.03**	**8.5**			**42.5**	**-2.0**	**0.65**	**11.0**

Not including vaccines (ATC J07) and oxygen (V03AN01)

*calculated on the total expenditure for medicines purchased directly from public health facilities in class C

Section 3

Consumption and expenditure by therapeutic class

General data on expenditure and consumption by ATC group

This section aims to analyse the trend of public pharmaceutical expenditure, including gross NHS expenditure under approved care regime and the cost of medicines purchased directly by public health facilities, by ATC 1st level, by therapeutic category and by active ingredient. In 2021, the NHS pharmaceutical expenditure, expressed as a per capita value, was 396.81 euros, with a 2.8% decrease compared to the previous year (Table 3.1). This trend was mainly determined by the increase in expenditure for public health facilities (233.53 euros; +4.8%), while the expenditure on class A drugs under approved care regime remained almost stable (163.28 euros; +0.2%).

Overall, the most significant increase in NHS expenditure was due to dermatological drugs (+32.2%) and sensory organs drugs (+11.8%), whose per capita values were respectively 3.35 and 6.74 euros. On the contrary, the most marked reduction was recorded for systemic hormonal preparations excluding sex hormones (-7.6%) and for antimicrobials for systemic use (-5.5%). Within the categories with the greatest expenditure, the increase is noteworthy for drugs of the gastrointestinal tract (+7.2%) and for antineoplastics and immunomodulators (+4.5%), which have constantly increased over the last four years (Figure 3.1).

With regard to consumption (Table 3.2), cardiovascular drugs represent the highest number of doses consumed (503.6 DDD/1000 inhabitants per day), stable compared to the previous year, and account for approximately 38.5% of all DDD consumed. These are followed by drugs acting on the gastrointestinal system and metabolism (318.3 DDD/1000 inhabitants per day; up 10.1%; Figure 3.2), on blood and blood forming organs (140.2 DDD/1000 inhabitants per day; +2.6%) and on the central nervous system (95.4 DDD/1000 inhabitants per day; +1.2%).

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 6.1 billion euros, an incidence of 20.2% on total pharmaceutical expenditure and a per capita value of 111.98 euros. As expected for this category, the largest share of expenditure (94.8%) refers to purchases by public health facilities. Gastrointestinal drugs account for 13.5% of total expenditure and represent, in absolute values, the most privately purchased category in the case of both class A drugs (305 million euros) and self-medication drugs (647 million euros). Medicines acting on the central nervous system have the highest absolute expenditure value of class C drugs sold upon prescription (1.01 billion euros) and in fact represent 34.2% of the total expenditure in this reimbursement range. As for purchases by public health facilities, 43.8% (equal to 5.8 billion euros) refers to antineoplastics and immunomodulators; as for class A drugs, 28.8% relates to cardiovascular drugs, for a total expenditure of 2.9 billion euros.

The most consumed privately purchased class A drugs (Table 3.4) are cardiovascular system drugs (32.8 DDD/1000 inhabitants per day), while drugs acting on the nervous system are the most used within class C drugs with prescription (64.2 DDD/1000 inhabitants per day); gastrointestinal drugs rank first for consumption within self-medication drugs (31.4 DDD/1000 inhabitants per day). Blood and blood-forming organs drugs (50.6 DDD) show the highest consumption within public health facilities, while cardiovascular drugs are the most used in class A, with 486.9 DDD (48.0% of the total).

Figure 3.2 shows the 2017-2021 trend in consumption by ATC 1st level, with no particular variations, except for gastrointestinal drugs, which in 2021 reported almost the same levels as in 2019, after the decrease recorded in 2020.
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 163.3 euros, the Northern and Central Regions report lower values, respectively 149.0 and 162.1 euros, while the Southern Regions show a higher value, equal to 184.6 euros (+13% compared to the national average). The greatest variability, highlighted by the variation coefficient, is observed for the ATC "Various" (130%), where per capita expenditure ranges from a value of 0.48 euros in Calabria to 0.01 euros in Piedmont. The Northern Regions on average show higher values (0.18 euros), compared to the Southern (0.13 euros) and the Central Regions (0.06 euros). A large variability is also observed for ATC "Blood and blood forming organs" drugs (CV 56%), as the expenditure values range from 12.7 euros in Lombardy to 2.2 euros in Liguria. Cardiovascular system drugs report the largest proportion of expenditure under approved care regime in all regions, followed by central nervous system drugs and, to a lesser extent, by respiratory drugs. The greatest differences between the Regions are recorded for blood drugs, probably due to the different use of alternative drug dispensing methods (e.g. direct and "on-behalf" distribution).
The trend in drug consumption (Table 3.6) shows a greater use in the South (1,242.6 DDD/1000 inhabitants per day) and in the Centre (1,149.9 DDD/1000 inhabitants per day) compared to the North (1049.8 DDD/1000 inhabitants per day), confirming the larger variability for the "Various" ATC (CV 91%), which however shows very low values of DDD/1000 inhab. per day. The ATC "Antineoplastics and immunomodulators" (CV 28%) follows, reporting the highest value in Campania (19.2 DDD/1000 inhab. per day) and the lowest in the Province of Bolzano (6.1 DDD/1000 inhab.per day). The first three categories with the highest consumption (ATC A, B and C) account for over 70% of the doses in all regions.
Table 3.7 shows the regional trend of per capita expenditure on 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 241.5 euros and 250.2 euros, compared to the Northern Regions (218.5 euros). Drugs in the "Various" category, musculoskeletal and respiratory system drugs report the largest regional variability (CV 32%). Per capita expenditure of the "Various" class ranges from 13.3 euros in Sardinia to 4.4 euros in the Province of Trento, from a maximum of 5 euros in the Marche to a minimum of 1 euro in Valle d'Aosta for ATC M; as for ATC R, it ranges from 11.8 euros in Basilicata to 4.1 euros in Valle d'Aosta and Molise. The antineoplastics and immunomodulators category represents, in almost all the Regions, about half of the expenditure of public health facilities.
However, when analyzing consumption (Table 3.8), the greatest heterogeneity in the Regions is observed for genitourinary drugs (CV 89%), with a difference between the maximum value (9.6 DDD/1000 inhabitants per day in Emilia Romagna) and the minimum value (0.6 DDD/1000 inhabitants per day in Molise) up to 9 DDD. Respiratory drugs (ATC R) record a CV of 53% with a maximum value of 5.1 DDD in Emilia Romagna and a minimum in Molise with 0.8 DDD/1000 inhabitants per day. The category with the highest consumption in all Regions is ATC B with values ranging between 14% and 45%, which (together with ATC

A) accounts for over 60% 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 euros of per capita expenditure. Information is also provided on prescribed doses and average cost per day of therapy. The variation compared to the previous year is calculated for all indicators, together with the mix effect (Table 3.9 and Figure 3.7). Compared to 2020, class A medicines provided under approved care regime show reductions in expenditure (-0.5%), prices (-0.4%), average DDD cost (-2.6%) and deviation towards less expensive medicines (mix effect: -2.2%), while consumption increases by 2.2%. However, there are many differences between the therapeutic categories. As regards cardiovascular system drugs, the stability of expenditure was due to a positive mix effect (+1.2%) and to an increase in the average DDD cost (+0.8%), offset by a reduction in both consumption (-0.5%) and prices (-0.4%). As for gastrointestinal system drugs, despite a shift towards less expensive medicines (mix effect: -6.4%), a 2.9% increase in expenditure is reported due to an increase in consumption (+9.9%). Respiratory drugs show the greatest reduction in terms of expenditure, (-6.5%), owing to the combined effect of the reduction in DDD (-5.7%) and prices (-1.2%) and to resorting to more expensive medicines (+0.4%). When analyzing the individual therapeutic categories, acid pump inhibitors show the highest value of per capita expenditure (11.48 euros), with a 4.1% negative mix effect and a 3.8% increase in consumption, followed by statins (HMG-CoA reductase inhibitors) with 8.14 euros, with all indicators stable compared to 2020. Adrenergic drugs combined with corticosteroids or others, excluding anticholinergics (7.81 euros) belonging to respiratory system drugs, show a reduction in all indicators (expenditure: -8.2%, DDD: -5.5%, prices: -2.1%, mix effect: -0.8%).
The highest consumption, besides vitamin D and analogues (142.5 DDD), is mainly attributable to cardiovascular drugs, in particular non-combined ACE-inhibitors (82.4 DDD/1000 inhabitants per day), HMG-CoA reductase inhibitors (81.7 DDD/1000 inhabitants per day), followed by acid pump inhibitors (76.2 DDD/1000 inhabitants) and by platelet aggregation inhibitors (60.9 DDD/1000 inhabitants per day). The trend in vitamin D expenditure (+20.8%) is entirely due to the increase in consumption (+20.4%), while acid pump inhibitors show a stable expenditure, offset by a negative mix effect (-4.1%) and by an increase in consumption (+3.8%). The expenditure on GLP-1 receptor analogues increases by 53.3% due to a 35.6% increase in consumption and a greater use of more expensive medicines (mix effect: +11.9%).
Considering the percentage of expenditure by therapeutic category (Table 3.10), hydroxychloroquine and the combination calcipotriol/betamethasone are the molecules accounting for more than half of the value recorded for the entire category, respectively equal to 73.2% and 63.4%. When analyzing consumption, in addition to hydroxychloroquine, which represents 87.4% of the doses of the entire category, 58.7% of consumption of the ATC category systemic hormones (excluding sex hormones and insulins) relates to levothyroxine, while acetylsalicylic acid accounts for 50.2% of the doses related to the ATC category blood and blood forming organs.
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 3647.5 million euros. Overall, eleven molecules belong to the category of medicines acting on the

cardiovascular system and are mainly represented by atorvastatin (273.7 million), bisoprolol (160.9 million), omega-3 (123.4 million, rising from rank 13th in 2020 to 11th in 2021) and ramipril (119.6 million); other ten belong to the category of drugs acting on the gastrointestinal system and metabolism: pantoprazole (260.5 million), cholecalciferol (246.9 million), lansoprazole (135.6 million), esomeprazole (132.2 million) and omeprazole (131.9 million). The combination olmesartan/amlodipine (from 36th to 29th rank), ezetimibe (from 25th to 19th) and rosuvastatin (from 29th to 24th) are the substances showing the greatest variation in rank compared to 2020.

Table 3.12 shows the regional trend of the ranks for the first 30 active ingredients, showing that cholecalciferol ranks 12th in Tuscany and is among the top 3 drugs in almost all the other Regions. Enoxaparin, the 10th most expensive active ingredient, ranks over 300th in Piedmont, Province of Trento, Emilia Romagna and Marche (Regions where it is mainly supplied by direct distribution) while it ranks 2nd in Lazio and 3rd in Lombardy and in the Province of Bolzano, where it is mainly supplied by approved care regime.

In 2021, the drugs supplied under approved care regime with the highest average cost per day of therapy were teriparatide (15.65 euros; a 6.6% decrease compared to 2020), followed by ceftriaxone (11.99 euros) and cyclosporine (8.12 euros; Table 3.13). No active ingredient shows significant increases, with the exception of the triple combination vilanterol/fluticasone furoate/umeclidinium, whose average cost increased by 5.3% compared to the previous year, settling at 2.83 euros. Dulaglutide, a GLP-1 analogue, is the substance with the greatest change in expenditure compared to 2020 (+40.6%), followed by three combinations reporting an increase of more than 30%: glycopyrronium/ beclomethasone/formoterol, ezetimibe/rosuvastatin, and vilanterol/fluticasone fluroate/umeclidinium (Table 3.14).

The combination salmeterol/fluticasone (-29.2%), teriparatide (-26%), ceftriaxone (-11.7%) and tiotropium (-10%) are the first four substances with the greatest variation in approved care expenditure between 2021 and 2020 (Table 3.15). Cholecalciferol with 140 DDD accounts for 12.4% of the consumption in class A-NHS approved care regime; ramipril with less than half the DDD (62.4) is the second most consumed molecule, followed by atorvastatin (50.2 DDD) and acetylsalicylic acid (45 DDD). The first thirty substances represent more than 58% of the total expenditure (Table 3.16).

Table 3.17 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 amlodipine) show no particular differences in rank within the Regions.

Table 3.18 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 euros of per capita expenditure. Information is also provided on prescribed doses and average cost per day of therapy. The variation compared to the previous year is calculated for all indicators, together with the mix effect.

In 2021, per capita expenditure on drugs purchased directly by public health facilities was 233.53 euros, up 4.1% compared to the previous year. It was reported a decrease in consumption (-0.7%) and prices (-5.4%), an increase in the average cost per day of therapy (+4.8%) and a shift towards more expensive medicines (mix effect +10.8%). Antimicrobial drugs for systemic use record a decrease in expenditure (-6.4%), consumption (-9.5%) and

prices (-12%) despite the use of higher-cost drugs (mix effect: +17.6%) and an average cost per DDD up +3.4% compared to 2020. The figure of the mix effect of the category can be explained by the trend of the mix effect of the influenza vaccines (+70.8%), of the nucleosides and nucleotides -excluding reverse transcriptase inhibitors (+111.2%) and of third-generation cephalosporins (+48.7%). It is noteworthy that the 13% increase in expenditure on gastrointestinal tract and metabolism drugs is almost entirely attributable to the use of more expensive drugs (mix effect: +10%), while the increase in consumption is more limited (+2.8%); as for cardiovascular system drugs, consumption and prices decreased by -5.2% and -2.4% respectively, therefore the 9.7% increase in expenditure is exclusively due to the mix effect, which increased by 18.6% (Table 3.18). Antineoplastic and immunomodulatory drugs are within the first 4 most expensive therapeutic categories; in this category, PD-1/PDL-1 inhibitors and interleukin inhibitors record the highest increases in expenditure (respectively 20% and 17.8%), while poly (ADP-ribose) polymerase (PARP; ATC L01XK) inhibitors, indicated in ovarian or breast cancer used in second line in patients with advanced tumour stage or with BRCA mutations, report changes in expenditure by 92%.
Table 3.19 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 80% of dermatological drugs, atovaquone (74.3% of antiparasitic drugs), aflibercept (43.4% of sensory organs drugs) and nusinersen (34.7% of musculoskeletal system drugs).
With reference to the first thirty most expensive active ingredients, which represent 31.4% of the total expenditure by healthcare facilities, 19 molecules belong to the category of antineoplastic and immunomodulatory drugs and 5 to blood and blood-forming organs drugs. Pembrolizumab and lenalidomide show the highest values, respectively 6.41 euros and 5.47 euros (Table 3.20), with reversed ranks compared to 2020. These are followed by daratumumab with 4.07 euros, nivolumab with 3.70 euros and ibrutinib with 3.39 euros. Remdesivir shows a particularly interesting trend, shifting from rank 74th in 2020 to 12th in 2021, due to its widespread use for the treatment of the Sars-Cov-2 infection during the COVID-19 pandemic. Dulaglutide, an antidiabetic administered weekly, moves from rank 44th to rank 18th; while dupilumab, a monoclonal antibody indicated for the treatment of atopic dermatitis, shifts from rank 70th to 28th. The top 5 most expensive drugs show no particular differences in the regional ranks with the exception of nivolumab, which in the Province of Trento ranks 43rd while ranking between 4th and 5th in most of the other regions (Table 3.21).
With regard to the top 30 active substances showing the greatest variation in expenditure (Table 3.22), thirteen belong to the category of antineoplastic drugs and immunosuppressants, although the largest increases are related to the dolutegravir/lamivudine combination (>400%), used for the treatment of HIV, to the influenza vaccine (>250%) and to remdesivir and semaglutide (>150%), a GLP-1 analogue administered once weekly. The drugs with the greatest expenditure reduction (Table 3.23) are bevacizumab (-57.5%), dolutegravir (-37.7%) and octocog-alfa (-29.7%). Agalsidase alfa and imiglucerase, used as enzyme therapy for Fabry disease and Gaucher disease respectively, albutrepenonacog alfa, indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B and human acid algucosidase indicated in Pompe disease, are the first four active ingredients with an average cost per DDD greater than 1,000

euros (Table 3.24). Some fourteen molecules belong to the category of antineoplastic and immunomodulating agents. Within the most consumed drugs, the first five active ingredients, with more than 5 DDD, belong to the blood and blood-forming organs category: sodium chloride (5.8 DDD), clopidogrel (5.8 DDD), enoxaparin (5.7 DDD), rivaroxaban (5.4 DDD) and cyanocobalamin (5.0 DDD) (Table 3.25).

Table 3.1 NHS per capita expenditure by ATC 1st level in descending order of expenditure: comparison 2021-2020

ATC 1st level	Per capita expenditure A-NHS Approved care regime (a)	Δ% 21-20	Per capita expenditure Public health facilities (b)	Δ% 21-20	NHS Expenditure (a+b)	Δ% 21-20
L	4.38	1.8	107.59	4.6	111.98	4.5
C	49.51	0.9	6.48	10.5	56.00	2.0
A	32.31	3.6	19.39	13.8	51.70	7.2
J	9.46	-4.9	32.77	-5.7	42.23	-5.5
B	7.61	-3.2	32.05	4.1	39.66	2.6
N	23.97	1.4	8.23	5.4	32.21	2.3
R	16.13	-5.9	6.24	31.3	22.37	2.2
M	5.18	3.1	3.82	3.0	9.00	3.1
H	3.82	-2.7	4.24	-11.5	8.06	-7.6
G	5.53	2.1	1.36	12.5	6.89	4.0
S	3.71	-4.7	3.03	41.9	6.74	11.8
V	0.14	-1.2	6.26	7.8	6.40	7.6
D	1.32	5.2	2.03	58.5	3.35	32.2
P	0.23	3.2	0.03	-31.5	0.25	-2.2
Total	**163.28**	**0.2**	**233.53**	**4.8**	**396.81**	**2.8**

A Gastrointestinal tract 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) by ATC 1st level in descending order of consumption: comparison 2021-2020

ATC 1st level	DDD/1000 inhab. per day Approved care regime (a)	Δ% 21-20	DDD/1000 inhab. per day Public health facilities (b)	Δ% 21-20	DDD/1000 inhab. per day NHS (a+b)	Δ% 21-20
C	486.89	0.4	16.68	-4.3	503.6	0.3
A	284.28	10.9	34.04	3.8	318.3	10.1
B	89.60	2.2	50.56	3.2	140.2	2.6
N	68.91	1.6	26.53	0.2	95.4	1.2
G	43.67	3.9	2.47	12.8	46.1	4.4
R	39.84	-4.8	1.98	-7.4	41.8	-4.9
M	37.61	3.5	5.56	7.4	43.2	4.0
H	36.79	2.6	4.69	-15.3	41.5	0.2
S	20.86	0.2	2.05	0.5	22.9	0.3
J	12.40	-4.1	5.74	-8.6	18.2	-5.6
L	6.30	-0.8	11.12	5.1	17.4	2.9
D	4.98	8.1	8.91	-11.7	13.9	-5.5
V	0.10	-2.3	3.17	1.8	3.3	1.7
P	1.00	0.0	0.01	-96.9	1.0	-17.1
Total	**1133.23**	**3.2**	**173.52**	**0.3**	**1306.8**	**2.8**

Table 3.3 Composition of 2021 pharmaceutical expenditure by ATC 1st level and reimbursement class (descending order for total expenditure)

ATC 1st level	Class A-NHS^		Class A medicines - private purchase		Class C with prescription		Self-medication pharmaceuticals (SOP and OTC)		Public health facilities§		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°
L	252	4.1	49	0.8	19	0.3	-	-	5,786	94.8	6,106
A	1,967	48.2	305	7.5	226	5.5	647	15.9	932	22.9	4,077
J	755	20.9	143	4.0	78	2.2	-	-	2,639	73.0	3,615
C	2,872	81.1	186	5.3	41	1.2	134	3.8	309	8.7	3,542
N	1,399	42.2	168	5.1	1,049	31.7	257	7.8	441	13.3	3,314
B	476	19.6	163	6.7	81	3.3	4	0.2	1,702	70.2	2,426
R	1,008	51.4	135	6.9	164	8.4	420	21.4	234	11.9	1,961
M	328	23.4	157	11.2	209	14.9	499	35.6	209	14.9	1,402
G	348	29.3	40	3.4	640	53.9	68	5.7	92	7.7	1,188
S	235	31.6	14	1.9	223	30.0	84	11.3	187	25.2	743
D	78	11.3	26	3.8	263	38.0	275	39.7	50	7.2	692
H	248	38.3	72	11.1	42	6.5	-	-	286	44.1	648
V	9	1.9	83	17.8	29	6.2	-	-	344	74.0	465
P	14	53.8	4	15.4	3	11.5	3	11.5	2	7.7	26
Total	**9,989**	**33.1**	**1,544**	**5.1**	**3,066**	**10.2**	**2,392**	**7.9**	**13,215**	**43.7**	**30,206**

^Expenditure for Class A net of Class C reimbursed (32.4 million); § Not including oxygen; ° Gross in million euros
* calculated on the category
Source: OsMed, Traceability of medicinal products

Table 3.4 Composition of 2021 consumption (in terms of DDD/1000 inhabitants per day), by ATC 1st level and reimbursement class (descending order of consumption)

	Class A-NHS^		Class A medicines - private purchase		Class C with prescription		Self-medication pharmaceuticals (SOP and OTC)		Public health facilities		Total
ATC 1st level	No.	%*	No.	%*	No.	%*	No.	%*	No.	%*	units
C	486.9	89.2	32.8	6.0	1.5	0.3	7.9	1.4	16.7	3.1	545.8
A	284.3	74.8	23.3	6.1	7.1	1.9	31.4	8.3	34.0	9.0	380.1
B	89.6	46.0	20.0	10.3	34.4	17.7	0.1	0.1	50.6	26.0	194.7
N	68.9	39.9	6.9	4.0	64.2	37.1	6.3	3.6	26.5	15.3	172.8
R	43.7	47.9	10.3	11.3	12.5	13.7	22.3	24.4	2.5	2.7	91.2
M	39.8	45.5	21.5	24.6	3.2	3.7	21.0	24.0	2.0	2.3	87.5
G	37.6	45.3	3.5	4.2	34.3	41.3	2.1	2.5	5.6	6.7	83.1
H	20.9	34.4	3.4	5.6	17.3	28.5	17.0	28.0	2.1	3.4	60.6
D	36.8	67.8	11.0	20.3	1.8	3.3	-	-	4.7	8.6	54.3
S	12.4	29.2	1.8	4.2	12.4	29.2	10.1	23.8	5.7	13.5	42.4
J	6.3	26.0	4.1	16.9	2.7	11.1	-	-	11.1	45.9	24.2
L	5.0	34.4	0.5	3.5	0.1	0.7	-	-	8.9	61.5	14.5
V	0.1	2.3	0.1	2.3	0.9	21.1	-	-	3.2	74.2	4.3
P	1.0	82.6	0.2	16.5	-	-	-	-	0.0	0.8	1.2
Total	**1133.2**	**64.5**	**139.5**	**7.9**	**192.4**	**11.0**	**118.2**	**6.7**	**173.5**	**9.9**	**1756.9**

* calculated on the category
Source: OsMed, Traceability of medicinal products

Figure 3.1 Trend of class A-NHS per capita and public health facilities expenditure in the period 2017-2021 by ATC 1st level

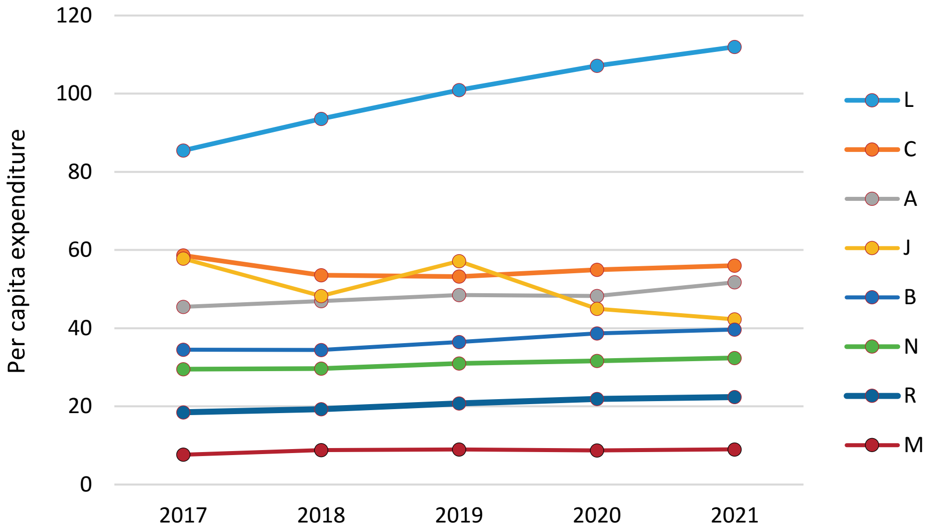


Figure 3.2 Trend of class A-NHS and public health facilities consumption in the period 2017-2021 by ATC 1st level

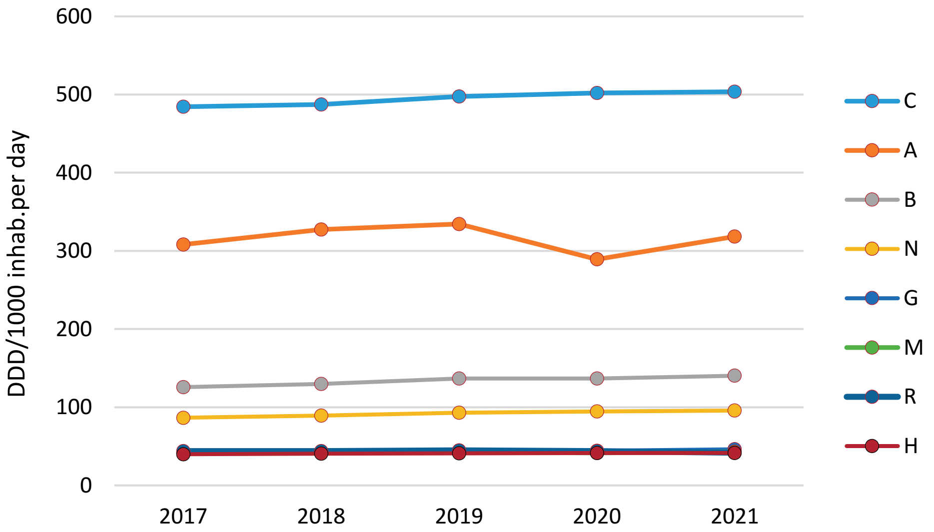


Table 3.5 Regional distribution by ATC 1st level of gross per capita approved care expenditure (on weighted population) for class A-NHS medicines: year 2021 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	25.1	2.8	43.0	1.2	5.0	3.5	7.0	4.3	4.1	23.6	0.2	14.2	4.1	0.0	138.1
Valle d'Aosta	24.8	2.4	37.2	1.1	5.2	3.1	6.3	3.6	4.2	23.4	0.2	14.5	3.5	0.0	129.6
Lombardy	41.8	12.6	46.5	1.1	5.8	3.8	7.5	6.9	4.0	28.3	0.3	15.2	3.1	0.5	177.4
Province of Bolzano	17.0	5.8	32.7	0.9	3.7	3.0	4.0	3.6	3.2	24.6	0.2	12.0	2.6	0.0	113.4
Province of Trento	26.4	5.2	38.8	1.4	5.0	3.6	6.9	4.6	4.3	23.0	0.3	14.6	2.8	0.0	136.8
Veneto	22.3	2.7	44.4	1.2	4.8	3.3	5.9	4.3	3.9	21.6	0.3	13.0	3.3	0.0	130.8
Friuli VG	26.0	5.5	45.4	1.3	4.6	3.6	5.5	4.8	4.5	24.2	0.3	13.2	4.1	0.1	143.1
Liguria	28.7	2.2	42.6	1.2	5.4	2.9	6.5	4.3	4.1	25.1	0.1	16.3	4.0	0.0	143.2
Emilia R.	21.6	3.3	46.5	1.2	5.5	2.6	6.1	1.1	3.9	16.7	0.3	13.1	4.7	0.0	126.8
Tuscany	22.5	4.3	42.6	1.3	5.0	3.9	7.1	0.6	4.0	22.2	0.3	16.1	4.7	0.0	134.7
Umbria	29.8	4.3	53.7	1.1	6.0	4.6	9.4	4.5	4.8	25.2	0.3	15.3	4.5	0.1	163.7
Marche	26.7	3.2	52.7	1.1	6.3	4.3	10.1	4.4	5.3	23.6	0.2	14.6	5.2	0.0	157.8
Lazio	33.1	12.7	53.9	1.3	5.7	4.9	11.1	4.6	6.2	25.3	0.2	18.5	3.9	0.1	181.6
Abruzzo	32.8	10.9	51.9	1.2	5.7	4.8	11.4	4.6	6.5	29.2	0.2	15.1	4.6	0.2	179.2
Molise	32.3	5.2	52.5	1.2	5.4	3.7	11.2	4.6	6.2	21.9	0.1	13.5	3.0	0.1	160.8
Campania	44.1	8.9	59.5	1.9	6.0	4.2	16.1	4.7	6.6	22.0	0.2	22.3	3.4	0.1	199.9
Puglia	35.0	10.7	55.6	1.3	6.0	4.3	13.2	4.6	7.5	25.3	0.1	17.9	3.3	0.0	184.9
Basilicata	40.5	10.3	54.5	1.5	6.4	4.4	11.4	4.4	7.2	24.1	0.1	18.3	3.7	0.1	186.8
Calabria	37.8	11.0	56.4	1.5	5.8	3.8	15.1	4.9	7.3	23.5	0.2	16.4	3.5	0.5	187.8
Sicily	35.8	7.5	55.8	1.4	5.6	3.8	12.1	4.2	6.4	22.6	0.2	16.5	3.1	0.1	175.0
Sardinia	33.6	4.2	48.7	1.5	5.4	3.6	9.6	5.1	6.7	27.3	0.2	17.5	3.4	0.1	167.0
Italy	**32.3**	**7.6**	**49.5**	**1.3**	**5.5**	**3.8**	**9.5**	**4.4**	**5.2**	**24.0**	**0.2**	**16.1**	**3.7**	**0.1**	**163.3**
North	30.1	6.5	44.9	1.2	5.3	3.4	6.7	4.7	4.0	23.9	0.3	14.2	3.6	0.2	149.0
Centre	28.6	8.1	50.1	1.3	5.6	4.4	9.5	3.3	5.3	24.1	0.3	17.0	4.4	0.1	162.1
South and Islands	37.8	8.9	55.8	1.5	5.8	4.1	13.4	4.6	6.8	23.9	0.2	18.3	3.4	0.1	184.6

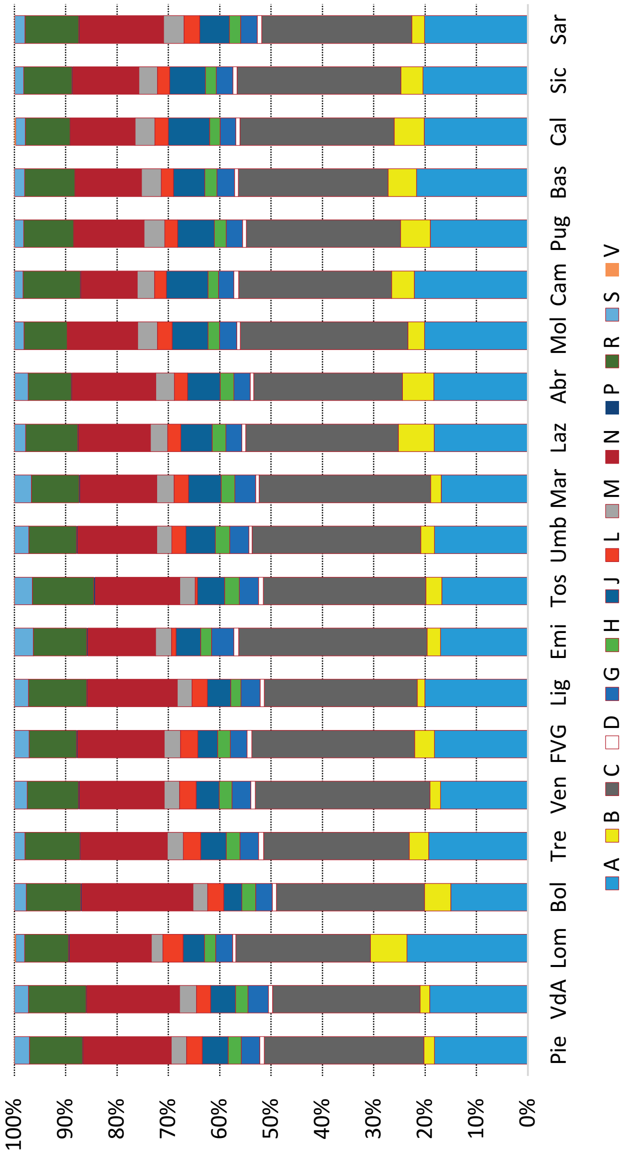

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Pie
VdA
Lom
Bol
Tre
Ven
FVG
Lig
Emi
Tos
Umb
Mar
Laz
Abr
Mol
Cam
Pug
Bas
Cal
Sic
Sar
A
B
C
D
G
H
J
L
M
N
P
R
S
V

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 2021 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	240.1	82.9	449.5	4.1	40.7	34.7	9.6	6.5	32.1	73.5	1.0	33.6	23.1	0.0	1031.4
Valle d'Aosta	238.4	65.0	374.6	3.6	38.8	30.4	8.9	5.5	32.1	64.8	1.0	34.7	19.2	0.0	917.0
Lombardy	301.6	78.2	455.0	3.6	40.3	27.0	9.9	8.5	27.3	71.9	1.2	35.7	17.2	0.3	1077.7
Province of Bolzano	196.2	56.4	353.5	3.5	29.8	28.6	6.1	5.8	23.1	74.5	0.8	27.4	15.8	0.0	821.4
Province of Trento	265.0	100.5	417.8	5.1	40.5	42.5	10.4	7.1	31.5	66.4	1.1	39.6	16.4	0.0	1043.8
Veneto	251.8	54.4	466.6	4.3	38.3	30.9	8.7	6.8	27.5	62.5	1.1	31.4	18.8	0.0	1003.1
Friuli VG	263.9	83.1	486.6	4.7	37.2	37.6	8.9	7.7	34.5	59.5	1.3	32.2	23.1	0.1	1080.4
Liguria	260.5	55.4	415.5	3.9	43.5	21.7	8.7	6.4	28.2	79.3	0.6	39.0	20.7	0.0	983.5
Emilia R.	240.5	100.8	501.7	4.5	44.1	40.8	9.7	2.6	31.2	65.0	1.1	34.1	27.2	0.0	1103.3
Tuscany	225.9	101.2	479.7	4.6	42.1	42.7	10.5	1.3	33.2	84.3	1.3	38.5	26.3	0.0	1091.7
Umbria	252.6	91.2	590.6	4.2	48.4	46.8	13.5	7.0	38.4	79.7	1.3	36.1	24.5	0.1	1234.5
Marche	227.0	88.2	505.6	3.8	51.4	41.9	13.4	6.5	42.4	71.6	1.0	32.7	30.1	0.1	1115.6
Lazio	276.0	114.3	498.9	5.1	46.4	44.2	14.1	6.9	43.8	67.4	1.1	45.2	21.9	0.1	1185.2
Abruzzo	289.4	116.0	476.9	4.8	45.4	42.5	15.2	6.5	49.2	75.9	0.9	36.9	26.2	0.2	1186.0
Molise	299.9	99.4	478.6	5.0	41.5	45.3	14.0	6.2	47.1	62.7	0.6	33.6	16.0	0.1	1150.0
Campania	401.8	86.1	542.2	8.5	48.5	36.3	19.2	6.2	46.9	60.3	0.8	59.2	18.2	0.1	1334.3
Puglia	321.0	112.5	512.7	5.3	48.6	45.6	16.5	6.7	54.2	65.5	0.6	47.1	19.1	0.1	1255.6
Basilicata	331.8	111.6	498.2	6.1	50.9	45.1	15.2	6.3	52.5	66.1	0.6	43.8	20.9	0.1	1249.1
Calabria	295.7	114.8	509.8	6.3	45.0	39.1	16.8	7.0	51.1	68.4	0.9	39.7	19.6	0.3	1214.3
Sicily	288.0	89.9	529.4	6.3	45.4	36.1	15.5	6.0	44.0	61.9	0.9	42.0	17.6	0.1	1182.9
Sardinia	324.3	85.5	467.8	5.4	45.4	45.3	11.3	7.9	47.3	77.8	1.0	44.6	19.7	0.1	1183.4
Italy	**284.3**	**89.6**	**486.9**	**5.0**	**43.7**	**36.8**	**12.4**	**6.3**	**37.6**	**68.9**	**1.0**	**39.8**	**20.9**	**0.1**	**1133.2**
North	266.0	77.2	459.9	4.0	40.5	31.7	9.4	6.7	29.1	69.2	1.1	34.3	20.5	0.1	1049.8
Centre	251.8	104.9	500.5	4.7	45.8	43.6	12.8	5.0	39.8	74.3	1.1	40.8	24.6	0.1	1149.9
South and Islands	330.5	97.9	517.2	6.5	46.9	39.9	16.4	6.5	48.4	65.2	0.8	47.2	19.1	0.1	1242.6

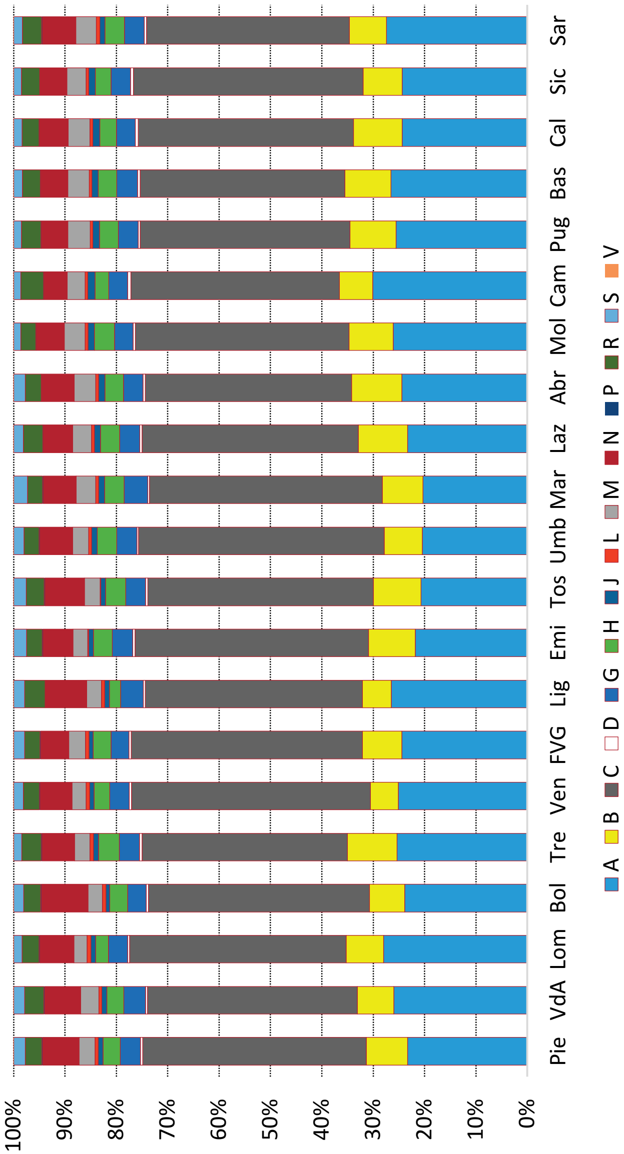

Sar
Sic
Cal
Bas
Pug
Cam
Mol
Abr
Laz
Mar
Umb
Tos
Emi
Lig
FVG
Ven
Tre
Bol
Lom
VdA
Pie
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
A
B
C
D
G
H
J
L
M
N
P
R
S
V

Table 3.7 Regional distribution by ATC 1st level of per capita expenditure (on weighted population) of medicines purchased by public health facilities: year 2021 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	18.2	30.9	6.5	2.3	1.2	3.9	28.9	100.0	3.4	7.6	0.0	5.8	3.4	5.9	218.0
Valle d'Aosta	9.2	29.9	5.0	1.5	1.5	3.2	26.4	78.8	1.0	6.5	0.1	4.1	1.6	7.0	175.9
Lombardy	12.1	25.2	4.0	1.8	1.1	3.8	38.1	87.7	3.7	5.2	0.1	5.4	2.3	5.2	195.7
Province of Bolzano	14.5	19.5	4.8	2.0	1.3	4.5	24.9	118.0	5.0	8.7	0.0	7.5	3.8	5.7	220.2
Province of Trento	22.5	29.3	4.6	1.6	1.8	3.9	27.2	83.0	2.0	6.7	0.0	7.2	3.7	4.4	197.9
Veneto	19.6	27.9	5.3	1.9	1.2	4.5	31.9	101.7	4.5	8.4	0.0	5.1	3.3	5.8	221.2
Friuli VG	19.4	27.2	6.3	1.8	1.4	4.0	29.1	119.3	3.9	7.7	0.0	5.9	4.1	5.7	235.7
Liguria	15.5	35.9	7.3	1.7	0.8	4.1	36.1	109.0	3.7	9.4	0.0	5.8	4.0	5.0	238.2
Emilia R.	20.6	35.0	5.8	2.1	1.7	4.5	38.9	117.3	3.5	11.4	0.1	6.9	2.6	6.8	257.1
Tuscany	16.8	33.3	6.8	2.1	1.5	4.4	35.0	111.5	3.5	10.0	0.0	6.2	2.9	6.8	240.8
Umbria	21.8	38.5	7.3	2.0	1.0	4.6	37.3	129.9	3.1	9.0	0.0	5.3	3.9	5.7	269.3
Marche	18.5	35.5	7.8	2.8	1.2	4.8	32.6	122.7	5.0	10.5	0.0	6.4	2.9	6.7	257.2
Lazio	19.9	32.1	6.1	1.6	1.8	4.0	36.3	106.5	4.7	8.1	0.0	5.0	2.4	4.9	233.3
Abruzzo	20.4	36.0	6.6	1.8	1.2	4.8	30.0	127.4	3.6	9.2	0.0	6.1	3.6	5.9	256.6
Molise	17.0	31.5	6.4	2.7	0.9	4.3	18.2	124.9	2.8	7.9	0.0	4.1	4.1	4.5	229.3
Campania	26.4	39.0	10.8	2.9	1.7	5.1	29.7	124.8	4.1	7.7	0.0	5.9	3.9	4.8	266.7
Puglia	24.1	37.1	8.1	2.5	1.4	4.2	31.1	117.1	3.7	10.0	0.0	9.0	3.8	8.3	260.3
Basilicata	22.5	30.5	9.5	2.7	1.3	3.8	25.2	117.7	1.5	7.9	0.0	11.8	3.3	9.6	247.3
Calabria	26.7	37.7	8.6	2.1	1.4	5.5	24.0	116.5	3.6	7.9	0.0	8.5	2.3	8.5	253.5
Sicily	22.6	31.8	6.3	1.6	1.3	3.8	28.1	97.6	3.5	8.8	0.0	8.2	2.6	7.3	223.5
Sardinia	19.6	33.4	6.2	1.5	0.8	3.2	25.4	122.5	3.7	8.0	0.0	4.7	3.8	13.3	246.2
Italy	**19.4**	**32.0**	**6.5**	**2.0**	**1.4**	**4.2**	**32.8**	**107.6**	**3.8**	**8.2**	**0.0**	**6.2**	**3.0**	**6.3**	**233.5**
North	16.5	28.9	5.2	2.0	1.3	4.1	34.6	100.1	3.8	7.6	0.0	5.8	2.9	5.7	218.5
Centre	18.9	33.4	6.6	1.9	1.5	4.3	35.5	112.0	4.2	9.1	0.0	5.6	2.7	5.8	241.5
South and Islands	23.8	35.7	8.2	2.2	1.4	4.4	28.4	115.7	3.7	8.6	0.0	7.4	3.4	7.4	250.2

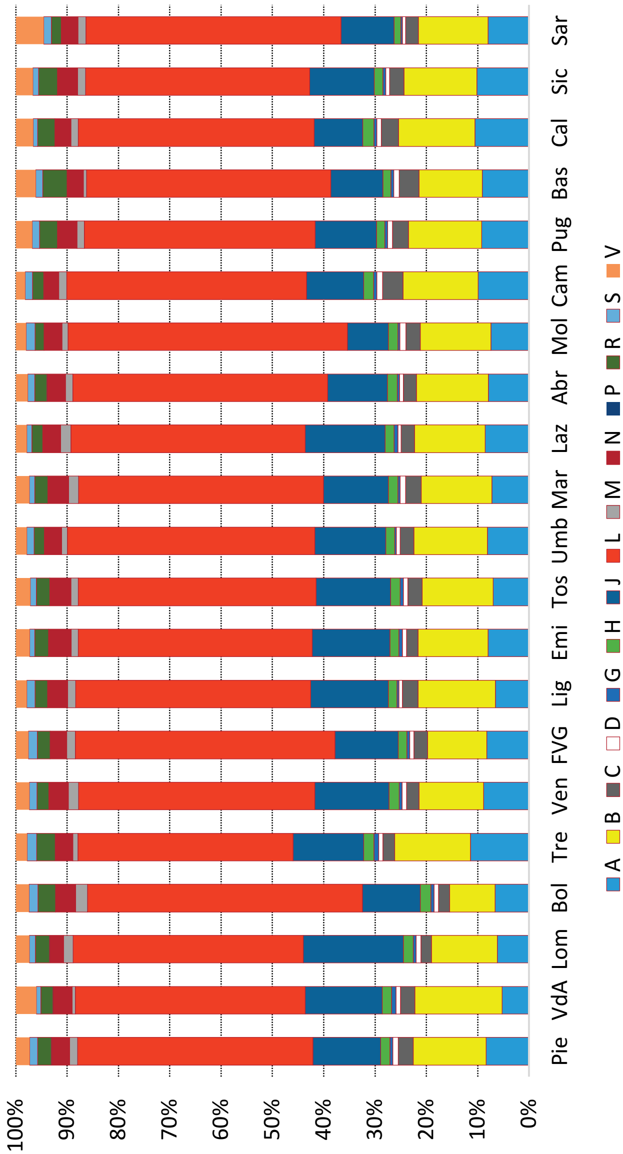

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Pie
VdA
Lom
Bol
Tre
Ven
FVG
Lig
Emi
Tos
Umb
Mar
Laz
Abr
Mol
Cam
Pug
Bas
Cal
Sic
Sar
A
B
C
D
G
H
J
L
M
N
P
R
S
V

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 2021 (Table and Figure)

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	37.6	54.3	21.1	8.6	2.1	5.0	5.3	10.4	5.6	31.0	0.0	2.5	2.0	4.4	189.9
Valle d'Aosta	21.1	48.8	20.4	8.5	4.8	5.8	5.5	6.7	4.0	33.7	0.0	4.0	1.5	4.8	169.7
Lombardy	19.4	29.3	9.6	6.3	1.9	3.3	6.5	7.7	5.3	15.8	0.0	1.6	2.0	3.2	112.0
Province of Bolzano	53.6	28.0	22.3	8.8	1.8	7.6	4.8	12.4	9.1	37.2	0.0	2.8	2.6	5.3	196.4
Province of Trento	46.5	52.0	21.1	8.8	3.3	5.1	5.0	10.0	5.1	30.0	0.0	2.2	2.5	6.9	198.7
Veneto	46.9	50.4	21.1	15.1	1.9	4.7	6.2	10.6	5.2	38.8	0.0	2.5	2.9	4.3	210.8
Friuli VG	40.6	47.5	19.4	10.9	2.2	6.1	6.2	12.1	5.2	34.6	0.0	2.6	2.2	4.5	194.0
Liguria	35.9	65.0	21.9	7.4	1.6	5.8	5.8	10.6	5.8	39.0	-0.1	2.4	2.7	3.8	207.6
Emilia R.	57.0	79.5	40.0	10.5	9.6	8.0	8.7	14.9	6.2	51.8	0.0	5.1	3.9	5.6	301.0
Tuscany	30.9	65.4	19.2	7.8	5.4	6.4	6.2	15.7	4.6	33.9	0.0	3.1	2.8	3.3	204.6
Umbria	37.7	67.0	23.8	18.1	2.2	4.2	5.6	11.5	3.9	40.3	0.0	1.8	3.0	3.7	222.9
Marche	31.8	101.1	15.2	10.5	2.7	5.8	5.4	12.5	7.0	24.1	0.0	1.5	2.2	4.3	224.0
Lazio	27.2	36.9	12.5	5.4	1.2	3.4	5.6	10.2	5.9	20.4	0.0	0.9	1.3	1.6	132.2
Abruzzo	31.4	34.2	12.1	8.4	0.8	4.8	4.9	12.1	7.2	17.9	0.0	1.3	1.8	2.1	138.9
Molise	29.5	50.2	11.8	4.2	0.6	4.2	3.4	11.1	5.7	19.1	0.0	0.8	1.8	2.0	144.4
Campania	32.8	56.5	11.7	6.0	0.9	4.5	4.6	11.8	5.5	19.4	0.0	1.3	1.2	1.8	158.0
Puglia	35.5	41.2	12.8	12.7	1.5	4.9	5.2	11.7	5.4	16.8	0.0	1.4	2.0	2.2	153.2
Basilicata	32.8	42.5	10.0	12.2	1.0	4.6	4.0	10.9	4.3	19.7	0.0	2.2	1.5	2.5	148.1
Calabria	35.2	46.5	12.5	11.0	1.0	4.2	3.5	10.5	5.1	18.0	0.0	1.0	0.9	1.9	151.3
Sicily	32.3	51.7	13.7	8.0	1.4	3.6	4.7	11.0	5.1	20.8	0.0	1.1	0.8	1.7	155.8
Sardinia	34.2	59.4	10.6	11.9	1.0	3.4	5.3	12.8	7.3	29.4	0.0	1.1	1.9	3.7	181.9
Italy	**34.0**	**50.6**	**16.7**	**8.9**	**2.5**	**4.7**	**5.7**	**11.1**	**5.6**	**26.5**	**0.0**	**2.0**	**2.0**	**3.2**	**173.5**
North	36.3	48.6	20.1	9.3	3.2	5.0	6.5	10.3	5.6	31.1	0.0	2.6	2.5	4.2	185.3
Centre	29.8	56.7	15.8	7.8	2.8	4.7	5.7	12.3	5.5	26.7	0.0	1.7	2.0	2.7	174.2
South and Islands	33.4	49.6	12.4	9.1	1.2	4.3	4.7	11.5	5.6	19.9	0.0	1.2	1.4	2.0	156.1

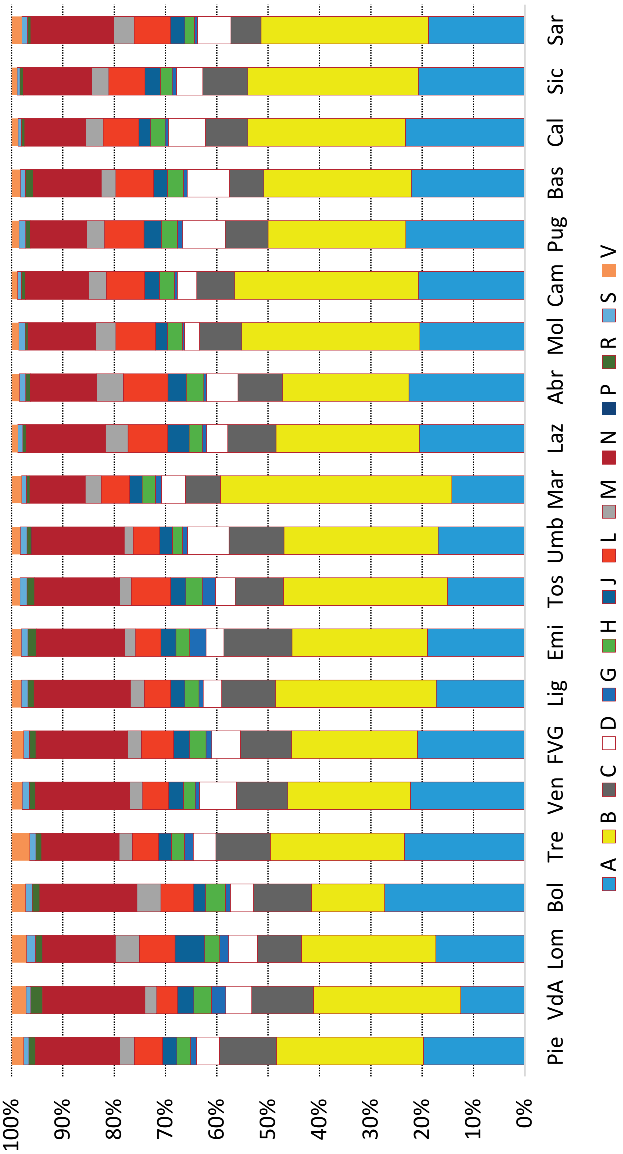

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Pie
VdA
Lom
Bol
Tre
Ven
FVG
Lig
Emi
Tos
Umb
Mar
Laz
Abr
Mol
Cam
Pug
Bas
Cal
Sic
Sar
A
B
C
D
G
H
J
L
M
N
P
R
S
V

Figure 3.7 Consumption, price and mix effect on variation of class A-NHS approved care pharmaceutical expenditure by ATC 1st level: comparison 2021-2020

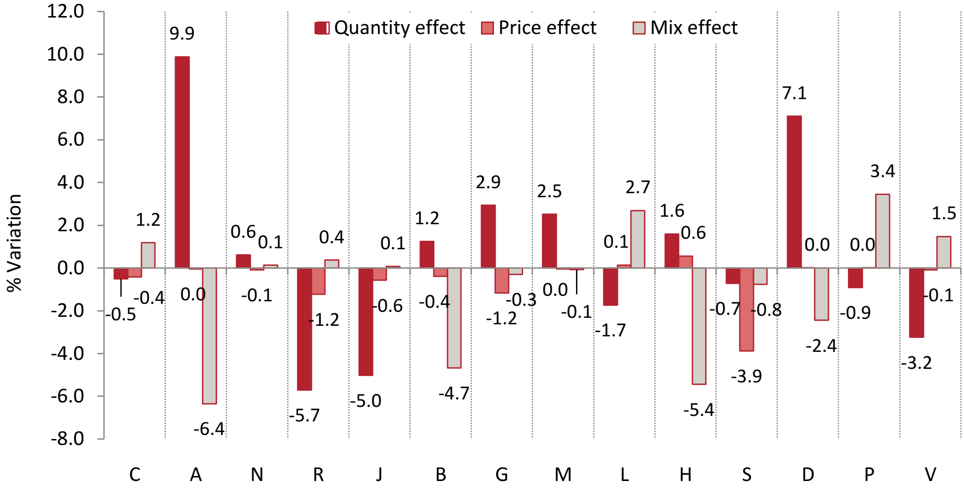


Table 3.9 Consumption, price and mix effect on variation of class A-NHS approved care pharmaceutical expenditure: comparison 2021-2020
(any ATC category includes the therapeutic subgroups in decreasing order of expenditure, up to the value of 0.10 euros of per capita expenditure)

ATC 4th level

Subgroup	Gross per capita expenditure	DDD/ 1000 inhab. per day	Δ % 21-20				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Italy	**163.28**	**1133.2**	**-0.5**	**2.2**	**-0.4**	**-2.2**	**-2.6**
C - Cardiovascular system	**49.51**	**486.9**	**0.3**	**-0.5**	**-0.4**	**1.2**	**0.8**
HMG-CoA reductase inhibitors	8.14	81.7	0.5	1.0	0.0	-0.5	-0.5
Angiotensin II receptor blockers (ARBs), not in combination	4.88	57.9	-0.8	-1.7	-0.1	1.0	0.9
Beta blockers, selective	4.86	40.6	2.1	0.4	0.0	1.7	1.6
Dihydropyridine derivatives	4.16	50.1	-2.3	-1.8	0.0	-0.4	-0.4
Angiotensin II receptor blockers (ARBs) and diuretics	3.90	32.5	-3.4	-3.0	0.0	-0.5	-0.5
ACE inhibitors, not in combination	3.71	82.4	-3.0	-2.8	0.6	-0.8	-0.2
Other lipid modifying agents	3.65	10.7	8.9	10.3	0.0	-1.1	-1.2
ACE inhibitors and diuretics	2.49	19.4	-4.7	-4.0	0.1	-0.8	-0.6
Lipid modifying agents in combination	2.24	11.3	13.4	37.8	-8.0	-10.6	-17.7
ACE inhibitors and calcium channel blockers	1.66	12.2	-1.2	0.3	0.0	-1.5	-1.5
Angiotensin II receptor blockers (ARBs) and calcium channel blockers	1.37	9.3	12.3	11.9	0.0	0.4	0.4
Alpha-adrenoreceptor blockers	1.25	7.6	-1.3	-1.2	0.0	-0.1	-0.1
Antiarrhythmic agents, class Ic	1.08	4.7	0.5	-1.3	0.0	1.9	1.9
Sulfonamides, not in combination	0.85	25.3	-3.8	-4.1	0.0	0.3	0.3
ACE inhibitors, other combinations	0.73	5.1	0.1	15.8	-9.3	-4.7	-13.6
Selective beta-blockers and thiazides	0.58	6.0	3.0	3.0	0.0	0.0	0.0
Organic nitrates	0.57	5.4	-14.2	-14.4	0.0	0.2	0.2
Aldosterone antagonists	0.55	3.3	-0.3	-2.0	0.0	1.8	1.8
Alpha and beta adrenoreceptor blockers	0.49	2.8	-7.8	-7.3	0.0	-0.5	-0.5
Fibrates	0.40	2.9	1.8	1.7	0.0	0.1	0.1
Angiotensin II receptor blockers (ARBs), other combinations	0.37	0.1	29.5	29.5	0.0	0.0	0.0
Antiarrhythmic agents, class III	0.26	2.8	-3.8	-3.7	0.0	-0.1	-0.1
Imidazoline receptor agonists	0.19	1.3	-7.1	-7.4	0.0	0.3	0.3
Benzothiazepine derivatives	0.16	0.9	-9.7	-9.7	0.0	0.0	0.0
Beta-blocking agents, not selective	0.14	1.5	-2.4	-2.5	0.0	0.1	0.1
Other cardiac preparations	0.13	0.4	-20.0	-10.4	0.0	-10.7	-10.7
Phenylalkylamine derivatives	0.12	1.0	-8.9	-9.6	0.4	0.4	0.8
High-ceiling diuretics in combination with potassium-sparing agents	0.12	0.6	-2.9	-2.7	0.0	-0.2	-0.2

ATC 4th level

Subgroup	Gross per capita expenditure	DDD/ 1000 inhab. per day	Δ % 21-20				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Sulfonamides, not in combination	0.12	1.7	-6.8	-8.7	0.6	1.4	2.0
Selective beta-blockers and other diuretics	0.12	1.6	-6.3	-6.6	0.1	0.1	0.3
A- Gastrointestinal system and metabolism	**32.31**	**284.3**	**2.9**	**9.9**	**0.0**	**-6.4**	**-6.4**
Proton pump inhibitors	11.48	76.2	-0.4	3.8	0.0	-4.1	-4.0
Vitamin D and analogues	4.82	142.5	20.8	20.4	0.0	0.4	0.4
Insulins and injectable analogues, fast-acting	3.43	7.2	-5.8	-5.0	-0.8	0.0	-0.8
Aminosalicylic acid and analogues	2.14	5.5	4.0	4.1	0.0	-0.1	-0.1
Biguanides	1.63	23.0	3.2	1.9	0.0	1.3	1.3
Antibiotics	1.48	2.0	0.7	0.6	0.0	0.1	0.1
GLP-1 (glucagon-like peptide-1) receptor analogues	1.31	0.5	53.3	35.6	1.0	11.9	13.1
Other anti-peptic antiulcer and gastroesophageal reflux disease	0.90	4.2	-1.2	-1.3	0.0	0.1	0.1
Bile acids and derivatives	0.90	2.7	9.7	6.5	1.1	1.9	3.1
Oral hypoglycemic agents, in combination	0.56	1.7	13.8	-9.4	0.7	24.7	25.6
Sulfonylureas	0.49	7.1	-5.5	-8.6	0.0	3.4	3.4
Aluminium, calcium and magnesium compounds in combination	0.41	1.8	0.6	0.2	0.0	0.3	0.3
Insulins and injectable analogues, long-acting	0.40	0.2	-48.2	-67.5	-0.8	60.7	59.5
Calcium, combinations with vitamin D and/or other pharmaceuticals	0.32	3.3	-0.4	-0.7	0.0	0.3	0.3
Corticosteroids for topical use	0.30	0.4	4.1	6.5	-0.2	-2.0	-2.2
Enzyme preparations	0.24	0.6	3.7	3.7	0.0	0.0	0.0
Other hypoglycaemic agents, excluding insulins	0.23	1.6	-14.7	-15.9	0.0	1.4	1.4
Dipeptil Peptidase 4 Inhibitors (DPP-4)	0.21	0.3	-0.8	-0.3	-0.2	-0.3	-0.6
Serotonin antagonists (5-HT3)	0.19	0.0	-5.9	4.2	-0.1	-9.6	-9.7
Alpha Glucosidase Inhibitors	0.13	0.5	-8.5	-8.6	0.0	0.2	0.2
Osmotic laxatives	0.11	1.0	-8.7	-6.5	-1.9	-0.5	-2.4
Thiazolidinediones	0.11	0.4	5.5	4.9	0.0	0.6	0.6
N- Central nervous system	**23.97**	**68.9**	**0.7**	**0.6**	**-0.1**	**0.1**	**0.0**
Other antiepileptics	4.77	6.4	3.0	2.4	0.0	0.6	0.6
Selective serotonin reuptake inhibitors	3.39	30.0	0.9	1.2	0.0	-0.3	-0.3
Other antidepressants	3.26	11.7	3.0	3.0	0.0	0.0	0.0
Other opioids	1.46	1.1	-1.6	-3.3	-0.8	2.5	1.7
Phenylpiperidine derivatives	1.34	0.6	-2.4	-2.8	-0.3	0.7	0.4
Natural opium alkaloids	1.14	0.6	-6.0	-4.3	-1.0	-0.7	-1.7

ATC 4th level

Subgroup	Gross per capita expenditure	DDD/ 1000 inhab. per day	Δ % 21-20 Expenditure	Δ % 21-20 DDD	Δ % 21-20 Prices	Δ % 21-20 Mix	Δ % average DDD cost
Dopamine agonists	1.11	1.0	-5.8	-6.6	0.0	0.9	0.9
Diazepines, oxazepines, thiazepines and oxepins	1.02	1.3	7.8	4.5	0.0	3.2	3.2
5-HT1 selective receptor agonists	1.01	0.9	1.2	1.1	0.0	0.1	0.1
Fatty acid derivatives	0.99	2.3	0.3	-0.6	0.2	0.7	0.9
Type B monoamine oxidase inhibitors	0.77	1.6	-1.8	-1.7	0.0	-0.1	-0.1
DOPA and derivatives	0.72	2.1	-3.1	-1.7	0.0	-1.4	-1.4
Opioids in combination with non-opioid analgesics	0.53	1.4	-2.1	-1.2	-1.1	0.2	-0.9
Carboxamide derivatives	0.48	1.8	-2.1	-3.3	1.0	0.2	1.3
Amides	0.36	0.3	2.8	2.8	0.0	0.0	0.0
Oripavine derivatives	0.29	0.2	17.4	10.6	0.0	6.2	6.2
Other antipsychotics	0.26	0.4	3.5	3.8	-1.8	1.5	-0.3
Non-selective monoamine reuptake inhibitors	0.16	1.0	1.0	1.0	1.0	-1.0	0.0
Anticholinesterases	0.14	0.4	-4.3	-3.6	-0.6	-0.2	-0.8
R- Respiratory system	**16.13**	**39.8**	**-6.5**	**-5.7**	**-1.2**	**0.4**	**-0.9**
Adrenergics in combination with corticosteroids or others, excluding anticolinergics	7.81	12.7	-8.2	-5.5	-2.1	-0.8	-2.9
Anticolinergics	3.06	5.7	-7.6	-8.5	-0.3	1.3	1.0
Combination of adrenergics with anticolinergics including triple combinations with corticosteroids	1.89	2.4	6.5	1.2	-0.6	5.9	5.2
Glycocorticoids	1.26	3.4	-9.1	-10.9	-0.9	2.9	2.0
Other antihistamines for systemic use	0.66	6.0	-3.6	-3.5	0.0	-0.1	-0.1
Selective agonists of beta2-adrenergic receptors	0.51	3.1	-13.6	-10.8	0.0	-3.1	-3.1
Leukotriene receptor antagonists	0.46	2.0	-7.3	-6.1	0.0	-1.3	-1.3
Piperazine derivatives	0.40	4.1	0.9	0.5	0.0	0.4	0.4
J- General antimicrobials for systemic use	**9.46**	**12.4**	**-5.5**	**-5.0**	**-0.6**	**0.1**	**-0.5**
Penicillin combinations, including betalactamase inhibitors	2.19	4.2	-3.9	-4.7	0.0	0.9	0.9
Third generation cephalosporins	1.97	1.3	-9.5	-6.2	0.0	-3.5	-3.5
Macrolides	1.17	2.6	-6.3	-8.0	-0.3	2.1	1.9
Fluoroquinolones	1.08	1.4	-5.5	-6.4	-0.3	1.2	1.0
Triazole and tetrazole derivatives	0.85	0.5	-2.7	-2.5	0.0	-0.2	-0.2
Other antibacterials	0.63	0.4	0.3	0.3	0.0	0.0	0.0
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.55	0.3	-9.5	-2.2	-8.4	1.1	-7.4
Specific immunoglobulins	0.39	0.0	-7.7	-10.2	0.0	2.7	2.7
Broad-spectrum penicillins	0.15	0.7	-11.7	-12.4	-0.3	1.1	0.8

ATC 4th level

Subgroup	Gross per capita expenditure	DDD/ 1000 inhab. per day	Δ % 21-20				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
B - Blood and blood-forming organs	**7.61**	**89.6**	**-3.9**	**1.2**	**-0.4**	**-4.7**	**-5.1**
Platelet aggregation inhibitors, excl. heparin	2.96	60.9	-4.4	-1.1	-1.6	-1.8	-3.3
Heparins	2.47	3.0	10.1	13.5	-0.1	-2.9	-3.0
Folic acid e derivatives	0.51	6.6	8.9	10.3	-0.1	-1.1	-1.2
Bivalent iron, oral preparations	0.36	2.9	6.8	7.2	0.0	-0.4	-0.4
Direct Xa factor inhibitors	0.29	0.2	-60.7	-57.3	0.0	-7.8	-7.8
Blood substitutes and plasma protein fractions	0.25	0.0	6.7	7.7	0.0	-0.9	-0.9
Solutions affecting the electrolyte balance	0.17	0.2	3.8	-5.0	9.2	0.0	9.3
Vitamin K antagonists	0.12	2.9	-17.5	-17.5	0.0	0.1	0.1
Other antianemic preparations	0.11	0.0	-22.8	-19.2	0.0	-4.5	-4.5
Vitamin B12 (cyanocobalamin and derivatives)	0.10	12.3	13.5	14.0	0.0	-0.4	-0.4
G - Genito-urinary system and sex hormones	**5.53**	**43.7**	**1.4**	**2.9**	**-1.2**	**-0.3**	**-1.5**
Alpha adrenergic receptor antagonists	2.88	27.7	0.8	3.9	-1.9	-1.2	-3.0
Testosterone-5-alpha reductase inhibitors	1.59	10.9	-2.0	-1.0	-0.1	-0.9	-1.0
Prolactin inhibitors	0.17	0.1	2.2	0.9	0.0	1.3	1.3
Gonadotropins	0.16	0.0	54.6	3.9	-0.6	49.7	48.8
Other estrogens	0.13	0.8	4.8	5.1	0.0	-0.3	-0.3
Pregnene derivatives (4)	0.12	0.9	20.8	20.3	0.0	0.4	0.4
M - Musculo-skeletal system	**5.18**	**37.6**	**2.4**	**2.5**	**0.0**	**-0.1**	**-0.1**
Biphosphonates	1.33	6.9	-0.1	0.4	-0.2	-0.4	-0.6
Preparations inhibiting formation of uric acid	0.87	10.6	4.3	2.6	0.0	1.7	1.7
Acetic acid derivatives and related substances	0.78	4.8	3.5	3.7	0.0	-0.2	-0.2
Coxib	0.70	4.1	8.9	9.1	0.0	-0.2	-0.2
Propionic acid derivatives	0.67	5.4	5.1	3.4	0.0	1.6	1.6
Biphosphonates, combinations	0.42	2.0	-5.4	-5.0	0.0	-0.4	-0.4
Other non-steroidal anti-inflammatory/anti-rheumatic pharmaceuticals	0.16	1.9	3.3	2.8	0.0	0.5	0.5
Oxicam-derivatives	0.12	0.8	-1.5	-1.8	0.0	0.3	0.3
L- Antineoplastic and immunomodulatory drugs	**4.38**	**6.3**	**1.1**	**-1.7**	**0.1**	**2.7**	**2.9**
Aromatase inhibitors	2.23	3.0	1.3	0.8	0.0	0.5	0.5
Other immunosuppressants	0.78	1.6	0.6	-0.4	0.0	1.0	1.0
Calcineurin inhibitors	0.55	0.2	-7.1	-6.4	0.0	-0.8	-0.8
Colony stimulating factors	0.19	0.0	72.2	56.2	0.0	10.2	10.2
Other antineoplastics	0.17	0.3	5.2	1.0	4.3	-0.1	4.1

ATC 4th level

Subgroup	Gross per capita expenditure	DDD/ 1000 inhab. per day	Δ % 21-20 Expenditure	Δ % 21-20 DDD	Δ % 21-20 Prices	Δ % 21-20 Mix	Δ % average DDD cost
Antiandrogens	0.12	0.2	-13.7	-13.8	0.0	0.1	0.1
H - Systemic hormonal preparations, excl. sex hormones	**3.82**	**36.8**	**-3.4**	**1.6**	**0.6**	**-5.4**	**-4.9**
Glycocorticoids	1.44	13.5	4.4	3.9	1.8	-1.3	0.5
Thyroid hormones	1.26	21.6	7.1	0.5	0.0	6.6	6.6
Parathyroid hormones and analogues	0.78	0.1	-26.5	-21.3	-0.1	-6.5	-6.6
Vasopressin and analogues	0.13	0.1	-0.5	-1.0	0.0	0.5	0.5
S - Sensory organs	**3.71**	**20.9**	**-5.3**	**-0.7**	**-3.9**	**-0.8**	**-4.6**
Beta-blockers	2.13	11.6	-6.6	-2.7	-3.9	0.0	-4.0
Prostaglandin analogues	1.19	5.6	-7.5	-2.4	-4.5	-0.8	-5.3
Carbonic anhydrase inhibitors	0.26	1.8	20.7	23.7	0.0	-2.4	-2.4
Sympathomimetics for treatment of glaucoma	0.10	1.5	-2.3	-1.0	-0.9	-0.3	-1.2
D - Dermatologicals	**1.32**	**5.0**	**4.5**	**7.1**	**0.0**	**-2.4**	**-2.4**
Other antipsoriatic agents for topical use	0.89	2.5	1.6	1.8	0.1	-0.3	-0.2
Retinoids for acne treatment	0.11	0.2	23.3	24.0	0.0	-0.6	-0.6
P - Antiparasitic, insecticide and repellent pharmaceuticals	**0.23**	**1.0**	**2.5**	**-0.9**	**0.0**	**3.4**	**3.4**
Aminoquinolines	0.17	0.9	-1.7	-0.9	0.0	-0.9	-0.9
V - Various	**0.14**	**0.1**	**-1.9**	**-3.2**	**-0.1**	**1.5**	**1.4**
Pharmaceuticals for treatment of hyperkalemia and hyperphosphatemia	0.12	0.1	-0.2	-1.6	0.0	1.4	1.4

Table 3.10 2021 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 *per capita* expenditure	%*	Δ % 21-20	DDD/ 1000 inhab. per day	%*	Δ % 21-20	Average DDD cost	Δ % 21-20
C - Cardiovascular system	**49.51**		**0.9**	**486.9**		**0.4**	**0.28**	**0.8**
atorvastatin	4.62	9.3	2.8	50.2	10.3	3.0	0.25	0.1
bisoprolol	2.72	5.5	4.4	12.3	2.5	4.2	0.60	0.5
omega 3	2.08	4.2	7.8	4.9	1.0	9.1	1.17	-0.9
ramipril	2.02	4.1	0.0	62.4	12.8	-0.8	0.09	1.0
olmesartan	1.78	3.6	7.7	15.5	3.2	7.8	0.31	0.1
amlodipine	1.62	3.3	-0.4	28.1	5.8	0.3	0.16	-0.4
ezetimibe	1.56	3.2	12.3	5.8	1.2	13.2	0.74	-0.6
nebivolol	1.53	3.1	2.0	16.5	3.4	2.4	0.25	-0.1
simvastatin	1.45	2.9	-4.9	12.2	2.5	-4.7	0.33	0.1
rosuvastatin	1.41	2.9	5.0	14.9	3.1	6.0	0.26	-0.7
olmesartan/amlodipine	1.31	2.6	12.4	8.9	1.8	12.1	0.40	0.5
doxazosin	1.25	2.5	-0.6	7.6	1.6	-0.3	0.45	-0.1
olmesartan/hydrochlorothiazide	1.22	2.5	5.4	10.0	2.1	5.8	0.33	-0.2
ezetimibe/ simvastatin	1.20	2.4	2.1	5.0	1.0	2.5	0.66	-0.1
ezetimibe/ rosuvastatin	1.03	2.1	31.3	6.3	1.3	91.6	0.45	-31.3
flecainide	0.89	1.8	3.2	3.0	0.6	4.0	0.82	-0.5
barnidipine	0.88	1.8	-1.6	4.9	1.0	-1.4	0.50	0.1
perindopril/ amlodipine	0.83	1.7	-1.2	5.3	1.1	0.0	0.43	-0.9
lercanidipine	0.78	1.6	-1.5	9.5	1.9	-1.2	0.22	0.0
losartan	0.74	1.5	-5.5	7.1	1.5	-5.2	0.29	-0.1
furosemide	0.72	1.5	-3.0	24.1	4.9	-3.1	0.08	0.4
zofenopril	0.68	1.4	-0.8	4.5	0.9	-0.9	0.41	0.3
valsartan/ hydrochlorothiazide	0.67	1.4	-5.4	6.1	1.3	-5.0	0.30	-0.2
valsartan	0.67	1.3	-1.7	9.9	2.0	-1.3	0.19	-0.2
irbesartan	0.67	1.3	-4.8	8.1	1.7	-4.7	0.22	0.1
zofenopril/hydrochlorothiazide	0.64	1.3	-1.2	4.1	0.8	-0.8	0.43	-0.1
perindopril/indapamide/amlodipine	0.61	1.2	-2.0	4.2	0.9	16.4	0.40	-15.6
irbesartan/ hydrochlorothiazide	0.59	1.2	-5.1	5.1	1.0	-4.4	0.32	-0.5
ramipril/hydrochlorothiazide	0.57	1.1	0.0	6.6	1.4	0.1	0.24	0.2
telmisartan	0.53	1.1	-4.3	8.6	1.8	-4.3	0.17	0.2
A - Gastrointestinal tract and metabolism	**32.31**		**3.6**	**284.3**		**10.9**	**0.31**	**-6.4**
pantoprazole	4.40	13.6	3.3	27.5	9.7	8.7	0.44	-4.6

Therapeutic category	Gross *per capita* expenditure	%*	Δ % 21-20	DDD/ 1000 inhab. per day	%*	Δ % 21-20	Average DDD cost	Δ % 21-20
cholecalciferol	4.17	12.9	23.4	140.0	49.3	21.8	0.08	1.6
lansoprazole	2.29	7.1	-4.5	13.8	4.9	-1.8	0.45	-2.5
esomeprazole	2.23	6.9	1.8	15.3	5.4	7.9	0.40	-5.4
omeprazole	2.23	6.9	-1.6	17.6	6.2	2.3	0.35	-3.6
mesalazine	2.07	6.4	4.2	5.2	1.8	4.1	1.09	0.4
metformin	1.63	5.0	4.0	23.0	8.1	2.9	0.19	1.3
insulin lispro	1.49	4.6	-4.5	3.3	1.1	-3.9	1.25	-0.3
insulin aspart	1.41	4.4	-5.3	2.8	1.0	-3.2	1.37	-1.9
rifaximin	1.38	4.3	1.9	1.8	0.6	2.2	2.08	0.0
ursodeoxycholic acid	0.87	2.7	10.7	2.6	0.9	7.6	0.92	3.2
sodium alginate/potassium bicarbonate	0.87	2.7	-0.4	4.1	1.4	-0.2	0.59	0.1
N- Central nervous system	**23.97**		**1.4**	**68.9**		**1.6**	**0.95**	**0.0**
levetiracetam	1.62	6.7	0.9	2.2	3.2	1.5	2.02	-0.3
fentanyl	1.34	5.6	-1.7	0.6	0.9	-1.8	5.77	0.4
pregabalin	1.30	5.4	5.7	2.3	3.3	5.4	1.54	0.6
tapentadol	1.22	5.1	0.1	0.5	0.8	1.2	6.25	-0.9
paroxetine	1.01	4.2	0.6	7.9	11.5	0.8	0.35	0.0
escitalopram	0.97	4.0	1.3	7.6	11.0	2.0	0.35	-0.4
valproic acid	0.96	4.0	1.2	2.3	3.3	0.4	1.16	1.0
naloxone/ oxycodone	0.89	3.7	-5.4	0.4	0.5	-2.4	6.50	-2.8
venlafaxine	0.80	3.4	1.0	3.6	5.3	2.4	0.61	-1.1
sertraline	0.80	3.3	4.7	8.7	12.6	4.8	0.25	0.2
duloxetine	0.79	3.3	3.0	3.2	4.7	3.9	0.67	-0.6
vortioxetine	0.72	3.0	12.1	1.7	2.5	12.4	1.14	0.0
lacosamide	0.68	2.8	11.5	0.3	0.5	11.8	5.38	0.0
rotigotine	0.65	2.7	-6.3	0.3	0.5	-6.4	5.42	0.4
quetiapine	0.60	2.5	6.4	0.5	0.7	6.5	3.47	0.2
lamotrigin	0.45	1.9	2.0	0.7	1.0	2.1	1.78	0.2
trazodone	0.40	1.7	1.4	1.1	1.6	1.5	0.98	0.2
citalopram	0.40	1.7	-1.2	3.9	5.7	-0.8	0.28	-0.1
safinamide	0.39	1.6	1.1	0.2	0.4	3.0	4.36	-1.6
pramipexole	0.37	1.5	-1.4	0.4	0.6	-1.9	2.31	0.7
lidocaine	0.36	1.5	3.5	0.3	0.4	3.8	3.61	0.0
mirtazapine	0.35	1.5	1.6	1.7	2.5	1.9	0.57	-0.1
levodopa/ benserazide	0.35	1.4	-1.2	1.0	1.5	-1.0	0.92	0.0
gabapentin	0.34	1.4	3.0	0.4	0.6	3.0	2.15	0.3
buprenorphine	0.29	1.2	18.2	0.2	0.3	11.6	4.46	6.2
R - Respiratory system	**16.13**		**-5.9**	**39.8**		**-4.8**	**1.11**	**-0.9**
beclomethasone/ formoterol	2.47	15.3	-2.1	3.9	9.8	-1.8	1.73	0.0
fluticasone furoate/vilanterol	2.35	14.6	-0.6	3.7	9.3	-0.4	1.74	0.0

Therapeutic category	Gross *per capita* expenditure	%*	Δ % 21-20	DDD/ 1000 inhab. per day	%*	Δ % 21-20	Average DDD cost	Δ % 21-20
budesonide/ formoterol	1.41	8.8	-3.1	2.0	5.1	-2.2	1.90	-0.6
salmeterol/ fluticasone	1.23	7.6	-29.2	2.3	5.8	-15.5	1.46	-15.9
tiotropium	1.17	7.2	-10.0	2.1	5.3	-10.0	1.53	0.2
umeclidinium	0.84	5.2	5.8	1.5	3.6	6.1	1.59	0.0
aclidinium	0.60	3.7	-9.9	1.0	2.6	-8.8	1.59	-0.9
glycopyrronium/ beclomethasone/ formoterol	0.50	3.1	31.4	0.5	1.1	31.8	3.06	0.0
vilanterol/ fluticasone furoate/ umeclidinium	0.47	2.9	31.1	0.5	1.1	24.9	2.83	5.3
beclomethasone	0.47	2.9	-7.6	1.3	3.2	-7.9	1.00	0.6
montelukast	0.46	2.9	-6.7	2.0	5.1	-5.2	0.62	-1.3
glycopyrronium	0.41	2.6	-14.5	0.7	1.9	-14.3	1.51	0.0
J - Antimicrobials	**9.46**		**-4.9**	**12.4**		**-4.1**	**2.09**	**-0.5**
amoxicillin/ clavulanic acid	2.07	21.9	-3.6	4.2	33.6	-3.8	1.36	0.5
ceftriaxone	0.82	8.7	-11.7	0.2	1.5	-12.4	11.99	1.0
azithromicyn	0.72	7.6	2.0	1.3	10.8	1.7	1.48	0.6
cefixime	0.69	7.3	0.9	0.8	6.6	1.0	2.33	0.2
fluconazole	0.68	7.2	-1.8	0.3	2.7	-1.2	5.55	-0.4
fosfomycin	0.63	6.7	1.0	0.4	3.0	1.2	4.63	0.1
ciprofloxacin	0.59	6.2	1.7	0.6	5.1	1.9	2.57	0.1
clarithromycin	0.39	4.1	-15.7	1.2	9.8	-14.6	0.88	-1.0
levofloxacin	0.35	3.7	-10.6	0.7	5.2	-10.6	1.49	0.2
human immunoglobulin antihepatitis B	0.33	3.5	-6.2	0.0	0.0	-5.5	312.04	-0.5
B - Blood and blood-forming organs	**7.61**		**-3.2**	**89.6**		**2.2**	**0.23**	**-5.1**
enoxaparin	2.21	29.0	16.0	2.7	3.1	19.4	2.20	-2.6
acetylsalicylic acid	1.18	15.5	0.8	45.0	50.2	1.4	0.07	-0.4
clopidogrel	1.16	15.3	-0.1	5.6	6.3	0.5	0.57	-0.4
folic acid	0.51	6.7	9.7	6.6	7.4	11.3	0.21	-1.2
ferrous sulfate	0.26	3.4	8.8	2.3	2.6	9.1	0.31	0.0
human albumin	0.25	3.3	7.4	0.0	0.0	8.7	51.79	-0.9
G - Genito-urinary system and sex hormones	**5.53**		**2.1**	**43.7**		**3.9**	**0.35**	**-1.5**
tamsulosin	1.12	20.2	1.9	10.8	24.8	2.8	0.28	-0.6
dutasteride	1.04	18.8	-1.8	8.3	19.1	-0.5	0.34	-1.1
alfuzosin	0.89	16.0	2.6	9.4	21.4	2.8	0.26	0.1
silodosin	0.71	12.8	1.2	6.2	14.2	15.2	0.31	-11.9
finasteride	0.55	9.9	-0.4	2.6	5.8	1.2	0.59	-1.3

Therapeutic category	Gross *per capita* expenditure	%*	Δ % 21-20	DDD/ 1000 inhab. per day	%*	Δ % 21-20	Average DDD cost	Δ % 21-20
M - Musculo-skeletal system	**5.18**		**3.1**	**37.6**		**3.5**	**0.38**	**-0.1**
alendronic acid	0.78	15.1	2.2	4.1	10.9	3.8	0.52	-1.2
diclofenac	0.60	11.6	6.2	4.1	10.9	6.2	0.40	0.3
etoricoxib	0.59	11.4	10.6	3.5	9.2	11.3	0.46	-0.3
febuxostat	0.51	9.9	6.3	2.1	5.6	6.8	0.67	-0.2
alendronic acid/cholecalciferol	0.42	8.1	-4.8	2.0	5.3	-4.1	0.58	-0.4
risendronic acid	0.37	7.1	-2.5	2.1	5.6	-1.5	0.48	-0.7
allopurinol	0.36	7.0	3.3	8.5	22.5	2.8	0.12	0.7
ibuprofen	0.28	5.5	14.3	1.9	5.0	14.3	0.41	0.2
L - Antineoplastic and immunomodulating agents	**4.38**		**1.8**	**6.3**		**-0.8**	**1.90**	**2.9**
letrozole	1.41	32.2	3.2	1.7	27.2	3.8	2.26	-0.3
methotrexate	0.69	15.7	2.2	1.3	21.1	1.8	1.41	0.7
ciclosporin	0.48	10.9	-9.2	0.2	2.5	-7.5	8.12	-1.5
exemestane	0.44	10.1	6.4	0.5	8.6	7.0	2.23	-0.3
anastrozole	0.37	8.5	-6.6	0.8	11.9	-5.9	1.36	-0.6
H - Systemic hormones	**3.82**		**-2.7**	**36.8**		**2.6**	**0.28**	**-4.9**
levothyroxine	1.22	31.9	8.2	21.6	58.7	1.5	0.15	7.0
teriparatide	0.78	20.4	-26.0	0.1	0.4	-20.6	15.65	-6.6
prednisone	0.68	17.8	2.4	6.8	18.4	3.8	0.28	-1.1
betamethasone	0.26	6.8	-3.1	1.7	4.6	-2.7	0.42	-0.2
methylprednisolone	0.20	5.1	1.5	3.0	8.2	2.5	0.18	-0.7
S - Sensory organs	**3.71**		**-4.7**	**20.9**		**0.2**	**0.49**	**-4.6**
tafluprost	0.50	13.4	3.7	1.6	7.5	4.0	0.86	0.0
timolol/ bimatoprost	0.43	11.7	-1.8	1.4	6.7	-1.8	0.85	0.3
dorzolamide/ timolol	0.40	10.7	21.5	2.7	13.0	17.4	0.40	3.8
timolol	0.36	9.8	2.6	3.1	14.8	0.0	0.32	2.8
bimatoprost	0.32	8.6	-22.1	1.8	8.5	-4.1	0.49	-18.5
tafluprost/timolol	0.25	6.9	11.8	0.7	3.5	12.1	0.96	0.0
timolol/ brinzolamide	0.24	6.4	-40.3	1.2	5.9	-26.4	0.53	-18.7
travoprost	0.20	5.5	-5.7	1.0	4.7	-5.8	0.57	0.4
latanoprost	0.17	4.6	-1.8	1.3	6.2	-0.3	0.37	-1.1
D - Dermatologicals	**1.32**		**5.2**	**5.0**		**8.1**	**0.73**	**-2.4**
calcipotriol/betamethasone	0.84	63.4	3.5	2.4	47.6	4.2	0.97	-0.4
isotretinoin	0.11	8.4	24.1	0.2	4.4	25.2	1.38	-0.6
clobetasol	0.08	5.9	13.0	1.0	20.1	23.7	0.21	-8.4
diclofenac	0.06	4.8	15.9	0.1	1.2	17.8	2.95	-1.4
terbinafine	0.05	3.8	4.0	0.1	2.0	3.9	1.41	0.4

Therapeutic category	Gross *per capita* expenditure	%*	Δ % 21-20	DDD/ 1000 inhab. per day	%*	Δ % 21-20	Average DDD cost	Δ % 21-20
P - Antiparasitic products	**0.23**		**3.2**	**1.0**		**0.0**	**0.62**	**3.4**
hydroxychloroquine	0.17	73.2	-1.1	0.9	87.4	0.1	0.52	-0.9
mefloquine	0.02	8.2	88.1	0.0	0.4	88.6	13.27	0.0
mebendazole	0.02	8.1	-7.3	0.1	7.7	-7.7	0.65	0.7
metronidazole	0.01	5.2	15.6	0.0	3.1	16.1	1.03	-0.1
tinidazole	<0.005	2.2	12.5	0.0	0.5	12.8	2.71	0.0
V - Various	**0.14**		**-1.2**	**0.1**		**-2.3**	**3.78**	**1.4**
sevelamer	0.05	39.2	2.1	<0.05	27.4	2.7	5.40	-0.3
polystyrene sulfonate	0.04	31.6	1.5	<0.05	43.0	1.9	2.78	-0.1
sucroferric oxyhydroxide	0.02	12.0	0.7	<0.05	5.4	0.9	8.44	0.0
calcium acetate/magnesium carbonate	0.01	4.4	-11.4	<0.05	16.3	-11.2	1.02	0.0
deferoxamine	0.01	3.9	-10.5	<0.05	0.7	-10.0	19.62	-0.2

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

Table 3.11 First thirty active ingredients by approved care NHS expenditure (class A-NHS): comparison 2021-2020

ATC	Active substance	Expenditure *(million)*	%*	Gross *per capita* expenditure	Rank 2021	Rank 2020	Average DDD cost	Δ % 21-20
C	atorvastatin	273.7	2.8	4.62	1	1	0.25	0.1
A	pantoprazole	260.5	2.7	4.40	2	2	0.44	-4.6
A	cholecalciferol	246.9	2.6	4.17	3	3	0.08	1.6
C	bisoprolol	160.9	1.7	2.72	4	4	0.60	0.5
R	beclomethasone/formoterol	146.2	1.5	2.47	5	5	1.73	0.0
R	fluticasone furoate/vilanterol	139.3	1.4	2.35	6	7	1.74	0.0
A	lansoprazole	135.6	1.4	2.29	7	6	0.45	-2.5
A	esomeprazole	132.2	1.4	2.23	8	9	0.40	-5.4
A	omeprazole	131.9	1.4	2.23	9	8	0.35	-3.6
B	enoxaparin	130.9	1.4	2.21	10	14	2.20	-2.6
C	omega 3	123.4	1.3	2.08	11	13	1.17	-0.9
A	mesalazine	122.8	1.3	2.07	12	12	1.09	0.4
J	amoxicillin/clavulanic acid	122.5	1.3	2.07	13	10	1.36	0.5
C	ramipril	119.6	1.2	2.02	14	11	0.09	1.0
C	olmesartan	105.4	1.1	1.78	15	16	0.31	0.1
A	metformin	96.6	1.0	1.63	16	19	0.19	1.3
C	amlodipine	96.0	1.0	1.62	17	17	0.16	-0.4
N	levetiracetam	95.7	1.0	1.62	18	18	2.02	-0.3
C	ezetimibe	92.6	1.0	1.56	19	25	0.74	-0.6
C	nebivolol	90.6	0.9	1.53	20	22	0.25	-0.1
A	insulin lispro	88.1	0.9	1.49	21	20	1.25	-0.3
C	simvastatin	86.1	0.9	1.45	22	21	0.33	0.1
R	budesonide/formoterol	83.8	0.9	1.41	23	24	1.90	-0.6
C	rosuvastatin	83.7	0.9	1.41	24	29	0.26	-0.7
A	insulin aspart	83.6	0.9	1.41	25	23	1.37	-1.9
L	letrozole	83.6	0.9	1.41	26	26	2.26	-0.3
A	rifaximin	81.7	0.8	1.38	27	28	2.08	0.0
N	fentanyl	79.5	0.8	1.34	28	27	5.77	0.4
C	olmesartan/amlodipine	77.7	0.8	1.31	29	36	0.40	0.5
N	pregabalin	76.8	0.8	1.30	30	32	1.54	0.6
	Total	**3,647.5**	**37.7**					
	Total expenditure class A-NHS	**9,672.4**						

* Calculated on overall expenditure under approved care regime

Table 3.12 2021 regional ranks of the first 30 active ingredients by consumption under approved care regime (class A-NHS)

Rank	Active substance	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	5	2	3	1	1	2	1	1	2	1	3	3	3	3	1	3	1	1
2	pantoprazole	1	2	4	1	5	3	3	1	2	2	1	2	1	2	4	2	2	2	2	4
3	cholecalciferol	3	1	2	4	2	5	2	3	6	12	3	3	4	1	1	1	3	1	3	2
4	bisoprolol	6	10	10	7	7	4	4	6	3	6	8	5	6	5	5	7	4	4	5	5
5	beclomethasone/ formoterol	4	4	7	5	6	7	10	5	7	3	5	11	9	18	23	11	14	10	19	15
6	fluticasone furoate/vilanterol	5	6	9	30	9	8	12	7	11	4	6	4	10	8	10	10	11	13	9	8
7	lansoprazole	25	7	29	61	1	2	8	4	4	8	28	6	8	9	2	14	5	8	22	13
8	esomeprazole	7	3	6	9	4	10	9	10	12	21	13	21	15	7	14	5	13	5	8	20
9	omeprazole	14	30	12	75	29	20	26	16	27	17	11	54	14	13	6	4	17	6	4	3
10	enoxaparin	386	277	3	3	303	226	7	247	310	143	186	432	2	6	156	8	6	150	16	6
11	omega 3	31	9	24	60	21	17	21	17	17	27	10	10	5	12	12	6	7	15	6	11
12	mesalazine	8	17	19	15	14	9	13	8	8	7	12	7	12	16	24	17	8	9	13	9
13	amoxicillin/clavulanic acid	10	16	21	19	8	18	18	13	13	11	9	8	11	10	7	9	9	12	10	10
14	ramipril	9	13	22	8	11	6	5	19	5	5	4	23	13	20	22	21	25	21	21	17
15	olmesartan	33	14	25	16	20	19	14	9	30	37	14	16	16	14	9	12	10	14	12	7
16	metformin	19	18	34	39	28	22	22	32	20	13	22	24	17	19	18	24	15	17	18	12
17	amlodipine	15	29	23	28	17	14	17	25	10	9	7	12	24	30	25	25	31	35	31	27
18	levetiracetam	12	19	17	6	13	11	11	11	209	211	18	9	18	11	27	16	21	18	14	18
19	ezetimibe	20	34	26	36	27	16	20	15	9	19	20	13	19	27	21	28	48	41	33	22
20	nebivolol	17	27	33	56	43	24	24	23	23	18	16	14	27	22	16	18	19	20	25	19
21	insulin lispro	30	23	28	44	37	15	31	53	443	10	15	44	53	28	17	19	23	11	11	14
22	simvastatin	28	35	32	17	25	21	27	46	14	15	26	19	28	37	20	31	22	26	35	24
23	beclomethasone/ formoterol	34	32	27	10	18	12	28	21	15	20	53	32	35	39	31	27	32	27	38	32
24	rosuvastatin	24	39	20	21	19	28	23	34	18	25	30	20	26	31	34	38	29	23	29	49

Rank	Active substance	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Sicily	Sardinia
25	insulin aspart	13	26	39	14	31	43	40	31	422	35	19	27	21	25	35	15	34	37	17	16
26	letrozole	11	24	18	11	10	13	16	12	240	199	29	15	29	23	13	26	28	22	32	26
27	rifaximin	18	25	43	152	50	34	52	29	16	30	27	17	23	33	50	23	20	16	26	47
28	fentanyl	29	15	30	24	12	35	6	14	39	29	64	36	36	17	8	44	30	57	28	25
29	olmesartan/ amlodipine	47	21	36	23	30	36	38	20	43	45	33	25	31	24	26	22	16	24	24	28
30	pregabalin	16	8	31	27	23	37	33	26	31	52	17	29	20	35	38	39	37	38	45	35

Table 3.13 First thirty active ingredients* with highest average cost per day of therapy under approved care regime compared to the previous year: comparison 2021-2020

ATC	Active substance	Average DDD cost	Δ % 21-20	Per capita expenditure	Δ % 21-20	DDD/1000 inhab. per day	Δ % 21-20
H	teriparatide	15.65	-6.6	0.78	-26.0	0.1	-20.6
J	ceftriaxone	11.99	1.0	0.82	-11.7	0.2	-12.4
L	ciclosporin	8.12	-1.5	0.48	-9.2	0.2	-7.5
N	naloxone/oxycodone	6.50	-2.8	0.89	-5.4	0.4	-2.4
N	tapentadol	6.25	-0.9	1.22	0.1	0.5	1.2
N	fentanyl	5.77	0.4	1.34	-1.7	0.6	-1.8
J	fluconazole	5.55	-0.4	0.68	-1.8	0.3	-1.2
N	rotigotine	5.42	0.4	0.65	-6.3	0.3	-6.4
N	lacosamide	5.38	0.0	0.68	11.5	0.3	11.8
A	dulaglutide	4.84	2.6	0.87	40.6	0.5	37.4
J	fosfomycin	4.63	0.1	0.63	1.0	0.4	1.2
N	quetiapine	3.47	0.2	0.60	6.4	0.5	6.5
R	glycopyrronium/beclomethasone/formoterol	3.06	0.0	0.50	31.4	0.5	31.8
R	vilanterol/fluticasone furoate/umeclidinium	2.83	5.3	0.47	31.1	0.5	24.9
J	ciprofloxacin	2.57	0.1	0.59	1.7	0.6	1.9
J	cefixime	2.33	0.2	0.69	0.9	0.8	1.0
L	letrozole	2.26	-0.3	1.41	3.2	1.7	3.8
B	enoxaparin	2.20	-2.6	2.21	16.0	2.7	19.4
A	rifaximin	2.08	0.0	1.38	1.9	1.8	2.2
N	levetiracetam	2.02	-0.3	1.62	0.9	2.2	1.5
R	budesonide/formoterol	1.90	-0.6	1.41	-3.1	2.0	-2.2
R	fluticasone furoate/vilanterol	1.74	0.0	2.35	-0.6	3.7	-0.4
R	beclomethasone/formoterol	1.73	0.0	2.47	-2.1	3.9	-1.8
R	umeclidinium	1.59	0.0	0.84	5.8	1.5	6.1
R	aclidinium	1.59	-0.9	0.60	-9.9	1.0	-8.8
N	pregabalin	1.54	0.6	1.30	5.7	2.3	5.4
R	tiotropium	1.53	0.2	1.17	-10.0	2.1	-10.0
J	azithromicyn	1.48	0.6	0.72	2.0	1.3	1.7
R	salmeterol/fluticasone	1.46	-15.9	1.23	-29.2	2.3	-15.5
L	methotrexate	1.41	0.7	0.69	2.2	1.3	1.8

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

Table 3.14 First thirty active ingredients* with highest variation in expenditure under approved care regime compared to the previous year: comparison 2021-2020

ATC	Active substance	Per capita expenditure	Δ % 21-20	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
A	dulaglutide	0.87	40.6	0.5	37.4	4.84	2.6
R	glycopyrronium/ beclomethasone/formoterol	0.50	31.4	0.5	31.8	3.06	0.0
C	ezetimibe/rosuvastatin	1.03	31.3	6.3	91.6	0.45	-31.3
R	vilanterol/fluticasone furoate/umeclidinium	0.47	31.1	0.5	24.9	2.83	5.3
A	cholecalciferol	4.17	23.4	140.0	21.8	0.08	1.6
B	enoxaparin	2.21	16.0	2.7	19.4	2.20	-2.6
C	olmesartan/amlodipine	1.31	12.4	8.9	12.1	0.40	0.5
C	ezetimibe	1.56	12.3	5.8	13.2	0.74	-0.6
N	vortioxetine	0.72	12.1	1.7	12.4	1.14	0.0
N	lacosamide	0.68	11.5	0.3	11.8	5.38	0.0
A	ursodeoxycholic acid	0.87	10.7	2.6	7.6	0.92	3.2
M	etoricoxib	0.59	10.6	3.5	11.3	0.46	-0.3
B	folic acid	0.51	9.7	6.6	11.3	0.21	-1.2
H	levothyroxine	1.22	8.2	21.6	1.5	0.15	7.0
C	omega 3	2.08	7.8	4.9	9.1	1.17	-0.9
C	olmesartan	1.78	7.7	15.5	7.8	0.31	0.1
N	quetiapine	0.60	6.4	0.5	6.5	3.47	0.2
M	febuxostat	0.51	6.3	2.1	6.8	0.67	-0.2
M	diclofenac	0.60	6.2	4.1	6.2	0.40	0.3
R	umeclidinium	0.84	5.8	1.5	6.1	1.59	0.0
N	pregabalin	1.30	5.7	2.3	5.4	1.54	0.6
C	olmesartan/ hydrochlorothiazide	1.22	5.4	10.0	5.8	0.33	-0.2
C	rosuvastatin	1.41	5.0	14.9	6.0	0.26	-0.7
N	sertraline	0.80	4.7	8.7	4.8	0.25	0.2
C	nebivolol/ hydrochlorothiazide	0.48	4.6	4.6	5.0	0.28	-0.2
C	bisoprolol	2.72	4.4	12.3	4.2	0.60	0.5
A	mesalazine	2.07	4.2	5.2	4.1	1.09	0.4
A	metformin	1.63	4.0	23.0	2.9	0.19	1.3
S	tafluprost	0.50	3.7	1.6	4.0	0.86	0.0
D	calcipotriol/betamethasone	0.84	3.5	2.4	4.2	0.97	-0.4

* 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 compared to the previous year: comparison 2021-2020

ATC	Active substance	Per capita expenditure	Δ % 21-20	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
R	salmeterol/fluticasone	1.23	-29.2	2.3	-15.5	1.46	-15.9
H	teriparatide	0.78	-26.0	0.1	-20.6	15.65	-6.6
J	ceftriaxone	0.82	-11.7	0.2	-12.4	11.99	1.0
R	tiotropium	1.17	-10.0	2.1	-10.0	1.53	0.2
R	aclidinium	0.60	-9.9	1.0	-8.8	1.59	-0.9
L	ciclosporin	0.48	-9.2	0.2	-7.5	8.12	-1.5
C	carvedilol	0.49	-7.2	2.8	-6.5	0.48	-0.5
N	rotigotine	0.65	-6.3	0.3	-6.4	5.42	0.4
A	insulin glulisine	0.51	-6.3	1.1	-6.0	1.32	0.0
C	losartan	0.74	-5.5	7.1	-5.2	0.29	-0.1
N	naloxone/oxycodone	0.89	-5.4	0.4	-2.4	6.50	-2.8
C	valsartan/hydrochlorothiazide	0.67	-5.4	6.1	-5.0	0.30	-0.2
A	insulin aspart	1.41	-5.3	2.8	-3.2	1.37	-1.9
C	irbesartan/hydrochlorothiazide	0.59	-5.1	5.1	-4.4	0.32	-0.5
C	simvastatin	1.45	-4.9	12.2	-4.7	0.33	0.1
C	irbesartan	0.67	-4.8	8.1	-4.7	0.22	0.1
A	lansoprazole	2.29	-4.5	13.8	-1.8	0.45	-2.5
A	insulin lispro	1.49	-4.5	3.3	-3.9	1.25	-0.3
C	telmisartan	0.53	-4.3	8.6	-4.3	0.17	0.2
C	telmisartan/hydrochlorothiazide	0.51	-3.7	4.0	-3.3	0.35	-0.1
J	amoxicillin/clavulanic acid	2.07	-3.6	4.2	-3.8	1.36	0.5
R	budesonide/formoterol	1.41	-3.1	2.0	-2.2	1.90	-0.6
C	furosemide	0.72	-3.0	24.1	-3.1	0.08	0.4
C	candesartan	0.48	-2.8	8.6	-2.8	0.15	0.3
R	beclomethasone/formoterol	2.47	-2.1	3.9	-1.8	1.73	0.0
C	perindopril/indapamide/amlodipine	0.61	-2.0	4.2	16.4	0.40	-15.6
G	dutasteride	1.04	-1.8	8.3	-0.5	0.34	-1.1
J	fluconazole	0.68	-1.8	0.3	-1.2	5.55	-0.4
C	valsartan	0.67	-1.7	9.9	-1.3	0.19	-0.2
N	fentanyl	1.34	-1.7	0.6	-1.8	5.77	0.4

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

Table 3.16. First thirty active ingredients by consumption under approved care regime (class A-NHS): comparison 2021-2020

ATC	Active substance	DDD/1000 inhab. per day	%*	Rank 2021	Rank 2020	Average DDD cost	Δ % 21-20
A	cholecalciferol	140.0	12.4	1	1	0.08	1.6
C	ramipril	62.4	5.5	2	2	0.09	1.0
C	atorvastatin	50.2	4.4	3	3	0.25	0.1
B	acetylsalicylic acid	45.0	4.0	4	4	0.07	-0.4
C	amlodipine	28.1	2.5	5	5	0.16	-0.4
A	pantoprazole	27.5	2.4	6	6	0.44	-4.6
C	furosemide	24.1	2.1	7	7	0.08	0.4
A	metformin	23.0	2.0	8	8	0.19	1.3
H	levothyroxine	21.6	1.9	9	9	0.15	7.0
A	omeprazole	17.6	1.6	10	10	0.35	-3.6
C	nebivolol	16.5	1.5	11	11	0.25	-0.1
C	olmesartan	15.5	1.4	12	12	0.31	0.1
A	esomeprazole	15.3	1.4	13	13	0.40	-5.4
C	rosuvastatin	14.9	1.3	14	15	0.26	-0.7
A	lansoprazole	13.8	1.2	15	14	0.45	-2.5
C	bisoprolol	12.3	1.1	16	17	0.60	0.5
C	simvastatin	12.2	1.1	17	16	0.33	0.1
B	cyanocobalamin	11.0	1.0	18	21	0.02	-0.2
G	tamsulosin	10.8	1.0	19	18	0.28	-0.6
C	olmesartan/hydrochlorothiazide	10.0	0.9	20	22	0.33	-0.2
C	valsartan	9.9	0.9	21	19	0.19	-0.2
C	lercanidipine	9.5	0.8	22	20	0.22	0.0
G	alfuzosin	9.4	0.8	23	23	0.26	0.1
C	olmesartan/amlodipine	8.9	0.8	24	31	0.40	0.5
N	sertraline	8.7	0.8	25	29	0.25	0.2
C	telmisartan	8.6	0.8	26	24	0.17	0.2
C	candesartan	8.6	0.8	27	25	0.15	0.3
M	allopurinol	8.5	0.7	28	30	0.12	0.7
G	dutasteride	8.3	0.7	29	28	0.34	-1.1
C	irbesartan	8.1	0.7	30	26	0.22	0.1
	Total	**660.4**	**58.3**				
	Total DDD class A-NHS	**1133.2**					

*calculated on overall expenditure under approved care regime

Table 3.17 2020 regional ranks of the first 30 active ingredients by consumption under approved care regime (class A-NHS)

Rank	Active substance	Piedmonte	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	2	2	2	2	2	2	2	2	4	2	3	3	2	4	4	3	2
3	atorvastatin	4	4	3	3	4	3	3	3	4	3	4	3	4	4	4	3	3	3	4	3
4	acetylsalicylic acid	3	3	6	4	3	5	4	5	3	4	3	2	3	2	2	5	2	2	2	4
5	amlodipine	5	8	4	7	8	4	5	6	5	5	5	5	7	6	8	7	9	9	9	8
6	pantoprazole	6	5	5	5	12	10	6	4	10	10	7	7	5	5	10	4	5	5	7	10
7	furosemide	7	10	7	8	6	6	8	13	7	7	6	6	9	9	5	14	7	8	8	7
8	metformin	8	7	8	11	10	8	9	9	8	8	9	9	8	7	9	9	6	7	6	6
9	levothyroxine	9	9	13	6	7	9	7	22	6	9	8	8	6	8	6	12	8	6	10	11
10	omeprazole	14	18	11	65	21	19	18	15	27	18	13	38	11	11	11	6	17	10	5	5
11	nebivolol	10	12	12	24	17	11	13	10	15	11	10	10	13	13	12	11	11	11	13	12
12	olmesartan	22	13	14	14	15	16	11	8	25	23	12	12	10	12	13	10	10	13	11	9
13	esomeprazole	12	6	9	15	9	15	14	12	19	26	15	20	16	10	18	8	14	12	12	17
14	rosuvastatin	11	17	10	9	11	13	10	16	12	15	16	11	14	16	22	15	16	14	15	21
15	lansoprazole	29	15	25	61	5	7	15	7	11	21	33	15	12	15	7	16	12	17	21	15
16	bisoprolol	23	23	16	13	13	14	12	11	13	19	25	16	21	18	19	18	21	23	18	18
17	simvastatin	21	21	15	12	14	17	17	30	14	16	19	14	19	25	15	20	18	19	24	14
18	cyanocobalamin	15	26	19	76	39	49	29	27	9	6	11	35	23	27	44	34	26	28	17	43
19	tamsulosin	13	14	18	16	20	22	16	14	17	17	14	17	25	22	21	22	28	25	27	27
20	olmesartan/hydrochlorothiazide	32	16	26	21	22	23	19	17	43	49	37	24	26	19	25	13	13	16	14	20
21	valsartan	27	27	23	31	29	32	23	28	16	12	18	18	29	24	29	29	25	15	23	19
22	lercanidipine	18	11	22	10	32	12	20	29	20	30	24	22	24	31	27	24	39	50	34	26
23	alfuzosin	43	53	31	85	37	25	50	26	30	33	55	21	22	21	32	17	20	20	22	13
24	olmesartan/amlodipine	40	20	24	19	24	27	27	20	42	40	32	25	28	20	24	19	19	26	20	25
25	sertraline	17	29	21	20	19	20	34	19	18	13	27	28	45	29	42	60	48	52	33	45
26	telmisartan	20	39	29	28	18	40	26	33	35	36	17	33	17	26	23	26	30	36	19	28
27	candesartan	28	73	36	18	43	38	32	21	32	28	26	23	27	23	14	25	15	29	31	22
28	allopurinol	24	22	46	33	34	36	24	36	21	20	20	13	31	17	16	36	22	21	28	35
29	dutasteride	35	37	28	32	26	24	28	23	34	31	21	19	30	28	35	37	24	24	30	33
30	irbesartan	37	30	33	64	73	46	40	25	37	32	22	32	18	37	17	31	29	32	32	16

Table 3.18 Consumption, price and mix effects on the variation of pharmaceutical expenditure on medicines provided by public health facilities: comparison 2021-2020 (any ATC category includes the therapeutic subgroups in decreasing order of expenditure, up to the value of 0.10 euros of per capita expenditure)

ATC 1st level Subgroups	Gross *per capita* expenditure	DDD/ 1000 inhab. per day	Δ % 21-20				Δ % Average DDD cost
			Expen diture	DDD	Prices	Mix	
Italy	**233.53**	**173.5**	**4.1**	**-0.7**	**-5.4**	**10.8**	**4.8**
L- Antineoplastic and immunomodulatory drugs	**107.59**	**11.1**	**3.9**	**4.1**	**-6.0**	**6.2**	**-0.2**
Selective immunosuppressants	14.95	1.4	10.3	9.4	-2.3	3.2	0.8
PD-1/PDL-1 inhibitors	12.05	0.3	20.5	32.5	-8.1	-1.0	-9.1
Other immunosuppressants	10.00	0.5	1.0	3.8	-7.4	5.0	-2.8
Interleukin inhibitors	8.53	0.8	17.8	19.9	-0.1	-1.7	-1.7
Tumor necrosis factor alpha inhibitors (TNF-alpha)	5.04	1.5	-14.0	10.3	-9.2	-14.1	-22.0
HER2 inhibitors (human epid. growth factor 2 receptor)	4.63	0.2	-13.4	1.1	-17.3	3.6	-14.3
Other kinase protein inhibitors	4.28	0.1	4.7	1.7	0.4	2.5	2.9
CD38 inhibitors	4.08	0.1	14.4	43.9	-19.6	-1.1	-20.5
Cyclin-dependent kinase inhibitors (CDK)	3.44	0.1	-0.2	18.0	-16.6	1.4	-15.4
BCR-ABL tyrosine kinase inhibitors	3.42	0.2	-3.2	-1.9	-1.6	0.4	-1.3
Bruton tyrosine kinase (BTK) inhibitors	3.40	0.1	18.0	18.0	0.0	0.0	0.0
Epidermal growth factor receptor (EGFR) tyrosine kinase inhib.	2.62	0.1	22.0	4.1	0.5	16.1	17.1
Antiandrogens	2.28	0.6	22.3	0.1	-1.2	23.7	22.2
Other antineoplastics	2.20	0.1	28.8	4.9	6.7	15.0	22.7
Other hormone antagonists and related substances	1.98	0.1	1.7	-5.4	-0.5	8.1	7.6
Gonadotropin-releasing hormone analogues	1.89	1.1	-0.2	-4.3	3.8	0.4	4.2
Janus-associated kinase (JAK) inhibitors	1.87	<0.05	15.1	13.7	0.1	1.1	1.2
Interferons	1.76	0.4	-9.5	-11.6	-1.3	3.7	2.4
VEGF/VEGFR inhibitors (angiogenic growth factor)	1.54	0.1	-46.8	-8.6	-16.7	-30.2	-41.8
Serine-threonine kinase B-RAF (BRAF) inhibitors	1.35	<0.05	8.0	6.5	-2.1	3.7	1.5
CD20 inhibitors	1.35	0.5	-15.7	-0.4	-14.5	-0.9	-15.3
Anaplastic lymphoma kinase inhibitors (ALK)	1.29	<0.05	2.9	13.0	-7.7	-1.3	-9.0
Other monoclonal antibodies and antibody-drug conjugates	1.21	<0.05	0.3	15.7	-14.9	1.8	-13.3
Pyrimidine analogues	1.16	0.4	-24.6	-7.1	-4.8	-14.7	-18.8

ATC 1st level Subgroups	Gross *per capita* expenditure	DDD/ 1000 inhab. per day	Δ % 21-20				Δ % Average DDD cost
			Expen diture	DDD	Prices	Mix	
EGFR inhibitors (epidermal growth factor receptor)	1.12	<0.05	-3.7	-1.3	-2.3	-0.1	-2.4
Poly (ADP-RIBOSE) polymerase (PARP) inhibitors	1.06	<0.05	92.3	65.4	-11.3	31.0	16.3
Proteasome inhibitors	0.86	<0.05	-12.2	-11.3	-5.6	4.8	-1.0
Calcineurin inhibitors	0.86	0.4	-7.3	-4.2	0.0	-3.2	-3.2
Folic acid analogues	0.84	0.1	-19.8	0.9	-17.3	-3.8	-20.5
Taxanes	0.68	0.2	-8.2	4.2	-10.5	-1.6	-11.9
Mitogen-activated protein kinase (MEK) inhibitors	0.67	<0,05	-1.1	7.7	-1.7	-6.5	-8.1
Other immunostimulating agents	0.61	0.1	-12.0	-5.5	-10.5	4.0	-6.9
Cytostatics	0.52	<0.05	133.8	79.8	30.1	0.0	30.1
Anthracyclines and related substances	0.52	0.1	5.2	-0.6	0.7	5.0	5.8
Rapamycin and mammalian target of rapamycin (MTOR) inhibitors	0.48	<0.05	-2.2	11.2	-3.9	-8.5	-12.0
Colony stimulating factors	0.40	0.1	-26.2	-2.7	-9.6	-16.2	-24.2
Hedgehog pathway inhibitors	0.39	<0.05	4.2	28.0	0.2	-18.7	-18.6
Inhib. tyrosine kinase receptor vascular endothelial growth factor (VEGFR)	0.33	<0.05	859.6	920.5	-6.1	0.1	-6.0
Antiestrogens	0.31	0.2	-44.4	-12.2	-5.5	-33.0	-36.7
Other alkaloids derived from plants and other natural products	0.29	<0.05	-14.1	-0.1	-13.9	-0.1	-14.0
Vinca alkaloids and analogues	0.17	<0.05	-22.7	-9.6	-10.7	-4.2	-14.5
Antineoplastics in combination	0.15	<0.05	7.0	6.5	0.4	0.0	0.4
Epidermal growth factor receptor 2 tyrosine kinase inhibitors (HER2)	0.13	<0.05	-11.4	-11.2	-0.3	0.0	-0.3
Phosphatidylinositol-3-kinase (PI3k) inhibitors	0.12	<0.05	-26.7	-25.2	-0.2	-1.9	-2.1
Nitrogen mustard analogues	0.11	0.1	-12.2	-3.6	-2.0	-7.1	-9.0
J - General antimicrobials for systemic use	**32.77**	**5.7**	**-6.4**	**-9.5**	**-12.0**	**17.6**	**3.4**
Antivirals for treatment of HIV infections, combinations	8.29	1.4	2.3	0.4	-0.2	2.1	1.9
Influenza vaccines	3.07	0.8	97.3	13.7	1.5	70.8	73.5
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	2.36	0.1	138.0	14.2	-1.4	111.2	108.3
Human normal immunoglobulin	1.99	<0.05	-6.9	-9.5	1.8	1.4	2.9
Pneumococcal vaccines	1.93	0.1	-15.0	-13.0	0.7	-3.0	-2.4
Meningococcal vaccines	1.93	0.1	-6.3	-4.4	-1.3	-0.7	-2.0

ATC 1st level Subgroups	Gross *per capita* expenditure	DDD/ 1000 inhab. per day	Δ % 21-20 Expen diture	DDD	Prices	Mix	Δ % Average DDD cost
Antivirals for treatment of HCV infections	1.44	<0.05	-72.1	-13.0	-68.6	2.2	-67.9
Integrase inhibitors	1.43	0.3	-33.0	-30.7	0.0	-3.4	-3.4
Human papillomavirus vaccines	1.19	<0.05	21.6	21.9	-0.2	0.0	-0.2
Bacterial and viral vaccines in combination	0.89	0.1	-7.9	3.2	-7.9	-3.1	-10.8
Antibiotics	0.71	<0.05	29.3	27.2	0.1	1.5	1.6
Measles vaccines	0.61	<0.05	13.7	3.1	0.6	9.6	10.3
Combination of penicillins, incl. beta-lactamase inhibitors	0.61	0.4	-5.3	-8.1	-1.3	4.2	3.0
Third generation cephalosporins	0.59	0.3	-0.3	-21.4	-14.4	48.7	26.8
Other antibacterials	0.53	0.1	15.0	28.2	1.7	-11.8	-10.3
Other antivirals	0.42	<0.05	-2.8	-14.9	-0.9	15.2	14.2
Antiviral monoclonal antibodies	0.41	<0.05	8.9	9.1	0.0	-0.2	-0.2
Other antifungals for systemic use	0.36	<0.05	-19.7	9.7	-11.0	-17.7	-26.7
Varicella Zoster vaccines	0.35	<0.05	14.3	-0.5	0.3	14.5	14.9
Carbapenems	0.31	0.1	22.8	0.0	-2.7	26.2	22.8
Specific immunoglobulins	0.30	<0.05	-5.6	1.3	-3.4	-3.5	-6.8
Rotavirus diarrhea vaccines	0.29	<0.05	-3.7	10.2	2.0	-14.3	-12.6
Nucleosides and nucleotides inhibitors of reverse transcriptase	0.29	0.7	-20.6	-13.0	-15.9	8.5	-8.7
Glycopeptide antibacterials	0.26	<0.05	-12.1	-12.6	-2.9	3.5	0.5
Other cephalosporins and penems	0.24	<0.05	-42.9	-57.3	-62.6	258.3	33.6
Polymyxins	0.20	<0.05	-9.8	-4.7	-3.2	-2.2	-5.4
Non-nucleosides inhibitors of reverse transcriptase	0.18	0.1	-21.4	-21.1	-1.6	1.3	-0.3
Fluoroquinolones	0.12	0.2	-4.6	-25.2	2.6	23.8	27.6
Pertussis vaccines	0.11	<0.05	-4.3	0.6	-4.9	0.0	-4.9
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.11	0.1	-5.1	3.8	-2.1	-6.6	-8.6
Other aminoglycosides	0.10	<0.05	-6.9	-10.6	-1.7	6.0	4.1
B - Blood and blood-forming organs	**32.05**	**50.6**	**3.4**	**2.2**	**-3.0**	**4.3**	**1.2**
Coagulation factors	7.82	0.1	-5.1	-0.2	-0.5	-4.4	-4.9
Direct Xa factor inhibitors	7.48	12.5	4.8	14.7	-9.7	1.2	-8.6
Other antianemic preparations	2.51	3.6	-10.8	0.7	-7.7	-4.1	-11.4
Other hemostatics for systemic use	2.49	0.1	31.7	17.0	-5.1	18.5	12.5
Platelet aggregation inhibitors, excl. heparin	2.36	9.7	-2.7	3.1	-3.7	-2.1	-5.7
Heparins	2.11	6.5	9.8	-10.2	14.6	6.8	22.4

ATC 1st level Subgroups	Gross *per capita* expenditure	DDD/ 1000 inhab. per day	Δ % 21-20 Expenditure	DDD	Prices	Mix	Δ % Average DDD cost
Direct thrombin inhibitors	1.31	2.4	-12.8	-5.5	-6.2	-1.7	-7.8
Solutions affecting the electrolyte balance	0.96	6.8	5.0	0.7	4.5	-0.2	4.3
Parenteral nutritional solutions	0.81	0.7	-1.6	-7.4	-4.2	10.9	6.2
Other antithrombotics	0.73	0.5	40.3	16.3	4.1	15.8	20.6
Medicines used in hereditary angioedema	0.60	<0.05	48.7	105.9	3.8	-30.4	-27.8
Hypertonic solutions	0.53	0.1	0.3	7.9	-7.2	0.2	-7.0
Iron, parenteral preparations	0.41	0.1	29.4	29.0	0.4	0.0	0.3
Local hemostatics	0.39	<0.05	20.0	15.6	3.4	0.4	3.8
Blood substitutes and plasma protein fractions	0.33	0.1	33.3	27.6	0.2	4.3	4.5
Protease inhibitors	0.26	<0.05	8.7	-3.7	-1.5	14.5	12.9
Fibrinogen	0.25	<0.05	488.1	500.9	-0.9	-1.2	-2.1
Enzymes	0.25	<0.05	-8.4	-7.3	-0.3	-0.8	-1.1
Isotonic solutions	0.19	0.1	8.2	9.0	-1.3	0.6	-0.7
Hemofiltrates	0.11	<0.05	14.0	11.8	-2.1	4.3	2.0
A- Gastrointestinal system and metabolism	**19.39**	**34.0**	**13.0**	**2.8**	**-0.1**	**10.0**	**9.9**
Enzymes	5.28	<0.05	8.1	10.9	1.4	-3.6	-2.5
GLP-1 (glucagon-like peptide-1) receptor analogues	3.53	3.3	41.2	27.8	0.2	10.3	10.5
Insulins and injectable analogues, long-acting	3.00	6.8	3.6	3.9	-2.2	1.8	-0.4
Oral hypoglycemic agents, in combination	2.16	5.4	6.6	2.6	0.5	3.4	3.9
Dipeptil Peptidase Inhibitors 4 (DPP-4)	1.32	3.1	0.6	1.5	-0.5	-0.3	-0.8
Various products for gastrointestinal system and metabolism	1.23	<0.05	18.7	3.4	-2.9	18.3	14.9
SGLT2 cotransporter inhibitors (sodium-glucose type 2)	1.00	2.0	32.9	28.4	1.1	2.5	3.6
Bile acids and derivatives	0.32	0.1	85.3	-27.7	0.1	155.8	156.2
Proton pump inhibitors	0.24	3.6	13.5	-2.0	-1.3	9.1	15.8
Antibiotics	0.19	0.2	9.0	-1.5	1.2	9.3	10.6
Insulins and injectable analogues, fast-acting	0.17	0.9	-15.5	-9.7	-1.6	-4.9	-6.4
Serotonin antagonists (5-HT3)	0.17	0.1	6.5	-3.8	-2.5	13.1	10.8
Amino acids and derivatives	0.14	0.1	-1.2	-3.5	-1.4	3.3	2.4
Polyvitamins, not in combination	0.13	0.1	-21.9	-12.7	-10.5	0.0	-10.5
N- Central nervous system	**8.23**	**26.5**	**4.6**	**-0.7**	**0.5**	**4.8**	**5.4**
Other antipsychotics	2.94	2.7	2.8	2.7	0.1	-0.2	0.1
Other medicines for the nervous system	0.83	0.1	51.7	13.0	-2.6	37.7	34.2
Other antiepileptics	0.60	1.2	13.9	4.6	-0.8	9.7	8.8
DOPA and derivatives	0.52	0.2	-4.9	-14.6	-0.5	12.0	11.4

ATC 1st level Subgroups	Gross *per capita* expenditure	DDD/ 1000 inhab. per day	Δ % 21-20 Expenditure	Δ % 21-20 DDD	Δ % 21-20 Prices	Δ % 21-20 Mix	Δ % Average DDD cost
Medicines used in opioid addiction	0.45	3.3	-8.4	-2.9	-4.6	-1.1	-5.7
Diazepines, oxazepines, thiazepines and oxepins	0.34	3.5	-15.0	-4.5	7.7	-17.3	-11.0
Calcitonin gene-related peptide antagonists	0.33	0.2	774.5	138.0	310.3	-10.4	267.4
Other general anesthetics	0.23	0.3	-22.7	-35.4	-3.8	15.4	19.7
Halogenated hydrocarbons	0.19	<0.05	-0.1	10.7	-4.2	-5.8	-9.7
Amides	0.16	2.0	1.3	11.7	-6.6	-2.9	-9.3
Other hypnotics and sedatives	0.13	<0.05	-37.3	-22.3	-17.6	-2.0	-19.3
Other dopaminergic substances	0.13	0.1	16.6	16.6	0.5	-0.5	0.0
Anticholinesterases	0.12	1.0	-23.4	-4.9	-10.1	-10.4	-19.4
Indole derivatives	0.10	0.1	20.6	23.0	0.0	-1.9	-1.9
C - Cardiovascular system	**6.48**	**16.7**	**9.7**	**-5.2**	**-2.4**	**18.6**	**15.8**
Other lipid modifying agents	1.66	0.6	41.5	27.0	-1.4	13.0	11.4
Other cardiac preparations	1.49	2.4	0.1	0.4	-0.9	0.6	-0.2
Antihypertensives for pulmonary arterial hypertension	1.31	0.1	-11.6	-3.9	-4.8	-3.4	-8.1
Angiotensin II receptor blockers (ARBs), other combinations	1.14	0.8	30.0	30.0	0.0	0.0	0.0
Vasopressin antagonists	0.21	<0.05	10.4	31.7	-9.4	-7.5	-16.2
Other inotropic substances	0.13	<0.05	-8.0	9.9	-14.2	-2.4	-16.2
Adrenergics and dopaminergics	0.13	1.0	1.7	18.4	0.9	-14.9	-14.1
V - Various	**6.26**	**3.2**	**7.1**	**0.8**	**-0.1**	**6.3**	**6.2**
Iron chelating agents	1.53	0.1	-3.7	-3.2	-0.2	-0.5	-0.6
Water-soluble, nephrotropic, low osmotic radiological contrast media	1.26	0.1	11.2	9.5	0.2	1.3	1.6
Antidotes	0.93	0.1	21.5	21.6	0.1	-0.2	-0.1
Other diagnostic radiopharmaceuticals for cancer detection	0.43	<0.05	19.0	17.6	3.4	-2.2	1.2
Paramagnetic contrast agents	0.42	<0.05	13.8	14.3	-1.0	0.6	-0.5
Various therapeutic radiopharmaceuticals	0.27	<0.05	-13.1	-8.4	-9.5	4.8	-5.1
Detoxifying substances for cytostatic treatments	0.27	0.2	12.1	0.7	4.1	7.0	11.4
Pharmaceuticals for treatment of hyperkalemia and hyperphosphatemia	0.20	0.2	-14.5	-1.1	-10.4	-3.5	-13.5
Iodine-123I compounds	0.16	<0.05	32.4	37.0	-0.2	-3.1	-3.3
Various thyroid diagnostic radiopharmaceuticals	0.14	<0.05	-5.3	-4.4	5.4	-6.0	-0.9
Solvents and thinners, including cleaning solutions	0.12	2.2	18.6	-0.2	7.3	10.8	18.9
Allergenic extracts	0.11	0.2	2.2	-2.7	-0.5	5.5	5.0

ATC 1st level Subgroups	Gross *per capita* expenditure	DDD/ 1000 inhab. per day	Δ % 21-20 Expenditure	DDD	Prices	Mix	Δ % Average DDD cost
R- Respiratory system	**6.24**	**2.00**	**30.4**	**-8.2**	**-4.8**	**49.2**	**42.1**
Other preparations for the respiratory system	3.51	<0.05	57.2	91.5	-8.7	-10.1	-17.9
Other systemic drugs for obstructive airway disorders	2.12	0.2	9.7	10.6	-2.0	1.2	-0.8
Mucolytics	0.26	0.2	-3.4	-11.6	-0.3	9.5	9.2
H - Systemic hormonal preparations, excl. sex hormones	**4.24**	**4.7**	**-12.1**	**-16.1**	**-2.5**	**7.5**	**4.8**
Somatostatin and analogues	1.54	0.2	-6.6	-3.9	0.0	-2.8	-2.8
Somatropin and somatropin agonists	1.21	0.3	-11.8	-4.8	-5.7	-1.8	-7.4
Other antiparathyroid substances	0.58	0.4	-27.0	-2.1	-7.8	-19.2	-25.5
Other hormones of the anterior pituitary lobe and analogues	0.42	<0.05	-5.3	-5.6	0.3	0.0	0.3
Glycocorticoids	0.33	3.3	-7.1	-20.4	3.2	13.1	16.7
M - Musculo-skeletal system	**3.82**	**5.6**	**2.3**	**6.4**	**-5.9**	**2.3**	**-3.8**
Other drugs for musculoskeletal system disorders	1.86	<0.05	-0.1	-2.5	-3.3	6.0	2.5
Other drugs acting on bone structure and mineralization	1.38	3.9	22.4	15.2	-0.5	6.8	6.2
Other muscle relaxants with peripheral action	0.23	<0.05	16.8	18.7	-0.9	-0.8	-1.6
Other quaternary ammonium compounds	0.15	0.2	-57.0	-39.0	-42.4	22.3	-29.5
S - Sensory organs	**3.03**	**2.0**	**40.9**	**-0.4**	**0.7**	**40.6**	**41.5**
Antineovascularization substances	2.17	0.1	44.1	27.6	0.7	12.2	12.9
Corticosteroids, not in combination	0.43	0.2	13.9	15.7	0.1	-1.6	-1.5
D - Dermatologicals	**2.03**	**8.9**	**57.5**	**-12.6**	**-5.7**	**91.1**	**80.1**
Substances for dermatitis, excluding corticosteroids	1.61	0.2	86.0	99.9	-10.5	4.0	-7.0
Biguanides and amidines	0.10	1.6	8.9	-4.8	9.2	4.8	14.5
G - Genito urinary system and sex hormones	**1.36**	**2.5**	**11.8**	**11.7**	**-6.3**	**6.6**	**0.0**
Gonadotropins	0.95	0.1	27.4	22.1	-4.9	9.8	4.4
Medicines used in erectile dysfunctions	0.12	0.3	-28.5	-2.4	-9.0	-19.5	-26.7
Prostaglandins	0.10	0.1	-9.3	-5.4	-6.2	2.3	-4.1
P - Antiparasitic, insecticide and repellent pharmaceuticals	**0.03**	**<0.05**	**-32.0**	**-97.0**	**-35.2**	**3472.9**	**2145.7**

Table 3.19 2021 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	NHS *per capita* expenditure	%	Δ % 21-20	DDD/ 1000 inhab. per day	%	Δ % 21-20	Average DDD cost	Δ % 21-20
L- Antineoplastic and immunomodulatory drugs	**107.59**		**4.6**	11.1		**5.1**	**26.50**	**-0.2**
pembrolizumab	6.41	6.0	32.0	0.2	1.7	53.3	93.03	-13.7
lenalidomide	5.47	5.1	1.2	0.1	1.1	9.6	122.78	-7.4
daratumumab	4.07	3.8	14.9	0.1	0.7	43.8	149.45	-19.9
nivolumab	3.70	3.4	-1.8	0.1	0.8	-0.5	110.72	-1.1
ibrutinib	3.39	3.2	18.8	0.1	0.6	19.1	129.92	0.0
dimethyl fumarate	2.64	2.5	6.2	0.2	2.0	6.4	32.88	0.1
osimertinib	2.48	2.3	33.2	<0.05	0.4	31.5	148.33	1.6
pertuzumab	2.44	2.3	-10.3	0.1	0.5	14.9	112.39	-21.7
fingolimod	2.32	2.2	-3.3	0.1	1.1	-1.4	53.90	-1.6
eculizumab	2.15	2.0	8.7	<0.05	0.1	10.0	766.98	-0.9
ustekinumab	2.05	1.9	10.7	0.3	2.8	17.8	17.88	-5.8
enzalutamide	2.02	1.9	16.2	0.1	0.6	19.5	83.50	-2.5
abiraterone	1.90	1.8	3.5	0.1	0.5	3.8	85.31	-0.1
secukinumab	1.89	1.8	0.6	0.2	1.5	4.4	30.60	-3.4
ruxolitinib	1.87	1.7	15.9	<0.05	0.4	14.8	110.85	1.2
palbociclib	1.86	1.7	-24.5	0.1	0.7	-4.1	68.37	-21.1
natalizumab	1.74	1.6	2.9	0.1	0.9	16.3	50.03	-11.3
ocrelizumab	1.73	1.6	40.2	0.1	0.9	40.3	48.32	0.1
adalimumab	1.56	1.4	-13.0	0.6	5.8	18.1	6.60	-26.1
etanercept	1.50	1.4	-15.4	0.3	2.6	1.3	14.14	-16.2
nintedanib	1.32	1.2	17.9	<0.05	0.4	17.4	76.34	0.7
interferon beta 1a	1.22	1.1	-10.7	0.3	2.8	-11.0	10.63	0.6
vedolizumab	1.21	1.1	15.6	0.1	0.9	16.4	32.52	-0.4
nilotinib	1.17	1.1	-3.2	<0.05	0.2	-2.9	131.33	0.0
abatacept	1.14	1.1	0.5	0.1	0.6	0.5	49.36	0.3
trastuzumab	1.11	1.0	-28.4	0.2	1.6	-2.5	17.59	-26.4
dabrafenib	1.11	1.0	1.7	<0.05	0.3	1.9	105.73	0.1
rituximab	1.09	1.0	-20.2	0.4	4.0	0.2	6.68	-20.1
trastuzumab emtansine	1.07	1.0	4.3	<0.05	0.1	13.8	193.74	-8.1
ribociclib	1.06	1.0	43.1	<0.05	0.4	49.6	68.02	-4.1
tocilizumab	1.02	1.0	4.9	0.1	1.0	5.7	25.46	-0.5
teriflunomide	1.02	0.9	10.3	0.1	0.9	11.3	27.15	-0.7
alectinib	1.02	0.9	2.0	<0.05	0.2	10.3	162.41	-7.3
leuprorelin	1.01	0.9	2.3	0.2	1.6	-5.7	15.96	8.8
atezolizumab	1.00	0.9	26.0	<0.05	0.2	42.1	107.94	-11.1
bevacizumab	1.00	0.9	-57.5	0.1	0.8	-8.4	29.48	-53.5
canakinumab	0.98	0.9	12.1	<0.05	0.2	1.8	157.13	10.4
pirfenidone	0.97	0.9	-4.7	<0.05	0.4	-4.4	64.42	-0.1
olaparib	0.96	0.9	85.3	0.0	0.2	58.5	132.20	17.2
ixekizumab	0.96	0.9	37.6	0.1	0.8	38.0	30.30	0.0
dasatinib	0.92	0.9	-4.3	<0,05	0.2	-2.4	101.53	-1.7
triptorelin	0.87	0.8	-1.3	0.9	7.9	-2.7	2.73	1.7

ATC 1st level Subgroups	NHS *per capita* expenditure	%	Δ % 21-20	DDD/ 1000 inhab. per day	%	Δ % 21-20	Average DDD cost	Δ % 21-20
golimumab	0.87	0.8	-18.0	0.1	1.1	-2.4	19.61	-15.8
venetoclax	0.87	0.8	55.4	<0.05	0.1	48.1	158.44	5.2
pomalidomide	0.86	0.8	0.3	<0.05	0.1	21.2	246.11	-17.1
pemetrexed	0.82	0.8	-19.6	<0.05	0.3	12.7	69.57	-28.5
tacrolimus	0.79	0.7	-6.1	0.4	3.2	-2.4	6.14	-3.5
imatinib	0.71	0.7	-1.5	0.1	0.8	-2.0	21.78	0.8
J- General antimicrobials for systemic use	**32.77**		**-5.7**	**5.7**		**-8.6**	**15.63**	**3.4**
remdesivir	2.25	6.9	>100	<0.05	0.3	>100	374.71	-1.3
emtricitabine/tenofovir alafenamide /bictegravir	1.81	5.5	35.5	0.2	4.3	35.9	19.96	0.0
thirteen-valent pneumococcal vaccine	1.74	5.3	-16.9	0.1	1.7	-17.2	48.84	0.7
emtricitabine/rilpivirine/tenofovir alafenamide	1.52	4.6	-12.8	0.2	3.6	-12.6	19.96	0.0
inactivated virus, surface antigen, adjuvanted influenza vaccine	1.51	4.6	>100	0.3	4.8	28.1	14.99	185.3
B group meningococcal vaccine	1.50	4.6	-7.7	0.1	1.2	-6.8	62.29	-0.7
human normal immunoglobulin by extravascular administration	1.20	3.7	-6.1	<0.05	0.2	-10.1	352.39	4.8
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.19	3.6	22.5	<0.05	0.8	23.0	69.31	-0.2
dolutegravir/lamivudine	1.08	3.3	>100	0.2	3.1	>100	16.60	0.0
dolutegravir/abacavir/ lamivudine	1.05	3.2	-23.1	0.1	2.3	-22.9	21.48	0.0
inactivated, split virus tetravalent influenza vaccine	0.99	3.0	11.3	0.4	6.4	-5.5	7.34	18.1
dolutegravir	0.95	2.9	-37.7	0.2	2.8	-37.5	16.42	0.0
emtricitabine/tenofovir alafenamide/ darunavir/cobicistat	0.82	2.5	-2.5	0.1	1.8	-2.2	21.85	0.0
human normal immunoglobulin by intravascular administration	0.78	2.4	-6.5	<0.05	0.1	-6.5	319.70	0.3
amphotericin B	0.71	2.2	30.2	<0.05	0.3	28.5	100.39	1.6
glecaprevir/pibrentasvir	0.71	2.2	-15.7	<0.05	0.3	-11.0	107.91	-5.0
sofosbuvir/velpatasvir	0.63	1.9	-84.0	<0.05	0.4	-3.0	71.64	-83.5
measles mumps rubella and varicella vaccine	0.57	1.8	18.1	<0.05	0.6	15.7	46.80	2.4
hexavalent vaccine	0.56	1.7	-18.5	0.1	0.9	-9.5	29.43	-9.6
emtricitabine/tenofovir alafenamide	0.51	1.6	-25.7	0.1	2.1	-25.5	11.29	0.0
piperacillin/tazobactam	0.50	1.5	-3.7	0.1	2.4	0.9	10.10	-4.3

ATC 1st level Subgroups	NHS *per capita* expenditure	%	Δ % 21-20	DDD/ 1000 inhab. per day	%	Δ % 21-20	Average DDD cost	Δ % 21-20
raltegravir	0.48	1.5	-19.5	0.1	2.4	-18.9	9.51	-0.5
ceftazidime/avibactam	0.47	1.4	10.2	<0.05	0.1	36.6	194.45	-19.1
dolutegravir/rilpivirine	0.44	1.3	68.6	0.1	1.1	69.1	18.31	0.0
palivizumab	0.41	1.3	9.7	<0.05	0.0	10.2	807.14	-0.2
darunavir/cobicistat	0.41	1.3	-22.1	0.1	1.6	-21.9	12.25	0.0
B - Blood and blood-forming organs	**32.05**		**4.1**	**50.6**		**3.2**	**1.74**	**1.2**
rivaroxaban	3.03	9.4	-1.9	5.4	10.8	7.7	1.53	-8.7
apixaban	2.70	8.4	0.4	4.4	8.7	11.2	1.69	-9.5
edoxaban	1.75	5.5	33.8	2.7	5.4	47.8	1.76	-9.2
enoxaparin	1.70	5.3	12.2	5.7	11.2	-9.1	0.82	23.7
octocog alfa	1.66	5.2	-29.7	<0.05	0.0	-28.9	332.46	-0.8
dabigatran	1.29	4.0	-12.6	2.4	4.8	-4.5	1.46	-8.2
emicizumab	1.27	4.0	68.1	<0.05	0.0	75.6	753.71	-4.0
epoetin alfa	1.06	3.3	-9.5	2.1	4.1	14.1	1.39	-20.5
efmorocotog alfa	1.03	3.2	-0.6	<0.05	0.0	-0.5	357.17	0.2
ticagrelor	0.97	3.0	-1.1	1.1	2.1	-2.7	2.45	1.9
darbepoetin alfa	0.91	2.8	-4.5	0.4	0.8	-2.0	5.89	-2.3
eltrombopag	0.81	2.5	5.5	<0.05	0.1	15.3	49.37	-8.3
albutrepenonacog alfa	0.80	2.5	9.7	<0.05	0.0	10.2	1086.69	-0.1
sodium chloride	0.77	2.4	6.0	5.8	11.4	1.4	0.37	4.9
treprostinil	0.59	1.9	-4.2	<0.05	0.0	-2.5	548.24	-1.4
activated heptacog alfa (recombinant DNA coagulation factor VII)	0.59	1.9	-28.3	<0.05	0.0	-28.2	4082.80	0.1
moroctocog alfa	0.59	1.8	-22.8	<0.05	0.0	-20.4	333.43	-2.8
epoetin zeta	0.45	1.4	-17.9	1.1	2.1	-13.2	1.15	-5.2
damoctocog alfa pegol	0.44	1.4	>100	<0.05	0.0	>100	329.94	1.5
romiplostim	0.41	1.3	14.8	<0.05	0.0	15.6	50.40	-0.4
carboxymaltose iron	0.41	1.3	30.4	0.1	0.3	30.3	8.46	0.4
lonoctogoc alfa	0.40	1.2	-0.7	<0.05	0.0	0.8	320.34	-1.2
glucose/sodium chloride/calcium chloride/ magnesium chloride/sodium bicarbonate/sodium lactate	0.39	1.2	-1.7	0.1	0.2	10.4	10.04	-10.7
A- Gastrointestinal system and metabolism	**19.39**		**13.8**	**34.0**		**3.8**	**1.56**	**9.9**
dulaglutide	1.88	9.7	44.5	2.3	6.8	41.8	2.23	2.2
insulin glargine	1.55	8.0	-0.4	4.7	13.7	3.9	0.91	-3.9
recombinant human acid alglucosidase	1.29	6.7	6.9	<0.05	0.0	7.2	1062.23	0.0
agalsidase alfa	0.88	4.6	6.2	<0.05	0.0	-0.2	1692.37	6.8
semaglutide	0.87	4.5	>100	0.2	0.5	>100	13.33	-8.7
agalsidase beta	0.77	4.0	28.1	<0.05	0.0	28.7	483.60	-0.2
imiglucerase	0.77	4.0	-2.0	<0.05	0.0	-1.7	1096.50	0.1
insulin degludec	0.72	3.7	6.3	1.4	4.2	9.3	1.38	-2.5
sitagliptin	0.60	3.1	1.1	1.4	4.0	4.5	1.21	-3.0
insulin degludec/liraglutide	0.57	2.9	22.4	0.4	1.2	21.8	3.98	0.7

ATC 1st level Subgroups	NHS *per capita* expenditure	%	Δ % 21-20	DDD/ 1000 inhab. per day	%	Δ % 21-20	Average DDD cost	Δ % 21-20
sitagliptin/metformin	0.54	2.8	-9.6	1.4	4.1	-6.6	1.06	-3.0
linagliptin	0.54	2.8	5.3	1.3	3.8	5.4	1.14	0.2
idursulfase	0.53	2.7	6.4	<0.05	0.0	0.6	2877.24	6.0
dapagliflozin	0.45	2.3	38.9	0.9	2.7	39.1	1.33	0.2
dapagliflozin/metformin	0.45	2.3	22.9	0.9	2.7	23.2	1.33	0.0
liraglutide	0.44	2.3	-26.1	0.5	1.3	-26.3	2.65	0.7
migalastat	0.37	1.9	11.9	<0.05	0.0	12.2	465.68	0.0
empagliflozin	0.36	1.9	9.5	0.8	2.3	6.2	1.30	3.4
exenatide	0.33	1.7	40.6	0.3	1.0	45.6	2.66	-3.2
eliglustat	0.31	1.6	10.1	<0.05	0.0	10.4	622.68	0.0
velaglucerase alfa	0.28	1.5	6.9	<0.05	0.0	0.5	1096.94	6.6
elosulfase alfa	0.27	1.4	6.2	<0.05	0.0	6.5	2992.00	0.0
N- Central nervous system	**8.23**		**5.4**	**26.5**		**0.2**	**0.85**	**5.4**
paliperidone	1.53	18.5	2.6	0.8	3.1	3.7	5.10	-0.8
aripiprazole	1.08	13.2	9.2	1.1	4.2	5.5	2.64	3.7
levodopa/carbidopa	0.49	5.9	-2.6	0.1	0.4	-7.0	12.91	5.0
patisiran	0.45	5.5	>100	0.0	0.0	>100	516.03	0.0
risperidone	0.31	3.8	-11.7	0.7	2.5	-3.2	1.27	-8.5
methadone	0.31	3.7	-2.8	2.4	9.0	-2.2	0.35	-0.3
lacosamide	0.18	2.2	21.7	0.1	0.3	19.4	6.19	2.2
tafamidis	0.18	2.2	-20.6	0.0	0.0	-3.4	226.37	-17.5
propofol	0.17	2.0	-28.4	0.3	1.1	-36.9	1.56	13.8
erenumab	0.16	2.0	>100	0.1	0.4	74.0	4.00	284.5
quetiapine	0.16	2.0	-14.7	1.5	5.6	-1.9	0.30	-12.8
levetiracetam	0.15	1.9	-11.7	0.4	1.6	-7.2	1.00	-4.6
dexmedetomidine	0.13	1.6	-36.9	0.0	0.0	-21.6	31.02	-19.3
sevoflurane	0.13	1.5	0.4	0.0	0.0	7.5	59.44	-6.4
opicapone	0.12	1.4	21.4	0.1	0.4	20.9	3.26	0.7
rivastigmine	0.10	1.3	-23.1	0.4	1.5	-10.4	0.73	-13.8
olanzapine	0.10	1.2	-9.6	1.6	6.0	-2.9	0.17	-6.6
galcanezumab	0.10	1.2	>100	0.0	0.2	>100	6.67	132.9
perampanel	0.10	1.2	12.4	0.1	0.2	13.7	4.61	-0.9
buprenorphine/naloxone	0.10	1.2	-26.3	0.2	0.6	-7.6	1.56	-20.1
lurasidone	0.09	1.1	23.1	0.1	0.5	27.4	2.09	-3.1
paracetamol	0.09	1.1	-5.7	3.4	12.8	17.1	0.07	-19.2
C - Cardiovascular system	**6.48**		**10.5**	**16.7**		**-4.3**	**1.06**	**15.8**
ranolazine	1.40	21.6	1.5	1.3	8.0	1.8	2.86	0.0
sacubitril/valsartan	1.14	17.5	30.9	0.8	4.6	31.3	4.08	0.0
macitentan	0.94	14.5	0.7	0.0	0.2	0.9	87.71	0.0
evolocumab	0.86	13.3	51.5	0.2	1.1	52.1	13.10	-0.2
alirocumab	0.66	10.1	39.9	0.2	1.3	48.0	8.44	-5.3
V - Various	**6.26**		**7.8**	**3.2**		**1.8**	**5.41**	**6.2**
deferasirox	1.40	22.3	-2.9	0.0	1.1	-2.8	109.79	0.1
sugammadex	0.80	12.8	20.3	0.0	0.8	22.9	81.39	-1.9
iomeprol	0.51	8.2	17.3	0.0	0.6	14.1	72.53	3.0
fluorodeoxyglucose (18F)	0.32	5.2	14.7	0.0	0.1	18.5	401.07	-2.9
iodinaxol	0.23	3.6	3.7	0.0	0.3	6.7	75.88	-2.5
lutetium oxodotreotide (177Lu)	0.22	3.6	-12.1	0.0	0.0	-0.4	14141.40	-11.5

