Medicines use in Italy

National Report

Year 2020

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The original numeration of tables and figures was left unchanged
in order to allow easy data consultation.

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Marco De Martino, Linda Pierattini, Marta Toma.

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Italian Medicines Agency (AIFA)
Director General:
Nicola Magrini

Working group:

Coordination:
Agnese Cangini, Filomena Fortinguerra, Andrea Pierantozzi, Simona Zito, Francesco Trotta, Giuseppe Traversa – Italian Medicines Agency (AIFA)
Roberto Da Cas – National Institute of Health (ISS)

Italian Medicines Agency (AIFA)
HTA & Pharmaceutical Economy Division:
Domenico Caiazza, Eleonora Capannini, Antonio La Greca, Marzia Petrelli, Giovanni Polimeni, Maria Paola Trotta
Health Budget Monitoring and Regional Relations Office:
Agnese Cangini, Aurora Di Filippo, Filomena Fortinguerra, Ramon Frulio, Francesca Gallinella, Maria Alessandra Guerrizio, Mariarosaria Italiano, Marco Marinelli, Roberto Marini, Federica Milozzi, Serena Perna, Andrea Pierantozzi, Linda Pierattini, Emanuela Pieroni, Matteo Sacconi, Daniela Settesoldi, Francesco Trotta, Simona Zito
Information and Communication Technology (ICT) Department:
Andrea Fabrizi, Marco Fontanella, Giuliano Pistolesi, Maurizio Trapanese
Monitoring Registers Office:
Valeria Angelini, Giorgia Bartoccioni, Alessia Cirilli, Simone Celant, Antonietta Colatrella, Susanna Di Segni, Pier Paolo Olimpieri, Daniele Ricagni, Pierluigi Russo, Valentina Summa, Luca Tomassini

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

Ministry of Health
Directorate General for the Healthcare Statistical and Information System
Claudia Biffoli, Chiara Brutti

Ministry of the Economy and Finance
Treasury Department
Luciana Patrizi, Antonietta Cavallo, Sara Guerrini, Marco Martino

SOGEI - Società Generale d'Informatica S.P.A.
Silvio Andreoli, Stefania Chiapparino, Cinzia Friguglietti, Donato Sanson

For the analysis of the appropriateness of prescription:
Società Italiana di Medicina Generale e delle Cure Primarie (SIMG)
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 (Reggio Emilia Local Health Authority), Pier Mannuccio Mannucci (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan), Giampiero Mazzaglia (Bicocca University of Milan), Francesco Perrone (National Cancer Institute, Naples), Evelina Tacconelli (Department of Diagnostics and Publich Health, University di Verona), Nicola Vanacore (ISS)

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Rome during lockdown, 18 March 2020

Introduction

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The Medicines Utilisation Monitoring Centre (OsMed) has published the 21st *National Report on Medicines Use in Italy*, which contains an increasingly comprehensive and critical description of pharmaceutical care in Italy. With its over 800 pages, the Report exceeds the readability threshold, which legitimises it as a work of reference, leading to imagine new future formats based on the "paper short, online long" formula.

Worthy of note is the involvement of experts in the main therapeutic areas, who have been called on to provide a critical analysis of the data in light of the best available evidence, in order to offer insights into optimal use of medicinal products as well as new detailed information and analyses.

The Report also features a new structure. All information relating to each individual therapeutic category has been gathered to provide a more comprehensive overview and to facilitate reading. An epidemiological framework, trends in consumption and expenditure, the analysis of regional variability are provided for each category; in some cases, indicators of exposure, adherence and persistence to pharmacological treatment in the population are also described, as well as prescriptive profiles by general practitioners (GPs). Finally, some key messages and areas of possible improvement of the appropriateness of use are provided together with possible actions to be implemented.

Given the importance of patent-expired biological medicines, a new in-depth analysis of biosimilars has been conducted. In particular, for each category, the evolution of the biosimilars market penetration and their impact on the overall efficiency of direct purchases have been analysed. In addition, in view of the possible implications on price dynamics, the level of market concentration for patent-expired biological medicines has been assessed.

The chapter on international comparison has been enriched with new insights into specific types of medicines, such as patent-expired biological medicines and orphan drugs.

In the analysis of adherence to pharmacological treatment, the yearly trend has also been assessed with the aim of verifying any changes occurring during the pandemic. Similarly, in addition to prevalence, the incidence of the disease and the change compared to the previous year has also been evaluated through the analysis of prescription by GPs.

Pharmaceutical care is one of the most relevant parts of healthcare, both in universal systems such as Italy, and in mixed systems. In this regard, more background data have been provided that offer an overview of pharmaceuticals with other health data from other European countries.

The OsMed Report not only provides an assessment of the time trend of medicines consumption and expenditure, but also allows to evaluate prescriptive patterns and to capture any health changes in the population through pharmaceutical care. Therefore, the Report represents a tool of information and governance with respect to the overall sustainability of the national health system (NHS).
Despite being the cornerstone of OsMed, the Report is not the only tool for analysing pharmaceutical care. However, it has become a guide for a whole series of in-depth studies and other reports on special populations, such as the health of the elderly, perinatal health, COVID-19 and other areas related to the organisation of the national and regional health system, such as regional repayment plans.

Finally, the interactive OsMed report published online on the AIFA website should be mentioned, since it offers the possibility to search data at different levels of detail. Therefore, the scope of the Report is extended to meet specific information needs.

OsMed as a whole should be seen not only as an important epidemiological monitoring centre, but also as a fundamental support for the governance of the NHS and the Regions and a valuable research tool: a valuable asset of AIFA and the NHS that has been made available to all.

Nicola Magrini
AIFA Director General

Summary

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The Report describes the use of medicines by using the various information flows available, which allow to obtain a comprehensive picture of pharmaceutical care in the inpatient and outpatient settings, both when costs are borne by the NHS and when they are borne by the citizen through private purchases.
OsMed data 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 measuring adherence and persistence indicators, 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 2020 the **overall pharmaceutical expenditure** (both public and private) amounted to 30.5 billion euros and was stable compared to the previous year. It represents an important component of the national health expenditure, accounting for 1.8% of gross domestic product (GDP). **Public expenditure**, worth 23.4 billion euros, accounts for 76.5% of total pharmaceutical expenditure and 18.9% of public health expenditure, and has remained almost stable compared to 2019 (-0.8%).
In 2020, the **overall outpatient pharmaceutical expenditure**, both public and private, amounted to 20.5 billion euros, down by 2.6% compared to the previous year. A reduction in both public and private outpatient expenditure can be observed.
Public outpatient expenditure, including expenditure on Class A medicines provided under approved care regime and direct and *per conto* distribution, was equal to 11.9 billion euros, down 3.0% compared to 2019. This trend was mainly driven by a reduction in direct and *per conto* distribution (-4.9%).
The citizen pharmaceutical expenditure, including cost sharing (regional tickets and difference between the price of patent-expired medicine and reference price) for privately purchased class A medicines and class C medicines totalled 8.7 billion euros, with a decrease of 2.0% compared to 2019. Almost all components registered a reduction compared to 2019, in particular expenditure for self-medication (-10.8%) and citizen cost sharing (-6.0%). Conversely, expenditure for class C medicines requiring a medical prescription increased by 6.6%.
In 2020, 17 packs per citizen and 993.1 doses per 1000 inhabitants under approved care regime were consumed every day, showing a stable trend compared to the previous year (-0.3%).
Within outpatient care, both public and private, **almost 2 billion packs were dispensed**, with a slight reduction compared with the previous year (-1.0%). Considering class A medicines, again compared with the previous year, privately purchased packs increased by 13.9%, while those supplied under direct and *per conto* distribution decreased by 9.5%.

The **main components of change** in gross expenditure under approved care regime in 2020, compared to the previous year (-2.7%), show stable consumptions (-0.3% in terms of DDD), a slight reduction in average prices (-0.7%) and a trend in the prescription of less expensive products (mix effect: -1.6%).
The **region with the highest per capita gross expenditure** for A-NHS medicines was Campania (197.3 euros per capita), while the lowest value was found in the Bolzano area (114.4 euros per capita), with a 72% difference between the two regions. As regards consumption, the region with the highest levels was Campania (1123.8 DDD/1000 inhabitants per day), while the lowest consumption was found in the Bolzano area (708.4 DDD/1000 inhabitants per day).
Expenditure on medicines purchased by public health facilities was around 13.5 billion euros (222.87 euros per capita), almost stable both in terms of expenditure (+0.9%) and consumption (+1.5%), compared to the previous year.
Regions with the highest spending values were Campania (256.55 euros per capita), Umbria (251.77 euros per capita) and Puglia (248.77 euros per capita). Conversely, Valle d'Aosta (163.07 euros per capita), Trento area (184.80 euros per capita) and Lombardy (186.98 euros per capita) showed the lowest values.
In 2020, **approximately over 6 out of 10 citizens received at least one prescription**, with a difference between men and women of 57.4% and 65.5%, respectively. Per capita expenditure and consumption increase with age, especially regarding the population over 64 years of age, which accounts for more than 60% of expenditure and about 70% of doses. Regions in the North of Italy have a lower prevalence (59.6%) compared to the Centre (64.8%) and the South (65.8%).
In 2020, **over 3.4 million children and adolescents** (35.7% of the overall paediatric population) received at least one pharmaceutical prescription, with pre-school children (1-5 years of age) accounting for 46.4%. However, compared with the previous year, the number of prescriptions and prescribed packs showed a significant decrease (-32.7% and -32.9% respectively). Antiinfectives for systemic use continue to be the most consumed medicines, followed by medicines for the respiratory system. However, both categories register a reduction in prescriptions compared to the previous year, probably due to the COVID-19 health emergency. Central nervous system medicines rank third among the most prescribed medicines, accounting for 10.7% of the total consumption, with a 4.2% increase compared to 2019, contrary to the previous two categories.

In the **elderly population**, the average expenditure per user was equal to 560 euros (601 euros for men and 527 euros for women) and almost all the geriatric population (96%) received at least one pharmacological prescription during the year. On average, each user consumed more than 3 doses per day, with higher levels recorded among men than women. In addition, each user took 7.3 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. Both genders registered a progressive growth in the number of different active ingredients taken, which increased with age. During 2020, 65.8% of users aged ≥65 years received prescriptions for at least 5 different substances (i.e. polypharmacy) and approximately one subject in four (26.1%) took at least 10 different active ingredients.

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. Conversely, class C medicines requiring a prescription show a decreasing trend. The analysis of the **time trend of prices** for medicines shows a growth in the average price per pack and per dose for class A medicines under approved care regime and an increase in outpatient class C medicines requiring prescription. Insights into specific, recently patented molecules show that patent expiry can affect price reductions, especially in the case of medicines purchased directly from public facilities and dispensed under direct and *per conto* distribution.

The **international comparison** section compares the Italian pharmaceutical assistance with nine other European countries, in terms of medicines dispensed in the outpatient and inpatient settings. 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 compared to other European countries, although Italy ranks second and first in the incidence of spending and consumption of biosimilars, respectively. 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, in relation to medicines dispensed in the outpatient and inpatient settings. A further analysis was devoted to the expenditure on orphan drugs in the period 2018-2020. With 25.3 euros per capita, Italy ranks fifth in orphan drugs expenditure, after France (31.6 euros), Austria (30.9 euros), Germany (27.8 euros) and Spain (27.2 euros). Compared with the previous year, in 2020 most countries recorded a reduction in orphan drugs expenditure, which was more pronounced for Belgium (more than 20% change).

Section 2. Detailed analysis of expenditure and consumption of medicines

In 2020, **patent-expired medicines** accounted for 67.6% of expenditure and 84.8% of consumption under class A medicines under approved care regime. The percentage share of generic medicines, excluding those with patent coverage, accounted for 20.5% of expenditure and 30.7% of consumption. Citizen cost-sharing for the amount exceeding the reference price of patent-expired medicines (hereinafter “cost-sharing”) was equal to 18.07 euros per capita (approximately 1.1 billion euros), representing 72% of the total citizen cost-sharing and showing a higher per capita value in the South and the Islands (23.0 euros) compared to the Centre (19.88 euros) and the North (13.88 euros) 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 available for longer time and a positive trend for more recent ones (anti TNF-alpha, bevacizumab, fast acting insulin, long acting insulin, rituximab and trastuzumab) are confirmed, although a certain regional variability in consumption and incidence of expenditure remains.

As regards **class C medicines reimbursed by the NHS under approved care regime**, the total expenditure (358,377 users, 65.7% women and 34.3% men) doubled compared to the previous year, from a value of almost 19 million euros to around 39 million euros, representing 0.4% of the gross expenditure under approved care regime. Total expenditure for C-NN medicines doubled compared with the previous year, amounting to around 96 million euros (1.60 euros per capita).

Regarding **class C medicines dispensed directly by public health facilities**, per capita expenditure was equal to 9.25 euros, with a 14.8% increase compared to 2019.

In 2020 expenditure for **medicines dispensed via direct (DD) and *per conto* (DPC) distribution** equalled 8.4 billion euros, with 75.6% attributable to DD and 24.4% to DPC. Class H medicines represented the largest share of expenditure (50.9% class H and 48.9% class A).

In 2020, the total per capita expenditure for **medicines dispensed under inpatient and ambulatory care** amounted to 168.05 euros per capita (10 billion euros), increasing by 3.7% compared to 2019. Pembrolizumab is the main active ingredient dispensed in the hospital and ambulatory setting, followed by nivolumab and daratumumab.

Expenditure for **class C medicines** equalled approximately 5.7 billion euros in 2020, showing a stable trend compared to 2019. Out of this amount, 57.8% (3.3 billion euros) relates to prescription medicines, whereas 42.2% (2.4 billion euros) relates to self-medication medicines (SOP and OTC), including those sold in shops. In 2020, too benzodiazepines, contraceptives and medicines used to treat erectile dysfunction are the categories with the highest incidence on expenditure. An analysis on NSAIDs and antipyretics showed that paracetamol and ibuprofen are the active ingredients with the highest incidence on expenditure and consumption for this class of pharmaceuticals. A further analysis has been devoted to antitussives, which recorded a consumption of 11.3 DDD and a per capita expenditure of 3.4 euros, with a reduction of 16.4% and 27.1%, respectively, compared to 2019. Also for antihistamines, a decrease compared to 2019 was recorded, with a consumption going from 1.8 DDD/1000 inhabitants in 2019 to 1.3 DDD/1000 inhabitants in 2020. In 2020, cholecalciferol, pantoprazole and ketoprofen registered the highest incidence on expenditure among **class A medicines privately purchased by citizens**. After ranking first in 2019, amoxicillin in combination with clavulanic acid ranked fourth in 2020, recording a reduction in private expenditure.

Among **self-medication medicines**, propionic acid derivatives account for 10.1% of total expenditure and the active ingredients with the highest expenditure are diclofenac, ibuprofen and paracetamol.

Section 3. Consumption and expenditure by therapeutic category

In 2020, per capita pharmaceutical expenditure, including medicines purchased directly by public health facilities and those dispensed under the approved care regime, amounted to 385.88 euros, with a slight reduction compared to the previous year. Consumption remained at 1,163.4 DDD/1000 inhabitants, and was stable compared with 2019.

Cardiovascular medicines represent the therapeutic category with the highest expenditure (49.05 euros per capita) and consumption (484.7 DDD) **in the approved care regime**, whereas, **antineoplastic and immunomodulating agents as well as medicines for blood and blood forming organs** show the highest expenditure (102.88 euros per capita) and consumption (49.0 DDD) **among medicines purchased directly by public health facilities**.

Within the approved care regime, the active ingredients with the highest incidence on expenditure are atorvastatin (268.1 million euros), pantoprazole (253.8 million euros) and cholecalciferol (201.4 million euros). The latter goes down in the ranking from first to third as a result of a reduction in expenditure of about 28%, probably due to application of AIFA Note 96.

The molecules with the highest variation in expenditure compared to the previous year are ezetimibe/rosuvastatin, dulaglutide and the perindopril/indapamide/amlodipine combination. Within the approved care regime, ramipril, atorvastatin and acetylsalicylic acid continue to be the most consumed active ingredients.

Taking into account medicines purchased by public health facilities, the active ingredients with the highest incidence on expenditure are cancer drugs, such as lenalidomide (322.2 million euros), pembrolizumab (289.8 million euros) and the sofosbuvir/velpatasvir combination (233.5 million euros) for the treatment of chronic hepatitis C.

Bictegravir/emtricitabine/tenofovir alafenamide for the treatment of HIV, hemicizumab for the treatment of haemophilia A and osimertinib for the treatment of non-small cell lung cancer are the active ingredients with the greatest variation in expenditure compared to 2019.

For each level I ATC, after presenting the overall data on expenditure, consumption and exposure, insights are given for the most relevant 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 prescriptive profiles in the general practice. As regards the main chronic diseases, there were no significant differences compared to the previous year, suggesting the possible efficacy of the measures put in place to balance the continuity of treatment and the containment of COVID-19 infections.

The assessment of adherence and persistence indicators was carried out using the flow data of the *Tessera sanitaria* for the following categories of pharmaceuticals: antidiabetics, anticoagulants, antiaggregants, lipid-lowering agents, antihypertensives, antidepressants, medicines for benign prostate hypertrophy, osteoporosis, asthma and COPD. The therapeutic category with the highest percentage of highly-adherent subjects (with treatment coverage greater than or equal to 80% of the observed period) is that of medicines for osteoporosis (67.7%) followed, for the male population alone, by medicines for benign prostatic hypertrophy (62.8%) and finally by anti-aggregating agents (59.7%). Conversely, the therapeutic

categories with the highest percentages of low-adherent subjects (with treatment coverage less than 40% of the observed period) are those of 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 antiaggregants (52.0%).
Finally, a description is given of the prescriptive 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 2020, 166 registries were available online (intended as single IT entities active during 2020). In particular, during the year 24 new registries were released online, 10 registries were modified, adding a new indication to the monitoring or the extension of an indication already monitored, whereas 24 registries were closed. In 2020, medicines for the cardiovascular system and those in the "Various" and "Dermatological" categories recorded a increase of more than 50% in terms of new patients, while "Blood and blood forming organs", including the therapeutic plans of the new oral anticoagulants, still remain the category that includes the highest number of patients within the Monitoring Registries platform.
The following data are presented: main characteristics of patients treated with new oral anticoagulants (NAOs) for the prevention of stroke and systemic embolism in case of non-valvular atrial fibrillation (NVAF); treatments initiated with PCSK9 inhibitors in hypercholesterolaemia; treatments with anti-neovascularisation medicines for intravitreal use; CAR-T cell therapy; ALK inhibitors (ALKi) for the treatment of patients with non-small cell lung cancer.
Finally, data on reimbursements paid by companies in 2020, following the application of Managed Entry Agreements (MEAs) 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 343.7 million euros, with a financial impact of MEAs on the NHS expenditure of 1.5%.

Section 5. Innovative medicines and Orphan medicines

During 2020, 40 medicines benefited from the **innovation requirement** (full or conditioned), mainly belonging to the antineoplastics category; 9 of these medicines were declared innovative during 2020.
The expenditure and consumption of innovative medicines during 2017-2020 were analysed and assessed in accordance with AIFA decision no. 519 of 31 March 2017, as updated by decision no. 1535 of 12 September 2017.
In 2020, expenditure for innovative medicines amounted to 2.0 billion euros, showing an increase compared to 2019 (+16.0%). Pembrolizumab is the active ingredient with the greatest impact on expenditure for innovative medicines (14.4%), together with nivolumab (11.2%) and daratumumab (10.5%).
In terms of consumption, in 2020 the daily doses dispensed were 19.1 million, compared to 14.4 million in 2019, resulting in an increase of 32.6%. The molecule with the highest consumption was pembrolizumab (approx. +70%), against a slight increase in expenditure.
During 2020, the European Medicines Agency (EMA) granted the authorisation to a total of 20 new **orphan medicines**. As of 31 December 2020, out of a total of 118 orphan medicines authorised by EMA, 97 were available in Italy. Of the remaining 21, 5 have been marketed as of 2021, 12 are undergoing a price and reimbursement procedure and 4 have not applied for price and reimbursement in Italy.
Expenditure on orphan drugs of class H, A, and C, including purchase by public health facilities and the supply under approved care regime, was around 1.4 billion euros in 2020, corresponding to 6.0% of the NHS expenditure.
With reference to therapeutic categories, most of the expenditure related to antineoplastic and immunomodulating agents (64.3%), musculo-skeletal system medicines (8.3%) and gastrointestinal tract and metabolism (7.2%). Analysis by type of substance shows that most orphan medicines are synthesis molecules (59.0%), followed by monoclonal antibodies (30.0%).
The active ingredients with the greatest consumption and expenditure in 2020 are daratumumab and ibrutinib with an increase in expenditure by 3.1% and 29.3% and in consumption by 35.0% and 29.1%, respectively.

Section 1

General characteristics of medicines use in Italy

1.1 General data on expenditure and consumption

In 2020, the overall pharmaceutical expenditure (both public and private) amounted to 30.5 billion euros. This expenditure represents an important part of healthcare expenditure, accounting for 1.8% of the gross domestic product at current prices. Medicinal products dispensed to citizens were mostly reimbursed by the NHS and provided through public and private local pharmacies (32.1%). Gross public expenditure, equal to 23.4 billion euros, accounts for 76.5% of total pharmaceutical expenditure and for 18.9% of public health expenditure, and has remained almost stable compared to 2019 (-0.8%). Medicines purchased by the citizen amount to around 7.2 billion euros, and mainly concern class C prescription medicines (10.7% of total expenditure). Compared with 2019, total pharmaceutical expenditure shows a slight decrease (-0.9%). This trend is mainly attributable to a reduction in gross expenditure under approved care regime (-2.7%), in direct and *per conto* distribution expenditure (-4.9%), in self-medication medicines expenditure (-10.8%) and in the private purchase of class A medicines (-1.1%). Conversely, an increase in expenditure for class C prescription medicines is observed (+6.6%; 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 is smaller compared to Northern Regions (Table 1.1.2).

Figure 1.1.1 shows that public territorial expenditure has been decreasing over the last four years; conversely, hospital expenditure and for class A medicines purchased privately by citizens is constantly growing.

Figure 1.1.2 shows the comparison between pharmaceutical expenditure borne by the NHS and planned funding, corresponding to the sum of pharmaceutical expenditure caps as defined by the legislation (including funds for innovative medicines) over the period 2013-2020. The biggest differences between the overall cap and the pharmaceutical expenditure borne by the NHS were observed in 2015 and 2016, before gradually narrowing in the period 2017-2019, until 2020 when a slight deviation between the two values is observed. This trend suggests substantial control of NHS expenditure in recent years. However, it should be stressed that the alignment of NHS expenditure to the overall cap, which is clear in 2020, does not lead to an absence of overruns in pharmaceutical expenditure, in particular concerning direct purchases, given the presence of separate caps for the approved care regime and direct purchases.

The incidence of public expenditure over GDP is higher in Southern Regions (2.3%) compared to the Centre (1.4%) and the North (1.09%) of Italy, with a national quota of 1.4%. The incidence of public pharmaceutical expenditure over GDP in Calabria (2.56%) is more than 3 times higher than in the Autonomous Province (AP) 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).

After a period of increasing trend, consumption has been stable since 2012 for A-NHS medicines dispensed under approved care regime. Similarly, consumption of medicines purchased by public health facilities showed a growing trend from 2006 to 2013, and then

became stable thereafter. Regarding consumption of class C medicines with prescription, no significant changes were recorded in the period 2004-2020 (Figure 1.1.4).

Table 1.1.1. Composition of pharmaceutical consumption: comparison 2020-2019

	Expenditure *(million)*	**%**	**Δ % 20-19**
Gross expenditure under approved care regime^	9,820.4	32.15	-2.7
of which oxygen and vaccines	80.0	-	0.5
Class A direct and *per conto* distribution	4,259.4	13.94	-4.9
Local health authorities, Hospitals, Healthcare residences and prisons*	9,284.4	30.40	3.4
of which oxygen and vaccines	800.2	-	1.3
Public expenditure	**23,364.2**	**76.49**	**-0.8**
A private	1,527.7	5.00	-1.1
C with prescription	3,269.1	10.70	6.6
OTC and SOP	2,133.7	6.99	-10.8
Shops	249.7	0.82	-3.7
Private expenditure	**7,180.3**	**23.51**	**-1.1**
Total	**30,544.5**	**100.00**	**-0.9**

^ Including expenditure for class C reimbursed medicines (32.4 million euros)

* Does not include expenditure for class A medicines under direct and *per conto* distribution

Table 1.1.2. Composition of total pharmaceutical expenditure in 2020 by Region

	Gross Expenditure under approved care regime[1]		Class A private		Class C with prescription		Self-medication (public and private pharmacies)		Shops		Public facilities		Total^
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°	%	€°
Piedmont	627	28	158	7	259	12	175	8	19	1	990	44	2,228
Valle d'Aosta	17	29	6	10	7	12	6	10	1	2	22	37	59
Lombardy	1,787	36	289	6	582	12	397	8	42	1	1,902	38	4,999
A.P. of Bolzano	57	27	10	5	19	9	19	9	-	-	108	51	213
A.P. of Trento	73	32	6	3	23	10	21	9	2	1	100	44	225
Veneto	648	29	119	5	245	11	187	8	18	1	1,051	46	2,268
Friuli VG	187	30	33	5	58	9	46	7	4	1	299	48	627
Liguria	244	28	58	7	114	13	75	8	8	1	389	44	888
Emilia Romagna	565	26	82	4	241	11	168	8	27	1	1,063	50	2,146
Tuscany	525	27	86	4	214	11	149	8	22	1	949	49	1,945
Umbria	149	33	5	1	41	9	26	6	4	1	231	51	456
Marche	247	32	20	3	70	9	47	6	7	1	393	50	784
Lazio	1,042	35	127	4	330	11	214	7	17	1	1,290	43	3,020
Abruzzo	236	33	37	5	61	9	41	6	6	1	333	47	714
Molise	51	34	6	4	13	9	8	5	1	1	72	48	151
Campania	1,052	33	172	5	381	12	199	6	22	1	1,373	43	3,199
Puglia	724	34	80	4	183	9	117	6	16	1	995	47	2,115
Basilicata	101	35	10	3	22	8	14	5	3	1	141	49	291
Calabria	350	36	33	3	89	9	51	5	8	1	449	46	980
Sicily	858	36	171	7	232	10	125	5	13	1	990	41	2,389
Sardinia	280	33	21	3	86	10	48	6	11	1	406	48	852
Italy	**9,820**	**32**	**1,528**	**5**	**3,269**	**11**	**2,134**	**7**	**250**	**1**	**13,544**	**44**	**30,545**
North	4,205	31	761	6	1,548	11	1,094	8	120	1	5,923	43	13,651
Centre	1,963	32	237	4	654	11	436	7	49	1	2,862	46	6,201
South and Islands	3,652	34	530	5	1,067	10	603	6	80	1	4,758	45	10,690

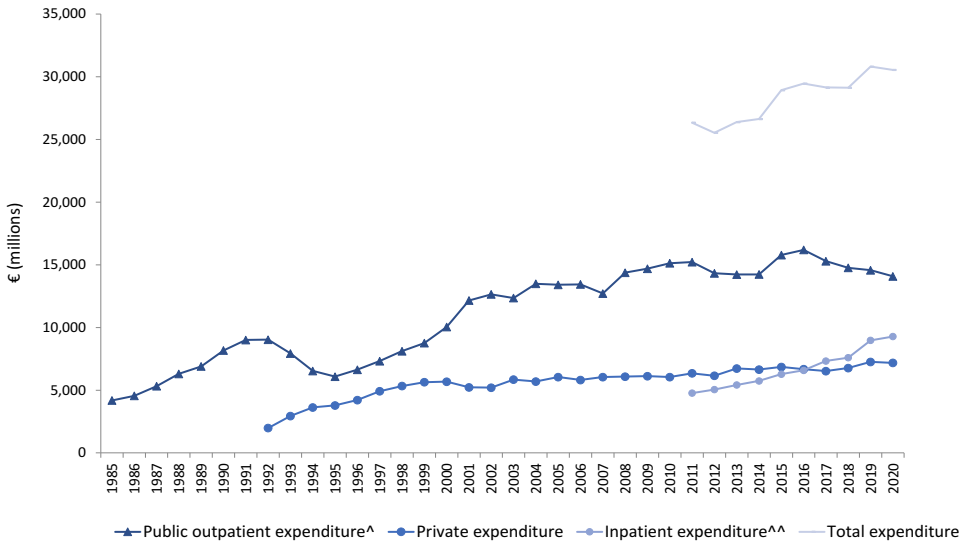
[1]The expenditure refers to class A-NHS medicines and class C medicines (32.4 million euros) reimbursed by the NHS

^Calculated without including expenditure on oxygen and shops

°Million euros

* Calculated on overall regional expenditure

Figure 1.1.1. Pharmaceutical expenditure in the period 1985-2020 (Figure and Table)



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

^ Inclusive of pharmaceutical expense under approved care regime (gross of pay-back and discount) and of direct and *per conto* distribution of class A-NHS medicines, including the share paid by citizens

^^ Expenditure by public health facilities (gross of pay-back) net of direct and *per conto* distribution of class A-NHS medicines

* Including expenditure on oxygen.

Figure 1.1.2. NHS expenditure and funding of pharmaceutical expenditure in the period 2013-2020

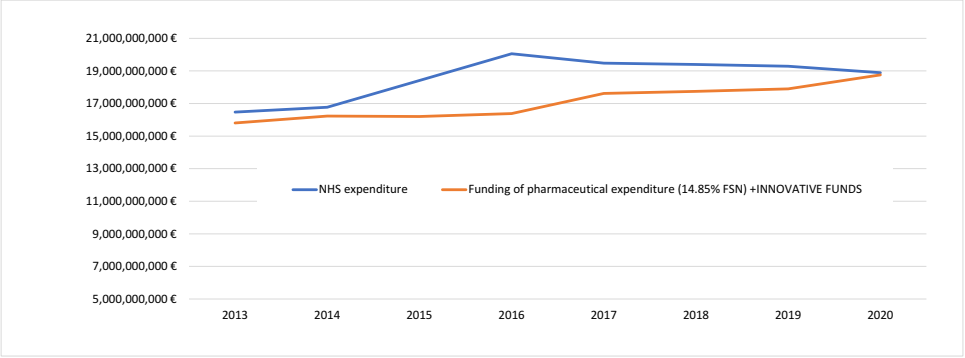


Table 1.1.3. Regional incidence of public pharmaceutical expenditure over GDP: period 2016-2020

Region	Inc. % 2016	Inc. % 2017	Inc. % 2018	Inc. % 2019	Inc. % 2020
Piedmont	1.19	1.15	1.11	1.18	1.27
Valle d'Aosta	0.82	0.77	0.76	0.80	0.86
Lombardy	0.93	0.90	0.87	0.93	1.00
A.P. of Bolzano	0.64	0.64	0.61	0.65	0.71
A.P. of Trento	0.80	0.80	0.78	0.82	0.89
Veneto	1.02	1.00	0.96	1.01	1.11
Friuli VG	1.19	1.26	1.19	1.27	1.36
Liguria	1.27	1.23	1.24	1.25	1.36
Emilia Romagna	1.02	0.99	0.98	1.01	1.08
Tuscany	1.35	1.25	1.17	1.21	1.34
Umbria	1.62	1.60	1.59	1.64	1.79
Marche	1.53	1.53	1.47	1.52	1.64
Lazio	1.17	1.16	1.14	1.18	1.25
Abruzzo	1.67	1.66	1.68	1.71	1.85
Molise	1.86	1.84	1.80	1.94	2.07
Campania	2.27	2.16	2.11	2.25	2.38
Puglia	2.47	2.38	2.30	2.32	2.45
Basilicata	1.91	1.91	1.80	1.91	2.04
Calabria	2.46	2.40	2.39	2.46	2.56
Sicily	2.16	2.08	2.02	2.12	2.22
Sardinia	2.16	2.14	1.93	1.95	2.13
Italy	**1.34**	**1.30**	**1.26**	**1.32**	**1.41**
North	1.02	0.99	0.96	1.01	1.09
Centre	1.29	1.26	1.21	1.25	1.35
South and Islands	2.22	2.15	2.09	2.17	2.29

Figure 1.1.3. Relationship between per capita public pharmaceutical expenditure and per capita regional income in 2020

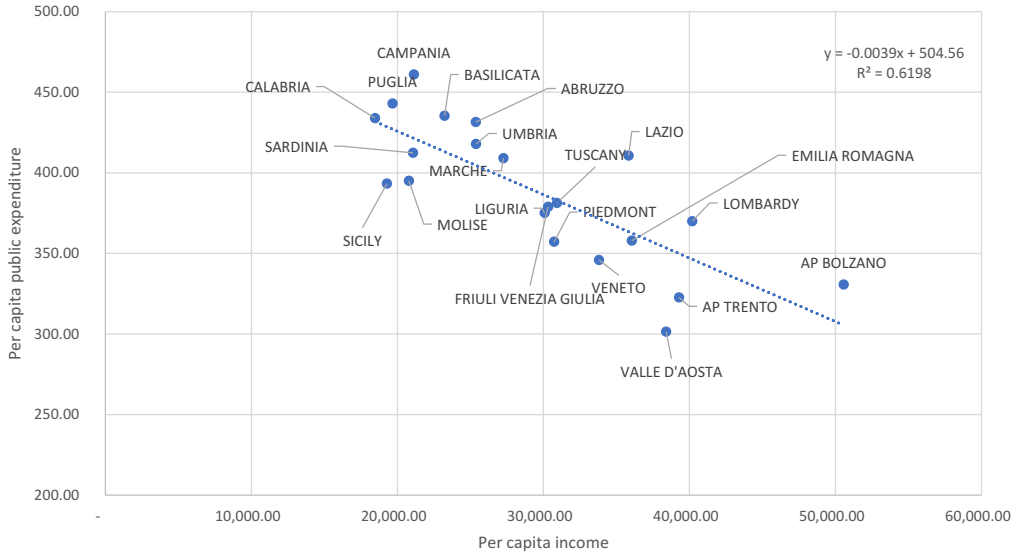
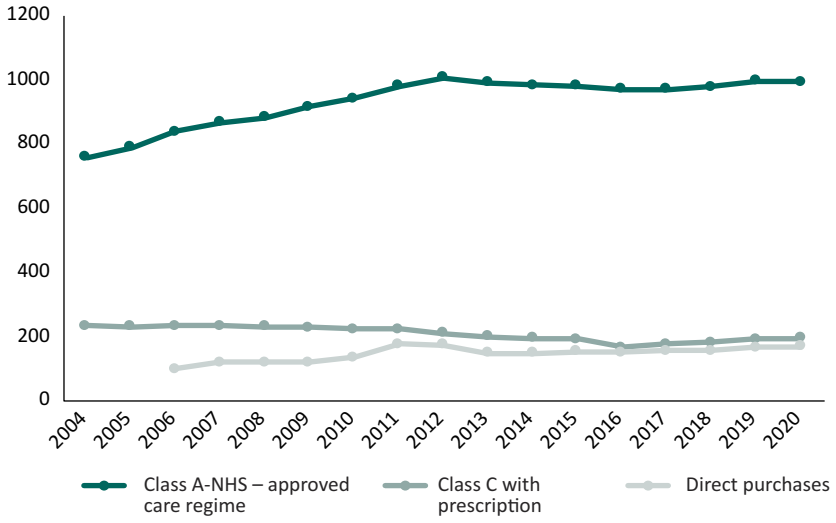


Figure 1.1.4. Consumption (DDD/1000 inhabitants per day) in the period 2004-2020 (Figure and Table)



Year	DDD/1000 inhab. per day		
	Approved care regime class A-NHS	Class C with prescription	Direct purchases
2004	759.7	235.9	
2005	788.6	231.7	
2006	838.1	235.4	100.6
2007	866.8	235.0	121.7
2008	882.8	231.9	120.4
2009	915.1	229.6	120.9
2010	942.8	223.8	136.5
2011	980.8	225.7	178.8
2012	1006.6	212.2	175.1
2013	990.8	202.4	150.9
2014	983.5	195.8	151.2
2015	980.0	193.0	154.3
2016	971.4	168.2	151.4
2017	969.4	178.8	158.3
2018	978.8	183.6	157.0
2019	996.3	193.2	167.8
2020	993.1	196.5	170.3

1.2 Outpatient pharmaceutical expenditure and consumption

In 2020, the overall outpatient pharmaceutical expenditure, both public and private, amounted to 20,542 million euros, down by 2.6% compared to the previous year (Table 1.2.2). The NHS outpatient pharmaceutical expenditure includes medicines supplied under the approved care regime (7,615 million) and class A medicines supplied through direct and *per conto* distribution channels (4,259 million) (Tables 1.2.1 and 1.2.2). Public outpatient expenditure amounted to 11,875 million euros (199.1 euros per capita), representing 57.8% of total outpatient pharmaceutical expenditure, and down by 3.0%, compared with 2019. This decrease was mainly due to a 4.9% reduction in expenditure on class A medicines supplied through direct and *per conto* distribution, as well as to a 1.9% reduction in net approved care regime expenditure.

Citizens pharmaceutical expenditure (Table 1.2.1 and Figure 1.2.1), including citizen cost sharing (regional tickets and difference between the patent-expired price and the corresponding reference price), expenditure on privately purchased class A medicines and for class C medicines amounted to € 8,668 million euros (down 2.0% compared to 2019). This was influenced by a reduction in expenditure on class A medicines (from 1,544 million euros to 1,528 million euros, -1.1%) and by a reduction in the purchase of self-medication medicines (-10.8%). In addition, there has been a reduction in expenditure on citizen cost sharing (-6.0%) and in the number of medicines dispensed by shops (-3.7%). The considerable increase in class C medicines with prescription is worthy of note (+6.6%).

The citizen cost-sharing (Tables 1.2.1 and 1.2.2) amounted to 1,487 million euros (approximately 24.9 euros per capita), accounting for 15.1% of gross expenditure under approved care regime. Compared with 2019, a reduction in expenditure was mainly determined by the ticket expenditure for prescription/package (-10.9%) and partially by a reduction in the share exceeding the reference price of patent-expired medicines (-4.0%).

In line with data from the previous three years, the amount of packages supplied under approved care regime registered a decrease (-4.6%) also in 2020. During 2020 (Table 1.2.3), an average of 993.1 daily doses per 1000 inhabitants (DDD) of NHS reimbursed class A medicines were consumed, accounting to over 1 billion packages dispensed (17 packs per capita). In 2019, the amount was 996.3 DDD.

The region with the highest per capita gross expenditure for A-NHS medicines was Campania (197.3 euros per capita), while the lowest value was found in the A.P. of Bolzano (114.4 euros per capita), with a 72% difference between the two regions (Table 1.2.4). Regarding consumption, the region with the highest levels was again Campania (1,123.8 DDD/1000 inhabitants per day), while the lowest consumption was found in the A.P. of Bolzano (708.4 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 116.2 euros per capita. A fair variability across Italian Regions emerges, with Liguria registering the highest value (146.3 euros per capita) and Umbria registering the minimum value (78.3 euros) (Table 1.2.4).

Contrary to class A medicines reimbursed by the NHS, Northern Regions showed higher private expenditure than Central and Southern Regions.
At national level, net expenditure amounted to 7,615.4 million euros, with the highest levels, in absolute terms, recorded in Lombardy (1,386.5 million euros), Lazio (800.7 million euros) and Campania (771.8 million euros). Both expenditure for fixed co-payment (ticket) and citizen cost sharing of the difference between the price of the patent-expired medicinal product and the corresponding reference price were lower than in 2019. With regard to the fixed co-payment, the biggest changes were recorded in the A.P. of Trento (-97.6%), Umbria (-85.9%) and Basilicata (-45.6%), while as for citizen cost sharing, the largest reductions in the reference price were observed in Marche (-5.6%), Piedmont (-5.5%) and Sicily (-5.4%; Table 1.2.5).
An analysis of the relationship between average cost and consumption under approved care regime (Table and Figure 1.2.6) shows that Campania, Calabria, Lazio, Basilicata, Abruzzo and Puglia are the regions with consumption and cost per DDD above the national average. Conversely, Emilia Romagna, Tuscany, A.P. of Trento, Friuli Venezia Giulia, Veneto, Piedmont, Valle d'Aosta and A.P. of Bolzano are those with the lowest consumption and average cost than the national average.
The main elements (e.g. quantity, prices and mix effect) of the change in gross expenditure under approved care regime in 2020, compared with the previous year (-2.7%), show a stable consumption of prescribed pharmaceuticals (-0.3% in terms of DDD), a slight reduction in average prices (-0.7%), linked in part to an increasing use of patent-expired products, and finally to the prescription of less expensive products (mix effect: -1.6%). Compared with 2019, the average DDD cost decreased by 2.3% due to the expiry of the patent for widely used molecules (Figure 1.2.2 and Table 1.2.7). Against these national average values, regional variability is very broad: change in prices compared to the previous year ranges between -4.3% in Valle d'Aosta to +0.9% in Lombardy. The mix effect varies between -2.7% in Puglia to +1.9% in Valle d'Aosta. Consumption ranges between -2.1% in Piedmont and +1.6% in Sardinia.
Table 1.2.8 shows data on class A outpatient expenditure (approved care regime and direct and *per conto* distribution) and private expenditure (class A, C, self-medication). The A.P. of Bolzano has the lowest public outpatient expenditure (169.6 euros per capita), while Campania, Puglia and Basilicata are the regions with the highest public outpatient expenditure (280.6, 273.3 and 268.5 euros per capita, respectively). Considering also private expenditure, the A.P. of Bolzano (267.0 euros per capita) and Campania (423.4 euros per capita) are the regions with the lowest and highest level of expenditure, respectively (Table and Figure 1.2.8).

Table 1.2.1. Comparison of public and private outpatient expenditure (2016-2020)

		2016 *(million)*	2017 *(million)*	2018 *(million)*	2019 *(million)*	2020 *(million)*	Δ % 17-16	Δ % 18-17	Δ % 19-18	Δ % 20-19
1	Net expenditure under approved care regime	8,254	8,120	7,781	7,764	7,615	-1.6	-4.2	-0.2	-1.9
2	Class A medicines through direct and *per conto* distribution	5,556	4,792	4,620	4,481	4,259	-13.8	-3.6	-3.0	-4.9
1+2	**Public outpatient expenditure**	**13,810**	**12,913**	**12,402**	**12,245**	**11,875**	**-6.5**	**-4.0**	**-1.3**	**-3.0**
3	Citizen cost-sharing	1,540	1,549	1,608	1,582	1,487	0.6	3.8	-1.6	-6.0
4	Private purchases of class A medicines	1,309	1,317	1,360	1,544	1,528	0.6	3.3	13.5	-1.1
5	Class C medicines with prescription	2,642	2,813	2,875	3,066	3,269	6.5	2.2	6.6	6.6
6	Self-medication pharmaceuticals	2,429	2,109	2,270	2,392	2,134	-13.2	7.6	5.4	-10.8
7	Shops	301	286	266	259	250	-5.0	-7.0	-2.5	-3.7
3+4+5	**Total private expenditure**	**8,220**	**8,076**	**8,379**	**8,843**	**8,668**	**-1.8**	**3.8**	**5.5**	**-2.0**
	Total pharmaceutical expenditure	**22,030**	**20,988**	**20,781**	**21,088**	**20,542**	**-4.7**	**-1.0**	**1.5**	**-2.6**
	Share (%) borne by the NHS	62.7	61.5	59.7	58.1	57.8				

Source: OsMed analysis from "Traceability of medicines" flow (for private expenditure data). Analysis from IMS Health data for the estimate of private expenditure for 2016.

Table 1.2.2. Outpatient pharmaceutical expenditure: comparison 2016-2020

		2016 *(million)*	2017 *(million)*	2018 *(million)*	2019 *(million)*	2020 *(million)*	Δ % 17-16	Δ % 18-17	Δ % 19-18	Δ % 20-19
1+2+3+4	**Gross expenditure under approved care regime**	**10,638**	**10,499**	**10,141**	**10,089**	**9,820**	**-1.3**	**-3.4**	**-0.5**	**-2.7**
1+2	Citizen cost-sharing	1,540	1,549	1,608	1,582	1,487	0.6	3.8	-1.6	-6.0
1	Fixed co-payment (ticket)	518	499	482	459	409	-3.7	-3.4	-4.7	-10.9
2	Reference price share	1,022	1,050	1,126	1,123	1,078	2.7	7.2	-0.3	-4.0
3	Discount^	845	830	751	743	717	-1.8	-9.5	-1.1	-3.4
4	**Net expenditure under approved care regime**	**8,254**	**8,120**	**7,781**	**7,764**	**7,615**	**-1.6**	**-4.2**	**-0.2**	**-1.9**
5	Class A medicines through direct and *per conto* distribution°	5,556	4,792	4,620	4,481	4,259	-13.8	-3.6	-3.0	-4.9
4+5	**Public outpatient expenditure**	**13,810**	**12,913**	**12,402**	**12,245**	**11,875**	**-6.5**	**-4.0**	**-1.3**	**-3.0**

^Including the discount per price charged to pharmacies; extra-discounts following AIFA Decision of 15 June 2012 and art. 15, paragraph 2, of Law 135/2012 as well as both the discount from AIFA Decision of 30 December 2005, and the pay-back on agreement under art. 11, paragraph 6, of Law 122/2010, temporarily modified by Law 135/2012, charged to industry

°Expenditure for direct and *per conto* distribution of class A, including - in the case of Regions with missing data - 40% of pharmaceutical expenditure outside the approved care regime recorded with the "Traceability of medicines" flow, pursuant to Law 222/2007. In 2020 no Region implemented this condition.

Source: OsMed analysis from NSIS data

Figure 1.2.1. Outpatient pharmaceutical consumption: comparison 2014-2020

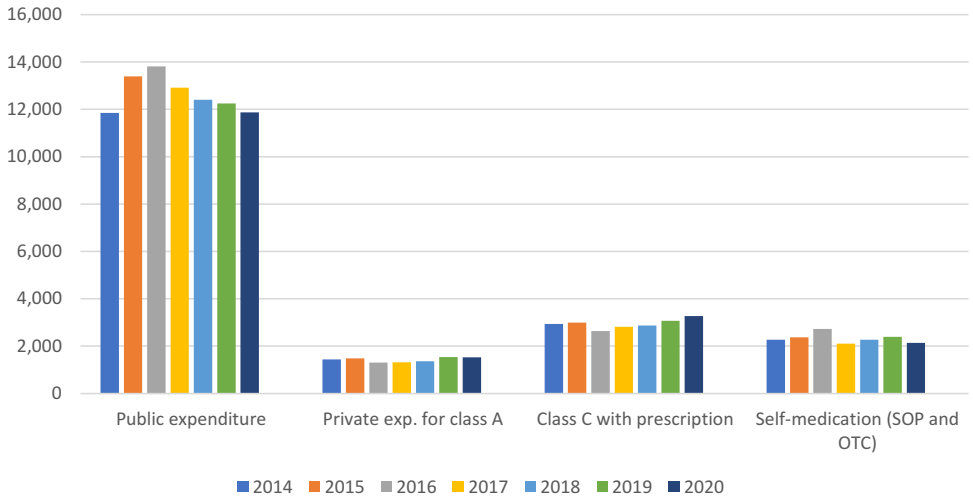


Table 1.2.3. Comparison of consumption for public and private outpatient care (2016-2020)

		2016 *(million)^*	2017 *(million)^*	2018 *(million)^*	2019 *(million)^*	2020 *(million)^*	Δ % 17-16	Δ % 18-17	Δ % 19-18	Δ % 20-19
	Prescriptions#	587	581	576	570	541	-1.0	-0.9	-1.0	-5.2
1	Approved care regime	1,117	1,110	1,102	1,083	1,034	-0.6	-0.7	-1.7	-4.6
2	Class A medicines paid by citizens*	210	216	162	190	217	2.9	-25.0	17.4	13.9
3	Direct and *per conto* distribution of class A medicines	86	105	105	112	101	22.1	0.0	6.6	-9.5
1+2+3	**Total class A medicines**	**1,414**	**1,430**	**1,369**	**1,385**	**1,351**	**1.1**	**-4.3**	**1.2**	**-2.4**
4	Class C medicines with prescription	209	222	229	234	243	6.2	3.2	2.1	4.0
5	Self-medication pharmaceuticals (SOP and OTC)	259	231	241	242	248	-10.8	4.3	0.6	2.2
6	Shops	32	30	29	28	27	-6.3	-3.3	-4.0	-1.9
4+5+6	**Total Class C medicines**	**501**	**484**	**498**	**504**	**518**	**-3.4**	**2.9**	**1.2**	**2.8**
1+2+3 +4+5	Total packs	1,915	1,914	1,867	1,889	1,870	-0.1	-2.5	1.2	-1.0
	DDD/1000 inhab. per day[#]	971.4	969.7	978.8	996.3	993.1	-0.2	0.9	1.8	-0.3

^Only the number of prescriptions and packs is expressed in millions of units

[#] Related to the consumption of class A medicines dispensed under the approved care regime.

* The amount of private expenditure of medicines reimbursed by the NHS is obtained by calculating the difference between the total expenditure (estimated through the "Traceability of medicines" flow data) and the expense borne by the NHS (obtained from OsMed data).

Source: OsMed analysis from "Traceability of medicines" flow (for private expenditure data). Analysis from IMS Health data for the estimate of private expenditure for 2016.