ATC 1st level Subgroups	NHS *per capita* expenditure	%	Δ % 21-20	DDD/ 1000 inhab. per day	%	Δ % 21-20	Average DDD cost	Δ % 21-20
gadobutrol	0.20	3.2	17.6	0.0	0.2	20.8	77.71	-2.3
iopromide	0.18	2.9	6.7	0.0	0.3	7.9	56.52	-0.8
iodine ioflupane (123I)	0.16	2.6	33.3	0.0	0.0	38.3	839.38	-3.3
rasburicase	0.14	2.3	17.5	0.0	0.0	15.0	806.55	2.5
tecnetium pertecnetate (99 mTc)	0.13	2.0	-4.4	0.0	0.0	-5.6	331.97	1.6
iobitridol	0.12	1.9	8.9	0.0	0.2	6.4	48.68	2.6
iopamidol	0.11	1.8	24.0	0.0	0.4	15.4	26.37	7.8
deferiprone	0.11	1.7	-5.4	0.0	0.6	-1.6	16.10	-3.6
lanthanum	0.09	1.4	-19.9	0.0	1.2	-5.7	6.09	-14.8
R- Respiratory system	**6.24**		**31.3**	**2.0**		**-7.4**	**8.65**	**42.1**
ivacaftor	1.31	21.0	87.5	0.0	0.4	>100	495.55	-26.8
lumacaftor/ivacaftor	1.18	18.9	-15.0	0.0	0.4	-13.2	418.52	-1.8
omalizumab	0.97	15.5	9.8	0.1	5.2	9.3	25.66	0.7
elexacaftor/tezacaftor/ ivacaftor	0.86	13.7	0.0	0.0	0.4	0.0	292.59	-
mepolizumab	0.63	10.1	-1.3	0.1	2.9	8.6	30.15	-8.9
H - Systemic hormonal preparations, excl. sex hormones	**4.24**		**-11.5**	**4.7**		**-15.3**	**2.47**	**4.8**
somatropin	1.20	28.4	-11.2	0.3	5.8	-3.9	12.19	-7.4
octreotide	0.75	17.7	-1.9	0.1	2.3	-1.8	18.71	0.2
lanreotide	0.67	15.9	-3.3	0.1	2.1	-2.4	19.11	-0.6
pegvisomant	0.42	9.9	-4.7	0.0	0.4	-4.7	69.51	0.3
etelcalcetide	0.38	8.9	12.3	0.1	2.2	13.4	10.02	-0.7
M - Musculo-skeletal system	**3.82**		**3.0**	**5.6**		**7.4**	**1.88**	**-3.8**
nusinersen	1.32	34.7	-14.8	0.0	0.2	-11.0	405.64	-4.0
denosumab	1.19	31.1	15.6	3.8	69.2	16.3	0.85	-0.3
ataluren	0.31	8.2	9.2	0.0	0.0	9.1	1581.39	0.3
Clostridium botulinum type A toxin	0.23	5.9	17.6	0.0	0.1	19.9	120.91	-1.6
onasemnogene abeparvovec	0.22	5.6	0.0	0.0	0.0	0.0	254807.45	-
S - Sensory organs	**3.03**		**41.9**	**2.0**		**0.5**	**4.05**	**41.5**
aflibercept	1.31	43.4	55.0	0.0	0.4	55.7	492.66	-0.1
ranibizumab	0.82	27.1	28.9	0.1	5.0	27.0	21.81	1.8
dexamethasone	0.39	13.0	16.7	0.2	11.9	16.7	4.43	0.3
voretigene neparvovec	0.21	6.8	0.0	0.0	0.0	0.0	298014.15	-
brolucizumab	0.04	1.3	0.0	0.0	0.0	0.0	398.27	-
D - Dermatologicals	**2.03**		**58.5**	**8.9**		**-11.7**	**0.62**	**80.1**
dupilumab	1.61	79.2	88.0	0.2	1.7	111.1	29.01	-10.7
silver sulfadiazine	0.06	2.9	6.3	0.7	7.8	4.4	0.23	2.1
chlorhexidine/isopropyl alcohol	0.06	2.8	1.0	0.1	0.7	4.8	2.66	-3.3
povidone iodine	0.06	2.7	-3.5	0.9	9.8	27.8	0.18	-24.3
sodium hypochlorite	0.04	1.7	-34.7	2.4	27.1	-35.6	0.04	1.8

ATC 1st level Subgroups	NHS *per capita* expenditure	%	Δ % 21-20	DDD/ 1000 inhab. per day	%	Δ % 21-20	Average DDD cost	Δ % 21-20
G - Genito urinary system and sex hormones	**1.36**		**12.5**	**2.5**		**12.8**	**1.51**	**0.0**
follitropin alfa from recombinant DNA	0.37	26.9	28.6	0.1	2.2	34.0	18.30	-3.7
menotropin	0.23	17.2	23.0	0.0	1.9	24.3	13.47	-0.8
follitropin alfa/lutropin alfa	0.16	11.8	43.6	0.0	0.1	-48.5	214.23	179.3
dinoprostone	0.09	6.8	-5.8	0.0	1.9	-5.7	5.35	0.1
follitropin beta	0.08	6.0	25.4	0.0	0.3	25.3	27.22	0.4
testosterone	0.07	5.1	11.7	0.1	5.7	18.0	1.33	-5.1
tadalafil	0.06	4.7	-32.4	0.2	8.0	-1.9	0.89	-30.9
P - Antiparasitic, insecticide and repellent pharmaceuticals	**0.03**		**-31.5**	**0.0**		**-96.9**	**11.45**	**>100**
atovaquone	0.02	74.3	9.9	0.0	63.6	24.4	13.39	-11.4
permethrin	<0.005	18.1	25.8	0.0	20.2	35.8	10.29	-7.0
pentamidine isethionate	<0.005	2.9	-1.9	0.0	3.2	-1.5	10.51	-0.2
metronidazole	<0.005	2.5	-4.5	0.0	86.5	-5.6	0.34	1.4
dihydroartemisinin/ piperaquine tetraphosphate	<0.005	1.9	68.0	0.0	3.0	70.1	7.28	-1.0

Table 3.20 First thirty active ingredients purchased by public health facilities in terms of expenditure: comparison 2021-2020

ATC	Active substance	Expenditure *(million)*	%*	Per capita expenditure	Rank 2021	Rank 2020	Average DDD cost	Δ % 21-20
L	pembrolizumab	379.8	2.7	6.41	1	2	93.03	-13.7
L	lenalidomide	323.9	2.3	5.47	2	1	122.78	-7.4
L	daratumumab	240.8	1.7	4.07	3	5	149.45	-19.9
L	nivolumab	219.0	1.6	3.70	4	4	110.72	-1.1
L	ibrutinib	201.1	1.5	3.39	5	7	129.92	0.0
B	rivaroxaban	179.4	1.3	3.03	6	6	1.53	-8.7
B	apixaban	160.0	1.2	2.70	7	9	1.69	-9.5
L	dimethyl fumarate	156.5	1.1	2.64	8	10	32.88	0.1
L	osimertinib	147.2	1.1	2.48	9	18	148.33	1.6
L	pertuzumab	144.4	1.0	2.44	10	8	112.39	-21.7
L	fingolimod	137.6	1.0	2.32	11	12	53.90	-1.6
J	remdesivir	133.3	1.0	2.25	12	74	374.71	-1.3
L	eculizumab	127.6	0.9	2.15	13	16	766.98	-0.9
L	ustekinumab	121.4	0.9	2.05	14	19	17.88	-5.8
L	enzalutamide	119.5	0.9	2.02	15	24	83.50	-2.5
L	abiraterone	112.6	0.8	1.90	16	20	85.31	-0.1
L	secukinumab	111.9	0.8	1.89	17	17	30.60	-3.4
A	dulaglutide	111.1	0.8	1.88	18	44	2.23	2.2
L	ruxolitinib	110.7	0.8	1.87	19	27	110.85	1.2
L	palbociclib	110.0	0.8	1.86	20	11	68.37	-21.1
J	emtricitabine/ tenofovir alafenamide/ bictegravir	107.3	0.8	1.81	21	42	19.96	0.0
B	edoxaban	103.7	0.7	1.75	22	43	1.76	-9.2
J	thirteen-valent pneumococcal vaccine	103.3	0.7	1.74	23	15	48.84	0.7
L	natalizumab	103.3	0.7	1.74	24	25	50.03	-11.3
L	ocrelizumab	102.3	0.7	1.73	25	46	48.32	0.1
B	enoxaparin	100.7	0.7	1.70	26	32	0.82	23.7
B	octocog alfa	98.6	0.7	1.66	27	13	332.46	-0.8
D	dupilumab	95.2	0.7	1.61	28	77	29.01	-10.7
L	adalimumab	92.2	0.7	1.56	29	21	6.60	-26.1
A	insulin glargine	92.1	0.7	1.55	30	28	0.91	-3.9
	Total	**4,346.6**	**31.4**					
	Total expenditure by public health facilities	**13,883.2**						

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

Table 3.21 2021 regional ranks by expenditure relating to the first thirty active ingredients purchased by public health facilities

Rank	Active substance	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	1	1	4	3	1	1	1	1	1	1	1	1	6	1	1	1	3	1
2	lenalidomide	2	3	2	2	1	1	2	2	2	2	2	2	2	2	3	3	2	2	1	2
3	daratumumab	3	0	3	3	3	2	7	3	3	4	6	8	3	5	4	5	4	9	5	6
4	nivolumab	5	10	5	5	43	6	9	5	4	3	9	3	4	4	11	2	9	11	7	5
5	ibrutinib	4	18	4	4	7	5	6	6	6	6	3	6	5	10	8	11	3	5	16	9
6	rivaroxaban	8	7	9	11	11	4	3	8	9	10	7	4	10	11	5	6	10	3	10	10
7	apixaban	7	4	10	154	2	245	4	7	8	7	4	9	7	13	24	10	11	18	22	8
8	dimethyl fumarate	11	15	17	14	17	8	10	23	13	5	8	11	11	6	10	32	12	10	15	13
9	osimertinib	13	32	8	16	21	7	5	13	11	9	11	10	9	20	46	28	23	44	50	17
10	pertuzumab	17	5	15	9	41	12	12	11	12	13	12	14	17	9	13	4	13	7	19	35
11	fingolimod	9	11	16	8	10	14	28	10	29	32	23	15	13	3	15	8	6	25	14	26
12	remdesivir	14	6	13	125	105	26	55	4	10	16	18	7	6	8	130	72	26	6	32	25
13	eculizumab	6	2	14	6	34	31	16	29	7	11	15	12	58	17	17	23	37	4	31	55
14	ustekinumab	24	75	31	12	23	22	14	26	24	21	20	24	26	27	30	7	8	13	35	4
15	enzalutamide	19	45	37	21	6	15	8	25	15	15	10	13	22	16	33	17	21	26	24	33
16	abiraterone	26	8	32	7	102	17	26	18	25	14	32	25	23	19	31	21	16	29	40	27
17	secukinumab	10	23	43	15	44	23	21	34	27	18	33	17	54	14	12	9	14	17	8	31
18	dulaglutide	28	126	883	69	12	9	20	30	35	26	29	35	24	30	47	30	5	24	9	3
19	ruxolitinib	25	63	25	48	68	20	34	16	28	36	14	32	21	37	14	13	7	33	25	20
20	palbociclib	39	16	28	13	39	21	15	21	16	31	24	18	12	22	58	19	43	54	42	21
21	emtricitabine/tenofovir alafenamide/bictegravir	18	46	6	35	27	69	38	15	37	8	21	29	14	89	366	44	51	94	234	61
22	edoxaban	32	27	19	33	15	11	22	22	18	19	31	23	36	49	84	47	38	794	45	32
23	thirteen-valent pneumococcal vaccine	145	34	18	23	22	16	17	33	19	69	43	34	20	29	32	20	32	41	53	12
24	natalizumab	16	48	40	17	16	13	23	17	22	39	53	64	37	25	2	49	47	146	37	11
25	ocrelizumab	22	12	44	18	33	19	27	12	21	24	102	46	38	12	1	22	48	106	33	48
26	enoxaparin	21	51	216	62	5	10	35	20	5	12	5	5	66	44	16	42	106	19	57	73
27	octocog alfa	87	1020	30	149	8	118	277	78	53	84	183	68	8	24	51	16	15	46	4	15
28	dupilumab	23	47	21	37	32	34	49	44	47	29	46	16	49	42	18	14	30	23	39	44
29	adalimumab	88	134	50	22	31	36	11	54	34	55	30	36	64	18	20	12	22	27	2	39
30	insulin glargine	30	28	26	51	24	24	31	57	36	41	19	44	53	34	34	37	61	35	29	16

Table 3.22 First thirty active ingredients* with highest variation in expenditure on medicines purchased by public health facilities compared to the previous year: comparison 2021-2020

ATC	Active substance	Per capita expenditure	Δ % 21-20	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
J	dolutegravir/lamivudine	1.08	413.2	0.2	414.6	16.60	0.0
J	inactivated virus, surface antigen, adjuvanted influenza vaccine	1.51	264.4	0.3	28.1	14.99	185.3
J	remdesivir	2.25	157.9	0.0	161.9	374.71	-1.3
A	semaglutide	0.87	154.8	0.2	179.7	13.33	-8.7
D	dupilumab	1.61	88.0	0.2	111.1	29.01	-10.7
R	ivacaftor	1.31	87.5	0.0	156.7	495.55	-26.8
L	olaparib	0.96	85.3	0.0	58.5	132.20	17.2
B	emicizumab	1.27	68.1	0.0	75.6	753.71	-4.0
L	venetoclax	0.87	55.4	0.0	48.1	158.44	5.2
S	aflibercept	1.31	55.0	0.0	55.7	492.66	-0.1
C	evolocumab	0.86	51.5	0.2	52.1	13.10	-0.2
A	dulaglutide	1.88	44.5	2.3	41.8	2.23	2.2
L	ribociclib	1.06	43.1	0.0	49.6	68.02	-4.1
L	ocrelizumab	1.73	40.2	0.1	40.3	48.32	0.1
L	ixekizumab	0.96	37.6	0.1	38.0	30.30	0.0
J	emtricitabine/tenofovir alafenamide/bictegravir	1.81	35.5	0.2	35.9	19.96	0.0
B	edoxaban	1.75	33.8	2.7	47.8	1.76	-9.2
L	osimertinib	2.48	33.2	0.0	31.5	148.33	1.6
L	pembrolizumab	6.41	32.0	0.2	53.3	93.03	-13.7
C	sacubitril/valsartan	1.14	30.9	0.8	31.3	4.08	0.0
S	ranibizumab	0.82	28.9	0.1	27.0	21.81	1.8
A	agalsidase beta	0.77	28.1	0.0	28.7	483.60	-0.2
L	atezolizumab	1.00	26.0	0.0	42.1	107.94	-11.1
J	human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.19	22.5	0.0	23.0	69.31	-0.2
V	sugammadex	0.80	20.3	0.0	22.9	81.39	-1.9
L	ibrutinib	3.39	18.8	0.1	19.1	129.92	0.0
L	nintedanib	1.32	17.9	0.0	17.4	76.34	0.7
L	enzalutamide	2.02	16.2	0.1	19.5	83.50	-2.5
L	ruxolitinib	1.87	15.9	0.0	14.8	110.85	1.2
L	vedolizumab	1.21	15.6	0.1	16.4	32.52	-0.4

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

Table 3.23 First thirty active ingredients* with highest reduction in expenditure on medicines purchased by public health facilities compared to the previous year: comparison 2021-2020

ATC	Active substance	Per capita expenditure	Δ % 21-20	DDD/1000 inhab. per day	Δ % 21-20	Average DDD cost	Δ % 21-20
L	bevacizumab	1.00	-57.5	0.1	-8.4	29.48	-53.5
J	dolutegravir	0.95	-37.7	0.2	-37.5	16.42	0.0
B	octocog alfa	1.66	-29.7	0.0	-28.9	332.46	-0.8
L	trastuzumab	1.11	-28.4	0.2	-2.5	17.59	-26.4
L	palbociclib	1.86	-24.5	0.1	-4.1	68.37	-21.1
J	dolutegravir/abacavir/lamivudine	1.05	-23.1	0.1	-22.9	21.48	0.0
L	rituximab	1.09	-20.2	0.4	0.2	6.68	-20.1
L	pemetrexed	0.82	-19.6	0.0	12.7	69.57	-28.5
L	golimumab	0.87	-18.0	0.1	-2.4	19.61	-15.8
J	thirteen-valent pneumococcal vaccine	1.74	-16.9	0.1	-17.2	48.84	0.7
L	etanercept	1.50	-15.4	0.3	1.3	14.14	-16.2
R	lumacaftor/ivacaftor	1.18	-15.0	0.0	-13.2	418.52	-1.8
M	nusinersen	1.32	-14.8	0.0	-11.0	405.64	-4.0
L	adalimumab	1.56	-13.0	0.6	18.1	6.60	-26.1
J	emtricitabine/rilpivirine/tenofovir alafenamide	1.52	-12.8	0.2	-12.6	19.96	0.0
B	dabigatran	1.29	-12.6	2.4	-4.5	1.46	-8.2
H	somatropin	1.20	-11.2	0.3	-3.9	12.19	-7.4
L	interferon beta 1a	1.22	-10.7	0.3	-11.0	10.63	0.6
L	pertuzumab	2.44	-10.3	0.1	14.9	112.39	-21.7
B	epoetin alfa	1.06	-9.5	2.1	14.1	1.39	-20.5
J	B group meningococcal vaccine	1.50	-7.7	0.1	-6.8	62.29	-0.7
J	human normal immunoglobulin by intravascular administration	0.78	-6.5	0.0	-6.5	319.70	0.3
J	human normal immunoglobulin by extravascular administration	1.20	-6.1	0.0	-10.1	352.39	4.8
L	tacrolimus	0.79	-6.1	0.4	-2.4	6.14	-3.5
L	pirfenidone	0.97	-4.7	0.0	-4.4	64.42	-0.1
B	darbepoetin alfa	0.91	-4.5	0.4	-2.0	5.89	-2.3
L	dasatinib	0.92	-4.3	0.0	-2.4	101.53	-1.7
L	fingolimod	2.32	-3.3	0.1	-1.4	53.90	-1.6
L	nilotinib	1.17	-3.2	0.0	-2.9	131.33	0.0
V	deferasirox	1.40	-2.9	0.0	-2.8	109.79	0.1

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

Table 3.24 First thirty active ingredients by average cost per day of therapy for medicines purchased by public health facilities*: comparison 2021-2020

ATC	Active substance	Average DDD cost	Δ % 21-20	Per capita expenditure	Δ % 21-20	DDD/1000 inhab. per day	Δ % 21-20
A	agalsidase alfa	1692.4	6.8	0.88	6.2	0.0	-0.2
A	imiglucerase	1096.5	0.1	0.77	-2.0	0.0	-1.7
B	albutrepenonacog alfa	1086.7	-0.1	0.80	9.7	0.0	10.2
A	recombinant human acid alglucosidase	1062.2	0.0	1.29	6.9	0.0	7.2
L	eculizumab	767.0	-0.9	2.15	8.7	0.0	10.0
B	emicizumab	753.7	-4.0	1.27	68.1	0.0	75.6
R	ivacaftor	495.6	-26.8	1.31	87.5	0.0	156.7
S	aflibercept	492.7	-0.1	1.31	55.0	0.0	55.7
A	agalsidase beta	483.6	-0.2	0.77	28.1	0.0	28.7
R	lumacaftor/ivacaftor	418.5	-1.8	1.18	-15.0	0.0	-13.2
M	nusinersen	405.6	-4.0	1.32	-14.8	0.0	-11.0
J	remdesivir	374.7	-1.3	2.25	157.9	0.0	161.9
B	efmorocotog alfa	357.2	0.2	1.03	-0.6	0.0	-0.5
J	human normal immunoglobulin by extravascular administration	352.4	4.8	1.20	-6.1	0.0	-10.1
B	octocog alfa	332.5	-0.8	1.66	-29.7	0.0	-28.9
J	human normal immunoglobulin by intravascular administration	319.7	0.3	0.78	-6.5	0.0	-6.5
R	elexacaftor/tezacaftor/ivacaftor	292.6	-	0.86	0.0	0.0	0.0
L	pomalidomide	246.1	-17.1	0.86	0.3	0.0	21.2
L	trastuzumab emtansine	193.7	-8.1	1.07	4.3	0.0	13.8
L	alectinib	162.4	-7.3	1.02	2.0	0.0	10.3
L	venetoclax	158.4	5.2	0.87	55.4	0.0	48.1
L	canakinumab	157.1	10.4	0.98	12.1	0.0	1.8
L	daratumumab	149.5	-19.9	4.07	14.9	0.1	43.8
L	osimertinib	148.3	1.6	2.48	33.2	0.0	31.5
L	olaparib	132.2	17.2	0.96	85.3	0.0	58.5
L	nilotinib	131.3	0.0	1.17	-3.2	0.0	-2.9
L	ibrutinib	129.9	0.0	3.39	18.8	0.1	19.1
L	lenalidomide	122.8	-7.4	5.47	1.2	0.1	9.6
L	pertuzumab	112.4	-21.7	2.44	-10.3	0.1	14.9
L	ruxolitinib	110.9	1.2	1.87	15.9	0.0	14.8

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

Table 3.25 First thirty active ingredients purchased by public health facilities in terms of consumption: comparison 2021-2020

ATC	Active substance	DDD/ 1000 inhab. per day	Δ % 21-20	Rank 2021	Rank 2020	Per capita expenditure	Δ % 21-20	Average DDD cost	Δ % 21-20
B	sodium chloride	5.8	1.4	1	2	0.77	6.04	0.37	4.9
B	clopidogrel	5.8	13.9	2	3	0.12	9.94	0.06	-3.2
B	enoxaparin	5.7	-9.1	3	1	1.70	12.22	0.82	23.7
B	rivaroxaban	5.4	7.7	4	5	3.03	-1.89	1.53	-8.7
B	cyanocobalamin	5.0	-0.8	5	4	0.01	0.49	<0.005	1.5
A	insulin glargine	4.7	3.9	6	6	1.55	-0.38	0.91	-3.9
B	apixaban	4.4	11.2	7	8	2.70	0.39	1.69	-9.5
C	furosemide	4.0	-8.5	8	7	0.05	-1.93	0.03	7.5
M	denosumab	3.8	16.3	9	10	1.19	15.64	0.85	-0.3
N	paracetamol	3.4	17.1	10	11	0.09	-5.69	0.07	-19.2
A	cholecalciferol	2.9	10.0	11	12	0.01	-10.72	0.01	-18.7
B	edoxaban	2.7	47.8	12	16	1.75	33.77	1.76	-9.2
B	dabigatran	2.4	-4.5	13	13	1.29	-12.56	1.46	-8.2
D	sodium hypochlorite	2.4	-35.6	14	9	0.04	-34.65	0.04	1.8
N	methadone	2.4	-2.2	15	14	0.31	-2.77	0.35	-0.3
A	dulaglutide	2.3	41.8	16	21	1.88	44.53	2.23	2.2
B	epoetin alfa	2.1	14.1	17	17	1.06	-9.54	1.39	-20.5
V	sodium chloride	1.8	-1.9	18	15	0.05	13.62	0.07	16.2
C	ramipril	1.6	-8.5	19	18	<0.005	1.41	<0.005	11.2
N	olanzapine	1.6	-2.9	20	19	0.10	-9.63	0.17	-6.6
A	pantoprazole	1.5	16.4	21	30	0.12	26.70	0.22	9.2
N	quetiapine	1.5	-1.9	22	22	0.16	-14.72	0.30	-12.8
A	insulin degludec	1.4	9.3	23	28	0.72	6.26	1.38	-2.5
C	atorvastatin	1.4	-12.4	24	20	<0.005	-74.13	<0.005	-70.4
A	sitagliptin/metformin	1.4	-6.6	25	23	0.54	-9.58	1.06	-3.0
N	lidocaine	1.4	7.6	26	32	0.08	4.06	0.17	-3.0
B	clopidogrel/acetylsalicylic acid	1.4	2.3	27	26	0.14	-29.03	0.28	-30.4
A	sitagliptin	1.4	4.5	28	29	0.60	1.07	1.21	-3.0
C	ranolazine	1.3	1.8	29	27	1.40	1.53	2.86	0.0
A	linagliptin	1.3	5.4	30	34	0.54	5.31	1.14	0.2

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

Therapeutic categories with highest prescription

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, in addition to the epidemiological classification, the temporal trend of consumption and expenditure along with national and regional data; where possible, the indicators are analysed of exposure and adherence to drug treatment in the population as well as the prescribing profiles in General Practice. 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 drugs dispensed through local pharmacies, including “on-behalf” distribution (so-called Art.50 flow/Health Card). The data relating to epidemiology and prescribing profiles in General Practice were obtained through a network of General Practitioners (GPs) bringing together all information relating to patients to Health Search-IQVIA Health LPD.

The categories that will be examined in depth are the following:

- **Antineoplastic and immunomodulating agents**
  - Antineoplastics pharmaceuticals
  - 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
  - Anti-HCV antivirals
  - Antifungals for systemic use
- **Blood and blood-forming organs**
  - Anticoagulants
  - Coagulation factors
  - Platelet aggregation inhibitors
- **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**
- **Medicines used in critically ill patients**

Medicines used in the treatment of COVID-19 patients

For categorization, please refer to Appendix 3.

3.1 Antineoplastic and immunomodulating agents

Antineoplastic and immunomodulating agents are the therapeutic category with the highest public expenditure in 2021, amounting to 6,633 million euros (28.2% of overall expenditure), with a 4.5% increase compared to the previous year (Box. Main indices of expenditure, consumption and exposure).

The overall per capita expenditure on such medicines was 111.98 euros, mainly due to the purchase by public health facilities (107.59 euros per capita), thus recording a sharp increase compared to the previous year (+4.6%). On the contrary, the contribution by the approved care regime was lower (4.38 euros per capita) (Table 3.1).

Consumption for this category of drugs was 17.4 DDD/1000 inhabitants per day, with a 2.9% increase compared to 2020 (Table 3.2), which confirms the growing trend of the last eight 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 gender 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 (4.9% compared to 3.8% 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 (24.5 euros per capita compared to 13.8 euros in women).

As for approved care regime, per capita expenditure was 4.38 euros, up 1.1% compared to 2020; this trend was caused by a reduction in consumption (-1.7%) and a slight shift towards more expensive medicines (mix effect: +2.7%); however, prices are stable (+0.1%) (Table 3.9). Under this supply regime, aromatase inhibitors are the first category both in terms of expenditure (2.23 euros per capita) and consumption (3.0 DDD), followed by other substances with immunosuppressive action and calcineurin inhibitors (belonging to the class of immunosuppressants), with a per capita expenditure respectively of 0.78 euros and 0.55 euros and 1.6 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 (1.41 euros) and by consumption (1.7 DDD) (Table 3.10). It is the only antineoplastic drug within the first 30 active ingredients for expenditure under approved care regime (Table 3.11), and, together with ciclosporine and methotrexate, it is listed within the first thirty active ingredients with the highest average DDD cost (Table 3.13). Cyclosporine, with a reduction of 9.2%, is listed within the first thirty active ingredients with the greatest reduction in the approved care expenditure (Table 3.15). However, no active ingredient in this therapeutic category is included in the top 30 active ingredients with the highest consumption under approved care regime (Table 3.16).

As regards the purchases by public health facilities, an increase was reported in expenditure (+3.9%) and consumption (+4.1%) compared to 2020, although a 6.6% reduction in prices was also recorded. This category reported a shift towards more expensive medicines, as in 2020 (mix effect: +6.2%) (Table 3.18). Selective immunosuppressants are the first category in terms of per capita expenditure (14.95 euros), with a 10.3% increase compared to the previous year; they also record an increase in consumption (+9.4%) and a shift towards more expensive drugs (mix effect: +3.2%), while reporting a reduction in prices (-2.3%). PD-1/PDL-1 inhibitors, which include nivolumab and pembrolizumab, rank second (12.05 euros), while other immunosuppressants (10.00 euros) rank third by expenditure. For these two categories, increases were recorded both in terms of expenditure and consumption compared to the previous year. Especially for PD-1/PDL-1 inhibitors, an increase is recorded by 20.5% in expenditure and by 32.5% in consumption, although both prices and mix effect are decreasing (respectively -8.1% and -1.0%). The average cost per day of therapy recorded a -9.1% reduction.

On the other hand, expenditure on anti-TNF-alpha is reduced by 14.0% although consumption is up by 10.3%. The expenditure trend is attributable to the reduction in prices (-9.2%), due to the presence on the market of biosimilars of some molecules belonging to these sub-categories. Similarly, against a slight increase in consumption (+1.1%), the expenditure on HER2 inhibitors has decreased, given the significant reduction in prices (-17.3%) caused by the presence on the market of trastuzumab biosimilars, a molecule belonging to to this sub-category.

In 2021, pembrolizumab, surpassing lenalidomide, is the drug with the highest value of per capita expenditure (6.41 euros), which alone accounts for 6.0% of expenditure on this category (Table 3.19). This active ingredient recorded a 32% increase in expenditure and a 53% increase in terms of DDD compared to the previous year, driven by the numerous reimbursed indication extensions. Similarly to 2020, this drug recorded a reduction in the average DDD cost, although with a smaller change compared to 2020 (-13.7% compared to 38.6%), owing to the negotiated discounts. In third rank for expenditure is daratumumab, an anti CD38 monoclonal antibody, authorized, for example, as monotherapy for patients with relapsed/refractory multiple myeloma or not eligible for stem cell treatment; with a per capita expenditure of 4.07 euros, it recorded an increase in both expenditure (+ 14.9%) and consumption (+ 43.8%), reducing its average DDD cost by -19.9%. Pembrolizumab, lenalidomide and daratumumab also rank within the top three most expensive drugs purchased by public health facilities (Table 3.20). As many as 13 active ingredients belonging to the category of antineoplastics and immunomodulators appear in the list of the first thirty drugs with the greatest variation in expenditure compared to the previous year; the first is olaparib, which records a variation of 85.3%, against a per capita cost of 0.96 euros (Table 3.22). Bevacizumab is the first active ingredient with the greatest reduction in expenditure in 2021 compared to the previous year, recording a variation of -57.5%, against a smaller reduction in consumption (-8.4%; Table 3.23). 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 767 euros, stable compared to 2020. The other 13 active ingredients have an average cost that varies between a maximum of 246.1 euros and a minimum of 110.9 euros (Table 3.24)

No drug belonging to the antineoplastic and immunomodulatory category is listed within the first thirty drugs purchased by public facilities for consumption, calculated as DDD per 1000 inhabitants per day (Table 3.25).

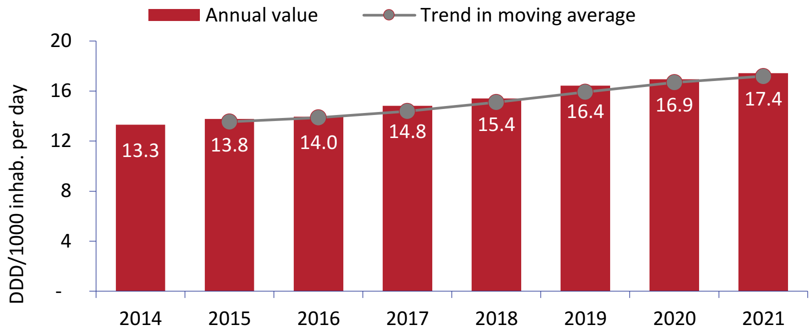
For further information on the use of medicines related to the same therapeutic area, analyzes have been developed on the historical series of consumption by active ingredient and by Region. These analyzes concerned oncological and immunosuppressive medicines and immunomodulatory drugs (Tables 3.1.1 and following).

Main indices of expenditure, consumption and exposure

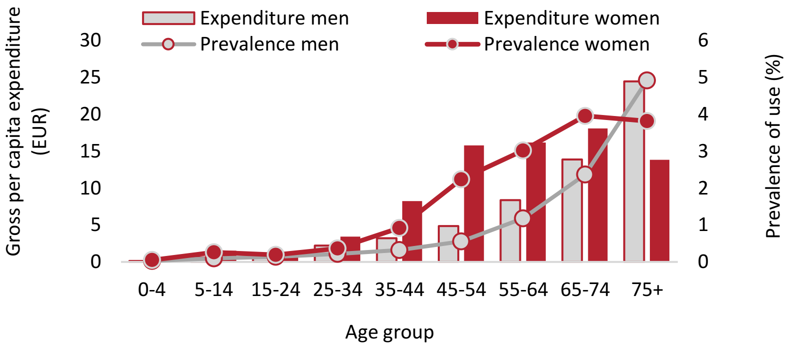
Antineoplastic and immunomodulating agents

Public expenditure* in million euros (% on total)	**6,633.1**	**(28.2)**
Δ % 2021-2020		4.5
Regional range of gross per capita expenditure:	82.4	134.4
DDD/1000 inhab. per day* (% on total)	**17.4**	**(1.3)**
Δ % 2021-2020		2.9
Regional range of DDD/1000 inhab. per day:	12.2	20.7

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



Distribution by age and gender of expenditure, prevalence of use and consumption under approved care regime and "on-behalf" distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.1	0.2	0.2	0.1	0.2	0.1
5-14	0.6	1.5	1.0	0.4	1.4	0.9
15-24	1.1	1.2	1.1	0.6	0.8	0.7
25-34	2.2	3.4	2.8	1.0	1.8	1.4
35-44	3.2	8.2	5.7	1.5	6.3	3.9
45-54	4.8	15.8	10.4	2.6	16.9	9.8
55-64	8.4	16.2	12.4	5.3	19.0	12.3
65-74	13.9	18.1	16.1	10.3	24.0	17.5
75+	24.5	13.8	18.1	26.6	21.1	23.3

3.1.1 Antineoplastic medicines

Epidemiological framework

Neoplastic diseases are characterized by an uncontrolled proliferation of cells that originates from mutations of genes involved in cellular regulation. According to the WHO, various primary prevention measures can be implemented, such as campaigns against tobacco use (responsible for 25% of cancer deaths), vaccinations for known carcinogenic viral agents (e.g. HBV, HPV), as well as secondary prevention measures through screening campaigns on the population at risk (e.g. mammography every two years in women between 50 and 69 years, search for faecal occult blood in people over 50s). It is estimated that at least 7 million deaths from cancer could be avoided over the next decade through prevention and screening programs; in fact in Europe, the United States and other Western countries, about 40% of new cancer cases and 50% of cancer deaths are potentially preventable as they are caused by modifiable risk factors.

In Italy, behavioural (and modifiable) risk factors are held responsible for approximately 65,000 cancer deaths each year; in both sexes, smoking is the risk factor with the greatest impact, with at least 43,000 annual cancer deaths attributable. As we know, the scenario determined by the SARS-CoV-2 epidemic caused a slowdown in the implementation of screening programs, especially during the initial stages of the emergency. This has had an effect on the early diagnosis of many diseases, including cancer. In summary, the data show a decrease in the number of operated cancers in 2020, both for breast cancer (the most frequent cancer in the female gender, accounting for about 30% of all female cancers) and for colorectal cancer (12% prevalence in the male gender).

National data on consumption and expenditure

In the last eight years, expenditure on cancer drugs has almost doubled (+96%), going from 34.8 euros in 2014 to 68.2 euros in 2021 and recording a +10.1% average annual increase. At the same time, the average DDD cost increased by 66%, shifting from 10.9 to 18.1 euros (Figure 3.1.1a). Consumption shows a 2.4% average annual increase, with 10.3 DDD/1000 inhabitants per day in 2021 (Table 3.1.1a). The first three categories with the highest expenditure are monoclonal antibodies (mAbs). Immune check-point inhibitors rank first (12.33 euros), with a significant increase in expenditure (+21.6%) and consumption (+33.8%), despite a reduction in the average DDD cost (-8.8%) compared to 2020. The reasons for this increasing 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 positive results of therapeutic improvement.

MAbs blocking growth factors (6.22 euros) rank second, with a decrease in all the indicators considered (expenditure -25.2%; consumption -1.4%; average DDD cost -24.0%) compared to 2020, due to the presence of biosimilars for some drugs of this class (bevacizumab and trastuzumab). CAR-Ts are the category with the highest expenditure variation (>100%), and also record a 65% increase in the average DDD cost. Finally, an increase is recorded in expenditure (+20.7%) and in the average DDD cost (25.3%) of the anti-androgens used in the treatment of prostate cancer, related to the availability of new drugs.

The trend of the individual active ingredients follows the trend of the categories; in fact, pembrolizumab (6.41 euros) and daratumumab (4.07 euros) are at the top of the list. Daratumab has the highest average DDD cost (149.45 euros), although down by almost 20% compared to the previous year, while the lowest-cost active ingredient is palbociclib (68.37 euros), down by 21.1%.

Analyzing the regional per capita expenditure compared to the national average value (68.23 euros), the Regions of the Centre tend to spend more (73.30 euros) than the Regions of the South (70.65 euros) and the North (64.38 euros) (Table 3.1.1b). All Regions, with the exception of Sardinia and Basilicata, record an increase in per capita expenditure in 2021 compared to the previous year. The Marche Region shows the highest consumption (11.8 DDD/1000 inhabitants per day), while Emilia Romagna has the highest increase in consumption compared to the previous year (+11.4%). The average DDD cost for this category of drugs in 2021 was 18.08 euros, with a 3.8% increase compared to the previous year; the greatest increases are recorded in Valle d'Aosta (+32.8%) and in Lazio (+11.0%).

Figure 3.1.1a Antineoplastic medicines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

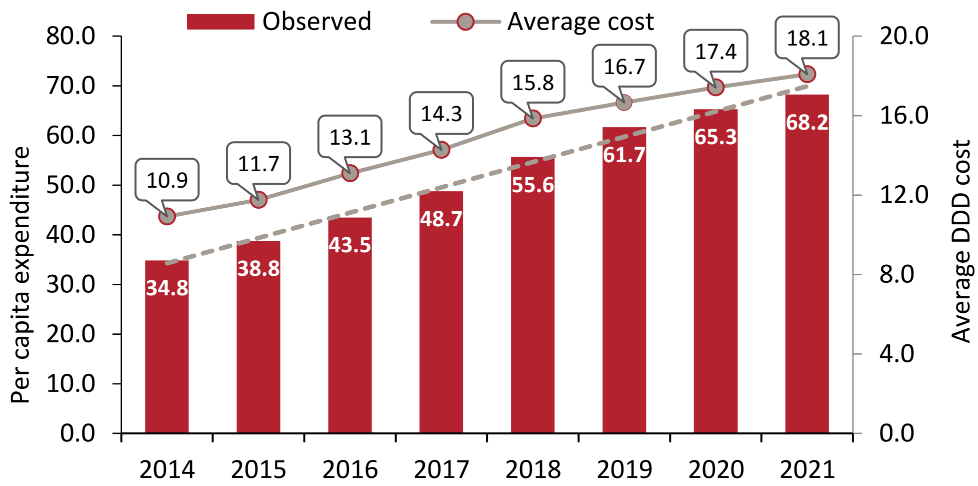


Table 3.1.1a Antineoplastic medicines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Monoclonal antibodies inhibiting immune check points	12.33	21.6	50.5	0.3	33.8	94.2	103.78	-8.8
Monoclonal antibodies blocking growth factors	6.22	-25.2	-3.9	0.4	-1.4	4.9	47.22	-24.0
Monoclonal antibodies acting on specific targets	5.89	5.8	9.3	0.5	5.2	4.4	30.11	0.8
Cytostatic antineoplastics - other cytostatics	4.61	16.5	11.8	0.5	3.3	4.6	27.99	13.0
Endocrine therapy - aromatase inhibitors	4.26	2.0	7.7	3.7	2.5	5.8	3.18	-0.2
Multitarget tyrosin kinase inhibitors in comb. with VEGFR	4.15	8.6	10.7	0.1	8.9	16.0	106.32	0.0
CDK protein kinase inhibitors	3.44	0.5	-	0.1	19.1	-	68.39	-15.4
BRC-ABL tyrosin kinase inhibitors	3.42	-2.5	-4.9	0.2	-1.0	3.4	58.28	-1.3
Bruton tyrosine kinase (BTK) inhibitors	3.40	18.8	-	0.1	19.1	-	129.92	0.0
EGFR tyrosin kinase inhibitors	2.75	20.7	11.5	0.1	3.7	4.4	124.19	16.8
Endocrine therapy – antiandrogens	2.40	20.7	37.7	0.8	-3.4	-4.9	8.09	25.3
Cytostatic antineoplastics – antimetabolites	2.13	-21.6	-3.7	0.6	-6.0	-5.0	9.44	-16.4
Endocrine therapy - hormones and GnRH analogues	1.96	0.5	0.1	1.1	-3.0	1.4	4.83	3.9
JAK tyrosin kinase inhibitors	1.87	15.9	102.5	0.0	14.8	107.5	110.85	1.2
Monoclonal antibodies conjugated with drugs	1.62	-4.0	27.2	0.0	9.6	33.3	219.20	-12.2
BRAF tyrosin kinase inhibitors	1.35	8.8	15.3	0.0	7.5	34.5	111.08	1.5
ALK tyrosin kinase inhibitors	1.29	3.6	-	0.0	14.1	-	150.96	-9.0
CAR-T	0.82	>100	-	0.0	77.4	-	196697.03	65.1
Cytotoxic antineoplastics - products of natural derivation – taxanes	0.68	-7.6	3.6	0.2	5.2	3.1	10.26	-11.9
MEK tyrosin kinase inhibitors	0.67	-0.4	-	0.0	8.8	-	58.43	-8.1
Cytotoxic antineoplastics - cytotoxic antibiotics - anthracyclines and related substances	0.52	5.9	0.0	0.1	0.4	-1.2	13.45	5.8
MTOR protein kinase inhibitors	0.48	-1.4	-10.9	0.0	12.3	-5.5	93.44	-12.0

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Cytotoxic antineoplastics - products of natural derivation – others	0.48	-16.6	-0.8	0.1	-9.8	-1.1	23.52	-7.2
Other protein kinase inhibitors	0.45	68.9	-	0.0	65.0	-	413.25	2.6
Endocrine therapy - antiestrogens	0.39	-39.5	-4.5	1.0	-8.4	-2.6	1.10	-33.7
Cytostatic antineoplastics - alkylating agents	0.37	1.8	-9.5	0.2	2.0	-4.0	5.62	0.1
Combination of antineoplastic agents	0.15	7.7	-	0.0	7.5	-	3819.32	0.4
Cytostatic antineoplastics – platinum compounds	0.09	-10.6	-2.3	0.2	0.2	0.0	1.11	-10.6
Cytotoxic antineoplastics – other cytotoxic antibiotics	0.05	119.2	-8.1	0.0	47.0	-3.5	3.25	49.5
Antineoplastic medicines	**68.23**	**4.6**	**10.1**	**10.3**	**1.0**	**2.4**	**18.08**	**3.8**
pembrolizumab	6.41	32.0	-	0.2	53.3	-	93.03	-13.7
daratumumab	4.07	14.9	-	0.1	43.8	-	149.45	-19.9
nivolumab	3.70	-1.8	-	0.1	-0.5	-	110.72	-1.1
ibrutinib	3.39	18.8	-	0.1	19.1	-	129.92	0.0
osimertinib	2.48	33.2	-	0.0	31.5	-	148.33	1.6
pertuzumab	2.44	-10.3	38.0	0.1	14.9	41.6	112.39	-21.7
enzalutamide	2.02	16.2	105.1	0.1	19.5	119.3	83.50	-2.5
abiraterone	1.90	3.5	10.9	0.1	3.8	13.5	85.31	-0.1
ruxolitinib	1.87	15.9	102.5	0.0	14.8	107.5	110.85	1.2
palbociclib	1.86	-24.5	-	0.1	-4.1	-	68.37	-21.1

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	58.38	10.1	15.85	60.07	10.0	16.47	2.9	-0.7	3.9	8.6	2.1	6.3
Valle d'Aosta	43.74	8.7	13.81	47.63	7.1	18.34	8.9	-17.8	32.8	9.0	-0.7	9.7
Lombardy	56.89	10.3	15.16	59.82	10.2	16.05	5.1	-0.4	5.9	10.9	1.4	9.4
Province of Bolzano	71.79	8.5	23.14	72.13	8.9	22.26	0.5	4.7	-3.8	9.9	4.0	5.6
Province of Trento	46.84	9.5	13.45	51.54	9.7	14.55	10.0	2.0	8.2	9.7	3.4	6.1
Veneto	61.50	10.2	16.52	64.38	10.2	17.24	4.7	0.6	4.4	9.8	2.4	7.2
Friuli VG	72.62	11.1	17.95	75.58	11.0	18.86	4.1	-0.7	5.1	8.9	1.7	7.1
Liguria	70.91	10.7	18.07	73.93	10.8	18.74	4.3	0.9	3.7	11.0	2.4	8.4
Emilia R.	67.79	9.4	19.66	73.08	10.5	19.08	7.8	11.4	-3.0	11.0	3.0	7.7
Tuscany	68.14	10.3	18.00	68.28	10.1	18.60	0.2	-2.8	3.3	7.3	1.8	5.4
Umbria	78.44	11.0	19.54	86.05	11.2	21.02	9.7	2.3	7.6	12.6	3.8	8.4
Marche	75.91	11.8	17.57	77.26	11.8	17.99	1.8	-0.3	2.4	9.8	2.9	6.7
Lazio	67.04	10.6	17.25	73.60	10.5	19.14	9.8	-0.8	11.0	11.9	2.0	9.7
Abruzzo	70.68	11.0	17.55	75.33	10.9	18.87	6.6	-0.6	7.5	8.5	2.1	6.2
Molise	66.19	9.6	18.76	66.30	10.2	17.82	0.2	5.7	-5.0	11.6	4.4	6.9
Campania	78.22	10.4	20.62	80.04	10.7	20.43	2.3	3.5	-0.9	10.2	3.7	6.3
Puglia	71.56	10.4	18.80	72.75	10.5	19.02	1.7	0.8	1.2	9.0	2.0	6.9
Basilicata	77.57	10.3	20.56	74.21	9.7	20.90	-4.3	-5.6	1.6	9.2	3.2	5.7
Calabria	63.40	9.5	18.25	67.41	10.0	18.42	6.3	5.7	0.9	11.4	3.7	7.4
Sicily	55.49	9.4	16.05	59.40	9.5	17.08	7.1	0.9	6.4	11.1	3.1	7.7
Sardinia	68.16	11.4	16.37	67.44	11.0	16.85	-1.1	-3.6	2.9	8.6	3.6	4.8
Italy	**65.27**	**10.2**	**17.41**	**68.23**	**10.3**	**18.08**	**4.6**	**1.0**	**3.8**	**10.1**	**2.4**	**7.5**
North	61.27	10.1	16.60	64.38	10.2	17.21	5.1	1.6	3.7	10.2	2.1	7.9
Centre	69.41	10.7	17.70	73.30	10.6	18.96	5.6	-1.1	7.1	10.1	2.2	7.7
South and Islands	68.46	10.2	18.37	70.65	10.3	18.75	3.2	1.4	2.1	10.0	3.1	6.7

Key message

- Data on consumption of antineoplastic medicines are consistent with a consolidating use in clinical practice, especially as regards monoclonal antibodies acting on immune check-point mechanisms. This **upward consumption trend** is likely to increase, especially in light of the probable further extensions of indications of use, in combination with other drugs in various solid tumors, which reported positive results of therapeutic improvement.
- Another relevant phenomenon is the **increase in the expenditure and average cost per day of therapy of anti-androgens** used in the treatment of prostate cancer, related to the availability of new drugs; in the future this data could lead to an increase in consumption linked to the use of these drugs in therapeutic stages earlier than the disease stage.
- It is noteworthy that, compared to 2020, the expenditure on antibodies blocking the action of growth factors (-25.2%) has decreased much more significantly than the reduction in consumption (expenditure -25.2%; consumption -1.4%), due to the presence of biosimilars of bevacizumab and trastuzumab.
- There is still a **variability in per capita expenditure between the Centre-South and the North**, which could be due to the still widespread phenomenon of mobility between the Regions.

References

- AIRTUM Working Group. I numeri del cancro in Italia. I Registri Tumori di popolazione in Italia: la Banca Dati AIRTUM, 2020.
- IARC. International Agency for Research on Cancer. WHO outlines steps to save 7 million lives from cancer. Press release N° 279, 4 February 2020. Available at the address https://www.iarc. who.int/wp-content/uploads/2020/02/pr279_E.pdf/
- Serraino D, Carreras G, Fratino L. Fattori di rischio per i tumori: impatto su incidenza e mortalità. I numeri del cancro in Italia. I Registri Tumori di popolazione in Italia: la Banca Dati AIRTUM, 2020.

3.1.2 Immunosuppressants and immunomodulating agents

Epidemiological framework

Immunosuppressive drugs inhibit the immune response, therefore, in addition to being used in various anticancer therapies, they are often used in organ transplants and in autoimmune diseases. According to the National Transplant Center, 71 organ transplants from 49 COVID-19 positive donors were carried out in Italy during the pandemic emergency. A specific experimental program active since November 2020 made it possible to carry out organ transplants from donors who tested positive for coronavirus and who died from other causes, on recipients who were positive at the time of transplant or already immunized due to previous disease or vaccination.

The immunosuppressive and immunomodulatory drugs used for the treatment of autoimmune diseases, from a therapeutic point of view, are mainly directed against the cytokine pathways, including tumor necrosis factor (TNF-α), a pro-inflammatory cytokine implicated in the pathogenesis of various intestinal (Crohn's disease), cutaneous (plaque psoriasis) and joint (rheumatoid arthritis) diseases. One of the drawbacks of the therapeutic use of immunosuppressants is the increased risk of serious infections, which is particularly important during the SARS-CoV-2 pandemic. With press release no. 664, AIFA published a list of the main immunosuppressive drugs in order to facilitate the selection of people requiring the additional dose of vaccine.

Autoimmune diseases are characterized by an exaggerated immune response leading to damage and dysfunction of specific organs and tissues; despite the enormous progress in the diagnosis and treatment of these diseases, there is still a scarcity of data on the etiological events causing their development, although such data show an interaction between genetic, environmental and lifestyle factors. The overall prevalence of autoimmunity is about 3-5% in the general population. However, this indicator varies according to the different autoimmune diseases, age, sex, and other demographic characteristics. These diseases have significant gender differences in terms of pathogenesis, prevalence, clinical picture, response to therapy and, therefore, survival. In general, women show stronger humoral and cellular immune responses than men and this is thought to play a major role in the different susceptibility to the development of autoimmune diseases.

National data on consumption and expenditure

In the past eight years expenditure on immunosuppressants and immunomodulating agents has increased by about 43%, shifting from 21.5 euros per capita in 2014 to 30.8 euros in 2021, with a 5.3% average annual increase. At the same time, the average DDD cost has increased by 14.2%, going from 24.4 to 20.9 euros (Figure 3.1.1a). Consumption shows a 8.9% average annual increase, with 4.2 DDD/1000 inhabitants per day in 2021 (Table 3.1.2a). In 2021, the two categories with the greatest expenditure are interleukin inhibitors (8.53 euros), up 18.7% compared to 2020, and other immunosuppressants (7.34 euros), whose values instead remain almost stable compared to the previous year (+0.1%). TNF-α inhibitors, despite increasing in consumption (+11.4%) in 2021, record a decrease in expenditure (-13.4%), owing to the reduction in the average DDD cost (-22.0%) compared to the previous year, maybe due to the use of biosimilar drugs. The calcineurin inhibitors subgroup also shows a reduction of all the indicators considered. On the other hand, immunosuppressive monoclonal antibodies show increases in both expenditure (+12.3%) and consumption (+21.0%), against a reduction in the average DDD cost (-7.0%).

Analyzing the trend of the individual active ingredients, lenalidomide records the highest expenditure value, confirming the growing trend in the last 8 years for both expenditure and consumption (CAGR 2014-2021: expenditure +12.4%, consumption +16.5%), although the average DDD cost recorded a 7.4% decrease last year. The largest increases in expenditure were observed for canakinumab (+12.1%), vedolizumab (+15.6%) and ustekinumab (+10.7%), indicated in the treatment of moderate to severe active ulcerative colitis and in patients with Crohn's disease, who have shown an inadequate response or have become intolerant to anti-TNF-α. The greatest reduction in expenditure is instead recorded for golimumab (-18.0%), which also shows a reduction of 15.8% in the average DDD cost, and for etanercept (-14.4%), for which the reduction in DDD average cost stood at 16.2%, probably due to the presence of biosimilars on the market.

Analyzing the regional variability (Table 3.1.2b) of per capita expenditure, the Southern Regions show a higher value (34.21 euros) than the national average (30.80 euros), while those of the Centre (29.58 euros) and the North (28.94 euros) show lower values. The significant regional variability is underlined by the lowest value in Valle d'Aosta (23.17 euros) and the highest in Calabria (40.87 euros). Valle d'Aosta and Lombardy are the Regions with a lower use of drugs compared to the national value (respectively 2.7 and 3.4 DDD/1000 inhabitants per day), compared to a higher average DDD cost. On the contrary, the Province of Bolzano and Friuli VG have a higher consumption, respectively 5.6 and 5.2 DDD/1000 inhabitants per day, but with a lower average DDD cost than the national value. Compared to the previous year, Emilia Romagna in 2021 shows the greatest increase in both per capita expenditure (+18.6%) and consumption (+16.5%). Emilia-Romagna, Piedmont and Valle d'Aosta are the only Regions with an increase in the average DDD cost in 2021; Valle d'Aosta records a higher value (+14.4%) than Emilia Romagna (+2.1%) and Piedmont (+1.4%).

Figure 3.1.2a Immunosuppressants and immunomodulating agents, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

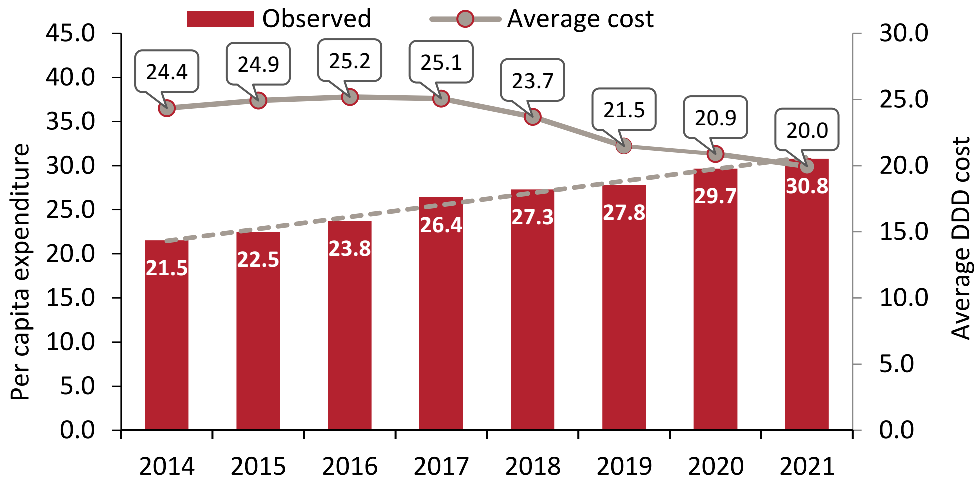


Table 3.1.2a Immunosuppressants and immunomodulating agents, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Interleukin inhibitors	8.53	18.7	29.9	0.8	21.1	34.2	27.99	-1.7
Other immunosuppressants	7.34	0.1	14.7	0.2	5.7	15.8	111.51	-5.0
Tumor necrosis factor alpha inhibitors (TNF-alpha)	5.04	-13.4	-9.6	1.5	11.4	7.4	9.12	-22.0
Immunosuppressant monoclonal antibodies	3.56	12.3	16.8	0.1	21.0	54.8	72.77	-7.0
Calcineurin inhibitors	1.41	-6.6	-3.0	0.6	-4.0	0.2	6.75	-2.4
Selective T cell co-stimulation modulators	1.16	0.8	12.3	0.1	1.0	10.4	48.68	0.0
Selective immunosuppressants	1.06	2.3	9.7	0.6	0.7	5.7	4.95	1.8
JAK tyrosin kinase inhibitors	1.05	28.4	-	0.1	36.3	-	24.65	-5.5
MTOR protein kinase inhibitors	0.68	2.4	4.0	0.1	2.2	6.0	17.42	0.4
Growth factors	0.59	-8.9	-11.6	0.1	0.7	1.0	14.88	-9.3
Other immunomodulators	0.32	8.9	7.3	0.0	2.9	6.1	169.98	6.1
Interferons	0.08	28.0	-31.2	0.0	-9.9	-34.1	24.51	42.5
Immunosuppressants and immunomodulating agents	**30.80**	**3.8**	**5.3**	**4.2**	**8.9**	**8.3**	**19.95**	**-4.5**
lenalidomide	5.47	1.2	12.4	0.1	9.6	16.5	122.78	-7.4
eculizumab	2.15	8.7	9.1	0.0	10.0	12.2	766.98	-0.9
ustekinumab	2.05	10.7	17.4	0.3	17.8	24.8	17.88	-5.8

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
secukinumab	1.89	0.6	-	0.2	4.4	-	30.60	-3.4
adalimumab	1.56	-13.0	-13.0	0.6	18.1	11.3	6.60	-26.1
etanercept	1.50	-15.4	-11.6	0.3	1.3	1.1	14.14	-16.2
vedolizumab	1.21	15.6	-	0.1	16.4	-	32.52	-0.4
abatacept	1.14	0.5	12.1	0.1	0.5	10.2	49.36	0.3
tocilizumab	1.02	4.9	11.7	0.1	5.7	18.8	25.46	-0.5
canakinumab	0.98	12.1	38.0	0.0	1.8	42.9	157.13	10.4

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	28.67	3.8	20.58	30.82	4.0	20.87	7.5	6.3	1.4	7.3	9.8	-2.2
Valle d'Aosta	20.41	2.8	20.27	23.17	2.7	23.19	13.5	-0.5	14.4	9.6	5.2	4.2
Lombardy	24.86	3.2	21.10	25.72	3.4	20.43	3.5	7.2	-3.2	4.7	6.9	-2.1
Province of Bolzano	32.33	4.9	18.08	35.23	5.6	17.26	9.0	14.4	-4.5	5.4	10.1	-4.2
Province of Trento	23.00	3.5	17.81	25.00	4.0	17.15	8.7	13.2	-3.7	7.4	10.1	-2.4
Veneto	27.46	3.8	19.79	28.67	4.3	18.22	4.4	13.8	-8.0	5.2	9.3	-3.8
Friuli VG	36.27	4.7	20.95	35.14	5.2	18.65	-3.1	9.1	-11.0	7.1	8.7	-1.5
Liguria	26.53	3.3	22.19	26.35	3.6	20.05	-0.7	10.3	-9.7	6.9	7.9	-0.9
Emilia R.	28.32	3.9	19.89	33.58	4.5	20.30	18.6	16.5	2.1	8.9	10.2	-1.1
Tuscany	31.60	4.2	20.64	31.97	4.4	19.75	1.2	6.0	-4.3	3.6	7.2	-3.4
Umbria	34.48	3.9	24.17	35.49	4.3	22.71	2.9	9.8	-6.0	7.1	8.8	-1.6
Marche	36.88	4.3	23.52	37.47	4.5	22.91	1.6	4.6	-2.6	6.7	8.9	-2.0
Lazio	24.76	3.7	18.49	24.86	3.9	17.45	0.4	6.7	-5.7	2.8	8.2	-5.0
Abruzzo	37.50	4.2	24.15	38.43	4.4	23.75	2.5	4.5	-1.6	7.4	9.0	-1.5
Molise	37.72	3.7	27.60	36.02	3.8	25.79	-4.5	2.5	-6.6	5.2	7.7	-2.3
Campania	35.16	4.2	22.73	36.12	4.7	21.12	2.8	10.9	-7.1	5.9	8.5	-2.3
Puglia	34.80	4.4	21.76	34.45	4.7	20.06	-1.0	7.7	-7.8	2.4	6.9	-4.2
Basilicata	34.98	4.2	22.94	34.46	4.5	20.91	-1.5	8.4	-8.9	5.3	8.3	-2.8
Calabria	38.82	4.2	25.42	40.87	4.6	24.42	5.3	9.9	-3.9	6.2	8.1	-1.7
Sicily	27.52	4.2	17.92	28.33	4.5	17.21	3.0	7.5	-3.9	4.9	8.7	-3.5
Sardinia	31.70	4.1	21.26	33.23	4.5	20.41	4.8	9.5	-4.0	3.2	6.7	-3.3
Italy	**29.67**	**3.9**	**20.88**	**30.80**	**4.2**	**19.95**	**3.8**	**8.9**	**-4.5**	**5.3**	**8.3**	**-2.8**
North	27.19	3.6	20.48	28.94	4.0	19.80	6.5	10.4	-3.3	6.3	8.7	-2.2
Centre	29.28	3.9	20.37	29.58	4.2	19.40	1.0	6.4	-4.8	4.0	8.0	-3.7
South and Islands	33.49	4.2	21.68	34.21	4.6	20.45	2.1	8.6	-5.7	4.8	8.0	-3.0

Key message

- In 2021, the two categories with the **highest per capita expenditure** are **interleukin inhibitors** (8.53%), which increased compared to the previous year, and other **immunosuppressants** (7.34 euros), which remain **stable**. The subgroup of TNF-α inhibitors records the greatest reductions in expenditure (-13.4%)
- Lenalidomide shows the highest expenditure value, although the largest increases were observed for vedolizumab (+15.6%) and ustekinumab (+10.7%), both indicated for the treatment of moderate to severe active ulcerative colitis and in patients with Crohn's disease who have shown an inadequate response or have become intolerant to anti-TNF-α. A decrease in expenditure is recorded for golimumab (-18.0%) and etanercept (-14.4%), attributable to a reduction in the average DDD cost (-15.8% and -16.2%), probably due to the presence of biosimilars on the market.
- Although all the Italian regions (with the exception of Piedmont, Valle d'Aosta and Emilia Romagna) show a reduction in the average cost per day of therapy; the Regions of the **South** record a **higher per capita expenditure** (34.21 euros) **than the national average** (30.80 euros), unlike the Regions of the Centre (29.58 euros) and the North (28.94 euros), which instead show lower values.

References

- Centro Nazionale Trapianti, Istituto Superiore di Sanità. Trapianti, i dati 2019: quasi 4mila vite salvate ma aumentano i no alla donazione. Available at the address http://www.trapianti.salute. gov.it/trapianti/dettaglioComunicatiNotizieCnt.jsp?lingua=italiano&area=cnt&menu=media&- sottomenu=news&id=538/
- Krensky, Alan M et al. Immunosuppressants and tolerogens. Brunton LL et al., eds. Goodman & Gilman’s: the pharmacological basis of therapeutics. 13th edition. New York: McGraw-Hill, 2017.
- Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F, Shoenfeld Y. Sex-based differences in auto- immune diseases. Ann Ist Super Sanita 2016; 52(2):205-12.
- Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med 2015; 278(4):369-95.

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. Although death rates from cardiovascular diseases have decreased in recent years, 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 and alcohol, further accentuated during the COVID-19 pandemic. In particular, between 2009 and 2019 the prevalence of arterial hypertension increased from 25.7% to 31.1%, the prevalence of ischemic heart disease increased from 3.9% to 4.8%, the prevalence of ischemic stroke increased from 2.7% to 4.4%, while the prevalence of heart failure stands at 1.3%.
In 2021, cardiovascular drugs are the second therapeutic category with the highest public expenditure, equal to 3,318 million euros and 14.1% of total public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure on these drugs was equal to 56.0 euros, of which 88% refers to the approved care regime (49.51 euros 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 (+0.9%); the purchase by public health facilities is significantly lower (6.48 euros per capita) despite a marked increase compared to the previous year (+10.5%) (Table 3.1).
Cardiovascular drugs are confirmed to be the most used: the consumption for this therapeutic category was equal to 503.6 DDD/1000 inhabitants per day, remaining substantially unchanged compared to the previous year (+0.3%), of which 96.5% of the total doses refers to the approved care regime (486.9 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%). In addition, the NHS per capita expenditure also increases with age, reaching 180.3 euros per capita in people aged 75 or over (193.6 euros per capita in men and 171.0 euros per capita in women).

With regard to the approved care regime (Table 3.9), the change in expenditure (+0.3%) was driven by the shift of prescription towards higher-cost specialties (mix effect: +1.2%), while both consumption and prices remain stable compared to the previous year (respectively -0.5% and -0.4%). The average DDD cost is also stable compared to 2020. In 2021 HMG-CoA reductase inhibitors (statins) remain the active ingredients with the highest per capita expenditure (8.14 euros), showing an increase, both in terms of expenditure (+0.5%) and consumption (+1.0%) compared to the previous year, as well as a reduction in the average cost per day of therapy (-0.5%) and a shift towards lower cost specialties (mix effect: -0.5%). Angiotensin II receptor blockers are the second category with the highest per capita expenditure on this ATC (4.88 euros), showing a decrease in almost all the indicators considered (expenditure -0.8%, DDD -1.7%, prices -0.1%). The major changes in expenditure compared to 2020 are instead attributable to other combinations of angiotensin II receptor blockers (+29.5%) and to the combinations of various lipid-lowering drugs (+ 13.4%).

In 2021 atorvastatin confirms as the molecule with the highest per capita expenditure (4.62 euros), increasing by 2.8% compared to the previous year, and also recording a 3.0% increase in consumption (Table 3.10). Atorvastatin represents 9.3% of approved care pharmaceutical expenditure on this category, followed by bisoprolol and omega 3, with per capita expenditure values of 2.72 and 2.08 euros respectively.

Among the top 30 active ingredients for expenditure under approved care regime, atorvastatin records the highest figure (273.7 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 50.2 DDD (Table 3.16) and showing a reduced regional variability in terms of consumption (Table 3.17). The ezetimibe/rosuvastatin combination shows the greatest variation in per capita expenditure (+31.3%), due to a variation in consumption of +91.6% and a reduction of 31.3% in the average cost per day of therapy, attributable to the patent expiry and the consequent market entry of equivalent medicines (Table 3.14). Compared to the previous year, the first thirty active ingredients with the greatest reduction under approved care include 12 active ingredients belonging to the category of cardiovascular system drugs; the first is carvedilol, which records a reduction by 7.2% compared to 2020, with an expenditure of 0.49 euros per capita (Table 3.15).
As regards cardiovascular medicines purchased directly by public health facilities (Table 3.18), per capita expenditure is equal to 6.48 euros, with a 9.7% increase compared to the previous year, against a decrease in consumption (-5.2%) and in prices (-2.4%). The increase in expenditure compared to 2020 was therefore driven by a shift towards more expensive medicines (mix effect +18.6%). The average DDD cost consequently recorded a sharp increase by 15.8% compared to 2020.

The “Other lipid-lowering substances”, including PCSK-9 inhibitors, in 2021 are the category with the highest per capita expenditure (1.66 euros) and an increase of 41.5% compared to 2020, surpassing other cardiac preparations (1.49 euros) and drugs used in the treatment of pulmonary arterial hypertension (1.31 euros).
Over half (54%) of the expenditure incurred by public health facilities for cardiovascular drugs relates to three active ingredients: ranolazine, macitentan and the sacubitril/valsartan combination. In 2021 ranolazine confirms again as the active ingredient with the highest per capita expenditure (1.40 euros), followed by the sacubitril/valsartan combination (1.14 euros), originator of the therapeutic class called ARNI (Angiotensin Receptor-Neprilysin Inhibitors [NEP]), which recorded a significant increase of about 30% in consumption and expenditure (Table 3.19). In particular, significant increases in expenditure concern two PCSK9 inhibitors, evolocumab and alirocumab (+51.5% and +39.9%, respectively). Evolocumab, together with sacubitril/valsartan, is listed within the first thirty active ingredients with the greatest variation in expenditure among the drugs purchased by public health facilities (Table 3.22). Four active ingredients belonging to the cardiovascular system category are in the list of the first 30 most consumed drugs purchased by public health facilities: furosemide 4.0 DDD, ramipril 1.6 DDD, atorvastatin 1.4 DDD and ranolazine 1.3 DDD (Table 3.25).
For further information on the use of medicines related to the same therapeutic area, analyzes have been developed on the historical series of consumption by active ingredient

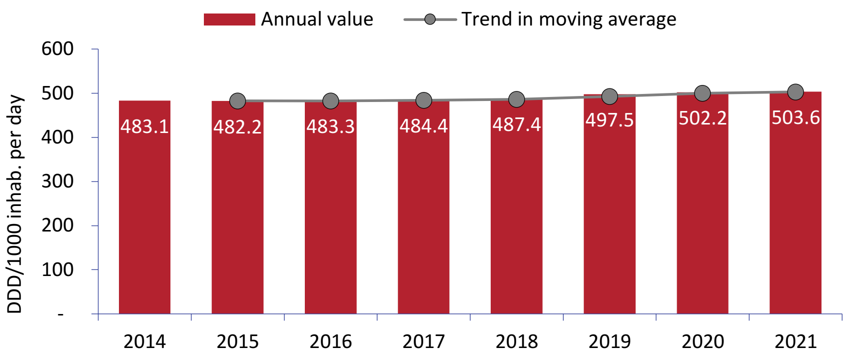
and by Region. Such analyses focused on medicines for hypertension and heart failure and on lipid-lowering drugs (Tables 3.2.1 and following). Moreover, the section dedicated to monitoring registries contains a focus on PCSK9 inhibitors, which provides a description of the baseline characteristics of patients undergoing treatment and their regional distribution (Section 4).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

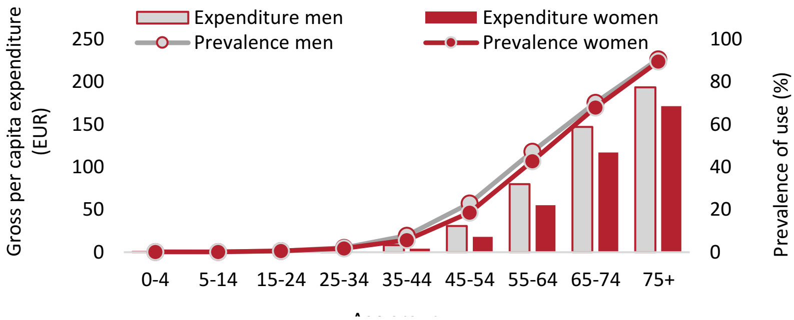
Cardiovascular system

Public expenditure* in million euros (% on total)	**3,318.1**	**(14.1)**
Δ % 2021-2020		2
Regional range of gross per capita expenditure:	37.5	70.3
DDD/1000 inhab. per day* (% on total)	**503.6**	**(38.5)**
Δ % 2021-2020		0.3
Regional range of DDD/1000 inhab. per day:	375.8	614.4

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



Distribution by age and gender of expenditure, prevalence of use and consumption under approved care regime and "on-behalf" distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure Men	Women	Total	DDD/1000 inhab. per day Men	Women	Total
0-4	0.2	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	1.7	0.9	1.3	14.9	7.9	11.5
35-44	8.3	4.0	6.1	75.7	38.0	56.9
45-54	30.7	17.9	24.3	289.6	173.0	230.7
55-64	80.0	55.1	67.2	752.4	518.0	631.8
65-74	147.2	116.8	131.2	1368.8	1075.0	1213.6
75+	193.6	171.0	180.3	1869.4	1654.3	1741.0

3.2.1 Medicines for hypertension and heart failure

Epidemiological framework

High blood pressure affects approximately 1.13 billion people globally. In Italy it affects 55-59% of the population over the age of 18. This clinical condition represents the main modifiable risk factor for coronary heart disease, stroke, heart failure and renal failure, which contribute to the premature death of many people. However, it is necessary to contextualize the data, correlating them with the progressive ageing of the population, with higher sedentary lifestyle and obesity, which will cause a further increase in the prevalence of this disease in the future. It is now clear that the correct treatment of hypertension, besides preventing numerous deaths of cardiovascular origin, also allows a considerable saving of economic resources. Nevertheless, there is a high share of hypertensive patients who are not treated or who are poorly adherent to the prescribed therapy. In fact, although effective therapies are available, only one in three hypertensive patients is adequately treated. In clinical practice, the use of a single active ingredient in monotherapy for the treatment of arterial hypertension may not guarantee the achievement and stable maintenance of recommended optimal blood pressure over time. On the other hand, the growing increase in the dosage and/or number of drugs can lead to a reduction in patient compliance with therapy. Poor adherence, in addition to exposing the patient to potential cardiovascular clinical outcomes due to lack of blood pressure control, strongly affects healthcare costs through an increase in hospitalizations for cardiovascular events and the consumption of drugs prescribed following worsening and/or complications of pre-existing (cardiovascular and non-cardiovascular) clinical conditions.

National data on consumption and expenditure

Consumption of medicines for hypertension and heart failure has been basically stable over the last eight years (CAGR +0.0%), recording a value of 375.4 DDD in 2021 and an average cost per day of therapy of 0.25 euros, with a 1.6% increase compared to the previous year (Figure 3.2.1a). The per capita expenditure for these drugs, equal to 34.35 euros, remains unchanged compared to 2020, although recording an average annual reduction rate of 1.1%, calculated starting from 2014 (Table 3.2.1a). Beta blockers are the therapeutic category with the highest per capita expenditure (5.59 euros), showing a 1.9% increase compared to the previous year and an average cost per day of therapy of 0.34 euros, slightly higher than the value observed for the entire therapeutic class. The DDD/1000 inhabitants per day were 45.7, stable compared to 2020 (+0.5%). Analysing the trend of expenditure and consumption for this subgroup over time, an annual increase can be noted, over the period 2014-2021, by respectively 2.7% and 1.3%.
ACE inhibitors remain the category with the highest consumption (84.3 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 3.72 euros, albeit with a tendential reduction over time in all the values considered (CAGR expenditure -2.7%, CAGR consumption -1.0%). Bisoprolol is the substance with the highest per capita expenditure, recording a value of 2.73 euros, a 4.2% increase compared to the previous year, while ramipril recorded the highest value of DDD/1000 inhabitants per day (64.0).

Particularly interesting is the increase in both expenditure (+30.8%) and consumption (+31.2%) 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 analysis of regional consumption (Table 3.2.1b) shows that in 2021 Umbria is the Region reporting the highest value (488.1 DDD/1000 inhabitants per day), while the Province of Bolzano is confirmed to have the lowest value (277.2 DDD/1000 inhabitants per day). Compared to the national average, the Northern Regions showed a lower consumption (359.3 compared to 375.4 DDD/1000 inhabitants per day), while those of the Centre and the South have higher values, equal to respectively 388.1 and 390.8 DDD/1000 inhabitants per day.

By analyzing the regional variability, compared to the national average, Umbria, Tuscany and Emilia Romagna consumed the greatest quantities of drug with a lower average cost; Lazio, Marche, Campania, Puglia, Basilicata, Calabria and Sicily recorded both a consumption and an average DDD cost higher than the national value; Friuli Venezia Giulia showed a consumption in line with the national average, but a lower average DDD cost; Abruzzo, Molise, Sardinia and Liguria consumed the least quantities of the drug, but with an average cost per day of therapy higher than the national values (Table 3.2.1b).

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

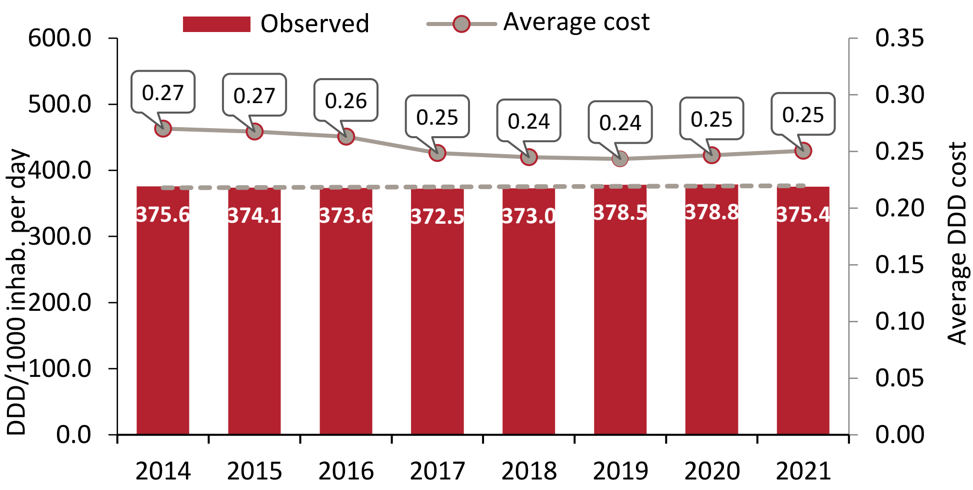


Table 3.2.1a Medicines for hypertension and heart failure, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ% 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ% 21-20	CAGR % 14-21	Average DDD cost	Δ% 21-20
Beta blockers	5.59	1.9	2.7	45.7	0.5	1.3	0.34	1.7
Angiotensin II antagonists	4.88	-0.1	-2.9	58.4	-0.9	0.5	0.23	1.0
Calcium channel blockers (dihydropyridines)	4.18	-1.6	-1.7	51.2	-1.0	-0.8	0.22	-0.3
Angiotensin II receptor blockers and diuretics (combinations)	3.90	-2.7	-7.2	32.5	-2.1	-2.8	0.33	-0.4
ACE inhibitors	3.72	-2.4	-2.7	84.3	-2.0	-1.0	0.12	-0.1
ACE inhibitors and diuretics (combinations)	2.49	-4.0	-5.1	19.5	-3.2	-3.5	0.35	-0.6
ACE inhibitors and calcium channel blockers (combinations)	1.66	-0.5	4.2	12.2	1.3	9.1	0.37	-1.5
Angiotensin II receptor blockers and neprilysin inhibitor	1.51	30.8	-	0.9	31.2	-	4.57	-0.1
Angiotensin II receptor blockers and calcium channel blockers (combinations)	1.37	13.1	5.4	9.3	13.0	19.0	0.40	0.4
Alpha-adrenoreceptor antagonists	1.26	-0.6	0.0	7.8	-0.5	0.0	0.44	0.1
High-ceiling diuretics, plain or in combination with potassium-sparing agents	1.03	-3.1	-0.5	30.0	-3.9	0.2	0.09	1.2
Beta blockers and diuretics (combinations)	0.70	2.0	1.0	7.6	1.7	2.6	0.25	0.6
Perindopril/indapamide/ amlodipine	0.61	-2.0	-	4.2	16.5	-	0.40	-15.6
Potassium-sparing diuretics	0.58	0.1	1.1	3.6	-1.6	0.3	0.44	2.0
Calcium channel blockers (not dihydropyridines)	0.28	-8.7	-8.6	2.0	-9.1	-8.1	0.39	0.8
Thiazides and similars (including combinations)	0.22	-5.3	-3.6	3.8	-5.2	-5.3	0.16	0.2
Imidazoline receptor agonists	0.20	-6.8	-7.3	1.4	-6.9	-5.7	0.39	0.4
ACE inhibitors, other combinations	0.11	18.9	-	0.9	19.3	-	0.33	0.0
Aliskiren plain or in combination	0.04	-18.1	-17.1	0.1	-17.8	-17.0	0.89	-0.1
Alpha-2 adrenergic receptor agonists	<0,005	60.3	-6.8	0.0	55.5	-6.8	0.36	3.4
Medicines for hypertension and heart failure	**34.35**	**0.4**	**-1.1**	**375.4**	**-0.9**	**0.0**	**0.25**	**1.6**
bisoprolol	2.73	4.2	6.6	12.6	3.9	6.3	0.59	0.6
ramipril	2.02	0.0	-0.3	64.0	-1.0	0.4	0.09	1.2
olmesartan	1.78	7.7	-3.4	15.5	7.9	11.4	0.31	0.1
amlodipine	1.62	-0.4	0.1	29.0	0.1	0.4	0.15	-0.2
nebivolol	1.53	2.0	2.5	16.7	2.3	3.1	0.25	-0.1
sacubitril/valsartan	1.51	30.8	-	0.9	31.2	-	4.57	-0.1
olmesartan/amlodipine	1.31	12.4	4.8	8.9	12.1	18.2	0.40	0.5
doxazosin	1.25	-0.7	0.1	7.8	-0.5	0.1	0.44	0.1
olmesartan/ hydrochlorothiazide	1.22	5.6	-7.1	10.0	5.8	6.2	0.33	0.1
barnidipine	0.88	-1.6	0.8	4.9	-1.4	1.1	0.50	0.0

Table 3.2.1b Medicines for hypertension and heart failure, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	30.92	363.7	0.23	30.92	361.6	0.23	0.0	-0.6	0.8	-1.7	-0.2	-1.6
Valle d'Aosta	27.52	310.3	0.24	27.69	307.4	0.25	0.6	-0.9	1.8	-2.4	-1.6	-0.9
Lombardy	30.88	344.9	0.24	31.23	342.9	0.25	1.1	-0.6	2.0	-1.2	-0.6	-0.6
Province of Bolzano	23.80	280.9	0.23	23.80	277.2	0.24	0.0	-1.3	1.6	-2.4	-1.2	-1.2
Province of Trento	26.45	328.4	0.22	26.51	326.0	0.22	0.2	-0.7	1.3	-1.8	-0.4	-1.4
Veneto	30.55	368.1	0.23	30.52	361.9	0.23	-0.1	-1.7	1.9	-2.0	-0.9	-1.1
Friuli VG	30.70	383.5	0.22	31.05	373.6	0.23	1.1	-2.6	4.1	-2.0	-0.4	-1.6
Liguria	30.27	329.4	0.25	30.48	328.0	0.25	0.7	-0.4	1.4	-2.2	-0.9	-1.3
Emilia R.	31.89	408.9	0.21	32.80	412.0	0.22	2.9	0.8	2.4	-0.4	-0.1	-0.3
Tuscany	29.89	380.0	0.21	30.21	380.5	0.22	1.1	0.1	1.2	-0.8	0.3	-1.1
Umbria	39.31	494.0	0.22	39.47	488.1	0.22	0.4	-1.2	1.9	0.3	0.7	-0.4
Marche	35.59	377.6	0.26	36.11	377.6	0.26	1.5	0.0	1.7	-0.8	0.2	-1.0
Lazio	36.62	385.2	0.26	36.48	380.2	0.26	-0.4	-1.3	1.2	-0.8	0.2	-1.0
Abruzzo	36.50	370.9	0.27	36.34	366.2	0.27	-0.4	-1.3	1.1	-0.5	0.3	-0.9
Molise	37.25	373.9	0.27	37.32	374.1	0.27	0.2	0.0	0.4	-1.4	0.3	-1.7
Campania	41.23	408.8	0.28	41.62	406.2	0.28	1.0	-0.6	1.9	-0.3	1.0	-1.3
Puglia	39.00	394.6	0.27	38.62	386.3	0.27	-1.0	-2.1	1.4	-1.4	-0.1	-1.3
Basilicata	39.29	377.8	0.28	40.44	381.3	0.29	2.9	0.9	2.2	0.2	1.0	-0.8
Calabria	40.36	398.8	0.28	40.25	390.9	0.28	-0.3	-2.0	2.0	-0.8	0.2	-1.0
Sicily	39.34	412.0	0.26	39.05	404.9	0.26	-0.7	-1.7	1.3	-0.6	0.8	-1.4
Sardinia	31.82	343.5	0.25	31.58	338.9	0.26	-0.7	-1.3	0.9	-2.7	-0.6	-2.1
Italy	**34.20**	**378.8**	**0.25**	**34.35**	**375.4**	**0.25**	**0.4**	**-0.9**	**1.6**	**-1.1**	**0.0**	**-1.1**
North	30.72	361.6	0.23	31.02	359.3	0.24	1.0	-0.6	1.9	-1.4	-0.5	-0.9
Centre	34.53	390.8	0.24	34.64	388.1	0.24	0.3	-0.7	1.3	-0.7	0.3	-1.0
South and Islands	39.01	396.2	0.27	38.96	390.8	0.27	-0.1	-1.4	1.5	-0.8	0.5	-1.3

Exposure and adherence in population

Health Card data were collected to perform an analysis aimed at estimating exposure to drugs for hypertension and heart failure in the general population, as well as adherence and persistence to treatment.

Exposure was higher in the over 75 age groups, with a slightly higher prevalence in men. In 2021, the largest doses of such medicines were consumed by men up to 74 years of age, while no significant differences were recorded in the population aged over 85 (Figure 3.2.1b).

In 2021, about a quarter of the Italian population used these drugs, with a higher prevalence in the South and the Islands (28.5%) and in the Centre (27.1%), than in the North (25.0%) (Table 3.2.1c). Molise was the Region with the highest prevalence of use (31.9%), while the Province of Bolzano reported the lowest value (18.4%). The median age of users is 70 years and each patient uses about 498.9 DDD per year. Half of the exposed population is treated with a number of DDDs greater than 378, indicating the simultaneous intake of different molecules during the year, while only 3% of users received a single prescription.

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 275,546 new users, with a median age of 63 years (IQR 55-72) and a greater proportion of women than men (52.7% vs 47.3%).

The percentage of people with high and low adherence to treatment with drugs for hypertension was 53% and 18%, respectively (Table 3.2.1d). Low adherence tends to increase with age, recording the highest value in people aged over 85 (23.7%) and in women compared to men (20.8% and 14.8% respectively). Stratifying by age and geographical area, the highest percentage of low adherence was observed in users aged over 85 residing in Southern Italy (26.5%). High adherence, on the other hand, tends to decrease with increasing age, showing a greater value in the 55-64 age group (54.7%) and is higher in men than women, (respectively 57.8% and 48.6%). Users residing in Northern Italy and aged between 55 and 64 years showed the greatest percentage value of high adherence (56.4%).

Analysing the persistence to medicines for hypertension and heart failure (Table 3.2.1e and Figure 3.2.1c), about half of the new users are found to be persistent to treatment after one year (53.1%), with a rather similar trend by geographic area (North 53.4%, Centre 54.4% and South 51.9%), although the North and the Centre record a minimal improvement in persistence compared to 2020, respectively by +2% and +4%. Men showed higher persistence percentages than women, with values of 57.5% and 49.1% respectively.

For these drugs, the median time to discontinuation is greater than 365 days (Figure 3.2.1c). 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 45.4% at 24 months from the beginning of the treatment (Table 3.2.1f and Figure 3.2.1d).

Figure 3.2.1b Distribution of prevalence of use and consumption of medicines for hypertension and heart failure under approved care regime and "on-behalf" distribution (year 2021)

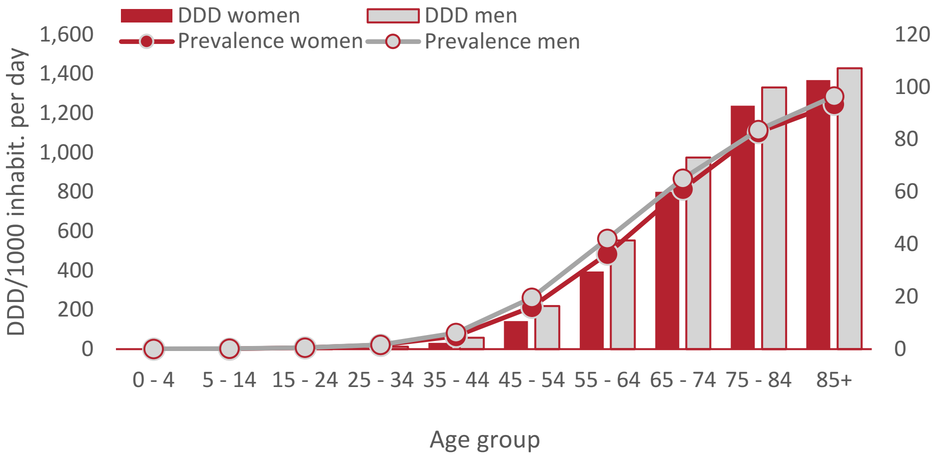


Table 3.2.1c Exposure and duration of therapy with medicines for hypertension and heart failure by Region under approved care regime and "on-behalf" distribution (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	men	women	total					
Piedmont	26.9	28.8	27.9	72	114.2	475.0	364.0	2.8
Valle d'Aosta	23.4	24.9	24.1	71	114.5	448.5	357.3	2.4
Lombardy	23.7	24.7	24.2	71	125.7	498.4	378.7	2.4
Province of Bolzano	17.9	18.9	18.4	72	117.9	482.3	364.0	2.7
Province of Trento	22.3	23.0	22.6	71	111.0	485.2	373.5	2.4
Veneto	24.6	25.0	24.8	71	120.9	512.9	390.0	2.4
Friuli VG	26.1	27.0	26.6	72	122.4	524.9	392.0	2.4
Liguria	27.5	29.4	28.5	73	115.3	441.2	356.0	3.3
Emilia R.	25.5	27.4	26.5	71	115.9	521.7	392.0	2.7
Tuscany	25.8	27.7	26.8	72	114.0	518.7	392.0	4.4
Umbria	30.5	32.5	31.5	71	129.2	570.1	420.0	3.2
Marche	27.6	29.4	28.5	72	127.9	485.4	378.0	3.0
Lazio	26.7	28.2	27.5	70	129.3	487.0	387.3	3.0
Abruzzo	28.2	30.7	29.5	70	119.5	449.1	361.3	3.4
Molise	30.1	33.7	31.9	70	122.4	444.3	364.0	3.0
Campania	27.7	29.6	28.6	67	132.7	472.7	367.3	2.7
Puglia	28.3	31.0	29.7	70	121.9	457.2	364.0	2.9
Basilicata	29.1	32.8	31.0	69	130.2	449.6	364.0	3.6
Calabria	29.0	31.5	30.3	69	127.0	452.0	364.0	3.3
Sicily	26.9	30.0	28.5	70	127.9	496.5	381.5	3.3
Sardinia	26.0	**27.9**	27.0	71	120.1	466.7	364.0	3.0
Italy	**25.6**	**27.4**	**26.5**	**70**	**125.9**	**498.9**	**378.0**	**3.0**
North	24.3	25.6	25.0	71	122.3	507.1	380.0	2.6
Centre	26.2	28.0	27.1	71	127.0	513.9	392.0	3.5
South and Islands	27.2	29.7	28.5	69	129.2	478.9	364.0	3.1

Table 3.2.1d Indicators of adherence to treatment with drugs for hypertension and heart failure in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

	Total N=275.546				North N=124.177				Centre N=60.958				South N=90.411			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*^																
45-54 years	16.4	16.3	16.9	4	15.1	14.9	15.5	4	16.6	16.9	17.3	2	17.6	17.6	18.3	4
55-64 years	16.1	16.5	16.9	2	15.0	15.6	15.9	2	16.0	16.7	17.0	2	17.4	17.6	18.0	2
65-74 years	17.7	18.2	17.9	-2	16.7	16.7	16.7	0	17.5	19.2	18.4	-4	19.2	19.7	19.3	-2
75-84 years	20.2	21.1	20.2	-4	18.8	19.7	18.5	-6	20.8	21.5	21.3	-1	22.2	23.4	22.6	-3
≥85 years	25.0	25.8	23.7	-8	22.8	23.3	21.8	-6	25.7	27.3	24.3	-11	28.2	28.8	26.5	-8
Women	20.5	20.9	20.8	0	19.1	19.4	19.4	0	20.8	22.2	21.5	-3	22.1	22.2	22.3	0
Men	14.7	15.1	14.8	-2	13.9	14.2	13.8	-3	14.7	15.1	15.1	0	15.8	16.3	16.0	-2
Total	**17.7**	**18.1**	**18.0**	**-1**	**16.6**	**16.9**	**16.8**	**-1**	**18.0**	**18.8**	**18.5**	**-2**	**19.1**	**19.4**	**19.3**	**-1**
High adherence*^																
45-54 years	54.8	54.9	54.0	-2	56.7	56.8	55.6	-2	55.8	55.9	55.5	-1	52.3	52.2	51.3	-2
55-64 years	55.4	54.6	54.7	0	56.5	56.0	55.9	0	56.7	55.7	56.4	1	53.5	52.2	52.1	0
65-74 years	53.9	53.0	53.9	2	54.6	54.3	54.5	0	55.9	53.5	54.9	3	51.8	51.1	52.2	2
75-84 years	49.5	48.2	49.7	3	50.6	49.5	51.1	3	50.0	48.7	50.2	3	47.3	45.6	46.5	2
≥85 years	41.0	40.9	42.7	4	42.1	43.0	44.6	4	41.2	39.5	42.5	8	39.0	38.8	39.6	2
Women	48.7	48.1	48.6	1	49.9	49.5	49.9	1	49.5	48.4	49.4	2	46.7	46.1	46.3	0
Men	58.0	57.3	57.8	1	58.7	58.5	58.6	0	59.5	58.2	59.4	2	56.2	55.2	55.6	1
Total	**53.1**	**52.5**	**53.0**	**1**	**54.1**	**53.8**	**54.0**	**0**	**54.1**	**53.0**	**54.1**	**2**	**51.2**	**50.5**	**50.8**	**1**

*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, who received a first prescription in the period 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.
Percentages of people with low/high adherence relating to the specific category.
Median follow-up time (IQR): 327 (279-348).

Table 3.2.1e Persistence after one year of treatment with medicines for hypertension and heart failure in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

Persistence after 12 months	Total N=275.546				North N=124.177				Centre N=60.958				South N=90.411			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54 years	55.0	54.6	54.3	0	55.2	55.4	54.9	-1	55.4	54.6	55.7	2	54.6	53.7	52.9	-2
55-64 years	55.4	54.7	55.1	1	55.4	54.9	55.5	1	56.4	54.9	56.6	3	55.0	54.3	53.8	-1
65-74 years	53.5	53.0	53.9	2	53.1	53.1	53.8	2	54.7	52.8	55.6	5	53.5	52.9	52.9	0
75-84 years	49.0	47.5	48.8	3	49.0	48.0	49.6	3	49.4	47.8	50.1	5	48.6	46.4	46.2	0
≥85 years	41.1	40.5	42.8	5	41.0	41.4	44.2	7	40.9	40.0	42.9	7	41.4	39.5	40.1	1
Women	48.9	48.2	49.1	2	48.7	48.4	49.4	2	49.3	47.7	50.3	6	48.9	48.1	47.9	0
Men	57.5	56.9	57.5	1	57.1	57.0	57.8	1	58.4	57.3	59.0	3	57.6	56.4	56.2	0
Total	**53.0**	**52.3**	**53.1**	**1**	**52.7**	**52.5**	**53.4**	**2**	**53.5**	**52.2**	**54.4**	**4**	**53.0**	**52.1**	**51.9**	**0**

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 3.2.1c 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)

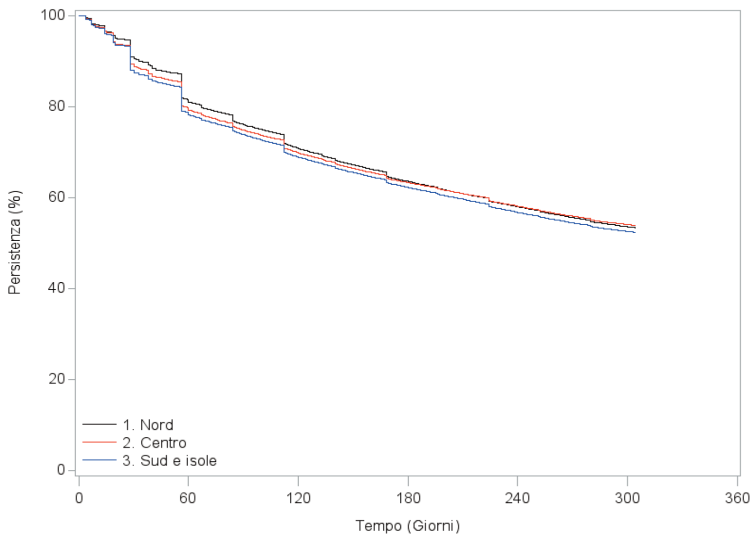
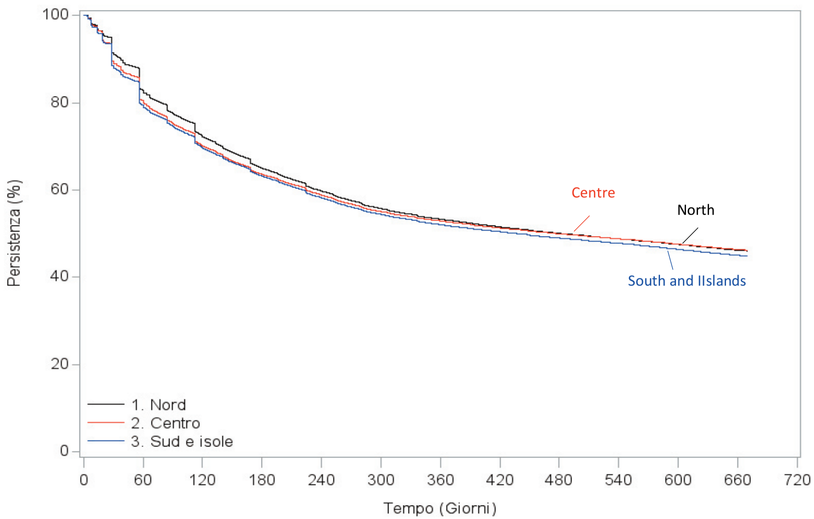


Table 3.2.1f Persistence to treatment with medicines for hypertension and heart failure in the population aged ≥45 years in 2021 with 2 years of follow-up

Persistence (%)	Total N=233.188			North N=103.271			Centre N=48.360			South N=81.557		
	12 months	18 months	24 months	12 months	18 months	24 months	12 months	18 months	24 months	12 months	18 months	24 months
45-54 years	55.4	51.2	48.5	56.7	52.4	49.6	55.4	51.7	49.1	54.0	49.7	47.0
55-64 years	54.8	50.6	48.0	55.2	50.9	48.2	55.0	51.1	48.7	54.3	50.0	47.4
65-74 years	52.2	47.9	45.3	52.3	47.8	45.3	52.0	48.0	45.8	52.1	47.8	45.1
75-84 years	46.5	42.2	39.7	47.1	42.5	40.0	47.2	43.0	40.4	45.1	41.1	38.4
≥85 years	40.2	35.2	32.9	41.1	35.7	33.6	39.6	34.6	32.0	39.1	35.1	32.6
Women	47.9	43.5	40.8	48.2	43.6	40.9	47.6	43.4	41.0	47.8	43.4	40.6
Men	57.1	53.0	50.4	57.4	53.1	50.6	57.5	53.6	51.2	56.4	52.4	49.8
Total	**52.3**	**48.0**	**45.4**	**52.6**	**48.2**	**45.6**	**52.2**	**48.2**	**45.8**	**51.9**	**47.7**	**45.0**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions in 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 2 years

Figure 3.2.1d Time (in days) to discontinuation of treatment with medicines for hypetension after 2 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)



Epidemiology and prescribing profiles in General Medicine

The data relating to epidemiology and prescribing profiles were obtained through a network of GPs "approved" according to a series of quality criteria in data recording, homogeneously distributed throughout Italy, bringing together to Health Search-IQVIA Health LPD all information relating to: diagnosis of pathology, demographic information, pharmaceutical prescription, as well as outpatient specialist services, laboratory parameters and exemptions for disease or disability.

The analyses focused on the prevalence and incidence of hypertension in the population treated by the 800 GPs of the HS network for the years 2019, 2020 and 2021. In addition, the prevalence of use of drugs was assessed, considering the most used therapeutic categories, as well as the related trend.

In 2021 the incidence of hypertension in the population cared for by the GPs of the HS network was 16.4‰, with an increase by 3.5% compared to the previous year (Table 3.2.1g). In fact, observing the incidence estimates in the three years considered, 2021 recorded a growth in disease diagnoses, compared to the sharp decline observed in 2020.

Analyzing the estimate on a geographical basis, it is possible to note a higher value in the South and in the Islands (17.7‰), compared to the Centre (16.7‰) and the North (15.2‰) for the year 2021. Compared to the incidence of hypertension in 2020, a reduction in the estimate was found only for the Regions of the Centre (-7.4%). The analysis by gender shows overlapping values between men and women (16.1‰ and 16.7‰), although the greatest estimate growth compared to 2020 was observed for the female gender (6.2%). Stratifying the analysis by age group for 2021, an increase is reported in the incidence with increasing age of patients. Furthermore, compared to the previous years, this is increasing for all the groups considered, with the exception of patients aged ≥85 years (-5.1%).

The prevalence figure, equal to 29.7%, is slightly higher than in the previous two years, with a comparable value for men and women. The highest prevalence is recorded in the South and the Islands (32.4%), compared to the Centre (28.6%) and the North (28.0%). The analysis by age group showed an increase in prevalence with increasing age, with the peak in patients aged ≥85 years (74.0%) (Table 3.2.1h).

In 2021, the prevalence of use of antihypertensive drugs estimated in people diagnosed with hypertension was 76.0%, with a slight stabilization of the trend compared to 2019 and 2020. The highest estimates are observed in the Centre (78.7%), compared to the South (75.6%) and the North (75.2%); this is also the only geographic area showing an increase (albeit slight) in the prevalence of drug use compared to 2020 (0.3%) (Table 3.2.1i). Stratifying the analysis by gender, women show a higher estimante of prevalence of use than men (79.6% vs. 72.4%), who are also associated with a -2.0% reduction in the estimate compared to 2020.

The analysis by age group shows that people aged between 75 and 84 have the highest estimate (89.9%). Finally, only the 46-65 age group recorded a negative change in the prevalence of use compared to the previous year (-2.1%).

Analyzing the prevalence of use according to the therapeutic categories, the highest estimate is recorded for beta-blocking drugs (29.8%) and for ACE-inhibitors (18.6%), as highlighted by the national data of consumption and expenditure (Table 3.2.1j). In patients also suffering from heart failure, beta-blockers were confirmed as the most used category (64.3%), followed by high-ceiling diuretics in combination with potassium-sparing agents (61.6%). Furthermore, in the case of comorbidity with diabetes mellitus, besides beta-blockers, there was a significant prevalence of use for dihydropyridine calcium channel blockers (23.8%).

Finally, the trend of prevalence of use (2019-2021) for the first six most used therapeutic categories (year 2021) (beta-blockers, ACE-inhibitors, calcium channel blockers (dihydropyrimidines), angiotensin II antagonists, angiotensin II antagonistis and diuretics (combinations) and diuretics) was substantially stable over the period, with slight variations in the estimates. In general, all categories recorded a decrease in the estimate of prevalence of use between 2019 and 2020; however, this trend seemed to stabilize between 2020 and 2021. Only the category of beta-blockers reported a slight increase in the estimate of prevalence of use, which in fact goes from 29.5% (2020) to 29.8% (2021) (Figure 3.2.1e).

Table 3.2.1g Incidence of hypertension in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographic area (years 2019-2021)

	Incidence of Hypertension (‰)			
	2019	**2020**	**2021**	**Δ % 21-20**
Geographic analysis				
North	16.1	14.3	15.2	6.7
Centre	21.6	18.0	16.7	-7.4
South and Islands	19.3	16.6	17.7	6.4
Analysis by gender				
Men	18.8	16.0	16.1	0.8
Women	17.9	15.7	16.7	6.2
Analysis by age				
≥45 years	3.7	3.1	3.4	10.3
46-65	24.7	20.5	22.2	8.5
66-74	47.6	43.6	48.4	11.1
75-84	47.5	53.1	59.6	12.3
≥85	25.6	45.9	43.5	-5.1
Total	**18.3**	**15.9**	**16.4**	**3.5**

Indicators used:

Incidence of hypertension: number of patients with a “first” diagnosis of hypertension recorded during the year [**numerator**], out of the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Table 3.2.1h Prevalence of hypertension in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographic area (years 2019-2021)

	Prevalence of Hypertension (‰)			
	2019	2020	2021	Δ % 21-20
Geographic analysis				
North	27.2	27.4	28.0	2.0
Centre	27.8	28.0	28.6	2.1
South and Islands	31.8	32.0	32.4	1.4
Analysis by gender				
Men	28.9	29.1	29.9	2.4
Women	29.1	29.2	29.6	1.3
Analysis by age				
≥45 years	3.3	3.5	3.9	11.4
46-65	27.0	28.7	30.8	7.4
66-74	55.1	57.4	60.0	4.6
75-84	66.5	68.3	70.5	3.3
≥85	70.7	72.2	74.0	2.5
Total	**29.0**	**29.2**	**29.7**	**1.9**

Indicators used:
Prevalence of hypertension: number of patients diagnosed with hypertension **[numerator]**, out of the total population eligible for assistance [**denominator**]

Table 3.2.1i Prevalence of use of antihypertensive drugs in patients with hypertension and comparison 2021-2020: analysis by gender, age group and geographic area (years 2019-2021)

	Prevalence of use (%) of antihypertensive drugs			
	2019	2020	2021	Δ % 21-20
Geographic analysis				
North	76.1	75.5	75.2	-0.4
Centre	80.4	78.5	78.7	0.3
South and Islands	78.2	76.8	75.6	-1.6
Analysis by gender				
Men	75.2	73.9	72.4	-2.0
Women	80.1	79.2	79.6	0.5
Analysis by age				
≥45 years	41.4	35.1	35.4	0.9
46-65	71.1	67.0	65.6	-2.1
66-74	84.4	82.1	82.1	0.0
75-84	88.4	87.4	89.9	2.9
≥85	83.8	85.2	87.2	2.3
Total	**77.7**	**76.6**	**76.0**	**-0.8**

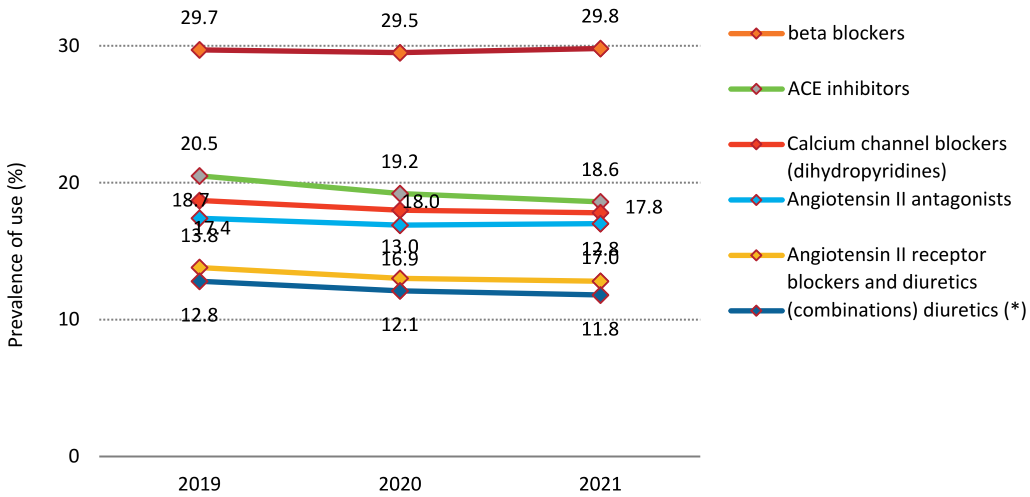
Indicators used:
Prevalence of use of medicines for hypertension: number of patients treated with medicines for hypertension [**numerator**] on the total number of patients diagnosed with hypertension [**denominator**]

Table 3.2.1j Prevalence of use of antihypertensive drugs in patients with hypertension (with and without concomitant diseases^): analysis by therapeutic category and comparison 2021-2020

Analysis by therapeutic category	Prevalence of use (%)						
	Hypertension	Δ % 21-20	Hypertension NA*	Diabetes mellitus	CV diseases	Heart failure	Chronic kidney disease
ACE inhibitors	18.6	-3.1	16.4	21.0	25.0	26.9	21.4
ACE inhibitors and calcium channel blockers (combinations)	4.8	0.0	4.7	5.5	5.0	2.5	4.2
ACE inhibitors and diuretics (combinations)	9.1	-3.2	9.2	9.7	8.8	4.2	6.7
ACE inhibitors, other combinations	0.4	33.3	0.4	0.4	0.4	0.3	0.3
Alpha-2 adrenergic receptor agonists	-	-	-	-	-	-	-
Imidazoline receptor agonists	0.5	-16.7	0.3	1.1	1.0	1.3	2.0
Alpha-adrenoreceptor antagonists	4.3	0.0	3.2	7.0	6.3	6.1	10.2
Aliskiren plain or in combination	0.0	-	0.0	0.0	0.0	0.1	0.0
Angiotensin II receptor blockers and neprilysin inhibitor	0.2	0.0	0.1	0.5	0.7	3.9	0.6
Angiotensin II antagonists	17.0	0.6	15.4	19.1	20.4	19.4	24.0
Angiotensin II receptor blockers and calcium channel blockers (combinations)	3.7	12.1	3.5	4.5	4.0	2.2	3.7
Angiotensin II receptor blockers and diuretics (combinations)	12.8	-1.5	12.3	15.5	13.8	6.9	11.9
Beta blockers	29.8	1.0	23.8	38.9	48.3	64.3	44.1
Beta blockers and diuretics (combinations)	3.4	3.0	3.8	3.1	2.3	1.1	2.0
Calcium channel blockers (dihydropyridines)	17.8	-1.1	14.7	23.8	25.4	18.6	29.4
Calcium channel blockers (not dihydropyridines)	0.9	-10.0	0.6	1.2	1.9	1.9	1.3
High-ceiling diuretics, plain or in combination with potassium-sparing agents	11.8	-2.5	7.0	20.1	22.8	61.6	33.1
Potassium-sparing diuretics	3.0	0.0	1.6	5.3	6.4	26.8	7.3
Olmesartan/amlodipine/hydrochlorothiazide	-	-	-	-	-	-	-
Perindopril/indapamide/amlodipine	1.7	21.4	1.4	2.6	2.0	1.0	1.8
Thiazides and similars (including combinations)	3.3	-5.7	3.2	3.6	3.6	3.5	4.0

Some estimates of prevalence of use may be affected by the type of supply regime and by an exclusively specialist prescription
^The categories are not mutually exclusive
*None of the comorbidities listed below in the table CV diseases: cardiovascular diseases
Indicator used: **Prevalence of use of antihypertensive drugs**: number of patients treated with a specific therapeutic category [**numerator**], out of the total number of hypertensive patients with or without diagnosis of diabetes mellitus or heart failure or chronic kidney disease or cardiovascular disease (coronary or cerebral ischemic) [**denominator**]

Figure 3.2.1e Prevalence of use of antihypertensive drugs in patients with hypertension: analysis by therapeutic category (for the first 6 OsMed cathegories) (years 2019-2021)



(*) high-ceiling diuretics, plain or in combination with potassium-sparing agents

Indicators used:
Prevalence of use of medicines for hypertension: number of patients treated for a specific therapeutic category [**numerator**] on the total number of patients diagnosed with hypertension [**denominator**]

Key message

- **Consumption of drugs for hypertension and heart failure** appears stable over the last eight years, with 375.4 DDD/1000 inhabitants per day. Almost all the most used categories recorded a stable or slightly reduced consumption compared to 2020, with the exception of angiotensin II receptor antagonists and neprilysin inhibitor, which recorded an increase of 31.2% and the combination of antagonists of the angiotensin II receptor and calcium channel blockers, which showed an increase of 13.1% compared to the previous year.
- Among beta-blockers, **bisoprolol has been the most used and steadily increasing drug** since 2014 (CAGR: +6.6%), probably attributable to the greater tolerability of the active ingredient and the possible administration in a single daily dose and the wide possibility of titrating the dose, thus enhancing patient compliance.
- In terms of consumption, **large regional variability is confirmed**. In 2021, the difference between the highest and lowest values observed in the individual Regions was equal to 210.9 DDD/1000 inhabitants per day, i.e. a 76% difference in percentage terms. This variability cannot be completely explained by geographical differences in the prevalence of arterial hypertension and heart failure which, although significantly different, does not appear statistically significant, but rather by a different regional prescribing attitude.
- Regional variability is confirmed, albeit to a lesser extent, also for issues relating to **prescriptive appropriateness**. In particular, the analysis of data from the Health Card shows a proportion of patients with low adherence to treatment equal to 16.8% in the North and 19.3% in the South and Islands. Therefore, a different prescribing attitude could be hypothesized in Northern Italy, whereby the doctor tends to postpone the drug prescription only after a careful evaluation of the effects associated with lifestyle modification programs. This would not only explain the different prevalence of use (North 25.0% vs South and Islands 28.5%), but also the different adherence shown by patients.
- The data relating to DDD per user (national average 498.9) confirms the tendency by the Italian doctors to use combinations of different drugs to achieve the therapeutic target. Since antihypertensive drugs interfere with various synergistic pathophysiological mechanisms responsible for arterial hypertension, the **combined strategy** is associated with greater efficacy in reducing cardiovascular events and allows for a reduction in the dosage of individual active ingredients, with a consequent reduction of potential adverse events.
- Consumption increases with increasing age up to a maximum of 1428 DDD in men over 85 years of age, and the same applies to the prevalence of use (96.4%). This trend could be partially explained by the **greater fragility of the elderly population**, generally undergoing polytherapy, which also makes them more frequently at risk of adverse drug reactions. In addition, considering that these drugs are used for a wide range of diseases (e.g. angina pectoris, heart failure, atrial fibrillation, renal failure, hepatic decompensation), a strategy should be carefully implemented of therapeutic re-evaluation through the control of drug prescriptions, accompanied by a intensive monitoring of blood pressure values.

- Data from General Practice indicate an increase in the incidence of arterial hypertension (mostly in the 66-74 and 75-84 age groups), probably due to new diagnoses not made in 2020 because of the SARS-CoV-2 pandemic. The prevalence of hypertension (mostly in the ≤ 65 years range) also recorded an increase compared to 2020 (+1.9%). The cohort of patients diagnosed with hypertension recorded a **prevalence of use** equal to 76.0%, about 0.8% less than 2020. Some regional variability is also observed in the prevalence of arterial hypertension, with higher levels in the South and in the Islands (32.4%), compared to the Centre (28.6%) and the North (28.0%).

References

- Haeusler KG, Huttner HB, Kuramatsu JB. Comment on 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2019; 40(25):2092.
- Mennini FS, Marcellusi A, von der Schulenburg JM et al. Cost of poor adherence to anti-hypertensive therapy in five European countries. Eur J Health Econ 2015; 16(1):65-72.
- Morganti A, Nardin C, Pauletto P, Trimarco B. La gestione del paziente iperteso nella pratica cli- nica. AboutOpen 2017; 3(1):24-2.
- NICE guideline [NG136]. Hypertension in adults: diagnosis and management. Available at the address https://www.nice.org.uk/guidance/ng136/
- Rea F, Corrao G, Merlino L. Initial antihypertensive treatment strategies and therapeutic inertia. Hypertension 2018; 72(4):846-53.
- Shani M, Lustman A, Vinker S. Adherence to oral antihypertensive medications, are all medica- tions equal? J Clin Hypertens (Greenwich) 2019; 21(2):243-8.
- Tocci G, Ferrucci A, Pontremoli R et al. Blood pressure levels and control in Italy: comprehensive analysis of clinical data from 2000-2005 and 2005-2011 hypertension surveys. J Hum Hypertens 2015; 29:696-701.
- Torlasco C, Faini A, Makil E. Nation-wide hypertension screening in Italy: data from May Measure- ments Month 2017-Europe. Eur Heart J Suppl 2019; 21(Suppl D): D66-D70.
- Townsend N, Wilson L, Bhatnagar P et al. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J 2016; 37(42):3232-45.
- Vandenberghe D, Albrecht J. The financial burden of non-communicable diseases in the Euro- pean Union: a systematic review. Eur J Public Health 2019; ckz073.
- Vidal-Petiot E, Elbez Y, Lüscher TF. The 2018 ESC-ESH guidelines for the Management of arterial hypertension leave clinicians facing a dilemma in half of the patients. Eur Heart J 2018; 39(45):4040-1.
- Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Associ- ation Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018; 71: e127-e248.
- Williams B, Mancia G, Spiering W et al., on behalf of ESC Scientific Document Group. 2018 ESC/ ESH guidelines for the management of arterial hypertension. Eur Heart J 2018 Sep 1; 39(33):3021- 104.

3.2.2 Lipid-lowering medicines

Epidemiological framework

Dyslipidemias are a major modifiable risk factor for cardiovascular diseases, in particular for coronary heart disease, stroke, heart failure and renal failure. It has long been known that lipid-lowering drugs used in the treatment of dyslipidemias have a favorable cost-effectiveness ratio, with benefits in both primary and secondary prevention. In Italy lipid-lowering drugs, with the exception of new monoclonal antibodies, are prescribed by GPs in accordance with Note 13, which limits their reimbursement by the National Health System (NHS). Statins are generally the first-line treatment, while the ezetimibe/statin combination is considered second choice. Based on the score assigned, patients are divided into different risk categories:

- medium risk (who are recommended a lifestyle correction for a period of at least 6 months);
- moderate risk;
- high risk;
- very high risk.

Note 13 establishes that treatment with lipid-lowering drugs can be reimbursed by the NHS up to the age of 80, since beyond that age there is insufficient evidence to support a real benefit.

For the treatment of familial dyslipidemia, high-risk clinical conditions, in statin-intolerant patients, alternatively ezetimibe is reimbursed in monotherapy. For some of these dyslipidemias, fibrates in combination with N3 PUFAs can also be used as second-line treatment. In some conditions, it is also possible to prescribe bile acid sequestering resins in third-line treatment.

National data on consumption and expenditure

Consumption of lipid-lowering drugs has shown a 38% increase over the years, moving from 79 DDD/1000 inhabitants per day in 2014 to 109.1 in 2021 (CAGR +4.7%). The average DDD cost, on the other hand, recorded a 30% decrease, going from 0.57 euros in 2014 to 0.40 in 2021 (Figure 3.2.2a). The per capita expenditure value for these drugs was equal to 16.12 euros, up 8.0% compared to the previous year, although the value of the CAGR, calculated for the last eight years, shows a slight decrease by 0.4% (Table 3.2.2a). Statins not in combination with other molecules are the therapeutic category with the highest per capita expenditure (8.14 euros), up 1.1% 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 expenditure and consumption trend for this subgroup over the last eight years shows an annual reduction of 3.7%, compared with an increase in consumption of 3.0%. Ezetimibe in combination, on the other hand, represents the second category with the highest expenditure, recording a value of 2.25 euros, up 13.6% compared to the previous year. For this class, an equally important increase was observed in terms of consumption (+38.5%), which stands at 11.4 DDD/1000 inhabitants per day. Particularly interesting is the reduction in the average cost per day of ezetimibe therapy, especially in combination (-17.8%), probably attributable to patent expiries in recent years.

Therefore, the expenditure trend overall appears to be consistent with the reimbursement indications of Note 13. Among lipid-lowering drugs, the active ingredient volanesorsen showed the highest average DDD cost (8190.19 euros). This drug is indicated as a dietary adjuvant in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk of pancreatitis, who do not adequately respond to diet and triglyceride-lowering therapy. The second class with the highest average DDD cost is microsomal triglyceride transport protein (MTP) inhibitors, including the active ingredient lomitapide, authorized as adjuvant therapy in adult patients with homozygous familial hypercholesterolemia (HoFH), with an average DDD cost equal to 811.11 euros, although showing a 6.1% decrease compared to the previous year. On the other hand, particularly interesting is the increase, compared to 2020, in expenditure and consumption (respectively by 46.2% and 49.9%) of PCSK-9 inhibitors, which rank third for average DDD cost.

Atorvastatin is the active ingredient with the highest per capita expenditure (4.62 euros), up 2.7% compared to 2020, and 6.0% in the last eight years; however, it recorded the lowest average DDD cost, equal to 0.25 euros. The consumption value was 51.6 DDD/1000 inhabitants per day, a 2.5% 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 13.10 euros and 8.44 euros; they are among the top ten active ingredients per annual expenditure.

Campania in 2021 recorded the highest value in terms of consumption, with 127.9 DDD/1000 inhabitants per day, while Valle d'Aosta recorded the lowest value, equal to 69.3 DDD (Table 3.2.2b). In general, the consumption data of the Regions of the Centre is aligned with the national value, respectively 108.6 and 109.1 DDD/1000 inhabitants per day. The North showed a lower dose consumption (102.3 DDD/1000 inhabitants per day), while the South showed a higher value (119.04 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. Piedmont, Valle d'Aosta, Liguria, Abruzzo, Molise consumed the least quantities of the drug, but at the highest cost per day of therapy. Campania, Puglia, Basilicata, Calabria and Lazio are the regions consuming the largest quantities and with the highest cost.

Figure 3.2.2a Lipid-lowering medicines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

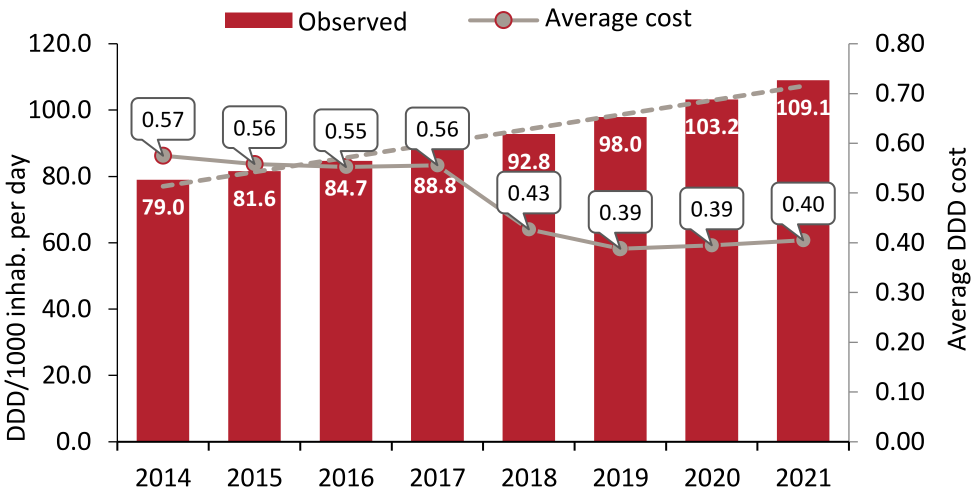


Table 3.2.2a Lipid-lowering medicines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Statins, plain	8.14	1.1	-3.7	83.4	1.6	3.0	0.27	-0.2
Ezetimibe in combination	2.25	13.6	-2.3	11.4	38.5	18.3	0.54	-17.8
Omega 3	2.09	8.0	0.4	5.0	8.6	4.7	1.15	-0.4
Ezetimibe	1.57	11.9	8.3	5.9	13.1	22.7	0.73	-0.8
PCSK9 inhibitors	1.52	46.2	-	0.4	49.9	-	10.58	-2.2
Fibrates	0.40	2.4	1.4	2.9	2.6	1.9	0.38	0.1
MTP inhibitor	0.12	-0.9	-	0.0	5.7	-	811.11	-6.1
Amlodipine/atorvastatin/perindopril	0.02	>100	-	0.1	98.3	-	0.45	5.1
Other lipid modifying agents	0.02	-	-	0.0	-	-	8190.19	-
Statins in combination	<0.005	>100	-	<0.05	>100	-	0.22	-1.5
Lipid-lowering medicines	**16.12**	**8.0**	**-0.4**	**109.1**	**5.6**	**4.7**	**0.40**	**2.5**
atorvastatin	4.62	2.7	6.0	51.6	2.5	6.6	0.25	0.5
omega 3	2.09	8.0	0.4	5.0	8.6	4.7	1.15	-0.4
ezetimibe	1.57	11.9	8.3	5.9	13.1	22.7	0.73	-0.8
simvastatin	1.45	-5.0	-3.4	12.3	-5.0	-3.4	0.32	0.3
rosuvastatin	1.41	4.9	-15.9	15.0	5.9	0.9	0.26	-0.6
ezetimibe/simvastatin	1.21	1.3	-10.6	5.1	2.2	5.3	0.66	-0.6
ezetimibe/rosuvastatin	1.03	31.3	-	6.3	91.5	-	0.45	-31.2
evolocumab	0.86	51.4	-	0.2	52.1	-	13.10	-0.2
alirocumab	0.66	39.9	-	0.2	48.0	-	8.44	-5.2
fenofibrate	0.38	2.9	2.0	2.7	3.1	2.5	0.38	0.1

Table 3.2.2b Lipid-lowering medicines, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	12.29	84.4	0.40	13.36	89.8	0.41	8.8	6.5	2.4	-1.0	4.4	-5.3
Valle d'Aosta	9.57	66.3	0.39	10.48	69.3	0.41	9.5	4.5	5.0	-2.4	2.7	-5.0
Lombardy	12.79	94.7	0.37	13.87	101.5	0.37	8.4	7.1	1.5	-1.2	4.9	-5.8
Province of Bolzano	9.57	84.2	0.31	10.19	88.8	0.31	6.4	5.5	1.2	-0.4	6.0	-6.1
Province of Trento	11.78	88.9	0.36	12.72	96.8	0.36	8.0	8.9	-0.5	-0.8	5.8	-6.3
Veneto	13.39	101.4	0.36	14.26	107.4	0.36	6.5	5.9	0.9	-1.5	4.6	-5.8
Friuli VG	14.24	110.7	0.35	14.38	110.2	0.36	1.0	-0.5	1.7	-1.8	4.4	-6.0
Liguria	13.26	87.6	0.41	14.70	93.3	0.43	10.9	6.5	4.4	0.1	4.7	-4.3
Emilia R.	13.50	107.6	0.34	15.10	115.2	0.36	11.8	7.0	4.8	1.1	4.9	-3.6
Tuscany	12.58	94.3	0.36	13.64	100.2	0.37	8.4	6.2	2.4	1.0	4.9	-3.6
Umbria	14.62	100.2	0.40	16.19	106.3	0.42	10.8	6.1	4.6	3.2	5.7	-2.3
Marche	16.32	115.8	0.39	17.79	123.9	0.39	9.0	7.0	2.1	-0.5	4.8	-5.1
Lazio	17.26	106.5	0.44	18.16	110.6	0.45	5.2	3.9	1.5	-2.0	3.1	-5.0
Abruzzo	15.28	98.8	0.42	16.53	104.1	0.43	8.1	5.4	2.9	0.9	5.6	-4.4
Molise	14.12	87.4	0.44	15.27	93.3	0.45	8.2	6.8	1.6	-1.8	4.7	-6.2
Campania	20.21	120.9	0.46	22.56	127.9	0.48	11.6	5.8	5.8	3.1	6.1	-2.8
Puglia	16.87	112.1	0.41	17.99	117.5	0.42	6.6	4.8	2.0	-1.4	4.6	-5.7
Basilicata	16.01	104.2	0.42	18.13	111.8	0.44	13.2	7.2	5.9	3.0	5.9	-2.7
Calabria	17.01	107.5	0.43	18.37	112.1	0.45	7.9	4.3	3.8	-1.1	4.1	-5.0
Sicily	16.17	113.0	0.39	17.04	117.8	0.40	5.4	4.2	1.4	-0.1	5.1	-4.9
Sardinia	17.32	119.2	0.40	18.02	124.4	0.40	4.0	4.4	0.0	-3.7	3.6	-7.0
Italy	**14.92**	**103.2**	**0.39**	**16.12**	**109.1**	**0.40**	**8.0**	**5.6**	**2.5**	**-0.4**	**4.7**	**-4.9**
North	12.93	96.2	0.37	14.03	102.3	0.38	8.5	6.3	2.3	-0.8	4.8	-5.3
Centre	15.43	103.3	0.41	16.51	108.6	0.42	7.0	5.2	2.0	-0.7	4.0	-4.6
South and Islands	17.48	113.4	0.42	18.89	119.0	0.43	8.1	5.0	3.2	0.3	5.1	-4.6

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 (expressed as DDD/1000 inhabitants per day) in the 75-84 age group, then decreases in the over 85 group (Figure 3.2.2b). Analysing exposure by gender, men were clearly more exposed than women, regardless of age. Furthermore, prevalence of use tends to be higher in the Southern regions (15.2%), compared to Central (13.8%) and Northern regions (12.3%) (Table 3.2.2c).

Analysis of the therapy duration showed that half of the users were treated for a period of at least eight months (median DDD 228), although even lower values were recorded in Southern regions (median DDD 224). About half of the observed users are 71 years old. Prevalence of use of lipid-lowering agents in the population is 13.5% and, on average, each user is treated for 285.4 days (about 10 months); in addition, 3.8% of users received only one prescription.

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. Therefore, in order to achieve the expected benefit, besides choosing the most appropriate treatment, it is essential that the patient takes the drugs continuously. Failure to adhere to lipid-lowering treatment, in fact, leads to negative effects both in terms of public health (increase in the number of potentially preventable events) and health costs due to an ineffective therapy or costs linked to possible side effects requiring further treatments, therapeutic adjustments or hospitalizations. However, numerous studies indicate that adherence to statin treatment is limited. For this reason, using Health Card data, an analysis was performed to estimate the 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 245,367 new users, with a median age of 67 years (IQR 58-73), and a greater proportion of women than men (53.7% vs 46.3%).

The percentage of patients with high and low adherence to treatment was respectively 42.8% and 15.1% (Table 3.2.2d). As in the case of antihypertensives, low adherence tends to increase with age, recording the highest value in people over 85 (19%) and in women (17%) compared to men (13%). Users residing in Northern Italy and aged between 55 and 64 years have a higher percentage value of high adherence, equal to 46.8%.

Analysing persistence to lipid-lowering drugs, there is an overall improvement compared to the previous year (Δ% 21-20 +3%) (Table 3.2.2e); less than half of new users were found to be persistent to treatment (48.5%), with a trend similar to the national value in the Central Regions (49.2%), a higher value in the Northern Regions (50.8%) and a lower value in the Southern Regions (45.3%). Men recorded higher persistence rates (52.5%) than women (45.1%). By evaluating the persistence for different time intervals, the percentage of patients persistent to treatment decreases as the observation time increases, going from 45.4% at 12 months from the beginning of treatment (Table 3.2.2e, Figure 3.2.2c) to 36.4% at 24 months from the beginning of treatment (Table 3.2.2f, Figure 3.2.2d).

Figure 3.2.2b Distribution of prevalence of use and consumption of medicines for lipid-lowering drugs under approved care regime and “on-behalf” distribution in 2021

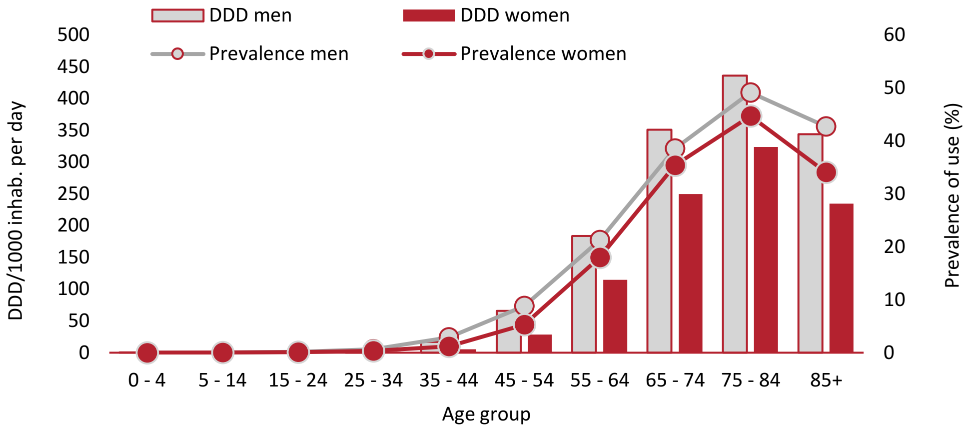


Table 3.2.2c Exposure and duration of therapy with lipid-lowering medicines by Region under approved care regime and "on-behalf" distribution (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	men	women	total					
Piedmont	13.0	11.7	12.3	72	97.3	270.2	224.0	2.9
Valle d'Aosta	10.0	8.6	9.3	72	100.2	262.2	205.3	2.3
Lombardy	12.9	11.6	12.3	71	103.5	293.9	240.0	2.6
Province of Bolzano	9.4	8.3	8.9	73	98.8	325.8	261.3	2.2
Province of Trento	11.7	10.8	11.3	72	103.4	297.7	240.0	2.3
Veneto	13.0	11.5	12.3	72	107.7	311.9	242.7	2.3
Friuli VG	13.4	12.2	12.8	73	108.4	323.9	261.3	1.9
Liguria	13.3	12.7	13.0	73	101.6	275.3	236.0	4.0
Emilia R.	13.8	13.5	13.6	72	98.6	275.0	224.0	2.8
Tuscany	13.3	12.6	13.0	73	95.6	284.1	224.0	5.9
Umbria	14.3	13.8	14.0	72	105.8	281.1	240.0	4.8
Marche	15.7	15.3	15.5	72	108.7	295.6	240.0	3.3
Lazio	14.3	14.3	14.3	71	114.4	274.7	232.0	3.5
Abruzzo	14.1	13.8	13.9	70	108.0	272.5	224.0	4.8
Molise	14.1	14.0	14.1	71	106.7	254.4	224.0	4.1
Campania	15.7	16.1	15.9	68	105.7	266.0	224.0	4.6
Puglia	15.4	15.8	15.6	70	101.0	266.0	224.0	3.4
Basilicata	15.0	15.3	15.1	70	98.8	267.8	224.0	5.5
Calabria	15.3	15.3	15.3	69	102.3	256.6	213.3	6.1
Sicily	15.2	15.8	15.5	70	101.9	267.8	224.0	5.2
Sardinia	14.3	15.6	15.0	71	112.9	309.9	242.7	3.6
Italy	**13.7**	**13.3**	**13.5**	**71**	**105.9**	**285.4**	**228.0**	**3.8**
North	12.8	11.8	12.3	72	104.0	295.3	240.0	2.7
Centre	13.9	13.6	13.8	72	109.4	285.8	240.0	4.4
South and Islands	15.0	15.4	15.2	70	105.7	273.5	224.0	4.7

Table 3.2.2d Indicators of adherence to treatment with lipid-lowering drugs in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

	Total N=245.367				North N=104.352				Centre N=51.788				South N=89.227			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*^																
45-54 years	16.1	15.7	14.3	-8	13.4	12.9	12.2	-5	15.9	16.3	14.6	-10	18.5	17.7	16.3	-8
55-64 years	15.4	15.1	14.1	-7	12.9	13.1	11.7	-11	15.5	15.2	14.2	-7	17.9	16.9	16.6	-2
65-74 years	16.6	16.1	15.2	-5	14.5	14.1	13.0	-8	16.5	16.2	15.5	-4	18.8	18.0	17.7	-2
75-84 years	17.4	16.8	16.7	-1	15.6	15.0	14.5	-3	17.2	17.7	17.4	-2	20.0	18.8	19.5	4
≥85 years	18.8	19.1	19.0	0	16.8	17.3	16.1	-7	18.9	19.1	20.2	6	21.1	21.1	22.1	5
Women	18.4	18.0	17.0	-6	16.1	16.1	40.5	153	18.5	18.4	38.1	108	20.6	19.6	35.3	80
Men	14.4	13.9	13.0	-6	12.4	11.9	51.2	330	14.0	14.1	48.2	241	16.7	15.8	45.0	185
Total	**16.5**	**16.0**	**15.1**	**-6**	**14.3**	**14.0**	**12.9**	**-8**	**16.4**	**16.4**	**15.5**	**-6**	**18.8**	**17.9**	**17.5**	**-2**
High adherence*^																
45-54 years	40.2	41.7	42.7	2	43.1	45.9	46.2	1	41.7	40.8	42.8	5	37.2	38.6	39.3	2
55-64 years	41.5	42.2	43.8	4	44.6	45.1	46.8	4	42.1	42.8	44.2	3	38.2	39.4	40.5	3
65-74 years	40.3	41.8	42.6	2	42.7	44.7	45.3	1	40.9	41.8	42.2	1	37.5	38.8	39.5	2
75-84 years	40.6	41.9	42.2	1	43.1	43.9	44.5	1	40.9	42.0	41.5	-1	37.2	39.2	39.1	0
≥85 years	40.7	41.6	40.9	-2	43.0	44.4	43.5	-2	42.5	42.2	41.4	-2	36.8	38.1	37.0	-3
Women	35.7	37.2	38.1	2	38.2	39.5	40.5	3	36.4	37.0	38.1	3	32.9	35.0	35.3	1
Men	46.3	47.2	48.4	2	48.8	50.2	51.2	2	47.1	47.7	48.2	1	43.1	43.8	45.0	3
Total	**40.7**	**41.9**	**42.8**	**2**	**43.4**	**44.8**	**45.6**	**2**	**41.4**	**42.0**	**42.7**	**2**	**37.6**	**39.0**	**39.7**	**2**

*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, who received a first prescription in the period 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.

Percentages of people with low/high adherence relating to the specific category.

Median follow-up time (IQR): 322 (257-345).

Table 3.2.2e Persistence after one year of treatment with lipid-lowering drugs in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

Persistence after 12 months	Total N=245.367				North N=104.352				Centre N=51.788				South N=89.227			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54 years	46.1	46.5	48.2	4	48.6	49.7	51.2	3	47.7	46.4	48.7	5	43.3	44.0	45.0	2
55-64 years	48.3	48.7	50.3	3	51.0	51.2	53.1	4	49.6	48.6	51.6	6	45.2	46.5	46.7	0
65-74 years	47.8	48.0	49.1	2	49.5	50.1	51.0	2	47.9	48.2	50.3	4	46.0	45.9	46.2	1
75-84 years	45.9	45.6	45.9	1	47.6	47.1	48.1	2	45.6	45.5	45.4	0	43.9	43.7	42.8	-2
≥85 years	43.0	42.7	42.5	0	44.8	45.8	45.4	-1	43.9	43.0	42.8	0	40.4	39.1	38.5	-2
Women	43.1	43.6	45.1	3	44.5	45.1	46.8	4	43.6	43.3	45.7	6	41.5	42.3	42.7	1
Men	51.5	51.3	52.5	2	53.9	53.9	55.2	2	52.1	51.6	53.4	3	48.5	48.4	48.5	0
Total	**47.1**	**47.2**	**48.5**	**3**	**49.1**	**49.4**	**50.8**	**3**	**47.6**	**47.2**	**49.2**	**4**	**44.7**	**45.1**	**45.3**	**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 statistical methods)

Figure 3.2.2c 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)

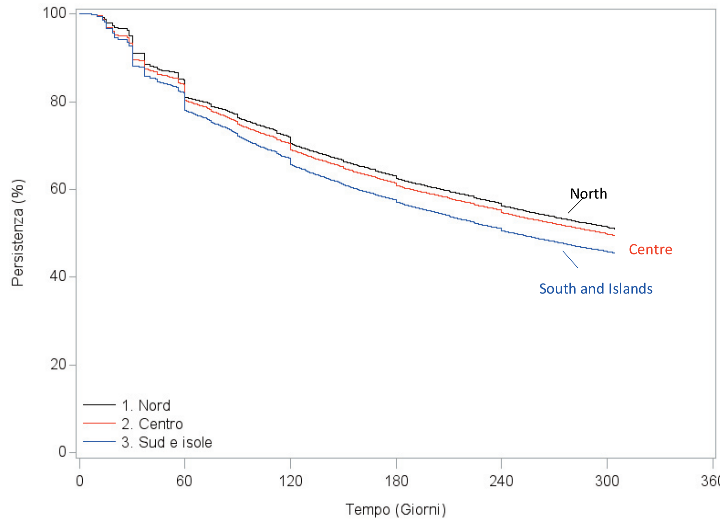
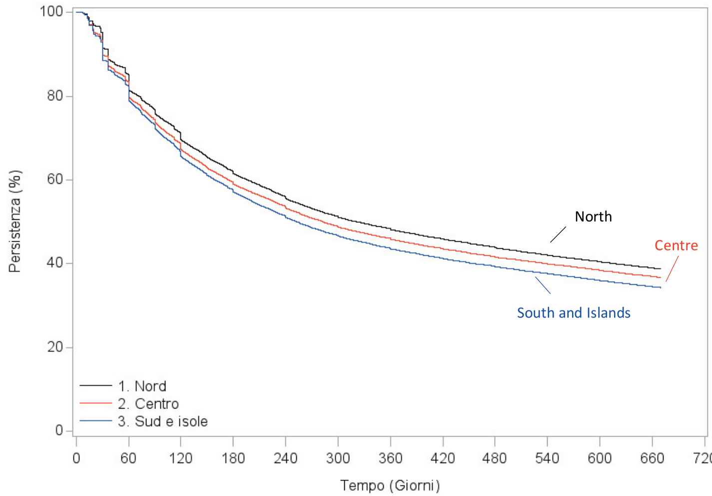


Table 3.2.2f Persistence to treatment with lipid-lowering drugs in the population aged ≥45 years in 2021 with 2 years of follow-up

Persistence (%)	Total N=215.768			North N=85.417			Centre N=43.858			South N=86.493		
	12 months	18 months	24 months	12 months	18 months	24 months	12 months	18 months	24 months	12 months	18 months	24 months
45-54 years	45.5	39.5	36.3	48.8	43.0	39.9	45.4	39.1	36.0	42.9	36.8	33.6
55-64 years	47.1	41.2	38.0	50.0	43.8	40.7	46.9	41.5	38.4	44.6	38.6	35.5
65-74 years	46.0	40.1	37.2	48.4	42.4	39.4	46.3	40.6	37.7	43.5	37.7	34.7
75-84 years	43.1	37.2	34.3	44.5	38.5	35.7	43.0	37.3	34.4	41.2	35.4	32.5
≥85 years	40.2	34.1	31.0	43.6	37.5	34.3	40.4	33.3	30.4	36.5	31.0	27.8
Women	41.5	35.3	32.2	43.3	36.9	33.7	41.2	35.1	32.1	40.0	33.9	30.8
Men	49.8	44.2	41.3	52.5	46.8	44.0	50.1	44.6	41.7	46.7	41.2	38.2
Total	45.4	39.5	36.4	47.8	41.7	38.8	45.4	39.5	36.6	43.0	37.2	34.1

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 2 years

Figure 3.2.2d Time (in days) to discontinuation of treatment with lipid-lowering drugs after 2 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)



Epidemiology and prescribing profiles in General Medicine

The data relating to epidemiology and prescribing profiles were obtained through a network of GPs "approved" according to a series of quality criteria in data recording, homogeneously distributed throughout Italy, bringing together to Health Search-IQVIA Health LPD all information relating to: diagnosis of pathology, demographic information, pharmaceutical prescription, as well as outpatient specialist services, laboratory parameters and exemptions for disease or disability.

The analyses focused on the prevalence and incidence of hypetension in the population treated by the 800 GPs of the HS network for the years 2019, 2020 and 2021. In addition, the prevalence of use of drugs was assessed, considering the most used therapeutic categories, as well as the related trend.

The incidence of dyslipidemia in the population assisted by the GPs of the HS network in 2021 was 14.2‰, an increase of 38.9% compared to 2020 (Table 3.2.2g). In detail, the incidence of polygenic hypercholesterolemia stands at 13.2, while the incidence of hyperlipidemias associated with moderate or severe chronic renal failure stands at 1.5‰. By analyzing the incidence of this condition on a geographical basis, it is possible to note a higher value of patients who are incident in the Centre and in the South and Islands (14.7‰ each), compared to the North (13.7‰). Furthermore, for all three areas considered, the incidence estimates showed a sharp increase compared to 2020.

The analysis by gender shows higher values in women (16.6‰) than in men (11.8‰), while stratifying by age, the highest incidence is observed in the 66-74 age group (32.6‰). Compared to the 2020 estimates, a negative change in the incidence of disease (-1.7%) was recorded only for people aged 85 or over.

As regards the prevalence, this is equal to 19.6%, with a 5.4% increase compared to the previous year (Table 3.2.2h), and with a value of 20.6% for women and 18.6% for men. Stratifying the analysis by age group, the highest prevalence is found in people aged between 75 and 84 (41.0%).

In 2021, the prevalence of use of lipid-lowering drugs in patients suffering from dyslipidemia (Table 3.2.2i) was 47.9%, a 2.6% increase compared to the previous year and with higher values in the South (51.4%) than the Centre (47.5%) and the North (44.8%). The age stratification shows a higher prevalence of use in people aged between 75 and 84 years (66.1%); this estimate, however, tends to decrease in patients over 85 (54.0%). Analyzing the prevalence of use according to the different categories of dyslipidemia, patients suffering from hyperlipidemia with moderate to severe chronic renal failure show the highest estimate (56.9%), while only 32.8% of patients with other dyslipidemias, which include dysbetalipoproteinemias, hyperchylomicronemias, hypertriglyceridemias, drug-induced hyperlipidemias, received at least one prescription of a lipid-lowering drug in the year. Analyzing the prevalence of use of lipid-lowering drugs stratified by therapeutic category (Table 3.2.2j), statins are the most used category (39.7%), regardless of the type of dyslipidemia considered. The maximum value is recorded in patients with hyperlipidemia associated with moderate to severe chronic renal failure (47.0%), followed by those with familial dyslipidemia (42.2%), polygenic hypercholesterolemia (40.1%), and finally by patients with other dyslipidemias (16.4%). The latter category shows a percentage of prevalence of use equal to 10.9% and 11.9% for omega-3 and fibrates respectively.

Analyzing the trend of prevalence of use (2019-2021) stratified by therapeutic category, substantially stable trends are observed for all classes over the period (Figure 3.2.2e). Finally, the analysis of the prevalence of use of statins in patients aged ≥80 years in primary prevention shows that 39.8% of patients were treated with these drugs during 2021 (Table 3.2.2k), a percentage which stands at 36.4% for non-diabetic patients over eighty.