Table 1.2.4. Regional variability of pharmaceutical consumption through local, public and private pharmacies: year 2020 (Table and Figure)

Region	Class A medicines reimbursed by the NHS					Private purchases of class A, class C SOP and OTC medicines (per capita expenditure)	
	Gross expenditure A-NHS^	Gross expenditure (per capita) in absolute terms	Δ % 20-19	DDD/ 1000 inhab. per day	Δ % 20-19	Gross	Δ % 20-19
Piedmont	625	138.2	-4.8	911.8	-1.8	130.8	-11.5
Valle d'Aosta	17	131.9	-3.1	821.1	-0.5	141.5	4.9
Lombardy	1,759	176.4	0.0	920.1	-0.8	127.1	-1.2
A.P. of Bolzano	57	114.4	-2.8	708.4	-1.8	97.5	-9.0
A.P. of Trento	73	135.6	-2.3	902.4	-0.6	94.2	-8.4
Veneto	644	131.0	-3.3	869.3	-1.7	112.2	-8.0
Friuli VG	186	144.6	-3.0	961.2	0.2	106.6	-19.2
Liguria	243	144.2	-3.8	866.8	-1.1	146.3	-3.0
Emilia Romagna	562	123.6	-2.8	943.5	0.9	108.0	-4.8
Tuscany	521	134.7	-3.1	968.4	-0.1	116.1	0.1
Umbria	149	164.1	-3.2	1121.2	0.4	78.3	27.5
Marche	247	157.7	-5.0	1002.5	-1.3	87.1	30.8
Lazio	1,034	182.1	-4.5	1071.4	-1.3	118.2	-4.4
Abruzzo	234	177.8	-2.9	1043.2	0.3	105.7	6.6
Molise	51	163.1	-3.1	1004.0	0.2	84.0	-7.8
Campania	1,038	197.3	-2.6	1123.8	0.8	142.8	21.4
Puglia	718	185.0	-3.8	1106.6	-0.2	97.9	-16.7
Basilicata	101	181.4	-1.8	1062.5	1.5	81.8	-4.4
Calabria	348	188.8	-4.0	1108.9	0.3	94.0	5.0
Sicily	836	178.1	-1.4	1083.6	1.0	112.6	22.0
Sardinia	279	167.8	-0.9	1019.8	1.4	93.5	-11.0
Italy	**9,722**	**163.0**	**-2.7**	**993.1**	**-0.3**	**116.2**	**-0.8**
North	4,166	148.3	-2.1	907.8	-0.8	121.1	-6.0
Centre	1,951	162.3	-4.1	1033.1	-0.8	110.4	1.3
South and Islands	3,606	184.6	-2.6	1091.3	0.6	112.6	7.0

Amounts in million euros
^Expenditure for class A medicines net of class C reimbursed medicines (32.4 million euros) and including expenditure for vaccines

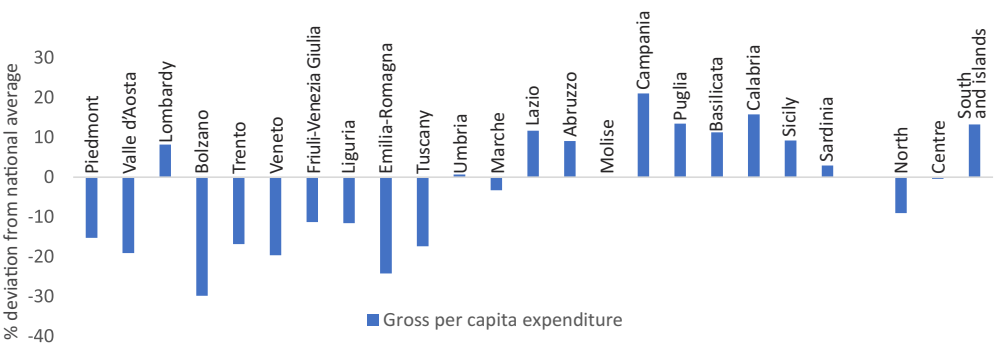


Table 1.2.5. Composition of expenditure for medicines supplied under approved care regime in 2020

Region	Gross expenditure *(million)*	Citizen cost-sharing				Discount *(million)*	Net expenditure^ *(million)*
		Fixed co-payment (ticket)	Δ % 20-19	Reference price	Δ % 20-19		
Piedmont	626.8	00.3	-23.1	63	-5.5	41.59	522.1
Valle d'Aosta	17.0	1.4	-7.7	2	-2.4	1.02	12.9
Lombardy	1787.1	118.1	-9.7	137	-4.1	145.34	1,386.5
A.P. of Bolzano	57.0	4.1	-5.4	6	-3.5	4.14	42.9
A.P. of Trento	73.1	0.1	-97.6	7	-2.6	4.91	61.3
Veneto	647.9	54.3	-7.9	68	-2.8	42.28	483.4
Friuli VG	186.8	0.0	-	19	-3.3	12.66	155.4
Liguria	244.0	17.4	-5.6	25	-4.8	16.03	185.4
Emilia R.	565.1	2.1	-38.7	64	-2.0	34.37	464.8
Tuscany	525.0	12.0	-37.1	52	-3.3	36.34	424.9
Umbria	149.5	0.4	-85.9	18	-1.9	10.11	120.9
Marche	246.9	0.0	-	29	-5.6	17.41	200.3
Lazio	1042.1	20.3	-10.7	140	-4.6	81.19	800.7
Abruzzo	236.0	6.9	-8.2	27	-3.6	15.95	186.0
Molise	51.3	2.5	-4.3	7	-3.2	3.05	39.1
Campania	1052.2	71.2	-6.4	131	-3.0	78.30	771.8
Puglia	723.6	42.7	-6.4	84	-4.8	54.22	542.3
Basilicata	101.3	3.5	-45.4	12	-1.6	6.93	78.4
Calabria	350.2	9.2	-9.0	46	-4.9	22.31	273.0
Sicily	857.7	42.8	-5.8	113	-5.4	69.96	632.0
Sardinia	279.9	0.0	-	29	-2.7	19.44	231.5
Italy	**9,820.2**	**409.3**	**-10.9**	**1,078**	**-4.0**	**717.57**	**7,615.4**

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

Source: Italian Medicines Agency DCR (Summary Accounting Statement)

Table 1.2.6. Regional variability of 2020 pharmaceutical consumption under approved care regime by quantity, average cost per day of therapy and expenditure (% deviations from national average)

Region	% deviation from national average			Type of expenditure
	DDD/1000 inhab. per day	Average DDD cost	Gross per capita expenditure	
Campania	13	7	21	1
Calabria	12	4	16	2
Puglia	11	2	13	3
Lazio	8	3	12	4
Basilicata	7	4	11	5
Lombardy	-7	18	9	6
Sicily	9	0	9	7
Abruzzo	5	4	9	8
Sardinia	3	0	3	9
Umbria	13	-11	0	10
Molise	1	-1	0	11
Marche	1	-4	-3	12
Friuli VG	-3	-8	-11	13
Liguria	-13	1	-12	14
Piedmont	-8	-8	-15	15
Trento	-9	-9	-17	16
Tuscany	-3	-15	-18	17
Valle d'Aosta	-17	-2	-19	18
Veneto	-12	-8	-20	19
Emilia R.	-5	-20	-24	20
Bolzano	-29	-2	-30	21

Figure 1.2.2. Trend of class A-NHS pharmaceutical expenditure under approved care regime in the period 2010-2020: consumption, price and mix effect

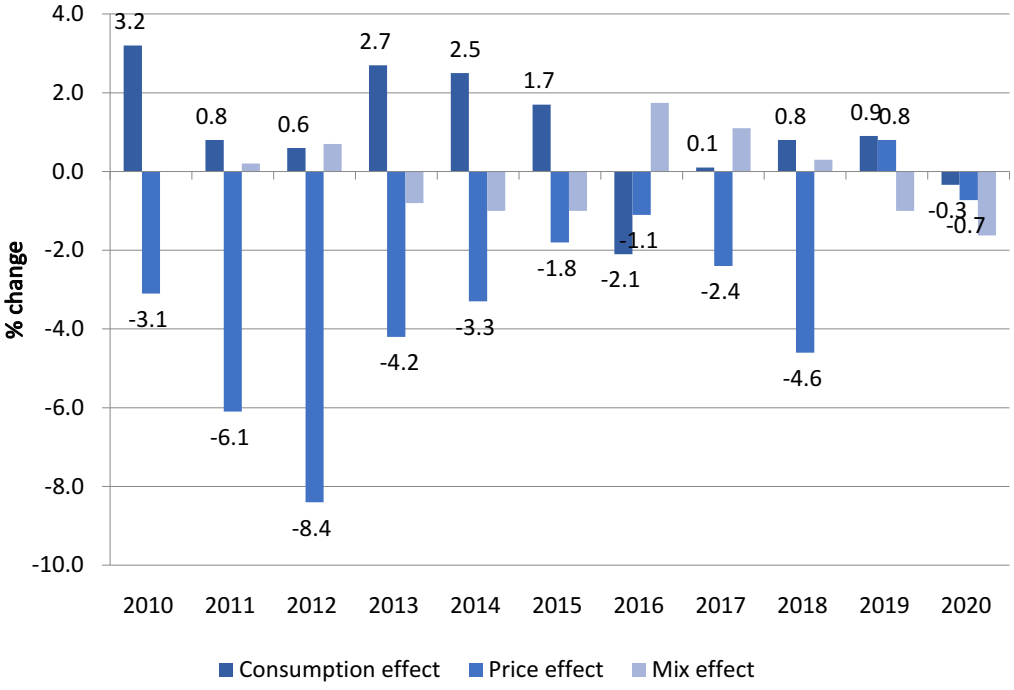


Table 1.2.7. Consumption, price and mix effect on the variation in class A-NHS pharmaceutical expenditure under approved care regime: comparison 2020-2019

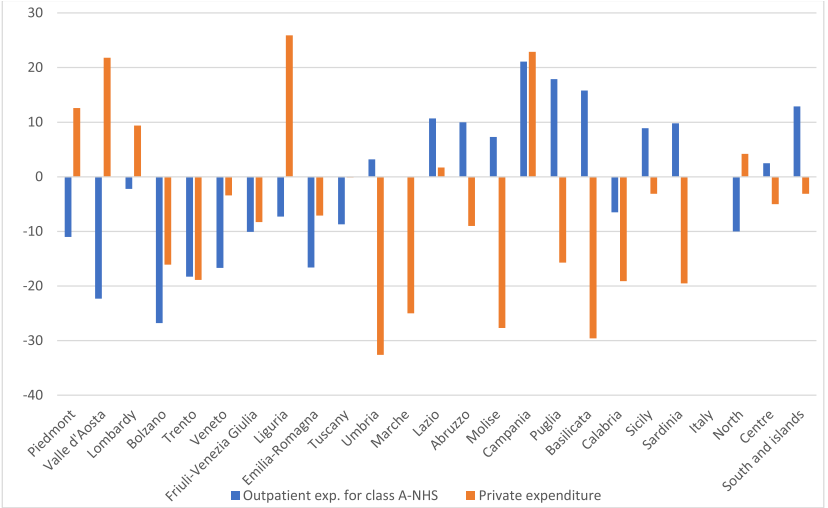
Region	Gross expenditure 2020 *(million)*	Δ % 20-19				Δ % cost average DDD
		Expenditure	DDD	Prices	Mix	
Piedmont	625.4	-4.8	-2.1	-1.0	-1.7	-2.8
Valle d'Aosta	16.9	-3.1	-0.7	-4.3	1.9	-2.5
Lombardy	1759.1	0.0	-0.6	-0.9	1.5	0.6
A.P. of Bolzano	56.9	-2.8	-1.4	-2.2	0.7	-1.5
A.P. of Trento	72.7	-2.3	-0.1	-1.9	-0.3	-2.2
Veneto	643.9	-3.3	-1.6	-1.0	-0.8	-1.7
Friuli VG	185.6	-3.0	0.0	-1.3	-1.7	-3.0
Liguria	243.1	-3.8	-1.7	-1.3	-0.9	-2.2
Emilia Romagna	562.2	-2.8	0.9	-1.2	-2.5	-3.7
Tuscany	520.5	-3.1	-0.3	-1.1	-1.8	-2.9
Umbria	149.3	-3.2	0.2	-2.2	-1.3	-3.4
Marche	246.6	-5.0	-1.6	-1.2	-2.3	-3.5
Lazio	1034.3	-4.5	-1.3	-1.4	-1.8	-3.2
Abruzzo	234.4	-2.9	0.2	-1.4	-1.8	-3.1
Molise	50.7	-3.1	-0.2	-2.8	-0.2	-3.0
Campania	1038.1	-2.6	0.8	-1.1	-2.4	-3.5
Puglia	718.0	-3.8	-0.2	-0.9	-2.7	-3.6
Basilicata	100.8	-1.8	1.0	-1.9	-0.9	-2.8
Calabria	347.9	-4.0	0.0	-1.4	-2.5	-3.9
Sicily	836.4	-1.4	0.8	-1.0	-1.2	-2.2
Sardinia	279.3	-0.9	1.6	-1.3	-1.2	-2.5
Italy	**9,722.0**	**-2.7**	**-0.3**	**-0.7**	**-1.6**	**-2.3**

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

Table 1.2.8. Per capita outpatient pharmaceutical expenditure (public and private) in 2020 (weighted population) % deviation from national average (Figure)

Region	Public outpatient^ expenditure for class A-NHS medicines (per capita)	Per capita private expenditure (A, C, SOP and OTC)	Outpatient pharmaceutical expenditure (per capita)
Piedmont	206.3	130.8	337.1
Valle d'Aosta	180.2	141.5	321.7
Lombardy	226.7	127.1	353.8
Bolzano	169.6	97.5	267.0
Trento	189.4	94.2	283.6
Veneto	193.2	112.2	305.4
Friuli VG	208.4	106.6	315.0
Liguria	214.8	146.3	361.1
Emilia Romagna	193.3	108.0	301.4
Tuscany	211.7	116.1	327.8
Umbria	239.2	78.3	317.5
Marche	231.9	87.1	319.0
Lazio	256.5	118.2	374.7
Abruzzo	254.9	105.7	360.6
Molise	248.8	84.0	332.8
Campania	280.6	142.8	423.4
Puglia	273.3	97.9	371.2
Basilicata	268.5	81.8	350.2
Calabria	216.7	94.0	310.7
Sicily	252.4	112.6	365.1
Sardinia	254.5	93.5	348.0
Italy	**231.8**	**116.2**	**348.0**
North	208.7	121.1	329.8
Centre	237.6	110.4	348.0
South and Islands	261.6	112.6	374.2

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



1.3 Medicines purchased by public health facilities

Expenditure on the purchase of medicines by public health facilities (hospitals, direct and *per conto* distribution) amounted to around 13.5 billion euros (222.87 euros per capita; Table 1.1.1 and Table 1.3.1) and registered a limited increase (+0.9%) compared to 2019. Consumption, with an average of 170.3 DDD/1000 inhabitants per day, increased compared to the previous year (+1.5%). 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 real pharmaceutical dose administered to the patient. Although this assumption is also valid in cases where DDD is used to parametrize outpatient consumption (for example in the paediatric population), it becomes even more valid in an inpatient setting, where the dose of a medicine can vary depending on the patient's care needs. Regions with the highest expenditure were Campania (256.55 euros per capita), Umbria (251.77 euros per capita) and Puglia (248.77 euros per capita). Conversely, Valle d'Aosta (163.07 euros per capita), the A.P. of Trento (184.80 euros per capita) and Lombardy (186.98 euros per capita) showed the lowest values.

Most Regions registered an increase in expenditure, with the largest changes compared to 2019 emerging in Tuscany (+6.7%), Liguria (+5.5%) and Abruzzo (+5.2%).

In terms of consumption, Emilia Romagna (298.88 DDD) and Lombardy (108.92 DDD) represent the regions with the highest and lowest levels of consumption, respectively. In 2020, almost all Regions recorded an increase in consumption compared to 2019, with the exception of Marche (-6.1%), Friuli Venezia Giulia (-5.8%) and Emilia Romagna (-5.2%). Molise and Piedmont recorded the largest increases (+13.6% and +7.3%, respectively).

An analysis of the relationship between average cost and purchases of medicines by public health facilities (Table and Figure 1.3.2) shows that only Friuli Venezia Giulia consumes more quantities of and more expensive active ingredients. Molise, Basilicata, Lazio, Calabria, Campania, Puglia, Lombardy, Abruzzo, Sardinia and Sicily registered lower consumption, but with an average cost per DDD higher than the national average. Emilia Romagna, Marche, Veneto, Tuscany, Umbria, Liguria, Piedmont, Valle d'Aosta, A.P. of Bolzano and A.P. of Trento consumed higher quantities but with a lower average cost per DDD. Table 1.3.3 analyses the elements that contributed to the change in expenditure for purchases by public health facilities. Expenditure under approved care regime in 2020 increased by 0.6% at national level, driven by a 1.5% increase in consumption, a 6.2% price reduction and a shift in purchases towards more expensive specialities (mix effect: +5.5%). The average cost per DDD is also reduced by 0.9%, with the largest changes recorded in Molise (-11.5%), Sicily (-5.6%) and Campania (-5.3%). The highest increases in average cost per DDD were observed in Marche (+10.6%), Friuli Venezia Giulia (+6.0%) and Veneto (+4.0%).

Table 1.3.1. Expenditure and consumption for medicines purchased by public health facilities: comparison 2020-2019 (weighted population) (Table and Figure)

Region	Per capita NHS expenditure		DDD/1000 inhab. per day	
	€	Δ % 20-19	NO.	Δ % 20-19
Piedmont	214.04	2.7	192.73	7.3
Valle d'Aosta	163.07	0.7	181.21	4.0
Lombardy	186.98	-1.2	108.92	-0.2
A.P. of Bolzano	213.47	0.5	185.03	4.0
A.P. of Trento	184.80	1.5	183.28	4.4
Veneto	211.82	4.7	212.98	0.4
Friuli VG	230.71	0.1	174.48	-5.8
Liguria	228.09	5.5	211.94	8.4
Emilia Romagna	230.16	-1.3	298.88	-5.2
Tuscany	242.49	6.7	211.01	3.4
Umbria	251.77	3.3	218.14	4.2
Marche	247.93	4.1	222.06	-6.1
Lazio	223.60	1.2	134.22	3.0
Abruzzo	248.16	5.2	147.03	5.4
Molise	224.24	0.9	128.84	13.6
Campania	256.55	-0.9	152.10	4.4
Puglia	248.77	-1.6	150.55	3.1
Basilicata	247.40	-0.6	145.43	3.0
Calabria	237.16	-1.4	140.21	1.5
Sicily	203.75	-2.6	135.60	2.9
Sardinia	238.29	2.0	168.19	6.7
Italy	**222.87**	**0.9**	**170.31**	**1.5**
North	207.46	1.0	183.66	0.2
Centre	234.97	3.5	176.70	1.6
South and Islands	237.58	-0.8	147.17	3.9

Source: OsMed analysis from NSIS data concerning the "Traceability of medicines" flow - Ministerial Decree 15 July 2004

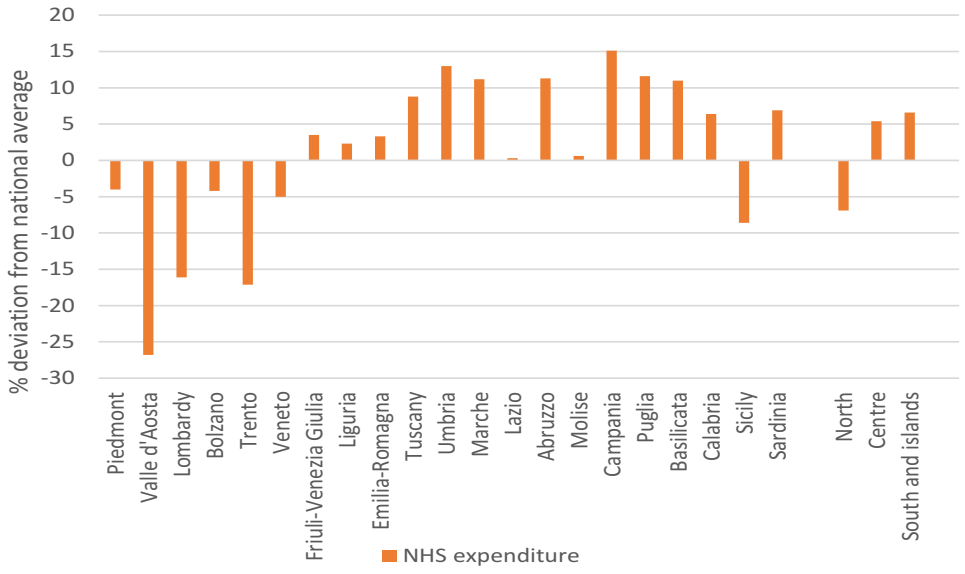


Table 1.3.2. Regional variability of consumption of medicines purchased by public health facilities in 2020 by quantity, average cost per day of therapy and expenditure (% deviations from national average)

Region	% deviation from national average			Type of expenditure
	DDD/1000 inhab. per day	Average cost per DDD	Gross per capita expenditure	
Campania	-11	29	15	1
Umbria	28	-12	13	2
Puglia	-12	26	12	3
Abruzzo	-14	29	11	4
Marche	30	-15	11	5
Basilicata	-15	30	11	6
Tuscany	24	-12	9	7
Sardinia	-1	8	7	8
Calabria	-18	29	6	9
Friuli VG	2	1	4	10
Emilia Romagna	75	-41	3	11
Liguria	24	-18	2	12
Molise	-24	33	1	13
Lazio	-21	27	0	14
Piedmont	13	-15	-4	15
Bolzano	9	-12	-4	16
Veneto	25	-24	-5	17
Sicily	-20	15	-9	18
Lombardy	-36	31	-16	19
Trento	8	-23	-17	20
Valle d'Aosta	6	-31	-27	21

Table 1.3.3. Consumption, price and mix effect on the variation of expenditure for medicines purchased by public health facilities: comparison 2020-2019

Region	Gross expenditure 2020 *(million)*	Δ % 20-19				Δ % 20-19 average DDD cost
		Expenditure	DDD	Prices	Mix	
Piedmont	968.86	2.1	7.0	-6.9	2.5	-4.5
Valle d'Aosta	20.91	0.3	3.9	-11.5	9.1	-3.4
Lombardy	1,864.77	-1.3	0.1	-6.6	5.7	-1.3
A.P. of Bolzano	106.20	0.7	4.5	-8.5	5.4	-3.6
A.P. of Trento	99.07	1.7	5.0	-10.1	7.7	-3.1
Veneto	1,040.72	4.6	0.6	-4.7	9.0	4.0
Friuli VG	296.08	-0.3	-6.0	-7.9	15.1	6.0
Liguria	384.58	4.6	7.7	-6.8	4.1	-2.9
Emilia Romagna	1,047.10	-1.6	-5.2	-6.1	10.5	3.8
Tuscany	937.32	6.2	3.2	-7.4	9.6	2.9
Umbria	229.18	2.8	4.0	-9.2	8.9	-1.1
Marche	387.71	3.6	-6.4	-6.3	18.0	10.6
Lazio	1,269.76	1.0	3.0	-5.9	4.2	-2.0
Abruzzo	327.19	4.8	5.2	-5.2	5.1	-0.4
Molise	69.74	0.2	13.2	-7.7	-4.0	-11.5
Campania	1,349.55	-1.1	4.5	-6.1	0.8	-5.3
Puglia	965.58	-1.9	3.1	-7.1	2.5	-4.8
Basilicata	137.47	-1.3	2.5	-5.5	2.0	-3.7
Calabria	436.93	-2.0	1.2	-6.2	3.2	-3.2
Sicily	956.93	-3.0	2.7	-6.3	0.7	-5.6
Sardinia	396.51	1.9	6.9	-7.4	2.9	-4.7
Italy	**13,292.17**	**0.6**	**1.5**	**-6.2**	**5.5**	**-0.9**

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, 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 *per conto* distribution, a description of the distribution of consumption and expenditure, as well as 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 reimbursed by the NHS (*Tessera sanitaria*) and provided through public and private pharmacies. This flow covers the whole Italian population.

Overall, in 2020 a little less than 40 million people received at least one pharmaceutical prescription, with a prevalence of use equal to 62.8%, a per capita expenditure equal to 195 euros and a consumption of 1,033 DDD/1000 inhabitants per day (this suggests that, on average, every Italian citizen received a dose of medication every day of the year) (Tables 1.4.1 and 1.4.2).

There is a slight difference in the exposure to medication between the two genders, with a prevalence of 57.4% in men and of 65.5% in women. As far as consumption and expenditure are concerned, the number of doses registered are 1,038 DDD in men and 1,028 in women, whereas pharmaceutical expenditure is equal to 192 euros per capita in men and 197 euros per capita in women (Table 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 +64 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 subjects in younger age groups (Table 1.4.1). This result is due to both change in the prevalence of use and consumption. The prevalence of use ranges from about 50% in children and adults up to 50 years of age, to over 95% in the elderly population aged 74 years and above. It then decreases in the 75-79 age group, but equals 100% in the population aged +79 years. Consumption is maintained between 274 and 428 DDD/1000 inhabitants per day in the 40-49 age group and reaches over 3,000 in the population over 75 years of age (Figure 1.4.1-1.4.2 and Table 1.4.1). This shows that a patient aged over 75 years is administered at least 3 daily defined doses every day of the year. The population over 64 years of age accounts for more than 60% of expenditure and about 70% of DDD (Table 1.4.1).

Gender differences can be seen especially in the 20-64 age group, where women show a prevalence of use higher than men (Figure 1.4.1). Compared with a national prevalence of use of 62.8%, values at regional level range between 48.5% in the A.P. of Bolzano and 70.5% in Molise (Table 1.4.2). Generally, Northern Regions have a lower prevalence (59.6%) compared to Central (64.8%) and Southern (65.8%) ones. Expenditure of 328 euros was incurred for each user in the South, compared with 314.5 euros in the Centre and 294.0 euros in the North. These differences are also due to increased consumption and probably also to the prescription of more expensive specialties and to a reduced use of generic medicines. Higher doses per user are given in the Centre (615.9 DDD) and in the South (609.1 DDD) compared to the North (586.7 DDD). This may reflect a different epidemiological pattern of disease severity and the presence of comorbidity. The average

age of users is significantly higher in the Centre (65 years), compared to the North and the South (57 years).

Table 1.4.1. Breakdown of outpatient expenditure and consumption by age group in 2020

Age group	Gross per capita expenditure					Total expenditure			DDD/1000 inhab. per day	
	Men	Women	Total	%	% cum.	Men	Women	Total	%	% cum.
0-4	13	11	12	0.2	0.2	32	27	29	0.1	0.1
5-9	19	16	17	0.4	0.6	37	30	33	0.1	0.3
10-14	29	22	26	0.6	1.3	47	37	43	0.2	0.4
15-19	37	24	31	0.8	2.0	68	67	68	0.3	0.8
20-24	32	32	32	0.8	2.8	85	102	93	0.4	1.2
25-29	36	38	37	1.0	3.8	102	127	114	0.6	1.8
30-34	42	50	46	1.3	5.1	127	165	146	0.8	2.6
35-39	52	64	58	1.8	6.9	177	212	194	1.1	3.7
40-44	68	78	73	2.6	9.6	269	278	274	1.9	5.6
45-49	94	101	97	4.0	13.6	440	417	428	3.3	8.9
50-54	133	136	135	5.7	19.2	698	635	666	5.3	14.1
55-59	201	188	195	7.6	26.8	1,122	953	1,035	7.6	21.8
60-64	292	256	273	9.1	36.0	1,685	1,360	1,516	9.6	31.3
65-69	406	346	374	11.2	47.1	2,371	1,899	2,124	11.9	43.3
70-74	545	468	504	14.4	61.5	3,201	2,620	2,892	15.6	58.8
75-79	617	529	569	12.9	74.4	3,582	2,975	3,246	13.9	72.7
80-84	737	627	673	12.9	87.2	4,211	3,529	3,813	13.7	86.4
85+	791	627	681	12.8	100.0	4,425	3,552	3,841	13.6	100.0
Total	**192**	**197**	**195**			**1,038**	**1,028**	**1,033**		

Figure 1.4.1. Trend in prevalence of use of outpatient pharmaceuticals by age and gender in 2020

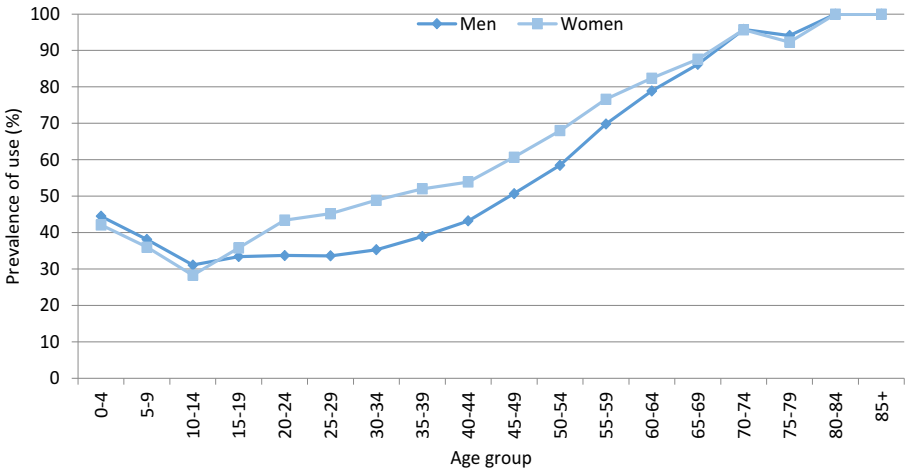


Figure 1.4.2. Trend in outpatient DDD/1000 inhabitants per day in 2020 by age and gender

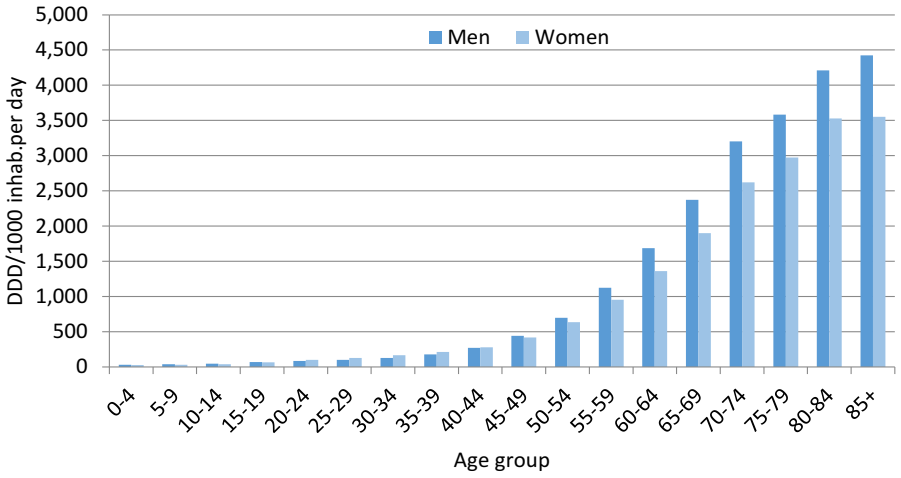


Table 1.4.2. Prevalence and intensity of use in an outpatient setting by Region (2020)

Region	Prevalence (%)	Average age	M/W	Per user expenditure	DDD per user	Packs per user
Piedmont	61.8	55	0.82	286.2	599.2	27.8
Valle d'Aosta	59.6	53	0.82	256.7	537.1	25.5
Lombardy	58.2	56	0.84	340.9	585.6	27.3
A.P. of Bolzano	48.5	53	0.82	261.4	520.0	23.6
A.P. of Trento	62.8	54	0.84	253.9	538.6	26.1
Veneto	57.4	56	0.84	274.7	585.1	26.5
Friuli VG	61.4	55	0.81	310.7	630.2	29.4
Liguria	61.9	55	0.80	311.4	603.9	28.3
Emilia R.	62.9	55	0.83	221.1	574.6	26.6
Tuscany	62.5	57	0.82	269.6	619.7	28.0
Umbria	67.9	55	0.82	328.8	667.3	31.1
Marche	67.2	55	0.84	299.4	602.4	28.4
Lazio	65.1	64	0.82	343.7	609.1	29.5
Abruzzo	70.3	55	0.85	305.5	575.0	28.1
Molise	70.5	55	0.85	314.7	574.7	28.4
Campania	65.7	56	0.84	343.9	605.3	30.1
Puglia	69.0	55	0.84	325.2	591.5	29.3
Basilicata	69.4	55	0.84	319.1	592.8	29.5
Calabria	62.5	55	0.84	352.9	642.0	32.2
Sicily	62.8	55	0.83	318.9	630.4	29.9
Sardinia	66.0	56	0.82	302.5	610.5	29.2
Italy	**62.8**	**55**	**0.83**	**310.3**	**600.7**	**28.5**
North	59.6	57	0.83	294.0	586.7	27.2
Centre	64.8	65	0.82	314.5	615.9	29.0
South and islands	65.8	57	0.84	328.0	609.1	29.8

1.5. Trend in pharmaceutical consumption on a monthly basis

Figure 1.7.1 shows the trend in consumption of class A-NHS medicines in DDD/1000 inhabitants per day during the period 2004-2020.
Over the last seventeen years, pharmaceutical consumption has registered a growing trend, increasing from 763.8 DDD/1000 inhabitants per day in 2004 to 993.1 DDD/1000 inhabitants per day in 2020.
In addition to being characterised by an increasing trend, pharmaceutical consumption is associated with seasonal variations, as shown by peaks identifiable on a monthly basis (see Figure 1.7.1).
As a result of this seasonality, during the first half of 2020 consumption was higher than the annual average by 10%. In contrast, during the second half of the year, consumption decreased by 2%. In particular, consumption in August were 17% lower than the average.
Generally, systemic antimicrobials and respiratory medicines are the therapeutic categories on which consumption seasonality has the highest impact. Figure 1.7.2 shows the time trend of DDD/1000 inhabitants per day of class C medicines with prescription starting from January 2004. The trend in consumption could be affected by regulatory decisions granting (or not) the status of reimbursed medicine over time. Starting from 2004, a downward trend in consumption of such medicines has been observed, with an average change ranging from 236.5 DDD in 2004 to 197.1 DDD in 2020 (-17%). Similarly to 2019, a 2% increase in the consumption of these medicines was registered in 2020 compared to the previous year (for further details Section 2.6). In 2020 the highest average consumption was recorded in September (231.8 DDD/1000 inhabitants per day) and January (215.4 DDD/1000 inhabitants per day), whereas the lowest levels were observed in August (157.0 DDD/1000 inhabitants per day).
Figure 1.7.3 shows the trend in consumption of medicines purchased by public health facilities in the period 2006-2020. Consumption shows a growing trend, with an average ranging from 100.6 DDD/1000 inhabitants per day during 2006 up 170.3 DDD/1000 inhabitants per day in 2020. During 2020 the lowest levels of consumption were observed in August (100.3 DDD/1000 inhabitants per day) and May (125.8 DDD/1000 inhabitants per day), whereas March (240.7 DDD/1000 inhabitants per day) and January (221.8 DDD/1000 inhabitants per day) registered the highest 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 since it is impacted by such purchases by public health facilities. This may be verified by looking at irregularities in the volume of monthly purchases by public health facilities registered over the last fifteen years.

Figure 1.7.1. Consumption trend of class A-NHS medicines (DDD/1000 inhab. per day) under approved care regime, period 2004-2020

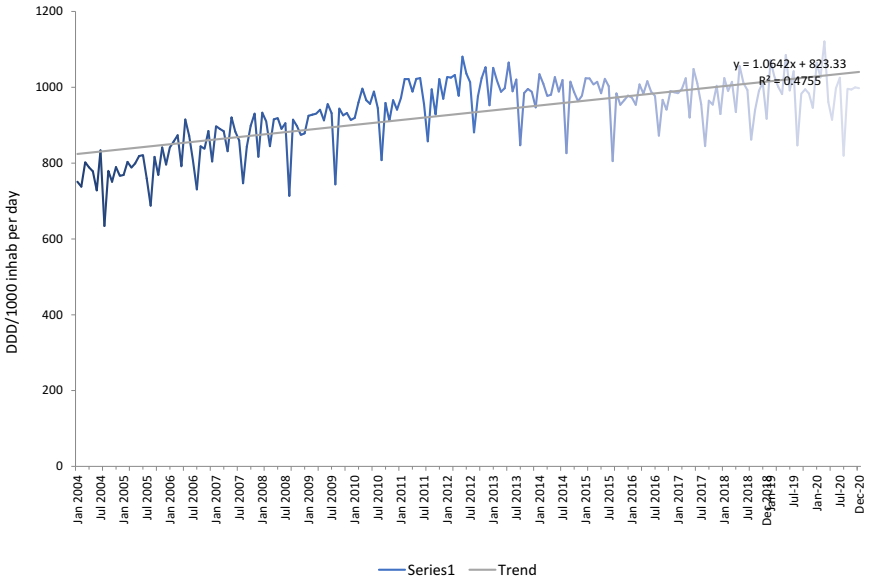


Figure 1.7.2. Consumption trend of class C medicines with prescription (DDD/1000 inhab. per day), period 2004-2020

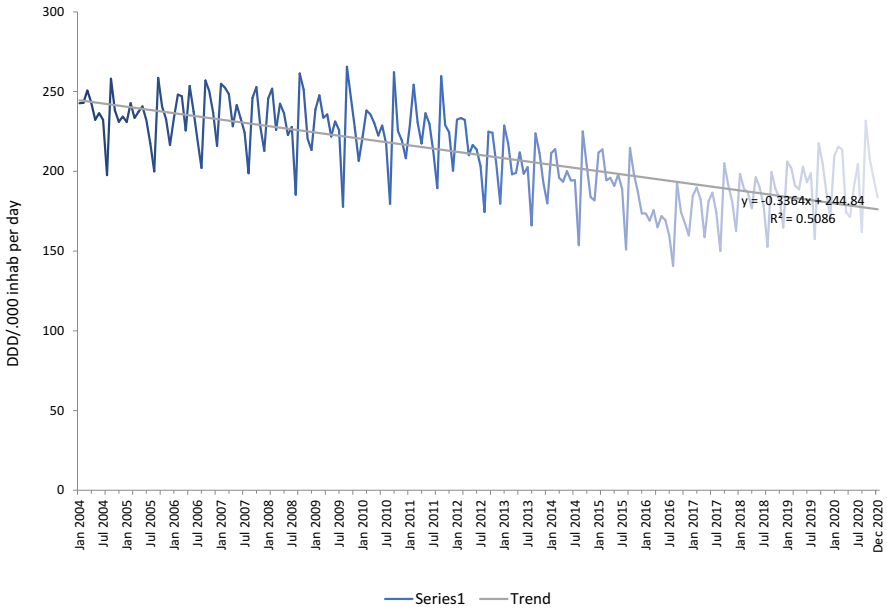
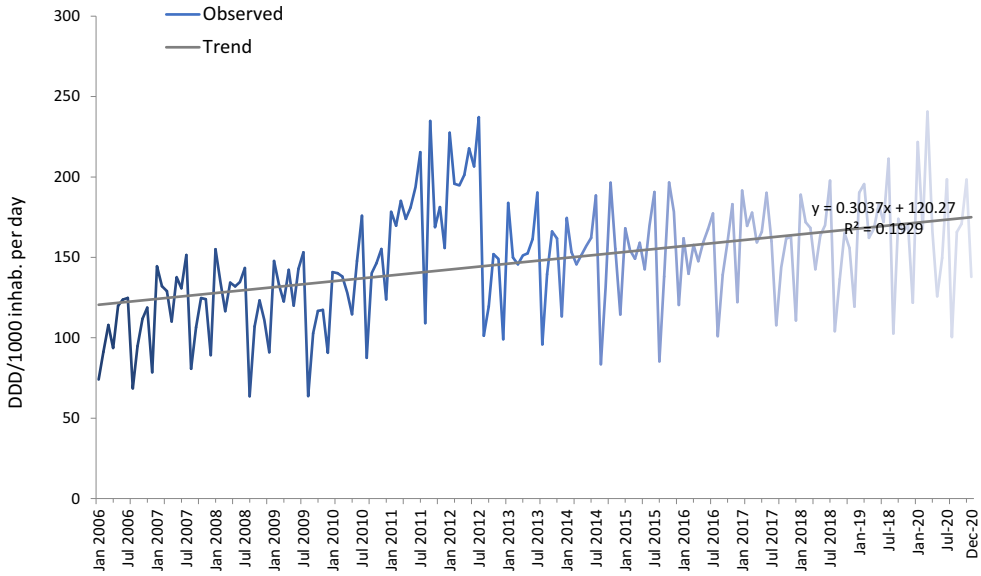


Figure 1.7.3. Consumption trend of medicines purchased by public health facilities (DDD/1000 inhab. per day), period 2006-2020



1.6 Time trend in pharmaceutical prices

Data in Figure 1.8.1 show the trend in average weighted price per package and average weighted price per DDD of class A-NHS medicines in the period between January 2004 and December 2020. The time series show a decreasing trend for both prices, especially from 2006 and in the period 2011-2012. This decline was mostly driven by the patent expiring of important pharmaceutical molecules (such as valsartan and atorvastatin) during that period, by measures of price reduction implemented at national level at the beginning of 2006, and by the economic effects resulting from AIFA decision of 8 April 2011. These measures resulted in a reduction in reference prices of medicinal products included in Transparency Lists, on the basis of a comparison between prices of generic medicines in Italy and the same pharmaceutical packages marketed in Germany, UK, France and Spain. Also in 2018 there was a reduction in average prices, taking into account the entry into the market of generic medicines of high consumption molecules such as rosuvastatin, the simvastatin/ezetimibe combination, and tadalafil and dutasteride.

Figure 1.8.2 shows the trend in average weighted price per package and per DDD of class C medicines with prescription in the period 2004-2020. Looking at monthly data of time series, the trend of the two indexes shows a steady growth from 10.13 euros per package (0.61 euros per DDD) in 2004 up to 13.4 euros per package (0.76 euros per DDD) in 2020, resulting in an increase of +32.3% and of +24.6% respectively, compared to 2004. 2019 is an odd year in which pharmaceutical companies are allowed to change the price of these medicines, and an increase of 5.6% was recorded compared to 2018[1] 2020 was an even year and prices remained somewhat stable, with an average change of approximately 2% (for further details see Section 2.6).

Figure 1.8.3 shows the trend in average weighted price per package and per DDD of medicines purchased by public health-facilities in the period 2006-2020. Average prices increased from 2006 to 2010; they remained stable between 2011 and 2012, and then increased again in the period 2013-2017. Since 2018, a slowdown in growth has been observed, probably due to the marketing of biosimilars and generics of highly used medicines. In this section, some categories of medicines, for which biosimilars and generics were marketed in the above mentioned period, are therefore further explored with the aim of analysing the time trend of average price both for package and DDD.

Figure 1.8.4 shows the trend over the period 2016-2020 relating to teriparatide prices, whose first biosimilar was placed on the market in September 2019. This molecule is mainly dispensed through the approved care regime channel, with 74% of the doses provided by public and private local pharmacies.

Within direct purchases, there was a decrease in prices with a 17.3% change in the price per package and in the price per DDD in the 12 months following the marketing of its biosimilar compared to the previous 12 months. Concerning the approved care regime, the price reduction was much lower, by around 7.5%.

Figure 1.8.5 shows the trend in average prices per DDD and per package of trastuzumab purchased by public health facilities.

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

The biosimilar of trastuzumab was placed on the Italian market in September 2018. By analysing the trend in prices in the 12 months prior to and after the marketing of the biosimilar, the price per DDD and the price per package show a decrease of 32.5% and 39.8% respectively. A further analysis (Figure 1.8.6) concerns the price of bevacizumab whose biosimilar was marketed in June 2020. Values increased from an average price per DDD of 74.2 euros in May 2020 to 47.2 euros in December 2020, showing an overall deviation of 36.4% of the price per DDD (for further details see Section 2.1 and Section 4). As regards pegfilgrastim, whose biosimilar has been marketed since February 2019, there is a 30% price reduction both per DDD and per package in the 12 months following the marketing of the biosimilar, compared to the same period prior to marketing (Figure 1.8.7). Figure 1.8.8 represents the trend in price per DDD and per package of miglustat, whose generic has been marketed since February 2019. Comparing the 12 months before and after the marketing of the generic, a price reduction per DDD and per package of approximately 10% emerged. If, on the other hand, the price in the month preceding the marketing of the generic and the last price recorded in December 2020 is taken as reference, a much larger reduction (+60%) can be seen. Figure 1.8.9 presents the trend in price per DDD and per package of glatiramer, whose complex generic has been marketed since March 2017. Price reductions appears as of July 2018 and the change between the price recorded in June 2018 and that recorded in December 2020 is around -65%, both per DDD and per package. Figure 1.8.10 shows the trend in prices per DDD and per package for gefitinib and erlotinib, both EGFR tyrosine kinase inhibitors. The generic of gefitinib was marketed in July 2019, and by comparing the 12 months before and after its placing on the market, a reduction of almost 60% can be seen. The marketing in April 2020 of the generic of erlotinib resulted in a 35% price reduction, after comparing the price in March 2020 and the last recorded price in December 2020. In July 2019, the generic of another cancer drug, dasatinib, a BCR-ABL tyrosine kinase inhibitor, became available. Its marketing resulted in a price reduction of 16% both per DDD and package between the 12 months prior and after the placing on the market (Figure 1.8.11).

Figure 1.8.1. Trend in average price of class A-NHS medicines under approved care regime in the period 2004-2020

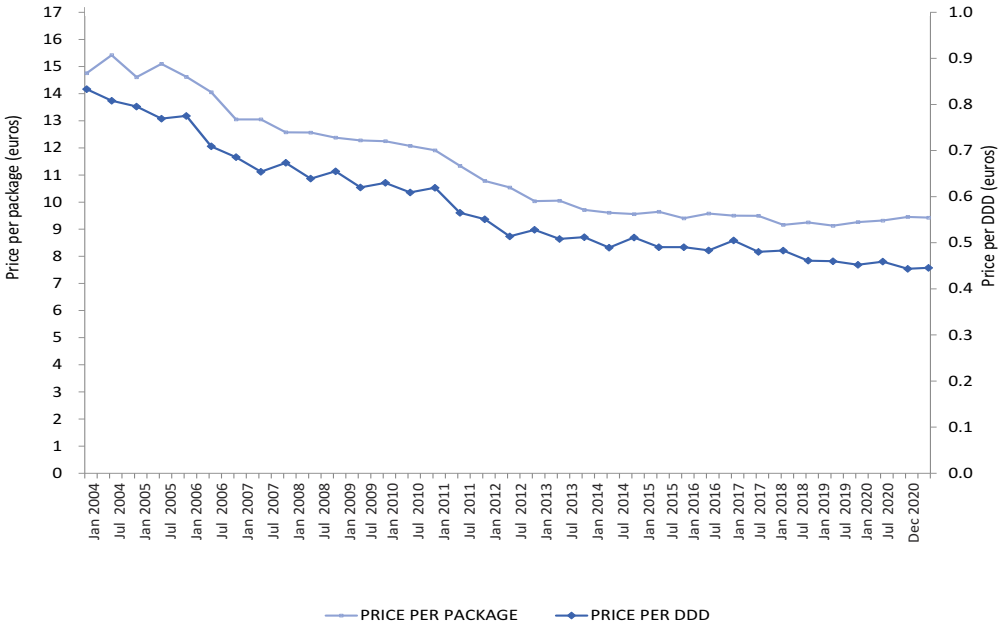


Figure 1.8.2. Trend in average price of class C medicines with prescription in the period 2004-2020

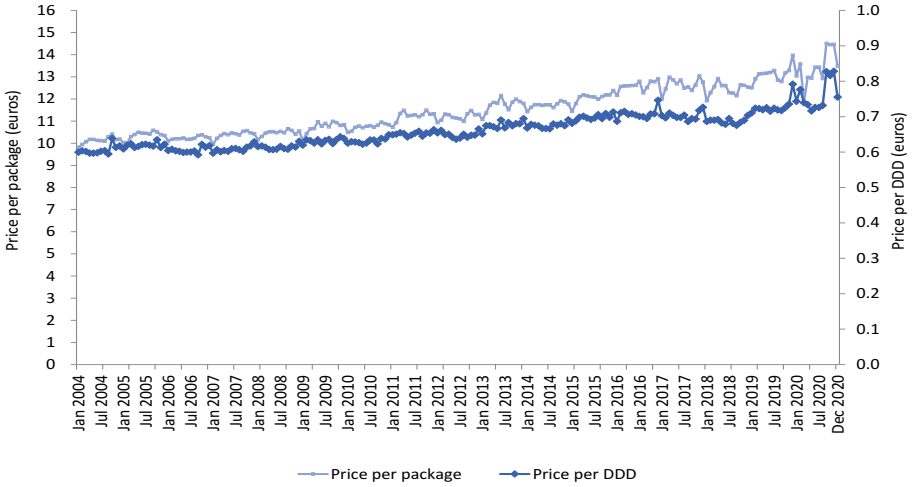


Figure 1.8.3. Trend in average price of medicines purchased by public health facilities in the period 2006-2020

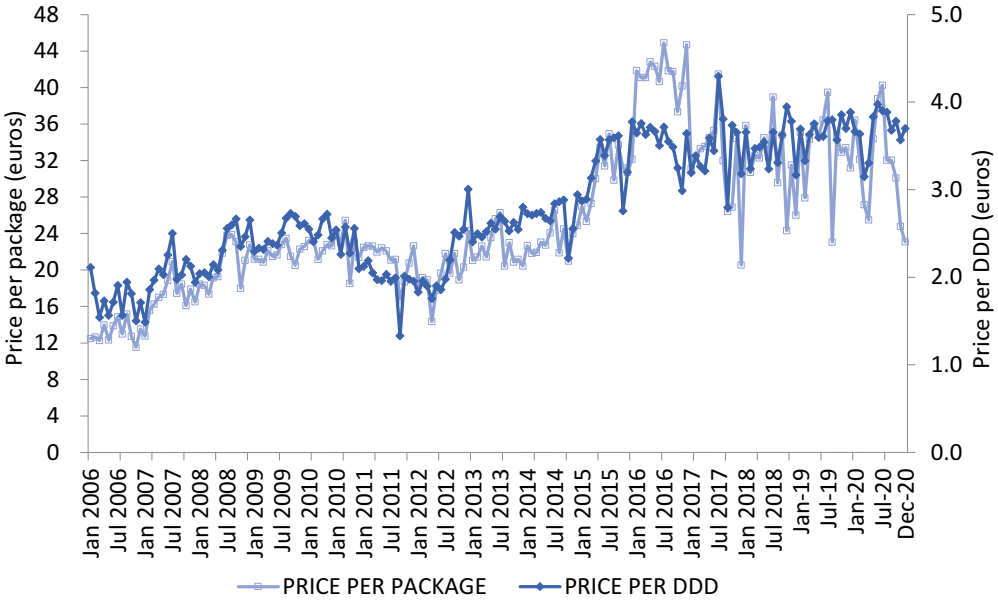


Figure 1.8.4. Trend in average price for teriparatide in the period 2016-2020

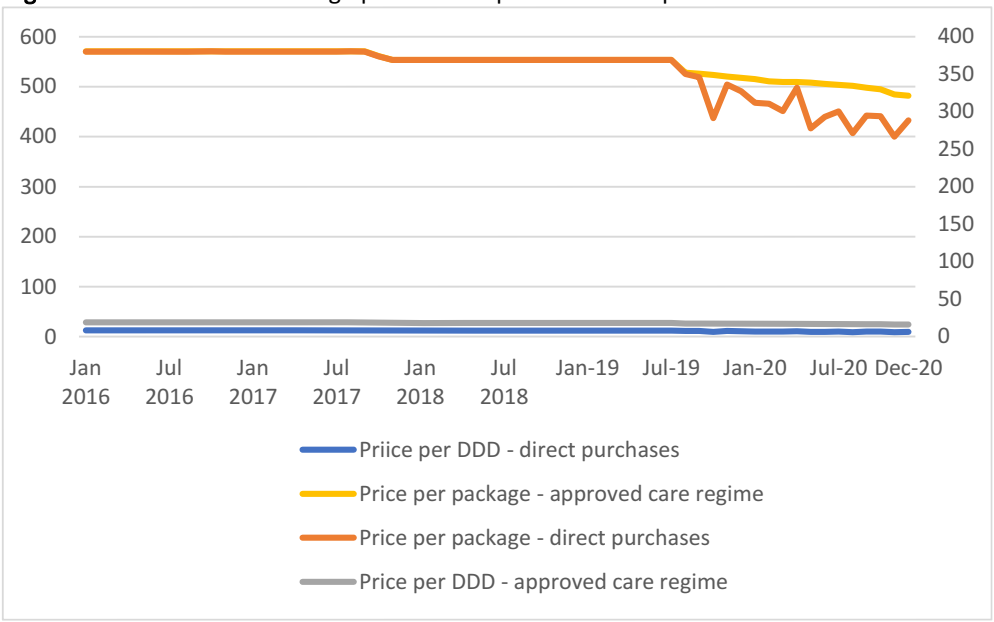


Figure 1.8.5. Trend in average price for trastuzumab in the period 2016-2020

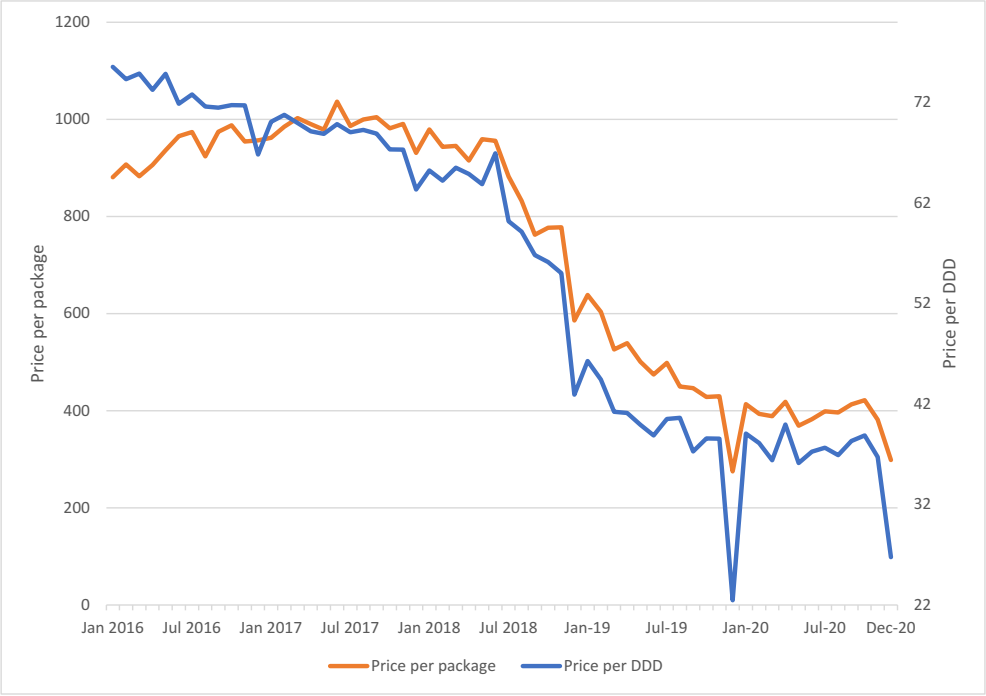


Figure 1.8.6. Trend in average price for bevacizumab in the period 2016-2020

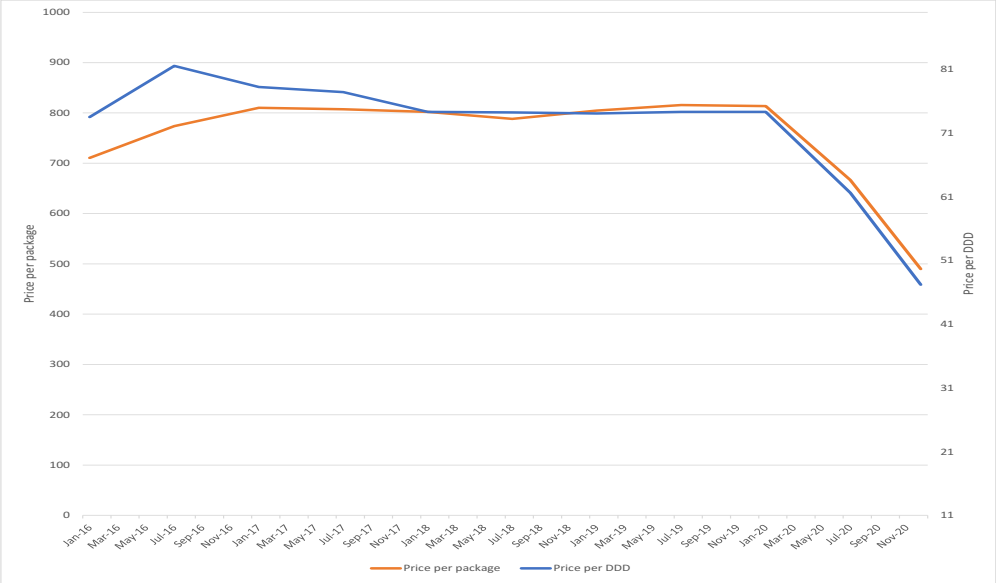


Figure 1.8.7. Trend in average price for pegfilgrastim in the period 2016-2020

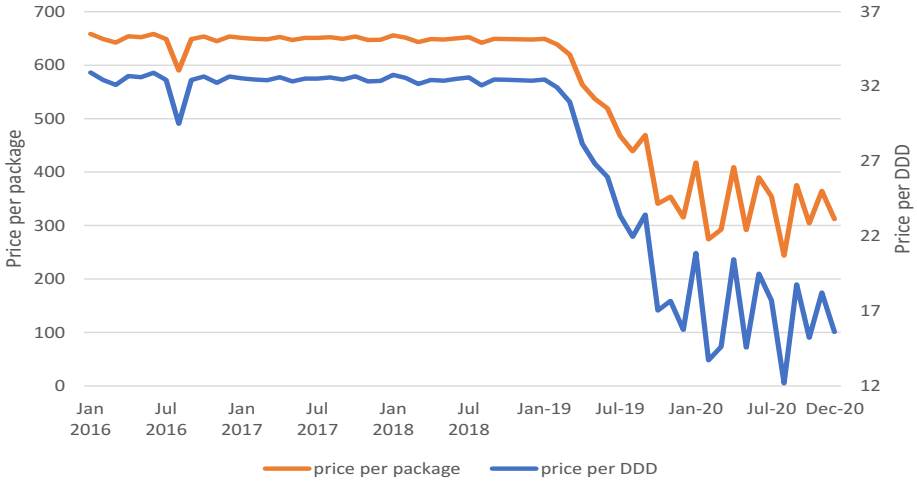


Figure 1.8.8. Trend in average price for miglustat in the period 2016-2020

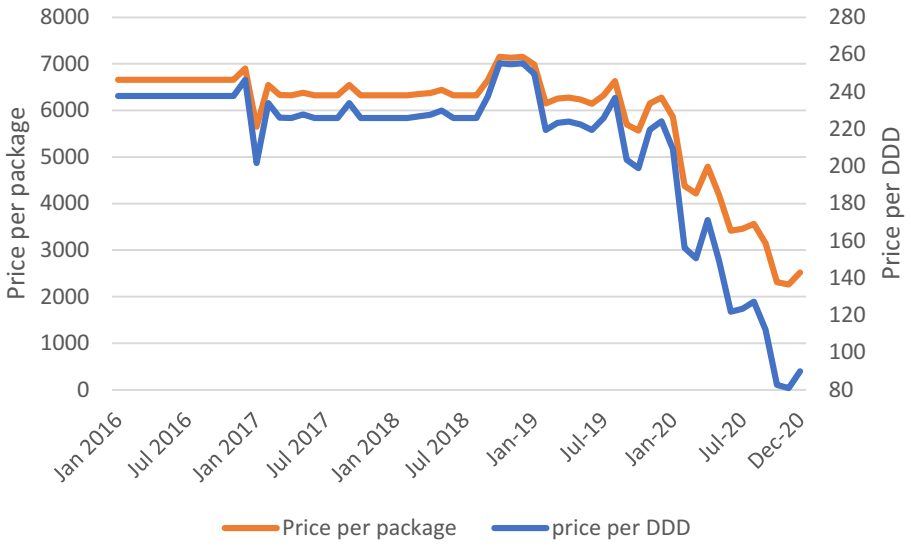


Figure 1.8.9. Trend in average price for glatiramer in the period 2016-2020

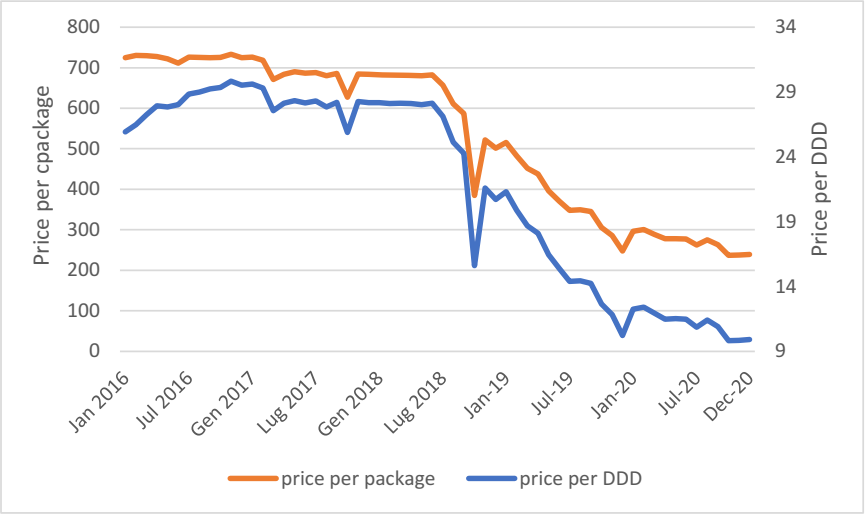


Figure 1.8.10. Trend in average price for gefitinib and erlotinib in the period 2016-2020

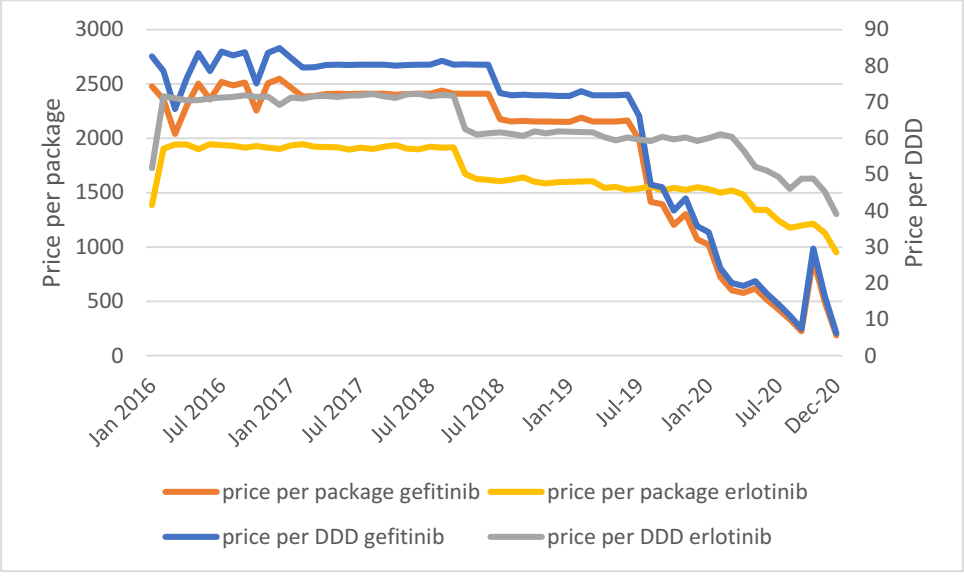
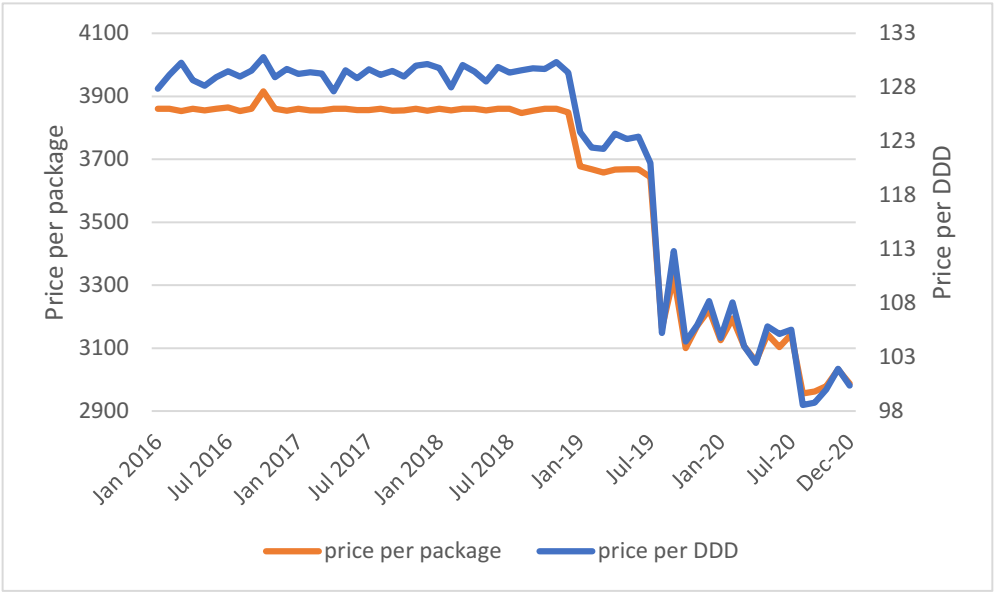


Figure 1.8.11. Trend in average price for dasatinib in the period 2016-2020



1.7 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;
- penetration of generics and biosimilars;
- level of market concentration in relation to patent-expired biological medicinal products;
- expenditure for orphan medicines;
- price comparison analysis in the year 2020.

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 obtained on patent coverage, medicinal product, biological medicinal products/biosimilars, orphan designation. Data on inpatient treatments include accredited private hospitals. The outpatient data includes the private purchase by citizens and is net of direct and *per conto* distribution. In addition to Italy, 9 countries were considered for the purposes of the international comparison: Germany, Belgium, Austria, Spain, France, Sweden, Portugal, United Kingdom (UK) and Poland.

In Italy, the share of total pharmaceutical expenditure on GDP was 1.7%, only below Spain (2.0%) and Portugal (1.8%). Sweden (0.9%) and the UK (1.1%) show the lowest percentages (Figure 1.9.1). All countries, with the exception of Poland and Sweden, registered an increase in the weight of pharmaceutical expenditure on GDP in 2020 compared to 2019. This trend was mainly due to a decline in GDP in all countries, as pharmaceutical expenditure increased.

The overall pharmaceutical expenditure in Italy, including public and private outpatient expenditure as well as inpatient expenditure, was 473 euros per capita. It was lower than the expenditure recorded in Germany (573 euros), Belgium (532 euros) and Austria (528 euros), but higher than that of Poland (182 euros), Portugal (352 euros) and United Kingdom (365 euros) (Figure 1.9.2). There are important differences in the distribution of pharmaceutical expenditure between the two supply channels: total inpatient pharmaceutical expenditure ranges from 66% in Italy to 23% and 27% in Germany and Poland, respectively.

The international comparison was also carried out in terms of standard units (SU), i.e. the smallest 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 already been 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 standard minimum unit (e.g. inhalation).

The comparison in terms of standard unit shows that Italy has a per capita consumption of 840 Sus, lower than all countries considered (average of countries: 1,103 SUs per capita). This mainly depends on the outpatient channel that is lower compared with all other countries. As for the inpatient channel, Italy ranks third in the per capita consumption with 65 SUs, only after the United Kingdom (72 SUs) and Germany (68 SUs).

As far as outpatient expenditure is concerned, the highest share of expenditure in Italy is represented by cardiovascular medicines, equal to 20.3% and higher than the value recorded in other countries. In Sweden expenditure for this therapeutic class represents only 5.5% of outpatient expenditure. In the UK and Spain (both 23.7%), medicines for the central nervous system have the highest incidence on expenditure. Again, the United Kingdom (13.1%), followed by Poland (13.0%), is the country with the highest incidence of expenditure on medicines in the respiratory system. Medicines for gastrointestinal tract disorders account for most of the spending in Portugal (21.5%), the UK (20.0%) and Spain (20.0%). In Sweden (10.0%) and France (9.7%), the value of expenditure for antimicrobial medicines is double than the same value in Italy (4.4%) (Table 1.9.1).

Italy (25.9%) ranks first in terms of incidence of medicines consumption in the cardiovascular system (Table 1.9.2), closely followed by Portugal (22.5%). The percentage of SUs consumed for medicines in the central nervous system (14.2%) is lower than almost all the countries considered: Spain 26.0%, Sweden 24.7%, France 23.2%, Portugal 22.4%, Belgium 21.6%, United Kingdom 21.2%. Only Germany shows a lower percentage (13.5%). The percentage of consumption of medicines in the respiratory system is reduced in Italy (12.0%), lower than all other countries considered, with the exception of Portugal (9.9%). Antimicrobials for systemic use (that in Italy are mainly represented by antibiotics (J01) in the outpatient setting), show the largest share of consumption, which is lower only than in Poland and France. These countries have an outpatient consumption of antibiotics above the European average and higher than Italy.

As for inpatient care (Table 1.9.3), the main item of expenditure in Italy is for antineoplastics (40.5%), even though higher values may be observed in nearly all countries involved in the analysis, with the exception of Germany (36.4%). In Germany (22.0%), Portugal (20.1%), Spain (19.1%) and Italy (17.6%), expenditure for antimicrobials has a greater impact than in other countries. In 2019, the impact of this category on inpatient expenditure was higher (22.6%) and even higher than almost all countries, with the exception of Germany and Spain. Italy and Sweden have high incidences of expenditure on haematological medicines (13.0% and 13.1%, respectively) (Table 1.9.3).

Central nervous system medicines are the first in terms of incidence on inpatient consumption (25.8%), although their weight is lower than in other countries (Sweden 39.5%; Belgium 36.0% and France 33.2%). Similarly to spending, Italy has the highest incidence of consumption for haematological medicines (22.6%) and gastrointestinal medicines (17.6%). On the other hand, the percentage of SUs consumed in hospitals is low for respiratory system medicines, equal to 3.1% compared to the percentage found in all other countries: the highest values are registered in Portugal (23.8%), the United Kingdom (16.5%), Spain (14.1%) and Austria (13.2%) (Table 1.9.4).

Large differences are found, both in outpatient and inpatient settings, among active ingredients representing the main cost items. For example, cholecalciferol ranks 4th in Italy and 122nd in France. Regarding 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, the 5th active ingredient for consumption in Italy, ranks over 100th in France and the United Kingdom. In addition to the different prescriptive profiles, these differences could also be attributed to the different medicines reimbursement modalities.

With regard to inpatient care, the sofosbuvir/velpatasvir combination, indicated in the treatment of the HCV infection, ranks 4th in terms of expenditure, while it is over 600th in Austria and over 350th in Germany. In addition to the different epidemiology of the condition in various countries, these differences may be attributable to the various dispensation channels. Since anti-HCV medicines are dispensed via direct and *per conto* distribution in Italy, they are part of the inpatient channel, whereas in other countries they are considered as part of the outpatient channel. Pembrolizumab ranks among the top three active ingredients in all countries analysed. Active ingredients that are highly consumed in hospitals show great variability: apixaban ranks 1st in Italy for inpatient consumption, but over 200th in Poland and Portugal. Similar to HCV medicines, these differences can be explained by the differing dispensation channels for new oral anticoagulants (Tables 1.9.5-1.9.8).

In Italy, expenditure on generic medicines is still low (39.9%, third last in a 10-country ranking) compared to other European countries. The percentage of outpatient expenditure on generic medicines in the countries analysed ranges between 31.8% in Belgium and 67.5% in Poland (Figure 1.9.4). The percentage of consumption ranges between 46.7% in Belgium and 81.4% in Germany (Figure 1.9.5). Italy ranks 8th with a incidence of generic medicines equal to 52.2%.

The penetration of biosimilars in terms of expenditure and consumption was also analysed (Figures 1.9.6 and 1.9.7). Italy ranks 2nd and 1st in the incidence in expenditure and consumption of biosimilars, respectively. Figure 1.9.8 shows the penetration of biosimilars in terms of expenditure and consumption for individual molecule. Among the countries analysed, the highest percentage of biosimilar consumption is recorded for infliximab, rituximab and trastuzumab. Low percentages of biosimilar penetration are observed in all countries for bevacizumab and teriparatide.

Figure 1.9.9 shows the market concentration and market shares of competitors for single, patent-expired product by country, through the Herfindhal-Hirschman (HHI) index. This index is commonly used to quantify the level of market competition and is defined as the sum of squares of 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 of which holds a small market share. With the exception of Poland and Sweden, insulin lispro has a high concentration index in all countries considered. This is because, in addition to the reference product, there is only one biosimilar with still minimal market shares. Teriparatide and bevacizumab also generally have high concentration indices, given their recent entry into the biosimilar market. Infliximab is generally characterised by a low concentration index as there is a variety of market competitors with a fair distribution of market shares. Even trastuzumab has a low concentration rate in most countries analysed, although its first biosimilar was authorised in Europe in 2018.

With 25.3 euros per capita, Italy ranks fifth in orphan drugs expenditure, after France (31.6 euros), Austria (30.9 euros), Germany (27.8 euros) and Spain (27.2 euros). Compared with the previous year, in 2020 most countries recorded a reduction in orphan drugs expenditure, which was more pronounced in Belgium, with a change of more than 20% (Figure 1.9.10).

Figures 1.9.11 and 1.9.12 show a comparison of the weighted average price (realizable value) for consumption in 2020, referred to outpatient as well as inpatient medications. Figure 1.9.13 shows a price comparison in the overall market, including both outpatient and inpatient medicines. The analysis considered medicinal products that are identical or have a similar packaging than those marketed in Italy. Therefore, the percentage of expenditure of products in common with the country of comparison (Italy) was calculated out of the total expenditure found in each specific country. The average price in this basket was calculated as the ratio of expenditure to the dosage units dispensed in each country. This approach makes it possible to overcome the problem of the various ways in which medicines are supplied in the different countries. The Italian territorial distribution channel does not include medicines supplied via direct and *per conto* distribution. Conversely, they are included in the hospital channel. For example, unlike other countries, the Italian territorial 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. Considering medicines dispensed through the territorial channel, Figure 1.9.11 shows that all countries considered have average prices higher than Italy, with a price difference ranging from +23.2% in Poland to +190.3% in Germany. The situation is different when looking at medicines dispensed through the hospital pharmacies, for which Belgium, France, Germany and Portugal have prices lower than Italy, with differences ranging from -48.1% in Portugal to -12.6% in Belgium. Italy has lower prices compared with Sweden (+640.2%), United Kingdom (+382.5%), Austria (+230.9%), Poland (+191.7%) and Spain (+13.4%) (Figure 1.9.12). When looking at the overall market, including both outpatient and inpatient medicines, Italy shows lower prices than Germany (+98.9%), Belgium (+71.1%) Sweden (+47.7%), Austria (+27.0%), United Kingdom (+7.6%) and Spain (+6.5%). France (-22.4%), Portugal (-32.5%) and Poland (-35.8%) have lower prices than Italy (Figure 1.9.13). When interpreting the results, it is important to consider the medicines that Italy has in common with other countries, in particular whether they are included in the country's pharmaceutical expenditure. In the overall market, the largest expenditure coverage is found in Spain (67.5%), while the lowest is found in Germany (24.3%). 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.

Figure 1.9.1. International comparison: incidence of public pharmaceutical expenditure over GDP in the period 2016-2020

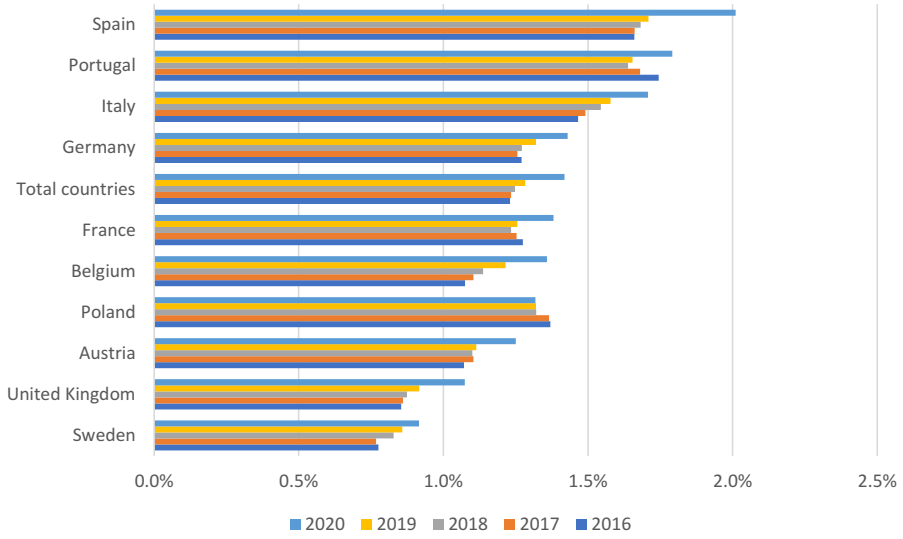


Figure 1.9.2. International comparison of overall per capita pharmaceutical expenditure by dispensation channel. Year 2020

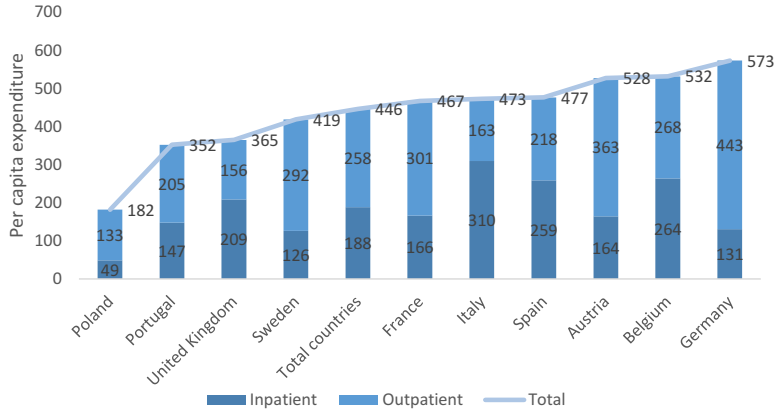


Figure 1.9.3. International comparison of overall per capita pharmaceutical consumption (standard unit per inhabitant) by dispensation channel. Year 2020

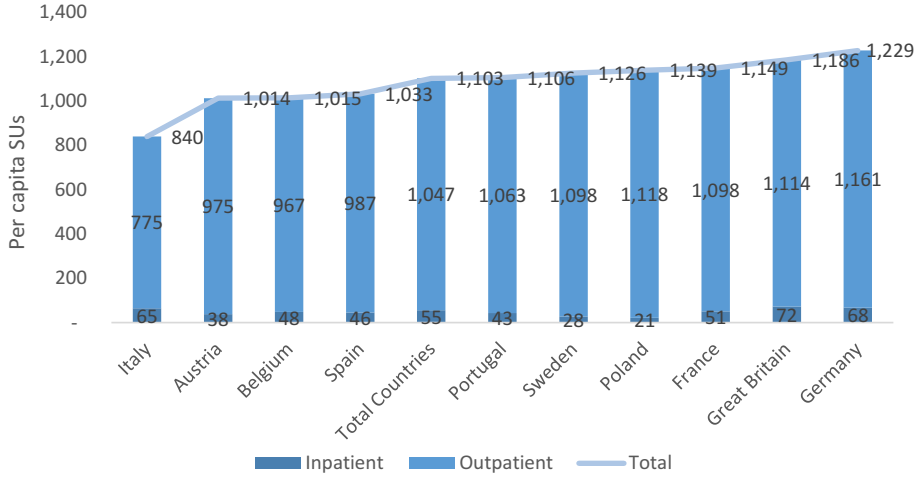


Table 1.9.1. International comparison of the proportion of outpatient pharmaceutical expenditure* 2020 by 1st level of ATC classification

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
C - Cardiovascular system	20.3	10.8	11.2	8.5	7.7	17.2	18.8	15.4	5.5	11.9
N - Nervous system	19.1	14.9	18.0	14.4	14.8	15.5	19.2	23.7	18.0	23.7
A - Alimentary tract and metabolism	17.6	10.5	14.1	11.7	12.0	18.0	21.5	20.0	12.8	20.0
R - Respiratory system	11.2	8.3	10.0	8.6	7.7	13.0	8.7	9.8	8.7	13.1
G - Genito-urinary and sex hormones	6.9	2.3	4.7	3.5	2.7	5.9	5.6	5.9	4.1	5.3
M - Musculo-skeletal system	5.6	5.1	4.6	2.9	4.2	4.9	5.4	4.0	3.8	2.4
J - Antiinfectives for systemic use	4.4	6.5	9.0	9.7	8.3	4.5	4.2	2.9	10.0	2.7
D - Dermatologicals	3.9	3.2	3.6	2.2	3.1	3.1	2.7	2.6	2.4	3.1
B - Blood and blood forming organs	3.5	8.1	10.0	8.4	8.3	12.0	9.4	7.6	8.5	9.2
S - Sensory organs	3.4	0.7	1.1	5.2	3.1	1.8	1.8	2.1	1.8	2.8
H - Systemic hormonal preparations, excluding sex hormones and insulins	2.1	1.9	2.3	2.7	2.2	1.5	0.9	2.0	2.4	2.5
L - Antineoplastic and immunomodulating agents	1.5	26.0	10.9	21.4	23.5	1.7	0.5	3.6	21.5	2.8
V - Various	0.3	1.4	0.2	0.6	2.2	0.7	1.1	0.5	0.5	0.2
P - Antiparasitic products, insecticides and repellents	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.2

* medicines dispensed by local pharmacies, net of direct and *per conto* distribution

Table 1.9.2. International comparison of the proportion of territorial consumption* 2020 by 1st level of ATC classification

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
C - Cardiovascular system	25.9	19.1	18.0	16.4	21.9	22.0	22.5	18.0	17.3	16.0
A - Alimentary tract and metabolism	17.1	14.6	16.0	17.9	13.3	22.7	14.2	15.1	17.1	16.2
N - Nervous system	14.2	15.4	21.6	23.2	13.5	14.3	22.4	26.0	24.7	21.2
R - Respiratory system	12.0	22.0	18.0	14.5	16.3	14.5	9.9	13.8	16.4	19.4
S - Sensory organs	8.1	5.4	5.1	7.3	8.9	4.8	4.9	6.6	5.3	6.5
M - Musculo-skeletal system	6.0	7.6	5.2	4.9	5.7	6.7	7.8	5.9	3.6	2.9
B - Blood and blood forming organs	5.4	4.7	5.9	4.3	5.0	4.6	4.5	4.6	4.9	4.1
H - Systemic hormonal preparations, excluding sex hormones and insulins	3.8	3.3	2.5	2.6	4.0	2.6	2.0	2.7	2.6	2.7
D - Dermatologicals	2.9	4.0	3.0	3.8	4.0	3.0	3.8	3.2	4.3	7.1
G - Genito-urinary and sex hormones	2.7	1.9	2.6	2.2	2.4	2.6	2.6	2.0	2.0	2.0
J - Antiinfectives for systemic use	1.4	0.9	1.3	1.7	0.7	1.5	1.0	1.3	0.9	1.3
L - Antineoplastic and immunomodulating agents	0.4	0.6	0.7	0.5	0.5	0.3	0.2	0.6	0.8	0.4
V - Various	0.2	0.6	0.1	0.5	3.5	0.4	3.8	0.1	0.1	0.1
P - Antiparasitic products, insecticides and repellents	0.0	0.1	0.1	0.1	0.4	0.1	0.2	0.1	0.1	0.2

* medicines dispensed by local pharmacies, net of direct and *per conto* distribution

Table 1.9.3. International comparison of the proportion of inpatient pharmaceutical expenditure for 2020 by 1st level of ATC classification

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
L - Antineoplastic and immunomodulating agents	40.5	54.0	58.4	47.8	36.4	49.6	44.1	48.2	40.6	45.2
J - Antiinfectives for systemic use	17.6	15.9	8.8	11.4	22.0	11.4	20.1	19.1	13.0	16.4
B - Blood and blood forming organs		13.0	9.2	9.5	10.8	11.6	5.0	5.7	5.7	13.1	6.1
N - Nervous system	9.9	7.4	6.5	13.5	15.3	19.7	11.7	9.1	10.6	7.2
A - Alimentary tract and metabolism	7.2	4.6	6.1	6.5	5.0	1.7	7.3	4.0	5.7	4.4
R - Respiratory system	2.6	1.0	1.9	1.0	1.2	2.3	2.8	4.3	1.4	7.3
C - Cardiovascular system	2.5	2.3	1.7	2.9	2.1	3.0	1.6	2.3	1.8	1.7
M - Musculo-skeletal system	1.9	1.6	1.9	2.5	2.0	1.3	1.6	2.1	4.0	3.1
H - Systemic hormonal preparations, excl. sex hormones and insulins	1.7	0.8	0.8	0.9	0.9	2.5	1.7	1.4	0.8	1.2
S - Sensory organs	1.0	1.4	3.2	0.5	1.7	2.5	1.5	2.1	7.9	5.4
D - Dermatologicals	0.9	0.2	0.2	1.1	0.8	0.3	1.1	1.1	0.2	0.8
V - Various	0.8	0.7	0.6	0.6	0.8	0.3	0.6	0.2	0.7	0.5
G - Genito-urinary system and sex hormones	0.5	0.7	0.5	0.5	0.3	0.3	0.2	0.3	0.3	0.5
P - Antiparasitic products, insecticides and repellents	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0

Table 1.9.4. International comparison of the proportion of inpatient pharmaceutical consumption for 2020 by 1st level of ATC classification

Level I ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
N - Nervous system	25.8	25.1	36.0	33.2	18.8	27.5	13.7	21.9	39.5	18.9
B - Blood and blood forming organs	22.6	4.6	4.5	4.2	3.1	5.8	2.2	2.7	5.8	4.1
A - Alimentary tract and metabolism	17.6	12.9	11.3	14.3	13.5	16.7	7.1	7.6	16.6	12.3
C - Cardiovascular system	10.9	12.6	8.0	8.0	9.2	13.6	5.6	5.8	7.9	5.4
J - Antiinfectives for systemic use	4.9	4.0	4.5	3.4	2.8	6.3	8.8	6.8	5.5	6.8
L - Antineoplastic and immunomodulating agents	4.7	0.6	3.2	0.7	0.3	2.4	10.0	3.0	1.2	4.0
S - Sensory organs	3.3	10.5	12.2	8.9	9.7	7.7	8.8	19.6	4.4	16.6
R - Respiratory system	3.1	13.2	11.6	12.6	12.1	6.2	23.8	14.1	6.6	16.5
D - Dermatologicals	2.8	5.5	3.6	8.6	12.3	3.9	14.4	13.5	2.6	8.4
H - Systemic hormonal preparations, excluding sex hormones and insulins	1.5	2.0	1.4	1.8	1.6	2.7	1.9	1.9	5.8	2.8
M - Musculo-skeletal system	1.2	6.0	2.4	1.7	4.1	4.6	1.3	2.3	2.2	1.6
V - Various	1.0	2.0	0.5	1.9	11.9	1.0	1.6	0.2	0.8	1.1
G - Genito-urinary and sex hormones	0.7	0.9	0.9	0.9	0.6	1.3	0.8	0.5	1.1	1.4
P - Antiparasitic products, insecticides and repellents	0.0	0.0	0.0	0.1	0.1	0.2	0.1	0.0	0.0	0.1

Table 1.9.5. International comparison of the first ten active ingredients in Italy: outpatient expenditure 2020*

Active ingredient	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
paracetamol	1	180	4	3	255	24	9	11	11	24
pantoprazole	2	35	5	54	40	14	32	25	418	297
atorvastatin	3	30	17	34	112	9	6	1	81	2
cholecalciferol	4	76	30	122	76	30	69	81	84	51
diclofenac	5	21	10	61	36	4	21	66	62	99
ibuprofen	6	36	25	88	27	3	5	23	49	111
amoxicillin/ clavulanic acid	7	121	82	79	152	56	37	82	599	342
bisoprolol	8	70	65	44	204	7	36	92	180	76
beclomethasone/formoterol	9	57	18	66	31	29		20	92	4
esomeprazole	10	137	114	25	271	129	18	22	114	115

* medicines dispensed by local pharmacies, net of direct and *per conto* distribution

Table 1.9.6. International comparison of the first ten active ingredients in Italy: territorial consumption 2020*

Active ingredient	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
acetylsalicylic acid	1	5	2	4	3	3	6	7	14	19
metformin	2	10	4	3	12	2	3	8	3	5
levothyroxine	3	3	6	5	2	5	11	5	13	8
bisoprolol	4	8	7	7	8	7	13	14	29	16
pantoprazole	5	6	3	15	7	11	12	33	133	179
atorvastatin	6	12	11	8	19	10	5	10	8	6
diclofenac	7	2	8	6	6	4	8	17	25	59
paracetamol	8	15	1	1	27	15	2	1	1	2
furosemide	9	37	87	14	87	40	15	20	30	38
ramipril	10	36	91	22	5	9	41	53	56	13

* medicines dispensed by local pharmacies, net of direct and *per conto* distribution

Table 1.9.7. International comparison of the first ten active ingredients in Italy: inpatient expenditure 2020

Active ingredient	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
pembrolizumab	1	1	1	1	2	3	2	2	2	3
lenalidomide	2	162	4	5	166	6	8	3	122	8
nivolumab	3	2	2	2	6	2	10	8	5	22
sofosbuvir/velpatasvir	4	670	41	174	365	18	74	10	94	11
adalimumab	5	163	240	386	101	39	17	1	309	1
epoetin alfa	6	192	59	120	148	126	247	79	1052	99
human immunoglobulin	7	7	5	3	1	47	3	7	3	5
rivaroxaban	8	153	235	188	145	120	651	407	307	195
ibrutinib	9	272	9	303	255	11	13	4	330	9
apixaban	10	151	203	115	116	266	534	387	139	141

Table 1.9.8. International comparison of the first ten active ingredients in Italy: inpatient consumption 2020

Active ingredient	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
apixaban	1	57	84	33	63	231	271	168	39	45
quetiapine	2	14	33	133	55	11	61	27	78	119
dabigatran	3	209	207	290	370	163	616	340	277	458
rivaroxaban	4	148	171	145	163	102	423	297	213	117
clopidogrel	5	120	98	136	124	128	236	162	135	83
ranolazine	6	392			330	1270	971	610		315
metformine/sitagliptin	7	195	807	358	317	1084		649	592	1352
lidocaine	8	7	1	5	16	7	13	91	2	92
furosemide	9	20	74	13	48	3	18	19	12	43
enoxaparin	10	9	22	17	45	13	27	29	161	46

Figure 1.9.4. International comparison of the proportion of outpatient expenditure in 2020 for patent-expired medicines

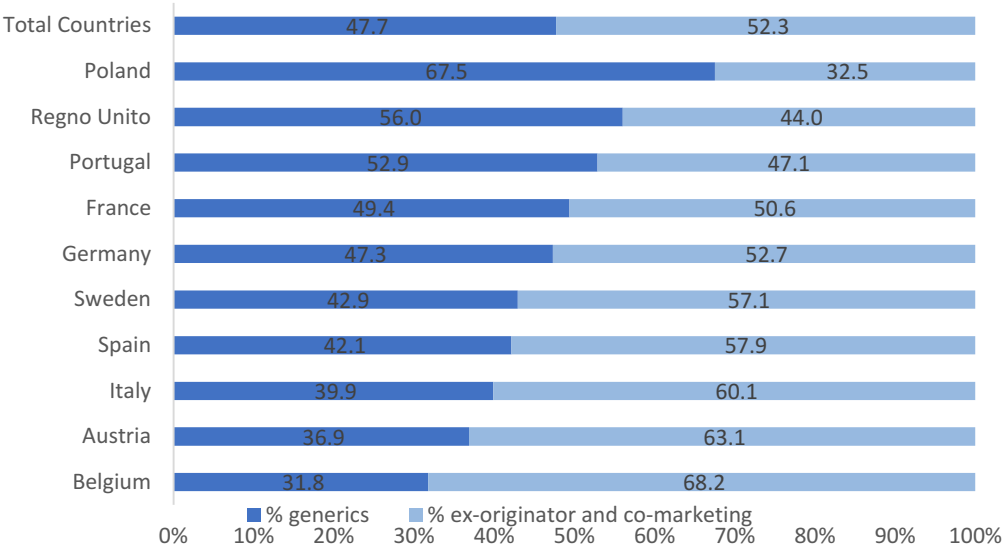


Figure 1.9.5. International comparison of the proportion of outpatient consumption in 2020 for patent-expired medicines

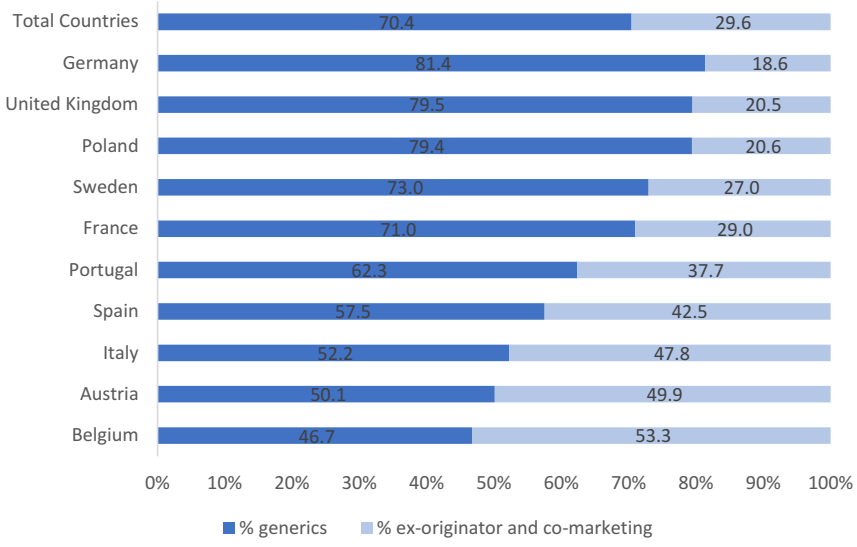


Figure 1.9.6. International comparison of the proportion of biosimilar pharmaceutical expenditure for 2020

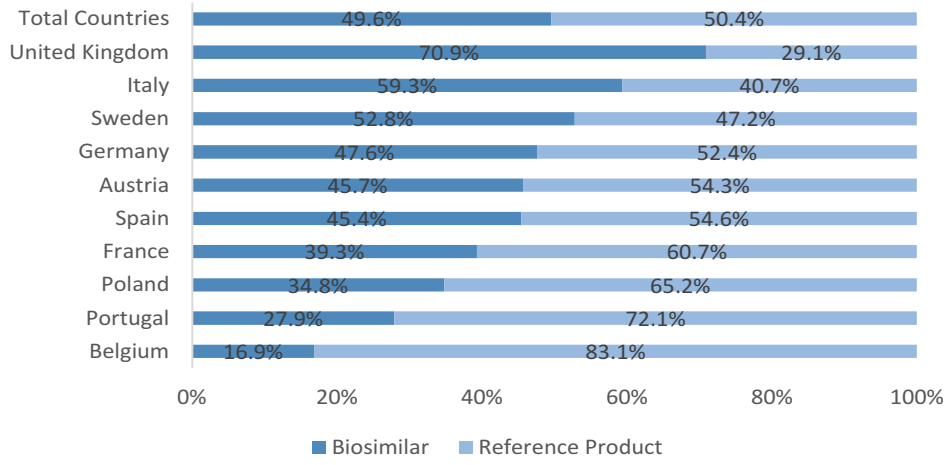


Figure 1.9.7. International comparison of the proportion of biosimilar pharmaceutical consumption for 2020

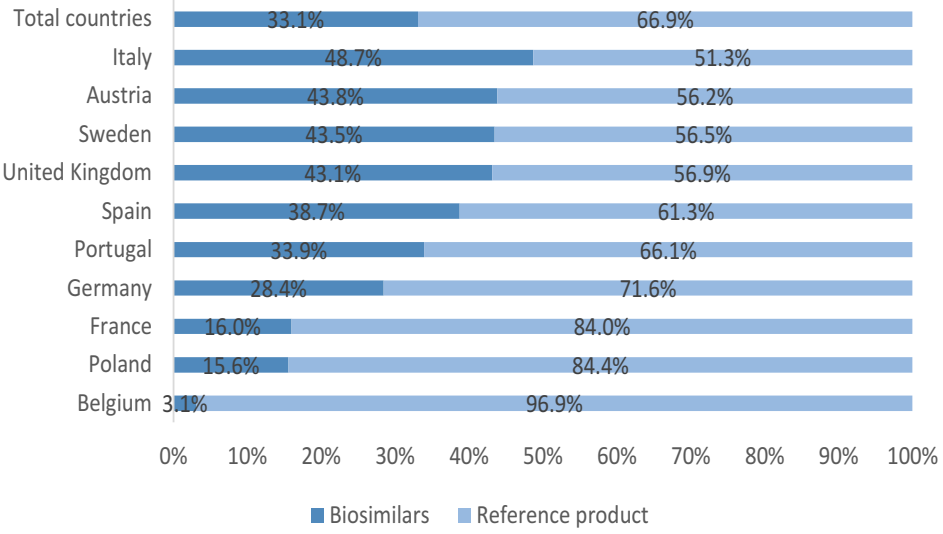


Figure 1.9.8. Proportion of consumption (standard units) of biosimilars by country and molecule in 2020

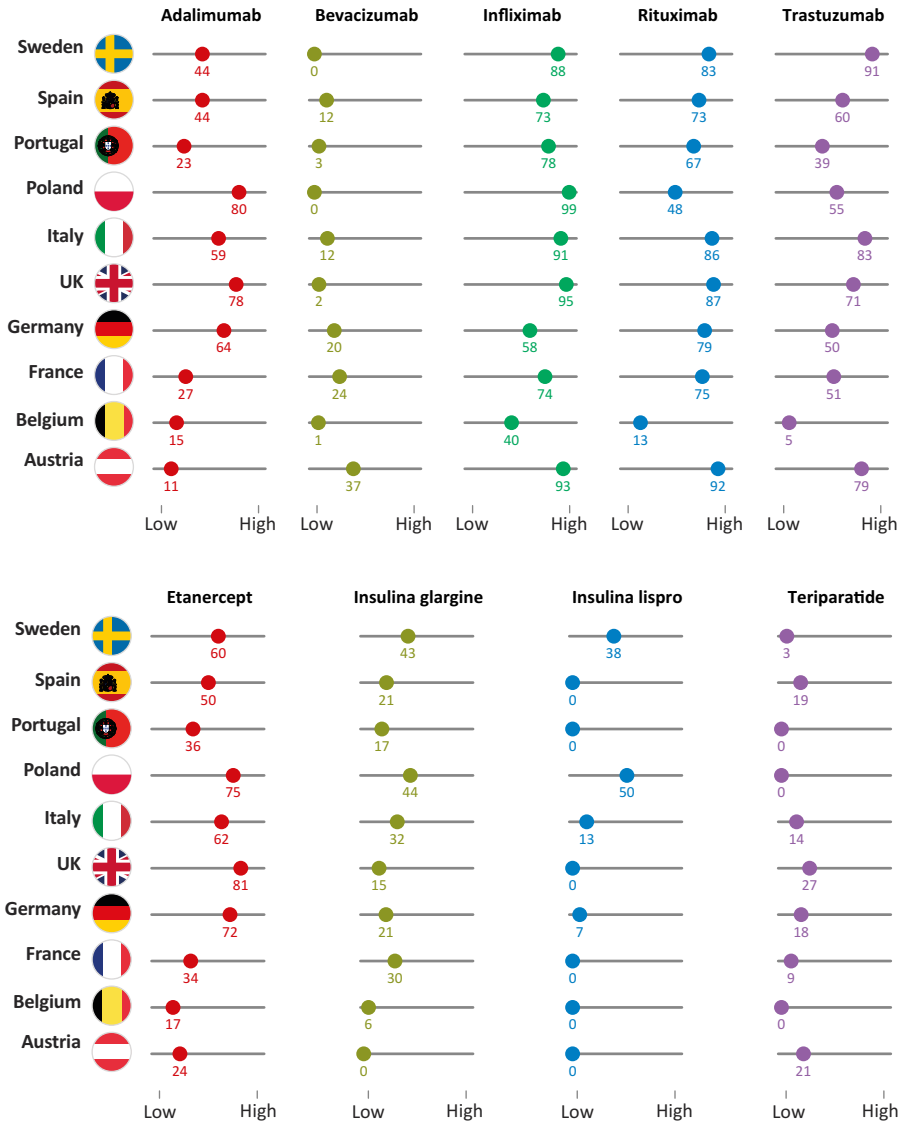
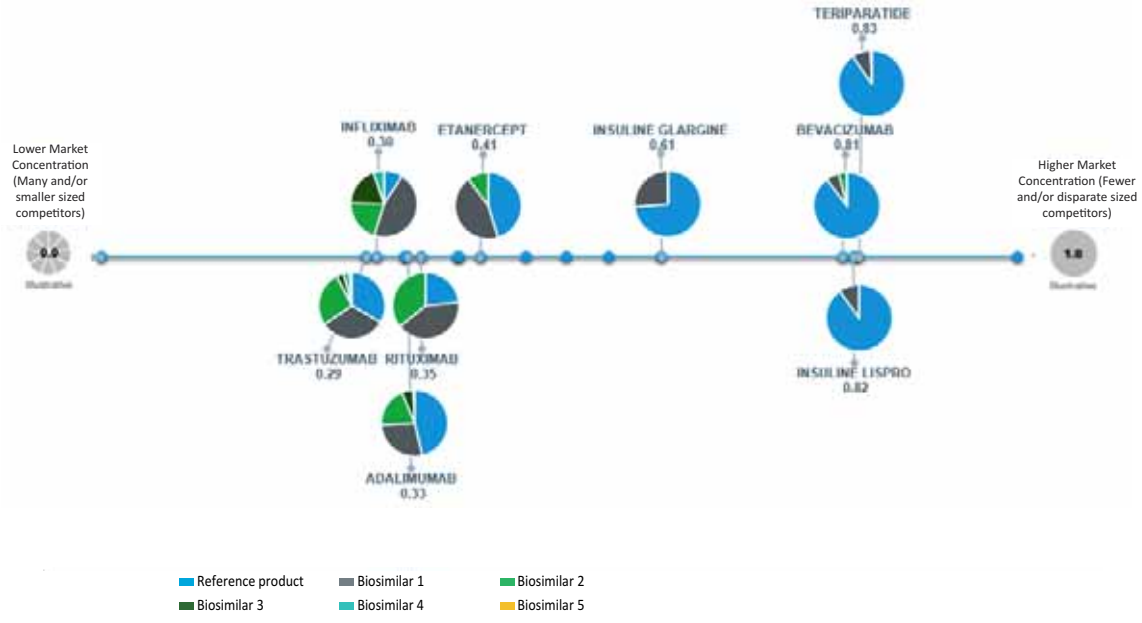


Figure 1.9.9. Patent expired biologic medicines: Herfindahl-Hirschman Index (HHI) and market shares by competitor, year 2020

Italy



Austria

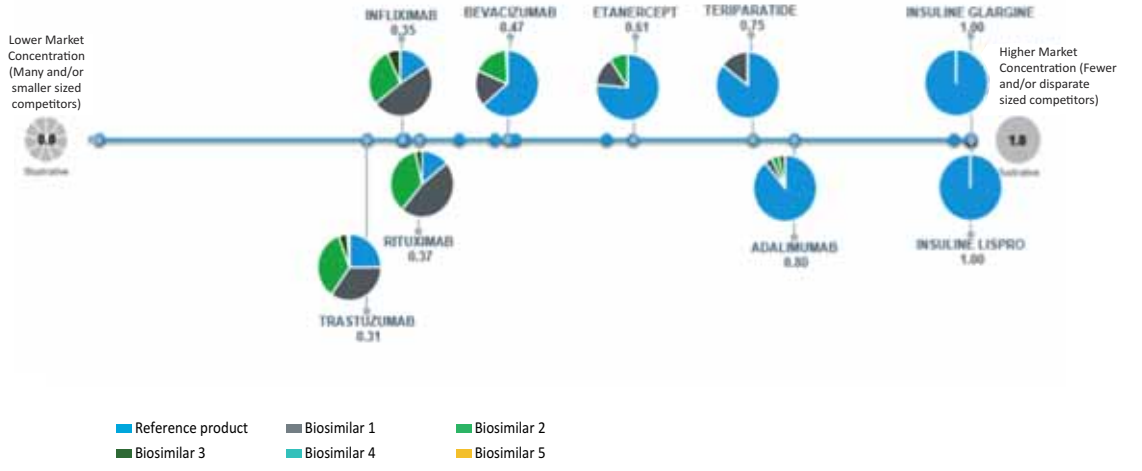
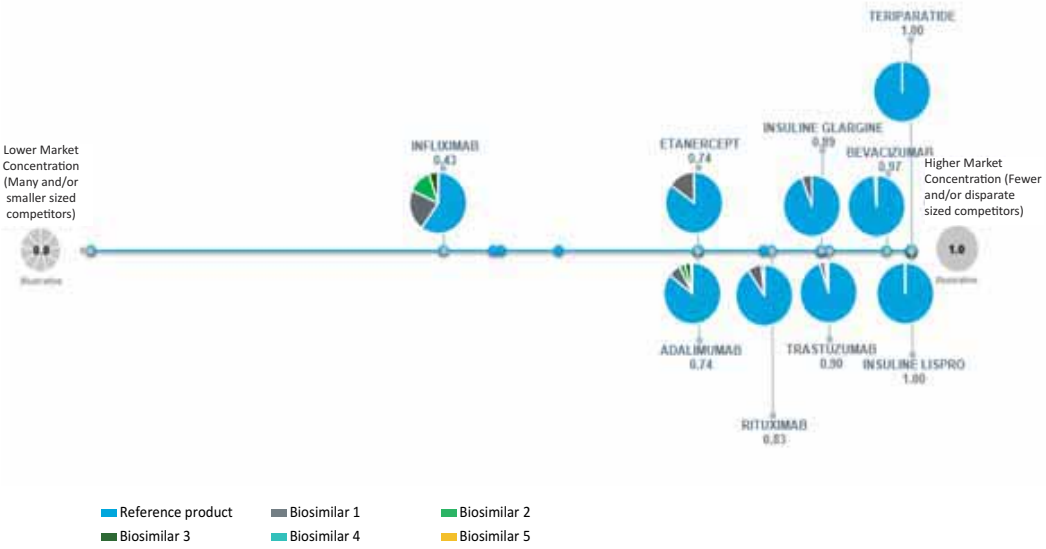