Table 3.2.2g Incidence of dyslipidemia and its different forms in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: stratified analysis by gender, age group and geographic area (Year 2021)

	Incidence (‰)					
	Dyslipidemia	Δ % 21-20	Polygenic hypercholesterolemia	Familial dyslipidemia	Other dyslipidemias*	Hyperlipidemias with moderate/severe CRF**
Geographic analysis						
North	13.7	50.6	12.7	0.6	0.4	1.5
Centre	14.7	22.9	13.7	0.6	0.5	1.7
South and Islands	14.7	36.4	13.4	0.8	0.4	1.6
Analysis by gender						
Men	11.8	31.8	10.8	0.6	0.6	1.4
Women	16.6	44.6	15.6	0.8	0.3	1.7
Analysis by age						
≥45 years	3.7	39.7	3.1	0.3	0.2	0.2
46-65	22.1	50.3	20.4	1.2	0.6	2.0
66-74	32.6	39.2	30.9	1.0	0.7	4.3
75-84	21.2	22.0	20.1	0.7	0.4	4.0
≥85	8.0	-1.7	7.5	0.3	0.2	1.9
Total	**14.2**	**38.9**	**13.2**	**0.7**	**0.4**	**1.5**

*Other dyslipidemias: dysbetalipoproteinemias, hyperchilomicronemias, hypertriglyceridemias, drug-induced hyperlipemia
**Chronic renal failure

Indicators used:
Incidence of dyslipidemia: number of patients with a "first" diagnosis of dyslipidemia recorded during the year [**numerator**], out of the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Incidence of different forms of dyslipidemia: number of patients with a "first" diagnosis of polygenic hypercholesterolemia or familial dyslipidemia or with other dyslipidemias (dysbetalipoproteinemias, hyperchylomicronemias, hypertriglyceridemias, drug hyperlipemia) [**numerator**], out of the total population at risk (disease free) at the beginning of the period **[denominators]**

Incidence of hyperlipidemias with moderate/severe CRF: number of patients with a "first" diagnosis of hyperlipidemia and with moderate or severe CRF [**numerator**], out of the total population at risk (disease free) at the beginning of the period [**denominators**]

Table 3.2.2h Incidence of dyslipidemia and its different forms in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: stratified analysis by gender, age group and geographic area

	Prevalence (%)					
	Dyslipidemia	Δ % 21-20	Polygenic hypercholesterolemia	Familial dyslipidemia	Other dyslipidemias *	Hyperlipidemias with moderate/ severe CRF**
Geographic analysis						
North	19.2	4.9	17.7	1.4	0.3	3.6
Centre	18.9	6.2	17.2	1.5	0.4	3.5
South and Islands	20.4	5.7	18.3	2.1	0.5	4.0
Analysis by gender						
Men	18.6	5.7	16.7	1.6	0.6	3.8
Women	20.6	5.6	18.9	1.8	0.2	3.7
Analysis by age						
≥45 years	3.8	11.8	3.1	0.6	0.2	0.3
46-65	22.1	10.5	19.8	2.2	0.5	2.8
66-74	39.6	6.7	36.6	3.0	0.7	8.3
75-84	41.0	4.3	38.6	2.4	0.5	11.7
≥85	34.0	4.6	32.3	1.6	0.4	12.1
Total	**19.6**	**5.4**	**17.8**	**1.7**	**0.4**	**3.8**

*Other dyslipidemias: dysbetalipoproteinemias, hyperchilomicronemias, hypertriglyceridemias, drug-induced hyperlipemia **Chronic renal failure

Indicators used:

Prevalence of dyslipidemia: number of patients diagnosed with hypertension [**numerator**], out of the total population eligible for assistance [**denominator**]

Prevalence of the different forms of dyslipidemia: number of patients with a diagnosis of polygenic hypercholesterolemia or familial dyslipidemia or other dyslipidemias (dysbetalipoprotheinemias, hyperchylomicronemias, hypertriglyceridemias, drug-induced hyperlipemia) [**numerator**], out of the total population eligible for assistance [**denominator**]

Incidence of hyperlipidemias with moderate/severe CRF: number of patients with diagnosis of hyperlipidemia and with moderate or severe CRF **[numerator]**, out of the total population eligible for assistance [**denominators**]

Table 3.2.2i Prevalence of use of lipid-lowering medicines in patients with dyslipidemia (general and in its various forms) and comparison 2021-2020: stratified analysis by gender, age group and geographic area (year 2021)

	Prevalence of use (%)					
	Dyslipidemia	Δ % 21-20	Polygenic hypercholesterolemia	Familial dyslipidemia	Other dyslipidemias*	Hyperlipidemias with moderate/ severe CRF**
Geographic analysis						
North	44.8	2.5	44.6	52.4	29.5	53.0
Centre	47.5	2.2	47.2	58.0	33.9	56.5
South and Islands	51.4	2.6	51.4	58.9	34.9	61.3
Analysis by gender						
Men	45.9	0.7	46.1	52.8	31.0	56.8
Women	49.6	4.2	49.1	59.6	38.1	57.0
Analysis by age						
≥45 years	13.6	10.6	12.1	24.4	13.1	16.9
46-65	36.8	5.1	35.9	51.1	26.9	42.8
66-74	58.7	4.3	58.1	72.2	49.2	61.8
75-84	66.1	4.6	65.8	76.8	52.0	68.6
≥85	54.0	2.1	53.8	61.9	46.4	57.1
Total	**47.9**	**2.6**	**47.7**	**56.4**	**32.8**	**56.9**

*Other dyslipidemias: dysbetalipoproteinemias, hyperchilomicronemias, hypertriglyceridemias, drug-induced hyperlipemia **Chronic renal failure

Indicators used:

Prevalence of use of lipid-lowering medicines in patients with dyslipidemia and its different forms: number of patients treated with lipid-lowering medicines [**numerator**] out of the total of patients diagnosed with dyslipidemia and polygenic hypercholesterolemia or familial dyslipidemia or with other dyslipidemias (dysbetalipoprotheinemias, hyperchylomicronemias, hypertriglyceridemias, drug hyperlipemia) [**denominators**]

Prevalence of use of lipid-lowering drugs in patients with dyslipidemia and moderate/severe CRF: number of patients treated for a specific therapeutic category [**numerator**] on the total number of patients diagnosed with dyslipidemia and moderate/severe IRC [**denominators**]

Table 3.2.2j Prevalence of use (%) of lipid-lowering medicines in patients with dyslipidemia and its different forms and by therapeutic category: comparison 2021-2020

Analysis by therapeutic category	Prevalence of use (%)					
	Dyslipidemia	Δ % 21-20	Polygenic hypercholesterolemia	Familial dyslipidemia	Other dyslipidemias *	Hyperlipidemias in patients with moderate or severe CRF**
amlodipine/ atorvastatin/ perindopril	-	-	-	-	-	-
ezetimibe	3.3	13.8	3.2	5.3	1.3	4.0
ezetimibe in combination	6.0	39.5	5.8	9.3	2.8	7.5
fibrates	2.3	-4.2	2.0	4.7	11.1	2.5
MTP inhibitor	-	-	-	-	-	-
PCSK9 inhibitors	0	--	-	0.1	-	0.1
omega 3	3.4	3.0	3.0	7.5	10.9	4.7
statins, plain	39.7	0.0	40.1	42.2	16.4	47.0
statins in combination	-	-	-	-	-	-

Some estimates of prevalence of use may be affected by the type of supply regime and by an exclusively specialist prescription

*Other dyslipidemias: dysbetalipoproteinemias, hyperchilomicronemias, hypertriglyceridemias, drug-induced hyperlipemia

**CRF: chronic renal failure

Indicators used:

Prevalence of use of lipid-lowering medicines in patients with dyslipidemia and its different forms: number of patients treated with la specific therapeutic category [**numerator**] out of the total of patients diagnosed with dyslipidemia and polygenic hypercholesterolemia or familial dyslipidemia or with other dyslipidemias (dysbetalipoprotheinemias, hyperchylomicronemias, hypertriglyceridemias, drug hyperlipemia) [**denominators**]

Prevalence of use of lipid-lowering drugs in patients with dyslipidemia and moderate/severe CRF: number of patients treated for a specific therapeutic category [**numerator**] on the total number of patients diagnosed with dyslipidemia and moderate/severe IRC [**denominators**]

Table 3.2.2k Proportion of patients (total and non-diabetic) using statins in primary prevention within the population aged ≥80 and comparison 2021-2020 (year 2021)

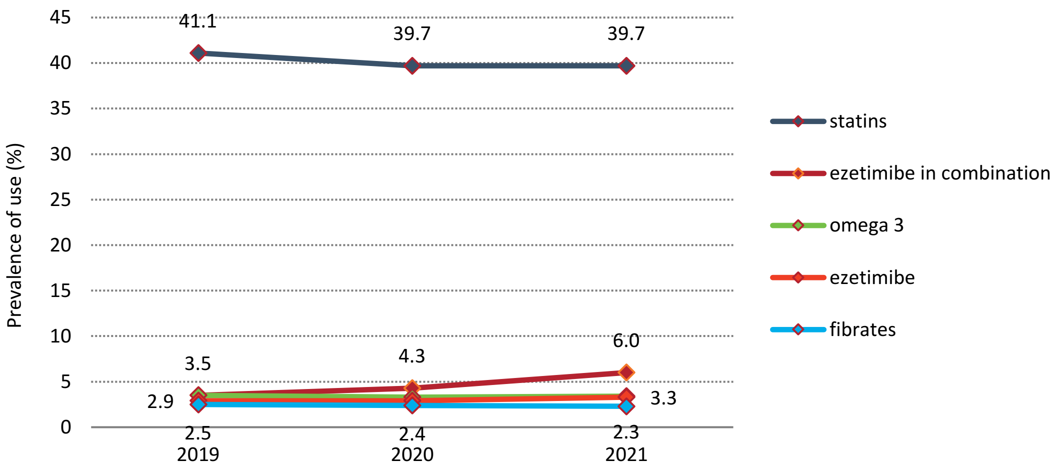
	Prevalence of use total population (%)	Δ% 21-20	Non diabetics	Δ% 21-20
Geographic analysis				
North	37.3	3.3	34	4.0
Centre	39.2	2.6	35.8	2.3
South and Islands	43.0	4.1	39.5	5.3
Analysis by gender				
Men	34.9	2.3	30.9	3.0
Women	43.9	5.0	40.8	5.4
Analysis by age				
80-84	56.8	3.8	53.7	3.9
85-90	50.5	1.6	48	1.5
90+	38.9	3.7	36.1	3.1
Total	**39.8**	**3.6**	**36.4**	**4.3**

Indicators used:

Proportion of patients using statins in primary prevention within the population aged ≥80: number of patients treated with statins for primary prevention and aged ≥80 [**numerator**] on the total of the population eligible for assistance aged ≥80 [**denominator**]

Proportion of non-diabetic patients using statins in primary prevention within the population aged ≥80: number of non-diabetic patients treated with statins for primary prevention and aged ≥80 [**numerator**] on the total of the population eligible for assistance aged ≥80 [**denominator**]

Figure 3.2.2e Prevalence of use of lipid-lowering medicines in patients with dyslipidemia: analysis by therapeutic category (years 2019-2021)



Indicators used:

Prevalence of use of lipid-lowering drugs in patients with dyslipidemia: number of patients treated for a specific therapeutic category [**numerator**] on the total number of patients diagnosed with dyslipidemia [**denominators**]

Key message

- Lipid-lowering drugs over the years have seen a **constant increase in consumption** (CAGR +4.7%), which in 2021 was 109.1 DDD/1000 inhabitants per day. In parallel, the average cost per day of therapy appears to be increasing compared to 2020, probably due to the market entry of new active ingredients.
- **PCSK9 inhibitors confirm the increasing trend**, both in terms of expenditure and consumption, compared to 2020. These drugs, authorized by the EMA since 2015, have shown a good efficacy profile in patients with familial hypercholesterolemia resistant to conventional therapy, together with an acceptable safety profile. In addition, recent studies have confirmed their effectiveness even in patients at high/very high cardiovascular risk and/or in secondary prevention. New epidemiological studies estimate the size of the population eligible for treatment with PCSK9 to be over 100,000 people, confirming the need to continue the **supervisory activity on prescribing appropriateness** through the AIFA registries, in light of the health costs incurred for this category of lipid-lowering drugs.
- The proportion of people with high **adherence to lipid-lowering drugs is significantly lower** than that observed for drugs for arterial hypertension and heart failure. Although the elderly population, as is the case with most drugs, is characterized by probable cognitive deterioration, comorbidities, multiple treatments and changes in socio-economic conditions that affect compliance with therapy, the more limited adherence may be partially attributed to the likely low safety profile of lipid-lowering drugs, generally perceived by the population at risk. Also, the absence of immediate unfavorable symptoms due to treatment discontinuation, as is otherwise the case for the failure to take antihypertensive drugs and for heart failure, promotes discontinuation of such medicines.
- The extreme regional variability is also confirmed for this therapeutic category, with the North showing a higher adherence profile than the Central and Southern Regions and Islands. This data appears even more significant because the greater consumption of these drugs is recorded precisely in the South and in the Islands which, not necessarily, are at higher risk (and therefore require treatment), as there are no substantial differences in the regional distribution of cardiovascular risk.
- Both consumption and exposure reach a peak in the 75-84 age group and subsequently decrease in the over 85s, as already observed for hypertension and heart failure drugs. Adherence also decreases with increasing age, with minimum values in patients aged 85 or over. Several meta-analyzes suggest a beneficial effect of lipid-lowering drugs in terms of reducing the risk of cardiovascular events even for **very elderly patients**. Efficacy of these drugs in primary prevention has not yet been demonstrated for this age group; however, data from General Practice confirm their wide use both in the over 85s and in the over 90s.

References

- Arca M, Ansell D, Averna M et al. Statin utilization and lipid goal attainment in high or very-high cardiovascular risk patients: insights from Italian general practice. Atherosclerosis 2018; 271:120-7.
- Blackburn DF, Dobson RT, Blackburn JL, Wilson TW. Cardiovascular morbidity associated with nonadherence to statin therapy. Pharmacotherapy 2005; 25(8):1035-43.
- Byrne P, Cullinan J, Smith A et al. Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews. BMJ Open 2019; 9(4): e023085.
- Chou R, Dana T, Blazina I, Daeges M et al. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016; 316(19):2008-24.
- Corrao G, Conti V, Merlino L, Catapano AL, Mancia G. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. Clin Ther 2010; 32(2):300-10.
- European Association for Cardiovascular Prevention & Rehabilitation; Reiner Z, Catapano AL, De Backer G et al., ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32(14):1769-818.
- Ferrajolo C, Arcoraci V, Sullo MG et al. Pattern of statin use in southern Italian primary care: can prescription databases be used for monitoring long-term adherence to the treatment? PLoS One 2014; 9(7): e102146.
- Official Gazette, no. 156 (Resolution no. 617/2014, of 8-7-2014). Modification to Note no. 13 referred to in Resolution of 26 March 2013.
- Maggioni AP, Rossi E, Cinconze E et al. Use and misuse of statins after ACS: analysis of a prescrip- tion database of a community setting of 2,042,968 subjects. Eur J Prev Cardiol 2014; 21(9):1109- 16.
- Martin-Ruiz E, Olry-de-Labry-Lima A, Ocaña-Riola R. Systematic review of the effect of adherence to statin treatment on critical cardiovascular events and mortality in primary prevention. J Cardi- ovasc Pharmacol Ther 2018; 23(3):200-15.
- Rannanheimo PK, Tiittanen P, Hartikainen J. Impact of statin adherence on cardiovascular mor- bidity and all-cause mortality in the primary prevention of cardiovascular disease: a population-based cohort study in Finland. Value Health 2015; 18(6):896-905.
- Sessa M, Rafaniello C, Scavone C et al. Preventable statin adverse reactions and therapy discontinuation. What can we learn from the spontaneous reporting system? Expert Opin Drug Saf 2018; 17(5):457-65.

3.2.3 Acute Coronary Syndrome

Epidemiological framework

Acute coronary syndrome (ACS) includes a series of clinical alterations, of laboratory and electrocardiographic parameters, with a partial or complete obstruction of the coronary arteries and consequent ischemia, which, if continued for a sufficiently long period of time, involves heart attack following myocardial cell necrosis. Of all deaths due to cardiovascular diseases, about 7 million are related to ischemic heart disease, of which about 1.8 million are attributable to ACS and sudden deaths. In Italy, the number of people affected yearly by coronary events exceeds 135,000 cases, of which about 45,000 are fatal.

In most European countries, a decrease has been observed in the mortality rate from ischemic heart disease, as well as from myocardial infarction. The patient who is able to survive becomes chronically ill, with major impacts on the quality of life and on economic and social costs. As indicated in numerous guidelines, it is extremely important to modify and improve unhealthy behaviours, to treat pharmacologically and to monitor the evolution of pathologies associated with the onset of ACS, not only in primary prevention, but also and above all in secondary prevention (characterized by several critical issues), although this is a key point in the management of the ACS patient. However, the pharmacological management of these patients appears to be associated with a progressive reduction in terms of therapeutic adherence, as well as with a complete treatment discontinuation in some cases. This exposes the patient to a high risk of further acute coronary events or death and, more generally, it can strongly affect both the patient's health and quality of life and the health costs associated with the increase in hospitalizations.

Epidemiology and prescribing profiles in General Medicine

The data relating to epidemiology and prescribing profiles were obtained through a network of GPs “approved” according to a series of quality criteria in data recording, homogeneously distributed throughout Italy, bringing together to Health Search-IQVIA Health LPD all information relating to: diagnosis of pathology, demographic information, pharmaceutical prescription, as well as outpatient specialist services, laboratory parameters and exemptions for disease or disability.

The analyses focused on the prevalence and incidence of acute coronary syndrome (ACS) in the population treated by the 800 GPs of the HS network for the years 2019, 2020 and 2021. In addition, it was assessed the prevalence of use of drugs for treatment of ACS, considering the most used therapeutic categories, for the same years.

In 2021, the incidence of ACS (first event considering the whole clinical history available) in the population eligible to medical assistance by GPs of the HS network was 0.8‰, with a -7.0% variation compared to the previous year (Table 3.2.3a). Overall, there is a slight reduction in the incidence of the disease starting from 2019, equal to about 0.1 percentage points per year.

Analyzing the incidence of this condition on a geographical basis, no substantial differences are recorded, although the Northern Regions show a slightly higher incidence (0.9‰) than the Centre (0.8‰) and the South and Islands (0.7 ‰). Compared to 2020, the greatest variation in terms of new diagnoses is observed in the Centre (-19.4%) and in the South

(-9.2%). Probably these variations are due to the reduced mobility of the patients, caused by the pandemic, which resulted in less access to health facilities used for diagnosis.
With regard to the prevalence of ACS, equal to 1.6%, it does not show particular differences between the different geographic areas. On the other hand, there is a lower prevalence of the disease in women (0.8%) than in men (2.3%); men also show a positive change in the prevalence estimate compared to 2020 (0.7%). Finally, the prevalence of the disease increases with increasing age, reaching the maximum value of 5.1% in people aged at least 85 years (Table 3.2.3b).
The prevalence of use of drugs (i.e., ACE inhibitors, sartans, beta-blockers, antiplatelet agents and lipid-lowering drugs) in patients with ACS was 85.9% in 2021 (Table 3.2.3c), a slightly lower figure compared to the previous year (-1.2%). The use of these drugs tends to be greater in the Centre (86.8%), compared to the South and Islands (85.6%) and the North (85.8%), while women (90.3%) and patients aged 75 to 84 years (95.3%) show the highest estimates. In terms of variation compared to the previous year, men record a -2.0% decrease, while the stratification by age group shows an estimate reduction in younger people.
Analyzing the prevalence of use according to the therapeutic categories selected, in 2021 lipid-lowering drugs (Table 3.2.3d) show the highest estimate (75.9%), followed by antiplatelet agents (70.8%) and beta-blockers (65.9%). The estimates are substantially overlapping with 2020, despite slight variations.

Table 3.2.3a Incidence of acute coronary syndrome in the population eligible for medical assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographic area (years 2019-2021)

	Incidence (‰)*			Δ %
	2019	2020	2021	21-20
Geographic analysis				
North	1.1	0.9	0.9	0.0
Centre	1.1	1.0	0.8	-19.4
South and Islands	1.0	0.8	0.7	-9.2
Analysis by gender				
Men	1.4	1.2	1.2	-1.7
Women	0.7	0.6	0.4	-20.0
Analysis by age				
≥45 years	0.1	0.1	0.0	-33.3
46-65	1.0	0.9	0.9	2.4
66-74	2.0	1.7	1.7	-4.6
75-84	2.6	2.0	2.0	-0.5
≥85	2.7	2.5	2.1	-14.2
Total	**1.0**	**0.9**	**0.8**	**-7.0**

*First event considering the patient's entire clinical history

Indicators used:
Incidence of acute coronary syndrome: number of patients with a “first” diagnosis of acute coronary syndrome recorded during the year [**numerator**], out of the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Table 3.2.3b Prevalence of acute coronary syndrome in the population eligible for medical assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographic area (years 2019-2021)

	Prevalence (%)			Δ %
	2019	2020	2021	21-20
Geographic analysis				
North	1.6	1.6	1.6	2.5
Centre	1.6	1.6	1.5	-0.6
South and Islands	1.5	1.5	1.5	-0.5
Analysis by gender				
Men	2.4	2.3	2.3	0.7
Women	0.8	0.8	0.8	-0.9
Analysis by age				
≥45 years	0.0	0.1	0.1	7.5
46-65	1.1	1.2	1.3	9.3
66-74	3.3	3.4	3.6	6.7
75-84	4.2	4.2	4.3	1.6
≥85	4.9	5.0	5.1	2.2
Total	**1.6**	**1.5**	**1.6**	**0.8**

Indicators used:
Prevalence of acute coronary syndrome: number of patients diagnosed with acute coronary syndrome [**numerator**], on the total population eligible for assistance [**denominator**]

Table 3.2.3c Prevalence of use of ACE inhibitors, sartans, beta-blockers, antiplatelet agents and lipid-lowering medicines in patients with acute coronary syndrome and comparison 2021-2020: analysis by gender, age group and geographic area (years 2019-2021)

	Prevalence of use (%)			Δ %
	2019	2020	2021	21-20
Geographic analysis				
North	85.7	86.7	85.8	-1.0
Centre	87.3	86.7	86.8	0.1
South and Islands	88.2	87.3	85.6	-1.9
Analysis by gender				
Men	86.3	86.1	84.4	-2.0
Women	88.7	89.3	90.3	1.1
Analysis by age				
≥45 years	64.7	60.7	60.6	-0.2
46-65	82.5	79.9	76.4	-4.4
66-74	87.9	88.0	85.5	-2.8
75-84	92.3	92.1	95.3	3.5
≥85	87.8	89.7	91.9	**2.5**
Total	**86.9**	**86.9**	**85.9**	**-1.2**

Indicators used:

Prevalence of use of medicines for acute coronary syndrome: number of patients treated with ACE inhibitors, sartans, beta-blockers, antiplatelet agents and medicines for acute coronary syndrome [**numerator**] on the total of patients diagnosed with acute coronary syndrome [**denominator**]

Table 3.2.3d Prevalence of use of ACE inhibitors, sartans, beta-blockers, antiplatelet agents and lipid-lowering medicines in patients with acute coronary syndrome and comparison 2021-2020: analysis by therapeutic category (years 2019-2021)

Analysis by therapeutic category	Prevalence of use (%)			
	2019	2020	2021	Δ % 21-20
ACE inhibitors	44.3	43.1	41.5	-3.7
Sartans	25	25.0	25.4	1.6
Beta blockers	66.4	66.3	65.9	-0.6
Platelet aggregation inhibitors	73	72.0	70.8	-1.7
Lipid-lowering agents	76.3	76.2	75.9	-0.4

Indicators used:

Prevalence of use of medicines for acute coronary syndrome: number of patients treated with a specific therapeutic category [**numerator**] on the total number of patients diagnosed with acute coronary syndrome [**denominator**]

Key message

- Long-term management of patients with acute coronary syndrome (ACS) aims to prevent further thrombotic events, reduce cardiac work and ward off complications. Therefore, **drug therapy** involves the use of:
  - antiplatelet agents for a period of no less than 12 months from discharge as prevention strategies in the formation of blood clots;
  - ACE inhibitors-sartans, which showed a protective effect in post-ACS patients regardless of the blood pressure target;
  - beta-blockers, which reduce heart rate, blood pressure and contractility, thus mitigating the work of the heart and the need for oxygen.
- **LDL hypercholesterolemia** is a known risk factor associated with the development of atherosclerosis and its complications, and the reduction of LDL levels plays a key role in significantly reducing the recurrence of cardiovascular events in secondary prevention. The guidelines of the European Society of Cardiology recommend the early administration of lipid-lowering agents in ACS patients, their long-term maintenance as well as achieving the target cholesterol values in the follow-up.
- **General practice data** suggest a predominantly appropriate use of these drugs in the management of patients with ACS; in fact, over 80% of patients have at least one of the above therapeutic categories.

References

- Borja Ibanez, Stefan James, Stefan Agewall, Manuel J Antunes et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal, 2017; 39 (2): 119–177
- Jean-Philippe Collet, Holger Thiele, Emanuele Barbato et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal 2020; 42 (14): 1289–1367
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2):271–80.

3.3 Gastrointestinal system and metabolism

Medicines for gastrointestinal system and metabolism were the third therapeutic category with the highest public expenditure in 2021, equal to 3,064.2 million euros and 13.0% of overall public expenditure (See Main indices of expenditure, consumption and exposure). Total per capita expenditure for these pharmaceuticals was 51.70 euros (+7.2% compared to the previous year), mainly due to the NHS outpatient care (32.31 euros per capita). Conversely, expenditure due to purchases by public health facilities is lower (19.39 euros per capita), with a 13.8% increase compared to 2020 (Table 3.1). In 2021 consumption for this pharmaceutical category was equal to 318.3 DDD/1000 inhabitants per day, increasing by 10.1% compared to 2020 (Table 3.2).
The analysis of the drug use profile by age group and gender, including NHS outpatient care and distribution on behalf, 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 expenditure borne by the NHS shows a similar trend, reaching the maximum value of 128.8 euros in the over 75 age group, with a slightly higher expenditure for males.

As regards NHS outpatient care, expenditure in absolute terms increased by 2.9% compared to the previous year (Table 3.9). This trend was determined by an increase in consumption (+9.9%) and a shift in prescription towards less expensive medicinal products (mix effect: -6.4%), while prices remain stable (-0.1%).

Proton pump inhibitors rank first in terms of expenditure (11.48 euros per capita) and second in terms of consumption (76.2 DDD/1000 inhabitants per day), recording an increase in use (+3.8%), a slight decrease in expenditure (-0.4%) and a use of less expensive medicinal products (mix effect: -4.1%). Vitamin D and analogues rank second by gross per capita expenditure (4.82 euros), registering a remarkable increase in expenditure (+20.8%) and consumption (+20.4%) in 2021, despite the introduction of AIFA Note 96. A greater use of more expensive products was also observed for this category of medicines (mix effect: +0.4%). Conversely, calcium in combination with vitamin D and/or other pharmaceuticals recorded a slight reduction in both expenditure (-0.4%) and consumption (-0.7%).

In 2021 too a further increase was reported in expenditure and consumption for GLP-1 receptor analogues (+53.3% and +35.6%, respectively). Oral hypoglycaemic agents in combination recorded an increase in expenditure (+13.8%), against a slight contraction in consumption (-9.4%), a shift in prescriptions towards more expensive products (mix effect: +24.7%) and an increase in the average cost per day of therapy (+25.6%), probably due to the increase in prescription of fixed combinations ofglyphzine with dipeptidyl-peptidase IV inhibitors.

Pantoprazole and cholecalciferol are the molecules with the highest per capita expenditure (4.40 euros and 4.17 euros, respectively). Together, they constitute the main cost item of the NHS outpatient pharmaceutical expenditure relating to medicines for the gastrointestinal system (26.5%) (Table 3.10). These two molecules also rank in the first places among the first 30 active ingredients by NHS outpatient expenditure (260.5 and 246.9 million euros, respectively) (Table 3.11).

Two active ingredients belonging to this category of pharmaceuticals are included in the list of medicines with the highest cost per day of therapy under the approved care regime: dulaglutide (4.84 euros) and rifamixin (2.08 euros) (Table 3.13).

Dulaglutide is among the top 30 active ingredients with the greatest variation in NHS outpatient expenditure compared with the previous year (+40.6%), showing a +37.4% variation in consumption. It is followed by cholecalciferol (+23.4% in per capita expenditure and +21.8% in consumption), and by ursodeoxycholic acid and mesalazine (Table 3.14).

Compared with 2020, insulin glulisine (fast-acting insulin), insulin aspart, insulin lispro, together with lansoprazole, rank among the top thirty most cost-reducing active ingredients for the NHS outpatient expenditure (-6.3%, -5.3%, -4.5 % and -4.5%, respectively; Table 3.15). Reductions in expenditure are accompanied by reductions in consumption: -6.0% for insulin glulisine, -3.9% for insulin lispro, -3.2% for insulin aspart and -1.8% for lansoprazole.

Six out of thirty most consumed active ingredients under the approved care regime (Table 3.16) belong to the category of medicinal products for gastrointestinal system and metabolism. Cholecalciferol ranks first with 140.0 DDD/1000 inhabitants per day, and becomes the most prescribed active ingredient within this category also in 2021. It is followed by pantoprazole (27.5 DDD/1000 inhabitants per day) and metformin (23 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, compared with 2020 expenditure increased by 13.0%, consumption increased by 2.8% (Table 3.18), prices slightly decreased (-0.1%), and prescriptions focused on more expensive products (mix effect: +10.0%). The highest expenditure increases were recorded for bile acids and derivatives (+85.3%), GLP-1 receptor analogues (+41.2%), and for SGLT2 inhibitors (+32.9%). Enzymes such as recombinant human acid alglucosidase, agalsidase alfa, agalsidase beta, imiglucerase, idursulfase, velaglucerase alfa and elosulfase alfa account for 26.2% 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 (Table 3.19). Dulaglutide (GLP-1 analogue) is the active ingredient with the highest per capita expenditure (1.88 euros) in 2021, with a steady increase compared with the previous year (+44.5%). It accounts for 9.7% of expenditure by public health facilities for medicinal products in this category, with a 41.8% increase in consumption compared to the previous year (Table 3.17). Insulin glargine is the second active ingredient with the highest per capita expenditure after dulaglutide. It is also the only active ingredient in this category to rank among the top 30 active ingredients with the highest expenditure by health facilities (Table 3.20).

Semaglutide, a GLP-1 receptor agonist, is among the top 30 active ingredients with the greatest variation in pharmaceuticals purchased by public health facilities compared with the previous year (+154.8%). It also registers a similar trend in terms of consumption (+179.7%). It is followed by dulaglutide (+44.5% in per capita expenditure and +41.8% in consumption), and by agalsidase beta (+28.1% in per capita expenditure despite negligible consumption, mainly due to the molecule's high average cost per DDD [483.60 euros]) (Table 3.22).

No active ingredient in the gastrointestinal system and metabolism category is included in top thirty most cost-reducing active ingredients purchased by public health facilities compared to the previous year (Table 3.23).

Agalsidase alfa and imiglucerase rank first and second among the top 30 active ingredients for average cost per day of therapy, equal to 1692.4 euros and 1096.5 euros, respectively. They are followed by recombinant human acid alglucosidase (4th place, 1062.2 euros) and agalsidase beta (483.6 euros) (Table 3.24).

With a consumption of 4.7 DDD/1000 inhabitants per day, insulin glargine is the 6th most consumed active ingredient purchased by public health facilities in 2021 (Table 3.25). It is followed by cholecalciferol (11th place in 2021 vs 12th in 2020), with 2.9 DDD/1000 inhabitants per day. An increase in pantoprazole consumption is registered (21st place in 2021 vs 30th place in 2020), with 1.5 DDD/1000 inhabitants per day, along with dulaglutide (16th place in 2021 vs 21st place in 2020), with 2.3 DDD/1000 inhabitants per day.

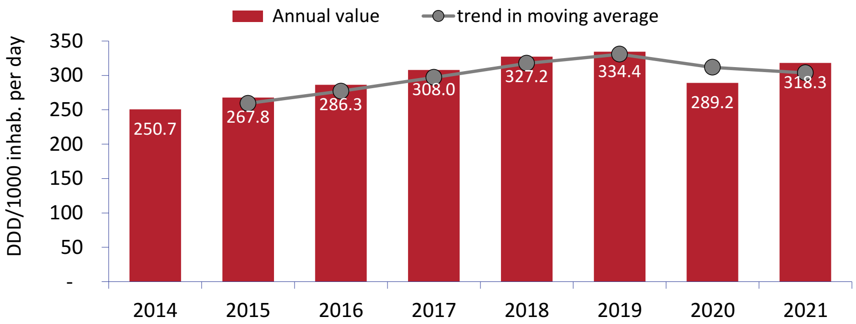
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by region and on the efficiency in the absorption of resources according to the presence of off-patent medicines and on a regional basis. These analyses focused on 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

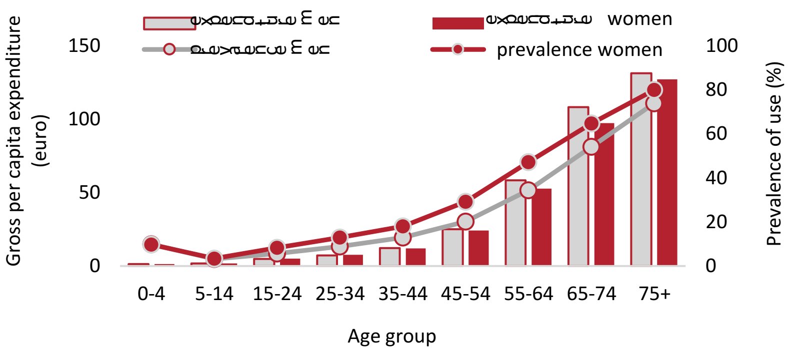
Gastrointestinal system and metabolism

Public expenditure* in million euros (% over total)	**3,064.2**	**(13.0)**
Δ % 2021-2020		7.2
Regional range for gross expenditure (per capita):	31.5	70.6
DDD/1000 inhab. per day* (% over total)	**318.3**	**(24.4)**
Δ % 2021-2020		10.1
Regional range for DDD/1000 inhab. per day:	249.8	434.7

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



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and on behalf distribution in 2021 (Figure and Table)



Breakdown of expenditure and consumption under approved care regime by age group in 2017

Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**
0-4	1.4	1.3	1.4	63.8	62.2	63.0
5-14	1.8	1.9	1.8	19.5	20.9	20.2
15-24	4.9	4.9	4.9	23.9	35.8	29.6
25-34	7.3	7.7	7.5	34.1	57.1	45.4
35-44	12.2	12.1	12.1	57.6	98.7	78.1
45-54	25.0	24.1	24.6	118.0	226.7	172.9
55-64	58.3	52.6	55.4	271.0	492.2	384.8
65-74	108.2	97.4	102.5	532.6	849.1	699.8

3.3.1 Antidiabetics

Epidemiological framework

Diabetes is a chronic disease characterised by the presence of high blood glucose levels (hyperglycaemia) and due to an abnormal amount or function of insulin. The two most common forms of diabetes are type 1 diabetes, also called insulin-dependent diabetes or juvenile diabetes, which accounts for about 10% of cases of diabetes, and diabetes mellitus, the most common form of diabetes, accounting for 90% of cases and that develops predominantly from the age of 40.
The prevalence of the disease is strongly correlated with age: it affects more than 20% of people over 75 years of age. About 70% of patients are over 65 years old. The constant increase in the number of people with diabetes is mainly linked to the aging of the population, coupled with the improvement of therapies and survival rates, the forecasting of diagnoses (which reveals previously unknown cases), the increased survival rates of patients with diabetes, and the prevalence of the main risk factors for the disease, such as overweight and physical inactivity. In 2016 in Italy the National Institute of Statistics (ISTAT) estimated at about 3.2 million people suffered with diagnosed diabetes (90% type 2), with a prevalence of 5.3% (3.8% in 2000). This disease is most common in the South of Italy, where the age-standardised prevalence rate is 5.8% versus 4.0% in the North. In terms of mortality, the South shows significantly higher levels for both genders. Diabetes is more common in men than women. Although it is known that overweight and physical inactivity are more frequent in the South, it is not yet clear whether the incidence of diabetes differs between **these populations**.

National data on consumption and expenditure

The consumption of medicines for diabetes increased slightly over the period 2014-2021, from 61.8 to 65.1 DDD every thousand inhabitants per day, with an average annual change (CAGR) of 0.7% (Figure and Table 3.3.1a). Conversely, the cost per day of therapy increased on average by approximately 5.1% every year, indicating an increasing use of high-cost pharmaceuticals such as GLP-1 analogues, gliptins and glyphozines. In 2021, the per capita expenditure was 19.89 euros, an 8.7% increase compared with the previous year. The average DDD cost was 0.84 euros, a 7.8% increase compared with the previous year.
The most used antidiabetics are metformin (about 30 DDD/1000 inhabitants per day when used alone or in combination with other medicines, accounting for 46% of the total) and insulin (about 15 DDD/1000 inhabitants per day, accounting for 23% of the total). Secretagogues (sulfonylureas alone or in combination, and glinides) still represent the third most widely used category (with a consumption of 9.6 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 6 DDD, considering also combinations with metformin or glitazone) although with a significant slowdown in growth and unlike gliflozins and GLP1 analogues, which show a sharp increase compared with the previous year (+30% each). The gliflozin/gliptin and GLP1 analogue/basal insulin combinations are currently characterised by marginal consumption shares (0.5 DDD each).

Overall, insulin is the most important item cost for the treatment of diabetes. However, although short and long acting insulin analogues represent the second and third most per capita expensive pharmaceuticals in 2021, they show a slight contraction in consumption against a higher contraction in expenditure compared with the previous year, probably due to lower costs of some insulins (especially basal, such as insulin glargine and degludec).
The most important increases in expenditure depend on GLP1 analogues (+45.3%) and gliflozins (+35.3%) and, subsequently, by GLP1 analogue/basal insulin (+19%) and gliflozin/metformin (+17.7%) combinations. The increase in expenditure corresponds to an increase in consumption for this category of pharmaceuticals. In the case of GLP1 analogues, the largest increase in expenditure over consumption could be due to a preference towards higher-cost long-acting analogues, as also shown by the top ten active ingredients for expenditure.
The active ingredient with the highest per capita expenditure is dulaglutide, a long-acting GLP-1 analogue (2.74 euros and +43.3% compared with 2020, due to a 41% increase in consumption and an average DDD cost of 2.69 euros). Metformin ranks second in terms of expenditure with 1.64 euros, showing a stable trend in terms of consumption and expenditure and an average DDD cost of 0.19 euros, the lowest of all. The active substance with the greatest increase in expenditure and consumption (>100%) is semaglutide, which also registers the highest cost per day of therapy (16.06 euros), despite a 10.6% decrease compared with 2020. The insulin degludec/liraglutide combination continues to record significant increases in expenditure and consumption (>20%) also in 2021. This medicinal product also shows the highest cost per day of therapy (4.97 euros).
Insulin degludec is the active ingredient with the largest contraction in per capita expenditure compared with the previous year (-20.2%), as a result of the reduction in the average DDD cost of the molecule (-17.8%) in 2021. No SGLT2 inhibitors are included in the top 10 active ingredients for expenditure.
In line with the prevalence of diabetes, in 2021 Southern Regions recorded a 36% higher consumption than the Northern Regions (78.2 vs 57.5 DDD) and a 13% higher consumption compared with the national average (65.1 DDD) (Table 3.3.1b). The South registers the largest increases in expenditure (+9.0%) and consumption (+1.9%) compared with the previous year. An even more marked variability is observed between the different regions: the Autonomous Province of Bolzano (39.1 DDD) consumes less than half of the doses of Calabria (87.4 DDD) and Sicily (85.0 DDD). The Autonomous Province of Trento (+6.8%) and Sicily (+5.1%) are the Regions with the highest increase compared to the previous year. Valle d’Aosta, on the other hand, is the Region in which consumption has decreased markedly (-13.9%). As with consumption, Southern Regions have the highest per capita expenditure (22.84 euros) for this category of medicines compared with other geographical areas, up 9% compared to the previous year, although both the average cost per DDD (0.80 euros) and the average annual change (CAGR) over the period 2014-2021 (3.3%) are lower than the national average.

Figure 3.3.1a Antidiabetics, temporal trend in per capita expenditure and average cost per day of therapy (2014-2021)

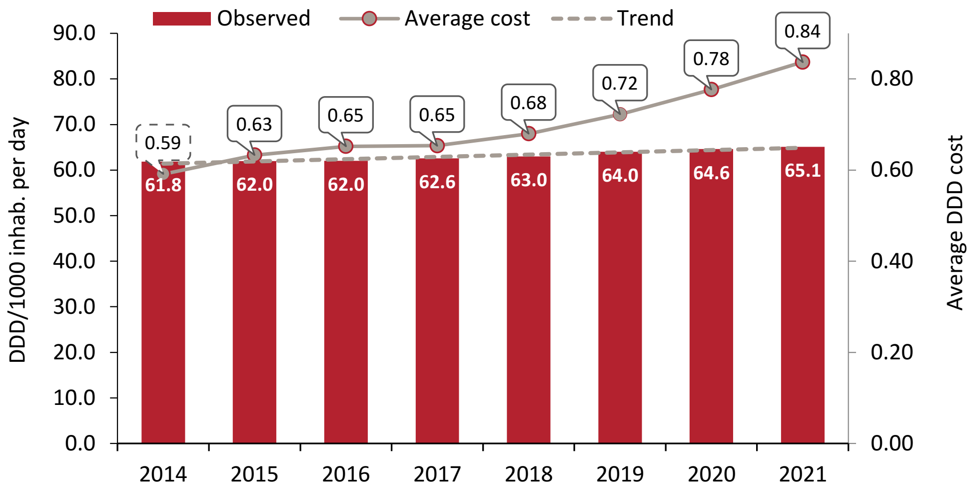


Table 3.3.1a Antidiabetics, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
GLP-1 (glucagon-like one) analogues	4.84	45.3	30.3	3.8	30.1	30.8	3.46	12.0
Fast acting insulins	3.60	-5.7	-1.2	8.1	-4.6	-0.3	1.22	-0.8
Long acting insulins	2.43	-14.3	-0.2	6.4	-2.7	3.1	1.04	-11.6
Metformin	1.64	3.8	2.8	23.4	2.3	2.0	0.19	1.8
Gliptins (DPP-4 inhibitors) plain	1.53	1.1	9.4	3.3	2.3	13.3	1.25	-0.9
Glifozins (SGLT2 inhibitors) plain	1.09	35.3	-	2.1	30.2	-	1.40	4.2
Gliptins (DPP-4 inhibitors) in combination with metformin	1.06	-8.1	-0.4	2.6	-8.1	4.0	1.11	0.3
Glifozins (SGLT2 inhibitors) in combination with metformin	0.99	17.7	-	2.0	17.7	-	1.34	0.3
Insulins combined with GLP-1 (glucagon-like one) analogues	0.98	19.0	-	0.5	19.3	-	4.86	0.1
Sulfonylureas plain	0.49	-4.8	-2.1	7.1	-8.7	-6.2	0.19	4.4
Gliptins (DPP-4 inhibitors) in combination with glifozins (SGLT2 inhibitors)	0.32	>100	-	0.5	>100	-	1.91	-4.9
Repaglinide	0.23	-14.1	-11.1	1.6	-15.8	-11.9	0.39	2.3
Glitaziones in combination	0.19	-8.4	-13.8	0.8	-9.3	-6.5	0.64	1.2
Acarbose	0.13	-8.0	-4.7	0.5	-8.0	-3.6	0.72	0.3
Glitazones plain	0.13	9.4	-3.5	0.9	7.6	-0.2	0.41	1.9
Gliptins (DPP-4 inhibitors) in combination with pioglitazone	0.09	12.6	74.0	0.2	8.6	80.8	1.18	3.9
Combined insulins (long/intermediate with fast)	0.09	-23.2	-21.1	0.2	-23.0	-20.3	1.22	0.0

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Sulfonylureas in combination with metformin	0.07	-21.1	-20.5	0.9	-21.0	-20.6	0.21	0.2
Intermediate acting insulins	<0.005	-24.0	-43.8	0.0	-26.5	-36.2	0.49	3.6
Antidiabetics	**19.89**	**8.4**	**5.9**	**65.1**	**0.8**	**0.7**	**0.84**	**7.8**
dulaglutide	2.74	43.3	-	2.8	41.0	-	2.69	1.9
metformin	1.64	3.8	2.8	23.4	2.3	2.0	0.19	1.8
insulin glargine	1.61	-10.8	-2.6	4.7	-1.7	2.3	0.93	-9.0
insulin lispro	1.58	-6.2	-3.1	3.8	-5.3	-0.9	1.15	-0.6
insulin aspart	1.54	-6.0	-2.5	3.2	-4.1	-2.1	1.33	-1.7
semaglutide	1.28	>100	-	0.2	>100	-	16.06	-10.6
insulin degludec/liraglutide	0.87	20.9	-	0.5	21.2	-	4.97	0.0
insulin degludec	0.73	-20.2	91.1	1.4	-2.7	107.8	1.39	-17.8
linagliptin	0.73	4.9	34.2	1.5	5.2	38.0	1.31	0.0
sitagliptin	0.61	0.1	2.7	1.4	4.0	6.8	1.23	-3.5

Table 3.3.1b Antidiabetics, temporal trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	15.74	60.7	0.71	17.00	60.1	0.77	8.0	-0.9	9.2	4.6	0.2	4.5
Valle d'Aosta	10.97	59.9	0.50	10.63	51.6	0.56	-3.1	-13.9	12.8	0.8	-2.2	3.0
Lombardy	23.07	58.1	1.08	24.66	57.6	1.17	6.9	-0.8	8.1	10.8	0.5	10.2
A.P. of Bolzano	11.75	40.8	0.79	11.72	39.1	0.82	-0.2	-4.3	4.6	2.6	-1.4	4.1
A.P. of Trento	14.33	49.5	0.79	16.41	52.9	0.85	14.5	6.8	7.5	7.0	1.2	5.7
Veneto	14.97	54.2	0.75	16.52	55.4	0.82	10.3	2.3	8.1	5.6	0.9	4.7
Friuli VG	15.74	60.1	0.72	17.68	61.0	0.79	12.3	1.4	11.1	6.2	0.9	5.3
Liguria	12.78	49.9	0.70	13.92	49.7	0.77	8.9	-0.5	9.7	4.4	-0.5	4.9
Emilia R.	12.50	62.1	0.55	13.51	61.4	0.60	8.1	-1.1	9.6	5.2	0.8	4.4
Tuscany	14.07	55.9	0.69	14.96	56.5	0.73	6.3	1.0	5.5	3.5	-0.4	3.9
Umbria	18.91	61.0	0.85	20.47	61.6	0.91	8.2	1.0	7.4	5.6	1.0	4.5
Marche	15.97	59.4	0.73	17.22	60.4	0.78	7.8	1.7	6.3	8.1	2.6	5.3
Lazio	17.75	65.4	0.74	19.23	65.5	0.80	8.3	0.2	8.4	5.5	0.5	4.9
Abruzzo	19.96	67.8	0.80	19.47	64.5	0.83	-2.5	-4.9	2.8	2.7	0.2	2.5
Molise	19.64	68.2	0.79	20.13	68.3	0.81	2.5	0.1	2.7	4.8	0.8	3.9
Campania	21.02	74.4	0.77	22.68	75.7	0.82	7.9	1.6	6.4	4.4	1.5	2.8
Puglia	20.92	76.8	0.74	23.47	77.8	0.83	12.2	1.3	11.1	6.6	0.8	5.7
Basilicata	21.04	77.1	0.75	22.96	79.3	0.79	9.2	2.8	6.5	6.1	1.8	4.2
Calabria	22.85	85.7	0.73	24.51	87.4	0.77	7.2	2.0	5.4	4.8	1.5	3.2
Sicily	20.41	80.9	0.69	23.38	85.0	0.75	14.6	5.1	9.3	3.8	1.1	2.7
Sardinia	21.20	70.5	0.82	21.66	69.8	0.85	2.2	-0.9	3.4	2.6	0.6	1.9
Italy	**18.36**	**64.6**	**0.78**	**19.89**	**65.1**	**0.84**	**8.4**	**0.8**	**7.8**	**5.9**	**0.7**	**5.1**
North	17.39	57.6	0.82	18.78	57.5	0.90	8.0	-0.2	8.6	7.5	0.5	6.9
Centre	16.43	61.2	0.73	17.69	61.6	0.79	7.7	0.7	7.3	5.2	0.5	4.7
South and Islands	20.95	76.7	0.75	22.84	78.2	0.80	9.0	1.9	7.3	4.5	1.1	3.3

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 analysis of the population shows an increasing use of pharmaceuticals for diabetes with increasing age, with higher prevalence (24.5%) and consumption (243.3 DDD) values in men aged 75 to 84 years, in agreement with the epidemiology of the condition (Figure 3.3.1b). This difference between men and women is found in all age groups, with a more marked trend in the 55 to 84 age group, while in the over 85 group this difference is slightly reduced. On average, prevalence is equal to 6.1%, ranging from a minimum of 5.2% 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 (8.6%), whereas the Autonomous Province of Bolzano shows a prevalence of use slightly over 3.5%. As already highlighted, prevalence is higher among men than women (6.7% and 5.6%, respectively). The median age of users is 71, with no specific differences at regional level. The cost per user was 303.9 euros. Lombardy has four times higher values (468.2 euros) than Emilia Romagna (121.7 euros), which is well below the national average (303.9 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: 364.3) and half of them are treated for at least 10 months a year (9 months in Central regions). Subjects receiving a single prescription account for 3.5%, ranging from a minimum of 5% in Friuli and Sardinia to a maximum of 5.2% in Emilia Romagna. When reading this indicator, it should be taken into account that values can be influenced both by the number of subjects starting treatment at the end of the observation period (incident cases) and by those who stopped therapy in the first months of the year (e.g. side effects, hospitalisation and death).

Concerning 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 69,489 new users, with a median age of 67 years (IQR interquartile range: 58-76), with a smaller proportion of women than men (53.3% vs 46.7%).

The percentage of subjects with high and low adherence to antidiabetic treatment was equal to 29.5% and 27.9%, respectively (Table 3.3.1d). In particular, the highest percentages of high adherence were observed in subjects aged between 45 and 54 years (37.1% in total: 45.0% in the North, 32.0% in the Centre and 33.7% in the South). Then, they decrease with increasing age. The highest percentage of subjects with low adherence is recorded in subjects living in the South and aged at least 85 years (40.5%). In general, men have a higher percentage of high adherence than women (32.8% vs 25.7%). Compared with **2020**, a decrease in subjects with low adherence (-4%) and an increase in subject with high adherence (+2%) are found at national level. The North registers the greatest reduction in subjects with low adherence (-6%), while high adherence increases in the North and the South (+5%) but reduces in the Centre (-6%).

In 2021, the percentage of subjects persisting to treatment at 12 months was higher in the Northern Regions (45.0%) than the Centre (41.8%) and the South (41.8%). Women have a lower percentage of persistence to treatment at 12 months than men (39.2% vs 46.1%) (Table 3.3.1e).

The probability of being persistent decreases with increasing age: in 2021 persistent subjects at 12 months vary from 48.8% to 29.1%, starting from the 45-54 age group up to subjects aged at least 85.

If the median time to discontinuation of antidiabetic treatment is taken into account, a 50% probability of discontinuing treatment is achieved at approximately 211 days, with values ranging from 238 days in the North to 193 days in the South (Figure 3.3.1c).

Over the three-year period 2019-2021, an overall slight improvement in the adherence and persistence indicators can be observed. However, in the Centre the number of subjects with high adherence drops by 6% in the same year, despite the largest increase in persistent subjects at 12 months (+15%) (Tables 3.3.1d and 3.3.1e).

Figure 3.3.1b Breakdown of prevalence of use and consumption of antidiabetics under approved care regime and distribution on behalf in 2021

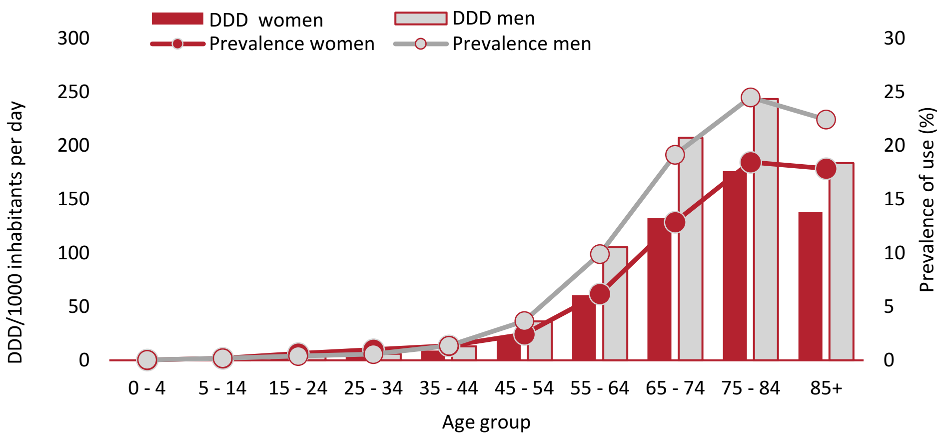


Table 3.3.1c Exposure and duration of therapy with antidiabetics by Region under approved care regime and distribution on behalf (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	men	women	total					
Piedmont	6.7	5.2	5.9	72	290.6	375.7	308.0	2.5
Valle d'Aosta	5.4	4.0	4.7	72	234.5	439.7	336.0	1.5
Lombardy	5.9	4.5	5.2	72	468.2	395.8	332.0	2.5
A.P. of Bolzano	3.9	3.1	3.5	72	344.3	396.2	336.0	2.2
A.P. of Trento	5.2	4.2	4.7	72	270.0	339.8	277.5	2.3
Veneto	5.6	4.1	4.9	72	311.2	387.8	330.0	2.4
Friuli VG	6.7	4.9	5.8	73	305.8	388.9	318.8	2.2
Liguria	6.0	5.0	5.5	74	260.4	346.1	293.5	3.7
Emilia R.	5.8	4.6	5.2	72	121.7	296.5	232.0	3.6
Tuscany	6.7	5.8	6.2	72	222.4	320.1	254.8	5.2
Umbria	7.2	5.9	6.5	73	322.4	350.9	300.0	3.7
Marche	6.6	5.2	5.9	72	284.2	373.0	306.0	3.4
Lazio	7.2	6.5	6.8	70	269.7	335.2	270.0	4.2
Abruzzo	7.3	6.3	6.8	72	294.3	355.0	300.0	3.9
Molise	8.2	6.8	7.5	71	276.5	334.5	300.0	3.7
Campania	7.6	6.5	7.1	70	293.4	355.9	308.0	3.5
Puglia	8.0	7.4	7.7	71	333.7	353.0	294.0	3.4
Basilicata	8.2	7.5	7.9	71	290.6	365.7	309.1	3.3
Calabria	9.1	8.2	8.6	70	239.0	349.1	292.5	4.3
Sicily	8.4	7.5	7.9	71	251.9	352.5	289.5	3.7
Sardinia	7.2	5.9	6.5	71	323.2	383.6	336.0	3.5
Italy	**6.7**	**5.6**	**6.1**	**71**	**303.9**	**364.3**	**300.0**	**3.5**
North	5.8	4.5	5.2	72	335.7	377.6	300.0	2.7
Centre	6.8	6.0	6.4	71	265.7	342.2	270.0	4.5
South and Islands	7.9	6.9	7.4	71	291.9	361.7	300.0	3.7

Table 3.3.1d Indicators of adherence to treatment with antidiabetics in the population aged ≥45 years during 2019-2021 and 2021-2020 change

	Total N=69,489				North ^ N=24,462				Centre N=17,738				South N=27,289			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*^																
45-54	21.6	22.3	21.7	-3	16.4	17.2	16.0	-7	25.0	25.7	25.1	-2	23.5	24.5	24.3	-1
55-64	23.8	25.4	24.3	-4	18.3	20.4	18.6	-9	27.0	27.5	26.9	-2	26.4	28.2	27.1	-4
65-74	28.6	30.0	29.5	-1	22.3	24.6	24.1	-2	32.8	32.0	31.3	-2	32.0	33.6	33.3	-1
75-84	34.5	34.0	33.5	-1	29.5	30.7	29.5	-4	36.8	35.3	35.1	-1	38.4	37.0	36.8	0
≥85	34.6	36.9	37.1	0	29.8	32.5	32.1	-1	38.7	37.6	39.9	6	36.8	41.3	40.5	-2
Women	31.1	32.3	31.7	-2	25.5	27.8	26.7	-4	34.4	34.0	34.0	0	33.8	35.1	34.3	-2
Men	25.2	25.9	24.6	-5	20.6	22.0	20.1	-8	28.5	28.0	26.9	-4	27.6	28.5	27.5	-4
Total	**27.9**	**28.9**	**27.9**	**-4**	**22.8**	**24.6**	**23.0**	**-6**	**31.4**	**30.9**	**30.3**	**-2**	**30.6**	**31.6**	**30.7**	**-3**
High adherence*^																
45-54	37.8	36.8	37.1	1	45.5	42.8	45.0	5	32.7	33.4	32.0	-4	35.0	33.9	33.7	-1
55-64	32.6	32.4	33.5	3	40.0	38.9	41.3	6	27.7	28.7	28.7	0	29.3	29.3	30.4	4
65-74	27.1	26.3	26.5	1	31.7	31.0	32.4	4	22.9	24.3	21.9	-10	25.3	23.2	24.3	5
75-84	23.5	24.1	23.8	-1	27.2	27.2	27.0	-1	20.2	22.4	20.3	-10	21.3	21.5	22.8	6
≥85	23.6	23.9	21.5	-10	27.5	26.7	25.2	-6	19.7	27.1	20.5	-24	22.1	18.8	18.3	-2
Women	26.3	25.9	25.7	-1	31.7	30.3	31.1	3	22.2	24.2	21.8	-10	24.0	23.0	23.7	3
Men	31.7	31.6	32.8	4	36.3	35.8	38.3	7	27.4	29.2	28.0	-4	29.8	28.9	30.6	6
Total	**29.2**	**28.9**	**29.5**	**2**	**34.3**	**33.4**	**35.15**	**5**	**24.9**	**26.7**	**25.1**	**-6**	**27.1**	**26.1**	**27.4**	**5**

*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 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.

† Percentages of subjects with low/high adherence relating to the specific category.

Median follow-up time (IQR): 327 (280-348).

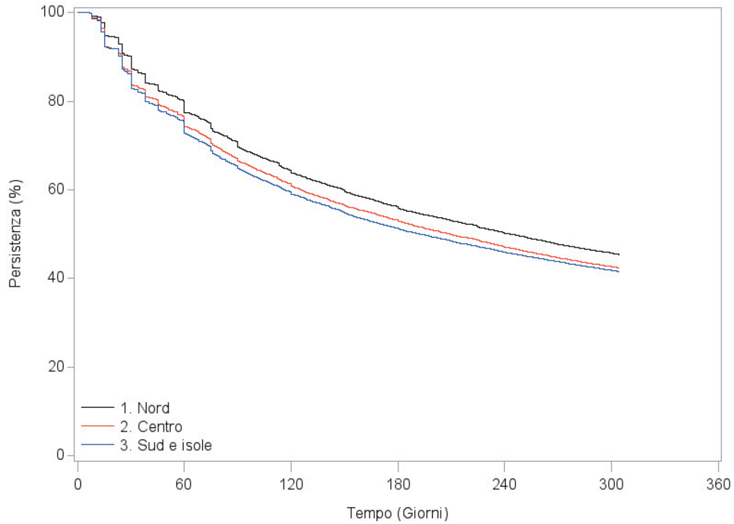
^ Excluding Emilia Romagna

Table 3.3.1e Persistence to treatment with antidiabetics after one year in the population aged ≥45 years during 2019-2021 and 2021-2020 change

Persistence at 12 months	Total N=69,489				North ^ N=24,462				Centre N=17,738				South N=27,289			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54	46.8	44.6	48.8	9	49.7	48.8	52.7	8	43.9	39.7	46.0	16	46.2	44.1	47.4	8
55-64	45.4	44.4	47.3	7	49.2	46.7	51.2	10	41.4	42.0	44.7	7	44.6	43.8	45.9	5
65-74	41.2	39.5	42.5	8	42.4	41.4	43.8	6	38.5	37.6	43.1	15	41.7	39.0	41.0	5
75-84	34.0	32.5	35.5	9	35.2	34.1	36.6	7	32.2	29.7	35.8	21	33.7	32.3	34.0	5
≥85	28.8	26.9	29.1	8	31.5	29.4	32.9	12	25.5	24.7	28.8	17	28.3	25.7	25.1	-2
Women	37.7	36.1	39.2	9	39.4	38.4	41.5	8	34.8	32.9	37.8	15	37.9	36.0	38.1	6
Men	43.4	42.0	46.1	10	45.1	43.3	47.7	10	40.5	39.7	45.4	14	43.5	42.0	44.9	7
Total	**40.8**	**39.2**	**42.9**	**9**	**42.6**	**41.1**	**45.0**	**9**	**37.7**	**36.4**	**41.8**	**15**	**40.9**	**39.1**	**41.8**	**7**

Persistence to treatment was evaluated only for new users with at least 2 prescriptions. A treatment interruption occurs if the subject does not receive a prescription within 60 days (for more details please refer to the statistical methods).
^ Excluding Emilia Romagna

Figure 3.3.1c 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



Key message

• Consumption of pharmaceuticals against diabetes mellitus appears stable over the past eight years, with 65.1 DDD/1000 inhabitants per day in 2021. The stability in consumption is accompanied by a constant increase in expenditure due to the introduction, over the last decade, of therapeutic categories with a new mechanism of action and still covered by a patent. These increases are observed in particular for GLP-1 analogues, SGLT2 inhibitors and GLP-1 analogue/basal insulin combinations. The progressive shift in therapeutic options from "traditional" pharmaceuticals to more recent medicines is due to the inability to induce hypoglycaemia, a characteristic common to all newer categories. Last year increased preference for two specific therapeutic categories (GLP1-RA and SGLT2i) is consistent with the growing evidence of their benefit also for some important chronic complications (cardiovascular and renal) and with current national and international guidelines emphasising their importance in the treatment of type 2 diabetes. It will be interesting to assess the effect of the introduction of AIFA Note 100 in January 2022, which extended the prescription of the three most recent categories of pharmaceuticals to general practitioners, and provided indications of preferential use in different clinical conditions.

• Metformin, alone or in combination with other medicines, remains the most widely used pharmaceutical for the treatment of diabetes. It is followed by insulin, which registers a slight decrease. Secretagogues (sulfonylureas and glinides) rank third, and their de-prescription is now recommended. However, their use cannot can still not be considered marginal, albeit in sharp reduction compared to the previous year.

• In terms of expenditure, overall insulin is the most important item. However, there is a higher contraction in expenditure against a slight reduction in consumption, probably as a result of the lower cost of some insulins, especially basal insulin.

• The largest increases in expenditure for some categories (such as GLP1 and gliflozins) go hand in hand with the increase in consumption and, only for GLP1 analogues, with the preference for more expensive long-acting analogues with weekly administration.

• Semaglutide is the most expensive treatment option (per day of therapy) and shows significant increases in expenditure and consumption. Similarly, the GLP1 analogue/basal insulin combination shows high variations for all indicators.

• As with most major therapeutic categories, a wide and growing regional variability in terms of consumption and prevalence of use is confirmed in 2021. In this case, this data appears in line with the epidemiology of diabetes mellitus which, as shown in the PASSI project, is more prevalent in the South and in the Islands than compared with the Centre and the North. The data is also consistent with the geographical breakdown of the main risk factors such as obesity and reduced physical activity.

• 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, and fractures). In parallel, reducing long-term complications becomes secondary.

• Analysis of adherence to treatment with antidiabetics 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).

References

- Ministry of Health *Relazione al Parlamento 2021 sul diabete mellito* https://www.salute.gov.it/imgs/C_17_pubblicazioni_3229_allegato.pdf
- American Diabetes Association Professional Practice Committee. *9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022; 45 (Suppl. 1): S125–S143 43 https://doi.org/10.2337/dc22-S009
- Guidelines of *Società Italiana di Diabetologia* (SID) and *Associazione dei Medici Diabetologi* (AMD). *La terapia del diabete mellito di tipo 2.* https://snlg.iss.it/?cat=6
- Italian Medicines Agency (AIFA) AIFA Note 100 on the prescription of SGLT2 inhibitors, GLP1 receptor agonists, DPP4 inhibitors, and their combinations in the treatment of type 2 diabetes mellitus; https://www.aifa.gov.it/nota-100
- Bonora E, Kiechl S, Willeit J et al. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. Diabetes 2004; 53:1782-9.
- Brocco S, Visentin C, Fedeli U et al. Monitoring the occurrence of diabetes mellitus and its major complications: the combined use of different administrative databases. Cardiovasc Diabetol 2007; 6:5.
- Gnavi R, Canova C, Picariello R et al. Mortality, incidence of cardiovascular diseases, and educa- tional level among the diabetic and non-diabetic populations in two large Italian cities. Diabetes Res Clin Pract 2011; 92:205-12.
- Gnavi R, Migliardi A, Maggini M, Costa G. Prevalence of and secular trends in diagnosed diabetes in Italy: 1980-2013. Nutr Metab Cardiovasc Dis 2018; 28:219-25.
- Gnavi R, Petrelli A, Demaria M, et al. Mortality and educational level among diabetic and nondiabetic people in the Turin Longitudinal Study: a 9 year follow up.Int J Epidemiol 2004; 33:864-71.
- Minardi V, Ferrante G, Possenti V et al. I numeri di PASSI. Anche i dati di sorveglianza confer- mano: il diabete è associato allo svantaggio economico-sociale. Epidemiol Prev 2011; 35(1):59. Available at

https://www.ep.epiprev.it/rubriche/anche-i-dati-di-sorveglianza-confer- mano-il-diabete-eassociato-allo-svantaggio-economico-sociale/

- Onder G, Bonassi S, Abbatecola AM et al. Geriatrics Working Group of the Italian Medicines Agency. High prevalence of poor quality drug prescribing in older individuals: a nationwide report from the Italian Medicines Agency (AIFA). J Gerontol A Biol Sci Med Sci. 2014; 69(4):430-7.

3.3.2 Medicines for peptic ulcer and GERD

Epidemiological framework

Like the rest of the world, for years Italy has been experiencing an overuse of medicines for gastric acidity and, in particular, of proton pump inhibitors (PPIs). This is due to a number of different factors, including an increase in disorders related to gastric acidity. Data in Italy show an increase in the prevalence of gastroesophageal reflux disease (GERD), which increased from 7.9% in 2009 to 18.7% in 2018. All this does not justify such a high increase in the prescription of these drugs, especially since products that can be purchased without a prescription are not taken into account. Therefore, it is crucial to identify possible inappropriate uses in order to rationalise the prescription, avoid exposing patients to health risks and reduce expenditure. As shown in numerous studies, the improper use of these medicines does not belong to a specific setting, but encompasses different settings (both hospital and territorial) and the guidelines can provide valuable support to reduce the direct and indirect costs related to such improper use. A successful pharmacological management of these conditions should presuppose a constant evaluation of the disorder, so as to limit the use of these medicines to when strictly necessary.

National data on consumption and expenditure

In 2021, on average, the consumption of medicines for peptic ulcer and GERD was 86.3 DDD/1000 inhabitants per day, with a 2.7% decrease compared to 2014 and a 0.4% average annual change rate in the 2014-2020 period (Figure 3.3.2a). Over the last 8 years, the average DDD cost has decreased from 0.54 to 0.42 euros. Per capita expenditure for these medicines was 13.08 euros, down by 0.6% compared to the previous year and with a 4% average annual reduction in the period 2014-2020 (Table 3.3.2a). With 79.8 DDD, proton pump inhibitors account for over 90% of the consumption of medicines for peptic ulcer and GERD, up by 4.5% compared to 2020. They are the category with the highest consumption and expenditure. A per capita expenditure of 11.71 euros is registered, although the average DDD cost is the lowest (0.40 euros). The second high-expenditure category (0.90 euros) is represented by other medicines for peptic ulcer, including the group of alginates and sucralfate, followed by antacids (0.42 euros), which consist of magnesium and aluminium salts. Pantoprazole is the molecule with the highest per capita expenditure (4.52 euros) and the highest consumption (29.0 DDD/1000 inhabitants per day), followed by omeprazole, esomeprazole and lansoprazole, with consumption values of 18.6, 15.4 and 14.9 DDD, respectively. They are followed by the sodium alginate/potassium bicarbonate combination (4.1 DDD). All proton pump inhibitors, with the exception of lansoprazole (-2.0%) and rabeprazole (-1.1%) show increasing consumption. Except for sucralfate, magaldrate and the sodium alginate/potassium bicarbonate combination, the average cost per day of therapy is down for all molecules belonging to this category (0.42 euros average DDD cost and -3.3% compared to 2020). Despite the increase in consumption, pantoprazole has recorded a decline in expenditure due to a reduction in the average cost per day of therapy.

Analysing the regional variability (Table 3.2.2b), the South of Italy shows higher consumption (104.2 DDD/1000 inhabitants per day) compared with the Centre (79.2 DDD) and the North (76.8 DDD). Consumption in Campania (127.2 DDD/1000 inhabitants per day) is more than double than the Autonomous Province of Bolzano (48.7 DDD). Compared with the previous year, in 2021 all regions recorded an increase in consumption, with Friuli Venezia Giulia showing the most marked increase (+10.4%), and a reduction in average cost for DDD, which is generally fairly aligned between the different regions. Consistently with the observed consumption, the South if Italy shows higher per capita expenditure (16.27 euros) compared with the Centre (12.20 euros) and the North (11.24 euros).

Figure 3.3.2a Medicines for peptic ulcer and GERD, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

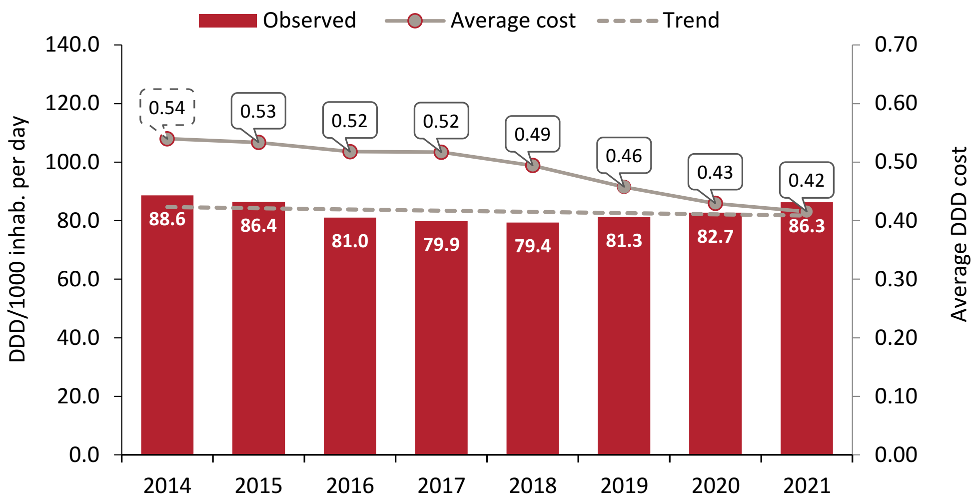


Table 3.3.2a Medicines for peptic ulcer and GERD, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Proton pump inhibitors	11.71	0.5	-4.2	79.8	4.5	-0.1	0.40	-3.5
Other medicines for peptic ulcer and gastroesophageal reflux disease GERD	0.90	-0.5	1.4	4.3	-0.4	1.1	0.58	0.2
Antacids	0.42	1.0	0.8	2.0	2.4	0.6	0.57	-1.1
H2 receptor antagonists	0.04	163.5	-28.9	0.1	180.3	-33.5	0.70	-5.7
Prostaglandins	0.01	-14.4	-11.9	0.0	-13.3	-11.0	1.00	-1.0
Medicines for peptic ulcer and GERD	13.08	0.6	-4.0	86.3	4.3	-0.4	0.42	-3.3
pantoprazole	4.52	3.9	-1.3	29.0	9.0	4.2	0.43	-4.5
omeprazole	2.31	-1.7	-5.5	18.6	1.3	-1.4	0.34	-2.7
lansoprazole	2.30	-4.3	-8.2	14.9	-2.0	-5.3	0.42	-2.1
esomeprazole	2.24	1.9	-2.7	15.4	7.7	2.1	0.40	-5.2
sodium alginate/potassium bicarbonate	0.87	-0.3	1.6	4.1	-0.2	1.4	0.59	0.1
magaldrate	0.41	0.9	0.8	1.9	0.9	0.5	0.61	0.3
rabeprazole	0.33	-2.5	-5.5	1.9	-1.1	-4.7	0.48	-1.2
famotidine	0.04	>100	38.4	0.1	>100	40.2	0.71	-2.7
sucralfate	0.03	-4.4	-4.1	0.2	-4.8	-4.8	0.48	0.7
misoprostole	0.01	-14.4	-11.9	0.0	-13.3	-11.0	1.00	-1.0

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	10.26	69.4	0.40	10.53	72.4	0.40	2.6	4.4	-1.5	-6.2	-2.0	-4.3
Valle d'Aosta	10.89	71.5	0.42	10.88	74.4	0.40	-0.1	4.0	-3.7	-4.4	-0.7	-3.7
Lombardy	11.93	79.5	0.41	12.18	83.2	0.40	2.1	4.6	-2.1	-1.7	2.3	-4.0
A.P. of Bolzano	7.19	46.4	0.42	7.25	48.7	0.41	0.8	4.9	-3.7	-1.2	1.7	-2.9
A.P. of Trento	12.80	83.9	0.42	12.93	87.6	0.40	1.0	4.5	-3.1	-1.0	3.0	-3.9
Veneto	9.75	66.8	0.40	9.82	68.8	0.39	0.7	2.9	-1.9	-5.9	-2.3	-3.7
Friuli VG	10.20	64.1	0.43	10.76	70.7	0.42	5.5	10.4	-4.1	-4.6	-0.8	-3.8
Liguria	14.80	95.7	0.42	14.66	98.8	0.41	-0.9	3.2	-3.8	-3.0	0.5	-3.4
Emilia R.	10.07	67.2	0.41	10.53	71.3	0.40	4.6	6.1	-1.2	-3.8	-1.2	-2.7
Tuscany	9.27	60.8	0.42	9.35	63.3	0.40	0.9	4.1	-2.7	-5.4	-1.6	-3.9
Umbria	13.43	84.1	0.44	13.07	85.3	0.42	-2.7	1.4	-3.7	-4.0	-0.4	-3.6
Marche	10.39	63.9	0.44	10.43	66.6	0.43	0.4	4.2	-3.3	-6.7	-2.9	-3.9
Lazio	14.73	90.1	0.45	14.47	92.4	0.43	-1.7	2.6	-3.9	-5.2	-1.6	-3.7
Abruzzo	14.11	84.6	0.46	14.23	89.4	0.44	0.9	5.7	-4.3	-2.1	1.0	-3.1
Molise	13.97	85.5	0.45	14.22	91.3	0.43	1.8	6.9	-4.5	-3.5	0.1	-3.6
Campania	20.13	121.9	0.45	20.03	127.2	0.43	-0.5	4.4	-4.4	-0.4	3.5	-3.8
Puglia	14.48	87.3	0.45	14.48	91.2	0.43	0.0	4.4	-4.0	-6.3	-2.6	-3.8
Basilicata	15.86	91.0	0.48	16.19	98.6	0.45	2.1	8.4	-5.6	-0.8	2.4	-3.1
Calabria	16.70	97.7	0.47	16.23	101.0	0.44	-2.8	3.4	-5.7	-5.1	-2.2	-3.0
Sicily	15.07	96.2	0.43	15.09	100.1	0.41	0.1	4.0	-3.5	-5.1	-1.4	-3.8
Sardinia	14.02	89.4	0.43	14.12	93.7	0.41	0.7	4.8	-3.6	-5.3	-2.1	-3.3
Italy	**13.00**	**82.7**	**0.43**	**13.08**	**86.3**	**0.42**	**0.6**	**4.3**	**-3.3**	**-4.0**	**-0.4**	**-3.7**
North	11.00	73.4	0.41	11.24	76.8	0.40	2.2	4.7	-2.1	-3.7	0.0	-3.7
Centre	12.31	76.8	0.44	12.20	79.2	0.42	-0.9	3.0	-3.6	-5.3	-1.6	-3.7
South and Islands	16.32	99.8	0.45	16.27	104.2	0.43	-0.3	4.4	-4.2	-3.7	-0.1	-3.6

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 distribution on behalf.

An analysis of prescription in the population shows an increasing use with increasing age but no meaningful differences between men and women (Figure 3.3.2b). 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 17.8%) and the median age of users is 68 year. Analysing the regional variability, the prevalence of use is reportedly higher in the South (24.4%), compared with the Centre (19.6%) and the North (16.6%). Over the year, each user consumed 150.8 doses of the medicines, equivalent to 5 months of treatment, and 16.6% of users received only one prescription. Overall, the average cost per user for this category was equal to 64.3 euros.

Figure 3.3.2b Distribution of 2021 prevalence of use and consumption of medicines for peptic ulcer and GERD under approved care regime and distribution on behalf

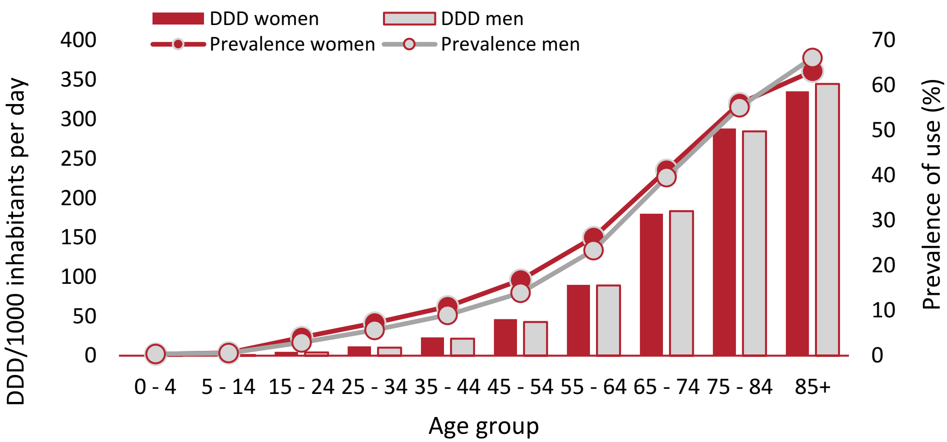


Table 3.3.2c Exposure and duration of therapy with medicines for peptic ulcer and GERD by region under approved care regime and distribution on behalf (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	men	women	total					
Piedmont	16.4	20.3	18.4	69	58.4	138.9	112.0	15.8
Valle d'Aosta	15.1	18.5	16.8	69	64.2	150.3	112.0	15.3
Lombardy	15.4	18.8	17.1	69	68.4	167.4	136.0	14.2
A.P. of Bolzano	9.2	10.9	10.0	70	64.6	138.9	93.3	18.2
A.P. of Trento	15.2	18.3	16.8	68	72.9	170.5	130.7	16.0
Veneto	12.6	15.2	13.9	70	68.8	163.3	112.0	16.7
Friuli VG	15.0	18.7	16.9	70	66.2	150.4	112.0	14.2
Liguria	19.8	24.8	22.4	72	70.2	163.8	140.0	12.8
Emilia R.	14.5	18.3	16.4	69	60.7	137.3	90.0	17.0
Tuscany	14.9	18.1	16.5	71	57.0	134.5	88.7	21.8
Umbria	19.7	23.8	21.8	70	61.5	141.4	112.0	18.3
Marche	16.6	19.2	17.9	71	58.4	132.5	98.0	18.3
Lazio	19.7	24.6	22.3	67	62.9	145.2	108.0	16.3
Abruzzo	20.8	25.3	23.1	68	60.7	138.1	98.0	18.1
Molise	21.2	25.4	23.4	69	63.0	146.6	112.0	16.2
Campania	25.6	30.8	28.3	64	64.3	148.6	112.0	15.9
Puglia	20.4	23.9	22.2	68	62.7	143.6	112.0	16.1
Basilicata	23.6	28.5	26.1	67	61.0	134.6	103.3	17.8
Calabria	22.9	26.9	24.9	68	61.9	141.7	112.0	15.9
Sicily	20.9	25.9	23.5	69	61.5	147.4	112.0	17.8
Sardinia	19.7	25.0	22.4	67	63.7	153.3	112.0	18.2
Italy	**17.8**	**21.7**	**19.8**	**68**	**64.3**	**150.8**	**112.0**	**16.6**
North	14.8	18.3	16.6	69	66.4	157.8	112.0	15.5
Centre	17.6	21.6	19.6	69	61.5	142.4	100.0	18.3
South and Islands	22.0	26.6	24.4	67	63.5	147.9	112.0	16.9

Prescribing profiles in General Medicine

Analyses of the overall prescriptions of all antacid/antisecretory/gastroprotective medicines and related indications by GPs of the HS network for 2021 (Table 3.3.2d) show that in more than 40% of cases the diagnosis concerns gastroesophageal reflux disease (GERD). Lower percentages concern a diagnosis of gastritis (11.8%) and other gastrointestinal disorders (11.5%). Prescriptions for the treatment of gastroduodenal peptic ulcer and the eradication of Helicobacter pylori in 2021 were lower than in the past, equal to 3.3% and 1.3%, respectively.
Regarding prescriptions of these medicines for MRGE, 55.0% of all prescriptions of other antacid/antisecretory/gastroprotector medicines, such as sucralfate and misoprostol, report this indication, compared to 52.2% for H2 or anti-H2 receptor antagonists (e.g. ranitidine), 47.3% for antacids and 38.7 % for PPIs. Gastritis is indicated in 19.6% of antacid prescriptions and 11.1% of PPI prescriptions. By contrast, 8.3% and 10.2% of anti-H2 prescriptions report indications for the treatment of gastroduodenal peptic ulcer and other gastrointestinal disorders, respectively. Finally, for the eradication of Helicobacter pylori, the percentage distribution is similar among the classes analysed, with slightly higher values for other antacid/antisecretory/gastroprotector medicines (1.4%).
In 2021, around 19% of prescriptions for antacids/antisecretors/gastroprotectors medicines (mainly PPIs) relate to gastroprotection in patients with cardio-metabolic disorders treated with potentially gastrolesive medicines (e.g. platelet aggregation inhibitors and anticoagulants). In addition, 9.3% of prescriptions (PPIs and antacids as the most used classes) refer to patients treated with pain medications (e.g. NSAIDs and Coxib), whereas 2.2% refer to patients suffering from other respiratory disorders and receiving potentially gastrolesive medicines (e.g. corticosteroids). Table 3.3.2e shows estimates of prevalence of use for antacids/antisecretors/gastroprotectors in patients on chronic therapy (i.e. with at least 4 prescriptions during the year) with potentially gastrolestive pharmaceuticals.
The analysis shows that antacids/antisecretors/gastroprotectors are prescribed in 65.9% of chronic users of corticosteroids, 66.5% of those taking platelet aggregation inhibitors(e.g. low-dose acetylsalicylic acid, ticlopidine, prasugrel, etc.), 62.7% of continuous users of NSAIDs/Coxib, and 55.1% of users of anticoagulants (e.g. vitamin K inhibitors and new oral anticoagulants). The use of antacids/antisecretors/gastroprotectors is significantly higher in the South and the Islands and in women, and shows an increasing trend with increasing age.
Finally, analysing the prevalence of use (2019-2021) of antacids/antisecretors/gastroprotectors prescribed in patients on chronic therapy with gastrolesive medicines, a broadly stable trend emerges for all four therapeutic categories considered (Figure 3.3.2c).

Table 3.3.2d Percentage distribution of indications reported in prescriptions of antacid/antisecretory/gastroprotective medicines

	Distribution (%)				
	Antacid/antisecretor/ gastroprotective medicines	PPIs	Antacids	Anti H2	Others
Reported indication*					
GERD	40.8	38.7	47.3	52.2	55.0
Gastritis	11.8	11.1	19.6	15.9	14.0
Gastro-duodenal peptic ulcer	3.3	3.5	2.5	8.3	2.3
HP eradication	1.3	1.3	1.3	1.1	1.4
Other gastrointestinal disorders	11.5	11.3	13.4	10.2	12.4
Protective therapy in case of treatment for					
Cardiometabolic disorders	18.6	21.2	4.5	2.6	4.2
Pain	9.3	9.6	9.8	9.2	7.1
Respiratory disorders	2.2	2.1	2.6	2.4	2.9
Other	14.4	14.6	15.2	15.8	12.5

*Not mutually exclusive. Indicator used:

Percentage distribution of indications reported in prescriptions of antacid/antisecretory/gastroprotective medicines: number of prescriptions of antacid/antisecretory/gastroprotective medicines for each indication reported by the doctor [**numerators**], over total prescriptions of antacid/antisecretory/gastroprotective medicines **[denominators]**

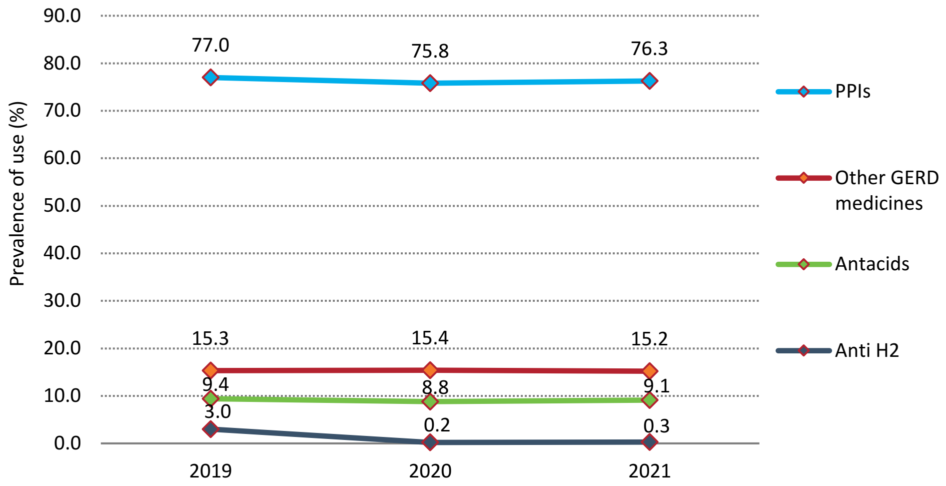
Table 3.3.2e Prevalence of use of antacid/antisecretory/gastroprotective medicines in patients on chronic therapy with gastrolesive medicines* (2021)

	Prevalence of use (%)			
	NSAIDs/Coxib	Platelet aggregation inhibitors (low dose ASA, ticlopidine, prasugrel, etc.)	Corticosteroids	Anticoagulants (AVK, NAO, etc.)
Geographic analysis				
North	56.2	60.0	64.1	50.3
Centre	57.5	63.9	60.3	51.9
South and Islands	67.5	72.8	70.2	63.0
Analysis by gender				
Men	57.4	63.6	62.0	51.4
Women	65.5	70.0	68.4	59.0
Analysis by age				
≤45	42.8	48.2	42.6	27.0
46-65	54.5	54.7	59.9	43.2
66-74	66.8	65.4	66.7	51.8
75-84	71.5	70.6	74.7	59.2
≥85	71.6	72.5	74.2	59.0
Total	**62.7**	**66.5**	**65.9**	**55.1**

*At least 4 prescriptions in the previous 12 months. Indicator used:

Prevalence of use of antacid/antisecretory/gastroprotective medicines in patients on chronic therapy with gastrolesive medicines (NSAIDs/Coxib, platelet aggregation inhibitors, corticosteroids and anticoagulants): number of patients treated with antacid/antisecretory/gastroprotective medicines [**numerator**], over total subjects on chronic therapy (at least 4 prescriptions in the previous 12 months) with NSAIDs/Coxib, platelet aggregation inhibitors, corticosteroids and anticoagulants [**denominators**]

Figure 3.3.2c Prevalence of use of antacid/antisecretory/gastroprotective medicines in patients on chronic therapy with gastrolesive medicines*: analysis by therapeutic category (2019-2021)



*At least 4 prescriptions in the previous 12 months.

Indicator used:

Prevalence of use of antacid/antisecretory/gastroprotective medicines in patients on chronic therapy with gastrolesive medicines (NSAIDs/Coxib, platelet aggregation inhibitors, corticosteroids and anticoagulants): number of patients treated with a specific category of antacid/antisecretory/gastroprotective medicines [**numerator**], over total subjects on chronic therapy (at least 4 prescriptions in the previous 12 months) with NSAIDs/Coxib, platelet aggregation inhibitors, corticosteroids and anticoagulants [**denominators**]

Key message

- **The consumption trend appears to be slightly decreasing**, equal to 86.3 DDD/1000 inhabitants per day in 2021. This trend in consumption is accompanied by a constant reduction in expenditure (CAGR 2014-2020: -4.0%) and in the average DDD cost. Proton pump inhibitors (PPIs) account for over 90% of expenditure and consumption. Therefore, the observed trends can essentially be attributed to this class of medicines. However, it is important to note that other major categories, such as antacids and H2 receptor antagonists, are predominantly over-the-counter pharmaceuticals. Consequently, a large share of use of these medicines is not considered in this analysis since they are purchased privately.

- As with most of the main therapeutic categories, **a large and growing regional variability in terms of consumption and prevalence of use** is confirmed in 2021. As already noted, the use of these medicines in Campania (consumption: 127.2 DDD/1000 inhabitants per day; prevalence of use: 28.3%) is more than twice compared with that of Bolzano (consumption: 48.7 DDD/1000 inhabitants per day; prevalence of use: 10.0%). This data is in line with what has been observed in many therapeutic categories and, in addition to differences in prescriptions by doctors, could be attributed to the private purchase of both OTC and SOP medicines, as well as class A medicines. Indeed, data on private purchases suggest a high consumption of PPIs in particular in Northern Italy.

- Unlike many therapeutic categories, **consumption and prevalence of use of medicines for peptic ulcer and GERD do not decrease in the over 85 age group**. This data confirms that this age group is characterised by both the increased use of potentially gastrolesive medicines and the high prevalence of gastrointestinal symptoms such as dyspepsia, reflux and epigastric burning symptoms as well as a corresponding treatment for the relief of these symptoms. Although available data do not allow an accurate assessment of prescriptive appropriateness, the information obtained from the Health Card, associated with consumption data and general medicine data allow to formulate some hypotheses:
  - **PPIs are recommended as first line treatment of gastroduodenal ulcers and GERD**, requiring at least 4-8 weeks of treatment. Available data show a national estimate of 150.8 DDD per user, which should reassure about the adequacy of the treatment duration.
  - The high percentage of users with a prescription, associated with the prevalent consumption of PPIs, and the data from General Practitioners, confirm that **these medicines are also used in the treatment of upper digestive tract disorders** for which there is no indication to inhibit gastric 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 still high use of non-PPI antacid medicines has no valid counterparts in the pathophysiology of upper digestive tract disorders, with the exception of a small percentage of patients. A potentially improper use of these medicines can expose the patient to a reduced absorption of nutrients and other pharmaceuticals.

References

- Agenzia Italiana del Farmaco (AIFA). Nota 1. 29 ottobre 2004. http://www.agenziafarmaco.gov.it/content/nota-1/
- Agenzia Italiana del Farmaco (AIFA). Nota 48. http://www.agenziafarmaco.gov.it/content/nota- 48/
- Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gas- troenterology 2017; 152(4):706-15.
- Gyawal CP. Proton pump inhibitors in gastroesophageal reflux disease: friend or foe. Curr Gastro- enterol Rep 2017; 19(9):46.
- Heidelbaugh JJ, Kim AH, Chang R et al. Overutilization of proton-pump inhibitors: what the clini- cian needs to know. Therap Adv Gastroenterol 2012; 5(4):219-32.
- Kanno T, Moayyedi P. Proton pump inhibitors in the elderly, balancing risk and benefit: an age-old problem. Curr Gastroenterol Rep 2019; 21(12):65.
- Ladd AM, Panagopoulos G, Cohen J et al. Potential costs of inappropriate use of proton pump inhibitors. Am J Med Sci 2014; 347(6):446-51.
- Lodato F, Poluzzi E, Raschi E et al. Appropriateness of PPI prescription in patients admitted to hospital: attitudes of general practitioners and hospital physicians in Italy. Eur J Intern Med 2016; 30:31-36.
- Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complica- tions and risks. Nat Rev Gastroenterol Hepatol 2017; 14(12):697-710.
- National Institute for Excellence (NICE). NICE guidelines [CG184]. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Published date: 03 September 2014. Last updated: 18 October 2019. Available at https://www.nice.org.uk/guid- ance/cg184/
- Savarino V, Marabotto E, Zentilin P et al. The appropriate use of proton-pump inhibitor. Minerva Med 2018; 109(5):386-99.
- Sigterman KE, van Pinxteren B, Bonis PA et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2013; 2013(5):CD002095.
- Vakil N. Prescribing proton pump inhibitors: is it time to pause and rethink? Drugs 2012; 72(4):437-45.
- Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. Drug Saf 2014; 37(4):201-11.

3.3.3 Metabolic disorders

Epidemiological framework

This section reports the data on expenditure and consumption for medicines for the treatment of lysosomal storage disorders (LSD), disorders caused by congenital amino-acid transport and metabolism defects, urea cycle disorders, juvenile neuronal ceroid lipofuscinosis, hereditary transthyretin-mediated amyloidosis, hypophosphatasia, lipodystrophy, acute liver porphyria, and Wilson’s disease. This is a set of rare genetic diseases, mostly hereditary, caused by an enzymatic deficiency that results in an accumulation of complex substrates in different body tissues and organs. In many cases, these conditions occur in the first few days after birth.

Lysosomal storage diseases (LSD), which represent the largest group of disorders within this category, are hereditary metabolic disorders caused by the lack of activity of lysosomal enzymes, resulting in the progressive accumulation of complex substrates in different tissues and organs. Clinical manifestations of such diseases may concern the musculoskeletal system, liver and spleen, heart, lungs and the central nervous system. Lysosomal diseases are classified according to the biochemical characteristics of the accumulated substrate. Although these diseases are rare when taken individually, their overall prevalence is relatively high compared to other groups of rare diseases (about 1 in 8,000 live births). The most common diseases include lipid storage diseases (Fabry disease, Gaucher disease, Pompe disease, lysosomal acid lipase deficiency), mucopolysaccharide storage diseases (i.e. mucopolysaccharidosis) or oligosaccharide storage diseases (such as alpha-mannosidosis), as well as glycoprotein storage diseases and glycogenosis. Symptoms may emerge at a variable age: in some cases, during intrauterine or neonatal time, during the paediatric age, or late adulthood. In recent years, thanks to a better understanding of the pathophysiology of LSD, important advances have been made in the development of highly innovative therapeutic approaches. These approaches include strategies that aim to increase the residual activity of the missing enzyme, such as hematopoietic stem cell transplantation (HSCT), enzyme replacement therapy (ERT), pharmacological chaperone therapy (PCT), gene therapy (GT), as well as approaches based on the substrate reduction therapy (SRT).
Congenital amino-acid transport and metabolism defects are congenital metabolic disorders caused by the deficiency of an enzyme involved in the metabolism and/or transport of amino acids. The clinical picture is variable and generally depends on the substrate accumulation caused by the enzyme defect, as well as on the lack of the downstream product and the severity of the enzyme deficit. Phenylketonuria, homocystinuria, manifest nephropathic cystinosis, type 1 hereditary tyrosinaemia belong to this group of diseases.

Urea cycle defects (UCD) are genetic diseases caused by a deficiency of the enzymes necessary for the urea incorporation of ammonium, which, as such, is eliminated with urine. Ammonium is a product of protein metabolism and a highly toxic substance for the central nervous system. As a group, the incidence of these disorders is about one in 35,000 newborns, although this is probably an underestimate because many cases remain undiagnosed.

The other medicines in this category include those for the treatment of:

- lipodystrophy, a group of rare diseases characterised by partial or complete deficiency of adipose tissue and possible accumulation of fat in liver and muscles, resulting in serious metabolic complications, including insulin resistance, hypertriglyceridaemia and liver steatosis;
- hypophosphatasia, a rare and potentially fatal genetic metabolic disorder caused by mutations of the gene encoding for alkaline phosphatase (ALP);
- juvenile neuronal ceroid lipofuscinosis (JNCL), a group of genetically heterogeneous ceroid lipofuscinoses, characterised by onset in early school age with vision loss as a result of retinopathy, epilepsy and decline in intellectual and motor skills;
- hereditary transthyretin-mediated amyloidosis, a progressively disabling and often fatal disease, caused by an accumulation of amyloid proteins that damage organs and tissues, such as heart and peripheral nerves;
- acute liver porphyria, a family of rare genetic diseases characterised by acute neurovisceral attacks (with or without skin signs), with the risk of developing irreversible progressive neuropathy, and chronic debilitating symptoms that have a negative impact on the quality of life;
- Wilson’s disease, a hereditary condition characterised by reduced elimination of copper in the bile by the liver.

National data on consumption and expenditure

Over the last few years, medicines for the treatment of diseases resulting from impaired cellular metabolism has recorded negligible consumption, 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 2021, the expenditure of these medicines reached a total of 7.2 euros per capita, up by 14% compared with the previous year, and an average DDD cost of 450.9 euros, up by 9.2% compared with the previous year (Table and Figure 3.3.a).

Overall, medicines for the treatment of lysosomal storage diseases record the highest per capita expenditure (5.94 euros per capita) of their category, followed by medicines for the treatment of congenital amino-acid transport and metabolism defects (0.24 euros).

The highest per capita expenditure is for Fabry disease, with 1.65 euros for enzyme replacement therapy (average DDD cost of 782.19 euros) and 0.37 euros for chaperone therapy (average DDD cost of 465.68 euros).

Pompe disease ranks second for expenditure, with only one enzyme therapy available (recombinant human acid alpha-glucosidase), with a per capita expenditure of 1.29 euros in 2021 (+6.9% compared with 2020) and an average DDD cost of 1062.23 euros (stable compared with the previous year). This active ingredient is also the first among those with the highest expenditure within the category, followed by agalsidase alfa (0.88 euros per capita, +6.2% compared with 2020) and agalsidase beta (0.77 euros, +28.1% compared with 2020). Both are used in the treatment of Fabry disease.

The third group of medicines with the highest expenditure within the category includes the enzyme replacement therapy for type 1 Gaucher's disease, with an expenditure of 1.05 euros and an average DDD cost of 1096.62 euros. Finally, the group of medicines for the treatment of hereditary transthyretin-mediated amyloidosis recorded the largest change in expenditure compared with the previous year (+70.9%), mainly attributable to the active ingredient patisiran.

There is a high variability in expenditure at regional level, ranging from a minimum value found in Valle d'Aosta (2.82 euros per capita) to a maximum value found in Campania (10.79 euros per capita) (Table 3.3.3b). The lowest average DDD cost (298.84 euros) was observed in Valle d'Aosta, whereas the highest value (896.98 euros) was observed in the Autonomous Province of Bolzano. Bolzano also recorded the greatest increase in consumption (+54.7%) and the average cost per day of therapy (+28.4%).

Figure 3.3.3a Metabolic disorders, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

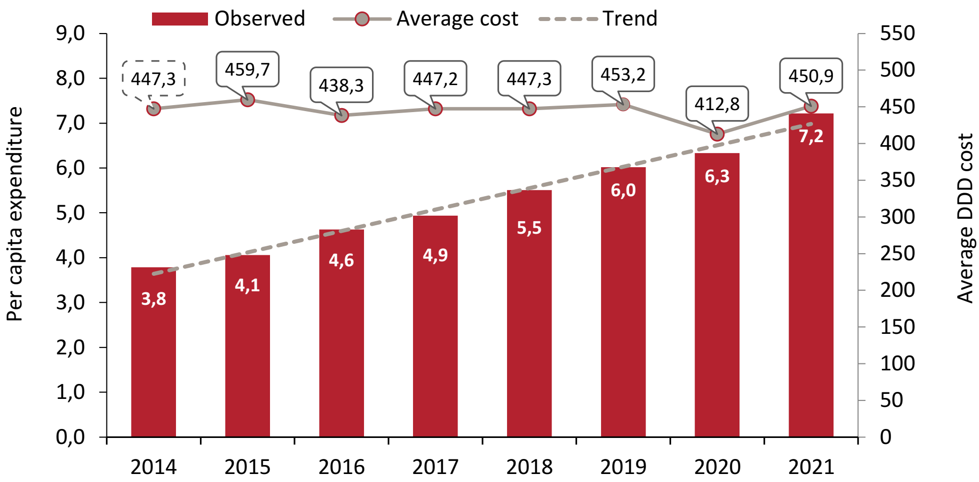


Table 3.3.3a Metabolic disorders, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD Cost	Δ % 21-20
Lysosomal storage diseases - Fabry disease - enzyme replacement therapy	1.65	15.4	8.1	<0.05	20.1	11.7	782.19	-3.6
Lysosomal storage diseases - Pompe disease - enzyme replacement therapy	1.29	6.9	6.4	<0.05	7.2	7.1	1062.23	0.0
Lysosomal storage diseases - type 1 Gaucher disease - enzyme replacement therapy	1.05	0.3	2.5	<0.05	-1.1	2.2	1096.62	1.7
Hereditary transthyretin-mediated amyloidosis	0.68	70.9	24.9	<0.05	55.2	27.3	376.06	10.4
Lysosomal storage diseases - mucopolysaccharidosis II - enzyme replacement therapy	0.53	6.4	2.3	<0.05	0.6	2.1	2877.24	6.0
Lysosomal storage diseases - Fabry disease - chaperone therapy	0.37	11.9	-	<0.05	12.2	-	465.68	0.0
Lysosomal storage diseases - type 1 Gaucher disease - chaperone therapy	0.36	2.3	18.0	<0.05	14.5	13.4	317.86	-10.4
Lysosomal storage diseases - mucopolysaccharidosis IV-A (Morquio's syndrome) - enzyme replacement therapy	0.27	6.2	-	<0.05	6.5	-	2992.00	0.0
Congenital amino-acid transport and metabolism defects - phenylketonuria	0.19	8.0	8.4	<0.05	10.0	9.5	155.66	-1.6
Lysosomal storage diseases - mucopolysaccharidosis I - enzyme replacement therapy	0.18	5.0	6.5	<0.05	5.3	6.5	1433.74	0.0
Lysosomal storage diseases - mucopolysaccharidosis VI - enzyme replacement therapy	0.15	24.8	9.4	<0.05	25.2	7.9	2869.64	0.0

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD Cost	Δ % 21-20
Lysosomal storage diseases - Liposomal acid lipase deficiency - enzyme replacement therapy	0.09	19.1	-	<0.05	13.3	-	1281.40	5.4
Wilson's disease	0.09	53.8	43.1	<0.05	-13.6	3.0	40.86	78.6
Urea cycle disorders	0.08	-2.4	11.1	<0.05	-0.6	15.7	60.77	-1.5
Acute hepatic porphyria	0.08	-	-	<0.05	-	-	854.52	-
Juvenile neuronal ceroid lipofuscinosis	0.07	-	-	<0.05	-	-	1110.13	-
Lipodystrophy	0.03	>100	-	<0.05	>100	-	762.76	-30.3
congenital amino-acid transport and metabolism defects - homocystinuria	0.03	-21.6	2.2	<0.05	-21.3	3.8	13.33	-0.1
congenital amino-acid transport and metabolism defects - type 1 hereditary tyrosinemia	0.02	-11.3	-3.0	<0.05	0.3	5.1	63.72	-11.3
Lysosomal storage diseases - alpha-mannosidosis - enzyme replacement therapy	0.01	64.1	-	<0.05	>100	-	665.54	-18.4
Congenital amino-acid transport and metabolism defects - manifest nephropathic cystinosis	0.01	-9.3	4.8	<0.05	-13.1	1.4	25.85	4.7
Medicines for metabolic disorders	**7.22**	**14.0**	**9.7**	**<0.05**	**4.7**	**9.5**	**450.89**	**9.2**
recombinant human acid alglucosidase	1.29	6.9	6.4	<0.05	7.2	7.1	1062.23	0.0
agalsidase alfa	0.88	6.2	3.6	<0.05	-0.2	3.5	1692.37	6.8
agalsidase beta	0.77	28.1	16.1	<0.05	28.7	16.1	483.60	-0.2
imiglucerase	0.77	-2.0	1.2	<0.05	-1.7	1.2	1096.50	0.1
idursulfase	0.53	6.4	2.3	<0.05	0.6	2.1	2877.24	6.0
patisiran	0.45	>100	-	<0.05	>100	-	516.03	0.0
migalastat	0.37	11.9	-	<0.05	12.2	-	465.68	0.0
eliglustat	0.31	10.1	-	<0.05	10.4	-	622.68	0.0
velaglucerase alfa	0.28	6.9	6.8	<0.05	0.5	5.8	1096.94	6.6
elosulfase alfa	0.27	6.2	-	<0.05	6.5	-	2992.00	0.0

Table 3.3.3b Metabolic disorders, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: 2014-2021 comparison

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	5.05	<0.05	470.44	5.66	<0.05	503.34	12.2	5.1	7.0	7.3	9.2	-1.8
Valle d'Aosta	2.93	<0.05	312.21	2.82	<0.05	298.84	-4.0	0.6	-4.3	107.7	22.5	69.6
Lombardy	5.55	<0.05	402.48	6.03	<0.05	432.84	8.5	1.2	7.5	8.2	11.4	-2.8
Bolzano	2.44	<0.05	698.36	4.83	<0.05	896.98	98.2	54.7	28.4	11.6	10.2	1.3
Trento	7.72	0.1	400.95	8.16	0.1	351.77	5.6	20.7	-12.3	8.5	12.4	-3.4
Veneto	5.54	<0.05	327.40	6.34	<0.05	378.68	14.4	-0.8	15.7	9.0	9.7	-0.7
Friuli VG	5.16	<0.05	545.26	6.13	<0.05	520.83	18.8	24.7	-4.5	13.0	11.4	1.4
Liguria	3.92	<0.05	331.24	4.57	<0.05	374.91	16.7	3.4	13.2	8.0	12.1	-3.6
Emilia R.	7.18	<0.05	525.36	8.53	<0.05	523.53	18.8	19.6	-0.3	9.9	11.5	-1.5
Tuscany	6.57	0.1	355.57	6.45	<0.05	377.40	-1.8	-7.2	6.1	10.7	10.1	0.5
Umbria	6.81	<0.05	401.32	6.63	<0.05	444.79	-2.6	-11.9	10.8	7.0	5.8	1.1
Marche	5.48	<0.05	472.83	5.90	<0.05	516.34	7.7	-1.1	9.2	2.9	2.8	0.1
Lazio	6.25	<0.05	406.85	7.61	<0.05	465.66	21.8	6.7	14.5	15.0	14.5	0.4
Abruzzo	6.17	<0.05	412.33	6.60	<0.05	443.81	6.9	-0.4	7.6	6.6	7.2	-0.5
Molise	3.77	<0.05	271.26	4.69	<0.05	301.86	24.6	12.3	11.3	11.1	13.7	-2.2
Campania	9.06	<0.05	496.67	10.79	0.1	534.09	19.1	11.0	7.5	9.7	9.5	0.2
Puglia	6.45	<0.05	388.93	7.31	<0.05	421.53	13.3	4.8	8.4	13.0	7.6	5.0
Basilicata	6.32	<0.05	461.82	7.29	<0.05	441.04	15.3	21.1	-4.5	11.4	11.2	0.1
Calabria	8.67	<0.05	539.57	10.02	<0.05	604.09	15.5	3.4	12.0	9.1	4.5	4.4
Sicily	7.29	0.1	386.94	8.77	0.1	428.87	20.4	8.9	10.8	8.7	7.6	1.1
Sardinia	5.44	0.1	255.69	5.84	0.1	300.75	7.5	-8.4	17.6	12.7	5.4	6.9
Italy	**6.33**	**<0.05**	**412.79**	**7.22**	**<0.05**	**450.89**	**14.0**	**4.7**	**9.2**	**9.7**	**9.5**	**0.1**
North	5.59	<0.05	416.83	6.35	<0.05	448.01	13.6	6.0	7.5	8.8	10.9	-1.8
Centre	6.30	<0.05	393.57	6.94	<0.05	438.27	10.3	-0.7	11.4	11.1	10.7	0.4
South and Islands	7.41	<0.05	419.09	8.64	0.1	460.58	16.5	6.3	9.9	9.9	7.7	2.0

Key message

- Although medicines for metabolic disorders have recorded negligible consumption over the years, a **progressive increase in per capita expenditure** was reported, due to the marketing of medicines for the treatment of diseases, which in many cases were orphan.
- Pharmaceuticals for the **treatment of lysosomal storage diseases** account for 82% of the expenditure for the entire category, with Fabry disease medicines ranking first. **Recombinant human acid alglucosidase**, an enzyme replacement therapy for the treatment of Pompe disease, is the active ingredient with the greatest expenditure.
- At regional level, a **high variability in expenditure** is reported, with Campania recording a per capita expenditure almost four times higher than that of Valle d'Aosta. Bolzano has the highest average cost per day of therapy, as well as the highest increases in consumption (+54.7%) and average cost (+28.4%) related to 2021.

References

- Araújo-Vilar D, Santini F. Diagnosis and treatment of lipodystrophy: a step-by-step approach. J Endocrinol Invest 2019; 42(1):61-73.
- Ballabio A, Gieselmann V. Lysosomal disorders: From storage to cellular damage. Biochim Biophys Acta 2009; 1793:684-96.
- Coutinho MF, Alves S. From rare to common and back again: 60 years of lysosomal dysfunction. Mol Genet Metab 2016; 117(2):53-65.
- Dionisi-Vici C, Rizzo C, Burlina AB et al. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr 2002; 140:321-7.
- Finsterer J, Iglseder S, Wanschitz J, Topakian R, Löscher WN, Grisold W. Hereditary transthyretin-related amyloidosis. Acta Neurol Scand 2019; 139(2):92-105.
- Ganesh R, Abinesh R, Janakiraman L. Clinical spectrum of inherited disorders of metabolism. Indian J Pediatr 2019; 86(10):892-6.
- Matsumoto S, Häberle J, Kido J, Mitsubuchi H, Endo F, Nakamura K. Urea cycle disorders-update. J Hum Genet 2019; 64(9):833-47.
- Ortolano S, Viéitez I, Navarro C, Spuch C. Treatment of lysosomal storage diseases: recent patents and future strategies. Recent Pat Endocr Metab Immune Drug Discov 2014; 8:9-25.
- Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. Annu Rev Med 2015; 66:471-86.
- Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ. Lysosomal storage diseases. Nat Rev Dis Primers 2018; 4(1):27.
- Schwartzlow C, Kazamel M. Hereditary transthyretin amyloidosis: clinical presentation and management updates. J Clin Neuromuscul Dis 2020; 21(3):144-56.
- Simon S, Resch H, Klaushofer K, Roschger P, Zwerina J, Kocijan R. Hypophosphatasia: from diagnosis to treatment. Curr Rheumatol Rep 2018; 20(11):69.

3.4 General antimicrobials for systemic use

General antimicrobials for systemic use are the fourth therapeutic category with the highest public expenditure for 2021, equal to 2504.0 million euros and 11.6% of overall public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these medicines was 42.23 euros, mainly due to expenditure by public health facilities to purchase these medicines (32.77 euros per capita). Conversely, expenditure under approved care regime was lower (9.46 euros per capita). Both expenditure under approved care regime and expenditure by public health facilities continued to register a significant reduction compared to 2020, (-4.9% and -5.7%, respectively) (Table 3.1).
Consumption for this category of medicines was equal to 18.2 DDD/1000 inhabitants per day, with a -5.6% decrease compared to 2020 (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 (23.5 DDD/1000 inhabitants per day) than in women (20.5 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 20.8 euros and 18.3 euros per capita in men and women respectively, in subjects over 75 years of age.
As regards approved care regime, the -4.9% change compared to 2020 is due to a decrease in consumption (-5.0%). Prices and mix effect remain broadly stable (Table 3.9).
Within this distribution channel, penicillin combinations, including beta-lactamase inhibitors, are the category with the highest expenditure (2.19 euros), and register a reduction in expenditure and consumption (-3.9% and -4.7%, respectively). These are followed by third generation cephalosporins with an expenditure of 1.97 euros per capita (-9.5%) (Table 3.9). All categories recorded a reduction in both expenditure and consumption, with the exception of “other antibacterials” which show stable consumption and expenditure (both +0.3% compared to the previous year).
Amoxicillin in combination with clavulanic acid is the first active ingredient in the category by per capita expenditure (2.07 euros) and consumption (4.2 DDD), showing a reduction both in expenditure (-3.6%) and consumption (-3.8%) (Table 3.10). It is also the only active ingredient in this category listed within the top 30 molecules with the greatest impact on expenditure under approved care regime (Table 3.11). Ceftriaxone (11.99 euros), fluconazole (5.55 euros) phosphomycin (4.63 euros), cefixime (2.33 euros) and azithromycin (1.48 euros) are among the top thirty active ingredients with the highest average cost per day of therapy under approved care regime (Table 3.13). Amoxicillin in combination with clavulanic acid (-3.6%), ceftriaxone (-11.7%) and fluconazole (-1.8%) are included in the top thirty active ingredients with the largest reduction in expenditure under approved care regime compared to 2020 (Table 3.15). For all three active ingredients, the reduction in expenditure is associated with a reduction in consumption, while the average DDD cost

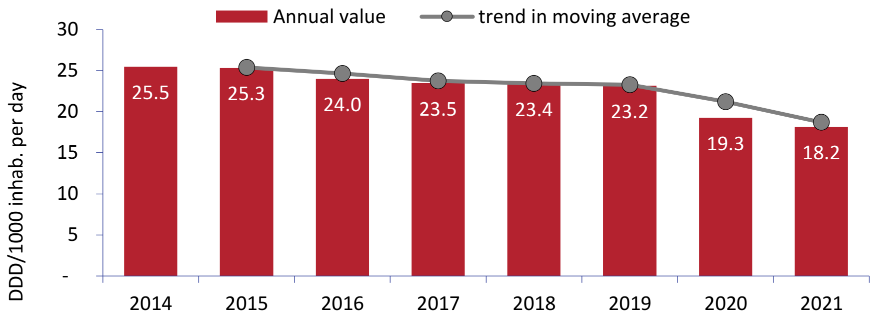
remains almost stable, with a slight increase only for ceftriaxone (+1.0%). No active ingredient in the antimicrobials category is included in the list of the top thirty active ingredients for consumption under approved care regime.
As for purchases by public health facilities, a significant reduction in expenditure (-6.4%) was recorded compared to 2020, against a slight reduction in consumption (-9.5%) and of prices (-12.0%), with a positive mix effect (+17.6%) (Table 3.18).
For direct purchases, antivirals for the treatment of HIV infections in combination (ATC level IV) are the highest expenditure subcategory (8.29 euros per capita), followed by influenza vaccines (3.07 euros per capita). The latter category showed a sharp increase in expenditure (+97.3%) mainly due to a shift in prescription towards more expensive medicines (mix effect: +70.8%) and, less markedly, to an increase in consumption (+13.7%). The first category for increased expenditure and consumption is represented by antivirals for systemic use - nucleosides and nucleotides, excluding reverse transcriptase inhibitors, which include remdesivir. On the contrary, the most important reduction in expenditure is registered with antivirals for the treatment of HCV infections (72.1%). This is due to a reduction in consumption (-13.0%) and in prices (-68.6%). A sharp decrease in the average DDD cost (-67.9%) is also found compared with 2020.
Within antimicrobials, the first active ingredients for expenditure are remdesivir (2.25 euros per capita), indicated in the treatment of COVID-19, the emtricitabine/tenofovir alafenamide/bictegravir combination (1.81 euros per capita), indicated in the treatment of adults with HIV-1 infection, and the 13-valent pneumococcal vaccine (1.74 euros per capita; Table 3.19). While the first two show an increase in both expenditure and consumption, the 13-valent pneumococcal vaccine shows a 16.9% reduction in expenditure and a 17.2% reduction in consumption. Table 3.20 shows the first thirty active ingredients in terms of expenditure purchased by public health facilities.
In addition, remdesivir and the emtricitabine/tenofovir alafenamide/bictegravir combination, together with the dolutegravir/lamivudine combination, the inactivated influenza vaccine and the human papilloma virus vaccine, are included in top 30 active ingredients with a greater variation in expenditure compared with the previous year: dolutegravir/lamivudine (>100%), inactivated influenza vaccine (>100%), remdesivir (>100%), emtricitabine/tenofovir alafenamide/bictegravir (+35.5%) and human papilloma virus vaccine (+22.5%) (Table 3.22). Seven active ingredients in antimicrobials category are among those with the largest reductions in expenditure. The first three are: dolutegravir (-37.7%), dolutegravir/abacavir/lamivudine (-23.1%) and 13-valent pneumococcal vaccine (-16.9) (Table 3.23). Conversely, among the top thirty active ingredients in terms of average cost per day of therapy for medicines purchased by public health facilities, remdesivir (374.7 euros) and human normal immunoglobulin for intravenous administration (319.7 euros) can be found (Table 3.24). No medicines belonging to the antimicrobials category can be found in the top thirty active ingredients in terms of consumption purchased by public health facilities (Table 3.25).
Analyses of the historical series of consumption and expenditure by active ingredient and by Region have been carried out to get more information on the use of medicines belonging to the same therapeutic area. These analyses focused on antibiotics, antifungals, anti-HIV and anti-HCV antivirals and vaccines (Table 3.4.1 and following).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

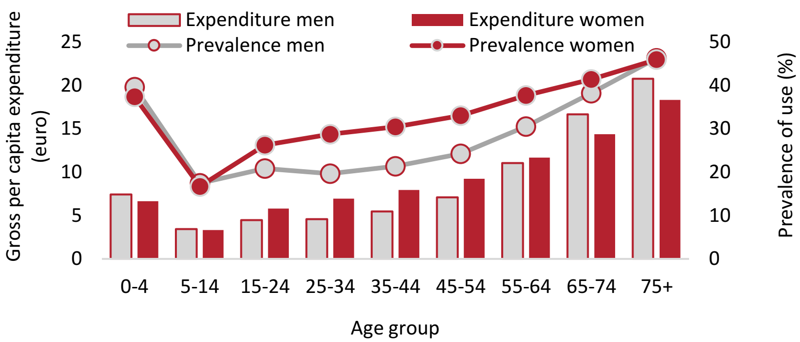
Antimicrobials for systemic use

Public expenditure* in million euros (% over total)	**2,504.0**	**(10.6)**
Δ % 2021-2020		-5.9
Regional range for gross expenditure (per capita):	28.9	47.4
DDD/1000 inhab. per day* (% over total)	**18.2**	**(1.4)**
Δ % 2021-2020		-5.7
Regional range for DDD/1000 inhab. per day:	10.8	23.7

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



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and on behalf distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	7.4	6.7	7.0	10.8	9.7	10.2
5-14	3.4	3.3	3.4	5.2	4.9	5.0
15-24	4.5	5.8	5.1	7.6	9.0	8.3
25-34	4.6	6.9	5.7	7.0	10.0	8.5
35-44	5.5	7.9	6.7	8.2	11.3	9.7
45-54	7.1	9.2	8.2	10.0	12.9	11.5
55-64	11.0	11.7	11.4	13.9	15.7	14.9
65-74	16.7	14.4	15.4	19.3	18.3	18.8
75+	20.8	18.3	19.3	23.5	20.5	21.7

3.4.1 Antibiotics

Epidemiological framework

Antimicrobials, including antibiotics, have had and still have a significant impact on human health. Together with vaccines, they have helped reduce mortality, prolong lifespan and improve quality of life. In every region of the world, the effects of resistance, i.e. the inability of an antibiotic, administered at therapeutic doses, to reduce the survival or inhibit the replication of a pathogenic bacterium, are being tested in clinical practice. In recent years, this phenomenon has significantly increased due to increased use of these pharmaceuticals (including inappropriate use). The loss of effectiveness of currently available antibiotics risks putting health systems under pressure, causing both an increased infection-related mortality and higher health and social costs. According to the "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis", the latest report published in The Lancet in 2022, the world's antibiotic-resistance-related deaths are estimated at around 4.95 million in 2019 and about 1.27 million are directly attributable to resistant bacterial strains. These estimates indicate that antibiotic resistance is a priority global public health problem, the extent of which is comparable to that of diseases such as HIV and malaria. However, antibiotic resistance shows a pejorative trend where there is no proper use of the pharmaceutical through stewardship and infection control strategies. The data show that the six pathogens associated with bacterial resistance are *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa.* The medicines most frequently causing the onset of resistance are third-generation cephalosporins and fluoroquinolones and carbapenems. Recently, in order to improve patient care through appropriate use of antimicrobials, the National Plan against Antimicrobial Resistance (PNCAR 2017-2020) has been approved in Italy, and a Coordination Technical Group has been established with the task of overseeing the implementation of the objectives set out in the plan. Among the areas of intervention, the PNCAR provides for the surveillance of antibiotic consumption for both human and veterinary use, with the common goal of reducing the frequency of infections with antibiotic resistant microorganisms. Pending the approval of the new National Plan, which has been delayed due to the pandemic, the PNCAR 2017-2020 has been extended for 2021.

National data on consumption and expenditure

Over the last eight years, a steady decrease in the consumption of antibiotics has been observed (CAGR -5.8%), with values shifting from 19.7 DDD in 2014 to 13.0 DDD in 2021. The most important decrease was recorded in 2020 compared to 2019 (-21.7%), whereas the decline in consumption in 2021 compared with 2020 was more contained (-6.1%; Figure 3.4.1a and Table 3.4.1a). Conversely, the average DDD cost has seen an increasing trend in the last two years and in 2021 the average cost was equal to 2.34 euros, an increase of 2.0% compared to 2020.

Penicillin combinations, almost entirely represented by amoxicillin+clavulanic acid, remain the category of antibiotics with the highest prescription (4.6 DDD), with an expenditure of 2.79 euros per capita in 2021 (-4.1% and -3.5% compared to 2020 for consumption and expenditure, respectively). Macrolides and lincosamides follow for consumption (2.7 DDD), whereas for expenditure, the second category is represented by third generation cephalosporins (2.56 euros per capita), as in 2020. Most of the subgroups of antibiotics recorded a reduction in consumption compared to the previous year. Important changes among high-consumption medicines were observed for third generation cephalosporins (-8.1%), macrolides and lincosamides (-12.7%) and fluoroquinolones (-7.8%). In particular, the decline found for macrolides and lincosamides is likely linked to the awareness campaign for a more appropriate use of macrolides and more generally of antibiotics in positive COVID-19 subjects. However, further awareness campaigns are still needed.

The subgroup that registered the highest increase both in terms of expenditure and consumption, is that of beta-lactamase resistant penicillins (>100%), although their expenditure and consumption levels are very low. The DDD cost for this sub-group also increased significantly (>100%). The second subgroup with the highest change in terms of expenditure and consumption is represented by nitrofuran derivatives. This change is attributable to the reclassification of nitrofurantoin in class A in early 2020. Concerning carbapenems, despite a stable consumption (+0.9%), there is a significant increase in expenditure (+23.6%) combined with an increase in average DDD cost (+22.8%). 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 4.5 DDD, followed by azithromycin and clarithromycin. All these molecules recorded a decrease in consumption compared to 2020: -4.3%, -9.4% and -15.9%, respectively. Again in 2021, there was an important increase in consumption of avibactam/ceftazidime, a combination of a third generation cephalosporin with a beta-lactamase inhibitor (+36.6% compared to 2020), against a lower increase in expenditure (+10.2%) due to the reduction in the average DDD cost (-19.1%). Similarly, the piperacillin/tazobactam combination, a broad-spectrum penicillin plus a beta-lactamase inhibitor, showed an increase in consumption (+1.1%), although smaller than in 2020. At the same time, a reduction in per capita expenditure (-2.4%) was registered as a result of the reduction in average DDD cost (-3.2%). Fosfomycin recorded a slight increase in expenditure (+1.8%), despite a strong increase in consumption (+7.0%), due to an increase in the DDD cost (+5.3%). Despite a decreasing trend in consumption in all Regions, a wide variability is still observed, with values ranging from 7.6 DDD in Bolzano to 19.1 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 (16.72 euros) and a minimum value recorded in Bolzano (6.10 euros). Consumption decreased in all Regions, with the largest variations observed in Veneto (-11.1%), Lombardy (-10.8%) and Piedmont (-10.5%) compared with 2020. With regard to per capita expenditure, compared to 2020, a reduction is recorded in all Regions, with the exception of Emilia Romagna (+1.8%) and Puglia (+0.3%). The largest decreases are found in Liguria (-16.5%), Molise (-12.2%) and Piedmont (-8.7%). The average DDD cost, equal to 2.34 euros at national level, varies between the maximum value of Liguria (-2.82 euros) and the minimum value of Trento (2.09 euros). The average DDD cost showed a slight increase compared to 2020 (+2.0%), with very heterogeneous variations at regional level, i.e. between -8.0% in Liguria and +9.1% in Emilia Romagna. 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 (2014-2021)

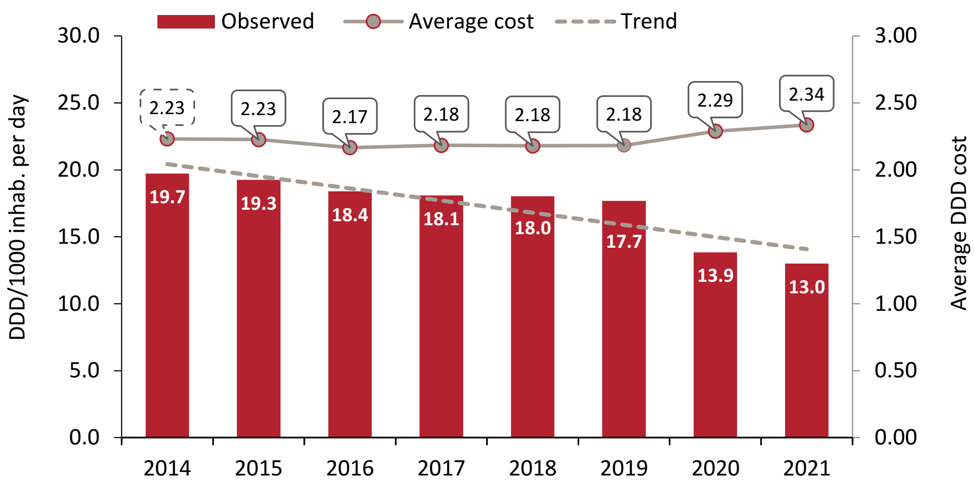


Table 3.4.1a Antibiotics, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Penicillin combinations (including beta lactamase inhibitors)	2.79	-3.5	-3.3	4.6	-4.1	-4.8	1.66	0.9
Third-generation cephalosporins	2.56	-6.9	-4.1	1.5	-8.1	-4.1	4.54	1.7
Macrolides and lincosamides	1.23	-8.8	-6.1	2.7	-12.7	-6.1	1.23	4.8
Fluroquinolones	1.20	-4.7	-10.4	1.5	-7.8	-11.0	2.12	3.6
Other antibacterials	1.16	7.2	-4.0	0.5	6.0	2.8	6.74	1.4
Glycopeptides	0.33	-10.1	-12.2	0.0	-11.3	-5.3	19.99	1.6
Carbapenems	0.31	23.6	-6.5	0.1	0.9	-2.6	14.31	22.8
Other cephalosporins and penems	0.24	-42.5	101.0	0.0	-56.9	78.3	228.39	33.6
Broad-spectrum penicillins	0.22	-5.0	-6.1	0.7	-11.7	-10.5	0.84	7.9
Polymyxin	0.20	-9.2	0.0	0.0	-3.8	1.0	34.08	-5.4
Tetracyclines	0.17	-2.9	-13.2	0.4	6.5	0.9	1.23	-8.5
Aminoglycosides	0.14	-3.1	-6.1	0.0	-5.2	-6.9	8.40	2.5
First-generation cephalosporins	0.11	2.1	-1.2	0.1	5.3	-1.7	2.95	-2.7
Sulphonamides (plain and in combination)	0.07	-1.3	1.4	0.4	-1.0	1.4	0.53	0.0
Fourth-generation cephalosporins	0.07	-0.3	-0.8	0.0	1.5	2.1	21.81	-1.5
Second-generation cephalosporins	0.07	-12.8	-14.2	0.1	-13.3	-13.4	1.79	0.8
Beta-lactamase resistant penicillins	0.07	>100	22.8	0.0	>100	7.4	6.79	>100
Nitrofuran derivatives	0.05	100.7	88.6	0.1	99.5	59.6	0.92	0.9
Other combinations	0.05	12.3	-	0.0	12.8	-	6.70	-0.2
Monobactams	0.04	-7.0	-1.5	0.0	-6.7	-1.5	88.12	0.0
Imidazole derivatives	0.01	-0.9	-1.0	0.0	-3.5	0.0	1.04	2.9
Beta-lactamase sensitive penicillins	<0.005	-88.2	-30.8	0.0	-86.1	-29.5	46.15	-15.0
Amphenicols	<0.005	-27.3	-5.7	0.0	-28.3	-7.6	6.52	1.8
Antibiotics	**11.09**	**-4.5**	**-5.2**	**13.0**	**-6.1**	**-5.8**	**2.34**	**2.0**
amoxicillin/clavulanic acid	2.15	-3.9	-5.0	4.5	-4.3	-5.0	1.32	0.7
ceftriaxone	0.89	-12.8	-8.0	0.4	-17.2	-4.8	6.39	5.6
fosfomycin	0.81	7.0	4.6	0.4	1.8	1.3	5.66	5.3
azithromicyn	0.74	-2.5	0.4	1.4	-9.4	0.3	1.45	7.9
cefixime	0.70	0.5	-3.1	0.8	0.0	-2.9	2.28	0.8
piperacillin/tazobactam	0.62	-2.4	7.9	0.1	1.1	7.0	11.87	-3.2
ciprofloxacin	0.60	1.6	-8.4	0.7	0.0	-7.8	2.41	1.8
ceftazidime/avibactam	0.47	10.2	-	0.0	36.6	-	194.45	-19.1
levofloxacin	0.45	-9.3	-10.4	0.7	-13.4	-12.6	1.68	5.1
clarithromycin	0.41	-18.5	-11.9	1.3	-15.9	-10.2	0.89	-2.8

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	9.49	11.7	2.21	8.67	10.5	2.26	-8.7	-10.5	2.3	-5.7	-6.2	0.4
Valle d'Aosta	8.41	11.6	1.97	8.26	10.5	2.15	-1.7	-9.5	9.0	-6.8	-6.6	-0.3
Lombardy	8.74	11.5	2.07	8.16	10.3	2.17	-6.7	-10.8	4.9	-4.7	-6.2	1.6
Bolzano	6.47	8.0	2.20	6.10	7.6	2.21	-5.7	-5.9	0.4	-6.6	-6.7	0.1
Trento	8.89	11.9	2.03	8.49	11.1	2.09	-4.5	-6.9	2.8	-5.5	-5.4	-0.1
Veneto	9.70	11.1	2.38	9.04	9.9	2.50	-6.7	-11.1	5.2	-4.4	-6.5	2.2
Friuli VG	8.49	10.7	2.17	8.34	10.2	2.24	-1.7	-4.4	3.0	-3.7	-5.2	1.7
Liguria	12.02	10.7	3.06	10.04	9.8	2.82	-16.5	-8.9	-8.0	-3.2	-5.4	2.3
Emilia R.	8.85	12.3	1.97	9.01	11.5	2.15	1.8	-6.4	9.1	-4.8	-6.0	1.3
Tuscany	10.38	12.5	2.27	9.98	11.8	2.32	-3.8	-5.4	1.9	-5.7	-6.5	0.8
Umbria	15.47	15.9	2.65	14.56	14.7	2.71	-5.9	-7.5	2.1	-3.4	-5.7	2.4
Marche	13.57	14.7	2.52	13.11	14.0	2.58	-3.3	-5.3	2.4	-4.8	-5.9	1.1
Lazio	13.56	15.1	2.45	12.46	14.2	2.40	-8.1	-5.9	-2.1	-5.1	-5.6	0.6
Abruzzo	15.23	16.9	2.46	14.12	15.8	2.44	-7.3	-6.5	-0.6	-3.7	-5.1	1.5
Molise	12.79	14.9	2.34	11.23	14.1	2.18	-12.2	-5.3	-7.1	-7.2	-6.2	-1.0
Campania	16.90	19.4	2.39	16.72	19.1	2.40	-1.0	-1.3	0.5	-5.1	-4.9	-0.2
Puglia	14.35	17.0	2.30	14.39	16.7	2.37	0.3	-2.1	2.8	-6.5	-6.2	-0.4
Basilicata	14.66	16.0	2.51	13.57	15.7	2.37	-7.5	-1.8	-5.6	-4.3	-5.3	1.0
Calabria	15.14	16.9	2.45	14.85	16.4	2.48	-1.9	-2.9	1.3	-5.2	-5.4	0.2
Sicily	13.04	16.4	2.17	12.82	15.8	2.22	-1.7	-3.9	2.5	-5.5	-5.0	-0.5
Sardinia	9.29	12.3	2.06	8.83	11.4	2.12	-5.0	-7.4	2.8	-6.7	-6.4	-0.3
Italy	**11.60**	**13.9**	**2.29**	**11.09**	**13.0**	**2.34**	**-4.5**	**-6.1**	**2.0**	**-5.2**	**-5.8**	**0.7**
North	9.19	11.5	2.19	8.62	10.4	2.28	-6.2	-9.5	4.0	-4.8	-6.1	1.4
Centre	12.68	14.3	2.43	11.91	13.4	2.43	-6.1	-5.8	-0.1	-5.1	-5.9	0.9
South and Islands	14.41	17.0	2.31	14.11	16.5	2.34	-2.0	-3.0	1.3	-5.5	-5.4	-0.1

Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to antibiotics in the general population in 2021. 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. Almost 26.7% of users receive only one prescription per year. There is a higher prevalence of use in women than in men (32.7% vs. 26.7%), with the largest differences in the 35-54 age group. This is likely due to antibiotic use in the treatment of cystitis in women.

More than 42% of users receive only one prescription during the year. Users receive an average of 14.1 doses per year at a cost of 25.7 euros per user.

Similarly to consumption, a greater prevalence of use is reported in the South (37.3%) and the Centre (31.1%) compared to the North (23.3%) of Italy. The South also features a higher number of DDD per user (South: 14.5 DDD *vs* Centre: 14.1 DDD and North: 13.7 DDD) and a higher cost per user than the Centre and the North (28.5 euros in the South and 26.2 euros in the Centre compared to 22.1% in the North; Table 3.4.1c).

Figure 3.4.2b Distribution of prevalence of use and consumption of antibiotics for systemic use under approved care regime and on behalf distribution in 2021

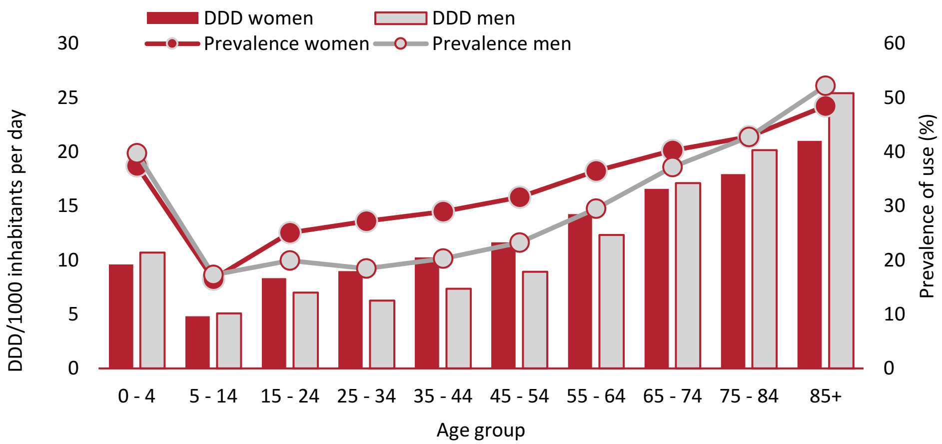


Table 3.4.2c Exposure and duration of therapy with antibiotics for systemic use by Region under approved care regime and on behalf distribution (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	men	women	total					
Piedmont	22.7	28.4	25.6	55	21.8	13.2	10.0	42.9
Valle d'Aosta	19.0	24.6	21.9	55	21.7	13.7	10.0	40.2
Lombardy	20.9	25.8	23.4	52	22.7	14.0	10.0	40.1
Bolzano	13.8	17.8	15.8	49	18.6	11.8	8.0	52.1
Trento	21.4	27.1	24.3	51	21.4	13.7	10.0	41.1
Veneto	19.1	24.2	21.7	53	21.7	13.5	10.0	43.3
Friuli VG	18.1	23.9	21.1	55	22.3	15.1	12.0	34.0
Liguria	21.7	26.7	24.3	58	23.7	13.1	10.0	41.8
Emilia R.	21.7	27.4	24.6	53	20.3	13.0	9.0	44.8
Tuscany	24.9	30.6	27.8	56	22.3	13.2	8.0	50.4
Umbria	30.1	36.8	33.6	56	25.2	14.4	10.0	40.1
Marche	30.9	37.1	34.1	54	25.5	13.6	10.0	42.7
Lazio	28.7	35.9	32.5	55	28.4	14.5	10.0	38.9
Abruzzo	34.1	41.1	37.7	54	25.5	13.8	10.0	44.2
Molise	33.9	40.7	37.4	56	26.9	13.7	10.0	42.3
Campania	36.2	43.3	39.8	53	32.6	15.3	10.0	36.0
Puglia	35.7	42.7	39.3	54	27.2	14.1	10.0	42.2
Basilicata	34.0	41.3	37.7	55	25.7	14.0	10.0	41.8
Calabria	33.6	39.0	36.3	57	31.2	15.0	10.0	39.0
Sicily	33.7	40.0	36.9	55	25.2	13.8	10.0	44.4
Sardinia	25.0	31.7	28.4	54	23.4	13.4	10.0	46.3
Italy	**26.5**	**32.4**	**29.5**	**54**	**25.7**	**14.1**	**10.0**	**42.0**
North	20.6	25.8	23.3	53	22.1	13.7	10.0	42.3
Centre	27.7	34.2	31.1	55	26.2	14.1	10.0	43.0
South and Islands	33.9	40.5	37.3	54	28.5	14.5	10.0	41.2

Key message

- A **downward trend in consumption** is observed in all Regions, with the most important changes in Veneto (-11.1%), Lombardy (-10.8%) and Piedmont (-10.5%). At national level, consumption recorded a -6.1% decrease. Considering that most antibiotic consumption is attributable to provision at local level, it can be inferred that the PNCAR objective of reducing consumption locally has been achieved. It will be necessary to continue monitoring prescriptive appropriateness by applying prescribing quality indicators. In 2020, there was a worsening of the indicator assessing the use of broad-spectrum antibiotics compared to the consumption of narrow-spectrum antibiotics (OsMed Report. Antibiotics use in Italy. Year 2020). In addition, it will be useful to specifically evaluate consumption in hospitals, considering the impact of the COVID-19 pandemic on the consumption of antibiotics in the inpatient setting.

- Although total NHS consumption (approved care regime and direct purchases) shows a reduction in the use of azithromycin, an increase in consumption (+1.7%) is seen when assessing the approved care regime alone (+1.7%; see Table 3.10). It should be noted that the information sheet published by AIFA on 9 April 2020 in the context of COVID-19 established the use of azithromycin outside the indications registered exclusively in randomised clinical trials or in case of bacterial superinfections.

- There continues to be an increase in the use of the combination of a **third generation cephalosporin with a beta-lactamase inhibitor, ceftadime/avibactam**, indicated for the treatment of infections caused by MDR microorganisms and included in the Reserve group of the WHO AWaRe classification. Therefore, they should be used as a last resort and only in the most severe cases. This once again underlines the need for monitoring of clinical appropriateness of antibiotics, especially the latest generation ones.

- Despite the decreasing trend in consumption in all Regions, a **wide variability** is still observed, with an increasing North-South gradient. The differences are mainly due to both the number of subjects receiving at least one prescription and to the number of prescriptions dispensed to the individual patient, resulting in a greater number of doses per user in the South and Centre than in the North. In this regard, in view of the ongoing use of the Electronic Health Report, it seems useful and necessary to carry out a more careful monitoring of the prescriptive appropriateness within the territory, with the creation of local and national networks for the evaluation of the parameters indicating that an ongoing infection requiring therapy.

References

- European Centre for Disease Prevention and Control. Giornata europea degli antibiotici. Un'in- iziativa europea per la salute. Scheda informativa per esperti. Available at https://antibiotic.ecdc.europa.eu/it/cosa-dovete-sapereschede-informative/scheda-informativa-esperti

- Hooper DC, Shenoy ES; Varughese CA. Treatment and prophylaxis of bacterial infections. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's principles of internal medicine, 20e ed. New York: McGraw-Hill, 2018
- Osservatorio Nazionale sull'impiego dei Medicinali. L'uso degli antibiotici in Italia. Rapporto Nazi- onale 2019. Roma: Agenzia Italiana del Farmaco, 2020. Available at https://www.aifa.gov.it/-/l-uso-degli-antibiotici-in-italia-rapporto-nazionale-anno-2019/
- World Health Organization. Antimicrobial resistance. Present situation. Drug resistance in bacteria. 13 October 2020. Available at https://www.who.int/news-room/fact-sheets/ detail/antimicrobial-resistance/
- World Health Organization. The 2019 WHO AWaRe classification of antibiotics for evaluation and monitoring of use. Geneva: World Health Organization, 2019. (WHO/EMP/IAU/2019.11). Available at https://www.who.int/publications/i/item/WHOEMPIAU2019.11/

3.4.2 Anti-HIV antivirals

Epidemiological framework

Human immunodeficiency viruses (HIV) are lentiviruses, a family of retroviruses leading to a persistent chronic infection with gradual onset of clinical symptoms. The virus attacks the immune system, specifically CD4 cells by destroying them and thus weakening the immune response of the person. This results in an increased susceptibility to other infections and certain types of cancer such as Kaposi's sarcoma. According to WHO estimates at the end of 2020, 37.7 million people had HIV infection, and over two-thirds of them (25.4 million) lived in African regions. HIV continues to be a major public health problem globally, and has been responsible for approximately 36.3 million deaths so far. There is no treatment for HIV infection. However, with increased access to effective HIV prevention, diagnosis, treatment and care, even for opportunistic infections, HIV infection has become a manageable chronic health condition. Based on the analysis of data originating from the surveillance of new diagnosed HIV infections, in 2020, 1303 new HIV infections were reported in Italy, with an incidence of 2.2 new cases per 100,000 inhabitants. Additionally, more than 1/3 of people with a new HIV diagnosis finds out to be HIV positive due to the presence of HIV-related symptoms or conditions. The incidence of new HIV diagnoses has been steadily decreasing since 2012, while the number of deaths of people with AIDS remains stable. In 2020, the highest incidences were recorded in Valle d'Aosta, Liguria, Trento and Lazio. In 79.9% of cases, people who found to be HIV positive in 2020 were male. The median age is 40 years for both sexes and the highest incidence is found in the 25-29 age group (5.5 new cases per 100,000 inhabitants) and 30-39 age group (5.2 new cases per 100,000 inhabitants). Data also indicate that the incidence of new cases observed in Italy is lower than the average incidence observed among EU Member States (3.3 new cases per 100,000 inhabitants). Additionally, since 2018, a decrease in cases for all modes of transmission is being observed.

National data on consumption and expenditure

In 2021, per capita expenditure for anti-HIV antivirals was equal to 10.4 euros, almost stable (+0.3%) compared to the previous year. This trend was determined by a slight reduction (-10.4%) in the average DDD cost compared to a slight increase (+4.7%) in doses (Table and Figure 3.4.2a). In general, compared to 2014, the expenditure for this category of medicines recorded a reduction of 14% and an average annual decrease rate (CAGR) of 2.1%. The average DDD cost has shown a decreasing trend since 2018 and was equal to 10.9 euros in 2021.

The total consumption for this category of medicines was 2.6 DDD per 1000 inhabitants per day, down 10.4% compared to the previous year, and with an average annual growth rate (CAGR) of 0.3% over the period 2014-2021.

Antivirals in co-formulated regimens with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and 1 integrase inhibitor (INSTI) account for 30% of the expenditure for this category of pharmaceuticals, with a 4.3% reduction compared to 2020 and an average annual growth rate (CAGR) of 82.5% compared to 2014. Both consumption and average

DDD cost of these medicines see a reduction by 1.2% and 2.9% respectively, compared to 2020.

Considering the trend in consumption, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) show the highest value, equal to 1.0 DDD per 1000 inhabitants per day, despite a decrease (-14.4%) compared to the previous year, which corresponds to a per capita expenditure of 0.86 euros, -24.6% compared to 2020. All subgroups record reductions both in expenditure and consumption, with the exception of co-formulated regimens with 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) and 1 integrase inhibitor (INSTI), as well as co-formulated regimens of 1 nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) and 1 integrase inhibitor (INSTI).

The bictegravir/emtricitabine/tenofovir alafenamide combination ranks first among the active substances with the highest expenditure (1.81 euros per capita) (Table 3.4.2a). This combination (+35.5%) and the dolutegravir/rilpivirine combination (+68.6%) record an increase in expenditure compared to the previous year. They are followed by the emtricitabine/rilpivirine/tenofovir alafenamide combination, with 1.52 euros per capita and a reduction of 12.8%.

Regional per capita expenditure (Table 3.4.2.b) varies widely in 2021, ranging from a minimum value of 2.81 euros in Molise (-14.7% compared to 2020), to a maximum of 17.07 euros in Lombardy (-3.5% compared to 2020). Molise and Lazio are the regions with a number of doses and a cost that are higher than the national average. Conversely, all Regions of the South, with the exception of Abruzzo, register consumption and average DDD cost below the national average. All Regions, with the exception of Valle d'Aosta and Emilia Romagna, show a reduction in expenditure, with the largest decreases being recorded in Bolzano (-29.7%), Basilicata (-28.4%) and Molise (-14.7%). Consumption is also decreasing in all Regions, with the exception of Molise, and the greatest changes are observed in Bolzano (32.3%), Tuscany (-25.3%) and in Calabria (-23.9%).

Figure 3.4.2a Anti-HIV antivirals, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

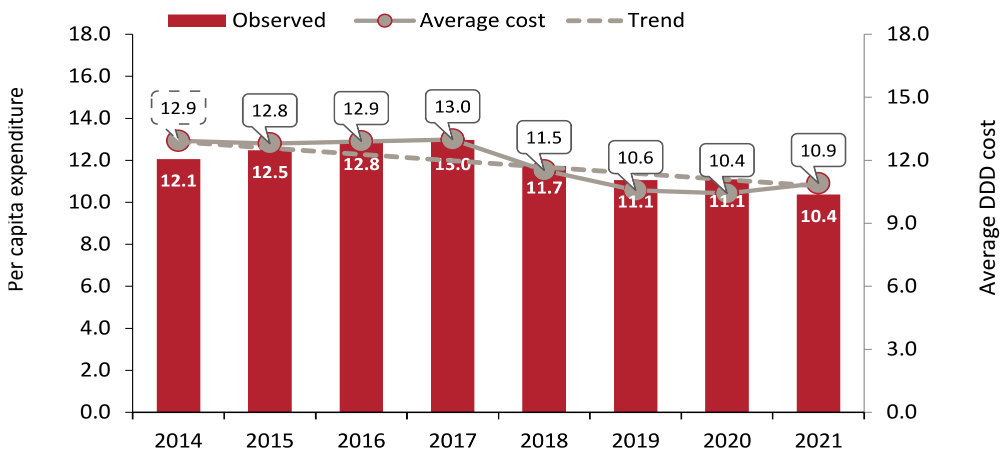


Table 3.4.2a Anti-HIV antivirals, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Co-formulated regimens (2 NRTIs + 1 INSTI)	3.15	-4.3	82.5	0.4	-1.2	88.9	20.93	-2.9
Co-formulated regimens (2 NRTIs + 1NNRTI)	1.75	-12.4	-1.9	0.3	-10.0	0.5	18.09	-2.5
INSTI	1.43	-32.6	6.4	0.3	-30.0	9.0	13.20	-3.4
Co-formulated regimens (1 NNRTI + 1 INSTI)	1.08	>100	-	0.2	>100	-	16.60	0.0
NRTI	0.86	-24.6	-23.0	1.0	-14.4	-3.4	2.36	-11.7
Co-formulated regimens (2 NRTIs + 1 IP)	0.82	-2.5	-	0.1	-2.2	-	21.85	0.0
IPS	0.56	-36.4	-20.8	0.2	-39.6	-16.1	8.81	5.5
Co-formulated regimens (1 NRTI + 1 INSTI)	0.44	68.6	-	0.1	69.1	-	18.31	0.0
NNRTI	0.18	-20.9	-15.2	0.1	-20.4	-11.2	4.82	-0.3
Other anti-HIV antivirals	0.09	-19.9	-14.5	0.0	-20.2	-11.7	34.17	0.6
Anti-HIV antivirals	**10.37**	**-6.5**	**-2.1**	**2.6**	**-10.4**	**0.3**	**10.91**	**4.7**
bictegravir/emtricitabine/ tenofovir alafenamide	1.81	35.5	-	0.2	35.9	-	19.96	0.0
emtricitabine/rilpivirine/ tenofovir alafenamide	1.52	-12.8	-	0.2	-12.6	-	19.96	0.0
dolutegravir/lamivudine	1.08	>100	-	0.2	>100	-	16.60	0.0
dolutegravir/abacavir/ lamivudine	1.05	-23.1	-	0.1	-22.9	-	21.48	0.0
dolutegravir	0.95	-37.7	95.0	0.2	-37.5	95.2	16.42	0.0
cobicistat/darunavir/ emtricitabine/tenofovir alafenamide	0.82	-2.5	-	0.1	-2.2	-	21.85	0.0
emtricitabine/tenofovir alafenamide	0.51	-25.7	-	0.1	-25.5	-	11.29	0.0
raltegravir	0.48	-19.5	-8.8	0.1	-18.9	-2.1	9.51	-0.5
dolutegravir/rilpivirine	0.44	68.6	-	0.1	69.1	-	18.31	0.0
darunavir/cobicistat	0.41	-22.1	-	0.1	-21.9	-	12.25	0.0

Table 3.4.2b Anti-HIV antivirals, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	11.61	2.7	11.74	10.08	2.3	12.09	-13.2	-15.5	3.0	-1.4	0.2	-1.5
Valle d'Aosta	6.34	1.8	9.38	7.41	1.8	11.07	16.9	-0.7	18.1	4.3	6.4	-2.0
Lombardy	17.69	4.1	11.84	17.07	3.8	12.31	-3.5	-7.0	4.0	-2.1	-1.1	-1.0
Bolzano	8.42	1.9	12.36	5.92	1.3	12.86	-29.7	-32.3	4.1	-3.4	-4.2	0.8
Trento	8.67	2.0	11.74	8.02	1.8	12.31	-7.5	-11.5	4.8	0.1	1.2	-1.2
Veneto	9.39	2.9	8.98	8.89	2.5	9.65	-5.4	-11.7	7.5	-2.3	0.1	-2.5
Friuli VG	7.62	2.3	9.25	7.35	2.1	9.59	-3.6	-6.9	3.7	0.0	3.4	-3.3
Liguria	10.96	2.4	12.45	10.63	2.2	13.48	-3.0	-10.2	8.3	-1.5	-1.0	-0.4
Emilia R.	12.50	4.4	7.81	12.67	4.2	8.30	1.3	-4.5	6.3	-3.5	1.2	-4.7
Tuscany	13.49	3.4	10.86	12.08	2.5	13.05	-10.4	-25.3	20.2	-0.6	0.3	-0.9
Umbria	10.47	2.1	13.67	10.20	2.0	13.72	-2.6	-2.7	0.4	-0.1	-0.3	0.2
Marche	10.85	2.6	11.49	9.69	2.3	11.42	-10.7	-9.9	-0.6	-1.6	0.7	-2.3
Lazio	14.04	3.4	11.41	12.55	2.9	11.92	-10.6	-14.2	4.5	-2.7	-1.0	-1.7
Abruzzo	8.03	1.9	11.39	7.23	1.8	11.04	-10.0	-6.9	-3.1	0.5	3.4	-2.8
Molise	3.29	0.9	9.51	2.81	1.0	8.02	-14.7	1.5	-15.7	-2.2	4.1	-6.1
Campania	6.51	2.0	8.82	6.08	1.9	8.56	-6.6	-3.6	-2.9	-2.7	2.8	-5.4
Puglia	7.18	2.2	8.75	7.10	2.2	8.88	-1.2	-2.3	1.5	-3.5	1.7	-5.1
Basilicata	4.91	1.2	11.52	3.52	1.1	8.79	-28.4	-5.9	-23.7	-2.5	2.7	-5.0
Calabria	3.80	1.2	8.31	3.53	1.0	10.17	-7.2	-23.9	22.3	-3.1	0.3	-3.5
Sicily	7.05	1.8	10.67	6.32	1.6	10.61	-10.4	-9.6	-0.5	-0.9	2.0	-2.9
Sardinia	10.06	3.4	8.14	9.33	2.7	9.40	-7.3	-19.5	15.5	-5.3	-0.2	-5.0
Italy	**11.09**	**2.9**	**10.42**	**10.37**	**2.6**	**10.91**	**-6.5**	**-10.4**	**4.7**	**-2.1**	**0.3**	**-2.4**
North	13.17	3.4	10.52	12.55	3.1	11.01	-4.7	-8.7	4.7	-2.1	-0.1	-2.0
Centre	13.18	3.2	11.34	11.85	2.6	12.32	-10.1	-17.0	8.6	-1.7	-0.4	-1.4
South and Islands	6.83	2.0	9.29	6.33	1.8	9.42	-7.2	-8.3	1.4	-2.6	1.9	-4.4

Key message

- The use of **co-formulated antiretroviral regimens** represents the main item of expenditure and consumption within the antiretroviral class. This confirms the need for these therapies to combine efficacy and tolerability with simplification.
- **Regional per capita expenditure records a wide variability in 2021**, ranging from a minimum value of 2.81 euros in Molise to a maximum of 17.07 euros in Lombardy. The latter, together with Lazio and Tuscany, is the Region with a number of doses and cost above the national average. This trend may reflect the different epidemiology of the disease among the Italian regions. However, it seems useful to initiate computerised anonymization processes for patients undergoing antiretroviral therapies not only for a better definition and evaluation of the progress of the infection, but also for a more accurate control of therapeutic outcomes.

References

- Regine V, Pugliese L, Boros S, Santaquilani M, Ferri M, Suligo B. Aggiornamento delle nuove diag- nosi di infezione da HIV e dei casi di Aids in Italia al 31 dicembre 2019. Not Ist Super Sanità 2020; 33(11):3-59
- World Health Organization. Health Topics HIV/AIDS. Available at ttps://www.who.int/health-topics/hiv-aids#tab=tab_1
- Flexner CW. Antiretroviral agents and treatment of HIV infection. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's: the pharmacological basis of therapeutics, 13e ed. New York: McGraw-Hill, 2017.
- Dorucci M, Regine V, Pezzotti P, Mammone A, Girardi E, Suligoi B and the HIV Surveillance System Group. Demographic and socio-economic determinants of poor HIV-risk perception at first HIV diagnosis: analysis of the HIV surveillance data, Italy 2010-2016. Ann Ist Super Sanità 2020; 56(3):267-76.
- The INSIGHT START Study Group; Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretro- viral therapy in early asymptomatic HIV infection. N Engl J Med 2015; 373(9):795-807.