Figure 1.9.9. Continued

Belgium



France

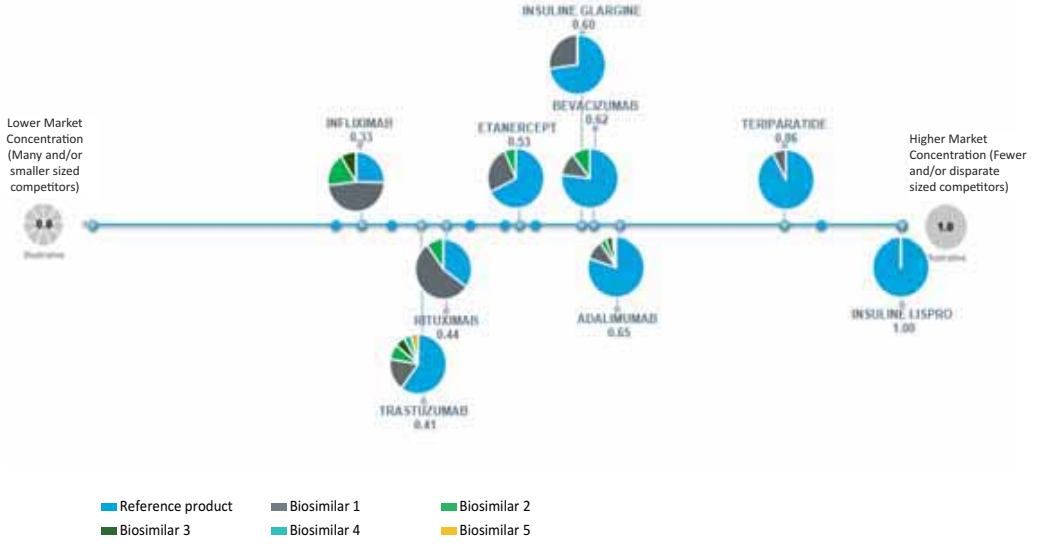
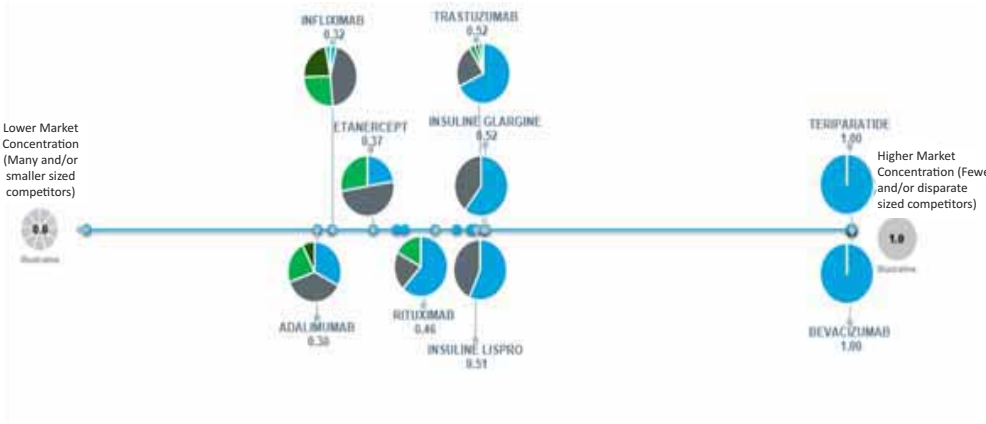


Figure 1.9.9. Continued

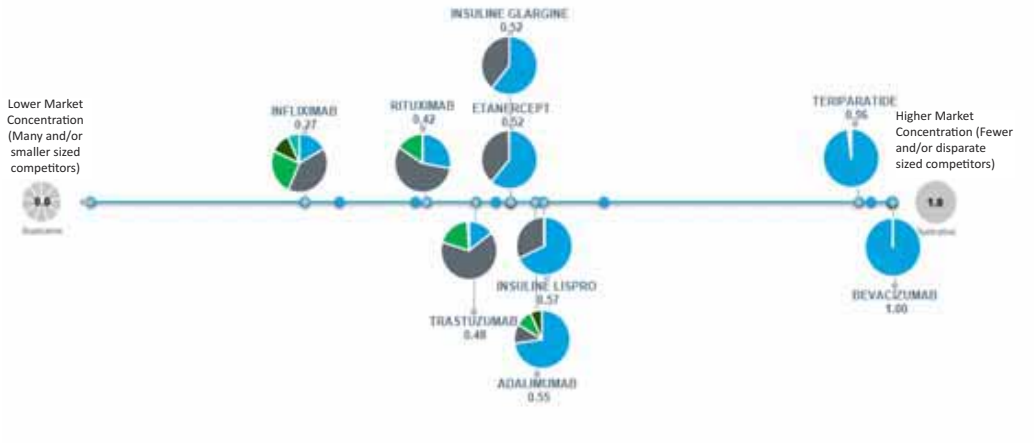
Poland



Portugal

Figure 1.9.9. Continued

Sweden



United Kingdom

Figure 1.9.9. Continued

Spain

Germany

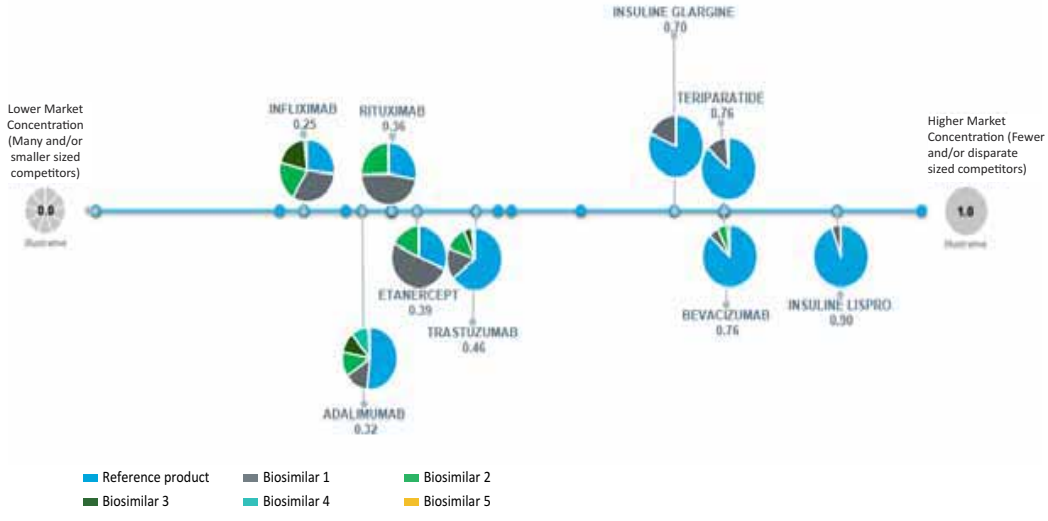


Figure 1.9.10. Trend in per capita expenditure for orphan drugs in the period 2018-2020

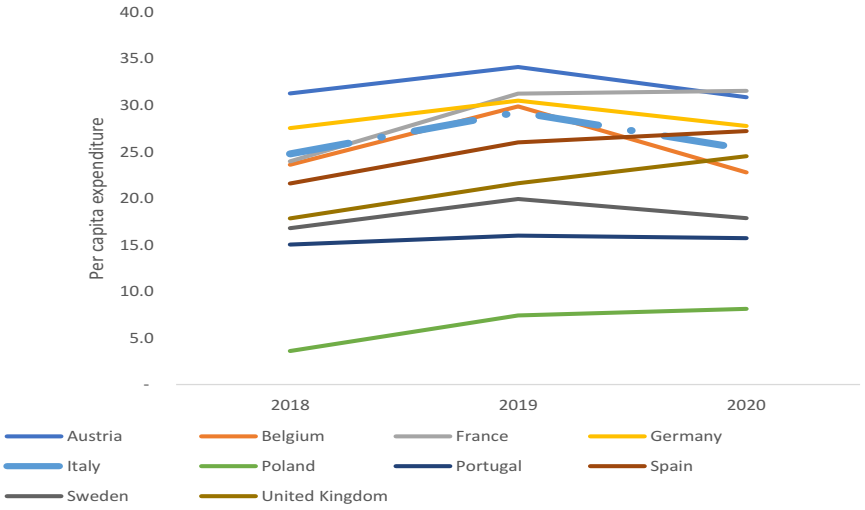
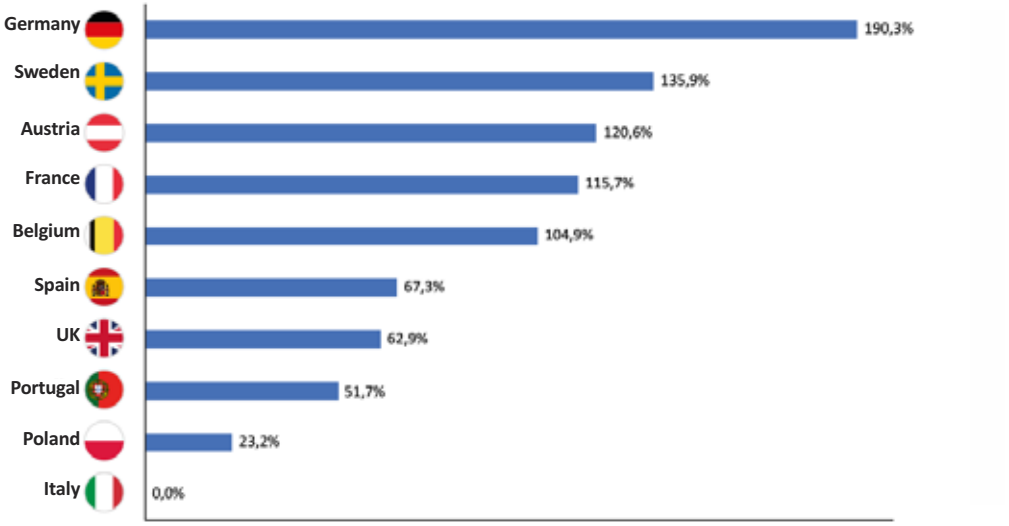


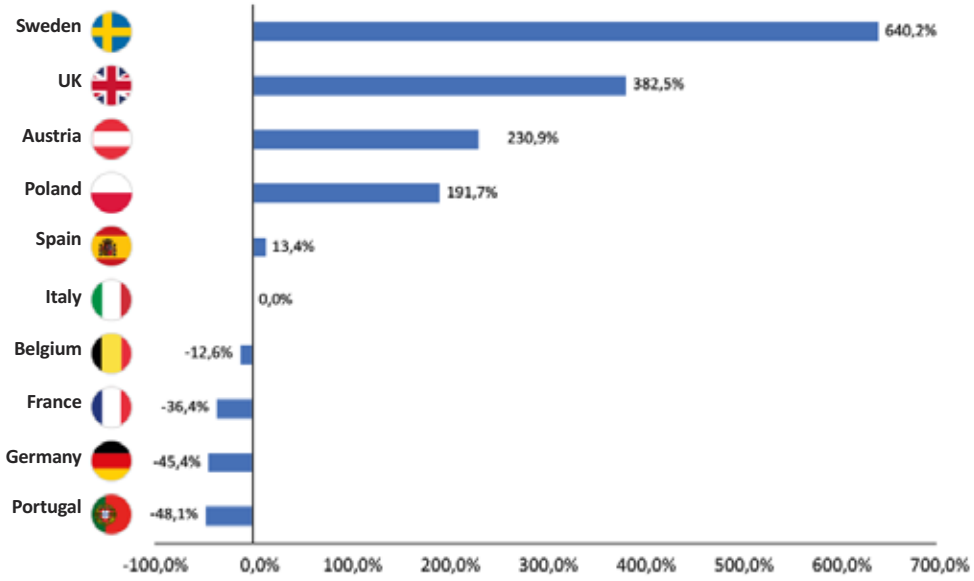
Figure 1.9.11. International comparison of pharmaceutical prices (realizable prices) in 2020: outpatient care



Common basket between Italy and other countries concerning channel, ATC IV, molecule, product, pack

Coverage (%)	Germany	Sweden	Austria	France	Belgium	Spain	UK	Portugal	Poland	Italy
	6.1	14.1	28.7	29.5	18.9	42.7	33.9	38.9	20.1	100

Figure 1.9.12. International comparison of pharmaceutical prices (realizable prices) in 2020: inpatient care*

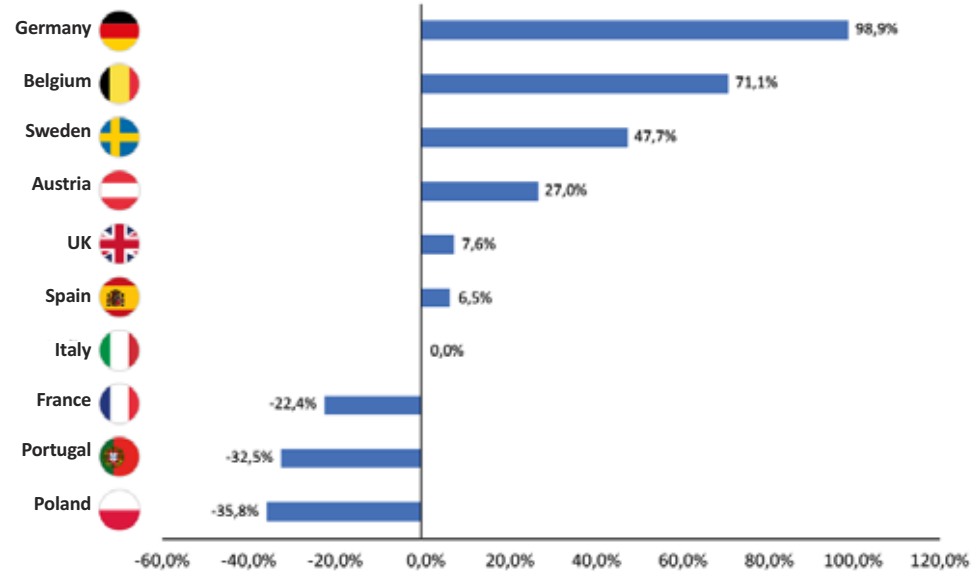


Common basket between Italy and other countries concerning channel, ATC IV, molecule, product, pack

*Inpatient channel (including per conto distribution in Italy)

Coverage (%)	Sweden	UK	Austria	Poland	Spain	Italy	Belgium	France	Germany	Portugal
	57.0	34.2	60.6	41.3	86.6	100.0	86.3	73.1	61.3	82.0

Figure 1.9.13. International comparison of pharmaceutical prices in 2020 (realizable prices): inpatient and outpatient care



Common basket between Italy and other countries concerning channel, ATC IV, molecule, product, pack

Coverage (%)	Germany	Belgium	Sweden	Austria	UK	Spain	Italy	France	Portugal	Poland
	24.3	55.5	30.4	44.0	35.5	67.5	100.0	48.0	57.7	27.5

Sources

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

European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA. Annual Epidemiological Report 2019. Stockholm: ECDC, 2020.

Section 2

Detailed analysis of expenditure and consumption of medicines

2.1 Patent-expired medicines and biosimilars

Patent-expired medicines under approved care regime

In 2020, patent-expired medicines accounted for 67.6% of expenditure and 84.8% of consumption under class A approved care regime. The percentage share of generic medicines, i.e. medicines based on active ingredients with expired patents, excluding those with patent coverage, accounted for 20.5% of expenditure and 30.7% 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 patent-expired medicines amounted to 110.17 euros, a reduction of almost 2% compared to 2019, although an increase in the percentage share of total expenditure can be seen from 67.3% in 2019 to 67.6%. Taking into account the last two years, the percentage of expenditure on generic medicines has also increased slightly from 29.8% to 30.4% (Table 2.1.1). The Southern regions (69.6%) and the Centre (68.3%) have the highest share of expenditure, both in comparison with the Northern Regions (65.5%) and the Italian average (67.6%). In fact, the lowest value was recorded in the A.P. of Bolzano (76.51 euros), while the highest in Campania (139.72 euros). An opposite trend is observed when considering the percentage of expenditure on generic medicines: the Northern Regions on average show higher values (39.2%), compared to the Southern (27.8%) and Central Regions (22.1%).

In 2020, 842.28 daily doses per 1000 inhabitants were consumed for patent-expired medicines, an increase of almost 1% compared to the previous year, corresponding to 84.8% of total DDD. On the other hand, the percentage of use of generic medicines, which was 36.2% in 2020, remains stable (Table 2.1.2). The Northern Regions consume a greater percentage of generic medicines (45.9%), compared to the Central (33.9%) and Southern Regions (26%), in fact the highest value was recorded in the A.P. of Trento (51.2%), while the lowest in Basilicata (22.3%).

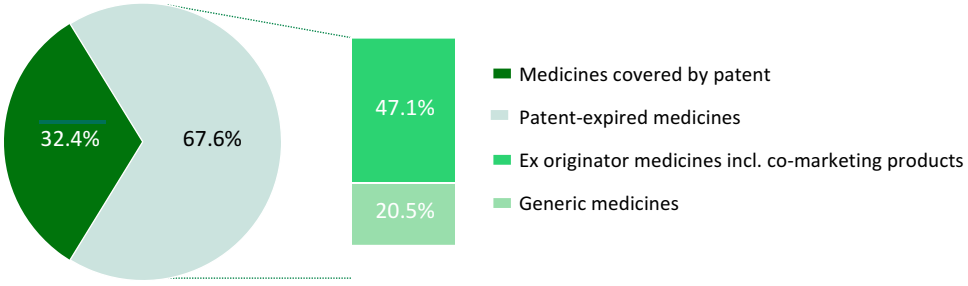
In the use of patent-expired medicines, the regional heterogeneity in terms of both expenditure and consumption is plain to see. The composition of expenditure on medicines under approved care regime (Figure 2.1.5) shows that the use of generic medicines is lower in Calabria, Basilicata and Campania (19%), whereas the highest values are recorded in the A.P. of Trento (44%), Lombardy (43%) and Friuli Venezia Giulia (42 %).

The three therapeutic categories with a higher incidence of expenditure on patent-expired medicines (Table 2.1.3) are cardiovascular medications (91.1%), as well as medications acting on the genitourinary system (88.7%) and on the musculoskeletal system (86.6%). For ATC code G in particular, the patent expiration of silodosin and solifenacin is likely to have contributed to these developments. For the ATC codes V (Various), L (Antineoplastic and immunomodulating agents) and A (Alimentary tract and metabolism), the highest percentages of expenditure on generic medicines were 36.1%, 29.1% and 25.9%, respectively.

When looking at consumption, medicines acting on the cardiovascular system (94.9%) and on the genitourinary system (91.5%) confirm the trend shown for expenditure. The category of antiinfectives for systemic use, on the other hand, has a higher incidence of consumption (92.0%) compared to that of expenditure (85.0%).

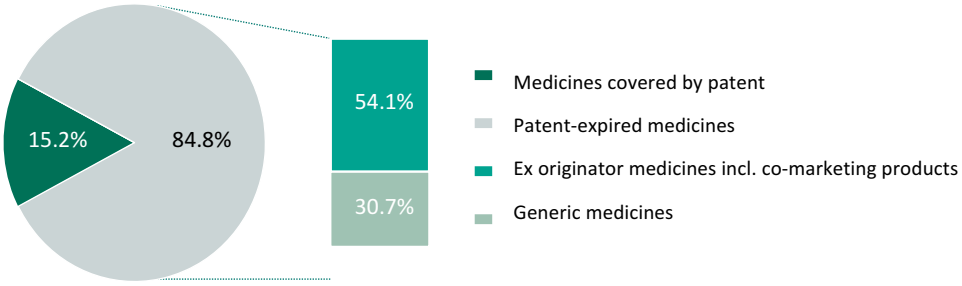
Categories with the highest incidence of consumption of generic medicines are: ATC code L (39.4%), ATC code A (39.3%) and ATC code N (36.2%).
As for expenditure on the top 30 active ingredients of class A-NHS (private purchase) with expired patent, more than half belong to cardiovascular medications, followed by medications acting on the gastrointestinal system and metabolism (Table 2.1.4). In 2020, atorvastatin is the most expensive active substance, with an absolute value of 268.1 million, up by 4.2% compared to the previous year, and a percentage of generics equal to 37.1%, followed by pantoprazole (253.8 million euros) and cholecalciferol (201.4 million euros). The active substances with the highest incidence of expenditure on generic medicines are lansoprazole (70.8%) and pantoprazole (56.3%). The incidence of cholecalciferol (17.7%) and the combination of amoxicillin and clavulanic acid (17.8%) is very low: they represent the active substances with higher reduction in spending, -28.4% and -26.1% respectively. Among the active substances with higher consumption, three act on the cardiovascular system and three on the gastrointestinal system and metabolism: ramipril (62.9 DDD/1000 inhabitants die), atorvastatin (48.7 DDD/1000 inhabitants die), amlodipine (27.9 DDD/1000 inhabitants die) act on the cardiovascular system; pantoprazole (25.3 DDD/1000 inhabitants die), metformin (22.4 DDD/1000 inhabitants die), omeprazole (17.2 DDD/1000 inhabitants die) on the gastrointestinal system.
The largest increase in spending from 2019 to 2020 is due to expenditure on ezetimibe (+14.3%) amounting to 83 million euros in 2020.

Figure 2.1.1. Expenditure on medicines supplied under approved care regime (class A-NHS) and broken down by patent coverage in 2020



Generics are medicinal products containing active substances with expired patents, with the exception of those which have benefited from patent cover, pursuant to Article 1(a) 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 2020



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

Figure 2.1.3. Trends in the impact of expenditure on generic and patent-expired medicines on the total spending on medicines under approved care regime (class A-NHS): comparison 2011-2020

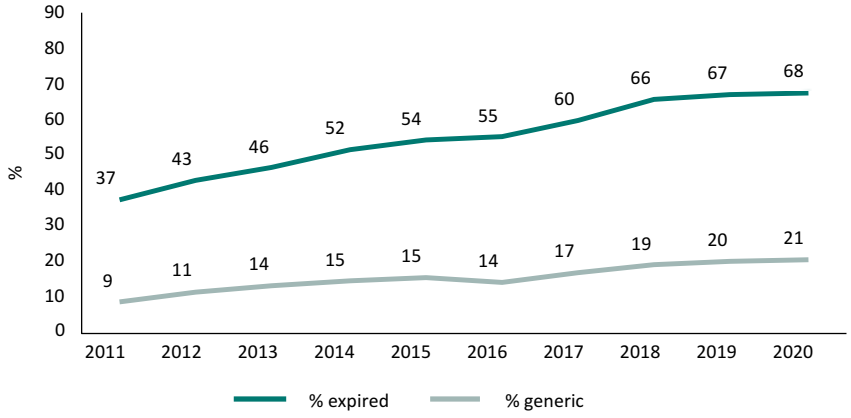


Table 2.1.1. Regional expenditure under approved care regime of medicinal products with expired patent* (class A-NHS): comparison 2020-2019

Region	Per capita expenditure (euros)		% of total expenditure		% generic expenditure**	
	2019	2020	2019	2020	2019	202
Piedmont	96.54	93.88	66.9	68.0	36.5	37.2
Valle d'Aosta	88.98	87.88	65.6	66.6	36.4	36.5
Lombardy	106.94	105.50	60.7	59.8	41.6	42.6
AP of Bolzano	78.40	76.51	66.5	66.9	36.4	36.7
AP of Trento	98.43	96.18	70.7	70.9	43.3	43.7
Veneto	93.20	91.27	68.9	69.6	35.7	36.0
Friuli VG	100.18	96.87	67.5	67.0	37.6	41.7
Liguria	101.45	99.29	68.3	68.9	34.4	34.8
Emilia R.	91.33	89.98	72.0	72.8	36.9	36.9
Tuscany	91.37	89.36	66.0	66.4	36.3	37.1
Umbria	118.94	117.54	70.5	71.6	27.7	27.5
Marche	114.53	110.06	69.4	69.8	24.9	25.5
Lazio	129.16	124.69	67.9	68.5	23.6	23.9
Abruzzo	126.38	123.89	69.3	69.7	26.3	27.1
Molise	119.27	116.85	71.3	71.6	24.4	24.3
Campania	141.49	139.72	69.9	70.8	19.4	19.3
Puglia	132.82	128.67	69.3	69.6	23.9	24.4
Basilicata	123.85	123.48	67.5	68.1	18.8	19.2
Calabria	137.18	133.91	70.2	70.9	18.8	19.2
Sicily	123.11	122.02	68.5	68.5	20.6	21.0
Sardinia	112.18	113.05	66.3	67.4	30.4	30.6
Italy	**112.40**	**110.17**	**67.3**	**67.6**	**29.8**	**30.4**
North	98.94	97.09	65.5	65.5	38.4	39.2
Centre	114.32	110.88	67.8	68.3	27.3	27.8
South and Islands	130.56	128.55	69.1	69.6	21.8	22.1

*Transparency lists published by AIFA over the years 2019-2020 have been used
**Calculated on the expenditure of patent-expired medicines

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

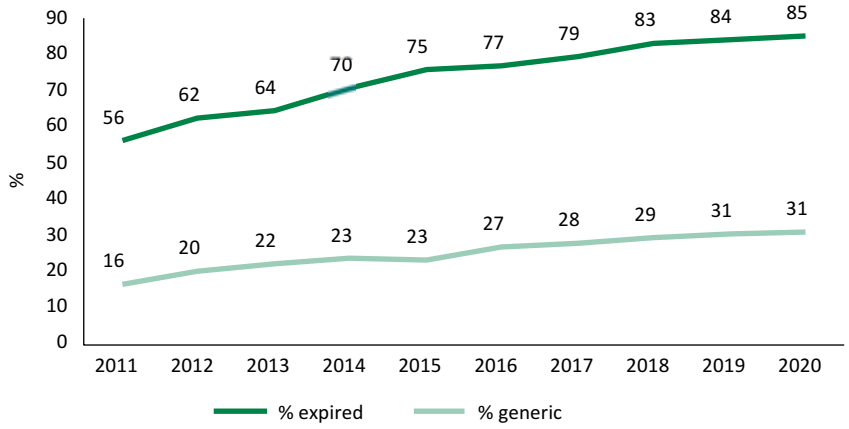


Table 2.1.2. Regional expenditure under approved care regime of medicinal products with expired patent* (class A-NHS): comparison 2020-2019

Region	DDD/1000 inhab. per day		% of total DDDs		% generic consumption**	
	2019	2020	2019	2020	2019	2020
Piedmont	772.74	769.77	83.2	84.4	44.1	44.3
Valle d'Aosta	684.19	691.08	82.9	84.2	44.5	43.7
Lombardy	770.23	772.75	83.0	84.0	48.5	48.7
A.P. of Bolzano	608.91	606.69	84.4	85.6	43.6	43.2
A.P. of Trento	772.74	776.56	85.1	86.1	51.5	51.2
Veneto	741.90	741.18	83.9	85.3	43.6	43.3
Friuli VG	813.71	820.90	84.8	85.4	44.9	48.9
Liguria	730.15	732.86	83.3	84.5	41.2	41.0
Emilia R.	794.29	809.61	84.9	85.8	44.4	44.4
Tuscany	792.07	802.48	81.7	82.9	44.6	45.2
Umbria	950.60	967.63	85.1	86.3	33.3	32.8
Marche	851.19	854.83	83.8	85.3	30.2	30.3
Lazio	914.18	913.02	84.2	85.2	28.5	28.1
Abruzzo	869.03	884.00	83.6	84.7	30.6	30.5
Molise	845.78	857.16	84.4	85.4	26.5	26.3
Campania	937.67	958.87	84.1	85.3	24.2	23.4
Puglia	930.87	939.68	83.9	84.9	27.7	27.6
Basilicata	868.66	894.37	83.0	84.2	22.4	22.3
Calabria	925.88	940.27	83.7	84.8	22.3	22.3
Sicily	904.45	923.19	84.3	85.2	24.9	25.0
Sardinia	834.30	859.73	83.0	84.3	35.9	35.8
Italy	**834.12**	**842.28**	**83.7**	**84.8**	**36.2**	**36.2**
North	765.96	769.28	83.7	84.7	45.7	45.9
Centre	869.43	874.03	83.5	84.6	33.9	33.9
South and	910.34	927.77	83.9	85.0	26.2	26.0

*Transparency lists published by AIFA over the years 2019-2020 have been used

**Calculated on the expenditure of patent-expired medicines

Figure 2.1.5. Composition by Region of 2020 expenditure on patent-expired medicines under approved care regime (class A-NHS)

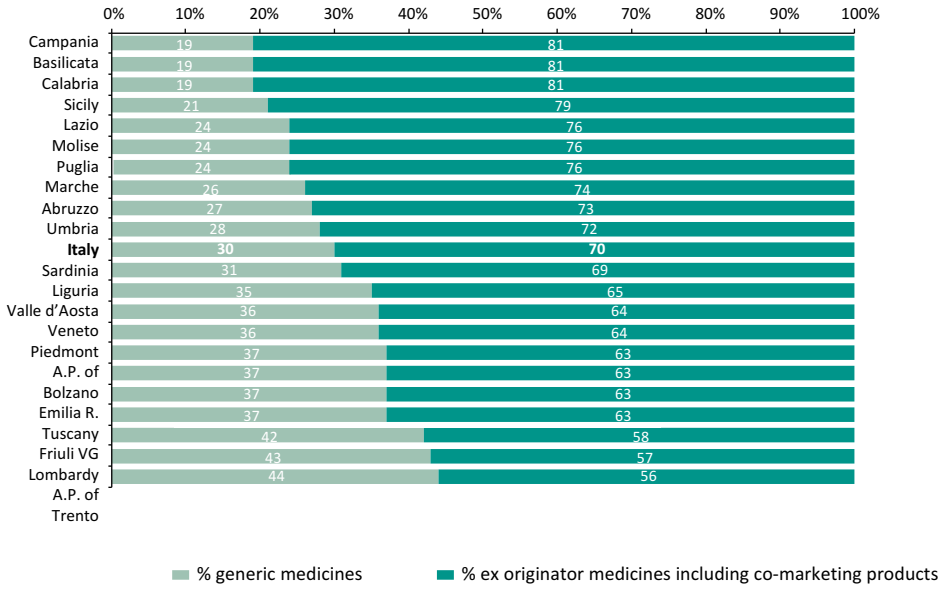


Table 2.1.3. Incidence of 2020 expenditure and consumption of patent-expired medicines* under approved care regime (class A-NHS) by ATC 1st level

ATC 1st level	Expenditure under approved care regime		Consumption (DDDs) under approved care regime	
	% expired patent	% generic**	% expired patent	% generic**
A	64.8	25.9	82.5	39.9
B	41.6	11.0	66.6	15.6
C	91.1	25.9	94.9	35.2
D	30.5	5.1	28.7	3.2
G	88.7	23.2	91.5	28.2
H	39.1	2.7	76.5	4.3
J	85.0	21.0	92.0	24.1
L	85.6	29.1	87.3	39.4
M	86.6	17.8	89.3	27.4
N	57.5	22.9	77.6	36.2
P	74.8	0.4	83.0	0.6
R	20.3	2.9	44.8	10.8
S	38.9	4.7	48.4	9.1
V	42.1	36.1	27.0	25.1

*Transparency lists published by AIFA in 2020 have been used
** Calculated on overall expenditure under approved care regime

Table 2.1.4. Expenditure and consumption of the top 30 active substances with expired patent* under approved care regime (class A-NHS): comparison 2020-2019

ATC	Active substance	Expenditure *(million)*	Δ % 20-19	% generic**	DDD/1000 inhab. per day	Average DDD cost
C	atorvastatin	268.1	4.2	37.1	48.7	0.25
A	pantoprazole	253.8	-4.2	56.3	25.3	0.46
A	cholecalciferol	201.4	-28.4	17.7	9.7	0.95
C	bisoprolol	155.2	5.4	31.6	11.8	0.60
A	lansoprazole	143.0	-6.0	70.8	14.1	0.47
A	omeprazole	135.0	-5.2	40.3	17.2	0.36
A	esomeprazole	129.6	-4.5	37.2	14.2	0.42
J	amoxicillin/ clavulanic acid	127.5	-26.1	17.8	4.3	1.35
C	ramipril	120.4	-1.6	38.6	62.9	0.09
C	omega 3	115.2	0.7	37.8	4.5	1.18
C	olmesartan	98.5	8.8	20.5	14.4	0.31
C	amlodipine	96.8	2.2	32.6	27.9	0.16
N	levetiracetam	93.6	2.5	39.0	2.1	2.03
A	metformin	93.5	1.8	34.5	22.4	0.19
C	simvastatin	91.2	-3.7	51.8	12.8	0.33
C	nebivolol	89.4	2.9	23.3	16.1	0.25
C	ezetimibe	83.0	14.3	36.6	5.1	0.74
L	letrozole	81.6	7.8	44.9	1.7	2.26
C	rosuvastatin	80.3	6.5	23.6	14.0	0.26
C	doxazosin	74.8	1.7	29.8	7.6	0.45

*Transparency lists published by AIFA in 2020 have been used

** Calculated on overall expenditure under approved care regime

Expenditure on sharing of the reference price of patent-expired medicines

In 2020, expenditure on sharing of the amount in excess of the reference price of patent-expired medicines (hereinafter share) amounted to 18.07 euros per capita (approximately 1.1 billion euros). This value represents 72.5% of the total citizen's share (including the ticket per prescription and/or packaging) and shows a reduction of 3.7% compared to the previous year (Table 2.1.5).
Expenditure per capita per share is highest in the South and the Islands (23.0 euros), while the lowest is in the North with 13.88 euros (Figure and Table 2.1.5), deviating from the national average of +27.3% and -23.2% respectively. Campania and Calabria are the regions with the highest spending values (24.90 euros and 24.82 euros, respectively), while Trento and Bolzano have the lowest values of 11.76 euros and 12.57 euros, respectively.
An analysis of the correlation between shared expenditure and regional per capita income shows that the regions with the lowest income are those with the highest share. In particular, for Calabria, Campania and Sicily, which have a low per capita income, slightly above 10 000 euros, 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 (8.8%), beta-blockers (7.3%), angiotensin II receptor antagonists, in combination and alone (6.1% and 5.2%), ACE-inhibitors in combination (5.1%) These categories make up about one third of total expenditure (Table 2.1.6). Compared to 2020, the spending value of treatments for peptic ulcer (-38.5%) and other beta-lactam antibiotics (-22.6%) is significantly reduced. This trend is mainly due to the reduction in shared expenditure on pantoprazole (-55.6%), thanks to the realignment of some products to the reference price, and to the reduction in expenditure on the sharing of amoxicillin/clavulanic acid (-21.1%), which can be due to the reduction in consumption of this substance in 2020 compared to 2019 (Table 2.1.7). On the other hand, expenditure on miotic and antiglaucomatous preparations (+36.0%) and medications used for benign prostatic hypertrophy increases (+22.6%).
Among the top 20 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, atorvastatin and ramipril cover 11.1% 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 ACE inhibitors not associated (C09A). 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 for peptic ulcer and gastro-oesophageal reflux disease (A02B), beta-blockers (C07A) and medications used to treat benign prostatic hypertrophy (G04C) it is observed that the use of generic medicines increases 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 most products with an average difference of less than 3 euros are under approved care regime (72.7%). Only 0.5% 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 sharing in the reference price of expired 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 their wider use.

Table 2.1.5. Distribution of share on reference price by Region (year 2020)

Region	Per capita expenditure	Δ % 20-19	Δ % national average
Piedmont	13.87	-4.9	-23.3
Valle d'Aosta	13.00	-2.0	-28.1
Lombardy	13.76	-4.1	-23.9
A.P. of Bolzano	11.76	-3.6	-34.9
A.P. of Trento	12.57	-2.8	-30.4
Veneto	13.82	-2.7	-23.5
Friuli VG	14.57	-2.9	-19.4
Liguria	14.89	-3.9	-17.6
Emilia R.	14.04	-1.8	-22.3
Tuscany	13.38	-2.9	-26.0
Umbria	19.82	-1.4	9.7
Marche	18.68	-5.1	3.4
Lazio	24.64	-4.3	36.3
Abruzzo	20.59	-3.2	13.9
Molise	21.41	-2.6	18.5
Campania	24.90	-2.8	37.8
Puglia	21.73	-4.5	20.2
Basilicata	22.43	-0.9	24.1
Calabria	24.82	-4.4	37.3
Sicily	24.05	-5.0	33.1
Sardinia	17.37	-1.0	-3.9
Italy	**18.07**	**-3.7**	**-**
North	13.88	-3.5	-23.2
Centre	19.88	-3.9	10.0
South and Islands	23.00	-3.7	27.3

Table 2.1.6. Top 20 therapeutic categories with the largest share of expenditure on reference price (year 2020)

3rd level ATC	Description	Total expenditure	Δ % 20-19	%*	% cum.
C10A	Lipid modifying agents, not combined	93,963,421	-2.6	8.8	8.8
C07A	Beta blockers	77,997,222	2.4	7.3	16.1
C09D	Angiotensin II antagonists in association	64,356,393	-2.1	6.1	22.2
C09C	Angiotensin II antagonists	55,222,316	-2.3	5.2	27.4
C09B	Angiotensin-converting enzyme inhibitors associated	53,863,503	-1.8	5.1	32.5
N06A	Antidepressants	52,907,761	4.4	5.0	37.5
C09A	Angiotensin-converting enzyme inhibitors not associated	49,342,766	-3.4	4.6	42.1
G04C	Medicines used in benign prostatic hypertrophy	47,706,516	22.6	4.5	46.6
B01A	Antithrombotics	41,625,359	1.6	3.9	50.5
A02B	Treatments for peptic ulcer	39,921,984	-38.5	3.8	54.3
M01A	Non-steroidal anti-inflammatory and anti-rheumatic drugs	36,128,263	-5.6	3.4	57.7
C08C	Selective calcium channel blockers with prevalent vascular effect	35,775,229	-0.6	3.4	61.1
N03A	Anti-epileptics	30,066,050	0.9	2.8	63.9
A10B	Oral hypoglycemic agents	29,291,652	-2.2	2.8	66.7
A11C	Vitamins A and D, including their combinations	27,523,447	-27.4	2.6	69.3
S01E	Antiglaucoma and miotic preparations	24,639,870	36.0	2.3	71.6
J01C	Beta-lactam antibacterials, penicillins	19,220,932	-22.6	1.8	73.4
J01D	Other beta-lactam antibacterials	17,262,275	-28.8	1.6	75.0
R06A	Antihistamines for systemic use	16,399,673	7.0	1.5	76.5
M05B	Drugs affecting mineralisation and bone structure	13,489,473	-5.9	1.3	77.8

* Calculated on overall shared expenditure

Table 2.1.7. Top 30 substances with the largest share of expenditure on reference price (year 2020)

ATC 5th	Active substance	Total	Δ % 20-19	%*	% cum.
C07AB07	bisoprolol	51,530,424	4.3	4.9	4.9
C10AA05	atorvastatin	37,849,475	-3.6	3.6	8.5
C09AA05	ramipril	27,408,488	-1.2	2.6	11.1
A11CC05	cholecalciferol	24,742,668	-29.7	2.3	13.4
B01AC06	acetylsalicylic acid	24,190,454	1.3	2.3	15.7
C08CA01	amlodipine	20,954,886	2.0	2.0	17.7
J01CR02	amoxicillin/clavulanic acid	16,867,413	-21.1	1.6	19.3
C09CA08	olmesartan	16,287,868	5.2	1.5	20.8
A10BA02	metformin	16,093,173	-2.4	1.5	22.3
C10AX06	omega 3	15,959,168	-4.2	1.5	23.8
B01AC04	clopidogrel	15,420,859	-0.3	1.5	25.3
G04CA02	tamsulosin	14,935,997	-0.7	1.4	26.7
C09DA08	olmesartan/hydrochlorothiazide	14,873,930	5.6	1.4	28.1
C09BB04	perindopril/amlodipine	13,565,460	-2.8	1.3	29.4
C10AA07	rosuvastatin	12,731,980	-0.9	1.2	30.6
C07AB12	nebivolol	12,682,425	0.2	1.2	31.8
G04CB02	dutasteride	12,642,238	-2.0	1.2	33.0
M01AB05	diclofenac	12,163,230	-1.3	1.1	34.1
C09DB02	olmesartan/amlodipine	11,997,430	0.6	1.1	35.2
C10AA01	simvastatin	11,823,858	-4.0	1.1	36.3
N06AB10	escitalopram	11,573,858	-0.7	1.1	37.4
C02CA04	doxazosin	11,555,552	2.9	1.1	38.5
A02BC02	pantoprazole	11,473,668	-55.6	1.1	39.6
N03AX16	pregabalin	10,934,542	6.0	1.0	40.6
C09CA07	telmisartan	10,854,179	0.6	1.0	41.6
J01XX01	fosfomycin	10,837,238	-0.6	1.0	42.6
A05AA02	ursodeoxycholic acid	10,755,452	29.7	1.0	43.6
H03AA01	levothyroxine	10,741,631	-1.7	1.0	44.6
C09BA05	ramipril/hydrochlorothiazide	10,441,561	-6.2	1.0	45.6
C09DA03	valsartan/hydrochlorothiazide	10,431,564	-7.5	1.0	46.6

* Calculated on overall shared expenditure

Table 2.1.8. Distribution by geographical area, gender and age of patients using generic medicines for the top 10 therapeutic categories (3rd level ATC) at the largest share of expenditure on the reference price (year 2020)

	A02B	B01A	C07A	C09A	C09B	C09	C09D	C10A	G04C	N06A
Geographical area										
North	69.3	23.0	58.6	63.6	33.2	45.3	37.1	59.1	55.6	53.6
Centre	56.9	20.5	43.5	50.5	23.7	35.9	29.7	47.6	42.3	45.1
South	47.7	17.4	33.5	37.9	18.0	27.4	23.7	39.2	31.7	33.9
Gender										
Women	56.7	17.9	43.6	51.1	25.0	34.5	28.4	46.8	-	45.4
Men	59.5	22.9	50.4	54.2	26.2	38.2	32.3	51.6	44.1	46.5
Age group										
<50	49.0	9.1	44.4	55.6	23.4	39.0	33.4	52.7	39.3	46.6
50-60	55.3	21.0	45.9	55.7	26.0	38.7	33.6	53.2	41.2	48.2
60-70	57.9	22.8	45.8	53.3	26.2	36.5	31.1	50.5	43.6	46.8
70-80	60.4	21.3	45.9	50.9	25.2	34.6	28.4	47.4	44.4	45.3
>80	64.3	20.6	49.4	51.0	25.9	35.2	28.3	46.5	45.6	42.7
Total	**57.9**	**20.4**	**46.6**	**52.7**	**25.6**	**36.2**	**30.2**	**49.2**	**44.0**	**45.8**

A02B: Treatments for peptic ulcer
B01A: Antithrombotics
C07A: Beta blockers
C09A: Angiotensin-converting enzyme inhibitors not associated
C09B: Angiotensin-converting enzyme inhibitors associated
C09C: Angiotensin II antagonists
C09D: Angiotensin II antagonists in association
C10A: Lipid modifying agents, not combined
G0AC: Medicines used in benign prostatic hypertrophy
N06A: Antidepressants

Table 2.1.9. Average difference between the public price and the reference price and share of expenditure under approved care regime and under direct and *per conto* distribution (year 2020)

Average difference between retail price and reference price (euros)	% expenditure under approved care regime*	% expenditure under direct and per conto distribution **
<1	10.0	2.2
≥1 <2	31.3	3.0
≥2 <3	31.3	2.5
≥3 <5	18.1	5.7
≥5 <20	8.7	13.0
≥20	0.5	73.6

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

Patent expired biologic medicines

Analysing the level of competition in the biosimilar market (HHI) and the market shares per competitor (Figure 2.1.7), it is clear that bevacizumab is the active substance with the higher concentration in the market (HHI = 0.76), where the originator has the largest market share, despite competition from two other biosimilars. Teriparatide and insulin glargine have a value of HHI of 0.62 and 0.59, respectively, although the largest market share belongs to the originator, which competes with only one type of biosimilar in the case of insulin glargine. The situation is different for somatropin (HHI 0.55) and insulin lispro (0.50), where the largest market share is made of a single biosimilar on the market. Epoetin (HHI 0.41), follitropin alpha (HHI 0.49) and etanercept (HHI 0.37) have greater competitiveness, in fact there are two other competitors in addition to the originator. Rituximab (HHI 0.32) has a fair distribution of market shares between the originator and the two available biosimilars. Infliximab (HHI 0.32) has a low market concentration, although the largest share is held by a biosimilar. Finally, trastuzumab and adalimumab have the lowest value of HHI (0.25 and 0.26), a high-competitive index, in which there are at least 4 competitors.

Analysing the trend in expenditure and consumption of expired 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 50% and 60% (Figure 2.1.13, 2.1.14 and 2.1.17). 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, 28.1%), the highest percentage of consumption is attributable to adalimumab biosimilars (26.1%), which are increasing for the indicators considered (+42.6% and +76%). Analysing the trend over the last decade it is observed a clear reduction in reference product expenditure for both adalimumab and etanercept (Figure 2.1.8). In the case of growth factors it can also be noted that, for expenditure, there is the highest incidence for the originator of pegfilgrastim (Figure 2.1.12), as for consumption the highest incidence is attributable to the biosimilar (31.1%), which has significantly increased compared to the previous year (91.3% and >100%). Long-acting insulins have higher consumption and spending values for reference products (35%), although more than a third of expenditure is attributable to other types of long-acting insulin currently available (Figure 2.1.15).

Rituximab and trastuzumab, which are the only two molecules to have two different formulations available (subcutaneous and intravenous) have a high incidence both for spending and consumption of the biosimilar (Figure 2.1.16 and 2.1.19). In particular, for trastuzumab significant increases are observed compared to the previous year. As for epoetin and low molecular weight heparins, there is a higher incidence of both consumption and expenditure on biosimilars (Figures 2.1.10 and 2.1.11).

Bevacizumab, whose biosimilar was first marketed in Italy in 2020, has a high percentage of both consumption (86.4%) and expenditure (94.2%) on the originator, although there has been a high increase in both indicators for the biosimilar (Figure 2.1.9). Also for teriparatide, there is a similar trend with a reference product incidence of 76.8% and 82.5%, though important increases in the corresponding biosimilar are observed (Figure 2.1.18).

Considering only the trend in expenditure and consumption of the reference product and the biosimilar, purchased directly by public facilities (Table 2.1.11), it is noted that for adalimumab, fast acting insulin and pegfilgrastim there is a higher incidence of expenditure on the reference product, but a higher incidence of consumption of the biosimilar. For bevacizumab, etanercept, follitropins, long acting insulin and teriparatide there is a higher incidence of the originator for all the indicators considered, as for low-molecular-weight heparin (LMWH), epoetin, filgrastim, infliximab, rituximab, somatropin and trastuzumab the greatest incidences are shown for biosimilars.
Analysing the regional variability in the consumption of expired biological medicines, Campania, Molise, Puglia, Calabria, the Provinces of Bolzano and Trento, Liguria and Umbria tend to consume more former originator products, whereas Emilia Romagna, Marche and Tuscany are the Italian regions with the highest consumption of biosimilars.
Analysing the regional variability in the consumption of expired patent biologics, it is observed that that Campania, Molise, Puglia, Calabria, the Provinces of Bolzano and Trento, Liguria and Umbria tend to consume more former originator products, whereas Emilia Romagna, Marche and Tuscany are the Italian regions with the highest consumption of biosimilars.
In the case of anti-TNF-alpha therapies, there are important differences for etanercept, whose reference product shows very low values in Valle d'Aosta and the Provinces of Bolzano and Trento, while higher values are registered in Abruzzo, Molise, Calabria and Campania. Sardinia, on the other hand, differs in its increased spending on the biosimilar. Bevacizumab and teriparatide, whose patent has expired recently, have a low market penetration of the biosimilar, in particular Abruzzo and Basilicata use only the former originator products for both molecules. For growth factors, the highest proportion of expenditure is shown for the biosimilar filgrastim, especially in Valle d'Aosta, the A.P. of Trento and Emilia Romagna. Sardinia and the A.P. of Bolzano, on the contrary, record the highest values for pegfilgrastim biosimilar. As for epoetins, follitropin and insuline fast acting, former originators are less used, and in some regions they are completely replaced by biosimilars or other molecules belonging to the same therapeutic category. Low molecular weight heparins show high variability: while in Umbria and in the Provinces of Trento and Bolzano the use of biosimilar is practically non-existent, in Emilia Romagna and Marche the percentage is among the highest. Lombardy, Apulia and Sicily, on the other hand, have the largest share of spending on other molecules. Particularly interesting is the different expenditure shown for rituximab and trastuzumab, the subcutaneous formulation of which shows higher values especially in Lombardy, Campania and Basilicata.
Analysing the regional variability in terms of biosimilar consumption and the average DDD cost of expired patent biologics, it is shown that in Emilia Romagna, Marche, Tuscany, Veneto and Piedmont the higher consumption of biosimilar corresponds to an average DDD cost lower than the national average. On the contrary, Basilicata, Friuli Venezia Giulia and Sardinia have a higher cost of expired patent biologics, despite a higher consumption of biosimilars. Calabria and Abruzzo have the highest values of cost per day of therapy compared to a lower consumption of biosimilars.
Regional trends are confirmed by analysing the average cost compared to the consumption of the molecule (originator + biosimilar).

Compared to the previous figure, however, it is worth noting the shift of Umbria, Liguria and the A.P. of Trento that move from the dial of lower consumption of the biosimilar to the dial of greater consumption of the molecule, while maintaining a lower cost per day of therapy. This can indicate efficiency of procurement procedures for the purchase of medicines.
There is a linear correlation between biosimilar consumption on total direct purchases and average cost per day of therapy with hospital pharmaceuticals and medicinal products reimbursed by the Italian National Health Service. Regions with higher biosimilar consumption and lower DDD cost are: Friuli Venezia Giulia, Piedmont, Veneto, Tuscany and Emilia Romagna. Basilicata and Sardinia show once again consumption of biosimilars and average costs higher than the national average. This indicates a need for improving procurement procedures for the purchase of medicines. As far as companies producing former originator medicines are concerned, it is noted that a single company accounts for 19% of the expenditure of expired patent biologics in Italy. This company is the one with the highest total turnover. As for biosimilars, although companies are numerically higher than those of former originators, it is noted that the largest market shares for expired patent biologics are held by companies that also have higher turnover levels.