3.4.3 Vaccines

Epidemiological framework

In Italy, the vaccination strategy is regulated by the National Vaccine Prevention Plan (PNPV), and its vaccination schedule. The aim is harmonising the vaccination strategies in place in the country, in order to guarantee the full benefits of vaccination to the entire population, both in terms of personal protection and collective prevention. Vaccination coverage (VC) is the main indicator of vaccination strategies, as they provide information on their actual implementation on the territory and on the efficiency of the vaccination system. In Italy, the coverage is monitored annually and a survey conducted at the end of the first half of 2020 shows a decrease in vaccination activities by almost all local health authorities. The primary course shows a not negligible decrease, with values well below the threshold guaranteeing herd immunity. As of 31 December 2020, the national coverage at 24 months (relating to children born in 2018) against polio (used as proxy for vaccinations contained in the hexavalent vaccine) falls to 94.02%, down by almost a percentage point compared to 2019.With the exception of VC for rotavirus (introduced for all newborns from the 2018 cohort), which improved in 2020 (+36.65%), there was a worsening of the indicators for vaccinations against measles, chickenpox, as well as for meningococcal B and pneumococcal vaccination. A negative general trend is also confirmed by national vaccination coverage at 36 months. This information is useful to monitor the proportion of children vaccinated later and who were not compliant with the vaccination schedule in the previous year. It should be stressed that if vaccinations are carried out later than required by the vaccination schedule, children are exposed to an unnecessary risk of infectious diseases, which are more frequent and more serious early in life. Coverage at 36 months shows higher values than those recorded in the previous year for the same birth cohort. With regard to vaccination coverage in adolescents, people aged 16 and 18 years were taken into account. Specifically, for the latter age group, a significant worsening of vaccination coverage is found, against an improvement observed in recent years with anti-difteric vaccination (fifth dose), which in the sixteen-year-olds decreased by 8.38% compared to 2019.

National data on consumption and expenditure

Expenditure for vaccines more than doubled from 2014 to 2021, from 4.8 euros to 10.5 euros per capita. Unlike 2020, an increase in vaccine expenditure is observed in 2021, up 11.8% compared to 2020. Similarly, after a reduction in 2020, the average DDD cost registered a new increase in 2021, +6.6% compared to 2020 (Figure 3.4.3a and Table 3.4.3a).

The flu vaccine represents the first item of expenditure in this category, accounting for almost 30% of the total (3.10 euros per capita in 2021, +100.9% compared to the previous year), with an average annual increase (CAGR) of 25.2% over the period 2014-2021. It is followed by the conjugated polysaccharide pneumococcal vaccine that in 2021 recorded a 24.1% decrease compared to the previous year (last year it was the first item of expenditure). Expenditure is therefore equal to 1.79 euros per capita.

Almost all of expenditure for conjugated polysaccharide pneumococcal vaccine (1.75 euros per capita) is attributable to the 13-valent conjugated vaccine (PCV13), which shows a 24.5% reduction in expenditure and a 20.8% reduction in consumption. This vaccine is indicated for infants and children up to 5 years of age and is effective against the 13 strains responsible for most of the most serious infections. It is an inactivated and conjugated vaccine obtained with fragments of the bacterium and then bound to a protein capable of increasing its effectiveness.

Although with much lower expenditure and consumption levels than the conjugated polysaccharide pneumococcal vaccine, there is an increase in both expenditure (+11.6%) and consumption (16.9%) for the pneumococcal 23 vaccine, which can be administered from 2 years of age.

The conjugated polysaccharide pneumococcal vaccine is followed by the meningococcal B vaccine (1.50 euros per capita) and the papilloma virus vaccine (1.19 euros per capita) (Table 3.4.3a). While the former continue to see a 7.7% contraction in expenditure, the papilloma virus vaccine shows a 22.4% increase in expenditure. Prevention of invasive meningococcal B disease, the incidence of which is higher in children under the age of 5 and especially in the first year of life (3.44 per 100,000 in the first year and 1.07 per 100,000 between 1-4 years), then decreasing with increasing age, with a further slight peak in adolescents aged 15-19 years (0.52 per 100,000), is one of the objectives of the PNPV. The administration of the 3 initial doses of the meningococcal B vaccine (recommended for all newborns) should be given in the first year of life. Since the maximum incidence of invasive diseases caused by this etiological agent is detected in the first two years of life, it is crucial to start the administration cycle as soon as possible. The MMRV vaccine, fourth in terms of expenditure with 0.57 euros per capita, recorded a 18.1% increase in expenditure and a 15.7% increase in consumption, while a decrease in expenditure and consumption of the MPR vaccine continued to be observed (-24.5% and -21.3%, respectively).

Among the categories with the highest expenditure, a contraction is recorded in the hexavalent vaccine (diphtheria/tetanus/pertussis/haemophilusinfluenza B/poliomyelitis/hepatitis B, -18.5%), in the attenuated rotavirus vaccine (-3.0%) and in the DTP vaccine (diphtheria/tetanus/pertussis; -3.7%). In addition, a reduction in vaccine expenditure for the live attenuated varicella zoster virus (-15.1%), probably due to the entry into the market in 2021 of the vaccine for the adjuvanted recombinant varicella zoster virus, should also be highlighted.

Southern Regions (with 11.08 euros per capita and a 18.2% increase over 2020) register the highest expenditure, while Northern and Central Regions have fairly similar values (10.41 euros per capita and 9.96 euros per capita, respectively) (Table 3.4.3b). It is noted that the North and the South register a sharp increase compared to the previous year (+13.4% and +18.2%, respectively), while the Centre shows a 1.5% decrease. Emilia Romagna is the Region with the highest expenditure (12.38 euros per capita), followed by Sicily (12.07 euros) and Puglia (12.05 euros). Emilia Romagna (30.5%) is also one of the Regions with the greatest increase compared to the previous year, together with Molise (41.7%), Friuli Venezia Giulia (39.9%) and Valle d’Aosta (38.9%). Lombardy, Bolzano, Trento, Veneto, Emilia Romagna, Lazio, Campania and Sicily record a consumption and average DDD cost above the national average. Piedmont, Liguria, Valle d’Aosta, Tuscany, Basilicata, Sardinia and Calabria show values below the national average for both indicators (Table 3.4.3b).

Figure 3.4.3a Vaccines, 2014-2021 temporal trend of per capita expenditure and average cost per day of therapy

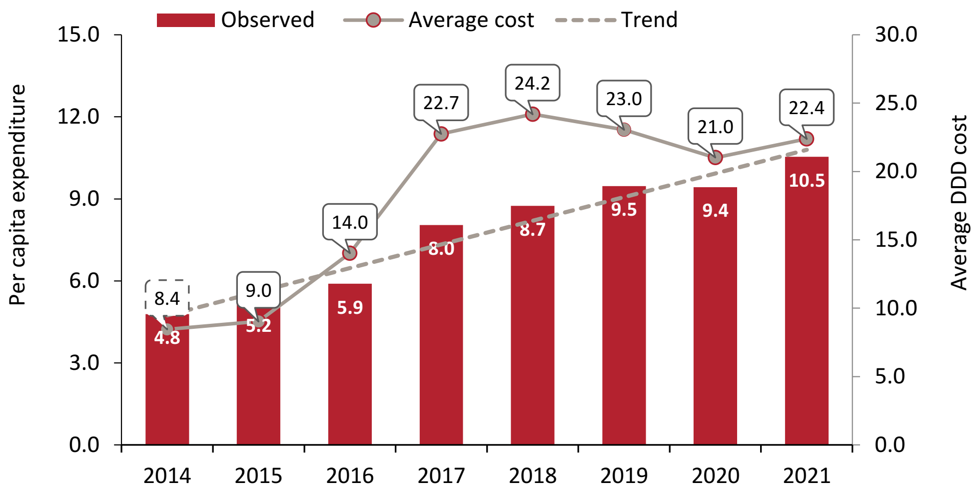


Table 3.4.3a Vaccines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Influenza vaccine	3.10	100.9	25.2	0.8	10.9	-6.0	11.07	81.7
Pneumococcal polysaccharide conjugate vaccine	1.79	-24.1	3.9	0.1	-20.2	3.4	48.21	-4.7
Meningococcal B vaccine	1.50	-7.7	54.6	0.1	-6.8	54.7	62.29	-0.7
Papillomavirus vaccine	1.19	22.4	17.7	0.0	23.1	9.8	69.26	-0.2
MMRV vaccine (measles/mumps/rubella/varicella)	0.57	18.1	17.9	0.0	15.7	20.1	46.80	2.4
Hexavalent vaccine (diphtheria/tetanus/pertussis/ Haemophilus Influenzae B/poliomyelitis/hepatitis B)	0.56	-18.5	-10.8	0.1	-9.5	-2.8	29.43	-9.6
Tetravalent meningococcal conjugate vaccine	0.40	2.9	33.0	0.0	6.7	37.2	29.78	-3.3
Tetravalent vaccine (diphtheria/tetanus/pertussis/ poliomyelitis)	0.33	20.5	11.7	0.0	24.5	11.3	18.71	-2.9
Rotavirus attenuated vaccine	0.29	-3.0	27.0	0.0	11.3	35.9	22.91	-12.6
Live attenuated varicella zoster vaccine	0.18	-15.1	164.4	0.0	-15.8	160.6	96.67	1.0
Pneumococcal 23 vaccine	0.15	11.6	37.7	0.0	16.9	32.2	21.36	-4.3
DTP vaccine (diphtheria /tetanus/pertussis)	0.11	-3.7	1.5	0.0	1.5	2.5	13.04	-4.9
Live attenuated varicella vaccine	0.09	2.5	-3.4	0.0	4.1	-1.9	32.36	-1.2
Adjuvanted recombinant varicella zoster vaccine	0.08	-	-	0.0	-	-	288.15	-
Hepatitis B vaccine	0.04	-4.1	-2.4	0.0	6.1	-2.6	16.55	-9.4
MMR vaccine (measles/mumps/rubella)	0.03	-24.5	-17.8	0.0	-21.3	-16.7	9.07	-3.8
Meningococcal C conjugate vaccine	0.03	-4.1	-15.2	0.0	-16.4	-16.8	11.45	15.0
Hepatitis A vaccine	0.03	-32.8	-8.8	0.0	-28.9	-6.1	16.64	-5.2
Encephalitis vaccine	0.03	-40.3	19.2	0.0	-38.8	20.1	36.78	-2.2
DT vaccine (diphtheria /tetanus)	0.01	-3.0	-7.8	0.0	-11.7	-15.8	4.69	10.2
Tetanus vaccine	0.01	3.3	-9.8	0.0	-4.7	-17.5	4.33	8.6
Haemophilus influenzae B vaccine	<0.005	-18.4	12.4	0.0	-20.4	8.8	14.72	2.8
Yellow fever vaccine	<0.005	4.7	-11.8	0.0	-2.2	-16.1	18.34	7.3
Typhus vaccine	<0.005	-10.1	-15.3	0.0	15.4	-10.9	2.58	-21.9
Hepatitis A and B vaccine	<0.005	-47.2	-12.8	0.0	-46.3	3.6	30.81	-1.4
Poliomyelitis inactivated vaccine	<0.005	-30.6	-9.5	0.0	-31.4	-12.4	7.71	1.5
Rabies vaccine	<0.005	-50.4	-6.5	0.0	-49.5	-15.0	49.50	-1.5

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Cholera vaccine	<0.005	584.7	-19.7	0.0	580.6	-22.4	25.50	0.9
Trivalent vaccine (diphtheria/tetanus/poliomyelitis)	<0.005	-64.2	-29.9	0.0	-64.1	-32.2	12.85	0.0
Vaccines	**10.54**	**11.8**	**11.9**	**1.3**	**5.1**	**-2.6**	**22.39**	**6.6**
thirteen-valent pneumococcal vaccine	1.75	-24.5	3.6	0.1	-20.8	2.9	48.93	-4.5
influenza vaccine (surface antigen, inactivated, adjuvanted)	1.52	>100	26.9	0.3	29.7	11.1	14.99	185.2
group B meningococcal vaccine	1.50	-7.7	54.6	0.1	-6.8	54.7	62.29	-0.7
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.19	22.5	-	0.0	23.0	-	69.31	-0.2
tetravalent influenza vaccine (split virion, inactivated)	0.99	11.5	114.3	0.4	-5.4	119.8	7.35	18.2
measles, mumps, rubella and varicella vaccine	0.57	18.1	17.9	0.0	15.7	20.1	46.80	2.4
diphtheria/hepatitis B (recombinant)/ Haemophilus Influenzae B conjugate (adjuvanted)/ acellular pertussis/inactivated poliomyelitis/ tetanus vaccine	0.56	-18.5	-10.8	0.1	-9.5	-2.8	29.43	-9.6
diphtheria/pertussis/poliomyelitis/ tetanus vaccine	0.33	20.5	11.7	0.0	24.5	11.3	18.71	-2.9
meningococcal ACWY-tetanus toxoid conjugate vaccine	0.30	5.3	38.8	0.0	9.1	43.2	29.44	-3.3
tetravalent influenza vaccine (surface antigen, inactivated)	0.21	90.8	-	0.1	86.7	-	7.59	2.5

Table 3.4.3b Vaccines, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	6.87	1.0	19.24	7.19	1.0	20.38	4.8	-0.8	5.9	9.8	4.1	5.5
Valle d'Aosta	6.12	1.0	16.74	8.50	1.1	21.64	38.9	7.7	29.3	10.7	5.4	5.0
Lombardy	9.89	1.1	24.51	10.68	1.3	23.14	7.9	14.6	-5.6	14.7	-11.2	29.2
Bolzano	9.52	1.0	26.93	10.81	1.2	25.20	13.6	21.7	-6.4	10.7	-11.0	24.4
Trento	11.21	1.4	22.49	11.89	1.4	23.91	6.0	0.0	6.3	12.5	6.9	5.2
Veneto	10.19	1.3	21.29	11.03	1.3	23.47	8.2	-1.6	10.3	11.3	-1.0	12.4
Friuli VG	8.41	1.1	20.33	11.77	1.6	20.38	39.9	39.9	0.3	11.6	0.2	11.4
Liguria	7.45	1.1	18.25	8.84	1.2	19.63	18.7	10.7	7.6	11.6	5.3	5.9
Emilia R.	9.49	1.3	19.28	12.38	1.5	22.81	30.5	10.6	18.3	15.3	-1.9	17.5
Tuscany	9.68	1.4	18.44	8.84	1.2	19.84	-8.6	-14.8	7.6	15.5	-7.6	25.0
Umbria	7.99	1.2	17.66	10.20	1.2	22.96	27.7	-1.5	30.0	12.2	4.1	7.8
Marche	8.16	1.2	18.42	9.18	1.2	20.78	12.5	0.0	12.8	12.3	5.9	6.1
Lazio	11.27	1.5	21.02	10.89	1.3	22.72	-3.4	-10.4	8.1	13.7	3.7	9.6
Abruzzo	7.77	1.0	21.68	9.66	1.2	22.90	24.3	18.0	5.6	12.4	3.8	8.2
Molise	7.58	1.0	21.62	10.75	1.4	21.06	41.7	45.9	-2.6	11.3	5.3	5.7
Campania	9.60	1.3	20.49	11.32	1.3	23.27	17.9	4.1	13.6	13.3	2.0	11.0
Puglia	10.93	1.4	21.13	12.05	1.6	20.79	10.3	12.4	-1.6	6.6	2.1	4.5
Basilicata	7.55	0.9	22.67	9.12	1.2	21.04	20.7	30.5	-7.2	6.7	-0.3	7.1
Calabria	8.44	1.1	20.34	10.43	1.2	23.30	23.5	8.2	14.5	12.0	-0.1	12.1
Sicily	10.04	1.2	22.41	12.07	1.3	24.79	20.2	9.0	10.6	8.4	-2.2	10.8
Sardinia	6.47	0.9	19.68	7.86	1.1	20.21	21.5	18.6	2.7	9.1	0.9	8.1
Italy	**9.43**	**1.2**	**21.01**	**10.54**	**1.3**	**22.39**	**11.8**	**5.1**	**6.6**	**11.9**	**-2.6**	**14.9**
North	9.18	1.2	21.59	10.41	1.3	22.48	13.4	9.2	4.1	13.0	-5.2	19.2
Centre	10.10	1.4	19.66	9.96	1.3	21.60	-1.5	-10.1	9.9	13.9	-0.8	14.8
South and Islands	9.38	1.2	21.17	11.08	1.3	22.73	18.2	10.4	7.4	9.7	0.7	8.9

Key message

- The **influenza vaccine represents the first item of expenditure** in this category, accounting for 30% of the total, up 100.9% compared to the previous year. This is due to an increase in adherence to the vaccination campaign during the pandemic, allowing for a simplification of the diagnosis and management of suspected cases due to symptoms overlapping with COVID-19.
- **Unlike 2020, there is an increase in vaccine expenditure at national level, although a decline still seen for several sub-groups**: conjugated polysaccharide pneumococcal vaccine (-24.1%), meningococcal B vaccine (-7.7%), hexavalent vaccine (diphtheria/tetanus/pertussis/haemophilus influenzae B/poliomyelitis/hepatitis B); -18.5%), attenuated rotavirus vaccine (-3.0%), live attenuated varicella zoster virus (-15.1%) and DTP vaccine (diphtheria/tetanus/pertussis; -3.7%)

References

- Ministero della Salute. Direzione Generale della prevenzione sanitaria. Aggiornamento vaccini disponibili contro SARS-CoV-2/COVID-19 e aggiornamento note informative del consenso. Circo- lare del Ministero della Salute 21 aprile 2021, n. 0016722. Available at https://www. aifa.gov.it/documents/20142/1446021/79916_1.pdf/
- Ministero della Salute. Direzione Generale della prevenzione sanitaria. Impatto dell'emergenza COVID-19 sulle attività di vaccinazione – analisi del fenomeno e raccomandazioni operative. Cir- colare del Ministero della Salute 30 luglio 2020, n. 25631. Available at https://www. trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2020&codLeg=75346&parte=1%20 &serie=null/
- Ministero della Salute. Direzione Generale della prevenzione sanitaria. Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2020-2021. Circolare del Ministero della Salute 04 giugno 2020, n. 19214. Available at https://www.trovanorme.salute.gov.it/norme/ renderNormsanPdf?anno=2020&codLeg=74451&parte=1%20&serie=null/
- Ministero della Salute. Piano nazionale di prevenzione vaccinale 2017-2019. Available at https://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf/

3.4.4 Anti-HCV antivirals

Epidemiological framework

Hepatitis C virus (HCV) is transmitted via parenteral or, less commonly, sexual route even from an infected mother to her baby (vertical transmission), and causes inflammation and necrosis of the liver. HCV infections can be asymptomatic and about 30% of infected people spontaneously eliminate the virus within 6 months of infection without any treatment. However, the remaining 70% develops a chronic infection that increases the risk of cirrhosis, ranging from 15% to 30% within 20 years, liver failure and hepatocellular carcinoma. Assessing the stage and severity of liver disease is an important aspect of treating people with chronic viral hepatitis. In fact, subjects with cirrhosis require additional monitoring for potential complications, such as the appearance of hepatocellular carcinoma, a condition that can also evolve to a terminal stage with a high risk of mortality (median survival of 2 years), for which a liver transplant is necessary. In Italy, SEIEVA surveillance is carried out, coordinated by the *Istituto Superiore di Sanità*, which, alongside the Information System of Infectious Diseases, analyses the epidemiological aspects of acute infections caused by viral hepatitis. Monitoring for 2021 shows that 24 new cases of acute hepatitis C have been reported, with an incidence of 0.05 cases per 100,000 inhabitants, confirming a general decreasing trend over the last 13 years. Over 80% of cases are over 35 years of age and, as in previous years, there is a higher prevalence of cases among men (2/3 in 2021). According to those results, hospital-acquired exposure is always the main risk factor (45.5% of cases), while there is a sharp decrease in cases (from 42.1% in 2020 to 13.6% in 2021) attributable to the use of aesthetic treatments (such as manicures, piercings and tattoos), a very significant risk factor in previous years. Conversely, in 2021 the percentage of cases reporting sexual exposure increased again. However, for the first time in the last 30 years, there were no cases in people living with hepatitis C positive patients. From a clinical point of view, there were no deaths, cases of fulminant hepatitis or encephalopathies.

National data on consumption and expenditure

In 2021 the use of anti-HCV antivirals decreased sharply. Per capita expenditure for this category of medicines stood at 1.4 euros (-71.9% compared to 2020). The reduction in expenditure is associated with a sharp decrease in the average DDD cost (-67.9%) and with a less marked reduction in consumption (-12.1%) (Figure and Table 3.4.4a). In general, in the period 2014 to 2021, this category of medicines recorded an average annual growth rate (CAGR) of expenditure of 5.5% and a decrease in consumption of 12.1%.
The glecaprevir/pibrentasvir combination is the medicine with the highest per capita expenditure (0.71 euros), down 15.7% compared with the previous year. Similarly, the average DDD cost also shows similar reductions (-5.0%). It is followed by the sofosbuvir/velpatasvir combination (0.63 euros) and an 84.0% reduction, due to a sharp decrease in the average DDD cost (-83.5%). This trend in expenditure and average cost is also observed for all other medicines in the category.
Sardinia is the Region with the highest expenditure (2.18 euros per capita), followed by Campania (2.02 euros per capita) and Emilia Romagna (1.74 euros per capita). Bolzano and

Molise, on the other hand, are the Regions with the lowest expenditure (0.60 euros and 0.70 euros, respectively) (Table 3.4.4b). All regions registers a sharp decline in expenditure compared to the previous year, with the maximum change recorded in Molise (82.3%) and the minimum in Emilia Romagna (-56.0%).

Figure 3.4.4a Anti-HCV antivirals, 2014-2021 temporal trend of per capita expenditure and average cost per day of therapy

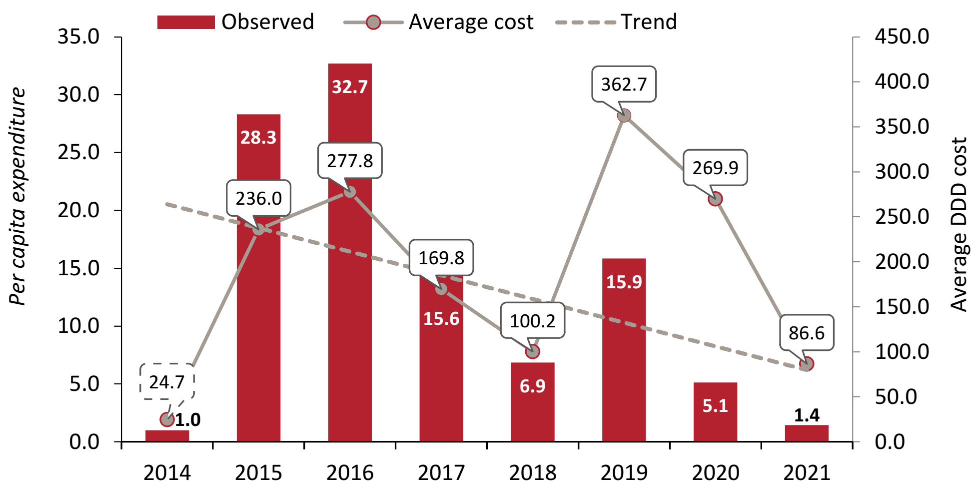


Table 3.4.4a Anti-HCV antivirals, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Anti-HCV antivirals in combination	1.44	-71.9	-	0.0	-9.7	-	87.34	-68.8
Other HCV antivirals	<0.005	-58.7	-51.0	0.0	-43.4	-23.6	21.07	-26.8
Anti-HCV antivirals	**1.44**	**-71.9**	**5.5**	**0.0**	**-12.1**	**-11.8**	**86.58**	**-67.9**
glecaprevir/pibrentasvir	0.71	-15.7	-	0.0	-11.0	-	107.91	-5.0
sofosbuvir/velpatasvir	0.63	-84.0	-	0.0	-3.0	-	71.64	-83.5
elbasvir/grazoprevir	0.05	-44.8	-	0.0	-44.6	-	77.25	-0.1
sofosbuvir/velpatasvir/ voxilaprevir	0.05	-80.8	-	0.0	-20.0	-	107.92	-75.9
sofosbuvir	<0.005	-64.9	-51.0	0.0	-53.6	-23.6	21.07	-24.1
ledipasvir/sofosbuvir	<0.005	-39.6	-	0.0	-39.4	-	0.04	0.0

Table 3.4.4b Anti-HCV antivirals, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants die) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	6.40	0.1	293.90	1.61	0.1	87.27	-74.9	-15.2	-70.3	12.0	-8.2	22.1
Valle d'Aosta	4.82	0.1	235.07	1.25	0.0	94.28	-74.1	-35.4	-59.9	5.8	-13.1	21.6
Lombardy	5.59	0.1	266.34	1.50	0.0	87.76	-73.2	-18.4	-67.1	10.7	-8.3	20.7
Bolzano	1.99	0.0	202.52	0.60	0.0	80.97	-69.8	-24.2	-60.0	11.9	-9.3	23.3
Trento	7.14	0.1	286.79	1.51	0.0	84.32	-78.8	-27.8	-70.6	33.0	5.6	26.0
Veneto	4.59	0.0	278.33	1.38	0.0	86.16	-70.0	-2.7	-69.0	6.9	-9.7	18.4
Friuli VG	6.70	0.1	294.35	1.52	0.0	83.96	-77.3	-20.2	-71.5	14.7	-1.8	16.8
Liguria	4.40	0.0	264.82	1.18	0.0	87.38	-73.1	-18.2	-67.0	8.0	-9.3	19.1
Emilia R.	3.95	0.1	192.46	1.74	0.1	90.81	-56.0	-6.6	-52.8	2.6	-12.9	17.8
Tuscany	6.84	0.1	267.95	1.52	0.0	85.27	-77.8	-29.9	-68.2	7.8	-10.2	20.1
Umbria	4.91	0.0	275.72	1.43	0.0	81.24	-70.8	-0.8	-70.5	12.8	-5.2	19.0
Marche	4.59	0.0	259.17	1.37	0.0	83.62	-70.1	-7.1	-67.7	8.2	-11.2	21.9
Lazio	3.85	0.0	277.31	1.08	0.0	88.89	-71.9	-12.2	-67.9	8.0	-13.8	25.3
Abruzzo	2.79	0.0	214.21	1.05	0.0	88.76	-62.5	-9.3	-58.6	4.3	-14.0	21.2
Molise	3.98	0.0	287.36	0.70	0.0	92.75	-82.3	-45.1	-67.7	7.2	-18.6	31.7
Campania	7.52	0.1	304.46	2.02	0.1	86.12	-73.2	-4.9	-71.7	1.0	-16.2	20.6
Puglia	4.54	0.1	246.94	1.38	0.0	84.42	-69.6	-10.9	-65.8	1.2	-14.7	18.7
Basilicata	3.84	0.0	263.06	1.18	0.0	91.29	-69.4	-11.6	-65.3	2.5	-14.6	20.0
Calabria	3.26	0.0	333.03	0.84	0.0	78.14	-74.3	9.7	-76.5	-2.7	-14.0	13.2
Sicily	4.15	0.0	284.72	1.08	0.0	82.22	-74.0	-9.8	-71.1	-3.7	-15.9	14.5
Sardinia	5.79	0.1	279.20	2.18	0.1	89.59	-62.4	17.4	-67.9	15.4	-6.2	23.1
Italy	**5.13**	**0.1**	**269.92**	**1.44**	**0.0**	**86.58**	**-71.9**	**-12.1**	**-67.9**	**5.5**	**-11.8**	**19.7**
North	5.22	0.1	261.77	1.50	0.0	87.66	-71.3	-14.1	-66.5	8.5	-9.2	19.5
Centre	4.99	0.1	270.76	1.29	0.0	86.07	-74.2	-18.6	-68.2	8.3	-11.5	22.5
South and Islands	5.09	0.0	282.38	1.46	0.0	85.30	-71.4	-5.0	-69.8	1.1	-14.8	18.6

Key message

- **In 2021, the use of anti-HCV antivirals reduced significantly**, with a decrease in per capita expenditure by more than 70% compared to 2020. This is due to both a reduction in the average DDD cost and the reduction in the number of treatments initiated. The expansion of the treatment criteria in 2017 allowed access to therapy for all patients diagnosed with chronic hepatitis C, regardless of the level of fibrosis. Therefore, the reduction in treatments could be explained by the depletion of the number of patients with chronic hepatitis requiring treatment. Furthermore, the impact of the COVID-19 pandemic should not be overlooked, since the pandemic has often caused a reconversion of hospital wards used for liver diseases into wards used only for COVID-19 patients. This has resulted in a greater difficulty to identify HCV asymptomatic patients or people unaware of being infected. It should be recalled that within the HCV infection eradication plan in Italy, in 2020 free national screening was introduced for the elimination of the HCV virus, pursuant to Law no. 8 of 28 February 2020.
- A **marked regional variability in consumption** was recorded. In Campania and Trento, consumption was about 40% higher than the national average, while in Bolzano and Abruzzo, expenditure was lower than the national average (50% and 31%, respectively). The variability registered in treatments also reflects the different strategies followed for screening.

References

- ECDC. The sustainable development goals and hepatitis B and C in the EU/EEA. Technical report, marzo 2021. Available at https://www.ecdc.europa.eu/en/publications-data/hepati- tis-b-and-c-sustainable-development-goals-eu-eea
- Istituto Superiore di Sanità. Epidemiologia delle epatiti virali acute in Italia. Aggiornamento 2020. Bollettino SEIEVA 2021; 8. Available at https://www.epicentro.iss.it/epatite/bollet- tino/Bollettino-n-8-marzo-2021.pdf/
- Kiser JJ, Flexner CW. Treatment of viral hepatitis (HBV/HCV). In: Brunton LL, Hilal-Dandan R, Knoll- mann BC, eds. Goodman & Gilman's: the pharmacological basis of therapeutics, 13e ed. New York: McGraw-Hill, 2017.
- Legge 28 febbraio 2020, n. 8. Conversione in legge, con modificazioni, del decreto-legge 30 dicembre 2019, n. 162, recante disposizioni urgenti in materia di proroga di termini legislativi, di organizzazione delle pubbliche amministrazioni, nonché di innovazione tecnologica. (20G00021) (GU n.51 del 29-2-2020 - Suppl. Ordinario n. 10.)
- Ministero della Salute. Piano Nazionale per la prevenzione delle Epatiti Virali da virus B e C (PNEV), 27 ottobre 2015. Available at http://www.salute.gov.it/imgs/C_17_pubblica- zioni_2437_allegato.pdf/
- World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. Geneva: WHO, 2016. Available at https://apps.who.int/iris/ handle/10665/246177/
- World Health Organization. Hepatitis C. 27 July 2020. Available at https://www.who. int/news-room/fact-sheets/detail/hepatitis-c/

3.4.5 Antifungals for systemic use

Epidemiological framework

With more than 150 million cases of serious fungal infections and about 1.7 million deaths per year, invasive fungal infections are a global health problem associated with severe socio-economic consequences. These are infections that commonly develop in immunocompromised patients, such as people undergoing cancer chemotherapy, people with acquired immunodeficiency syndrome or people who have undergone organ transplantation. However, the overuse of antibiotics and the increasing use of medical devices, such as catheters or heart valves, are also important risk factors for the development of invasive fungal infections, including the extremely virulent strain of *Candida auris*.
Although there are pharmacological options for antifungal treatment, including azoles, with relatively high efficacy and low toxicity, in recent years their long-term use, including for prophylaxis, has favoured antifungal resistance with an increase of less sensitive strains.
WHO has identified this type of antimicrobial resistance as one of the dominant threats of 2019. Antimicrobial resistance to antifungals is the result of multiple factors and emerges from a number of molecular mechanisms. While some intrinsic resistance is found in nature, such as *C. krusei*, *C. glabrata* and fluconazole-resistant *Aspergillus* species, acquired resistance is instead a consequence of long-term therapies, widespread prophylaxis, or use of antifungals in agriculture, especially in the case of triazoles. Environmental exposure of A. fumigatus to triazole fungicides may explain their resistance in patients naïve to azoles. In addition, secondary resistance can occur after vertical and horizontal transmission in both animals and humans.

National data on consumption and expenditure

Over the last eight years, an average annual decrease (CAGR -4.3%) in expenditure for antifungals was recorded, with values shifting from 3.4 euros in 2014 to 2.5 euros in 2021. A 1.4% decrease was recorded compared to 2020 (Figure 3.4.5a and Table 3.4.5a). Consumption recorded a reduction of 1.4% compared to 2020, while in the period 2014-2021 the average annual change was -4.4%. The average DDD cost was stable over the time period analysed.

Triazole derivatives, mostly represented by fluconazole, are the category with both the highest consumption (0.6 DDD) and the highest expenditure, with a value of 1.39 euros per capita in 2021. This category observed both a contraction in consumption (-2.3%) and in expenditure (-7.6%) compared to 2020. It is followed by polyenes (0.71 euros per capita), represented exclusively by amphotericin B, with a strong 30.2% increase compared to the previous year.

The subgroup with the largest decrease in consumption is that of pyrimidine analogues (-23.2%), representing the one with the highest average DDD cost.
Fluconazole is the most consumed molecule (0.4 DDD), followed by itraconazole (0.2 DDD). On the other hand, the molecule with the highest expenditure is amphotericin B (0.71 euros per capita), with a +30.2% change compared to 2020, followed by fluconazole (0.69 euros

per capita) and isavuconazole. While the first recorded a decrease compared to the previous year (-1.9%), the second showed a significant increase in both expenditure and consumption (+25.9% and +21.7%, respectively).
Compared to 2020, almost all Regions register a reduction in expenditure, with the exception of Lombardy, Abruzzo, Trento, Campania, Puglia and Veneto (Table 3.4.5b). Change goes from -25.6% in Friuli Venezia Giulia to +11.0% in Lombardy.
No Region shows a consumption and an average DDD cost above the national average. Calabria, Sardinia, Puglia, Campania and Sicily have higher consumption levels and lower DDD cost than the national average.

Figure 3.4.5a Antifungals for systemic use, 2014-2021 temporal trend of per capita expenditure and average cost per day of therapy

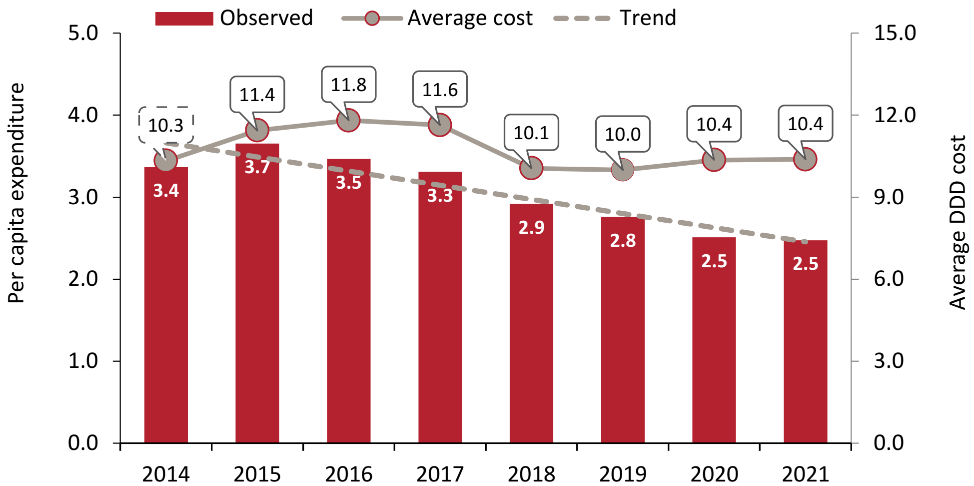


Table 3.4.5a Antifungals for systemic use, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Triazole derivatives	1.39	-7.6	-4.0	0.6	-2.3	-4.9	6.19	-5.2
Polyenes	0.71	30.2	6.4	0.0	28.5	4.8	100.39	1.6
Echinocandins	0.36	-19.1	-14.3	0.0	10.8	9.9	67.01	-26.8
Imidazole derivatives	0.02	1.2	82.2	0.0	1.3	59.0	9.47	0.1
Pyrimidine analogues	<0.005	-25.0	-12.1	0.0	-23.2	-11.7	141.46	-2.0
Antifungals	2.48	-1.4	-4.3	0.7	-1.4	-4.4	10.38	0.2
amphotericin B	0.71	30.2	6.4	0.0	28.5	4.8	100.39	1.6
fluconazole	0.69	-1.9	-4.6	0.4	-3.1	-4.0	4.84	1.5
isavuconazole	0.29	25.9	-	0.0	21.7	-	111.34	3.7
posaconazole	0.19	-44.4	-0.2	0.0	2.1	2.5	32.77	-45.4
itraconazole	0.18	-4.8	-7.7	0.2	-2.6	-7.6	2.55	-2.0
caspofungin	0.16	-25.6	-18.6	0.0	13.6	13.4	39.27	-34.3
micafungin	0.14	-1.6	0.2	0.0	18.0	1.5	327.89	-16.4
anidulafungin	0.05	-33.8	-19.1	0.0	-5.8	2.2	68.89	-29.5
voriconazole	0.04	7.9	-28.1	0.0	13.6	3.7	8.93	-4.7
ketoconazole	0.02	1.2	-	0.0	1.3	-	9.47	0.1

Table 3.4.5b Antifungals for systemic use, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	2.18	0.6	9.98	2.10	0.6	9.81	-3.3	-1.3	-1.7	-5.9	-3.4	-2.6
Valle d'Aosta	0.98	0.4	6.03	0.97	0.4	5.96	-0.5	1.0	-1.2	-5.2	-3.9	-1.3
Lombardy	2.03	0.5	11.63	2.25	0.5	12.45	11.0	4.0	7.0	-2.3	-3.9	1.7
Bolzano	2.28	0.3	19.85	1.72	0.3	16.47	-24.5	-8.8	-17.0	-6.6	-4.5	-2.1
Trento	1.37	0.5	6.92	1.44	0.5	7.45	4.7	-2.4	7.6	-5.7	-3.1	-2.6
Veneto	2.68	0.6	12.83	2.72	0.5	13.63	1.6	-4.1	6.2	-3.5	-5.0	1.5
Friuli VG	2.89	0.6	13.69	2.15	0.6	10.44	-25.6	-2.2	-23.7	-4.8	-4.3	-0.5
Liguria	3.68	0.6	15.65	3.59	0.7	14.70	-2.4	4.2	-6.1	-2.6	-2.9	0.3
Emilia R.	2.80	0.5	14.01	2.78	0.6	13.36	-0.8	4.3	-4.6	-0.3	-4.0	3.8
Tuscany	2.01	0.5	10.32	1.83	0.5	9.35	-8.8	0.9	-9.4	-7.8	-4.5	-3.4
Umbria	3.49	0.6	14.92	3.21	0.6	14.33	-8.1	-4.1	-3.9	-7.5	-5.3	-2.4
Marche	2.30	0.7	8.69	2.24	0.7	8.69	-2.4	-2.1	0.0	-3.6	-4.6	1.0
Lazio	2.41	0.7	9.91	2.30	0.6	9.88	-4.6	-4.0	-0.3	-6.6	-6.0	-0.7
Abruzzo	2.78	0.8	10.11	2.94	0.7	11.25	5.6	-4.9	11.3	-0.1	-3.9	4.0
Molise	1.44	0.6	6.91	1.21	0.6	5.93	-16.0	-1.9	-14.2	-11.5	-6.4	-5.5
Campania	2.77	0.8	8.97	2.83	0.8	9.29	2.2	-1.1	3.6	-3.4	-3.1	-0.3
Puglia	2.56	0.8	8.79	2.60	0.8	9.35	1.7	-4.1	6.3	-6.5	-5.3	-1.2
Basilicata	2.05	0.6	8.98	1.65	0.7	6.81	-19.3	6.7	-24.2	-8.7	-3.8	-5.1
Calabria	3.80	1.1	9.17	3.77	1.1	9.35	-0.9	-2.5	2.0	-2.0	-3.0	1.0
Sicily	2.55	0.9	7.43	2.34	0.9	7.26	-8.3	-5.9	-2.3	-5.9	-5.1	-0.9
Sardinia	2.92	0.8	9.78	2.68	0.8	8.99	-8.5	-0.1	-8.1	-4.3	-4.7	0.5
Italy	**2.51**	**0.7**	**10.36**	**2.48**	**0.7**	**10.38**	**-1.4**	**-1.4**	**0.2**	**-4.3**	**-4.4**	**0.1**
North	2.41	0.5	12.31	2.44	0.5	12.34	1.0	1.0	0.2	-3.1	-4.0	1.0
Centre	2.35	0.6	10.23	2.21	0.6	9.89	-5.9	-2.4	-3.3	-6.7	-5.3	-1.5
South and Islands	2.74	0.9	8.67	2.69	0.8	8.79	-2.0	-3.1	1.4	-4.5	-4.3	-0.2

Key message

- Overall, **expenditure and consumption of antifungals decreased compared to 2020** (-1.4%). Expenditure decreased by 27% in the 2014-2021 period, with an average annual change of 4.3%.
- **The greatest increases in consumption are recorded for amphotericin B**, which becomes the first molecule for expenditure in this category, and for isavuconeazole, also indicated for the treatment of invasive aspergillosis, a rare disease.
- In almost all Regions, there is a **reduction in expenditure** compared to 2020. A **wide variability remains in per capita expenditure**, ranging between 0.97 euros in Valle d'Aosta and 3.77 euros in Calabria.
- Strategies for the implementation of antifungal stewardship in the context of antimicrobial stewardship are desirable in the whole country.

References

- Houšť J, Spížek J, Havlíček V. Antifungal drugs. Metabolites 2020; 10(3):106.
- Kainz K, Bauer MA, Madeo F, Carmona-Gutierrez D. Fungal infections in humans: the silent crisis. Microb Cell 2020; 7(6):143-5

3.5 Blood and blood-forming organs

Medicines for blood and blood-forming organs represent the fifth therapeutic category with high public expenditure in 2021 (2,349.4 million euros), accounting for 10% of total public expenditure (Box Main indices of expenditure, consumption and exposure). Overall, per capita expenditure for these medicines was equal to 39.66 euros, mainly driven by the purchase by public health facilities (32.05 euros per capita), up from the previous year (+4.1%). The contribution resulting from purchases under approved care regime is smaller (7.61 euros per capita) (Table 3.1). Confirming the increasing trend observed in previous years, in 2021 the total NHS consumption for this category of medicines was 140.2 DDD per inhabitants per day (10.7% of the total), a 2.6% increase compared to the previous year (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 45-54 years, probably due to the different prevalence of cardio-cerebrovascular diseases. In the younger age groups, prevalence is higher in women than in men, probably due to a greater use of anti-anaemic preparations. At the same time, the per capita NHS expenditure shows a similar trend, reaching the maximum value of 97.5 euros per capita in the +75 age group (111.2 euros in men and 88.9 euros in women).

Concerning the approved care regime, expenditure recorded a reduction in 2021 compared to the previous year (-3.9%), together with an increase in consumption (+1.2%), with a shift in prescription towards less expensive specialties (mix effect: -4.7%) (Table 3.9).

The therapeutic categories that have the greatest impact on expenditure are platelet aggregation inhibitors (2.96 euros per capita) and heparins (2.47 euros per capita). Compared to the previous year, coagulation factor Xa inhibitors (10a), including apixaban, rivaroxaban and edoxaban, recorded a marked decrease in expenditure (-60.7%) and consumption (-57.3%), and a use of less expensive medicines (mix effect: -7.8%). However, expenditure for these medicines under approved care regime is marginal compared to that found for purchases by public health facilities (0.29 euros per capita), which show a steady increase after entry into market (Table 3.9). Vitamin K (AVK) antagonists also showed a decline in 2021 in terms of both consumption and per capita expenditure (-17.5%), although the latter is much lower (0.12 euros) than the rest of anticoagulants.
Enoxaparin, acetylsalicylic acid and clopidogrel represent the molecules with the highest cost per capita (2.21 euros, 1.18 euros and 1.16 euros, respectively). Overall, they are the main cost item of expenditure under approved care regime for medicines intended for blood and blood-forming organs (59.8%) (Table 3.10).

Enoxaparin is the only active ingredient in this category included in the top 30 medicines with the greatest impact on expenditure under approved care regime. It alone accounts for 29.0% of the total expenditure for this category (Table 3.11). In addition, together with folic acid, it is also included in the list of the top 30 active ingredients with the largest variation in expenditure under approved care regime compared to the previous year (+16.0% and +9.7%, respectively) (Table 3.14). None of the active ingredients belonging to the blood and blood-forming organs category are among the top 30 active ingredients with the greatest reduction in expenditure and with greatest change in the cost per day of therapy under the approved care regime (Table 3.13 and Table 3.15). Among the top 30 molecules with the greatest impact on consumption, acetylsalicylic acid (ASA), used at low doses as an aggregation inhibitor, and cyanocobalamin can be found (Table 3.16).

As regards purchases by public health facilities, compared to 2020, there was an increase in both expenditure (+3.4%) and consumption (+2.2%) and a shift towards more expensive specialties (mix effect +4.3%) (Table 3.18). The therapeutic category with the highest impact on expenditure is represented by coagulation factors, with a per capita expenditure of 7.82 euros, followed by factor Xa inhibitors (7.48 euros per capita). The most frequently used therapeutic categories include direct factor Xa inhibitors (12.5 DDD) and platelet aggregation inhibitors, excluding heparin (9.7 DDD). Rivaroxaban is the active ingredient that ranks first in terms of per capita expenditure (3.03 euros) among medicines purchased by public health facilities. It records a -1.9% reduction in expenditure and a 7.7% increase in consumption compared to the previous year (Table 3.19). It is also included in the top 30 active ingredients with the highest expenditure among medicines purchased by public health facilities (Table 3.20), followed by the other two Xa-inhibitor oral anticoagulants, apixaban and edoxaban. Finally, enoxaparin and octocog alfa, the latter being an hemophilia A short acting VIII coagulation factor, rank 26th and 27th.

The monoclonal antibody emicizumab and oral anticoagulant edoxaban rank eighth (+68.1%) and seventeenth (+33.8%), respectively, among the top 30 active ingredients with greater variation in expenditure compared to the previous year purchased by public health facilities (Table 3.22). Octocog alfa, dabigatran, epoietin alfa and darbopoietin beta are among the top 30 active ingredients with the greatest reduction in expenditure compared to the previous year (Table 3.23).

The top 30 active ingredients for average cost per day of therapy purchased by public health facilities include four coagulation factors, with values ranging from a maximum of 1086,7 euros for albutrepenonacog alfa to a minimum of 332.5 euros for octocog alfa (Table 3.24). Finally, 10 out of the first 30 active ingredients with the greatest consumption purchased by public health facilities belong to this therapeutic category (Table 3.25).

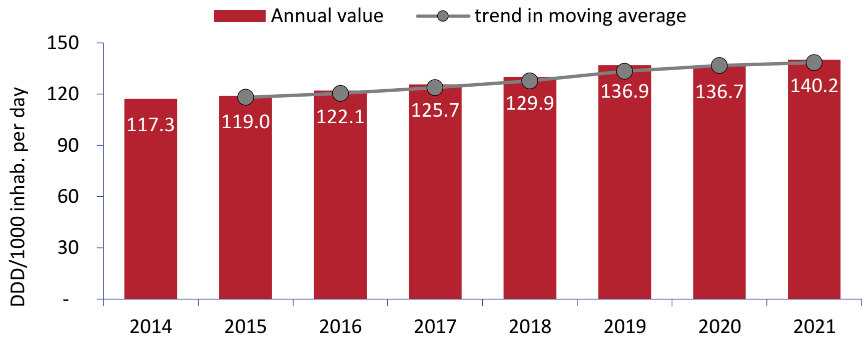
For further information on the use of medicines belonging to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region. These analyses covered anticoagulants, coagulation factors and platelet aggregation inhibitors (Table 3.5.1a and following).

Main indices of expenditure, consumption and exposure

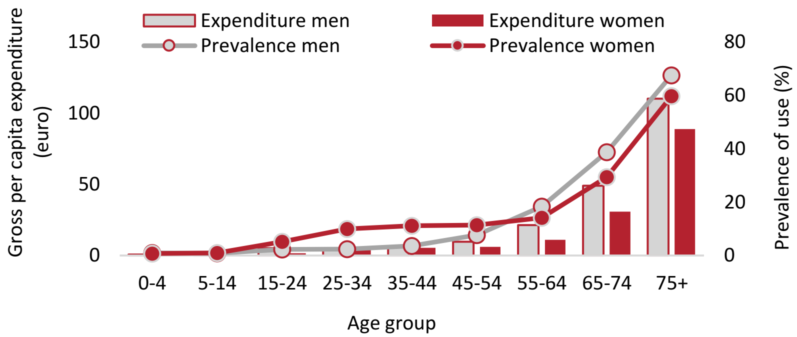
Blood and blood-forming organs

Public expenditure* in million euros (% over total)	**2,349.4**	**(10.0)**
Δ % 2021-2020		2.6
Regional range for gross expenditure (per capita):	25.3	48.7
DDD/1000 inhab. per day* (% over total)	**140.2**	**(10.7)**
Δ % 2021-2020		2.6
Regional range for DDD/1000 inhab. per day:	84.4	289.3

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



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and on behalf distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.8	0.4	0.6	1.5	1.2	1.3
5-14	2.4	0.4	1.4	1.2	1.3	1.3
15-24	5.2	1.5	3.4	4.0	9.6	6.7
25-34	4.9	3.8	4.4	5.7	24.5	14.9
35-44	6.0	5.3	5.7	12.3	30.2	21.2
45-54	9.6	6.0	7.8	39.6	36.1	37.9
55-64	21.3	11.1	16.0	124.1	72.4	97.5
65-74	49.0	30.7	39.4	309.0	201.4	252.2
75+	110.2	88.9	97.5	570.1	466.0	507.9

3.5.1 Anticoagulants

Epidemiological framework

Anticoagulants are administered parenterally, as in the case of heparin, low molecular weight heparins (LMWH) and fondaparinux, or orally, as in the case of vitamin K antagonists (AVKs; warfarin and acenocumarol), and new oral anticoagulants (NOAs/DOACs; dabigatran, rivaroxaban, apixaban, edoxaban). Anticoagulants administered parenterally have several indications, including prophylaxis of venous thromboembolism (VTE) and treatment of deep vein thrombosis (DVT). Nearly two-thirds of VTE cases are isolated in depth and are therefore DVT cases, whereas 80% of cases are proximal. According to the European Society of Cardiology, the incidence of venous thromboembolism increases progressively with age and this trend appears constant over time. At younger ages, women are more affected than males. However, this ratio is reverted in elderly. Recent studies on the European population have reported the incidence of DVT of 70-140 cases every 100,000 people per year. Even individuals with particular conditions, such as oncological diseases, are at risk of developing VTE that depends mainly on the type of condition. Therefore, the annual incidence rate varies between 0.5% and 20% according to the type of tumour and the body area concerned. VTE is a condition that can also occur during pregnancy and remains the leading cause of maternal mortality in industrialised countries. Pregnant women are at four to five times greater risk of developing thromboembolic events than non-pregnant women. Some oral anticoagulants, such as warfarin or dabigatran, have indications in the primary prevention of venous thromboembolic episodes. However, the main indication of these medicines is the treatment of atrial fibrillation (AF) or nonvalvular atrial fibrillation (NVAF) as well as AVKs. The prevalence of atrial fibrillation in Italy is around 1.9% of the general population and in between 2 and 3% in Europe. However, it is known that about 25% of cases are asymptomatic, so prevalence is often underestimated. In particular, there are more than 1 million patients with AF and the prevalence increases with age, affecting 4% of subjects aged 60 to 70 years and up to 10-15% subjects over 80.

National data on consumption and expenditure

From 2014 to 2021, the consumption of anticoagulants increased by 33.3%, going from 18.8 to 28.2 DDD (CAGR: +6.0%). In parallel, the average cost per day of therapy increased by 15.3%, from 1.22 euros to 1.44 euros (Figure 3.5.1a). The per capita expenditure on these medicines was 14.82 euros, up 2.6% compared to the previous year, which confirms the growth shown by the CAGR (8.5%) during 2014-2021 (Table 3.5.1a). The entry into market of NOAs may have contributed to increased consumption and expenditure for anticoagulants, given the ease of use and greater propensity to use by patients. However, in 2021 NOAs were the category with the highest use (15.2 DDD), with an increase compared to the previous year (+9.5%), although per capita expenditure slightly decreased in 2021 (-2.7% compared to 2020). The growth trend for this class of medicines is also confirmed by the CAGR values observed in the period 2014-2021 both for consumption (+38.0%) and expenditure (+29.3%). Low molecular weight heparins (LMWH) follow with a consumption of 9.1 DDD (-2.5% compared to 2020) and a per capita expenditure of 4.37 euros (+10.9%).

Expenditure and consumption of AVKs fell by about 17% compared to the previous year, confirming their downward trend (CAGR 2014-2021: -10% expenditure and -10.4% consumption). These trends most likely reflect the preference in clinical practice of direct oral anticoagulants (NOA/DOAC). These are not less effective compared to AVKs (warfarin and acecumarol) in preventing stroke/systemic thromboembolism in individuals with FANV, and in the prophylaxis of VTE and in treating deep vein thrombosis (DVT). However, their use is more practical for patients due to the fact that there is no need to monitor the blood coagulation status through INR (International Normalised Ratio) measurement. Moreover, the prescription of NOAs also by the general practitioner as more recently allowed according to AIFA Note 97 published in October 2020 (Determination No DG/1034/2020, Official Gazette, General Series No. 255 of 15 October 2020) may have affected in part these trends. It is expected that the forthcoming placing on the market of the respective generic medicines in the NOA class will help to change the trend in the related health expenditure without substantially changing their consumption.
Of the whole class of anticoagulants, enoxaparin is the most expensive active substance (3.91 euros per capita), up 14.3% compared to 2020, followed by the new four oral anticoagulants, rivaroxaban (3.06 euros), apixaban (2.92 euros), edoxaban (1.80 euros), dabigatran (1.31 euros). Among the latter, edoxaban suffered the largest reduction in the average cost per day of therapy (-22.0%) in 2021 compared to the previous year, although its cost is still higher than those of the other NOAs (1.79 euros). Although both rivaroxaban (5.5 DDD) and apixaban (4.5 DDD) have higher consumption than edoxaban (2.8 DDD), the latter still recorded the highest percentage increase in consumption (+28.8%).
Caplacizumab, a monoclonal antibody authorised in 2020 for episodes of acquired thrombocytopenic purpura (aTTP), in combination with plasmapheresis and immunosuppression, is the tenth active substance in the category. In 2021 it recorded a per capita expenditure of 0.29 euros, an approximately 94% increase compared to the previous year, suggesting an important unmet need for the disease, partially filled with this orphan medicine.
Regional variability in consumption is wide and ranges from a minimum of 20.5 DDD in Bolzano to 37.8 DDD in the autonomous province of Trento (Table 3.5.1b). In general, the Centre (30.1 DDD) and the North (28.8 DDD) tend to register higher consumption than the South (26.3 DDD/1000 inhabitants per day). Sicily is the region with the highest increase (+13.2%), while the Valle d’Aosta (-25.1%) and the autonomous province of Bolzano (-24.3%) are the regions with the largest reduction in consumption. Valle d’Aosta has an average cost per day of therapy (1.8 euros) higher than in the rest of the Italian Regions, while also recording the largest increase in 2021. In general, the Centre has higher per capita expenditure (15.66 euros) than the North (14.65 euros) and the South (14.53 euros), the latter substantially overlapping with each other. Umbria is the region with the largest per capita expenditure (18.62 euros), despite a lower average cost per DDD (1.39 euros). Conversely, Bolzano shows the lowest per capita expenditure (9.69 euros), mainly attributable to the reduction in consumption observed in 2021.

Figure 3.5.1a Anticoagulants, 2014-2021 temporal trend of consumption and average cost per day of therapy)

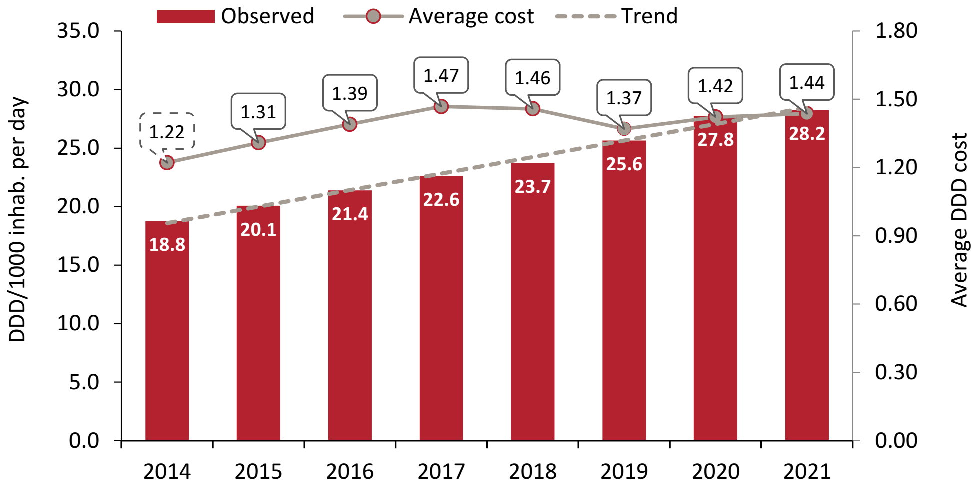


Table 3.5.1a Anticoagulants, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
NOAs	9.08	-2.7	29.3	15.2	9.5	38.0	1.64	-10.9
LMWH	4.37	10.9	-3.6	9.1	-2.5	-0.9	1.31	14.1
Fondaparinux	0.33	28.1	3.6	0.5	17.8	7.8	1.68	9.1
Monoclonal antibodies	0.29	93.7	-	0.0	88.3	-	3333.90	3.1
Antithrombotic enzymes	0.25	-7.8	0.6	0.0	-6.4	2.7	784.66	-1.1
Heparin and heparinoids	0.22	8.0	-8.4	0.4	-12.9	-7.1	1.68	24.3
Other antithrombotics	0.14	6.7	-	0.0	11.2	-	3893.34	-3.8
Vitamin K antagonists	0.12	-17.2	-10.6	3.0	-17.1	-10.4	0.11	0.2
Antithrombotics - direct thrombin inhibitors	0.02	22.1	-13.3	0.0	-51.1	-10.8	240.90	150.5
Anticoagulants	**14.82**	**2.6**	**8.5**	**28.2**	**1.7**	**6.0**	**1.44**	**1.1**
enoxaparin	3.91	14.3	-0.2	8.4	-1.4	1.7	1.27	16.2
rivaroxaban	3.06	-3.0	28.1	5.5	7.1	36.4	1.54	-9.2
apixaban	2.92	1.3	44.3	4.5	11.4	54.9	1.76	-8.8
edoxaban	1.80	0.2	-	2.8	28.8	-	1.79	-22.0
dabigatran	1.31	-13.0	8.5	2.4	-4.8	18.1	1.47	-8.4
calcium nadroparin	0.35	-10.2	-15.9	0.5	-9.2	-13.6	1.85	-0.8
fondaparinux	0.33	28.1	3.6	0.5	17.8	7.8	1.68	9.1
caplacizumab	0.29	93.7	-	0.0	88.3	-	3333.90	3.1
alteplase	0.18	11.0	12.5	0.0	10.5	12.4	823.80	0.7
heparin	0.15	-6.1	-7.3	0.3	-13.1	-7.1	1.23	8.4

Table 3.5.1b Anticoagulants, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	13.24	28.6	1.26	12.54	26.7	1.29	-5.3	-6.8	2.0	9.3	6.8	2.3
Valle d'Aosta	13.36	28.3	1.29	13.90	21.2	1.80	4.0	-25.1	39.3	15.2	1.8	13.1
Lombardy	17.50	27.2	1.76	16.20	27.2	1.63	-7.4	0.0	-7.2	10.0	7.0	2.8
Bolzano	11.62	27.1	1.17	9.69	20.5	1.30	-16.6	-24.3	10.5	4.1	0.0	4.1
Trento	14.43	36.3	1.08	17.07	37.8	1.24	18.3	4.1	13.9	18.1	7.4	9.9
Veneto	10.86	26.7	1.11	11.95	27.5	1.19	10.1	3.1	7.0	6.1	2.2	3.8
Friuli VG	16.19	33.2	1.33	17.22	34.3	1.38	6.3	3.2	3.3	10.6	6.0	4.3
Liguria	15.08	32.8	1.26	15.22	28.0	1.49	0.9	-14.6	18.5	9.6	3.1	6.3
Emilia R.	14.34	34.1	1.15	15.61	34.8	1.23	8.9	2.1	6.9	14.2	5.4	8.4
Tuscany	14.97	32.2	1.27	14.13	29.6	1.31	-5.6	-8.2	3.1	8.3	2.9	5.3
Umbria	16.79	34.4	1.33	18.62	36.8	1.39	10.9	7.1	3.8	15.1	6.6	8.0
Marche	15.55	34.2	1.24	15.90	35.5	1.23	2.3	3.7	-1.1	18.7	12.0	6.0
Lazio	15.12	26.0	1.59	16.17	27.8	1.59	6.9	7.0	0.2	7.3	7.2	0.1
Abruzzo	15.47	28.5	1.48	15.15	27.5	1.51	-2.1	-3.4	1.6	8.9	6.7	2.0
Molise	12.77	24.7	1.41	12.26	26.1	1.29	-4.0	5.8	-9.0	9.9	7.1	2.6
Campania	13.43	23.8	1.54	14.22	24.8	1.57	5.9	4.2	2.0	4.6	8.1	-3.2
Puglia	13.57	26.0	1.43	14.76	27.6	1.46	8.7	6.3	2.6	5.7	6.4	-0.7
Basilicata	13.59	24.9	1.49	13.81	26.8	1.41	1.6	7.6	-5.3	7.4	5.7	1.6
Calabria	12.89	23.1	1.53	14.29	25.5	1.54	10.9	10.4	0.7	2.5	5.2	-2.5
Sicily	12.72	21.1	1.65	14.41	24.8	1.59	13.2	17.9	-3.7	8.0	8.0	0.0
Sardinia	14.96	29.9	1.36	15.77	31.4	1.38	5.4	4.8	0.9	10.0	6.0	3.7
Italy	**14.44**	**27.8**	**1.42**	**14.82**	**28.2**	**1.44**	**2.6**	**1.7**	**1.1**	**8.5**	**6.0**	**2.3**
North	14.76	29.3	1.38	14.65	28.8	1.39	-0.7	-1.4	1.0	10.0	5.3	4.4
Centre	15.26	29.7	1.40	15.66	30.1	1.43	2.7	1.2	1.7	9.3	6.2	3.0
South and Islands	13.50	24.4	1.51	14.53	26.3	1.52	7.7	7.6	0.3	6.2	7.0	-0.8

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 2021, exposure to anticoagulants in the general population tends to increase with the age of patients for both genders, reaching a prevalence of use of 35.1% in men over 85, with greater use in men than in women for all age groups (Figure 3.5.1b).

The prevalence of use at national level was 6.0%, with values more or less overlapping in the Centre (6.7%), the South (5.9%) and the North (5.7%) (Table 3.5.1c). Veneto has the lowest prevalence (4.9%), while Marche has the highest prevalence (8.0%). The median age of users is 74 years and each user receives on average about 141.2 DDD of medicine per year with a cost per user of 215 euros. Half of the exposed population was treated with 80 DDD (equivalent to almost 3 months of therapy), while 19% of users received only one prescription. 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. In most cases this is indefinite for the prophylaxis of AF thromboembolism, whereas it is more time-limited for VTE prophylaxis and treatment of DVT in surgical and non-surgical patients.

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 55,897 individuals on anticoagulant therapy, of a median age of 76 years (IQR 67-82), and consisted of 52.5% women (Table 3.5.1d). The percentage of individuals with high and low adherence to treatment was 54.3% and 8.2%, respectively. 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 (8.6% 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 68.8%, and then decreases in the subsequent age groups, to 24.2% 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 (58.8% and 49.4%, respectively), with a more marked difference between genders in the North.

A comparison between 2021 and 2020 at national level shows that the percentage of users with low adherence has been broadly stable, with a minimum reduction of around 1%. 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 younger individuals (45-54 years of age) and older individuals (75-84 years of age), while the most significant increases in high adherence are observed in the North and the Centre, in particular, in individuals aged 55 to 84 years. Although there is an increase in users with high adherence, this appears to be overall sub-optimal. Taking into account the persistence to anticoagulant treatment (Table 3.5.1e), 66.2% of new users are still treated 12 months after the start of therapy. This means that within one year of treatment, approximately 34%

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 (66.7% vs 65.6%, respectively). If the average time to treatment discontinuation is taken into account, 50% of users discontinue anticoagulants after 282 days.

In general, a comparison of the persistence between 2020 and 2021 shows an increase in the percentage of persistent subjects at 12 months in all geographical areas, with more marked variations in the Centre (+13%) compared with the North and the South (+3%) (Table 3.5.1e). Even in this case, although there is an increase in the percentage of persistence for all regions, this appears to be suboptimal. In particular, while considering the impact of the different duration of anticoagulant therapy on the persistence depending on the approved indications, in light of the significant difference in prevalence in the general population of the main clinical indications for anticoagulant therapy (indefinite duration for AF prophylaxis and temporary duration for VTE), suboptimal adherence and persistence are mainly attributable to prophylaxis for the first clinical indication, justifiable by the low tolerance to chronic treatment by patients compared to a more limited treatment over time. It should be noted that, to some extent, the reduced adherence and persistence observed in people aged over 80 years may be influenced, albeit to a minimum, by a relative increase in the use of anticoagulants in the older population, for indications other than thromboembolic prevention in atrial fibrillation, such as VTE treatment and prophylaxis, whose recommended treatment duration is no more than six months in the prophylaxis of non-surgical patients at increased risk of venous thromboembolism and 28 days in post-surgical prophylaxis. Finally, in the North (63.8%) persistent individuals at 12 months are slightly fewer than in the Centre (67.3%) and in the South (69.0%) (Figure 3.5.1c).

Figure 3.5.1b Distribution of prevalence of use and consumption of anticoagulants under approved care regime (year 2021)

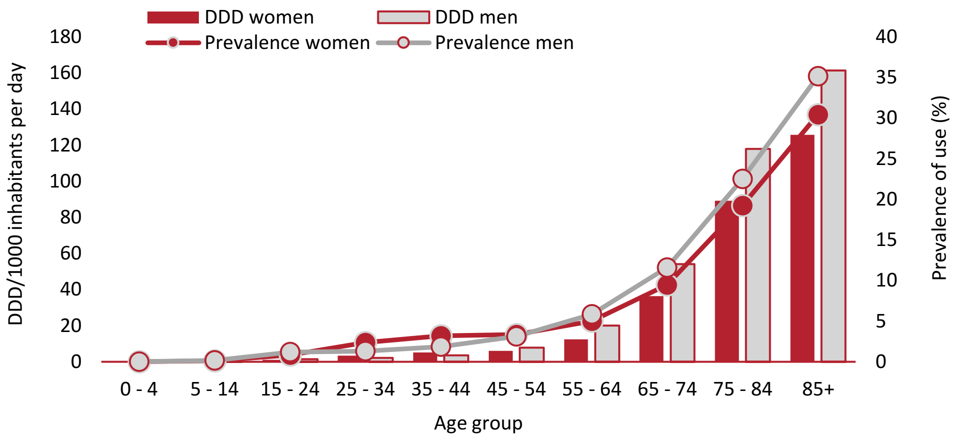


Table 3.5.1c Exposure and duration of anticoagulant therapy by Region under approved care regime and on behalf distribution (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	men	women	total					
Piedmont	5.5	5.6	5.6	75	193.8	149.4	112.0	17.5
Valle d'Aosta	5.7	5.5	5.6	74	204.5	147.8	100.0	11.7
Lombardy	5.9	6.2	6.1	72	250.4	139.8	80.0	18.7
Bolzano	5.3	5.1	5.2	74	211.5	148.0	113.0	14.7
Trento	6.2	6.0	6.1	72	148.2	135.2	80.0	16.7
Veneto	5.1	4.8	4.9	76	221.3	171.6	150.0	12.5
Friuli VG	5.9	5.7	5.8	77	250.0	175.9	160.0	10.5
Liguria	6.9	7.6	7.3	76	187.7	139.4	80.0	12.3
Emilia R.	5.6	5.7	5.7	75	177.4	144.6	105.0	22.9
Tuscany	6.4	7.1	6.8	75	162.8	126.5	68.0	21.7
Umbria	7.2	7.8	7.5	76	215.6	157.6	108.0	10.4
Marche	7.5	8.5	8.0	74	170.0	139.9	80.0	21.4
Lazio	5.9	6.7	6.3	73	227.4	138.4	75.0	21.2
Abruzzo	6.4	7.2	6.8	73	207.5	130.8	64.0	21.6
Molise	5.9	6.8	6.4	74	233.7	131.5	80.0	17.4
Campania	5.7	7.2	6.5	69	182.3	116.4	58.0	18.9
Puglia	5.3	6.1	5.7	74	302.9	146.9	94.5	15.4
Basilicata	6.0	7.6	6.8	73	202.6	138.2	80.0	16.2
Calabria	5.5	6.6	6.1	73	168.6	124.0	60.0	21.7
Sicily	4.8	5.6	5.2	73	210.4	125.4	60.0	23.0
Sardinia	5.6	6.2	5.9	74	205.7	159.0	110.0	20.0
Italy	**5.7**	**6.2**	**6.0**	**74**	**215.0**	**141.2**	**80.0**	**19.0**
North	5.6	5.8	5.7	74	220.8	150.0	100.0	17.5
Centre	6.3	7.1	6.7	74	199.8	138.0	75.0	20.8
South and Islands	5.4	6.4	5.9	72	217.2	131.6	63.0	19.7

Table 3.5.1d Indicators of adherence to treatment with anticoagulant medicines in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

	Total N=55,897				North ^ N=25,955				Centre N=12,909				South N=17,033			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*																
45-54	6.7	5.1	6.6	31	4.1	4.0	4.7	16	10.7	7.4	8.6	16	7.6	5.2	8.1	57
55-64	6.2	5.5	5.5	-1	5.1	4.3	4.3	0	8.8	6.4	6.4	0	6.1	6.6	6.5	-2
65-74	6.6	5.4	5.7	6	6.1	4.2	4.6	10	7.9	6.2	6.5	5	6.5	6.2	6.5	5
75-84	9.2	8.2	8.6	4	9.2	7.6	7.6	0	10.3	8.6	8.7	1	8.5	9.1	10.3	14
≥85	15.8	14.2	14.5	2	15.5	13.5	13.5	0	18.1	15.5	15.4	-1	14.5	14.3	15.2	6
Women	10.6	9.1	9.2	1	10.3	8.3	8.3	0	13.3	10.5	10.3	-2	9.3	9.3	9.7	5
Men	8.3	7.5	7.3	-2	7.9	6.6	6.2	-7	9.4	8.1	8.0	-1	8.2	8.3	8.6	4
Total	**9.4**	**8.3**	**8.2**	**-1**	**9.1**	**7.4**	**7.2**	**-3**	**11.3**	**9.3**	**9.1**	**-2**	**8.8**	**8.8**	**9.2**	**4**
High adherence*																
45-54	62.8	62.7	64.0	2	66.5	63.5	65.5	3	56.1	60.8	59.3	-2	62.1	62.6	65.0	4
55-64	64.9	66.1	69.8	6	65.3	66.1	70.1	6	61.0	64.2	68.8	7	66.5	67.2	69.9	4
65-74	64.0	67.2	68.8	2	63.5	68.3	70.5	3	60.0	65.4	67.0	2	66.9	66.9	67.7	1
75-84	47.0	50.1	49.5	-1	47.1	51.9	51.8	0	45.3	48.8	48.8	0	47.8	48.1	46.3	-4
≥85	25.5	25.9	24.2	-7	26.2	27.9	25.3	-9	22.9	25.4	24.3	-4	26.3	23.3	22.2	-5
Women	46.0	47.9	49.4	3	45.3	48.4	49.8	3	42.3	46.1	47.0	2	48.9	48.6	50.7	4
Men	53.1	55.8	58.8	5	53.4	57.5	60.8	6	49.6	53.4	56.6	6	54.8	55.0	57.3	4
Total	**49.6**	**52.0**	**54.3**	**5**	**49.6**	**53.2**	**55.72**	**5**	**46.0**	**49.8**	**52.0**	**4**	**51.8**	**51.8**	**54.0**	**4**

*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 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.
Percentages of people with low/high adherence relating to the specific category.
^ Excluding Emilia Romagna Median follow-up time (IQR): 334 (299-350).

Table 3.5.1e Persistence after one year of treatment with anticoagulant medicines in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

Persistence at 12 months	Total N=55,897				North ^ N=25,955				Centre N=12,909				South N=17,033			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54	55.9	56.1	57.7	3	56.0	54.7	54.9	0	47.2	56.7	58.1	2	60.6	57.8	61.4	6
55-64	61.8	62.6	65.6	5	58.5	60.8	62.0	2	57.4	59.9	66.4	11	67.6	66.4	69.7	5
65-74	67.2	68.8	71.3	3	64.6	68.6	70.3	3	61.8	64.6	70.5	9	73.2	71.7	73.1	2
75-84	63.5	64.9	67.5	4	59.4	64.0	65.7	3	60.3	61.2	69.3	13	71.2	68.9	69.2	0
≥85	53.7	53.8	57.5	7	49.0	52.3	52.5	0	50.3	51.8	62.1	20	62.5	57.6	61.7	7
Women	61.1	62.3	65.6	5	57.1	60.7	62.4	3	56.1	58.6	66.8	14	68.9	66.7	69.2	4
Men	62.8	63.8	66.7	5	59.5	63.2	65.0	3	59.1	60.7	67.9	12	69.5	66.9	68.7	3
Total	62.0	63.1	66.2	5	58.4	62.0	63.8	3	57.6	59.7	67.3	13	69.2	66.8	69.0	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

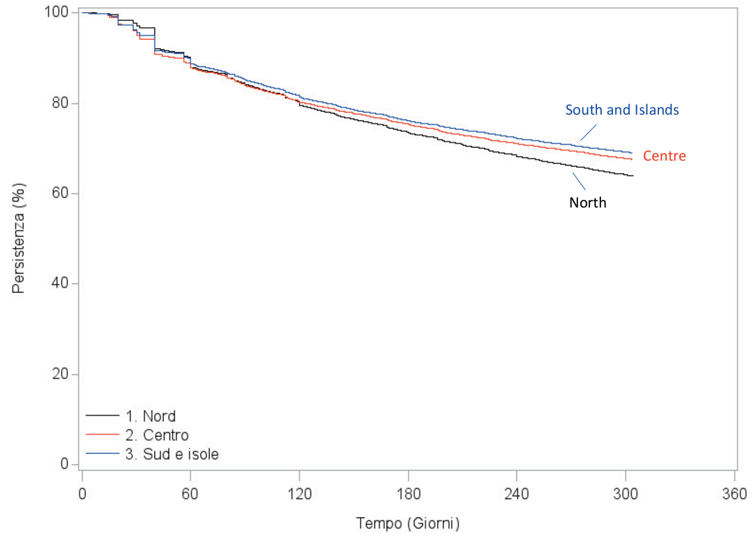


Figure 3.5.1c Time (in days) to discontinuation of anticoagulant treatment in the population aged ≥ 45 years stratified by geographical area. Curves are adjusted by gender and age (the Cox model was used for estimating the persistence curves). The North does not include Emilia Romagna

Key message

- As of 2014, Italy has seen **a significant increase in the consumption of anticoagulants** (CAGR: +6.0%), reaching 28.2 DDD/1000 inhabitants per day in 2021. At the same time, per capita expenditure increases by 2.6% compared to 2020, also given the fact that medicines with the highest consumption and expenditure, represented by NOAs, are still covered by patents. Overall, **NOAs record the highest consumption** at the expense of AVKs, which, on the other hand, show reduced consumption. These trends are partly attributable to the possibility of using NOAs in the prevention of stroke/systemic thromboembolism in individuals with FANV and in the treatment and prophylaxis of VTE, as an alternative to AVKs which, requiring periodic monitoring of the blood coagulation status, are preferred in medical prescription and, therefore, in clinical use. Moreover, as of October 2020, the prescription of NOAs by GPs and not just by specialists, as provided for in AIFA Note 97, may have affected the described patterns of consumption.
- In 2021, **the difference between the Region with the highest consumption compared to the Region with lower consumption increased** (17.3 DDD/1000 inhabitants per day), +12.1% compared to 2020 (15.2 DDD/1000 inhabitants per day). This variability, together with that observed in the prevalence of use, is not solely attributable to geographical differences in the prevalence of clinical indications for the use of such medicines, rather mainly to the different prescriptive attitude in AF thromboembolic prophylaxis, a clinical condition prevailing compared with VTE.
- The **adherence** analysis indicates that about 50% of the subjects considered have good therapeutic coverage, in particular those aged between 45 and 74 years. Conversely, among individuals aged over 80 years, only 24.2% show high adherence. This figure is comparable with the **persistence** analysis of treatment, which shows the same trend. If poor adherence and persistence in the older population can be explained mainly by individual socio-economic conditions and partial cognitive impairment with increasing age, which may affect compliance, suboptimal therapeutic coverage in the younger population cannot be attributed mainly to individual and patient-related reasons. Rather it is due to differences in medical care, diagnosis, clinical follow-up and prescriptive attitudes towards younger people, more often asymptomatic or with episodic/occasional atrial fibrillation.
- **Adherence and persistence analyses may be partly influenced by different clinical indications for anticoagulant therapy.** In particular, in light of the significant difference in prevalence in the general population of the main clinical indications for anticoagulant therapy (indefinite duration for AF prophylaxis and temporary duration for VTE), suboptimal adherence and persistence are mainly attributable to in AF thromboembolic prophylaxis for the first clinical indication, justifiable by the low tolerance and compliance to chronic treatment by patients compared to a more limited treatment over time. Moreover, the reduced adherence and persistence observed in individuals aged over eighty-five years could be influences, albeit to a minimal, by a relative increase in the use of anticoagulants for VTE treatment and prophylaxis in this subgroup, the recommended duration of treatment of which is generally temporary.

References

- Determina AIFA 1489/2016. Profilassi del tromboembolismo in gravidanza e puerperio per le pazienti a rischio GU Serie Generale n. 295 del 19-12-2016.
- Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromb oembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; 143(10):697-706.
- Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373-498.
- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-e496S.
- Mazzolai L, Aboyans V, Ageno W, et al. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. Eur Heart J 2018; 39(47):4208-18.
- Nota AIFA 97 per la prescrizione della terapia anticoagulante orale nei pazienti con Fibrillazione atriale non valvolare (FANV). Available at https://www.aifa.gov.it/documents/20142/1180832/NOTA_AIFA_%2097_17.06.2020.pdf/ (last accessed 27.04.2021).
- Per la prescrizione di EBPM nel paziente oncologico secondo Legge 648/96 “farmaci ad uso consolidato” http://www.aifa.gov.it/sites/default/files/All1_ONCOLOGIA_ADULTI_LUGLIO2016.pdf/
- SIMG-FCSA. Documento di consensus SIMG-FCSA sulle corrette procedure di anticoagulazione 2018. Available at https://simg.it/documenti/pdf/doc_finale_simg_fcsa_feb- braio_2018.pdf/
- Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021;160(6):e545-e608.

3.5.2 Coagulation factors

Epidemiological framework

Coagulopathies are a group of rare diseases, caused by mutations due to factors involved in blood clotting. In some cases they may occur with mild symptoms, while in others bleeding that can put the patient's life at risk. The main congenital coagulopathies are haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency), transmitted as a recessive character linked to chromosome X, and von Willebrand's disease (Von Willebrand factor deficiency), autosomal dominant transmission in the milder forms, or autosomal recessive in the most severe form. Deficiencies in all other coagulation factors (fibrinogen, prothrombin, factor V, factor VII, factor X, factor XI and factor XIII) are much rarer, but even in these cases, they can cause severe or mild haemorrhagic episodes. In Italy, the National Register of Congenital Coagulopathies collects data on the number and distribution of patients suffering from congenital haemorrhagic diseases, also implementing an epidemiological surveillance of complications. The latest available data refer to the report published in 2020 and come from 54 haemophilia centres (HC) present on the national territory. The prevalence in the female gender was significantly lower for haemophilia A and B as transmission of the two forms of haemophilia is linked to a genetic mutation on the X chromosome. Monitoring showed that 43.8% of patients had severe haemophilia A, 42.6% had mild haemophilia A and 13.6% moderate haemophilia A. In terms of prevalence, estimates were about 6.8/100,000 inhabitants with 13.8/100,000 male inhabitants. Among patients with haemophilia B, 33.9% had a severe form, 21.2% had a moderate form, and 44.9% had a mild form. The prevalence for this condition was 1.5/100,000 inhabitants, with 2.9/100,000 males. Finally, patients with von Willebrand's disease had a prevalence of 5.4/100,000 inhabitants. A specific analysis also considered individuals with a defect or deficiency relating to one of the other coagulation factors: these were 22% of the total patients enrolled in the register of coagulopathies.

National data on consumption and expenditure

In 2021, expenditure on coagulation factors reached 9.1 euros per capita, a +1.8% increase compared to 2020, showing a 3.0% average annual growth rate over the last 8 years (CAGR 2014-2021). The average cost per day of therapy also increased in the same period from 408.6 euros in 2014 to 417.5 euros in 2021 (despite a 2.1% decrease in the last year) (Figure and Table 3.5.2a).

Short-acting recombinant factors for the treatment of haemophilia A are the category with the highest expenditure, with a per capita value of 2.89 euros, a -24.9% decrease compared to 2020, and an average DDD cost of 341.82 euros, almost stable compared to the previous year (+0.7%). Short-acting recombinant medicines for factor VII deficiency and the activated human prothrombin antihaemophilic complex also showed a sharp reduction in expenditure (-28.3% and -24.1%, respectively), although these active ingredients have a high average DDD cost (4082.80 euros for short-acting recombinant medicines for factor VII and XI deficiency). On the other hand, there was an increase of 47.2% in expenditure for recombinant long-acting medicines for haemophilia A, which in 2021 recorded a value of 2.33 euros per capita, and of 68.1% for emicizumab, a monoclonal antibody for hemophilia A, with a expenditure of 1.27 euros per capita. These increases seem to be linked to an increase in consumption observed in 2021 for these medicines (+54.2% and +75.6%, respectively), after a reduction in the average DDD cost compared to the previous year (-4.3% and -4.0%).

The increases for recombinant long-acting factors for haemophilia A are attributable to factor VIII pegylated, damoctocog alfa pegol, which expenditure and consumption increase by more than 100% in 2021.

In parallel with expenditure, consumption of monoclonal antibody emicizumab in 2021 recorded an increase by more than 75% compared to the previous year. This medicine, initially authorised for routine prophylaxis in patients with haemophilia A with factor VIII inhibitors, can now also be used in patients with severe disease (congenital deficiency <1%), even in the absence of inhibitors.

Particularly interesting is the increase in expenditure and consumption recorded in 2021 for all coagulation factors used in the treatment of haemophilia B. Long-acting recombinant medicines record the largest per capita expenditure, equal to 1.10 euros, up 7.0% compared to 2020, ranking fourth for expenditure within the category of coagulation factors. Short-acting recombinant medicines follow despite a lower per capita expenditure (0.23 euros), but showing a 10.4% increase compared to the previous year. Expenditure increases are mainly due to the increase in consumption of these medicines (+10.4%), since the average DDD cost only recorded a slight increase compared to the previous year (+0.3%).

Analysing the individual active ingredients, it is possible to note that two drugs for haemophilia A rank at the top of the list: octocog alfa (a recombinant short-acting factor), with 1.67 euros, is the molecule with the highest expenditure, although with a 29.6% decrease compared to the previous year; efmorocotog alfa (the first long-acting recombinant factor available in Italy), with a per capita expenditure of 1.04 euros and a 0.5% decrease compared with 2020.

Regional per capita expenditure (Table 3.5.2b) varies widely, ranging from a minimum value of 4.33 euros in Bolzano (-27.8% compared to 2020) to a maximum of 12.33 euros in Campania (-10.4% compared to 2020). The Regions with the highest increases in expenditure are Molise (+28.5%) and Emilia Romagna (+28.0%), driven by a decrease in consumption. Conversely, the largest reductions are recorded in Friuli Venezia Giulia (-46.2%) and in Bolzano (-27.8%), due to a reduction in the average DDD cost in 2021 (-49.3% and -32.6%, respectively), and in Basilicata (-23.6%) due to a reduction in consumption (-30.6%). Friuli Venezia Giulia is the Region with the largest decreasing trend in terms of expenditure over the period 2014-2021 (-10.2%), while Umbria registers the highest average annual growth rate (+9.7%) over the same period.
Regarding consumption, increases in the North (+11.0%) and reductions in the South (-0.7%) are observed in 2021. The largest increases are found in Valle d'Aosta (+33.9%), Molise (+31.5%) and Emilia Romagna (+30.1%), while Basilicata is the Region with the highest reduction in consumption (-30.6%).

Figure 3.5.2a Coagulation factors, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

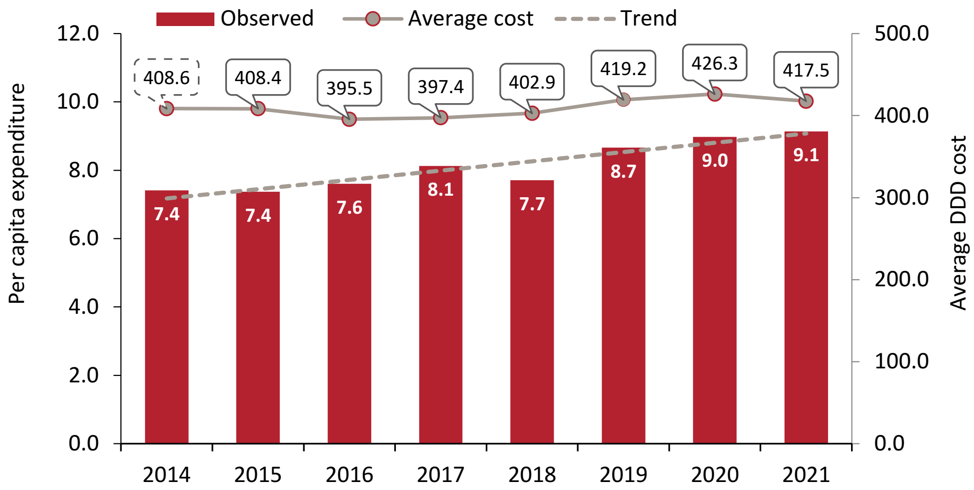


Table 3.5.2a Coagulation factors, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Haemophilia A (short acting recombinant)	2.89	-24.9	-6.6	0.0	-25.3	-5.9	341.82	0.7
Haemophilia A (long acting recombinant)	2.33	47.2	-	0.0	54.2	-	327.58	-4.3
Emicizumab	1.27	68.1	-	0.0	75.6	-	753.71	-4.0
Haemophilia B (long acting recombinant)	1.10	7.0	-	0.0	5.3	-	901.08	1.9
Factor VII deficiency (short acting recombinant)	0.59	-28.3	-7.0	0.0	-28.2	-5.8	4082.80	0.1
Haemophilia A (plasma derivatives)	0.36	-2.9	-6.8	0.0	-1.6	-6.1	254.23	-1.1
Haemophilia B (short acting recombinant)	0.23	10.4	-12.5	0.0	10.4	-12.7	379.92	0.3
Activated human antihemophilic prothrombin complex	0.13	-24.1	-15.5	0.0	-27.6	-16.1	11616.22	5.1
Combination of coagulation factors (plasma derivatives)	0.07	51.2	13.0	0.0	52.0	12.5	106.26	-0.3
Factor VII deficiency (plasma derivatives)	0.06	-4.4	4.3	0.0	3.0	4.3	359.90	-6.9
Other deficiencies of coagulation factors (long acting recombinant)	0.05	25.7	40.2	0.0	26.0	36.7	15524.20	0.0
Von Willebrand's disease (plasma derivatives)	0.02	282.0	-10.4	0.0	282.7	-10.4	71.90	0.1
Haemophilia B (plasma derivatives)	0.02	54.1	-3.4	0.0	78.9	-3.9	199.55	-13.6
Other deficiencies of coagulation factors (plasma derivatives)	0.01	-1.9	-	0.0	-1.7	-	5492.96	0.1
Coagulation factors	**9.14**	**1.8**	**3.0**	**0.1**	**4.2**	**2.7**	**417.52**	**-2.1**
octocog alfa	1.67	-29.6	-10.5	0.0	-28.9	-9.5	332.74	-0.7
emicizumab	1.27	68.1	-	0.0	75.6	-	753.71	-4.0
efmorocotog alfa	1.04	-0.5	-	0.0	-0.4	-	357.44	0.2
albutrepenonacog alfa	0.80	9.8	-	0.0	10.2	-	1087.36	-0.1
moroctocog alfa	0.60	-22.6	-7.6	0.0	-20.2	-6.4	334.50	-2.7
activated heptacog alfa (recombinant DNA coagulation factor VII)	0.59	-28.3	-7.0	0.0	-28.2	-5.8	4082.80	0.1
damoctocog alfa pegol	0.44	>100	-	0.0	>100	-	329.94	1.5
lonoctogoc alfa	0.40	-0.7	-	0.0	0.8	-	320.34	-1.2
factor VIII/von Willebrand's factor	0.36	-3.4	-6.1	0.0	-2.1	-5.3	255.38	-1.0
turoctocog alfa	0.33	-22.3	-	0.0	-19.3	-	322.59	-3.5

Table 3.5.2b Coagulation factors, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	7.37	0.0	417.37	8.49	0.1	450.17	15.2	7.1	7.9	1.1	-0.3	1.4
Valle d'Aosta	3.74	0.0	319.03	4.45	0.0	284.18	18.9	33.9	-10.9	4.6	9.9	-4.8
Lombardy	7.88	0.0	443.85	8.21	0.0	454.33	4.2	2.1	2.4	5.8	4.1	1.7
Bolzano	6.00	0.0	430.21	4.33	0.0	289.83	-27.8	7.5	-32.6	-4.0	-2.0	-2.0
Trento	4.53	0.0	353.11	5.06	0.0	359.59	11.6	9.9	1.8	1.8	1.9	-0.1
Veneto	6.55	0.0	449.20	7.17	0.0	396.78	9.5	24.3	-11.7	6.1	4.5	1.5
Friuli VG	7.91	0.0	1092.17	4.25	0.0	553.26	-46.2	6.4	-49.3	-10.2	-7.8	-2.6
Liguria	7.81	0.0	434.54	8.33	0.0	509.30	6.5	-8.9	17.2	7.8	3.2	4.5
Emilia R.	7.47	0.0	410.94	9.55	0.1	405.18	28.0	30.1	-1.4	6.8	8.1	-1.2
Tuscany	9.03	0.1	492.97	9.27	0.0	513.88	2.6	-1.3	4.2	3.7	3.5	0.2
Umbria	6.17	0.0	378.57	6.77	0.0	400.02	9.6	4.0	5.7	9.7	9.7	0.0
Marche	5.72	0.0	442.25	6.09	0.0	467.00	6.4	1.1	5.6	-0.9	0.4	-1.3
Lazio	11.35	0.1	368.26	10.84	0.1	342.42	-4.5	2.9	-7.0	2.0	3.1	-1.0
Abruzzo	11.19	0.1	423.84	11.66	0.1	435.89	4.2	1.6	2.8	5.3	4.0	1.2
Molise	5.41	0.0	365.69	6.95	0.1	358.45	28.5	31.5	-2.0	3.1	3.1	0.0
Campania	13.76	0.1	435.02	12.33	0.1	389.89	-10.4	0.3	-10.4	1.0	2.5	-1.4
Puglia	11.46	0.1	415.84	12.12	0.1	457.22	5.8	-3.5	10.0	3.1	1.2	1.8
Basilicata	7.68	0.1	374.28	5.86	0.0	413.13	-23.6	-30.6	10.4	-0.6	-3.1	2.6
Calabria	11.18	0.1	462.03	12.08	0.1	461.18	8.0	8.5	-0.2	4.1	1.7	2.3
Sicily	9.88	0.1	418.15	9.22	0.1	400.73	-6.6	-2.3	-4.2	1.3	1.4	-0.1
Sardinia	5.66	0.0	329.41	5.76	0.0	334.00	1.7	0.6	1.4	0.3	-0.6	0.9
Italy	**8.97**	**0.1**	**426.32**	**9.14**	**0.1**	**417.52**	**1.8**	**4.2**	**-2.1**	**3.0**	**2.7**	**0.3**
North	7.38	0.0	444.67	7.97	0.1	433.88	8.0	11.0	-2.4	4.3	3.4	0.8
Centre	9.48	0.1	405.56	9.41	0.1	396.26	-0.8	1.9	-2.3	2.6	3.3	-0.7
South and Islands	10.95	0.1	420.97	10.64	0.1	412.88	-2.9	-0.7	-1.9	2.1	1.7	0.3

Key message

- In 2021, coagulation factors recorded an increase in **overall per capita expenditure** (+1.8%), corresponding to an increase in consumption (+4.2%).
- **Short-acting recombinant medicines** for both the treatment of haemophilia A and haemophilia B, recorded a reduction in consumption also in 2021. However, consumption increased for **long-acting recombinant factors**, which, through a better pharmacokinetic profile compared to short-acting formulations, allow to increase the interval between infusions, with greater safety margins against haemorrhagic episodes, thus improving adherence to prophylaxis and the quality of life of patients.
- In 2021, consumption of **monoclonal antibody** emicizumab continues to increase (over 75%). This medicine, initially authorised for routine prophylaxis in patients with haemophilia A with factor VIII inhibitors, can now also be used in patients with severe disease (congenital deficiency <1%), even in the absence of inhibitors.
- Particularly interesting is the **increase in expenditure and consumption** recorded in 2021 for all **coagulation factors used in the treatment of haemophilia B**, with long-acting recombinant medicines recording the highest per capita expenditure.
- The observed **regional variability** is wide, but the pattern is in line with what is already known about the consumption of these medicines in Italy. The South and the Islands spend more than the Centre and the North. Lazio and Campania are the Regions with the highest expenditure on these medicines.

References

- Abbonizio F, Arcieri R, Giampaolo A; Associazione Italiana Centri Emofilia (AICE). Registro Nazion- ale Coagulopatie Congenite. Rapporto 2018 (Rapporti ISTISAN 20/14). Roma: Istituto Superiore di Sanità; 2020.
- Abbonizio F, Giampaolo A, Riccioni R, Arcieri R, Hassan HJ; Associazione Italiana Centri Emofilia (AICE). Registro Nazionale Coagulopatie Congenite. Rapporto 2016 (Rapporti ISTISAN 18/1). Roma: Istituto Superiore di Sanità; 2018.
- Berntorp E, Andersson NG. Prophylaxis for hemophilia in the era of extended half-life factor VIII/ factor IX products. Semin Thromb Hemost 2016; 42(5):518-25.
- Cancanelli L, Mirarchi SA, Pasut E, Salanitro MP, Stoppa S. L'impatto dei fattori a emivita prolun- gata sul consumo di FVIII: il punto di vista del farmacista ospedaliero. GIHTAD 2018; 11:7.
- Mannucci PM. Hemophilia therapy: the future has begun. Haematologica 2020; 105(3):545-53.

3.5.3 Platelet aggregation inhibitors

Epidemiological framework

Platelets provide the haemostatic cap in vascular sites with lesions and are responsible for pathological thromboses leading to cardio-cerebrovascular events, such as myocardial infarction, stroke and peripheral vascular thrombosis. Platelet aggregation inhibitors are used in the prevention of these events, and because molecules are available for different targets or distinct mechanisms, additive or synergic effects can also be exploited. The role of platelets in the onset of thrombosis is greater in arterial circulation than in venous circulation, because there are higher shear forces in the arteries that activate platelets. As a result, platelet aggregation inhibitors are more effective in arterial thrombosis than in venous thrombosis. According to data from the National Health Institute, cardiovascular diseases cause 44% of all deaths and represent the leading cause of death in Italy. In men mortality is negligible up to 40 years, emerges between 40 and 50 years and then grows exponentially with age. In women, it occurs about 10 years later, starting at 60 years of age and growing rapidly after the age of 70. According to data from the Ministry of Health, in 2019 cardiovascular disorders represented the main cause of hospitalisation in Italy (14.3% of the total number of discharges), with 7.2 days of average stay. However, it should be noted that, especially in recent years, the burden of cardiovascular diseases on hospitalisations is decreasing. Some medicines, such as treprostinil and selexipag are used as aggregation inhibitors in the treatment of pulmonary arterial hypertension, a rare and progressive respiratory disease that affects 50-60 individuals in a million. Data on the incidence of pulmonary hypertension and its subgroups globally are rather small. However, it is estimated that the most common forms are acquired or secondary, due to pre-existing cardio-pulmonary diseases. In Italy, it is estimated that approximately 3-4,000 patients are affected by this disease. However, especially due to the specificity of symptoms (dizziness, wheezing and fatigue) the possibility of undiagnosed cases should be considered.

National data on consumption and expenditure

The consumption of platelet aggregation inhibitors in the last eight years has remained almost stable, reaching 70.6 DDD/1000 inhabitants per day in 2021 (CAGR 2014-2020: +0.5%). Over the same period, the average DDD cost remained between 0.20 euros and 0.21 euros (Figure and Table 3.5.3a). Overall, per capita expenditure for these medicines was 5.32 euros in 2021, a slight decrease (3.0%) compared to the previous year (CAGR 2014-2020 +1.3%). $P2Y_{12}$ platelet receptor inhibitors have the highest per capita expenditure (1.51 euros, +0.2% compared to 2020), mostly attributable to chlorpidrogrel (1.28 euros, +0.7% compared to 2020). The acetylsalicylic acid subgroup alone or in combination has the highest consumption, reaching 54.1 DDD per 1000 inhabitants per day, mainly attributable to acetylsalicylic acid alone (46.1 DDD).
The acetylsalicylic acid and chlorpidrogrel combination ranks fifth among the most consumed medicines, reaching 2.2 DDD in 2021 (+3.9 % compared to 2020), with an average cost per day of therapy of 0.41 euros.
Ticagrelor, another $P2Y_{12}$ receptor inhibitors used in combination with acetylsalicylic acid for the prevention of athero-thrombotic events in patients with acute coronary syndrome

and at higher risk, ranks third for expenditure (0.98 euros per capita) and consumption (1.1 DDD), recording the highest average annual growth rate (CAGR) compared to 2014, both for expenditure (+9.6%) and consumption (11.3%).
Regional variability in consumption is wide and in 2021 ranges from a minimum value of 44.0 DDD in the autonomous province of Bolzano to a maximum value of 94.3 DDD in Molise (a difference more than double). Friuli Venezia Giulia is the Region with the highest change in consumption (+12.9%) compared to 2020, while in the autonomous province of Bolzano the doses contract the most (-2.6%) (Table 3.5.3b).
A high variability is also observed in the per capita expenditure of these medicines, with values ranging from a minimum of 2.99 euros in the autonomous province of Bolzano and Veneto and a maximum of 8.33 euros in Basilicata. With the exception of Veneto, Umbria and Marche, all Regions recorded a reduction in expenditure compared to the previous year, more marked in Molise (26.4%).
Although the average DDD cost of this category is rather low, it is evident that Lazio has an average cost per day of therapy more than twice than that of Emilia Romagna (0.28 euros and 0.13 euros, respectively).

Figure 3.5.3a Platelet aggregation inhibitors, temporal trend of per capita expenditure and average cost per day of therapy 2014-2021

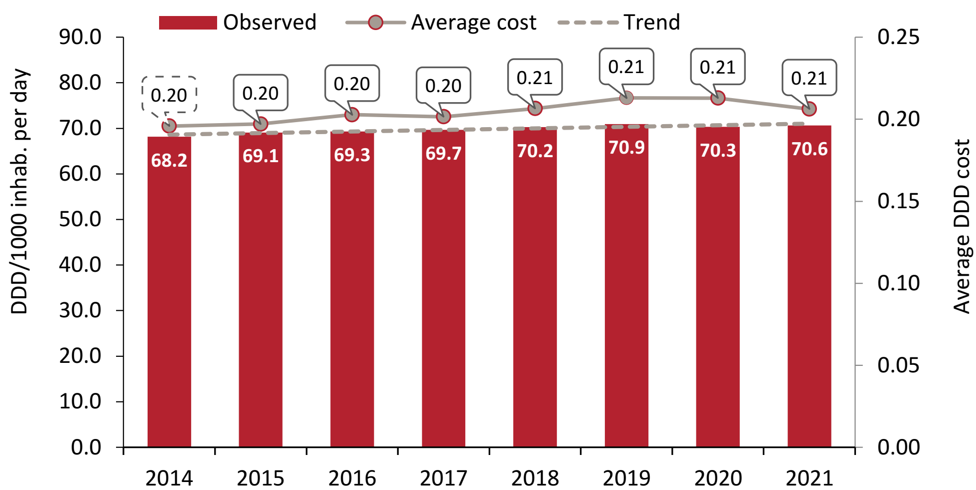


Table 3.5.3a Platelet aggregation inhibitors, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Per capita expenditure	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
P2Y12 platelet receptor inhibitors	1.51	0.2	-0.7	13.2	3.7	1.3	0.31	-3.1
Acetylsalicylic acid alone and in combination	1.44	-1.3	-0.5	54.1	-0.4	0.0	0.07	-0.6
Other platelet aggregation inhibitors	1.03	-0.3	3.5	0.0	9.6	-0.2	139.53	-8.8
Ticagrelor	0.98	-4.0	9.6	1.1	-4.0	11.3	2.46	0.3
Acetylsalicylic acid/clopidogrel	0.33	-23.7	1.3	2.2	3.9	8.1	0.41	-26.4
Glycoprotein IIb/IIIa inhibitors	0.03	-10.4	-23.2	0.0	-1.9	-6.0	81.09	-8.4
Platelet aggregation inhibitors	**5.32**	**-3.0**	**1.3**	**70.6**	**0.4**	**0.5**	**0.21**	**-3.1**
clopidogrel	1.28	0.7	3.6	11.4	6.8	7.1	0.31	-5.5
acetylsalicylic acid	1.18	0.5	1.3	46.1	0.7	0.8	0.07	0.0
ticagrelor	0.98	-4.0	9.6	1.1	-4.0	11.3	2.46	0.3
treprostinil	0.59	-4.2	3.0	0.0	-2.5	4.8	548.24	-1.4
clopidogrel/acetylsalicylic acid	0.33	-23.7	1.3	2.2	3.9	8.1	0.41	-26.4
selexipag	0.22	10.7	-	0.0	21.5	-	108.66	-8.6
acetylsalicylate lysine	0.20	-5.6	-2.9	6.7	-5.1	-2.3	0.08	-0.2
iloprost	0.18	6.0	-5.3	0.0	24.9	-2.6	87.64	-14.9
ticlopidine	0.15	-15.4	-14.0	1.6	-15.7	-14.2	0.25	0.7
acetylsalicylic acid/ magnesium hydroxide/algeldrate	0.05	-11.9	-9.6	1.3	-11.9	-9.7	0.11	0.3

Table 3.5.3b Platelet aggregation inhibitors, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	4.05	67.9	0.16	3.92	71.1	0.15	-3.0	4.7	-7.1	-1.4	-0.4	-1.0
Valle d'Aosta	3.19	58.0	0.15	3.12	60.8	0.14	-2.0	4.8	-6.2	-3.4	-3.1	-0.4
Lombardy	4.87	48.4	0.27	4.79	48.1	0.27	-1.7	-0.6	-0.8	2.0	-0.1	2.2
Bolzano	3.27	45.1	0.20	2.99	44.0	0.19	-8.4	-2.6	-5.8	1.0	-1.9	2.9
Trento	4.53	75.7	0.16	4.44	75.1	0.16	-2.0	-0.8	-1.0	-0.4	-0.1	-0.3
Veneto	2.92	48.0	0.17	2.99	46.8	0.17	2.3	-2.5	5.1	-1.0	0.9	-1.9
Friuli VG	3.86	61.8	0.17	3.80	69.8	0.15	-1.6	12.9	-12.6	-0.8	-1.4	0.6
Liguria	3.95	56.7	0.19	3.81	55.6	0.19	-3.7	-2.0	-1.5	0.1	-1.4	1.5
Emilia R.	3.90	83.8	0.13	3.88	82.0	0.13	-0.6	-2.1	1.9	-1.2	-0.8	-0.4
Tuscany	4.71	74.4	0.17	4.54	75.3	0.17	-3.5	1.2	-4.4	-0.3	-0.7	0.4
Umbria	6.00	76.5	0.21	6.31	76.1	0.23	5.1	-0.5	5.9	4.2	-0.1	4.3
Marche	4.68	86.2	0.15	4.67	84.6	0.15	0.0	-1.9	2.2	3.2	1.0	2.2
Lazio	8.41	80.7	0.28	8.12	80.3	0.28	-3.4	-0.5	-2.6	2.6	1.2	1.4
Abruzzo	8.67	92.1	0.26	7.92	91.2	0.24	-8.6	-1.0	-7.5	2.9	0.9	2.0
Molise	7.13	89.4	0.22	5.25	94.3	0.15	-26.4	5.5	-30.0	-2.7	1.0	-3.7
Campania	6.80	72.3	0.26	6.49	74.4	0.24	-4.5	2.9	-7.0	1.1	2.8	-1.7
Puglia	8.36	89.0	0.26	8.16	87.7	0.25	-2.4	-1.5	-0.7	3.4	1.1	2.3
Basilicata	9.31	83.9	0.30	8.73	88.3	0.27	-6.2	5.2	-10.6	4.9	1.9	3.0
Calabria	8.11	89.2	0.25	8.07	88.9	0.25	-0.5	-0.3	0.1	7.3	1.3	5.9
Sicily	5.22	81.4	0.18	4.85	82.9	0.16	-7.0	1.9	-8.5	-1.0	2.1	-3.1
Sardinia	3.99	74.1	0.15	3.89	72.9	0.15	-2.6	-1.7	-0.7	-2.0	-0.9	-1.0
Italy	**5.48**	**70.3**	**0.21**	**5.32**	**70.6**	**0.21**	**-3.0**	**0.4**	**-3.1**	**1.3**	**0.5**	**0.7**
North	4.10	58.8	0.19	4.03	59.0	0.19	-1.5	0.3	-1.5	0.2	-0.4	0.6
Centre	6.55	79.1	0.23	6.39	78.9	0.22	-2.5	-0.2	-2.0	2.1	0.5	1.6
South and Islands	6.82	81.5	0.23	6.50	82.2	0.22	-4.7	0.8	-5.2	1.8	1.6	0.2

Exposure and adherence in population

The data of the Health Card flow allowed to describe the trend of 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 2021, 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 (49.8%). In all age groups, men also consume more doses than women (Figure 3.5.3b).

The prevalence of use at national level was 9.2%, substantially overlapping with the South and the Islands (10.9%) and with the Centre (10.5%), and slightly reduced in the North (7.5%) (Table 3.5.3c). The autonomous province of Bolzano has the lowest prevalence (5.1%), while Molise has the highest (13.5%). The median age of users is 75 years and each individual receives an average of 267.5 DDD of the product during the year with a cost per user equal to 43.8 euros. Half of the nationally exposed population is treated for at least 10 months in one year (median DDD: 300). 4.3% of users at national level received only one prescription in the year, with a value ranging from a minimum of 2.1% in Valle d'Aosta to a maximum of 7.0% in Campania.

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 168.272 new users, with a median age of 70 years (IQR 62-78), made up of 48.7% of women.

In 2021, the proportion of subjects with high and low adherence to platelet aggregation inhibitors treatment was 60.4% and 7.0%, respectively (Table 3.5.3d). The percentage of individuals with low adherence tends to increase with age, recording the highest value in the over 85 age group (8.4%) and in women compared to men (7.8% and 6.2%, respectively). Stratified by age and geographical area, the largest proportion of individuals with low adherence is observed in the over 85 age group and in the Regions of Southern Italy (10.6%). High adherence, as expected, tends to decrease with increasing age, with a higher value in the age group between 45 and 54 years (63.3%), and to a slightly greater extent in men than in women (63.2% and 57.3%). Users in Northern Italy and aged between 45 and 54 years have the highest percentage of adherence (69.8%). The reduced adherence with age is due to the poor compliance that characterises the elderly population, affected by cognitive impairment, numerous comorbidities requiring numerous therapy and socio-economic conditions. In addition, the adverse effects represented most by major and minor haemorrhagic complications may be more frequent in the elderly population, who are at higher risk of bleeding as they progress in age and comorbidities.

A comparison of 2021 adherence data compared to 2020, in the Centre shows a slight increase in the percentage of subjects with high adherence (+4%) and a marked reduction in the percentage of individuals with low adherence (-24%), both above the national average (+1% and -9%, respectively). This trend could be explained by a greater awareness of the importance of cardiovascular prevention on the part of the general population.

Analysing the persistence of treatment with platelet aggregation inhibitors (Table 3.5.3e), it is evident that more than half of new users are persistent to treatment after one year

(52.8%), with slightly lower percentages in the South (48.9%) compared to the North (55.4%) and the Centre (54.9%). 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 (55.9% and 49.6%, respectively). For the North and the South, the data observed in 2021 are broadly similar to those of 2020, while the Centre shows an increase (+8%) of persistent individuals 12 months from the start of treatment compared to the previous year.
Finally, comparing persistence data among geographical areas (Figure 3.5.3c), platelet aggregation inhibitors show a median time to treatment discontinuation greater than 365 days in the Centre and the North, while the South records less than 289 days.

In general, both adherence and persistence to treatment with platelet aggregation inhibitors are suboptimal.

Figure 3.5.3b Distribution of the prevalence of use and consumption of platelet aggregation inhibitors under approved care regime and distribution on behalf (year 2021)

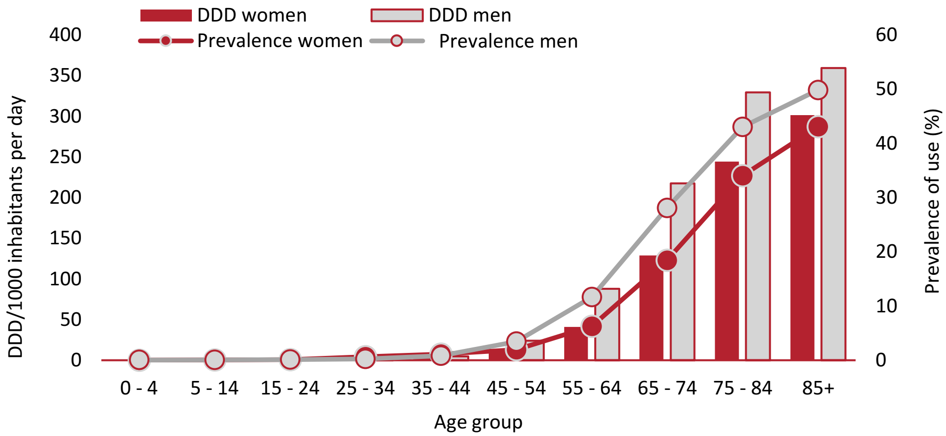


Table 3.5.3c Exposure and duration of therapy with platelet aggregation inhibitors by Region under approved care regime and distribution on behalf (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	Median DDD	Users with 1 prescription (%)
	men	women	total					
Piedmont	10.7	8.8	9.7	75	31.6	266.1	300.0	2.9
Valle d'Aosta	8.4	7.7	8.0	77	29.0	260.4	290.0	2.1
Lombardy	7.0	5.5	6.2	75	63.1	270.8	300.0	3.0
Bolzano	5.5	4.8	5.1	77	45.1	267.4	300.0	2.5
Trento	9.3	8.4	8.9	75	40.6	284.3	300.0	2.4
Veneto	6.7	4.7	5.7	75	41.3	277.8	300.0	2.3
Friuli VG	9.9	8.5	9.2	75	32.0	278.4	300.0	2.5
Liguria	8.6	8.5	8.5	79	36.2	241.5	270.0	4.3
Emilia R.	10.7	9.6	10.1	75	25.1	267.7	300.0	2.9
Tuscany	10.9	9.8	10.3	76	35.8	265.1	300.0	6.2
Umbria	11.1	9.3	10.2	76	38.4	274.7	300.0	4.7
Marche	12.3	10.6	11.4	76	33.6	272.3	300.0	3.6
Lazio	11.1	10.3	10.7	74	57.4	264.7	300.0	3.9
Abruzzo	13.2	12.1	12.6	74	54.2	264.6	300.0	4.5
Molise	13.9	13.1	13.5	74	32.5	263.2	300.0	4.0
Campania	10.8	10.0	10.4	72	44.3	238.0	252.0	7.0
Puglia	12.2	10.8	11.5	74	52.6	269.7	300.0	3.9
Basilicata	12.8	11.9	12.3	74	57.7	260.7	300.0	6.0
Calabria	12.4	12.0	12.2	74	52.5	256.7	280.0	5.6
Sicily	10.8	10.5	10.6	75	27.4	257.8	280.0	4.9
Sardinia	9.9	9.4	9.7	75	32.4	278.3	300.0	3.9
Italy	**9.8**	**8.7**	**9.2**	**75**	**43.8**	**267.5**	**300.0**	**4.3**
North	8.2	6.8	7.5	75	42.1	272.5	300.0	2.9
Centre	11.0	10.0	10.5	75	46.9	270.3	300.0	4.7
South and Islands	11.2	10.5	10.9	74	43.6	260.6	300.0	5.3

Table 3.5.3d Indicators of adherence to treatment with platelet aggregation inhibitors in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

	Total N=168,272				North N=62,293				Centre N=43,284				South N=62,695			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*																
45-54	7.6	7.3	6.6	-9	4.2	4.5	4.5	0	7.2	7.3	5.7	-22	10.6	9.5	8.9	-7
55-64	7.3	7.4	6.6	-12	4.5	4.7	4.1	-12	6.6	6.9	5.2	-25	9.8	9.9	9.5	-5
65-74	7.8	7.4	6.7	-8	5.5	5.0	4.6	-7	7.6	7.5	5.6	-26	9.8	9.3	9.5	2
75-84	8.1	8.0	7.4	-8	5.7	6.0	5.7	-5	7.8	8.3	6.6	-21	10.9	10.3	10.1	-2
≥85	9.1	8.3	8.4	1	6.7	5.9	6.8	17	9.7	9.5	8.0	-16	11.6	10.6	10.6	0
Women	8.8	8.4	7.8	-7	6.2	6.0	5.7	-6	8.5	8.4	6.8	-18	11.2	10.7	10.5	-1
Men	7.1	6.9	6.2	-11	4.7	4.7	4.5	-4	6.9	7.3	5.2	-29	9.4	9.0	8.8	-3
Total	**7.9**	**7.7**	**7.0**	**-9**	**5.4**	**5.3**	**5.1**	**-5**	**7.7**	**7.8**	**6.0**	**-24**	**10.3**	**9.8**	**9.7**	**-2**
High adherence*																
45-54	62.4	62.8	63.3	1	69.9	69.9	69.8	0	64.1	61.3	63.8	4	55.6	57.7	57.6	0
55-64	61.5	61.8	62.3	1	68.4	68.9	68.1	-1	62.0	61.3	63.6	4	55.6	56.2	56.7	1
65-74	59.7	60.1	60.9	1	65.6	65.5	65.6	0	59.2	60.1	62.0	3	55.3	55.6	56.1	1
75-84	58.0	58.2	58.4	0	63.0	62.3	61.6	-1	56.9	56.9	59.6	5	53.0	54.1	53.5	-1
≥85	55.4	56.4	55.9	-1	60.2	60.8	58.8	-3	53.9	54.3	56.2	3	50.8	52.0	51.8	0
Women	56.2	56.8	57.3	1	61.7	61.8	61.5	-1	56.5	56.2	58.4	4	51.2	52.5	52.8	1
Men	62.4	62.5	63.2	1	68.0	67.7	67.4	0	61.3	61.6	64.1	4	57.6	57.9	58.2	0
Total	**59.3**	**59.7**	**60.4**	**1**	**65.0**	**64.9**	**64.6**	**0**	**58.8**	**58.9**	**61.4**	**4**	**54.4**	**55.2**	**55.5**	**1**

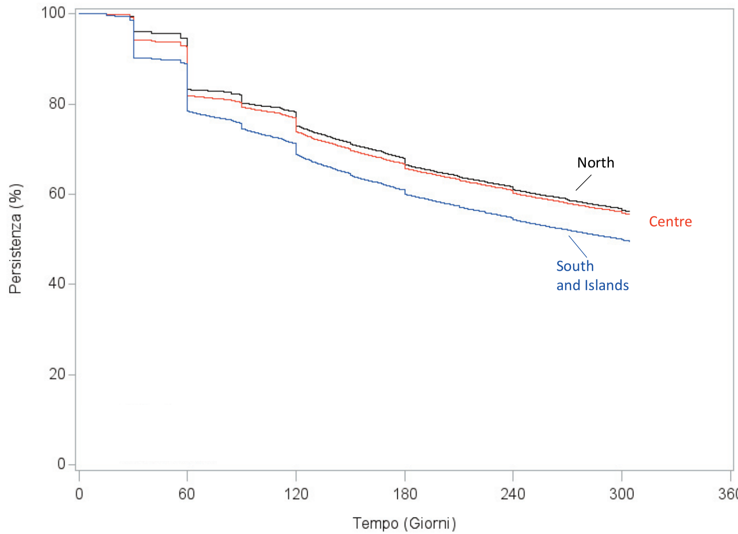
*Adherence to treatment was assessed during the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high 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, who received a first prescription in the period 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2019.
† Percentages of subjects with low/high adherence relating to the specific category.
Median follow-up time (IQR): 320 (259-344)

Table 3.5.3e Persistence after one year on treatment with platelet aggregation inhibitors in the population aged ≥ 45 years in the period 2019-2021 and variation 2021-2020

Persistence at 12 months	Total N=168,272				North N=62,293				Centre N=43,284				South N=62,695			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54	53.0	54.0	55.0	2	59.7	60.4	59.9	-1	53.2	51.8	54.9	6	47.7	49.9	50.9	2
55-64	53.6	54.7	55.8	2	59.5	60.5	60.2	0	53.5	53.9	58.0	8	48.9	50.4	50.6	0
65-74	52.6	52.8	54.1	2	56.5	56.7	56.6	0	52.6	52.3	56.9	9	49.5	49.9	49.9	0
75-84	49.9	49.5	49.9	1	53.2	52.1	51.8	-1	49.1	48.6	51.3	6	46.6	46.9	46.5	-1
≥85	46.7	47.2	47.1	0	49.6	50.4	48.2	-4	45.5	44.5	49.1	10	44.0	44.7	44.1	-2
Women	48.2	48.5	49.6	2	51.9	52.0	51.8	0	48.0	47.4	51.2	8	45.1	45.8	46.4	1
Men	54.5	54.9	55.9	2	58.6	58.6	58.6	0	54.0	53.8	58.2	8	50.9	51.8	51.5	-1
Total	**51.4**	**51.7**	**52.8**	**2**	**55.4**	**55.4**	**55.4**	**0**	**50.9**	**50.6**	**54.9**	**8**	**48.0**	**48.8**	**48.9**	**0**

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 3.5.3c Time (in days) to discontinuation of treatment with platelet aggregation inhibitors in the population aged ≥ 45 years stratified per year (2021-2020), the curves are adjusted for gender and age (the Cox model was used for estimating the persistence curves)



Key message

- **Consumption of platelet aggregation inhibitors** appears rather **stable** over the years considered (2014-2020), with 70.6 DDD/1000 inhabitants per day in 2021. However, compared to 2020, there is a minimum reduction in expenditure and consumption of acetylsalicylic acid alone or in combination (expenditure: -1.3%; consumption: -0.4%) and of ticagrelor (-4% for expenditure and consumption). However, the latter had recorded increases up to the previous year. Conversely, this minimum reduction is counterbalanced by a minimum increase in expenditure and consumption of other $P2Y_{12}$ platelet receptor inhibitors (expenditure: +0.2%; consumption: +3.7%).
- Despite the trend in the last year, **ticagrelor** is the platelet aggregation inhibitor with the greatest increase in expenditure (CAGR: +9.1%) and consumption (CAGR: +11.3%) in the 2014-2021 period. It is used in co-administration with acetylsalicylic acid in the prevention of atherothrombotic events following an acute coronary syndrome. Ticagrelor requires two daily administrations and has a higher cost than other medicines of the same class.
- The analysis on the consumption of platelet aggregation inhibitors indicates 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. Therefore, it can be assumed that among the measures chosen by prescribers to minimise the risk of bleeding there is the flexible use of dual therapy with the possibility of modulating the dose and the duration of treatment of the individual molecules. However, double aggregation inhibition provides for a defined period of therapy duration not exceeding 12 months. Therefore, it is also possible that the fixed combination is used for a fixed period and subsequently discontinued and that treatment is continued only with one platelet aggregation inhibitor in monotherapy as recommended, which would explain at least in part the difference in prescription between fixed or extemporaneous combinations of the two platelet aggregation inhibitors. In addition, in light of the recommendations for cardiovascular prevention in acute coronary syndrome, it is likely that extemporaneous combinations are preferred between low doses of acetylsalicylic acid (ASA) and the newest platelet aggregation inhibitors placed on the market, such as ticagrelor and pasugrel, of which fixed combinations are currently not available.
- Regional data show a **wide variability in consumption, expenditure and prevalence of use of platelet aggregation inhibitors**. In 2020, the Region with the highest consumption recorded a consumption twice as large as the Region with the lowest consumption (Molise: 93.4 DDD/1000 inhabitants per day vs Bolzano: 44.0 DDD/1000 inhabitants per day). As regards prevalence of use, the highest value was recorded in Molise (13.5%) and the lowest in Bolzano (5.1%). As already noted for anticoagulants, this variability is mainly due to the different prescriptive attitude of doctors rather than to a different prevalence of cardiovascular diseases in the various Regions. Although with sensitive geographical differences (North 64.9% and South and Islands 55.5%, respectively), the proportion of subjects with optimal adherence is around 60%. Unlike other therapeutic categories, **no significant reductions are observed with increasing**

age. In fact, in the over 85 years of age the proportion of subjects with high adherence remains stably above 50%. There is no supporting data, but it can be argued that this result is associated with good adherence to recommendations relating to secondary cardiovascular prevention.

- 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 their use in cardiovascular prevention.

References

- Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289-1367.
- Epicentro. Malattie cardiovascolari. Aggiornamenti. Available at https://www.epicen- tro.iss.it/cardiovascolare/aggiornamenti/ (last accessed 21.06.2021).
- Epicentro. Malattie cardiovascolari. Informazioni generali. Available at https://www. epicentro.iss.it/cardiovascolare/ (last accessed 21.06.2021).
- Galiè N, Humbert M, Vachiery J-L et al. ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016; 37(1): 67-119.
- Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-177.
- Osservatorio Ictus Italia. Rapporto sull'ictus in Italia 2018. Una fotografia su prevenzione, percorsi di cura e prospettive. https://www.epicentro.iss.it/cardiovascolare/2019/epicentro.iss.it/cardiovascolare/2019)
- Osservatorio Malattie Rare. Ipertensione polmonare cos'è. 25 Agosto 2010. https://www.osservatoriomalattierare.it/malattie-rare/ipertensione-polmonare/ https://www.osservatoriomalattierare.it/38-descrizioni/sezioni/102-che-cose-l-ipertensione-arteriosa-pol- monare/
- Regione Toscana. Ipertensione polmonare arteriosa idiopatica e raccomandazioni per la ges- tione delle altre forme di ipertensione polmonare. Scheda percorso diagnostico, terapeutico e assistenziale (PDTA) relativo a: ipertensione polmonare arteriosa idiopatica/RG0120. https://malattierare.toscana.it/static/media/uploads/PDTA/all19-dd-11505-2020_pdta_ipertensione_polmonare.pdf/
- Riassunto delle Caratteristiche del Prodotto. Cardioaspirin 100 mg. Made available by AIFA on 24/04/2021. https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_000022_024840_RCP.pdf&retry=0&sys=m0b1l3/
- Schulman S, Levi M. Antithrombotic therapy. In: Kaushansky K, Prchal JT, Burns LJ, Lichtman MA, Levi M, Linch DC. Williams Hematology, 10e ed. New York: McGraw-Hill, 2021.

3.6 Central Nervous System

In 2021, medicines acting on the central nervous system (CNS) rank sixth within the categories with the highest public expenditure, with 1,918.5 million euros, equal to 8.2% of total public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure was 32.21 euros, increasing by 2.3% compared to the previous year and mainly relating to NHS outpatient pharmaceutical care (23.97 euros per capita), with a slight increase compared to 2020 (+1.4%). The expenditure relating to the purchase by public health facilities is of lesser importance (8.23 euros per capita), however it recorded a +5.4% increase compared to the previous year (Table 3.1).

Analysing consumption under approved care regime, it is noteworthy that this category of drugs moves to fourth rank with 95.4 DDD/1000 inhabitants per day, a slight increase compared to the year 2020 (+1.2%); also in this case, the higher consumption is recorded in the context of the NHS ouptatient care with 68.9 DDD/1000 inhabitants per day, whereas purchasing by public facilities accounts for about one-third of the total (26.5 DDD) (Table 3.2). During 2014-2021, total consumption of CNS drugs increased by an average of 1.6 percent each year.

The analysis of the drug use profile by age group and gender in the context of local care (including approved care regime and per conto distribution) confirms the constant increase in the use of central nervous system drugs with increasing age, for both genders, with a higher prevalence of use in women from 25 years of age, consistent with epidemiological data on the frequency of neurological and psychiatric diseases. Men and women in the age group over 75 reach the highest level of prevalence (respectively 44.3% and 32.7%) and expenditure (respectively 79.03 and 61.10 euros per capita). In the age group 5-14 years, about one in 100 children receives at least one prescription of central nervous system drugs, mainly antidepressants, antipsychotics, and antiepileptics, during the course of a year.

As for NHS outpatient care, per capita expenditure for central nervous system drugs was 23.97 euros. The slight change in expenditure compared to 2020 was due to an increase in consumption (+0.6%), while both prices (-0.1%) and the mix effect (+0.1%) are stable, as is the average cost per day of therapy (Table 3.9). Analysing in detail the individual sub-categories, other antiepileptics, serotonin reuptake inhibitors (SSRIs) and other antidepressants have a greater impact on expenditure, with 4.77 euros, 3.39 euros and 3.26 euros respectively. However, in terms of consumption, SSRIs rank first with 30.0 DDD/1000 inhabitants per day and represent about half of the entire category, followed by other antidepressants with 11.7 DDD/1000 inhabitants per day (Table 3.9). All three sub-categories mentioned show increases compared to 2020 both in terms of expenditure and consumption and only SSRIs report a trend towards buying less expensive drugs (mix effect -0.3%) resulting in a slight decrease in the average cost per day of therapy for these drugs (-0.3%). Diazepines, oxazepines, thiazepines, and ossepines although with a per capita expenditure of 1.02 euros are the category that, together with oripavine derivatives, show a consistent increase in expenditure (+7.8%) and consumption (+4.5%) produced by a shift to more expensive drugs (mix effect: +3.2%).

Levetiracetam, fentanyl, and pregabalin are the molecules with the greatest impact on per capita spending in the category with 1.62, 1.34, and 1.30 euros per capita, respectively (Table 3.10), and are among the top 30 active ingredients with the highest spending in 2021 occupying the 18th, 28th, and 30th places, respectively (Tables 3.11 and 3.12). As many as 8 molecules (naloxone/oxycodone, tapentadol, fentanyl, rotigotine, lacosamide, quetiapine, levetiracetam, and pregabalin) are among the active ingredients with the highest cost per day of therapy (Table 3.13), while vortioxetine, lacosamide, and sertraline are among those with the greatest change in expenditure under approved care regime compared to 2020 (+12.1%, +11.5%, and +4.7%, respectively) (Table 3.14). Sertraline, recording the highest consumption and with 8.3 DDD/1000 inhabitants per day is also the only molecule in the category to fall within the first thirty most consumed active ingredients (Tables 3.16 and 3.17). Three molecules, rotigotine, naloxone/oxycodone and fentanyl, show the greatest variation in expenditure between 2020 and 2021 (Table 3.15).

As regards purchases by public health facilities, there was an increase by 4.6% in expenditure and, despite a reduction in consumption of 0.7%, a higher trend in using more expensive drugs is reported (mix effect +4.8%), resulting in an increase in prices of 0.5%, such factors led to 5.4% increase in the average cost per day of therapy compared to the previous year (Table 3.16). The sub-category of other antipsychotics records the largest share of expenditure (2.94 euros per capita), slightly increasing compared to 2020 (+2.8%), while diazepines, oxazepines, thiazepines and oxepines (3.5 DDD/1000 inhabitants per day) and the medicines used in opioid addiction (3.3 DDD/1000 inhabitants per day) are the highest consumption categories. Although both show a decrease in spending compared to 2020 (-15.0 % vs -8.4 %) and in average cost per day of therapy (-11.0 % vs -5.7 %). Other central nervous system drugs rank second in the category in terms of expenditure (0.83 euros): these drugs record a 51.7% expenditure increase determined by an increase in consumption (+13.5%) and mainly by greater use of more expensive drugs (mix effect +34.2% and average cost per DDD: +34.2%) compared to 2020 (Table 3.16). "Calcitonin gene-related peptide antagonists" are the drugs with the largest changes in spending, consumption and prices: +774.5%, +138.0% and +310.3% (Table 3.18). Erenumab and galcanezumab, anti-CGRP monoclonal antibodies and indicated for migraine, are the highest-spending molecules (0.16 and 0.10 euros per capita) in this category (Table 3.19).

The active substance with the highest incidence of expenditure (1.53%) is paliperidone with a unit cost per day of therapy of 5.10 euros (Table 3.19), which, however, is not among the highest in the category; in fact tafamidis and patisiran are the more expensive drugs in terms of average cost per DDD (respectively 516.03 and 226.37 euros).

No active ingredient belonging to this category of drugs is listed in the top 30 with the highest incidence of expenditure and highest average cost among drugs purchased by public facilities, nor in the top 30 with the greatest variation in expenditure compared to the previous year (Tables 3.18 and 3.20). Paracetamol, methadone, olanzapine, quetiapine and lidocaine, on the other hand, are among the 30 highest consumed molecules (Table 3.25).

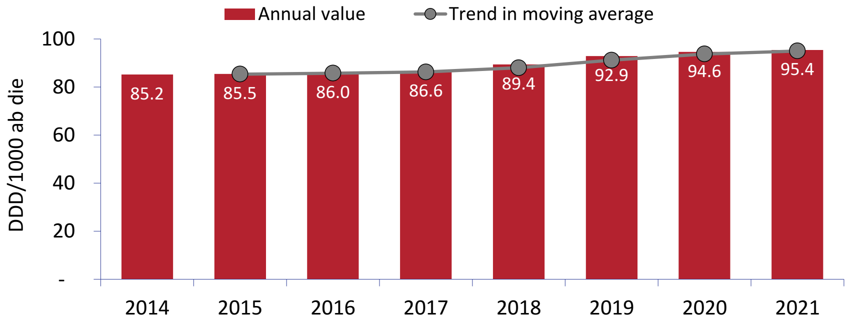
For further information on the use of medicines belonging to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region and on the efficiency in the absorption of resources according to the presence of off-patent medicines and on a regional basis. These analyses focused on medicines for multiple sclerosis, antidepressants, medicines for pain therapy, antiepileptics, antipsychotics, antiparkinsonian drugs, anti-migraines, anti-dementia drugs.

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

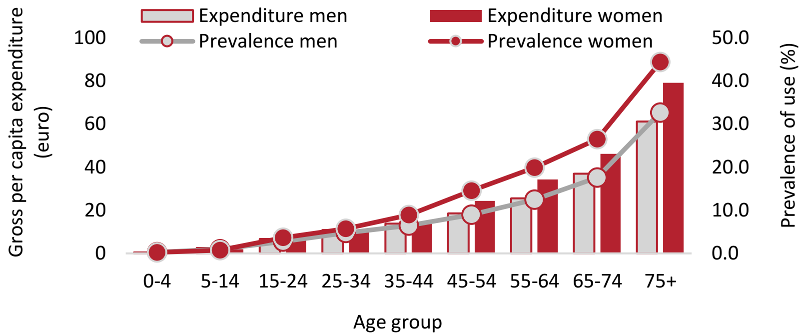
Central Nervous System

Public expenditure* in million euros (% over total)	**1,918.5**	**(8.2)**
Δ % 2021-2020		2.3
Regional range gross expenditure per capita:	28.2	38.5
DDD/1000 inhabitants per day* (% over total)	**95.4**	**(7.3)**
Δ % 2021-2020		1.2
Regional range DDD/1000 inhabitants per day	79.8	120.1

* *includes prescription under approved care regime and purchases from public health facilities*



Age and gender distribution of expenditure, prevalence of use, and consumption under approved care regime and distribution per conto 2021 (Figure and Table)



Age group	Gross per capita expenditure Men	Gross per capita expenditure Women	Gross per capita expenditure Total	DDD/1000 inhabitants per day Men	DDD/1000 inhabitants per day Women	DDD/1000 inhabitants per day Total
0-4	0.5	0.4	0.5	0.6	0.6	0.6
5-14	2.5	1.9	2.2	4.3	3.2	3.7
15-24	6.7	6.9	6.8	17.1	19.4	18.2
25-34	10.9	10.0	10.4	31.6	29.2	30.5
35-44	13.9	14.7	14.3	41.3	45.6	43.5
45-54	18.7	24.4	21.6	56.3	78.4	67.4
55-64	25.7	34.3	30.1	72.4	115.1	94.4
65-74	37.0	46.2	41.9	96.6	149.8	124.7
75+	61.2	79.2	71.9	164.9	236.1	207.4

3.6.1 Medicines for multiple sclerosis

Epidemiological framework

Multiple sclerosis (MS) is a neurodegenerative disease affecting the central nervous system described as an autoimmune demyelinating disease characterized by deterioration of the myelin sheath due to neuroinflammation. Multiple sclerosis can begin at any age in life, but it is most commonly diagnosed in young adults between the ages of 20 and 40 with nearly three times as many women as men affected. The disease appears to be characterized by a North-South gradient; in fact, it is more prevalent in areas far from the equator, such as northern Europe and the United States. There are about 2.8 million people with MS worldwide, including 1,200,000 in Europe and about 130,000 in Italy. According to a literature review in Italy there are many studies investigating the prevalence and incidence of MS cases but none with national representativeness. Prevalence estimates ranged widely from a minimum of 15.8 cases to a maximum of 197.8 cases per 100,000 population. Although quality of life and life expectancy have improved over the years there is still no drug therapy that can stop disease progression. However, several disease-modifying treatments are approved in Italy and are usually chosen according to the more or less severe forms of MS.

National data on consumption and expenditure

In recent years, consumption of medicines for multiple sclerosis has progressively increased with an average annual rate of 4.1%, shifting from 2.2 DDD/1000 inhabitants per day in 2014 to 2.9 DDD in 2021 (Figure 3.6.1a and Table 3.6.1a). The average cost per day of therapy has gradually increased over the past five years to reach 12.4 euros in 2021 partly explained by the introduction of monoclonal antibodies on the market. Immunosuppressive drugs account for about 70% of consumption of the entire category (2.0 DDD/1000 inhabitants per day) and this, despite the average cost per day of therapy being the lowest among other sub-categories, has an impact on per capita expenditure, which is more than a third of the entire category (4.07 out of 12.91 euros), with an increasing trend of 11.3% compared to previous year and in the 2014-2021 period (CAGR 36.0%). Monoclonal antibodies also have a significant impact on per capita expenditure (3.53 euros), and this is mainly due by a high average cost per day of therapy (49.96 euros) in the face of low levels of consumption (0.2 DDD/1000 inhabitants per day). Also fingolimod is reported to have a high per capita expenditure of 2.32 euros and low consumption (0.1 DDD) with an average cost per DDD of 53.90 euros. The only two sub-categories having decreased in terms of expenditure and consumption over the years are interferons and glatiramer; however, the level of spending on interferons can be explained by both a higher level of consumption and a cost per day of therapy that is 50 percent higher than that of glatiramer. In contrast, the categories with the largest increases in both spending and consumption are monoclonal antibodies and immunosuppressants (Table 3.6.1a). Analysing the active ingredients individually, methotrexate is reportedly the most used drug (1.4 DDD/1000 inhabitants per day equal to 50% of the entire category), but with a relatively low impact on per capita expenditure due to the average cost per day of therapy, which is the lowest in the category (1.37 euros) for patent expiration for several years. In addition to fingolimod, the most expensive drugs in terms of day of therapy are cladribine (49.43 euros) and monoclonal antibodies, including natalizumab (50.03 euros) and ocrelizumab (48.32 euros) more recently commercialized (since 2018) and whose spending is increasing compared to 2020 (+40.2%). The last two drugs, that record a similar level of spending, are mainly used as disease modifying in second-line treatment in the most advanced stages of the disease or in case of therapeutic failures with other first-line drugs, such as glatiramer in the relapsing and remitting forms and fingolimod in the highly active and in serious forms with rapid evolution.

In the Northern and Central areas, consumption of multiple sclerosis drugs is similar and in line with the national figure and rather stable compared to the previous year, while the Southern regions show higher consumption (3.1 DDD/1000 inhabitants per day) and costs in terms of both per capita expenditure and average cost per DDD (Table 3.6.1b). At the regional level, the highest consumption, in line with evidence in literature on the prevalence of condition, was observed in Sardinia (5.3 DDD), stable from the previous year (+1.7%) and with an average annual change of 2.9% between 2014 and 2021. In contrast, Valle d'Aosta is the region where the lowest consumption (2.4 DDD) is detected, less than half that of Sardinia. Consumption increases in almost all regions; while it decreases in Marche in Lazio and Basilicata. Molise (+12.4% of DDDs and +28.1% of spending) and Friuli Venezia Giulia (+5.6% DDDs and +10.9% of spending) are the regions noting the largest changes from 2020. Molise is also the region with the highest per capita expenditure (27.19 euros), determined by a high cost per day of therapy (22.45 euros) in the face, however, of consumption levels that are slightly higher than the national average (3.3 DDD/1000 inhabitants per day) and similar to those of the Province of Trento (3.4 DDD), which records a 60% lower average expenditure and cost per day of therapy.

Figura 3.6.1a Medicines for multiple sclerosis, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

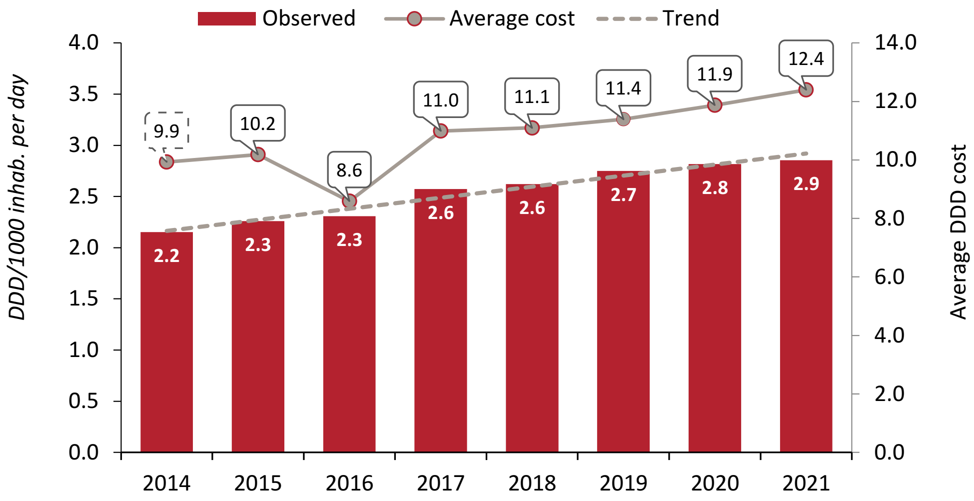


Table 3.6.1a. Medicines for multiple sclerosis, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Immunosuppressants	4.07	11.3	36.0	2.0	1.9	8.0	5.63	9.5
Monoclonal antibodies	3.53	18.3	16.9	0.2	27.3	19.2	49.96	-6.8
Fingolimod (modulator of the SP1 receptor)	2.32	-3.3	5.5	0.1	-1.4	7.5	53.90	-1.6
Interferons	1.69	-10.0	-9.7	0.4	-10.8	-9.8	12.56	1.2
Pyrimidine synthesis inhibitors	1.02	10.3	82.0	0.1	11.3	82.7	27.15	-0.7
Glatiramer	0.29	-26.9	-17.4	0.1	-5.1	-3.2	8.66	-22.8
Medicines for multiple sclerosis	**12.91**	**5.6**	**7.5**	**2.9**	**1.4**	**4.1**	**12.40**	**4.4**
dimethyl fumarate	2.64	6.2	-	0.2	6.4	-	32.87	0.1
fingolimod	2.32	-3.3	5.5	0.1	-1.4	7.5	53.90	-1.6
natalizumab	1.74	2.9	5.7	0.1	16.3	7.8	50.03	-11.3
ocrelizumab	1.73	40.2	-	0.1	40.3	-	48.32	0.1
interferon beta 1a	1.22	-10.8	-12.4	0.3	-11.0	-10.7	10.63	0.6
teriflunomide	1.02	10.3	82.0	0.1	11.3	82.7	27.15	-0.7
methotrexate	0.70	2.0	10.2	1.4	1.7	9.0	1.37	0.6
cladribine	0.59	55.6	-	0.0	60.6	-	48.43	-2.9
pegylated interferon beta 1a	0.39	-5.0	-	0.0	-4.7	-	29.71	0.0
glatiramer	0.29	-26.9	-17.4	0.1	-5.1	-3.2	8.66	-22.8

Table 3.6.1b Medicines for multiple sclerosis, regional trend of per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	12.93	2.9	12.39	13.32	2.9	12.75	3.0	0.3	2.9	8.1	4.6	3.3
Valle d'Aosta	11.79	2.3	13.76	11.54	2.4	13.38	-2.1	1.0	-2.8	7.2	3.6	3.5
Lombardy	8.60	2.6	9.17	9.11	2.6	9.54	5.9	2.1	4.0	7.9	4.0	3.7
Province of Bolzano	12.52	3.6	9.53	14.20	3.7	10.58	13.5	2.5	11.0	7.7	3.3	4.3
Province of Trento	10.08	3.4	8.15	10.95	3.4	8.70	8.6	2.0	6.8	7.6	4.9	2.6
Veneto	12.23	2.8	11.92	12.93	2.8	12.55	5.7	0.7	5.3	9.7	4.0	5.5
Friuli VG	12.04	3.5	9.41	13.36	3.7	9.90	10.9	5.6	5.3	6.7	2.5	4.1
Liguria	12.38	2.6	13.19	13.01	2.6	13.87	5.0	0.1	5.2	8.6	4.1	4.4
Emilia R.	10.60	2.4	11.94	11.69	2.5	12.70	10.3	4.0	6.4	9.6	4.7	4.7
Tuscany	11.49	2.5	12.55	11.88	2.5	12.95	3.4	0.5	3.2	7.2	4.5	2.6
Umbria	11.86	2.9	11.15	12.80	2.9	11.92	7.9	1.2	7.0	7.7	3.2	4.4
Marche	11.98	2.7	12.04	12.28	2.7	12.50	2.5	-1.0	3.8	5.9	2.7	3.1
Lazio	12.59	2.6	13.16	12.58	2.6	13.35	-0.1	-1.2	1.5	6.3	3.9	2.2
Abruzzo	17.03	3.1	14.92	18.18	3.1	15.85	6.7	0.8	6.2	8.3	4.8	3.4
Molise	21.23	3.0	19.64	27.19	3.3	22.45	28.1	12.4	14.3	18.9	7.9	10.3
Campania	12.65	2.6	13.23	13.24	2.6	13.75	4.7	1.0	4.0	7.1	4.4	2.6
Puglia	13.47	3.2	11.57	14.42	3.2	12.22	7.1	1.7	5.6	5.9	3.7	2.1
Basilicata	13.90	3.1	12.39	13.42	3.0	12.31	-3.5	-2.5	-0.7	7.5	4.9	2.5
Calabria	12.75	2.9	11.99	13.14	2.9	12.35	3.1	0.4	3.0	9.4	4.7	4.5
Sicily	13.01	2.9	12.17	14.05	3.0	12.83	8.0	2.7	5.4	6.6	4.7	1.8
Sardinia	25.14	5.2	13.25	26.89	5.3	13.98	7.0	1.7	5.5	4.7	2.9	1.8
Italy	**12.23**	**2.8**	**11.87**	**12.91**	**2.9**	**12.40**	**5.6**	**1.4**	**4.4**	**7.5**	**4.1**	**3.2**
North	10.75	2.7	10.86	11.44	2.8	11.37	6.4	1.9	4.7	8.5	4.1	4.2
Centro	12.10	2.6	12.65	12.33	2.6	12.99	1.9	-0.5	2.7	6.6	3.9	2.7
South and Islands	14.44	3.1	12.73	15.39	3.1	13.38	6.5	1.7	5.1	6.9	4.2	2.6

General data on expenditure and consumption by ATC group

This section aims to analyse the trend of public pharmaceutical expenditure, including gross NHS expenditure under approved care regime and the cost of medicines purchased directly by public health facilities, by ATC 1st level, by therapeutic category and by active ingredient. In 2021, the NHS pharmaceutical expenditure, expressed as a per capita value, was 396.81 euros, with a 2.8% decrease compared to the previous year (Table 3.1). This trend was mainly determined by the increase in expenditure for public health facilities (233.53 euros; +4.8%), while the expenditure on class A drugs under approved care regime remained almost stable (163.28 euros; +0.2%).

Overall, the most significant increase in NHS expenditure was due to dermatological drugs (+32.2%) and sensory organs drugs (+11.8%), whose per capita values were respectively 3.35 and 6.74 euros. On the contrary, the most marked reduction was recorded for systemic hormonal preparations excluding sex hormones (-7.6%) and for antimicrobials for systemic use (-5.5%). Within the categories with the greatest expenditure, the increase is noteworthy for drugs of the gastrointestinal tract (+7.2%) and for antineoplastics and immunomodulators (+4.5%), which have constantly increased over the last four years (Figure 3.1).

With regard to consumption (Table 3.2), cardiovascular drugs represent the highest number of doses consumed (503.6 DDD/1000 inhabitants per day), stable compared to the previous year, and account for approximately 38.5% of all DDD consumed. These are followed by drugs acting on the gastrointestinal system and metabolism (318.3 DDD/1000 inhabitants per day; up 10.1%; Figure 3.2), on blood and blood forming organs (140.2 DDD/1000 inhabitants per day; +2.6%) and on the central nervous system (95.4 DDD/1000 inhabitants per day; +1.2%).

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 6.1 billion, an incidence of 20.2% on total pharmaceutical expenditure and a per capita value of 111.98 euros. As expected for this category, the largest share of expenditure (94.8%) refers to purchases by public health facilities. Gastrointestinal drugs account for 13.5% of total expenditure and represent, in absolute values, the most privately purchased category in the case of both class A drugs (305 million euros) and self-medication drugs (647 million euros). Medicines acting on the central nervous system have the highest absolute expenditure value of class C drugs sold upon prescription (1.01 billion euros) and in fact represent 34.2% of the total expenditure in this reimbursement range. As for purchases by public health facilities, 43.8% (equal to 5.8 billion euros) refers to antineoplastics and immunomodulators; as for class A drugs, 28.8% relates to cardiovascular drugs, for a total expenditure of 2.9 billion euros.

The most consumed privately purchased class A drugs (Table 3.4) are cardiovascular system drugs (32.8 DDD/1000 inhabitants per day), while drugs acting on the nervous system are the most used within class C drugs with prescription (64.2 DDD/1000 inhabitants per day); gastrointestinal drugs rank first for consumption within self-medication drugs (31.4 DDD/1000 inhabitants per day). Blood and blood-forming organs drugs (50.6 DDD) show the highest consumption within public health facilities, while cardiovascular drugs are the most used in class A, with 486.9 DDD (48.0% of the total).

3.6.2 Antidepressants

Epidemiological framework

Depression is one of the leading causes of disability worldwide and one of the conditions that most impacts an individual's health and quality of life, as well as the health system. In fact, depression increases social and health care costs, personal suffering, psychosocial disability, and the risk of associated comorbidities and mortality. There are an estimated 3 million depressed people in Italy, including major depression and other types of depressive disorders. The epidemiological surveillance "Passi" showed that about 6% of adults between 18 and 69 years old reported depressive symptoms and perceived impairment in their psychological well-being. These symptoms are more frequent as age advances (about 8% among 50-69 year olds), in the female population (8% compared to 5% of men), among the socially disadvantaged classes due to economic hardship, and among those who report at least one diagnosis of a chronic condition (13%).

Although many effective treatments are available to date, depressive disorders are often underestimated and under-recognized, partly because of the accompanying stigma that results in poor patient referral for help, and partly because of a relative lack of training, time, and tools to enable rapid diagnosis. There are many possible therapeutic strategies that can be used, and a flexible approach in the treatment scheme is considered desirable, considering the marked inter-individual variation in efficacy and safety of various therapies. The initiation of antidepressant therapy usually assumes an evaluation of therapeutic efficacy after about 2-3 weeks of treatment. Depending on the response, a change in therapy may be necessary, due to reduced tolerance shown by the patient or lack of efficacy (in which case 1-2 additional weeks may be required). If the therapy is effective, it should instead be continued at full dose for a period of about 6 to 9 months, followed by a maintenance phase between 12 and 36 months. Despite this, numerous studies have shown that a small proportion of subjects are on continuous and appropriate treatment with these drugs, and only about 40% of newly treated subjects are characterized by a treatment duration of more than 3 months. All this has an impact on the effectiveness of drug treatments, resulting in increased complications in the treated population and increased spending on the NHS.

In this OsMed Report, antidepressant drugs were classified into four groups:

1. first-generation antidepressants or in combination (amitriptyline/chlordiazepoxide, perphenazine/amitriptyline, amitriptyline, clomipramine, dosulepine, maprotiline, nortrip- tiline, trimipramine);
2. SSRI antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline);
3. SNRI antidepressants (duloxetine, venlafaxine);
4. all others (agomelatine, bupropion, St. John's Wort dry extract, mianserin, mirtazapine, oxitriptan, reboxetine, vortioxetine, trazodone).

National data on consumption and expenditure

In 2021, daily consumption of antidepressants was 44.6 DDD per 1,000 inhabitants, up 2.4% over the previous year and with an average annual change of 1.9% since 2014. annual increase of 1.9% since 2014. The average cost per DDD in 2021 was 0.42 euros, which has remained stable since 2016 after the patent expiration of important active ingredients, such as escitalopram (2014), duloxetine (2015) (Figure 3.6.2a).

In 2021, consumption of antidepressants was 3.4% of the total consumption of drugs in Italy, with a 2.4% increase compared to 2020. Similarly, per capita expenditure shows a 2.6% increase, reaching 6.87 euros per capita in 2021 (Table 3.6.2a). SSRIs account for 70% (31.2 DDD) of consumption and 50% (3.40 euros per capita) of expenditure of the entire category. Both indicators show a 1.4% increase compared to 2020; greater variations are present, albeit with much lower levels of use, for other antidepressants (DDD: +4.8%, expenditure: +5.4%). This trend was mainly determined by vortioxetine (+12% for both indicators), a drug marketed in 2016 and indicated in the treatment of major depressive episodes in adults, which, while showing an effect on the cognitive system of elderly people, does not seem to show a superiority over other antidepressants. It should be highlighted that the cost per day of therapy with this drug is almost three times higher than the category average (1.13 vs 0.42 euro) (Table 3.6.2a). Paroxetine, with 1.02 euro per capita, stable compared to 2020, confirms as the most expensive molecule, while sertraline is the most consumed (9.3 DDD up 4.3% and average annual change of +3.6% compared to 2014). Bupropion records the highest average cost per DDD in the face, however, of more limited levels of consumption and per capita spending; it should be noted that this drug is also indicated as a treatment for smoking cessation.

Central regions have a level of use (50.4 DDD) about 10% higher than the North (46.9 DDD) and 33% higher than the South (37.7 DDD) (Table 3.6.2b). Confirming this, Tuscany is the Italian region with the highest use of antidepressant drugs, standing at 66 DDD/1000 inhabitants per day in 2021, a value almost double that of Campania and Basilicata (about 35 DDD), as also noted in 2020. All regions note increases in spending and consumption over the previous year, particularly Friuli Venezia Giulia (+8.6% and +7.3% respectively) even though it is the region that uses fewer antidepressants and at a lower cost than the national average. For antidepressants, limited regional variability is observed for the average cost per day of therapy. Marche and Sardinia are the regions with higher consumption and cost per day of therapy than the national average.

Figura 3.6.2a Antidepressants, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

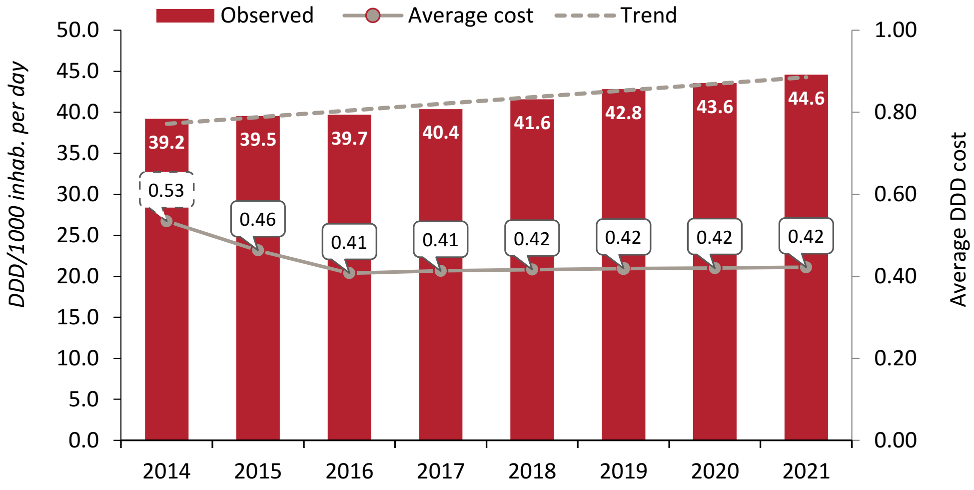


Tabella 3.6.2a Antidepressants, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
SSRI antidepressants	3.40	1.5	-2.7	31.2	1.9	0.9	0.30	0.0
Other antidepressants	1.71	5.4	11.4	5.3	4.8	9.8	0.88	0.8
SNRI antidepressants	1.60	2.0	-6.4	7.1	2.9	2.1	0.62	-0.7
Fisrt-generation antidepressants plain or in combination	0.16	1.1	-2.3	1.0	1.2	-1.5	0.42	0.2
Antidepressants	**6.87**	**2.6**	**-1.5**	**44.6**	**2.4**	**1.9**	**0.42**	**0.5**
paroxetine	1.02	0.5	-2.6	8.2	0.5	0.2	0.34	0.3
escitalopram	0.97	1.3	-6.4	7.7	2.0	0.9	0.34	-0.4
venlafaxine	0.80	1.0	0.9	3.8	2.1	1.3	0.58	-0.8
sertraline	0.80	4.7	3.2	9.3	4.3	3.6	0.24	0.6
duloxetine	0.80	3.0	-10.9	3.3	4.0	3.1	0.66	-0.7
vortioxetine	0.73	12.2	-	1.8	12.5	-	1.13	0.0
trazodone	0.44	1.1	6.0	1.3	0.9	6.8	0.92	0.5
citalopram	0.40	-1.3	-2.4	4.1	-1.4	-2.1	0.27	0.3
mirtazapine	0.35	1.6	2.3	1.9	1.4	2.8	0.51	0.4
bupropione	0.18	-0.9	-0.7	0.3	2.7	1.3	1.70	-3.3

Table 3.6.2b Antidepressants, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	7.17	49.2	0.40	7.32	50.4	0.40	2.2	2.5	0.0	-2.8	1.9	-4.5
Valle d'Aosta	6.40	42.1	0.41	6.60	43.6	0.41	3.2	3.4	0.0	-2.6	1.7	-4.2
Lombardy	6.08	40.7	0.41	6.30	42.3	0.41	3.7	3.9	0.1	-1.7	2.1	-3.7
Province of Bolzano	8.51	56.1	0.41	8.66	57.1	0.42	1.8	1.7	0.3	-2.6	1.3	-3.9
Province of Trento	6.49	43.2	0.41	6.72	45.1	0.41	3.5	4.3	-0.5	-0.6	2.4	-3.0
Veneto	6.29	42.2	0.41	6.45	43.1	0.41	2.6	1.9	0.9	-1.5	2.1	-3.5
Friuli VG	5.05	35.3	0.39	5.48	37.8	0.40	8.6	7.3	1.5	-2.6	1.5	-4.1
Liguria	8.86	57.9	0.42	8.99	58.7	0.42	1.4	1.4	0.2	-1.7	1.4	-3.0
Emilia R.	7.10	53.6	0.36	7.42	55.1	0.37	4.4	2.7	1.9	-1.2	1.4	-2.6
Tuscany	9.29	65.2	0.39	9.42	66.3	0.39	1.4	1.7	0.0	-1.1	1.3	-2.3
Umbria	8.21	57.1	0.39	8.31	57.6	0.40	1.3	0.9	0.7	-1.4	1.9	-3.2
Marche	7.39	45.6	0.44	7.56	46.7	0.44	2.4	2.5	0.2	-1.0	1.8	-2.7
Lazio	6.45	38.7	0.45	6.57	39.5	0.46	1.8	2.0	0.1	-1.7	2.0	-3.6
Abruzzo	7.35	42.9	0.47	7.53	43.6	0.47	2.5	1.8	1.0	0.0	2.5	-2.4
Molise	6.10	36.8	0.45	6.23	37.5	0.45	2.1	1.9	0.5	-1.9	1.8	-3.6
Campania	5.86	34.2	0.47	6.02	35.1	0.47	2.7	2.6	0.4	-0.4	2.6	-2.9
Puglia	5.84	35.2	0.45	5.94	35.8	0.45	1.7	1.4	0.5	-1.5	2.2	-3.6
Basilicata	5.65	34.1	0.45	5.84	34.9	0.46	3.4	2.4	1.2	-0.6	2.0	-2.5
Calabria	6.86	41.3	0.45	6.91	41.4	0.46	0.9	0.3	0.8	-1.3	1.8	-3.1
Sicily	6.00	35.2	0.47	6.09	35.7	0.47	1.6	1.3	0.5	-1.2	2.2	-3.3
Sardinia	7.59	47.1	0.44	7.81	48.2	0.44	3.0	2.4	0.9	-2.4	1.4	-3.7
Italy	**6.70**	**43.6**	**0.42**	**6.87**	**44.6**	**0.42**	**2.6**	**2.4**	**0.5**	**-1.5**	**1.9**	**-3.3**
North	6.63	45.5	0.40	6.85	46.9	0.40	3.3	3.0	0.6	-1.9	1.8	-3.6
Centre	7.62	49.5	0.42	7.74	50.4	0.42	1.7	1.8	0.1	-1.4	1.6	-2.9
South and Islands	6.23	37.0	0.46	6.36	37.7	0.46	2.1	1.7	0.6	-1.1	2.2	-3.2

Exposure and adherence in population

Health Card data allowed to describe the trend in prevalence and consumption by age class, gender and region and to calculate some indicators of intensity of use. Moreover, adherence and persistence was also estimated of chronic treatments with antidepressants.

Around 7% of the Italian population used antidepressant drugs in 2021: while in Tuscany and Liguria this percentage reaches 10%, in Campania the prevalence drops to 5.5%. In Southern Regions, the prevalence is reduced to 5.9% compared to 7.8% in the Center and 6.8% in the North (Table 3.6.c). As expected, consumption increases in relation to age, reaching a prevalence of 27.5% in women over the age of 85. The difference between genders persists in all age groups, with consumption levels that, in women, are more than double than men from the age of 45 years (Figure 3.6.2b).

Half of the users are over 67 years of age with no particular regional differences and each subject remains on treatment for 8 months on average, although half use antidepressant drugs for less than 6 months and one in ten receive only one prescription (12.2%), indicating how often these drugs are prescribed for clinical conditions unrelated to depressive pathology but which could be t.reated with non-pharmacological approaches (Table 3.6.2c) The average cost per user is 100 euros with slight differences between regions, with a minimum of 92.6 in Emilia Romagna and a maximum of 113.9 euros in the Province of Bolzano.

The study on adherence and persistence to treatment was conducted on a cohort of 119,871 new users of antidepressant drugs, 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), women account for about 67 percent of the total, and more than a third (37%) are over 75 years old.

In 2021 the percentage of subjects with high and low adherence to antidepressant treatment was respectively 38.5% and 27.0%, while the former increased by 3%, the proportion of low adherence decreased by 2% compared to 2020. In particular, the percentages of high adherence decrease with age, moving from 43.4% in subjects aged between 45 and 54 years to 24.4% in the over 85, and by geographical area with a maximum of 39.9% in the North and minimum of 37% in the Southern Regions, despite a median age of the subjects included in the study 2 years lower than the median of the other geographical areas. Men have a higher percentage of subjects with high adherence than women (40.0% vs 37.7%), while in women the percentage of low adherence approaches 27.2%. Compared with 2020, there is a 4% increase in high adherence in women and a 3% increase in men. For the low adherence indicator, there are differences between geographical areas, ranging from 26.5% in the North to 27.9% in the South, with a gradient by age with a maximum value of about 46% in the 85+ age group (Table 3.6.2d).

Taking into account the persistence to treatment at 12 months (calculated on new users with at least two antidepressant prescriptions and considering an interruption of at least 60 days) only one in three subjects (33.1%) remained persistent, there were no marked differences in gender and between geographical areas. Also confirmed in 2021 is a reduction in persistence with increasing age, shifting from 36.1% of the 45-54 age group up to 26.0% of subjects with at least 85 years. This gradient is found in every geographical area, even if the percentage variation is less marked for the South and the Islands (Δ% =-7.2%) compared to the North (Δ% =-11.1%) (Table 3.6.2e).

Considering the median time to discontinuation of antidepressant treatment, a 50% probability of discontinuing treatment is achieved at approximately 143 days, higher than the figure observed in 2020 (134 days) and with values in different geographical areas ranging from 149 days in the North, to 145 days in the Center and 133 days in the South and Islands (Figure 3.6.2e).

Figure 3.6.2b Distribution of prevalence of use and consumption of antidepressants under NHS outpatient care and per conto distribution (year 2021)

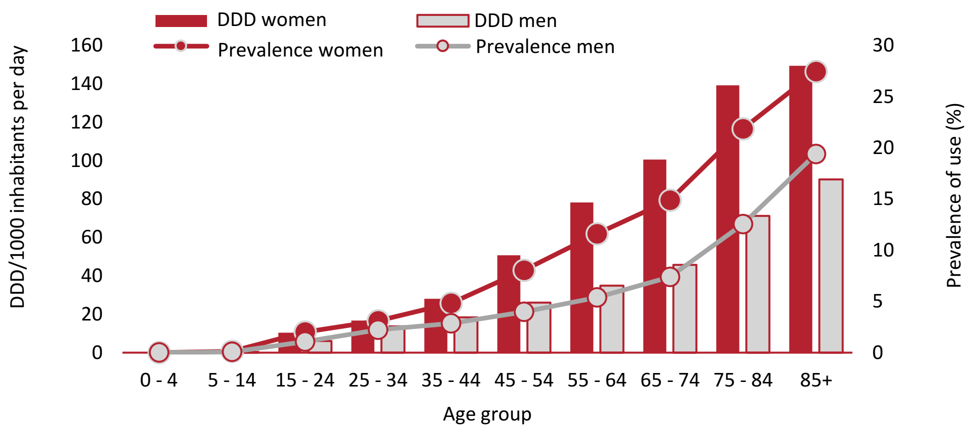


Tabella 3.6.2c Exposure and duration of therapy with antidepressants by Region under NHS outpatient care and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	5.2	10.8	8.1	68	93.5	225.6	180.0	10.9
Valle d'Aosta	4.3	9.3	6.8	69	95.2	214.3	170.0	10.4
Lombardy	4.0	8.5	6.3	66	97.7	236.0	196.0	9.5
Province of Bolzano	4.6	9.1	6.9	67	113.9	251.6	210.0	10.6
Province of Trento	3.9	8.4	6.2	65	101.7	238.3	180.0	10.4
Veneto	3.9	8.3	6.2	67	102.1	235.9	180.0	11.3
Friuli VG	3.5	8.2	5.9	67	95.5	217.4	180.0	10.0
Liguria	6.3	13.5	10.0	71	95.1	214.4	172.6	12.6
Emilia R.	4.8	10.3	7.6	68	92.6	225.0	180.0	10.9
Tuscany	6.5	13.8	10.3	69	93.7	231.2	180.0	14.0
Umbria	5.4	11.9	8.7	70	96.5	225.2	196.0	12.2
Marche	5.0	10.0	7.6	68	101.6	224.7	180.0	11.1
Lazio	4.1	8.4	6.3	66	101.8	221.6	180.0	11.4
Abruzzo	4.6	9.5	7.1	66	107.1	225.2	180.0	13.4
Molise	4.2	8.4	6.3	67	103.7	227.4	180.0	11.0
Campania	3.7	7.1	5.5	65	101.5	215.5	168.0	14.2
Puglia	3.9	7.5	5.8	66	100.5	218.5	168.0	13.0
Basilicata	4.0	7.9	6.0	66	98.3	213.3	168.0	13.8
Calabria	4.7	8.9	6.8	66	98.5	214.3	168.0	14.9
Sicily	3.9	7.7	5.9	67	100.8	214.0	168.0	14.9
Sardinia	4.2	10.1	7.2	66	111.7	249.8	224.0	11.1
Italy	**4.3**	**9.0**	**6.7**	**67**	**100.6**	**230.5**	**180.0**	**12.2**
North	4.3	9.2	6.8	67	98.6	234.4	180.0	10.8
Centre	5.0	10.4	7.8	68	99.8	230.3	180.0	12.7
South and Islands	3.9	7.8	5.9	66	104.0	223.7	174.0	14.0

Table 3.6.2d Indicators of adherence to treatment with antidepressants in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

	Total N=119.871				North N=56.062				Centre N=27.790				South N=36.019			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*^																
45-54 years	22.3	21.9	22.3	2	21.1	20.5	21.6	5	21.8	22.1	21.8	-2	24.4	23.8	23.7	0
55-64 years	22.1	22.2	22.0	-1	20.3	21.3	20.7	-3	22.1	22.1	22.2	0	24.6	23.6	23.5	0
65-74 years	24.3	24.6	23.7	-4	22.5	23.3	22.6	-3	24.6	23.9	23.3	-3	26.6	26.7	25.4	-5
75-84 years	29.5	30.4	30.5	0	28.3	29.6	30.3	2	29.2	29.9	29.0	-3	31.9	32.3	32.3	0
≥85 years	43.2	44.6	45.6	2	42.7	45.5	45.6	0	43.5	43.4	47.0	8	43.8	44.2	44.3	0
Women	27.6	28.0	27.2	-3	26.5	27.5	26.9	-2	27.7	27.5	26.8	-2	29.1	29.3	28.1	-4
Men	26.4	26.9	26.5	-1	24.8	25.8	25.6	-1	26.6	27.4	26.9	-2	28.5	28.0	27.6	-1
Total	**27.2**	**27.6**	**27.0**	**-2**	**26.0**	**27.0**	**26.5**	**-2**	**27.3**	**27.4**	**26.9**	**-2**	**28.9**	**28.9**	**27.9**	**-3**
High adherence*^																
45-54 years	42.2	42.6	43.4	2	44.0	45.1	44.6	-1	42.0	40.9	42.5	4	39.3	39.8	42.1	6
55-64 years	42.1	41.6	42.7	3	44.1	44.1	45.1	2	42.2	39.6	41.9	6	39.5	39.5	40.1	1
65-74 years	39.4	39.3	40.6	3	41.5	41.0	42.5	4	39.5	39.2	40.1	2	36.4	37.1	38.4	4
75-84 years	34.8	34.3	34.8	1	36.3	35.8	36.0	1	35.3	34.6	34.6	0	31.7	31.6	32.6	3
≥85 years	25.8	25.0	24.4	-3	26.6	25.2	25.1	0	25.5	25.2	22.6	-11	24.7	24.4	24.8	1
Women	36.5	36.4	37.7	4	37.8	38.0	39.0	3	36.6	35.7	36.6	2	34.5	34.4	36.5	6
Men	39.7	39.0	40.0	3	42.0	40.7	41.5	2	39.3	38.0	39.7	4	36.6	37.1	37.9	2
Total	**37.6**	**37.2**	**38.5**	**3**	**39.2**	**38.9**	**39.9**	**2**	**37.5**	**36.5**	**37.6**	**3**	**35.2**	**35.3**	**37.0**	**5**

*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, who received a first prescription in the period 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.
Percentages of people with low/high adherence relating to the specific category.
Median follow-up time (IQR): 306 (189-341)

Table 3.6.2e Persistence at 1 year with treatment with antidepressantsin the population aged ≥45 years during 2019-2021 and 2021-2020 change

Persistence after 12 months	Total N=119.871				North N=56.062				Centre N=27.790				South N=36.019			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54 years	34.5	35.6	36.1	1	36.7	37.2	37.1	0	33.4	34.7	36.2	4	32.1	33.9	34.5	2
55-64 years	33.7	33.9	34.9	3	35.7	35.9	36.7	2	33.2	32.8	35.0	7	31.3	32.0	32.3	1
65-74 years	32.7	32.4	33.7	4	33.7	33.3	34.7	4	33.1	33.0	34.5	5	31.2	30.8	31.6	3
75-84 years	31.3	31.1	31.6	2	32.1	31.5	32.0	1	30.8	31.5	32.6	3	30.4	29.9	30.3	1
≥85 years	26.9	26.2	26.0	-1	27.8	25.5	26.0	2	25.5	27.2	24.7	-9	26.5	26.3	27.3	4
Women	31.9	32.1	32.9	3	32.8	32.7	33.4	2	31.3	32.4	33.2	3	30.8	30.9	31.9	3
Men	32.8	32.4	33.5	4	34.8	33.9	35.0	3	32.1	31.5	33.7	7	30.3	30.7	31.1	1
Total	**32.2**	**32.2**	**33.1**	**3**	**33.5**	**33.1**	**33.9**	**3**	**31.6**	**32.1**	**33.4**	**4**	**30.6**	**30.9**	**31.7**	**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).

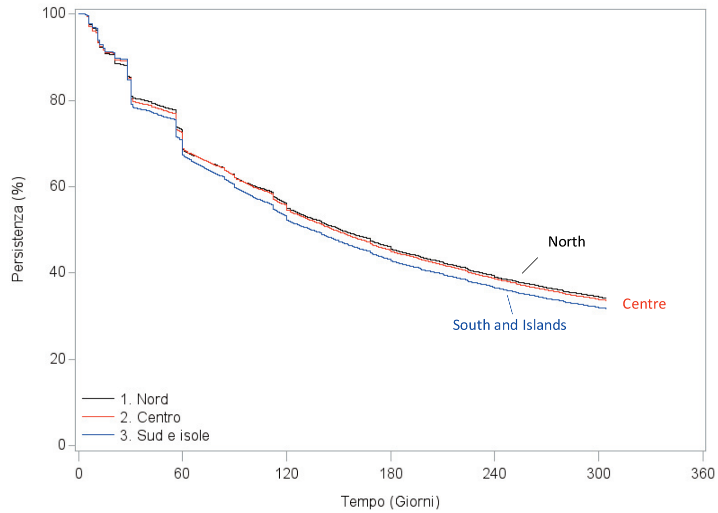


Figure 3.6.2c Time (in days) to discontinuation of treatment with antidepressants in the population aged ≥45 years stratified by geographical area. Curves are adjusted by gender and age (the Cox model was used to estimate persistence curves)

Epidemiology and prescribing profiles in General Medicine

The data relating to epidemiology and prescribing profiles were obtained through a network of GPs homogeneously distributed throughout the national territory bringing together all information relating to diagnosis of pathology, demographic information, pharmaceutical prescription, and more to Health Search-IQVIA Health LPD.

Analyses focused on the prevalence and incidence of depression in the years 2019, 2020, and 2021, as well as the prevalence of use of individual classes of antidepressant drugs in patients with the condition in the same years.

With regard to the incidence of depression in the population in the care of the 800 GPs in the HS network, 6.7 new cases of depression per 1,000 patients emerge in 2021; an increasing estimate (6.4 %) from the 2020 figure. Geographically, regions in Central Italy are characterized by a higher estimated incidence (7.3%), compared with those in the North (6.5%) and South and Islands (6.4%). Stratifying the analysis by sex, women appear to be characterized by a higher incidence of disease in 2021, with an estimated incidence about twice as high as that which emerged for men (9.0% vs. 4.4%). Moreover, if for men there is a decreasing trend in the incidence estimate between 2019 and 2020, which is also maintained for 2021, for women there is a growth in the incidence figure for the latter year. The analysis by age group showed an increase in prevalence with increasing age, with the peak in patients aged ≥85 years (14.4%) (Table 3.6.2f).

The prevalence of depression was 13.3% in 2021, an increase of 2.9% from 2020. Central Italian regions, although with slight differences from other geographical areas, show the highest prevalence estimate (13.6%) (Table 3.6.2g). As expected, women are found to have a higher estimated prevalence of depression than men (17.7% vs. 8.8%). In addition, an increasing trend in disease prevalence is observed as age increases, reaching the highest prevalence value in individuals 85 years of age and older (25.2%). In contrast, the percentage change between 2021 and 2020 is greatest in the younger age groups, and then tapers off as age increases.

About one in three patients diagnosed with depression are treated pharmacologically (30.9%) in 2021, a reduction of 0.3% from 2020. Furthermore, prevalence of use tends to be higher in the Central regions (34.9%), compared to Northern (32.3%) and Southern and insular (27.2%) regions and in women vs men (33.5% vs 25.6%). This prevalence also shows an increasing trend as age increases, rising from 36.1% in the 66-74 age group to 46.2% of the oldest individuals (≥85 years of age) (Table 3.6.2h).

Analyzing the prevalence of use by therapeutic category in 2021 (Table 3.6.2i) it is noted that SSRIs are the most widely used (23.6%), followed by SNRIs and other antidepressants (6.1%, each) and, finally, by first-generation antidepressants alone or in combination (2.4%). Analyzing the prevalences of use over the three-year period (2019-2021), there is a decreasing trend in estimates for first-generation antidepressants alone or in combination and for SSRIs. In contrast, for the category of SNRIs and other antidepressants a decrease in prevalence of use estimates emerges for 2020 (compared to 2019); however, estimates tend to increase again in 2021.

Table 3.6.2f Incidence of patients with depression in the population eligible for medical assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographical area (years 2019-2021)

	Incidence (‰)			Δ %
	2019	2020	2021	21-20
Geographic analysis				
North	6.6	5.9	6.5	10.0
Centre	9.2	7.8	7.3	-5.5
South and Islands	6.9	6.0	6.4	7.1
Analysis by gender				
Men	5.0	4.5	4.4	-1.1
Women	9.5	8.2	9.0	9.7
Analysis by age				
≥45 years	3.9	3.2	3.6	12.6
46-65	7.1	6.2	6.7	9.1
66-74	9.2	8.7	9.2	5.6
75-84	13.5	13.4	13.8	3.4
≥85 years	13.6	13.9	14.4	4.0
Total	**7.2**	**6.3**	**6.7**	**6.4**

Indicators used:

Incidence of depression: number of patients with a "first" diagnosis of depression recorded during the year [**numerator**], on the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Table 3.6.2g Incidence of patients with depression in the population eligible for medical assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographical area (years 2019-2021)

	Prevalence (%)			Δ %
	2019	2020	2021	21-20
Geographic analysis				
North	12.8	12.8	13.2	2.9
Centre	13.1	13.2	13.6	3.2
South and Islands	13.0	13.0	13.3	2.7
Analysis by gender				
Men	8.4	8.5	8.8	3.7
Women	17.2	17.2	17.7	3.0
Analysis by age				
≥45 years	5.5	5.5	5.9	7.2
46-65	14.3	14.6	15.3	4.9
66-74	18.1	18.6	19.2	3.0
75-84	20.5	21.3	22.3	4.9
≥85 years	23.9	24.4	25.2	3.4
Total	**12.9**	**12.9**	**13.3**	**2.9**

Indicators used:

Prevalence of depression: number of patients diagnosed with depression [**numerator**], on the total population eligible for assistance [**denominator**]

Tabella 3.6.2h Prevalence of use of antidepressants in subjects with depression and comparison 2021-2020: stratified analysis by gender, age group and geographic area (years 2019-2021)

	Prevalence of use (%)			Δ %
	2019	2020	2021	21-20
Geographic analysis				
North	32.9	32.2	32.3	0.3
Centre	35.8	35.3	34.9	-1.1
South and Islands	28.3	27.3	27.2	-0.4
Analysis by gender				
Men	26.7	25.9	25.6	-1.2
Women	34.1	33.4	33.5	0.3
Analysis by age				
≥45 years	18.3	17.2	16.8	-2.3
46-65	28.0	26.1	26.0	-0.4
66-74	37.3	35.0	36.1	3.1
75-84	46.3	43.7	45.6	4.3
≥85 years	45.2	45.0	46.2	2.7
Total	**31.8**	**31.0**	**30.9**	**-0.3**

Indicator used:

Prevalence of use of antidepressants: number of patients treated with antidepressants [**numerator**] on the total number of patients diagnosed with depression [**denominator**]

Table 3.6.2i Prevalence of use of antidepressants in subjects affected by depression and comparison 2021-2020: analysis by therapeutic category (years 2019-2021)

Analysis by therapeutic category	Prevalence of use (%)			Δ %
	2019	2020	2021	21-20
1st generation antidepressants, plain or in combination	2.6	2.5	2.4	-4.0
SNRI	6.3	6.0	6.1	1.7
SSRI	24.4	23.8	23.6	-0.8
Other antidepressants	5.9	5.9	6.1	3.4
Total	**31.8**	**31.0**	**30.9**	**-0.3**

Indicator used:

Prevalence of use of single classes of antidepressants: number of patients treated with antidepressants selected by therapeutic class [**numerator**] on the total number of patients diagnosed with depression [**denominator**]

Key message

- The **increase in the use of antidepressants** in 2021 is in line with the trend recorded in previous years and seems not to have been affected by the ongoing pandemic. Actually, the phenomenon appears more complex considering that, despite a national increase by 1.7%, there are **significant regional and macro-area differences**. This could be due to the combination of several 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 a possible different role of general practice in different areas of the country during the pandemic.

- The data on **exposure and adherence to treatment** in the population show the great level of inadequacy of these drugs compared with their under-use, if considering the indicators on the frequency of the disease. 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 drugs than conducting RCTs on very selected populations over a short period of time.**

References

- Bellón JÁ, Conejo-Cerón S, Moreno-Peral et al. Preventing the onset of major depression based on the level and profile of risk of primary care attendees: protocol of a cluster randomised trial (the predictD-CCRT study). BMC Psychiatry 2013; 13: 171.
- De Crescenzo F, Garriga C, Tomlinson A et al. Real-world effect of antidepressants for depressive disorder in primary care: protocol of a population-based cohort study. Evid Based Ment Health. 2020 Aug;23(3):122-126.
- Degli Esposti L, Piccinni C, Sangiorgi D et al. Patterns of antidepressant use in Italy: therapy dura- tion, adherence and switching. Clin Drug Investig 2015; 35(11):735-42.
- Global Burden of Disease. 2017 Disease and Injury Incidence and Prevalence Collaborators Global, regional, and national incidence, prevalence, and years lived with disability for 354 dis- eases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.
- Marengoni A, Onder G, Degli Esposti L et al. Adherence to selective serotonin and serotonin-nor- epinephrine reuptake inhibitor prescriptions affects overall medication adherence in older per- sons: evidence from the Italian Nationwide OsMed Health-DB Database. J Clin Psychiatry 2016; 77(12):1712-8.
- National Institute for Health and Care Excellence (NICE). Depression in adults: recognition and management. Clinical guideline [CG90]. Published date: 28 October 2009. Available at the address https://www.nice.org.uk/guidance/cg90
- Sorveglianza Passi. Sintomi depressivi nella popolazione adulta: prevalenze e caratteristiche socio-demografiche (Dati nazionali 2013).
- Taylor DM, Barnes RET, Young AH. The Maudsley prescribing guidelines in psychiatry. 13th edition. Hoboken, NJ: Wiley Blackwell 2018.
- Thornicroft G, Chatterji S, Evans-Lacko S et al. Undertreatment of people with major depressive disorder in 21 countries. Br J Psychiatry 2017; 210:119-24.

3.6.3 Medicines for pain therapy

(Includes pregabalin and gabapentin prescription for all authorized indications)

Epidemiological framework

Pain is a frequently occurring component in most diseases, so pain control assumes paramount importance in the clinical management of patients. In clinical pain syndromes, pain is often brought about by a combination of both inflammatory and neuropathic mechanisms. Painful manifestations can have negative consequences on various physiological functions, including autonomic hyperresponsiveness (increased blood pressure, heart rate, suppression of gastrointestinal motility, reduced secretions) and reduced mobility, leading to muscle atrophy, joint stiffening, and decalcification, all of which can also alter the subject's psychological state causing anxiety and depression. According to WHO, pain caused by tumors, occurs in 55% of patients undergoing cancer treatment, and particularly in 66% of patients in an advanced, metastatic or terminal state of the disease. Pain management, which allows an acceptable level of quality of life, becomes a major goal in these patients, especially if the disease is advanced. Chronic non-neoplastic pain is also a steadily increasing health problem, especially in wealthy countries, with significant social and economic costs. However, at present there are no epidemiological surveys available to define its true extent. A survey conducted in Europe in the early 2000s by telephone interviewing 46,000 people in 15 countries provided estimates of data on prevalence, severity, treatment modalities and impact of chronic pain. The survey found that about one-fifth (19%) of the European adult population suffers from chronic pain, and Italy ranks high with a prevalence of 26%, after Norway (30%) and Poland (27%). Epidemiological data regarding the practice of pain therapy in Italy are still poor, and to address this critical issue during 2017-2018, the Ministry of Health promoted several strategies, including a study with the aim of conducting a prevalence analysis of chronic pain pathology on a national and regional scale, associated with the health needs of the population studied (Ministry of Health, 2019). Of note in this context are the recent WHO guidelines on the treatment of chronic pain in children and the U.S. Centers for Disease Control and Prevention (CDC) guidelines, which contain recommendations urging general practitioners and specialists to limit opioid prescriptions in the treatment of chronic pain (not derived from cancer and not related to palliative care and end-of-life therapies).

National data on consumption and expenditure

The use of drugs for pain therapy has progressively increased over the years with an 1.7% average annual variation (CAGR), moving from 6.9 DDD/1000 inhabitants per day in 2014 to 7.7 DDD in 2021 (Figure 3.6.3a). The average cost per day of therapy instead has decreased of 10% since 2014 until it stabilized at 2.37 euros between 2018 and 2021. Major opioids plain or in combination are the sub-category accounting for about 65% of the expenditure of the entire category with 4.39 euros per capita and 35% of consumption, both indicators have slightly decreased since 2020. The most widely used drugs are those for neuropathic pain (up 6.5% compared to 2020), which, however, record a cost per day of therapy 3 times lower than opioids, which explains the lower per capita expenditure (1.66 euros) (Table 3.6.3a). On the other hand, minor opioids plain or in combination are the sub-category recording the greatest contractions both in terms of expenditure and consumption (-3,6% and -3,1% respectively) compared to 2020. Moreover, it is the category with the lowest average cost per DDD (0.92 euros). Analysing in detail the individual active ingredients, fentanyl, tapentadol and pregabalin, respectively with 1.39, 1.31 and 1.26 euros per capita, are the drugs with the greatest impact on expenditure; this is due, for fentanyl and tapentadol, to the high costs per day of therapy (respectively 4.95 and 6.12 euros), while for pregabalin to the high levels of consumption (2.6 DDD/1000 inhabitants per day). For other molecules, it is worth mentioning the year-on-year decrease for tramadol (-3.1%) and the combination of naloxone/oxycodone (-2.5%) while buprenorphine shows an increase of 10.3%. It should be mentioned that this molecule is also used as a maintenance treatment within the activities of drug addiction services (Table 3.6.3a)

At the macro-area level, consumption tends to increase from North to South, with the latter having the lowest levels of consumption (6.0 DDD), about 25% lower than the national average; in contrast, the Northern Regions have a 15% higher level of consumption (Table 3.6.3b). In the details of individual regions, the highest levels of consumption are found in Valle d'Aosta (10.3 DDD) and Friuli Venezia Giulia (9.6 DDD). These two regions, with positions reversed, are also those with the highest per capita spending (Friuli: 9.57 euros; Val d'Aosta: 8.40 euros). In contrast, Calabria, with 5.2 DDD, is the region with the lowest consumption nationwide. Overall, a clear variability in consumption compared to 2020 emerges, ranging from a decrease of 4.6% in Friuli Venezia Giulia to an increase of 12.1% in Calabria; there are smaller differences for expenditure and average DDD costs. For the latter indicator, however, it should be noted that Emilia Romagna has a value of 1.76 euros, 35% lower than that of Sardinia (2.76 euros).

Figure 3.6.3a Pain therapy, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

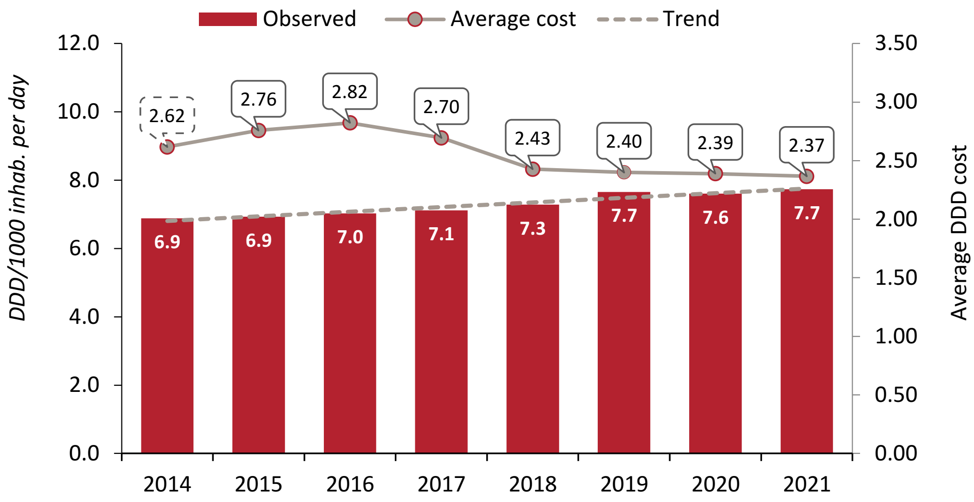


Table 3.6.3a Pain therapy, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Major opioids alone or in combination	4.39	-0.4	4.7	2.7	-0.7	2.8	4.49	0.5
Medications for neuropathic pain	1.66	4.9	-5.8	3.1	6.5	5.3	1.44	-1.3
Minor opioid alone or in combination	0.64	-3.6	-4.4	1.9	-2.1	-3.7	0.92	-1.3
Pain therapy	**6.68**	**0.5**	**0.2**	**7.7**	**1.7**	**1.7**	**2.37**	**-0.9**
fentanyl	1.39	-0.3	2.9	0.8	-3.4	1.8	4.95	3.5
pregabalin	1.31	5.6	-7.1	2.6	7.5	6.3	1.38	-1.5
tapentadol	1.26	1.8	11.8	0.6	3.9	12.1	6.12	-1.8
naloxone/oxycodone	0.90	-6.0	3.6	0.4	-2.5	5.7	6.17	-3.3
gabapentin	0.35	2.1	1.3	0.6	2.1	1.6	1.72	0.3
paracetamol/codeine	0.31	-1.7	-5.8	1.2	-1.7	-4.7	0.73	0.3
buprenorphine	0.29	17.7	10.8	0.2	10.3	4.7	4.29	7.0
paracetamol/oxycodone	0.25	-2.5	0.0	0.3	0.2	0.4	2.08	-2.5
tramadol	0.25	-6.1	-4.6	0.6	-3.1	-3.5	1.12	-2.9
oxycodone	0.15	-3.8	-3.4	0.1	-2.5	-0.9	3.02	-1.1

Table 3.6.3b Pain therapy, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	7.48	9.3	2.20	7.49	9.3	2.20	0.1	0.3	0.1	-0.8	1.3	-2.1
Valle d'Aosta	8.27	10.0	2.25	8.40	10.3	2.24	1.5	2.4	-0.6	-2.0	1.2	-3.2
Lombardy	8.34	8.8	2.58	8.37	8.9	2.57	0.4	1.3	-0.6	0.9	2.1	-1.2
Province of Bolzano	6.61	7.8	2.32	6.58	7.9	2.28	-0.5	1.5	-1.7	0.3	1.4	-1.1
Province of Trento	6.49	8.2	2.16	7.03	8.4	2.30	8.3	2.1	6.4	2.7	2.2	0.5
Veneto	6.40	7.7	2.27	6.38	7.7	2.27	-0.3	-0.2	0.2	0.4	1.5	-1.1
Friuli VG	10.15	10.0	2.76	9.57	9.6	2.74	-5.8	-4.6	-1.0	1.8	0.5	1.3
Liguria	7.55	9.2	2.24	7.80	9.5	2.24	3.2	3.6	-0.1	0.6	1.8	-1.2
Emilia R.	6.03	9.0	1.83	6.09	9.5	1.76	1.0	5.4	-3.9	-0.1	1.4	-1.5
Tuscany	6.22	8.6	1.99	6.21	8.7	1.94	-0.3	2.2	-2.1	-2.0	-0.7	-1.3
Umbria	6.31	8.0	2.15	6.33	8.1	2.15	0.3	0.8	-0.2	-0.4	3.0	-3.3
Marche	5.60	6.5	2.35	5.44	6.6	2.26	-2.9	1.0	-3.6	-1.1	0.4	-1.5
Lazio	6.51	7.4	2.42	6.58	7.6	2.38	1.1	3.0	-1.6	-0.3	2.5	-2.7
Abruzzo	6.22	6.1	2.77	6.24	6.2	2.75	0.3	1.1	-0.5	2.2	2.0	0.2
Molise	6.09	5.4	3.10	5.92	5.4	2.98	-2.7	1.3	-3.7	2.1	1.8	0.3
Campania	4.69	5.1	2.53	4.85	5.3	2.52	3.5	4.3	-0.5	-0.5	2.6	-3.0
Puglia	6.50	6.5	2.73	6.51	6.6	2.71	0.2	1.4	-0.9	1.5	2.3	-0.7
Basilicata	4.82	5.6	2.33	5.05	6.3	2.18	4.8	12.1	-6.3	1.3	3.4	-2.0
Calabria	5.07	5.2	2.64	5.06	5.2	2.64	-0.1	0.2	0.0	0.0	1.4	-1.5
Sicily	5.62	5.7	2.67	5.61	5.7	2.69	-0.1	-0.7	0.9	0.0	1.7	-1.7
Sardinia	7.85	7.8	2.75	8.16	8.1	2.76	3.9	4.0	0.2	2.0	2.6	-0.6
Italy	**6.65**	**7.6**	**2.39**	**6.68**	**7.7**	**2.37**	**0.5**	**1.7**	**-0.9**	**0.2**	**1.7**	**-1.4**
North	7.46	8.8	2.32	7.48	8.9	2.30	0.2	1.4	-0.9	0.4	1.6	-1.2
Centre	6.28	7.7	2.23	6.29	7.9	2.19	0.1	2.3	-1.9	-1.0	1.1	-2.0
South and Islands	5.71	5.9	2.66	5.78	6.0	2.65	1.4	2.1	-0.4	0.7	2.2	-1.5

Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to medicinìes used for pain therapy in the general population.

Exposure data indicate a prevalence of use that progressively increases with advancing age, reaching the highest values in the age group over 85s (Figure 3.6.3b). Advancing age also highlights gender differences both in terms of prevalence and consumption, in fact a higher prevalence can be noted in women which almost exceeds men by five percentage points, especially in the extreme age groups. In particular, in the over 85s age group, one in 4 women has received at least one prescription, while this percentage drops in men to 17.7%. A similar argument can be made in terms of consumption where significant differences appear in the 65-74 age group, reaching a difference of 50% in those over 85 years old (33.8 DDDs in women versus 22.0 DDDs in men). In detail, Tuscany is the Region with the highest level of prevalence (6.8%), whilAt the national level the prevalence of use is 5.3%, in detail Tuscany and Piedmont are the regions with the highest level of prevalence with 6.8%, while the Province of Bolzano records the lowest level (3.6%). Prevalence data do not show marked differences between macroareas with the Center recording the highest percentages, compared also to the national average (5.6% vs. 5.3%), while the South 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, and each prevalent user received at least one dose of medication per day for about 1.5 months of therapy with a cost per user of 121 euros with wide differences between regions (from a low of 86.8 in Basilicata to 175.5 euros in Friuli Venezia Giulia). In detail, Northern Regions have an average annual coverage that is approximately 26 days higher than Central and Southern Regions. Analysing the DDD indicator by user, however, 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) indicates that half of the users have been treated for less than two weeks. In addition, about one-third of subjects (34.5%) received only one prescription during the year, with Southern Regions reporting the highest levels of sporadic users (38.4%), and among these, Calabria is the Region with the highest percentage (39.5%) of sporadic users whereas Val d'Aosta has the lowest share at 25.7% (Table 3.6.3c).

Figure 3.6.3b Distribution of prevalence of use and consumption of medicines for pain therapy under NHS outpatient care and per conto distribution (year 2021)

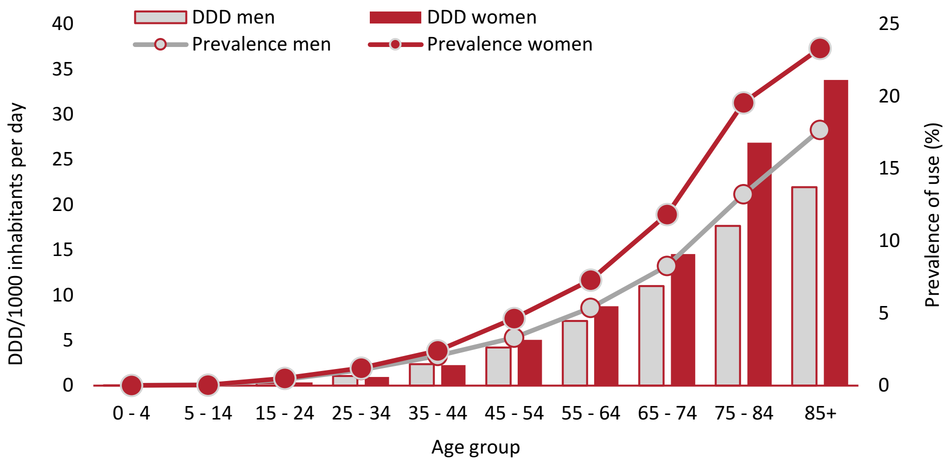


Table 3.6.3c Exposure and duration of medicines for pain therapy by Region under NHS outpatient care and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average median	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	5.4	8.2	6.8	70	110.6	45.6	10.7	33.4
Valle d'Aosta	4.4	6.6	5.5	71	146.9	56.0	15.0	25.7
Lombardy	4.0	6.3	5.1	71	156.2	56.3	15.0	29.7
Province of Bolzano	2.8	4.3	3.6	74	160.3	58.1	15.3	29.4
Province of Trento	4.1	6.4	5.3	70	123.7	47.8	10.7	31.9
Veneto	3.0	5.0	4.0	73	152.3	57.7	14.4	32.7
Friuli VG	4.2	6.8	5.5	72	175.5	57.9	15.0	26.9
Liguria	5.2	8.2	6.7	73	119.5	46.8	13.3	32.0
Emilia R.	4.5	7.2	5.9	70	96.0	44.5	10.7	34.7
Tuscany	5.1	8.3	6.8	72	89.0	40.6	10.7	37.5
Umbria	4.4	7.1	5.8	72	111.0	45.9	11.3	31.8
Marche	4.1	6.4	5.3	71	102.0	42.5	10.7	37.4
Lazio	3.8	6.3	5.1	70	124.8	49.4	14.0	29.6
Abruzzo	3.7	6.0	4.9	70	124.1	43.7	10.7	37.8
Molise	3.6	5.9	4.8	71	129.7	42.0	10.7	37.1
Campania	3.6	6.0	4.9	68	93.5	35.6	10.7	39.2
Puglia	4.7	7.5	6.1	70	103.0	37.0	10.7	39.0
Basilicata	4.4	7.2	5.8	70	86.8	36.1	10.7	37.9
Calabria	3.8	5.9	4.8	71	96.2	37.1	10.7	39.5
Sicily	3.6	5.7	4.7	71	115.4	41.7	10.7	37.1
Sardinia	4.1	6.7	5.4	70	154.6	52.8	14.0	32.3
Italy	**4.1**	6.5	**5.3**	**71**	**121.3**	**46.8**	**11.7**	**34.5**
North	4.1	6.5	5.3	71	135.2	52.1	14.0	32.1
Centre	4.3	6.9	5.6	71	108.8	45.6	11.7	34.0
South and Islands	3.9	6.2	5.1	70	109.1	39.8	10.7	38.4

Key message

- The combination of a decrease in the consumption of minor opioids and marked regional variability in the consumption of major opioids denotes, on the one hand, a focus on prescribing these drugs for the treatment of chronic pain alone, and on the other hand, how there is an urgent need to ensure access to palliative care and pain therapy in all territories in accordance with Law No. 38 of March 15, 2010.
- 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 drugs with the usual tools of training, residential 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.**

References

- Associazione Italiana di Oncologia Medica. Linee Guida AIOM 2018 nella terapia del dolore in oncologia. Available at the address https://www.aiom.it/wp-content/uploads/2020/10/2020_ LG_AIOM_Terapia_dolore.pdf
- Brunton LL et al., eds. Goodman & Gilman's manual of pharmacology and therapeutics. 2nd edition. New York: McGraw-Hill, 2014.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. MMWR Recomm Rep 2016; 65(No. RR-1):1-49. Available at the address https:// www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm
- Ministry of Health Direzione Generale della Programmazione Sanitaria. Disposizioni per garantire l'accesso alle cure palliative e alla terapia del dolore, 2020. Rapporto al Parlamento sullo stato di attuazione della Legge n. 38 del 15 marzo 2010. Years 2015-2017. Available at https://www.salute.gov.it/imgs/C_17_pubblicazioni_2814_allegato.pdf
- Vadalouca A, Alexopoulou-Vrachnou E, Rekatsina M, et al. The Greek Neuropathic Pain Registry: The structure and objectives of the sole NPR in Greece. Pain Pract. 2022 Jan;22(1):47-56.
- World Health Organization. Guidelines on the management of chronic pain in children. Geneva: World Health Organization, 2020. Available at the address https://extranet.who.int/iris/restricted/bitstream/handle/10665/337999/9789240017870-eng.pdf?sequence=1&isAllowed=y
- World Health Organization. WHO guidelines for the pharmacological and radiotherapeutic man- agement of cancer pain in adults and adolescents. Geneva: World Health Organization, 2018. Licence: CC BY-NC-SA 3.0 IGO.
- Yaksh T and Wallace M. Opioids, analgesia, and pain management. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's manual of pharmacology and therapeutics. 13th edition. New York: McGraw-Hill, 2017.

3.6.4 Anti-epileptics

(it does not include pregabalin and gabapentin prescription)

Epidemiological framework

According to the International League Against Epilepsy (ILAE), epilepsy is a disease "characterized by a persistent predisposition to develop seizures and by the neurobiological, cognitive, psychological, and social consequences of the condition. The definition of epilepsy requires the occurrence of at least one seizure." It is a chronic neurological disorder characterized by the occurrence of seizures, defined as clinical manifestations with paroxysmal occurrence, unpredictable recurrence in most cases, of very short duration, characterized by signs and/or symptoms due to abnormal neuronal activity. Syndromes often have age-dependent characteristics: age of onset and possibly remission, seizure triggers, circadian variations, and sometimes prognosis. Epidemiologically, it is estimated that in Italy about 500,000 people are affected by epilepsy and 30,000 are the new cases per year, with higher incidence in children and the elderly. About 6 million people in Europe have active phase epilepsy (i.e., with seizures that are persistent and/or still being treated). The prevalence of epilepsy in most developed countries ranges from 0.5 to 1% of the population, with peaks of higher incidence in children and the elderly. In three-quarters of cases, onset is before the age of 20; in one-quarter, seizures may be frequent and resistant to treatment.

National data on consumption and expenditure

In 2021, the consumption of antiepileptics stood at 10.8 DDD/1000 inhabitants per day, with an increase of 0.7% compared to the previous year, while an even greater increase was recorded for expenditure (+3.5%), equal to a value of 5.34 euros per capita (Table 3.6.4a). Since 2014 there has been an average annual increase of 1.2% in terms of consumption and 4.3% in terms of spending. At the same time, the average cost per day of therapy has shown steady growth from €1.11 in 2014 to €1.37 in 2021 (+23%) (Figure 3.6.4a).

Second generation antiepileptics are, with 2.81 euros per capita, the category with the highest expenditure, down 0.4% from 2020; these medicines represent more than half of the expenditure of antiepileptics (Tabelle 3.6.4.a). Second generation antiepileptics are the category most used in the population (5.7 DDD) even if they record a 2.5% contraction compared to 2020; third-generation antiepileptics, on the other hand, show an increase in consumption and spending (+15.1% and +14.1% respectively). Second generation antiepileptics are more tolerable and safe in women of childbearing age and the elderly, while third generation antiepileptics are mainly used in combined therapies. Cannabidiol records the highest expenditure in the category: €0.03 per capita and an average cost per DDD of €47.47. The drug was marketed in 2021 as an adjunctive therapy for seizures associated with complex tuberous sclerosis (TSC) and for the treatment of Dravet syndrome (DS) and Lennox-Gasteaux syndrome (LGS), in combination with clobazam, in patients of 2 years of age and older.

Levetiracetam and valproic acid, both with 2.6 DDD, are confirmed as the most used molecules with no significant changes from 2020. A similar trend is observed for lacosamide and perampanel showing increases in consumption of more than 13% (Table 3.6.4a). These new generation drugs 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.

Analyzing regional variability it is noted that there is a greater use of these drugs in South-Central areas. The regions with the highest consumption are Calabria (12.5 DDD), Umbria (12.3 DDD) and Abruzzo (12.2 DDD), while the three with the lowest are Valle d'Aosta, Lombardy and Veneto (Table 3.6.4b). Tuscany has the largest changes in spending (+28.3%), consumption (+7.9%) and average cost per DDD (+19.2%), compared to 2020. Compared to 2014, there is an average annual increase for all regions in both spending and consumption (with the exception of Valle d'Aosta).

Figure 3.6.4a Antiepileptics, temporal trend of consumption and average cost per day of therapy (2014-2021)

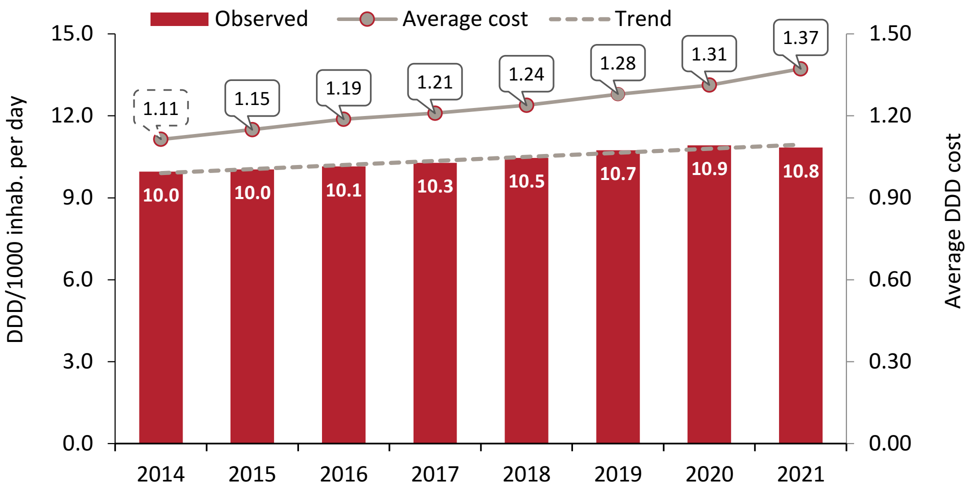


Table 3.6.4a Antiepileptics, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Second-generation antiepileptics	2.81	-0.4	2.3	4.6	-0.4	3.6	1.69	0.3
Fisrt-generation antiepileptics	1.41	1.5	1.0	5.7	-2.5	-1.4	0.68	4.4
Third-generation antiepileptics	1.19	14.1	19.7	0.6	15.1	22.7	5.18	-0.6
Cannabidiol	0.03	-	-	0.0	-	-	47.47	-
Antiepileptic medicines	**5.43**	**3.5**	**4.3**	**10.8**	**-0.7**	**1.2**	**1.37**	**4.6**
levetiracetam	1.77	-0.3	4.1	2.6	0.0	5.9	1.85	0.0
valproic acid	1.02	1.6	1.8	2.6	-0.3	1.2	1.09	2.2
lacosamide	0.86	13.5	17.9	0.4	13.1	18.4	5.54	0.6
lamotrigin	0.46	-0.4	3.7	0.8	1.7	4.9	1.52	-1.8
topiramate	0.30	1.5	-1.0	0.4	-3.4	-0.6	2.26	5.3
carbamazepine	0.25	-0.3	-1.1	1.2	-2.6	-1.7	0.55	2.6
oxcarbazepine	0.18	-3.0	-3.6	0.6	-2.9	-2.1	0.82	0.1
perampanel	0.13	11.3	-	0.1	13.3	-	5.24	-1.4
brivaracetam	0.09	37.4	-	0.1	36.1	-	2.93	1.2
clonazepam	0.07	3.2	0.4	0.4	2.7	0.3	0.45	0.7

Table 3.6.4b Antiepileptic medicines, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	5.21	10.8	1.32	5.35	10.6	1.38	2.7	-1.6	4.7	4.4	1.3	3.0
Valle d'Aosta	4.21	9.3	1.24	4.46	9.0	1.36	6.1	-2.7	9.3	4.8	-0.5	5.4
Lombardy	4.82	8.8	1.49	4.87	8.7	1.53	1.0	-1.5	2.8	4.7	1.1	3.5
Province of Bolzano	5.54	10.3	1.47	5.76	10.0	1.59	4.1	-3.1	7.8	2.7	1.0	1.7
Province of Trento	5.11	10.9	1.29	5.30	10.6	1.37	3.7	-2.5	6.7	4.1	-0.1	4.2
Veneto	4.75	9.8	1.32	5.08	9.9	1.41	6.9	0.1	7.1	5.0	0.9	4.0
Friuli VG	5.13	10.5	1.33	5.20	10.1	1.41	1.3	-3.9	5.6	5.4	1.0	4.4
Liguria	5.05	11.1	1.24	5.36	11.1	1.33	6.1	-0.4	6.8	4.0	0.9	3.1
Emilia R.	3.36	10.2	0.90	3.72	10.4	0.98	10.7	1.2	9.7	2.6	0.8	1.9
Tuscany	3.36	11.2	0.82	4.32	12.0	0.98	28.3	7.9	19.2	4.4	1.2	3.2
Umbria	5.41	12.5	1.18	5.56	12.3	1.24	2.7	-2.2	5.3	5.6	1.0	4.6
Marche	5.99	11.9	1.37	6.30	12.0	1.44	5.2	0.2	5.3	4.5	0.7	3.8
Lazio	5.89	11.6	1.39	6.06	11.5	1.44	2.9	-0.7	3.9	4.4	1.5	2.9
Abruzzo	6.55	12.4	1.45	6.66	12.2	1.49	1.7	-1.1	3.1	3.3	0.9	2.3
Molise	5.14	11.2	1.25	5.44	11.4	1.31	6.0	1.5	4.7	4.5	1.2	3.3
Campania	6.72	12.8	1.44	6.38	12.0	1.46	-5.1	-6.3	1.5	4.5	1.5	2.9
Puglia	5.84	11.5	1.39	5.97	11.4	1.44	2.1	-1.1	3.5	3.7	1.5	2.3
Basilicata	5.97	12.1	1.34	6.13	12.2	1.37	2.6	0.7	2.1	3.7	1.3	2.4
Calabria	6.46	12.5	1.41	6.75	12.5	1.48	4.6	-0.2	5.1	4.8	1.7	3.1
Sicily	6.01	11.6	1.41	6.16	11.6	1.46	2.6	-0.4	3.2	4.5	2.0	2.5
Sardinia	5.35	11.8	1.23	5.51	11.8	1.27	3.0	0.0	3.2	2.8	0.9	1.9
Italy	**5.24**	**10.9**	**1.31**	**5.43**	**10.8**	**1.37**	**3.5**	**-0.7**	**4.6**	**4.3**	**1.2**	**3.0**
North	4.68	9.8	1.30	4.86	9.7	1.37	4.0	-0.9	5.2	4.3	1.0	3.3
Centre	5.05	11.6	1.19	5.49	11.8	1.27	8.7	2.0	6.9	4.5	1.2	3.2
South and Islands	6.18	12.1	1.40	6.20	11.8	1.44	0.4	-2.1	2.9	4.2	1.5	2.6

Exposure in population

An analysis to estimate the exposure and intensity of use of antipsychotics in the Italian population was conducted using data from the Tessera Sanitaria.

As expected from the epidemiology of the condition, consumption increases with age and reaches a prevalence of use of 5% in the over 85 population 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 antiepileptics than women, with a slightly higher prevalence level (Figure 3.6.4b).

All the 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 59 years and each subject is treated on average for 6 months, costing 255.7 euros. Marked differences between macro-areas can be seen with the Center having a value of 16% lower than the national average while the North 8% higher. There are slight differences between regions, with a minimum of 145.8 in Tuscany and a maximum of 363.5 euros in the Province of Bolzano. The 9.1% receive only one prescription in a year, and half of the users are on treatment for less than 4 months (in Emilia-Romagna, Tuscany, and Lazio for less than 3 months) indicating that prescription is not in line with the main national and international guidelines on treatment of epilepsy (Table 3.6.4c).

Figure 3.6.4b Breakdown of prevalence of use and consumption of antiepileptics under approved care regime and per conto distribution in 2021

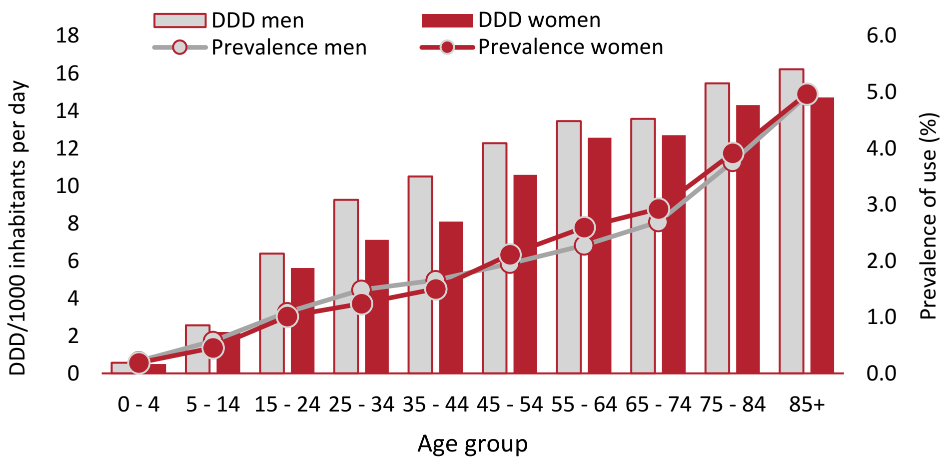


Table 3.6.4c Exposure and duration of therapy with antiepileptics by Region under NHS outpatient care and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average median	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	1.7	1.9	1.8	61	278.3	197.3	131.3	7.3
Valle d'Aosta	1.5	1.5	1.5	58	269.9	198.9	140.0	6.5
Lombardy	1.5	1.6	1.5	59	296.9	193.9	130.0	7.0
Province of Bolzano	1.3	1.3	1.3	58	363.5	222.3	149.3	6.9
Province of Trento	1.6	1.8	1.7	61	270.0	193.0	120.0	9.1
Veneto	1.3	1.4	1.4	58	337.9	227.6	160.0	5.8
Friuli VG	1.3	1.5	1.4	61	352.6	238.4	168.0	6.5
Liguria	2.1	2.5	2.3	62	222.8	160.7	100.0	9.0
Emilia R.	1.5	1.8	1.7	61	146.5	158.4	93.8	10.8
Tuscany	2.4	2.8	2.6	61	145.8	147.8	82.0	11.7
Umbria	2.0	2.2	2.1	63	261.3	194.0	120.0	8.4
Marche	2.1	2.3	2.2	61	274.6	189.0	120.0	7.8
Lazio	2.3	2.7	2.5	59	230.3	160.2	90.0	8.7
Abruzzo	2.3	2.5	2.4	61	269.7	181.4	114.0	10.7
Molise	2.3	2.5	2.4	60	235.6	176.7	112.0	8.2
Campania	2.0	2.2	2.1	56	272.0	187.4	115.0	9.2
Puglia	2.1	2.2	2.2	59	263.0	184.0	120.0	8.7
Basilicata	2.4	2.5	2.5	60	239.3	173.3	120.0	10.6
Calabria	2.4	2.6	2.5	60	247.9	172.2	100.0	11.1
Sicily	2.3	2.4	2.3	60	248.3	171.2	105.0	9.9
Sardinia	2.3	2.8	2.5	59	216.1	168.5	108.0	9.0
Italy	**1.9**	**2.1**	**2.0**	**59**	**255.7**	**184.0**	**114.3**	**9.1**
North	1.5	1.7	1.6	60	277.1	197.4	126.0	7.8
Centre	2.3	2.6	2.4	60	213.6	164.9	93.3	9.8
South and Islands	2.2	2.3	2.2	59	260.6	182.2	112.0	9.8

Key message

- From a public health perspective, a greater number of studies must be conducted on the use of these medicines in the real world in order to characterise their prescribing patterns, especially on the effectiveness of **third generation molecules**, such as lacosamide and perampanel, which have had 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.
- In general, the **change in the prescribing pattern** observed in the last seven years (decrease in the use of I generation drugs and an increase in those of II and III generation) requires an in-depth study on the clinical outcomes that have the greatest impact on the quality of life of patients.

References

- Hou L, Peng B, Zhang D, Yang J, Wang Y, Tong L, Li S, Wang Q, Zhao J. Clinical Efficacy and Safety of Lacosamide as an Adjunctive Treatment in Adults With Refractory Epilepsy. Front Neurol. 2021 Dec 3;12:712717.
- D'Souza W, Alsaadi T, Montoya J, Carreño M, Di Bonaventura C, Mohanraj R, Yamamoto T, McMurray R, Shastri O, Villanueva V; PERMIT study group. Perampanel for the treatment of patients with myoclonic seizures in clinical practice: Evidence from the PERMIT study. Seizure. 2022 Jun 14;9(5):e200005.
- Lega Italiana Epilessia LICE. https://www.lice.it/documenti/Lei%20web%2023-03-10_1.pdf
- National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. Clinical guideline [CG137]. Published: 11 January 2012. Last updated 12 May 2021. Available at the address www.nice.org.uk/guidance/cg137
- Téllez-Zenteno JF, Hernández-Ronquillo L, Buckley S, Zahagun R, Rizvi S. A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy. Epilepsia 2014; 55(6):829-34.

3.6.5 Antipsychotics

Epidemiological framework

Psychotic disorders such as schizophrenia, delusional disorder, and mood disorders (bipolar disorder type I) are widespread central nervous system disorders of a chronic and disabling nature that are a major problem in terms of social and public health costs. Clinically, psychotic disorders are united by positive symptoms that may include hallucinations, thought disturbances and lack of behavioral control. Such conditions are impediments to performing daily activities particularly in interpersonal relationships. Schizophrenia, according to WHO data, affects about 24 million people or 1 in 300 people (0.32%) worldwide, and the condition is associated with a risk of premature death 2-3 times higher than the general population. The disease occurs at similar rates in males and females; however, in males it seems to appear earlier. In addition to the positive symptoms, negative symptoms such as apathy, avolition, alogia, anhedonia, and cognitive deficits may also occur in schizophrenia, representing the most disabling aspect of the disorder. At the national level, according to the 2019 "Mental Health Report" published by the Ministry of Health, the prevalence of treated individuals (i.e., with at least one access during the year at Mental Health Department facilities or accredited Private Facilities) with schizophrenia or other functional psychosis was 164 per 10,000 population, slightly down from the year 2018, with a higher proportion of females (54.3% of cases) than males. When considering the composition by different age groups, the prevalence trend in 2019 reflects the aging of the general population, with a large proportion of patients over the age of 45 (68.7%). When considering the composition by different age groups, the prevalence trend in 2019 reflects the aging of the general population, with a large proportion of patients over the age of 45 (68.7%). In both sexes there are fewer patients under the age of 25 while the highest concentration is in the 45-54 and 55-64 age groups (45.8%).

National data on consumption and expenditure

From 2014 to 2021, the consumption of antipsychotic drugs increased by more than 20% switching from 8.3 in 2014 to 10.1 DDD in 2021; over the same period there was a reduction of 1.2% in terms of average annual variation (CAGR) of the average cost per DDD, standing at a value of 1.36 euros in 2021 (Figure 3.6.5a). On average, for each citizen, the expenditure was equal to 5.01 euros with an increase of 2.9% compared to 2020 and an average annual change of 2.6% from 2014 to 2021. The change in spending in 2021 was mainly driven by a 3.5% increase in average cost (Table 3.6.5a).
Atypical and other antipsychotics are confirmed as the category with the highest expenditure (4.71 euros per capita equal to about 94% of the total) and the highest consumption (7.9 DDD equal to 78% of the total), with an increase compared to 2020 of 3.3% and 1.3% respectively (Table 3.6.5a). In addition, atypical antipsychotics have a cost per day of therapy that is about 5 times higher than typical antipsychotics (€1.64 vs. €0.36), among them aripiprazole and paliperidone record values between €2.47 and €5, while clozapine records the largest variation from 2020 with 11.7%. Typical antipsychotics show reductions of 3.1% in expenditure and 5.1% in consumption (Table 3.6.5a).

Also in 2021 paliperidone and aripiprazole are at the first places in terms of expenditure (respectively 1.57 and 1.21 euros), with an increase of 2.4% and 9.1% compared to the previous year. Despite a reduced consumption in terms of prescribed doses, from 0.9 to 1.3 DDD, the high cost of both is determined by a high average cost per day of therapy. Haloperidol and lithium are the only typical antipsychotics present in the top ten with the highest cost, with opposite trends of -4.3%% and +3.9%, respectively; these two molecules are among those with the lowest average cost per DDD in the entire category. 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, as monotherapy or as a combination therapy with lithium and/or valproic acid. This molecule, although with an efficacy and safety profile comparable to other atypical antipsychotics, in the last year has shown an increase of 26.6% in terms of doses and 22.8% in terms of expenditure, with a cost per day of therapy equal to 2.24 euros compared to an average of 1.64 euros for atypical antipsychotics.
Important differences can be seen among the Regions; in fact, Sardinia with 13.2 DDDs has almost double the consumption of Valle d'Aosta (6.6) and, in general, in almost all regions of the Central and South (except Campania and Molise) there is a more pronounced use of these drugs than in the North (Table 3.6.5b). Abruzzo, although its consumption is slightly higher than the national average (10.4 vs. 10.1 DDD), is the region with the highest per capita expenditure (7.74 euros) due to higher use of high-cost drugs per day of therapy (2.04 euros). The largest increases in consumption over the previous year are in Calabria (+10.7%) and Basilicata (+10.6%); while Valle d'Aosta (-22.7%), Molise (-13.9%) and Sardinia (-10.3%) note the sharpest contraction.

Figure 3.6.5a Antipsychotics, temporal trend of consumption and average cost per day of therapy (2014-2021)

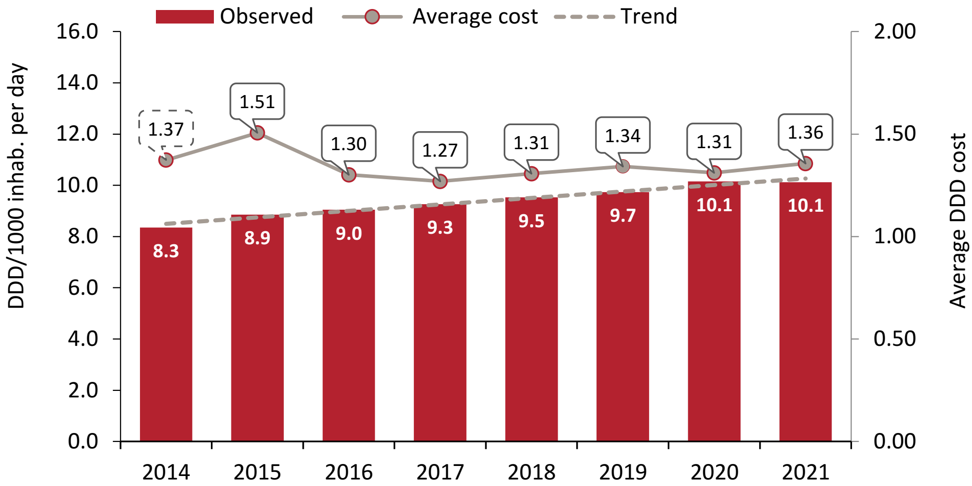


Table 3.6.5a Antipsychotics, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Atypical and other antipsychotics	4.71	3.3	2.8	7.9	1.3	4.7	1.64	2.4
Typical antipsychotics	0.30	-3.1	-0.6	2.3	-5.1	-2.2	0.36	2.4
Antipsychotic medicines	**5.01**	**2.9**	**2.6**	**10.1**	**-0.2**	**2.8**	**1.36**	**3.5**
paliperidone	1.57	2.4	10.1	0.9	3.4	11.0	5.00	-0.6
aripiprazole	1.21	9.1	12.8	1.3	6.7	25.7	2.47	2.6
quetiapine	0.77	1.1	-3.8	2.0	0.0	2.4	1.07	1.4
risperidone	0.39	-10.2	-7.6	0.8	-3.3	-0.6	1.28	-6.9
olanzapine	0.34	-2.1	-2.2	2.1	-1.9	1.4	0.45	0.1
clozapine	0.16	11.3	1.9	0.5	0.0	2.0	0.98	11.7
lurasidone	0.12	22.8	-	0.1	26.6	-	2.24	-2.8
haloperidol	0.08	-4.3	0.2	1.2	-3.6	0.2	0.19	-0.5
lithium	0.07	3.9	0.9	0.4	-4.6	0.9	0.53	9.1
amisulpride	0.06	-4.5	-3.1	0.1	-4.4	-2.9	1.63	0.1

Table 3.6.5b Antipsychotics, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	3.43	10.2	0.92	3.49	9.7	0.98	1.9	-4.8	7.3	-0.5	1.7	-2.2
Valle d'Aosta	3.27	8.6	1.04	3.27	6.6	1.35	0.1	-22.7	29.7	3.6	0.4	3.1
Lombardy	6.39	8.3	2.11	6.63	8.4	2.17	3.7	1.0	3.0	6.5	3.6	2.8
Province of Bolzano	5.28	9.5	1.52	5.14	9.7	1.45	-2.6	2.0	-4.2	4.1	1.6	2.5
Province of Trento	3.20	9.5	0.92	3.18	10.0	0.88	-0.5	4.8	-4.8	4.9	5.3	-0.3
Veneto	3.76	9.6	1.07	3.80	9.7	1.08	1.2	0.4	1.0	0.0	1.1	-1.2
Friuli VG	2.92	9.8	0.82	3.14	9.9	0.87	7.4	0.8	6.9	0.6	1.8	-1.2
Liguria	3.94	9.9	1.09	4.14	10.0	1.14	5.2	0.9	4.5	-0.1	3.2	-3.2
Emilia R.	3.44	10.3	0.91	3.61	10.2	0.97	5.0	-0.7	6.0	-0.9	1.3	-2.2
Tuscany	4.51	10.3	1.19	4.60	10.3	1.23	2.0	-0.6	2.9	8.1	3.5	4.5
Umbria	4.19	10.8	1.06	4.40	11.3	1.07	5.1	4.2	1.1	3.4	4.5	-1.1
Marche	5.88	11.7	1.38	5.97	11.3	1.45	1.5	-3.2	5.1	3.4	4.9	-1.5
Lazio	4.09	10.1	1.11	4.55	10.1	1.24	11.1	0.2	11.2	2.7	3.7	-1.0
Abruzzo	7.64	10.5	1.99	7.74	10.4	2.04	1.3	-1.1	2.7	0.4	1.9	-1.5
Molise	5.01	10.6	1.29	3.29	9.1	0.99	-34.3	-13.9	-23.5	-7.0	-0.2	-6.8
Campania	4.83	9.4	1.40	5.19	9.3	1.53	7.4	-1.4	9.3	3.6	2.1	1.4
Puglia	7.24	11.9	1.66	7.39	11.6	1.74	2.1	-2.3	4.8	6.3	3.4	2.8
Basilicata	5.44	10.3	1.44	6.73	11.4	1.62	23.6	10.6	12.1	4.4	3.7	0.6
Calabria	5.71	10.3	1.51	4.89	11.4	1.17	-14.5	10.7	-22.5	-0.9	3.4	-4.2
Sicily	4.40	11.7	1.03	4.37	12.1	0.99	-0.8	3.7	-4.1	-1.6	3.5	-4.9
Sardinia	5.25	14.7	0.97	5.18	13.2	1.07	-1.3	-10.3	10.4	-2.7	2.3	-4.9
Italy	**4.87**	**10.1**	**1.31**	**5.01**	**10.1**	**1.36**	**2.9**	**-0.2**	**3.5**	**2.6**	**2.8**	**-0.2**
North	4.58	9.4	1.34	4.73	9.3	1.39	3.3	-0.4	4.0	2.8	2.3	0.5
Centre	4.47	10.4	1.17	4.74	10.4	1.25	6.1	-0.2	6.6	4.3	3.9	0.5
South and Islands	5.54	11.1	1.36	5.59	11.1	1.38	0.9	-0.1	1.3	1.6	2.9	-1.2

Exposure in population

An analysis to estimate the exposure and intensity of use of antipsychotics in the Italian population was conducted using data from the Tessera Sanitaria.

Consistent with the epidemiology of the clinical conditions in which antipsychotics find use, the prevalence of use increases with age to 10.9% in women and 8.7% in men in the over-85 age group; up to age 64, however, men 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 a value of 1.8% in 2021, with a minimum of 1.1% in Veneto and a maximum of 2.8% in Sardinia. The Regions of the Center and South show greater exposure than the North (2.0% vs 1.5%). The median age of antipsychotic users is 66 years (North: 67 years, Centre: 68 years and South: 65 years). On average, each user is treated for more than 4 months (DDD per user: 131.5), and the average annual cost for each is 108.4 euros in Lombardy spending 5 times more than Liguria (233 vs. 37.9 euros). In addition, several regions have an expenditure above the national average of 131.5 euros indicating possible savings margins possibly resulting from a different drug distribution method. half of the users remain on treatment for less than two months (median DDD: 56 days) and 12.3% receives only one prescription during the year (Table 3.6.5c). These data may indicate that a large proportion of patients may experience significant side effects, particularly related to extrapyramidal disorders (e.g. dystonia, tremor, tardive dyskinesia), or that patients with schizophrenia do not respond to conventional antipsychotics.

Figure 3.6.5b Breakdown of prevalence of use and consumption of antipsychotics under approved care regime and per conto distribution in 2021

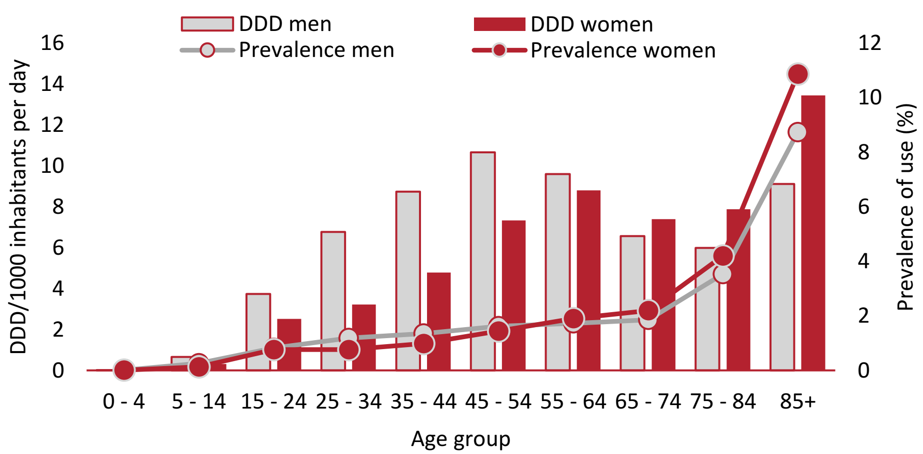


Table 3.6.5c Exposure and duration of therapy with antipsychotics by Region under NHS outpatient care and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average median	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	1.4	1.8	1.6	69	43.2	121.3	48.8	11.6
Valle d'Aosta	1.2	1.6	1.4	65	42.0	121.0	56.0	10.4
Lombardy	1.6	1.9	1.7	67	233.1	124.5	56.0	10.1
Province of Bolzano	1.1	1.5	1.3	65	101.1	102.0	48.4	13.6
Province of Trento	1.3	1.6	1.5	63	91.5	128.4	58.3	11.0
Veneto	1.0	1.2	1.1	62	83.4	131.1	60.0	13.7
Friuli VG	1.1	1.6	1.3	77	64.5	79.0	31.9	13.0
Liguria	1.7	2.3	2.0	73	37.9	98.5	41.3	13.2
Emilia R.	1.1	1.4	1.2	66	42.5	102.5	45.0	16.6
Tuscany	1.7	2.3	2.0	70	77.9	100.5	42.0	16.2
Umbria	1.7	2.5	2.1	79	52.0	82.8	37.5	13.1
Marche	1.8	2.2	2.0	68	61.8	122.9	56.0	12.2
Lazio	1.9	2.3	2.1	65	75.6	130.9	56.0	12.4
Abruzzo	2.1	2.6	2.4	70	175.5	123.7	52.5	12.4
Molise	2.0	2.4	2.2	69	61.2	135.1	62.5	10.1
Campania	1.6	1.7	1.6	63	87.2	148.6	60.0	11.6
Puglia	1.9	2.1	2.0	65	163.4	156.6	71.0	11.1
Basilicata	2.1	2.3	2.2	65	156.8	146.7	72.0	11.7
Calabria	1.9	2.0	1.9	62	103.2	154.8	73.1	12.1
Sicily	1.9	2.1	2.0	65	61.8	154.0	67.5	10.8
Sardinia	2.5	3.1	2.8	66	65.3	143.4	60.0	12.4
Italy	**1.6**	1.9	**1.8**	**66**	**108.4**	**131.5**	**56.0**	**12.3**
North	1.3	1.7	1.5	67	132.0	119.6	50.0	12.3
Centre	1.8	2.3	2.1	68	73.8	118.6	48.8	13.8
South and Islands	1.9	2.1	2.0	65	104.7	151.3	65.3	11.6

Key message

- **The 2021 data document considerable regional variability in antipsychotic use that cannot be attributed to a different prevalence of mental illness.**
- In terms of appropriateness, prescribing patterns for users of two antipsychotic medicines should be characterised in order to define the outcomes on the course of the disease. In general, 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, good agreement was documented between available evidence in RCTs and real-world evidence.

References

- Brambilla R, Vigna-Taglianti F. Il trattamento con antipsicotici e la mortalità dei pazienti ricoverati per schizofrenia e altri disturbi psicotici nella città di Torino. Department of Clinical and Biological Sciences, University of Turin Epidemiological Observatory of Addictions, Piedmont Region. 40th Congress Italian Epidemiology Association, Turin 19-21 October 2016. Available at the address http://www.epidemiologia.it/wp-content/uploads/2016/10/03_AIE-2016- Brambilla.pdf
- Epicentro. Istituto Superiore di Sanità. Salute mentale. Informazioni generali. Avaialble at https://www.epicentro.iss.it/mentale/mentale
- Epicentro. Istituto Superiore di Sanità. Schizofrenia. Informazioni generali. Avaialble at https://www.epicentro.iss.it/schizofrenia/
- Katona L, Bitter I, Czobor P. A meta-analysis of effectiveness of real-world studies of antipsychotics in schizophrenia: Are the results consistent with the findings of randomized controlled trials? Transl Psychiatry. 2021 Oct 6;11(1):510.
- Meyer JM. Pharmacotherapy of psychosis and mania. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's: the pharmacological basis of therapeutics, 13th edition. New York: McGraw-Hill, 2017.
- Ministero della Salute. Rapporto salute mentale. Analisi dei dati del Sistema Informativo per la Salute Mentale (SISM) Anno 2018. Available at the address http://www.salute.gov.it/imgs/C_17_ pubblicazioni_2932_allegato.pdf
- National Institute for Health and Care Excellence (NICE). Psychosis and schizophrenia in adults. Treatment and management. Clinical guideline [CG178]. Published: 12 February 2014. Last updated: 01 March 2014. Available at the address https://www.nice.org.uk/guidance/cg178
- Pasina L, Novella A, Cortesi L, Nobili A, Tettamanti M, Ianes A. Drug prescriptions in nursing home residents: an Italian multicenter observational study. Eur J Clin Pharmacol 2020; 76(7):1011-9.
- Piazza A, Tibaldi G, per conto del Gruppo di lavoro della Regione Emilia-Romagna. L'utilizzo degli antipsicotici nei Servizi Italiani. Un'esperienza di valutazione condivisa tra professionisti, familiari e utenti, in Emilia Romagna. SIEP, 2018. Società Italiana Epidemiologia Psichiatrica. Available at the address https://siep.it/lutilizzo-degli-antipsicotici-nei-servizi-italiani/

- World Health Organization. Mental health and substance use. Duration of antipsychotic treatment in individuals with a first psychotic episode. Inserted on 28 July 2020. Available at the address https:// www.who.int/teams/mental-health-and-substance-use/mental-health-gap-action-programme/ evidence-centre/psychosis-and-bipolar-disorders/duration-of-antipsychotic-treatment-in-individ- uals-with-a-first-psychotic-episode
- World Health Organization. Schizophrenia. Key facts. 4 October 2020. Available at the address https://www.who.int/news-room/fact-sheets/detail/schizophrenia

3.6.6 Antiparkinson medications

Epidemiological framework

Parkinson's disease is a chronic and progressive neurodegenerative disorder of the central nervous system, typically characterized by the presence of cardinal motor symptoms such as bradykinesia, rigidity and tremor, with which postural instability is associated. The predominantly motor involvement of the disease determines its usual classification among movement disorders. Parkinson's disease is the second most frequent neurodegenerative disorder, in terms of frequency, after Alzheimer's disease. In industrialized countries it has an incidence of about 12/100000 people per year with a prevalence of about 2 million affected individuals. The disease affects about 1% of the population over 60 years old and reaches 4% among those over 85 years old is slightly more common in the male sex than in the female (60% vs 40%). Although the prevalence increases progressively with age, cases in which the disease occurs before the age of 50 and even before the age of 40 (juvenile Parkinson's) are not uncommon. This suggests that an age-dependent biological factor, possibly in association with cumulative exposure to an environmental factor, is among the determining agents. In Italy there are currently an estimated 230,000 Parkinson's patients. The disease is slightly more common in men than in women (60% vs. 40%), and it is estimated that about 5% of all Parkinson's patients are younger than 50 years old while about 70% are older than 65 years. The number of cases is expected to double by 2030 due to the increasing aging of the general population.

National data on consumption and expenditure

In 2021, the consumption of antiparkinson's drugs reached 5.7 DDD/1000 inhabitants per day declining by 2.4% from 2020 and with an average annual increase of 0.8% between 2014 and 2021 (Figure 3.6.6a). On average, each day of therapy costs €1.64 (-8.3% compared to 2014), with values ranging between €1.31 for MAO inhibitors and €4.04 for COMT inhibitors. (Table 3.6.6a).

Among the categories of medicines that control the symptoms of the disease, dopa-derived agonists, plain or in combination, continue to be the most widely used in 2021 with 2.3 DDD (equal to 40% of the total antiparkinsonians) and an expenditure of €1.23 per capita (respectively -2.3% and -3.2% compared to 2020), followed by dopamine agonists, down 6.5% in terms of doses and 5.5% in terms of expenditure. COMT inhibitors, although accounting for a small share of consumption (0.1 DDD), are the category that shows the greatest increase in consumption (+14.6%) and expenditure (+2021%), with values exceeding 20% increase when compared to 2014 (Table 3.6.6a).

From the in-depth study by active ingredient, the highest consuming drugs appear to be levodopa and benserazide in combination (1.1 DDD), selegiline (1.0 DDD) and levodopa+carbidopa (0.9 DDD). The first two drugs show decreases compared to 2020 (1.8% and 0.7%, respectively), while the combination of levodopa and carbidopa is stable (+0.3%). Of note is the steady increase in opicapone consumption (+18.9%) over the previous year. This substance is the latest molecule to be marketed in the COMT inhibitor class and, due to its prolonged action, allows for daily single administration. The highest cost molecules per day of therapy, as they are still covered by patent, are rotigotine (5.59 euros, found in transdermal patch pharmaceutical form), safinamide (4.23 euros) and opicapone (4.01 euros) (Table 3.6.6a).

Among the different macroareas, the highest consumption is found in the Center with 6.2 DDD, 6DDD in the South and Islands, and 5.3 DDD in the North; in all areas there is a contraction in consumption, more than 2%, compared to 2020. Central regions also have a higher average cost per DDD (€1.75) than the South (€1.65), and the North (€1.58); in detail, the Center has an average cost 11% higher than the North. Among individual regions, the variability, in terms of consumption, ranges from 3.9 DDD in the Province of Bolzano to a maximum at 6.7 DDD in Marche. Overall, compared to 2020, there are decreases in consumption in all regions except Friuli Venezia Giulia (+4,0%). Sardinia has an average cost per DDD almost double that of Emilia Romagna (1.98 vs. 1.04); confirming this, spending in this region is found to have the lowest per capita spending (1.94 euros); while Abruzzo has the highest spending (4.76 euros).

Figure 3.6.6a Antiparkinsonians, temporal trend of consumption and average cost per day of therapy (2014-2021)

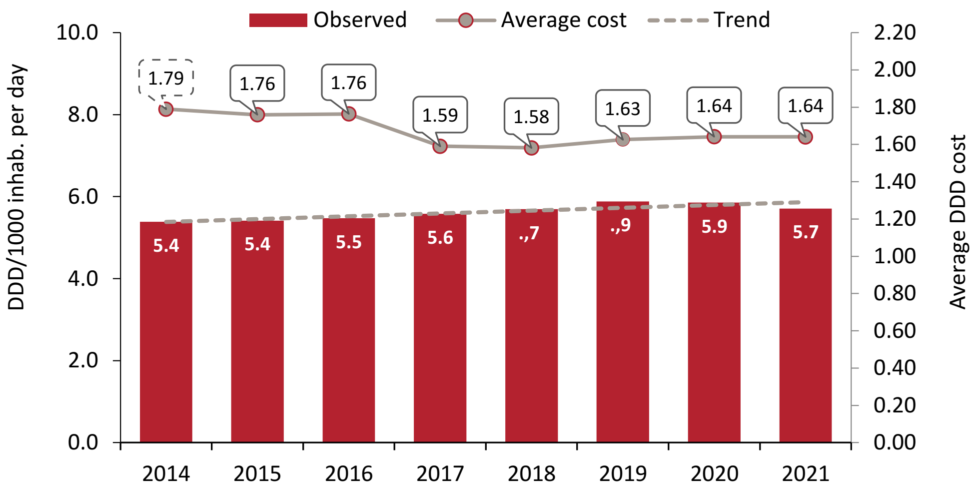


Tabella 3.6.6a Antiparkinsonians, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
DOPA-derived agonists alone or in combination	1.23	-3.2	0.3	2.3	-2.3	0.7	1.44	-0.6
Dopamine-agonists	1.16	-5.5	-2.3	1.1	-6.5	-3.8	2.85	1.4
MAO inhibitors	0.79	-1.1	-1.0	1.7	-0.8	5.6	1.31	-0.1
COMT inhibitors	0.19	12.5	22.6	0.1	14.6	24.4	4.04	-1.6
Anticolinergics	0.05	-2.5	-1.5	0.5	-2.5	-1.5	0.26	0.4
Amantadine	<0.005	-31.8	-13.8	0.0	-31.2	-20.0	0.67	-0.6
Antiparkinsonian medicines	**3.42**	**-2.7**	**-0.4**	**5.7**	**-2.4**	**0.8**	**1.64**	**0.0**
levodopa/carbidopa	0.68	-1.7	4.7	0.9	0.3	1.1	2.03	-1.7
rotigotine	0.68	-6.5	0.6	0.4	-6.6	0.7	5.29	0.5
safinamide	0.41	1.0	-	0.3	3.5	-	4.23	-2.1
pramipexole	0.38	-1.7	-4.3	0.5	-2.5	-3.0	2.16	1.1
levodopa/benserazide	0.35	-1.6	3.2	1.1	-1.8	2.8	0.90	0.5
rasagiline	0.27	-4.3	-13.8	0.4	-4.0	-2.4	2.03	0.0
opicapone	0.18	17.7	-	0.1	18.9	-	4.01	-0.7
melevodopa/carbidopa	0.16	-3.3	2.0	0.2	-3.6	0.9	1.83	0.5
selegiline	0.12	-1.1	4.0	1.0	-0.7	5.7	0.31	-0.1
ropinirole	0.10	-11.6	-9.3	0.3	-12.2	-8.7	0.96	1.0

Table 3.6.6b Antiparkinsonians, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	3.73	6.2	1.63	3.52	6.0	1.61	-5.6	-3.8	-1.6	-2.5	0.3	-2.8
Valle d'Aosta	3.60	6.0	1.63	3.45	6.0	1.57	-4.2	-0.4	-3.5	2.8	2.5	0.3
Lombardy	3.25	4.9	1.81	3.16	4.8	1.81	-2.6	-2.3	0.0	0.4	1.0	-0.6
Province of Bolzano	2.07	4.1	1.37	1.99	3.9	1.39	-4.1	-5.0	1.2	-1.1	-1.6	0.5
Province of Trento	3.12	4.7	1.81	3.13	4.7	1.84	0.2	-1.3	1.9	-0.4	-1.0	0.6
Veneto	3.48	5.8	1.64	3.42	5.7	1.65	-1.9	-2.3	0.7	0.1	0.4	-0.4
Friuli VG	2.64	5.1	1.42	2.80	5.3	1.45	5.9	4.0	2.2	-1.2	0.7	-1.9
Liguria	3.47	6.7	1.41	3.39	6.4	1.46	-2.3	-4.8	2.9	-0.1	0.2	-0.3
Emilia R.	1.94	5.3	1.00	1.94	5.1	1.04	-0.4	-3.9	4.0	-4.0	-0.6	-3.4
Tuscany	3.45	5.9	1.61	3.45	5.7	1.66	0.1	-2.6	3.1	-0.1	0.2	-0.3
Umbria	4.52	6.6	1.86	4.43	6.5	1.86	-2.0	-1.6	-0.1	-0.3	1.2	-1.5
Marche	3.87	6.8	1.55	3.76	6.7	1.55	-3.0	-2.4	-0.3	-1.5	0.1	-1.6
Lazio	4.48	6.6	1.86	4.34	6.4	1.84	-3.1	-1.9	-1.0	0.7	1.8	-1.1
Abruzzo	4.99	7.0	1.95	4.76	6.9	1.89	-4.7	-1.4	-3.1	-0.6	2.4	-2.9
Molise	3.94	5.9	1.82	3.62	5.8	1.70	-8.3	-1.2	-6.9	-1.8	1.1	-2.9
Campania	3.32	5.8	1.57	3.13	5.6	1.52	-5.7	-2.8	-2.7	-1.0	2.0	-2.9
Puglia	4.12	6.2	1.82	4.01	6.0	1.84	-2.8	-3.2	0.7	0.4	0.4	0.0
Basilicata	3.80	6.3	1.66	3.81	6.1	1.71	0.2	-2.7	3.2	0.6	1.6	-1.0
Calabria	3.55	5.9	1.64	3.48	5.9	1.62	-2.0	-0.4	-1.3	1.8	0.8	1.0
Sicily	3.51	6.5	1.48	3.43	6.4	1.47	-2.3	-1.6	-0.5	0.2	1.6	-1.4
Sardinia	4.08	5.6	2.01	3.91	5.4	1.98	-4.1	-2.7	-1.2	-1.1	1.3	-2.4
Italy	**3.52**	**5.9**	**1.64**	**3.42**	**5.7**	**1.64**	**-2.7**	**-2.4**	**0.0**	**-0.4**	**0.8**	**-1.2**
North	3.12	5.4	1.57	3.04	5.3	1.58	-2.4	-2.8	0.6	-0.9	0.3	-1.2
Centre	4.07	6.4	1.74	3.99	6.2	1.75	-2.1	-2.2	0.3	0.1	1.0	-0.9
South and Islands	3.75	6.1	1.67	3.61	6.0	1.65	-3.6	-2.2	-1.1	-0.1	1.4	-1.5

Exposure in population

Using Health Card data, an analysis was conducted to estimate the exposure and intensity of use of antiparkinson's drugs in the general population.
Epidemiological data on Parkinson's disease indicate that, in general, the disease manifests itself after the age of 60, although about 10% of patients are around 40 years of age. Parkinson's is a neurodegenerative and progressive disease, the prevalence data of drug use and consumption in fact show a sharp increase with age up to a value of 5.6% in the age range of 85 and over. In line with the epidemiology of the condition men have a greater use in age groups over 65 with differences in consumption ranging from 50% to 70% compared to women. For example, in the over 85 age group there is a 1% higher prevalence (5.6% vs 4.3%) (Figure 3.6.6b).
In Italy, about one in 100 people was treated with antiparkinsonian medicines in 2021, with a regional variability ranging from 0.6% in the Province of Trento to 1% in Liguria. Half of the users are older than 77 years and, on average, each subject has been treated for 251.9 days with an expenditure of 368.6 euros. For this last indicator there is wide regional variability with Emilia-Romagna having a cost per user 65% lower than Lombardy (176.8 vs. 459.5 euros) (Table 3.6.6c). This difference may depend on both the different mode of dispensing (direct vs. contracted distribution) and the effect of competitive bidding for these drugs. It should be noted, however, 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.

Figure 3.6.6b Distribution of prevalence of use and consumption of parkinson's medications under approved are regime and *per conto* distribution in 2021

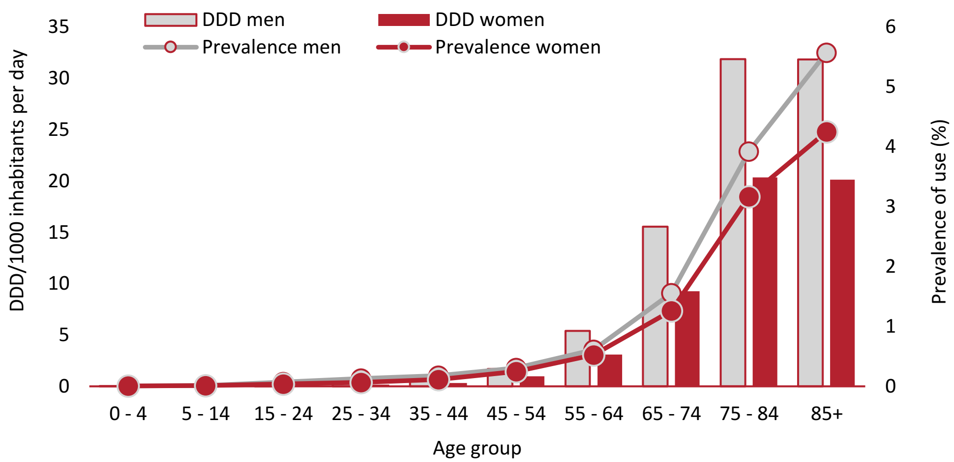


Tabella 3.6.6c Exposure and duration of therapy with antiparkinsonian medicines by Region under NHS outpatient care and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average median	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	0.8	0.8	0.8	78	348.4	250.1	125.0	7.6
Valle d'Aosta	0.7	0.8	0.7	76	447.8	277.0	136.9	8.8
Lombardy	0.6	0.6	0.6	77	459.5	268.2	140.0	6.4
Province of Bolzano	0.6	0.7	0.6	77	253.0	178.8	80.0	8.3
Province of Trento	0.6	0.5	0.6	75	374.8	252.4	133.3	6.9
Veneto	0.7	0.7	0.7	76	388.9	272.6	133.3	6.9
Friuli VG	0.6	0.7	0.6	78	389.8	277.7	133.3	7.4
Liguria	1.0	1.0	1.0	80	309.5	235.0	120.0	9.2
Emilia R.	0.7	0.7	0.7	78	176.8	200.0	102.0	7.9
Tuscany	0.8	0.9	0.9	79	339.1	226.4	108.0	10.9
Umbria	1.0	1.0	1.0	80	375.0	226.8	120.0	8.8
Marche	0.9	1.0	1.0	79	365.4	245.0	120.0	8.1
Lazio	0.8	0.8	0.8	78	448.2	274.9	140.0	8.2
Abruzzo	1.0	1.0	1.0	78	398.9	244.0	125.0	9.2
Molise	0.9	0.8	0.8	77	360.6	251.1	151.2	7.3
Campania	0.8	0.8	0.8	77	338.9	241.4	120.0	10.6
Puglia	0.9	0.9	0.9	77	374.8	238.4	120.0	8.1
Basilicata	0.9	0.8	0.9	76	340.8	255.9	140.0	9.0
Calabria	0.9	0.8	0.9	74	303.7	234.4	120.0	10.8
Sicily	0.9	0.9	0.9	76	306.4	239.7	132.0	9.6
Sardinia	0.8	0.8	0.8	73	368.5	249.2	137.7	9.1
Italy	**0.8**	0.8	**0.8**	**77**	**368.6**	**251.9**	**125.0**	**8.6**
North	0.7	0.7	0.7	78	368.6	255.3	126.7	7.4
Centre	0.8	0.9	0.9	78	403.6	256.1	121.3	9.2
South and Islands	0.9	0.8	0.8	76	346.5	244.7	125.0	9.7

Key message

- The wide regional variability in the use of Parkinson's medications and some specific categories (MAO inhibitors and dopa-derivative agonists alone or in combination) as well as the finding that half of subjects are treated for less than 4 months and 8.7% received only one prescription during the year highlight the need to disseminate and implement more of the recommendations of the guidelines on the diagnosis and treatment of Parkinson's disease in order to pursue diagnostic and prescriptive appropriateness.
- The need to define **complex therapeutic schemes**, especially in moderate and advanced forms of the disease, with constant use of drugs with multiple active ingredients, calls for a rational diffusion in the territories of centers 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** in this disease also for non-motor symptoms, which have a considerable influence on the quality of life of patients and their families.

References

- Dorsey ER, Constantinescu R, Thompson JP et al. Projected number of people with Parkinson’s disease in the most populous nations, 2005 through 2030. Neurology 2007; 68(5):384-6.
- Linea Guida. Diagnosi e terapia della malattia di Parkinson. SNLG Linea Guida 2013; 24:1-250.
- Martinez-Martin P, Radicati FG, Rodriguez Blazquez C, Wetmore J, Kovacs N,Ray Chaudhuri K, Stocchi F; PDCS European Study Group. Extensive validation study of the Parkinson's Disease Composite Scale. Eur J Neurol. 2019 Oct;26(10):1281-1288.
- National Institute for Health and Care Excellence (NICE). Guidelines Parkinson’s disease. Quality standard [QS164]. Published: 9 February 2018. Available at the address www.nice.org.uk/guid- ance/qs164
- Von Campenhausen S, Bornschein B, Wick R et al. Prevalence and incidence of Parkinson’s disease in Europe. Eur Neuropsychopharmacol 2005; 15(4):473-90.

3.6.7 Antimigraine medicines

Migraine is a neurological disorder that is the third most common disease worldwide with a prevalence of 14%. It is also the second most disabling disease with 45.1 million people affected, according to data from the Global Burden of Disease study. Migraine involves more women than men with a male to female ratio of 1:2-3; however, it seems to be an under-diagnosed condition in men. In women, it appears mainly after menarche, and it is estimated that in the period between puberty and menopause, about 27% of women are affected; while in the pre-developmental stages there does not seem to be any significant difference in prevalence between men and women. Evidence about the disappearance of migraine with menopause is discordant, in fact, in 1/3 of women it persists in an unchanged form, while 1/3 on the contrary manifests worsening. Nationwide, several population studies have been conducted over the years in which high prevalences of the disease have been found. For example, in a population-based study conducted in the province of Pavia, it was found that among 487 subjects (58% women, 42% men), migraine had a sex-adjusted one-year prevalence of 42.9%. Specifically, there was a prevalence of 54.6% in females and 32.5% in males.

National data on consumption and expenditure

Over the past eight years, the consumption in terms of DDD/1000 inhabitants per day of drugs for the treatment of migraine is almost stable with slight average annual changes (CAGR 2.9%), as well as for total per capita expenditure (CAGR +0.1%), while the average cost per day of therapy (€3.53), compared to 2020, has increased by 15.2% entirely due to the introduction of monoclonal antibodies (€5.03) on the market (Figure 3.6.7a and Table 3.6.7a). In detail, within the category, triptans occupy almost all of the expenditure of the entire category (75%; 1.01 out of 1.34 euros per capita) and consumption (90%) with 0.9 DDD/1000 inhabitants per day. Monoclonal antibodies were recently (February 2019) approved through centralized procedure and are indicated for prophylaxis in patients who have recurrent migraine episodes and attacks (at least 4 migraine days per month). The impact on spending and quantities used of the single active ingredients, although still small in absolute values, is showing a significant increase over 2020: erenumab (+562.6% and +73.9%), galcanezumab (+1098.1% and +420.9%) and fremanezumab (+1363.8% and +1404.2%) (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 that increases the most in consumption levels is eletriptan (+4.4%), which, however, is also among those with the lowest consumption levels.

At the regional level, there are no major changes in consumption and spending either in terms of time (CAGR 2014-2021 of +2.9% and +0.1%, respectively) or geography: North (1.1 DDD), Centre (1.0 DDD) and South and Islands (0.9 DDD). In terms of comparison with the previous year, the Centre reports the largest increases in spending, consumption and average cost per day of therapy (+38.5%, +16.0% and +19.7%). Among regions, increases in consumption range from a low of +4.6% in the Province of Trento to a high of +29.5% in Molise, for spending from +9.5% in the Province of Trento to +60.7% in Abruzzo (Table 3.6.7b).

Figura 3.6.7a Antimigraine medicines, temporal trend of consumption and average cost per day of therapy (2014-2021)

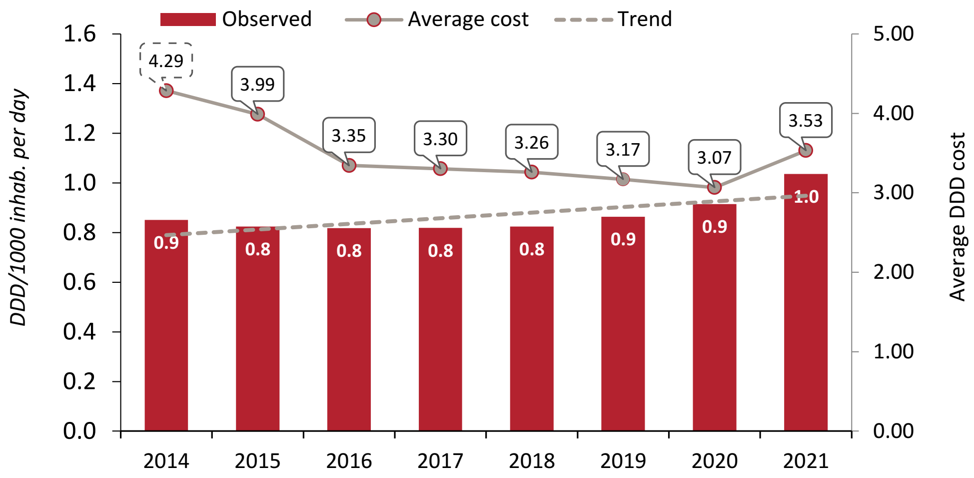


Tabella 3.6.7a Antimigraine medicines, per capita expenditure and consumption (DDD/1000 ab day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Triptans	1.01	2.0	-3.8	0.9	2.0	0.7	3.22	0.2
Monoclonal antibodies	0.33	774.2	-	0.2	140.1	-	5.03	265.0
Other antimigraine medicines	<0.005	-4.6	-26.1	0.0	2.3	-37.3	1.09	-6.4
Ergot alkaloids	<0.005	-25.9	-48.9	0.0	3.6	-48.2	0.29	-28.3
Antimigraine medicines	**1.34**	**30.1**	**0.1**	**1.0**	**13.2**	**2.9**	**3.53**	**15.2**
rizatriptan	0.23	2.9	1.0	0.2	3.2	1.8	2.86	0.0
sumatriptan	0.22	2.4	-2.0	0.2	0.6	-1.3	3.62	2.0
almotriptan	0.18	1.3	-7.3	0.2	1.4	0.2	3.21	0.1
eletriptan	0.17	4.0	-3.6	0.1	4.4	4.4	3.50	-0.2
erenumab	0.16	>100	-	0.1	73.9	-	4.00	>100
frovatriptan	0.14	-0.9	-8.0	0.1	-0.5	-0.7	3.20	-0.1
galcanezumab	0.10	>100	-	0.0	>100	-	6.67	>100
zolmitriptan	0.07	0.7	-1.2	0.1	3.5	0.2	2.95	-2.4
fremanezumab	0.06	>100	-	0.0	>100	-	7.01	-2.4
indomethacin/caffeine/ prochlorperazine	<0.005	-4.3	0.4	0.0	3.6	1.8	1.09	-7.3

Table 3.6.7b Antimigraine medicines, regional per capita expenditure, consumption (DDD/1000 inhabitants per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	1.14	1.0	3.05	1.38	1.1	3.31	21.3	12.1	8.5	-1.9	1.4	-3.3
Valle d'Aosta	1.17	1.2	2.70	1.62	1.3	3.43	38.2	8.8	27.4	-1.4	1.5	-2.8
Lombardy	0.99	0.9	3.08	1.26	1.0	3.50	27.2	12.4	13.5	-1.4	1.9	-3.2
Province of Bolzano	1.06	0.9	3.07	1.60	1.1	3.83	50.4	20.7	24.9	4.0	4.7	-0.7
Province of Trento	1.22	1.1	3.08	1.33	1.1	3.23	9.5	4.6	4.9	-2.0	0.8	-2.8
Veneto	1.19	1.1	3.06	1.51	1.2	3.49	27.3	11.8	14.1	-0.9	2.3	-3.1
Friuli VG	1.42	1.2	3.22	1.69	1.3	3.64	19.2	5.5	13.2	0.2	3.2	-3.0
Liguria	0.89	0.8	3.04	1.16	0.9	3.38	29.4	17.1	10.9	-0.6	2.3	-2.8
Emilia R.	1.30	1.2	2.97	1.76	1.4	3.56	35.7	13.6	19.7	1.7	3.9	-2.2
Tuscany	0.81	0.7	3.12	1.07	0.8	3.59	31.9	14.8	15.2	0.5	2.3	-1.7
Umbria	0.71	0.6	3.19	0.97	0.7	3.70	35.9	17.4	16.1	1.4	3.5	-2.1
Marche	0.99	0.9	3.07	1.37	1.0	3.60	37.8	17.8	17.3	1.2	4.0	-2.7
Lazio	1.07	1.0	2.98	1.53	1.1	3.67	42.3	16.0	23.0	1.9	4.7	-2.7
Abruzzo	0.85	0.9	2.65	1.37	1.0	3.57	60.7	19.3	35.0	2.3	4.3	-1.9
Molise	0.72	0.6	3.37	1.01	0.8	3.64	39.5	29.5	8.1	0.1	3.6	-3.4
Campania	0.76	0.7	3.05	1.07	0.8	3.70	42.2	17.7	21.2	2.8	4.6	-1.7
Puglia	1.09	0.9	3.16	1.35	1.1	3.51	23.5	11.3	11.3	0.2	3.0	-2.7
Basilicata	0.70	0.6	2.96	0.91	0.7	3.44	30.1	12.3	16.2	0.9	2.3	-1.3
Calabria	0.87	0.8	3.03	1.16	0.9	3.65	33.7	11.2	20.5	0.6	3.1	-2.5
Sicily	0.98	0.8	3.17	1.14	0.9	3.42	16.5	8.2	8.0	-1.5	1.9	-3.4
Sardinia	1.36	1.1	3.35	1.67	1.3	3.60	22.5	14.3	7.5	-1.6	1.8	-3.3
Italy	**1.03**	**0.9**	**3.07**	**1.34**	**1.0**	**3.53**	**30.1**	**13.2**	**15.2**	**0.1**	**2.9**	**-2.7**
North	1.12	1.0	3.05	1.43	1.1	3.48	27.6	12.3	13.9	-0.6	2.4	-2.9
Centre	0.95	0.9	3.04	1.32	1.0	3.64	38.5	16.0	19.7	1.4	3.9	-2.3
South and Islands	0.94	0.8	3.11	1.22	0.9	3.56	29.2	13.1	14.5	0.3	3.0	-2.6

Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure and intensity of use of thyroid medicines in the general population.

In the overall population, in 2021, there is a prevalence of use of 0.6% with a median age of users of 50 years, with no variability between regions (Table 3.6.7c). In line with the 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 age group 15-24 there is a progressive increase in the prevalence in women which reaches about 2% between the ages of 45 and 54, and then decreases in the following groups. Consumption levels also follow the same trend with a maximum value of 4.8 DDD reached in the same age group as the prevalence. A similar, but significantly less pronounced trend is seen in men, with higher prevalence (0.5%) and consumption (0.7 DDD) in the 45-54 age group.
Each user received, on average during the year, at least one dose of medicines for the treatment of migraine for about 50 days, with an expenditure of 156.8 euros (Tabella 3.6.7c). The cost goes from 124.3 in Calabria to 194.5 euros in Sardinia, which also has the highest intensity of use with 57.5 days per user.
For this indicator, too, the northern regions appear to have the highest levels of intensity of use with 51 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. From the results it is indeed observed that the median duration of treatment at the 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 for migraine medication in 2021, with Southern Regions recording the highest proportion (26.1%).

Figure 3.6.7b Breakdown of prevalence of use and consumption of antimigraine medicines under approved care regime and per conto distribution in 2021

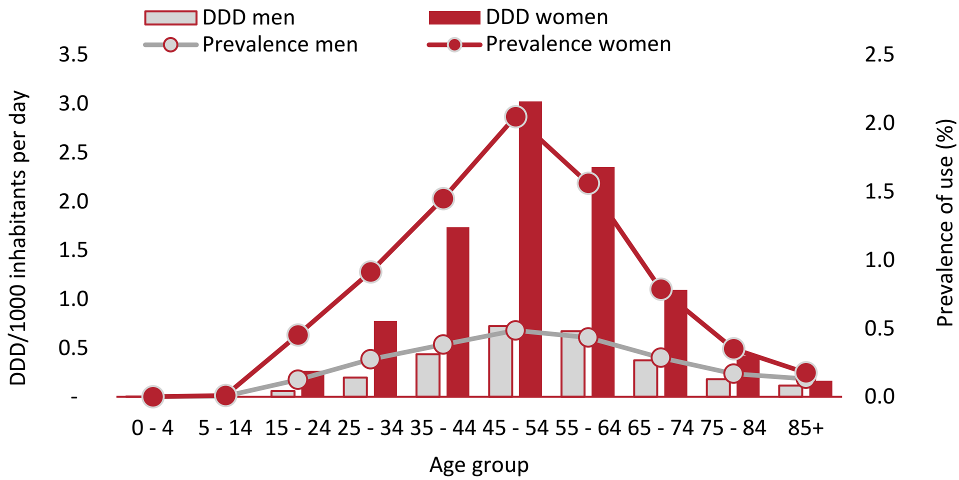


Table 3.6.7c Exposure and duration of therapy withantimigraine medicines by Region under NHS outpatient care and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average median	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	0.3	1.2	0.8	51	154.9	49.8	24.0	19.2
Valle d'Aosta	0.3	1.2	0.7	50	156.1	48.2	24.0	16.2
Lombardy	0.3	1.0	0.6	50	158.6	48.8	24.0	18.1
Province of Bolzano	0.2	1.0	0.6	49	136.4	41.2	24.0	19.5
Province of Trento	0.3	1.1	0.7	50	152.0	50.6	24.0	18.8
Veneto	0.3	1.1	0.7	50	167.6	52.3	24.0	20.0
Friuli VG	0.3	1.2	0.8	50	169.8	51.3	24.0	17.1
Liguria	0.3	1.0	0.7	52	141.6	45.3	24.0	22.0
Emilia R.	0.3	1.2	0.8	49	162.3	51.6	24.0	20.5
Tuscany	0.2	0.9	0.6	51	143.7	45.3	24.0	26.9
Umbria	0.2	0.7	0.5	51	146.0	45.1	24.0	25.4
Marche	0.3	1.1	0.7	50	142.2	44.7	24.0	23.0
Lazio	0.3	1.0	0.6	51	159.2	47.6	24.0	19.7
Abruzzo	0.3	0.9	0.6	51	144.8	46.0	24.0	26.5
Molise	0.2	0.8	0.5	51	148.3	45.4	24.0	23.7
Campania	0.3	0.8	0.5	50	131.5	40.4	18.0	26.1
Puglia	0.3	1.0	0.7	50	153.7	47.7	24.0	24.1
Basilicata	0.3	0.8	0.5	51	127.2	40.7	18.0	27.5
Calabria	0.3	0.9	0.6	52	124.3	37.9	12.0	30.5
Sicily	0.3	1.0	0.6	51	143.7	44.6	18.0	26.8
Sardinia	0.3	1.2	0.8	50	194.5	57.5	30.0	19.9
Italy	**0.3**	1.0	**0.6**	**50**	**156.8**	**48.7**	**24.0**	**22.4**
North	0.3	1.1	0.7	50	162.8	51.0	24.0	19.6
Centre	0.3	0.9	0.6	51	155.1	47.5	24.0	23.0
South and Islands	0.3	0.9	0.6	51	148.1	45.6	20.0	26.1

Key message

- The data on drug consumption, expressed as DDD per 1000 inhabitants/day in 2020, document a **wide regional variability** compared to the national average that cannot be explained by such a marked difference in the frequency of the disease.
- The introduction on the market of **monoclonal antibodies** raises the question of **evaluating the appropriateness** of these active ingredients (erenumab, galcanezumab and fremanezumab) in 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 observed 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, which allow to define the appropriateness of treatments.

References

- Allena M, Steiner TJ, Sances G et al. Impact of headache disorders in Italy and the public-health and policy implications: a population-based study within the Eurolight Project. J Headache Pain 2015; 16:100.
- Altamura C, Brunelli N, Marcosano M, Aurilia C, Egeo G, Lovati C, Favoni V, Perrotta A, Maestrini I, Schiano Di Cola F, d'Onofrio F, Finocchi C, Bertuzzo D, Bono F, Ranieri A, Albanese M, Messina R, Doretti A, Di Piero V, Cevoli S, Barbanti P, Vernieri F; GARLIT Study Group. Conversion from chronic to episodic migraine in patients treated with galcanezumab in real life in Italy: the 12-month observational, longitudinal, cohort multicenter GARLIT experience. J Neurol. 2022 Jun 28:1–10.
- Associazione Italiana per la lotta contro le Cefalee (AIC). La cefalea. Available at the address http://www.malditesta-aic.it/la-cefalea/
- Centro di Riferimento per la Medicina di Genere. Emicrania: una malattia di genere, impatto socio-economico in Italia. Istituto Superiore di Sanità. Ottobre 2018. Available at the address https://www.iss.it/documents/20126/0/Emicrania-una-patologia-di genere.pdf/d5c39e7f-bf711d3a-91ef-6d71efc87a6e?t=1576061517293
- *Die*ner HC, Tassorelli C, Dodick DW et al; International Headache Society Clinical Trials Standing Committee. Guidelines of the International Headache Society for controlled trials of acute treat- ment of migraine attacks in adults: Fourth edition. Cephalalgia 2019; 39(6):687-710.
- Diener HC, Tassorelli C, Dodick DW et al; International Headache Society Clinical Trials Committee. Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults. Cephalalgia 2020; 40(10):1026-44.
- GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the 24 2016. Lancet 2017; 390(10100):1211- 59.

- Matteo E, Favoni V, Pascazio A et al. Erenumab in 159 high frequency and chronic migraine patients: real-life results from the Bologna Headache Center. Neurol Sci 2020; 41(Suppl 2):483-4.
- Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 2017; 16(1):76-87.
- World Health Organisation. Headache disorders. 8 April 2016. Available at the address https:// www.who.int/news-room/fact-sheets/detail/headache-disorders

3.6.8 Antidementia medicines

Epidemiological framework

Dementias are a complex of chronic degenerative diseases comprising a set of conditions, the natural history of which is characterized by the more or less rapid progression of cognitive deficits, behavioral disorders, and functional impairment with loss of autonomy and self-sufficiency with varying degrees of disability and subsequent dependence on others. Dementia interferes with patients' social, work and relationship activities and causes a decline in their abilities. There are different forms of dementia, which are distinguished by the progression of the disease. Dementias can be reversible and irreversible. In recent years, a condition termed Mild Cognitive Impairment (MCI) or Prodromal Alzheiemer's Disease has been emerging, which is a risk factor in the onset of Alzheimer's dementia and is characterized by isolated or multiple cognitive impairment with very mild impairment in the performance of activities of daily living. The prevalence of dementia in industrialized countries is about 8% in those over the age of 65 and rises to more than 20% after the age of 80. According to some projections, dementia cases could triple in the next 30 years in Western countries. In Italy, there are an estimated 1.1 million people with dementia and about 900,000 with MCI. The economic and organizational consequences are easy to imagine, taking into account that the annual direct costs alone for each patient are, in several European studies, estimated to range from 9,000 to 16,000 euros depending on the stage of the disease. Estimates of calculations about the social and health care costs of dementia in Italy assume total figures of about 10-12 billion euros annually, and of these 6 billion for Alzheimer's disease alone.

National data on consumption and expenditure

In 2021 the medicines used in dementia recorded a slight reduction in consumption compared to 2020 (-4.2%), however, reaching 2.4 DDD/1000 inhabitants per day, with an average annual variation (CAGR) of +0.5% of consumption and -13.1% of expenditure in the 2014-2021 period, which stood at 0.44 euros per capita in 2020. In the same period, the average cost per day of therapy has more than halved, switching from 1.19 to 0.43 euros, this is mainly due to the patent expiry of all the molecules belonging to the category (Figure 3.6.8a and Table 3.6.8a). In detail, all drugs show reductions in spending (from -8% of donepezil to -21.4% of memantine) compared to 2020. Rivastigmine is the active ingredient that accounts for half of the spending in the entire category with 0.18 euros per capita, with an average cost per day of therapy more than double the category average (1.03 vs. 0.46 euros), while galantamine is the molecule that has the smallest impact on spending with 0.01 euros per capita, due to low consumption (Table 3.6.8a). At the regional level there is a minimum expenditure of 0.11 euros in Piedmont and a maximum of 0.94 euros in Umbria. For DDDs it ranges from 1.1 in the Province of Trento to 4.3 in the Province of Bolzano. Finally, the average cost ranges from a low of 0.17 euros in Piedmont to 0.98 in Lombardy. There is wide regional variability in all indicators from 2020. The range of expenditure ranges from -64.3% in Molise to +66.0% in Basilicata, the range of consumption ranges from -21.0% in Aosta Valley to +26.2% in Basilicata, and finally the range of average cost passes from -67.7% in Molise to +31.8% in Basilicata.

Figure 3.6.8a Antidementia medicines, temporal trend of consumption and average cost per day of therapy (2014-2021)

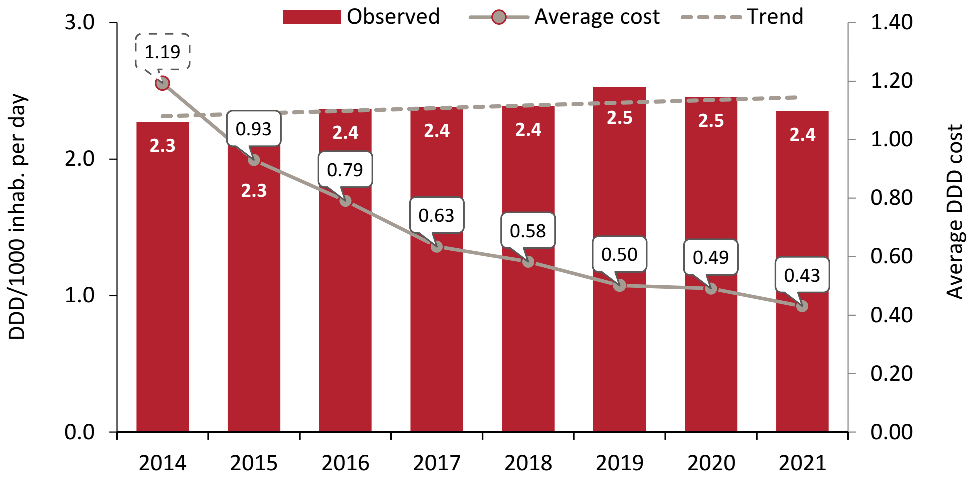


Table 3.6.8a Antidementia medicines, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Anticholinesterases	0.26	-13.6	-13.2	1.3	-3.6	-1.5	0.52	-10.1
Other antidementia medicines	0.11	-21.4	-12.9	1.0	-4.9	3.8	0.31	-17.2
Antidementia medicines	**0.37**	**-16.1**	**-13.1**	**2.4**	**-4.2**	**0.5**	**0.43**	**-12.3**
rivastigmine	0.18	-15.5	-15.0	0.5	-8.6	-4.2	1.03	-7.3
memantine	0.11	-21.4	-12.9	1.0	-4.9	3.8	0.31	-17.2
donepezil	0.06	-8.0	-5.4	0.8	-0.1	1.2	0.20	-7.7
galantamine	0.01	-9.8	-12.1	0.0	-12.1	-12.7	1.04	2.9

Table 3.6.8b Antidementia medicines ,regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	0.16	2.1	0.20	0.11	1.8	0.17	-29.3	-13.5	-18.1	-24.2	-2.6	-22.2
Valle d'Aosta	0.21	2.0	0.29	0.19	1.6	0.33	-11.2	-21.0	12.7	-18.8	-3.3	-16.0
Lombardy	0.81	2.2	1.02	0.75	2.1	0.98	-7.7	-3.4	-4.2	-5.2	0.6	-5.8
Province of Bolzano	0.98	4.5	0.60	0.88	4.3	0.56	-10.1	-3.8	-6.3	-5.1	2.9	-7.8
Province of Trento	0.18	1.1	0.47	0.14	1.1	0.36	-21.5	1.8	-22.7	-16.6	-2.7	-14.3
Veneto	0.25	2.6	0.26	0.20	2.4	0.22	-22.8	-7.7	-16.1	-20.0	0.4	-20.3
Friuli VG	0.38	1.7	0.61	0.44	2.0	0.59	15.8	19.8	-3.1	-10.6	0.4	-11.0
Liguria	0.38	4.0	0.26	0.33	3.7	0.24	-14.2	-6.3	-8.2	-17.2	0.4	-17.5
Emilia R.	0.21	1.9	0.29	0.16	2.0	0.22	-24.6	2.2	-26.0	-17.3	0.5	-17.7
Tuscany	0.51	3.5	0.40	0.28	3.2	0.24	-44.3	-7.9	-39.4	-19.7	0.5	-20.1
Umbria	1.02	4.3	0.65	0.94	4.1	0.63	-7.9	-3.8	-4.1	-8.7	3.0	-11.4
Marche	0.34	2.8	0.33	0.27	2.5	0.30	-21.0	-12.1	-9.8	-16.7	-0.4	-16.4
Lazio	0.37	2.8	0.36	0.31	2.6	0.33	-16.9	-7.8	-9.6	-15.8	1.4	-17.0
Abruzzo	0.63	3.9	0.44	0.54	3.7	0.40	-14.9	-5.4	-9.8	-18.4	0.1	-18.4
Molise	0.51	2.6	0.55	0.18	2.8	0.18	-64.3	10.8	-67.7	-16.5	7.5	-22.3
Campania	0.35	2.6	0.37	0.26	2.4	0.30	-26.3	-7.1	-20.4	-14.2	2.1	-15.9
Puglia	0.62	2.3	0.73	0.59	2.2	0.72	-5.1	-4.2	-0.7	-6.2	1.1	-7.2
Basilicata	0.37	1.8	0.57	0.62	2.3	0.75	66.0	26.2	31.8	-4.1	3.9	-7.8
Calabria	0.54	1.9	0.77	0.31	2.1	0.40	-41.6	11.0	-47.3	-18.7	-0.3	-18.4
Sicily	0.22	1.5	0.40	0.20	1.7	0.34	-5.6	12.5	-15.9	-15.7	-0.8	-15.0
Sardinia	0.31	2.2	0.38	0.17	2.1	0.22	-43.5	-4.0	-41.0	-25.0	-1.1	-24.2
Italy	**0.44**	**2.5**	**0.49**	**0.37**	**2.4**	**0.43**	**-16.1**	**-4.2**	**-12.3**	**-13.1**	**0.5**	**-13.5**
North	0.45	2.3	0.54	0.40	2.2	0.50	-11.3	-4.5	-6.8	-11.2	0.0	-11.2
Centre	0.46	3.1	0.40	0.34	2.9	0.33	-25.5	-7.9	-18.9	-16.1	1.0	-16.9
South and Islands	0.41	2.2	0.50	0.34	2.2	0.42	-17.4	-0.4	-16.8	-14.0	0.7	-14.6

Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to antidementia medicines in the general population.
The exposure data of antidementia medicines are in line with the prevalence data of the disease which in fact tends to occur mainly in the age group of the over-seventy-five year olds. In detail, the prevalence of use of these medicines goes from 0.4% in the 65-74 range, up to 2.5% in the more extreme ranges (85+ years). Women have a higher level of exposure in all age groups, particularly in those over 85 years old, a prevalence level of 2.8% is reached compared to 2.5% in men In this age group, women have a 20% higher consumption and a higher prevalence (19 vs 16 DDDs) than men (Figure 3.6.8d).
In the overall population, the prevalence of use is 0.3% with some differences between regions (Table 3.6.8c) with values ranging from 0.1% in the Province of Trento to 0.6% in Abruzzo and Umbria. As expected, the median age of users is 82 years and, even in this case, there are no differences among the individual Regions. On average, each user remained in treatment for 8 months with an expenditure of 117.6 euros and wide variability between regions: from 39.7 euros in Piedmont to 249.9 in Lombardy. Half of users remain in treatment for less than 224 days, with no substantial differences between the different geographical areas. In the details of the individual regions, the value ranges from the lowest in Val d'Aosta of 180 days to 300 in the Province of Bolzano (6 to 10 months). Nationwide, 7.6% of users received only one prescription during the year, the regions with the highest proportion of users with only one prescription are Sardinia, Lazio (11.5% and 10.6%, respectively) compared to Lombardy and Sicily where the lowest proportion is recorded (less than 4%). With regard to the calculation of the latter indicator, and for DDDs per user, it should be borne in mind that subjects who receive a first prescription toward the end of the year or subjects who discontinue therapy during the year due to side effects, hospitalizations, or death (outliers) tend to be included, however.

Figure 3.6.8d Distribution of 2021 prevalence of use and consumption of antidementia medicines under NHS outpatient care and per conto distribution

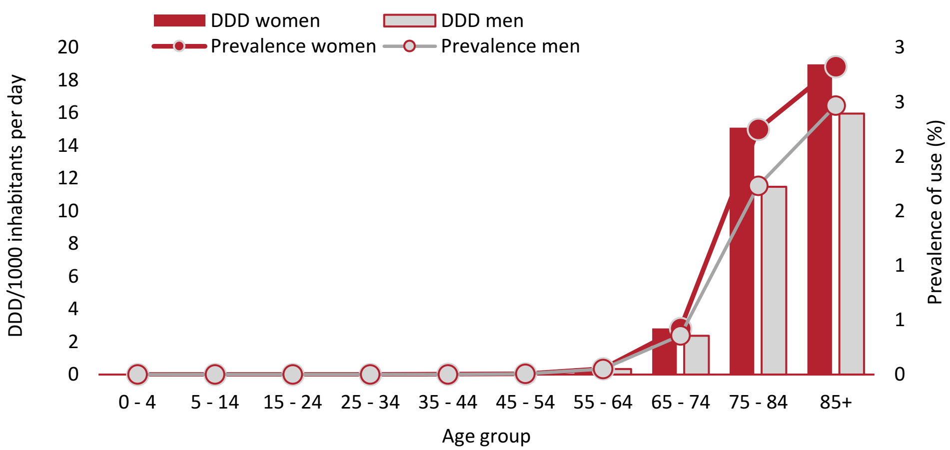


Table 3.6.8c Exposure and duration of therapy with antidementia medicines by Region under NHS outpatient care and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average median	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	0.2	0.4	0.3	81	39.7	241.1	224.0	5.3
Valle d'Aosta	0.2	0.4	0.3	81	82.0	227.1	180.0	4.7
Lombardy	0.2	0.4	0.3	82	249.9	255.8	224.0	3.8
Province of Bolzano	0.2	0.4	0.3	84	208.6	307.1	300.0	7.1
Province of Trento	0.1	0.1	0.1	81	92.2	239.2	205.3	5.3
Veneto	0.2	0.4	0.3	82	57.5	254.2	224.0	4.4
Friuli VG	0.2	0.3	0.3	82	167.7	265.5	252.0	4.2
Liguria	0.4	0.7	0.5	83	62.1	255.8	224.0	7.3
Emilia R.	0.2	0.3	0.2	82	63.3	210.0	196.0	9.5
Tuscany	0.3	0.5	0.4	83	79.1	244.7	205.3	9.8
Umbria	0.4	0.7	0.6	83	163.9	261.5	242.7	7.5
Marche	0.3	0.5	0.4	83	73.2	237.1	224.0	7.3
Lazio	0.3	0.5	0.4	82	83.4	236.6	202.3	10.6
Abruzzo	0.4	0.7	0.6	82	98.1	245.7	224.0	8.4
Molise	0.3	0.5	0.4	82	71.8	241.4	196.0	7.9
Campania	0.3	0.5	0.4	80	66.3	221.2	210.0	9.8
Puglia	0.3	0.4	0.3	81	219.3	239.1	224.0	9.1
Basilicata	0.2	0.4	0.3	82	182.0	252.0	242.7	9.5
Calabria	0.2	0.4	0.3	81	93.7	228.2	196.0	9.7
Sicily	0.1	0.2	0.2	80	97.8	253.8	224.0	3.9
Sardinia	0.2	0.4	0.3	82	60.1	242.8	224.0	11.5
Italy	**0.2**	0.4	**0.3**	**82**	**117.6**	**246.1**	**224.0**	**7.6**
North	0.2	0.4	0.3	82	137.2	252.4	224.0	5.3
Centre	0.3	0.5	0.4	82	90.4	244.0	210.5	9.7
South and Islands	0.2	0.4	0.3	81	113.2	238.9	224.0	8.8

Key message

- The Centers for the Diagnosis and Treatment of Dementia (CDCD) limited patient access in most Italian Regions during the COVID-19 pandemic. Furthermore, patients with dementia represent a category strongly affected by COVID-19 with a significant number of infected and deceased. These two phenomena are likely to have had an effect on the **overall reduction in drug consumption**. The same prevalence of use observed in 2020 is also noted for 2021, thus confirming the reduction from 2019 (to be verified)
- The regional variability in the use of memantine is probably affected by the territorial application of Note 85 in relation to the possibility of a **concomitant use of cholinesterase inhibitors and memantine** in moderate forms of the disease that requires more study and in the off-label use of memantine to treat behavioral disorders as well.
- There is a need to further characterise the use of **cholinesterase inhibitors in very early forms of the disease**, on the borderline between isolated cognitive impairment (ICD) and early dementia, as this subgroup of patients, between off-label and indicated use of the medicines, represents the target category of new antidementia medicines currently being tested and authorised.

References

- Bacigalupo I, Mayer F, Lacorte E et al. A systematic review and meta-analysis on the prevalence of dementia in Europe: estimates from the highest-quality studies adopting the DSM IV diagnostic criteria. J Alzheimers Dis 2018; 66(4):1471-81.
- Clerici F, Vanacore N, Elia A, et al. Memantine effects on behaviour in moderately severe to severe Alzheimer's disease: a post-marketing surveillance study. Neurol Sci. 2012 Feb;33(1):23-31.
- July J, Pranata R. Prevalence of dementia and its impact on mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. Geriatr Gerontol Int 2021; 21(2):172-7.
- National Institute for Health and Care Excellence (NICE). Dementia: assessment, management and support for people living with dementia and their carers. NICE guideline [NG97]. Published: 20 June 2018 www.nice.org.uk/guidance/ng97
- Petersen RC, Smith GE, Waring SC et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neuro 1999; 56(3):303-8.
- Sachdev PS, Lipnicki DM, Kochan NA et al; Cohort Studies of Memory in an International Consortium (COSMIC). The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: The COSMIC Collaboration. PLoS One 2015; 10(11):e0142388.
- Spalletta G, Porcari DE, Banaj N et al. Effects of COVID-19 infection control measures on appointment cancelation in an Italian outpatient memory clinic. Front Psychiatry 2020; 11:599844.

3.7 Respiratory system

Medicines for respiratory system are confirmed as the seventh therapeutic category with the highest public expenditure, amounting to EUR 1,325,5 million and 5.6% of total public expenditure. (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was 22.37 euros, mainly due to the outpatient pharmaceutical expenditure (16.13 euros per capita), reporting a -5.9% decrease compared to the previous year. Instead, expenditure due to purchases by public health facilities is lower (6.24 euros per capita), with a +31.3% increase compared to 2020 (Table 3.1).

Consumption for this category of drugs was 41.8 DDD/1000 inhabitants per day, with a 4.9% decrease compared to 2020 (Table 3.2).

Analysis of the drug use profile by age and gender, including NHS outpatient pharmaceutical care and distribution per conto, 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 grow with age and the highest value is reached in the age group over 75 years (101.7 DDD/1000 inhabitants per day), probably attributable to the treatment of chronic obstructive pulmonary disease (COPD). With regard to gender differences, there is a higher prevalence 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 the age, reaching the maximum value of 50 euros per capita in the age group over 75 years, with a different contribution from the two genders (65.6 euros in men and 39.4 euros in women).

As regards the NHS outpatient care, per capita expenditure was equal to 16.13 euros, with a 6.5% decrease compared to 2020. This trend was determined by a decrease in consumption (-5.7%) and prices (-1.2%), and a shift towards more expensive medicines (mix effect: +0.4%) (Table 3.9). There is also evidence of stability in the average cost per day of therapy (-0.9%). Within this channel, beta-adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics, represent the most expensive and consumed category, with EUR 7.81 per capita and 12.7 DDD/1000 inhabitants per day respectively. The beclomethasone/formoterol combination represents the drug with the highest expenditure impact (15.3%), followed by vilanterol/fluticasone furoate (14.6%) (Table 3.10). These active substances are LABA+ICS (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 of 146.2 and 139.3 million euros respectively (Table 3.11).

The triple combination vilanterol/umeclidinium/fluticasone furoate (LABA+LAMA+ICS), along with tiotropium and glycopyrrolate/beclomethasone/formoterol, are on the list of the top 30 active ingredients with the highest average cost per day of therapy, with an average DDD cost of €2.83, €1.53 and €3.06, respectively (Table 3.13). The triple combinations of glycopyrrolate/beclomethasone/formoterol and vilanterol/umeclidinium/fluticasone furoate fall into the list of the top 30 active ingredients with the greatest change in contracted pharmaceutical spending compared to 2020, both registering a 30% increase (Table 3.14). The same list includes umeclidinium, an anticholinergic bronchodilator used for COPD, with a change in spending of +5.8%, mainly due to an increase in consumption (+6.1%) (Table 3.14). Among the top 30 active ingredients with the greatest reduction in spending belonging to this category are salmeterol/fluticasone (-29.2%), tiotropium (-10.0%), aclidinium (-9.9%), budesonide/formeterol (-3.1%) and beclometasone/formeterol (-2.1%). Among the top thirty most used active ingredients dispensed under approved care regime, we find no drugs affecting the respiratory system (Table 3.16).

In terms of purchases by public health facilities, compared to 2020, there was an increase in expenditure (+30.4%), faced with a reduction in consumption (-8.2%), prices (-4.8%) and a shift in the purchase of pharmaceuticals towards more expensive specialties (mix effect: +49.2%; Table 3.18). The drugs with the greatest impact on spending, for this category, are ivafactor (21%) and the combination lumacaftor/ivacaftor (18.9%), used to treat cystic fibrosis, followed by omalizumab (15.5%), used in IgE allergic asthma (Table 3.19). Moreover, ivacaftor is (compared to 2020) on the list of the top 30 active ingredients involving changes in spending on medicines purchased by public health facilities, with an increase of 87.5% (Table 3.22), whereas in combination with lumafactor presents a 15% reduction in spending (Table 3.23). Among the top thirty active ingredients by average cost per day of therapy purchased by public facilities we find the combination elexacaftor/tezacaftor/ivacaftor, a recently marketed drug indicated for the treatment of cystic fibrosis, with a value of 299.6 euros and an expenditure of 0.86 euros per capita (Table 3.24).

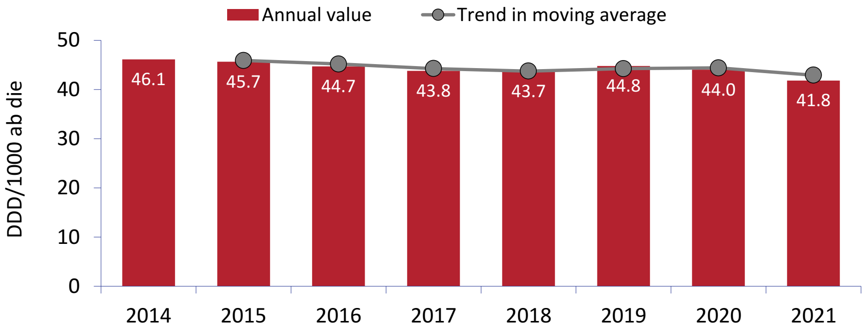
For further information on the use of medicines related to the same therapeutic area, analyzes have been developed on the historical series of consumption by active ingredient and by Region. These analyses focused on medicines for asthma and COPD and on medicines for the treatment of cystic fibrosis (Table 3.7.1 and following).

Main indices of expenditure, consumption and exposure

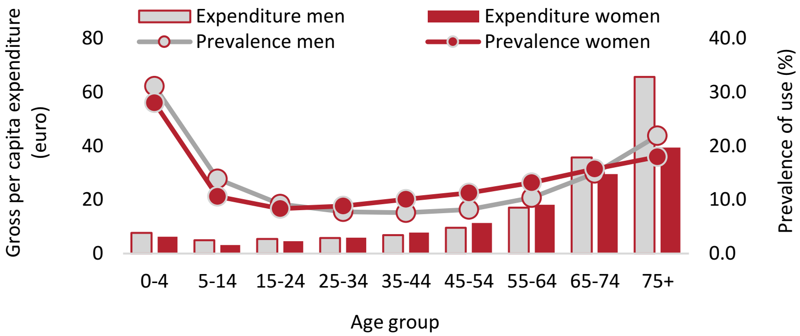
Respiratory system

Public expenditure* in million euros (% over total)	**1,325.5**	**(5.6)**
Δ % 2021-2020		2.2
Regional range gross expenditure per capita:	17.5	30.0
DDD/1000 inhabitants per day* (% over total)	**41.8**	**(3.2)**
Δ % 2021-2020		-4.9
Regional range DDD/1000 inhabitants per day	30.3	60.5

* *includes prescription under approved care regime and purchases from public health facilities*



Age and gender distribution of expenditure, prevalence of use, and consumption under approved care regime and distribution per conto 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhabitants per day		
	Men	Women	Total	Men	Women	Total
0-4	7.6	6.3	7.0	22.2	18.0	20.2
5-14	4.9	3.2	4.1	18.3	11.6	15.0
15-24	5.4	4.6	5.0	21.2	17.7	19.5
25-34	5.8	5.8	5.9	19.7	19.8	19.7
35-44	6.9	7.8	7.4	20.1	23.9	22.0
45-54	9.7	11.4	10.5	25.3	32.6	29.0
55-64	17.1	18.2	17.7	38.6	44.8	41.8
65-74	35.8	29.6	32.5	70.7	65.1	67.7
75+	65.6	39.4	50.0	126.6	85.0	101.7

3.7.1 Medicines for asthma and COPD

Epidemiological framework

Chronic respiratory diseases, and in particular asthma and chronic obstructive pulmonary disease (COPD), are a major public health problem. Worldwide, about 328 million people have COPD, a condition that ranks fourth in mortality and globally accounts for 6% of all causes of death. Although both asthma and COPD are characterized by airway obstruction due to chronic inflammation (in the case of asthma also to bronchial hyperactivity), they have different characteristics. In asthma, obstruction is caused primarily by bronchospasm and inflammation of the bronchial wall, has a variable course, and tends to be totally reversible, either spontaneously or as a result of drug therapies. In contrast, in COPD, obstruction is persistent and has a chronic course with variable progression of obstructive symptoms. The main determinants or risk factors implicated in the onset of COPD are cigarette smoking, air pollution, occupational exposure to dust and chemicals, and repeated lower respiratory tract infections in childhood. Asthma flare-ups originate from various causes, such as infectious (mostly viral) diseases, allergens, exercise, air pollutants, drugs, and food, and can be a cause of death, even in individuals who had not previously presented severe symptoms. The main trigger of COPD flare-ups is infectious etiology. Flare-ups are often the cause of respiratory failure in individuals with severe obstruction. For both obstructive diseases, lack of therapeutic adherence may play a predisposing role in the onset of flare-ups. Correct diagnosis and appropriate treatment are the basis for a better clinical course of the disease and are associated with an improvement in the patient's quality of life. In addition to lifestyle modifications (smoking cessation and increased physical activity), numerous drug therapies are available for the treatment of these conditions including drugs administered by inhalation, short-acting (SABA) and long-acting (LABA) beta2-agonists, inhaled corticosteroids (ICS), short-acting (SAMA) and long-acting (LAMA) anticholinergics, as well as oral medications such as theophylline and, for asthma, antileukotrienes (use in COPD is off-label). It should be pointed out that GOLD indications are not always in line with the indications of the drug data sheet, with possible issues of inappropriateness according to current regulations. In addition, the prescription of LABA+LAMA and triple IC- S+LABA+LAMA in the same device is subject to the specialist treatment plan. In the therapy of severe asthma, several monoclonal antibodies have recently been added, such as omalizumab, directed against IgE, benralizumab and mepolizumab, indicated as adjunctive therapy in the treatment of severe eosinophilic-type asthma, and dupilumab, which, in addition to being approved in atopic dermatitis, is also approved in severe asthma characterized by type 2 inflammation with increased eosinophils and/or exhaled nitric oxide fraction in inadequately controlled patients.

National data on consumption and expenditure

Over the past eight years there has been a decrease in asthma and COPD medication consumption, about 10.7% in 2021 compared with 2014 and with an average annual change of -1.6%. In 2021, consumption was 31.0 DDD, down by 6.3% from 2020. Spending reached 17.38 euros per capita with a change of +4.4% compared to the previous year and an average annual change of +0.7% over the 2014-2021 period. A day of therapy with these medicines cost EUR 1.54, increasing by 2.3% compared to the previous year (Figure and Table 3.7.1a).

Combined long-term beta2-agonists and inhaling corticosteroids (LABA+ICS) remain the most prescribed category in 2021, with consumption values of DDD 9.0/1000 inhabitants per day and expenditure per capita of EUR 5.42, down by 6.0% and 10.2% respectively compared to 2020, followed by long-term anticholinergics/antimuscarinics (LAMA), with 5.5 DDD, and ultra-LABA+ICS (5.5 DDD and + 9.4% compared to 2019) (-6.7% compared to 2020), and by Ultra-LABAs+ICSs, with 3.8 DDD. The growth trend in consumption is confirmed both for monoclonal antibodies (+12.5%), used in severe asthma not controlled with other therapies, and for the triple therapy LAMAs+LABAs+ICSs (+30.5%) which also recorded a strong increase in expenditure (+32.8%). On the other hand, the consumption of LABAs+LAMAs (-6.0%), SABAs (-8.4%) and antileukotrienes (-5,2%) is slightly decreasing. The top 3 substances prescribed are confirmed as beclomethasone+formoterol, fluticasone+vilanterol and salmeterol+fluticasone, decreasing by 1.6% and 0.5% in the case of the first two combinations; as for salmeterol+fluticasone, a decrease of 15.4% is recorded, compared to 2020.

Campania is confirmed as the region with the highest consumption (41.4 DDD) and the Province of Bolzano the one with the lowest (23.7 DDD). Consumption decreased in all Regions, with the largest variations observed in Friuli Venezia Giulia (-13.3%) and Valle d'Aosta (-9.8%) compared with 2020. Southern regions generally have both higher consumption (34.2 DDDs) and average cost per day of therapy (1.57 euros) than the national average (31.0 DDDs and 1.54 euros); in contrast, northern regions have lower consumption (28.3 DDDs) and average cost per day of therapy (1.51 DDDs) than the national average value. Despite the reduction in consumption and per capita spending throughout the country, the average cost per day of therapy increases by 2.3%; a greater increase is seen in Puglia (+5%) and Sicily (+4.3%). Only Marche has a reduction of -1.8% in average DDD cost compared to 2020 (Table 3.7.1b).