Figure 2.1.7. Expired Patent Biologics: Herfindahl-Hirschman Index (HHI) and market shares by competitor, year 2020

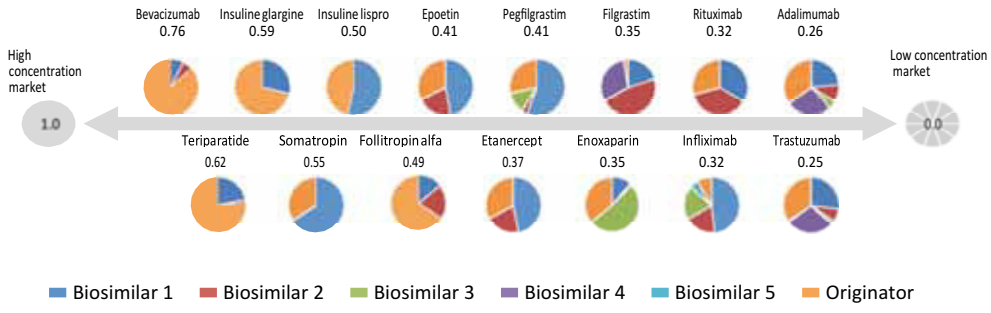


Table 2.1.10. Biosimilars, provision through public health facilities and NHS prescriptions 2020

Group and subgroup	Per capita expenditure	Inc. %	Δ % 20-19	DDD/1000 inhab. per day	Inc. %	Δ % 20-19
Anti-TNF alpha	**5.82**	**100**	**-16.6**	**1.36**	**100**	**6.1**
Biosimilar bevacizumab	0.67	11.54	42.6	0.36	26.07	76.03
Biosimilar etanercept	0.85	14.53	2.92	0.19	14.15	18.04
Biosimilar infliximab	0.51	8.72	-19.02	0.3	22.28	9.78
Originator adalimumab	1.12	19.21	-36.75	0.19	14.19	-31.6
Etanercept originator	0.93	15.95	-24.69	0.09	6.96	-24.07
Infliximab originator	0.12	1.98	-48.81	0.03	2.15	-39.4
Other anti-TNF alpha	1.63	28.08	-10.93	0.19	14.19	3.85
Bevacizumab	**2.35**	**100**	**-27.47**	**0.1**	**100**	**-**
Biosimilar	0.14	5.77	>100	0.01	13.62	>100
Originator	2.21	94.23	-31.65	0.09	86.38	-26.59
Low molecular weight	**1.97**	**100**	**28.07**	**7.25**	**100**	**7.7**
Biosimilar	1.1	55.68	91.15	3.99	55.08	32.04
Originator	0.42	21.17	-9.74	2.25	31.05	-13.09
Other low molecular weight heparin	0.46	23.16	-9.19	1.01	13.87	-9.69
Epoetins	**2.79**	**100**	**-8.66**	**3.6**	**100**	**1.5**
Biosimilar	1.3	46.75	-1.6	2.7	75.15	7.59
Originator	0.41	14.66	-17.7	0.36	10.04	-12.41
Other epoetins	1.08	38.6	-12.62	0.53	14.81	-13.98
Growth factors	**0.53**	**100**	**-20.64**	**0.1**	**100**	**7.1**
Biosimilar filgrastim	0.13	24.3	-1.67	0.05	45.95	5.62
Biosimilar pegfilgrastim	0.09	16.24	91.31	0.03	31.14	163.2
Originator filgrastim	0.04	7.04	12.82	0	1.31	15.03
Originator pegfilgrastim	0.15	27.87	-49.51	0.01	12.46	-51.4
Other growth factors	0.13	24.55	-21.74	0.01	9.14	-18.5
Follitropins	**0.72**	**100**	**-23.79**	**0.1**	**100**	**-**
Biosimilar	0.08	11.08	-13.83	0.01	14.21	-12.14
Originator	0.21	28.71	-26.88	0.03	27.1	-23.1
Other follitropin	0.43	60.22	-23.87	0.06	58.69	-21.15
Fast acting insulins	**0.2**	**100**	**1.3**	**0.94**	**100**	**8.5**
Biosimilar	0.04	19.36	68.19	0.25	26.56	66.67
Originator	0.04	20.29	-27.76	0.22	23.13	-19.27
Other long acting insulins	0.12	60.34	2.08	0.47	50.3	5.84
Long acting insulins	**2.35**	**100**	**2.87**	**6.08**	**100**	**4**
Biosimilar	0.28	11.76	10.93	0.88	14.4	13.04
Originator	0.81	34.28	-12.74	2.13	35.05	-11.19
Other insulin glargine	0.48	20.34	22.5	1.49	24.56	22.8
Other long acting insulins	0.79	33.61	9.45	1.58	25.99	8.52

Continued

Table 2.1.10. Continued

Group and subgroup	Per capita expenditure	Inc. %	Δ % 20-19	DDD/1000 inhab. per day	Inc. %	Δ % 20-19
Rituximab	**1.37**	**100**	**-21.75**	**0.45**	**100**	**-13.85**
Biosimilar IV	0.97	71.06	-12.3	0.31	70.39	0.68
Originator iv	0.09	6.58	-50.41	0.02	3.6	-50.21
Originator sc	0.31	22.37	-33.28	0.12	26.01	-33.19
Somatropins	**1.35**	**100**	**-0.5**	**0.28**	**100**	**4.51**
Biosimilar	0.25	18.8	6.75	0.07	24.54	8.75
Originator	0.21	15.72	-7.77	0.04	12.79	-5.41
Other somatropin	0.89	65.48	-0.56	0.18	62.67	5.15
Teriparatide	**0.15**	**100**	**-32.66**	**0.04**	**100**	**-19.98**
Biosimilar	0.03	17.46	1527.3	0.01	24.24	1591.7
Originator	0.12	82.54	-44.01	0.03	75.76	-38.67
Trastuzumab	**1.56**	**100**	**-30.02**	**0.18**	**100**	**-13.48**
Biosimilar iv	0.79	50.49	11.28	0.12	65.53	30.85
Originator iv	0.19	11.96	-58.45	0.01	4.82	-57.67
Originator sc	0.58	37.55	-45.38	0.05	29.65	-45.21

Figure 2.1.8. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): anti-TNF alpha

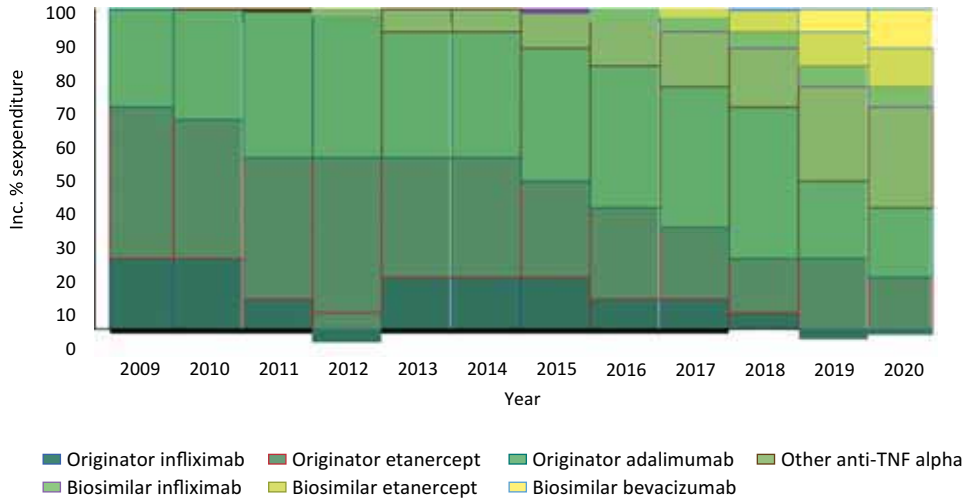


Figure 2.1.9. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: bevacizumab

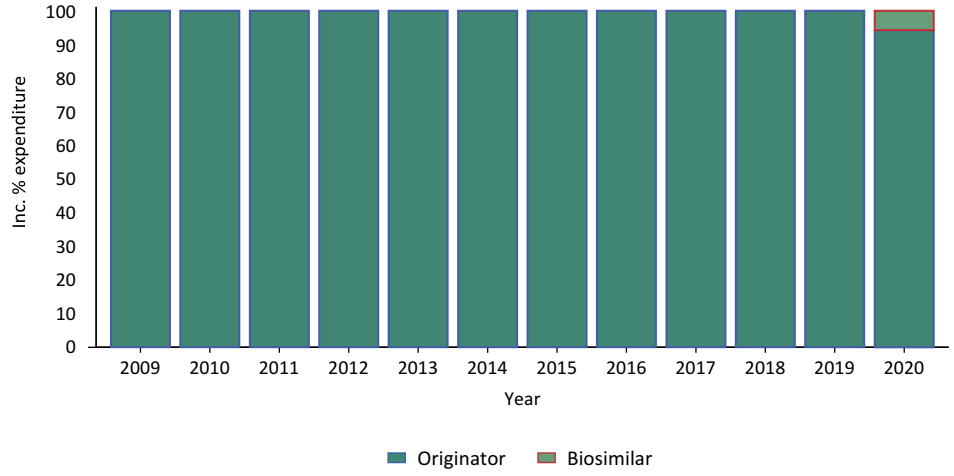


Figure 2.1.10. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (4th ATC level): low molecular weight heparins

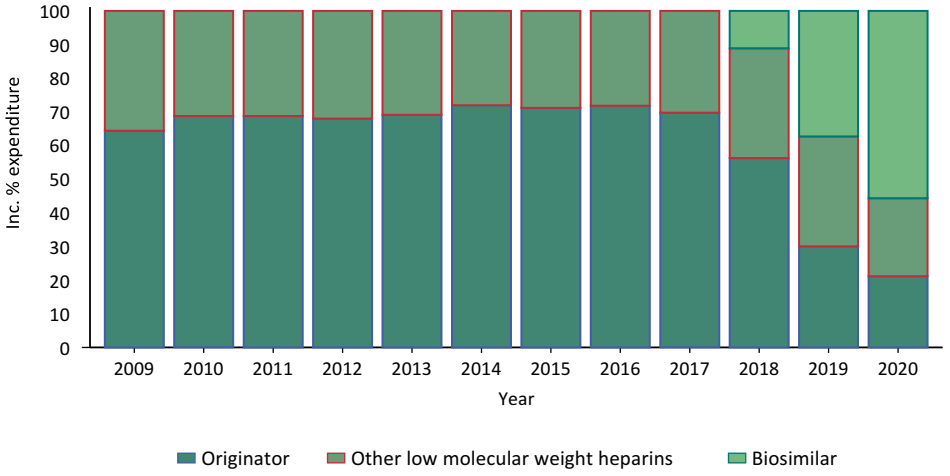


Figure 2.1.11. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (4th ATC level): anti-TNF alpha

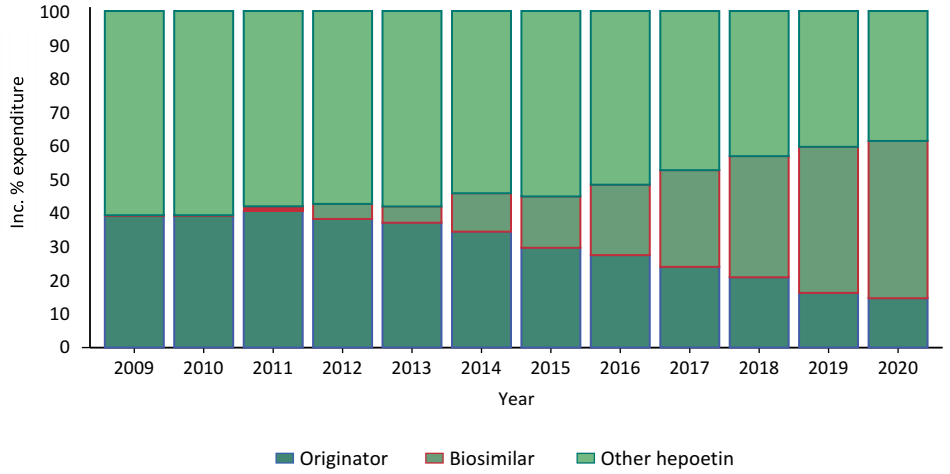


Figure 2.1.12. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (4th ATC level): anti-TNF alpha

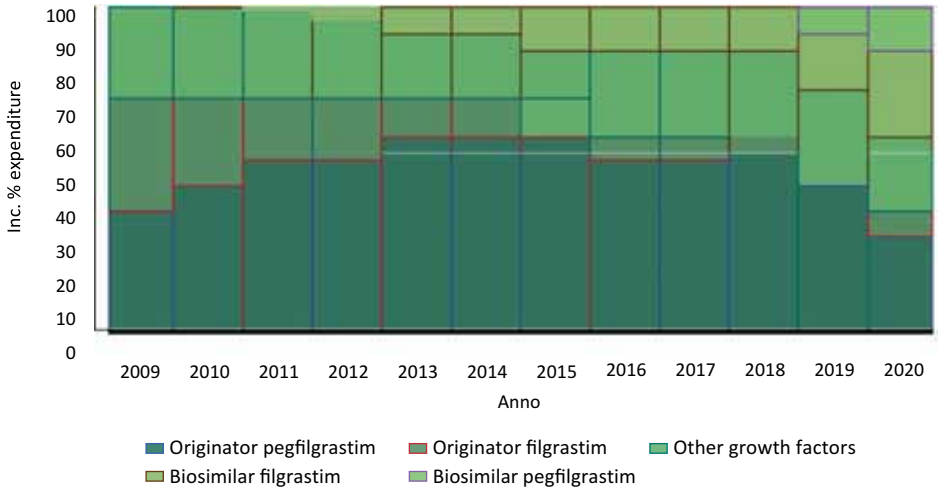


Figure 2.1.13. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (4th ATC level): follitropin

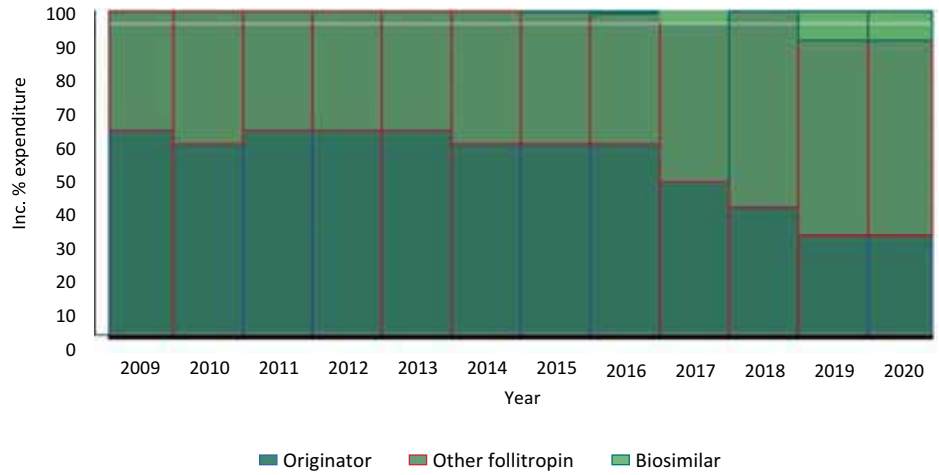


Figure 2.1.14. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (4th ATC level): fast acting insulins

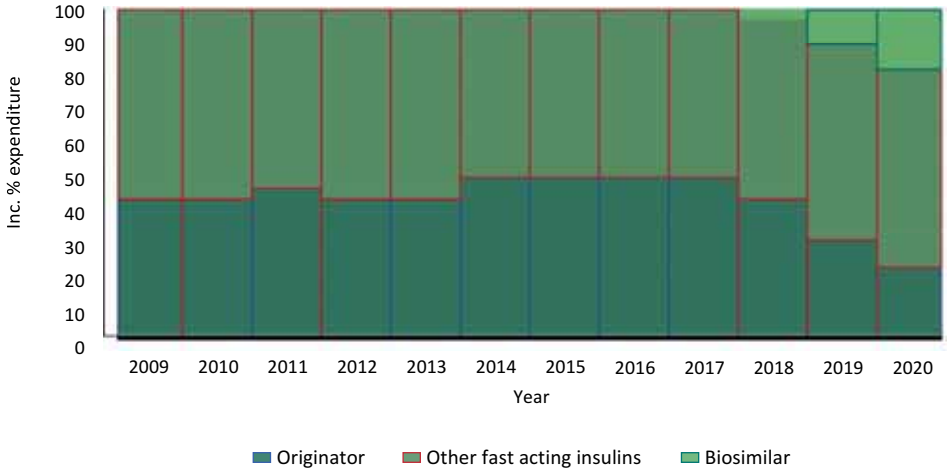


Figure 2.1.15. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): fast acting insulins

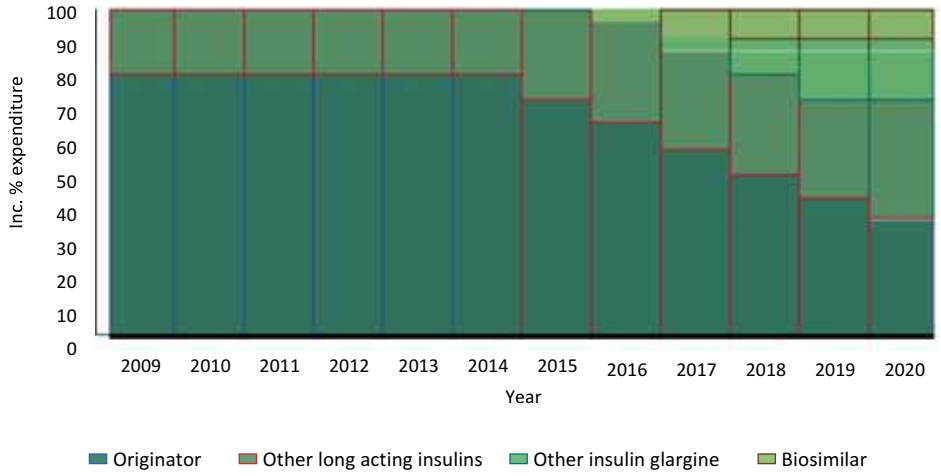


Figure 2.1.16. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: rituximab

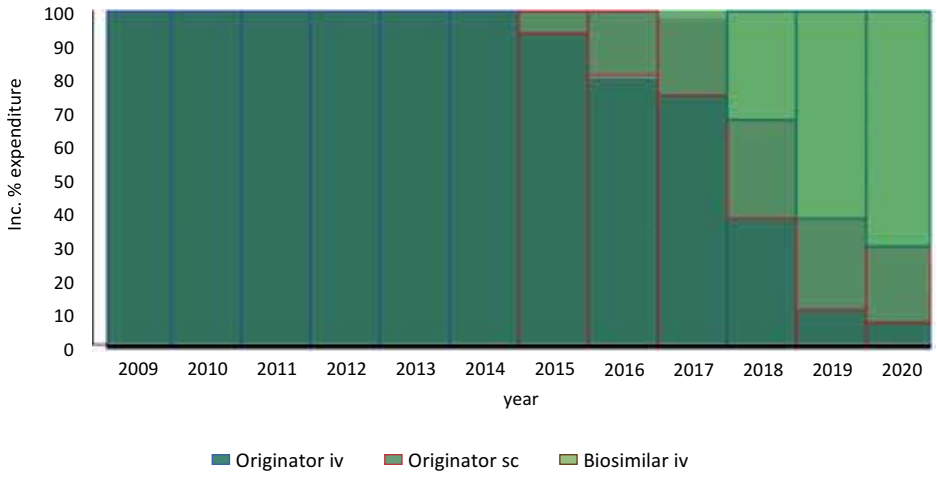


Figure 2.1.17. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category (ATC 4th level): somatropin

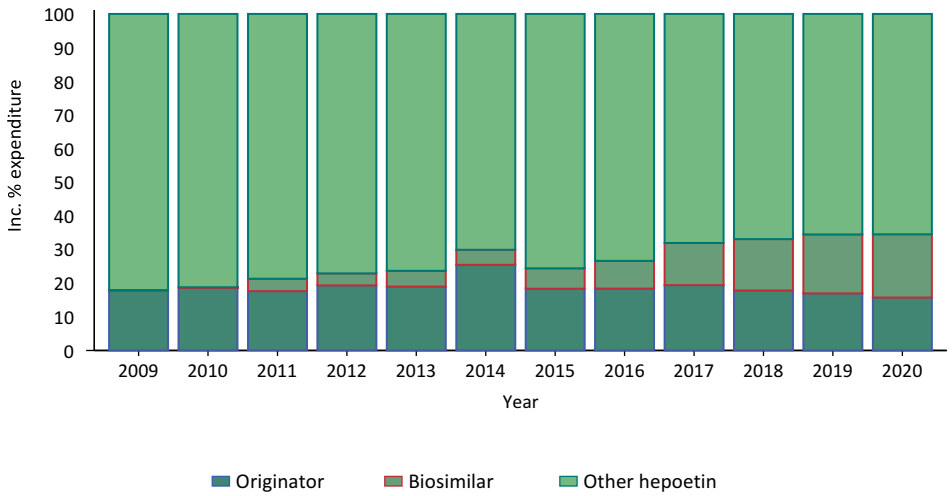


Figure 2.1.18. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: teriparatide

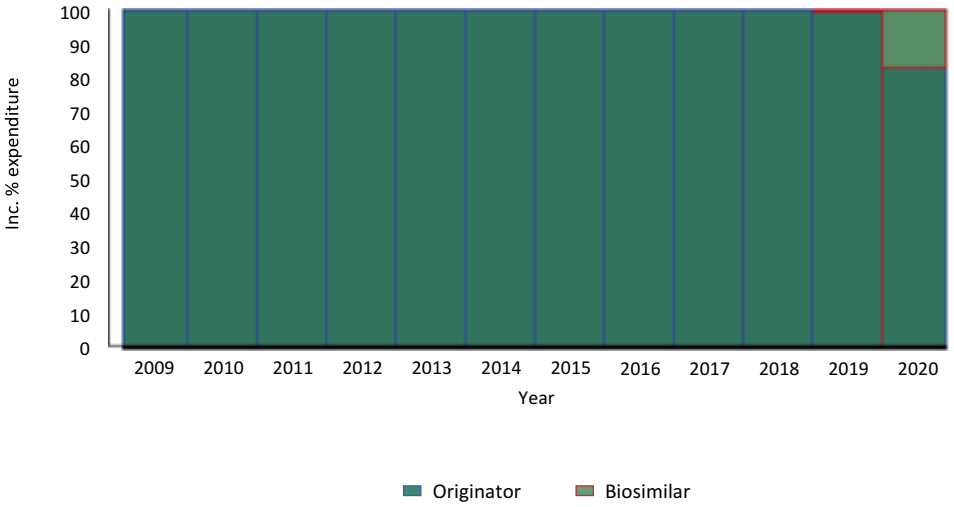


Figure 2.1.19. Incidence (%) of expenditure on biosimilar drugs compared to total expenditure for the therapeutic category: trastuzumab

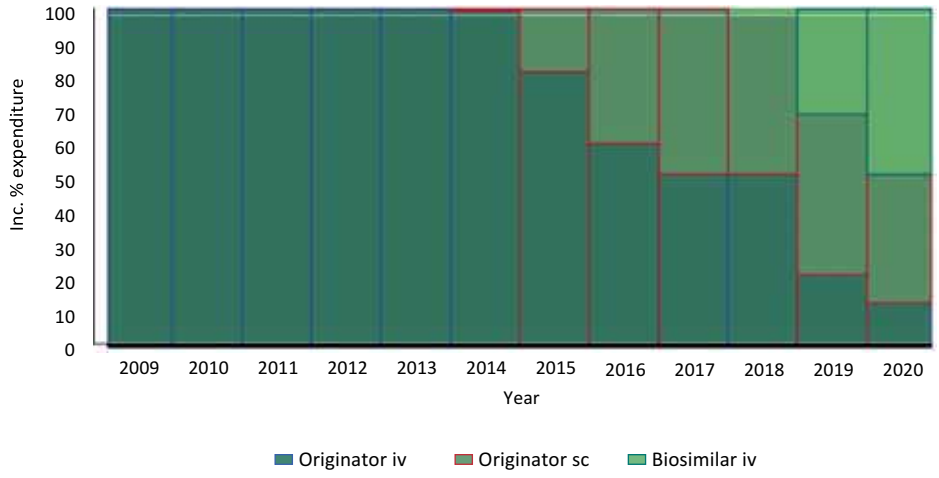


Table 2.1.11. Expired patent biosimilars, provision through public health facilities and NHS prescriptions 2020: comparison between biosimilar and originator drugs

Group and subgroup	Per capita expenditure	Inc. %	Δ % 20-19	DDD/1000 inhab. per day	Inc. %	Δ % 20-19
Adalimumab	**1.79**	**100**	**-20.06**	**0.55**	**100**	**13.24**
Biosimilar	0.67	37.53	42.6	0.36	64.76	76.03
Originator	1.12	62.47	-36.75	0.19	35.24	-31.6
Bevacizumab	**2.35**	**100**	**-27.47**	**0.1**	**100**	**-15.01**
Biosimilar	0.14	5.77	>100	0.01	13.62	>100
Originator	2.21	94.23	-31.65	0.09	86.38	-26.59
Low molecular weight heparins	**1.52**	**100**	**46.15**	**6.24**	**100**	**11.22**
Biosimilar	1.1	72.45	91.15	3.99	63.95	32.04
Originator	0.42	27.55	-9.74	2.25	36.05	-13.09
Epoetin	**1.71**	**100**	**-5.99**	**3.07**	**100**	**4.77**
Biosimilar	1.3	76.13	-1.6	2.7	88.22	7.59
Originator	0.41	23.87	-17.7	0.36	11.78	-12.41
Etanercept	**1.77**	**100**	**-13.65**	**0.29**	**100**	**-0.21**
Biosimilar	0.85	47.68	2.92	0.19	67.02	18.04
Originator	0.93	52.32	-24.69	0.09	32.98	-24.07
Filgrastim	**0.17**	**100**	**1.25**	**0.05**	**100**	**5.85**
Biosimilar	0.13	77.54	-1.67	0.05	97.23	5.62
Originator	0.04	22.46	12.82	-	2.77	15.03
Follitropin	**0.29**	**100**	**-23.66**	**0.04**	**100**	**-19.65**
Biosimilar	0.08	27.84	-13.83	0.01	34.39	-12.14
Originator	0.21	72.16	-26.88	0.03	65.61	-23.1
Infliximab	**0.62**	**100**	**-26.89**	**0.33**	**100**	**2.47**
Biosimilar	0.51	81.5	-19.02	0.3	91.21	9.78
Originator	0.12	18.5	-48.81	0.03	8.79	-39.4
Fast acting insulins	**0.08**	**100**	**0.14**	**0.47**	**100**	**11.45**
Biosimilar	0.04	48.83	68.19	0.25	53.45	66.67
Originator	0.04	51.17	-27.76	0.22	46.55	-19.27
Long acting insulins	**1.08**	**100**	**-7.71**	**3.01**	**100**	**-5.28**
Biosimilar	0.28	25.54	10.93	0.88	29.12	13.04
Originator	0.81	74.46	-12.74	2.13	70.88	-11.19
Pegfilgrastim	**0.24**	**100**	**-30.73**	**0.04**	**100**	**16.36**
Biosimilar	0.09	36.82	91.31	0.03	71.42	163.2
Originator (v and subq)	0.15	63.18	-49.51	0.01	28.58	-51.4
Rituximab	**1.37**	**100**	**-21.75**	**0.45**	**100**	**-13.85**
Biosimilar	0.97	71.06	-12.3	0.31	70.39	0.68
Originator	0.4	28.94	-38.13	0.13	29.61	-35.86
Somatropins	**0.47**	**100**	**-0.39**	**0.11**	**100**	**3.45**
Biosimilar	0.25	54.46	6.75	0.07	65.74	8.75

Continued

Table 2.1.11.
Continued

Group and subgroup	Per capita expenditure	Inc. %	Δ % 20-19	DDD/1000 inhab. per day	Inc. %	Δ % 20-19
Originator	0.21	45.54	-7.77	0.04	34.26	-5.41
Teriparatide	**0.15**	**100**	**-**	**0.04**	**100**	**-19.98**
Biosimilar	0.03	17.46	1527.3	0.01	24.24	>100
Originator	0.12	82.54	-44.01	0.03	75.76	-38.67
Trastuzumab	**1.56**	**100**	**-**	**0.18**	**100**	**-13.48**
Biosimilar	0.79	50.49	11.28	0.12	65.53	30.85
Originator	0.77	49.51	-49.24	0.06	34.47	-47.38
Total	**15.14**	**100**	**-**	**14.96**	**100**	**4.15**
Biosimilar	7.21	47.6	12.41	9.29	62.12	21.58
Originator	7.94	52.4	-31.65	5.67	37.88	-15.67

2.2 Out-of-pocket medication consumption

Expenditure for class C medicines equalled approximately 5.7 billion euros in 2020, showing a stable trend compared to 2019. 57.8% (3.3 billion euros) of this amount relates to prescription medicines, whereas 42.2% (2.4 billion euros) relates to self-medication medicines (OTC), including those sold in shops.
The 6.6% increase compared to the previous year in the expenditure of class C prescription drugs is mainly driven by an increase in prices (+1.0%) and an increase in quantities of 1.3%, while the mix effect remained almost stable (-0.4%; Figure 2.6.1).
Benzodiazepines are the most purchased category, accounting for 18.7% of expenditure and about 27.9% of DDDs in class C with prescription. Among them, benzodiazepine derivatives rank first among the most expensive categories, with a spending of over 400 million euros and 28 DDD. Both indicators show an increase of around 9.5% compared to the previous year (Table 2.6.1). Anilides come second and are the category with the highest increase (+49%) compared to 2019, counting for 9% of total expenditure equal to 294.2 million euros. Other categories with a level of expenditure above 200 million euros are medicines used in erectile dysfunction (-7.9% of expenditure and +5.6% of doses) and fixed-dose oestrogen-progestogen combinations (approximately +3% of expenditure and doses). The high adhesion to the pneumococcal vaccination observed during the SARS-CoV-2 pandemic led to an increase in spending on these vaccines by more than 100% (Table 2.6.1). The first six substances in terms of expenditure are the same as in 2019 Paracetamol, with 285.4 million euros or 8.7% of the total Class C, ranks first and shows an increase of 51.8% compared to 2019, which rises to +25.5% when considering the doses used. This medicine, mainly used in paediatric for its analgesic and antipyretic action, has been included in protocols for the home treatment of patients with COVID-19 in case of fever or joint and muscle pain. Followed by two benzodiazepines (alprazolam: 132.8 million; lorazepam: 120.3 million euros) with increases between +13.7% and +9.2% and two molecules (tadalafil: 102.9 million euros; sildenafil: 84.6 million euros) used in erectile dysfunction, the expenditure of which is reduced by 6.2% and 8.4% respectively, although for tadalafil there is an 11.1% increase in doses (Table 2.6.2). In addition to alprazolam and lorazepam, among the most expensive substances there are several benzodiazepines placed as follows: 8° zolpidem, 9° lormetazepan, 10° bromazepam, 11° delorazepam and 13° triazolam.
Among self-medication medicines, propionic acid derivatives account for 10.1% of total expenditure and they amounted to 215.4 million euros, down by 1.5% compared to 2019. Ibuprofen is the most widely used molecule in this category and ranks, with 133.1 million euros, the second most expensive substance, surpassed only by diclofenac with 135.0 million. Both molecules show reductions ranging from 30.1% for diclofenac to 4.6% for ibruprofen (Tables 2.6.3 and 2.6.4). Topical non-steroidal anti-inflammatory agents are the second most expensive category (183.5 million euros, -23.5% compared to 2019), followed by anilides with 156.2 million. Mucolitics are the category with the largest contraction in expenditure (-39.2%).
At regional level, there is moderate variability in spending and consumption on OTC medicines and Class C prescription medicines.

This trend can be explained mainly by regional differences in income but also by a different attitude of doctors and patients in the use of these medicines. For example, while for Class C medicines, Campania's per capita expenditure is almost twice that of the A.P. of Bolzano (72.30 euros vs 37.70 euros), for OTC medicines Liguria spends 80% more than Basilicata (44.30 vs. 24.30) and in the North they spend over 25% more than in the South. The highest increases in Class C medicines consumption were recorded in Umbria (+45.9%) and Marche (+44.3%), for OTC medicines they were also recorded in Umbria (+27.0%) and Marche (+24.9%), while the biggest reductions were observed in the A.P. of Bolzano (-11.5%) and Sardinia (-9.1%) (Table and Figure 2.6.5).

The wider differences between Regions emerge from the analysis of private spending on Class A medicines, with Valle d'Aosta spending 9 times higher than Umbria (39.50 vs. 5.20) and, in general, with Northern Regions (26.90 euros per capita) spending almost 40% more than Central Regions (19.40 euros) (Table and Figure 2.6.6). Cholecalciferol, pantoprazole, ketoprofen and the amoxicillin/clavulanic acid association are at the top with a cost of more than 40 million euros. Cholecalciferol shows a considerable increase in private spending by more than 100%. Ketoprofen (74.2%) and ibuprofen (62.9%) are the substances with the highest percentage of private spending, calculated on the total expenditure on the molecule. As for pump inhibitors, in addition to the aforementioned pantoprazole, among the top 20 active ingredients at the highest expense, there are also esomeprazole, lansoprazole and omeprazole, whose share of private expenditure is between 17% and 20% (Table 2.6.7).

The cost breakdown of the consumption of Class A medicines shows that about 2/3 of private spending relates to medicines whose price is lower than 6 euros (63.3%) and only 13.8% is on medicines with a price above 10 euros. However, there is wide regional variability in the distribution of consumption, mainly in the price range above 10 euros, with a maximum of 19.5% in Marche and a minimum of 8.4% in Sicily (0.9%), while consumption is more homogeneous for medicines with a price below 6 euros (Table 2.6.8).

In 2020, expenditure on OTC medicines sold in retail settings amounted to 249.7 million euros, decreasing by 3.7% compared to the previous year. The highest per capita expenditure is recorded in Sardinia (6.50 euros) and Emilia Romagna (5.80 euros), while in the A.P. of Bolzano and Sicily the lowest values are observed (0.50 euros and 2.70 euros, respectively). There are no particular differences in expenditure between different geographical areas, ranging from 4.10 euros per capita in Central-South to 4.30 euros in the North. In terms of expenditure, the first three medicines that are most sold in retailing pharmacies are ibuprofen (0.28 euros per capita), diclofenac (0.27 euros) and paracetamol (0.25 euros) representing around 20% of total spending (Tables 2.6.9a and 2.6.9b).

Figure 2.6.1 Trend of expenditure on Class C medicines with prescription in the period 2012-2020: consumption, price and mix effect

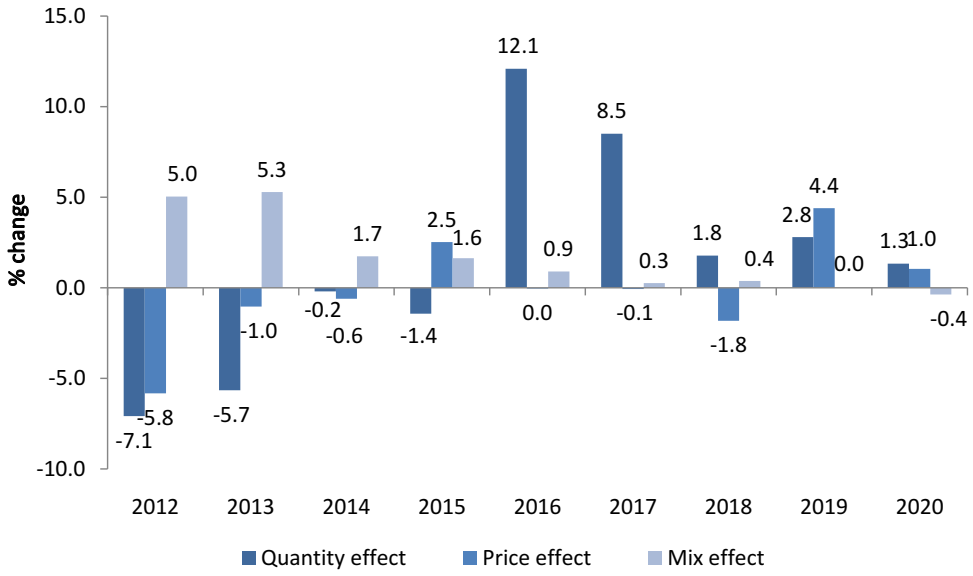


Table 2.6.1. First 20 therapeutic categories of Class C medicines with prescription

1st ATC level	Subgroup	DDD/1000 inhab. per day	Δ % 20-19	Expenditure *(million)*	%*	Δ % 20-19
N	Benzodiazepine derivatives (anxiolytics)	28.0	9.4	401.0	12.3	9.5
N	Anilides	7.2	24.1	294.2	9.0	49.0
G	Medications for erectile dysfunction	1.9	5.6	212.9	6.5	-7.9
G	Fixed-dose oestrogen/progestogen	20.1	2.6	208.9	6.4	2.9
N	Benzodiazepine derivatives	21.4	8.1	140.6	4.3	7.6
D	Corticosteroids in combination with antibiotics	4.6	2.2	88.5	2.7	3.9
N	Benzodiazepine analogues	5.6	12.0	69.3	2.1	14.4
S	Antibacterial-corticosteroid combinations	2.9	-12.1	65.7	2.0	-11.1
R	Corticosteroids	4.7	-2.1	65.4	2.0	-0.6
A	Osmotic laxatives	2.0	11.1	64.7	2.0	9.8
M	Other centrally acting muscle relaxants	1.1	0.0	60.1	1.8	-3.4
N	Other psychostimulants and nootropics	1.2	0.0	55.4	1.7	0.2
R	Mucolytics	4.8	-15.8	51.9	1.6	-15.3
N	Antivertigo preparations	2.8	3.7	50.2	1.5	4.6
B	Heparins	2.2	10.0	49.5	1.5	9.5
M	Other muscle relaxants with peripheral	0.0	-	42.7	1.3	9.2
M	Biphosphonates	0.0	-	42.7	1.3	-9.5
G	Progestogens and estrogens, sequential preparations	3.5	2.9	42.0	1.3	7.7
N	Benzamides	0.3	0.0	38.7	1.2	9.0
J	Pneumococcal vaccines	0.0	-	35.8	1.1	>100

* Calculated on overall expenditure

Table 2.6.2. First 20 active substances of Class C with prescription at higher expense in 2020

1st ATC level	Active substance	DDD/1000 inhab. per day	Δ % 20-19	Expenditure *(million)*	%*	Δ % 20-19
N	paracetamol	6.9	25.5	285.4	8.7	51.8
N	alprazolam	10.5	12.9	132.8	4.1	13.7
N	lorazepam	10.8	8.0	120.3	3.7	9.2
G	tadalafil	1.0	11.1	102.9	3.1	-6.2
G	sildenafil	0.7	0.0	84.6	2.6	-8.4
D	gentamicin/betamethasone	4.0	2.6	74.5	2.3	3.5
G	drospirenone/ethinylestradiol	5.7	-1.7	69.4	2.1	-1.4
N	zolpidem	5.4	12.5	66.6	2.0	14.8
N	lormetazepam	15.3	9.3	63.9	2.0	9.8
N	bromazepam	1.5	7.1	51.1	1.6	2.0
N	delorazepam	2.6	13.0	47.5	1.5	11.2
A	macrogol 3350/sodium chloride/sodium	1.7	13.3	45.2	1.4	14.7
N	triazolam	3.8	8.6	44.5	1.4	8.3
R	acetylcysteine	4.0	-13.0	43.3	1.3	-13.1
M	Clostridium botulinum type A toxin	0.0	-	42.7	1.3	9.2
M	thiocolchicoside	0.5	-16.7	40.7	1.2	-4.0
G	dienogest/ethinylestradiol	3.6	16.1	39.8	1.2	15.0
N	levo-acetylcarnitine	0.8	0.0	39.7	1.2	-0.5
N	betahistine	2.2	4.8	36.2	1.1	5.5
G	dienogest/estradiol	2.6	13.0	35.7	1.1	10.9

* Calculated on overall expenditure

Table 2.6.3. First 20 therapeutic categories of OTC medicines at higher cost in 2020

1st ATC level	Subgroup	DDD/1000 inhab. per day	Δ % 20-19	Expenditure *(million)*	%*	Δ % 20-19
M	Propionic acid derivatives	5.1	0.0	215.4	10.1	-1.5
M	Topical nonsteroidal anti-inflammatory drugs	14.5	0.7	183.5	8.6	-23.5
N	Anilides	4.0	-4.8	156.2	7.3	-10.9
A	Other agents for local oral treatment	4.8	-4.0	106.5	5.0	-3.4
A	Antidiarrheal microorganisms	2.3	-14.8	104.3	4.9	-25.6
R	Mucolytics	3.5	-23.9	75.7	3.5	-39.2
C	Bioflavonoids	4.1	5.1	73.2	3.4	3.7
D	Imidazole and triazole derivatives	3.0	3.4	63.8	3.0	5.3
N	alicylic acid and derivatives	1.3	0.0	53.9	2.5	-1.3
R	Sympathomimetics, non-	8.8	-10.2	49.2	2.3	-29.8
A	Enemas	1.9	5.6	46.7	2.2	6.1
G	Imidazole derivatives	1.4	7.7	45.6	2.1	6.8
R	Antiseptics	1.0	0.0	43.9	2.1	5.3
A	Contact laxatives	3.9	-4.9	40.0	1.9	-1.7
S	Sympathomimetics used as decongestants	7.9	11.3	38.5	1.8	8.8
C	Corticosteroids	1.9	0.0	30.9	1.4	5.8
A	Osmotic laxatives	2.8	0.0	30.4	1.4	-2.9
A	Antipropulsives	0.3	-25.0	30.0	1.4	-18.5
R	Sympathomimetics	0.3	0.0	26.1	1.2	-19.7
R	Other cough suppressants	1.3	-18.8	25.3	1.2	-18.9

* Calculated on overall expenditure

Table 2.6.4. First 20 OTC active ingredients at higher cost in 2020: comparison 2019-2020

1st ATC level	Active substance	DDD/1000 inhab. per day	Δ % 20-19	Expenditure *(million)*	Δ % 20-19	%*	% OTC	% OTC
M	diclofenac (M02AA15)	11.9	-0.8	135.0	-30.1	6.3	6.5	93.5
M	ibuprofen (M01AE01)	2.3	-4.2	133.1	-4.6	6.2	15.3	84.7
N	paracetamol	2.7	8.0	108.4	1.6	5.1	93.5	6.5
A	flurbiprofen	3.3	-10.8	74.3	-9.2	3.5	0.0	100.0
A	probiotic	1.8	-18.2	72.8	-27.9	3.4	0.0	100.0
C	diosmin/hesperidin	3.2	3.2	59.5	3.8	2.8	100.0	0.0
M	ketoprofen	1.1	0.0	47.4	-3.3	2.2	0.0	100.0
N	acetylsalicylic acid/ascorbic acid	1.1	-8.3	44.9	-2.6	2.1	0.0	100.0
R	naphazoline (R01AA08)	6.1	-10.3	33.4	-7.0	1.6	0.0	100.0
A	loperamide	0.3	-25.0	29.7	-18.2	1.4	18.2	81.8
R	carbocisteine	1.7	-19.0	27.3	-24.0	1.3	7.6	92.4
A	glycerol (A06AG04)	1.5	7.1	25.5	12.8	1.2	0.0	100.0
M	diclofenac (M01AB05)	0.5	25.0	24.5	25.0	1.1	0.0	100.0
A	glycerol (A06AX01)	3.9	2.6	24.0	7.1	1.1	2.4	97.6
M	ibuprofen (M02AA13)	1.7	0.0	22.6	9.7	1.1	8.6	91.4
N	paracetamol/ascorbic acid/phenylephrine	0.4	-33.3	21.1	-26.5	1.0	0.0	100.0
S	naphazoline (S01GA01)	5.5	17.0	20.4	15.3	1.0	0.0	100.0
M	naproxen	0.8	14.3	19.9	7.0	0.9	1.6	98.4
G	clotrimazole/metronidazole	0.7	16.7	19.9	22.8	0.9	100.0	0.0
D	tioconazole	0.4	0.0	19.8	11.9	0.9	0.0	100.0

*Calculated on overall expenditure

Table 2.6.5. 2020 local pharmaceutical prescriptions of Class C OTC medicines with prescription and deviation (%) of gross expenditure from national average

Region	Class C with prescription				Self-medication (OTC)			
	Per capita expenditure	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19	Per capita expendi-ture	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Piedmont	57.30	2.9	219.7	-0.4	38.70	-8.3	138.0	6.5
Valle d'Aosta	54.00	-2.7	242.6	-5.7	44.20	-13.7	137.9	-6.7
Lombardy	58.30	6.0	208.5	-1.9	39.80	-10.2	127.2	-1.9
AP of Bolzano	37.70	-6.7	141.6	-5.6	39.10	-18.5	118.9	-11.5
AP of Trento	43.00	-4.4	169.6	-4.2	39.50	-14.3	125.4	-6.0
Veneto	49.90	-2.9	193.8	-3.1	38.20	-13.0	121.8	-5.4
Friuli VG	45.20	-0.9	177.2	-1.7	35.80	-11.2	116.3	-4.4
Liguria	67.40	-2.2	271.7	-0.7	44.30	-12.3	152.1	-3.7
Emilia R.	52.90	-0.9	200.6	-2.0	37.00	-11.9	121.2	-2.1
Tuscany	55.30	3.4	227.6	-1.0	38.70	-8.7	129.9	-0.3
Umbria	44.60	41.1	152.8	45.9	28.30	14.6	91.3	27.0
Marche	44.60	38.5	163.6	44.3	29.90	13.7	98.8	24.9
Lazio	58.00	2.7	195.2	-0.8	37.80	-15.2	126.9	-6.3
Abruzzo	46.20	-2.3	153.4	-2.4	31.00	-14.1	102.4	-4.0
Molise	40.90	2.5	153.2	-2.5	25.40	-11.5	85.4	-2.7
Campania	72.30	31.0	207.9	12.7	37.80	-4.1	130.1	7.5
Puglia	47.20	-0.2	165.6	-2.5	30.10	-12.8	110.9	11.7
Basilicata	40.20	-1.2	147.4	-4.5	24.30	-13.2	80.1	-2.1
Calabria	48.10	8.6	195.7	6.2	27.90	-11.4	92.3	-1.2
Sicily	49.50	24.1	164.2	22.0	26.70	-12.7	89.8	-2.8
Sardinia	51.90	-2.3	213.2	-5.1	28.90	-17.2	90.4	-9.1
Italy	**54.80**	**7.0**	**197.1**	**2.0**	**35.80**	**-10.5**	**119.3**	**-0.1**
North	55.10	1.7	207.1	-1.8	39.00	-11.0	127.9	-1.7
Centre	54.40	7.7	198.3	4.6	36.30	-9.3	121.5	-0.1
South and Islands	54.60	14.9	182.0	7.2	30.90	-10.2	105.6	2.8

*Including drugs classified in Class C - Non-negotiated

Table 2.6.6. 2020 expenditure and consumption of Class A out-of pocket medicines and deviation (%) of gross expenditure from national average

Region	Per capita expenditure	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Piedmont	34.70	-30.5	206.7	6.7
Valle d'Aosta	39.50	54.3	176.8	-10.3
Lombardy	28.70	-2.4	216.8	4.1
AP of Bolzano	20.60	9.6	136.3	3.0
AP of Trento	11.40	-1.7	73.9	3.6
Veneto	23.70	-10.2	188.3	0.5
Friuli VG	25.50	-44.6	153.5	28.9
Liguria	34.40	9.9	268.4	11.8
Emilia R.	18.10	1.1	118.4	18.0
Tuscany	21.60	9.1	169.8	32.4
Umbria	5.20	>100	33.9	>100
Marche	12.60	55.6	50.3	>100
Lazio	22.10	-0.9	144.5	8.8
Abruzzo	28.30	79.1	106.5	15.3
Molise	17.70	-21.0	110.5	-2.8
Campania	32.60	42.4	225.2	39.4
Puglia	20.50	-42.6	124.8	1.7
Basilicata	17.30	2.4	116.9	-1.3
Calabria	17.70	30.1	125.1	58.8
Sicily	17.30	>100	133.7	>100
Sardinia	12.50	-26.5	80.4	-23.0
Italy	**23.90**	**-2.4**	**164.8**	**17.1**
North	26.90	-12.1	190.1	6.4
Centre	19.40	7.2	132.0	22.7
South and Islands	22.40	13.7	148.5	39.2

*Including drugs classified in Class C - Non-negotiated

Table 2.6.7. First 20 Class A active substances paid out of pocket in descending order of expenditure in 2020

ATC 1st level	Active substance	DDD/1000 inhab. per day	Δ % 20-19	Expenditure *(million)*	Δ % 20-19	%*	% medicines paid out of pocket**
A	cholecalciferol	4.5	>100	61.2	>100	4.3	23.2
A	pantoprazole	5.4	17.4	52.2	7.0	3.7	16.7
M	ketoprofen	8.2	0.0	47.3	0.2	3.3	74.2
J	amoxicillin/clavulanic acid	1.5	-6.3	45.7	-7.5	3.2	25.5
A	esomeprazole	3.5	34.6	34.2	27.1	2.4	20.6
A	lansoprazole	3.3	17.9	33.0	10.7	2.3	18.7
A	omeprazole	4.1	20.6	32.5	13.2	2.3	18.8
M	ibuprofen	2.8	0.0	26.2	2.3	1.8	62.9
B	acetylsalicylic acid	15.9	24.2	25.9	23.3	1.8	26.9
M	diclofenac	2.7	12.5	24.0	15.4	1.7	41.1
R	cetirizine	3.0	20.0	19.2	18.5	1.3	52.9
H	levothyroxine	8.2	22.4	18.8	22.1	1.3	21.8
R	beclomethasone	0.8	0.0	17.9	-5.8	1.3	36.3
H	betamethasone	2.0	5.3	17.8	6.6	1.2	51.6
C	rosuvastatin	2.9	16.0	17.1	17.1	1.2	17.5
C	omega 3	0.6	20.0	16.4	15.5	1.2	12.5
B	enoxaparin	0.3	0.0	15.6	14.7	1.1	7.1
J	fosfomycin	0.1	0.0	14.9	6.4	1.0	24.7
J	azithromicyn	0.4	33.3	14.3	57.1	1.0	24.1
C	ramipril	6.9	27.8	13.9	28.7	1.0	10.3

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

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

Table 2.6.8. Breakdown of consumption by price range of Class A medicines paid out of pocket by citizens in 2020

Region	<2 € %	≥2 <3 € %	≥3 <6 € %	≥6 <10 € %	≥10 <30 € %	≥30 € %
Piedmont	8.7	11.7	32.3	29.5	14.2	3.6
Valle d'Aosta	10.1	20.8	28.2	21.8	13.7	5.5
Lombardy	11.4	20.7	31.2	23.1	12.1	1.5
AP of Bolzano	8.0	17.9	34.6	23.9	13.3	2.3
AP of Trento	12.6	10.3	33.8	27.3	14.8	1.2
Veneto	12.2	21.4	32.5	20.8	11.8	1.4
Friuli VG	6.5	9.3	33.8	31.3	16.5	2.6
Liguria	11.7	19.5	31.9	23.0	12.9	1.0
Emilia R.	9.7	11.1	38.0	25.4	14.4	1.5
Tuscany	11.4	16.8	36.5	22.7	11.8	0.9
Umbria	17.6	7.1	41.9	22.7	10.1	0.5
Marche	15.7	5.4	33.9	25.5	13.8	5.7
Lazio	11.0	16.4	34.0	23.2	13.9	1.6
Abruzzo	12.8	13.3	34.0	22.7	11.9	5.2
Molise	9.3	14.7	36.1	25.5	13.1	1.3
Campania	12.4	23.8	32.2	19.6	9.8	2.2
Puglia	12.8	15.0	35.3	21.9	12.6	2.3
Basilicata	10.1	21.0	34.4	21.8	11.3	1.3
Calabria	10.1	26.0	37.4	17.8	7.5	1.1
Sicily	11.0	25.5	34.8	20.4	7.8	0.6
Sardinia	16.0	14.7	33.3	21.4	12.9	1.6
Italy	**11.3**	**18.6**	**33.4**	**22.9**	**12.0**	**1.8**
North	10.7	17.6	32.5	24.4	12.9	1.9
Centre	11.6	15.7	35.1	23.1	13.0	1.5
South and Islands	12.1	21.7	34.0	20.4	9.9	1.8

Table 2.6.9a. Expenditure and consumption of OTC medicines provided by retail pharmacies by Region in 2020 and deviation (%) from national average

Region	Expenditure *(million)*	Δ % 20-19	Per capita expenditure	DDD/1000 inhab. per day
Piedmont	19.3	-1.6	4.30	14.2
Valle d'Aosta	0.6	12.6	5.00	14.8
Lombardy	42.0	9.9	4.20	13.7
AP of Bolzano	0.3	-2.7	0.50	1.5
AP of Trento	1.5	-21.9	2.80	8.6
Veneto	17.8	-11.0	3.60	11.5
Friuli VG	3.9	10.5	3.10	9.9
Liguria	8.4	-17.4	5.00	18.1
Emilia R.	26.6	-13.8	5.80	20.2
Tuscany	21.8	16.5	5.60	18.3
Umbria	3.7	-3.8	4.10	14.4
Marche	6.5	-13.7	4.20	14.7
Lazio	17.0	-13.9	3.00	10.4
Abruzzo	6.3	-19.8	4.80	16.1
Molise	1.0	-15.5	3.20	11.0
Campania	21.8	35.9	4.10	14.5
Puglia	16.5	-12.0	4.20	14.5
Basilicata	3.1	-8.2	5.60	18.2
Calabria	8.4	-12.8	4.50	14.8
Sicily	12.5	-8.2	2.70	10.3
Sardinia	10.8	-23.1	6.50	20.2
Italy	**249.7**	**-3.7**	**4.20**	**14.1**
North	120.4	-3.8	4.30	14.3
Centre	49.1	-1.7	4.10	13.8
South and Islands	80.3	-4.8	4.10	14.2

Table 2.6.9b. First 20 OTC active substances provided by retail pharmacies in descending order of expenditure in 2020

ATC	Active substance	Per capita expenditure	Δ % 20-19	Inc. %	% cum.	DDD/1000 inhab. per day
M	ibuprofen	0.28	-5.2	6.8	6.8	0.3
M	diclofenac (M02AA15)	0.27	-28.4	6.5	13.3	1.4
N	paracetamol	0.25	8.1	5.9	19.2	0.5
A	flurbiprofen	0.15	-19.0	3.5	22.7	0.4
M	ketoprofen	0.14	3.4	3.5	26.2	0.2
C	diosmin/hesperidin	0.13	32.1	3.2	29.3	0.4
A	probiotic	0.12	-39.4	2.9	32.2	0.2
R	naphazoline	0.12	-22.5	2.8	35.0	1.3
A	glycerol (A06AG04)	0.09	-37.0	2.1	37.1	0.3
N	acetylsalicylic acid/ascorbic acid	0.09	9.8	2.1	39.2	0.1
A	glycerol (A06AX01)	0.07	-51.2	1.6	40.8	0.7
D	escin/l-thyroxine	0.06	-	1.4	42.3	0.1
M	diclofenac (M01AB05)	0.05	-86.3	1.2	43.5	0.1
A	bisacodyl	0.05	0.7	1.2	44.7	0.2
A	loperamide	0.05	-20.2	1.1	45.8	0.0
R	dichlorophenyl carbinol/amylmetacresol/ascorbic	0.04	12.0	1.1	46.9	0.0
N	paracetamol/ascorbic acid/phenylephrine	0.04	-14.3	1.0	47.9	0.0
N	nicotine	0.04	5.8	1.0	48.9	0.0
A	magnesium hydroxide/algeldrate/dimethicone	0.04	-	1.0	49.9	0.0
M	naproxen	0.04	1.1	1.0	50.9	0.1

Section 3

Consumption and expenditure by therapeutic class

This section aims to analyse the trend of public pharmaceutical expenditure, including gross expenditure under approved care regime and the cost of medicines purchased directly by public health facilities, by level I ATC, by therapeutic categories and by active ingredient.
In 2020, the NHS pharmaceutical expenditure, expressed as a per capita value, was equal to 385.88 euros, down by 0.5% compared with the previous year (Table 3.1). This reduction is largely influenced by a 2.4% decrease in expenditure for class A medicines under approved care regime, compared to 2019, with a value of 163.01 euros. On the other hand, medicines purchased directly by public health facilities record a 222.87 euros expenditure, with a 0.9% increase.
Overall, the most significant increase in NHS expenditure is due to dermatologicals (+17.9%), antineoplastics and immunosuppressants (+6.2%), medicines acting on blood and blood forming organs (+6.1%), whose per capita values are equal to 2.53, 107.19 and 38.64 euros, respectively.
With regard to consumption (Table 3.2), cardiovascular medicines represent the highest number of doses consumed (502.2 DDD/1000 inhabitants per day), and account for approximately 43% of all DDD consumed. These are followed by drugs acting on the alimentary tract and metabolism (181.4 DDD/1000 inhabitants per day), on blood and blood forming organs (136.7 DDD/1000 inhabitants per day) and on the central nervous system (94.5 DDD/1000 inhabitants per day). However, the largest increases compared to 2019 are recorded for antiparasitics (+26.2%), dermatologicals (+8.5%) and antineoplastic and immunomodulating agents (+3.0%).
Public and private expenditure by level I ATC (Table 3.3) shows that antineoplastic and immunomodulating agents have the highest expenditure, with a value of 6.4 billion euros, an incidence of 21.5% on total pharmaceutical expenditure and a per capita value of 108.1 euros, thus confirming the trend of the previous year (Figure 3.1). Gastrointestinal medicines account for 13.4% of total expenditure and represent the most privately purchased category both in the case of class A medicines (323 million euros) and self-medication drugs (583 million euros). Medicines acting on the central nervous system have the highest absolute expenditure value for class C medicines under prescription (1.2 billion euros) and account for 37.4% of the total expenditure in this reimbursement range.
As regards consumption (Table 3.4), the most consumed privately-purchased class A drugs are cardiovascular system medicines (40.0 DDD/1000 inhabitants per day), while medicines acting on the nervous system are most used within class C with prescription (70.4 DDD/1000 inhabitants per day); gastrointestinal medicines rank first for consumption of self-medication drugs (31.5 DDD/1000 inhabitants per day).
Figure 3.1 shows the total per capita expenditure for level I ATC, highlighting a ranking change (compared to 2019) of the ATC of general antimicrobials for systemic use which ranked second in decreasing order of value in 2019, while they were fifth in 2020.
Table 3.5 shows the trend in gross per capita expenditure of class A drugs under approved care regime, stratified by Region and geographic area. Overall, compared to the national value of 163.01 euros, the Northern and Central Regions report lower values, 148.28 and 162.31 euros respectively. Southern Regions show a higher value, equal to 184.62 euros. The greatest variability, highlighted by the variation coefficient, is observed for the “Miscellaneous” ATC (>100%), where per capita expenditure ranges from a value of 0.49 euros in Calabria to 0.02 euros in Emilia Romagna, Liguria and Piedmont.