Figure 3.7.1a Therapies for asthma and COPD, temporal trend of consumption and average cost per day of therapy (2014-2021)

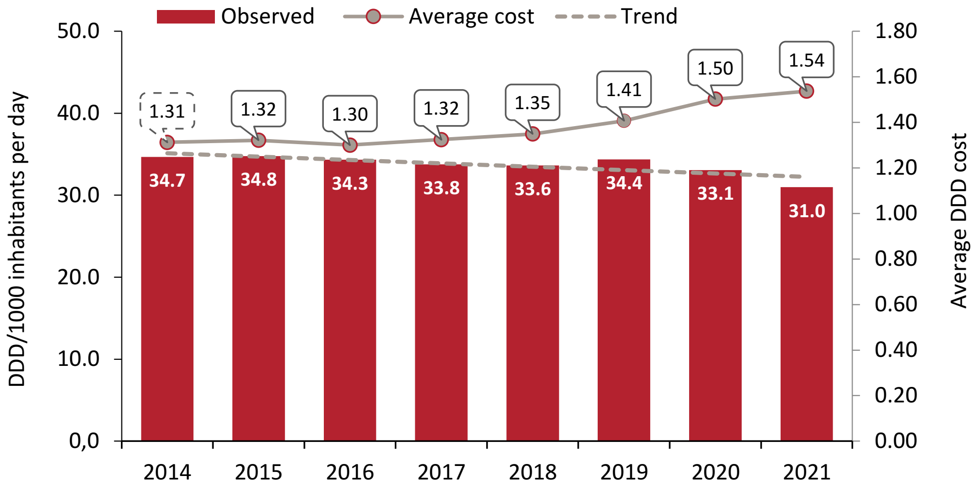


Table 3.7.1a Therapies for asthma and COPD, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
LABAs+ICS	5.42	-10.2	-5.2	9.0	-6.0	-2.2	1.66	-4.3
LAMAs	3.07	-6.8	-1.2	5.5	-6.7	-0.3	1.54	0.2
Ultra-LABAs+ICSs	2.37	-0.7	-	3.8	-0.5	-	1.72	0.1
Monoclonal antibodies	2.12	9.8	29.2	0.2	12.5	32.1	27.68	-2.2
ICSs	1.28	-8.9	-9.8	3.5	-11.0	-9.7	0.99	2.6
LAMAs+LABAs+ICSs	1.01	32.8	-	1.0	30.5	-	2.89	2.0
LABAs+LAMAs	0.82	-9.7	321.9	1.1	-6.0	182.7	2.01	-3.6
Antileukotrienes (LTRAs)	0.46	-6.7	-2.2	2.1	-5.2	-0.6	0.61	-1.2
LABAs	0.20	-14.4	-12.0	0.6	-13.0	-11.8	0.97	-1.3
SABAs	0.17	-8.0	-7.5	2.4	-8.4	-5.5	0.19	0.7
Ultra-LABAs	0.16	-16.5	-13.5	0.4	-16.4	-13.7	1.07	0.2
SABAs+SAMAs	0.11	-12.2	-8.5	0.5	-15.0	-8.6	0.65	3.6
SABAs+ICSs	0.10	-11.0	-8.2	0.2	-11.1	-8.1	1.21	0.4
Theophylline-based bronchodilators	0.05	-13.7	-10.2	0.4	-12.6	-12.1	0.34	-1.0
SAMAs	0.04	-23.2	-12.9	0.5	-25.0	-7.1	0.24	2.7
PDE-4 inhibitors	<0.005	-13.0	-13.7	0.0	-15.8	-13.3	1.56	3.6
Chromones	<0.005	-88.9	-44.9	0.0	-88.9	-43.8	0.63	0.1
Medicines for asthma and COPD	**17.38**	**-4.4**	**0.7**	**31.0**	**-6.3**	**-1.6**	**1.54**	**2.3**
beclomethasone/ formoterol	2.50	-1.9	5.0	4.0	-1.6	5.5	1.72	-0.1
fluticasone furoate/ vilanterol	2.37	-0.7	-	3.8	-0.5	-	1.72	0.1
budesonide/formoterol	1.42	-3.1	2.6	2.1	-2.3	4.7	1.87	-0.6
salmeterol/fluticasone	1.25	-29.0	-17.4	2.4	-15.4	-12.1	1.43	-15.9
tiotropium	1.20	-9.9	-10.0	2.2	-10.1	-8.6	1.49	0.4
omalizumab	0.97	8.1	15.6	0.1	8.6	19.4	25.70	-0.2
umeclidinium	0.85	5.7	-	1.5	6.0	-	1.59	0.0
mepolizumab	0.63	-1.3	-	0.1	8.6	-	30.16	-8.9
aclidinium	0.61	-9.9	7.7	1.0	-9.0	7.3	1.58	-0.7
glycopyrronium/ beclomethasone/ formoterol	0.53	33.5	-	0.5	34.8	-	2.99	-0.7

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	17.05	29.7	1.57	16.33	28.0	1.60	-4.2	-5.9	2.2	0.6	-1.7	2.3
Valle d'Aosta	17.50	32.9	1.45	16.13	29.6	1.49	-7.8	-9.8	2.5	-2.9	-4.1	1.2
Lombardy	16.91	30.8	1.50	16.09	28.8	1.53	-4.8	-6.4	1.9	0.4	-1.1	1.5
Province of Bolzano	13.82	25.4	1.49	12.89	23.7	1.49	-6.7	-6.5	0.0	0.1	-1.6	1.7
Province of Trento	15.43	30.5	1.38	14.64	28.8	1.39	-5.1	-5.6	0.8	0.0	-1.3	1.3
Veneto	15.07	28.4	1.45	14.29	26.2	1.50	-5.2	-7.7	3.0	0.7	-1.6	2.3
Friuli VG	16.49	31.8	1.42	14.33	27.5	1.42	-13.1	-13.3	0.5	0.2	-1.3	1.6
Liguria	18.49	33.3	1.51	17.59	31.2	1.54	-4.8	-6.3	1.9	1.5	-0.9	2.4
Emilia R.	15.33	30.7	1.37	15.23	29.4	1.42	-0.7	-4.0	3.8	0.3	-1.8	2.1
Tuscany	18.75	33.9	1.51	17.74	31.8	1.53	-5.4	-6.3	1.2	1.3	-1.2	2.5
Umbria	17.32	31.7	1.49	16.17	28.9	1.53	-6.6	-8.8	2.6	1.0	-1.4	2.5
Marche	17.58	29.2	1.64	15.95	27.1	1.61	-9.3	-7.4	-1.8	-0.4	-2.0	1.7
Lazio	20.18	36.7	1.50	19.00	33.9	1.54	-5.9	-7.7	2.3	0.1	-2.1	2.3
Abruzzo	17.77	29.9	1.62	16.51	27.9	1.62	-7.1	-6.8	-0.1	1.6	-0.9	2.5
Molise	14.58	25.2	1.58	14.26	24.1	1.62	-2.2	-4.5	2.6	-0.1	-2.2	2.2
Campania	23.08	43.0	1.47	22.35	41.4	1.48	-3.2	-3.8	0.9	1.3	-0.8	2.1
Puglia	20.24	35.3	1.57	19.90	33.1	1.65	-1.7	-6.1	5.0	0.4	-3.0	3.4
Basilicata	22.56	35.6	1.73	21.79	34.0	1.75	-3.4	-4.5	1.4	2.4	-1.8	4.3
Calabria	19.51	32.8	1.62	18.76	30.4	1.69	-3.8	-7.4	4.1	1.4	-1.8	3.2
Sicily	18.43	33.3	1.51	17.90	31.1	1.58	-2.8	-6.6	4.3	1.2	-1.6	2.9
Sardinia	19.03	35.8	1.45	18.28	33.8	1.48	-3.9	-5.6	2.1	-0.9	-2.5	1.6
Italy	**18.18**	**33.1**	**1.50**	**17.38**	**31.0**	**1.54**	**-4.4**	**-6.3**	**2.3**	**0.7**	**-1.6**	**2.3**
North	16.35	30.3	1.47	15.60	28.3	1.51	-4.6	-6.5	2.3	0.5	-1.4	1.9
Centre	19.17	34.5	1.52	17.98	31.9	1.54	-6.2	-7.3	1.5	0.5	-1.8	2.3
South and Islands	20.20	36.2	1.53	19.57	34.2	1.57	-3.2	-5.5	2.8	0.9	-1.7	2.7

Exposure and adherence in population

The prevalence of drug use for asthma and COPD was 8.9% at national level in 2021. Prevalence, similarly to consumption, shows higher levels in the extreme age groups; in particular in the pediatric population 0-4 years of age, with a percentage of 30.2% and 27.2%, in men and women respectively, and in the age group equal to or greater than 85 years of age with a percentage of 22.4% and 15.0%, in men and women respectively (Figure 3.7.1b). It should be noted that for asthma the diagnosis is often made in paediatric age, frequently by free choice pediatricians, while for COPD it is usually considered an age greater than or equal to 45 years.

Making a comparison of the different geographical areas, higher levels are observed in the South (10.5%), compared to the Centre (9.2 %) and the North of Italy (7.6 %). The median age of users was lower than in 2020 (53 years), and an average of 121.6 DDDs were dispensed per usermwith a cost of 176 euros. The 38% of users, with no differences across geographic areas, received only one prescription in the year (Table 3.7.1c).

For this reason, using Health Card data, an analysis was performed to estimate the adherence and persistence of treatments for obstructive airway diseases, focusing attention on new users, of at least 45 years, and considering a one-year follow-up.

The study population includes a total of 117,143 new users of treatments for obstructive airway diseases. The median age of the cohort is 68 years (interquartile range [IQR]: 58-78), with a greater proportion of women than men (55.5% vs 44.5 %).

The percentage of subjects with high and low adherence to the treatment was 24.2% and 43.5% respectively, showing an increase in subjects with high adherence (+4%), mainly in men (+8%), and a decrease in subjects with low adherence (-1%), compared to 2020. High adhesion rates increase slightly by age group, with a moderate decline for the older group of the population In general, men have a higher percentage of subjects with high adherence than women (26.8% vs 22.2%). The proportion of subjects with high adherence to treatment was higher in the North (26.8%) and the Centre (25.5%) compared to the South and the Islands (22.2%) (Table 3.7.1d).

Taking into consideration persistence to treatment with treatments for obstructive airway diseases, at 12 months persistent subjects ranged from 8.1% to 12.9% starting from the age group of 45-54 years up to subjects aged 85 years or more, with the highest value found for those aged 75-84 years (13.5%). Men recorded higher persistence rates than women (13,7% vs 9,4%) (Tabella 3.7.1e).

If considering the median time to discontinuation of treatment, a 50% probability of discontinuing treatment is achieved at approximately 60 days, such probability is higher in the South and Islands (Figure 3.7.1c).

Figure 3.7.1b Breakdown of prevalence of use and consumption of medicines for asthma and COPD under approved care regime and per conto distribution in 2021

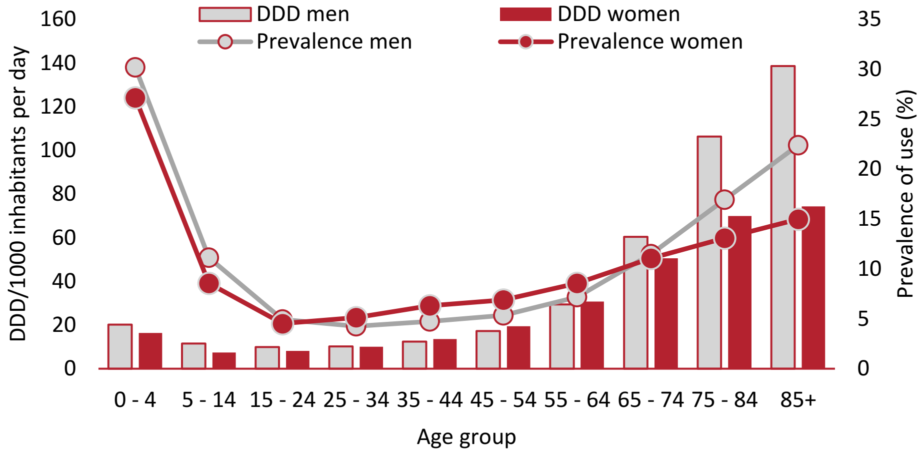


Table 3.7.1c Exposure and duration of therapy with medicines for asthma and COPD by Region under approved care regime and per conto distribution (year 2021)

Region	Prevalence of use (%)			Average median	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	7.0	6.9	6.9	56	234.8	145.4	60.0	32.6
Valle d'Aosta	8.2	8.3	8.3	51	167.0	121.1	41.3	35.8
Lombardy	7.8	7.8	7.8	49	183.8	127.6	50.0	35.6
Province of Bolzano	6.6	6.3	6.5	45	163.9	115.9	30.0	38.5
Province of Trento	9.2	9.0	9.1	44	147.4	106.6	30.0	39.1
Veneto	7.3	7.0	7.1	49	172.5	126.6	41.7	36.9
Friuli VG	7.0	6.9	7.0	56	194.9	142.9	50.0	35.0
Liguria	8.7	8.8	8.8	57	190.1	135.1	55.0	32.3
Emilia R.	8.4	8.5	8.4	49	143.6	107.8	30.0	40.3
Tuscany	7.6	7.6	7.6	57	208.5	146.5	60.0	35.5
Umbria	8.4	8.2	8.3	58	180.6	127.0	34.8	41.2
Marche	7.9	7.5	7.7	54	192.0	128.1	42.7	39.7
Lazio	10.2	11.1	10.7	53	173.8	112.3	30.7	37.9
Abruzzo	8.8	8.8	8.8	53	185.4	114.5	30.0	43.6
Molise	8.4	8.3	8.4	58	170.8	110.7	30.0	43.3
Campania	13.0	13.7	13.4	51	151.9	102.6	30.0	38.8
Puglia	9.5	8.9	9.2	56	174.4	125.4	45.0	37.9
Basilicata	9.3	9.2	9.3	59	186.5	130.0	45.0	39.0
Calabria	9.4	9.3	9.4	59	171.9	111.5	31.3	41.4
Sicily	9.5	9.5	9.5	57	154.6	112.9	35.0	40.5
Sardinia	9.9	10.6	10.2	54	164.4	122.2	33.3	40.3
Italy	**8.8**	**8.9**	**8.8**	**53**	**176.0**	**121.6**	**40.0**	**38.1**
North	7.6	7.6	7.6	51	183.3	128.0	46.3	36.4
Centre	8.9	9.2	9.1	55	186.8	124.9	40.7	38.0
South and Islands	10.4	10.5	10.4	54	163.0	113.2	33.3	39.9

Table 3.7.1d Indicators of adherence to treatment with medicines for asthma and COPD in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

	Total N=117,143				North ^ N=33,316				Centre N=26,805				South N=57,022			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*^																
45-54 years	55.0	49.7	48.6	-2	51.6	45.5	41.8	-8	54.8	49.7	48.7	-2	57.3	52.4	52.7	0
55-64 years	51.8	44.7	44.8	0	49.6	40.7	38.8	-5	52.2	44.3	44.6	1	52.9	47.2	48.0	2
65-74 years	48.8	42.8	42.3	-1	46.3	39.4	37.4	-5	47.9	40.9	40.3	-2	50.7	45.7	45.9	0
75-84 years	46.1	41.1	39.8	-3	44.5	38.2	34.3	-10	44.6	39.9	36.9	-7	48.2	43.8	44.9	2
≥85 years	48.9	43.2	42.5	-2	48.6	41.2	39.5	-4	46.5	41.2	39.3	-5	50.5	45.9	46.2	1
Women	51.9	45.4	46.1	2	50.0	42.1	40.4	-4	50.5	43.7	44.7	2	53.9	48.5	50.2	4
Men	47.2	42.2	40.2	-5	44.6	38.7	35.1	-9	47.0	41.8	38.0	-9	48.9	44.7	44.1	-1
Total	**49.9**	**44.0**	**43.5**	**-1**	**47.7**	**40.6**	**38.0**	**-6**	**49.1**	**42.9**	**41.8**	**-2**	**51.8**	**46.8**	**47.5**	**1**
High adherence*^																
45-54 years	15.8	18.0	20.4	13	17.3	19.1	22.9	20	16.3	18.9	20.3	8	14.6	16.9	19.0	12
55-64 years	18.6	22.1	23.1	5	20.4	25.1	25.6	2	18.9	22.5	24.3	8	17.4	20.0	21.2	6
65-74 years	20.9	24.2	25.2	4	22.7	26.9	27.8	3	22.0	25.7	26.6	3	19.3	21.9	23.2	6
75-84 years	22.3	25.9	27.0	4	24.3	28.2	29.5	5	22.9	27.6	28.8	4	20.6	23.4	24.5	5
≥85 years	21.4	25.3	25.2	0	22.7	27.5	27.9	1	23.8	26.4	26.5	0	19.1	23.1	22.8	-1
Women	18.6	22.0	22.2	1	19.8	24.2	24.3	0	19.9	23.4	23.2	-1	16.9	19.9	20.5	3
Men	21.7	24.7	26.8	8	24.1	27.3	29.8	9	22.0	25.8	28.6	11	20.1	22.5	24.2	8
Total	**19.9**	**23.2**	**24.2**	**4**	**21.7**	**25.6**	**26.8**	**5**	**20.8**	**24.4**	**25.5**	**4**	**18.3**	**21.0**	**22.2**	**5**

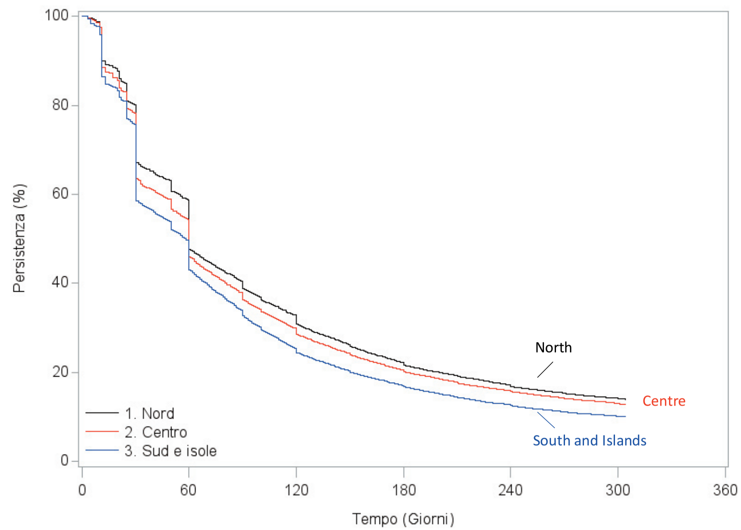
*Adherence to treatment was assessed during the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high 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, who received a first prescription in the period 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.
Percentages of people with low/high adherence relating to the specific category.
^ Excluding Emilia Romagna
Median follow-up time (IQR): 244 (114-330)

Table 3.7.1e Persistence after one year of treatment with medicines for asthma and COPDin the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

Persistence after 12 months	Total N=117,143				North ^ N=33,316				Centre N=26,805				South N=57,022			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54 years	5.2	6.5	8.1	25	6.6	8.0	10.3	28	5.5	6.2	8.5	37	4.2	5.6	6.6	17
55-64 years	6.9	9.2	9.9	7	8.7	11.3	11.8	4	6.2	9.1	10.8	18	6.1	8.0	8.5	6
65-74 years	8.9	11.0	12.3	12	11.0	13.3	14.9	12	8.9	11.8	13.7	16	7.7	9.2	10.3	12
75-84 years	10.2	12.3	13.5	10	11.9	14.3	15.2	6	9.8	12.6	15.2	21	9.1	10.7	11.6	9
≥85 years	9.5	10.8	12.9	19	9.8	11.3	14.6	29	10.0	10.7	12.8	20	9.0	10.5	11.8	13
Women	6.5	8.2	9.4	14	7.9	9.8	11.4	15	6.7	8.6	10.3	20	5.5	7.0	7.8	10
Men	10.4	12.6	13.7	9	12.5	14.9	15.9	6	10.0	12.8	15.2	19	9.4	10.9	11.8	8
Total	**8.2**	**10.1**	**11.3**	**12**	**9.9**	**12.0**	**13.4**	**11**	**8.1**	**10.3**	**12.4**	**20**	**7.2**	**8.7**	**9.6**	**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 3.7.1c Time (in days) to discontinuation of treatment with medicines for asthma and COPDin 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



Epidemiology and prescribing profiles in General Medicine

The data relating to epidemiology and prescribing profiles were obtained through a network of GPs homogeneously distributed throughout the national territory bringing together all information relating to diagnosis of pathology, demographic information, pharmaceutical prescription, and more to Health Search-IQVIA Health LPD.

For the OsMed Report 2021, the incidence and prevalence of asthma or COPD for the years 2019, 2020, and 2021 were analyzed, as well as their changes between 2021 and 2020. In addition, the prevalence of medication use for the treatment of these conditions for the same three years was analyzed.

The incidence of asthma in the population in the care of the 800 GPs in the HS network was 2.4% in 2021. Although it emerges with a reduction in the estimate of 18.1% from the previous year, it is still evident how this change is less than the reduction observed between 2019 and 2020. Regarding new COPD diagnoses in 2021, a disease incidence of 1.6% is observed, up from 2020 (12.9%) (Table 3.7.1f). Stratifying the analysis by geographic area, a reduction in the estimated incidence of asthma from 2020 emerges as 20.8% for the North, 17.2% for the Center, and 16.5% for the South and Islands. The opposite trend is observed for COPD, with an increase in estimates for all three areas considered.

From the analysis by sex, men show the greatest reduction in the incidence of asthma compared to 2020 (-21.4%); a reduction that also increases as age increases. In contrast, for COPD, the greatest growth in incidence is observed in women (13.9%), and in the 46-65 age group (25.0%).

When analyzing the prevalence of asthma in 2021, it was 8.8%, a slight increase from 2020 (4.2%). In contrast, for COPD, a disease prevalence of 2.9% is observed, with a decrease of 0.7% from the previous year (Table 3.7.1g).

When analyzing the geographical distribution, for both asthma and COPD, it is possible to see a higher prevalence value in the regions of the South and Islands (11.2% for asthma and 3.6% for COPD) than in the Center (7.4% for asthma and 3.0% for COPD) and the North (7.4% for asthma and 2.2% for COPD). Compared with 2020, asthma prevalence appears to be increasing for all three geographic areas, in contrast to the findings for COPD.

Asthma is more common in women (9.6% vs 8.1%), while COPD shows a higher prevalence in men (3.4% vs 2.4%). As with the geographic analysis, there is a growth in asthma prevalence estimates in both sexes from 2020, and a reduction in COPD. Stratifying the analysis by age group, while for asthma there appears to be no marked differences in prevalence in accordance with age, for COPD this ranges from 0.2% of younger individuals to 11.6% of those over 85.

The prevalence of medication use for the treatment of asthma and COPD was 21.9% and 38.9%, respectively, a decrease from 2020 (asthma: -11.0%; COPD: -2.8%). Geographically, the highest prevalences of use are found in the North for both respiratory diseases, while the highest change, relative to 2020, emerges in the Center (for COPD) and the South and Islands (for asthma). Stratifying the analysis by sex, the highest prevalences of use are found in women and men in the treatment of asthma and COPD, respectively. For both conditions, however, the largest reductions in estimates are observed in males (asthma: -12.1%; COPD: -3.7%).

Finally, for both disease conditions, the prevalence of use increases with increasing age, with a decline in patients aged 85 years or older (Table 3.7.1h).

In 2021, the most widely used drugs for the treatment of asthma appear to be LABAs in combination with ICSs (LABA+ICS: 12.0%), followed by SABA (alone) (4.8%), ICS (alone) (4.0%), and ULTRA-LABA+ICS (3.7%) (Table 3.7.1i). Almost all of the therapeutic categories considered are characterized by a reduction in the estimated prevalence of use compared to 2020; reductions particularly evident for SABA+SAMA (-36.4%), SAMA (-33.3%), theophylline bronchodilators (-25.0%), ICS (-24.5%), and LABA (-20.0%).

In patients with COPD, the highest prevalence of use is observed for LAMA (alone) (18.1%), followed by LABA in combination with ICS (LABA+ICS: 11.8%), by ULTRA-LABA+ICS (7.2%) and by ICS (alone) (5.5%). Almost all of the therapeutic categories considered are characterized by a reduction in the estimated prevalence of use compared to 2020; reductions are particularly evident for SABAs+SAMAs (-25.9%), SAMAs (-25.0%), theophylline bronchodilators (-21.1%), ICS (-20.3%), and SABAs+ICSs (-20.0%). Only for the fixed triple combination LAMA+LABA+ICS (30.0%), the LABA+LAMA combination (6.8%), and the ULTRA-LABA+ICS category is there a positive change in the prevalence estimate.

Finally, when analyzing the trend of prevalence of use of drugs for the treatment of asthma (Figure 3.7.1d-A) during 2019-2021, a decreasing trend emerges for all therapeutic categories. Similar trend emerges in patients with COPD (Figure 3.7.1d-B), although less markedly. In addition, for some therapeutic categories there is a rebound in prevalence of use estimates, after a contraction seen between 2019 and 2020.

Table 3.7.1f Incidence of patients with asthma and COPD in the population eligible for medical assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographical area (years 2019-2021)

	Asthma				COPD			
	Incidence (‰) 2019	Incidence (‰) 2020	Incidence (‰) 2021	Δ% 21-20	Incidence (‰) 2019	Incidence (‰) 2020	Incidence (‰) 2021	Δ% 21-20
Geographic analysis								
North	3.2	2.2	1.7	-20.8	1.6	1.0	1.2	27.1
Centre	4.4	2.6	2.2	-17.2	2.6	1.6	1.8	11.1
South and Islands	6.2	4.1	3.4	-16.5	2.6	1.8	1.9	4.4
Analysis by gender								
Men	3.7	2.6	2.0	-21.4	2.5	1.6	1.8	11.9
Women	5.3	3.3	2.8	-14.7	1.9	1.2	1.4	13.9
Analysis by age								
≥45 years	4.2	2.9	2.4	-16.4	0.1	0.1	0.1	-16.7
46-65	4.5	2.9	2.4	-18.4	1.5	1.0	1.2	25.0
66-74	5.2	3.0	2.6	-13.1	4.8	3.1	3.5	15.4
75-84	4.9	3.0	2.2	-26.2	6.3	4.4	5.4	21.9
≥85 years	4.4	2.7	2.1	-21.4	6.3	4.9	5.7	16.2
Total	**4.5**	**2.9**	**2.4**	**-18.1**	**2.2**	**1.4**	**1.6**	**12.9**

Indicators used:

Incidence of asthma: number of patients with a "first" diagnosis of asthma recorded during the year [**numerator**], on the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Incidence of COPD: number of patients with a "first" diagnosis of COPD recorded during the year [**numerator**], on the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Table 3.7.1g Incidence of patients with asthma and COPD in the population eligible for medical assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: analysis by gender, age group and geographical area (years 2019-2021)

	Asthma				COPD			
	Prevalence (%) 2019	Prevalence (%) 2020	Prevalence (%) 2021	Δ% 21-20	Prevalence (%) 2019	Prevalence (%) 2020	Prevalence (%) 2021	Δ% 21-20
Geographic analysis								
North	7.0	7.1	7.4	3.8	2.3	2.2	2.2	-1.0
Centre	7.0	7.1	7.4	3.9	3.2	3.1	3.0	-2.1
South and Islands	10.5	10.8	11.2	4.3	3.7	3.6	3.6	-0.4
Analysis by gender								
Men	7.5	7.7	8.1	4.4	3.5	3.4	3.4	-1.2
Women	9.0	9.2	9.6	4.2	2.5	2.5	2.4	-0.3
Analysis by age								
≥45 years	8.7	8.9	9.2	4.2	0.2	0.2	0.2	7.5
46-65	8.1	8.3	8.7	4.8	1.6	1.7	1.8	8.4
66-74	8.1	8.3	8.5	2.2	5.5	5.8	6.2	6.7
75-84	8.0	8.2	8.5	2.7	9.1	9.3	9.6	3.0
≥85 years	7.2	7.4	7.8	4.6	11.5	11.5	11.6	1.1
Total	**8.3**	**8.5**	**8.8**	**4.2**	**3.0**	**2.9**	**2.9**	**-0.7**

Indicators used:

Prevalence of asthma: number of patients diagnosed with asthma[**numerator**], on the total population eligible for assistance [**denominator**]

Prevalence of COPD: number of patients diagnosed with COPD[**numerator**], on the total population eligible for assistance [**denominator**]

Table 3.7.1h Prevalence of use of medicines for asthma and COPD in patients with these conditions and comparison 2021-2020: stratified analysis by gender, age group and geographic area

	Asthma				COPD			
	Prevalence (%) 2019	Prevalence (%) 2020	Prevalence (%) 2021	Δ% 21-20	Prevalence (%) 2019	Prevalence (%) 2020	Prevalence (%) 2021	Δ% 21-20
Geographic analysis								
North	27.6	26.6	24.0	-9.8	43.4	41.8	41.1	-1.7
Centre	26.5	25.5	22.4	-12.2	41.9	39.6	38.8	-2.0
South and Islands	24.8	22.7	20.1	-11.5	40.6	38.8	37.3	-3.9
Analysis by gender								
Men	24.4	23.1	20.3	-12.1	43.1	41.1	39.6	-3.7
Women	27.5	25.8	23.3	-9.7	40.1	38.6	38.0	-1.6
Analysis by age								
≥45 years	21.0	19.2	17.1	-10.9	13.4	11.4	10.2	-10.5
46-65	29.3	27.2	23.8	-12.5	32.3	28.0	26.1	-6.8
66-74	32.4	29.9	27.6	-7.7	44.7	41.2	40.6	-1.5
75-84	31.0	29.3	27.4	-6.5	49.1	47.0	47.2	0.4
≥85 years	24.3	24.2	22.8	-5.8	43.5	43.5	43.4	-0.2
Total	**26.1**	**24.6**	**21.9**	**-11.0**	**41.8**	**40**	**38.9**	**-2.8**

Indicator used:

Prevalence of use of medicines for asthma: number of patients treated with medicines for asthma[**numerator**] on the total number of patients diagnosed with asthma[**denominator**]

Prevalence of use of medicines for COPD: number of patients treated with medicines for COPD[**numerator**] on the total number of patients diagnosed with COPD[**denominator**]

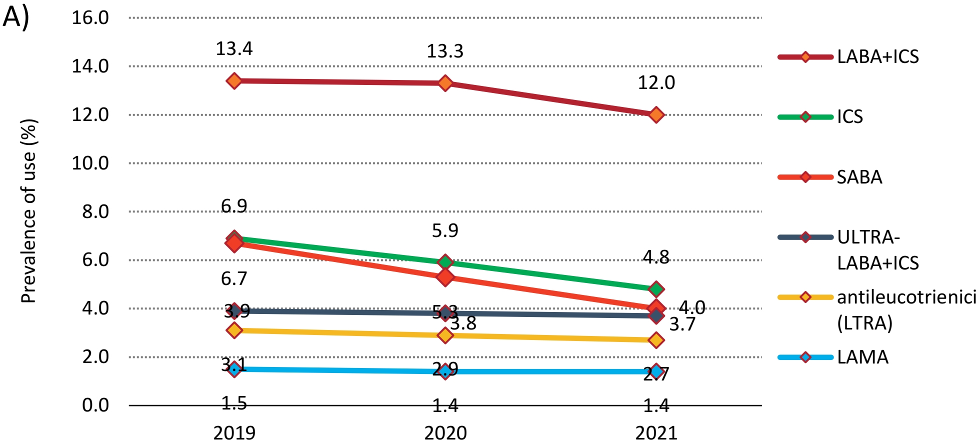
Table 3.7.1i Prevalence of use of medicines for asthma and COPD in patients with these conditions and comparison 2021-2020: analysis by therapeutic category (year 2021)

	Prevalence of use (%)			
	Asthma	Δ% 21-20	COPD	Δ% 21-20
Monoclonal antibodies	0.1	0.0	0.0	0.0
Antileukotrienes (LTRAs)	2.7	-6.9	0.6	0.0
Theophylline-based bronchodilators	0.3	-25.0	1.5	-21.1
Chromones	0.0	0.0	0.0	0.0
ICSs	4.0	-24.5	5.5	-20.3
PDE-4 inhibitors	0.0	0.0	0.0	0.0
LABAs	0.4	-20.0	1.1	-15.4
LABAs+ICS	12.0	-9.8	11.8	-5.6
LABAs+LAMAs	0.1	0.0	4.2	10.5
LAMAs	1.4	0.0	18.1	-2.7
LAMAs+LABAs+ICSs	0.1	0.0	3.4	30.8
SABAs	4.8	-18.6	2.8	-17.7
SABAs+ICSs	0.5	-16.7	0.4	-20.0
SABAs+SAMAs	0.7	-36.4	2	-25.9
SAMAs	0.2	-33.3	0.9	-25.0
ULTRA-LABAs	0.0	0.0	1.4	-6.7
ULTRA-LABAs+ICSs	3.7	-2.6	7.2	1.4

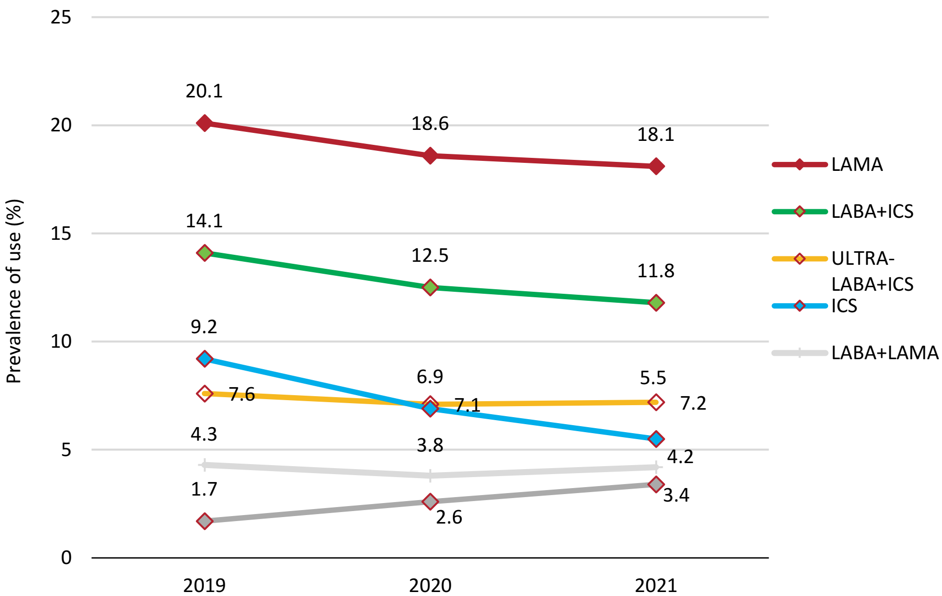
Indicator used:
Prevalence of use of medicines for asthma: number of patients treated with a specific therapeutic category prescribed for asthma[**numerator**] on the total number of patients diagnosed with asthma[**denominator**]
Prevalence of use of medicines for COPD: number of patients treated with a specific therapeutic category prescribed for COPD[**numerator**] on the total number of patients diagnosed with COPD [**denominator**]

Figure 3.7.1e Prevalence of use of medicines for asthma (A) and COPD (B) in patients with these conditions: analysis by therapeutic category (years 2019-2021)

A)



B)



Indicator used:
Prevalence of use of medicines for asthma: number of patients treated with a specific therapeutic category prescribed for asthma[**numerator**] on the total number of patients diagnosed with asthma[**denominator**]
Prevalence of use of medicines for COPD: number of patients treated with a specific therapeutic category prescribed for COPD[**numerator**] on the total number of patients diagnosed with COPD [**denominator**]

Key message

- A steady reduction in asthma and COPD drug consumption is observed over the past eight years (CAGR 14-21: -1.6%), which stands at 31.0 DDD/1000 inhabitants per day in 2021. In contrast, spending shows a steadily increasing trend (CAGR 14-21: 0.7%) with a per capita expenditure of 17.38 euros in 2021. This trend suggests the use of high-cost drugs as confirmed by the increasing consumption of the triple combination LABA+LAMA+ICS (+30.5% over 2020) and monoclonal antibodies for severe asthma (+12.5% over 2020).

- Within the category, LABA+ICS and LAMA account for about 50% of total consumption in 2021. However, it is interesting to note that all drugs, including fixed combinations, show a reduction in consumption compared to 2020, with the exception of omalizumab (+8.6%), umeclidinium (+6.0%) and mepolizumab (+8.6%).

- Regional data indicate wide variability in asthma and COPD drug consumption, spending, and exposure. In 2021, Campania was the region with the highest expenditure (22.4 euros per capita), consumption (42.4 DDD/1000 inhabitants per day) and prevalence of use (13.0%), about twice as high as the Province of Bolzano, which recorded the lowest figure for all three measures analyzed.

- The distribution of prevalence of use and consumption by age for asthma and COPD drugs in 2021 shows a bimodal pattern with peak consumption in the most extreme age groups. This observation is in line with the epidemiology of respiratory diseases with asthma having a prevalent onset during pediatric age and COPD in adulthood.

- Despite significant geographic differences (North: 64.9% vs South and Islands: 55.2%), there is a proportion of subjects with optimal adherence around 24.2%. Unlike other therapeutic categories, no significant reductions are observed with increasing age. However, the proportion of those with low adherence remains particularly high (43.5%) but shows a decreasing trend from 2020 in both the North (-6%) and the Center (-2%), but not in the South and Islands.

- Data from general practice, focused specifically on individuals with the two diseases, shows a prevalence of use in asthma patients of 27.9% and in COPD of 47.7% in 2021. In this analysis the previously observed north-south trend appears reversed, with higher prevalence of use in the north than in the south for both asthma (North: 29.8% vs South 25.8%) and COPD (Northern: 50.6% vs South 45.8%).

References

- Devereux G, Cotton S, Fielding S et al. Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with COPD: a randomized clinical trial. JAMA 2018; 320(15): 1548-59.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2019. URL: http://www.ginasthma.org (last access May 2020).
- Global Initiative for Chronic Obstructive Lung Diseas (GOLD). Global Strategy for Prevention, Diagnosis and Management of COPD. Updated 2019 URL: https://goldcopd.org (last access May 2020).
- Quaderi SA, Hurst JR. The unmet global burden of COPD. Glob Health Epidemiol Genom. 2018 Apr 6;3:e4.
- Rolnick SJ, Pawloski PA, Hedblom BD et al. Patient characteristics associated with medication adherence. Clin Med Res. 2013;11(2):54-65.
- Sanduzzi A, Balbo P, Candoli P, et al. COPD: adherence to therapy. Multidiscip Respir Med 2014: 9, 60.
- Taube C, Bramlage P, Hofer A et al. Prevalence of oral corticosteroid use in the German severe asthma population. ERJ Open Res. 2019 Oct 30;5(4).

3.7.2 Medicines for cystic fibrosis

Epidemiological framework

Cystic fibrosis (CF) is an autosomal recessive genetic disease with an ominous prognosis that indifferently affects both sexes with a prevalence of 1/2500 individuals. The cause of the disease lies in a mutation in the gene that codes for the cellular transport protein CFTR (Cystic Fibrosis Transmebrane Regulator). According to the European Cystic Fibrosis Society, the [delta]FC508 mutation is the most common in Europe. The CFTR protein is present on the cell surface of mucus-producing organs; therefore, CF is a systemic disease that alters the function of various organs such as the lungs, liver, pancreas, and intestines. To date, life expectancy has greatly improved in Europe, and in Italy, due to continuous therapeutic and care advances, 20% of those diagnosed with CF are over 36 years old. According to the 2017-2018 Report of the Italian Cystic Fibrosis Registry (RIFC), the estimated CF prevalence in 2017 and 2018 was 9.2 patients per 100,000 residents. The 51.65% of patients were male with the largest proportion between 7 and 35 years of age. The incidence was 1 case in 5,214 live births in 2017 and 1 case in 5,442 in 2018, similar to the data collected in 2015-2016.

National data on consumption and expenditure

Per capita spending on cystic fibrosis drugs has increased significantly for the past seven years, reaching EUR 3.70 in 2021 (+52.9% compared to 2020 and CAGR 2014-2021 +61.0%). The cost per DDD also showed a major increase from EUR 21.4 in 2014 to EUR 184.0 in 2021, with a growth of 21.7% over 2020 (Figure and Table 3.7.2a).

The largest expenditure category is represented by CFTR modulator therapies (EUR 3.43 per capita), predominantly impacted by ivacaftor (1.31 euros per capita; +87.5% over 2020) and the lumacaftor/ivacaftor association (1.18 euros per capita). The category "Mucolytic agents" includes the active ingredient DNAse, indicated in patients with cystic fibrosis to improve pulmonary function; although this has a minor impact on the overall expenditure of the category of cystic fibrosis drugs, in 2021 it recorded a decrease in both expenditure (-1.5%) and consumption (-1.3%).

Although with low spending and consumption values, it is noticeable that ivacaftor/tezacaftor continues to show increases in both per capita spending and consumption, by 22.5% and 63.0% respectively (Table 3.7.2a). The market entry of a new treatment for cystic fibrosis, the triple combination elexacaftor/tezacaftor/ivacaftor, is highlighted.

This confirms a marked variability between the various regions, with the South and the Islands presenting a higher weighted per capita expenditure than the rest of Italy and 20% higher than the national average figure (Table 3.7.2b).

Basilicata, Calabria, Sicily, Apulia, Umbria and the Provinces of Bolzano and Trento have per capita expenditure values above the national average; in contrast, Valle d’Aosta, Molise, Veneto, Sardinia, Piedmont, Latium, Tuscany, Abruzzo, Liguria, Lombardy and Campania have expenditure values below the national average. The average DDD cost, equal to 184.0

euros at national level, varies between the maximum value of Emilia Romagna (271.1 euros) and the minimum value of Valle d'Aosta (79.3 euros).

Figure 3.7.2a Medications for cystic fibrosis, temporal trend of expenditure and average cost per day of therapy (2014-2021)

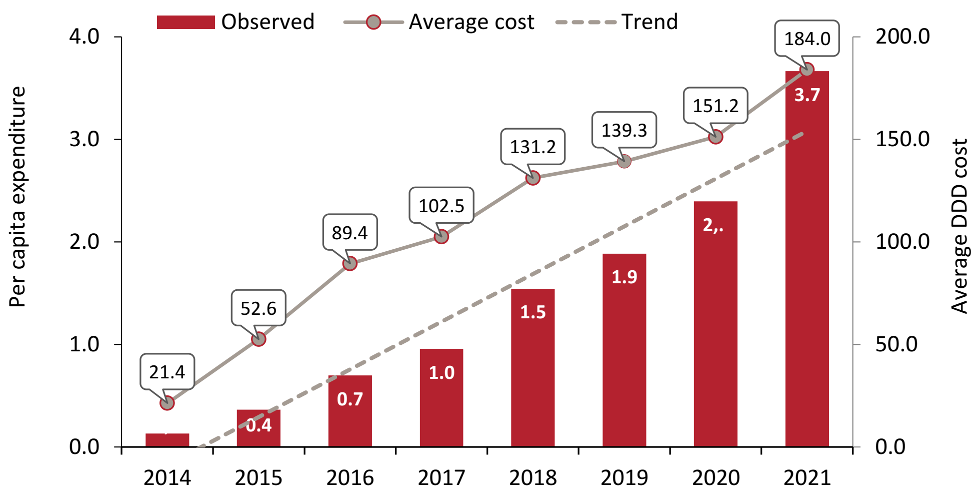


Tabella 3.7.2a Medicines for multiple sclerosis, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhabitants per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
CFTR modulator therapies	3.43	59.0	-	0.0	94.2	-	390.26	-17.9
Mucolytics with specific action	0.24	-1.5	8.9	0.0	-1.3	9.0	21.31	0.1
Medicines for cystic fibrosis	**3.67**	**52.9**	**61.0**	**0.1**	**26.0**	**18.4**	**184.00**	**21.7**
ivacaftor	1.31	87.5	-	0.0	156.7	-	495.55	-26.8
lumacaftor/ivacaftor	1.18	-15.0	-	0.0	-13.2	-	418.52	-1.8
elexacaftor/tezacaftor/ ivacaftor	0.86	-	-	0.0	-	-	292.59	-
desossiribonucleasi	0.24	-1.5	8.9	0.0	-1.3	9.0	21.31	0.1
ivacaftor/tezacaftor	0.08	22.5	-	0.0	63.0	-	208.86	-24.6

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost	Expenditure per capita	DDD/ 1000 inhabitants per day	Average DDD cost
Piedmont	1.88	0.1	99.09	2.72	0.1	132.37	44.6	8.5	33.6	48.9	14.7	29.8
Valle d'Aosta	1.42	0.1	76.00	1.62	0.1	79.32	13.6	9.1	4.4	43.2	19.0	20.3
Lombardy	2.04	0.0	135.81	3.40	0.1	174.65	66.0	29.5	28.6	62.6	20.6	34.9
Province of Bolzano	3.94	0.1	109.08	5.70	0.1	133.40	44.6	18.6	22.3	44.2	11.3	29.6
Province of Trento	3.06	0.1	144.31	5.42	0.1	190.59	76.9	34.3	32.1	61.1	18.1	36.4
Veneto	1.61	0.0	91.31	2.80	0.1	127.15	73.7	25.1	39.2	50.6	17.0	28.7
Friuli VG	1.98	0.0	212.43	3.57	0.0	257.32	80.1	49.1	21.1	79.2	25.7	42.5
Liguria	1.87	0.0	123.76	3.21	0.1	158.11	71.4	34.6	27.8	51.2	13.8	32.8
Emilia R.	2.17	0.0	251.51	3.70	0.0	271.07	70.9	59.0	7.8	82.8	27.1	43.8
Tuscany	1.76	0.0	119.78	3.45	0.1	178.38	95.7	31.7	48.9	58.5	17.3	35.1
Umbria	2.87	0.0	166.73	3.33	0.1	168.30	16.3	15.5	0.9	49.8	11.6	34.3
Marche	2.25	0.0	136.42	3.79	0.1	174.28	68.3	32.1	27.7	56.2	16.0	34.7
Lazio	1.97	0.0	120.15	3.03	0.1	165.25	53.8	12.2	37.5	49.2	11.3	34.0
Abruzzo	2.06	0.0	128.44	3.48	0.1	165.53	68.7	31.3	28.9	62.8	21.8	33.7
Molise	1.00	0.0	89.55	2.12	0.0	125.32	111.3	51.4	39.9	42.2	10.7	28.5
Campania	2.74	0.0	171.70	3.58	0.1	195.88	30.4	14.6	14.1	63.4	19.3	36.9
Puglia	3.55	0.0	223.82	5.30	0.1	238.49	49.2	40.4	6.6	79.6	27.3	41.0
Basilicata	4.81	0.1	187.28	6.85	0.1	225.09	42.4	18.8	20.2	48.0	5.9	39.7
Calabria	4.42	0.1	206.06	4.84	0.1	196.99	9.5	14.8	-4.4	66.4	21.1	37.4
Sicily	3.78	0.0	242.85	5.27	0.1	234.45	39.2	44.5	-3.5	82.3	27.5	43.0
Sardinia	1.68	0.0	111.44	2.54	0.0	165.35	51.3	2.3	48.4	64.5	23.1	33.7
Italy	**2.40**	**0.0**	**151.24**	**3.67**	**0.1**	**184.00**	**52.9**	**26.0**	**21.7**	**61.0**	**18.4**	**36.0**
North	2.00	0.0	130.25	3.30	0.1	169.01	65.1	27.6	29.8	58.9	18.3	34.2
Centre	2.01	0.0	126.04	3.29	0.1	171.06	63.7	20.9	35.7	53.0	13.7	34.5
South and Islands	3.21	0.0	194.30	4.42	0.1	211.38	37.9	27.1	8.8	69.5	22.0	38.9

Key message

- Consumption of drugs has steadily increased over the past eight years both in consumption (CAGR 14-21: 18.4%) and per capita expenditure (CAGR 14-21: 61.0%), standing at 0.1 DDD/1000 inhabitants per day and 3.67 euros per capita in 2021, respectively. The increase in spending is also matched by the increase in the cost per DDD for these drugs from 21.4 euros in 2014 to 184.0 euros in 2021.

- Expenditure data are certainly affected by the recent approval under NHS reimbursability of new and promising CFTR protein modulators, drugs with an estimated average cost per DDD in 2021 of 390.3 euros compared with an estimated 21.3 euros for specific-action mucolytics.

- It is confirmed, as in most therapeutic categories, that there is wide geographic variability in both expenditure and consumption. The trend always sees regions in the South and Islands having a greater impact than those in the North both in terms of per capita spending (North: 3.3 euros vs. South and Islands: 4.4 euros) both in terms of average DDD cost (North: 169.0 euros vs. South and Islands: 211.4 euros). However, more detailed analysis indicates that the highest average cost per DDD is observed in Emilia Romagna (271.1 euros), followed by Friuli VG (257.3 euros) and Puglia (238.5 euros).

References

- Cartabellotta A, Furnaru ML. Guidelines for the diagnosis and treatment of cystic fibrosis. Evidence 2008; 10(1):e10000176.
- European Cystic Fibrosis Society. Patient registry-annual data report, version 1.4, 2018. Available at the address https://www.ecfs.eu/sites/default/files/general-content-files/working-groups/ ecfs-patient-registry/ECFSPR_Report_2018_v1.4.pdf
- Lega Italiana Fibrosi Cistica. What is cystic fibrosis? Available at the address https://www.fibrosicis- tica.it/fibrosi-cistica/cose-la-fibrosi-cistica/
- Lega Italiana Cystic Fibrosis. Report 2015-2016. Epidemiol Prev 2019; 43(4) Suppl 1:1-36.

3.8 Musculo-skeletal system

Medications for the musculoskeletal system represent the eighth largest category by public expenditure in 2021, amounting to 533.5 million euros, and 2.3% of public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these medicines was 9.00 euros, mainly due to the outpatient pharmaceutical expenditure (5.18 euros per capita), reporting a +3.1% increase compared to the previous year; similarly, the expenditure relating to the purchase by public health facilities also increased (+3.0%), setting at 3.82 euros per capita (Table 3.1).

Consumption for this pharmaceutical category was equal to 43.2 DDD/1000 inhabitants per day, increasing by 4.0% compared to 2020. Even in terms of utilization, it is possible to highlight a large difference between NHS outpatient medicine utilization (37.6 DDD/1000 inhabitants per day) and public health facilities medicine utilization (5.6 DDD/1000 inhabitants per day).

Although it does not belong to the ATC M category according to the WHO classification, vitamin D has been included, by therapeutic analogy, in the medicines used for the treatment of osteoporosis. For further information, please refer to section 3.8.1.

The analysis of the medicine use profile by age group and gender, including approved care regime and per conto distribution, confirms the constant increase, both in terms of expenditure and prevalence of use, in the use of these medicines with increasing age, for both genders, with the highest prevalence of use in the over 75 years (prevalence: 46.1% in women and 41.7% in men; expenditure: 25.66 euros in women and 12.42 in men) and with women recording greater use than men in all age groups. The highest consumption values are reached in the age group over 75 years (women 153.6 and men 110.4 DDD/inhabitants per day). This difference is likely due to the higher use of osteoporosis medications among women or other osteo-articular diseases.

As regards the NHS outpatient care, per capita expenditure was equal to 5.18 euros, with a 2.4% increase compared to 2020 (Table 3.9). This trend was determined exclusively by an increase in consumption (+2.5%) while prices, the average cost for DDD and the mix effect remain stable. Within the regimen of this distributing channel, bisphosphonates had the greatest impact on expenditure (1.33 euros per capita), stable compared to 2020. These are followed by preparations inhibiting uric acid production, with a per capita expenditure of 0.87 euros, an increase of 4.3% due to the combined effect of a 2.6% increase in consumption and a shift towards more expensive molecules (mix effect: +1.7%). The coxib category is the one that shows the greatest variation in expenditure and consumption (+8.9% and +9.1% respectively). The category that instead shows the greatest contractions is that of bisphosphonates in association (-5.4% of expenditure and +5.0% of DDD). Among bisphosphonates, alendronic acid is the active ingredient with the greatest impact on spending (0.78 euros per capita, equal to 15.1% of the category) with a 2.2% increase compared to 2020 while allopurinol is the one with the highest consumption (8.5 DDD/inhabitants per day and +22.5%). Diclofenac is the second active ingredient with the highest per capita expenditure (0.60 euros) and alone accounts for 11.6% of the expenditure for the category followed by etoricoxib with 0.59 euros, with an increase of 10.6% compared to 2020 (Table 3.10). It should be noted that for febuxostat, after a reduction in expenditure and consumption in 2020 due to the patent expiry, in 2021 there was an increase in both indicators of 6.3% and 6.8% respectively. Ibuprofen in 2021 recorded increases in expenditure and consumption of 14.3%, this aspect is attributable to its use for the symptomatic treatment of COVID-19 at home according to AIFA recommendations.

No medicine in this category is among the top 30 active ingredients representing the highest agreed expenditure, the highest average cost for DDD and the highest expenditure reduction. Etoricoxib, febuxostat and diclofenac are among the top 30 active ingredients with the greatest variation in the agreed expenditure (Table 3.14). Allopurinol ranks 28th for consumption under the approved care regime (Table 3.16 and 3.17).

On the side of public health facilities, in 2021 there was an increase in expenditure (+2.3%) determined both by an increase in consumption (+6.4%) and by a shift towards more expensive medicines (mix effect: +2.3%) offset by a price reduction of 5.9% (Table 3.18). The category "other medicines acting on bone structure and demineralisation", represented mainly by denosumab, recorded increases in consumption and mix effect of 15.2% and 8.6% respectively, resulting in a 22.4% increase in expenditure. It is worth noting that, after the substantial increase in use observed in 2020 of quaternary ammonium compounds (a category that includes pancuronium, vecuronium, rocuronium and atracurium) in intensive care for performing intubations of patients with COVID-19, a 39% decrease in DDDs and a 57% decrease in expenditure is observed in 2021, confirming a reduction in cases hospitalised in intensive care.

Considering the active ingredients featuring the highest expenditure, nusinersen, indicated for the treatment of spinal muscular atrophy (SMA), still ranks first in per capita expenditure (1.32 euros) and alone accounts for 35% of the category's expenditure, although a 14.8% reduction is observed (Table 3.19). This active ingredient is also among the top 30 ones with the highest expenditure reduction and the highest average cost for DDD (Tables 3.23 and 3.24). Denosumab and ataluren, authorised for the treatment of osteoporosis/bone mass loss and Duchenne muscular dystrophy (nmDMD) respectively, with 1.19 and 0.31 euros are the second and third active ingredient by expenditure (Table 3.19), denosumab appears among the top 30 active ingredients with the highest consumption (ninth place).

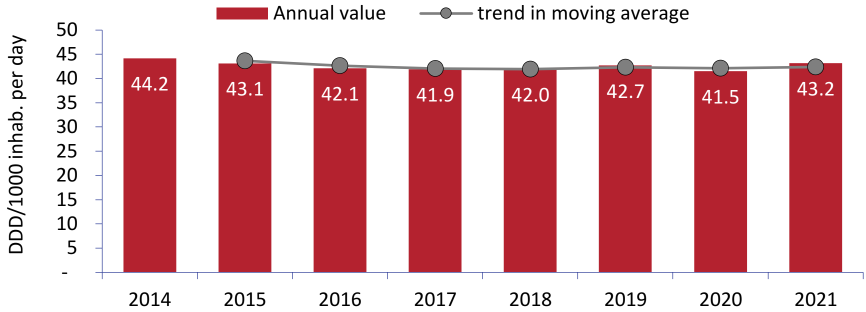
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by Region and on the efficiency in the absorption of resources according to the presence of off-patent medicines and on a regional basis. These analyses focused on osteoporosis medications and nonsteroidal anti-inflammatory drugs (Sections 3.8.1 and 3.8.2).

Main indices of expenditure, consumption and exposure

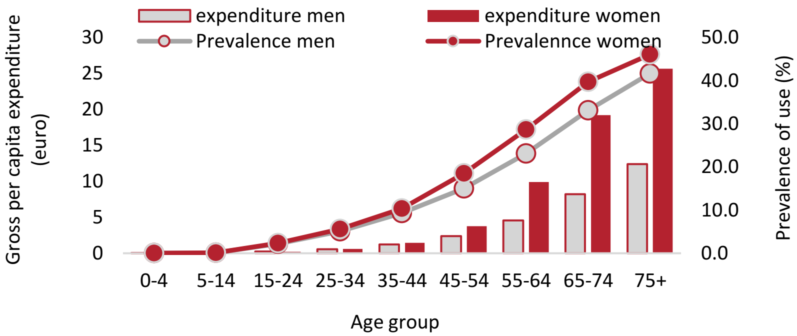
Musculo-skeletal system

Public expenditure* in million euros (% over total)	**533.5**	**(2.3)**
Δ % 2021-2020		3.1
Regional range for gross expenditure (per capita):	5.3	11.1
DDD/1000 inhab. per day* (% over total)	**43.2**	**(3.3)**
Δ % 2021-2020		4.0
Regional range for DDD/1000 inhab. per day:	32.2	59.6

* *includes NHS outpatient prescriptions and purchases by public health facilities*



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and *per conto* distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	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	0.2	0.2	0.2	1.7	1.7	1.7
25-34	0.6	0.6	0.6	4.3	4.3	4.3
35-44	1.2	1.4	1.3	9.3	9.9	9.6
45-54	2.4	3.8	3.1	18.9	24.4	21.6
55-64	4.6	10.1	7.4	37.9	58.6	48.5
65-74	8.2	19.5	14.2	72.0	111.1	92.6
75+	12.4	26.0	20.5	110.4	153.6	136.2

3.8.1 Medicines for osteoporosis

Epidemiological framework

Osteoporosis is a condition characterised by a reduction in bone mass and skeletal alterations with a consequent increase in fragility and a greater risk of fractures that can usually be located in the spine, at the proximal ends of the femur and humerus and at the distal end of the radius. Two different types of osteoporosis are schematically identified: primary osteoporosis (juvenile, postmenopausal, male and senile osteoporosis) and secondary osteoporosis caused by diseases or medicines (prolonged intake of glucocorticoids). From an epidemiological point of view, it is estimated that in Italy about 3.5 million women and 1 million men have osteoporosis and the numbers seem destined to grow with the expected increase in the over-65-year-old population over the next 25 years. With regard to fractures, in the population over fifty the annual number of hip fractures is around 90,000, while it is believed that there are approximately 70,000 vertebral fractures, probably underestimated because they are largely asymptomatic. Fractures have a significant impact on the patient's health and quality of life, as they are not only associated with a 5-8 times increased risk of death in the first three months following the event (vertebral and hip fracture), but they also involve a more or less significant loss of self-sufficiency, sometimes definitive, with the possible need, in the long term, to institutionalise the patient. Osteoporosis can be countered with a preventive approach (measures to slow down demineralisation), or with treatments to be used in subjects suffering from osteoporosis at high risk of fracture (with or without pre-existing fractures). The pharmacological treatment of osteoporosis is based on the use of two specific categories of medicines, which aim to reduce the risk of fractures: anti-catabolics and anabolics. In Italy, several medicines with an anti-resorptive effect are available, while the category of anabolic medicines until 2021 was limited to teriparatide only, while from 2022 the marketing of romosozumab (anabolic and anti-resorptive) is destined to change the prescribing profile. Non-pharmacological measures are based on the elimination of modifiable risk factors and on an appropriate nutritional approach, for example based on calcium (a substance with a primary role in the genesis of osteoporosis) which, if taken in adequate quantities and in appropriate ways, increases bone matrix density in younger subjects, maintains it in adults and slows down its loss in women after the menopause. Calcium supplementation often has to be associated with vitamin D replacement therapy (on average the diet contributes only 20% of the requirement while the remainder is produced by the effect of type B ultraviolet rays on the skin), which in its active form, called 1-25 (OH) 2 cholecalciferol or calcitriol, modulates the intestinal absorption of calcium and phosphorus necessary for proper bone mineralisation. Historically, there is an agreement of opinion on the fact that vitamin D promotes bone health and, together with calcium (when indicated), helps protect against demineralisation (particularly in the elderly). However, on the basis of extensive reviews of epidemiological studies and randomized clinical trials, the indiscriminate efficacy of vitamin D in reducing the risk of fracture has been questioned and the real usefulness of vitamin D supplements is one of the most debated issues to date, also to hypothesise extra-skeletal actions. When analysing the appropriateness of prescribing the various active ingredients, it must therefore be recognised that it is complex to define a threshold for intervention due to the interaction of several risk factors, as well as the different efficacy, adherence and safety profiles and the different cost of the medicines available.

The finding of inconsistencies between the parameters adopted in the past and those suggested by the WHO in the definition of the recommended daily doses for vitamin D, led to the correction of the parameters previously in use with obvious implications in the calculation of the DDD for the year 2021. For fairness of presentation and reliability, in the analysis of the annual prescription variations, the correct parameters were also applied in the calculation of the average cost per day of therapy as well as the DDD for the years 2016-2020.

National data on consumption and expenditure

The trend in osteoporosis medicine consumption (including vitamin D and metabolites) shows a significant increase between 2014 and 2019 with a 26% decrease in 2020 due to the entry into force of AIFA Note 96 and a new 20.7% increase in 2021 (Figure and Table 3.8.1a). Over the entire period, the average cost per therapy day remained fairly stable, settling at 0.16 euros in 2021. Per capita expenditure for these medicines was 9.33 euros (+9% compared to the previous year).

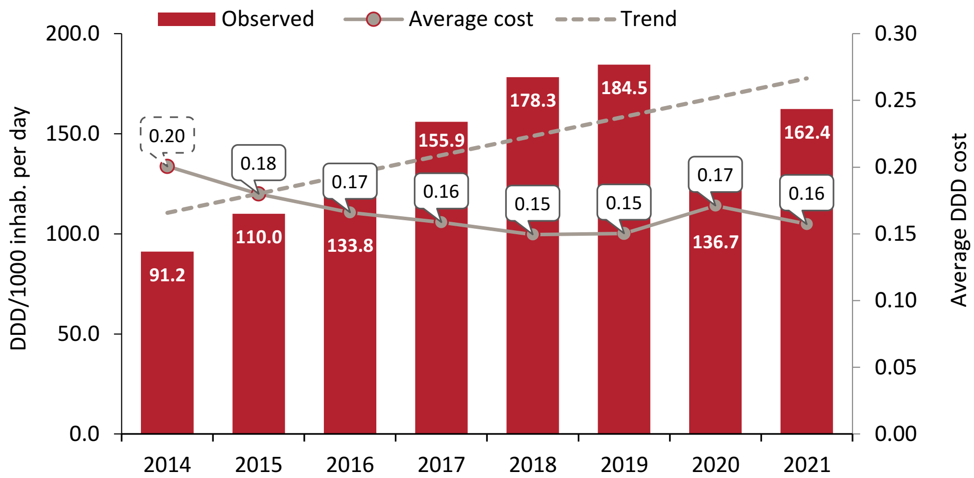
The expenditure for vitamin D and analogues (5.16 euros per capita) represents about 50% of the expenditure of the entire category with a 20% increase compared to 2020. The reason for this increase is mainly due to the unproven protective effect against COVID and only partially to the physiological dilution of the note's dampening effect on prescribing. This underlines the wide use of cholecalciferol and metabolites for extra-skeletal indications for which the RCTs have not provided evidence of efficacy.

Monoclonal antibodies, mainly represented by the antiresorptive denosumab, occupy the second place in terms of expenditure with 1.39 euros, a 23.2% increase compared to 2020 despite representing a small share of consumption (3.9 DDD/1000 inhabitants per day). On the contrary teriparatide, an off-patent biological medicine, approved to treat postmenopausal women at increased risk of fracture or adults suffering from glucocorticoid-induced osteoporosis, shows a significant percentage reduction in both expenditure (-27.3%) and consumption (-20.9%).

Analysing the individual active ingredients, cholecalciferol represents the molecule with the highest per capita expenditure (4.18 euros) and consumption (142.9 DDD/1000 inhabitants per day), followed by teriparatide, which, despite the availability of biosimilar medicines, records the highest cost per day of therapy of the entire category (14.23 euros), slightly decreasing with respect to 2020 (-7.8%).

Analysing regional consumption (Table 3.8.1b) it appears that the macro-areas of the South and the Islands (178.0 DDD/1000 inhabitants per day) have a 30% higher consumption than the Central Regions (137.2 DDD/1000 inhabitants per day) and the Northern Regions (162.3 DDD/1000 inhabitants per day), with increases respectively of 21.4% and 7.7% over the previous year. Similarly, in the South there is a 12% increase in expenditure compared to 4.5% in the Centre and 8.3% in the North. Among the individual Regions, Campania records the highest consumption (226.6 DDD) while Valle d'Aosta records the lowest consumption (127 DDD) with an almost 80% difference between the two of them. As regards the variations compared to 2020, in all the Regions there is an increase in consumption with Molise increasing by 30% while Veneto by 8.4%, in terms of expenditure the same differences are noted at the regional level.

Figure 3.8.1a Osteoporosis medications*, temporal trend of consumption and average cost per day of therapy (2014-2021)



** excluding raloxifene*

Table 3.8.1a Osteoporosis medications, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Vitamin D and analogues	5.16	19.9	10.6	148.7	20.7	9.7	0.09	-0.4
Monoclonal antibodies for osteoporosis	1.39	23.2	22.8	3.9	16.3	20.9	0.99	6.2
Bisphosphonates alone	1.37	0.7	-2.2	7.0	1.2	0.1	0.54	-0.2
Teriparatide	0.87	-27.3	0.1	0.2	-20.9	0.9	14.23	-7.8
Biphosphonates in combination	0.42	-4.8	-13.3	2.0	-4.1	-7.6	0.58	-0.4
Calcium	0.10	-10.4	-2.8	0.6	-36.9	-13.2	0.47	42.5
SERMs - Selective oestrogen receptor modulators	0.01	4.4	-5.4	0.0	3.0	-5.3	0.76	1.7
Medicines for osteoporosis	**9.33**	**9.0**	**4.9**	**162.4**	**18.8**	**8.6**	**0.16**	**-8.0**
cholecalciferol	4.18	23.3	14.2	142.9	21.6	10.6	0.08	1.7
denosumab	1.19	15.7	20.2	3.9	16.3	20.9	0.85	-0.3
teriparatide	0.87	-27.3	0.1	0.2	-20.9	0.9	14.23	-7.8
alendronic acid	0.78	2.2	3.6	4.2	3.6	5.3	0.52	-1.1
alendronic acid cholecalciferol	0.42	-4.8	-13.3	2.0	-4.1	-7.6	0.58	-0.4
risendronic acid	0.37	-2.5	-5.8	2.1	-1.6	-4.0	0.48	-0.7
calcium/cholecalciferol	0.32	0.3	-6.7	3.4	0.3	-7.3	0.26	0.3
calcifediol	0.23	25.7	15.8	0.2	25.8	15.7	0.07	12.4
alfacalcidol	0.22	12.2	14.5	1.3	12.7	14.8	0.45	-0.2
calcitriol	0.22	-2.2	0.2	1.0	-1.4	-0.4	0.60	-0.6

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	6.97	116.7	0.16	7.34	138.8	0.14	5.2	19.0	-11.4	4.1	8.7	-4.2
Valle d'Aosta	7.02	111.6	0.17	6.84	127.7	0.15	-2.5	14.4	-14.6	4.1	11.8	-6.9
Lombardy	8.88	150.9	0.16	9.80	179.1	0.15	10.4	18.7	-6.7	7.1	11.1	-3.5
Province of Bolzano	7.51	136.5	0.15	7.85	158.8	0.14	4.6	16.3	-9.9	4.9	2.6	2.2
Province of Trento	7.09	137.4	0.14	7.76	161.9	0.13	9.5	17.8	-6.8	6.6	9.0	-2.2
Veneto	6.34	151.8	0.11	6.68	164.6	0.11	5.3	8.4	-2.6	0.7	-2.6	3.4
Friuli VG	7.42	126.3	0.16	8.61	164.3	0.14	16.0	30.1	-10.6	6.7	9.6	-2.7
Liguria	8.06	122.6	0.18	8.34	143.3	0.16	3.5	16.9	-11.2	4.6	8.9	-3.9
Emilia R.	6.23	128.4	0.13	6.79	154.0	0.12	9.0	20.0	-8.9	2.3	5.1	-2.7
Tuscany	6.53	114.8	0.16	6.63	130.8	0.14	1.5	13.9	-10.7	1.2	3.0	-1.8
Umbria	7.06	112.6	0.17	7.97	137.7	0.16	12.9	22.3	-7.4	7.7	11.3	-3.2
Marche	8.58	100.6	0.23	9.44	128.5	0.20	10.1	27.8	-13.6	4.9	7.8	-2.7
Lazio	10.17	122.7	0.23	10.52	143.8	0.20	3.5	17.1	-11.4	4.1	10.9	-6.1
Abruzzo	10.61	133.1	0.22	11.78	166.5	0.19	11.0	25.1	-11.0	4.2	7.7	-3.2
Molise	8.62	128.4	0.18	10.11	171.5	0.16	17.3	33.6	-12.0	7.1	13.3	-5.5
Campania	11.74	183.9	0.17	13.45	226.6	0.16	14.6	23.2	-6.8	13.0	22.5	-7.7
Puglia	9.91	152.1	0.18	10.87	181.2	0.16	9.7	19.1	-7.7	2.8	8.5	-5.3
Basilicata	10.17	143.5	0.19	11.48	181.7	0.17	12.9	26.6	-10.6	7.8	14.5	-5.8
Calabria	8.92	110.8	0.22	10.16	138.2	0.20	13.9	24.7	-8.4	5.7	13.6	-6.9
Sicily	9.19	111.2	0.23	10.15	133.3	0.21	10.5	19.9	-7.6	4.1	12.4	-7.4
Sardinia	8.59	170.9	0.14	9.42	196.5	0.13	9.7	15.0	-4.3	-1.5	9.8	-10.3
Italy	**8.56**	**136.7**	**0.17**	**9.33**	**162.4**	**0.16**	**9.0**	**18.8**	**-8.0**	**4.9**	**8.6**	**-3.4**
North	7.52	138.4	0.15	8.14	162.3	0.14	8.3	17.3	-7.4	4.7	6.0	-1.3
Centre	8.56	116.5	0.20	8.94	137.2	0.18	4.5	17.7	-11.0	3.7	7.6	-3.7
South and Islands	10.06	146.6	0.19	11.27	178.0	0.17	12.0	21.4	-7.5	5.8	13.6	-6.8

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 on the basis on the prevalence of osteoporotic disease in the population, the exposure was significantly higher for women than men (19.8% vs 5.2%), this difference persists in all age groups reaching a maximum value of 48.7% for women in the 75-84 age group and 22.3% for men aged 85 years and over (Figure 3.8.1d). Investigating the trend of the prevalence of use by geographical area (Table 3.8.1d), it is evident that the Southern Regions record a higher figure (14.8%) than both the Central (11.5%) and the Northern Regions (11.4%) and that Abruzzo is the Region with the highest exposure in the general population (17.1%), in women (25.9%) and also in men (7.9%). The median age of the patients was 68 years and, for each user, the annual expenditure was 67.4 euros with a regional range between 43.4 euros in Emilia Romagna and 79.6 euros in Lazio. On average, each user received 454 doses of osteoporosis medicines and half of the users were treated for more than 10 months and 14.7% received only one prescription.

Concerning 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 41,571 new users, with a median age of 69 years (IQR 61-76) and a greater proportion of women than men (91.7% vs 8.3%). The percentage of subjects with high and low adherence to osteoporosis treatments was respectively 68.8% and 7% (Table 3.8.1d). High adherence also registered a 2% increase and was higher in subjects aged 45-54 years resident in the North (75.9%). Low adherence tends to increase with age, going from 6.8% for the 45-54 age group to 9.9% in the over 85 age group, a percentage which has increased since the previous year, while it is stable for the other age groups. There are differences between men and women in terms of adherence to therapy with the former having the highest level of low adherence (11.4% vs. 6.6%). Patients older than 85 years resident in Central Italy had the highest value of low adherence, 12.2%.

Analysing the persistence to medicines for osteoporosis (Table 3.8.1e), it can be highlighted that about half of the new users are found to be persistent to treatment after one year (51.5%), with a better trend in the North (56.5%) and in the Centre (53.3%), compared to the South, where less than half of patients did not observe an interruption in treatment for a period of less than 60 days (45.1%). Women were more persistent than men (52.3% and 42.8%), who also showed a 9% decrease in the number of persistent subjects compared to the previous year. Comparing the persistence data between 2020 and 2021 (Figure 3.8.1c), no obvious differences were found and it is possible to note that, for these medicines, the median time to discontinuation is 365 days. This discontinuation time decreases progressively with age and in the population over the age of 85 it is 227 days; moreover, gender differences are found with men having a lower persistence to treatment than women (224 vs 365 days).

Figure 3.8.1b Breakdown of prevalence of use and consumption of medicines for osteoporosis under approved care regime and per conto distribution in 2021

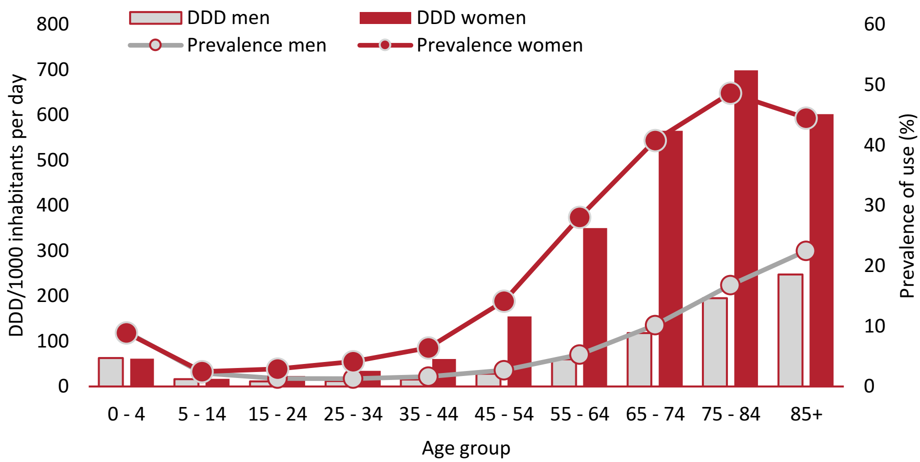


Table 3.8.1c Distribution of prevalence of use and consumption of osteoporosis medicines under approved care regime and per conto distribution (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD age	Users with 1 prescription (%)
	men	women	total					
Piedmont	4.5	17.4	11.1	70	62.6	451.6	340.0	13.6
Valle d'Aosta	4.5	16.0	10.4	69	60.1	435.2	312.5	6.2
Lombardy	5.5	19.4	12.6	68	73.6	501.1	375.0	9.0
Province of Bolzano	3.6	12.4	8.0	70	65.2	557.8	375.0	13.2
Province of Trento	5.5	17.6	11.7	66	60.1	462.5	312.5	9.0
Veneto	4.4	14.9	9.7	68	58.9	586.7	400.0	17.2
Friuli VG	5.7	19.4	12.7	69	69.0	479.6	348.0	11.9
Liguria	4.4	19.0	12.0	73	71.1	452.4	375.0	12.2
Emilia R.	4.6	17.8	11.4	68	43.4	444.1	278.0	15.7
Tuscany	3.9	15.3	9.7	70	58.0	489.1	306.0	28.9
Umbria	4.6	20.0	12.6	69	63.9	404.7	250.0	20.0
Marche	4.5	18.2	11.5	70	74.0	399.3	250.0	15.5
Lazio	4.7	20.0	12.6	68	79.6	405.3	250.0	13.7
Abruzzo	7.9	25.9	17.1	67	66.4	352.9	250.0	19.8
Molise	6.8	25.9	16.5	67	63.5	398.7	250.0	13.1
Campania	7.2	25.0	16.3	65	70.6	461.2	355.5	10.0
Puglia	6.5	24.5	15.7	67	62.1	405.9	250.0	17.1
Basilicata	6.0	25.8	16.0	66	72.1	416.7	300.0	12.7
Calabria	5.9	22.1	14.2	67	64.3	340.9	250.0	17.1
Sicily	4.8	20.4	12.8	69	69.0	361.7	250.0	16.3
Sardinia	4.6	21.4	13.1	68	67.7	558.3	406.0	22.4
Italy	**5.2**	19.6	**12.6**	**68**	**67.4**	**453.9**	**308.0**	**14.7**
North	4.9	17.7	11.4	69	64.6	497.1	375.0	12.5
Centre	4.4	18.1	11.5	69	72.5	430.2	250.0	18.6
South and Islands	6.1	23.1	14.8	67	67.9	418.4	250.0	15.2

Table 3.8.1d Indicators of adherence to treatment with osteoporosis medicines in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

	Total N=41.571				North N=16.764				Centre N=9.271				South N=15.536			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*^																
45-54 years	7.2	7.0	6.8	-2	4.7	4.9	5.2	5	6.8	6.6	4.8	-27	8.6	9.1	9.8	7
55-64 years	6.2	6.1	6.4	5	4.9	5.3	4.9	-6	6.4	6.5	6.5	0	6.6	6.8	7.9	17
65-74 years	6.8	6.5	6.5	0	5.3	5.1	5.4	6	6.2	6.5	6.7	2	7.7	7.9	7.7	-3
75-84 years	7.4	7.2	7.8	9	5.8	5.9	6.4	10	7.2	7.5	9.1	21	8.5	8.6	8.8	3
≥85 years	9.8	8.1	9.9	23	8.7	6.8	7.3	8	8.8	9.2	12.2	32	11.0	9.0	11.3	26
Women	6.7	6.5	6.6	2	5.5	5.3	5.4	1	6.5	6.7	6.9	4	7.5	7.6	7.8	3
Men	10.7	9.4	11.4	20	6.6	6.7	7.9	19	9.4	10.5	12.0	14	14.2	12.6	15.7	25
Total	**7.1**	**6.8**	**7.0**	**4**	**5.6**	**5.5**	**5.6**	**3**	**6.8**	**7.0**	**7.3**	**5**	**7.9**	**7.9**	**7.3**	**-8**
High adherence*^																
45-54 years	64.8	68.5	71.1	4	72.6	73.2	75.9	4	66.4	69.2	74.3	7	60.2	63.7	64.1	1
55-64 years	67.8	68.7	70.6	3	71.4	71.5	74.2	4	68.5	69.6	71.3	2	65.9	65.6	66.6	2
65-74 years	68.0	68.0	69.5	2	72.8	72.0	73.3	2	68.0	68.2	68.9	1	65.8	64.4	66.0	2
75-84 years	67.5	67.2	66.5	-1	70.2	70.6	68.8	-3	69.0	66.9	66.4	-1	64.9	63.4	63.4	0
≥85 years	62.5	64.7	62.7	-3	64.6	67.4	65.6	-3	65.4	63.0	62.9	0	59.4	62.5	59.6	-5
Women	67.3	67.7	69.1	2	70.8	71.1	72.3	2	68.3	67.9	69.6	2	65.0	64.4	65.4	2
Men	66.1	67.8	65.8	-3	73.1	71.9	70.5	-2	66.2	67.6	64.1	-5	61.2	62.5	60.2	-4
Total	**67.2**	**67.7**	**68.8**	**2**	**71.0**	**71.2**	**72.15**	**1**	**68.1**	**67.9**	**69.2**	**2**	**64.7**	**64.2**	**65.1**	**1**

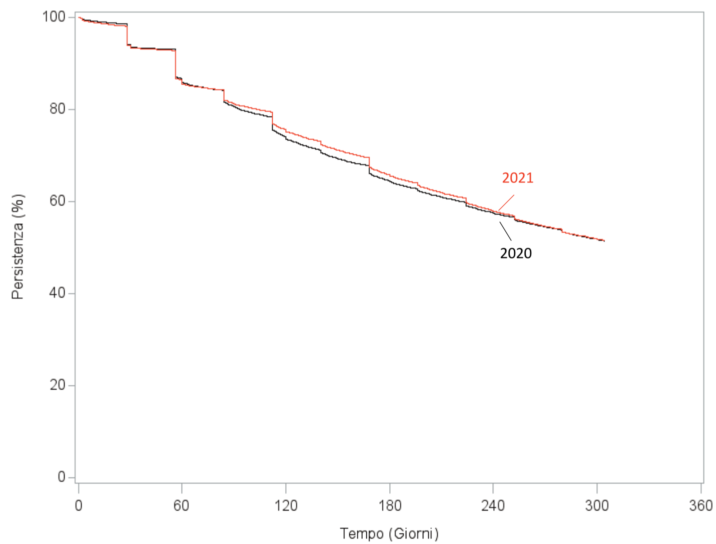
*Adherence to treatment was assessed during the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high 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 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.
Percentages of subjects with low/high adherence relating to the specific category.
Median follow-up time (in days) (IQR): 311 (190-342).

Table 3.8.1e Persistence after one year of treatment with medicines for osteoporosis in the population aged ≥45 years in the period 2019-2021 and variation 2021-2020

Persistence after 12 months	Total N=41.571				North N=16.764				Centre N=9.271				South N=15.536			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54 years	51.1	54.7	55.4	1	58.8	59.6	60.6	2	54.1	58.9	62.4	6	45.9	47.8	45.5	-5
55-64 years	51.8	54.1	55.1	2	58.0	59.0	60.4	2	55.6	56.4	58.6	4	47.2	48.3	47.7	-1
65-74 years	49.9	51.3	51.8	1	57.6	57.3	57.2	0	50.5	53.0	52.9	0	46.0	44.9	45.6	2
75-84 years	47.9	48.7	48.0	-1	54.0	53.2	52.1	-2	48.8	46.9	47.7	2	43.7	44.3	42.9	-3
≥85 years	41.4	43.7	41.8	-4	44.5	48.9	48.6	-1	44.4	41.1	37.1	-10	37.8	39.1	37.4	-5
Women	49.8	51.2	52.3	2	55.9	56.2	57.1	2	51.7	52.4	54.2	3	45.7	45.8	46.1	1
Men	43.5	47.1	42.8	-9	53.0	53.8	50.4	-6	42.9	44.0	42.6	-3	37.3	39.7	32.6	-18
Total	**49.3**	**50.9**	**51.5**	**1**	**55.6**	**55.9**	**56.5**	**1**	**50.9**	**51.7**	**53.3**	**3**	**45.1**	**45.4**	**45.1**	**-1**

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

Figure 3.8.1c Time (in days) to discontinuation of treatment with osteoporosis medicines in the population aged ≥45 years stratified by year (2021-2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Epidemiology and prescribing profiles in General Medicine

The data relating to epidemiology and prescribing profiles were obtained through a network of GPs homogeneously distributed throughout the national territory bringing together all information relating to diagnosis of pathology, demographic information, pharmaceutical prescription, and more to Health Search-IQVIA Health LPD.

For the OsMed 2021 Report, the analyses focused on estimates of the prevalence and incidence of osteoporosis, as well as with or without a previous vertebral or femoral fracture, in the population in charge of the 800 GPs of the HS network for the years 2019, 2020 and 2021. Furthermore, the prevalence of use of medicines, including the most frequently used therapeutic classes, and related trends were calculated for the three-year period 2019-2021.

The incidence of osteoporosis in 2021 was equal to 5.7 ‰, a 14.9% increase compared to 2020. In addition, about 4 new cases out of 1000 do not have a previous vertebral or femur fracture (Table 3.8.1f). Geographically, the incidence of osteoporosis is higher in the South and Islands (6.6‰) than in the North (5.1‰) and the Centre (5.4‰). For all three geographical areas, there is an increase in the estimated incidence compared to 2020, with the highest value for the North (18.8%).

Stratifying the analysis by gender, women show a higher incidence estimate (9.6 ‰) than men, with a +18.5 variation compared to 2020, while by age, an increase in the estimate emerges as the latter increases. Analysing the percentage change compared to the previous year, an increase in the diagnosis of the disease is observed for all age groups; this increase is particularly evident in the younger age groups.

The prevalence of osteoporosis in the population eligible for assistance by the GPs of the HS network in 2021 stood at 9.3% (Table 3.8.1g), a 1.1% increase compared to 2020. This prevalence shows a growing geographical gradient, going from a minimum value of 7.7% of the Northern Regions to 8.8% of the Central Regions, up to a maximum value of 11.5% in the South and in the Islands. Moreover, only the latter geographic area is characterised by an increase in the prevalence estimate (1.3%) compared to 2020.

The prevalence of osteoporosis is higher in women than in men (15.6% vs. 2.9%), with a stable trend over the three years considered. In general, the prevalence increases with age, although the most marked increase is observed from the age of 66 years onwards (in women mainly due to post-menopausal osteoporosis), reaching a maximum value of 37.5% in subjects aged 85 years and over. As in the case of incidence, all age groups show an increase in the estimated prevalence of the disease compared to 2020.

The prevalence of osteoporosis patients without a previous vertebral or femur fracture stands at 6.8% of the population eligible for assistance, with estimates varying according to geographical area (5.1% in the North, 5.9% in the Centre and 9.1% in the South and Islands). Analysing this prevalence according to age group, it reaches its highest value in subjects aged 85 years or over (22.7%).

Table 3.8.1h shows how in 2021 51% of subjects with osteoporosis were treated with at least one medicine, a 4.1% increase compared to 2020. In addition, stratification by age shows an increase in the prevalence of use up to the age groups 66-74 years (58.1%; Δ% 21-20: 6.2%) and 75-84 years (58.2%; Δ% 21-20: 4.1%), and then a decrease in the oldest age groups (≥85: 48.3%). Overall, the prevalence of use in each of the age groups increased compared to that observed for 2020.

Stratifying the analysis according to the presence or absence of a previous vertebral or femur fracture, a prevalence of use equal to respectively 55.8% and 37.9% emerges for non-fractured and fractured osteoporosis patients.

In the latter group, the highest estimate is found in the age group 75-84 years (52.5%), whereas in patients without previous fracture the peak prevalence of use is found in the age group 66-74 years (60.6%).

Calculating the prevalence of use of the main therapeutic categories used in the treatment of osteoporosis, the category of vitamin D and analogues shows, also for 2021, the highest estimate (46.9%), followed by bisphosphonates alone (10.4%) and bisphosphonates in combination (2.9%) (Table 3.8.1i). Analysing the trend in prevalence of use over the last three years, a decline in estimates is observed for all therapeutic categories (with the exception of monoclonal antibodies) between 2019 and 2020; however, these estimates increase again during 2021 (Figure 3.8.1d). Only calcium is associated with a decrease in the prevalence of use in the latter year as well.

Table 3.8.1f Incidence of osteoporosis (with or without previous vertebral or femur fracture) in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: stratified analysis by gender, age group and geographic area (2019-2021)

	Osteoporosis Incidence (‰)			Δ%	Previous vertebral or femur fracture (2021)	
	2019	2020	2021	21-20	without	with
Geographic analysis						
North	5.7	4.3	5.1	18.8	3.3	1.9
Centre	6.8	5.1	5.4	5.5	3.6	1.8
South and Islands	8.3	5.7	6.6	15.6	5.1	1.5
Analysis by gender						
Men	2.5	2.1	2.2	6.7	0.9	1.4
Women	11.5	8.1	9.6	18.5	7.5	2.1
Analysis by age						
≤45	0.6	0.4	0.6	30.2	0.3	0.3
46-65	6.9	4.7	6.1	29.2	5.1	0.9
66-74	13.9	9.8	11.7	19.1	9.1	2.6
75-84	16.5	14.5	16.9	16.1	9.7	7.2
≥85	16.9	21.0	22.4	6.9	8.1	14.3
Total	**6.9**	**5.0**	**5.7**	**14.9**	**4.0**	**1.7**

Indicators used:

Incidence of osteoporosis: number of patients with a "first" diagnosis of osteoporosis recorded during the year [**numerator**], on the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Incidence of osteoporosis in patients with or without previous vertebral or femur fracture: number of patients with a "first" diagnosis of osteoporosis recorded during the year with or without previous vertebral or femur fracture [**numerator**], on the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

Table 3.8.1g Prevalence of osteoporosis (with or without previous vertebral or femur fracture) in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2021-2020: stratified analysis by gender, age group and geographic area (2019-2021)

	Osteoporosis				Previous vertebral or femur fracture (2021)	
	Prevalence (%)			Δ%		
	2019	2020	2021	21-20	without	with
Geographic analysis						
North	7.7	7.6	7.7	1.3	5.1	2.6
Centre	8.9	8.8	8.8	0.0	5.9	2.9
South and Islands	11.6	11.5	11.5	0.0	9.1	2.4
Analysis by gender						
Men	2.8	2.8	2.9	3.6	1.1	1.9
Women	15.5	15.4	15.6	1.3	12.3	3.3
Analysis by age						
≤45	0.8	0.8	0.9	12.5	0.2	0.7
46-65	5.5	6	6.6	10.0	5.1	1.5
66-74	17.7	18.4	19.1	3.8	15.6	3.5
75-84	26.1	27	28.6	5.9	21.1	7.5
≥85	35.4	36	37.5	4.2	22.7	14.8
Total	**9.4**	**9.2**	**9.3**	**1.1**	**6.8**	**2.6**

Indicators used:
Prevalence of osteoporosis: number of patients diagnosed with osteoporosis [**numerator**], out of the total population eligible for assistance [**denominator**]
Prevalence of osteoporosis in patients with or without previous vertebral or femur fracture: number of patients diagnosed with osteoporosis with or without previous vertebral or femur fracture [**numerator**], out of the total population eligible for assistance [**denominator**].

Table 3.8.1h Prevalence of use of medicines for the treatment of osteoporosis in the population with osteoporosis, with or without previous vertebral or femur fracture, and comparison 2021-2020: stratified analysis by gender, age groups and geographical area (2019-2021)

	Osteoporosis				Previous vertebral or femur fracture (2021)	
	Prevalence of use (%)			Δ%		
	2019	2020	2021	21-20	without	with
Geographic analysis						
North	53.5	49.7	51.4	3.4	58.8	36.6
Centre	53.3	48.1	48.8	1.5	54.1	37.2
South and Islands	57.8	48.7	51.6	6.0	54.5	39.9
Analysis by gender						
Men	23.8	22.0	23.2	5.5	37.1	15.3
Women	60.6	53.6	56.0	4.5	57.3	50.7
Analysis by age						
≤45	19.2	8.6	8.7	1.2	29.4	3.5
46-65	57.8	41.5	43.4	4.6	50.0	21.9
66-74	63.0	54.7	58.1	6.2	60.6	46.2
75-84	54.0	55.9	58.2	4.1	60.0	52.5
≥85	40.6	46.5	48.3	3.9	49.9	45.7
Total	**55.4**	**49.0**	**51.0**	**4.1**	**55.8**	**37.9**

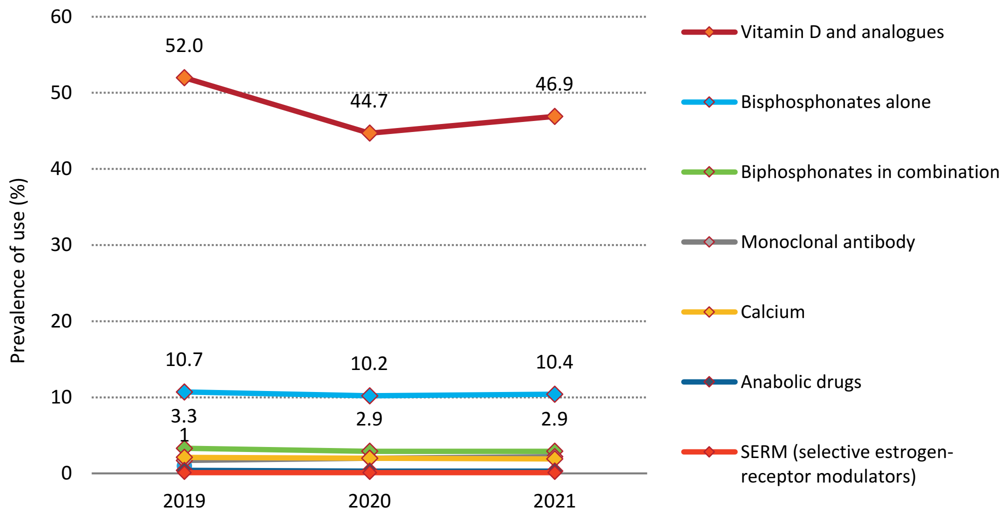
Indicator used:
Prevalence of use of medicines for osteoporosis: number of patients treated with medicines for osteoporosis [**numerator**] on the total number of patients diagnosed with osteoporosis [**denominator**]
Prevalence of use of medicines for osteoporosis in patients with or without previous vertebral or femur fracture: number of patients treated with medicines for osteoporosis [**numerator**] on the total number of patients diagnosed with osteoporosis with or without previous vertebral or femur fracture [**denominator**]

Table 3.8.1i Prevalence of use of medicines for the treatment of osteoporosis in the population with osteoporosis, with or without previous vertebral or femur fracture, and comparison 2021-2020: stratified analysis by therapeutic category (2019-2021)

	Osteoporosis				Previous vertebral or femur fracture (2021)	
	Prevalence of use (%)			Δ %		
	2019	2020	2021	21-20	without	with
Bisphosphonates alone	10.7	10.2	10.4	2.0	11.3	7.9
Biphosphonates in combination	3.3	2.9	2.9	0.0	3.1	2.3
Monoclonal antibody	1.7	2.0	2.2	10.0	2.1	2.8
SERM (selective estrogen-receptor modulators)	0.1	0.1	0.1	0.0	0.1	0
Anabolic drugs	0.4	0.3	0.3	0.0	0.2	0.6
Double-acting medicines	-	-	-	-	-	-
Vitamin D and analogues	52.0	44.7	46.9	4.9	51.4	34.7
Calcium	2.1	2.0	1.9	-5.0	2.0	1.6
Other medicines for osteoporosis	-	-	-	-	-	-
Total	**10.7**	**10.2**	**10.4**	**2.0**	**11.3**	**7.9**

Indicators used:
Prevalence of use of medicines for osteoporosis: number of patients treated with medicines for osteoporosis [**numerator**] on the total number of patients diagnosed with osteoporosis [**denominator**]
Prevalence of use of medicines for osteoporosis in patients with or without previous vertebral or femur fracture: number of patients treated with a specific therapeutic category [**numerator**] on the total number of patients diagnosed with osteoporosis with or without previous vertebral or femur fracture [**denominator**]

Figure 3.8.1d Prevalence of use of medicines for the treatment of osteoporosis in the population with osteoporosis: analysis by therapeutic category (2019-2021)



Prevalence of use of medicines for osteoporosis: number of patients treated with a specific therapeutic category [**numerator**] on the total number of patients diagnosed with osteoporosis [**denominator**]

Key message

- The most relevant data in the overall analysis of osteoporosis therapy is a **decrease in the use of medicines**, more than 14%, after years of almost uninterrupted growth (+28.9% from 2014 to 2019).
- Despite a reduction compared to the maximum peak of 2019 of 21.3% and 24.6%, respectively, **consumption and expenditure for vitamin D and analogues** recorded an increase in the approve care channel compared to 2020. This increase can be attributed to the dilution of the effects of the application of Note 96 and the inappropriate prescription of vitamin D as a protective anti-COVID. Cholecalciferol, however, is third in terms of reduced NHS outpatient expenditure with 201.4 million euros, despite the important reduction recorded compared to 2019, when it occupied 1st place with 257 million euros.
- The analysis of components of this trend, involving both use (-21.7%) and induced expenditure (-24.1%), cannot disregard the **evaluation of trends** of other medicines used for this disease, even if they belong to different ATC codes (e.g. cholecalciferol or analogues and teriparatide).
- The **increase in prescribing the monoclonal antibody denosumab** which bucked the trend may be motivated by greater confidence in medication management, as well as by unavailability of strontium ranelate as an alternative to bisphosphonates.
- Analysis of **osteoporosis medicine prescription trends by individual Region** shows a greater medicine consumption in the Southern Regions, contrary to what might be expected given the greater exposure based on latitude.
- Analysis of **persistence** in therapy continues to show a troubling lack of adherence to treatments that may help explain a large proportion of treatment failures.
- The survey on **general practice** showed a dramatic decline in new cases that can be related to reduced access to diagnostic and treatment sites due to the pandemic.

References

- Barrionuevo P, Kapoor E, Asi N et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. J Clin Endocrinol Metab 2019; 104(5):1623-30.
- Beaudart C, Biver E, Bruyère O et al. Quality of life assessment in musculo-skeletal health. Aging Clin Exp Res 2018; 30(5):413-8.
- Cesareo R, Attanasio R, Caputo M et al. AME and Italian AACE Chapter. Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocronologist (AACE) position statement: clinical management of vitamin D deficiency in adults. Nutrients 2018; 10(5):546.
- Kanis JA, Cooper C, Rizzoli R et al. Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation

(IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2019; 30(1):3-44.

- Nuti R, Brandi ML, Checchia G et al. Guidelines for the management of osteoporosis and fragility fractures. Intern Emerg Med 2019; 14(1):85-102.
- Svedbom A, Hernlund E, Ivergård M et al. UE Review Panel of IOF. Osteoporosis in the European Union: a compendium of country-specific reports. Arch Osteoporos 2013; 8(1):137.

3.8.2 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Epidemiological framework

Depending on the type of pathology and the inflammatory response, different therapeutic strategies are adopted. Several classes of medicines, in particular NSAIDs, perform their main therapeutic effects as pain relief of inflammatory origin by blocking the formation of prostaglandins. NSAIDs are antipyretic, analgesic and anti-inflammatory, often used "as needed", as they provide symptomatic relief from pain, mainly of mild or moderate inflammatory type associated mainly with musculoskeletal disorders, but also with menstrual disorders, due to headache and toothache. Musculoskeletal disorders concern a broad spectrum of inflammatory and degenerative diseases that include osteo-tendon and joint inflammation (epicondylitis, bursitis, arthritis), nerve compression disorders (carpal tunnel syndrome, lumbosciatalgia), osteoarthritis, myalgia, lower back pain and various other local pain syndromes. In over 90% of cases the painful symptoms resolve within 6 weeks and only 2-7% of subjects develop a chronic form of low back pain characterised by periodic relapses and exacerbations. In the United States, musculoskeletal disorders are detected in more than 20% of outpatient visits during the year (approximately 315 million visits) and an estimated 54.4 million (1 in 5 adults) of inhabitants have been diagnosed with arthritis. Musculoskeletal pains are also very common in the European States. Several population studies estimate, for example, an annual prevalence of pain in the upper limbs, shoulders and neck, of about 30-40% and anti-inflammatory medicines are used in 50% of cases regardless of the type of diagnosis.

National data on consumption and expenditure

In 2021 downward trend in NSAID consumption found up to 2020 stops (Figure and Table 3.8.2a). In detail, in the last year there was a 5.5% increase in consumption (17.8 DDD), while the cost per day of therapy remained stable at 0.38 euros. Extending the analysis to the last eight years, however, an average annual variation decreasing by 3.4% is observed. As regards the NHS outpatient care, per capita expenditure was equal to 2.48 euros, with a 5.9% increase compared to 2020 and the main therapeutic categories (traditional NSAIDs and Coxibs) show increases of 5.0% and 9.7% respectively. Traditional NSAIDs represent the category with the highest per capita expenditure (1.65 euros) and consumption (12.8 DDD, a 4.6% increase), both accounting for about 70% of the entire category. The second category with the highest expenditure (0.70 euros) and consumption (4.2 DDD/1000 inhabitants per day, a 10.1% increase), is represented by Coxibs, which show a stability in the average DDD cost (-0, 1%). Analysis of individual molecules shows a similar trend as seen for the categories. In particular, the active ingredient with the highest expenditure is represented by diclofenac (0.61 euros), followed by etoricoxib (0.59 euros) and ketoprofen (0.27 euros), he first two increasing by 6.1% and 10.6% respectively, while the expenditure for ketoprofen remains stable (-0.3%). Important increases in expenditure and consumption were recorded for ibuprofen (+15.3% and +13.9% respectively). Ketorolac, approved only for the short-term (maximum five days) treatment of moderate-to-severe postoperative pain, is the molecule with the highest DDD cost (0.53 euros), decreasing by 8.1% compared to 2020, while consumption increases by 10.2%.

Analysing the regional variability of NSAID consumption (Table 3.8.2b), it can be seen that the Southern Regions (25.8 DDD/1000 inhabitants per day) have a consumption which is more than double that of the Northern Regions (12.4 DDD/1000 inhabitants per day) and 50% higher than those of the Centre (17.6 DDD/1000 inhabitants per day). Calabria, Campania and Puglia are the Regions with the highest spending value, srespectively 28.2, 27.9 and 27.1 DDD, while Lombardy, Province of Bolzano, Trento and Emilia Romagna record the lowest values (11.2, 11.4 and 11.7 DDD) On average, in the macro-areas of the North there was an increase in consumption compared to 2020 that was higher than the national average (+7.9%), with Emilia Romagna recording the highest figure (+16.7%), while in Sicily there were less marked increases (+1.1%). Since the average cost per DDD is rather similar in the various Italian Regions, those with the highest consumption, such as Calabria, Campania and Puglia, are also those with the highest expenditure with 3.82, 3.86, 3.85 euros respectively.

Figure 3.8.2a Nonsteroidal anti-inflammatory drugs (NSAIDs), temporal trend of consumption and average cost per day of therapy (2014-2021)

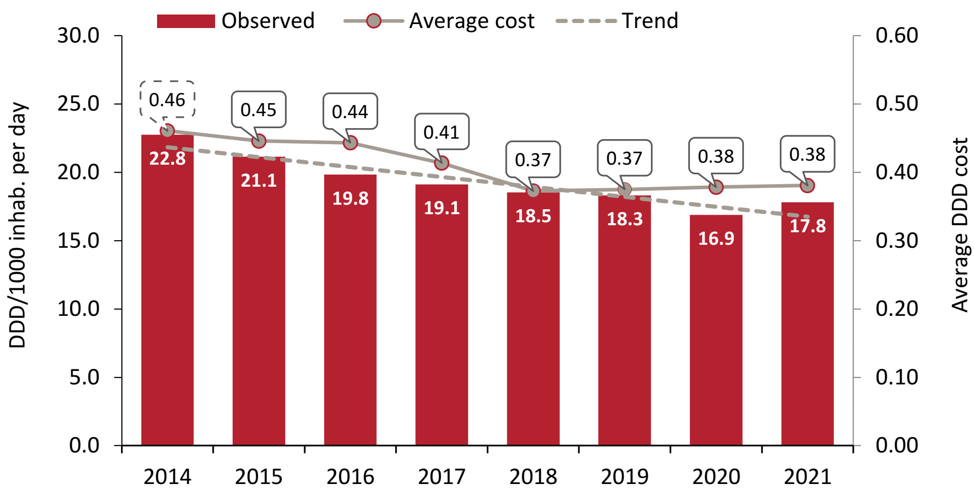


Table 3.8.2a Nonsteroidal anti-inflammatory drugs (NSAIDs), per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Traditional NSAIDs	1.65	5.0	-3.5	12.8	4.6	-3.6	0.35	0.7
Coxib	0.70	9.7	-10.3	4.2	10.1	-1.9	0.46	-0.1
Oxicam	0.12	-0.8	-5.6	0.8	-0.8	-6.3	0.38	0.2
Other nonsteroidal anti-inflammatory anti-rheumatic medicines	0.01	-9.1	-13.9	0.0	-11.1	-16.8	0.65	2.5
Nonsteroidal anti-inflammatory drugs (NSAIDs)	**2.48**	**5.9**	**-6.0**	**17.8**	**5.5**	**-3.4**	**0.38**	**0.7**
diclofenac	0.61	6.1	0.2	4.2	5.9	0.0	0.40	0.4
etoricoxib	0.59	10.6	-9.6	3.5	11.3	-1.1	0.46	-0.3
ibuprofen	0.30	15.3	-1.8	2.0	13.9	-1.3	0.40	1.5
ketoprofen	0.27	-0.3	-6.9	2.7	-0.6	-6.3	0.28	0.6
nimesulide	0.15	4.5	-5.4	1.9	3.8	-5.8	0.22	1.0
celecoxib	0.12	5.0	-12.6	0.7	4.3	-5.3	0.47	1.0
ketorolac	0.10	0.9	-4.3	0.5	10.2	-3.4	0.53	-8.1
piroxicam	0.08	-0.8	-3.6	0.5	-0.4	-4.2	0.45	-0.1
aceclofenac	0.07	-5.3	-10.8	0.4	-5.2	-9.7	0.50	0.2
dexibuprofen	0.06	3.8	-1.8	0.3	4.1	-1.8	0.49	0.0

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	1.86	13.4	0.38	2.01	14.4	0.38	8.0	7.1	1.1	-5.7	-3.4	-2.4
Valle d'Aosta	2.10	15.1	0.38	2.23	15.8	0.39	5.9	4.1	2.1	-7.0	-4.8	-2.3
Lombardy	1.41	10.3	0.37	1.55	11.2	0.38	9.6	8.5	1.3	-5.6	-2.5	-3.2
Province of Bolzano	1.43	10.8	0.36	1.53	11.4	0.37	7.2	5.9	1.5	-8.3	-4.6	-3.9
Province of Trento	2.01	14.9	0.37	2.19	16.3	0.37	9.2	9.4	0.0	-3.4	-0.3	-3.2
Veneto	1.52	11.1	0.37	1.58	11.5	0.38	4.3	3.9	0.6	-7.5	-4.4	-3.2
Friuli VG	2.32	17.8	0.36	2.38	18.1	0.36	2.4	1.5	1.3	-5.4	-2.0	-3.5
Liguria	1.69	11.7	0.39	1.80	12.4	0.40	6.5	5.7	1.1	-6.7	-3.5	-3.3
Emilia R.	1.39	10.1	0.38	1.56	11.7	0.36	11.8	16.7	-3.9	-4.8	-2.4	-2.4
Tuscany	1.71	12.5	0.37	1.81	13.2	0.38	5.8	5.5	0.6	-6.6	-4.5	-2.2
Umbria	1.77	13.0	0.37	1.87	13.7	0.37	5.7	5.2	0.8	-5.2	-3.0	-2.2
Marche	1.80	12.5	0.39	1.91	13.3	0.39	6.3	6.4	0.2	-7.2	-4.5	-2.9
Lazio	2.98	21.5	0.38	3.10	22.4	0.38	4.1	3.9	0.5	-6.9	-3.6	-3.4
Abruzzo	2.58	18.4	0.38	2.76	19.6	0.39	7.2	6.5	0.9	-4.6	-2.2	-2.5
Molise	3.14	21.5	0.40	3.36	22.9	0.40	7.0	6.2	1.0	-5.9	-3.0	-3.1
Campania	3.59	26.2	0.37	3.86	27.9	0.38	7.4	6.4	1.2	-4.4	-2.2	-2.2
Puglia	3.67	26.0	0.39	3.85	27.1	0.39	4.9	4.1	1.0	-7.0	-5.1	-2.0
Basilicata	3.11	22.2	0.38	3.43	24.4	0.39	10.5	9.9	0.9	-4.0	-2.0	-2.1
Calabria	3.86	27.8	0.38	3.92	28.2	0.38	1.7	1.5	0.5	-5.7	-3.5	-2.3
Sicily	3.22	22.9	0.38	3.28	23.2	0.39	2.0	1.1	1.1	-6.4	-3.7	-2.8
Sardinia	3.47	24.9	0.38	3.67	26.1	0.38	5.7	5.1	0.9	-6.5	-4.3	-2.4
Italy	**2.34**	**16.9**	**0.38**	**2.48**	**17.8**	**0.38**	**5.9**	**5.5**	**0.7**	**-6.0**	**-3.4**	**-2.7**
North	1.57	11.5	0.38	1.70	12.4	0.38	8.0	7.9	0.3	-5.9	-3.0	-3.0
Centre	2.32	16.8	0.38	2.44	17.6	0.38	4.9	4.7	0.5	-6.8	-3.9	-3.0
South and Islands	3.44	24.7	0.38	3.61	25.8	0.38	4.9	4.2	1.0	-5.8	-3.5	-2.4

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.

During the year 2021, about 15 out of 100 citizens received at least one prescription of NSAIDs, with a higher exposure level in women: 17.1% compared to 12.8% in men. As expected, on the basis of the epidemiology of some clinical conditions such as arthritis and osteoarthritis in which these medicines are used, consumption increases with age until it reaches a maximum value of 50.4 in women and 34.6 DDD/1000 inhabitants per day in men in the 75-84 age group. In this same group, the prevalence of use is between 35.4% in women and 28.3% in men (Figure 3.8.2b), while up to the age of 44 it does not reach 10%, and in any case in all groups women show higher values than men.

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 (20.5%), compared to the Centre (16.1%) and especially the North (10.3%), with a maximum level of 23.1% in Puglia and a minimum of 6.2% in the Province of Bolzano. In assessing these territorial differences, the possible greater use of private purchase of Class A or self-medication medicines in the Northern Regions must be taken into account. As expected, this category of medicines is used as needed and for short periods, in fact half of the users are treated with NSAIDs for one month a year and 50.2% receive only one prescription.

Figure 3.8.2b Distribution of prevalence of use and consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) under approved care regime and per conto distribution (year 2021)

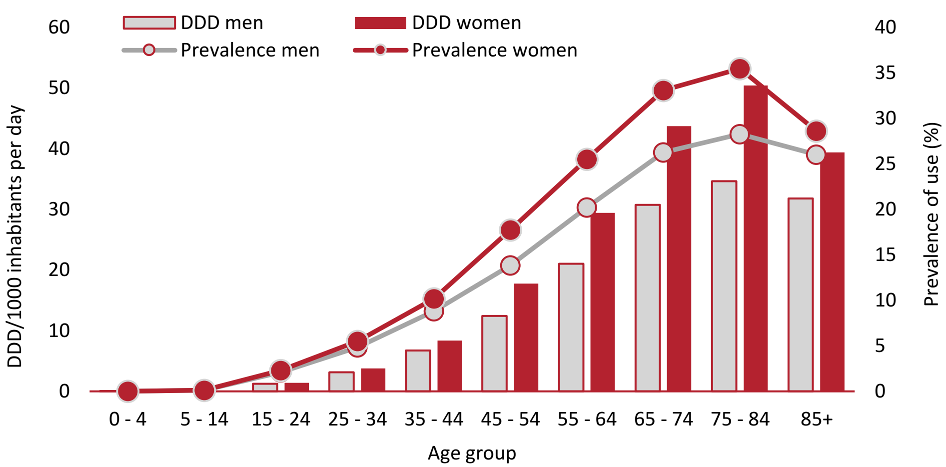


Table 3.8.2c Exposure and duration of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) by Region under approved care regime and per conto distribution (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	10.6	14.6	12.7	64	16.1	41.2	25.0	52.8
Valle d'Aosta	9.9	14.2	12.1	63	17.6	44.8	30.0	52.5
Lombardy	7.4	10.7	9.1	64	16.1	41.3	30.0	53.9
Province of Bolzano	5.0	7.3	6.2	67	21.1	53.1	30.0	49.3
Province of Trento	11.1	14.7	12.9	61	15.8	41.7	28.3	50.2
Veneto	7.2	10.5	8.9	64	17.2	43.6	30.0	54.7
Friuli VG	12.0	16.6	14.4	63	16.8	45.1	30.0	48.9
Liguria	10.2	14.0	12.2	67	15.5	37.8	21.0	55.9
Emilia R.	9.2	12.3	10.8	62	13.3	33.0	20.0	55.5
Tuscany	11.2	14.9	13.1	64	13.8	35.5	20.0	56.1
Umbria	12.6	15.9	14.3	63	13.4	34.9	20.0	55.7
Marche	12.2	15.2	13.7	64	14.0	34.4	20.0	56.8
Lazio	16.5	21.7	19.2	62	15.7	40.8	28.5	48.1
Abruzzo	17.1	21.7	19.5	63	14.0	35.5	20.0	53.5
Molise	19.0	24.1	21.6	65	16.3	39.9	24.0	48.3
Campania	17.8	24.1	21.0	61	16.7	43.3	30.0	46.9
Puglia	20.5	25.7	23.1	63	16.0	40.8	30.0	46.0
Basilicata	18.8	24.4	21.6	63	15.7	40.0	26.9	49.4
Calabria	17.4	22.8	20.1	67	18.7	48.4	30.0	43.2
Sicily	15.5	20.3	18.0	66	17.5	44.4	30.0	46.3
Sardinia	19.2	25.0	22.2	63	16.8	43.1	30.0	46.0
Italy	**12.7**	17.0	**14.9**	**63**	**16.1**	**41.3**	**30.0**	**50.2**
North	8.5	12.0	10.3	64	15.9	40.6	25.0	54.0
Centre	13.9	18.2	16.1	63	15.0	38.6	22.5	51.8
South and Islands	17.8	23.2	20.5	63	16.8	43.0	30.0	46.9

Key message

- In 2021 there is **an increase in the consumption of NSAIDs**, which returns to pre-pandemic levels with 17.8 DDD/1000 inhabitants per day, a 5.5% increase compared to 2020 but with an average annual reduction of 3.4% over the period 2014-2021.
- The main therapeutic categories (NSAIDs and Coxibs) show an **increase in expenditure and consumption compared to 2020**, although the trend of the average DDD cost is stable. The category with the highest per capita expenditure and consumption is represented by **traditional NSAIDs**, for which a value of 1.65 euros and a consumption of 12.8 DDD/1000 inhabitants per day are observed.
- **Diclofenac** is confirmed as the active ingredient with the highest expenditure (0.61 euros), followed by heterocoxib (0.59 euros), ibuprofen (0.30 euros) and ketoprofen (0.27 euros).
- During the year 2021, about 15 out of 100 citizens received at least one prescription of NSAIDs, with a higher **exposure** level in women than men: 17.1% vs 12.8% and an **increase in prevalence with increasing age**.
- **Days of therapy** per user indicate treatment of approximately one and a half months, although half of users receive only one prescription, highlighting as-needed use of these medications.
- For this category, there is a high level of private purchasing (see Section 2), which limits the possibility of adequate monitoring of the prescribing appropriateness of these medicines 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 to use a NSAID, account should be taken both of the medicine's overall benefit/risk profile and of the characteristics of populations that might present contraindications or risk factors predisposing to the occurrence of side effects.

References

- Aifa. Important Information Note on ketorolac trometamine available at the link https://www.aifa.gov.it/-/nota-informativa-importante-su-ketorolac-trometamina. Last update 15 April 2015.
- Cush JJ. Approach to articular and musculoskeletal disorders. In: Jameson JL et al., eds. Harrison's principles of internal medicine. 20th edition. New York: McGraw-Hill, 2018.
- Feleus A, Bierma-Zeinstra SM, Miedema HS, et al. Management in non-traumatic arm, neck and shoulder complaints: differences between diagnostic groups. Eur Spine J 2008; 17(9):1218-29.
- Grosser Tilo et al. Pharmacotherapy of inflammation, fever, pain, and gout. In: Brunton LL, et al., eds. Goodman & Gilman's: the pharmacological basis of therapeutics. 13th edition. New York: McGraw-Hill, 2017.

- Smyth EM, et al. Lipid-derived autacoids: eicosanoids and platelet-activating factor In: Brunton LL, et al., eds. Goodman & Gilman's: the pharmacological basis of therapeutics. 13th edition. New York: McGraw-Hill, 2017.
- Van Tulder M, Becker A, Bekkering T et al.; COST B13 Working Group on guidelines for the man- agement of acute low back pain in primary care. Chapter 3. European guidelines for the man- agement of acute nonspecific low back pain in primary care. Eur Spine J 2006; 15 Suppl 2(Suppl 2):S169-91.

3.9 Systemic hormonal preparations, excluding sex hormones and insulins

In 2021, the therapeutic category of systemic hormone preparations, excluding sex hormones and insulins (H), ranks ninth in terms of public spending, accounting for EUR 477.4 million and 2.0% of total public spending (Box. Main indices of expenditure, consumption and exposure). The overall per capita expenditure for such medicines was 8.06 euros, mainly due to the purchase by public health facilities with 4.24 euros per capita, a 11.5% decrease. On the contrary, the contribution provided through the NHS outpatient care was lower (3.82 euros per capita), a 2.7% decrease compared to the previous year (Table 3.1).

Consumption for this category of medicines was 41.5 DDD/1000 inhabitants per day in 2021, with a slight 0.2% increase compared to 2020, confirming the growing trend of the last eight years (CAGR 2014-2021: +0.8%), which places this category in eighth place in terms of consumption (Table 3.2). The analysis of the medicine use profile by age group and gender, including outpatient pharmaceutical expenditure and per conto distribution, shows a progressive increase in the use of medicines belonging to this category with increasing age for both genders, with a more marked increase from 55 years on. However, use remains consistently higher in women than in men, with the exception of the group aged between 5 and 14, which is likely justified by the trend toward early corticosteroid use and treatment of subclinical hypothyroidism as early as pediatric age. About one in three women in the age group over the age of 75 receives at least one prescription over the course of one year. At the same time, NHS per capita expenditure also increases with the age of patients, reaching the maximum level of 12.2 euros per capita (14.4 in women and 9.0 in men) in subjects over 75 years of age.

As for outpatient expenditure, per capita expenditure was 3.82 euros, with a 3.4% decrease compared to the previous year. Where consumption increases slightly by 1.6%, there is a recourse to less expensive specialties (mix effect: -5.4%) and a 4.9% reduction compared to 2020 in the average cost per day of therapy (Table 3.9).

Categories having the greatest impact on the cost of pharmaceuticals under approved care regime are glucocorticoids (1.44 euros per capita, equal to 38% of the total of the category), followed by thyroid hormones (1.26 euros per capita). Glycocorticoids show an increase in both expenditure and consumption (+4.4% and +3.9% respectively) compared to the previous year with a shift towards less expensive specialties (mix effect -1.3%). Thyroid hormones, which have the highest consumption in the whole group of systemic hormonal preparations, also recorded an increase in both expenditure and consumption compared to 2020 (+7.1% and +0.5% respectively), with a higher propensity to use more expensive medicines (mix effect +6.6 %). Parathyroid hormones continue to record a decrease in expenditure and consumption (-26.5% and -21.3% respectively) and a 6.6% reduction in the average DDD cost, which can be explained by the recent patent expiry of teriparatide. The most expensive active ingredient is levothyroxine (1.22 euros), followed by teriparatide (0.78 euros; Table 3.10): both molecules are the most prescribed molecules within the respective category. In particular, levothyroxine consumption (21.6 DDD) accounts for 60% of systemic hormonal preparations (36.8 DDD). Levothyroxine also ranks 14th among the

30 active ingredients with the highest variation in NHS outpatient expenditure compared to 2020 (+8.2%) (Table 3.14) and 9th among the active ingredients with the greatest consumption (Table 3.16). Teriparatide, on the other hand, ranks first among the medicines with the highest cost per day of therapy (Table 3.13) and second among the active ingredients with the greatest reduction in expenditure (Table 3.15).

With regard to purchases by public health facilities, compared to 2020, there was a marked reduction in expenditure (-12.1%) and in consumption (-16.1%) and a smaller reduction in prices (-2.5%), despite a shift towards more expensive medicinal products (mix effect: +7.5%) with a corresponding increase in the average cost per day of therapy (+4.8%) (Table 3.18).

The category with the greatest impact on expenditure is represented by somatostatin and analogues (1.54 euros per capita), a 6.6% reduction compared to 2020 and accounting for 36.0% of the expenditure of the entire class, followed by somatotropin and analogues (1.21 euros per capita). Compared to 2020, there is a decrease in consumption for both subcategories (-3.9% and -4.8% respectively); however, for somatotropin and analogues there was a more marked reduction in prices (-5.7% vs. 0.0%) and in the average cost per day of therapy (-7.4% vs. -2.8%) (Table 3.19).

Somatropin is the active substance that ranks first in this category of medicines both in terms of consumption (0.3 DDD per 1000 inhabitants per day) and per capita expenditure (1.20 euros, -11.2% vs. 2020), while etelcalcetide, indicated for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease undergoing haemodialysis, is the active ingredient that registers the greatest increase in per capita expenditure compared to 2020 (+12.3%) (Table 3.19).

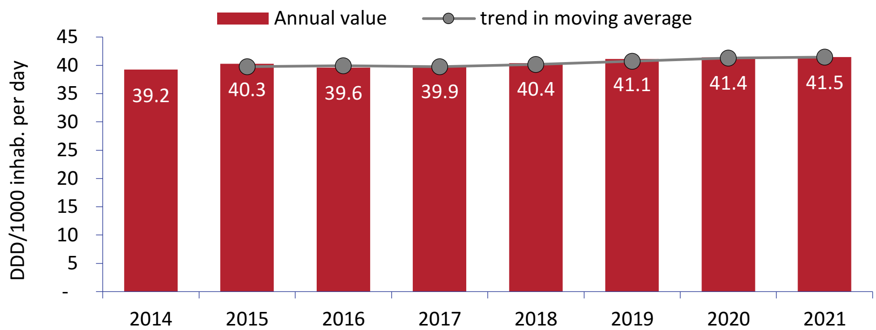
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by Region and on the efficiency in the absorption of resources according to the presence of off-patent medicines and on a regional basis. Such analyses focused on medicines for thyroid medicines (Tables 3.9.1).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

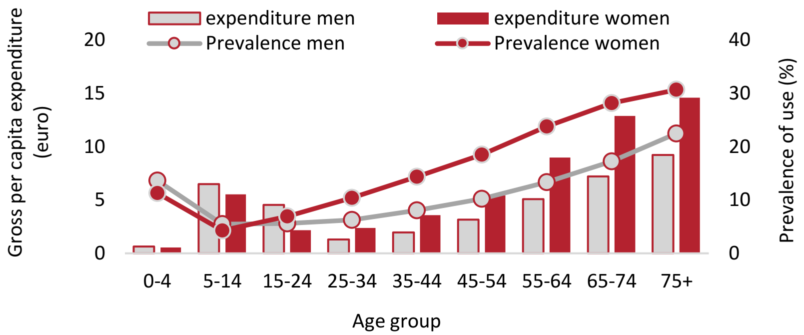
Systemic hormonal preparations, excluding sex hormones

Public expenditure* in million euros (% over total)	**477.4**	**(2.0)**
Δ % 2021-2020		-7.6
Regional range for gross expenditure (per capita):	6.3	9.6
DDD/1000 inhab. per day* (% over total)	**41.5**	**(3.2)**
Δ % 2021-2020		0.2
Regional range for DDD/1000 inhab. per day:	27.5	51.0

* *includes NHS outpatient prescriptions and purchases by public health facilities*



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and *per conto* distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.6	0.6	0.6	3.1	2.6	2.9
5-14	6.5	5.5	6.0	3.8	3.3	3.6
15-24	4.6	2.2	3.4	6.0	8.4	7.2
25-34	1.3	2.4	1.8	8.3	19.4	13.8
35-44	2.0	3.6	2.8	12.5	33.0	22.8
45-54	3.1	5.4	4.3	19.1	50.4	34.9
55-64	5.1	9.0	7.1	30.3	74.0	52.8
65-74	7.2	12.9	10.2	44.5	94.6	71.0
75+	9.2	14.6	12.4	59.7	99.1	83.2

3.9.1 Thyroid medicines

Epidemiological framework

Thyroid diseases mainly concern hyperthyroidism, characterised by the excessive synthesis and/or secretion of thyroid hormones, and hypothyroidism which is the most common thyroid disease, characterized by an insufficient action of thyroid hormones at the tissue level with consequent slowing down of all metabolic processes. Basedow-Graves syndrome, also called “Graves disease” is the most common form of hyperthyroidism (autoimmune pathogenesis); it is 7-8 times more common in women and usually appears before the age of 40. Hyperthyroidism is a rare condition and the prevalence data present in the literature on the Italian population are somewhat lacking and often refer to limited territorial areas or hospital cases rather than to the national level. An Italian retrospective study conducted on administrative databases of the Piedmont Region between 2012 and 2018 estimated a prevalence of the condition of 756 per 100,000 inhabitants and an incidence of 81 per 100,000 individuals per year. In the study, women showed two distinct peaks in incidence at the age of 30 and 50, respectively, while after the age of 60, the trend became similar between the genders. As far as hypothyroidism is concerned, the two most common forms are congenital hypothyroidism (IC), caused by alterations in the embryogenesis of the thyroid gland, and acquired hypothyroidism (AI), or post-natal onset, caused by a deficiency in hormone production by the thyroid gland (primary hypothyroidism), mainly due to autoimmune thyroid diseases, such as Hashimoto's thyroiditis. In this case too, the epidemiological data, especially prevalence data, available in the literature on the Italian population are somewhat lacking and often refer to limited territorial areas or hospital settings. According to the latest available Health Search data relating to 2011, the prevalence of hypothyroidism (congenital, post-surgical and primary) was 3.7%, with a tendency to increase with age and with a higher incidence in women than men (2/1,000/year vs 2/10,000/year) with a F/M ratio of 10:1. Primary hypothyroidism is more frequent in North-Eastern and Central Italy, while congenital and post-surgical hypothyroidism prevail in the South and Islands. According to the latest data from the National Registry (1999-2005 period), congenital hypothyroidism has an incidence of approximately 1 case per 2,300 live births in Italy, and approximately 1 case per 803 new births in Calabria, a historically endemic region. Less common forms, such as secondary or tertiary hypothyroidism, due to hypothalamic-pituitary dysfunction, are found in only 1% of cases. While treatment of hypothyroidism is normally intended to be lifelong unless remission occurs (described in 20% of cases), administration to control thyroid hyperplasia should be discontinued by menopause or the age of 60 because of the risk of developing osteoporosis.

National data on consumption and expenditure

Over the past 8 years, thyroid medication consumption has remained stable with slight mean annual variations (CAGR: +1.5%) (Figure 3.9.1.a). A slightly more marked increase was recorded starting from 2018 (22.1 DDD/1000 inhabitants per day) up to 23.4 DDD/1000 inhabitants per day in 2021, a 1.4% increase compared to 2020. In recent years there has been also the greatest variation in terms of the average cost per day of therapy, which has risen overall by 41%, from 0.11 euros in 2014 to 0.15 euros in 2021, most likely due to the use of more expensive medicines.

Out of a per capita expenditure of 1.32 euros and consumption levels of 23.4 DDD/1000 inhabitants per day, thyroid hormones account for almost the whole category (about 95%) with 1.26 euros and 22.0 DDD respectively. In particular, in the last eight years, against a limited increase in consumption (CAGR: +1.5%), there have been more marked variations in terms of expenditure (CAGR: +6.7%) with an increase of 7.5% compared to 2020 (Table 3.9.1a).

What emerged for thyroid hormones is also reflected in the analysis of individual active ingredients. In fact, levothyroxine, a medicine authorised for hypothyroidism and non-toxic thyroid hyperplasia or in the prevention of relapse after partial removal of thyroid tissue, accounts for almost all the subgroup's prescriptions, registering in 2021 an expenditure of 1.23 euros per capita, in constant and progressive increase over the years (CAGR: +7% and Δ % 21-20: +7.9%), and consumption levels equal to 22 DDD/1000 inhabitants per day. On the contrary, the use of antithyroid preparations (thiamazole) has decreased slightly over the years (CAGR: -0.9%).

According to prevalence data in literature, Regions of the Centre show the highest levels of consumption of medicines for the thyroid gland in the last two years, reaching the value of 28.6 DDD/1000 inhabitants per day in 2021, a 1.7% increase compared to 2020 (Table 3.9.1b) Lazio is the Region with the highest consumption (31.0 DDD), followed by Umbria and Basilicata (both with 30.6 DDD), while Tuscany is the one with the greatest increase compared to 2020 (+6.5%) and in Friuli consumption is reduced by 1.9%.

Figure 3.9.1a Thyroid medicines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

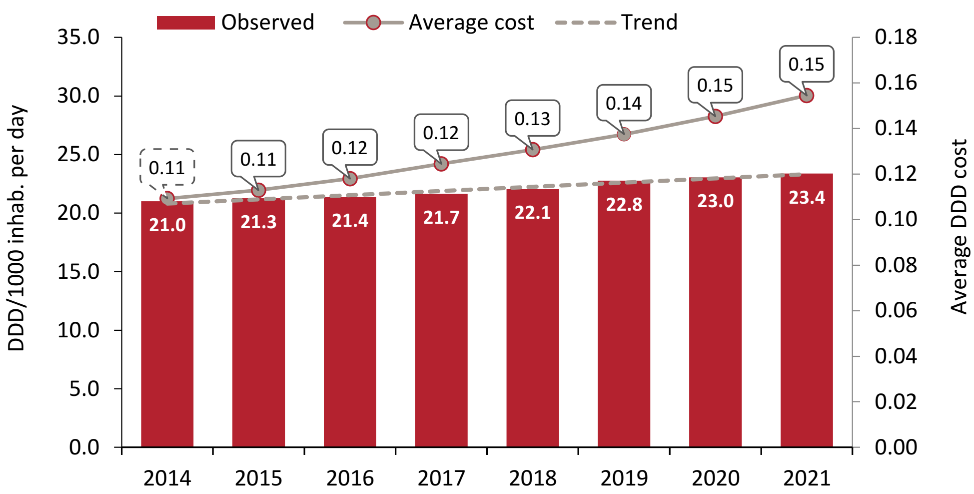


Table 3.9.1a Thyroid medicines, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Thyroid hormones	1.26	7.9	7.0	22.0	1.5	1.7	0.16	6.6
Antithyroid preparations	0.06	0.4	0.5	1.4	0.4	-0.9	0.11	0.2
Thyroid medicines	**1.32**	**7.5**	**6.7**	**23.4**	**1.4**	**1.5**	**0.15**	**6.3**
levothyroxine	1.23	8.2	7.2	22.0	1.5	1.7	0.15	7.0
thiamazole	0.06	0.4	0.5	1.4	0.4	-0.9	0.11	0.2
liothyronine	0.04	-3.5	2.2	0.0	-3.2	2.2	2.07	0.0

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	1.10	22.3	0.13	1.18	22.7	0.14	7.6	1.4	6.4	6.5	2.1	4.4
Valle d'Aosta	0.97	19.7	0.13	1.04	20.2	0.14	7.1	2.5	4.7	0.1	-2.8	3.0
Lombardy	0.88	15.8	0.15	0.96	16.2	0.16	8.9	2.5	6.5	8.4	2.4	5.9
Province of Bolzano	0.96	22.1	0.12	0.99	22.0	0.12	2.6	-0.4	3.3	3.9	0.5	3.3
Province of Trento	1.60	29.5	0.15	1.67	29.6	0.15	4.8	0.4	4.6	7.2	2.3	4.9
Veneto	1.27	20.1	0.17	1.40	20.4	0.19	9.5	1.2	8.5	9.8	2.0	7.6
Friuli VG	1.33	26.5	0.14	1.42	26.0	0.15	6.9	-1.9	9.3	7.1	2.1	4.9
Liguria	0.63	11.2	0.15	0.68	11.3	0.16	7.8	0.9	7.0	5.6	-0.6	6.2
Emilia R.	1.32	29.4	0.12	1.43	30.2	0.13	8.1	2.8	5.4	5.0	1.2	3.7
Tuscany	1.09	23.8	0.13	1.21	25.4	0.13	10.8	6.5	4.3	5.6	1.9	3.7
Umbria	1.60	30.1	0.14	1.69	30.6	0.15	5.9	1.5	4.6	7.5	2.9	4.5
Marche	1.21	26.0	0.13	1.27	26.4	0.13	5.4	1.6	4.0	5.2	1.7	3.4
Lazio	1.77	31.2	0.15	1.88	31.0	0.17	6.4	-0.7	7.4	6.3	0.5	5.8
Abruzzo	1.38	25.2	0.15	1.46	25.2	0.16	5.3	0.2	5.5	7.8	2.4	5.3
Molise	1.67	30.9	0.15	1.79	31.1	0.16	7.5	0.7	7.0	5.2	0.5	4.6
Campania	1.06	18.7	0.15	1.15	19.1	0.16	8.6	1.9	6.9	6.0	1.3	4.6
Puglia	1.55	28.4	0.15	1.64	28.5	0.16	5.7	0.5	5.5	6.7	2.2	4.4
Basilicata	1.39	29.0	0.13	1.51	30.6	0.13	8.6	5.6	3.1	6.1	2.4	3.7
Calabria	1.21	23.9	0.14	1.28	23.7	0.15	5.6	-0.9	6.9	4.8	0.6	4.2
Sicily	1.26	22.2	0.16	1.34	22.2	0.17	6.2	0.1	6.4	7.3	1.7	5.6
Sardinia	1.46	28.9	0.14	1.56	28.9	0.15	6.6	0.0	6.8	5.2	-0.2	5.3
Italy	**1.23**	**23.0**	**0.15**	**1.32**	**23.4**	**0.15**	**7.5**	**1.4**	**6.3**	**6.7**	**1.5**	**5.1**
North	1.08	20.4	0.14	1.16	20.8	0.15	8.3	1.7	6.8	7.3	1.8	5.4
Centre	1.47	28.1	0.14	1.57	28.6	0.15	7.3	1.7	5.8	6.1	1.2	4.9
South and Islands	1.29	23.7	0.15	1.38	23.9	0.16	6.7	0.7	6.2	6.4	1.5	4.9

Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure and intensity of use of thyroid medicines in the general population.

As expected, based on epidemiological evidence of the condition, women use more medicines than men. Consumption levels increase progressively with age to reach for both genders higher values in the 75-84 age group: 71.2 DDD in women and 24.9 DDD in men. The trend in prevalence is in line with consumption and for women, in the 65-74 and 75-84 age groups, there are percentage values of 15.3% and 16.4% respectively, more than 3 times higher than for the men of the same age groups; however, the greatest differences between men and women are observed in the 35-44 age group (5.7% vs 1.0%) (Figure 3.9.1c).

The prevalence of use in the Italian population is equal to about 5.1% with a median age of 64 years and a male to female ratio of 1:4 (1.9%/8.2%). Liguria, despite its higher median age (75 years), has the lowest prevalence of use (3.0%) at regional level, while Molise, whose treated population is slightly younger than the national population (63 years vs. 64), has a prevalence of use of 7.3%, which reaches 11.7% in women. 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. Confirming the non-chronic use of these medicines and the fact that the cost per DDD is not high, it should be emphasised that the average expenditure per user is just over 25 euros. In this case the regional range varies from 21.1 euros in Marche to 32.5 euros in Veneto (equal to a 55% difference; Table 3.9.1c). Approximately 6% of the users received only one prescription in 2021, with, in this case, wide variability in the various Regions: in fact, it goes from 2.9% in the Province of Trento to 9.4% in Liguria.

Figure 3.9.1d Breakdown of prevalence of use and consumption of thyroid medicines under approved care regime and per conto distribution in 2021

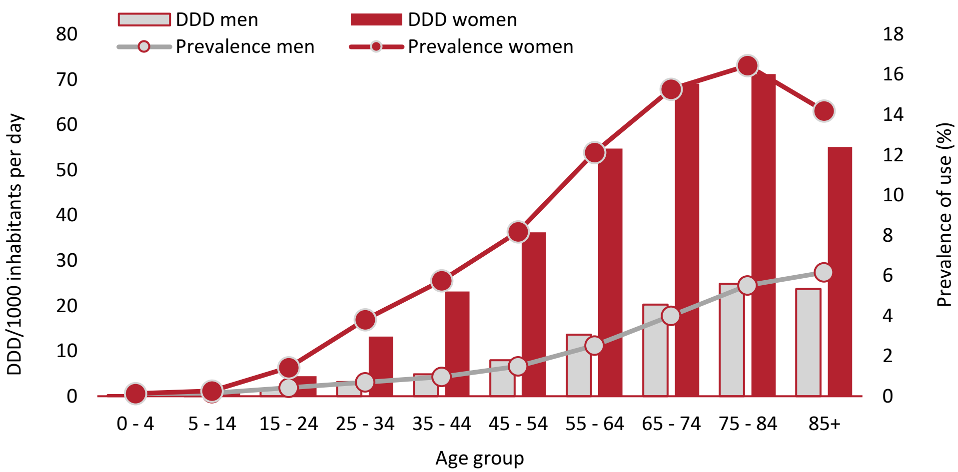


Table 3.9.1c Exposure and duration of therapy with thyroid medicines by Region under approved care regime and per conto distribution (year 2021)

Region	Prevalence of use (%)			Median age	Cost per user	DDD per user	DDD median	Users with 1 prescription (%)
	men	women	total					
Piedmont	2.0	9.0	5.6	66	21.8	149.7	133.3	5.8
Valle d'Aosta	1.6	7.8	4.8	67	21.7	150.1	133.3	3.6
Lombardy	1.3	5.8	3.6	64	26.1	160.0	150.0	4.9
Province of Bolzano	1.7	7.1	4.4	67	20.5	157.8	150.0	3.8
Province of Trento	2.3	10.3	6.3	61	25.3	161.1	150.0	2.9
Veneto	1.5	6.9	4.3	62	32.5	168.2	150.0	4.7
Friuli VG	2.1	9.9	6.1	65	24.5	160.6	150.0	3.7
Liguria	1.1	4.7	3.0	75	24.5	141.0	133.3	9.4
Emilia R.	2.3	10.3	6.4	64	21.5	161.1	150.0	4.1
Tuscany	2.3	9.6	6.0	66	20.6	155.4	141.7	8.1
Umbria	2.7	11.3	7.1	64	24.7	160.9	150.0	5.9
Marche	2.3	9.8	6.2	65	21.1	158.4	150.0	5.9
Lazio	2.4	10.6	6.6	64	27.9	166.3	150.0	4.4
Abruzzo	2.2	9.0	5.7	64	26.0	163.5	150.0	6.1
Molise	2.8	11.7	7.3	63	26.2	164.1	150.0	5.2
Campania	1.6	6.8	4.3	61	24.5	148.3	133.3	8.5
Puglia	2.3	10.1	6.3	62	25.4	161.1	150.0	4.7
Basilicata	2.6	10.5	6.6	63	23.2	170.2	166.7	6.4
Calabria	2.1	8.3	5.2	65	23.8	160.5	150.0	8.1
Sicily	1.7	7.6	4.7	65	27.7	166.6	150.0	6.8
Sardinia	2.0	9.8	6.0	64	27.0	181.4	175.0	4.6
Italy	**1.9**	**8.2**	**5.1**	**64**	**25.5**	**162.8**	**150.0**	**5.7**
North	1.6	7.4	4.6	65	25.3	160.8	150.0	4.9
Centre	2.3	10.1	6.3	65	25.0	163.9	150.0	5.9
South and Islands	1.9	8.2	5.1	63	26.0	163.8	150.0	6.6

Key message

- Over the last 8 years, thyroid hormone **consumption** has stabilised around values between 22 and 23 DDD/1000 inhab. per day with a +1.5% average annual variation.
- **Thyroid hormones** are the category with the highest consumption in 2021 (23.4 DDD/1000 inhabitants per day) with an increase in doses of 1.4% and in the average cost per day of therapy of 6.3%, compared to the previous year.
- According to **prevalence data in literature**, Regions of the Centre show the highest levels of consumption (28.6 DDD/1000 inhabitants per day), compared to the Southern (23.9) and the Northern Regions (20.8), and of prevalence (6.3%) compared to a national average equal to 5.1%.
- **Levothyroxine**, in addition to being the active ingredient with the highest per capita expenditure, ranks 14th among the 30 active ingredients with the greatest variation in NHS outpatient spending compared to 2020 (+8.2%) and 9th among the active ingredients with the highest consumption (21.6 DDD). If the consumption of this molecule is slightly increasing (+1.5%), the significant growth of the average DDD cost (+6.3%) is particularly evident.
- As expected, **women** have higher levels of **use** than men with a ratio of 4:1; the prevalence in women is 8.2% while in men it is 1.9%.
- 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.

References

- Campo S, Cricelli C, Lapi F, Medea G, Pecchioli S. La patologia tiroidea nella Medicina generale italiana. Studio epidemiologico e considerazioni sul management clinico del paziente. Rivista SIMG 2013; 5:7-11. Available at the address https://www.simg.it/Riviste/rivista_simg/2013/05_2013/2. pdf/
- Caputo M, Pecere A, Sarro A, et al. Incidence and prevalence of hyperthyroidism: a popula- tion-based study in the Piedmont Region, Italy. Endocrine 2020; 69(1):107-12.
- Chiovato L, Magri F, Carlé A. Hypothyroidism in context: where we've been and where we're going. Adv Ther 2019; 36(Suppl 2):47-58.
- Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and preva- lence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014; 99(3):923- 31.
- Istituto Superiore di Sanità. Convegno "Ipotiroidismo congenito in Italia". Roma, 3 luglio 2009. ISTISAN Congressi 09/C5. Available at the address https://www.iss.it/documents/20126/0/2009.pdf/731fb718-2b2e-8459-9272-eb76c3796934?t=1609404310274
- Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid 2014; 24(12):1670-751.

- Ragusa F, Fallahi P, Elia G, et al. Hashimotos' thyroiditis: epidemiology, pathogenesis, clinic and therapy. Best Pract Res Clin Endocrinol Metab 2019; 33(6):101367.
- Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diag- nosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016; 26(10):1343-421.
- van Trotsenburg AS, Stoupa A, Léger J, et al. Congenital hypothyroidism: a 2020-2021 consensus guidelines update An ENDO-European Reference Network (ERN) initiative endorsed by the Euro- pean Society for Pediatric Endocrinology and the European Society for Endocrinology. Thyroid 2021; 31(3):387-419.

3.10 Genito-urinary system and sex hormones

In 2021, medicines affecting the genito-urinary system and sex hormones were the 10th therapeutic category with the highest public expenditure, equal to 409.4 million euros and 1.7% of overall public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure for these medicines was 6.89 euros, mainly relating to NHS outpatient pharmaceutical care (5.53 euros per capita), with a 2.1% increase compared to 2020. Expenditure by public health facilities is lower than the agreed one (1.36 euros per capita), but shows a 12.5% increase compared to the previous year (Table 3.1).

On the other hand, this category of medicines ranks fifth in terms of NHS consumption with 46.2 DDD/1000 inhabitants per day, a 4.4% increase compared to 2020, with a rather steady trend in recent years (CAGR 2014-2021: +0.9%; Table 3.2).

The analysis of the medicine use profile by age group and gender, including outpatient pharmaceutical expenditure and per conto distribution, confirms an almost exclusive use of this class of medicines in men aged 55 and over, essentially due to the treatment of prostatic hypertrophy. The prevalence of use of these medicines in men over 75 years of age reaches 40% of the population in this age group. At the same time, NHS per capita expenditure also increases with the age of patients, reaching the maximum level of 53.1 in men 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 11.5 euros per capita.

As for NHS outpatient care, per capita expenditure for medicines affecting the genito-urinary system and sex hormones is 5.53 euros decreasing compared to 2020. This trend was determined exclusively by an increase in consumption (+2.9%) while the average cost for DDD shows a -1.5% reduction and there is a recourse to less expensive specialties (mix effect -0.3%) (Table 3.9). Within this channel, alpha-adrenergic receptor antagonists are the therapeutic subcategory that accounts for more than half of spending and consumption in the whole category, with 2.88 euros per capita expenditure and 27.7 DDD/1000 inhabitants per day, followed by testosterone-5-alpha reductase inhibitors, with 1.59 euros and 10.9 DDD (Table 3.9). While testosterone-5-alpha reductase enzyme inhibitor medicines show slight contractions in expenditure and consumption compared to 2020 (-2.0% and -1.0% respectively), alpha-adrenergic receptor antagonists show increases especially in terms of consumption (+ 3.9%) with a slight increase in expenditure (+ 0.8%) due to a shift towards less expensive specialties (mix effect: -1.2%). The molecules with the greatest impact on per capita expenditure in the category are tamsulosin (1.12 euros) and dutasteride (1.04 euros) which represent about 40% of the entire category (Table 3.10) and which together with alfuzosin fall within among the top 30 most consumed active ingredients (Table 3.16). Dutasteride is the only molecule in the category which is among the 30 active ingredients with the highest expenditure reduction (Table 3.15).

In terms of purchases by public health facilities, there was an increase in both per capita expenditure (+11.8%) and consumption (+11.7%) and a shift towards more expensive medicines (mix effect: +6.6%), while the average cost per day of therapy remained stable (Table 3.18). The gonadotropin subcategory records the highest expenditure per capita

(0.95 euros), accounting for 70% of the category; it is also the one where the largest increases over 2020 are recorded (+27.4% per expenditure and +22.1% per DDD). These medicines are adenohypophyseal hormone analogues that are used both to restore hormone balance, such as in the treatment of infertility, and to treat conditions requiring a decrease in hormone levels (e.g., prostate cancer, surgical removal of fibroids, or early menarche) since a negative feedback system suppressing adenohypophyseal hormone production can be exploited.

The active ingredient with the highest incidence of expenditure (27%) is represented by follitropin alpha from recombinant DNA with a cost per day of therapy equal to 18.30 euros and a consumption of 0.1 DDD, which represents less than 1% of the whole category, although an increase of 34% over the previous year (Table 3.19). Similarly, the expenditure for menotropin and the follitropin alfa/lutropin alfa combination has also grown in the last year (+ 23.0% and + 43.6% respectively).

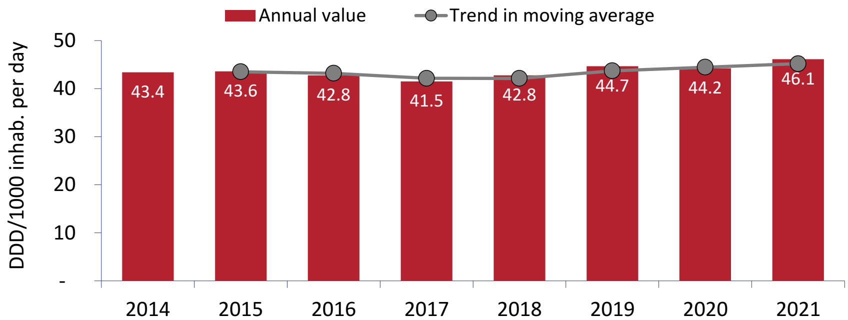
For further information on the use of medicines belonging to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region and on the efficiency in the absorption of resources according to the presence of off-patent medicines and on a regional basis. These analyses focused on medicines for genitourinary disorders (Section 3.10.1).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

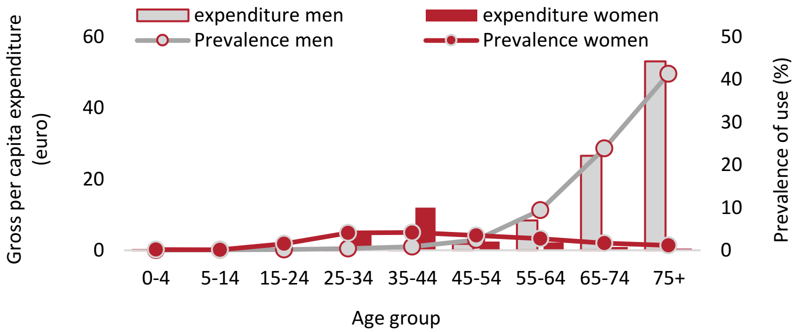
Genito-urinary system and sex hormones

Public expenditure* in million euros (% over total)	**409.4**	**(1.7)**
Δ % 2021-2020		4.0
Regional range for gross expenditure (per capita):	5.0	7.7
DDD/1000 inhab. per day* (% over total)	**46.1**	**(3.5)**
Δ % 2021-2020		4.4
Regional range for DDD/1000 inhab. per day:	31.5	54.1

* *includes NHS outpatient prescriptions and purchases by public health facilities*



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and *per conto* distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.0	0.0	0.0	0.0	0.1	0.1
5-14	0.0	0.0	0.0	0.1	0.2	0.2
15-24	0.3	0.7	0.5	0.5	4.0	2.2
25-34	0.6	5.4	3.0	1.2	11.3	6.2
35-44	1.0	11.9	6.5	2.6	14.6	8.6
45-54	1.8	2.5	2.1	11.8	14.5	13.1
55-64	8.4	2.2	5.2	68.2	15.1	40.9
65-74	26.6	0.9	13.0	222.2	7.8	108.9
75+	53.1	0.5	21.7	432.2	4.0	176.6

3.10.1 Medicines for genitourinary disorders

Epidemiological framework

Disorders of the genito-urinary system cover a range of clinical conditions that depend on the nature and aetiology of the disorder and the gender and age at which they appear. Benign prostatic hypertrophy (BPH) and urinary incontinence are the most common clinical conditions. BPH is a widespread condition, showing a prevalence in the male population of 15.8% in 2018, a marked increase from the 9.5% recorded in 2007, and an increasing geographical gradient from North to South and East to West. BPH is strongly correlated with age, so much so that it is, after hypertension, the most frequent disease among men over the age of 50. In particular, according to data presented to the Senate in 2019 by the Prevention and Research in Oncology Foundation, more than 6 million Italians over 50 are affected, and prevalence estimates range from 50% among men aged 50-60 up to 90% in the over-80s. To date, the aetiology of this disorder has not yet been fully clarified; however, a familiarity is hypothesised as an increased incidence is observed among relatives of individuals who have already been diagnosed with BPH. In addition, several preventable behavioural and clinical risk factors have been identified, including low levels of physical activity, high body mass index and previous history of hypertension, diabetes, hypercholesterolaemia and cardiovascular disease.

National data on consumption and expenditure

Between 2014 and 2021, consumption of medications for genito-urinary disorders increased from 31.8 to 39.4 DDD/1000 inhabitants per day, representing a mean annual increase (CAGR) of 3.1% (Figure and Table 3.10.1a). In the same period, the average cost per day of therapy decreased from 0.48 euros in 2014 to 0.32 euros in 2021 (CAGR: -33.3%), with the largest decrease in average cost for DDD occurring in 2017 due to the patent expiration of dutasteride, one of the most widely used medicines. On the other hand, as regards per capita expenditure (4.56 euros), the values are stable compared to 2020 (+0.7%).

Medicines for BPH account for almost all the consumption of the category of medicines for genito-urinary disorders (39.0 out of 39.4 DDD), with a slight increase compared to 2020 (+3.2%), and of the per capita expenditure (4.48 out of 4.56 euros), while the use of medicines for incontinence and urinary frequency disorders is marginal (0.4 DDD), but with an average annual increase since 2014 of 11.7% (+36% compared to 2020) (Table 3.10.1a).

Similar to the year 2020, the most prescribed medicines for 2021 are tamsulosin, dutasteride, alfuzosin, and silodosin with year-over-year increases ranging from -0.8% for dutasteride to +15.3% for silodosin. Although these are the medicines with the highest consumption, they record the lowest average cost per day of therapy of the category, ranging between 0.26 euros (alfuzosin) and 0.34 euros (dutasteride), about half that of tolterodine, a medicine indicated in the symptomatic treatment of urgency incontinence and/or increased urinary frequency and urgency in patients with overactive bladder syndrome which records the highest average cost per DDD of the whole category with 0.65 euros.

As for expenditure, doxazosin is the medicine for which the largest reduction in per capita expenditure is observed (-7.3%), while solifenacin registers the largest increases in expenditure (+328.4%) and in consumption (+453.8%) compared to 2020, probably linked to the patent expiry of the molecule, which occurred in February 2020 and for which several equivalent products are currently available. Although still small, tolterodine use has increased of 15.4% since the previous year, with an average annual increase of 51.7% since 2014. This medicine, together with oxybutynin and solifenacin, is included in AIFA Note 87, which limits its reimbursement (only for packages negotiated in class A/RR) to patients with urgency urinary incontinence, in cases where the urination disorder is related to diseases of the central nervous system (e.g. stroke, Parkinson's disease, trauma, tumours, spina bifida, multiple sclerosis).

At the macro-area level, there is a North-South gradient of increase both in terms of expenditure (from 4.09 euros in the North to 5.05 in the South) and in consumption (from 36.2 DDD in the North to 42.7 in the South) with a difference for both indicators of around 20% (Table 3.10.1b). The Marche is the Region with the highest consumption and expenditure (48.1 DDD and 5.65 euros), while the lowest values are recorded in the Province of Bolzano (24.2 DDD and 2.62 euros). In all the Regions there are increases in consumption ranging from + 1.1% in Calabria and Sicily to + 8.5% in Friuli Venezia Giulia.

Figure 3.10.1a Medicines for genitourinary disorders, temporal trend of consumption and average cost per day of therapy (2014-2021)

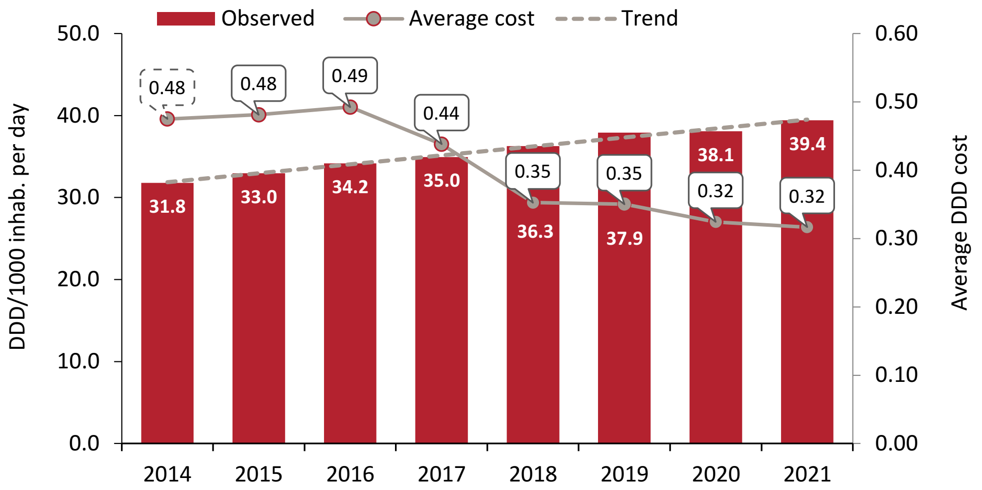


Table 3.10.1a Medicines for genitourinary disorders, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Medicines for benign prostatic hypertrophy	4.48	0.4	-2.8	39.0	3.2	3.1	0.31	-2.5
Medicines for incontinence and urinary frequency disorders	0.08	24.0	9.3	0.4	36.0	11.7	0.58	-8.5
Other medicines for benign prostatic hypertrophy	<0.005	2.6	-1.1	0.0	0.1	-2.8	1.17	2.7
Medicines per genitourinary disorders	**4.56**	**0.7**	**-2.7**	**39.4**	**3.5**	**3.1**	**0.32**	**-2.4**
tamsulosin	1.12	1.7	1.9	11.1	2.7	2.3	0.28	-0.6
dutasteride	1.04	-1.9	-10.7	8.4	-0.8	3.8	0.34	-0.9
alfuzosin	0.89	2.6	3.0	9.4	2.6	3.0	0.26	0.3
silodosin	0.71	1.4	1.7	6.2	15.3	9.2	0.31	-11.7
finasteride	0.55	-0.5	-0.9	2.6	0.8	-0.4	0.57	-1.0
terazosin	0.15	-5.5	-5.4	1.2	-4.9	-5.1	0.33	-0.4
oxybutynin	0.05	3.4	4.5	0.2	3.9	4.6	0.61	-0.3
doxazosin	0.02	-7.3	-7.6	0.2	-7.1	-7.6	0.42	0.0
solifenacin	0.02	328.4	31.4	0.1	453.8	51.7	0.43	-22.4
tolterodine	0.01	13.8	30.2	0.0	15.4	51.7	0.65	-1.1

Table 3.10.1b Medicines for genitourinary disorders, temporal trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	4.17	35.4	0.32	4.16	36.6	0.31	-0.1	3.5	-3.2	-3.6	2.1	-5.6
Valle d'Aosta	3.57	30.3	0.32	3.53	31.1	0.31	-1.2	2.6	-3.4	-4.8	1.3	-6.0
Lombardy	3.88	33.5	0.32	3.94	35.4	0.31	1.6	5.4	-3.3	-3.3	3.1	-6.2
Province of Bolzano	2.60	23.2	0.31	2.62	24.2	0.30	1.1	4.2	-2.7	-3.9	1.7	-5.5
Province of Trento	3.99	33.7	0.32	4.09	36.0	0.31	2.5	6.6	-3.6	-3.4	3.2	-6.4
Veneto	3.94	33.5	0.32	3.98	34.6	0.31	0.8	3.5	-2.4	-2.8	3.2	-5.8
Friuli VG	3.68	31.4	0.32	3.86	34.1	0.31	4.9	8.5	-3.0	-3.6	2.7	-6.2
Liguria	4.56	38.8	0.32	4.59	40.3	0.31	0.7	3.9	-2.8	-3.5	2.6	-6.0
Emilia R.	4.44	39.0	0.31	4.54	40.1	0.31	2.3	3.0	-0.4	-1.3	2.7	-3.9
Tuscany	4.30	37.1	0.32	4.33	38.6	0.31	0.7	4.0	-2.8	-2.8	2.9	-5.6
Umbria	5.39	44.9	0.33	5.38	45.8	0.32	-0.3	2.1	-2.1	-3.1	3.2	-6.1
Marche	5.67	46.7	0.33	5.65	48.1	0.32	-0.4	3.0	-3.0	-3.6	2.8	-6.2
Lazio	4.86	39.8	0.33	4.86	40.9	0.33	-0.1	2.8	-2.6	-3.2	2.5	-5.6
Abruzzo	4.71	39.9	0.32	4.74	41.2	0.32	0.6	3.2	-2.2	-2.6	3.6	-6.0
Molise	4.57	36.9	0.34	4.66	38.5	0.33	1.9	4.4	-2.1	-2.2	3.5	-5.5
Campania	5.09	41.5	0.33	5.16	42.9	0.33	1.4	3.3	-1.6	-0.8	4.5	-5.1
Puglia	5.20	43.1	0.33	5.23	44.2	0.32	0.5	2.5	-1.7	-2.3	4.0	-6.0
Basilicata	5.62	45.8	0.34	5.69	47.2	0.33	1.2	3.0	-1.5	-1.3	4.6	-5.6
Calabria	5.04	40.8	0.34	4.96	41.2	0.33	-1.7	1.1	-2.5	-3.2	2.8	-5.8
Sicily	5.04	42.1	0.33	4.99	42.6	0.32	-1.0	1.1	-1.8	-2.5	3.2	-5.5
Sardinia	4.60	38.8	0.32	4.68	41.0	0.31	1.8	5.7	-3.5	-1.7	3.9	-5.4
Italy	**4.52**	**38.1**	**0.32**	**4.56**	**39.4**	**0.32**	**0.7**	**3.5**	**-2.4**	**-2.7**	**3.1**	**-5.6**
North	4.04	34.7	0.32	4.09	36.2	0.31	1.4	4.3	-2.6	-3.0	2.8	-5.6
Centre	4.83	40.2	0.33	4.83	41.5	0.32	0.1	3.1	-2.7	-3.2	2.7	-5.7
South and Islands	5.04	41.6	0.33	5.05	42.7	0.32	0.3	2.6	-1.9	-2.0	3.8	-5.6

Exposure and adherence in population

Using Health Card data it was possible to describe the trend of prevalence and consumption by age group and Region and to calculate some indicators of intensity of use of medicines for genito-urinary disorders, represented for 99% by medicines for the treatment of BPH. In addition, patient adherence and persistence to treatment was estimated by taking into account only BPH medications.

From the in-depth study conducted in the male population (in women the use of these medicines is insignificant and therefore it has not been represented graphically), it is noted an increase in the use of medicines for genito-urinary disorders with increasing age, with higher values of prevalence (48.5%) and consumption (497.0 DDD/1000 inhabitants per day) in men over 85, in accordance with the epidemiological data in the literature on the prevalence of BPH in the male population. In the 75-84 age group the prevalence and consumption values are lower than in the next age group (39.2% and 406.2 DDD), while in the 65-74 age group the prevalence is 23.8% and then falls below 10% from the age of 64 onwards (Figure 3.10.1c). At national level, prevalence in males is 8.5%, ranging from a minimum of 7.7% in the Northern areas to a maximum of 9.1% in the Central and Southern Regions. The highest prevalence value is recorded in the Marche region (10.3%), followed by Basilicata (10.2%) and Umbria (10.1%), while the Province of Bolzano, with a prevalence of 5.2%, shows the lowest value. As expected on the basis of BPH prevalence, the median age of users is 74 years, with no particular differences between the different Regions (Table 3.10.1c).

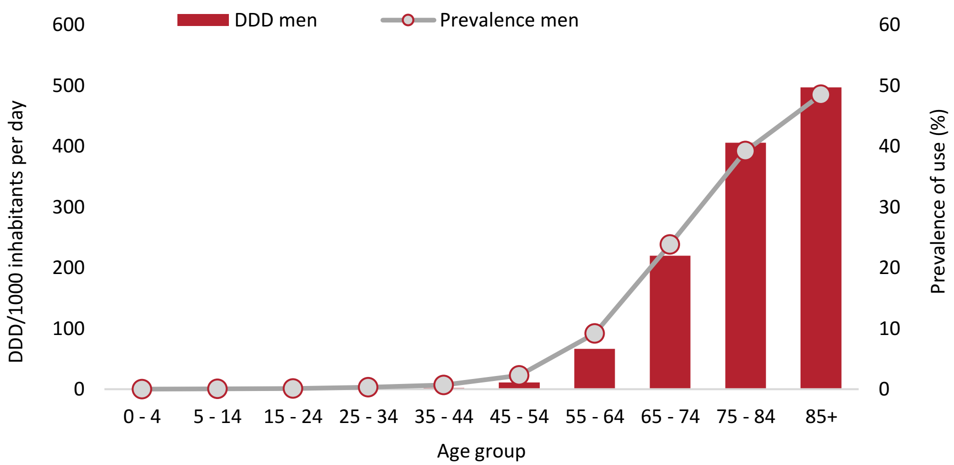
In accordance with the main guidelines on the treatment of BPH that provide for the treatment of a condition that has now become chronic, each user has received on average at least one dose of medicine per day for about 11 months of therapy: with regional differences ranging from from just under 290 days in Val d'Aosta and in the Province of Bolzano to over 340 days in the Province of Trento, Veneto, Friuli VG, Umbria, the Marche and Puglia. Analysing the DDD indicator by user, however, 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, which is not influenced by extreme values, was also taken into consideration: the result obtained (median DDD equal to 320 days) made it possible to confirm the data obtained previously. These data are also confirmed by the proportion of users with 1 prescription, which in 2021 showed a 6.9% decrease compared to the previous years. Also in this case there are marked regional differences with Tuscany which has a double percentage compared to that of Friuli Venezia Giulia (10.1% vs 5.0%). On average, the expenditure per user in 2021 was equal to 106.7 euros, in the Province of Bolzano this expenditure is equal to 21% and so lower than that of the Marche (88.7 euros vs 112.8 euros) (Table 3.10.1c).

As for the adherence and persistence analyses, the data on exposure to BPH medicines refer to a cohort of new male users over 45 years old, which were followed considering the one-year follow-up. In detail, the study population includes a total of 88,773 new users with a median age of 68 years (IQR 61-75). The percentage of subjects with high adherence is

63.7% and follows a normal distribution in which it tends to increase progressively from the age of 45 to reach the highest value (64.8%) in the 65-74 age group, then it decreases again in the following age groups (60.5% in the over 85s; Table 3.10.1d). This trend is found in all macro-areas, users residing in Central Italy and aged between 55 and 64 years showed the highest percentage value of high adherence (65.7%), while the lowest value is found in the South in the age group 85+ years with 59.1%. For low adherence to treatment (10.0% in total), on the other hand, an opposite trend is observed, with the highest percentage in the 45-54 age group and in the over-80s (12.4% and 10.7% respectively), while the 65-74 age group is the one that records the lowest percentage of users with low adherence (9.3%). In this case, too, the trend is similar in the three macro-areas, but it is Regions of the South that show the highest percentages of low adherence for all age groups.

An analysis of persistence data, on the other hand, shows that about half of users (49.3%), over a period of 1 year, stopped therapy for at least 60 days; these data are slightly lower than those of 2020. In detail, while in Northern Regions there are more persistent medication users (52.2%), in the South there are the lowest rates (48.9%), and this occurs regardless of the age group considered. In all three macroareas, however, the highest percentage of persistent users is concentrated in the 65-74 age groups (Table 3.10.1e). Comparing the persistence data (Figure 3.10.1c) there are differences between geographical macro-areas: the median time to discontinuation is over one year in the North, 300 days in the Centre and 275 days in the South.

Figure 3.10.1d Distribution of 2021 prevalence of use and consumption of medicines for genitourinary disorders under approved care regime and per conto distribution



Note: The use of medications for genitourinary disorders in women is not significant, so the chart shows data only for the male population

Table 3.10.1c Exposure and duration of therapy with medicines for genitourinary disorders by Region under approved care regime and per conto distribution (year 2021)

Region	Prevalence of use (%)	Median age	Cost per user	DDD per user	DDD age	Users with 1 prescription (%)
Piedmont	8.8	75	99.9	315.1	320.0	5.5
Valle d'Aosta	7.8	74	90.0	283.8	300.0	7.3
Lombardy	7.5	74	103.1	335.4	330.0	6.1
Province of Bolzano	5.2	76	88.7	287.3	300.0	8.7
Province of Trento	7.1	75	108.3	341.0	330.0	7.7
Veneto	7.1	74	110.1	344.6	340.0	6.7
Friuli VG	7.6	75	107.8	341.0	336.0	5.0
Liguria	10.0	75	101.7	319.4	320.0	6.4
Emilia R.	8.4	75	105.7	329.0	320.0	6.2
Tuscany	9.1	75	97.7	314.0	320.0	10.1
Umbria	10.1	75	112.2	344.4	340.0	6.9
Marche	10.3	74	112.8	348.8	345.0	7.4
Lazio	9.0	73	106.0	325.4	320.0	6.7
Abruzzo	9.1	74	105.4	333.1	330.0	8.3
Molise	9.2	74	105.6	319.4	320.0	6.9
Campania	9.4	72	101.5	308.1	320.0	6.6
Puglia	9.2	73	111.2	342.7	340.0	5.9
Basilicata	10.2	73	111.9	337.6	340.0	7.3
Calabria	9.3	73	104.2	316.0	320.0	7.7
Sicily	9.2	73	107.0	332.8	336.0	7.5
Sardinia	9.2	73	104.3	334.0	330.0	7.7
Italy	**8.5**	**74**	**106.7**	**334.0**	**320.0**	**6.9**
North	7.7	75	105.9	336.4	320.0	6.3
Centre	9.1	74	106.8	332.4	320.0	8.0
South and Islands	9.1	73	107.4	331.2	320.0	7.1

Table 3.10.1d Indicators of adherence to treatment with medicines for genitourinary disorders in the population aged ≥45 years in 2021 and percentage change compared to the previous year

	Total N=88.773				North N=36.968				Centre N=19.412				South N=32.393			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
Low adherence*^																
45-54 years	14.3	13.9	12.4	-11	12.9	12.1	11.1	-8	13.5	12.9	12.1	-6	15.8	15.7	13.6	-13
55-64 years	10.2	10.5	9.9	-5	9.3	9.4	8.8	-7	10.2	10.4	9.5	-8	11.2	11.6	11.3	-3
65-74 years	9.4	9.4	9.3	-2	8.4	8.9	8.4	-5	9.8	9.1	8.7	-5	10.2	10.2	10.6	4
75-84 years	10.0	10.3	10.1	-1	9.1	9.2	9.0	-2	10.1	10.7	10.7	0	11.2	11.5	11.5	0
≥85 years	11.6	11.0	10.7	-2	10.3	9.8	9.7	-1	12.6	12.4	11.0	-11	12.7	11.8	12.2	4
Total	**10.3**	**10.3**	**10.0**	**-3**	**9.2**	**9.3**	**8.9**	**-5**	**10.4**	**10.3**	**9.8**	**-5**	**11.3**	**11.4**	**11.4**	**0**
High adherence*^																
45-54 years	56.9	58.2	60.9	5	56.9	58.0	61.6	6	58.3	60.8	61.8	2	56.0	57.0	59.9	5
55-64 years	62.9	62.9	64.6	3	62.6	63.9	65.0	2	64.0	62.3	65.7	5	62.6	62.3	63.7	2
65-74 years	64.2	64.4	64.8	1	65.2	64.8	65.3	1	64.1	65.0	65.6	1	63.1	63.7	63.8	0
75-84 years	62.8	62.3	62.6	1	63.8	63.5	63.9	1	62.9	61.7	61.9	0	61.4	61.0	61.0	0
≥85 years	60.1	60.0	60.5	1	62.0	61.6	61.9	0	58.7	58.9	59.7	1	58.5	58.6	59.1	1
Total	**62.7**	**62.8**	**63.7**	**1**	**63.5**	**63.6**	**64.4**	**1**	**63.0**	**62.8**	**64.2**	**2**	**61.7**	**61.9**	**62.7**	**1**

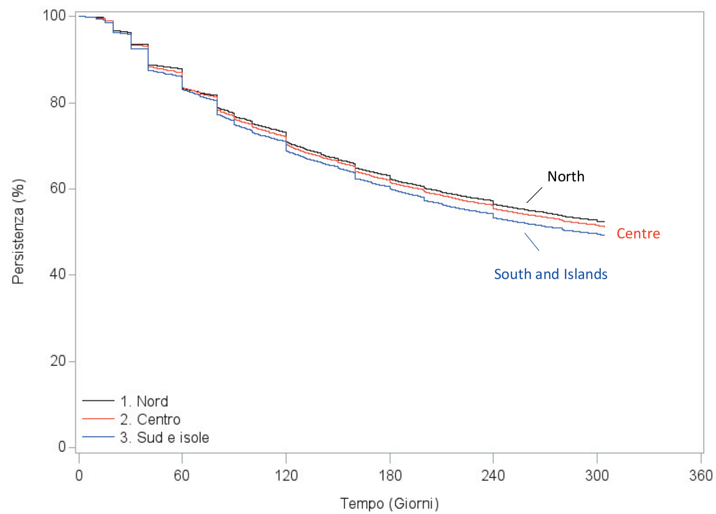
*Adherence to treatment was assessed during the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period, whereas high 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 01/10/2020-31/12/2020, not treated in the previous months starting from 01/01/2020.
Percentages of subjects with low/high adherence relating to the specific category.
Median follow-up time (IQR): 320 (215-345).

Table 3.10.1e Persistence after one year of treatment with medicines for genitourinary disorders in the population aged ≥45 years in 2021 and percentage change compared to the previous year

Persistence after 12 months	Total N=88.773				North N=36.968				Centre N=19.412				South N=32.393			
	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20	2019	2020	2021	Δ % 21-20
45-54 years	39.8	41.5	44.2	6	40.8	42.7	46.0	8	42.1	41.8	44.3	6	37.9	40.5	42.6	5
55-64 years	49.2	49.0	51.0	4	50.0	50.8	52.4	3	49.3	48.3	51.8	7	48.5	47.5	49.2	4
65-74 years	51.5	51.6	52.1	1	52.8	52.8	53.0	0	52.2	52.2	52.5	1	49.8	50.1	50.8	1
75-84 years	51.8	50.9	51.4	1	53.2	52.7	53.0	1	51.3	50.3	51.3	2	50.2	48.8	49.1	1
≥85 years	50.0	49.6	49.0	-1	52.7	51.0	51.1	0	48.8	48.5	49.0	1	47.3	47.4	45.9	-3
Total	**50.1**	**49.9**	**50.7**	**2**	**51.5**	**51.6**	**52.2**	**1**	**50.2**	**49.8**	**51.0**	**3**	**48.3**	**48.2**	**48.9**	**2**

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

Figure 3.10.1c Time (in days) to discontinuation of treatment with medicines for genitourinary disorders 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)



Key message

- In the field of medicines for genitourinary disorders, reference is mainly made to medicines used for the treatment of BPH in men, for which there is a **progressive increase in consumption** in line with increase in prevalence of the disease, probably due to the development of new knowledge leading to improvement in diagnostic techniques, greater attention to 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. Moreover, each user on average received at least one dose of the medicine per day for about 11 months of therapy, confirming a chronic use of these medicines, with slight interregional variations with respect to the national average.
- Against an increase in consumption, per capita expenditure on these medicines, after a steady decline in previous years, rose slightly in 2021. This trend is attributable to the gradual reduction in the impact of the patent expiry of some molecules between the years 2017 and 2018.
- Adherence and persistence to treatment with medicines for BPH do not present critical issues and indicate a **good patient compliance** to therapy, although lower percentages of high-adherent patients from 75 years of age are observed in all geographical areas and lower shares of persistent subjects in Southern Regions, regardless of the age group considered.

References

- Da Maso L, Zucchetto A, Tavani A et al. Lifetime occupational and recreational physical activity and risk of benign prostatic hyperplasia. Int J Cancer 2006; 118:2632-5.
- Fondazione PRO. Conferenza stampa “Ipertrofia prostatica benigna”. Rome, 18th September 2019. https://fondazionepro.it/wp-content/uploads/2020/11/Rassegna-stam- pa-aggiornata-ipertrofia-prostatica-1.pdf
- Health Search – Research Institute of SIMG. XII and XIII Annual reports, editions 2019 and 2020. https://www.healthsearch.it/report/
- Kosilov KV, Alexandrovich LS, Gennadyevna KI, et al. Social, economic, and medical factors associated with solifenacin therapy compliance among workers who suffer from lower urinary tract symptoms. Int Neurourol J 2016; 20:240-9.
- Mirone V, Carrieri G, Morgia G et al. Risk factors for benign prostatic enlargement: the role of lifestyle habits at younger age. Arch It Urol Androl 2017; 89(4):253-8.
- Piccinelli C, Carnà P, Stringhini S et al. The contribution of behavioural and metabolic risk fac- tors to socioeconomic inequalities in mortality: the Italian Longitudinal Study. Int J Public Health 2018; 63(3):325-35.
- Italian Society of Urology (SIU). EAU guidelines for the treatment of non-neurogenic male lower urinary tract symptoms and cervico-prostatic obstruction. Collane Linee Guida. Edition 2019. Available at the address http://www.andrologia-urologia.it/andrurl/ghid-cont/ uploads/2019/09/LG2018_LUTS.pdf

3.11 Sense organs

In 2021, medicines for sense organs are confirmed in 11th place in terms of public spending, amounting to about 399.5 million euros (1.7% of total spending; Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these medicines was 6.74 euros, mainly due to the NHS outpatient expenditure (3.71 euros per capita), reporting a -4.7% decrease compared to the previous year. Expenditure due to purchases of these medicines by public health facilities is slightly lower (3.03 euros per capita), but, on the contrary, shows a marked increase over 2020 of 41.9% (Table 3.1).

Consumption for this category of medicines was 22.9 DDD/1000 inhabitants per day, stable compared to 2020 (Table 3.2).

The analysis of the medicine use profile by age group and gender, including NHS outpatient pharmaceutical expenditure and per conto distribution, confirms an almost exclusive use of this class of medicines in subjects aged up to 55 years old, with an increase in the subsequent age groups up to about 10% in men over 55.. Consumption remains slightly higher in men than in women, in all age groups, with the values differing most in the 75+ age group (96.7 DDD in men vs. 84.6 in women). At the same time, NHS per capita expenditure also increases with the age of patients, reaching the maximum level of 15.9 euros per capita (17.3 in men and 15.0 in women) in subjects over 75 years of age.

As for NHS outpatient care, a significant reduction was recorded in expenditure (-5.3%) compared to 2021, against a slight reduction in consumption (-0.7%) and a more marked price reduction (-3.9%), with a shift towards less expensive medicines (mix effect: -0.8%; Table 3.9). Within this distribution channel, beta-blockers are the subcategory with the highest expenditure (2.13 euros) and consumption (11.6 DDD). Prostaglandin analogues follow, with values of 1.19 and 5.6 DDD, respectively. The only category to record an increase in consumption in 2021 (+23.7%) is that of carbonic anhydrase inhibitors, medicines capable of decreasing the formation of aqueous humour and thus reducing endocular pressure (Table 3.9). The increase observed for this category is mainly supported by the dorzolamide/timolol combination, which shows a 17.4% increase in consumption. Timolol alone or in combination with other active ingredients accounts for about 47% of the expenditure of the entire category (Table 3.10).

In terms of purchases by public health facilities, an important increase in expenditure was recorded, determined exclusively by a shift towards the purchase of more expensive substances (mix effect: +40.6%) and a slight increase in prices (+0.7%); while consumption remained stable (-0.4%; Table 3.18). The therapeutic category with the greatest impact on spending is antineovascular agents, which account for 70% of expenditure, such as medicines for the treatment of neovascular (exudative) age-related macular degeneration (AMD) and for the treatment of visual decline caused by diabetic macular edema (DME), whose consumption is stable compared to 2020 (Table 3.18). Within this subgroup, aflibercept is the active ingredient with the highest expenditure (1.31 euros) and an impact on category expenditure of around 43%, followed by ranibizumab (0.82 euros and an impact of around 27%) (Table 3.19). Tafluprost is among the first 30 active ingredients with the greatest variation in agreed expenditure (Table 3.14); while aflibercet and ranibizumanb are among the first 30 active ingredients with the greatest variation in expenditure for medicines purchased in public facilitieses, in the same sphere aflibercet is in eighth place among the medicines with the highest average cost per day of therapy.

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 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 medicines for eye disorders (Section 3.11.1).

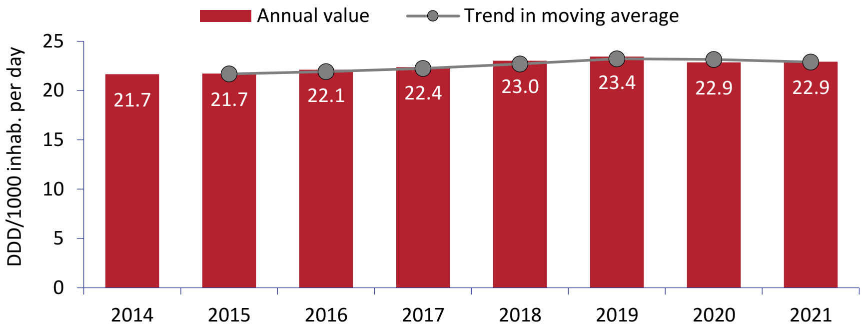
Moreover, the section dedicated to Monitoring registries contains a focus on acitve ingredients used in the treatment of AMD, which provides a description of the baseline characteristics of patients undergoing treatment and their regional distribution (Section 4).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

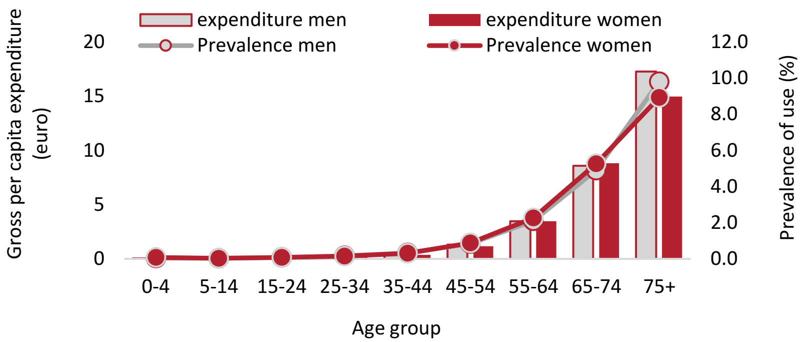
Sensory organs

Public expenditure* in million euros (% over total)	**399.5**	**(1.7)**
Δ % 2021-2020		11.8
Regional range for gross expenditure (per capita):	5.1	8.4
DDD/1000 inhab. per day* (% over total)	**22.9**	**(1.8)**
Δ % 2021-2020		0.3
Regional range for DDD/1000 inhab. per day:	17.8	32.3

* *includes NHS outpatient prescriptions and purchases by public health facilities*



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and *per conto* distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.0	0.0	0.0	0.2	0.2	0.2
5-14	0.0	0.0	0.0	0.3	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	1.2	0.9	1.0
35-44	0.5	0.4	0.4	2.7	2.1	2.4
45-54	1.3	1.2	1.2	7.4	6.6	7.0
55-64	3.5	3.5	3.5	19.6	19.5	19.5
65-74	8.6	8.8	8.7	47.9	49.2	48.6
75+	17.3	15.0	15.9	96.7	84.6	89.5

3.11.1 Medicines for eye disorders

Epidemiological framework

The most common eye disorders, often age-related, are glaucoma, cataracts, maculo-papular degeneration and diabetic retinopathy (a consequence of macro- and micro-vascular changes in diabetes). According to the WHO, worldwide at least 2.2 billion people have a visual impairment or blindness, and of these about 1 billion have a preventable or treatable visual impairment. Although the prevalence of visual impairment worldwide has decreased since the first estimates in the 1990s, thanks to the greater availability of scientific knowledge and care services, in the most industrialised countries, including Italy, we are nevertheless witnessing an increase in the prevalence and incidence of age-related degenerative eye diseases. These pathologies are extremely disabling and estimates indicate that the number of people with visual impairment could triple in the coming decades. Diabetic retinopathy is the leading cause of vision loss in working age in most developed countries, and particularly affects people aged between 20 and 65. In contrast, at an older age, the leading cause of visual impairment is age-related macular degeneration, followed by glaucoma, which causes mixed damage by affecting both central and peripheral vision. Diabetic retinopathy affects approximately 146 million people worldwide. This is a complication of diabetes and is characterised by the formation of new blood vessels with increased retinal vascular permeability and altered blood flow, all of which can lead to retinal ischaemia. As regards macular degeneration, it is estimated that in 2020, around 195.6 million people aged between 30 and 97 were affected worldwide. This is a multifactorial disease that affects the central area of the retina, known as the macula, which can be involved in choroidal neovascularisation (CNV), causing retinal thickening with oedema or atrophy with a progressive decrease in visual acuity and distortion of vision. The main risk factors are smoking, excessive exposure to unprotected sunlight and blue light, obesity, cardiovascular and lipid metabolism disorders, and family history.
The prevalence of glaucoma is also high, with approximately 76 million people worldwide suffering from the disease, and it is estimated that there will be a gradual increase over the years, especially in relation to increased life expectancy. Glaucoma is characterised by progressive loss of retinal nerve fibre layer tissue and loss of the visual field. Risk factors include increased intraocular pressure, positive family history of glaucoma, African-American ethnicity, myopia, diabetes and hypertension. The above-mentioned visual problems represent a public health problem in many countries, including Italy, where it is estimated that around 5.4% of people over 65 suffer from severe visual impairment.

National data on consumption and expenditure

Over the past eight years, consumption of medicines used for eye disorders has remained nearly stable, increasing from 19.8 DDD in 2014 to 21.0 DDD in 2021, with a mean annual variation of 0.8% (Figure and Table 3.11.1a). By analysing variation between 2020 and 2021 it is noted a slight 0.5% decrease in consumption. Over the same period, the average cost per day of therapy increased by 12.2% to 0.86 euros in 2021 (0.76 euros in 2020), probably due to the increase in the cost of anti-neovascularising agents (+12.9%) and parasympathomimetic medicines (+26.8%). Similarly to 2020, also for 2021, the highest consumption is represented by antiglaucoma preparations, which in detail concern more antiglaucoma/beta-blockers alone or in combination (12.1 DDD/1000 inhabitants per day) and antiglaucoma/prostanglandin analogues (5.6 DDD). This aspect is also reflected in per capita spending, which for the former is 2.18 euros and for the latter 1.19 euros. Neovascularising agents, at 2.17 euros, show a significant decrease in per capita spending compared to 2020 (+45.0%), although they remain the medicines with the highest average cost per day of therapy of the whole category (53.83 euros). Timolol alone or in combination represents the active ingredient with the highest expenditure (1.73 euros per capita) and consumption (9.5 DDD). They are followed in spending by aflibercept (1.31 euros) and ranibizumab (0.82 euros), medicines indicated in the treatment of neovascular (exudative) age-related macular degeneration (AMD), which however show an important decrease compared to 2020 (+55% and +28.9%, respectively). The level of expenditure for these two medicines, in the presence of low consumption levels, is determined by a high average cost per DDD (492.66 euros and 21.81 euros, respectively).

Starting from 1 January 2021 (Italian Official Journal no. 323 of 31 December 2020), Note 98 has come into force to regulate methods of prescription, intravitreal administration and use by the National Health Service of anti-VEGF medicines for the treatment of maculopathy. As part of the Note, in consideration of the scientific evidence available, the AIFA CTS expressed its opinion on the overlap of the anti-VEGF aflibercept, bevacizumab, brolucizumab and ranibizumab in relation to the AMD treatment indication (See Appendix 1 for more details on Note 98).

For further discussion regarding the use of these medicines, see Section 4 on Monitoring Registries ("Anti-neovascular Drugs for Intravitreal Use") (Tables 4.1.11 and 4.1.12).

At the regional level there is a clear variability in consumption with values ranging from 16.0 DDD in Molise to 30.5 DDD in Marche (a difference of 90%) (Table 3.11.1b). Umbria is the Region with the highest level of expenditure per capita while Valle d'Aosta records the lowest expenditure (8.20 and 5.0 euros respectively, a difference equal to 65%). Campania is the Region with the highest expenditure variation compared to the previous year (+33.6%) and Calabria the one with the smallest increase (+2.7%). As far as consumption is concerned, we go from -12.7% in Friuli to +2.6% in Emilia Romagna (Table 3.11.1b).

Figure 3.11.1a. Medicines for eye disorders, temporal trend of consumption and average cost per day of therapy (2014-2021)

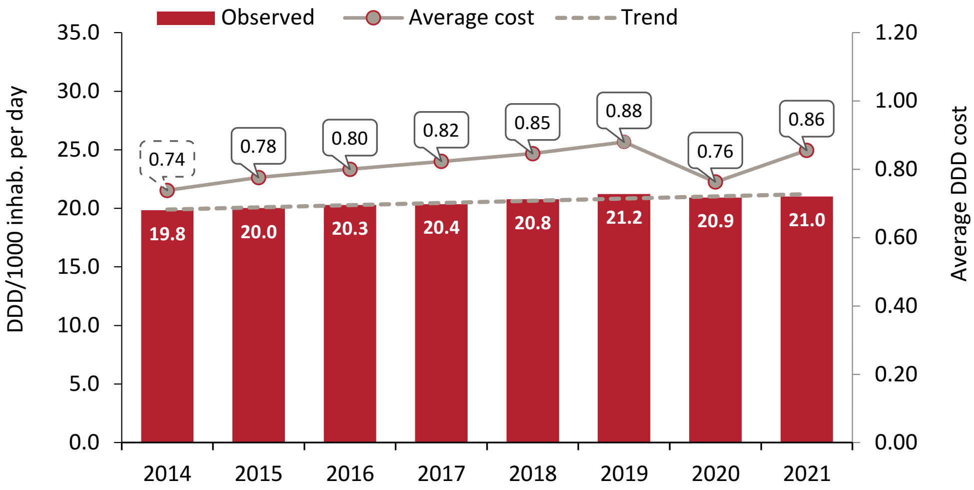


Table 3.11.1a Medicines for eye disorders, per capita expenditure and consumption (DDD/1000 ab day) by therapeutic category and by substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Antiglaucoma preparations - beta blocker alone or in combination	2.18	-4.1	1.2	12.1	0.8	1.1	0.50	-4.6
Antineovascular agents	2.17	45.0	5.3	0.1	28.8	-5.1	53.83	12.9
Antiglaucoma preparations - prostaglandin analogues	1.19	-7.0	-1.2	5.6	-1.7	0.1	0.58	-5.1
Corticosteroids	0.40	16.6	13.8	0.2	16.7	14.1	4.46	0.2
Antiglaucoma preparations - carbonic anhydrase inhibitors	0.21	2.2	-3.3	1.4	2.0	-0.5	0.42	0.5
Other ophthalmological medicines (gene therapy)	0.21	-	-	0.0	-	-	298014.15	-
Antiglaucoma preparations sympathomimetics	0.10	-1.5	2.7	1.5	-0.1	2.3	0.18	-1.2
Other ophthalmological medicines	0.06	-39.4	39.1	0.0	>100	29.1	9.99	-93.0
Corticosteroids (intravitreal implants)	0.02	-9.8	-	0.0	-9.0	-	6607.22	-0.6
Antiglaucoma preparations parasympathomimetics	0.01	30.0	-0.1	0.0	2.8	-8.7	0.95	26.8
Other ophthalmological medicines (cell therapy)	<0.005	-	-	0.0	-	-	94310.54	-
Antiglaucoma preparations - others	<0.005	-6.8	-2.5	0.0	-9.6	-4.4	0.37	3.4
Medicines for eye disorders	**6.56**	**12.4**	**3.0**	**21.0**	**0.5**	**0.8**	**0.86**	**12.2**
aflibercept	1.31	55.0	34.2	0.0	55.7	40.5	492.66	-0.1
ranibizumab	0.82	28.9	-6.5	0.1	27.0	-5.9	21.81	1.8
tafluprost	0.50	3.7	9.2	1.6	4.0	9.2	0.86	0.0
timolol/bimatoprost	0.43	-1.9	2.8	1.4	-2.0	2.3	0.85	0.3
dorzolamide/timolol	0.40	21.5	4.6	2.7	17.1	4.4	0.40	4.0
dexamethasone	0.39	16.7	13.4	0.2	16.6	14.3	4.42	0.3
timolol	0.36	2.6	3.4	3.1	-0.1	-0.3	0.32	3.0
bimatoprost	0.32	-22.2	-4.5	1.8	-4.3	-0.5	0.49	-18.5
timolol/brinzolamide	0.29	-29.4	-0.8	1.6	-7.0	4.7	0.49	-23.9
tafluprost/timolol	0.25	11.8	-	0.7	12.1	-	0.96	0.0

Table 3.11.1b Medicines for eye disorders, regional trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	6.62	22.9	0.79	7.31	23.2	0.86	10.5	1.3	9.3	4.9	0.9	3.9
Valle d'Aosta	4.72	19.5	0.66	5.00	19.2	0.71	5.9	-1.6	7.9	-0.2	-1.0	0.8
Lombardy	4.26	16.8	0.69	5.25	17.2	0.84	23.2	2.4	20.6	-0.1	1.0	-1.0
Province of Bolzano	5.58	16.0	0.95	6.14	16.2	1.04	9.9	1.7	8.4	3.4	2.0	1.4
Province of Trento	5.57	16.6	0.92	6.27	16.8	1.02	12.7	1.4	11.5	4.3	1.6	2.7
Veneto	5.71	19.0	0.82	6.32	19.2	0.90	10.7	1.2	9.7	3.9	1.2	2.7
Friuli VG	7.92	26.6	0.81	7.96	23.2	0.94	0.5	-12.7	15.4	1.8	0.4	1.4
Liguria	6.79	21.1	0.88	7.69	21.4	0.99	13.3	1.1	12.4	1.2	0.3	1.0
Emilia R.	6.61	27.2	0.66	7.05	27.9	0.69	6.5	2.6	4.2	3.8	1.5	2.2
Tuscany	6.54	26.4	0.68	7.33	26.3	0.76	12.2	-0.6	13.1	1.2	0.3	0.9
Umbria	7.55	24.9	0.83	8.20	24.8	0.90	8.5	-0.3	9.2	6.0	1.2	4.7
Marche	7.62	30.0	0.69	7.93	30.5	0.71	4.0	1.7	2.6	2.0	1.0	1.0
Lazio	5.68	22.0	0.71	6.18	21.8	0.78	8.9	-0.7	9.9	1.8	-0.1	1.8
Abruzzo	7.77	26.4	0.80	8.02	26.2	0.84	3.2	-0.9	4.4	3.3	0.5	2.8
Molise	6.39	16.3	1.07	6.97	16.0	1.19	9.0	-1.5	11.0	3.8	0.2	3.7
Campania	5.38	18.1	0.81	7.19	18.2	1.08	33.6	0.9	32.8	7.9	1.2	6.6
Puglia	6.39	19.2	0.91	6.87	19.3	0.98	7.4	0.1	7.6	3.8	0.7	3.0
Basilicata	6.61	20.8	0.87	6.79	21.1	0.88	2.8	1.5	1.6	2.3	1.4	0.9
Calabria	5.54	19.8	0.76	5.69	19.6	0.79	2.7	-1.0	4.0	3.0	0.6	2.4
Sicily	5.15	17.7	0.80	5.57	17.7	0.86	8.3	0.2	8.4	3.3	1.4	1.9
Sardinia	5.95	19.7	0.82	7.00	19.8	0.97	17.8	0.5	17.5	3.8	0.2	3.6
Italy	**5.84**	**20.9**	**0.76**	**6.56**	**21.0**	**0.86**	**12.4**	**0.5**	**12.2**	**3.0**	**0.8**	**2.1**
North	5.64	20.5	0.75	6.36	20.8	0.84	12.7	1.0	11.9	2.4	1.0	1.4
Centre	6.35	24.7	0.70	6.93	24.6	0.77	9.2	-0.3	9.7	1.9	0.3	1.6
South and Islands	5.80	19.1	0.83	6.62	19.2	0.95	14.1	0.2	14.2	4.6	0.9	3.6

Key message

- On average, from 2014 to 2021, medicines for eye disorders **show stability in terms of consumption**, however between 2021 and 2020 there is an increase in both expenditure and average cost per day of therapy probably due to the increase in the cost of anti-neovascularising agents and parasympathomimetic medicines.

- Starting from January 2021, **AIFA Note 98** came into force which regulates the methods of prescription, intravitreal administration and use by the National Health Service of anti-VEGF medicines for the treatment of maculopathy.

- Antiglaucoma preparations are also the most widely used medicines for 2021. Overall, compared to 2020, there are variations in consumption in all Regions, in particular there is a marked reduction in Friuli Venezia Giulia.

- In general, **medicines available for the treatment of eye disorders** do not lead to a complete resolution of the disease, though they play a key role in delaying its course, and this can have a significant impact in terms of improving the quality of life not only in elderly patients but mainly in younger ones.

References

- Effron, David, et al. Age-related macular degeneration. The atlas of emergency medicine. 5th edition. Knoop KJ et al., eds. New York: McGraw-Hill, 2021.
- Henderer JD and Rapuano CJ. Ocular pharmacology. Brunton LL et al., eds. Goodman & Gilman's: the pharmacological basis of therapeutics. 13th edition. New York: McGraw-Hill, 2017.
- National Eye Institute (NEI). Eye health data and statistics. Last updated: July 17, 2019. Available at the address https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educa- tors/eye-health-data-and-statistics/
- Powers, Alvin C. et al. Diabetes mellitus: complications. Jameson JL et al., eds. Harrison's principles of internal medicine. 20th edition. New York: McGraw-Hill, 2018.
- Report of the Minister of Health on the status of implementation of policies concerning the prevention of blindness, education and visual rehabilitation (Law 284/97). Data 2017. 28 December 2018. Available at the address http://www.salute.gov.it/imgs/C_17_pubblicazioni_2825_allegato.pdf/
- World Health Organization. WHO launches first World report on vision. October 2019. Available at the address https://www.who.int/news/item/08-10-2019-who-launches-first-world-report- on-vision/
- World Health Organization. World report on vision. Geneva: World Health Organization, 2019. Licence: CC BY-NC-SA 3.0 IGO.

3.12 Miscellaneous

In 2021, the therapeutic category of "Miscellaneous" medicines ranks 12th in terms of public spending, accounting for 379.2 million euros and 1.6% of total public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure for these medicines reached 6.40 euros, an increase of 7.6% compared to the previous year deriving, almost entirely, from the purchase by public health facilities (6.26 euros per capita). On the contrary, the contribution provided through the NHS outpatient care was lower (0.14 euros per capita) (Table 3.1).

Consumption for this category of medicines was 3.3 DDD/1000 inhabitants per day, with a +1.7% increase compared to 2020, with a stable trend over the last 5 years (Table 3.2).

The analysis of the medicine use profile by age group and gender, including NHS outpatient pharmaceutical expenditure and per conto distribution, shows a marginal use of these medicines for both genders up to the age group between 45 and 54 years old, followed by a progressive increase with age. Prevalence is highest in those over 75 years of age, recording for men and women values of 4.2% and 3.7%, respectively. At the same time, NHS per capita expenditure also increases with the age of patients, reaching the maximum level of 10.69 euros per capita in men and 8.66 in women over 75 years of age.

As for NHS outpatient care, per capita expenditure was 0.14 euros, decreasing of 1.9% compared to 2020, and with a corresponding reduction in consumption (-3.2%), a shift in prescription towards more expensive medicinal products (mix effect: +1.5%) and substantial stability in prices (-0.1%; Table 3.9). ATC 4th level includes miscellaneous medicines, such as medicines for the treatment of hyperkalemia and hyperphosphatemia (0.12 euros per capita), having the greatest impact on pharmaceutical spending under approved care regime. The active ingredient with the highest expenditure (0.05 euros) is sevelamer, authorised for the control of hyperphosphatemia in patients undergoing hemodialysis or peritoneal dialysis and for the control of hyperphosphatemia 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 36% on the total expenditure. This is followed by polystyrene sulphonate, approved for the treatment of hyperkalaemia, which with an expense of 0.04 euros records an incidence of expenditure of about 30% (Table 3.10).

Among medicines purchased by public health facilities, there was an increase in expenditure (+7.1%), consumption (+0.8%), average cost per day of therapy (+6.2%) and a shift to more expensive medicines (mix effect +6.3%) and price stability (-0.1%; Table 3.18). The category with the greatest impact on expenditure is reconfirmed as that of iron chelating substances (1.53 euros per capita), followed by radiological, water-soluble, nephrotropic and low osmolar contrast agents (1.62 euros) and antidotes (0.93 euros); for the latter two categories an increase in expenditure of 11.2% and 21.5% respectively (Table 3.18).

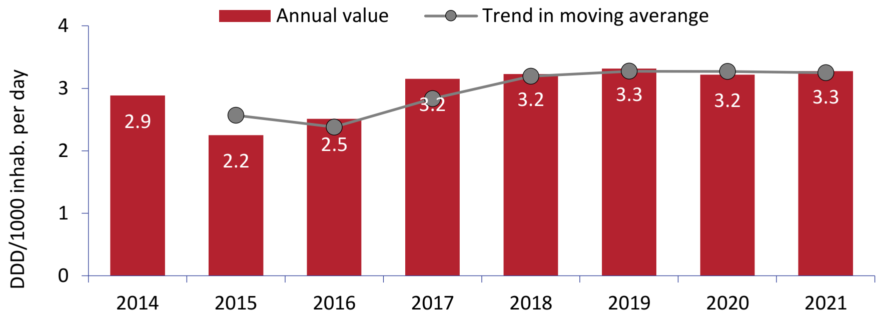
Among iron chelators, deferasirox, has a per capita expenditure of 1.40 euros and impacts 22% on category expenditure (Table 3.19). This is authorised for the treatment of chronic iron overload due to frequent haemotrasfusions in patients with beta thalassemia majors aged 6 years and over or in other groups of patients where deferoxamine is contraindicated or inadequate. In second place is sugammadex, antagonist of rocuronium- or vecuronium-induced block, with a per capita expenditure of 0.80 euros and an impact of 13 % on the expenditure for the category; this active ingredient, compared to 2020, recorded increases of about 20% in terms of both expenditure and consumption. Moreover, sugammadex is among the medicines with the greatest change in expenditure in 2021-2020 purchased by public health facilities, while deferasirox is among the top 30 active ingredients with the greatest reduction in expenditure (Tables 3.22 and 3.23).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

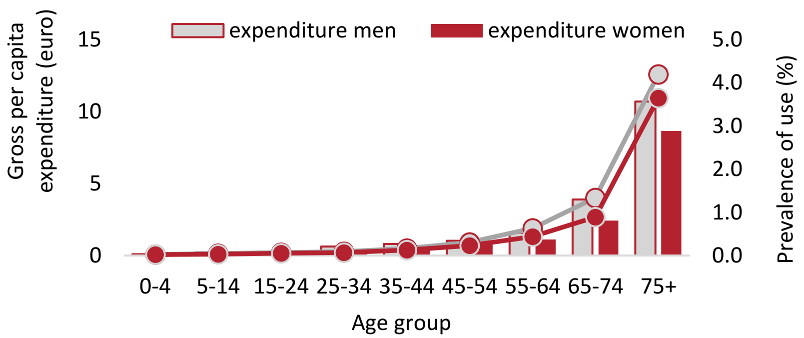
Various

Public expenditure* in million euros (% over total)	**379.2**	**(1.6)**
Δ % 2021-2020		7.6
Regional range for gross expenditure (per capita):	4.4	13.4
DDD/1000 inhab. per day* (% over total)	**3.3**	**(0.3)**
Δ % 2021-2020		1.7
Regional range for DDD/1000 inhab. per day:	1.7	6.9

** includes NHS outpatient prescriptions and purchases by public health facilities*



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and per conto distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.1	0.1	0.1	0.0	0.0	0.0
5-14	0.3	0.2	0.2	0.1	0.1	0.1
15-24	0.3	0.3	0.3	0.1	0.1	0.1
25-34	0.7	0.4	0.5	0.1	0.1	0.1
35-44	1.0	0.9	1.0	0.2	0.1	0.1
45-54	1.2	1.2	1.2	0.2	0.1	0.2
55-64	1.7	1.2	1.4	0.4	0.2	0.3
65-74	4.0	2.5	3.2	0.6	0.3	0.5
75+	10.9	8.8	9.7	0.9	0.4	0.6

3.12.1 Contrast agents

General framework

Contrast media (contrast agents) represent an indispensable diagnostic tool for clinical practice. In general, contrast agents are substances suitable for modifying the X-ray absorption of organs and tissues, which are similar in composition and/or thickness to surrounding organs and apparatuses, thus improving the image of different diagnostic techniques. The substances used are characterised by chemical, physical (osmolarity) and biological properties, which correspond to different clinical uses and toxicity profiles. Currently, the most commonly used contrast agents in radiology are barytes (ATC V08B) and iodates (ATC V08A). Barytes are exclusively barium sulphate suspensions, which can increase organ and tissue opacity, although their use is limited to radiography of the gastrointestinal tract. Iodine compounds, on the other hand, represent a category of molecules of varying complexity containing one or more iodine atoms, the use of which has led to a formidable advance in radiodiagnostics, allowing the visualisation of most organs and systems. Although Magnetic Resonance Imaging (MRI) is capable of generating good contrast between tissues, the use of specific contrast agents has made this technique increasingly precise, allowing it to be used extensively, especially for analyses of the central nervous system. A contrast agent for MRI must be able to interact magnetically with the nuclei of hydrogen atoms in water and possess a magnetic moment. Most of these substances are, in fact, paramagnetic ion complexes or superparamagnetic magnetite particles, which contain lanthanide elements such as gadolinium ($Gd3+$) or manganese in the $Mn2+$ transition state. These substances are also classified according to characteristics such as:

- chemical composition (including the presence or absence of metal atoms);
- route of administration;
- magnetic properties;
- effect on magnetic resonance imaging;
- biodistribution (extracellular fluid, blood pool and target/organ-specific agents).

Contrast agents used in ultrasound imaging, which uses non-ionising radiation of a mechanical nature, were introduced when Gramiak and his co-workers first described the echocardiographic contrast effect in 1968. Most of them consist of gas-filled microbubbles, which greatly enhance Doppler signals and, in some cases, even greyscale images.

National data on consumption and expenditure

In 2021, the use of contrast media increased by 12% to a value similar to that observed in 2019 after the reduction in 2020, due to the lower number of diagnostic tests performed during the COVID-19 pandemic. On the other hand, the average cost per DDD progressively increased, reaching a value of 51.17 euros in 2021, a 1.7% increase compared to the previous year (Figure 3.12.1a). Similarly, in terms of per capita spending (1.75 euros), there is a 13.7% increase in the period 2021-2020 with an annual reduction of 2.1% since 2014. The therapeutic category with the highest per capita expenditure (1.27 euros) is represented by radiological contrast agents, which are up by 12.0%, while in second place are contrast agents for MRI, with 0.42 euros a 14.5% decrease. The category with the greatest increase in expenditure are contrast media for ultrasound which, despite having an expenditure equal to 0.07 euros, recorded a 47.7% increase (Table 3.12.1a). The active ingredient with the highest spending is represented by iomeprol (0.51 euros; +17.3% compared to 2020), a radiological contrast agent (iodinated, non-ionic, monomeric), with high solubility in water, low chemotoxicity, osmolality and viscosity. In second place is iodixanol (0.23 euro; + 3.7%), another radioactive iodine (dimeric, nonionic, iso-osmolal), characterized by diagnostic efficacy similar to that of other medicines in the same category (ATC V08AB). The active ingredients gadobutrol (medicine containing gadolinium and the macrocyclic ligand butrol), used for contrast intensification in MRI, and iopromide, diagnostic iodate (used for angiography, contrast enhancement in computed tomography, urography, visualization of body cavities), present a per capita expenditure equal to 0.20 and 0.18 euros respectively. The active ingredient with the most important expenditure increase in 2021 is iopamidol with +24.0%, a low osmolality monomeric non-ionic contrast medium used for brain radiological examinations, computerized axial tomography, angiography, urography, venography, arthrography.

Analysing the regional variability, it emerges that the Regions of the Centre show higher values (2.02 euros), compared to the Northern (1.67 euros) and the Southern Regions (1.71 euros). A possible explanation for the difference between the North and the other geographical areas could depend on a greater recourse to private facilities not affiliated with the SSN for the performance of diagnostic examinations. The lowest per capita expenditure values are found in Lombardy, with 1.39 euros, while the highest are found in Friuli (2.43 euros). Compared to the previous year, a more marked increase in expenditure was recorded in the Central Regions (+14.3%), among these Tuscany shows a 20.1% increase, while Campania is the one with the greatest variation compared to the other Regions with +29.8%. The average cost per DDD of Province of Bolzano is about 3 times lower than that of Puglia (27.98 euros vs. 79.54 euros).

Figure 3.12.1a Contrast agents, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

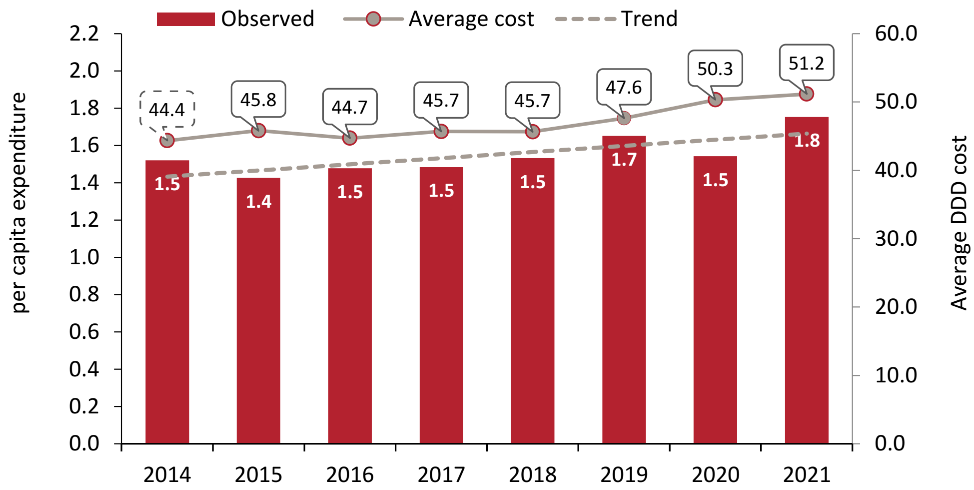


Table 3.12.1a Contrast agents, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Radiocontrast agents	1.27	12.0	1.7	0.1	10.8	-0.8	50.93	1.3
MRI contrast agents	0.42	14.5	3.6	0.0	15.4	3.5	48.77	-0.5
Contrast agents for ultrasound	0.07	47.7	4.3	0.0	17.8	0.9	84.84	25.7
Contrast agents	**1.75**	**13.7**	**2.1**	**0.1**	**12.1**	**0.0**	**51.17**	**1.7**
iomeprol	0.51	17.3	3.4	0.0	14.1	-0.4	72.53	3.0
iodinaxol	0.23	3.7	0.6	0.0	6.7	0.5	75.88	-2.5
gadobutrol	0.20	17.6	6.7	0.0	20.8	7.4	77.71	-2.3
iopromide	0.18	6.7	-2.2	0.0	7.9	-2.2	56.52	-0.8
iobitridol	0.12	8.9	-0.2	0.0	6.4	0.5	48.68	2.6
iopamidol	0.11	24.0	6.5	0.0	15.4	0.2	26.37	7.8
gadoxetic acid	0.08	17.3	9.6	0.0	16.3	8.3	175.64	1.1
ioexol	0.08	8.8	7.3	0.0	7.5	8.0	31.46	1.5
gadoteridol	0.06	19.8	30.5	0.0	19.2	27.1	25.70	0.8
sulfur hexafluoride	0.05	17.5	0.9	0.0	17.8	0.8	67.50	0.0

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 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	1.47	0.1	50.47	1.58	0.1	47.74	7.8	14.2	-5.4	0.1	-0.2	0.3
Valle d'Aosta	2.29	0.1	61.47	2.63	0.1	58.92	14.8	20.1	-4.2	-0.4	-3.2	2.9
Lombardy	1.19	0.1	43.77	1.39	0.1	44.94	16.8	14.1	2.7	-0.6	-1.4	0.8
Province of Bolzano	1.53	0.1	28.10	1.65	0.2	27.98	7.8	8.6	-0.4	2.5	-2.4	5.1
Province of Trento	1.36	0.1	31.33	1.45	0.1	33.65	6.1	-0.9	7.4	3.9	0.7	3.2
Veneto	1.74	0.1	42.26	1.91	0.1	43.05	9.4	7.7	1.9	1.9	1.4	0.5
Friuli VG	2.12	0.1	64.90	2.43	0.1	61.49	14.7	21.4	-5.3	1.7	1.1	0.6
Liguria	1.19	0.1	27.67	1.45	0.1	27.95	21.8	20.9	1.0	4.1	1.8	2.2
Emilia R.	1.73	0.1	34.36	1.99	0.2	34.52	15.1	14.9	0.5	2.3	0.5	1.9
Tuscany	1.99	0.1	45.20	2.39	0.1	47.99	20.1	13.5	6.2	3.5	0.7	2.7
Umbria	2.10	0.1	50.89	2.26	0.1	51.70	7.4	6.0	1.6	0.5	-1.6	2.1
Marche	1.98	0.1	46.15	2.21	0.1	47.34	11.6	9.1	2.6	2.6	1.3	1.3
Lazio	1.50	0.1	66.09	1.68	0.1	66.90	11.7	10.7	1.2	1.9	-0.9	2.8
Abruzzo	1.90	0.1	60.01	2.13	0.1	59.28	11.8	13.4	-1.2	2.9	0.2	2.6
Molise	1.42	0.1	58.53	1.63	0.1	52.87	14.8	27.5	-9.7	2.4	-0.2	2.6
Campania	0.99	0.0	61.13	1.29	0.1	70.14	29.8	13.5	14.7	7.0	2.9	4.0
Puglia	1.82	0.1	76.32	1.93	0.1	79.54	5.9	1.9	4.2	2.9	-1.4	4.4
Basilicata	2.11	0.1	70.60	2.15	0.1	72.13	1.7	-0.2	2.2	1.1	-2.6	3.8
Calabria	1.55	0.1	71.87	1.77	0.1	71.77	14.2	14.7	-0.1	4.9	0.4	4.5
Sicily	1.51	0.1	75.17	1.65	0.1	76.02	9.0	8.1	1.1	2.2	-0.9	3.2
Sardinia	1.80	0.1	70.48	2.16	0.1	70.58	20.1	20.2	0.1	1.2	-1.6	2.9
Italy	**1.54**	**0.1**	**50.33**	**1.75**	**0.1**	**51.17**	**13.7**	**12.1**	**1.7**	**2.1**	**0.0**	**2.1**
North	1.47	0.1	41.28	1.67	0.1	41.37	13.3	13.3	0.2	1.0	0.0	1.0
Centre	1.77	0.1	52.56	2.02	0.1	54.24	14.3	11.1	3.2	2.4	0.0	2.4
South and Islands	1.50	0.1	69.80	1.71	0.1	72.18	13.7	10.2	3.4	3.4	-0.2	3.6

Key message

- **Contrast media** (mdc), thanks to their ability to modify the X-ray absorption of organs and tissues (similar in composition and/or thickness to surrounding body parts), are now an indispensable and indispensable diagnostic tool in clinical practice.
- In 2021, the **use** of contrast media increased by 12% to a value similar to that observed in 2019 after the reduction in 2020, due to the lower number of diagnostic tests performed during the COVID-19 pandemic.
- **Per capita expenditure** has increased in recent years, registering a value equal to 1.75 euros in 2021, a 13.7% increase compared to the previous year; consequently, the average cost per day of therapy also increased by 1.7%.
- **Radiological contrast agents** represent the category that records the highest per capita expenditure and consumption values, both of which are up by more than 10% compared to 2020, confirming the progressive recovery of clinical activities that were considerably reduced during the COVID-19 pandemic.
- Analysing **regional variability**, it emerges that the Regions of the Centre show higher values (2.02 euro), compared to those of the North (1.67 euro) and the South (1.71 euro). A possible explanation for the difference between the North and the other geographical areas could depend on a greater recourse to private facilities not affiliated with the SSN for the performance of diagnostic examinations.

References

- Buschur M, Aspelin P. Contrast media: history and chemical properties. Interv Cardiol Clin 2014; 3(3):333-9.
- Cosgrove D. Ultrasound contrast agents: an overview. Eur J Radiol 2006; 60(3):324-30.
- Dooley M, Jarvis B. Iomeprol. Drugs 2000; 59(5): 1169-1186.
- Forsberg F, Merton DA, Liu JB, Needleman L, Goldberg BB. Clinical applications of ultrasound contrast agents. Ultrasonics 1998; 36(1):695-701.
- Lohani S, Rudnick MR. Contrast media-different types of contrast media, their history, chemical properties, and relative nephrotoxicity. Interv Cardiol Clin 2020; 9(3):279-92.
- Meth MJ, Maibach HI. Current understanding of contrast media reactions and implications for clinical management. Drug Saf 2006; 29(2):133-41.
- Pasternak JJ, Williamson EE. Clinical pharmacology, uses, and adverse reactions of iodinated con- trast agents: a primer for the non-radiologist. Mayo Clin Proc 2012; 87(4):390-402.
- Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nat Rev Drug Discov 2020; 19(9):589-608.
- Spencer CM, Goa KL. Iodixanol. Drugs 1996; 52(6): 899-927.

3.12.2 Radiopharmaceuticals

General framework

A radiopharmaceutical is any medicine that, once ready for use, includes one or more radionuclides and is therefore constituted by the combination of the radioactive isotope, responsible for activity (diagnostic and/or therapeutic), and of a compound that determines biological properties of the medicine. The radioactivity of these medicines is used both for diagnostic purposes, exploiting the emission of electromagnetic radiation (gamma or X-rays), and for therapeutic applications, where the ionising radiation emitted as the radionuclide decays is used to destroy cells.

Radiopharmaceuticals are generally classified according to their chemical structure, mechanism of localisation and possible therapeutic action, as well as into positive or negative indicators, depending on the type of visualisation produced in the specific diagnostic application. A positive indicator radiopharmaceutical accumulates electively where the pathological process takes place, directly highlighting the site of the specific metabolic alteration, while a negative indicator radiopharmaceutical accumulates in the normal, functioning parenchyma of an organ, highlighting a defect in uptake of the pathological process. The same substance, however, can act as both a positive and negative indicator, depending on the different applications. Technetium (^{99m}TC) pertechnetate, for example, is a negative indicator in the case of non-functioning nodular pathology, but becomes positive in the case of thyroid hyperfunction.

In the therapeutic field, radiopharmaceuticals are widely used in the treatment of cancer (radiopharmaceutical therapy, RPT) in which, unlike radiotherapy, radiation is not administered outside the body, but delivered systemically or locoregionally, with the aim of targeting only the neoplastic cells, minimising exposure to other cells. In fact, cytotoxic radiation is delivered directly to target cells or the microenvironment, either directly or by exploiting delivery vehicles capable of binding to endogenous targets or accumulating by altering the physiological mechanisms characteristic of the neoplasm. Unlike biological therapy, it is much less dependent on understanding signalling pathways and identifying the cancer phenotype, allowing for a targeted therapeutic approach. Of particular interest is the emerging field of theranostics, in which diagnosis and targeted therapy are combined to achieve a personalised therapeutic approach to the patient. In clinical nuclear medicine practice, theranostics are often constructed using the same molecule labelled with two different radionuclides, one for imaging and the other for therapy. The in vivo distribution of the diagnostic radionuclide can, in fact, be determined by means of detection obtained by single photon emission computed tomography (SPECT) or positron emission tomography (PET), providing a substantial advantage over existing therapies.

National data on consumption and expenditure

In 2021 the per capita expenditure of radiopharmaceuticals was equal to 1.15 euros, recording a growth trend of 7.7% compared to the previous year, in line with the increase already observed in 2020 (Figure 3.12.2a). The average cost per day of radiopharmaceutical therapy has increased by more than 50% in the last eight years, going from a value of 299.7 euros in 2014 to 455.1 euros in 2021. Analysing the trend over the years, however, a 18.8% decrease in the period 2015-2018 is observed, followed by an increase of over 70% in the last three years. The category with the highest expenditure is represented by radiodiagnostics for tumor detection (0.43 euros per capita), followed by radiopharmaceuticals for therapeutic oncological use (0.27 euros). These two categories show an opposite trend, while the former increase by 18% compared to 2020, the latter decrease by 12.5%. Thyroid and central nervous system (CNS) radiodiagnostics show a value of per capita expenditure of 0.14 (down 4.7%) and 0.20 euros (up 47.7%) respectively. The first active ingredient by expenditure is represented by fluorodeoxyglucose (18F), a radiodiagnostic for tumor detection that records a per capita expenditure of 0.32 euros, followed by lutetium (177Lu) oxodotreodite (0.22 euros, a 12.1% reduction compared to 2020), indicated in adult patients for the treatment of well-differentiated, progressive, non-removable or metastatic somatostatin receptor-positive gastroenterohepatic neuroendocrine tumors (NET-GEP). Technetium(99mTC) pertechnetate and iodine ioflupane (123I), two radiodiagnostics used respectively for the thyroid and the central nervous system, instead record a per capita expenditure of 0.13 and 0.16 euros respectively (the first registers a 4.4% contraction while the second a 33.3% increase). For these medicines, it should be noted that the average cost per DDD may be influenced by the presence of some medicinal products in class Cnn. The profound regional variability (CV 49.1%), increasing compared to 2020, is particularly evident considering the difference found between the maximum value of per capita expenditure recorded in Basilicata, equal to 2.89 euros (+23.8% compared to 2020) and the minimum observed in Sardinia (0.58 euros), a 5.5% increase compared to the previous year (Table 3.12.2b). The only Regions that show contractions in spending compared to the previous year are Campania, the Province of Trento and Emilia Romagna (-19.7%, -11.2%, -10.3% respectively). Regions of the North (1.15 euros) and those of the Centre (1.23 euros) show greater spending than those of the South and Islands (1.10 euros) and a higher increase (+18%).

Figure 3.12.2a Radiopharmaceuticals, temporal trend of per capita expenditure and average cost per day of therapy (2014-2021)

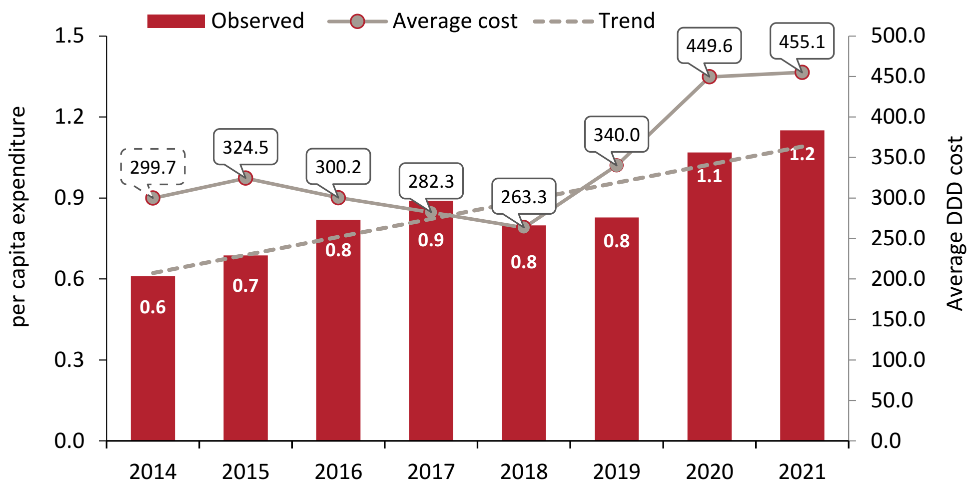


Table 3.12.2a Radiopharmaceuticals, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/ 1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Radiopharmaceuticals for cancer detection	0.43	18.8	11.6	0.0	18.0	-0.1	503.37	1.0
Oncological therapeutic radiopharmaceuticals	0.27	-12.5	78.3	0.0	-7.6	67.7	8966.44	-5.1
CNS diagnostic radiopharmaceuticals	0.20	37.7	3.8	0.0	33.9	2.1	691.56	3.2
Thyroid diagnostic radiopharmaceuticals	0.14	-4.7	-0.8	0.0	-3.5	17.9	222.59	-0.9
Radiopharmaceuticals for the detection of inflammation and infections	0.03	-1.3	18.0	0.0	37.0	-29.6	12165.79	-27.8
Cardiovascular system diagnostic radiopharmaceuticals	0.02	7.8	-11.2	0.0	14.4	-6.7	128.96	-5.5
Iodized radiopharmaceuticals for therapeutic use	0.02	6.8	29.5	0.0	-1.2	84.9	210.80	8.4
Respiratory system diagnostic radiopharmaceuticals	0.01	16.8	14.4	0.0	-18.4	12.3	63.51	43.5
Other diagnostic radiopharmaceuticals	0.01	19.1	-	0.0	-19.5	-	927.81	48.2
Hepatic and reticuloendothelial system diagnostic radiopharmaceuticals	0.01	16.2	-15.4	0.0	2.7	-3.7	37.55	13.4
Skeletal system diagnostic radiopharmaceuticals	<0.005	37.2	-	0.0	32.0	-	111.11	4.2
Renal system diagnostic radiopharmaceuticals	<0.005	-72.5	-12.4	0.0	-30.0	-13.8	59.98	-60.7
Radiopharmaceuticals with analgesic/ anti-inflammatory action	<0.005	21.8	-13.3	0.0	-16.4	-7.0	3333.72	46.2
Radiopharmaceuticals	**1.15**	**7.7**	**9.5**	**0.0**	**6.7**	**3.1**	**455.13**	**1.2**
fluorodeoxyglucose (18f)	0.32	14.7	11.4	0.0	18.5	0.1	401.07	-2.9
lutetium oxodotreotide (177lu)	0.22	-12.1	-	0.0	-0.4	-	14141.40	-11.5
iodine ioflupane (123i)	0.16	33.3	2.9	0.0	38.3	3.0	839.38	-3.3
tecnetium pertecnetate (99mtc)	0.13	-4.4	12.9	0.0	-5.6	19.1	331.97	1.6
fluoromethylcholine (18f)	0.07	31.5	-	0.0	27.8	-	2407.25	3.1
radium dichloride (223Ra)	0.05	-14.2	47.3	0.0	-14.2	55.7	3240.30	0.3
sodium iodide (131i)	0.03	-1.1	160.3	0.0	-0.8	198.6	92.70	-0.1
flutemetamol (18f)	0.03	>100	-	0.0	>100	-	1219.12	3.9
gallium citrate (67Ga)	0.03	-2.6	-	0.0	-22.6	-	67342.50	26.1
edotreotide	0.02	60.3	-	0.0	-20.6	-	8972.92	102.5

Table 3.12.2b Radiopharmaceuticals, temporal trend of per capita expenditure, consumption (DDD/1000 inhab. per day) and average cost per day of therapy: comparison 2014-2021

Region	2020			2021			Δ % 21-20			CAGR % 14-21		
	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	0.91	0.0	479.10	1.00	0.0	520.33	10.1	1.6	8.6	6.4	0.1	6.3
Valle d'Aosta	1.54	0.0	571.85	2.12	0.0	593.54	37.3	32.6	3.8	0.9	-4.9	6.1
Lombardy	1.12	0.0	575.97	1.17	0.0	591.30	3.9	1.5	2.7	11.4	-0.9	12.4
Province of Bolzano	0.86	0.0	529.90	0.83	0.0	497.86	-3.6	2.9	-6.0	5.0	-2.4	7.5
Province of Trento	0.87	0.0	523.01	0.77	0.0	450.18	-11.2	3.4	-13.9	5.5	6.3	-0.8
Veneto	0.99	0.0	592.04	1.03	0.0	603.41	3.4	1.8	1.9	6.2	1.7	4.4
Friuli VG	0.90	0.0	464.04	0.85	0.0	414.13	-6.2	5.4	-10.8	4.4	2.8	1.6
Liguria	1.07	0.0	426.77	1.03	0.0	407.74	-4.0	0.8	-4.5	2.9	-2.3	5.3
Emilia R.	1.77	0.0	711.74	1.59	0.0	608.54	-10.3	5.2	-14.5	9.9	-1.3	11.4
Tuscany	1.29	0.0	378.54	1.42	0.0	359.90	10.4	16.4	-4.9	3.5	1.9	1.7
Umbria	0.60	0.0	254.56	0.71	0.0	311.50	18.3	-3.0	22.4	0.8	5.6	-4.6
Marche	1.58	0.0	314.60	1.79	0.0	354.29	12.9	0.6	12.6	3.2	-2.7	6.1
Lazio	0.94	0.0	523.30	1.04	0.0	536.62	11.1	8.6	2.5	19.6	9.4	9.3
Abruzzo	0.49	0.0	108.38	0.94	0.0	241.17	91.0	-13.9	122.5	5.9	16.7	-9.2
Molise	0.67	0.0	297.27	0.73	0.0	391.67	9.8	-16.4	31.8	-0.4	-15.7	18.2
Campania	0.78	0.0	475.91	0.62	0.0	364.93	-19.7	5.0	-23.3	8.3	10.7	-2.1
Puglia	1.27	0.0	436.99	1.69	0.0	552.71	33.3	5.7	26.5	17.1	1.4	15.5
Basilicata	2.33	0.0	325.53	2.89	0.0	372.09	23.8	8.6	14.3	11.9	-1.2	13.2
Calabria	1.48	0.0	565.50	2.07	0.0	655.09	40.0	21.2	15.8	31.1	19.9	9.3
Sicily	0.70	0.0	239.73	0.80	0.0	219.02	13.4	24.5	-8.6	18.8	26.1	-5.8
Sardinia	0.55	0.0	306.39	0.58	0.0	317.40	5.5	2.1	3.6	-6.4	0.4	-6.7
Italy	**1.07**	**0.0**	**449.58**	**1.15**	**0.0**	**455.13**	**7.7**	**6.7**	**1.2**	**9.5**	**3.1**	**6.1**
North	1.15	0.0	573.20	1.15	0.0	560.80	0.1	2.6	-2.2	8.3	-0.5	8.8
Centre	1.11	0.0	399.60	1.23	0.0	409.67	11.4	9.0	2.5	7.6	2.5	5.0
South and Islands	0.93	0.0	347.67	1.10	0.0	377.19	18.5	9.5	8.5	13.1	8.8	4.0

Key message

- A **radiopharmaceutical** is a medicine consisting of the combination of the radioactive isotope, responsible for the diagnostic and/or therapeutic activity, and a compound that determines the biological properties of the molecule, and therefore, may include one or more radionuclides.

- In 2021 the **per capita expenditure on radiopharmaceuticals** was equal to 1.15 euros, confirming a growth trend of 7.7% compared to the previous year, already highlighted in 2019, after years of wide variability. This figure would seem to be determined by an increase in the average cost per day of therapy, which in the last eight years has increased by more than 50% but which may be influenced by the presence of some medicinal products in the Cnn class.

- The categories of radiodiagnostic medicines and therapeutic oncological radiopharmaceuticals are among those with the highest expenditure, representative of the categories are respectively the **active principles fluorodeoxyglucose (18F) and lutetium (177Lu) oxodotreodite** which have the highest values of per capita expenditure; however for the first there is an almost 15% increase compared to 2020 while the second records a reduction of over 12%.

- The profound **regional variability** (CV 49.1%), increasing compared to 2020, is particularly evident considering the difference found between the maximum value of per capita expenditure recorded in Basilicata, equal to 2.89 euros (+23.8% compared to 2020) and the minimum observed in Sardinia (0.58 euros), a 5.5% increase compared to the previous year.

References

- Brugarolas P. et al. Fifty years of radiopharmaceuticals. J Nucl Med Technol 2020; 48(Suppl 1): 34S-39S.
- Caratteristiche generali dei radiofarmaci. SpringerLink [Internet]. Available at the address https:// link.springer.com/chapter/10.1007/978-88-470-1685-9_3/
- Legislative decree 219/2006. Implementation of Directive 2001/83/EC (and subsequent amending directives) on a Community code relating to medicinal products for human use. Available at the address https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:decreto.legislativo:2006-04-24;219!vig=/
- Herrmann K, Schwaiger M, Lewis JS et al. Radiotheranostics: a roadmap for future development. Lancet Oncol 2020; 21(3):e146-e156.
- Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nat Rev Drug Discov 2020, 19.9: 589-608.
- St James S, Bednarz B, Benedict S et al. Current status of radiopharmaceutical therapy. Int J Radiat Oncol Biol Phys 2021; 109(4):891-901.
- Vermeulen K, Vandamme M, Bormans G, Cleeren F. Design and challenges of radiopharmaceu- ticals. Semin Nucl Med 2019; 49(5):339-56.

3.13 Dermatologicals

In 2021, dermatologicals were the 13th therapeutic category with the highest public expenditure, amounting to 199.2 million euros, and corresponding to 0.8% of total public expenditure (Box Main indexes of expenditure, consumption and exposure). The overall per capita expenditure on these medicines is 3.35 euros, a sharp increase over the previous year (+32.2%) and similarly distributed for NHS outpatient pharmaceutical care (1.32 euros per capita, a 5.2% increase compared to the previous year) and public health facilities (2.03 euros), which show a significant increase compared to 2020 (+58.5%) (Table 3.1).

Consumption for this category of medicines was 13.9 DDD/1000 inhabitants per day, a 5.5% decrease compared to 2020 mainly in public health facilities (-11.7%; Table 3.2), while for the NHS pharmaceutical assistance there are increases in consumption (+ 8.1%).

The analysis of the medicine use profile by age group and gender, including NHS outpatient pharmaceutical expenditure and per conto distribution, shows an increase in the prevalence of use and consumption of dermatological medicines, starting from 15 years for both genders. In particular in males over 75 years of age, a prevalence of about 3.6% is reached and a consumption of 192.7 DDD/1000 inhabitants per day. In women there is a less evident trend with increasing age, similarly to men the prevalence of use reaches the highest level in the age group above 75 years, standing at 2.2%. Per capita expenditure borne by the NHS increases with the age of patients, reaching a maximum value of 2.3 euros per capita in the over 65s (3.2 euros in men and 1.6 euros in women).

As for NHS outpatient care, per capita expenditure was 1.32 euros, with a 4.5% increase. This trend was mainly determined by an increase in the prescribed doses (+ 7.1%) and a shift in prescription towards less expensive medicinal products (mix effect: -2.4%). The category that has the greatest impact on the NHS outpatient expenditure is represented by other antipsoriatic medicines for topical use (0.89 euros per capita) (Table 3.9). The medicine with the highest expenditure and consumption is the calcipotriol/betamethasone combination, which accounts for 65% of gross expenditure and 48% of consumption for the category (Table 3.10), a 4.2% increase compared to 2020. The isotretinoin, a medicine indicated for the treatment of severe acne in patients resistant to both systemic antibacterials and topical therapy, is up by 25% compared to the previous year in terms of both expenditure and consumption.

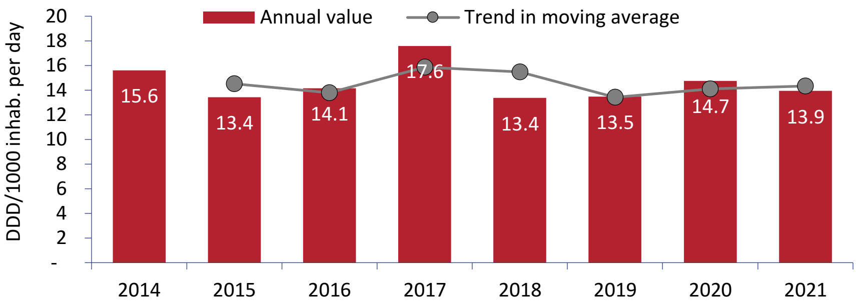
Among medicines purchased by public health facilities, there was an increase in expenditure (>50%) and a decrease in consumption (-12.6%) (Table 3.18) against a significant shift (mix effect: +91.1%) towards more expensive medicines. The active ingredient with the highest expenditure is dupilumab (1.61 euros per capita), a monoclonal antibody that falls on the list of innovative medicines and is used for the treatment of moderate to severe atopic dermatitis in adult patients and adolescents (aged 12-17 years) eligible for systemic therapy. This medicine accounts for 80% of the entire category and is up more than 90% by 2020 in terms of expenditure and 111% in terms of DDDs, which could be attributed to the extension of the indication of this medicine for the treatment of nasal polyposis as of December 2020. The average cost per day of treatment equal to 29.01 euros is the highest in the category. Sodium hypochlorite, on the other hand, is the active ingredient that records the highest levels of consumption (2.4 DDD/1000 ab day) (Table 3.19).

Main indices of expenditure, consumption and exposure

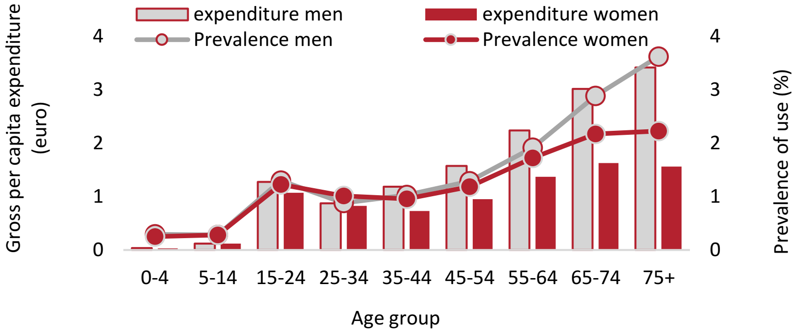
Dermatologicals

Public expenditure* in million euros (% over total)	**199.2**	**(0.8)**
Δ % 2021-2020		32.0
Regional range for gross expenditure (per capita):	2.6	4.8
DDD/1000 inhab. per day* (% over total)	**13.9**	**(1.1)**
Δ % 2021-2020		-5.5
Regional range for DDD/1000 inhab. per day:	9.2	22.3

* *includes NHS outpatient prescriptions and purchases by public health facilities*



Breakdown of expenditure, prevalence of use and consumption under approved care regime by age and gender and per conto distribution in 2021 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.0	0.0	0.0	0.4	0.3	0.4
5-14	0.1	0.1	0.1	0.6	0.6	0.6
15-24	1.3	1.1	1.2	3.4	3.0	3.2
25-34	0.9	0.8	0.9	3.0	2.8	2.9
35-44	1.2	0.7	1.0	4.1	2.8	3.5
45-54	1.6	0.9	1.3	5.5	3.7	4.6
55-64	2.2	1.4	1.8	8.0	5.4	6.7
65-74	3.0	1.6	2.3	11.1	7.0	8.9
75+	3.4	1.6	2.3	13.0	7.1	9.5

3.14 Medicines used in critically ill patients

General framework

In view of the strong impact that the COVID-19 health emergency has had on the National Health Service, particularly on the ability to manage critically ill hospitalized patients, this section presents data on the expenditure and consumption of medicines used in intensive or subintensive care units during 2021, where critically ill patients with COVID-19 were cared for.

The infection caused by the new coronavirus SARS-CoV-2, in fact, causes in the most severe cases a severe bilateral interstitial pneumonia, accompanied by a severe hypoxemic respiratory failure that rapidly worsens in an Acute Respiratory Distress Syndrome (ARDS), the most common form of organ failure found in patients affected by COVID-19, which requires complex mechanical and pharmacological supportive therapies to stabilize and monitor the vital functions of these patients.

National data on consumption and expenditure

Utilization of medicines generally used in critically ill patients stood at 97.3 packages per 10,000 inhabitants per day in 2021, an increase of about 12.8% compared to the previous year and an average annual variation of 8% over the 2014-2021 period. Per capita expenditure, on the other hand, showed a 2.4% decrease compared to 2020, settling at a value of 7.31 euros and maintaining an average annual growth rate from 2014 to 2021 substantially stable (CAGR 14-21: 0.7%). The average cost per package was 2.06 euros, a 13.2% decrease compared to the previous year (Table 3.14a).

Analysing the monthly trend over the last three years (Figure 3.14a) shows that in the months corresponding to the peak of SARS-CoV-2 infections for the years 2020 and 2021 (March-April and November-December) in 2021, there is a substantial increase in consumption (in packages per 10. 000 inhab. per day) for the months of March-April, equal to 26.0%, compared to the same months of 2020, while in correspondence with the second peak of infections there is a reduction in consumption, equal to 23.3%, confirming a lower incidence of hospitalisations in the critical area for COVID-19 thanks to the protective effects of the vaccines, which in that period had reached coverage of about 80% of the population for the complete cycle and just under 30% for the booster dose (ISS, 2021).

As expected on the basis of the number of admissions recorded in Italian intensive care units, there was a very high use of oxygen with 83.2 packages per 10,000 inhabitants per day, which alone accounted for 59% of expenditure and 85% of total consumption, an increase of 2.2% and 16.2% respectively over the previous year. Significant reductions in the use of several injectable medicines were observed, including: curare (-39.8%), ascorbic acid (-31.4%), cortisone (-25.6%), general anaesthetics (-21.5%) and antithrombotic medicines (-18.8%) (Table 3.14a). Other injectables such as cardiac stimulants (+32.1%), local anaesthetics (+18%), antidotes (+15.4%), antiemetics (+9.5%) and NSAIDs (+5.8%), on the contrary, show an increase in consumption. In detail, the medicine that reported the greatest increase in both expenditure and consumption compared to the previous year is sugammadex (+20.3% per capita expenditure, +22.9 packages per 10,000 inhab. per day), a medicine used to antagonize neuromuscular block induced by rocuronium in operative procedures (Table 3.14a).

At the national level there was an increase in consumption (+12.8%) accompanied, however, by a reduction in expenditure and in the average cost per package (-2.4% and -13.2%) compared to the previous year (Table 3.14 b). The Northern Regions recorded a consumption of 94.5 packages per 10,000 inhabitants per day, which is just below the national average (about -3%). The Central Regions, on the other hand, recorded the highest consumption with 105.6 packages per 10,000 inhab. per day, an increase of 20.3% compared to last year and 8.5% compared to the national average. The Southern Regions also recorded a 26.7% increase in consumption compared to 2020 with 96.3 packages per 10,000 inhab. per day, remaining however below the national average (Table 3.14b). Compared to the previous year, the Northern and Central Regions, on the other hand, showed a reduction in per capita expenditure and in the average cost per package (North: -8.3% and -9.7%, Centre -1, 4% and -17.8%), while in the Southern Regions there is a slight increase in expenditure (+ 3.6%) and a substantial reduction in the average cost per package compared to last year (-18%).

In particular, only for Valle d'Aosta, Lombardy and Liguria, the reduction in expenditure is accompanied by that of consumption; while for Piedmont, Province of Bolzano, Province of Trento, Veneto, Tuscany, Puglia and Basilicata there is an increase in consumption accompanied, however, by a reduction in the expenditure more or less contained. In Friuli VG, Emilia Romagna, Umbria, Marche, Lazio, Abruzzo, Molise, Campania, Calabria, Sicily and Sardinia, there is an increase in both expenditure and consumption. In almost all the Regions, except Lombardy and Liguria, there is a more or less consistent reduction in the average cost per package compared with the previous year.

Figure 3.14.a Medications used in critically ill patients, monthly trend in packages/10,000 inhabitants per day: comparison 2021-2019

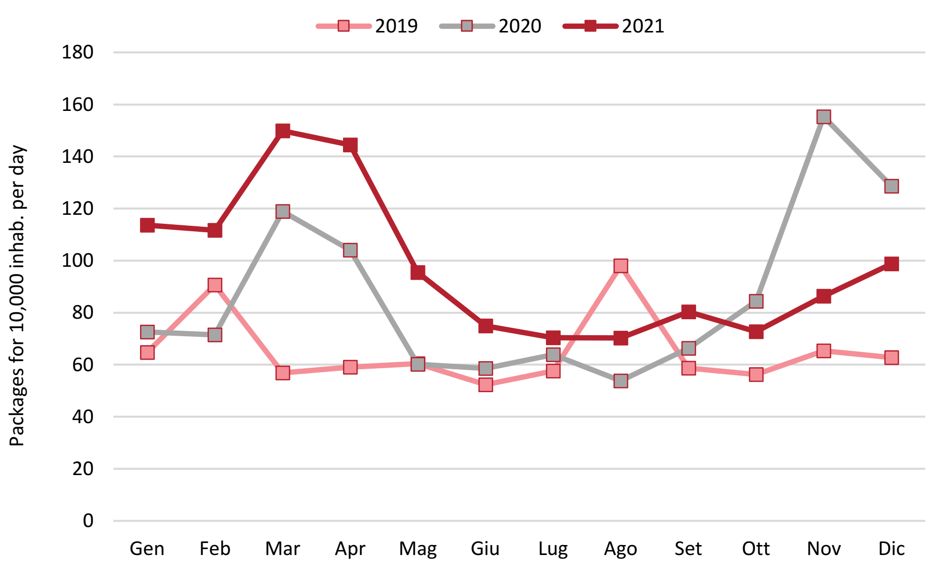


Table 3.14a Medications used in critically ill patients, per capita expenditure and consumption (DDD/10,000 inhab. per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	Packages per 10,000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average cost per package	Δ % 21-20
Oxygen	4.31	2.2	-1.2	83.2	16.2	10.2	1.42	-11.8
Injectable antidotes	0.93	22.3	21.8	0.3	15.4	-1.7	89.87	6.3
Injectable general anaesthetics	0.50	-13.9	-3.0	1.2	-21.5	2.5	11.32	10.0
Injectable antihemorrhagics	0.28	6.5	8.4	0.4	-12.8	-8.2	19.29	22.5
Injectable cardiac stimulants	0.26	-2.6	14.1	2.4	32.1	7.5	2.92	-26.1
Injectable thrombolytics	0.25	-7.8	0.6	0.1	-18.8	2.6	64.97	13.9
Injectable corticosteroids	0.19	-14.3	-4.4	2.4	-25.6	-6.3	2.16	15.5
Injectable hypnotics and sedatives	0.19	-35.7	33.2	0.5	-10.0	5.2	10.05	-28.4
Injectable curares	0.15	-56.6	4.5	0.3	-39.8	4.7	14.30	-27.7
Injectable local anaesthetics	0.08	3.7	-14.0	1.5	18.0	-1.9	1.41	-11.9
Injectable antiemetics	0.07	-17.2	-12.3	1.7	9.5	8.7	1.15	-24.2
Injectable NSAIDs	0.04	0.1	-7.5	1.2	5.8	-4.8	0.82	-5.1
Injectable pain therapy	0.03	-7.7	-1.9	1.5	2.2	-2.8	0.62	-9.4
Injectable anxiolytics	0.03	-6.9	6.4	0.2	-10.8	-1.8	4.17	4.6
Injectable ascorbic acid	0.01	-38.0	8.6	0.3	-31.4	31.9	0.47	-9.3
Injectable xanthines	<0.005	-36.3	-12.5	<0,05	-41.8	-14.9	1.03	9.8
Injectable mucolytics	<0.005	-21.8	-22.6	<0,05	-26.4	-24.6	3.82	6.4
Injectable Acetylcysteine	<0.005	>100	>100	<0,05	>100	>100	2.13	-2.7
Medicines for critical conditions	**7.31**	**-2.4**	**0.7**	**97.3**	**12.8**	**8.0**	**2.06**	**-13.2**
oxygen	4.31	2.2	-1.2	83.2	16.2	10.2	1.42	-11.8
sugammadex	0.80	20.3	23.5	<0.05	22.9	23.0	813.89	-1.9
human alpha 1 antitrypsin	0.24	12.0	16.3	<0.05	13.8	17.3	246.78	-1.3
alteplase	0.18	11.0	12.5	<0.05	12.3	13.1	313.83	-0.9
propofol	0.17	-28.4	4.4	0.5	-28.8	2.1	9.38	0.7
dexmedetomidine	0.13	-36.9	-	<0.05	-20.7	58.9	151.51	-20.1
levosimendan	0.13	-7.4	-	<0.05	13.0	13.2	582.08	-17.8
sevoflurane	0.13	0.4	-9.6	<0.05	13.1	-7.0	96.55	-11.0
methylprednisolone	0.11	-9.5	-4.3	1.2	-16.1	-5.0	2.42	8.2
rocuronium	0.08	-22.4	18.0	0.2	-36.0	25.1	12.59	21.6

Table 3.14b Medications used in critically ill patients, regional trend of expenditure consumption (packages/10,000 inhabitants per day) on weighted population: comparison 2020-2021

Region	Per capita expenditure			Packages per 10,000 inhab. per day			Average cost per package		
	2020	2021	Δ % 21-20	2020	2021	Δ % 21-20	2020	2021	Δ % 21-20
Piedmont	8.12	8.03	-1.0	103.2	104.3	1.0	2.15	2.11	-1.7
Valle d'Aosta	10.79	10.25	-5.0	287.4	275.8	-4.0	1.03	1.02	-0.7
Lombardy	6.55	6.02	-8.0	102.0	93.9	-7.9	1.75	1.76	0.2
Province of Bolzano	7.17	6.91	-3.7	58.8	71.0	20.7	3.33	2.66	-20.0
Province of Trento	4.98	4.11	-17.4	60.7	60.8	0.3	2.24	1.85	-17.4
Veneto	7.39	5.25	-28.9	77.5	83.0	7.1	2.61	1.74	-33.4
Friuli VG	5.77	6.10	5.8	80.1	101.4	26.6	1.97	1.65	-16.2
Liguria	6.00	5.70	-5.0	97.0	90.1	-7.1	1.69	1.73	2.5
Emilia R.	6.92	7.08	2.2	82.9	99.5	20.0	2.28	1.95	-14.5
Tuscany	6.84	6.21	-9.2	106.9	127.1	18.9	1.75	1.34	-23.5
Umbria	5.82	6.45	10.9	84.9	104.6	23.3	1.87	1.69	-9.8
Marche	7.00	7.05	0.8	124.5	148.4	19.2	1.54	1.30	-15.2
Lazio	5.80	5.94	2.3	65.1	79.4	22.0	2.44	2.05	-15.9
Abruzzo	8.27	9.17	10.8	95.1	112.4	18.2	2.38	2.24	-5.9
Molise	8.38	9.52	13.6	86.9	121.8	40.3	2.64	2.14	-18.8
Campania	7.39	7.73	4.6	73.4	93.6	27.5	2.75	2.26	-17.8
Puglia	10.69	9.52	-10.9	85.4	112.2	31.5	3.42	2.32	-32.1
Basilicata	8.85	8.79	-0.7	82.7	98.9	19.7	2.92	2.43	-16.8
Calabria	9.28	9.82	5.8	69.0	87.6	26.9	3.67	3.07	-16.4
Sicily	9.75	11.08	13.6	73.1	93.0	27.1	3.64	3.26	-10.4
Sardinia	8.85	9.01	1.8	58.8	67.8	15.2	4.11	3.64	-11.4
Italy	**7.50**	**7.31**	**-2.4**	**86.3**	**97.3**	**12.8**	**2.37**	**2.06**	**-13.2**
North	6.94	6.36	-8.3	92.8	94.5	1.8	2.04	1.85	-9.7
Centre	6.29	6.21	-1.4	87.8	105.6	20.3	1.96	1.61	-17.8
South and Islands	9.03	9.36	3.6	76.0	96.3	26.7	3.25	2.66	-18.0

Key message

- Utilization of medicines generally used in critically ill patients stood at 97.3 packages per 10,000 inhabitants per day in 2021, an increase of about 12.8% compared to 2020 accompanied by a reduction in expenditure (-2.4%) and the average cost per package (-13.2%).
- As expected on the basis of the number of admissions recorded in Italian intensive care units, there was a very high use of oxygen, which alone accounted for 59% of expenditure and 85% of total consumption, an increase of 2.2% and 16.2% respectively over the previous year. Strong reductions in consumption were also observed for several **injectable medicines**, including curares, corticosteroids, general anaesthetics and antithrombotic medicines; while significant increases were seen for cardiac stimulants in particular.
- At the regional level, there was a reduction in the average cost per package almost everywhere. Only in three Regions is there a reduction in both expenditure and consumption (Valle d'Aosta, Lombardy and Liguria). In other Regions there is a reduction in expenditure but an increase in consumption (Piedmont, Province of Bolzano, Province of Trento, Veneto, Tuscany, Apulia and Basilicata) while in most there is an increase in consumption and expenditure. In general, the Northern Regions recorded the most consistent reductions in per capita expenditure (-8.3%), and average cost per package (- 9.7%), with a slight increase in consumption (+1.8% in packages per 10,000 inhab. per day). In the Central and Southern Regions, on the other hand, significant increases in consumption are recorded, respectively +20.3% and +26.7%, accompanied by a substantial reduction in the average cost per package (respectively -17.8% and -18%) and by minimal changes in per capita expenditure (-1.4% and 3.6% respectively).

References

- Chanques G, Constantin JM, Devlin JW et al. Analgesia and sedation in patients with ARDS. Inten- sive Care Med 2020; 46(12):2342-56.
- Florio G, Zanella A, Pesenti A. Preparedness of ICU networks for pandemics. Curr Opin Crit Care 2021; 27(1):13-19.
- Grieco DL, Maggiore SM, Roca O et al. Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. Intensive Care Med 2021; 1-16.
- Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19. Aggiornamento nazionale: 21 dicembre 2021.

3.15 Medicines used in the treatment of COVID-19 patients

General framework

The objective of this section is to provide an overview of the use of the most widely used medicines at the national level in the treatment of patients with COVID-19 during 2021.

The medicines included in the analysis are those used outside clinical trials and marketed for other indications, which have been made available to patients, despite the absence of a specific therapeutic indication for COVID-19, on the basis of scientific evidence that is often quite limited. For these medicines the Technical-Scientific Committee of AIFA has prepared information sheets, continuously updated on the basis of the availability of new evidence on efficacy and safety, which outline the therapeutic guidelines within which it is possible to envisage a controlled and safe use in the context of health emergency from COVID-19, and include both medicines for home management (e.g. corticosteroids and heparins) and medicines that can be used in hospitals (e.g. remdesivir), distinguishing those which, according to the AIFA guidelines, represent the standard of care (in green), from those not recommended in clinical practice (in red) and those that can be used are in selected cases (in yellow) (data updated to 11 July 2022).

National data on consumption and expenditure

The medicine utilization trend in the treatment of patients with COVID-19 has increased in the last eight years, standing at 12.0 DDD/1000 inhabitants per day in 2021, although there is a 5% decrease compared to 2020. The total per capita expenditure for these medicines amounted to 10.4 euros per capita, increased by 23.4% compared to the previous year, with an average annual growth rate (CAGR) of 0.2%. The average cost per therapy day increased by 30.3% in the last year, switching from 1.82 euros in 2020 to 2.38 euros in 2021 (Table 3.15a and Figure 3.15a).

The direct-acting antiviral remdesivir, the first antiviral medicine to be granted conditional authorisation by the European Medicines Agency (EMA) for the treatment of COVID-19 disease in adults and adolescents (aged 12 years or older and weighing at least 40 kg) with pneumonia requiring supplemental oxygen therapy, accounts for almost 22% of the per capita expenditure on COVID-19 medicines, with a value equal to 2.25 euros, a sharp increase compared to 2020 (+157.9%), although the average cost per DDD equal to 374.41 euros fell by 1.3%.

Low molecular weight heparins represent almost half of the consumption of medicines that can be used in the context of COVID-19, with a value of 6.2 DDD/1000 inhabitants per day, being second as a per capita expense item, equal to 1.92 euros, an increase of 10.2% compared to 2020, attributable to a 21.8% increase in the average cost per day of therapy, although this is very low (0.85 euros).

After heparins, among the medicines with the highest consumption, injectable antipyretics and non-injectable corticosteroids follow, with consumption equal respectively to 3.1 DDD/1000 inhabitants per day (+20.7% compared to 2020) and 1.1 DDD/1000 inhabitants per day (-12.5% compared to 2020) (Table 3.15a).

According to the indications of the AIFA fact sheet (updated to 6 October 2020), the use of corticosteroids is recommended in hospitalized subjects with severe COVID-19 disease who require oxygen supplementation, in the presence or absence of mechanical ventilation (invasive or noninvasive); moreover, in the aforementioned population, the use of corticosteroids should be considered a standard of care because it is the only treatment that has demonstrated a benefit in terms of reduced mortality.

All Janus kinase inhibitors show an increase in consumption (ruxolitinib +14.8%; baricitinib +14.9%; tofacinib +32.6%) with an overall per capita expenditure of 2.82 euros, while the consumption of monoclonal antibodies remained unchanged, with the exception of the human monoclonal anti-interleukin 1 beta antibody, canakinumab, which showed an increase in all the indicators considered (expenditure +12.1%, DDD +1.8%, average cost DDD +10.4%) and tocilizumab, which recorded an increase in DDD of 5.7% (Table 3.15a).

The lopinavir/ritonavir combination (expenditure -88.4%; DDD -86.8%) and the darunavir/cobicistat combination (expenditure -22.1%; DDD -21.9%), whose off-label use in the early stages of the epidemic had been allowed as an alternative to lopinavir/ritonavir, showed significant reductions in expenditure and consumption following AIFA's suspension, in the light of the literature evidence, of the authorisation for off-label use of the medicine outside clinical trials.
Azithromycin, an antibiotic belonging to the macrolide class, also recorded a strong contraction in its indicators (expenditure -67.4%; DDD -73.5%) compared to 2020, which could be explained by the excessive and indiscriminate use of this antibiotic in the initial stages of the pandemic; subsequently, greater therapeutic appropriateness led to a reduction in consumption. AIFA has strongly discouraged the use of azithromycin for COVID; as amply demonstrated by numerous well-conducted clinical studies published in the best international journals, there is no evidence that the use of azithromycin has a protective effect on the evolution of COVID-19, neither in terms of reducing transmission, nor in terms of healing time, or mortality.

The consumption and expenditure of hydroxychloroquine also appear to be entirely negligible in the course of 2021. It is useful to point out that the evidence collected on the therapeutic use of hydroxychloroquine has demonstrated a complete lack of efficacy of this medicine, in the face of an increase in adverse events following its administration. Therefore, there is currently no indication for treatment with hydroxychloroquine for COVID-19 patients.

At the regional level, there is a marked variability in consumption, with Emilia Romagna and Umbria having three times higher consumption than Puglia and Lazio (23.2 and 19.3 vs. 6.2 and 6.5 DDD). A reduction in consumption is observed in twelve Regions, while for the other Regions there are more or less marked increases (from +6.8% in Friuli VG to +67.1% in Sardinia). Overall, at the national level there is a reduction in consumption (-5.0%) and an increase in expenditure (+23.4%) and average cost per day of therapy (+30.3%). More doses are used in the North (14.4 DDD) than in the Centre (11.2 DDD) and the South (9.1 DDD). The Regions with the highest average cost per day of therapy are Puglia and Calabria (4.53 euros and 4.0 euros), almost three times higher than the cost recorded in the Province of Bolzano (1.52 euros) (Table 3.15b).

Figure 3.15a Medicines used in the treatment of COVID-19 patients, temporal trend of consumption and average cost per day of therapy (2014-2021)

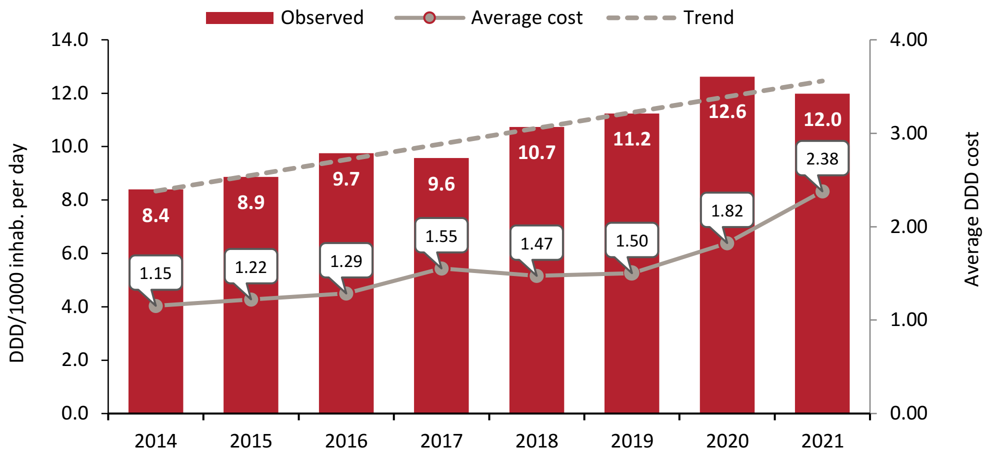


Table 3.15a Medicines used in the treatment of COVID-19 patients, per capita expenditure and consumption (DDD/1000 inhabitants per day) by therapeutic category and substance: comparison 2014-2021

Subgroups and substances	Expenditure *per capita*	Δ % 21-20	CAGR % 14-21	DDD/1000 inhab. per day	Δ % 21-20	CAGR % 14-21	Average DDD cost	Δ % 21-20
Remdesivir*	2.25	157.9	-	<0.05	161.9	-	374.71	-1.3
LMWH	1.92	10.2	0.0	6.2	-9.2	0.0	0.85	21.8
Ruxolitinib	1.87	15.9	1.0	<0.05	14.8	1.1	110.85	1.2
Tocilizumab	1.02	4.9	0.1	0.1	5.7	0.2	25.46	-0.5
Canakinumab	0.98	12.1	0.4	<0.05	1.8	0.4	157.13	10.4
Baricitinib	0.69	14.9	-	0.1	14.9	-	27.66	0.3
Darunavir/cobicistat	0.41	-22.1	-	0.1	-21.9	-	12.25	0.0
Fondaparinux	0.30	27.1	0.1	0.5	17.4	0.1	1.56	8.6
Tofacitinib	0.26	22.0	-	<0.05	32.6	-	21.35	-7.7
Sarilumab	0.16	-0.2	-	<0.05	0.5	-	26.36	-0.4
Non-injectable cortisones	0.15	7.8	0.1	1.1	-12.5	0.0	0.39	23.5
Heparin and heparinoids	0.13	-1.4	-0.1	0.3	-12.0	-0.1	1.12	12.3
Anakinra	0.12	6.9	0.1	<0.05	7.4	0.1	28.19	-0.2
Injectable antipyretics	0.09	-6.9	-0.1	3.1	20.7	0.5	0.08	-22.7
Non-injectable antipyretics	0.02	-10.7	0.0	0.4	-9.4	0.0	0.17	-1.2
Azithromicyn	0.02	-67.4	0.0	0.1	-73.5	0.0	0.73	23.1
Lopinavir/ritonavir	<0.005	-88.4	-0.5	<0.05	-86.8	-0.4	4.49	-12.4
Colchicine	<0.005	-47.1	0.1	<0.05	-48.5	0.1	0.09	3.1
Hydroxychloroquine	<0.005	0.0	-1.0	<0.05	0.0	-1.0	0.35	66.6
Medicines used to treat COVID-19	**10.40**	**23.4**	**0.2**	**12.0**	**-5.0**	**0.1**	**2.38**	**30.3**

Note: green=standard of care; yellow=usable in selected cases; red=not recommended in clinical practice according to AIFA guidelines (figure updated 11 July 2022).

* For remdesivir the complete expenditure and consumption data are partially tracked in the flows used in this Report.

Table 3.15b Medicines used in the treatment of COVID-19 patients, regional trend in expenditure, consumption (DDD/1000 inhabitants per day of therapy) and average cost per day of therapy: comparison 2021-2020

Region	Per capita expenditure			DDD/1000 inhab. per day			Average DDD cost		
	2020	2021	Δ % 21-20	2020	2021	Δ % 21-20	2020	2021	Δ % 21-20
Piedmont	9.35	10.09	8.0	17.2	13.1	-23.5	1.49	2.10	41.6
Valle d'Aosta	7.23	11.23	55.4	19.1	11.6	-39.3	1.04	2.66	156.9
Lombardy	6.11	7.57	23.9	10.1	9.0	-10.9	1.65	2.30	39.4
Province of Bolzano	7.87	7.42	-5.8	16.2	13.4	-17.7	1.32	1.52	14.8
Province of Trento	8.47	9.38	10.8	17.8	14.8	-16.8	1.30	1.74	33.5
Veneto	8.68	10.17	17.1	21.2	19.0	-10.2	1.12	1.47	30.9
Friuli VG	8.24	9.46	14.7	10.6	11.4	6.8	2.11	2.28	7.7
Liguria	10.76	12.99	20.8	19.9	14.2	-28.8	1.47	2.51	70.2
Emilia R.	10.46	14.32	36.9	19.4	23.2	19.7	1.47	1.69	14.7
Tuscany	11.94	12.68	6.2	17.7	14.0	-21.1	1.84	2.49	35.0
Umbria	10.74	14.74	37.3	18.0	19.3	7.1	1.63	2.09	28.6
Marche	9.80	13.49	37.7	16.9	16.8	-0.7	1.58	2.20	39.0
Lazio	6.66	9.46	42.0	7.0	6.5	-7.1	2.60	3.98	53.3
Abruzzo	8.36	11.69	39.8	8.9	10.0	12.9	2.57	3.19	24.2
Molise	10.92	10.05	-8.0	8.6	11.0	27.4	3.46	2.50	-27.6
Campania	8.71	10.25	17.6	9.7	8.8	-10.0	2.44	3.20	31.1
Puglia	8.14	10.24	25.7	6.2	6.2	-0.6	3.58	4.53	26.8
Basilicata	8.43	12.58	49.2	13.8	15.0	8.5	1.66	2.30	38.0
Calabria	8.74	11.08	26.8	7.1	7.6	7.0	3.36	4.00	18.9
Sicily	7.70	10.10	31.1	7.2	7.8	9.3	2.94	3.53	20.2
Sardinia	7.82	9.39	20.1	11.1	18.6	67.1	1.92	1.38	-27.9
Italy	**8.43**	**10.40**	**23.4**	**12.6**	**12.0**	**-5.0**	**1.82**	**2.38**	**30.3**
North	8.24	9.98	21.1	15.6	14.4	-8.1	1.44	1.91	32.1
Centre	9.08	11.42	25.8	12.6	11.2	-10.8	1.97	2.79	41.5
South and Islands	8.29	10.37	25.2	8.3	9.1	8.6	2.72	3.14	15.6

Key message

- In 2021, the consumption of medicines used for the treatment of COVID-19 disease stood at 12 DDD/1000 inhabitans per day (-5.0% compared to 2020), with the **average cost per day of therapy increasing** by 33.3%.
- **Low molecular weight heparins** accounted for almost half of the consumption of medicines used to treat COVID-19, with a value of 6.2 DDD/1000 inhabitants per day, and about 27% of expenditure (1.92 euros per capita), though the corresponding average cost per day of therapy turns out to be very low (0.85 euros).
- The direct-acting antiviral remdesivir, the first antiviral medicine to be granted conditional authorisation by the European Medicines Agency (EMA) for the treatment of the coronavirus disease 2019 accounts for almost 22% of the per capita expenditure on COVID-19 medicines, with a value equal to 2.25 euros, a sharp increase compared to 2020 (+157.9%).
- At the regional level, there is a marked variability in consumption, with Emilia Romagna and Umbria having three times higher consumption than Puglia and Lazio (23.2 and 19.3 vs. 6.2 and 6.5 DDD). A reduction in consumption is observed in twelve Regions, while for the other Regions there are more or less marked increases (from +6.8% in Friuli VG to +67.1% in Sardinia).

References

- Italian Medicines Agency (AIFA) COVID-19: AIFA fact sheet regarding the use of corticosteroids in the treatment of adult patients with COVID-19. 6 October 2021
- Italian Medicines Agency (AIFA) COVID-19: AIFA fact sheet regarding the use of corticosteroids in the treatment of adult patients with COVID-19 (first publication: 6 October 2020. Available at the address https://www.aifa.gov.it/documents/20142/1123276/Corticoster- oidi_06.10.2020.pdf/
- Italian Medicines Agency (AIFA) COVID-19: AIFA fact sheet regarding the use of azithromycin in the treatment of adult patients with COVID-19. Update of 5 May 2020 (first publication: 9 April 2020). Available at the address https://www.aifa.gov.it/documents/20142/1123276/azitromicina_05.05.2020.pdf/
- Italian Medicines Agency (AIFA) COVID-19: AIFA fact sheet regarding the use of hydroxychloroquine in the treatment of adult patients with COVID-19. Update of 22 December 2020 (first publication: 2 April 2020).
- Kashour Z, Riaz M, Garbati MA et al. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis. J Antimicrob Chemother 2021; 76:30-42.
- RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020; 383(21):2030-40.

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. This is because they allow the application of specific conditions of eligibility for reimbursement of a medicine, in a specific therapeutic indication, signed 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 itself 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 first concerns 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**). Moreover, in a simpler way, there are the **Web-based therapeutic plans** (Web-based TPs), which focus on aspects inherent to the prescription of the medicine and the eligibility criteria, as well as, in some cases, on the possible evaluation and re-evaluation of the results of the therapy. Lastly, at the end of 2019 **Simplified Multidrug Monitoring Registries** were introduced, which are a tool for prescribing and monitoring the use of multiple medicinal products within the same therapeutic indication. This particular Registry has been 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) 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 (Law n. 145 of 30 December 2018, Italian Official Journal n. 302 of 31 December 2018), the allocation of resources to the Regions for the purchase of innovative medicines (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.

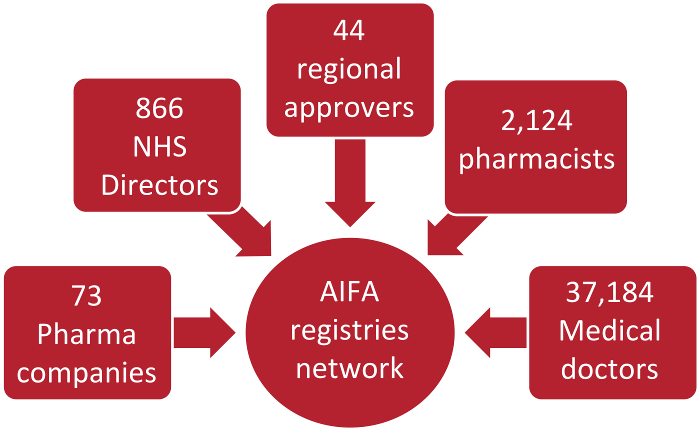
AIFA Registries and the Regions

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 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 about 1,536 active health facilities (with at least one treatment started in 2021), in all 21 Italian Regions and Autonomous Provinces, 44 regional managers, 866 health directors, 37,184 doctors registered on the platform and 2,124 pharmacists (Figure 4.1.1). 73 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 2021



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 AP Therapeutic Plans)
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 multi-drug cards share a very similar structure to those reported above, but provide for a very limited collection of data as required and approved by the CTS. It should be noted that, in these cases, the eligibility form allows the selection of the drug used and the associated therapeutic indication. As of 31 December 2021, 162 Registries were available online (intended as single IT entities active during 2021) (Table 4.1.1). In particular, during the year 24 new Registries were released online, 13 Registries were modified, adding a new indication to the monitoring or with the extension of an indication already monitored, while 25 Registries were closed
The real-time updated list of all medicines subject to active and closed monitoring is available at the following link: http://www.aifa.gov.it/content/lista-aggiornata-dei-registri-e-dei-piani-terapeutici-web-based.

Data on Monitoring Registries

Table 4.1.1 Summary data of the Monitoring Registries present on the web platform: cumulative trend 2019-2021

	2019	N. 2020	2021	Δ % 21-20
Registries*	166	166	162	-2.40
web-based TPs*	14	13	14	7.7
Treatments	2,735,876	3,217,598	3,787,682	17.72
Patients	2,289,421	2,657,393	3,093,372	16.41

*Registries intended as single active IT entities are counted (therefore all previous and inactive versions of a Registry that have occurred over time are excluded from the calculation)

In 2021, the ATC categories D *"Dermatological"*, N “*Nervous system*” and R “*Respiratory system*” recorded a relative increase of more than 50% in terms of new patients, while category B *"Blood and blood forming organs"*, including the therapeutic plans of the new oral anticoagulants, still remains the category that collects the highest number of patients within the platform of the Monitoring Registries (Tables 4.1.2 and following).

Table 4.1.2 Number of patients* by ATC category (I level) in the period 2019-2021

ATC Code	No. of patients			Incidence %			Δ %	
	2019	2020	2021	2019	2020	2021	20-19	21-20
A	73	82	109	0.0	0.0	0.0	12.33	32.93
B	1,274,971	1,487,193	1,682,593	52.9	52.8	50.9	1665	13.14
C	45,913	71,695	107,119	1.9	2.5	3.2	56.15	49.41
D	5,427	8,221	12,734	0.2	0.3	0.4	51.48	54.90
H	238	248	263	0.0	0.0	0.0	4.20	6.05
J	200,481	236,396	335,842	8.3	8.4	10.2	17.91	42.07
L	412,897	465,891	518,528	17.1	16.5	15.7	12.83	11.30
M	227,420	261,198	306,898	9.4	9.3	9.3	14.85	17.50
N	12,485	17,124	27,389	0.5	0.6	0.8	37.16	59.95
R	3,668	4,717	7,444	0.2	0.2	0.2	28.60	57.81
S	226,839	263,185	304,510	9.4	9.3	9.2	16.02	15.70
V	704	1,087	1,475	0.0	0.0	0.0	54.40	35.69
Total	**2,411,116**	**2,817,037**	**3,304,904**	**100**	**100**	**100**	**16.84**	**17.32**

*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 PTs per ATC category (Level I) in the period 2019-2021

ATC Code	No. of Registries			No. of TPs			Total		
	2019	2020	2021	2019	2020	2021	2019	2020	2021
A	3	4	4	0	0	0	3	4	4
B	3	1	2	8	8	8	11	9	10
C	6	6	3	1	1	1	7	7	4
D	2	2	2	0	0	0	2	2	2
H	1	1	1	0	0	0	1	1	1
J	10	8	11	0	0	0	10	8	11
L	127	124	117	0	0	0	127	124	117
M	3	3	4	2	1	1	5	4	5
N	3	7	9	2	2	2	5	9	11
R	4	5	4	1	1	2	5	6	6
S	2	3	3	0	0	0	2	3	3
V	2	2	2	0	0	0	2	2	2
Total	**166**	**166**	**162**	**14**	**13**	**14**	**180**	**179**	**176**

Table 4.1.4 Number of patients* enrolled per ICD-11 category (years 2019-2021)
ICD: International Classification of Diseases

ICD 11	No. of Patients			Incidence %			Δ %	
	2019	2020	2021	2019	2020	2021	20-19	21-20
Mental and behavioural disorders	1,605	3,327	5,063	0.1	0.1	0.2	107.29	52.18
Diseases of the blood and blood-forming organs	5,954	6,815	7,240	0.3	0.2	0.2	14.46	6.24
Diseases of the circulatory system	1,291,360	1,515,680	1,727,885	54.7	55.0	53.5	17.37	14.00
Diseases of the immune system	1,712	2,066	2,583	0.1	0.1	0.1	20.68	25.02
Diseases of the musculoskeletal system and connective tissue	200,226	230,520	272,009	8.5	8.4	8.4	15.13	18.00
Diseases of the nervous system	12,931	16,009	24,539	0.5	0.6	0.8	23.80	53.28
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	434	616	771	0.0	0.0	0.0	41.94	25.16
Diseases of the respiratory system	12,429	14,444	17,503	0.5	0.5	0.5	16.21	21.18
Skin diseases	5,615	9,114	15,373	0.2	0.3	0.5	62.32	68.67
Eye diseases	248,560	282,906	323,171	10.5	10.3	10.0	13.82	14.23
Diseases of the endocrine glands of nutrition and metabolism and immune disorders	15,413	22,253	33,288	0.7	0.8	1.0	44.38	49.59
Infectious and parasitic diseases	198,313	233,004	331,262	8.4	8.5	10.2	17.49	42.17
Tumors	364,358	416,216	468,023	15.4	15.1	14.5	14.23	12.45
Total	**2,362,034**	**2,756,094**	**3,231,834**	**100**	**100**	**100**	**16.68**	**17.26**

*The Table reports the number of *naïve* patients by ICD-11 code. For each patient, only the first treatment carried out with a medicine belonging to a specific ICD-11 code is counted.

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 clinical trials with the awareness that the benefit-risk profile of the approved medicinal product may vary in population treated in real clinical practice.

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 there is a higher incidence 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 and L. 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 S begins to be relevant, up to 100,000 patients entered in the age group 70-79,

Table 4.1.5 Number of patients by age group and gender in the Registries (year 2021)

Age group	Men		Women	
	No. of patients	Inc %	No. of patients	Inc %
<40	30,565	4.7	26,923	4.6
40-49	59,069	9.0	48,187	8.2
50-59	122,545	18.7	97,448	16.5
60-69	160,236	24.4	133,928	22.7
70-79	191,940	29.3	174,508	29.6
≥80	91,756	14.0	108,715	18.4
Total	**656,111**	**100.0**	**589,709**	**100.0**

Table 4.1.6 Number of patients by age group and gender in the Therapeutic Plans (year 2021)

Age group	Men		Women	
	No. of patients	Inc %	No. of patients	Inc %
<40	15,848	1.7	11,495	1.0
40-49	27,370	2.9	25,334	2.3
50-59	77,304	8.2	68,170	6.1
60-69	181,919	19.4	170,861	15.4
70-79	327,479	34.9	364,406	32.9
≥80	309,233	32.9	468,369	42.2
Total	**939,153**	**100.0**	**1,108,635**	**100.0**

Table 4.1.7 Number of patients* in ATC categories (level I) until 2021

ATC code	<40			40-49			50-59			60-69			70-79			≥80		
	M	F	tot	M	F	tot	M	F	tot	M	F	tot	M	F	tot	M	F	tot
A	70	17	87	3	5	8	2	8	10	2	1	3	0	0	0	1	0	1
B	10,678	8,400	19,078	23,819	14,131	37,950	66,586	31,347	97,933	162,033	101,815	263,848	299,274	271,919	571,193	288,206	404,385	692,591
C	1,571	512	2,083	5,140	1,338	6,478	14,385	4,339	18,724	22,008	7,762	29,770	23,692	9,510	33,202	11,267	5,595	16,862
D	3,321	2,754	6,075	946	849	1,795	994	1,075	2,069	751	683	1,434	526	400	926	260	175	435
H	21	57	78	9	66	75	14	37	51	10	25	35	2	17	19	0	5	5
J	15,349	8,407	23,756	34,634	14,328	48,962	59,001	28,366	87,367	36,960	30,288	67,248	34,839	40,064	74,903	15,019	18,587	33,606
L	6,607	9,218	15,825	13,768	22,797	36,565	38,436	46,487	84,923	78,175	66,162	144,337	97,332	72,237	169,569	35,235	32,074	67,309
M	844	2,655	3,499	1,410	10,732	12,142	4,519	35,604	40,123	10,159	67,206	77,365	14,086	91,456	105,542	8,728	59,499	68,227
N	5,401	3,500	8,901	1,981	4,818	6,799	2,085	5,194	7,279	1,154	2,238	3,392	426	470	896	78	44	122
R	1,187	1,355	2,542	324	514	838	366	522	888	835	521	1,356	1,048	357	1,405	324	91	415
S	1,685	1,746	3,431	4,671	3,719	8,390	14,764	12,160	26,924	32,466	28,678	61,144	51,073	57,765	108,838	38,617	57,166	95,783
V	13	10	23	47	38	85	150	83	233	315	109	424	425	93	518	173	19	192
Total	**46,747**	**38,631**	**85,378**	**86,752**	**73,335**	**160,087**	**201,302**	**165,222**	**366,524**	**344,868**	**305,488**	**650,356**	**522,723**	**544,288**	**1,067,011**	**397,908**	**577,640**	**975,548**

*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.

PCSK9 inhibitors in the treatment of hypercholesterolemia

The two lipid-lowering medicines with anti-PCSK9 action, evolocumab and alirocumab, have been reimbursed since 2017. The current indications charged to the NHS, common to both medicines, are the following:

- *in primary prevention in patients aged ≤80 years with heterozygous familial hypercholesterolemia and LDL-C levels ≥130 mg/dl, despite therapy for at least 6 months with high potency statin at maximum tolerated dose + ezetimibe or with demonstrated intolerance to statin and/or ezetimibe;*
- *in secondary prevention in patients aged ≤80 years with heterozygous familial hypercholesterolaemia or non-familial hypercholesterolaemia or mixed dyslipidemia and LDL-C levels ≥70 mg/dl*[1] *despite therapy for at least 6 months with high potency statin at maximum tolerated dose + ezetimibe or after a single LDL-C detection in case of recent AMI (last 12 months) or multiple CV events or with demonstrated intolerance to statins and/or ezetimibe.*

Evolocumab, in line with the broader authorised indication, is also reimbursed in homozygous familial hypercholesterolemia for patients aged 12-80 years.
As of 31 December 2021, 30,167 treatments were started, of which 16,921 with evolocumab and 13,255 with alirocumab (Table 4.1.8).
The trend of treatments initiated per month from the start of monitoring is shown in Figure 4.1.2. A significant and progressive increase in the number of new treatments for both medicines, with a constant relationship between them, can be observed.
The decline relative to the month of August is constant for all the years of observation, therefore it can be considered physiological in the annual trends of the new treatments initiated.
65% of the treatments involved male subjects, while the median age was 63 years (range 12-84. Consistent with the different prevalence of forms of hypercholesterolemia, most prescriptions were made in subjects diagnosed with non-familial hypercholesterolemia (52.7%), followed by those for mixed dyslipidemia (28.8%). Both of these forms of hypercholesterolemia recorded a slight increase in the relative frequency of treatments initiated compared to the year 2020. On the other hand, there is a slight decrease compared to 2020 for forms of familial hypercholesterolemia (heterozygous form (18.0 % vs 20.9 %) and homozygous form (0.5 % vs 0.6 %)). Please note that for the form of homozygous familial hypercholesterolemia only evolocumab is authorised.
A marginal share of patients (n = 367, equal to 1.2% of the total) appears to be treated with one of the two medicines after having already been treated by the NHS with another antiPCSK9, then suspended for different reasons.
88.8% of subjects undertook treatment in secondary cardiovascular prevention while the remaining 11.2% in primary prevention. As regards the relevant comorbidities, 71.4% of the entire sample had cardiovascular disease, 63.9% arterial hypertension and 20.9% diabetes

[1] Starting from 16/06/2022, C-LDL values for patients aged ≤ 80 with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia or mixed dyslipidemia in secondary prevention have been modified to 70 mg/dl. As of 31/12/2021, the reimbursed indication provided for threshold value of 100 mg/dl.

mellitus. Only 6.5% of subjects have no relevant comorbidities at baseline. Furthermore, 13.8% of subjects have a current smoking habit, 35.9% reports a previous smoking habit and the remaining 50.3% does not have a smoking history.
Compared to the conditions that led to the initiation of treatment with an inhibitor (PCSK9i), 52.1% of patients have statin intolerance. Furthermore, among patients receiving a high-potency statin at the maximum tolerated dose, 22.2% uses atorvastatin and 25.7% rosuvastatin. 10.6% of total patients treated with PCSK9 inhibitors is intolerant to ezetimibe, with a similar percentage between alirocumab (10.1 %) and evolocumab (10.9 %) (Table 4.1.9).
In conclusion, populations treated with evolocumab and alirocumab confirm to have fairly homogeneous baseline characteristics, without significant deviations from what was found for 2020. Compared to comorbidities, more patients with arterial hypertension treated with evolocumab are confirmed compared to those treated with alirocumab (65.3 % vs 62.1 %). Also in relation to the type of hypercholesterolemia, the following characteristics are confirmed, compared to the year 2020: a higher percentage of subjects with heterozygous familial hypercholesterolemia treated with alirocumab and, conversely, a higher percentage of subjects with non-familial hypercholesterolemia treated with evolocumab. The percentages of patients with mixed dyslipidemia were similar for both medicines.
The regional distribution of patients shows that Campania has the highest number of subjects in treatment (22.1% of the national total), followed by Lombardy (11.5%) and Lazio (9.6%). These three Regions alone represent almost 43.2% of all subjects treated with PCSK9 inhibitors (Table 4.1.10).

Table 4.1.8 Characteristics of patients at initiation of treatment with anti PCSK9

Medicine	Alirocumab N (%)	Evolocumab N (%)	Total N (%)
Total patients	13,255 (43.9%)	16,921 (56.1%)	30,176 (100%)
Women	4,667 (35.2%)	5,883 (34.8%)	10,550 (35.0%)
Men	8,588 (64.8%)	11.038 (65.2%)	19,626 (65.0%)
Median age (range)	62 (18 - 80)	63 (12 - 84)	63 (12 - 84)
Previous anti-pcsk9 treatment	180 (1.4%)	187 (1.1%)	367 (1,2%)
Types of hypercholesterolemia			
HoFH*	0 (0.0%)	150 (0.9%)	150 (0.5%)
HeFH	2,520 (19.0%)	2,921 (17.3%)	5,441 (18.0%)
noFH	6,787 (51.2%)	9,111 (53.8%)	15,898 (52.7%)
MD	3,948 (29.8%)	4,739 (28.0%)	8,687 (28.8%)
Use in CV prevention			
Primary prevention	1,519 (11.5%)	1,859 (11.0%)	3,378 (11.2%)
Secondary prevention	11,736 (88.5%)	15,062 (89.0%)	26,798 (88.8%)
Relevant co-morbidities§			
Cardiovascular disease (heart disease)	9,281 (70.0%)	12,270 (72.5%)	21,551 (71.4%)
Cerebrovascular disease (previous stroke)	1,123 (8.5%)	1,280 (7.6%)	2,403 (8.0%)
Peripheral arterial disease	2,589 (19.5%)	3,032 (17.9%)	5,621 (18.6%)
Diabetes mellitus	2,884 (21.8%)	3,416 (20.2%)	6,300 (20.9%)
Arterial hypertension	8,225 (62.1%)	11,051 (65.3%)	19,276 (63.9%)
None	1,009 (7.6%)	960 (5.7%)	1,969 (6.5%)
Smoking habit			
Present	1,784 (13.5%)	2,387 (14.1%)	4,171 (13.8%)
Previous	4,617 (34.8%)	6,214 (36.7%)	10,831 (35.9%)
Absent	6,854 (51.7%)	8,320 (49.1%)	15,174 (50.3%)
Use of statins			
Intolerance to statins	6,744 (50.9%)	8,984 (53.1%)	15,728 (52.1%)
Statin in combination, treatment with^			
atorvastine	3,020 (22.8%)	3,681 (21.8%)	6,701 (22.2%)
rosuvastatina	3,491 (26.3%)	4,256 (25.2%)	7,747 (25.7%)

HoFH: homozygous familial hypercholesterolaemia ; HeFH: heterozygous familial hypercholesterolemia
noFH: non-familial hypercholesterolemia ; MD: mixed dyslipidemia
*Only evolocumab has an indication in HoFH
§You can select multiple items
^For 12 treatments there is no information on the statin used in combination

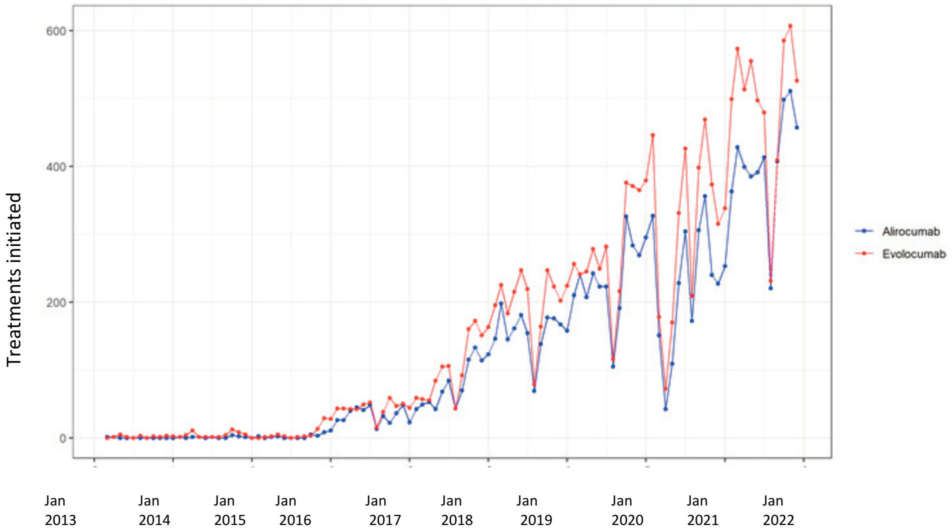
Table 4.1.9 Number of ezetimibe intolerant patients at initiation of anti PCSK-9 treatment

Medicine	Alirocumab N (%)	Evolocumab N (%)	Total N (%)
Use of di ezetimibe			
Intolerant to ezetimibe	1,336 (10.1)	1,851 (10.9)	3,187 (10.6)

Table 4.1.10 Regional distribution of prescribing centers and of patients starting treatment

Region	No. Of centres		No. Of patients undergoing treatment		Total No. (%)
	Alirocumab	Evolocumab	Alirocumab	Evolocumab	
Abruzzo	7	6	278	371	649 (2.2)
Basilicata	5	9	216	455	671 (2.2)
Calabria	10	17	439	877	1,316 (4,4)
Campania	46	65	2,502	4,169	6,671 (22.1)
Emilia R.	16	15	591	812	1,403 (4.6)
Friuli VG	13	12	193	286	479 (1.6)
Lazio	25	25	1,704	1,183	2,887 (9.6)
Liguria	17	17	805	589	1,394 (4.6)
Lombardy	81	87	1,332	2,147	3,479 (11.5)
Marche	12	15	206	449	655 (2.2)
Molise	5	4	164	29	193 (0.6)
Piedmont	29	27	1,597	1,154	2,751 (9.1)
A.P. of Bolzano	7	5	60	40	100 (0.3)
A.P. of Trento	2	2	46	44	90 (0.3)
Puglia	12	13	667	1,308	1,975 (6.5)
Sardinia	6	8	292	384	676 (2.2)
Sicily	23	20	481	431	912 (3)
Tuscany	19	20	789	1,142	1,931 (6.4)
Umbria	10	9	289	235	524 (1.7)
Valle d'Aosta	1	1	20	51	71 (0.2)
Veneto	12	12	584	765	1,349 (4.5)
Total	**358**	**389**	**13,255**	**16,921**	**30,176 (100)**

Figure 4.1.2 Treatments initiated with anti-PCSK9 medicines in December 2021 (monthly trend)



Intravitreal anti-VEGF medicines

Anti-neovascularization agents (VEGF inhibitors) are reimbursed by the NHS in different therapeutic indications for intravitreal administration (IVT); however, the data shown refer to the treatment of neovascular (exudative) age-related macular degeneration (AMD). In particular, the data are referred to authorised uses in this indication (aflibercept brolucizumab, pegaptanib and ranibizuma) as well as to bevacizumab, even though it is not authorised for this indication, added to the list of medicines under Law 648/96. Since 1 January 2019, upon request of the marketing authorisation holder, the withdrawal of the MA for the medicinal product Macugen® (pegaptanib) became effective in Europe [*Commission implementing decision* C (2018) 9064 final, 17/12/2018] and its Registry closed starting from 1 September 2019. Information is referred to Monitoring Registries active starting from: 25 February 2013 for pegaptanib; 7 March 2013, for ranibizumab; 28 June 2014 and 19 June 2020 for bevacizumab respectively for Avastin® e Mvasi®; 15 April 2014 for aflibercept; 1 January 2021 for brolucizumab.
The registries of aflibercept, bevacizumab (with regards to Avastin®) and of ranibizumab were closed on 8 October 2019, with the introduction of a temporary paper-form and then, since 6 February 2020, of the new simplified form of monitoring of all anti-VEGF agents.
This new tool also has the purpose of collecting all the previous treatments, started in the old online Registries or in paper form, so as to allow the management of monitoring in a single platform. On the other hand, Beovu® (brolucizumab) and Mvasi® (bevacizumab) were inserted, at the same time of the entry into force of the relative reimbursement and 648/96 decisions, within the simplified monitoring platform.
Starting from 1 January 2021 (Italian Official Journal no. 323 of 31 December 2020), Note 98 came into force which regulates the methods of prescription, intravitreal administration and use by the NHS of anti-VEGF medicines for the treatment of maculopathy. As part of the Note, in consideration of the scientific evidence available, the AIFA CTS expressed its opinion on the overlap of the anti-VEGF aflibercept, bevacizumab, brolucizumab and ranibizumab in relation to the AMD indication.
It should be noted that the data reported here include both the treatments included in the old Monitoring Registries and those started directly within the simplified multi-drug form, established by 6 February 2020. Therefore, for the purposes of the analyses reported below, the treatments opened in the old Monitoring Registries and subsequently migrated to the simplified multi-drug card are considered as a single treatment.
As of 31 December 2021, a total of 320,862 eyes, almost 50,000 more than those resulting on 31 December 2020, were initiated for treatment for AMD (Table 4.1.11), 76.1% of which were treated as part of a unilateral therapy. The number of *naïve* patients (considering only first treatment with an intravitreal IVT anti-VEGF) is 214,806. More than a third of treatments (no. of eyes) were started with ranibizumab (115,723; 36.1%), followed by aflibercept (100,972; 31.5%), bevacizumab (100,488; 31.4%), brolucizumab (2,605; 0.8%) and finally, pegaptanib (1,074; 0.3%). The baseline characteristics of *naïve* patients show a higher prevalence of use in women (56.8%) than in men (43.2%), a median age of treated patients of 78 years (range 20-105 years), and the largest number of patients receiving first treatment with IVT anti-VEGF falling in the age group between 75 and 84 years.
19.9% of the treatments started refer to eyes previously treated with an anti-VEGF.

Specifically, 29.5% of the eyes treated with aflibercept, 20.2% of those treated with bevacizumab, 64.8% of those treated with brolucizumab and 7.0% of those treated with ranibizumab were previously treated with another anti-VEGF IVT.

The mean (median) number of injections per eye in the first year of treatment with an anti-VEGF IVT is 3.6, with a highest value for aflibercept of 3.8 (4), followed by bevacizumab with 3.6 (3), ranibizumab with 3.5 (3) and finally pegaptanib with a value of 2.6 (2). As far as brolucizumab is concerned, at the cut-off of the data (31/12/2021), no patient still had the minimum potential follow-up to calculate the average number of administrations in the first 12 months.

The trend of treatments initiated starting from 2013 to 31 December 2021 is shown in Figure 4.1.3.

Bevacizumab was the most used anti-VEGF (with about 1,825 new eyes treated per month of which about 1,200 treated with Avastin and about 625 treated with Mvasi), followed by aflibercept with 1,256 new eyes/month, ranibizumab with 739 new eyes/month and brolucizumab with 217 eyes/month. These values represent the initiated treatments (first prescription with a given medicine), regardless of whether the patient had already received administration for the same eye with other anti-VEGF. Data reveal a resumption of the number of new treatments initiated with anti-VEGF for AMD in 2021, after the decrease recorded in 2020 and in particular during the lockdown months (March-May).

The distribution of the percentage of switches on active patients by year and medicine of origin is shown in Figure 4.1.4. The main targets of switches appear in 2021, bevacizumab and aflibercept, with a decrease in the percentage of switches on active treatments for aflibercept (around 10%) and an increase for bevacizumab (around 18%).

The regional distribution shows that more than half of the treatments initiated with medicines for AMD are distributed over 5 Regions, Lombardy, Veneto, Lazio, Emilia Romagna and Tuscany. The regional distribution of prescribing centers and the treatments started are shown in Table 4.1.12, while the number of treatments started by Regions normalised on the basis of the resident population, is shown in Figure 4.1.5.

Table 4.1.11 Baseline characteristics of patients at the start of anti-VEGF treatment

	Aflibercept		Bevacizumab L.648/96)/ Avastin®		Bevacizumab (L.648/96)/ Mvasi®		Brolucizumab		Pegaptanib		Ranibizumab		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No. Of Patients*	56,374	26.2	58,712	27.3	3,573	1.7	695	0.3	720	0.3	94,732	44,1	214,806	100
Age, yy median (range)	77.8 (20.7 – 103.9)		79.4 (20.0 – 103.0)		79.6 (27.0 – 99.2)		77.3 (39.0 – 95.6)		80.4 (50.6 – 99.9)		77.9 (18.0 -105.0)		78.3 (18,0 - 105,0)	
-64	6,041	10.7	4,212	7.2	282	7.9	69	9.9	36	5.0	10,333	10.9	20,973	9.8
65 - 74	15,334	27.2	13,702	23.3	814	22.8	211	30.4	148	20.6	25,093	26.5	55,302	25.7
75 - 84	25,182	44.7	27,840	47.4	1,680	47.0	303	43.6	360	50.0	42,200	44.5	97,565	45.4
>85	9,817	17.4	12,958	22.1	797	22.3	112	16.1	176	24.4	17,106	18.1	40,966	19.1
Gender														
Women	31,344	55.6	34,315	58.4	2,131	59.6	377	54.2	355	49.3	53,585	56.6	122,107	56.8
Men	25,030	44.4	24,397	41.6	1,442	40.4	318	45.8	365	50.7	41,147	43.4	92,699	43.2
No. of treatments (eyes)	100,972	31.5	90,678	28.3	9,810	3.1	2,60 5	0.8	1,074	0.3	115,723	36.1	320,862	100.0
Previous anti-VEGF IVT treatment**	29,734	29.5	19,066	21.0	5,059	51.5	1,68 9	64.8	304	28.3	8,059	7.0	63,911	19.9%
Monocular treatment	73,968	84.6	67,168	85.1	8,152	90.8	2,277	93.3	1,058	99.2	91,473	88.3	244,096	76.1%
Biocular treatment	13,502	15.4	11,755	14.9	829	9.2	164	6.7	8	0.8	12,125	11.7	38,383	12.0%
Average (median-iqr) number of prescriptions in the first 12 months***	3.8 (4; 3-5)		3.6 (3; 2-5)				NA		2.6 (2; 1-3)		3.5 (3; 2-4)		3.6 (3; 2-5)	

*The row percentages are shown

**Considering only first treatm,ent with bevacizumad (regardless of the medicine used), the total numer of eyes previously treated with other anti-VEGF IVT (aflibercept, pegaptanib o ranibizumab) in the AMD indication is 20,267, equal to 33.7 of the observed switches.

***Average (median) number of administrations for patients with at least one year of potential follow-up as of 31/12/2021; for brolucizumab, no treatment has the minimum potential follow-up (1 year) necessary to calculate the average number of prescriptions in the first 12 months.

Figure 4.1.3 Monthly trend of treatments initiated with anti-VEGF IVT medicine from January 2013 to 2021 in Italy

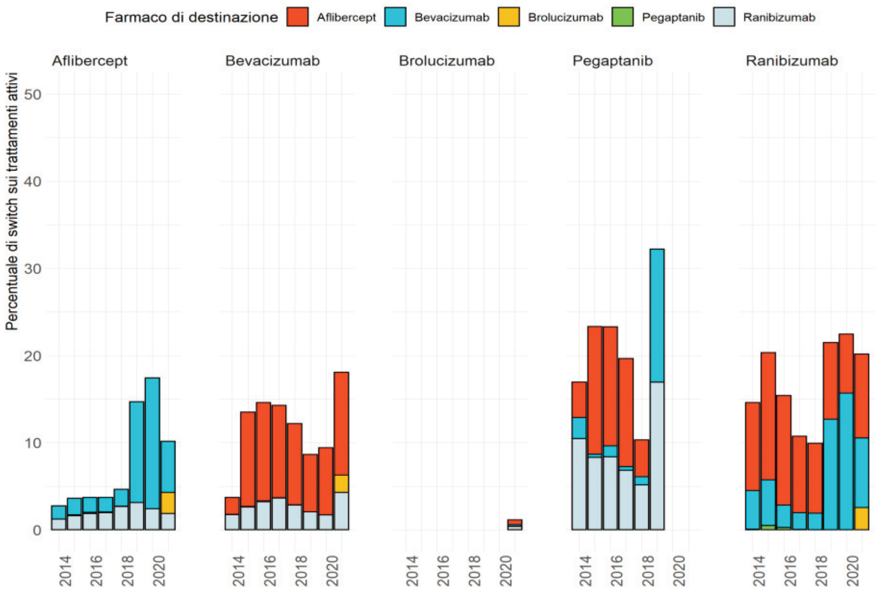
* The trends shown are net of migration from old Registries to multidrug anti-VEGF form.

Table 4.1.12 Regional distribution of prescribing centers and of patients starting treatment

Region	No. of active prescribing centers						No. of eyes					
	Aflibercept	Bevacizumab		Brolucizumab	Pegaptanib	Ranibizumab	Aflibercept	Bevacizumab		Brolucizumab	Pegaptanib	Ranibizumab
		Avastin	Mvasi					Avastin	Mvasi			
Abr	11	4	0	8	4	11	2,532	203	0	142	16	3,171
Bas	4	1	0	5	2	5	634	15	0	127	8	1,112
Cal	11	1	0	1	5	14	1,495	23	0	3	22	2,164
Cam	31	3	1	10	5	31	5,196	767	50	111	8	8,822
Emi	18	20	10	6	7	19	5,371	13,698	1,639	61	33	4,349
Fvg	6	6	0	2	0	6	2,805	5,508	0	26	0	2,456
Laz	30	20	6	11	10	33	11,786	5,613	1,162	399	49	10,434
Lig	9	8	2	5	4	8	3,848	4,767	31	81	10	4,424
Lom	69	65	3	36	23	75	20,909	20,389	304	707	260	27,236
Mar	14	14	3	8	8	15	2,583	5,549	502	169	94	3,636
Mol	5	1	0	1	0	5	502	41	0	5	0	939
Pie	25	19	3	11	6	26	9,215	8,465	172	75	28	5,415
Bol	3	3	2	1	1	3	1,145	1,456	208	16	2	889
Tre	2	2	2	1	0	2	733	1,456	51	3	0	613
Pug	28	7	1	22	25	38	7,060	474	88	311	296	10,561
Sar	8	2	0	0	5	8	2,236	159	0	0	39	3,671
Sic	23	10	2	17	6	24	6,630	491	351	271	17	6,975
Tus	17	14	16	1	11	21	7,264	4,583	3,687	1	104	8,645
Umb	7	7	5	3	0	7	1,625	870	526	18	0	2,840
Vda	1	1	0	0	1	1	286	1,236	0	0	5	81
Ven	28	28	10	15	15	29	7,117	14,915	1,037	79	83	7,290
Total	**350**	**236**	**66**	**164**	**138**	**381**	**100,972**	**90,678**	**9,808***	**2,605**	**1,074**	**115,723**

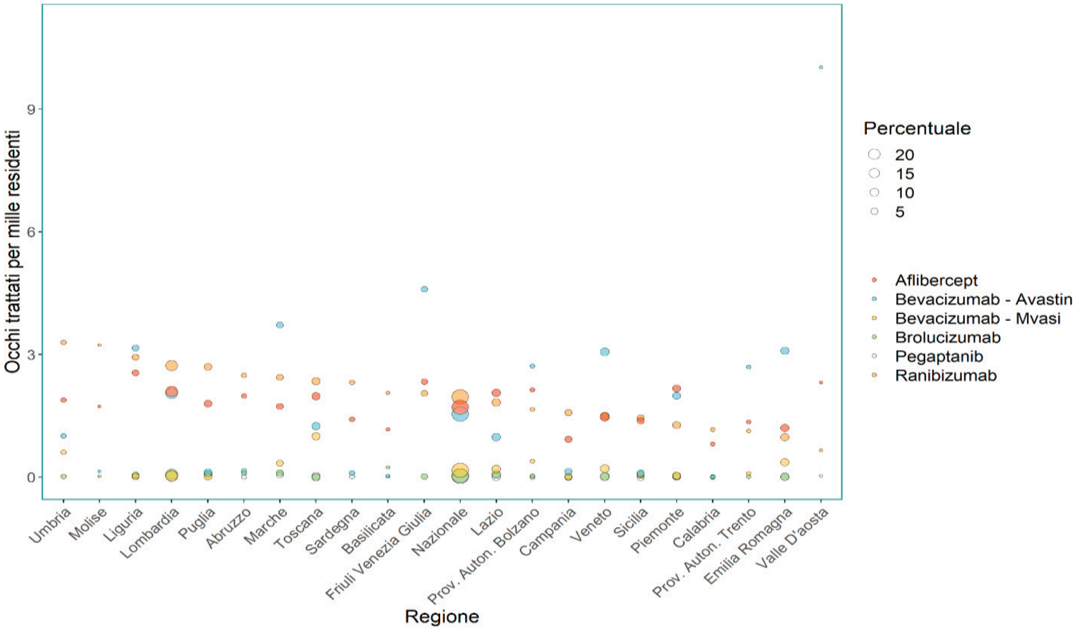
* the Region in charge of the 2 treatments initiated with the medicinal product Mvasi® is unknown

Figure 4.1.4 Percentage of patients who changed treatment out of total ongoing patients by year and medicine of origin. Target medicines are shown using different colours



The number of ongoing patients is defined as the difference in the number of cumulative treatments started up to the year considered, minus the number of cumulative treatments discontinued in the same year (for example, total treatments inserted until 2018 minus total treatments discontinued until 2018). Discontinued treatment means both treatment with a completed End of Treatment card and treatment without a completed End of Treatment card and with a period without further dispensing of the medicine of more than 180 days from the extraction date. The year of interruption coincides with the date of the last day with dispensation of the medicine.

Figure 4.1.5 Regional distribution of eyes treated (per 1000 inhabitants)



Cell therapy based on Chimeric Antigen Receptor T cell (CAR-T)

CAR-T, advanced therapy medicinal products (ATMP) based on the use of genetically modified autologous T lymphocytes to express a Chimeric Antigen Receptor (CAR) have recently entered clinical practice. In particular, tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) are two CAR-T products designed to recognise the CD19 antigen, a surface molecule physiologically expressed by B lymphocytes and present in most cancers of the B lymphocyte line.