The Northern Regions, on average, show higher values (0.18 euros), compared to the Southern (0.14 euros) and the Central Regions (0.05 euros). A large variability is also observed for ATC drugs "Blood and blood forming organs" (CV 56.2%), as the expenditure values range from 14.96 euros in Lombardy to 2.26 euros in Liguria. The trend in drug consumption (Table 3.6) shows a greater use in the South (1,091.3 DDD/1000 inhabitants per day) and in the Centre (1,033.1 DDD/1000 inhabitants per day) compared to the North (907.8 DDD/1000 inhabitants per day) and confirms the larger variability for the "Miscellaneous" ATC (CV 84.2%), which however shows very low values of DDD/1000 inhab. per day. The ATC "Antineoplastics and immunomodulators" (CV 25.8%) follows, whose highest value is reported in Lombardy (8.6 DDD/1000 inhab. per day) and the lowest in Tuscany (1.2 DDD/1000 inhab.per day). Table 3.7 shows the regional trend of per capita expenditure of drugs purchased by public health facilities by level I ATC. In general, the Central and Southern Regions show a higher per capita expenditure, respectively of 237.58 euros and 234.97 euros, compared to the Northern Regions (207.46 euros). Medicines in the "Miscellaneous" category and those of the respiratory system have the largest regional variability (CV 30.2%). In the latter case, per capita expenditure values range from 9.48 euros in Basilicata to 2.88 euros in Molise. However, when analysing consumption (Table 3.8), the greatest heterogeneity between the Regions is observed for genitourinary drugs (CV 86.5%), with a difference between the maximum value (8.4 DDD/1000 inhabitants per day of Emilia Romagna) and the minimum value (0.7 DDD/1000 inhabitants per day of Molise) up to 7.7 DDD, and for antiparasitics (CV 78.8%).

Table 3.9 shows, for each level I ATC category, the therapeutic subgroups in descending order of expenditure, sorted by per capita expenditure, up to the value of 0.10 euros 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 (Table 3.9 and Figure 3.2).

Compared to 2019, class A medicines provided under approved care regime show reductions in expenditure (-2.7%), consumption (-0.3%), prices (-0.6%), average DDD cost (-2.3%) and deviation towards less expensive medicines (mix effect: -1.8%). However, there are many differences between the therapeutic categories. A reduction or substantial stability of all indicators considered is observed in medicines for blood and blood-forming organs, for the genitourinary system, for the musculoskeletal system, systemic hormones (excluding sex hormones and insulins), and in medicines acting on sensory organs and in the category "Miscellaneous". The greatest reduction in expenditure concerns antimicrobials for systemic use (-21.5%), whose reduction can be explained by the net decrease in consumption (-22.9%), although a shift can be noted towards more expensive medicines (mix effect: +1.8%) and a consequent increase in the average cost per day of therapy (+1.9%). Antiparasitic and dermatological medicines record a reduction in expenditure, by 4.5% and 4.3% respectively, with an increase or substantial stability in consumption, probably attributable to a shift towards less expensive drugs (mix effect: -10.9% and -5.9%). Finally, respiratory medicines show an increase in expenditure (+1.3%), against a slight reduction in consumption (-0.8%) and a shift towards more expensive medicines (mix effect: +2.6%).

Analysing the individual therapeutic categories, the highest per capita expenditure value regards proton pump inhibitors (11.45 euros), followed by adrenergics in combination with corticosteroids or others, excluding anticholinergics (8.45 euros) belonging to respiratory system drugs, and HMG-CoA reductase inhibitors (4.88 euros). Thiazolidinediones used in diabetes, gonadotropins, folic acid analogues used as antineoplastic agents, sympathomimetics used in glaucoma (S01EA) and pregnene derivatives are the categories with the lowest per capita expenditure, equal to 0.10 euros. The highest consumption is mainly attributable to cardiovascular drugs, in particular non-combined ACE inhibitors (84 DDD/1000 inhabitants per day), HMG-CoA reductase inhibitors (80 DDD/1000 inhabitants per day), followed by proton pump inhibitors (72.7 DDD/1000 inhabitants) and by platelet aggregation inhibitors (61 DDD/1000 inhabitants per day).
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 76.3% and 64.5%. When analysing consumption, in addition to hydroxychloroquine, which represents 87.4% of the doses of the entire category, 59.4% of consumption of the systemic hormones ATC category (excluding sex hormones and insulins) relates to levothyroxine, and 50.6% of the doses of the blood and blood forming organs ATC category are attributable to acetylsalicylic acid.
The first thirty active ingredients for class A pharmaceutical expenditure under approved care regime (Table 3.11) represent 37% of the total class A-NHS expenditure, equal to an absolute value of 3,596 million euros. Overall, ten molecules belong to the category of medicines acting on the cardiovascular system and are mainly represented by atorvastatin (268.1 million), bisoprolol (155.2 million) and ramipril (120.4 million), while other ten belong to the category of drugs acting on the alimentary tract and metabolism, mainly represented by proton pump inhibitors: pantoprazole (253.8 million), lansoprazole (143 million), esomeprazole (130.8 million) and cholecalciferol (201.4 million). Table 3.12 shows the regional trend of the ranks for these active ingredients. In 2020, the greatest variation in the pharmaceutical expenditure under approved care regime was observed for the ezetimibe/rosuvastatin combination, driven by an increase in consumption, but by a reduction in the average cost per day of therapy, attributable to the patent expiry of the originator (Table 3.13). The first thirty active ingredients by consumption represent 52.4% of all the doses used of class A drugs (Table 3.14). In particular, the first molecules by consumption are confirmed: ramipril, which accounts for 6.3% of consumption of class A drugs under approved care regime; atorvastatin (4.9% of DDD); acetylsalicylic acid (4.5%); amlodipine (2.8%). Particularly interesting is the shift in rank of cholecalciferol, from rank 14 in 2019 to 19 in 2020, probably due to the effects of Note 96. Table 3.15 shows the regional ranks of the first 30 active ingredients in consumption relating to outpatient pharmaceutical expenditure.
Table 3.16 shows, with regard to purchases by health facilities, for each level I ATC category, the therapeutic subgroups in descending order of expenditure, sorted by per capita expenditure up to the value of 0.10 euros per capita expenditure. Information is also provided on prescribed doses and average cost per day of therapy. The variation compared to 2019 is calculated for all indicators (Table 3.16). In 2020, per capita expenditure for drugs purchased directly by public facilities was 222.87 euros, substantially stable compared to the previous year (+0.6%).

Similarly, an increase in consumption is reported (+1.5%) and a shift towards more expensive medicines (mix effect 5.5%) against a reduction in prices (-6.2%) and in the average cost per day of therapy (-0.9%). A reduction can be noted of all the indicators considered for antimicrobials for systemic use, for ophthalmologicals, which also record significant reductions in prices, and for drugs acting on the genitourinary system. On the other hand, dermatological drugs show the greatest increase in expenditure (+51.4%), while antiparasitics have the greatest variation in consumption (>100%). Finally, a shift is reported towards more expensive medicines for the respiratory system, for dermatological medicines and for drugs acting on the cardiovascular system. Monoclonal antibodies are the category with the highest per capita expenditure (25.71 euros), followed by selective immunosuppressants (13.47 euros). Direct Xa factor inhibitors are the most consumed therapeutic category (10.8 DDD/1000 population per day), followed by platelet aggregation inhibitors, with a value of 9.3 DDD/1000 inhabitants per day, and by heparins (7.2 DDD/1000 inhabitants per day).
On the other hand, the most expensive active ingredients are lenalidomide and pembrolizumab, respectively 5.40 euros and 4.86 euros (Table 3.17). Finally, while dupilimumab accounts for 66.8% of the dermatological drugs expenditure, denosumab represents 63.6% of the doses consumed for musculoskeletal system drugs. With reference to the first thirty active ingredients by expenditure (Table 3.18), which as a whole account for 32.8% of the total expenditure by health facilities, it is evident that more than a third refers to antineoplastic drugs and immunosuppressants. Particularly interesting is the trend of osimertinib, which shifted from rank 74 in 2019 to 18 in 2020, probably due to the extension of indication of the drug in the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) locally advanced or metastatic with mutations activating the epidermal growth factor receptor (EGFR), authorised with Resolution no. 1742 of 29 November 2019.
Table 3.19 shows the regional ranks of the top 30 active ingredients by expenditure of medicines purchased directly by public health facilities. With regard to the top 30 active substances showing the greatest variation in expenditure (Table 3.20), more than half belong to antineoplastic drugs and immunosuppressants, although the largest increases are related to the combination bictegravir/emtricitabine/tenofovir alafenamide for the treatment of HIV and to emicizumab (>100%). The data observed for emicizumab are probably attributable to the extension of the indication occurred with Resolution no. 206 of 2020, which allows its use for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital deficiency of factor VIII, FVIII <1%) without factor VIII inhibitors. For each level I ATC, after showing the overall data on expenditure, consumption and exposure, in-depth analyses are provided, 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 of exposure and adherence to drug treatment in the population as well as the prescribing profiles in general practice are analysed. The national data on expenditure and consumption include both drugs supplied under approved care regime, including co-payments and discounts, and drugs purchased directly by public health facilities.

The exposure data and the adherence and persistence indicators were processed through the administrative flow of prescriptions for class A drugs dispensed through local pharmacies, including *per conto* distribution (so-called Art.50 flow/Health Card). The data relating to epidemiology and prescribing profiles were obtained through a network of GPs bringing together all information relating to patients to Health Search-IQVIA Health LPD.
Tables 3.21 and 3.22 show the data on expenditure, consumption and average cost per day of therapy of the categories that will be examined in depth in the following pages.

The analysed categories are the following:

- **Antineoplastic and immunomodulating agents**
  - Antineoplastics pharmaceuticals
  - Immunosuppressants and immunomodulating agents
- **Cardiovascular system**
  - Medicines for hypertension and heart failure
  - Lipid-lowering agents
  - Acute Coronary Syndrome
- **Alimentary tract and metabolism**
  - Antidiabetics
  - Medicines for peptic ulcer and GERD
  - Metabolic disorders
- **General antimicrobials for systemic use**
  - Antibiotics for systemic use
  - 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**
  - Multiple sclerosis
  - Antidepressants
  - 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**
- **Sensory organs**
  - Medicines for eye disorders
- **Miscellaneous**
  - Contrast agents
  - Radiopharmaceuticals
- **Dermatologicals**
- **Medicines used in critically ill patients**
- **Medicines used in the treatment of COVID-19 patients**

Table 3.1 NHS per capita expenditure by level I ATC in descending order of expenditure: comparison 2020-2019

Level I	Per capita exp. A-NHS Approved care regime (a)	Δ % 20-19	Per expenditure Public health facilities (b)	Δ % 20-19	NHS (a+b)	Δ % 20-19
L	4.30	2.3	102.88	6.4	107.19	6.2
C	49.05	2.2	5.87	13.5	54.92	3.3
A	31.20	-5.1	17.04	9.3	48.23	-0.5
J	9.94	-21.3	34.77	-21.2	44.71	-21.2
B	7.86	-1.3	30.78	8.1	38.64	6.1
N	23.65	1.1	7.81	6.0	31.47	2.3
R	17.13	1.6	4.76	21.8	21.89	5.4
M	5.02	-8.4	3.71	5.9	8.73	-2.8
H	3.93	-5.1	4.79	0.0	8.72	-2.4
G	5.42	-6.9	1.21	-21.7	6.63	-10.0
S	3.89	-1.1	2.14	-31.8	6.02	-14.7
V	0.14	-4.6	5.81	1.7	5.95	1.5
D	1.25	-4.0	1.28	51.9	2.53	17.9
P	0.22	-4.2	0.04	25.6	0.26	-0.6
Total	**163.01**	**-2.4**	**222.87**	**0.9**	**385.88**	**-0.5**

Table 3.2 NHS Consumption (DDD/1000 inhab. per day) by level I ATC in descending order of consumption: comparison 2020-2019

Level I ATC	DDD/1000 inhab. day Approved care regime (a)	Δ % 20-19	DDD/1000 inhab. per day public health facilities (B)	Δ % 20-19	DDD/1000 inhab.day NHS (a+b	Δ % 20-19
C	484.7	1.3	17.4	-7.0	502.2	1.0
A	151.0	-2.2	30.4	4.1	181.4	-1.2
B	87.7	-1.5	49.0	2.5	136.7	-0.1
N	67.8	1.5	26.6	3.1	94.5	1.9
G	42.0	-0.5	2.2	-9.7	44.2	-1.0
R	41.8	-0.8	2.1	-17.2	44.0	-1.7
M	36.4	-3.5	5.2	4.4	41.6	-2.6
H	35.9	0.3	5.5	3.5	41.4	0.7
S	20.8	-0.4	2.2	-19.9	23.1	-2.7
J	12.9	-22.9	6.3	-0.6	19.2	-16.8
L	6.4	1.8	10.6	3.8	16.9	3.0
D	4.6	0.6	9.3	12.9	13.9	8.5
V	0.1	-3.5	3.1	-2.8	3.2	-2.8
P	1.0	7.1	0.2	629.5	1.2	26.2
Total	**993.1**	**-0.3**	**170.3**	**1.5**	**1,163.4**	**-0.1**

Table 3.3. Composition of 2020 pharmaceutical expenditure by level I ATC and reimbursement class (descending order for total expenditure)

Level I ATC	Class A-NHS^		Private purchase of Class A		Class C with prescription		Self-medication SOP and OTC		Public health facilities (b)		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°
L	256,737,774	4.0	27,410,863	0.4	27,204,895	0.4		0.0	6,135,979,355	95.2	6,447,332,888
A	1,860,645,900	46.2	323,113,098	8.0	242,269,430	6.0	582,741,641	14.5	1,016,055,373	25.2	4,024,825,441
C	2,925,670,664	79.7	212,801,991	5.8	42,697,479	1.2	139,375,110	3.8	349,922,075	9.5	3,670,467,320
N	1,410,638,705	40.2	165,440,549	4.7	1,222,280,961	34.9	240,451,605	6.9	466,039,873	13.3	3,504,851,693
J	592,707,177	20.2	136,871,936	4.7	133,061,509	4.5		0.0	2,073,672,578	70.6	2,936,313,201
B	468,734,577	18.8	107,114,919	4.3	84,462,753	3.4	3,009,369	0.1	1,835,594,942	73.5	2,498,916,559
R	1,021,920,880	54.1	135,777,160	7.2	154,741,483	8.2	292,536,669	15.5	283,655,788	15.0	1,888,631,979
M	299,456,536	22.7	159,200,320	12.1	199,006,083	15.1	441,490,926	33.4	221,048,381	16.7	1,320,202,245
G	323,152,969	28.4	39,849,921	3.5	630,379,459	55.5	70,411,846	6.2	72,182,405	6.4	1,135,976,599
D	74,637,401	10.4	27,030,359	3.8	267,255,182	37.1	274,682,104	38.1	76,412,585	10.6	720,017,631
S	231,902,554	35.5	16,655,102	2.5	192,950,116	29.5	85,178,777	13.0	127,358,236	19.5	654,044,784
H	234,374,078	37.5	65,090,261	10.4	40,455,812	6.5		0.0	285,549,125	45.7	625,469,277
V	8,367,172	1.7	105,486,591	21.4	31,609,151	6.4	335,009	0.1	346,306,351	70.4	492,104,274
P	13,052,304	51.0	5,891,554	23.0	759,750	3.0	3,511,991	13.7	2,397,778	9.4	25,613,377
Total	**9,721,998,690**	**32.5**	**1,527,734,625**	**5.1**	**3,269,134,064**	**10.9**	**2,133,725,047**	**7.1**	**13,292,174,845**	**44.4**	**29,944,767,270**

^Expenditure for Class A net of Class C reimbursed (32.4 million)
§Excluding oxygen
°Gross in million euros
*Calculated on the category
Source: OsMed, Traceability of medicinal products

Table 3.4. Composition of 2020 consumption (in terms of DDD/1000 inhabitants per day), by level I ATC and reimbursement class (descending order of consumption)

Level I ATC	Class A-NHS^		Private purchase of Class A		Class C with prescription		Self-medication SOP and OTC		Public health facilities		Total units
	N.	%*	N.	%*	N.	%*	N.	%*	N.	%*	
C	484.7	87.8	40.0	7.2	1.7	0.3	8.5	1.5	17.4	3.2	552.4
A	151.0	60.4	29.2	11.7	7.7	3.1	31.5	12.6	30.4	12.2	249.8
B	87.7	45.1	23.8	12.2	32.9	16.9	1.0	0.5	49.0	25.2	194.4
N	67.8	37.8	8.1	4.5	70.4	39.3	6.4	3.6	26.6	14.9	179.3
M	36.4	41.3	22.5	25.5	3.0	3.4	21.1	23.9	5.2	5.9	88.1
R	41.8	48.4	11.4	13.2	11.7	13.5	19.4	22.4	2.1	2.5	86.5
G	42.0	48.6	4.7	5.5	35.3	40.9	2.2	2.5	2.2	2.5	86.4
H	35.9	63.0	13.5	23.7	2.0	3.5		0.0	5.5	9.7	56.9
D	4.6	8.6	4.4	8.1	17.2	32.1	18.1	33.8	9.3	17.4	53.5
S	20.8	44.6	2.1	4.5	10.7	22.9	10.8	23.1	2.2	4.8	46.6
J	12.9	49.4	4.0	15.4	2.9	11.2		0.0	6.3	24.0	26.2
L	6.4	36.1	0.5	2.7	0.2	1.0		0.0	10.6	60.2	17.6
V	0.1	2.4	0.1	2.5	1.0	22.4	0.0	1.0	3.1	71.8	4.3
P	1.0	62.4	0.4	21.8	0.0	1.4	0.0	0.9	0.2	13.4	1.6
Total	**993.1**	**60.4**	**164.8**	**10.0**	**196.5**	**12.0**	**119.0**	**7.2**	**170.3**	**10.4**	**1,643.8**

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

Figure 3.1. 2020 total per capita pharmaceutical expenditure by level I ATC

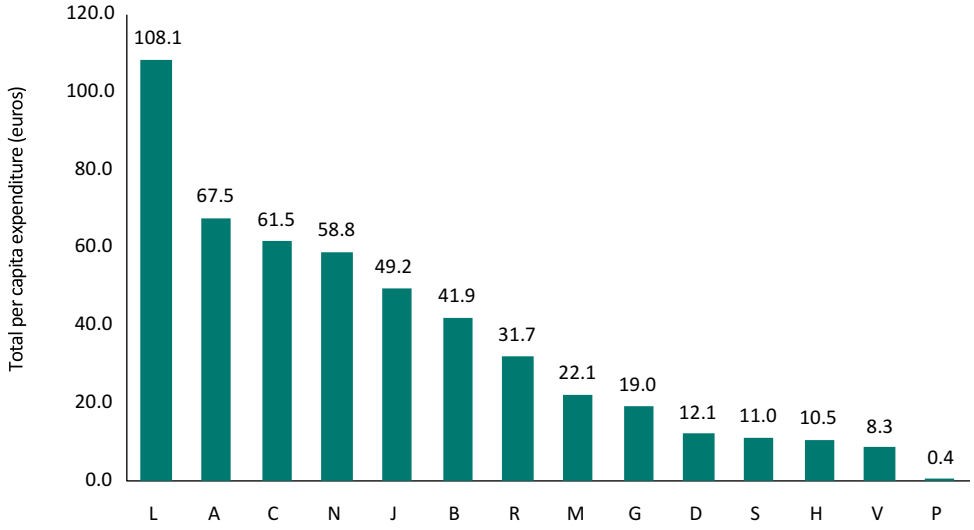


Table 3.5. Regional distribution by level I ATC of per capita gross expenditure under approved care regime (on weighted population) for class A-NHS medicines: year 2020

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	24.11	2.91	42.80	1.13	4.98	3.68	7.33	4.28	3.97	23.43	0.21	15.08	4.26	0.02	138.16
Valle d'Aosta	24.48	2.56	37.03	0.93	5.17	3.82	6.92	3.63	4.21	23.04	0.21	15.96	3.84	0.07	131.87
Lombardy	39.18	14.96	45.56	1.05	5.37	4.05	8.14	6.41	3.82	27.72	0.27	16.18	3.24	0.45	176.38
A.P. Bolzano	16.71	5.87	32.79	0.84	3.55	3.57	4.29	3.49	3.24	24.37	0.16	12.79	2.69	0.04	114.41
A.P. Trento	25.30	5.19	38.41	1.33	4.80	3.66	7.26	4.58	4.05	22.28	0.25	15.54	2.94	0.03	135.62
Veneto	21.86	2.68	44.24	1.15	4.74	3.12	6.29	4.20	3.82	21.36	0.24	13.90	3.43	0.04	131.05
Friuli VG	24.21	5.36	45.77	1.39	4.38	3.73	5.83	4.76	4.42	24.20	0.25	15.27	4.97	0.06	144.60
Liguria	28.24	2.26	42.14	1.12	5.33	3.25	6.98	4.45	4.02	24.77	0.12	17.36	4.13	0.02	144.18
Emilia R.	20.36	3.26	44.56	1.08	5.37	2.48	6.25	1.15	3.67	16.76	0.24	13.59	4.77	0.02	123.58
Tuscany	22.07	3.89	42.14	1.18	4.97	4.00	7.62	0.45	3.90	22.09	0.26	17.07	4.98	0.05	134.66
Umbria	29.46	4.16	53.11	1.12	6.07	4.42	10.08	4.36	4.64	25.20	0.28	16.40	4.68	0.07	164.06
Marche	25.50	3.24	51.68	1.04	6.36	4.49	10.62	4.23	5.12	23.48	0.23	16.20	5.42	0.04	157.66
Lazio	32.46	12.32	53.78	1.28	5.68	5.21	11.81	4.75	6.08	24.55	0.23	19.80	4.10	0.06	182.13
Abruzzo	31.43	9.72	51.49	1.17	5.60	4.90	12.15	4.68	6.29	28.84	0.20	16.21	4.90	0.18	177.76
Molise	30.83	6.54	52.48	1.13	5.30	3.52	11.69	4.82	5.91	23.62	0.13	13.91	3.17	0.08	163.12
Campania	42.69	8.32	58.79	1.77	5.88	4.08	16.25	4.63	6.33	21.68	0.19	23.14	3.49	0.12	197.34
Puglia	34.06	10.26	55.86	1.32	5.89	4.31	13.70	4.59	7.31	24.98	0.14	18.97	3.52	0.05	184.97
Basilicata	38.56	10.00	52.82	1.39	6.19	4.46	11.67	4.21	6.73	21.88	0.15	19.29	3.84	0.22	181.42
Calabria	37.43	10.38	56.58	1.51	5.75	3.85	15.75	4.86	7.21	23.44	0.19	17.62	3.75	0.49	188.83
Sicily	35.66	8.02	56.04	1.45	5.73	4.10	12.71	4.32	6.31	22.57	0.19	17.60	3.29	0.09	178.09
Sardinia	33.04	4.24	48.93	1.44	5.46	3.36	10.26	5.17	6.54	26.97	0.22	18.58	3.52	0.11	167.84
Italy	**31.2**	**7.8**	**49.0**	**1.25**	**5.4**	**3.93**	**9.9**	**4.30**	**5.02**	**23.6**	**0.2**	**17.1**	**3.8**	**0.1**	**163.01**
North	28.60	7.37	44.13	1.11	5.10	3.49	7.11	4.54	3.85	23.62	0.24	15.14	3.80	0.18	148.28
Centre	27.99	7.81	49.71	1.20	5.57	4.67	10.18	3.27	5.15	23.67	0.24	18.20	4.60	0.05	162.31
South and	36.90	8.59	55.74	1.49	5.78	4.10	13.85	4.61	6.62	23.69	0.18	19.35	3.57	0.14	184.62

Note: expenditure does not include oxygen

Table 3.6. Regional distribution by level I ATC of DDD/1000 inhabitants per day (on weighted population) for class A-NHS medicines under approved care regime: year 2020

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	129.3	80.0	447.0	3.7	39.3	33.8	10.1	6.6	30.9	72.2	0.9	35.1	22.9	0.0	911.8
Valle d'Aosta	135.5	66.7	377.9	3.5	37.3	30.6	10.0	5.8	31.9	63.6	1.0	37.8	19.3	0.1	821.1
Lombardy	152.0	77.4	451.3	3.3	38.2	26.2	10.8	8.6	26.1	70.0	1.2	37.7	16.9	0.3	920.1
A.P. Bolzano	83.9	57.2	352.8	3.0	28.4	28.5	6.5	5.8	22.9	73.9	0.7	29.1	15.6	0.0	708.4
A.P. Trento	132.7	98.6	414.4	4.8	37.7	41.4	10.9	7.1	30.0	65.1	1.1	42.2	16.3	0.0	902.4
Veneto	119.8	54.6	465.8	4.0	37.0	30.2	9.3	6.8	27.1	61.6	1.1	33.7	18.6	0.0	869.3
Friuli VG	127.8	82.8	499.9	4.6	34.7	37.6	9.4	7.7	34.0	57.8	1.1	37.3	26.5	0.1	961.2
Liguria	146.6	55.4	412.9	3.6	42.1	21.7	9.1	6.6	27.7	78.5	0.5	41.4	20.7	0.0	866.8
Emilia R.	114.1	93.9	483.2	3.9	41.6	39.5	9.8	2.7	29.1	63.3	1.0	34.9	26.2	0.0	943.5
Tuscany	118.7	95.3	473.7	4.3	40.4	40.7	11.1	1.2	31.7	83.4	1.2	40.3	26.5	0.0	968.4
Umbria	141.1	89.6	590.8	4.1	47.5	45.8	14.7	6.9	37.0	79.2	1.3	38.5	24.5	0.1	1121.2
Marche	125.0	87.9	498.3	3.5	49.9	40.8	13.9	6.3	40.8	70.6	1.0	34.7	29.7	0.1	1002.5
Lazio	163.0	112.3	500.9	4.8	44.9	43.8	14.8	6.9	42.7	65.9	1.1	47.9	22.2	0.1	1071.4
Abruzzo	153.1	111.3	476.6	4.5	43.8	42.4	16.1	6.6	47.5	74.8	0.9	39.1	26.5	0.1	1043.2
Molise	154.0	102.6	476.0	4.7	40.0	44.7	14.7	6.2	44.7	65.1	0.6	34.5	16.3	0.1	1004.0
Campania	202.6	83.4	539.6	7.8	46.5	34.3	19.2	6.2	44.8	59.5	0.9	60.7	18.1	0.1	1123.8
Puglia	171.1	111.7	517.0	5.0	47.2	44.6	16.9	6.8	52.8	64.7	0.6	49.0	19.2	0.1	1106.6
Basilicata	175.6	103.7	487.4	5.7	49.1	42.7	15.3	5.9	49.0	61.3	0.6	45.3	20.5	0.2	1062.5
Calabria	184.8	113.8	514.8	6.0	44.2	38.6	17.3	7.1	50.6	68.6	0.9	42.0	19.9	0.3	1108.9
Sicily	182.6	90.2	533.0	6.1	44.9	35.7	16.0	6.3	43.6	62.1	0.9	44.4	17.6	0.1	1083.6
Sardinia	163.5	85.5	467.8	5.0	43.2	44.3	12.1	8.0	46.1	77.3	1.0	46.1	19.7	0.1	1019.8
Italy	**151.**	**87.**	**484.7**	**4.6**	**42.**	**35.9**	**12.9**	**6.4**	**36.**	**67.8**	**1.0**	**41.**	**20.8**	**0.1**	**993.1**
North	133.5	75.4	455.4	3.7	38.6	30.9	10.0	6.8	28.0	67.7	1.1	36.3	20.3	0.1	907.8
Centre	142.2	101.9	498.6	4.4	44.3	42.6	13.5	5.0	38.5	73.2	1.1	43.0	24.7	0.1	1033.1
South and	181.6	96.5	518.3	6.1	45.5	38.9	16.8	6.6	47.1	64.7	0.8	49.2	19.1	0.1	1091.3

Note: expenditure does not include oxygen

Table 3.7. Regional distribution by level I ATC of per capita expenditure (on weighted population) of medicines purchased by public health facilities: year 2020

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	16.29	29.97	6.02	1.56	1.12	4.59	34.60	95.72	3.48	7.72	0.06	4.85	2.57	5.48	214.04
Valle d'Aosta	9.15	27.78	4.16	1.32	1.34	4.34	23.38	72.33	1.07	7.23	0.14	3.89	1.08	5.86	163.07
Lombardy	11.14	23.47	3.97	1.09	0.92	4.10	39.51	83.96	3.76	5.24	0.06	3.85	1.19	4.73	186.98
A.P. Bolzano	11.89	22.33	4.64	1.08	1.11	5.00	27.61	113.16	3.62	8.78	0.02	5.83	3.21	5.19	213.47
A.P. Trento	19.70	25.63	4.33	1.05	1.20	4.36	32.30	75.35	2.01	6.79	0.05	4.72	2.92	4.39	184.80
Veneto	17.00	25.49	4.71	1.42	1.04	5.10	34.21	97.00	5.82	8.18	0.05	3.81	2.59	5.42	211.82
Friuli VG	16.31	30.56	5.69	1.22	1.18	4.69	31.24	116.18	4.08	6.69	0.07	4.30	3.15	5.35	230.71
Liguria	13.51	34.99	6.22	1.10	0.87	4.59	38.10	105.39	3.01	8.59	0.05	4.23	2.89	4.54	228.09
Emilia R.	18.47	30.71	5.22	1.39	1.40	5.39	35.41	105.57	3.08	9.83	0.09	4.98	2.08	6.54	230.16
Tuscany	15.82	33.73	6.38	1.28	1.48	5.36	42.53	110.81	3.07	9.59	0.03	4.59	1.82	6.01	242.49
Umbria	19.92	35.53	6.12	1.23	0.98	4.89	37.13	120.45	3.45	8.69	0.04	4.83	3.10	5.41	251.77
Marche	16.96	33.82	7.12	1.54	1.18	5.61	33.31	120.54	4.97	9.76	0.03	4.82	2.38	5.89	247.93
Lazio	17.27	31.79	5.75	0.97	1.61	4.53	39.51	99.66	4.60	7.52	0.04	3.79	1.70	4.86	223.60
Abruzzo	20.10	38.30	5.93	1.05	1.13	6.29	29.37	120.57	3.26	9.16	0.06	4.89	3.05	5.02	248.16
Molise	16.07	32.33	6.12	1.43	1.40	6.12	19.73	120.35	2.78	7.23	0.01	2.88	3.37	4.42	224.24
Campania	22.68	39.25	9.00	1.84	1.51	5.41	33.03	121.41	3.43	7.57	0.01	4.91	1.98	4.51	256.55
Puglia	20.61	35.45	7.35	1.32	1.21	4.74	32.33	115.26	3.89	9.43	0.01	6.54	3.09	7.53	248.77
Basilicata	18.89	32.61	9.30	1.42	1.50	3.99	26.27	122.24	1.31	8.60	0.01	9.48	2.95	8.83	247.40
Calabria	23.17	35.95	7.23	1.44	1.72	5.98	23.00	110.11	3.26	8.39	0.01	7.61	1.90	7.40	237.16
Sicily	17.98	29.22	5.43	0.98	1.00	3.95	28.17	91.71	2.77	7.40	0.01	6.10	1.96	7.07	203.75
Sardinia	18.03	31.20	5.80	1.11	0.77	3.94	28.54	119.84	2.97	7.95	0.01	3.42	2.61	12.09	238.29
Italy	**17.0**	**30.7**	**5.87**	**1.28**	**1.2**	**4.7**	**34.77**	**102.8**	**3.71**	**7.8**	**0.0**	**4.7**	**2.1**	**5.8**	**222.8**
North	14.73	27.10	4.87	1.28	1.07	4.64	36.24	94.69	3.89	7.27	0.06	4.28	2.06	5.29	207.46
Centre	16.96	32.96	6.16	1.16	1.46	4.96	39.49	107.54	4.07	8.57	0.04	4.26	1.93	5.40	234.97
South and	20.40	34.72	7.13	1.36	1.26	4.89	29.74	111.80	3.23	8.14	0.01	5.74	2.37	6.80	237.58

Note: expenditure does not include oxygen

Table 3.8. Regional distribution by level I ATC of DDD/1000 inhabitants per day (on weighted population) of medicines purchased by public health facilities: year 2020

Region	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Piedmont	33.5	52.8	21.9	8.8	2.0	7.3	6.5	10.1	5.8	33.9	0.4	2.7	2.4	4.6	192.7
Valle d'Aosta	24.7	48.8	18.4	9.8	4.7	7.2	5.5	8.0	4.3	38.0	0.5	4.5	1.6	5.1	181.2
Lombardy	17.2	27.6	9.9	6.2	1.6	3.6	6.8	7.4	5.2	16.5	0.1	1.8	1.9	3.2	108.9
A.P. Bolzano	38.3	34.0	22.1	7.5	1.9	7.6	5.3	11.1	7.9	37.8	0.3	3.1	3.3	4.8	185.0
A.P. Trento	36.3	47.5	20.0	9.8	2.4	6.5	5.6	9.3	4.3	29.2	0.6	2.5	2.9	6.3	183.3
Veneto	39.5	49.5	23.4	18.5	1.7	5.6	7.2	10.0	5.1	41.7	0.3	3.0	3.3	4.2	213.0
Friuli VG	32.6	38.8	18.7	10.9	1.9	6.7	6.0	11.6	5.1	32.8	0.2	2.7	2.5	4.0	174.5
Liguria	29.2	73.7	21.4	8.8	1.4	6.8	6.4	10.0	5.5	39.3	0.4	2.5	3.0	3.6	211.9
Emilia R.	50.3	79.0	48.5	11.7	8.4	9.8	9.4	13.1	5.8	46.6	0.6	5.5	4.3	6.0	298.9
Tuscany	29.1	69.0	19.8	10.2	4.7	7.5	7.3	15.8	4.5	33.9	0.3	3.2	2.9	2.9	211.0
Umbria	33.3	61.1	24.9	21.2	2.1	5.1	5.8	10.8	3.8	40.8	0.1	2.1	3.5	3.6	218.1
Marche	29.1	100.0	15.7	10.3	2.1	6.3	6.0	12.5	6.5	25.1	0.4	1.6	2.3	4.2	222.1
Lazio	25.5	36.6	12.6	6.9	1.0	4.3	6.4	10.0	5.5	21.0	0.1	1.0	1.5	1.8	134.2
Abruzzo	32.6	38.8	13.6	9.2	0.8	5.5	5.1	11.8	6.6	17.3	0.1	1.3	2.1	2.0	147.0
Molise	27.8	42.1	9.0	5.2	0.7	5.0	3.1	10.1	5.5	15.6	0.1	0.9	1.8	1.9	128.8
Campania	31.1	54.2	10.4	5.3	0.9	4.8	4.8	11.0	5.0	20.3	0.1	1.3	1.2	1.6	152.1
Puglia	35.2	39.6	11.7	11.4	1.5	5.5	5.2	11.2	5.0	18.6	0.1	1.3	2.3	2.1	150.5
Basilicata	29.8	40.0	10.2	12.2	1.0	4.9	3.9	11.6	3.9	22.2	0.1	1.7	2.0	2.1	145.4
Calabria	31.9	43.2	11.4	11.5	0.9	4.4	3.7	9.4	4.5	15.7	0.0	1.0	1.0	1.6	140.2
Sicily	26.0	43.3	13.0	5.7	1.1	4.1	4.9	10.3	4.1	19.7	0.1	1.2	1.0	1.4	135.6
Sardinia	32.0	53.7	10.8	10.2	1.0	4.5	5.9	12.6	6.1	24.0	0.1	1.3	2.1	3.8	168.2
Italy	**30.4**	**49.**	**17.**	**9.3**	**2.2**	**5.5**	**6.3**	**10.**	**5.2**	**26.**	**0.2**	**2.1**	**2.2**	**3.1**	**170.3**
North	31.3	47.7	22.0	10.1	2.8	6.0	7.1	9.7	5.4	31.4	0.3	2.9	2.8	4.2	183.7
Centre	27.7	57.1	16.3	9.5	2.4	5.6	6.6	12.2	5.2	27.2	0.2	1.9	2.2	2.6	176.7
South and	30.8	45.9	11.6	8.1	1.1	4.8	4.9	10.9	4.9	19.5	0.1	1.2	1.5	1.9	147.2

Note: expenditure does not include oxygen

Figure 3.2. Consumption, price and mix effect on variation of class A-NHS pharmaceutical expenditure under approved care regime by level I ATC: comparison 2020-2019

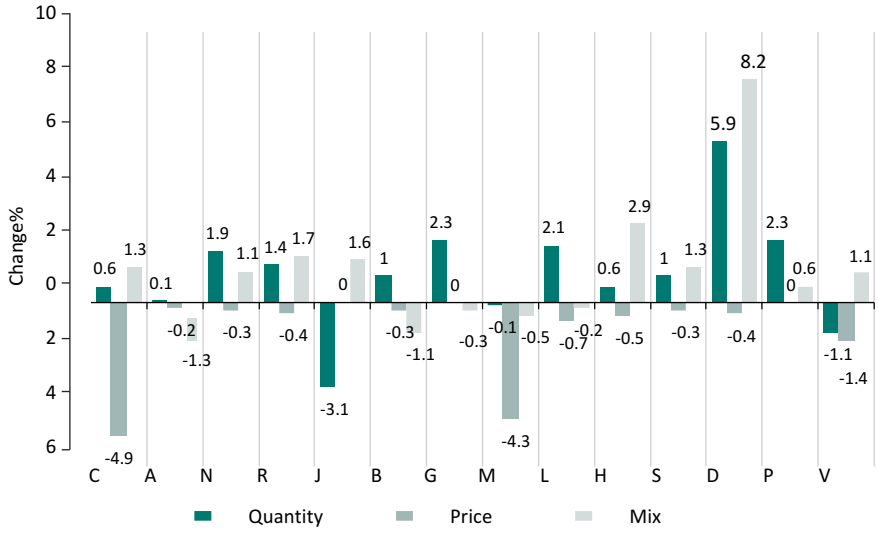


Table 3.9. Consumption, price and mix effect on variation of class A-NHS pharmaceutical expenditure under a pproved care regime by level I ATC: comparison 2020-2019 (any ATC category includes the therapeutic subgroups in decreasing order of expenditure, up to the value of 0.10 euros per capita expenditure)

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
TOTAL	**163.01**	**993.1**	**-2.7**	**-0.3**	**-0.6**	**-1.8**	**-2.3**
C - Cardiovascular system	**49.05**	**484.7**	**1.9**	**1.3**	**-0.3**	**0.9**	**0.6**
HMG-CoA reductase inhibitors	8.04	80.1	1.2	3.3	-1.0	-1.0	-2.1
Angiotensin II receptor blockers, plain	4.88	58.4	1.3	0.8	0.0	0.5	0.5
Beta blockers, selective	4.73	40.0	3.8	2.6	-0.1	1.3	1.2
Dihydropyridine derivatives	4.22	50.5	-0.6	0.7	0.0	-1.3	-1.3
Angiotensin II receptor blockers (ARBs) and diuretics	4.01	33.1	-1.9	-1.7	0.0	-0.2	-0.2
ACE inhibitors, not in combination	3.80	84.0	-2.9	-1.3	-0.1	-1.4	-1.6
Other lipid modifying agents	3.33	9.6	6.0	9.4	-0.8	-2.3	-3.1
ACE inhibitors and diuretics	2.59	20.1	-4.1	-3.4	0.0	-0.7	-0.7
Lipid modifying agents in combination	1.96	8.1	30.7	36.7	-0.1	-4.3	-4.4
ACE inhibitors and calcium channel blockers	1.67	12.0	-3.3	0.4	-2.5	-1.3	-3.7
Alpha-adrenoreceptor blockers	1.26	7.6	1.6	1.5	0.0	0.1	0.1
Angiotensin II receptor blockers (ARBs) and calcium channel blockers	1.21	8.3	13.5	16.5	0.0	-2.5	-2.5
Antiarrhythmic agents, class Ic	1.07	4.7	3.2	1.0	0.0	2.2	2.2
Sulfonamides, plain	0.88	26.1	0.2	0.2	0.0	0.0	0.0
ACE inhibitors, other combinations	0.72	4.4	31.0	30.9	0.0	0.0	0.0
Organic nitrates	0.66	6.3	-12.0	-12.0	0.0	0.0	0.0
Selective beta-blockers and thiazides	0.56	5.7	2.9	3.6	-0.3	-0.3	-0.7
Aldosterone antagonists	0.55	3.3	3.3	2.2	0.0	1.1	1.1
Alpha and beta adrenoreceptor blockers	0.53	3.0	-5.1	-4.6	0.0	-0.5	-0.5
Fibrates	0.39	2.8	1.9	1.7	0.0	0.1	0.1
Angiotensin II receptor blockers, other combinations	0.29	0.1	41.2	41.2	0.0	0.0	0.0
Antiarrhythmic agents, class III	0.26	2.9	-0.9	-0.9	0.0	0.1	0.1
Imidazoline receptor agonists	0.20	1.4	-4.2	-6.6	0.0	2.5	2.5
Benzodiazepine derivatives	0.18	1.0	-6.7	-6.6	0.0	-0.1	-0.1
Other cardiac preparations	0.17	0.5	-8.9	-15.3	0.0	7.6	7.6
Beta-blocking agents, not selective	0.14	1.6	-0.9	-1.0	0.0	0.1	0.1
Phenylalkylamine derivatives	0.13	1.1	-7.1	-7.7	0.0	0.6	0.6
Sulfonamides, plain	0.12	1.8	-5.6	-8.9	0.0	3.6	3.6
Selective beta-blockers and other diuretics	0.12	1.7	-5.1	-5.3	0.0	0.2	0.2
High-ceiling diuretics in combination with potassium-sparing agents	0.12	0.6	-1.5	-1.4	0.0	-0.1	-0.1
A – Alimentary tract and metabolism	**31.20**	**151.0**	**-5.4**	**-2.2**	**-0.1**	**-**	**-3.2**
Proton pump inhibitors	11.45	72.7	-4.9	4.7	0.0	-9.1	-9.1
Vitamin D and analogues	3.96	11.9	-24.6	-21.3	0.0	-4.2	-4.2

Continued

Table 3.9. continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Insulins and injectable analogues, fast-acting	3.62	7.5	-2.0	-1.3	-0.6	-0.1	-0.7
Aminosalicylic acid and analogues	2.04	5.2	4.0	4.2	-0.4	0.2	-0.2
Biguanides	1.57	22.4	1.8	0.7	0.0	1.1	1.1
Antibiotics	1.46	2.0	-4.9	-4.8	0.0	-0.2	-0.2
Other antipeptic antiulcer and gastroesophageal reflux disease	0.91	4.3	0.9	0.8	0.0	0.2	0.2
GLP-1 (glucagon-like peptide-1) receptor analogues	0.85	0.4	66.7	42.8	0.0	16.8	16.8
Bile acids and derivatives	0.81	2.5	8.4	3.9	2.6	1.8	4.4
Insulins and injectable analogues, long-acting	0.78	0.6	0.4	-1.9	0.2	2.1	2.3
Sulfonylureas	0.51	7.6	-3.4	-7.9	0.0	4.9	4.9
Oral hypoglycemic agents, in combination	0.49	1.8	35.7	-1.9	-2.3	41.5	38.3
Aluminium, calcium and magnesium compounds in combination	0.41	1.8	4.7	4.4	0.0	0.2	0.2
Calcium, combinations with vitamin D and/or other pharmaceuticals	0.32	3.3	-21.9	-22.1	0.0	0.3	0.3
Corticosteroids for topical use	0.28	0.4	-2.9	-2.6	0.0	-0.3	-0.3
Other hypoglycaemic agents, excluding insulins	0.27	1.9	-13.1	-13.3	0.0	0.2	0.2
Enzyme preparations	0.23	0.6	4.6	4.6	0.0	0.0	0.0
Dipeptil Peptidase 4 Inhibitors (DPP-4)	0.21	0.3	9.0	9.2	0.0	-0.3	-0.3
Serotonin antagonists (5HT3)	0.20	0.0	-6.6	-1.6	-0.3	-4.9	-5.1
Alpha Glucosidase Inhibitors	0.14	0.5	-7.9	-6.1	0.0	-1.9	-2.0
Osmotic laxatives	0.12	1.1	-3.7	-3.4	0.0	-0.4	-0.4
Calcium	0.11	0.8	-8.2	-36.7	0.0	45.1	45.1
Insulins and injectable analogues, intermediate or long-acting in combination with fast-acting	0.11	0.2	-23.8	-23.1	-1.0	0.0	-1.0
Thiazolidinediones	0.10	0.4	3.4	4.7	0.0	-1.2	-1.2
N- Central nervous system	**23.65**	**67.8**	**0.8**	**1.4**	**-0.2**	**-0.4**	**-0.6**
Other antiepileptics	4.60	6.2	4.1	4.0	-0.1	0.3	0.2
Selective serotonin reuptake inhibitors	3.33	29.3	0.9	1.6	0.0	-0.7	-0.7
Other antidepressants	3.14	11.3	3.9	3.9	0.0	0.1	0.1
Other opioids	1.48	1.1	-0.7	-3.0	0.0	2.4	2.4
Phenylpiperidine derivatives	1.37	0.6	-0.2	-0.9	0.0	0.7	0.7
Natural opium alkaloids	1.20	0.6	-6.3	-1.5	0.0	-4.8	-4.8
Dopamine agonists	1.17	1.1	-3.3	-5.5	0.0	2.4	2.4
5HT1 selective receptor agonists	0.99	0.8	-0.8	1.0	-1.0	-0.8	-1.8
Fatty acid derivatives	0.98	2.3	1.5	2.5	0.0	-1.0	-1.0
Diazepines, oxazepines, thiazepines and oxepins	0.94	1.2	3.1	2.4	0.0	0.7	0.7
Type B monoamine oxidase inhibitors	0.78	1.6	2.9	1.2	-0.2	1.9	1.7
DOPA and derivatives	0.73	2.1	-1.1	0.2	0.0	-1.3	-1.3