In pivotal clinical trials, immunotherapy with anti-CD19 CAR-T has made it possible to achieve lasting complete remissions in patients with lymphoproliferative neoplasms for which conventional chemotherapy was no longer an effective therapeutic option. Specifically, Yescarta has been eligible for reimbursement since November 2019 for the treatment of adult patients with Diffuse Large B-Cell Lymphoma (DLBCL) and Primary Mediastinal Large B-cell lymphoma (PMBCL) refractory or relapsing after two or more lines of systemic therapy. Kymriah, on the other hand, has been eligible for reimbursement since August 2019 for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in post-transplant recurrence or in second or further relapse, and for the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy. DLBCL and PMBCL are two forms of aggressive lymphoma, while ALL is the most common form of acute pediatric leukemia. Although these conditions respond well to first-line immunochemotherapy protocols, the prognosis of patients in advanced relapse/refractory settings is often ominous.

This paragraph briefly summarises the first data from the AIFA Monitoring Registries regarding the use of CAR-T marketed in Italy.

In consideration of the high expertise necessary to optimise the efficacy and safety of these treatments, CAR-T therapies can only be carried out in centers of reference identified by the Regions on the basis of a high level of specialisation in the management of cellular therapies, and subsequently “qualified” by the Marketing Authorisation Holder (AIC), in compliance with the specific risk management measures approved by the European Medicines Agency (EMA) for these products. The activation and qualification process of the centers for the provision of CAR-T therapies is still in progress: as of 31 December 2021 (Registries analysis date), 28 centers were qualified for the administration of Yescarta and Kymriah throughout the national territory (Table 4.1.15 for detail at regional level) but there is still a lack of homogeneity in the territorial distribution, with more than half of the qualified centers found in only 4 Regions (Lazio, Lombardy, Piedmont and Tuscany), although, compared to 2020, many more regions surveyed at least one patient for CAR-T infusion in 2021.

In total, 417 patients with aggressive large cell B lymphomas were entered in the AIFA Registries and considered eligible for CAR-T treatment (Kymriah n = 249, Yescarta n = 168, Table 4.1.13). The median age of these patients is 57 years (range 18-71) with a prevalence of male subjects (M/F ratio 1.4: 1), in line with what was expected on the basis of epidemiological data. The population of patients included in the AIFA Monitoring Registries is representative of the advanced disease setting for which these products are indicated: the median time from the diagnosis of lymphoma was 1.25 years, 33.1% of patients had

previously undergone at least 3 lines of systemic therapy and 98.8% were no longer eligible for hematopoietic stem cell transplant procedures, in most cases due to failure of a previous transplant (27.6% post-transplant recurrence) or failure to respond to salvage therapy (80%)[2].The data entered in the Monitoring Registries also confirm the high clinical risk of patients candidates for CAR-T therapy: 45.3% of patients had an IPI score ≥3, 78.7% a stage III/IV sec. Ann-Arbor and 59.2% refractory to previous treatments.
At the time of the analysis, 330 out of 417 patients eligible for treatment (79.1%) had undergone CAR-T cell infusion, with a median time from eligibility to infusion of 59 days. The discrepancy between the number of eligible and truly infused patients (Table 4.1.16) and the long time elapsing between the eligibility assessment and the infusion of genetically modified T cells can be attributed to various logistical factors (e.g. the time required for the patient's cell apheresis, shipping to the manufacturing center, manufacturing the CAR-T product, shipping to the patient treatment center) and clinical factors (e.g. disease progression and/or worsening of the general condition of the patient, appearance of complications that must be treated before infusion of CAR-T cells, death of the patient).
With regard to the ALL indication, 44 patients were entered in the AIFA Registries and considered eligible for treatment with tisagenlecleucel (Table 4.1.14). The median age of the patients is 15 years (range 2.9-26) with a prevalence of male subjects (M/F ratio 1.75: 1). Most patients had a ALL relapse after haematopoietic stem cell transplant procedure (45.5%) or a second or further relapse (40.9%), median time from diagnosis of ALL was 2.8 years, and in most of the cases there were no high-risk cytogenetic characteristics (68.2%). 50% of the patients included in the AIFA Registry had a suboptimal PS (Karnofsky-Lansky score ≤80%), and most (63.6%) had already undergone anti-CD19 immunotherapy (blinatumomab monotherapy in 64.3% of cases).
At the time of analysis, most of the patients eligible for treatment (33 out of 44, 75%) had undergone CAR-T cell infusion, with a median time from eligibility to infusion of 57 days. Again, the reasons for the discrepancy between eligible patients and infused patients must be ascribed to logistical and/or clinical issues.

[2] Patients with chemosensitive disease, i.e. who respond to salvage chemotherapy, are more likely to achieve long-term control of post-transplant disease. Failure of salvage therapy may preclude the possibility of undergoing hematopoietic stem cell transplantation

Table 4.1.13 Baseline characteristics for adult patients with diffuse large B cell lymphoma

Characteristics at baseline	Axicabtagene ciloleucel	Tisagenlecleucel	Total
Eligible patients	168 (100.0)	249 (100.0)	417 (100.0)
Gender			
Female	67 (39.9)	106 (42.6)	173 (41.5)
Male	101 (60.1)	143 (57.4)	244 (58.5)
Age at Registry entry (median years-range)	53.56 (18.02 – 70.94)	57.12 (21.93 – 71.01)	57.44 (18.02 – 71.01)
Time since first diagnosis (median years - iqr)	1.07 (0.75 – 21.65)	1.36 (0.82 – 18.40)	1.25 (0.77 – 2.63)
IPI Score			
0	10 (5.95)	11 (4.42)	21 (5.04)
1	39 (23.21)	38 (15.26)	77 (18.47)
2	47 (27.98)	83 (33.33)	130 (31.18)
3	48 (28.57)	82 (32.93)	130 (31.18)
4	21 (12.50)	29 (11.65)	50 (11.99)
5	3 (1.79)	6 (2.41)	9 (2.16)
Days from insertion to infusion (median days - range)	59.50 (50.00 – 70.00)	58.50 (47.00 – 77.00)	59.00 (49.00 – 73.00)
Number of previously administered systemic loines of therapy (including rituximab e antracicline)			
2	111 (66.07)	168 (67.47)	279 (66.91)
3	42 (25.00)	52 (20.88)	94 (22.54)
≥4	15 (8.93)	29 (11.65)	44 (10.55)
Patient candidate for ASCT			
No	167 (99.40)	245 (98.39)	412 (98.80)
yes	1 (0.60)	4 (1.61)	5 (1.20)
Performance Status (ECOG)			
0	130 (77.38)	164 (65.86)	294 (70.50)
1	38 (22.62)	85 (34.14)	123 (29.50)
Previous anti-CD19 therapy			
No	167 (99.40)	247 (99.20)	414 (99.28)
yes	1 (0.60)	2 (0.80)	3 (0.72)
Relapse after ASCT			
No	124 (73.81)	178 (71.49)	302 (72.42)
yes	44 (26.19)	71 (28.51)	115 (27.58)
Patient not eligible for ASCT			
Other (including transplant already performed)	29 (17.26)	52 (20.88)	81 (19.42)
Age/Comorbidity	3 (1.79)	7 (2.81)	10 (2.40)
Contraindications to maintenance regime	0 (0.00)	1 (0.40)	1 (0.24)
Failure to respond to rescue therapy	141 (83.93)	193 (77.51)	334 (80.10)
Stadium (Lugano mod. Ann Arbor criteria)			
I	1 (0.60)	1 (0.40)	2 (0.48)
I E	2 (1.19)	3 (1.20)	5 (1.20)
II	13 (7.74)	22 (8.84)	35 (8.39)
II bulky	18 (10.71)	7 (2.81)	25 (6.00)

Characteristics at baseline	Axicabtagene ciloleucel	Tisagenlecleucel	Total
II E	14 (8.33)	8 (3.21)	22 (5.28)
III	25 (14.88)	41 (16.47)	66 (15.83)
IV	95 (56.55)	167 (67.07)	262 (62.83)
Stage of the disease			
Recurrent DLBCL	34 (20.24)	95 (38.15)	129 (30.94)
Refractory DLBCL	93 (55.36)	154 (61.85)	247 (59.23)
Primary mediastinal DLBCL	41 (24.40)		41 (9.83)
Infusion occurred			
No	28 (16.67)	59 (23.7)	87 (20.86)
Yes	140 (83.33)	190 (76.30)	330 (79.14)
Treatment with FT card complete	67 (39.88)	124 (49.80)	191 (45.8)

Table 4.1.14 Baseline characteristics for pediatric and pediatric young adult and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL)

Characteristics at baseline	N (%)
Gender	
Female	16 (36.36)
Male	28 (63.63)
Age at Registry entry (median years-range)	15,11 (2.89-25.96)
Time since first diagnosis (median years - iqr)	2.77 (1.53 – 5.30)
Days from insertion to infusion (median days - range)	57.00 (49 - 74)
Diagnosis	
Post-transplant relapsed B-cell ALL	20 (45.45)
B-cell ALL in second or further relapse	18 (40.91)
Refractory B-cell ALL	6 (13.64)
Presence of high-risk genetic characteristics	
Other	8 (18.18)
Complex karyotype	3 (6.82)
Ph+ Chromosome	2 (4.55)
None	30 (68.18)
Rearrangement involving MLL/KMT2A	2 (4.55)
With failure of at least 2 lines of therapy with TKI (chromosome Ph+)	1 (2.27%)
Number of lines of systemic therapy	
2	6 (33.33)
3	5 (27.78)
≥4	7 (38.89)
Days since alloSCT (median - IQR)	392 (227-562)
Performance status Karnofsky.Lansky	
70	14 (31.82)
75	1 (2.27)
80	7 (15.91)
85	1 (2.27)
90	8 (18.18)
100	13 (29.55)
Previous anti-CD19 therapy	
No	16 (36.36)
Si	28 (63.64)
Percentage of blasts (median - IQR)	10.50 (6.75-42.50)
Anti-CD19 therapy	
Blinatumomab	18 (64.29)
Altro	10 (35.71)
Infusion occurred	
No	11 (25.00%)
Yes	33 (75.00%)
Treatments with FT card completed	12 (27.27%)

Table 4.1.15 Centers with at least one eligible patient in the CAR-T Registries

Region	Tisagenlecleucel		Axicabtagene ciloleucel		%
	LLA	DLBCL	DLBCL	Total	
Abruzzo	0	1	1	1	3.6
Basilicata	0	0	0	0	0.0
Calabria	0	1	1	1	3.6
Campania	0	1	0	1	3.6
Emilia R.	0	1	1	1	3.6
Friuli VG	0	1	0	1	3.6
Lazio	2	2	2	3	10.7
Liguria	0	1	1	1	3.6
Lombardy	6	6	6	7	25.0
Marche	0	0	1	1	3.6
Molise	0	0	0	0	0.0
Piedmont	1	2	1	3	10.7
A.P. of Bolzano	0	0	0	0	0.0
A.P. of Trento	0	0	0	0	0.0
Puglia	0	0	0	0	0.0
Sardinia	0	0	0	0	0.0
Sicily	0	2	2	2	7.1
Tuscany	1	0	1	3	10.7
Umbria	0	1	1	1	3.6
Valle d'Aosta	0	0	0	0	0.0
Veneto	0	2	1	2	7.1
Total	**10**	**21**	**19**	**28**	**100.0**

Table 4.1.16 Regional distribution of patients in the CAR-T Registries divided by eligible and infused patients

Region	Tisagenlecleucel					Axicabtagene ciloleucel		
	DLBLC		LLA		Total Infused	DLBLC		Total Infused
	Eligible	Infused	Eligible	Infused		Eligible	Infused	
Abruzzo	3	1	0	0	1	4	1	2
Basilicata	0	0	0	0	0	0	0	0
Calabria	14	9	0	0	9	5	4	13
Campania	3	1	0	0	1	0	0	1
Emilia R.	28	20	0	0	20	31	26	46
Friuli VG	4	3	0	0	3	0	0	3
Lazio	27	18	21	12	30	19	12	42
Liguria	16	15	0	0	15	4	2	17
Lombardy	98	80	19	18	98	71	65	163
Marche	0	0	0	0	0	2	1	1
Molise	0	0	0	0	0	0	0	0
Piedmont	13	11	2	1	12	2	2	14
A.P. of Bolzano	0	0	0	0	0	0	0	0
A.P of Trento	0	0	0	0	0	0	0	0
Puglia	0	0	0	0	0	0	0	0
Sardinia	0	0	0	0	0	0	0	0
Sicily	7	4	0	0	4	7	7	11
Tuscany	6	6	2	2	8	13	11	19
Umbria	16	11	0	0	11	3	2	13
Valle d'Aosta	0	0	0	0	0	0	0	0
Veneto	14	11	0	0	11	7	7	18
Total	**249**	**190**	**44**	**33**	**223**	**168**	**140**	**363**

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 various conditional reimbursement agreements (*Managed Entry Agreements*, MEAs) with pharmaceutical companies that can be managed both at the *patient level* through the Monitoring Registries 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 [3] in two main categories: a) outcome-based risk sharing agreements (*Performance-based Risk Sharing schemes*); and b) agreements of a purely financial nature (*Financial based schemes*). The first category, also known as outcome-based schemes, includes a series of agreements such as: *Payment by Result* (PbR - in which the risk of failure is entirely borne by the pharmaceutical company holder of the MA), *Risk Sharing* (RS - whose risk of failure is shared between the NHS and the pharmaceutical company), the *Success Fee* (SF - in which only the therapeutic success is borne by the NHS) and the recent *Payment at Result* (PaR model - which is essentially an SF with evaluations and payments of the only therapeutic success charged to the NHS, deferred in several times after the treatment). On the other hand, in the second category, only the *Cost Sharing* (CS) and *Capping* agreements are included among the financial MEAs that can be managed through Monitoring Registries.

- The **CS** provides for the application of a discount on the cost of the first cycles of therapy or the entire duration of treatment for all eligible patients. This tool is generally adopted in the context of financial uncertainty related to the impact of the drug rather than uncertainty about the results in terms of efficacy. According to the ***Capping*** model, the pharmaceutical company pays therapy costs when the quantities established by the agreement are exceeded. By way of example, in the negotiation with pharmaceutical companies the maximum cost of a treatment for the NHS can be fixed, providing for a maximum cost of the therapeutic schemes available.
- The RS model, compared to the CS, provides for a discount that applies only to patients not responding to treatment. The PbR model, on the other hand, extends the RS modalities by providing for full reimbursement by the pharmaceutical company of all patients who do not respond to treatment (payback by pharmaceutical companies of 100% of therapeutic failures). PbR is usually used in the case of medicines whose benefit/risk ratio presents a greater degree of uncertainty and requires a definition of non-response based on the evidence available from the pivotal clinical trials. SF is useful in the case of high-cost treatments, which involve financial exposure on the part of the

[3] Garrison Jr LP et al. Value in Health. 2013

healthcare company, only after having achieved therapeutic success. Conceptually identical to the PbR, instead of obtaining reimbursement of the cost of failure by the pharmaceutical company, with the SF the NHS only remunerates the therapeutic success once obtained. Finally, the PaR model recently introduced for advanced therapy medicines, CAR-Ts, which is in fact a SF model according to which the cost of the medicine is divided into one or more payment tranches to be made in set times only in the case of achievement of specific agreed outcomes (or maintenance of a benefit).

Figure 4.2.1 Percentage distribution of the types of risk sharing agreement (as of 31 December 2021) excluding PaR

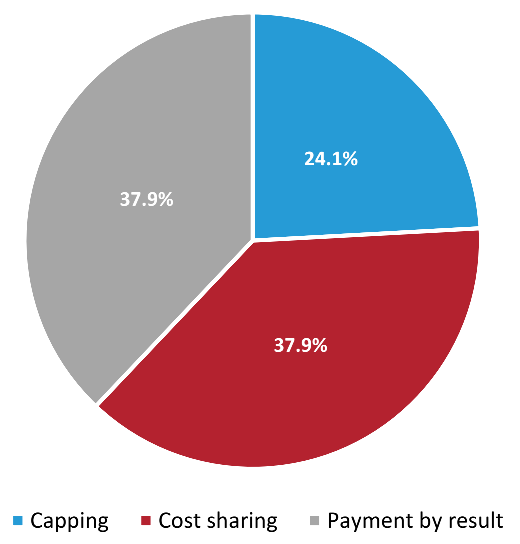


Figure 4.2.1 shows the percentage of each agreement, as of 31 December 2021.
At the end of 2021, 11 payment by result agreements (37.9 % of existing agreements) were active, making up the totality of outcome-based agreements integrated into the Registries platform. In fact, it is recalled that even though PaR agreements are managed through the platform, they use a different flow for the tracking of the amounts paid.
Financial agreements represent the majority of existing agreements, comprising a total of 18 agreements: 11 cost-sharing (37.9 % of existing agreements) and 7 capping (24.1 % of existing agreements).

Table 4.2.1 shows the reimbursements relating to MEAs detected by the Registries platform for the three-year period 2019-2021, divided by Region.
81.8% of the reimbursement obtained in 2021 (121.454.656, 99 euro) relates to financial agreements (Figure 4.2.2), with 69.9% of the reimbursement for Cost Sharing agreements and 11.9% for Capping agreements. Payment by Result and Risk Sharing cover instead 18.2% 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.
At ATC level (Figure 4.2.3), almost all of the reimbursement (95.2 %) are ascribable to antineoplastic and immunomodulatory medicines (L); general antimicrobials for systemic use (J) account for about 3 % of the reimbursements generated in 2021, while sensory organ drugs (S), nervous system drugs (N), endocrine system drugs (H) and muscle and skeletal (M) drugs add up to less than 2 % of 2021 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.

Table 4.2.1 Reimbursement obtained (€) for MEA online years 2019-2020-2021*

Region	Reimbursement 2019	Reimbursement 2020	Reimbursement 2021
Abruzzo	3,551,689	1,909,701	1,775,971
Basilicata	1,230,691	2,601,303	1,106,373
Calabria	2,733,155	2,787,310	1,872,137
Campania	15,570,670	12,658,095	15,569,723
Emilia R.	11,425,176	8,403,782	9,652,272
Friuli VG	2,341,654	3,520,923	2,508,802
Lazio	8,383,726	14,101,607	10,750,137
Liguria	3,261,973	2,994,895	2,266,187
Lombardy	20,938,350	17,307,750	19,686,427
Marche	3,766,917	3,309,402	2,519,704
Molise	251,825	417,356	501,225
Piedmont	6,346,751	6,317,278	7,044,898
A.P of Bolzano	1,902,342	1,162,700	1,015,011
A.P of Trento	680,717	984,236	456,463
Puglia	7,346,545	9,094,019	12,288,125
Sardinia	2,156,710	3,242,559	2,319,411
Sicily	9,676,137	6,049,224	7,740,633
Tuscany	8,643,847	8,838,372	12,343,935
Umbria	1,169,618	1,317,372	966,506
Valle d'Aosta	214,841	89,952	423,464
Veneto	7,774,687	7,669,111	8,647,254
Total	**119,368,022**	**114,776,947**	**121,454,657**

*Reimbursement reported for 2019, 2020 and 2021 is obtained using data updated to May 2019 and 2020 and June 2021.

Table 4.2.2 Reimbursements obtained by type of MEA (year 2021)

Region	Capping	Cost-sharing	Payment by result	Risk-sharing	Total
Abruzzo	386,133	1,114,967	274,871	0	1,775,971
Basilicata	117,459	792,031	196,883	0	1,106,373
Calabria	535,763	1,194,430	141,945	0	1,872,137
Campania	1,810,248	12,019,376	1,740,099	0	15,569,723
Emilia R.	913,280	7,247,626	1,491,366	0	9,652,272
Friuli VG	139,702	1,648,841	720,259	0	2,508,802
Lazio	1,700,907	7,593,604	1,455,626	0	10,750,137
Liguria	295,780	1,067,208	903,199	0	2,266,187
Lombardy	1,441,895	14,262,302	3,982,229	0	19,686,427
Marche	297,157	1,380,032	839,677	2,839	2,519,704
Molise	43,770	398,843	58,612	0	501,225
Piemonte	817,388	4,380,034	1,843,239	4,236	7,044,898
A.P of Bolzano	155,162	448,008	411,841	0	1,015,011
A.P of Trento	27,801	287,807	140,855	0	456,463
Puglia	2,037,911	8,881,410	1,368,804	0	12,288,125
Sardinia	762,032	1,076,976	480,402	0	2,319,411
Sicily	1,470,446	4,283,857	1,986,330	0	7,740,633
Tuscany	1,071,022	9,440,782	1,832,131	0	12,343,935
Umbria	8,183	874,135	84,189	0	966,506
Valle d'Aosta	0	359,945	63,519	0	423,464
Veneto	391,461	6,131,515	2,124,277	0	8,647,254
Total	**14,423,499**	**84,883,729**	**22,140,354**	**7,075**	**121,454,657**

Figure 4.2.2 Reimbursement 2021, percentages by type of agreement

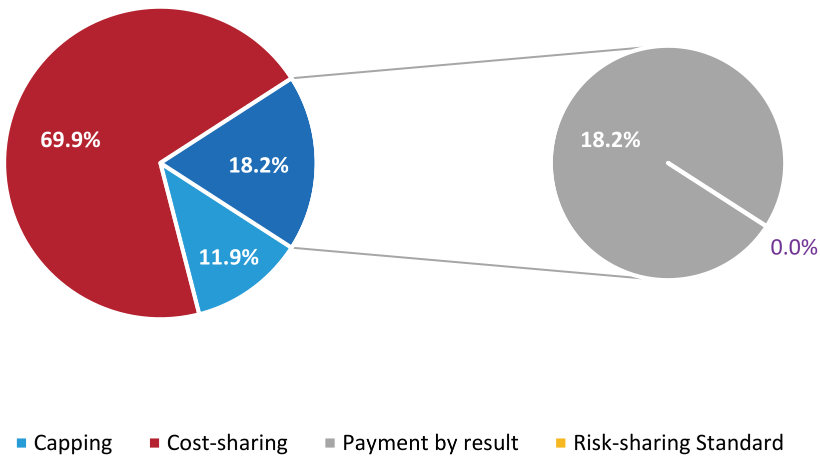
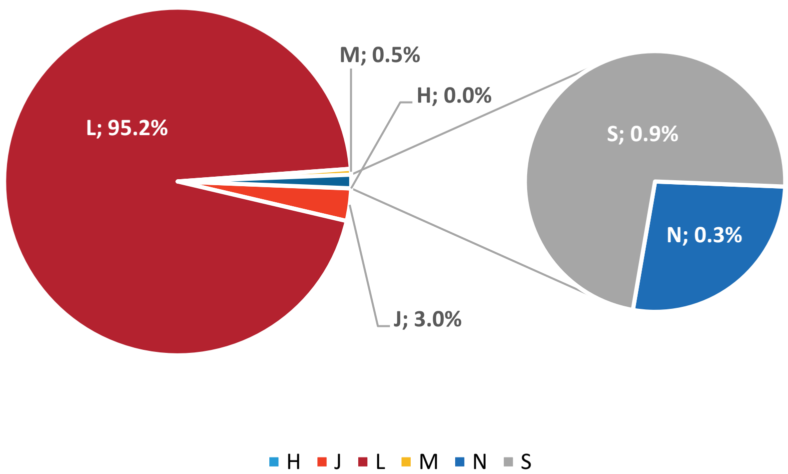


Figure 4.2.3 Reimbursement 2021, percentages for ATC level I



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, the Prices 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 2021 gave rise to reimbursements by companies for the application of expenditure ceilings and price/volume agreements. The medicines involved were a total of 18 (21 *paybacks*), for a total of 201.1 million euros (Tables 4.2.4a, 4.2.4b, 4.2.4c and 4.2.5). In particular, 83.3 million euros were paid by pharmaceutical companies for the application of the expenditure ceilings and the remaining 118.2 million for the application of price/volume agreements. Considering the reimbursement class, 86.9 million euros were paid for class A products and 114.2 million euros for class H products.

In addition, the *payback* percentage with respect to the expenditure ceiling has been reported in Table 4.2.4c.

In addition, a total of 183,833.58 million euros of payback derive from specialties subject to parallel trade (Table 4.2.3a).

Finally, Table 4.2.6 shows the measures that in 2021 gave rise to reimbursements by the companies in application of the “2015 Budget law” agreements. The medicines involved were a total of 41, for a total of 21.6 million euros (Table 4.2.7).

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
Brintellix	(Italian Official Journal General Series n. 80 dated 26-03-2020)	Price/volume
Cluviat	Italian Official Journal General Series n. 89 dated 03-04-2020)	Expenditure ceiling
Darzalex	(Italian Official Journal General Series n.192 dated 12-08-2021)	Price/volume
Kalydeco	(Italian Official Journal General Series n.89 dated 14-04-2021) (Italian Official Journal General Series n.278 dated 22-11-2021)	Expenditure ceiling
Keytruda	(Italian Official Journal General Series n.138 dated 11-06-2021)	Price/volume
Lojuxta	(Italian Official Journal General Series n.192 dated 12-08-2021)	Expenditure ceiling
Lybtayo	(Italian Official Journal General Series n.248 dated 16-10-2021)	Expenditure ceiling
Lysodren	(Italian Official Journal General Series n.28 dated 03-02-2021)	Expenditure ceiling
Oralair	(Italian Official Journal General Series n.138 dated 11-06-2021)	Expenditure ceiling
Orkambi	(Italian Official Journal General Series n.89 dated 14-04-2021) (Italian Official Journal General Series n.289 dated 04-12-2021)	Expenditure ceiling
Perjeta	(Italian Official Journal General Series n.192 dated 12-08 2021)	Price/volume
Samsca	(Italian Official Journal General Series n.57 dated 08-03-2021)	Expenditure ceiling
Striverdi Respimat	(Italian Official Journal General Series n.78 dated 31-03-2021)	Price/volume
Tagrisso	(Italian Official Journal General Series n.78 dated 31-03-2021)	Price/volume
Xadago	(Italian Official Journal General Series n.248 dated 16-10-2021)	Price/volume
Xagrid	(Italian Official Journal General Series n.260 dated 30-10-2021)	Expenditure ceiling
Zavicefta	(Italian Official Journal General Series n.198 dated 19-08-2021)	Expenditure ceiling
Zytiga	(Italian Official Journal General Series n.89 dated 14-04-2021) (Italian Official Journal General Series n.278 dated 22-11-2021) (Italian Official Journal General Series n.278 dated 22-11-2021)	Expenditure ceiling

Table 4.2.3a List of medicines subject to the payback mechanism for the application of expenditure ceilings and price/volume agreements- parallel trade

Company	Italian Official Journal	Type of agreement
GMM FARMA SRL	(Italian Official Journal General Series n.278 dated 22-11-2021	Price/volume
MEDWIN LTD	(Italian Official Journal General Series n.278 dated 22-11-2021)	Price/volume
MEDIFARM	(Italian Official Journal General Series n.289 dated 04-12-2021)	Price/volume

Table 4.2.4a Amounts (*millions of euros*) paid by companies to Regions in 2021 (Class A) - Expenditure ceilings

Region	Kalydeco	Oralair	Orkambi	Lojuxta	Lysodren	Xagrid	Total
Abruzzo	0.06	0.03	1.40		0.00	0.20	1.69
Basilicata	0.28	0.02	0.86		0.00	0.07	1.23
Calabria	1.24	0.05	1.46	0.01	0.00	0.20	2.96
Campania	1.42	0.01	557	0.13	0.00	0.54	7.67
Emilia R.	0.67	0.09	4.39	0.03	0.00	0.44	5.62
Friuli VG	0.11	0.01	1.33		0.00	0.09	1.55
Lazio	1.46	0.05	3.33	0.12	0.00	0.44	5.39
Liguria	0.22	0.00	1.44	0.01	0.00	0.15	1.83
Lombardy	0.76	0.28	9.62	0.03	0.00	0.46	11.14
Marche	0.06	0.02	1.79		0.00	0.24	2.12
Molise		0.01	0.10			0.04	0.14
Piedmont	0.47	0.09	3.95	0.02	0.00	0.43	4.97
A.P of Bolzano	0.05	0.02	0.62		0.00	0.06	0.76
A.P of Trento		0.01	0.85		0.00	0.02	0.88
Puglia	1.37	0.07	4.33	0.05	0.00	0.90	6.72
Sardinia	0.13	0.00	1.28	0.07	0.00	0.17	1.64
Sicily	1.67	0.02	6.57	0.07	0.00	0.36	8.70
Tuscany	0.39	0.04	3.16	0.02	0.00	0.27	3.88
Umbria	0.24	0.02	1.15		0.00	0.17	1.58
Valle d`Aosta		0.00	0.11		0.00	0.01	0.12
Veneto	0.13	0.11	3.16	0.02	0.00	0.32	3.75
Italy	**10.73**	**0.95**	**56.47**	**0.58**	**0.01**	**5.58**	**74.33**

Table 4.2.4b Amounts (*millions of euros*) paid by companies to Regions in 2021 (Class H) - Expenditure ceilings

Region	Cluviat	Libtayo	Samsca	Zytiga	Total
Abruzzo	0.3	43.1	11.2	183.6	238.2
Basilicata		29.8	0.2	68.1	98.1
Calabria		48.6	2.1	206.8	257.5
Campania		228.9	59.2	699.3	987.4
Emilia R.	62.2	136.5	43.8	489.6	732.0
Friuli VG		45.1	38.9	136.3	220.2
Lazio	23.5	99.9	9.4	485.6	618.3
Liguria		70.0	7.0	218.4	295.4
Lombardy	18.1	157.2	49.9	738.8	964.1
Marche	6.2	46.7	32.5	190.0	275.4
Molise		6.5	4.4	38.4	49.4
Piedmont	6.7	62.3	22.4	437.4	528.7
A.P of Bolzano		27.6	3.7	106.8	138.0
A.P of Trento	5.0	3.9	0.4	27.5	36.7
Puglia		197.8	36.5	568.9	803.2
Sardinia	1.0	39.2	7.8	265.9	314.0
Sicily		69.4	34.8	508.8	613.0
Tuscany	11.6	133.3	50.8	502.3	697.9
Umbria		20.4	9.1	97.0	126.5
Valle d'Aosta		0.0	1.0	24.8	25.8
Veneto	39.9	72.0	57.2	440.7	609.8
Italy	**174.3**	**1,538.1**	**482.3**	**6,435.0**	**8,629.7**

Table 4.2.4c Comparison between the amounts paid by companies to the Regions in 2021 with respect to the negotiated expenditure ceiling

Medicine	Amount paid (€)	Expenditure ceiling (€)	Weight of payback on expenditure ceiling (%)
Cluviat	174,348.09	800,000.00	21.79
Kalydeco	2,277,485.50	27,000,000.00	8.44
Kalydeco	8,451,596.60	29,250,000.00	28.89
Libtayo	1,538,094.60	11,900,000.00	12.93
Lojuxta	582,556.50	6,700,000.00	8.69
Lysodren	11,896.39	1,450,000.00	0.82
Oralair	954,803.76	2,800,000.00	34.10
Orkambi	29,436,911.65	33,000,000.00	89.20
Orkambi	27,033,233.90	33,000,000.00	81.92
Samsca	482,261.43	5,000,000.00	9.65
Xagrid	5,580,890.46	5,000,000.00	111.62
Zytiga	6,435,044.47	90,000,000.00	7.15

Table 4.2.5 Amounts (*millions* of euros) paid by companies to Regions in 2021 – Price/volume agreements (Class A and H)

Region	Brintellix	Darzalex	Keytruda	Perjeta	Striverdi Respimat	Tagrisso	Xadago	Zavicefta	Total
Abruzzo	0.32	0.22	0.55	1.85	0.00	0.15	0.32	0.10	3.51
Basilicata	0.06	0.21	0.20	1.59	0.00	0.03	0.06	0.04	2.18
Calabria	0.30	0.32	0.49	2.37	0.01	0.12	0.23	0.11	3.95
Campania	0.79	1.65	2.13	11.21	0.04	0.42	0.44	0.43	17.10
Emilia R.	0.24	1.52	2.52	2.89	0.01	0.58	0.19	0.25	8.20
Friuli VG	0.10	0.34	0.49	0.71	0.01	0.20	0.09	0.05	2.00
Lazio	0.71	1.81	2.62	4.87	0.04	0.64	0.85	0.82	12.35
Liguria	0.26	0.56	0.81	0.78	0.01	0.20	0.19	0.18	2.99
Lombardy	0.83	2.92	4.48	7.28	0.03	1.19	0.93	0.42	18.08
Marche	0.18	0.43	0.79	1.07	0.00	0.20	0.15	0.17	2.99
Molise	0.05	0.10	0.05	0.45	0.00	0.02	0.05	0.01	0.73
Piedmont	0.32	1.45	1.66	1.77	0.02	0.48	0.43	0.53	6.66
A.P. of Bolzano	0.06	0.28	0.28	0.20	0.01	0.06	0.01	0.01	0.91
A.P. of Trento	0.06	0.12	0.12	0.16	0.00	0.04	0.03	0.01	0.55
Puglia	0.45	1.16	1.65	4.99	0.01	0.36	0.52	0.26	9.41
Sardinia	0.23	0.52	0.54	1.19	0.01	0.14	0.15	0.13	2.92
Sicily	0.58	0.97	1.34	3.21	0.02	0.42	0.33	0.58	7.45
Tuscany	0.46	1.25	1.66	2.06	0.02	0.51	0.39	0.47	6.82
Umbria	0.09	0.28	0.49	0.74	0.00	0.10	0.09	0.22	2.02
Valle d’Aosta	0.02		0.05	0.03	0.00	0.01	0.01	0.02	0.14
Veneto	0.33	1.72	1.40	2.33	0.02	0.61	0.41	0.39	7.21
Italy	**6.43**	**17.84**	**24.31**	**51.74**	**0.28**	**6.50**	**5.88**	**5.19**	**118.17**

Table 4.2.5a Amounts (*millions* of euros) paid by companies to Regions in 2021 – Price/volume agreements Parallel trade (Class A)

Region	Payback
Abruzzo	4,459
Basilicata	1,206
Calabria	6,798
Campania	58,591
Emilia R.	3,267
Friuli VG	965
Lazio	32,238
Liguria	6,830
Lombardy	9,306
Marche	7,113
Molise	144
Piedmont	292
A.P of Bolzano	103
A.P of Trento	10,914
Puglia	15,516
Sardinia	1,802
Sicily	10,662
Tuscany	7,942
Umbria	774
Valle d'Aosta	234
Veneto	4,677
Italy	**183,834**

Note: amounts refer to companies MEDIFARM (Alphagan Medifarm, Aromasin, Blopress, Cipralex, Ciproxin, Coversyl, Diamicron, Lansox, Limpidex, Peptazol, Timogel, Xalatan**);** MEDIWIN LTD (Lyrica, Pantorc); GMM FARMA SRL (Alphagan, Augmentin, Brufen, Cardura, Ciproxin, Congrescor, Depakin, Depakin Chrono, Diamicron, Diflucan, Dostinex, Glucobay, Limpidex, Norvasc, Omnic, Pantorc, Peptazol, Singulair, Vasoretic, Xalatan, Zirtec)

Table 4.2.6 List of medicines subject to payback mechanism for the application of expenditure ceilings and "2015 Budget law" agreements

Medicine	Italian Official Journal (O.J.)
Accuretic	Italian Official Journal General Series n.278 dated 22-11-2021
Alendros	Italian Official Journal General Series n.6 dated 09-01-2021
Aprovel	Italian Official Journal General Series n. 81 dated 05-04-2019
Atimos	Italian Official Journal General Series n. 81 dated 05-04-2019
Bonviva	Italian Official Journal General Series n. 81 dated 05-04-2019
Cedravis	Italian Official Journal General Series n. 79 dated 25-3-2020
Cipralex	Italian Official Journal General Series n.260 dated 30-10-2021
Clexane	Italian Official Journal General Series n. 81 dated 05-04-2019
Coaprovel	Italian Official Journal General Series n. 81 dated 05-04-2019
Dumirox	Italian Official Journal General Series n. 81 dated 05-04-2019
Elopram	Italian Official Journal General Series n.260 dated 30-10-2021
Enapren	Italian Official Journal General Series n. 81 dated 05-04-2019
Entact	Italian Official Journal General Series n.260 dated 30-10-2021
Fevarin	Italian Official Journal General Series n. 81 dated 05-04-2019
Flutiformo	Italian Official Journal General Series n.122 dated 24-05-2021
Fluxum	Italian Official Journal General Series n. 81 dated 05-04-2019
Forzaar	Italian Official Journal General Series n. 81 dated 05-04-2019
Fosamax	Italian Official Journal General Series n. 81 dated 05-04-2019
Goltor	Italian Official Journal General Series n. 81 dated 05-04-2019
Gopten	Italian Official Journal General Series n. 81 dated 05-04-2019
Hizaar	Italian Official Journal General Series n. 81 dated 05-04-2019 I
Karvea	Italian Official Journal General Series n. 81 dated 05-04-2019 I
Karvezide	Italian Official Journal General Series n. 81 dated 05-04-2019
Liferol	Italian Official Journal General Series n. 81 dated 05-04-2019
Lortaan	Italian Official Journal General Series n. 81 dated 05-04-2019
Maveral	Italian Official Journal General Series n. 81 dated 05-04-2019
Medeoros	Italian Official Journal General Series n. 213 dated 27-8-2020
Mepral	Italian Official Journal General Series n. 32 dated 8-2-2020
Micardis	Italian Official Journal General Series n.232 dated 28-9-2021
Micardis plus	Italian Official Journal General Series n.232 dated 28-9-2021
Recombinate	Italian Official Journal General Series n. 81 dated 05-04-2019
Seropram	Italian Official Journal General Series n.260 dated 30-10-2021
Sinertec	Italian Official Journal General Series n. 81 dated 05-04-2019
Sinvacor	Italian Official Journal General Series n. 81 dated 05-04-2019
Triatec	Italian Official Journal General Series n. 81 dated 05-04-2019
Triatec hct	Italian Official Journal General Series n. 81 dated 05-04-2019
Urorec	Italian Official Journal General Series n. 81 dated 05-04-2019
Vasoretic	Italian Official Journal General Series n. 81 dated 05-04-2019
Zinadiur	Italian Official Journal General Series n. 38 dated 15-02-2020
Zinadril	Italian Official Journal General Series n. 38 dated 15-02-2020
Zoton	Italian Official Journal General Series n.278 dated 22-11-2021

Table 4.2.7 Amounts paid by companies to the Regions in 2021 for the application of the "2015 Budget law" agreements

Region	Payback 2015 *Budget Law*
Abruzzo	468,893.75
Basilicata	212,337.60
Calabria	816,177.00
Campania	2,443,972.54
Emilia R.	1,168,146.31
Friuli VG	380,652.56
Lazio	2,671,652.48
Liguria	567,192.13
Lombardy	3,183,525.06
Marche	580,663.24
Molise	143,185.10
A.P of Bolzano	107.776,06
A.P of Trento	128,212.81
Piedmont	1,583,410.40
Puglia	1,497,268.89
Sardinia	605,074.29
Sicily	2,012,042.01
Tuscany	1,199,720.10
Umbria	332,086.96
Valle D'Aosta	40,941.81
Veneto	1,497,414.42
Total	**21,640,345.50**

In 2021, the total reimbursements obtained by pharmaceutical companies following the application of the MEAs, both managed through the Registries and through monitoring flows, amounted to 344.4 million euros (Table 4.2.8). The greater contribution is attributable to reimbursements for MEAs managed through monitoring flows, mainly as a result of the application of price/volume agreements.
The *payback* paid by companies for the application of the MEAs affects NHS pharmaceutical expenditure by 1.4% in 2021; if we consider the *payback* relating to MEAs managed though Registries, the impact on NHS expenditure is 0.5%, while those related to MEA managed through monitoring flows is just below 1%.

Table 4.2.8 Impact of MEAs on pharmaceutical expenditure and expenditure overrun in 2021

	2020	2021
MEA reimbursements managed by Registries	114,776,947	121,454,657
MEA reimbursements managed through monitoring flows	228,820,009	222,954,773
Total REIMBURSEMENTS	**343,596,956**	**344,409,430**
Impact on NHS expenditure of MEAs managed by Registries (%)	0.49	0.51
Impact on NHS expenditure of MEAs managed through monitoring flows (%)	0.01	0.93
Total MEA impact on NHS expenditure (%)	1.47	1.44

Section 5

New therapeutic entities and orphan medicines

5.1 New therapeutic entities

An analysis of the new therapeutic entities for the period 2014-2021 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 2014-2021, 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 2021.
2) **Selection of molecules with a single specialty:** For each year, molecules with only one specialty (6-digit marketing authorisation) were considered and therefore molecules with more than one specialty on the market have been excluded. 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:** off-patent specialities 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 2021 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 class A and H molecules:** only molecules with prevalence class A and H in each year were subsequently selected.
6) **Selection of molecules not of known associations of active ingredients**: known associations of active ingredients have been eliminated
7) **Selection of molecules other than vaccines (J07):** molecules relating to "J07" vaccines have been excluded.

In conclusion, according to the criteria described above, the molecules analysed relating to new therapeutic entities followed from 2014 to 2021 in Italy are 218. (Table 5.1.1).

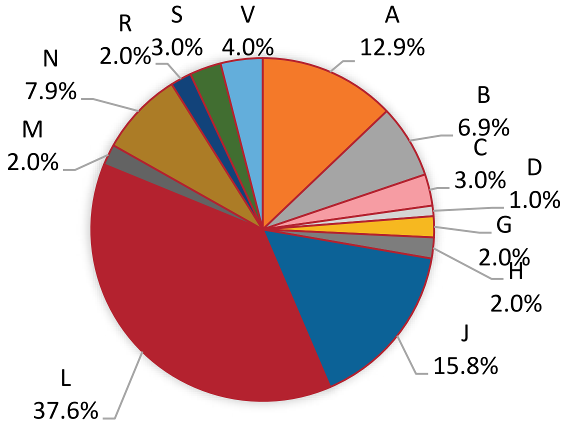
Table 5.1.1 shows for each year the number of new therapeutic entities both incident in the year and prevalent, as the respective movement over time is followed. The percentage of new therapeutic entities that have been granted the innovative status or have been designated and authorised as orphan drugs 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 and 2021, with 33, 33 and 35 new drugs, respectively. The proportion of orphan drugs increased over time from 10 % in 2013 to 27 % in 2021. Innovative medicines account for 16 % of new therapeutic entities marketed in 2021. New therapeutic entities are predominantly classified in class H, about 60 % in 2021.

Table 5.1.1 New therapeutic entities marketed in 2013-2021

	2014	2015	2016	2017	2018	2019	2020	2021
No. new therapeutic entities (Incident and prevalent)	**210**	**219**	**230**	**237**	**248**	**250**	**250**	**274**
No. new therapeutic entities (Incident)	29	24	24	33	33	21	19	35
No. new therapeutic entities	11	15	13	26	22	19	19	11
Of which orphans	28	32	40	51	58	62	65	74
(%)	(13%)	(15%)	(17%)	(22%)	(23%)	(25%)	(26%)	(27%)
Of which innovative	9	17	19	20	37	35	40	45
(%)	(4%)	(8%)	(8%)	(8%)	(15%)	(14%)	(16%)	(16%)
Of which Class A	85	91	94	96	95	90	92	94
(%)	(40%)	(42%)	(41%)	(41%)	(38%)	(36%)	(37%)	(34%)
Of which Class H	125	128	136	141	153	160	158	180
(%)	(60%)	(58%)	(59%)	(59%)	(62%)	(64%)	(63%)	(66%)

Figure 5.1.1 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 2014-2021 is attributable to the category “L: antineoplastics and immunomodulators" which represents 38 % of these drugs, in second place is the category “J: anti-infective for systemic use” with 16 % and third category “A: alimentary tract and metabolism “with 13 %. In a lower share there are the categories”B: blood and blood forming organs ", “C: cardiovascular system” and “R: respiratory system" that, as can be seen in the following tables, are categories of increasing economic importance.

Figure 5.1.1 New therapeutic entities incident and prevalent (N = 218) for ATC level I (period 2014-2021)



The expenditure for new incident and prevalent therapeutic entities amounted to around 5.371 million euros in 2014, up to around 8,291 million euros in 2021 (Table 5.1.2). On average, the expenditure for medicines disbursed under approved care regime from 2014 to 2021 represents a minority share (6 %) of the total expenditure for new therapeutic entities, while medicines purchased by public health facilities constitute the predominant share (94 %). 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 2021, 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 2021) (Table 5.1.3). The impact of the expenditure for new therapeutic entities on the total NHS expenditure recorded in each year from 2014 to 2021 increased over the years from 27 % in 2014 to 35 % in 2021. 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 200.4 million euros and the highest values were recorded in 2015 (512.6 million euros) and in 2017 (415.5 million euros). Among the incident of 2021, the most expensive molecules are elexacaftor/tezacaftor/ivacaftor, a drug for the treatment of cystic fibrosis, two gene therapies (onasemnogene abeparvovec, indicated in spinal muscular atrophy and voretigene neparvovec for the treatment of adults and children with vision loss due to inherited retinal dystrophy) and gilteritinib for the treatment of acute myeloid leukemia with values of respectively, 50, 69 million euros, 12.74 million euros,12.22 million euros and 11.34 million euros.

Tabella 5.1.2 NHS expenditure (in millions) for new therapeutic entities in the period 2013-2021

	2014	2015	2016	2017	2018	2019	2020	2021
New therapeutic entities (Incident and prevalent) (€)	**5,370.9**	**6,778.4**	**6,855.3**	**6,136.4**	**6,760.1**	**8,077.9**	**7,846.4**	**8,291.1**
Of which incident (€)	73.9	512.6	188.8	435.5	156.0	59.2	45.3	131.7
Of which approved class A (€)	583.1	342.7	330.2	396.5	398.5	307.0	307.4	284.8
Of which direct purchases class A (€)	1,337.6	2,676.6	2,650.9	1,794.6	2,021.2	2,688.5	2,274,2	2,256.4
Total class A (€)	1,920.7	3,019.3	2,981.1	2,191.2	2,419.7	2,995.5	2,581.6	2,541.3
Of which approved class H (€)	0.01	0.00	-	0.002	-	0.00	-	0.0
Of which direct purchases class H (€)	3,450.2	3,759.1	3,874.1	3,945.2	4,340.4	5,082.4	5,264.8	5,749.8
Total class H (€)	3,450.2	3,759.1	3,874.1	3,945.2	4,340.4	5,082.4	5,264.8	5,749.8
Of which orphans (%)	8.8	8.8	11.5	16.0	18.5	19.8	23.4	25.8
Of which innovative (%)	3.1	22.5	22.7	16.8	24.5	33.8	29.6	30.3
% on NHS total expenditure	**27.0**	**30.7**	**29.9**	**27.1**	**30.2**	**34.3**	**33.6**	**34.7**

The expenditure variance of new therapeutic entities compared to total NHS expenditure increased on average by 4 %: in particular, from 2016 to 2017 it decreased by 10 % and from 2018 to 2019 it increased by 19 %.

Figure 5.1.2 Annual trend of NHS expenditure for new incident and prevalent therapeutic entities and total NHS expenditure

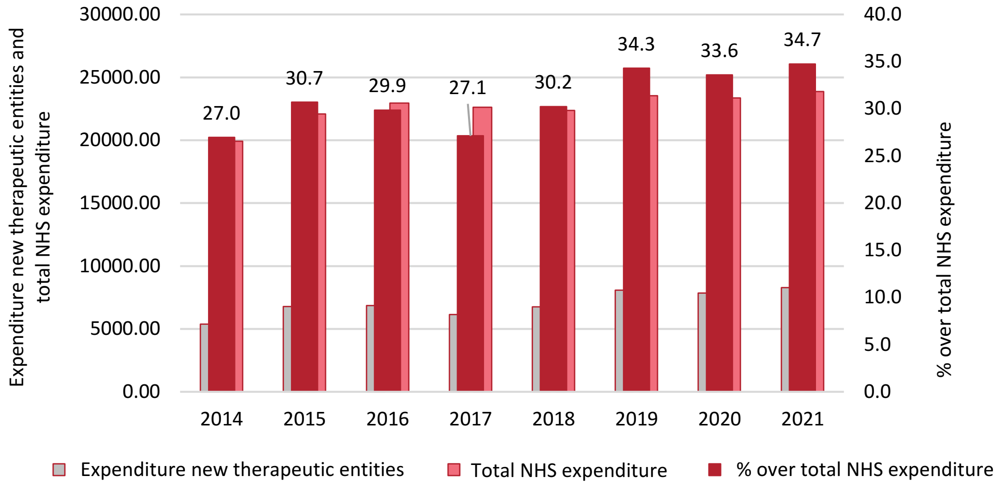
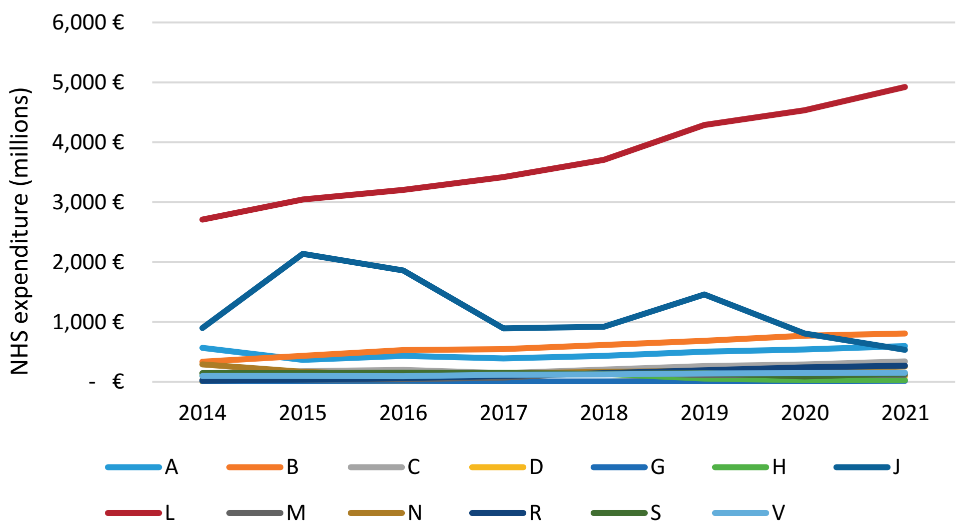


Figure 5.1.3 shows the trend in NHS expenditure for new incident and prevalent therapeutic entities by first level of ATC. As noted in Figure 5.1.3, category L, in addition to being the one with the highest number of medicines from new therapeutic entities, is also the one with the highest expenditure in the 2014-2021 observation period (from 2,709 million euros to 4,922 million euros, increasing by 92 %). The second and third categories, J and A, have different behaviours over time: J increased from 2013 to 2016 and since then a decrease in expenditure (CAGR 2014-2021 of -6.30 %) to 536 million euros in 2021 can be observed; category A grew with a 2014-2021 CAGR of 0.66 %, as well as category B (CAGR 2014-2021 11.56 %), category C (CAGR 2014-2021 11.35 %) and category R (CAGR 2014-2021 36.67 %).

Table 5.1.3 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 to 2021
A	0.66
B	11.56
C	11.35
D	53.57
G	4.66
H	-14.59
J	-6.30
L	7.75
M	17.65
N	-1.45
R	36.67
S	-0.76
V	5.80
Total	**5.58**



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

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 8.26 euros in 2014, to 10.3 euros in 2021. The peak was reached in 2015 reaching 11.97 euros.

Figure 5.1.4 Annual trend of average cost per DDD of new therapeutic entities over the period 2014-2021

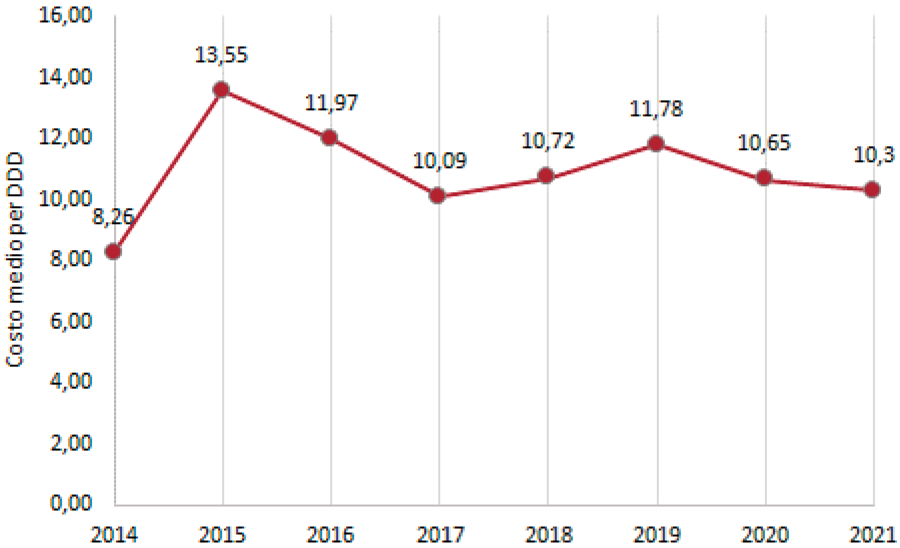


Table 5.1.3 shows the regional distribution of 2021 per capita expenditure of medicines concerning new therapeutic entities. Per capita expenditure on new therapeutic entities at national level was 140 euro, with a wide regional variability: the regions with the highest values are Umbria (161 euro) and Campania (160.6 euro), while the lowest values were recorded in Valle d'Aosta with 103.5 euro and in the AP of Trento with 113.2 euro. The regional expenditure trend from 2014 to 2021 is marked by an average annual positive variation in all regions, which at national level was 6.4 %. The biggest changes were recorded in the AP of Trento (+ 8.3 %), Emilia Romagna (+ 8.1 %) and Umbria (+ 8.0 %). The average DDD cost in 2021 was equal to 10.3 euro at national level, but fluctuates between the minimum value of 7.9 euro of the AP of Trento and a maximum of 16.2 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 number of DDDs registered for this region, probably related to higher-cost drugs.

Table 5.1.4 Regional variability in expenditure and average DDD cost of new therapeutic entities. Year 2021 and comparison 2014-2021

Region	Per capita expenditure 2021	Δ% compared to Italy average	CAGR 2014-2021	Average DDD cost 2021	Δ% compared to Italy average	CAGR 2014-2021
Piedmont	135.7	-29	6.63	10.2	-0.6	4.27
Valle d'Aosta	103.5	-26.0	7.69	10.0	-2.9	5.03
Lombardy	128.1	-8.4	6.44	10.5	1.8	2.90
A.P. Bolzano	134.2	-4.1	6.99	16.2	57.4	4.76
A.P Trento	113.2	-19.0	8.30	7.9	-22.8	-0.12
Veneto	125.8	-10.1	6.76	10.8	5.3	2.76
Friuli VG	144.6	3.4	7.62	10.1	-2.1	2.12
Liguria	143.0	2.3	6.85	10.2	-0.7	3.67
Emilia R.	145.6	4.1	8.14	11.5	11.9	3.15
Tuscany	144.2	3.1	5.55	11.1	8.1	2.81
Umbria	161.0	15.1	8.00	9.9	-3.5	4.52
Marche	147.8	5.7	6.08	10.4	1.0	1.57
Lazio	136.4	-2.5	5.43	9,6	-6.7	2.76
Abruzzo	144.7	3.5	4.92	10.4	1.0	3.46
Molise	140.8	0.7	7.21	10.4	1.0	3.51
Campania	160.6	14.8	6.89	10.6	3.1	4.03
Puglia	155.5	11.2	5.90	10.1	-1.7	2.17
Basilicata	138.7	-0.8	5.87	10.0	-2.9	3.73
Calabria	142.6	2.0	6.07	9.2	-10.4	3.59
Sicily	132.7	-5.2	6.32	9.3	-9.5	4.16
Sardinia	148.5	6.2	4.23	9.4	-8.7	2.38
Italy	**139.9**		**6.39**	**10.3**		**3.19**

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: 218). 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 5.1.5 shows the average turnover from the first year of marketing up to the 5th year. It is observed that the 65 molecules, since market entry, show an upward trend in turnover, rising on average from 0.8 million in the first year of commercialisation to 3.2 million in the last year analysed. 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 more than tripled 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=65)

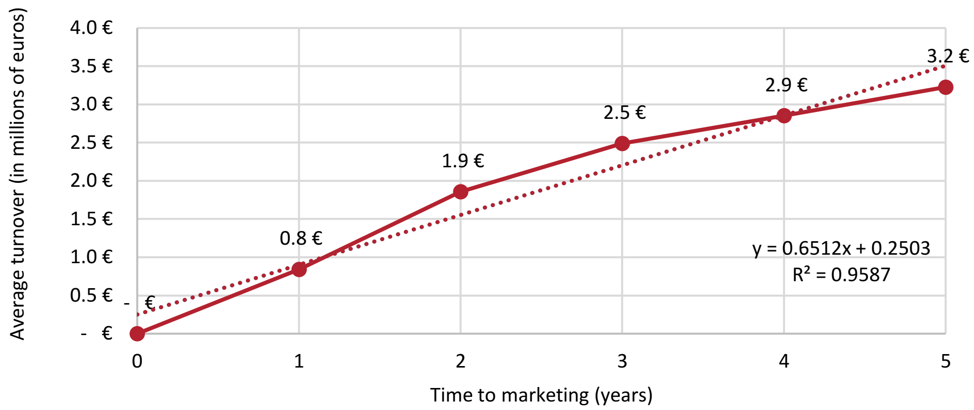


Figure 5.1.6 Percentage ratio between total expenditure at time Ti compared to expenditure at the time of first marketing T1. (molecules with at least 5 observation points; N=65)

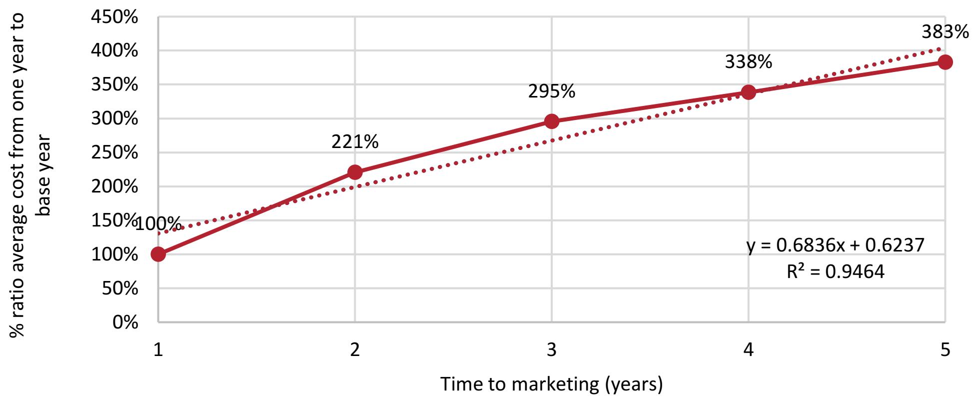
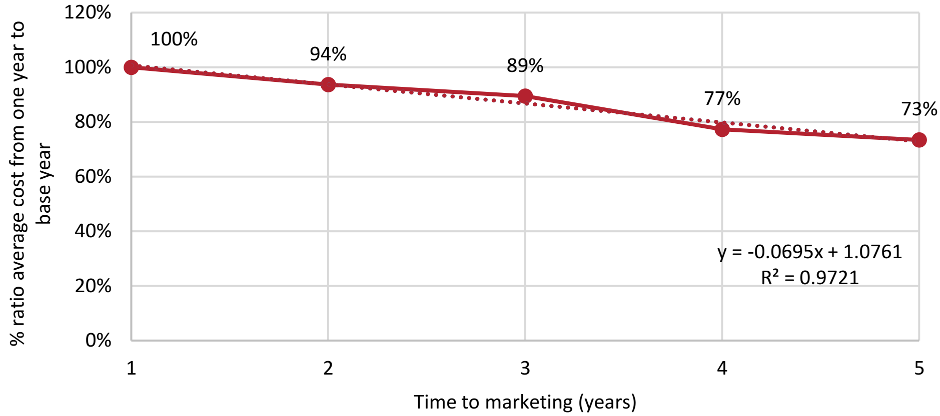


Figure 5.1.7 shows the percentage ratio between the average cost per DDD per year and the average cost in the first year. A downward trend can be observed, with a shift from 94 % in the second year to 73 % in the last year. This trend could be due to the effect of renegotiations, also following extensions of indications and purchasing procedures at regional level.

Figure 5.1.7 Percentage ratio between average DDD cost at time Ti compared to expenditure at the time of first marketing (T1) (molecules with at least 5 observation points; N=65)



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 (ex 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 2021, the EMA granted authorisation for a total of 13 new orphan medicines while AIFA made 18 available. The main therapeutic areas of medicines authorised under the centralised procedure by the EMA were antineoplastic agents (autologous T cell [Abecma], pemigatinib [Pemazyre] and ripretinib [Qinlock], tafasitamab [Minjuvi]), immunology (risdiplan [Evrysdi], selumetinib [Koselugo]) and vosoritide [Voxzogo]), endocrinology (somapacitan [Sogroya]), haematology (pegcetacoplan [Aspaveli]), metabolism (setmelanotide [Imcivree]), ophthalmology (satralizumab [Enspryng]), infectious diseases (artesunate [Artesunate Amivas]) and finally gastroenterology (odevixibat [Bylvay]).

Of the 13 drugs authorised by the EMA, 11 have initiated the process of negotiating the price and reimbursement and 2 are already on the market, including 1 in class C.

As of 31 December 2021, out of a total of 130 orphan medicines authorised by the EMA (Figure 5.2.1 and Figure 5.2.2), 122 were available in Italy of which:

- 24 (19.7%) in class A;
- 56 (45.9%) in class H;
- 12 (9.8%) in class C;
- 30 (24.6%) in class C-nn.

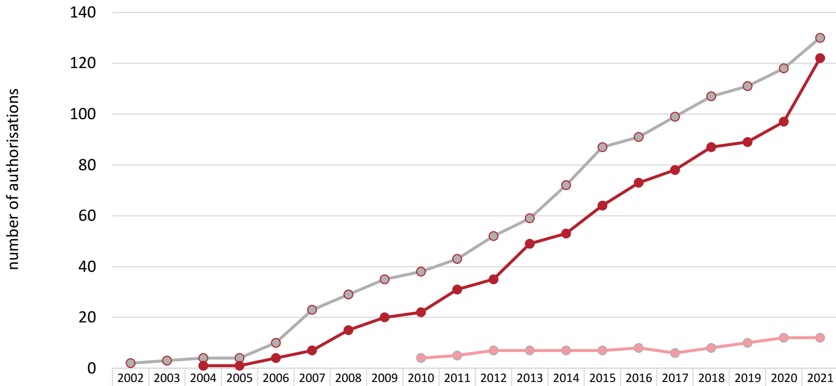
Of the 8 medicines authorised by the EMA but not available in Italy in 2021:

- 4 were marketed starting from 2022;
- 2 are in the phase of definition of price and reimbursement;
- 2 were not the subject of an application by the manufacturing companies for price and reimbursement.

The 4 medicines marketed starting from 2022 are: risdiplam, fedratinib, pretomanid and somapacitan.

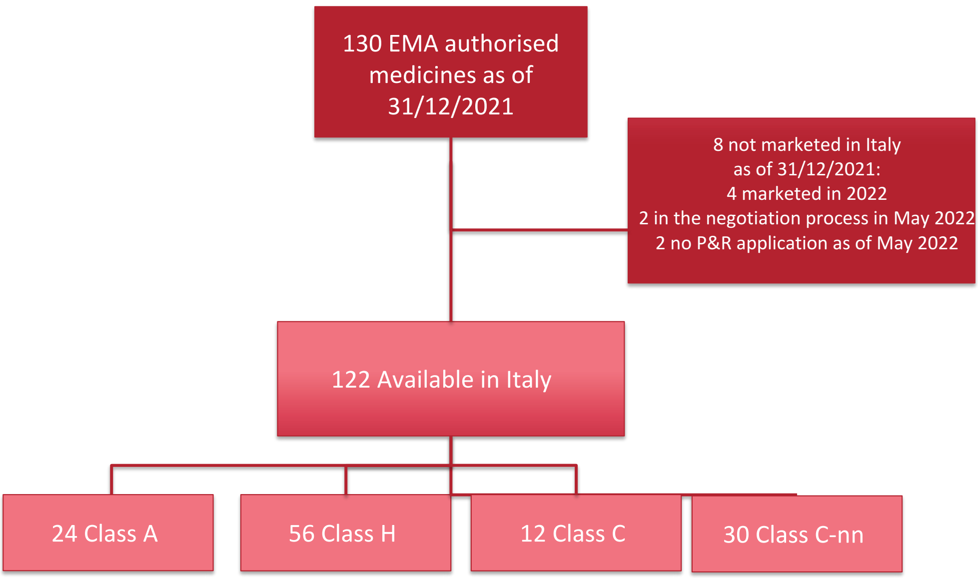
Interestingly, 37.7% of the medicines included in AIFA’s orphan list is subject to a Monitoring Register and 26% of the orphan drugs in the price and reimbursement phase have a *Managed Entry Agreement* (MEA) applied which can be either a financial agreement or an outcome-based agreement. Moreover, about 14% of medicines also obtained the innovativeness requirement (7 innovative oncological medicines and 10 innovative non-oncological medicines).

Figure 5.2.1 Comparison between medicines authorised with EMA centralised procedure and available in Italy (cumulative data 2002-2021)



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
EMA	2	3	4	4	10	23	29	35	38	43	52	59	72	87	91	99	107	111	118	130
AIFA			1	1	4	7	15	20	22	31	35	49	53	64	73	78	87	89	97	122
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
AIFA classe C									4	5	7	7	7	7	8	6	8	10	12	12

Figure 5.2.2 Comparison between number of orphan medicines authorised with EMA and AIFA centralised procedure as of 31 December 2021



Expenditure and consumption of orphan medicines

Table 5.2.1 Expenditure and consumption trend (agreed and direct purchases) for orphan medicines, years 2013-2021 in reimbursement class A-NHS, H-NHS, C, C-NN

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Expenditure orphan medicines (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
% Incidence of orphan medicines on pharmaceutical expenditure	6.4	7.1	6.7	4.2	4.5	5.8	6.8	6.1	6.4
% Incidence orphan direct purchase expenditure vs orphan expenditure (traceability+ OsMed)	100.0	100.0	100.0	99.7	99.6	99.7	99.9	100.0	100.0
Consumption (DDD) orphan medicines (OsMed + traceability, million)	5.6	6.1	6.7	7.0	7.2	8.8	10.1	8.1	8.4
% Incidence orphan medicines on consumption farmaci orfani sul consumo (OsMed + traceability)	0.002	0.002	0.003	0.026	0.026	0.031	0.035	0.029	0.030

The expenditure for orphan medicines, including the purchase by public health structures and the provision under the approved assistance regime, was approximately 1.53 billion euros in 2021 (+9.4% compared to 2020), corresponding to 6.4% of the pharmaceutical expenditure borne by the NHS. The incidence % on the expenditure for class C orphan medicines is equal to 0.94%, showing an increase in 2021 compared to trends of previous years (it was 0.47% in 2016). This is due to the increase in handling of class C drugs in 2021. Consumption of orphan medicines amounted to 8.4 million DDD (+3.7 million compared to the previous year), corresponding to 0.030% of the total consumption of medicines. In 2021 the incidence % on the consumption of class C orphan medicines was 2.2%, showing an increase compared to 2020 when an incidence of 1.39% was recorded (Table 5.2.1).

Table 5.2.2 Consumption and expenditure (approved and direct purchases) for orphan medicines by Region in 2021

Region	Expenditure (millions)	DDD (thousands)	Inc.% expenditure*	% direct purchases	Per capita expenditure	Δ % 21-20	DDD 1000 inhab. Per day	Δ % 21-20
Piedmont	107.4	628.7	7.0	100.0	24.0	4.1	0.4	199.6
Valle d'Aosta	1.9	10.1	0.1	100.0	14.8	34.6	0.2	207.0
Lombardy	253.3	1,244.7	16.5	99.8	25.6	15.9	0.3	208.6
A.P of Bolzano	14.0	75.5	0.9	100.0	28.3	8.9	0.4	200.6
A.P. of Trento	10.7	66.5	0.7	100.0	20.2	22.1	0.3	225.2
Veneto	124.1	699.6	8.1	100.0	25.4	7.2	0.4	209.8
Friuli VG	32.4	202.9	2.1	99.8	25.5	9.4	0.4	221.4
Liguria	45.6	261.7	3.0	100.0	27.3	5.8	0.4	208.2
Emilia R.	141.1	707.5	9.2	100.0	31.4	18.6	0.4	209.1
Tuscany	107.4	602.2	7.0	100.0	27.9	8.5	0.4	207.0
Umbria	29.9	154.9	1.9	99.8	33.0	13.4	0.5	201.0
Marche	43.3	258.4	2.8	99.9	28.0	6.7	0.5	197.5
Lazio	137.4	788.4	9.0	100.0	24.3	7.2	0.4	200.0
Abruzzo	33.2	199.4	2.2	100.0	25.4	16.1	0.4	196.2
Molise	5.8	34.3	0.4	100.0	19.1	4.3	0.3	197.1
Campania	131.4	713.0	8.6	100.0	25.2	7.4	0.4	195.7
Puglia	113.0	626.2	7.4	100.0	29.1	1.4	0.4	197.4
Basilicata	12.5	71.3	0.8	100.0	22.8	3.2	0.4	190.9
Calabria	46.2	242.8	3.0	100.0	25.4	14.0	0.4	205.4
Sicily	106.0	572.7	6.9	100.0	22.6	15.8	0.3	203.2
Sardinia	38.4	203.7	2.5	100.0	23.2	11.0	0.3	198.6
Italy	**1,535.1**	**8,364.5**	**100.0**	**100.0**	**25.9**	**10.2**	**0.4**	**203.5**
North	730.6	3,897.1	47.6	99.9	26.2	12.0	0.4	208.0
Centre	318.0	1,803.9	20.7	100.0	26.6	8.1	0.4	201.9
South and Islands	486.6	2,663.4	31.7	100.0	25.1	8.9	0.4	198.6

* Calculated on the total expenditure of orphan medicines nationwide

In terms of DDD, in 2021 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 Umbria (highest expenditure also in 2020) and Emilia Romagna, with an expenditure, respectively, of 33.0 and 31.4 euros compared to the national average of 25.9 euros, while the Regions with the lowest expenditure are Valle d'Aosta (also in 2020) and Molise with an expenditure of 14.8 and 19.1 euros respectively (Table 5.2.2).

Table 5.2.3 Consumption and expenditure (approved and direct purchases) for Class C* orphan medicines by Region in 2021

Region	DDD (thousands)	Spesa (thousands)	Per capita expenditure	Incidence % on consumption	Incidence % on expenditure
Piedmont	16.1	796	0.18	0.0008056	0.05
Valle d'Aosta	1.5	21	0.16	0.0030453	0.05
Lombardy	31.0	2,719	0.28	0.0007225	0.07
A.P of Bolzano	2.9	322	0.65	0.0015856	0.19
A.P of Trento	2.8	142	0.27	0.0011574	0.08
Veneto	18.2	2,098	0.43	0.0008402	0.12
Friuli VG	3.5	271	0.21	0.0005873	0.06
Liguria	6.0	380	0.23	0.0008288	0.06
Emilia R.	21.1	1,589	0.35	0.0009149	0.09
Tuscany	14.8	-493	-0.13	0.0008141	-0.03
Umbria	5.1	392	0.43	0.0010481	0.10
Marche	10.3	808	0.52	0.0013598	0.12
Lazio	22.1	1,106	0.20	0.0008125	0.05
Abruzzo	6.3	953	0.73	0.0009896	0.17
Campania	12.4	621	0.12	0.0004353	0.03
Puglia	10.0	1,236	0.32	0.0005010	0.07
Basilicata	2.4	92	0.17	0.0008609	0.04
Calabria	1.9	408	0.22	0.0002136	0.05
Sicily	10.8	934	0.20	0.0004732	0.05
Sardinia	2.1	518	0.31	0.0002517	0.07
Italy	**201.4**	**14,913**	**0.25**	**0.0007125**	**0.06**
North	103.2	8,337	0.30	0.0008214	0.08
Centre	52.3	1,813	0.15	0.0009042	0.04
South and Islands	45.9	4,762	0.25	0.0004627	0.06

*excluding medicines in C-NN

The expenditure on class C medicines in 2021 amounted to 14.9 million euro (in 2020 it was 14.3 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 only the centre Regions have per capita values significantly below the national average (0.30 euro per capita in northern regions, compared to 0,15 euro in centre regions and 0.25 in southern regions) (Table 5.2.3)

Table 5.2.4 Top ten Class-C^ orphan medicines per expenditure

Class	Active substance	Expenditure (€)	Consumption (DDD)
C	defibrotide	8,303,868	2,133
C	pitolisant	2,118,112	154,890
C	polatuzumab vedotin	1,806,621	4,200
C	tobramycin	1,090,805	12,274
C	cenegermin	512,116	1,197
C	mannitol	438,747	20,467
C	onasemnogene abeparvovec	260,008	1
C	clormetin	140,140	3,090
C	telotristat	35,923	1,410
	Total top 10 Class-C active substances	**14,706,340**	**199,662**
	Total remaining Class-C active substances *	**-206,169**	**-1,730**
	Total Class- C	**14,912,509**	**201,392**

^ excluding C-NN medicines
* Item “Total remaining Class-C active substances *” includes only product "EVRYSDI" (risdiplam) which generates an expenditure of 104 euros and product “STRENSIQ” (asphotase ALFA) which has a negative expenditure (returns of traceability) equal to -348,480 euro. The total expenditure for these two products therefore has a negative value of -348,376 euro.

The top 10 Class-C active ingredients in 2021 have an expenditure of approximately 14.7 million euro (98.6 %) most of which is associated with the active substance defibrotide, indicated in severe veno-occlusive disease (VOD) in patients undergoing hematopoietic stem cell transplantation. The consumption of the first 10 orphan drugs in Class-C was 199.662 DDDs, representing 99.1 % of the total consumption of orphan drugs in Class-C (Table 5.2.4).

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 2020-2021

Rank	First 30 orphan medicines (molecule)	Prevalent class in 2021	DDD (thousands)	Δ % 21-20	Expenditure (millions)	Δ % 21-20	Incidence % on consumption	Incidence % on expenditure	% direct purchases
1	daratumumab	H	1,611	42.4	240.8	14.1	17.2	14.9	100.0
2	ibrutinib	H	1,548	17.9	201.1	18.0	16.5	12.4	100.0
3	eculizumab	H	166	8.9	127.6	7.9	1.8	7.9	100.0
4	nusinersen	H	193	-11.9	78.5	-15.4	2.1	4.9	100.0
5	ivacaftor	A	156	>100	65.1	55.7	1.7	4.0	100.0
6	pirfenidone	H	890	-5.3	57.3	-5.4	9.5	3.5	100.0
7	macitentan	A	634	0.0	55.6	0.0	6.8	3.4	100.0
8	pomalidomide	H	206	20.1	50.7	-0.4	2.2	3.1	100.0
9	albutrepenonacog alfa	A	43	9.2	47.2	9.1	0.5	2.9	99.8
10	elexacaftor/tezacaftor/ ivacaftor	A	173	-	38.6	-	1.9	2.4	100.0
11	carfilzomib	H	254	-3.0	34.6	-3.1	2.7	2.1	100.0
12	tisagenlecleucel	H	0	79.8	31.0	>100	0.0	1.9	100.0
13	patisiran	H	52	>100	26.7	>100	0.6	1.7	100.0
14	niraparib	H	134	3.0	26.5	1.7	1.4	1.6	100.0
15	ponatinib	H	101	7.8	23.2	5.9	1.1	1.4	100.0
16	migalastat	A	48	11.1	22.2	11.1	0.5	1.4	100.0
17	Brentuximabvedotin	H	97	-5.5	20.8	-30.7	1.0	1.3	100.0
18	letermovir	H	55	9.5	19.4	3.4	0.6	1.2	100.0
19	ataluren	H	12	8.1	18.5	8.5	0.1	1.1	100.0
20	eliglustat	A	29	9.4	18.3	9.4	0.3	1.1	100.0
21	axicabtagene ciloleucel	H	0	69.6	17.4	>100	0.0	1.1	100.0
22	caplacizumab	H	5	86.5	17.1	92.3	0.1	1.1	100.0
23	isavuconazolo	H	154	20.5	17.1	25.0	1.6	1.1	99.8
24	eftrenonacog alfa	A	25	0.0	17.0	-0.1	0.3	1.0	100.0
25	velaglucerasi alfa	H	15	-0.4	16.9	6.1	0.2	1.0	100.0
26	elosulfase alfa	H	5	5.5	16.1	5.5	0.1	1.0	100.0

27	sorafenib	H	132	-24.7	15.7	-25.3	1.4	1.0	100.0
28	obinutuzumab	H	236	15.6	15.3	15.6	2.5	0.9	100.0
29	midostaurin	H	29	-0.9	15.1	-4.2	0.3	0.9	100.0
30	obeticholic acid	H	177	97.3	14.7	93.5	1.9	0.9	100.0
	Total first 30		**7,182**	**18.2**	**1,366.1**	**15.2**	**76.8**	**84.5**	**100.0**
	Other orphans		2,174	47.2	251.3	50.3	23.2	15.5	99.7
	Total orphans		**9,356**	**23.9**	**1,617.4**	**19.6**	**100.0**	**100.0**	100.0

The main active ingredients with the greatest consumption and expenditure in 2021 are again daratumumab and ibrutinib with an increase, respectively, of expenditure of 14.1% and 18.0% and consumption of 42.4% and 17.9%. Axicabtagene ciloleucel is the active ingredient that records the largest variance in expenditure together with patisiran, tisagenleucel, while as regards consumption, the major variance is recorded for patisiran and ivacaftor, both >100% (Table 5.2.5).

Table 5.2.6 Top 20 active principles (A and H) by expenditure variance in 2021 compared to 2020

Prevalent class	Active substance	Expenditure (millions)	Δ % 21-20	DDD (thousands)	Δ % 21-20
A	cannabidiol	1.7	>100	35.0	>100
H	cerliponase alfa	4.1	>100	3.1	>100
A	elexacaftor/tezacaftor/ivacaftor	38.6	>100	173.2	>100
H	givosiran	4.6	>100	5.3	>100
H	mogamulizumab	3.8	>100	13.0	>100
H	onasemnogene abeparvovec	12.7	>100	0.1	>100
H	voretigene neparvovec	12.2	>100	0.0	>100
H	gilteritinib	11.3	>100	34.8	>100
A	lanadelumab	13.2	>100	23.9	>100
H	axicabtagene ciloleucel	17.4	>100	0.1	69.6
H	inotersen	3.2	>100	9.2	>100
A	Chenodeoxycholic acid	2.5	>100	10.1	>100
H	patisiran	26.7	>100	51.7	>100
H	metreleptin	1.6	>100	2.1	>100
H	tisagenlecleucel	31.0	>100	0.2	79.8
H	burosumab	11.6	>100	61.7	>100
H	obeticholic acid	14.7	93.5	177.2	97.3
H	caplacizumab	17.1	92.3	5.1	86.5
H	gemtuzumab ozogamicin	4.3	56	0.3	56
A	ivacaftor	65.1	55.7	156.4	>100

* selected among active principles with an expenditure higher than 1 million euros

Among the top 20 active substances of Class A and H with the greatest variance in expenditure in 2021, the active substances with the highest values are ivacaftor with 65.1 million euros and a variance in expenditure of 55.7 % and elexacaftor/tezacaftor/ivacaftor with 38.6 million euros and a variance in expenditure > 100 % (Table 5.2.6).

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		1	1	1	1	2	1	1	1	2	2	1	1	1	1	2	3	1	1	1
2	ibrutinib	2	3	2	2	2	2	1	2	2	2	1	1	2	2	2	2	1	2	2	2	3
3	eculizumab	3	1	3	3	5	4	3	3	3	3	3	3	4	3	3	3	5	1	4	5	2
4	nusinersen	5		4	4	7	3	4	7	7	8	5	4	3	10	5	6	9	17	8	7	7
5	ivacaftor	8	15	9	5	4	8	8	8	8	7	10	8	5	9	13	5	3	4	3	3	12
6	pirfenidone	4	7	12	17	10	17	13	10	9	5	7	6	6	4	4	7	7	5	5	6	6
7	macitentan	6	6	8	8	11	6	5	6	4	9	12	5	14	5	6	15	6	6	6	12	5
8	pomalidomide	7		11	6	38	5	9	9	5	4	6	10	8	8	8	13	8	16	9	8	8
9	albutrepenona-cog alfa	13		7	48		7	6	4	6	6	18	12	12	7		10	4		11	14	
10	elexacaftor/tezacaftor /ivacaftor	14	14	10	7	3	9	7	13	11	12	28	7	11	11	9	16	10	7	15	11	15
11	carfilzomib	9	8	13	14	13	13	22	14	13	11	15	20	15	18	20	9	11	8	12	9	10
12	tisagenlecleucel	24		5			24	31	5	10	34	4	41	13	19		33	54		10	26	36
13	patisiran	33		20			26	12	20	16	28		15	7	15	7	34	17		51	4	
14	niraparib	16	9	19	10	12	16	11	21	14	15	21	16	10	16	10	19	12	20	18	13	17
15	ponatinib	21	12	25	11	24	28	18	32	18	19	23	17	18	12	14	17	13	14	7	10	32
16	migalastat	10	4	17			21	26	53	20	22	20		19	58	12	8	28		24	18	19
17	brentuximab vedotin	20	21	26	12	23	12	20	17	17	18	19	13	31	13	28	18	31	13	13	31	16
18	letermovir	29		14	9		25	15	16	29	21	8	14	24	25	19	36	22	37	19	36	20
19	ataluren	15		29			10	16	23	15	50		9	29	21		21	23	33	16	32	
20	eliglustat	17		22	18	9	11	25	36	19	27	17		17			50	46	19	38	16	9
21	axicabtagene ciloleucel	75		6			54		67	12	33	33	64	25	33		79			72	37	
22	caplacizumab	30	5	23			36		11	27	44	25	36	43	14	22	31	18	38	22	21	4
23	isavuconazolo	26		16	22	33	15	29	28	31	17	14	32	16	17	26	27	38	23	31	40	39
24	eftrenonacog alfa	11		21			42	49	18	46	35		26	21	6		25	14	18	56	20	
25	velaglucerasi alfa	48		33	19	8	38	21	52	40	23	13	11	38			14	15		17	15	14
26	elosulfase alfa	18	22	31		6	55			22	10	9	18	49			24	50	30	14	17	27
27	sorafenib	22		24	31	14	27	14	37	21	38	38	30	35	24	17	23	37	12	28	22	13
28	obinutuzumab	23		38	32	18	31	24	26	38	25	24	23	20	20	23	12	33	32	29	28	26
29	midostaurin	12		30	34	19	33	23	34	24	36	11	21	27	55	21	35	20	41	43	27	42
30	obeticholic acid	25	11	28	23	16	40	27	19	28	29	22	31	22	27	18	38	26	15	23	25	22

Analysing the first 30 orphan molecules by expense, a different behaviour among the different Regions can be observed. Almost all molecules are ranked differently in the various regions. The most significant cases concerns axicabtagene ciloleucel, ranked 75 in Piedmont, 54 in Veneto, 64 in Marche, 79 in Campania and 72 in Calabria compared to rank 21 of the Italian average (Table 5.2.7)

Table 5.2.8 2021 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	2		1	2	1	1	2	1	1	2	2	3	2	2	1	1	2	2	1	1	1
2	ibrutinib	1	1	2	1	2	2	1	2	2	1	1	1	1	3	2	3	1	1	3	2	3
3	pirfenidone	4	4	3	5	3	6	7	4	4	3	4	2	3	1	3	4	3	3	2	3	2
4	Hydrocortisone	3	5	10	23	13	4	4	6	6	6	3	5	4	4	5	2	5	4	5	4	5
5	macitentan	5	3	4	3	6	3	3	3	3	5	5	4	6	5	4	6	4	5	4	5	4
6	ciclosporin	15		5	10	4	5	5	5	5	4	32	6	18	36		9	12		10	8	19
7	carfilzomib	7	7	9	12	12	9	17	10	9	7	11	15	15	9	18	7	7	7	8	6	6
8	obinutuzumab	9		16	21	9	10	8	8	17	9	6	10	7	6	20	5	11	14	11	9	12
9	riociguat	6		7	4	15	11	6	7	41	10	14	20	9	13	7	8	6	32	6	11	11
10	pomalidomide	11		12	11	39	8	14	12	7	8	8	12	12	7	6	14	8	18	12	12	8
11	nusinersen	14		8	7	16	7	11	16	14	19	13	7	5	20	8	10	18	26	20	16	10
12	obeticholic acid	12	9	15	16	7	18	15	9	10	14	9	21	8	15	14	23	10	11	9	15	13
13	elexacaftor/tezacaftor/ivacaftor	19	16	11	9	5	12	12	14	13	13	24	8	16	12	10	16	13	8	14	13	14
14	eculizumab	8	6	14	8	17	21	16	19	8	11	15	11	20	11	9	12	17	9	16	21	9
15	ivacaftor	20	18	18	14	11	22	19	17	16	16	18	18	14	17	16	13	9	6	7	7	18
16	pitolisant	13	2	13	6	8	15	24	13	11	15	10	14	11	10		21	26	12	39	19	20
17	isavuconazolE	17		6	20	36	13	18	21	18	12	7	25	10	8	25	15	27	15	19	25	22
18	niraparib	18	14	19	13	14	23	13	22	15	20	17	17	13	14	11	19	15	19	15	18	16
19	sorafenib	16		17	22	10	19	10	26	12	24	23	22	24	16	15	11	22	10	17	17	7
20	ponatinib	24	15	23	15	22	26	20	30	20	22	21	19	17	18	19	17	16	16	13	14	29
21	brentuximab vedotin	22	21	22	19	30	20	21	20	19	21	19	16	22	19	28	20	24	13	18	24	15
22	ketoconazolE	10		21		18	17	9	11	23	26	12	9	30	22		27	19		24	32	37
23	pasireotide	21	20	26	26	31	14	34	15	37	25	16	26	19	21		24	30	24	31	20	27
24	burosumab	30		45	27		24		57	25	17			50	31		18	14		21	22	28

25	ixazomib	26		30	35	21	25	23	18	29	23	26	40	25	29		26	21	22	34	23	23
26	letermovir	31		24	17		29	22	23	27	27	28	23	26	25	22	32	29	35	23	29	24
27	patisiran	41		32			35	27	31	24	35		29	21	24	13	39	31		50	10	
28	migalastat	23	12	27			32	38	52	28	32	25		28	59	17	22	35		27	26	26
29	tafamidis	28		25	38		42	29	27	21	33		30	23	39	12	28	28		40	31	
30	carglumic acid	53		20	44	41	16		36	72	18	30	28			27	25	59			47	

The first active substances for consumption were again in 2021 ibrutinib, daratumumab and pirfenidone with moderate variability in regional ranks (Table 5.2.8). Orphan medicines also meeting the innovativeness requirement generated an expenditure in 2021 amounting to 477.4 million euros, an increase compared to 2020 in which the expenditure was equal to 373.5 million euros, in line with the increase in consumption (Table 5.2.9). In 2021, medicines meeting the innovativeness requirement were 17, compared to 11 in 2020 and 9 in 2019. Of these innovative orphan medicines, daratumumab and nusinersen are also among the top 30 most expensive orphan medicines, ranking first and fourth respectively.

Table 5.2.9 Orphan medicines accessing the fund for oncology and non-oncology innovative medicines: expenditure and consumption, years 2018-2021 (direct purchases)

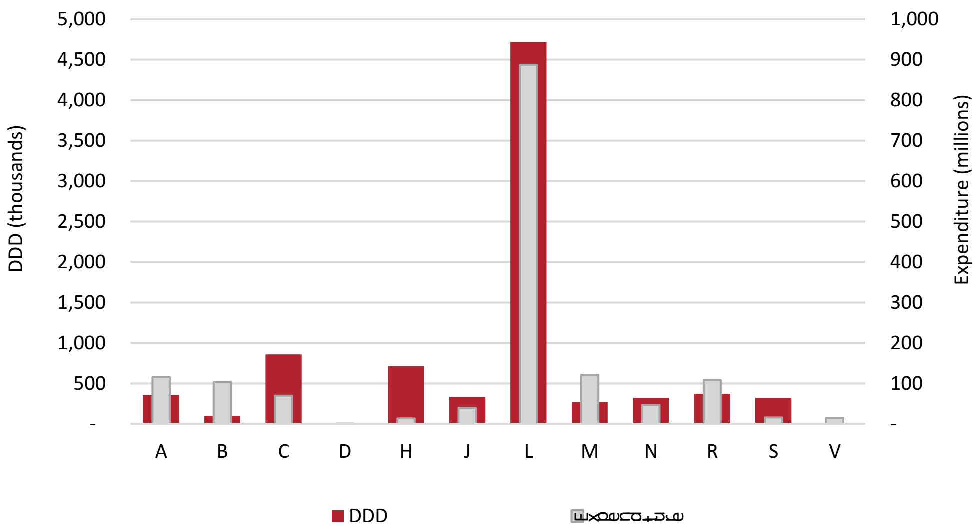
Active substance	Expenditure (millions)				DDD			
	2018	2019	2020	2021	2018	2019	2020	2021
axicabtagene ciloleucel	0.00	0.00	3.44	17.43	0	0	56	95
cenegermin	3.64	4.04	2.79	0.20	13,104	15,232	10,976	784
cerliponase alfa	0.00	0.00	0.00	4.13	0	0	0	3,101
cytarabine/daunorubicin	0.00	2.44	8.55	9.15	0	608	2,249	2,396
daratumumab	58.28	156.32	211.02	239.49	312,103	838,428	1,131,465	1,596,298
dinutuximab beta	0.00	3.22	5.13	3.38	0	926	1,414	886
elexacaftor/tezacaftor/ivacaftor	0.00	0.00	0.00	36.44	0	0	0	167,692
givosiran	0.00	0.00	0.00	4.57	0	0	0	5,344
ibrutinib	111.56	0.00	0.00	0.00	757,150	0	0	0
ivacaftor	11.10	0.00	0.00	40.03	16,492	0	0	119,215
letermovir	0.01	10.79	18.75	15.14	1	26,653	50,020	42,417
Lutezio oxodotreotide (177lu)	0.00	3.49	15.14	13.22	0	244	948	935
midostaurin	1.23	12.59	15.75	10.75	2,296	23,543	29,443	20,182
nusinersen	92.11	102.25	70.23	0.00	242,880	242,400	166,320	0
onasemnogene abeparvovec	0.00	0.00	0.00	12.48	0	0	0	49
patisiran	0.00	0.00	9.49	26.69	0	0	18,400	51,720
pomalidomide	18.63	0.00	0.00	0.00	61,859	0	0	0
tafamidis	0.00	0.00	0.00	1.13	0	0	0	5,790
tisagenlecleucel	0.00	1.19	13.24	30.95	0	12	84	151
voretigene neparvovec	0.00	0.00	0.00	12.22	0	0	0	41
Total	296.6	296.3	373.5	477.4	1,405,884.9	1,148,045.8	1,411,374.7	2,017,094.8

Expenditure for orphan drugs accessing funds increased in 2021 for both oncology and non-oncology innovative medicines. Although expenditure on innovative oncology drugs is higher than that of innovative non-oncology drugs, in 2021 the % increase compared to 2020 is higher for innovative non-oncological drugs (51.1 %) (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 2020-2021

Type of medicine	Expenditure		Δ %	DDD		Δ %
	2020	2021	21-20	2020	2021	21-20
Innovative oncology medicines	272	324	19.1	1,165,659	1,620,943	3.,1
Innovative non-oncology medicines	101	153	51.1	245,716	396,152	61.2

Figure 5.2.3 Expenditure and consumption of orphan medicines in Italy for ATC level I, year 2021 (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

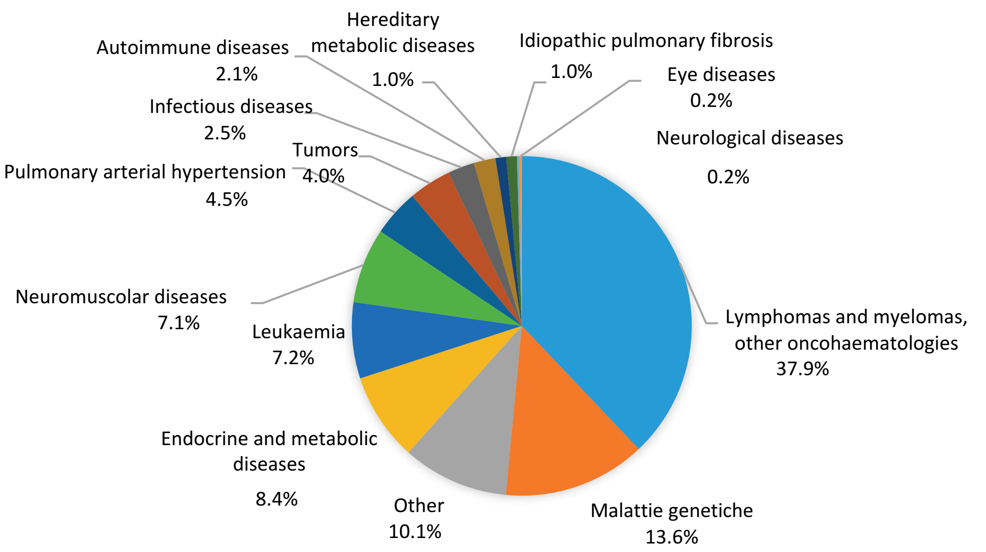
As regards therapeutic classes, the major expenditure was covered by antineoplastic agents and immuno-modulators (57.8%), followed by musculo-skeletal system medicines (7.9%), gastrointestinal tract and metabolism medicines (7.5%) and other (26.8%).

As regards consumption, the classes concerned are antineoplastics and immuno-modulators (56.4%), cardiovascular system medicines (10.3%) and systemic hormonal preparations, excluding sex hormones (8.6%), while the remaining 24.6% of consumption is represented by other (Figure 5.2.3).

Table 5.2.11 Expenditure and consumption of orphan medicines in Italy by therapeutic area: year 2021 (Table and Figure) (Class A, H, C, C-NN)

Therapeutic Area	Expenditure	Expenditure (millions)	Δ % 21-20	DDD	DDD (thousands)	Δ % 21-20	Per capita expenditure	DDD 1000 inhab. Per day	Inc.% expenditure *
Lymphomas and myelomas, other oncohaematologies	582,059,727	582	9.0	3,549,934	3,550	16.26	9.83	0.16	37.92
Genetic diseases	208,632,125	209	59.4	566,293	566	125.59	3.52	0.03	13.59
Other	155,185,001	155	24.4	210,874	211	24.27	2.62	0.01	10.11
Hereditary metabolic diseases	128,633,470	129	23.7	267,279	267	-5.57	2.17	0.01	8.38
Leukaemia	111,287,399	111	10.9	452,341	452	14.24	1.88	0.02	7.25
Neuromuscular diseases	109,740,516	110	-0.1	205,324	205	-10.85	1.85	0.01	7.15
Pulmonary arterial hypertension	68,667,795	69	2.1	858,305	858	2.85	1.16	0.04	4.47
Tumors	62,133,058	62	-8.4	271,763	272	-12.64	1.05	0.01	4.05
Infectious diseases	38,803,587	39	16.0	236,687	237	25.69	0.66	0.01	2.53
Autoimmune diseases	31,842,197	32	92.9	182,323	182	97.01	0.54	0.01	2.07
Endocrine and metabolic diseases	15,726,030	16	-12.3	811,576	812	-5.37	0.27	0.04	1.02
Idiopathic pulmonary fibrosis	15,432,004	15	-82.6	240,550	241	-81.60	0.26	0.01	1.01
Neurological diseases	3,778,895	4	114.2	189,876	190	44.54	0.06	0.01	0.25
Eye diseases	3,201,082	3	-41.4	321,336	321	1,004.51	0.05	0.01	0.21
Total	**1,535,122,888**	**1,535**	**9.4**	**8,364,460**	**8,364**	**2.82**	**25.92**	**0.39**	**100.00**

*Calculated on the total expenditure of orphan medicines nationwide

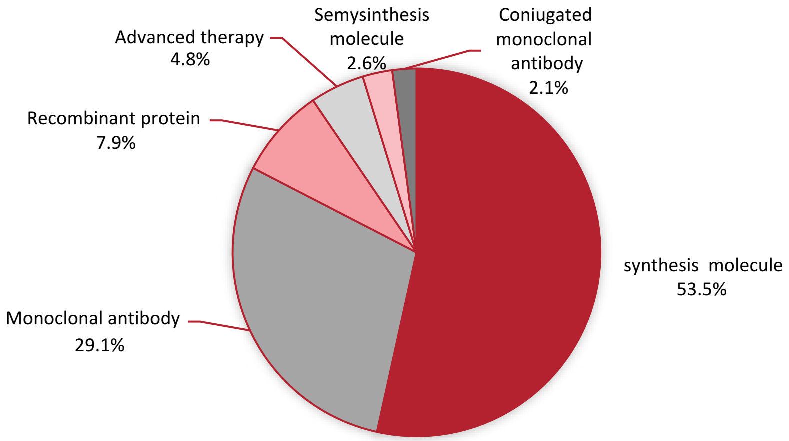


A further analysis of the distribution of orphan medicines expenditure by therapeutic area reveals that the highest incidence is found for medicines intended for the treatment of lymphomas, myelomas and genetic diseases (37.9% and 13.6% respectively), in line with the trend of the previous year. On the consumption side, the first in the ranking are medicines used in lymphomas, myelomas and other oncohaematologic diseases, followed by those for pulmonary arterial hypertension and endocrine and metabolic diseases (Table and Figure 5.2.11).

Analysis by product type shows that most orphan medicines are synthesis molecules (53.4% of incidence on expenditure), followed by monoclonal antibodies (29.1% of incidence on expenditure) (Table and Figure 5.2.12). Compared to 2020, there is a slight decrease in both the expenditure and consumption of synthetic molecules, while an increase is recorded for monoclonal antibodies.

Table 5.2.12 Expenditure and consumption of orphan medicines in Italy by type, year 2021 (Table and Figure) (Class A, H, C, C-NN)

Type of medicine	No. Of molecules	Expenditure (millions)	Δ % 21-20	DDD (thousands)	Δ % 21-20	Per capita expenditure	DDD 1000 inhab. Per day	Inc.% expenditure*
Synthesis molecule	58	821	-0.7	5,490	-11.23	13.85	0.25	53.46
Monoclonal antibody	11	447	17.9	2,138	38.72	7.55	0.10	29.13
Recombinant protein	14	121	6.7	198	-15.35	2.05	0.01	7.90
Advanced therapy	7	74	340.9	0	142.14	1.24	0.00	4.79
Semisynthesis molecule	9	40	44.1	428	574.42	0.68	0.02	2.61
Conjugated monoclonal antibodies	5	32	-17.4	110	-2.21	0.55	0.01	2.11
Total	**104**	**1.535**	**9.4**	**8,364**	**2.82**	**25.92**	**0.39**	**100.00**



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 authorized 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 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 foreseen 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 affordability and appropriateness.

Inclusion is carried out by AIFA upon documented request by Patient Associations, Scientific Societies, Health Authorities, Universities or upon 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 life-threatening conditions, when, according to the physician, 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 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 2021, 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 2021, intended for the treatment of rare diseases, both with and without orphan status.

Active ingredient	Therapeutic indication
cabozantinib	Treatment of patients with radioiodine-refractory differentiated thyroid cancer, progressing after up to two previous lines of therapy with vascular endothelial growth factor receptor (VEGFR) drugs
lenalidomide	At 10 mg per day dosage, on days 1 to 21 (of 28-day cycles), as maintenance treatment for adult patients with newly diagnosed multiple myeloma after autologous stem cell transplantation
venetoclax	Treatment of relapsed/refractory acute myeloid leukemia in combination with azacitidine or decitabine
peginterferone alfa 2 a (Pegasys)	Treatment of hairy cell leukemia

Table 5.2.14 Medicines intended for the treatment of rare diseases for which a program was activated in 2021 pursuant to Ministerial Decree 7th September 2017

Active substance (trade name)	Therapeutic indication	No. of patients included in the program
CARCIK-CD19 (Allogeneic T lymphocytes genetically engineered to express a specific CAR CD19 receptor)	Treatment of adult and paediatric patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (BCP-ALL) after Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for whom authorised therapeutic alternatives are not available	9
pralsetinib (Gavreto)	Treatment of adult patients suffering from advanced or metastatic RET-mutant medullary thyroid cancer (MTC) or RET fusion-positive thyroid cancer, who require systemic therapy	20
tebentafusp (Kimmtrak)*	Treatment of adult patients with HLA-A*02:01 positive metastatic uveal melanoma	16
zanubrutinib (Brukinsa)	Treatment of adult patients with Waldenström macroglobulinemia, for whom no authorised therapeutic alternatives are available	17
retifanlimab (Zynyz) *	Treatment of adult patients with squamous carcinoma of the anal canal (SCAC) who progressed following platinum-based chemotherapy	2
efgartigimod*	Treatment of patients with generalised Myasthenia Gravis (gMG), who do not benefit from currently available therapies	3
avalglucosidasi alfa (Nexviadyme)*	Enzyme replacement therapy for patients with Pompe disease who have demonstrated clinical decline while on treatment with alglucosidase alfa	2
difelikefalin (Kapruvia)	Treatment of pruritus associated with chronic kidney disease in adults on hemodialysis	0
olipudase alfa*	Enzyme replacement therapy for adult and paediatric patients (from 3 years of age) with chronic acid sphiningomielinase deficiency (ASMD)	3

* medicines granted orphan designation by the COMP

During the year 2021, 9 compassionate use programs were opened for rare diseases, 5 of which concerned medicines granted orphan designation by the COMP, for a total of 72 treated patients.

Table 5.2.15 Number of requests for access to the fund and number of actual accesses obtained in the year 2021

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
2021	1731	1349	1010	788

The resources allocated annually to the Fund have decreased over the years, and have halved from just over 20 million made available in 2010 to 10,651,389 euros in 2021. In face of such reduction, over time there has been a steady increase in requests for access to the Fund and, in the last two years, the reimbursements authorised to the NHS facilities have exceeded 50 million euros. The reduction in the capacity of the Fund for year 2021 was also affected by the decrease in promotional activities by pharmaceutical companies due to the pandemic. For these reasons, during 2021, activities related to the 5 % fund were temporarily suspended in order to initiate a process of rethinking and of simplification/optimisation of the system, with a particular effort to redefine rules and criteria to be used. New access criteria have also been defined to protect the sustainability of this tool designed 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, that is, the treatment of individual cases with an important or maximum therapeutic need.

The number of requests for access to the fund received during 2021 was 2.125; of these 1,731 concerned patients affected by rare disease, 1,349 patients with rare cancer. The fund was authorised for 1,010 applications related to rare diseases and 788 related to rare cancers.

Table 5.2.16 Top 10 medicines by number of requests for access to the 5% fund in year 2021

Medicine/Active substance	No. of requests
venetoclax (alone or in combination)	297
pembrolizumab (alone or in combination)	245
nivolumab (alone or in combination)	225
ruxolitinib (alone or in combination)	92
Bulevirtide	60
trifluridina/tipiracile	59
Ivosidenib	53
nintedanib	51
elexacaftor + ivacaftor + tezacaftor (alone or in combination)	51
olaparib	47

Table 5.2.17 Top 10 medicines with the greatest expenditure impact on the AIFA 5% fund for year 2021

Medicine/Active substance	Authorised expenditure (€)
venetoclax (alone or in combination)	4,403,173.95
tagraxofusp	3,822,995.00
ivosidenib	3,063,715.38
elexacaftor + ivacaftor + tezacaftor (alone or in combination)	2,906,169.27
eculizumab	2,829,374.48
pembrolizumab (alone or in combination)	2,708,290.13
nivolumab (alone or in combination)	2,663,710.83
blinatumomab	2,623,381.54
sebelipase alfa	2,606,303.12
bulevirtide	2,355,894.00

As can be seen from Tables 5.2.16 and 5.2.17, most of the requests concern the active ingredients venetoclax, nivolumab, pembrolizumab and ruxolitinib.

Venetoclax, which is also the active ingredient with the highest number of requests, is among the top 10 active ingredients by expense, followed by tagraxofusp, with an expenditure of 3,822,995.00 €.

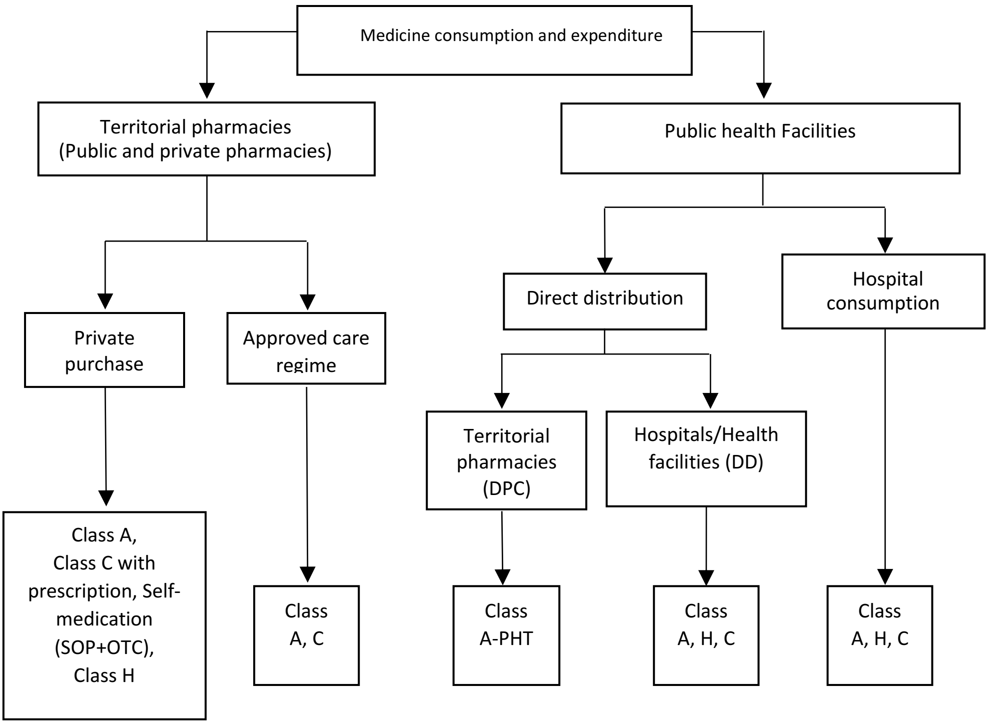
Appendix 2

Data source and methods

1. Pharmaceutical consumption and expenditure data

The 2021 National Report on Medicines Use in Italy provides a summary of data on consumption and expenditure of medicines supplied by the National Health Service (NHS) under approved care regime, direct and “on behalf” (per conto) and hospital distribution (Figure 1.1). Moreover, this Report describes consumption and expenditure of Class C medicines purchased directly by the citizen, in addition to the private purchase of Class A-H medicines.

Figure 1.1 Summary of Report data



The description of medicine consumption made available by the Report is based on the analysis and integration of data collected through different information flows:

- **OsMed (National Observatory on the Use of Medicines) flow.** The information flow of pharmaceutical services provided through pharmacies (both public and private) affiliated with the NHS was established pursuant to Law 448/1998 and subsequent amendments, implemented by the Ministerial Decree No. 245/2004[1]. This flow records the data of the prescriptions collected by Federfarma (National Federation of Private Pharmacies affiliated with the NHS) and by Assofarm (Association of Public Pharmacies), which receive data from their provincial offices and subsequently aggregate them at regional level. The OsMed flow has a variable degree of completeness by geographical area and by month; the national data coverage in 2021 was generally 96.3% of expenditure. The share of expenditure and missing consumption was obtained through an expansion, which uses as a reference value for pharmaceutical expenditure data from Summary accounting slips (Distinte Contabili Riepilogative, DCR), regularly updated by AIFA. In order to guarantee homogeneous comparisons between the Regions, the expansion procedure brings regional spending back to 100%, assuming that the distribution of missing data by specialty is not significantly different from the observed data and that the invariance of the retail price of the single medicinal package is guaranteed.
- **Purchase by public health facilities.** The Decree of the Minister of Health of 15 July 2004 provided for the establishment, within the New Health Information System (NSIS), of the "Drug Traceability flow”, aimed at tracking the movement of medicines with Marketing Authorization (MA) in the national territory and/or abroad. This flow is fed by pharmaceutical companies and intermediate distribution and detects the packages handled along the distribution chain, up to the final supply points: pharmacies, hospitals, clinics, shops, etc. The data analysed in this Report refer to the purchase of medicines (in terms of both quantity and economic value) by public health facilities (i.e. non-approved pharmaceutical assistance). Therefore, they relate to the supply of medicines by pharmaceutical companies to public health facilities (sell-in) which are subsequently used within the facilities themselves (i.e. sell-out of hospital consumption), or dispensed directly to the patient for their use also outside healthcare facilities (i.e. sell-out of direct and “on behalf” (*per conto)* distribution). Pursuant to Law 236/2016 (Budget Law 2017), Article 1, paragraph 398, the ceiling of hospital expenditure is calculated gross of the expenditure for Class A medicines in direct distribution and “on behalf” (*per conto*) distribution, and was therefore renamed “pharmaceutical expenditure ceiling for direct purchases”. The data used for monitoring compliance with the aforementioned ceiling are those collected from the Drug Traceability flow. The rules of data

[1] Art. 68, paragraph 9 of Law 23-12-1998, No. 448 as amended, implemented by Art. 18 of the Ministerial Decree 20-9-2004, No. 245 (“Regulation on the organisation and functioning of the Italian Medicines Agency, pursuant to Art. 48, paragraph 13, of Legislative Decree 30-9-2003, No. 269, converted into Law 24-11-2003, No. 3”).

transmission through the Drug Traceability flow provide for the daily transmission of data relating to the number of packages handled to the individual healthcare facility. However, since the sending of the economic value of the movements can also take place at a later stage, it is possible that the available data may include unexploited consumption.

- **Private purchase by the citizen.** In addition to the medicines reimbursed by the NHS, local pharmacies also dispense Class A and Class C medicines purchased privately by citizens (with or without a prescription). For Class C medicines, the analysis of pharmaceutical consumption by the citizen was carried out using the data collected through the Drug Traceability flow, established pursuant to the Decree of the Minister of Health of 15 July 2004, sent by the wholesalers to the central database of the Ministry of Health, with regard to medicines delivered to local pharmacies (sell-in). The private purchase of Class C medicines is estimated as the difference between what is purchased from pharmacies (Sell-in), compared to what is paid by the NHS (sell-out, i.e. the OsMed flow) and considers the citizen as a recipient. It should be noted that when analysing the consumptions related to a wide time span, any misalignment between sell-in and sell-out - consequent to the re-composition of the warehouse stocks of the pharmacy, which, on the contrary, could impact significantly on the single month- is minimised.
- **Direct and "on behalf" (*per conto)* distribution.** The information flow of pharmaceutical services carried out directly and *"on behalf" (per conto) was* established by the Decree of the Minister of Health of 31 July 2007 governing the New Health Information System (NSIS). This flow, fed by the Regions and the Autonomous Provinces of Trento and Bolzano, records the supply to patients of medicines paid by the NHS, for consumption in their own home, an alternative to the traditional supply at pharmacies, as well as those provided directly from health facilities pursuant to Law 405/2001, as amended. This flow includes pharmaceutical services provided: on discharge from hospitalisation or after specialist examination, limited to the first complete therapeutic cycle, to chronic patients subject to therapeutic plans or taken care of by facilities, in home care, residential or semi-residential care (i.e. direct distribution), by affiliated pharmacies, public or private, on behalf of the Local Health Authorities (i.e. "on behalf" distribution). The analysis is extended to the prescriptions of all medicines authorised for marketing in Italy and identified by the MA code, regardless of supply class and regime. However, in order to have a complete picture of the consumption and expenditure of medicines directly borne by public structures of the NHS, the analysis also includes foreign medicines not registered in Italy, medicines prepared in pharmacies on the basis of a medical prescription for a specific patient ("magistral formulas"), and medicines prepared in pharmacies according to the indications of the European Pharmacopoeia or national Pharmacopoeias in force in EU Member States ("officinal formulas"), which are directly provided to patients served by the pharmacy. For the purposes

of this Report, analyses on pharmaceutical performance in direct or “on behalf” (*per conto)* distribution have been carried out with exclusive reference to medicines provided with MA. The data of this information flow was used for periodic monitoring by AIFA of territorial pharmaceutical expenditure, as well as for the calculation of the deviation from the territorial pharmaceutical expenditure ceiling and for the allocation of budgets to pharmaceutical companies. Starting from 2017, in accordance with Law 236/2016 (Budget Law 2017), Article 1, paragraph 399, the territorial pharmaceutical expenditure ceiling, renamed "ceiling for pharmaceutical expenditure in approved regime", is calculated net of direct and “on behalf” (*per conto)* distribution.

- **Purchase of medicines by health facilities not directly managed by the NHS, but subsequently reimbursed.** In the information flow of pharmaceutical services carried out in direct or “on behalf” (*per conto)* distribution, the Regions and the Autonomous Provinces of Trento and Bolzano collect data concerning the supply of medicines through facilities not directly managed by the NHS. Such facilities proceed with the purchase of medicines, subsequently reimbursed by the NHS as a surplus compared to the rate reimbursed for the individual services provided (“extra-DRG”).

- **Pharmaceutical prescriptions**. The information flow for transmission of pharmaceutical prescriptions is provided by paragraph 5 of Art. 50 of the Decree Law of 30 September 2003, No. 269, converted, with modifications, by Law 24 November 2003, No. 326, as amended (Health Card). Structures providing health services (local health authorities, hospitals, hospitalisation and care institutes, university clinics, public and private pharmacies, specialist outpatient clinics and other accredited facilities) have an obligation to electronically transmit to the Ministry of Economy and Finance (MEF) prescriptions charged to the NHS. For the purpose of monitoring health expenditure, pursuant to the aforementioned provision, electronic transmission is requested for prescription data compliant with paragraph 2, Art. 50 - referred to as "red” prescriptions - regardless of the content of the prescription and the medicine supply method. This means that, in the case of prescription of medicines through “on behalf” (*per conto)* distribution or products related to supplementary assistance, reported on a "red prescriptions ", the relative data are subject to a transmission obligation, and incomplete, late or no transmission are sanctioned pursuant to Art. 50. The supplying structures can also transmit prescriptions written on different models (“white” prescriptions, or modules not processed by the Health Card System, such as the tracing form, class C prescriptions for exempt subjects) and prescriptions for different supply modes of pharmaceutical products: *“on behalf” (per conto)* distribution, direct distribution, additional home assistance and supplementary assistance. The data to be transmitted relates to the patient (fiscal code, Local Health Centre, etc.), to the prescription (prescription identification code, Local Health Centre that processed it, etc.), to the services provided (product code, MA code, license number, amount, etc.) and to the prescriber (physician's code, specialization, etc.). In the case of pharmaceutical

prescriptions, the transmission of prescription data by the supplying facilities (pharmacies open to the public) shall take place within the 10th day of the month following the use of the prescription (or according to the date reported on the MEF website), also through category associations and third parties specifically identified by such structures.
For the purposes of this Report, the data flow has been used for the analysis on the use of pharmaceuticals by age group and gender and for assessment of adherence and persistence. The data refer to all Italian Regions.

2. Classification systems

The drug classification system used in the Report is the one developed by the Oslo *Collaborating Centre for Drug Statistics Methodology* (http://www.whocc.no/) of the World Health Organisation (WHO), based on the ATC/DDD system (respectively: Anatomical-Therapeutic-Chemical category and Defined-Daily Dose). The ATC identifies a system for classifying the active ingredients of pharmaceuticals, grouping them in different categories on the basis of the apparatus/organ on which they exert their therapeutic action and according to their chemical and pharmacological properties. Each active ingredient is generally associated with a unique 5-level code; frequently the second, third and fourth levels are used to identify the pharmacological classes.
The defined-daily dose (DDD) represents the maintenance dose per day of therapy, in adult subjects, related to the main therapeutic indication of the substance (therefore it is a standard unit and not the recommended dose for the single patient). The DDD is generally assigned to an active ingredient already classified with a specific ATC code. The number of DDD prescribed refers to 1000 inhabitants for each day of the time period observed (week, month, year, etc.). The DDD allows to aggregate the prescriptions regardless of the prescribed substance, the administration route, the number of dosage units and the dosage of the single package, thus allowing time comparisons, between geographical areas and between therapeutic categories The WHO annually provides for a revision of the ATC and DDD classification; consequently, it is likely that consumption and spending by category change over time, depending at least in part on these updating processes.
Ultimately, DDD was used in the analysis of drug consumption to parametrize the number of packages delivered to patients, according to the formula shown in section 4. In some specific analyses, a grouping of different ATC and/or active ingredients was applied, in order to analyse consumption patterns according to the therapeutic field. The list of pharmaceuticals for direct distribution is represented by the Direct Distribution Guide (PHT - Guide for continuity of hospital-local assistance) in force since November 2004.
For equivalent medicines, the "transparency lists" were used, published monthly by AIFA, relating to the year 2021.

3. National population and standardisation of the Regional population

Regional variability of pharmaceutical expenditure and consumption, although mainly influenced by the different prescribing attitudes of physicians and by variability in epidemiological profiles, is also partly dependent on demographic characteristics (composition by age and gender). Therefore, in order to optimise the comparability between the Regions, the resident population in each Region measured by the Italian National Institute of Statistics (ISTAT) was recalculated taking into account the statistical weights provided by the Programming Department of the Ministry of Health.

Table 3.1 Statistical “weights” provided the Programming Department of the Ministry of Health

Age group	0	1-4	5-14	15-44 Men	15-44 Women	45-64	65-74	> 74
Weight	1	0.969	0.695	0.693	0.771	2.104	4.176	4.29

The procedure followed for the calculation of the weighted population was as follows: the number of the composition was identified by age group and gender of each Region (data source: http://demo.istat.it/); the number of residents in each class was then multiplied by the corresponding weight; then, the sum of the values thus obtained at regional level was re-proportioned to the Italian population of the reference year (59.236.213 inhabitants in 2021).
The implementation of this process of population standardisation implies that a Region with an older population than the national average will have a higher weighted population than the resident population and vice versa. Table 3.2 shows the resident population measured by the Italian National Institute of Statistics (ISTAT) and the weighted population for the years 2020 and 2021.

Table 3.2 Resident population measured by ISTAT and weighted population for 2020 and 2021

Region	Resident population as of 1.1.19	Weighted population 2020	Weighted resident population as of 1.1.2021	Weighted population 2021	Δ % 21-20 resident population	Δ % 21-20 Weighted population
Piedmont	4.311.217	4.526.583	4.274.945	4.473.927	-0.8	-1.2
Valle d'Aosta	125.034	128.252	124.089	126.972	-0.8	-1.0
Lombardy	10.027.602	9.973.090	9.981.554	9.882.363	-0.5	-0.9
Province of Bolzano	532.644	497.505	534.912	496.421	0.4	-0.2
Province of Trento	545.425	536.117	542.166	530.427	-0.6	-1.1
Veneto	4.879.133	4.913.136	4.869.830	4.894.740	-0.2	-0.4
Friuli VG	1.206.216	1.283.315	1.201.510	1.273.005	-0.4	-0.8
Liguria	1.524.826	1.686.057	1.518.495	1.668.564	-0.4	-1.0
Emilia R.	4.464.119	4.549.392	4.438.937	4.500.362	-0.6	-1.1
Tuscany	3.692.555	3.865.341	3.692.865	3.849.418	0.0	-0.4
Umbria	870.165	910.263	865.452	905.703	-0.5	-0.5
Marche	1.512.672	1.563.830	1.498.236	1.547.811	-1.0	-1.0
Lazio	5.755.700	5.678.841	5.730.399	5.663.187	-0.4	-0.3
Abruzzo	1.293.941	1.318.465	1.281.012	1.307.686	-1.0	-0.8
Molise	300.516	311.012	294.294	306.192	-2.1	-1.5
Campania	5.712.143	5.260.415	5.624.260	5.210.556	-1.5	-0.9
Puglia	3.953.305	3.881.368	3.933.777	3.881.453	-0.5	0.0
Basilicata	553.254	555.673	545.130	550.111	-1.5	-1.0
Calabria	1.894.110	1.842.325	1.860.601	1.822.155	-1.8	-1.1
Sicily	4.875.290	4.696.516	4.833.705	4.687.728	-0.9	-0.2
Sardinia	1.611.621	1.663.991	1.590.044	1.657.433	-1.3	-0.4
Italy	**59.641.488**	**59.641.488**	**59.236.213**	**59.236.213**	**-0.7**	**-0.7**
North	27.616.216	28.093.448	27.486.438	27.846.781	-0.5	-0.9
Centre	11.831.092	12.018.276	11.786.952	11.966.118	-0.4	-0.4
South and Islands	20.194.180	19.529.764	19.962.823	19.423.314	-1.1	-0.5

4. Indicators and measures of use of medicines

Analysis of the main expenditure components

The analysis is based on disaggregated data on pharmaceutical expenditure and DDDs in the current and previous years. These data are combined according to the following formula:

$$IV = \frac{S^{21}}{S^{20}} = \frac{\sum_i q_i^{21}}{\sum_i q_i^{20}} \times \frac{\sum_i p_i^{21} q_i^{20}}{\sum_i p_i^{20} q_i^{20}} \times \frac{\dfrac{\sum_i p_i^{21} q_i^{21}}{\sum_i q_i^{21}}}{\dfrac{\sum_i p_i^{21} q_i^{20}}{\sum_i q_i^{20}}}$$

Quantity effect | Price effect | Mix effect

where:
“i” varies in the "field" constituted by the packages present on the market (also for zero sale)
IV = index of variation in expenditure between 2021 and 2020
S_{21} = pharmaceutical expenditure in 2021
S_{20} = pharmaceutical expenditure in 2020
qi_{21} = quantity of the "i" package (expressed in DDD) sold in 2021
qi_{20}= quantity of the "i" package (expressed in DDD) sold in 2020
pi_{21} = average price in 2021 of the single DDD with the "i" package
pi_{20}= average price in 2020 of the single DDD with the "i" package

This indicator consists of three factors:

- the first factor (quantity effect) relates to variation in the quantities of pharmaceuticals consumed;
- the second factor (price effect) concerns changes in the price of pharmaceuticals;
- the third factor (mix effect) describes if, compared to the previous year, in the current year (considering current prices) more expensive medicinal products are consumed: if the indicator is greater than 1, high-price pharmaceuticals are mostly consumed; vice versa, if this factor is less than 1, in the current year medicines with lower prices are mostly consumed.

In the analysis of the one-year mix effect, the use of DDDs avoids the introduction of distortions induced by the change of packaging of some specialties present in the previous year with a different number of DDD per single piece.
This type of analysis partially records the effect due to the introduction of medicines belonging to categories for which therapeutic alternatives were previously absent. In this case an increase is expected in the total number of DDD prescribed, while the analysis does not apply to either price changes or the mix effect. The aforementioned limits do not concern the case of admission to the reimbursement of new molecules of therapeutic groups for which other reimbursable medicines were already available, because the analysis highlights both possible variations in the overall prescription volume and shifts in the type of prescriptions.
When reading the results, it should be taken into account that:

- the indices of variation were expressed as percentage changes;
- the deviation (%) of pharmaceutical expenditure does not exactly coincide with the sum of the three deviations calculated (quantity, prices, mix), since it is the result of a product.

Temporal dynamics of the prices of Class A-NHS, of Class C medicines with prescription and of medicines purchased by healthcare facilities

The data used for the analysis of price dynamics refer to the consumption of Class A-NHS medicines, of Class C medicines with prescription, of medicines purchased by public health facilities, collected and processed by OsMed. Prices relating to a single specialty are obtained as the ratio between the expenditure values (in euros) and the quantities sold (both in terms of DDD and packaging). Starting from the prices relating to single specialties, the Weighted Average Prices (PMP) were calculated for each month, for which the weights consist of either the number of DDD or the number of packages, according to the following formula:

$$PMP_i = \frac{\sum_{j=1}^{n} p_j^i q_j^i}{\sum_{j=1}^{n} q_j^i}$$

where:
n = is the number of specialties marketed in the month “i”
p_j^i= is the price of a DDD (or of a package) of the specialty “j” in the month “i”
q_j^i= is the number of DDDs (or of the packages) of the speciality “j” sold in the month “i”

The monthly temporal dynamics of prices is analysed in section 1. The growth value of the weighted average price per DDD in this analysis is different from the one calculated in the breakdown of the variation in pharmaceutical expenditure (price effect component). In the monthly price trend the index used takes into account all specialties marketed at that time; the price index used to break down the variation in expenditure is instead constructed using only the DDD relating to the specialties present in the period with which the comparison is made (previous year) and, therefore, does not take into account the new specialties marketed in the current year.

Herfindahl-Hirschman Index (HHI): it is defined as the sum of the squares of the market shares. The index assumes 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 agents, each of which holds a small market share. In order to be able to make comparisons taking into account the differences in formulation between the originator and biosimilars, the calculations were made on the defined daily doses (DDD) of each medicine in order to obtain a standardised daily dose.

Definition of the indicators

Coefficient of variation % (CV%): allows to evaluate the dispersion of the values around the mean regardless of the unit of measurement and is calculated according to the formula:

$$CV = \frac{\mathrm{DS}}{mean} \; X100$$

Packages/1000 inhabitants: average number of packages consumed by 1000 inhabitants in the given period

$$\text{CV} = \frac{\text{Total number of packages consumed in the given period}}{\text{No. of inhabitants}} \times 1000$$

Packages/10.000 inhabitants per day: average number of packages consumed daily by 10.000 inhabitants.

$$\frac{\text{Total number of packages consumed in the period}}{\text{No. of subjects x No. of days in the period}} \times 1000$$

Average DDD cost: indicates the average cost of a DDD (or a day of therapy). It is calculated as the ratio between total expenditure and the total number of doses consumed.

Average cost per user: indicates average expenditure for each user. It is calculated as the ratio between total expenditure and the total number of prevalent users (subjects who received at least one prescription during a given period of time).

DDD/1000 inhabitants per day: average number of doses of medicine consumed daily by 1000 inhabitants (or users).
For example, for the calculation of the DDD/1000 inhabitants per day of a given active ingredient, the value is obtained as follows:

$$\frac{\text{Total number of DDD consumed in the period}}{\text{No. of subjects x No. of days in the period}} \times 1000$$

DDD per user: it is an indicator of the average number of days of therapy. It is calculated as the ratio between the total DDD consumed and the total number of subjects who received at least one prescription during a period of time (users in the period).

DDD per user = (no. DDD consumed in the period/users in the period)

Standard deviation (DS): indicates the dispersion of data around a position index, which can be, for example, the arithmetic mean. If all the values in a dataset are very close together, the standard deviation will be close to zero. In such cases, the measured values of the data will all be close to the mean. A high standard deviation indicates that the values are spread out over a wider range.

Incidence of pathology: the Incidence (I) of a given condition in a population is the number of new cases that present the condition in a given period of time compared to the entire population at risk of presenting that same condition.

I = (n subjects with a "first" diagnosis of a specific pathology / total population at risk (free of the disease) at the beginning of the period) x 1000

Incidence of use: ratio between new users of medicine and reference population in a given period.

I = (new users in the period / reference population) x 100 (or x 1000)

Compound Annual Growth Rate (CAGR): is calculated through the nth root of the overall percentage rate where n is the number of years of the period considered.

Therefore:

$$CAGR = \left(\frac{x_f}{x_i}\right)^{\left(\frac{1}{n}\right)} - 1$$

where x_f represents the indicator calculated in the final period, x_i represents the indicator calculated in the initial period and n represents the number of years considered.

Median: in relation to an orderly distribution of values in a population (DDD, per capita expenditure) the median represents the value which divides the population into two equal parts**.**

Prevalence of pathology: the prevalence (P) of a given condition in a population is the number of patients who have the condition in a given period of time with respect to the entire population.

P = (no. of subjects presenting the condition/total population) X 100

Prevalence of use of medicines: the ratio between the number of subjects who received at least one prescription and the reference population (potential users) in a given period of time:

P = (no. users / population) x 100 (or x 1000 inhabitants, etc.)

Quartiles: values dividing the ordered distribution (expenditure, DDD, ...) into four parts of equal frequency.

- The first quartile is the value including 25% of the data (25th percentile);
- the second quartile is the value including 50% of the data (50th percentile), thus corresponding to the median;
- the third quartile is the value which includes 75% of the data (75th percentile).

The *Interquatile Range* is the region between the 25th and the 75th percentile

% deviation from average: the % deviation from average of Region i, with reference to an indicatr x (per capita expenditure, DDD/1000 inhabitants per day, etc.), is constructed as:

$$\frac{x_i - \text{Mean}}{\text{Mean}} \times 100$$

where x_i represents the indicator calculated in the Region *i* and Mean represents the average of the indicator calcluated for all Regions.

Gross expenditure: pharmaceutical expenditure calculated as the sum of the quantities sold multiplied by the retail price.

Net expenditure: expenditure actually borne by the NHS (share of gross pharmaceutical expenditure). Therefore, legal discounts and quotas paid by the citizen are not considered.

Per capita expenditure: represents the average expenditure on pharmaceuticals per recipient. It is calculated as total expenditure (gross or net) divided by the weighted population.

Users with one prescription only: percentage of subjects who received one prescription only compared to total number of users

$$\frac{\text{Users with 1 prescription}}{\text{Total no. of users}} \times 100$$

5. Indicators of adherence and persistence

The administrative database of prescriptions of Class A medicines dispensed on the national territory, was used to monitor the use of medicinal products for chronic therapies (so-called "art.50 flow"/Health Card provided for by article 50, paragraph 5, of Law Decree no. 269 dated 30 September 2003 converted with amendments into Law no. 326 dated 24 November 2003, as amended). In particular, the analysis of repeated prescriptions allowed to estimate adherence and persistence to the main treatments for such chronic therapies.
An analysis on new users aged at least 45 years was conducted, considering a one-year follow-up. In detail, new users were defined as individuals who received a prescription for medicines belonging to the considered therapeutic category in the period between 01/10/2020 and 31/12/2020 and who did not receive prescriptions for medicines belonging to the same category in the previous months starting from 01/10/2020. The year 2021 was therefore used for the follow-up of the subjects enrolled in 2020, in addition, new users who did not receive at least one medical prescription for any medicine in the last quarter of 2020 were excluded from the analysis, proxy of the status in life of the patient.

Adherence was assessed through the Medication Possession Rate (MPR) indicator, defined as the ratio between the number of dispensed therapy days (calculated on the basis of DDD) and the number of days in the time interval between the beginning of the first and the theoretical conclusion of the last prescription (defined as prescription date plus the days calculated on the basis of DDD), as supplied during the follow-up period; in formula:

$$MPR = \frac{\textit{number of therapy days}}{\textit{time interval between first and last prescription (plus days last prescription)}} \times 100$$

Low adherence to treatment is defined as therapeutic coverage lower than 40% in the observation period, whereas high adherence is defined as therapeutic coverage higher than or equal to 80% in the observation period (1).

Persistence is defined as "the time between the beginning and the interruption of a prescribed pharmacological treatment" and is a dynamic measure that describes the maintenance of the therapeutic regime over time, which is assumed to also include any gaps between one prescription and another, if the gap does not exceed a number of days set in advance, in this case, 60 days. Therefore, a subject who started pharmaceutical treatment on date t_0 was defined as "persistent" to treatment after x days from its start if he took the medicine without interruption until day ($t_0 + x$); consequently, an interruption occurs if, between the theoretical end (calculated on the basis of the DDD) of one prescription and the beginning of the next one or the end of the follow-up, a time gap greater than 60 days is observed. (2-4).

If a subject received a prescription before the theoretical end of the previous prescription, the prescription in question was considered sequential, so its start date was postponed to the day after the theoretical end of the previous prescription. Persistence at 12 months was estimated through the Kaplan-Meier analysis; the subjects were "censored" if at the end of the follow-up period they were still in therapy (persistent) or within the time gap between subsequent prescriptions that defines the maintenance of the therapeutic regime.

Prior to the computation of adherence and persistence, it was necessary to carry out a series of data normalization procedures. In particular, for subjects who received multiple prescriptions, relating to different medicines, on the same date, only the prescription with the longest duration was considered. Furthermore, if a subject received a prescription for a period of time that was entirely within the therapeutic coverage of a previous prescription, that prescription was not considered. For both the assessment of adherence and persistence, only subjects with at least 2 prescriptions were considered.

The results obtained were stratified by gender, age groups (45-54, 55-64, 65-74, 75-84, ≥85) and geographical distribution (North: Piedmont, Valle d'Aosta, Liguria, Lombardy, Province of Bolzano, Province of Trento, Veneto, Friuli Venezia Giulia, Emilia Romagna; Centre: Tuscany, Umbria, Marche, Lazio; South and Islands: Abruzzo, Molise, Campania, Puglia, Basilicata, Calabria, Sicily, Sardinia). Finally, in order to assess the trend over time, synthesis values obtained from 2019 to 2021 were reported and the percentage changes in adherence and persistence indicators compared to the previous year.

For each therapeutic class considered, the analyses carried out included only those Regions

in which the proportion of medicines provided under territorial assistance regime (approved and "on behalf" (*per conto)* distribution) was equal to or greater than 85% of the total (also including direct distribution, Health Ministry Decree of 31 July 2007 regulating the New Health Information System [NSIS] and Law 405/2001 and subsequent amendments).
Only for the categories of antihypertensives and lipid-lowering drugs an in-depth study was carried out considering a follow-up of 2 years and consequently the cohort of new users detected in the last quarter of 2019 and followed until the end of 2021.

Medicinal products and therapeutic classes considered

1. **Antidepressant medicines:**
   - Antidepressants (ATC: N06A)

2. **Lipid-lowering medicines:**
   - Hydroxymethylglutaryl-CoA reductase inhibitors (ATC: C10AA);
   - Fibrates (ATC: C10AB);
   - Omega-3 triglycerides (ATC: C10AX06);
   - Ezetimibe (ATC: C10AX09);
   - Lipid modifying agents, associations (ATC: C10B)

3. **Antiosteoporosis medicines:**
   - Raloxifene (ATC: G03XC01)
   - Bazedoxifene (ATC: G03XC02)
   - Bisphosphonates alone (ATC: M05BA)
   - Bisphosphonates in combination (ATC: M05BB)
   - Teriparatide (ATC: H05AA02)
   - Strontium ranelate (ATC M05BX03)

4. **Medicines for hypertension:**
   - Antihypertensives (ATC: C02A; C02C);
   - Diuretics (ATC: C03);
   - Beta blockers (ATC: C07);
   - Calcium channel blockers (ATC: C08);
   - Medicines for the renin-angiotensin system (ATC: C09)

5. **Medicines for benign prostatic hypertrophy (ATC: G04C)**

6. **Anticoagulant medicines:**
   - Direct thrombin inhibitors (ATC: B01AE*);
   - Direct Xa factor inhibitors (ATC: B01AF*);
   - Vitamin K antagonists (ATC: B01AA*)

7. **Antiplatelet medicines:**
   - Clopidogrel (ATC: B01AC04);
   - Ticlopidine (ATC: B01AC05);
   - Acetylsalicylic acid (ATC: B01AC06);
   - Prasugrel (ATC: B01AC22);
   - Ticagrelor (ATC: B01AC24);
   - Clopidogrel/ACETYLSALICYLIC acid (ATC: B01AC30);
   - Esomeprazole/acetylsalicylic acid (ATC: B01AC56).

8. **Antidiabetic medicines (ATC: A10*)**

9. **Medicines for asthma and COPD (ATC: R03*)**

Reference bibliography

1. Borghi C, Cicero AFG. Aderenza e persistenza in terapia. Giornale Italiano di Farmacoeconomia e Farmacoutilizzazione 2008; 1(2): 5-13.
2. Choi YJ, Ah YM, Kong J, et al. Implication of different initial beta blockers on treatment persis- tence: atenolol vs new-generation beta blocker, a population-based study. Cardiovasc Ther 2016; 34(4): 268-75.
3. Mazzaglia G. Brignoli O, Caputi AP, Claudio Cricelli C. Aderenza e persistenza: due elementi chiave per la determinazione dell'efficacia terapeutica in usual care. Farmacoeconomia e percorsi tera- peutici 2011; 12 (Suppl 2).
4. Santoni L, Dall'Asta G, Spampinato A, et al. Aderenza e persistenza alla terapia con statine: analisi di farmacoutilizzazione a partire dai database amministrativi di cinque ASL italiane. Giornale Ita- liano di Farmacoeconomia e Farmacoutilizzazione 2009; 2(1): 5-16.

6. Data relating to the prescription of medicines in General Practice

Health Search was founded in 1998 as a research unit of the Italian Society of General Medicine and Primary Care (SIMG). One of the main objectives of Health Search is to trace the care paths of Italian General Practitioners (GPs) through the systematic collection of all clinical information relating to patients. With this in mind, a network of GPs distributed homogeneously throughout the national territory brings together in Health Search-IQVIA Health Longitudinal Patient Database (Health Search-IQVIA Health LPD) all the information related to: demographic information, pathology diagnosis, pharmaceutical prescriptions, specialist outpatient services, laboratory parameters and exemptions for pathology or disability. This information, properly analysed, allows to describe in detail the state of health of a population and to develop indicators of appropriateness of drug use, understood as "specific and measurable elements of clinical practice, developed on the basis of solid scientific evidence and used as units of measurement of the quality of care[2] 2". They play a central role in performance improvement programs in healthcare and are frequently used at company level to monitor interventions to improve the diagnostic-therapeutic behavior of prescribers.
On the basis of compliance with a series of quality criteria in data recording, for each of the three years considered (i.e. 2019, 2020, 2021), 800 "validated" and active GPs in the specific year were selected for the OsMed 2021 Report. The data presented therefore refers to an overall population of patients, over the age of 14, who were found to be alive and registered in the lists of GPs in the aforementioned years.
Health Search/IQVIA Health LPD is a dynamic database subject to an annual update of the reference population on the basis of qualitative data imputation criteria. This update may involve slight variations in the values, even with respect to the data reported in the reports and publications of previous years.

Prevalence and prescribing profiles in General Practice

The prevalence and incidence of disease, in light of the widespread distribution of GPs in the area, guarantee solid information on the epidemiological impact of the conditions analysed in the Report. Furthermore, with regard to the prevalence of disease, this is the denominator for the calculation of the prevalence of use of medicines, for which any evidence of appropriateness or inappropriateness of prescription should be highlighted.
The peculiar feature of the Health Search/IQVIA Health LPD database, as well as of all primary care databases, is the fact that the data contained in it are able to bridge the information gaps related to the spread of chronic diseases. Therefore, General practice data represents a valuable source for monitoring the health status of the population and its taking charge, as well as to analyse the effect of specific phenomena on the health system of our country.

[2] By quality criteria we mean specific criteria of inclusion and exclusion required of doctors to enter the HS network, for further information please consult XIV Report Health Search 2021 (Report_XIII.pdf [healthsearch.it]

Construction of prescription indicators

The principles that inspired the choice of indicators were:

- the presence of solid scientific evidence regarding the data;
- a general consent expressed by the prescribers;
- applicability in different national and international contexts.

The set of indicators reported in this Report is organised on the basis of the clinical-epidemiological problem, explaining within it the pharmaceutical and therapeutic classes that have contributed to their realization.

For each clinical-epidemiological problem, the data of **prevalence of pathology** is reported, i.e. the number of patients who, in a given period of time, have the diagnosis of a given disease [**numerator**], out of the total population potentially assisted by the GPs of the network Health Search [**denominator**], as well as of **incidence of pathology** (per 1000 patients), estimated by considering the number of patients who underwent a "new" and "first" diagnosis of a given disease during the year [**numerator**], out of the total of the active population assisted by GPs of the Health Search network during the observation period as well as at “risk” (free of disease) at the beginning of the aforementioned period [**denominator**].
For each indicator of prevalence and incidence of pathology, the variation with respect to the estimate obtained for the previous year is reported (Δ % 2021-2020).
The prevalence of disease is reported as general data, as well as by gender, age group and geographical distribution of patients. Furthermore, when appropriate, the data is presented in greater detail, stratifying the subjects by the presence of comorbidities and certain risk factors.
Then, the **prevalence of medicine use** is reported, estimated by considering the number of patients who received at least one prescription of the medicine or of a specific therapeutic class during the year [**numerator**], out of the total number of patients identified on the basis of certain disease diagnoses [**denominator**]. Again, for each prevalence of use indicator, the change from the estimate obtained for the previous year is proposed (Δ% 2021-2020).
Finally, in some cases, the indications reported by the GP relating to the prescription of a certain medicine are described, presented in terms of the frequency of each indication [**numerator**] out of the total number of patients being treated with a certain medicine or with a given pathology [**denominator**].

The detailed description of each indicator is given at the bottom of the relevant table in Section 3.The criteria used to identify the pathologies and prescriptions examined are listed below.

Diseases and pathological conditions considered

1. Essential hypertension (ICD-9-CM: 401-404x, except 402.01, 402.11, 402.91, 404.01, 404.91)
2. Type II diabetes mellitus (ICD-9-CM: 250x, except 250.x1 and 250.x3)
3. Acute Coronary Syndrome (ICD-9-CM: 410-412x)
4. Coronary heart disease (ICD-9-CM: 410-414x)
5. Ischemic brain disorders (ICD-9-CM: 433-436x, 438x, 342x)
6. Cardiovascular diseases (ICD-9-CM: 410-414x, 433-436x, 438x, 342x)
7. Heart failure (ICD-9-CM: 428x, 402.01, 402.11, 402.91, 404.01, 404.91)
8. Peripheral arterial disease (PAD) (ICD-9-CM: V45.89, V49.7, 440.2x, 443.0x, 443.1x, 443.8x, 443.9x)
9. Chronic kidney disease (ICD-9-CM: 585, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93; 250.4, 581.1x, 581.8x, 583.81, 791.0x)
10. Hyperlipoproteinemia (ICD-9-CM: 272, 272.0x, 272.1x, 272.2x, 272.3x, 272.4x, 272.9x)
11. Polygenic hypercholesterolemia [(ICD9CM: 272, 272.0x, 272.2x with the exclusion of "Dysbetalipoproteinemia", 272.4x, 272.9x) and exclusion of the familial form]
12. Familial dyslipidemia (ICD-9-CM: 272.0-3x, familial forms only)
13. Vertebral fracture (ICD-9-CM: 805x)
14. Femur fracture (ICD-9-CM: 820x, 821.0x-821.2x)
15. Obesity (ICD-9-CM: 278.0x + BMI>30 kg/m2)
16. Atrial fibrillation (ICD-9-CM: 427.3x)
17. Peripheral arthropathies (ICD-9-CM: 415.1x,451.1x)
18. COPD (ICD-9-CM: 491.2x, 496x)
19. Asthma (ICD-9-CM: 493x)
20. Depression (ICD-9-CM: 290.21, 296.2-296.3x, 296.9x, 298.0x, 300.4x, 309.0309.1x, 309.28, 311x, V79.0)
21. Osteoporosis (ICD-9-CM: 820x, 821.0x, 821.2x, 805x, 812x, 813x, 733x associated with the term "osteoporosis")

Medicinal products and therapeutic classes considered

1. **Medicines for hypertension and heart failure (antihypertensive)**
   - ACE inhibitors (ATC: C09AA*)
   - Ace inhibitors and calcium channel blockers, in combination (ATC: C09BB*)
   - Ace inhibitors and diuretics, in combination (ATC: C09BA*)
   - Ace inhibitors, other combinations (perindopril, amlodipine e indapamide) (ATC: C09BX02)
   - Alpha-2 adrenergic agonists (ATC: C02AB01)
   - Imidazoline receptor agonists (ATC: C02AC01, C02AC05)
   - Alfablocants (ATC: C02CA, C02CA04, C02CA06)
   - Aliskiren (alone or in combination) (ATC: C09XA02, C09XA52)
   - Angiotensin II receptor antagonists and niprilysin inhibitor (ATC: C09DX04)
   - Angiotensin II receptor antagonists (ATC: C09CA*)

- Angiotensin II receptor antagonists and calcium antagonists (ATC: C09DB*)
- Angiotensin II receptor antagonists and diuretics (ATC: C09DA*)
- Beta Blockers, alone (ATC: C07AA*, C07AB*, C07AG01, C07AG02)
- Beta-blockers and diuretics, in combination (ATC: C07BB07, C07BB12, C07CA02, C07CB02, C07CB03)
- Calcium antagonists (dihydropyridines) (ATC: C08CA*)
- Calcium antagonists (non-dihydropyridine) (ATC: C08DA*)
- Diuretics with major diuretic action alone or in association with potassium-sparing diuretics (ATC: C03CA01, C03CA03, C03CA04, C03CC01, C03EB01)
- Potassium-sparing diuretics (ATC: C03DA*)
- Olmesartan/amlodipine/hydrochlorothiazide (ATC: C03DX03)
- Perindopril/indapamide/amlodipine (ATC: C03DX01)
- Thiazides and similar (including associations) (ATC: C03AA03; C03BA04; C03BA08; C03BA11; C03EA01; C03EA14)

2. Lipid-lowering medicines
- Statins (ATC: C10AA*)
- Acetylsalicylic acid/atorvastatin/ramipril (ATC: C10BX06)
- Amlodipine/atorvastatin/perindopril (ATC: C10BX11)
- Ezetimibe, alone (ATC: C10AX09)
- Ezetimibe in combination (ATC: C10BA02, C10BA06)
- Fibrates (ATC: C10AB02, C10AB04)
- MTP inhibitor (ATC: C10AX12)
- PCSK9 inhibitors (ATC: C10AX13, C10AX14)
- Omega-3 (ATC: C10AX06)
- Statins, alone (ATC: C10AA*)
- Statins, in combination (ATC: C10BA04, C10BX09)

3. Medicines for asthma and COPD
- Monoclonal antibodies (ATC: R03DX05, R03DX09, R03DX10)
- Antileukotrienes (LTRAs) (ATC: R03DC01, R03DC03)
- Theophylline-based bronchodilators (ATC: R03DA, R03DA01, R03DA04, R03DA05, R03DA08, R03DA11)
- Chromones (R03BC01, R03BC03)
- Inhaled corticosteroids (ICS) (ATC: R03BA*)
- PDE-4 inhibitors (ATC: R03DX07)
- Beta-2 long-acting agonists (LABA) (ATC: R03AC12, R03AC13, R03AC19, R03CC13)
- LABA+ICS (ATC: R03AK06, R03AK07, R03AK08, R03AK11)
- Long-acting antimuscarinic/anticholinergic (LAMA) (ATC: R03BB06, R03BB04, R03BB07, R03BB05)
- LABA+LAMA (ATC: R03AL03, R03AL04, R03AL05, R03AL06, R03AL07)
- LAMA+LABA+ICS (ATC: R03AL08, R03AL09)
- Beta-2 short-acting agonists (SABA) (ATC: R03AC02, R03AC03, R03AC04, R03CC02)
- SABA+ICS (ATC: R03AK, R03AK04, R03AK13)

- Antimuscarinic/short-acting anticholinergic (SAMA) (ATC: R03BB01, R03BB02)
- SABA+SAMA (ATC: R03AK03, R03AL01, R03AL02)
- Ultra-LABA (ATC: R03AC18)
- Ultra-LABA+ICS (ATC: R03AK10)

4. Antidepressants
- SSRI (ATC: N06AB*)
- SNRI (ATC: N06AX16, N06AX21)
- Tricyclic Antidepressants (ATC: N06AA*)
- Other reuptake inhibitors (NARI, SARI, NDRI) (ATC: N06AX05, N06AX12, N06AX18)
- Other Antidepressants (ATC: N06AX01, N06AX03, N06AX05, N06AX11, N06AX12, N06AX18, N06AX22, N06AX25, N06AX26, N06AX27)

5. Antacid/antisecretory/gastroprotective medicines
- IPP (ATC: A02BC*)
- Antacids (ATC: A02AA04, A02AD01, A02AD02, A02AF02, A02AH)
- H2 antagonists (ATC: A02BA01, A02BA02, A02BA03, A02BA04, A02BA06, A02BA53)
- Other medicines for peptic ulcer and gastroesophageal reflux disease (GERD) (ATC: A02BX02, A02BX05, A02BX08, A02BX13)
- Prostaglandins (ATC: A02BB01)

6. Sedative-hypnotic and anxiolytic medicines
- Anxiolytics (ATC: N05BA*)
- Hypnotics (ATC: N05CD*)
- Sedatives (ATC: N05CF*)

7. Antiosteoporosis medicines:
- Monoclonal antibody (ATC: M05BX04, M05BX05)
- Other medicines for osteoporosis (ATC: M05BX01)
- Bisphosphonates, alone (ATC: M05BA01, M05BA02, M05BA03, M05BA04, M05BA06, M05BA07, M05BA08)
- Bisphosphonates in combination (ATC: M05BB03)
- SERM selective estrogen receptor modulators (ATC: G03XC01, G03XC02; G03XC05)
- Teriparatide (ATC: H05AA02)
- Double-acting medicines (ATC: M05BX03)
- Vitamin D and analogues (A02AC01, A11CC03, A11CC04, A11CC05, A11CC06, A12AX)
- Calcium (A12AA03, A12AA04, A12AA20)

METHODOLOGICAL NOTE

Comparing the different editions of the Report, it should be considered that in drawing up the National Reports, updating operations are systematically carried out on the information recorded in the OsMed datawarehouse, and that may lead to slight differences in the values (expenditure, consumption, exposure) published in previous national Reports. Such updating activities may derive, for example, from the definition of new DDDs by the WHO, from the clarification of previously unavailable data (for example updated population data), from checks carried out on the basis of new data flows.

The data used in this report, acquired through the New Health Information System (NSIS), are updated as of 14 April 2022 and, therefore, do not take into account any further revisions by companies and Regions.

AGENZIA ITALIANA DEL FARMACO