Continued

Table 3.9. continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19 Expenditure	DDD	Prices	Mix	Δ % average DDD cost
Opioids in combination with non-opioid analgesics	0.54	1.4	-6.6	-7.8	0.3	1.1	1.4
Carboxamide derivatives	0.48	1.8	-0.8	-1.0	0.0	0.2	0.2
Amides	0.35	0.3	-4.9	-4.9	0.0	0.0	0.0
Other antipsychotics	0.25	0.4	0.1	7.6	-6.8	-0.2	-7.0
Oripavine derivatives	0.24	0.2	13.3	7.5	0.0	5.4	5.4
Non-selective monoamine reuptake inhibitors	0.15	1.0	-9.2	-4.4	-4.9	-0.1	-5.0
Anticholinesterases	0.14	0.4	-9.8	-5.6	-0.3	-4.1	-4.4
R- Respiratory system	**17.13**	**41.8**	**1.3**	**-0.8**	**-0.5**	**2.6**	**2.1**
Adrenergics in combination with corticosteroids or others, excluding anticolinergics	8.45	13.3	4.2	5.5	-1.3	0.0	-1.2
Anticolinergics	3.29	6.1	2.2	-0.4	0.5	2.1	2.6
Combination of adrenergics with anticolinergics including triple combination	1.76	2.4	23.2	6.3	0.7	15.0	15.9
Glycocorticoids	1.38	3.8	-27.0	-26.0	-0.1	-1.2	-1.3
Other antihistamines for systemic use	0.68	6.2	5.4	5.3	0.0	0.1	0.1
Selective agonists of beta2-adrenergic receptors	0.59	3.4	-13.0	-11.7	0.0	-1.5	-1.5
Leukotriene receptor antagonists	0.49	2.2	3.5	5.7	0.0	-2.1	-2.1
Piperazine derivatives	0.40	4.0	5.8	6.2	0.0	-0.3	-0.3
J- General antimicrobials for systemic use	**9.94**	**12.9**	**-21.5**	**-22.9**	**0.1**	**1.8**	**1.9**
Penicillin combinations, including betalactamase inhibitors	2.26	4.3	-25.4	-25.5	0.0	0.2	0.2
Third generation cephalosporins	2.16	1.4	-31.6	-30.5	0.0	-1.5	-1.5
Macrolides	1.24	2.8	-17.8	-20.5	-0.1	3.6	3.5
Fluoroquinolones	1.13	1.5	-21.7	-23.0	0.0	1.8	1.7
Triazole derivatives	0.87	0.5	-13.3	-14.3	0.0	1.1	1.1
Other antibacterials	0.62	0.4	-4.8	-4.7	0.0	-0.1	-0.1
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.60	0.3	-3.9	-2.8	0.0	-1.1	-1.1
Specific immunoglobulins	0.41	0.0	0.5	0.8	2.7	-2.9	-0.3
Broad-spectrum penicillins	0.16	0.8	-34.8	-33.3	-0.1	-2.0	-2.1
B- Blood and blood-forming organs	**7.86**	**87.7**	**-1.6**	**-1.5**	**-0.5**	**0.4**	**-0.1**
Platelet aggregation inhibitors, excl. heparin	3.07	61.0	-1.2	-0.6	-0.4	-0.2	-0.5
Heparins	2.23	2.6	-5.1	1.5	0.0	-6.4	-6.4
Direct Xa factor inhibitors	0.74	0.5	14.0	14.8	-0.6	-0.2	-0.8
Folic acid and derivatives	0.46	6.0	-5.0	-2.1	-1.5	-1.5	-3.0
Bivalent iron, oral preparations	0.34	2.7	-6.7	-6.4	0.0	-0.3	-0.3
Blood substitutes and plasma protein fractions	0.24	0.0	2.7	2.6	0.0	0.1	0.1
Solutions influencing the electrolyte balance	0.16	0.3	-1.7	-2.2	0.0	0.6	0.6
Vitamin K antagonists	0.15	3.5	-12.0	-11.6	0.0	-0.4	-0.4

Continued

Table 3.9.
continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19 Expenditure	DDD	Prices	Mix	Δ % average DDD cost
Other antianemic preparations	0.14	0.0	36.0	39.2	-0.2	-2.1	-2.3
G – Genito-urinary system and sex hormones	**5.42**	**42.0**	**-7.2**	**-0.5**	**-5.7**	**-1.1**	**-6.7**
Alpha adrenergic receptor antagonists	2.84	26.4	-10.7	0.6	-10.1	-1.3	-11.3
Testosterone-5-alpha reductase inhibitors	1.61	10.9	0.2	1.2	0.0	-1.0	-1.0
Prolactin inhibitors	0.16	0.1	0.6	-0.1	0.0	0.7	0.7
Other estrogens	0.12	0.7	2.4	2.6	0.0	-0.2	-0.2
Estrogen-progestogen, fixed combinations	0.11	0.5	0.5	0.0	0.0	0.5	0.5
Gonadotropins	0.10	0.0	-20.2	-19.6	-0.2	-0.5	-0.8
Pregnene derivatives	0.10	0.8	-19.3	-20.1	0.0	0.9	0.9
M - Musculo-skeletal system	**5.02**	**36.4**	**-8.7**	**-3.5**	**-4.0**	**-1.3**	**-5.3**
Biphosphonates	1.33	6.8	-1.5	-0.1	-0.7	-0.7	-1.4
Preparations inhibiting formation of uric acid	0.83	10.2	-22.5	1.3	-19.9	-4.5	-23.4
Acetic acid derivatives and related substances	0.75	4.6	-4.1	-4.2	-0.3	0.4	0.1
Coxib	0.64	3.8	-2.4	-2.0	0.0	-0.3	-0.3
Propionic acid derivatives	0.63	5.2	-13.9	-13.3	0.0	-0.6	-0.6
Biphosphonates, combinations	0.44	2.1	-7.0	-6.9	0.0	0.0	0.0
Other non-steroidal anti-inflammatory/anti-rheumatic pharmaceuticals	0.15	1.8	-6.1	-6.6	0.0	0.6	0.6
Oxicam-derivatives	0.12	0.8	-6.4	-8.0	0.0	1.8	1.8
L- Antineoplastic and immunomodulatory pharmaceuticals	**4.30**	**6.4**	**2.0**	**1.7**	**-0.1**	**0.5**	**0.3**
Aromatase inhibitors	2.18	3.0	6.0	5.5	0.0	0.5	0.5
Other immunosuppressants	0.77	1.6	2.9	1.8	0.0	1.2	1.1
Calcineurin inhibitors	0.59	0.2	-7.2	-7.5	-0.1	0.3	0.3
Other antineoplastics	0.16	0.3	3.7	4.0	0.0	-0.3	-0.3
Antiandrogens	0.14	0.3	-9.7	-9.7	0.0	0.0	0.0
Colony stimulating factors	0.11	0.0	20.0	36.6	-0.1	-12.1	-12.1
Folic acid analogues	0.10	0.1	-5.6	-5.5	0.0	0.0	0.0
H - Systemic hormonal preparations, excluding sex hormones	**3.93**	**35.9**	**-5.4**	**0.3**	**-0.9**	**-4.8**	**-5.7**
Glycocorticoids	1.37	12.9	-2.7	-1.1	0.0	-1.6	-1.6
Thyroid hormones	1.16	21.3	7.4	1.3	0.0	5.9	5.9
Parathyroid hormones and analogues	1.06	0.2	-15.1	-8.6	-3.0	-4.2	-7.1
Vasopressin and analogues	0.13	0.1	-9.6	-9.0	0.0	-0.7	-0.7
S - Sensory organs	**3.89**	**20.8**	**-1.3**	**-0.4**	**-0.9**	**0.0**	**-0.9**
Beta-blockers	2.26	11.8	-0.2	0.3	-0.7	0.3	-0.4
Prostaglandins analogues	1.28	5.7	-2.8	-0.9	-1.5	-0.4	-2.0
Carbonic anhydrase inhibitors	0.21	1.4	-4.0	-2.7	0.0	-1.3	-1.3
Sympathomimetics for treatment of glaucoma	0.10	1.5	-1.8	-2.0	0.0	0.2	0.2
D - Dermatologicals	**1.25**	**4.6**	**-4.3**	**0.6**	**1.1**	**-5.9**	**-4.9**
Other antipsoriatic agents for topical use	0.87	2.5	-1.2	-5.7	2.9	1.8	4.8

Continued

Table 3.9.
continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
P - Antiparasitic, insecticide and repellent pharmaceuticals	**0.22**	**1.0**	**-4.5**	**7.1**	**0.0**	**-10.9**	**-10.9**
Aminoquinolines	0.17	0.9	10.9	10.9	0.0	0.0	0.0
V - Miscellaneous	**0.14**	**0.1**	**-4.8**	**-3.5**	**0.0**	**-1.3**	**-1.3**
Pharmaceuticals for treatment of hyperkalemia and hyperphosphatemia	0.12	0.1	-3.4	-3.2	0.0	-0.2	-0.2

Table 3.10. 2020 expenditure and consumption of class A-NHS under approved care regime: most prescribed active ingredients by level I ATC (up to 75% of the category expenditure)

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
C - Cardiovascular system	**49.05**		**2.2**	**484.7**		**1.3%**	**0.28**	**0.6**
atorvastatin	4.50	9.2	4.5	48.8	10.1	4.8	0.25	-0.6
bisoprolol	2.60	5.3	5.7	11.8	2.4	5.1	0.60	0.2
ramipril	2.02	4.1	-1.4	62.9	13.0	-0.2	0.09	-1.4
omega 3	1.93	3.9	1.0	4.5	0.9	1.9	1.18	-1.1
olmesartan medoxomil	1.65	3.4	9.2	14.4	3.0	9.9	0.31	-0.9
amlodipine	1.63	3.3	2.6	28.0	5.8	2.7	0.16	-0.4
simvastatin	1.53	3.1	-3.4	12.8	2.6	-3.7	0.33	0.0
nebivolol	1.50	3.1	3.2	16.1	3.3	3.4	0.25	-0.5
ezetimibe	1.39	2.8	14.6	5.1	1.1	16.9	0.74	-2.2
rosuvastatin	1.35	2.7	6.8	14.0	2.9	7.7	0.26	-1.1
doxazosin	1.25	2.6	1.9	7.6	1.6	1.5	0.45	0.1
ezetimibe/simvastatin	1.18	2.4	5.3	4.8	1.0	5.5	0.66	-0.5
olmesartan/amlodipine	1.17	2.4	12.4	7.9	1.6	14.8	0.40	-2.4
olmesartan/hydrochlorothiazide	1.16	2.4	5.9	9.5	2.0	5.6	0.33	0.0
barnidipine	0.89	1.8	2.8	4.9	1.0	3.0	0.50	-0.4
flecainide	0.86	1.8	5.9	2.9	0.6	6.3	0.82	-0.6
perindopril/amlodipine	0.84	1.7	-0.7	5.3	1.1	-0.2	0.43	-0.8
lercanidipine	0.79	1.6	1.9	9.6	2.0	1.6	0.22	0.0
losartan	0.79	1.6	-2.5	7.5	1.5	-2.6	0.29	-0.2
ezetimibe/rosuvastatin	0.78	1.6	107.6	3.3	0.7	142.4	0.65	-14.6
furosemide	0.74	1.5	1.0	24.8	5.1	0.4	0.08	0.3
valsartan/hydrochlorothiazide	0.71	1.5	-5.6	6.4	1.3	-5.5	0.30	-0.3
irbesartan	0.70	1.4	-2.5	8.5	1.8	-2.8	0.22	0.1
zofenopril	0.68	1.4	1.5	4.5	0.9	0.9	0.41	0.3
valsartan	0.68	1.4	-2.5	10.0	2.1	-1.4	0.19	-1.4
zofenopril/hydrochlorothiazide	0.65	1.3	-0.2	4.1	0.8	-0.2	0.43	-0.3
perindopril/indapamide/amlodipine	0.62	1.3	31.7	3.6	0.7	31.4	0.47	0.0
irbesartan/hydrochlorothiazide	0.62	1.3	-3.8	5.3	1.1	-4.0	0.32	-0.1
ramipril/hydrochlorothiazide	0.57	1.2	-2.2	6.6	1.4	-1.2	0.23	-1.3
telmisartan	0.55	1.1	-0.5	9.0	1.9	-2.0	0.17	1.3
nitroglycerin	0.54	1.1	-12.2	4.5	0.9	-12.8	0.33	0.4
A- Alimentary tract and metabolism	**31.20**		**-5.1**	**151.0**		**-2.2**	**0.56**	**-3.2**
pantoprazole	4.26	13.6	-3.9	25.3	16.8	9.4	0.46	-12.4
cholecalciferol	3.38	10.8	-28.2	9.7	6.4	-26.4	0.95	-2.7
lansoprazole	2.40	7.7	-5.7	14.1	9.3	-0.6	0.47	-5.4
omeprazole	2.26	7.3	-4.9	17.2	11.4	3.9	0.36	-8.7
esomeprazole	2.19	7.0	-4.2	14.2	9.4	4.1	0.42	-8.2
mesalazine	1.99	6.4	4.7	5.0	3.3	4.9	1.08	-0.5
metformin	1.57	5.0	2.1	22.4	14.8	0.7	0.19	1.1

Continued

Table 3.10.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
insulin lispro	1.56	5.0	-3.2	3.4	2.2	-0.9	1.25	-2.5
insulin aspart	1.49	4.8	1.1	2.9	1.9	0.1	1.40	0.7
rifaximin	1.35	4.3	-4.4	1.8	1.2	-4.7	2.08	0.0
sodium alginate/potassium bicarbonate	0.87	2.8	1.6	4.1	2.7	1.2	0.59	0.1
N - Nervous system	**23.65**		**1.1**	**67.83**		**1.5**	**0.95**	**-0.6**
levetiracetam	1.60	6.8	2.3	2.2	3.2	2.9	2.03	-0.9
fentanyl	1.37	5.8	0.1	0.6	1.0	-0.9	5.76	0.7
pregabalin	1.23	5.2	7.5	2.2	3.2	7.1	1.53	0.1
tapentadol	1.22	5.2	0.7	0.5	0.8	0.5	6.30	0.0
paroxetine	1.01	4.3	-0.2	7.9	11.6	1.6	0.35	-2.0
escitalopram	0.95	4.0	1.0	7.4	11.0	1.1	0.35	-0.4
valproic acid	0.95	4.0	1.9	2.3	3.3	2.7	1.15	-1.0
naloxone/oxycodone	0.94	4.0	-7.7	0.4	0.6	-3.2	6.68	-4.9
venlafaxine	0.80	3.4	1.7	3.5	5.2	2.7	0.62	-1.3
duloxetine	0.77	3.2	1.9	3.1	4.6	2.2	0.68	-0.5
sertraline	0.77	3.2	4.4	8.3	12.2	3.7	0.25	0.4
rotigotine	0.69	2.9	-2.2	0.3	0.5	-2.5	5.39	0.0
vortioxetine	0.64	2.7	12.6	1.5	2.3	12.3	1.14	0.0
lacosamide	0.61	2.6	14.6	0.3	0.5	14.3	5.38	0.0
quetiapine	0.57	2.4	5.2	0.4	0.7	3.5	3.47	1.4
lamotrigine	0.44	1.9	0.8	0.7	1.0	0.6	1.77	0.0
citalopram	0.41	1.7	-0.8	3.9	5.8	-1.1	0.28	0.0
trazodone	0.40	1.7	2.5	1.1	1.6	2.9	0.98	-0.6
safinamide	0.39	1.6	7.8	0.2	0.4	10.1	4.43	-2.4
pramipexole	0.37	1.6	-2.0	0.4	0.7	-4.0	2.31	1.8
lidocaine	0.35	1.5	-4.7	0.3	0.4	-4.9	3.61	0.0
levodopa/benserazide	0.35	1.5	0.9	1.0	1.5	0.8	0.92	-0.2
mirtazapine	0.34	1.5	3.4	1.7	2.4	3.0	0.57	0.1
gabapentin	0.33	1.4	-0.8	0.4	0.6	-1.2	2.14	0.2
topiramate	0.28	1.2	-2.0	0.3	0.5	-2.1	2.41	-0.1
R - Respiratory system	**17.13**		**1.6**	**41.85**		**-0.8**	**1.12**	**2.1**
beclomethasone/formoterol	2.52	14.7	6.8	4.0	9.5	10.0	1.73	-3.2
fluticasone furoate/vilanterol	2.37	13.8	10.0	3.7	8.9	9.7	1.74	0.0
salmeterol/fluticasone	1.73	10.1	-5.2	2.7	6.5	-3.7	1.74	-1.8
budesonide/formoterol	1.46	8.5	7.6	2.1	5.0	8.0	1.91	-0.7
tiotropium	1.30	7.6	-2.3	2.3	5.6	-3.3	1.53	0.8
humeclidinium	0.80	4.7	24.8	1.4	3.3	21.5	1.59	2.4
aclidinium	0.67	3.9	-1.4	1.1	2.7	-1.6	1.61	0.0
beclomethasone	0.50	2.9	-26.8	1.4	3.3	-26.5	0.99	-0.7
montelukast	0.49	2.9	3.8	2.2	5.2	5.7	0.63	-2.1
glycopyrronium	0.48	2.8	-4.8	0.9	2.1	-5.1	1.51	0.0

Continued

Table 3.10.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
J - General antimicrobials for sistemic use	**9.94**		**-21.3**	**12.94**		**-22.9**	**2.10**	**1.9**
amoxicillin/clavulanic acid	2.15	21.6	-26.0	4.3	33.5	-25.5	1.35	-0.8
ceftriaxone	0.93	9.3	-27.9	0.2	1.7	-28.7	11.87	0.8
azithromicyn	0.71	7.1	2.6	1.3	10.2	2.7	1.47	-0.3
fluconazole	0.69	7.0	-12.9	0.3	2.6	-13.4	5.57	0.3
cefixime	0.69	6.9	-28.6	0.8	6.3	-28.6	2.33	-0.3
fosfomycin	0.62	6.3	-3.7	0.4	2.8	-4.6	4.62	0.7
ciprofloxacin	0.58	5.8	-13.9	0.6	4.8	-13.7	2.57	-0.4
clarithromycin	0.46	4.7	-35.7	1.4	11.0	-33.9	0.89	-3.0
levofloxacin	0.40	4.0	-28.3	0.7	5.6	-28.9	1.49	0.6
human immunoglobulin antihepatitis B	0.35	3.5	-2.9	0.0	0.0	-4.2	313.47	1.0
B - Blood and blood-forming organs	**7.86**		**-1.3**	**87.7**		**-1.5**	**0.24**	**-0.1**
enoxaparin	1.90	24.2	6.6	2.3	2.6	12.4	2.26	-5.4
acetylsalicylic acid	1.17	14.9	0.9	44.3	50.6	0.3	0.07	0.4
clopidogrel	1.16	14.8	1.0	5.6	6.4	1.4	0.57	-0.7
edoxaban	0.49	6.2	9.0	0.3	0.3	8.7	4.53	0.1
folic acid	0.46	5.9	-4.7	6.0	6.8	-2.0	0.21	-3.0
clopidogrel/acetylsalicylic acid	0.24	3.1	1.1	0.8	0.9	5.0	0.83	-4.0
ferrous sulfate	0.24	3.0	-5.9	2.1	2.4	-6.2	0.31	0.0
nadroparin calcium	0.24	3.0	-38.8	0.2	0.3	-38.8	2.91	-0.3
G - Genito-urinary system and sex	**5.42**		**-6.9**	**42.0**		**-0.5**	**0.3**	**-6.7**
tamsulosin	1.10	20.3	1.4	10.6	25.1	2.1	0.28	-1.0
dutasteride	1.06	19.5	1.1	8.4	19.9	1.9	0.35	-1.0
alfuzosin	0.86	16.0	5.0	9.1	21.7	4.7	0.26	0.0
silodosin	0.70	12.9	-35.0	5.4	12.8	-6.7	0.36	-30.6
finasteride	0.55	10.1	-0.7	2.5	6.0	-0.8	0.59	-0.1
M - Musculo-skeletal system	**5.02**		**-8.4**	**36.38**		**-3.5**	**0.38**	**-5.3**
alendronic acid	0.76	15.2	1.2	4.0	10.9	3.2	0.53	-2.2
diclofenac	0.57	11.3	-2.4	3.8	10.6	-3.0	0.40	0.4
etoricoxib	0.53	10.6	-1.7	3.1	8.6	-1.6	0.46	-0.4
febuxostat	0.48	9.6	-34.3	2.0	5.4	-6.7	0.67	-29.7
alendronic acid/cholecalciferol	0.44	8.8	-6.7	2.1	5.7	-6.9	0.58	0.0
risedronic acid	0.38	7.5	-3.8	2.1	5.9	-3.6	0.48	-0.5
allopurinol	0.35	6.9	4.2	8.2	22.7	3.5	0.12	0.5
ketoprofen	0.27	5.4	-13.9	2.6	7.2	-13.3	0.28	-1.0
L- Antineoplastic and immunomodulatory	**4.3**		**2.3**	**6.35**		**1.8**	**1.85**	**0.3**
letrozole	1.37	31.8	8.1	1.7	26.0	8.1	2.26	-0.3
methotrexate	0.67	15.6	4.3	1.3	20.6	3.2	1.40	0.8
ciclosporin	0.52	12.2	-8.3	0.2	2.7	-8.8	8.25	0.3

Table 3.10.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
exemestane	0.41	9.6	9.7	0.5	8.0	9.7	2.23	-0.3
anastrozole	0.40	9.3	-2.0	0.8	12.5	-1.8	1.37	-0.5
H - Systemic hormonal preparations, excluding sex	**3.93**		**-0.05**	**35.87**		**0.00**	**0.30**	**-0.06**
levothyroxine	1.13	28.7	7.8	21.3	59.4	1.4	0.14	6.1
teriparatide	1.06	26.9	-14.9	0.2	0.5	-8.6	16.75	-7.1
prednisone	0.66	16.9	1.0	6.5	18.2	1.0	0.28	-0.3
betamethasone	0.27	6.8	-17.7	1.7	4.9	-17.9	0.42	0.0
methylprednisolone	0.19	4.9	0.2	2.9	8.2	0.8	0.18	-0.9
S - Sensory organs	**3.89**		**-1.1**	**20.81**		**-0.4**	**0.51**	**-0.9**
tafluprost	0.48	12.3	7.1	1.5	7.3	6.8	0.86	0.0
timolol/bimatoprost	0.44	11.4	-1.7	1.4	6.8	-1.5	0.85	-0.5
bimatoprost	0.41	10.5	-12.1	1.8	8.9	-3.0	0.60	-9.6
timolol/brinzolamide	0.40	10.2	-7.8	1.7	8.0	-4.5	0.65	-3.7
timolol	0.35	9.1	2.6	3.1	14.8	-0.3	0.31	2.6
dorzolamide/timolol	0.33	8.4	12.1	2.3	11.1	11.6	0.39	0.2
tafluprost/timolol	0.23	5.9	18.5	0.6	3.1	18.2	0.96	0.0
travoprost	0.22	5.5	1.2	1.0	5.0	-0.1	0.56	1.1
latanoprost	0.18	4.5	-6.1	1.3	6.2	-6.3	0.37	-0.1
D - Dermatologicals	**1.25**		**-4.0**	**4.6**		**0.6**	**0.74**	**-4.9**
calcipotriol/betamethasone	0.81	64.5	0.2	2.3	49.4	-4.9	0.97	5.0
isotretinoin	0.09	7.1	17.3	0.2	3.8	18.9	1.39	-1.6
clobetasol	0.07	5.4	19.2	0.8	17.6	39.1	0.23	-14.6
diclofenac	0.05	4.4	-32.0	0.1	1.1	-20.7	2.99	-14.5
terbinafine	0.05	3.9	-18.6	0.1	2.0	-18.8	1.41	-0.1
P - Antiparasitic, insecticide and repellent	**0.22**		**-4.2**	**1.00**		**7.1**	**0.60**	**-10.9**
hydroxychloroquine	0.17	76.3	11.4	0.9	87.4	11.2	0.52	-0.2
mebendazole	0.02	9.0	-8.1	0.1	8.4	-8.3	0.64	-0.1
metronidazole	0.01	4.6	-12.9	0.0	2.7	-13.1	1.03	0.0
mefloquine	0.01	4.5	-67.1	0.0	0.2	-67.2	13.27	0.0
tinidazole	0.00	2.0	-28.4	0.0	0.4	-28.6	2.71	0.0
V - Miscellaneous	**0.14**		**-4.6**	**0.10**		**-3.5**	**3.73**	**-1.3**
sevelamer	0.05	37.9	3.0	0.0	26.1	2.7	5.42	0.0
polystyrene sulphonate	0.04	30.8	-4.0	0.0	41.2	-4.1	2.79	-0.1
sucroferric oxidroxide	0.02	11.8	-10.0	0.0	5.2	-10.3	8.44	0.0
calcium acetate/magnesium carbonate	0.01	4.9	-4.6	0.0	18.0	-4.9	1.02	0.0
deferoxamine	0.01	4.3	-17.7	0.0	0.8	-18.1	19.66	0.1

Table 3.11. First thirty active ingredients in terms of expenditure under approved care regime (class A-NHS): comparison 2020-2019

ATC	Active ingredient	Expend. *(million)*	%*	Gross per capita exp.	Rank 2020	Rank 2019	Average DDD	Δ % 20-19
C	atorvastatin	268.1	2.8	4.50	1	3	0.25	-0.6
A	pantoprazole	253.8	2.6	4.26	2	2	0.46	-12.4
A	cholecalciferol	201.4	2.1	3.38	3	1	0.95	-2.7
C	bisoprolol	155.2	1.6	2.60	4	6	0.60	0.2
R	beclomethasone/formoterol	150.3	1.5	2.52	5	8	1.73	-3.2
A	lansoprazole	143.0	1.5	2.40	6	5	0.47	-5.4
R	fluticasone furoate/vilanterol	141.1	1.5	2.37	7	10	1.74	0.0
A	omeprazole	135.0	1.4	2.26	8	7	0.36	-8.7
A	esomeprazole	130.8	1.3	2.19	9	9	0.42	-8.2
J	amoxicillin/clavulanic acid	127.9	1.3	2.15	10	4	1.35	-0.8
C	ramipril	120.4	1.2	2.02	11	11	0.09	-1.4
A	mesalazine	118.7	1.2	1.99	12	13	1.08	-0.5
C	omega 3	115.2	1.2	1.93	13	12	1.18	-1.1
B	enoxaparin	113.6	1.2	1.90	14	15	2.26	-5.4
R	salmeterol/fluticasone	103.4	1.1	1.73	15	14	1.74	-1.8
C	olmesartan	98.5	1.0	1.65	16	21	0.31	-0.9
C	amlodipine	97.0	1.0	1.63	17	17	0.16	-0.4
N	levetiracetam	95.5	1.0	1.60	18	19	2.03	-0.9
A	metformin	93.5	1.0	1.57	19	20	0.19	1.1
A	insulin lispro	92.8	1.0	1.56	20	16	1.25	-2.5
C	simvastatin	91.2	0.9	1.53	21	18	0.33	0.0
C	nebivolol	89.4	0.9	1.50	22	23	0.25	-0.5
A	insulin aspart	88.9	0.9	1.49	23	22	1.40	0.7
R	budesonide/formoterol	87.0	0.9	1.46	24	26	1.91	-0.7
C	ezetimibe	83.1	0.9	1.39	25	33	0.74	-2.2
L	letrozole	81.6	0.8	1.37	26	29	2.26	-0.3
N	fentanyl	81.4	0.8	1.37	27	25	5.76	0.7
A	rifaximin	80.7	0.8	1.35	28	24	2.08	0.0
C	rosuvastatin	80.3	0.8	1.35	29	30	0.26	-1.1
R	tiotropium	77.5	0.8	1.30	30	27	1.53	0.8
	Total	**3596.3**	**37.0**					
	Total expenditure A-NHS	**9722.0**						

* Calculated on overall expenditure under approved care regime

Table 3.12. 2020 regional ranks of the first 30 active ingredients under approved care regime (class A-NHS)

Rank	Active ingredi	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Calabria	Sicily	Sardinia
1	atorvastatin	2	5	4	2	3	1	1	2	1	1	2	1	2	2	3	3	1	2	1	1	1
2	pantoprazole	1	1	2	1	6	3	2	1	2	2	1	2	1	1	4	1	2	1	3	4	5
3	cholecalciferol	4	2	3	5	2	7	4	4	6	18	4	5	4	3	2	2	3	3	5	3	8
4	bisoprolol	6	11	10	7	7	6	6	6	5	6	9	4	7	5	5	8	5	4	4	5	11
5	beclomethasone/ formoterol	3	4	8	4	5	5	8	5	7	3	5	9	9	18	21	10	12	9	17	16	4
6	lansoprazole	22	7	30	57	1	2	7	3	3	8	20	6	8	8	1	13	4	7	18	8	2
7	futicasone furoate/vilanterol	5	6	9	33	10	8	10	7	12	4	6	3	11	7	10	9	9	13	10	7	9
8	omeprazole	14	26	11	77	27	21	35	15	31	16	10	52	14	11	6	4	16	6	2	2	3
9	esomeprazole	7	3	7	9	4	12	15	9	14	25	11	22	15	6	14	5	13	5	8	24	13
10	amoxicillin/ clavulanic acid	8	15	13	19	8	17	17	13	11	9	7	7	10	9	8	6	6	12	9	6	15
11	ramipril	10	12	20	10	12	4	5	18	4	5	3	23	13	19	23	20	24	19	20	17	20
12	mesalazine	9	16	22	20	14	9	14	8	8	7	12	8	12	17	26	18	8	11	14	10	22
13	omega 3	35	13	26	65	25	19	25	20	19	30	13	12	5	13	18	7	7	20	7	14	10
14	enoxaparin	246	234	1	3	423	229	9	296	271	313	306	551	3	12	160	11	14	167	28	11	207
15	salmeterol/ fluticasone	18	14	12	11	11	10	12	14	13	12	26	17	17	22	25	25	26	17	22	18	12
16	olmesartan	36	19	27	21	23	24	23	10	32	38	18	21	21	15	9	15	11	14	13	9	18
17	amlodipine	16	29	21	30	18	15	13	24	9	11	8	11	25	29	24	24	31	35	32	26	34
18	levetiracetam	12	18	17	6	13	11	11	11	186	349	17	10	18	10	28	17	21	15	16	19	21
19	metformin	21	20	38	40	29	22	24	36	22	15	23	26	20	20	20	27	15	18	19	12	30
20	insulin lispro	31	21	28	41	33	14	30	50	231	10	14	42	46	26	15	16	17	8	11	13	6
21	simvastatin	29	35	32	17	20	18	26	42	10	14	22	14	27	37	19	30	19	24	33	20	32
22	nebivolol	17	27	36	55	43	23	28	23	23	22	16	13	31	25	16	19	18	21	24	21	36
23	insulin aspart	13	23	39	18	28	37	32	33	244	31	15	28	16	21	31	14	35	33	15	15	7
24	budesonide /formotero	32	28	24	12	15	13	27	19	15	20	52	31	34	41	32	23	32	28	37	31	17
25	ezetimibe	30	36	33	38	32	20	16	22	16	26	27	20	23	32	27	32	57	54	38	25	25
26	letrozole	11	32	18	13	9	16	22	12	210	279	32	15	33	23	11	28	27	23	34	28	24
27	fentanyl	27	25	29	29	22	31	3	17	37	21	61	29	35	16	7	45	36	52	31	27	14
28	rifaximin	19	30	46	155	49	34	51	32	17	24	29	19	24	36	51	22	22	16	26	49	23
29	rosuvastatin	26	39	23	24	21	30	21	37	21	33	35	25	30	34	37	37	33	25	30	58	19
30	tiotropium	15	8	34	15	24	36	19	29	28	17	54	48	29	54	85	26	37	37	40	46	41

Table 3.13. First thirty active ingredients* with higher variation in expenditure under approved care regime compared to the previous year: comparison 2020-2019

ATC	Active ingredient	Per capita exp.	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19	Average DDD cost	Δ % 20-19
C	ezetimibe/rosuvastatin	0.78	107.6	3.3	142.4	0.65	-14.6
A	dulaglutide	0.62	36.1	0.4	32.8	4.72	2.2
C	perindopril/indapamide/ amlodipine	0.62	31.7	3.6	31.4	0.47	0.0
R	humeclidinium	0.80	24.8	1.4	21.5	1.59	2.4
C	ezetimibe	1.39	14.6	5.1	16.9	0.74	-2.2
N	lacosamide	0.61	14.6	0.3	14.3	5.38	0.0
N	vortioxetine	0.64	12.6	1.5	12.3	1.14	0.0
C	olmesartan/amlodipine	1.17	12.4	7.9	14.8	0.40	-2.4
R	fluticasone furoate/vilanterol	2.37	10.0	3.7	9.7	1.74	0.0
A	ursodeoxycholic acid	0.79	9.2	2.4	4.1	0.89	4.6
C	olmesartan	1.65	9.2	14.4	9.9	0.31	-0.9
B	edoxaban	0.49	9.0	0.3	8.7	4.53	0.1
L	letrozole	1.37	8.1	1.7	8.1	2.26	-0.3
H	levothyroxine	1.13	7.8	21.3	1.4	0.14	6.1
R	budesonide/formoterol	1.46	7.6	2.1	8.0	1.91	-0.7
N	pregabalin	1.23	7.5	2.2	7.1	1.53	0.1
C	rosuvastatin	1.35	6.8	14.0	7.7	0.26	-1.1
R	beclomethasone/formoterol	2.52	6.8	4.0	10.0	1.73	-3.2
B	enoxaparin	1.90	6.6	2.3	12.4	2.26	-5.4
C	olmesartan/ hydrochlorothiazide	1.16	5.9	9.5	5.6	0.33	0.0
C	flecainide	0.86	5.9	2.9	6.3	0.82	-0.6
C	bisoprolol	2.60	5.7	11.8	5.1	0.60	0.2
C	ezetimibe/simvastatin	1.18	5.3	4.8	5.5	0.66	-0.5
N	quetiapine	0.57	5.2	0.4	3.5	3.47	1.4
G	alfuzosin	0.86	5.0	9.1	4.7	0.26	0.0
A	mesalazine	1.99	4.7	5.0	4.9	1.08	-0.5
C	atorvastatin	4.50	4.5	48.8	4.8	0.25	-0.6
N	sertraline	0.77	4.4	8.3	3.7	0.25	0.4
L	methotrexate	0.67	4.3	1.3	3.2	1.40	0.8
R	montelukast	0.49	3.8	2.2	5.7	0.63	-2.1

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

Table 3.14. First thirty active ingredients by consumption under approved care regime (class A-NHS): comparison 2020-2019

ATC	Active ingredient	DDD/1000 inhab. per day	%*	Rank 2020	Rank 2019	Average DDD	Δ % 20-19
C	ramipril	62.9	6.3	1	1	0.09	-1.4
C	atorvastatin	48.8	4.9	2	2	0.25	-0.6
B	acetylsalicylic acid	44.3	4.5	3	3	0.07	0.4
C	amlodipine	28.0	2.8	4	4	0.16	-0.4
A	pantoprazole	25.3	2.6	5	6	0.46	-12.4
C	furosemide	24.8	2.5	6	5	0.08	0.3
A	metformin	22.4	2.3	7	7	0.19	1.1
H	levothyroxine	21.3	2.1	8	8	0.14	6.1
A	omeprazole	17.2	1.7	9	9	0.36	-8.7
C	nebivolol	16.1	1.6	10	10	0.25	-0.5
C	olmesartan	14.4	1.4	11	15	0.31	-0.9
A	esomeprazole	14.2	1.4	12	12	0.42	-8.2
A	lansoprazole	14.1	1.4	13	11	0.47	-5.4
C	rosuvastatin	14.0	1.4	14	16	0.26	-1.1
C	simvastatin	12.8	1.3	15	13	0.33	0
C	bisoprolol	11.8	1.2	16	17	0.6	0.2
G	tamsulosin	10.6	1.1	17	18	0.28	-1
C	valsartan	10.0	1.0	18	19	0.19	-1.4
A	cholecalciferol	9.7	1.0	19	14	0.95	-2.7
C	lercanidipine	9.6	1.0	20	21	0.22	0
B	cyanocobalamin	9.6	1.0	21	20	0.02	0.2
C	olmesartan/ hydrochlorothiazide	9.5	1.0	22	23	0.33	0
G	alfuzosin	9.1	0.9	23	27	0.26	0
C	telmisartan	9.0	0.9	24	22	0.17	1.3
C	candesartan	8.9	0.9	25	25	0.15	0
C	irbesartan	8.5	0.9	26	26	0.22	0.1
C	enalapril	8.4	0.8	27	24	0.15	-1.5
G	dutasteride	8.4	0.8	28	28	0.35	-1
N	sertraline	8.3	0.8	29	30	0.25	0.4
M	allopurinol	8.2	0.8	30	31	0.12	0.5
	Total	**520.1**	**52.4**				
	Total DDD class A-NHS	**993.1**					

*calculated on overall expenditure under approved care regime

Table 3.15. 2020 regional ranks of the first 30 active ingredients by consumption under approved care regime (class A-NHS)

Rank	Active ingredient	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Calabria	Sicily	Sardinia
1	ramipril	1	1	1	1	1	1	1	1	1	1	1	3	1	2	2	1	3	3	2	1	3
2	atorvastatin	3	3	2	2	3	2	2	2	3	2	3	2	3	3	3	2	2	2	3	2	2
3	acetylsalicylic acid	2	2	5	3	2	5	3	4	2	3	2	1	2	1	1	3	1	1	1	3	1
4	amlodipine	4	7	3	6	7	4	4	5	4	4	5	4	6	4	7	6	8	8	8	7	7
5	pantoprazole	6	4	4	4	11	9	8	3	8	9	6	6	4	8	10	4	6	6	7	10	10
6	furosemide	5	8	6	7	4	3	5	10	6	5	4	5	7	5	4	12	4	7	6	6	4
7	metformin	7	5	7	10	9	7	7	8	7	7	8	8	8	6	8	7	5	4	5	5	9
8	levothyroxine	8	9	12	5	6	8	6	20	5	8	7	7	5	7	5	11	7	5	9	9	5
9	omeprazole	13	18	10	61	19	19	25	13	29	16	10	35	10	9	9	5	15	9	4	4	6
10	nebivolol	9	11	11	25	18	10	11	9	14	10	9	9	12	10	11	9	9	10	11	11	14
11	olmesartan	22	13	13	13	14	18	13	7	26	23	11	13	11	12	12	10	10	11	10	8	12
12	esomeprazole	12	6	8	15	8	16	15	12	20	26	17	22	17	11	20	8	17	12	12	18	13
13	lansoprazole	28	12	24	57	5	6	12	6	9	17	31	14	9	13	6	15	11	15	19	14	8
14	rosuvastatin	10	17	9	9	10	13	9	15	15	18	20	10	13	16	22	16	16	14	14	23	11
15	simvastatin	18	21	14	11	13	14	14	27	11	12	15	12	18	19	14	17	13	18	21	13	17
16	bisoprolol	21	26	16	12	12	12	10	11	12	19	25	15	20	17	17	19	20	25	17	16	20
17	tamsulosin	11	14	18	14	20	22	16	14	16	15	12	17	24	23	19	25	29	24	26	26	18
18	valsartan	27	25	19	30	28	30	22	28	13	11	16	18	26	22	30	27	24	13	20	17	33
19	cholecalciferol	25	15	17	17	17	17	17	21	24	31	33	36	29	26	26	14	25	27	41	36	16
20	lercanidipine	16	10	21	8	32	11	23	30	19	29	23	19	23	28	28	23	37	49	32	24	32
21	cyanocobalamin	20	29	25	88	45	57	32	33	10	6	13	39	22	31	45	34	30	33	16	45	39
22	olmesartan/hydrochlorothiazide	37	20	28	20	23	24	26	17	43	44	39	23	27	18	23	13	14	16	13	21	15
23	alfuzosin	42	55	33	79	36	26	46	26	32	34	52	20	19	20	34	18	18	20	23	12	21
24	telmisartan	19	37	26	27	16	35	21	31	34	36	14	31	15	25	21	26	28	36	18	25	22
25	candesartan	29	73	35	18	41	36	27	18	31	24	24	21	25	21	13	24	12	28	27	19	23
26	ibesartan	36	27	30	58	66	44	39	22	35	30	21	30	16	34	15	29	27	29	28	15	49
27	enalapril	15	22	15	53	35	25	19	44	33	21	34	62	39	49	38	32	62	45	45	20	61
28	dutasteride	33	35	27	33	24	23	28	23	37	32	19	16	28	27	31	31	23	21	30	30	28
29	sertraline	17	30	23	21	21	21	35	19	17	14	26	27	45	30	44	61	52	51	33	47	25
30	Allopurinol	23	23	43	32	33	34	29	37	21	20	18	11	32	15	16	36	22	22	29	34	30

Table 3.16 Consumption, price and mix effects on the variation of pharmaceutical expenditure for medicines provided by public health facilities: comparison 2020-2019 (any ATC category includes the therapeutic subgroups in decreasing order of expenditure, up to the value of 0.10 euros per capita expenditure)

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
TOTAL	**222.87**	**170.3**	**0.6**	**1.5**	**-6.2**	**5.5**	**-0.9**
L - Antineoplastic and immunomodulating agents	**102.88**	**10.6**	**6.0**	**3.8**	**-6.6**	**9.4**	**2.2**
Monoclonal antibodies	25.71	1.1	-2.4	-2.0	-13.7	15.4	-0.4
Selective immunosuppressants	13.47	1.3	11.4	11.9	-1.5	1.1	-0.4
Other immunosuppressants	9.84	0.5	16.4	5.2	1.0	9.5	10.7
Interleukin inhibitors	7.19	0.7	22.4	24.0	-2.9	1.6	-1.3
Tumor necrosis factor alpha inhibitors (TNF-alpha)	5.82	1.4	-16.8	5.8	-10.2	-12.4	-21.4
Other kinase protein inhibitors	4.06	0.1	16.1	17.6	-1.6	0.3	-1.3
BCR-ABL tyrosine kinase inhibitors	3.51	0.2	-3.2	4.0	-1.2	-5.9	-7.0
Cyclin-dependent kinase inhibitors (CDK)	3.42	0.1	33.7	32.5	2.3	-1.3	0.9
Bruton tyrosine kinase (BTK) inhibitors	2.86	0.1	29.1	29.3	-0.2	0.0	-0.2
Epidermal growth factor receptor (EGFR) tyrosine kinase inhib.	2.14	0.1	42.7	18.1	-18.3	48.4	20.9
Other hormone antagonists and related substances	1.94	0.1	3.2	3.7	-1.7	1.2	-0.5
Interferons	1.93	0.4	-3.4	-4.2	-0.3	1.2	0.8
Other antineoplastics	1.92	0.1	37.0	15.0	-5.2	25.7	19.1
Gonadotropin-releasing hormone analogues (GnRH)	1.89	1.1	1.1	5.3	-2.5	-1.5	-4.0
Antiandrogens	1.86	0.6	22.7	-11.0	0.3	37.4	37.9
Janus kinase (JAK) inhibitors	1.61	0.0	16.3	15.2	-0.1	1.0	0.9
Pyrimidine analogues	1.53	0.4	-6.0	0.9	-6.9	0.1	-6.8
Anaplastic lymphoma kinase inhibitors (ALK)	1.24	0.0	30.6	26.1	0.7	2.8	3.5
Serine-threonine kinase B-RAF (BRAF) inhibitors	1.24	0.0	24.7	66.4	-24.0	-1.3	-25.0
Folic acid analogues	1.04	0.1	7.8	-3.1	0.1	11.2	11.3
Proteasome inhibitors	0.98	0.0	-27.4	5.0	-33.1	3.4	-30.9
Calcineurin inhibitors	0.92	0.4	3.5	7.1	-1.6	-1.8	-3.4
Taxanes	0.74	0.2	-10.8	-4.7	-11.4	5.4	-6.4
Other immunostimulating agents	0.69	0.1	-21.0	-5.1	-18.1	1.7	-16.8
Mitogen-activated protein kinase (MEK) inhibitors	0.67	0.0	32.3	86.5	-24.4	-6.2	-29.1
Antiestrogens	0.56	0.3	-15.4	-2.5	-11.5	-1.9	-13.2
Poly (ADP-RIBOSE) polymerase (PARP) inhibitors	0.55	0.0	42.2	91.3	-2.3	-23.9	-25.7
Colony stimulating factors	0.53	0.1	-20.9	6.8	-0.9	-25.3	-25.9
Anthracyclines and related substances	0.49	0.1	4.3	-0.7	0.9	4.1	5.0

Continued

Table 3.16
continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Rapamycin and mammalian target of rapamycin (MTOR) inhibitors	0.49	0.0	-9.2	3.4	-2.1	-10.3	-12.1
Hedgehog pathway inhibitors	0.38	0.0	-7.3	2.9	-0.2	-9.7	-9.9
Other alkaloids derived from plants and other natural products	0.34	0.0	4.7	4.5	0.1	0.1	0.2
Vinca alkaloids and analogues	0.21	0.0	-19.6	-3.1	-0.9	-16.4	-17.1
Phosphatidylinositol-3-kinase (PI3k) inhibitors	0.16	0.0	-10.9	-13.0	0.4	1.9	2.4
Epidermal growth factor receptor 2 tyrosine kinase inhibitors (HER2)	0.14	0.0	-4.5	-4.4	-0.1	0.0	-0.1
Antineoplastics in combination	0.14	0.0	251.1	269.7	-5.0	0.0	-5.0
Nitrogen mustard analogues	0.12	0.1	-14.3	-9.7	-0.5	-4.6	-5.1
Platinum compounds	0.10	0.2	8.1	-6.3	6.2	7.8	15.3
J- General antimicrobials for systemic use	**34.77**	**6.3**	**-21.4**	**-0.7**	**-11.8**	**-10.3**	**-20.9**
Antivirals for treatment of HIV infections, combinations	8.05	1.4	6.3	4.3	-0.6	2.6	1.9
Antivirals for treatment of HCV infections	5.13	0.1	-67.7	-56.6	-29.0	4.8	-25.6
Pneumococcal vaccines	2.26	0.1	26.6	30.3	-2.0	-0.9	-2.8
Integrase inhibitors	2.12	0.4	-3.4	-3.7	0.0	0.4	0.3
Human normal immunoglobulin	2.12	0.0	17.4	9.7	1.9	5.0	7.1
Meningococcal vaccines	2.05	0.1	-11.6	-9.7	-0.2	-1.9	-2.1
Influenza vaccines	1.54	0.7	40.2	28.8	1.7	7.0	8.8
Human papillomavirus vaccines	0.97	0.0	-11.0	-11.6	-0.4	1.0	0.6
Bacterial and viral vaccines in combination	0.96	0.1	-8.9	-8.3	-11.7	12.5	-0.6
Antivirals for systemic use	0.87	0.0	0.0	0.0	0.0	0.0	0.0
Specific immunoglobulins	0.70	0.0	-5.3	-13.9	-4.4	15.0	9.9
Penicillin combinations, including betalactamase inhibitors	0.64	0.5	-2.5	-19.2	1.2	19.1	20.8
Triazole derivatives	0.63	0.1	-2.9	-8.4	-2.6	8.9	6.0
Third generation cephalosporins	0.59	0.3	25.3	0.2	-2.6	28.3	25.0
Antibiotics	0.55	0.0	4.0	4.1	-0.1	0.0	-0.1
Measles vaccines	0.53	0.0	-13.5	-20.3	-1.3	9.9	8.5
Other antibacterials	0.45	0.1	-16.3	8.2	-19.5	-3.8	-22.6
Other antifungals for systemic use	0.44	0.0	-22.0	17.1	-7.6	-27.9	-33.4
Other antivirals	0.42	0.0	42.6	6.0	-3.3	39.0	34.5
Other cephalosporins and penems	0.42	0.0	64.9	74.6	-0.3	-5.3	-5.5
Nucleosides and nucleotides inhibitors of reverse transcriptase	0.36	0.8	-23.6	0.7	-4.3	-20.7	-24.1
Varicella Zoster virus vaccines	0.30	0.0	-27.5	-22.2	-1.6	-5.3	-6.8
Rotavirus diarrhea vaccines	0.30	0.0	-4.0	-1.7	-2.3	-0.1	-2.4
Glycopeptide antibacterials	0.29	0.0	-16.0	-6.1	-3.2	-7.6	-10.5
Carbapenems	0.25	0.1	2.1	15.5	-3.6	-8.3	-11.6

Continued

Table 3.16
continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Non-nucleosides inhibitors of reverse transcriptase	0.23	0.1	-22.5	-17.1	-1.5	-5.0	-6.5
Polymyxins	0.22	0.0	7.9	9.0	-0.2	-0.8	-1.0
Protease inhibitors	0.20	0.1	-50.8	26.5	-7.9	-57.8	-61.1
Fluoroquinolones	0.12	0.2	-3.2	-20.3	0.4	21.3	21.3
Pertussis vaccines	0.12	0.0	-16.8	-13.8	-2.7	-0.8	-3.5
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.11	0.1	-18.2	-4.1	2.4	-16.7	-14.7
Other aminoglycosides	0.10	0.0	-32.5	1.4	-53.9	44.3	-33.4
Tetracyclines	0.10	0.0	-34.3	16.3	-33.4	-15.2	-43.5
B- Blood and blood-forming organs	**30.78**	**49.0**	**7.8**	**2.5**	**-2.8**	**8.2**	**5.3**
Coagulation factors	8.18	0.1	-2.0	-1.5	-5.6	5.3	-0.6
Direct Xa factor inhibitors	7.09	10.8	16.0	20.4	-4.2	0.6	-3.7
Other antianemic preparations	2.79	3.6	-8.9	1.2	-5.5	-4.8	-10.0
Platelet aggregation inhibitors, excl. heparin	2.41	9.3	-0.5	-2.3	-3.3	5.4	1.8
Heparins	1.91	7.2	31.9	8.2	22.8	-0.8	21.9
Other hemostatics for systemic use	1.88	0.1	50.0	26.0	-10.1	32.5	19.1
Direct thrombin inhibitors	1.49	2.5	4.4	7.1	-3.1	0.7	-2.5
Solutions influencing the electrolyte balance	0.91	6.7	-0.6	-11.7	6.6	5.6	12.5
Parenteral nutritional solutions	0.82	0.7	16.1	1.3	0.3	14.3	14.7
Hypertonic solutions	0.52	0.1	76.7	56.8	4.5	7.9	12.7
Other antithrombotics	0.51	0.4	38.0	-5.8	0.2	46.3	46.5
Medicines used in hereditary angioedema	0.40	0.0	1.2	27.2	-5.0	-16.3	-20.5
Local hemostatics	0.32	0.0	-12.1	-12.2	-3.1	3.3	0.1
Iron, parenteral preparations	0.32	0.1	-1.3	-0.9	-0.4	-0.1	-0.5
Enzymes	0.27	0.0	1.6	4.0	-1.8	-0.5	-2.3
Blood substitutes and plasma protein fractions	0.24	0.0	-3.5	-7.9	-0.1	4.9	4.8
Protease inhibitors	0.24	0.0	6.7	-7.4	-1.1	16.5	15.2
Isotonic solutions	0.18	0.1	63.4	43.5	-3.7	18.2	13.9
Hemofiltrates	0.10	0.0	32.4	26.1	-7.8	13.9	5.0
A - Alimentary tract and metabolism	**17.04**	**30.4**	**9.0**	**4.0**	**-1.8**	**5.5**	**4.8**
Enzymes	4.85	0.0	-1.5	0.3	-0.9	-0.8	-1.8
Insulins and injectable analogues, long-acting	2.88	6.4	7.8	5.2	-0.8	3.2	2.4
GLP-1 (glucagon-like peptide-1) receptor analogues	2.48	2.5	32.7	23.4	-2.6	10.4	7.6
Oral hypoglycemic agents, in combination	2.01	5.2	0.5	2.0	-5.7	4.6	-1.4
Dipeptil Peptidase 4 Inhibitors (DPP-4)	1.31	3.0	7.5	8.5	-0.9	0.1	-0.9

Continued

Table 3.16
continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Various products for alimentary tract and metabolism	1.03	0.0	26.6	23.1	-2.2	5.2	2.9
SGLT2 cotransporter inhibitors (sodium-glucose type 2)	0.75	1.6	24.4	23.0	1.1	0.0	1.1
Proton pump inhibitors	0.21	3.7	89199.1	-3.6	-5.6	20.5	92565.5
Insulins and injectable analogues, fast-acting	0.20	0.9	1.0	8.2	-3.7	-3.1	-6.7
Antibiotics	0.17	0.3	8.6	1.0	-0.6	8.1	7.5
Bile acids and derivatives	0.17	0.1	-3.1	65.6	0.4	-41.7	-41.5
Polyvitamins, not in combination	0.17	0.1	46.4	30.5	12.2	0.0	12.2
Serotonin antagonists (5HT3)	0.15	0.1	-11.3	0.2	-0.9	-10.3	-11.5
Amino acids and derivatives	0.14	0.1	9.0	-1.2	-4.8	16.5	10.3
N- Central nervous system	**7.81**	**26.6**	**5.7**	**3.1**	**-2.1**	**4.9**	**2.6**
Other antipsychotics	2.84	2.6	2.3	3.9	-2.3	1.0	-1.6
Other medicines for the nervous system	0.54	0.1	45.3	-0.3	-0.2	46.1	45.8
DOPA and derivatives	0.54	0.3	5.7	-6.0	2.7	9.5	12.4
Other antiepileptics	0.53	1.2	23.5	18.6	2.2	1.9	4.1
Medicines used in opioid addiction	0.49	3.3	-7.3	0.4	-7.4	-0.3	-7.6
Diazepines, oxazepines, thiazepines and oxepins	0.40	3.6	-7.5	3.3	-1.3	-9.3	-10.4
Other general anesthetics	0.30	0.5	77.9	47.6	6.4	33.3	20.5
Other hypnotics and sedatives	0.21	0.0	42.8	220.7	-57.2	4.1	-55.5
Halogenated hydrocarbons	0.19	0.0	-23.4	-20.4	-2.3	-1.5	-3.8
Amides	0.16	1.8	-21.8	-10.3	-3.9	-9.3	-12.8
Anticholinesterases	0.15	1.0	-8.7	-7.5	-0.8	-0.6	-1.3
Other dopaminergic substances	0.11	0.1	10.5	10.4	2.1	-1.9	0.1
Anilides	0.10	2.9	6.6	17.5	28.2	-29.3	-9.3
C - Cardiovascular system	**5.87**	**17.4**	**13.2**	**-7.1**	**-3.7**	**26.4**	**21.8**
Other cardiac preparations	1.48	2.4	8.5	7.1	-1.5	2.9	1.3
Antihypertensives for pulmonary arterial hypertension	1.47	0.1	1.7	4.5	-3.7	1.1	-2.7
Other lipid modifying agents	1.17	0.4	27.7	10.8	-12.0	30.9	15.3
Angiotensin II receptor blockers (ARBs), other combinations	0.87	0.6	41.6	41.6	0.0	0.0	0.0
Vasopressin antagonists	0.18	0.0	11.8	23.3	-4.8	-4.8	-9.4
Other inotropic substances	0.14	0.0	3.4	4.5	-1.1	0.1	-1.1
Adrenergics and dopaminergics	0.12	0.8	19.3	10.3	0.5	7.6	8.1
V - Miscellaneous	**5.81**	**3.1**	**1.4**	**-2.8**	**0.9**	**3.4**	**4.4**
Iron chelating agents	1.58	0.1	0.7	2.0	0.0	-1.3	-1.2
Water-soluble, nephrotropic, low osmolar radiological contrast media	1.12	0.1	-6.8	-11.1	0.5	4.2	4.8
Antidotes	0.76	0.1	-5.5	-3.7	0.1	-2.1	-2.0

Continued

Table 3.16
continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Paramagnetic contrast agents	0.36	0.0	-5.0	-9.4	1.1	3.7	4.8
Other diagnostic radiopharmaceuticals for cancer detection	0.36	0.0	19.4	-0.8	12.1	7.4	20.3
Various therapeutic radiopharmaceuticals	0.31	0.0	190.8	73.9	6.8	56.6	67.3
Detoxifying substances for cytostatic treatments	0.24	0.2	2.5	-2.6	-7.5	13.8	5.3
Medicines for treatment of hyperkalaemia and hyperphosphatemia	0.23	0.2	-4.7	0.4	0.8	-5.8	-5.1
Various thyroid diagnostic	0.15	0.0	26.0	-2.9	-6.2	38.3	29.7
Iodine compounds - (123I)	0.12	0.0	-30.0	-30.1	-0.1	0.2	0.1
Allergenic extracts	0.11	0.2	22.4	17.6	1.9	2.1	4.1
Solvents and thinners, including cleaning solutions	0.10	2.2	2.9	-3.7	5.5	1.2	6.8
H - Systemic hormonal preparations, excluding sex	**4.79**	**5.5**	**-0.3**	**3.5**	**-3.2**	**-0.5**	**-3.7**
Somatostatin and analogues	1.64	0.2	5.3	5.7	-0.6	0.2	-0.4
Somatropin and somatropin agonists	1.36	0.3	-0.7	4.2	-4.6	-0.1	-4.8
Other antiparathyroid substances	0.79	0.4	-4.8	5.3	-6.9	-2.9	-9.5
Other hormones of the anterior pituitary lobe and analogues	0.44	0.0	4.0	4.0	-0.1	0.0	-0.1
Glycocorticoids	0.35	4.2	4.0	4.1	-0.6	0.4	-0.1
Parathyroid hormones and analogues	0.15	0.0	-32.9	-20.2	-8.7	-7.9	-15.8
R- Respiratory system	**4.76**	**2.1**	**21.4**	**-17.2**	**-0.5**	**47.3**	**46.7**
Other preparations for the respiratory	2.22	0.0	29.9	26.2	1.4	1.3	3.0
Other systemic drugs for obstructive airway disorders	1.92	0.2	23.9	23.7	-1.6	1.8	0.1
Mucolytics	0.27	0.2	12.2	-7.8	0.5	21.1	21.7
M - Musculo-skeletal system	**3.71**	**5.2**	**5.6**	**4.3**	**0.0**	**1.2**	**1.2**
Other drugs for musculoskeletal system disorders	1.85	0.0	-5.7	-35.0	-0.2	45.3	45.1
Other drugs acting on bone structure and mineralization	1.12	3.3	14.5	8.0	-3.4	9.8	6.1
Other quaternary ammonium compounds	0.35	0.4	458.6	233.5	114.5	-21.9	67.5
Other muscle relaxants with peripheral	0.19	0.0	-28.7	-26.6	-3.1	0.2	-2.9
S - Sensory organs	**2.14**	**2.2**	**-32.0**	**-19.9**	**-13.3**	**-2.1**	**-15.1**
Antineovascularisation substances	1.50	0.3	-37.1	-28.5	-16.7	5.6	-12.1
Corticosteroids, not in combination	0.37	0.2	-9.0	-13.5	4.2	1.0	5.2
Other ophthalmological drugs	0.10	0.1	-3.7	11.1	-7.5	-6.4	-13.4
D - Dermatologicals	**1.28**	**9.3**	**51.4**	**12.**	**0.0**	**34.**	**34.2**
Substances for dermatitis, excluding corticosteroids	0.86	0.1	89.0	73.6	-0.5	9.4	8.9
G - Genito-urinary system and sex hormones	**1.21**	**2.2**	**-22.0**	**-9.7**	**-2.5**	**-11.2**	**-13.5**
Gonadotropins	0.74	0.1	-24.3	-20.7	-2.8	-1.8	-4.6

Continued

Table 3.16
continued

Level I ATC Subgroups (level IV ATC)	Gross per capita expend	DDD/ 1000 inhab. per day	Δ % 20-19				Δ % average DDD cost
			Expenditure	DDD	Prices	Mix	
Medicines used in erectile dysfunctions	0.17	0.3	-17.3	5.7	-5.6	-17.1	-21.8
Prostaglandins	0.11	0.1	-10.2	-2.8	0.1	-7.6	-7.6
P - Antiparasitic, insecticide and repellent pharmaceuticals	**0.04**	**0.2**	**25.2**	**629.4**	**-3.2**	**-82.3**	**-82.8**

Table 3.17. 2020 expenditure and consumption of medicines supplied by public health facilities: most prescribed active ingredients by level I ATC (up to 75% of the category expenditure)

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
L - Antineoplastic and immunomodulating	**102.88**		**6.4**	**10.6**		**3.8**	**26.5**	**2.2**
lenalidomide	5.40	5.3	23.0	0.1	1.1	13.7	132.58	7.8
pembrolizumab	4.86	4.7	3.3	0.1	1.2	67.8	107.78	-38.6
nivolumab	3.77	3.7	-17.4	0.1	0.9	13.4	111.96	-27.4
daratumumab	3.54	3.4	35.4	0.1	0.5	35.0	186.5	0.0
ibrutinib	2.86	2.8	29.5	0.1	0.6	29.4	129.88	-0.2
pertuzumab	2.72	2.6	13.5	0.1	0.5	13.2	143.54	0.0
dimetilfumarate	2.49	2.4	11.3	0.2	2.0	11.9	32.86	-0.8
palbociclib	2.46	2.4	12.7	0.1	0.7	10.4	86.61	1.9
fingolimod	2.40	2.3	1.1	0.1	1.1	0.9	54.8	0.0
bevacizumab	2.35	2.3	-27.5	0.1	1.0	-15.2	63.43	-14.7
eculizumab	1.98	1.9	6.1	0.0	0.1	11.6	774.06	-5.2
secukinumab	1.88	1.8	9.0	0.2	1.5	8.8	31.67	-0.1
osimertinib	1.87	1.8	126.9	0.0	0.3	104.2	146.05	10.8
ustekinumab	1.85	1.8	8.4	0.3	2.5	12.6	18.97	-4.0
abiraterone	1.84	1.8	5.5	0.1	0.6	5.2	85.36	0.0
adalimumab	1.79	1.7	-20.1	0.5	5.2	12.9	8.93	-29.4
etanercept	1.77	1.7	-13.6	0.3	2.7	-0.5	16.88	-13.5
enzalutamide	1.74	1.7	19.3	0.1	0.5	19.0	85.65	0.0
natalizumab	1.69	1.6	8.7	0.1	0.8	9.5	56.38	-1.0
ruxolitinib	1.61	1.6	16.6	0.0	0.4	15.3	109.51	0.9
trastuzumab	1.56	1.5	-30.0	0.2	1.7	-13.7	23.9	-19.1
rituximab	1.37	1.3	-21.8	0.4	4.2	-14.1	8.37	-9.2
interferon beta 1a	1.36	1.3	-4.7	0.4	3.3	-4.6	10.57	-0.4
ocrelizumab	1.23	1.2	46.0	0.1	0.7	50.3	48.24	-3.1
nilotinib	1.21	1.2	-1.5	0.0	0.2	-1.7	131.34	-0.1
abatacept	1.14	1.1	3.9	0.1	0.6	2.6	49.23	1.0
nintedanib	1.12	1.1	22.2	0.0	0.4	19.0	75.81	2.4
dabrafenib	1.09	1.1	27.6	0.0	0.3	76.1	105.6	-27.7
golimumab	1.06	1.0	-12.4	0.1	1.2	2.8	23.29	-15
vedolizumab	1.04	1.0	12.5	0.1	0.8	24.8	32.65	-10.1
trastuzumab emtansine	1.03	1.0	12.9	0.0	0.1	12.6	210.87	0.0
pemetrexed	1.02	1.0	8.2	0.0	0.3	7.8	97.23	0.1
pirfenidone	1.02	1.0	8.0	0.0	0.4	7.8	64.46	-0.1
alectinib	1.00	1.0	46.3	0.0	0.1	44.6	175.14	0.9
leuproreline	0.99	1.0	-3.7	0.2	1.7	-3.6	14.67	-0.5
tocilizumab	0.98	0.9	23.2	0.1	1.0	28.2	25.59	-4.2
dasatinib	0.96	0.9	-11.8	0.0	0.2	-0.2	103.27	-11.9
teriflunomide	0.92	0.9	13.4	0.1	0.9	12.4	27.33	0.6
triptorelin	0.89	0.9	8.1	0.9	8.5	7.7	2.69	0.1

Continued

Table 3.17.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
ocrelizumab	0.87	0.9	29.7	0.0	0.2	48.0	142.33	-12.6
azacitidine	0.86	0.8	-9.3	0.0	0.1	5.6	301.11	-14.3
pomalidomide	0.85	0.8	10.5	0.0	0.1	14.2	296.78	-3.4
tacrolimus	0.84	0.8	4.7	0.4	3.4	8.5	6.36	-3.8
atezolizumab	0.80	0.8	17.6	0.0	0.2	42.7	121.47	-17.9
ribociclib	0.74	0.7	99.4	0.0	0.3	105.1	70.9	-3.1
imatinib	0.72	0.7	-4.7	0.1	0.9	3.0	21.61	-7.7
J - General antimicrobials for sistemic use	**34.77**		**-21.2**	**6.3**		**-0.6**	**15.11**	**-20.9**
sofosbuvir/velpatasvir	3.92	11.3	-68.8	0.0	0.4	-53.1	433.94	-33.7
thirteen-valent pneumococcal vaccine	2.10	6.0	26.1	0.1	1.9	28.3	48.5	-2.0
emtricitabine/rilpivirine /tenofovir alafenamide	1.74	5.0	0.4	0.2	3.8	0.1	19.96	0.0
B group meningococcal vaccine	1.63	4.7	-10.0	0.1	1.1	-10.1	62.7	-0.2
dolutegravir	1.52	4.4	-0.2	0.3	4.0	-0.4	16.42	0.0
dolutegravir/abacavir/ lamivudine	1.37	3.9	-4.8	0.2	2.8	-5.0	21.48	0.0
bictegravir/emtricitabine/ tenofovir alafenamide	1.34	3.8	606.1	0.2	2.9	604.2	19.96	0.0
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	0.97	2.8	-10.3	0.0	0.6	-10.6	69.43	0.1
inactivated, split virus tetravalent influenza vaccine	0.89	2.6	27.1	0.4	6.2	24.8	6.22	1.6
remdesivir	0.87	2.5	–	0.0	0.1	–	379.5	–
cobicistat/darunavir/e mtricitabine/tenofovir alafenamide	0.85	2.4	45.4	0.1	1.7	45.0	21.85	0.0
glecaprevir/pibrentasvir	0.84	2.4	-59.7	0.0	0.3	-57.7	113.59	-5.0
human immunoglobulin intravenous use	0.84	2.4	15.8	0.0	0.1	0.8	318.81	14.6
human immunoglobulin intravenous use	0.84	2.4	17.5	0.0	0.1	14.6	289.79	2.2
emtricitabine/tenofovir alafenamide	0.68	2.0	-25.2	0.2	2.6	-23.9	11.29	-1.9
diphtheria/recombinant hepatitis b/haemophilus influenzae b conjugate and adjuvanted/acellular pertussis/inactivated poliomyelitis/tetanus vacicne	0.68	2.0	-5.1	0.1	0.9	-2.7	32.57	-2.7
raltegravir	0.60	1.7	-9.8	0.2	2.7	-8.1	9.55	-2.1
elvitegravir/cobicistat/ emtricitabine/ tenofovir alafenamide	0.57	1.6	-58.1	0.1	0.9	-58.2	26.55	0.0

Continued

Table 3.17.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
amphotericin B	0.55	1.6	4.3	0.0	0.2	4.2	98.78	-0.1
darunavir/cobicistat	0.53	1.5	-17.9	0.1	1.9	-18.1	12.25	0.0
piperacillin/tazobactam	0.52	1.5	6.7	0.1	2.1	8.2	10.56	-1.7
measles mumps rubella and varicella vaccine	0.49	1.4	-10.0	0.0	0.5	-8.4	45.7	-2.1
human normal immunoglobulin by extravascular administration	0.44	1.3	22.3	0.0	0.0	24.4	483.22	-2.0
avibactam/ceftazidime	0.43	1.2	47.8	0.0	0.1	49.8	240.35	-1.6
inactivated virus, surface antigen, adjuvanted influenza vaccine	0.41	1.2	46.8	0.2	3.4	45.0	5.26	1.0
palivizumab	0.38	1.1	-4.2	0.0	0.0	-4.3	808.65	-0.1
posaconazole	0.35	1.0	-12.4	0.0	0.3	0.7	59.99	-13.3
B- Blood and blood-forming organs	**30.78**		**8.1**	**49.0**		**2.5**	**1.72**	**5.3**
rivaroxaban	3.09	10.0	19.0	5.0	10.3	21.8	1.67	-2.6
apixaban	2.69	8.7	5.4	3.9	8.0	10.9	1.86	-5.3
octocog alfa	2.37	7.7	-13.6	0.0	0.0	-12.6	335.08	-1.4
enoxaparin	1.52	4.9	46.2	6.2	12.7	10.9	0.67	31.4
dabigatran	1.48	4.8	4.3	2.5	5.2	7.1	1.59	-2.9
edoxaban	1.31	4.3	38.9	1.8	3.8	42.3	1.94	-2.7
epoetin alfa	1.17	3.8	-8.7	1.8	3.7	5.6	1.75	-13.7
efmorocotog alfa	1.04	3.4	9.5	0.0	0.0	7.5	356.6	1.5
ticagrelor	0.98	3.2	7.0	1.1	2.3	4.6	2.4	2.0
darbepoetin alfa	0.95	3.1	-9.6	0.4	0.9	-7.8	6.03	-2.3
activated heptacog alfa (recombinant DNA coagulation factor VII)	0.83	2.7	0.7	0.0	0.0	0.9	32,363.72	-0.5
moroctocog alfa	0.77	2.5	-4.0	0.0	0.0	-2.8	343.1	-1.5
eltrombopag	0.76	2.5	18.3	0.0	0.1	22.9	53.85	-4.0
emicizumab	0.75	2.5	174.2	0.0	0.0	264.4	784.88	-25
sodium chloride	0.73	2.4	-1.1	5.7	11.7	-12.5	0.35	12.7
albutrepenonacog alfa	0.72	2.4	9.1	0.0	0.0	8.9	1088.18	0.0
treprostinil	0.62	2.0	-2.1	0.0	0.0	5.6	556.21	-7.6
epoetin zeta	0.54	1.8	0.3	1.2	2.5	2.9	1.21	-2.8
amino acids/electrolytes/ glucose/lipids	0.45	1.5	33.0	0.1	0.1	30.9	18.06	1.3
dialysis solution	0.44	1.4	77.4	0.1	0.2	56.2	11.91	13.2
A- Alimentary tract and metabolism	**17.04**		**9.3**	**30.4**		**4.1**	**1.54**	**4.8**
insulin glargine	1.56	9.2	-0.2	4.5	14.7	2.2	0.95	-2.6
dulaglutide	1.30	7.6	42.4	1.6	5.3	39.4	2.18	1.9
human acid alglucosidase recombinant	1.21	7.1	0.4	0.0	0.0	-1.6	1062.24	1.7

Continued

Table 3.17.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
agalsidase alfa	0.83	4.9	-7.1	0.0	0.0	-2.7	1585.24	-4.8
imiglucerase	0.78	4.6	-3.8	0.0	0.0	-4.6	1095.92	0.6
insulin degludec	0.68	4.0	15.5	1.3	4.3	15.4	1.41	-0.2
agalsidase beta	0.60	3.5	5.5	0.0	0.0	4.5	484.37	0.6
liraglutide	0.60	3.5	-18.1	0.6	2.0	-14.1	2.64	-4.9
sitagliptin/metformin	0.60	3.5	2.5	1.5	4.9	2.6	1.09	-0.4
sitagliptin	0.60	3.5	10.7	1.3	4.3	10.6	1.25	-0.2
linagliptin	0.51	3.0	10.3	1.2	4.0	11.0	1.14	-0.9
idursulfase	0.49	2.9	-7.2	0.0	0.0	-2.7	2715.01	-4.9
insulin degludec/liraglutide	0.47	2.7	35.9	0.3	1.1	35.5	3.95	0.0
dapagliflozin/metformin	0.37	2.2	26.2	0.8	2.5	25.2	1.33	0.5
semaglutide	0.34	2.0	959.1	0.1	0.2	1226.5	14.6	-20.4
migalastat	0.33	2.0	57.8	0.0	0.0	57.8	465.68	-0.2
empagliflozin	0.33	2.0	11.8	0.7	2.4	10.3	1.25	1.1
dapagliflozin	0.33	1.9	31.0	0.7	2.2	30.5	1.33	0.1
eliglustat	0.28	1.6	41.0	0.0	0.0	40.6	622.68	0.0
velaglucerase alfa	0.27	1.6	1.9	0.0	0.0	6.4	1028.89	-4.5
elosulfase alfa	0.26	1.5	-1.3	0.0	0.0	-1.5	2992	0.0
vildagliptin/metformin	0.25	1.5	-9.5	0.6	2.1	-9.7	1.07	0.0
N- Nervous system	**7.81**		**6.0**	**26.6**		**3.1**	**0.80**	**2.6**
paliperidone	1.49	19.0	0.9	0.8	3.0	6.3	5.14	-5.4
aripiprazole	0.99	12.7	9.9	1.1	4.0	3.7	2.54	5.7
levodopa/carbidopa	0.50	6.4	7.9	0.1	0.4	-5.1	12.29	13.4
risperidone	0.35	4.5	-8.9	0.7	2.6	-0.3	1.39	-8.9
metadone	0.31	4.0	1.7	2.4	9.2	0.6	0.35	0.8
propofol	0.23	3.0	113.7	0.5	1.8	45.4	1.37	46.6
tafamidis	0.22	2.9	-8.5	0.0	0.0	-8.6	274.49	-0.1
dexmedetomidine	0.21	2.7	43.2	0.0	0.1	220.9	38.42	-55.5
quetiapine	0.19	2.4	-9.4	1.5	5.7	1.7	0.34	-11.1
levetiracetam	0.17	2.2	6.8	0.5	1.7	10.6	1.05	-3.7
patisiran	0.16	2.0	0.0	0.0	0.0	0.0	516.03	
lacosamide	0.15	1.9	43.5	0.1	0.3	62.1	6.05	-11.7
rivastigmine	0.13	1.7	-5.8	0.4	1.6	-4.8	0.85	-1.3
buprenorfine/naloxone	0.13	1.7	-27.2	0.2	0.7	0.1	1.96	-27.5
sevoflurane	0.13	1.6	-25.2	0.0	0.0	-20.9	63.48	-5.6
olanzapine	0.11	1.4	-3.0	1.6	6.1	6.0	0.19	-8.7
paracetamol	0.10	1.2	7.0	2.9	10.9	17.6	0.09	-9.3
opicapone	0.10	1.2	22.0	0.1	0.3	21.6	3.23	0.0
perampanel	0.09	1.1	17.1	0.1	0.2	16.6	4.65	0.2
midazolam	0.08	1.1	119.8	0.3	1.2	76.9	0.72	23.9
lidocaine	0.08	1.0	-9.8	1.3	4.8	-10.0	0.17	-0.1

Continued

Table 3.17.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
C - Cardiovascular system	**5.87**		**13.5**	**17.4**		**-7.0%**	**0.92**	**21.8**
ranolazine	1.38	23.5	10.3	1.3	7.5	10.6	2.86	-0.6
macitentan	0.93	15.9	6.4	0.0	0.2	8.0	87.72	-1.8
sacubitril/valsartan	0.87	14.8	42.0	0.6	3.3	41.6	4.08	0.0
evolocumab	0.57	9.7	31.5	0.1	0.7	53.2	13.12	-14.4
alirocumab	0.47	8.0	39.9	0.1	0.8	56.1	8.91	-10.6
ambrisentan	0.27	4.7	0.4	0.0	0.1	5.1	72.33	-4.7
V-Miscellaneous	**5.81**		**1.7**	**3.1**		**-2.8**	**5.10**	**4.4**
deferasirox	1.44	24.8	0.6	0.0	1.2	0.3	109.65	0.1
sugammadex	0.66	11.4	-5.6	0.0	0.7	-6.2	82.96	0.4
iomeprole	0.44	7.5	-4.9	0.0	0.5	-8.7	70.38	3.9
fludeoxyglucose (18 F)	0.28	4.8	12.0	0.0	0.1	-1.3	413.08	13.2
lutetium oxodotreotide (177Lu)	0.25	4.4	334.9	0.0	0.0	288.6	15,971.94	11.6
iodixanole	0.22	3.7	-10.0	0.0	0.2	-10.1	77.86	-0.1
iopromide	0.17	3.0	4.5	0.0	0.3	-7.5	56.99	12.7
gadobutrol	0.17	2.9	-1.8	0.0	0.2	-3.8	79.56	1.8
tecnetium pertecnetate (99 mTc)	0.13	2.3	46.2	0.0	0.0	21.6	326.81	19.9
iodine ioflupane (123I)	0.12	2.1	-29.8	0.0	0.0	-30.1	868.11	0.1
rasburicase	0.12	2.1	6.4	0.0	0.0	4.4	787.04	1.6
deferiprone	0.11	2.0	6.9	0.0	0.6	6.8	16.7	-0.2
iobitridole	0.11	1.9	-15.8	0.0	0.2	-20.3	47.43	5.4
lantanium	0.11	1.9	-0.3	0.0	1.3	-9.7	7.15	10.1
sevelamer	0.09	1.6	-8.5	0.2	5.0	5.0	1.63	-13.1
H - Systemic hormonal preparations, excluding sex hormones	**4.79**		**0.0**	**5.5**		**3.5**	**2.4**	**-3.7**
somatropin	1.35	28.3	-0.5	0.3	5.1	4.2	13.16	-4.8
octreotide	0.76	16.0	0.9	0.1	2.0	0.6	18.68	0.1
lanreotide	0.70	14.5	11.0	0.1	1.8	11.6	19.23	-0.8
pegvisomant	0.44	9.2	4.3	0.0	0.3	4.0	69.31	-0.1
cinacalcet	0.39	8.2	-24.1	0.1	2.0	-0.8	9.61	-23.7
R - Respiratory system	**4.76**		**21.8**	**2.1**		**-17.2**	**6.09**	**46.7**
lumacaftor/ivacaftor	1.39	29.2	19.1	0.0	0.4	16.2	426.32	2.2
omalizumab	0.88	18.6	7.1	0.1	4.4	7.6	25.49	-0.7
ivacaftor	0.70	14.7	40.0	0.0	0.1	32.3	676.64	5.5
mepolizumab	0.64	13.4	15.0	0.1	2.5	20.8	33.1	-5.1
benralizumab	0.39	8.2	146.1	0.0	1.8	143.9	28.02	0.6
M - Musculo-skeletal system	**3.71**		**5.9**	**5.2**		**4.4**	**1.95**	**1.2**
nusinersen	1.56	42.0	-9.0	0.0	0.2	-9.4	422.57	0.2
denosumab	1.03	27.7	5.8	3.3	63.6	7.9	0.85	-2.3
ataluren	0.29	7.7	24.5	0.0	0.0	27.5	1576.3	-2.6
cisatracurium	0.24	6.5	907.4	0.1	1.7	148.1	7.52	305
botulinum toxin of *Clostridium botulinum* type A	0.19	5.2	-28.5	0.0	0.1	-26.5	122.91	-2.9

Continued

Table 3.17.
Continued

Level I ATC Active ingredient	Gross expenditure (per capita)	%*	Δ % 20-19	DDD/1000 inhab. per day	%*	Δ % 20-19	Average DDD cost	Δ % 20-19
S - Sensory organs	**2.14**		**-31.8**	**2.2**		**-19.9**	**2.60**	**-15.1**
aflibercept	0.85	39.7	-28.7	0.2	9.6	-26.5	10.69	-3.3
ranibizumab	0.64	29.8	-45.3	0.1	3.6	-33.4	21.42	-18
dexamethasone	0.34	15.8	-9.1	0.2	9.3	-13.5	4.41	4.9
cenegermin	0.05	2.2	-30.7	0.0	0.0	-27.9	254.44	-4.1
cisteamine	0.04	2.1	87.1	0.0	0.0	86.6	155.57	0.0
D-Dermatologicals	**1.28**		**51.9**	**9.3**		**12.9**	**0.38**	**34.2**
dupilumab	0.86	66.8	91.7	0.1	0.8	92.0	32.5	-0.5
iodopovidone	0.06	4.5	2.0	0.7	7.3	-7.5	0.23	9.9
chlorhexidine/isopropyl alcohol	0.06	4.4	106.9	0.1	0.6	713.0	2.75	-74.6
silver sulfadiazine	0.06	4.3	0.4	0.7	7.2	-3.1	0.23	3.3
sodium hypochlorite	0.05	4.2	42.6	3.7	40.2	42.0	0.04	0.1
G - Genito-urinary system and sex hormones	**1.21**		**-21.7**	**2.2**		**-9.7**	**1.53**	**13.5**
follitropin alfa from recombinant DNA	0.29	23.6	-23.7	0.0	1.9	-19.9	19	-5.0
menotropin	0.19	15.7	-15.6	0.0	1.8	-15.5	13.57	-0.3
follitropin alfa/lutropin alfa	0.11	9.3	-25.1	0.0	0.2	-22.5	76.69	-3.7
dinoprostone	0.10	8.2	-0.9	0.1	2.3	-1.2	5.34	0.0
tadalafil	0.09	7.8	-21.3	0.2	9.3	8.3	1.28	-27.5
follitropin beta	0.07	5.4	-38.6	0.0	0.3	-39.0	27.11	0.4
testosterone	0.06	5.1	9.5	0.1	5.6	6.3	1.41	2.8

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

Table 3.18. First thirty active ingredients purchased by public health facilities in terms of expenditure: comparison 2020-2019

ATC	Active ingredient	Expenditure *(million)*	%*	Per capita expend	Rank 2020	Rank 2019	Average DDD	Δ % 20-19
L	lenalidomide	322.2	2.4	5.40	1	4	132.58	7.8
L	pembrolizumab	289.8	2.2	4.86	2	2	107.78	-38.6
J	sofosbuvir/velpatasvir	233.5	1.8	3.92	3	1	433.94	-33.7
L	nivolumab	224.6	1.7	3.77	4	3	111.96	-27.4
L	daratumumab	211.0	1.6	3.54	5	7	186.5	0.0
B	rivaroxaban	184.1	1.4	3.09	6	8	1.67	-2.6
L	ibrutinib	170.5	1.3	2.86	7	15	129.88	-0.2
L	pertuzumab	162.1	1.2	2.72	8	10	143.54	0.0
B	apixaban	160.5	1.2	2.69	9	9	1.86	-5.3
L	dimethyl fumarate	148.4	1.1	2.49	10	13	32.86	-0.8
L	palbociclib	146.7	1.1	2.46	11	16	86.61	1.9
L	fingolimod	143.2	1.1	2.40	12	11	54.8	0.0
B	octocog alfa	141.2	1.1	2.37	13	6	335.08	-1.4
L	bevacizumab	140.0	1.1	2.35	14	5	63.43	-14.7
J	thirteen-valent pneumococcal vaccine	125.2	0.9	2.10	15	27	48.5	-2.0
L	eculizumab	118.2	0.9	1.98	16	19	774.06	-5.2
L	secukinumab	112.1	0.8	1.88	17	24	31.67	-0.1
L	osimertinib	111.2	0.8	1.87	18	74	146.05	10.8
L	ustekinumab	110.4	0.8	1.85	19	26	18.97	-4.0
L	abiraterone	109.5	0.8	1.84	20	22	85.36	0.0
L	adalimumab	106.7	0.8	1.79	21	12	8.93	-29.4
L	etanercept	105.8	0.8	1.77	22	18	16.88	-13.5
J	emtricitabine/rilpivirine/ tenofovir alafenamide	104.0	0.8	1.74	23	23	19.96	0.0
L	enzalutamide	103.6	0.8	1.74	24	32	85.65	0.0
L	natalizumab	101.0	0.8	1.69	25	29	56.38	-1.0
J	B group meningococcal vaccine	97.1	0.7	1.63	26	20	62.7	-0.2
L	ruxolitinib	96.2	0.7	1.61	27	37	109.51	0.9
A	insulin glargine	93.1	0.7	1.56	28	28	0.95	-2.6
L	trastuzumab	92.8	0.7	1.56	29	14	23.9	-19.1
M	nusinersen	92.7	0.7	1.56	30	25	422.57	0.2
	Total	**4,357.30**	**32.8**					
	Total expenditure by public health facilities	**13,292.20**						

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

Table 3.19. 2020 regional ranks by expenditure relating to the first thirty active ingredients purchased by public health facilities

Rank	Active	Piedmont	Valle d'Aosta	Lombardy	Bolzano	Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Calabria	Sicily	Sardinia
1	lenalidomide	1	7	1	3	3	1	1	2	2	2	1	1	2	2	2	5	1	1	1	1	3
2	pembrolizumab	3	9	2	2	5	5	2	1	1	1	2	2	1	1	12	1	2	2	5	3	5
3	sofosbuvir/velpatasvir	2	3	3	31	1	4	3	9	14	3	6	5	11	27	8	2	4	11	12	5	6
4	nivolumab	5	13	4	5	41	8	10	4	3	4	8	4	4	7	6	3	3	12	7	6	7
5	daratumumab	4	0	6	1	10	2	15	3	4	5	7	10	5	21	9	7	5	7	27	11	9
6	rivaroxaban	7	8	11	8	13	3	6	7	5	10	5	3	8	3	3	10	9	6	15	9	10
7	ibrutinib	9	108	7	4	7	6	13	5	6	9	4	6	9	13	27	22	7	9	22	15	21
8	pertuzumab	15	6	15	6	22	9	7	11	8	11	13	12	16	11	14	4	10	4	8	28	11
9	apixaban	6	2	9	148	2	236	9	6	7	8	3	9	6	9	28	15	12	19	25	14	16
10	dimethyl	13	11	21	12	16	7	12	26	15	6	9	11	13	8	16	30	18	15	19	17	2
11	palbociclib	20	10	20	13	28	11	11	12	10	17	14	7	10	14	34	8	21	37	20	8	13
12	fingolimod	11	5	17	11	8	16	35	10	25	26	26	14	14	4	11	13	6	21	11	26	4
13	octocog alfa	48	14	22	80	15	40	115	20	35	49	108	40	3	6	38	6	8	22	3	2	23
14	bevacizumab	29	17	19	10	9	15	29	16	13	20	20	13	12	10	21	9	11	5	10	25	8
15	thirteen-valent pneumococca	74	22	14	22	21	14	18	28	17	13	34	26	7	28	29	17	27	42	39	13	43
16	eculizumab	8	1	16	9	25	27	17	15	12	15	24	16	52	17	7	25	34	13	30	45	18
17	secukinumab	10	27	50	18	36	24	22	32	24	24	39	21	46	16	10	16	15	23	9	27	24
18	osimertinib	18	34	13	19	30	13	14	27	16	19	23	23	22	26	59	51	40	70	62	33	36
19	ustekinumab	19	94	49	20	26	33	20	34	40	28	21	22	25	30	32	11	13	14	26	4	77
20	abiraterone	24	4	30	7	45	28	27	17	19	18	30	20	49	18	23	20	16	25	29	24	15
21	adalimumab	79	119	31	16	50	32	5	45	33	42	10	32	38	12	24	14	17	8	2	32	59
22	etanercept	58	74	47	44	65	29	8	36	27	29	12	17	21	5	17	18	35	24	6	36	12
23	emtricitabine/rilpivirine/tenofovir alafenamide	14	18	8	47	11	22	66	8	18	16	22	44	20	63	136	88	65	105	159	105	41
24	enzalutamide	17	49	33	28	4	26	16	31	26	22	15	15	29	19	42	24	30	28	31	34	34
25	natalizumab	16	58	38	17	19	12	26	23	20	52	55	67	28	31	4	42	45	113	37	10	17
26	B group meningococcal vaccine	53	43	23	37	23	23	49	55	29	45	44	56	19	34	55	35	22	46	42	19	40
27	ruxolitinib	28	79	29	42	83	30	46	25	37	50	37	39	31	41	15	21	14	44	34	20	103
28	insulin glargine	25	23	41	57	20	25	36	43	23	40	17	42	45	23	30	31	42	29	24	21	22
29	trastuzumab	26	20	39	40	66	37	25	38	34	69	51	33	26	15	13	12	55	3	18	53	31
30	nusinersen	39	0	18	41	59	20	21	86	52	66	18	18	15	109	41	47	28	200	50	42	81

Table 3.20. First thirty active ingredients* with highest variation in expenditure relating to medicines purchased by public health facilities compared to the previous year: comparison 2020-2019

ATC	Active ingredient	Per capita expenditure	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19	Average DDD cost	Δ % 20-19
J	bictegravir/emtricitabine/tenofovir alafenamide	1.34	606.1	0.2	604.2	19.96	0
B	emicizumab	0.75	174.2	0.0	264.4	784.88	-25
L	osimertinib	1.87	126.9	0.0	104.2	146.05	10.8
L	ribociclib	0.74	99.4	0.0	105.1	70.9	-3.1
D	dupilumab	0.86	91.7	0.1	92.0	32.5	-0.5
L	alectinib	1.00	46.3	0.0	44.6	175.14	0.9
B	enoxaparin	1.52	46.2	6.2	10.9	0.67	31.4
L	ocrelizumab	1.23	46.0	0.1	50.3	48.24	-3.1
J	cobicistat/darunavir/emtricitabine/ tenofovir alafenamide	0.85	45.4	0.1	45.0	21.85	0
A	dulaglutide	1.30	42.4	1.6	39.4	2.18	1.9
C	sacubitril/valsartan	0.87	42.0	0.6	41.6	4.08	0
R	ivacaftor	0.70	40.0	0.0	32.3	676.64	5.5
B	edoxaban	1.31	38.9	1.8	42.3	1.94	-2.7
L	daratumumab	3.54	35.4	0.1	35.0	186.5	0
L	canakinumab	0.87	29.7	0.0	48.0	142.33	-12.6
L	ibrutinib	2.86	29.5	0.1	29.4	129.88	-0.2
L	dabrafenib	1.09	27.6	0.0	76.1	105.6	-27.7
J	inactivated, split virus tetravalent influenza vaccine	0.89	27.1	0.4	24.8	6.22	1.6
J	thirteen-valent pneumococcal vaccine	2.10	26.1	0.1	28.3	48.5	-2
L	tocilizumab	0.98	23.2	0.1	28.2	25.59	-4.2
L	lenalidomide	5.40	23.0	0.1	13.7	132.58	7.8
L	ixekizumab	0.70	22.7	0.1	33.2	30.31	-8.1
L	nintedanib	1.12	22.2	0.0	19.0	75.81	2.4
L	enzalutamide	1.74	19.3	0.1	19.0	85.65	0
R	lumacaftor/ivacaftor	1.39	19.1	0.0	16.2	426.32	2.2
B	rivaroxaban	3.09	19.0	5.0	21.8	1.67	-2.6
B	eltrombopag	0.76	18.3	0.0	22.9	53.85	-4
L	atezolizumab	0.80	17.6	0.0	42.7	121.47	-17.9
J	human immunoglobulin intravenous use	0.84	17.5	0.0	14.6	289.79	2.2
L	ruxolitinib	1.61	16.6	0.0	15.3	109.51	0.9

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

Table 3.21. Largest prescription pharmaceutical groups in 2020

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Antineoplastic medicines	**3,893.4**	**16.9**	**65.28**	**5.8**	**10.2**	**1.0**
Monoclonal antibodies inhibiting immune check points	604.8	2.6	10.14	-0.6	0.2	42.2
Monoclonal antibodies blocking growth factors	495.9	2.2	8.32	-13.0	0.4	-10.0
Monoclonal antibodies acting on specific targets	331.9	1.4	5.57	12.8	0.5	-10.0
Endocrine therapy - aromatase inhibitors	248.9	1.1	4.17	4.9	3.6	4.0
Cytostatic antineoplastics - other cytostatics	236.2	1.0	3.96	0.3	0.4	5.7
VEGFR-associated multitarget tyrosin kinase inhibitors	228.2	1.0	3.83	15.4	0.1	16.6
BRC-ABL tyrosin kinase inhibitors	209.1	0.9	3.51	-2.9	0.2	4.0
CDK protein kinase inhibitors	204.2	0.9	3.42	34.1	0.1	32.5
Bruton tyrosine kinase (BTK) inhibitors	170.5	0.7	2.86	29.5	0.1	29.4
Cytostatic antineoplastics – antimetabolites	162.7	0.7	2.73	-1.3	0.7	-1.1
EGFR tyrosin kinase inhibitors	136.0	0.6	2.28	38.8	0.1	15.5
Endocrine therapy – antiandrogens	118.8	0.5	1.99	20.1	0.8	-10.6
Endocrine therapy - hormones and GnRH analogues	116.6	0.5	1.95	1.1	1.1	4.7
Monoclonal antibodies conjugated to drugs	100.8	0.4	1.69	8.1	0.0	12.6
JAK tyrosin kinase inhibitors	96.2	0.4	1.61	16.6	0.0	15.3
ALK tyrosin kinase inhibitors	74.0	0.3	1.24	30.9	0.0	26.1
BRAF tyrosin kinase inhibitors	74.0	0.3	1.24	25.1	0.0	66.4
Cytotoxic antineoplastics - products of natural derivation – taxanes	43.9	0.2	0.74	-10.5	0.2	-4.7
MEK tyrosin kinase inhibitors	40.1	0.2	0.67	32.6	0.0	86.6
Endocrine therapy - antiestrogens	38.3	0.2	0.64	-14.1	1.1	-3.8
Cytotoxic antineoplastics - products of natural derivation – others	34.1	0.1	0.57	-5.5	0.1	-1.3
Cytotoxic antineoplastics - cytotoxic antibiotics -anthracyclines and related substances	29.1	0.1	0.49	4.6	0.1	-0.7
MTOR protein kinase inhibitors	29.0	0.1	0.49	-8.9	0.0	3.4
Cytostatic antineoplastics - alkylating agents	21.8	0.1	0.36	-3.8	0.2	-8.2
CAR-T	16.7	0.1	0.28	1,304.3	0.0	1,066.9
Other protein kinase inhibitors	15.8	0.1	0.26	25.5	0.0	66.2
Combination of antineoplastic agents	8.6	0.0	0.14	252.1	0.0	269.7
Cytostatic antineoplastics – platinum compounds	5.7	0.0	0.10	8.4	0.2	-6.3
Cytotoxic antineoplastics – antibiotics	1.5	0.0	0.02	-62.5	0.0	-21.9
Cytotoxic -others						

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Antihypertensives	**2,040.8**	**8.9**	**34.22**	**1.7**	**378.9**	**0.1**
Beta blockers	328.3	1.4	5.50	3.1	45.5	1.8
Angiotensin II antagonists	291.5	1.3	4.89	1.6	58.9	0.8
Calcium channel blockers	253.4	1.1	4.25	-0.2	51.7	0.7
Angiotensin II receptor blockers and	239.0	1.0	4.01	-1.6	33.2	-1.7
ACE inhibitors	227.0	1.0	3.81	-2.6	86.0	-1.7
ACE inhibitors and diuretics	154.6	0.7	2.59	-3.8	20.1	-3.4
ACE inhibitors and calcium channel	99.7	0.4	1.67	-3.0	12.0	0.4
Alpha-adrenoreceptor antagonists	75.8	0.3	1.27	2.0	7.9	1.4
Angiotensin II receptor blockers and calcium channel blockers	72.0	0.3	1.21	13.8	8.3	16.5
Angiotensin II receptor blockers and neprilysin inhibitor	68.9	0.3	1.16	41.9	0.7	41.5
High-ceiling diuretics, plain or in combination with potassium-sparing agents	63.3	0.3	1.06	-0.2	31.2	-2.0
Beta blockers and diuretics	40.9	0.2	0.69	1.7	7.5	1.4
Perindopril/indapamide/amlodipine	37.3	0.2	0.62	31.7	3.6	31.4
Potassium-sparing diuretics	34.5	0.1	0.58	3.0	3.6	1.1
Calcium channel blockers (not	18.5	0.1	0.31	-6.6	2.2	-7.3
Thiazides and similars (including	14.1	0.1	0.24	-4.1	4.0	-5.4
Imidazoline receptor agonists	13.1	0.1	0.22	-3.1	1.5	-5.7
ACE inhibitors, other combinations	5.8	0.0	0.10	29.3	0.8	29.0
Aliskiren plain or in combination	3.1	0.0	0.05	-14.3	0.2	-13.7
Alpha-2 adrenergic receptor agonists	0.2	0.0	0.00	-52.1	0.0	-50.1
Immunosuppressants and immunomodulating agents	**1,769.8**	**7.7**	**29.67**	**6.6**	**3.9**	**9.4**
Other immunosuppressants	437.2	1.9	7.33	18.8	0.2	11.3
Interleukin inhibitors	429.0	1.9	7.19	22.7	0.7	24.0
Tumor necrosis factor alpha inhibitors (TNF-alpha)	347.0	1.5	5.82	-16.6	1.4	5.8
Immunosuppressant monoclonal antibodies	189.0	0.8	3.17	7.8	0.1	19.6
Calcineurin inhibitors	89.9	0.4	1.51	-0.7	0.6	1.9
Selective T cell co-stimulation modulators	68.4	0.3	1.15	4.1	0.1	2.9
Selective immunosuppressants	61.6	0.3	1.03	3.2	0.6	6.3
JAK tyrosin kinase inhibitors	48.7	0.2	0.82	51.0	0.1	45.4
MTOR protein kinase inhibitors	39.3	0.2	0.66	10.0	0.1	9.2
Growth factors	38.3	0.2	0.64	-15.8	0.1	7.8
Other immunomodulators	17.8	0.1	0.30	4.1	0.0	-11.0
Interferons	3.5	0.0	0.06	-19.8	0.0	-19.5
Antidiabetics	**1,095.0**	**4.8**	**18.36**	**8.7**	**64.6**	**0.9**
Fast acting insulins	227.4	1.0	3.81	-1.6	8.5	-0.3

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
GLP-1 (glucagon-like one) analogues	198.6	0.9	3.33	40.4	2.9	25.7
Combined insulins (long/intermediate with fast)	176.0	0.8	2.95	-0.4	6.8	1.9
Metformin plain and in combination	99.3	0.4	1.67	0.4	24.0	-0.9
Gliptins (DPP-4 inhibitors) plain	90.2	0.4	1.51	8.0	3.3	8.6
Gliptins (DPP-4 inhibitors) in combination	81.2	0.4	1.36	6.7	3.2	3.2
Glifozins combined with metformin	50.4	0.2	0.84	21.6	1.7	21.0
Insulins combined with GLP-1 (glucagon-like one) analogues	48.9	0.2	0.82	32.7	0.5	34.7
Glifozins (SGLT2 inhibitors) plain	48.0	0.2	0.81	24.9	1.6	22.8
Sulfonylureas, plain	30.6	0.1	0.51	-3.1	7.8	-8.1
Pioglitazone plain and in combination	19.4	0.1	0.33	-15.4	1.7	1.7
Repaglinide	16.0	0.1	0.27	-12.8	1.9	-13.4
Acarbose	8.6	0.0	0.14	-7.8	0.6	-6.3
Intermediate acting insulins	0.3	0.0	0.00	-11.7	0.0	-7.0
Asthma and COPD	**1,084.3**	**4.7**	**18.18**	**3.0**	**33.1**	**-3.8**
LABAs+ICSs	360.0	1.6	6.04	2.5	9.5	3.9
LAMAs	196.7	0.9	3.30	2.4	5.9	0.5
Ultra-LABAs+ICSs	142.2	0.6	2.39	9.8	3.8	9.4
Monoclonal antibodies	115.2	0.5	1.93	25.0	0.2	26.3
ICSs	83.6	0.4	1.40	-27.1	4.0	-26.9
LABAs+LAMAs	54.5	0.2	0.91	-1.0	1.2	-1.4
LAMAs+LABAs+ICSs	45.2	0.2	0.76	115.2	0.7	109.0
Antileukotrienes (LTRAs)	29.5	0.1	0.49	3.8	2.2	5.7
LABAs	13.9	0.1	0.23	-10.2	0.7	-10.3
Ultra-LABAs	11.2	0.0	0.19	-9.3	0.5	-9.8
SABAs	10.9	0.0	0.18	-19.2	2.6	-11.8
SABAs+SAMAs	7.5	0.0	0.13	-30.5	0.5	-30.1
SABAs+ICSs	6.8	0.0	0.11	-11.0	0.3	-11.8
Theophylline-based bronchodilators	3.3	0.0	0.06	-11.2	0.4	-11.2
SAMAs	3.2	0.0	0.05	-27.3	0.6	-31.0
PDE-4 inhibitors	0.3	0.0	0.01	-11.9	0.0	-11.7
Chromones	0.2	0.0	0.00	43.6	0.0	45.3
Lipid-lowering medicines	**890.1**	**3.9**	**14.92**	**7.6**	**103.2**	**5.4**
Statins, plain	480.2	2.1	8.05	1.5	82.1	2.7
Ezetimibe in combination	117.9	0.5	1.98	30.6	8.2	35.9
Omega 3	115.3	0.5	1.93	1.0	4.6	1.5
Ezetimibe	83.6	0.4	1.40	13.9	5.2	15.7
PCSK9 inhibitors	62.1	0.3	1.04	35.2	0.3	54.8
Fibrates	23.6	0.1	0.40	2.2	2.8	1.8
MTP inhibitor	6.9	0.0	0.12	-6.5	0.0	13.2
Amlodipine/atorvastatin/perindopril	0.6	0.0	0.01	2,149.5	0.1	2,137.4

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Statins in combination	0.0	0.0	0.00	3,686.0	0.0	4,174.3
Acetylsalicylic acid/atorvastatin/ramipril	0.0	0.0	0.00	-83.3	0.0	-83.3
Anticoagulants	**861.5**	**3.7**	**14.44**	**12.7**	**27.8**	**8.3**
NAO	556.7	2.4	9.33	14.0	13.9	17.5
EBPM	235.0	1.0	3.94	9.6	9.4	6.6
Antithrombotic enzymes	16.0	0.1	0.27	1.9	0.0	4.1
Fondaparinux	15.3	0.1	0.26	-6.3	0.5	-5.8
Heparin and heparinoids	12.0	0.1	0.20	5.1	0.4	1.6
Monoclonal antibody	8.9	0.0	0.15	0.0	0.0	0.0
Vitamin K antagonists	8.9	0.0	0.15	-12.0	3.7	-12.0
Other antithrombotics	7.8	0.0	0.13	6.1	0.0	6.4
Antithrombotics - direct thrombin inhibitors	0.9	0.0	0.02	78.1	0.0	313.1
Medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	**775.6**	**3.4**	**13.00**	**-4.2**	**82.7**	**1.8**
Proton pump inhibitors	695.2	3.0	11.66	-2.9	76.4	4.2
Other medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	54.2	0.2	0.91	1.2	4.3	0.8
Antacids	24.9	0.1	0.42	4.6	2.0	4.1
H2 receptor antagonists	0.8	0.0	0.01	-94.7	0.1	-97.1
Prostaglandins	0.5	0.0	0.01	-11.1	0.0	-9.4
Medicines for multiple sclerosis	**729.6**	**3.2**	**12.23**	**7.1**	**2.8**	**2.4**
Immunosuppressants	218.1	0.9	3.66	15.7	1.9	2.5
Monoclonal antibodies	177.8	0.8	2.98	16.5	0.2	25.1
Fingolimod (S1P receptor modulator)	143.2	0.6	2.40	1.2	0.1	0.9
Interferons	111.9	0.5	1.88	-2.8	0.4	-3.9
Pyrimidine synthesis inhibitors	55.1	0.2	0.92	13.4	0.1	12.4
Glatiramer	23.5	0.1	0.39	-32.9	0.1	-4.7
Antibiotics	**692.1**	**3.0**	**11.60**	**-17.6**	**13.9**	**-21.7**
Combinations of penicillins (including beta lactamase inhibitors)	172.8	0.8	2.90	-21.1	4.8	-25.0
Third-generation cephalosporins	164.0	0.7	2.75	-24.0	1.7	-26.3
Macrolides and lincosamides	80.7	0.4	1.35	-15.9	3.1	-16.7
Fluroquinolones	74.9	0.3	1.26	-20.0	1.7	-22.8
Other antibacterials	64.3	0.3	1.08	-9.7	0.4	-2.7
Other cephalosporins and penems	24.9	0.1	0.42	65.4	0.0	74.6
Glycopeptides	22.2	0.1	0.37	-13.6	0.1	-6.0
Carbapenems	14.9	0.1	0.25	2.4	0.1	15.5
Broad-spectrum penicillins	13.9	0.1	0.23	-24.6	0.8	-32.8
Polymyxin	13.0	0.1	0.22	8.2	0.0	9.0
Tetracyclines	10.2	0.0	0.17	-23.8	0.3	-2.9

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Aminoglycosides	8.5	0.0	0.14	-30.6	0.0	-6.9
First-generation cephalosporins	6.2	0.0	0.10	-20.5	0.1	-20.2
Second-generation cephalosporins	4.7	0.0	0.08	-39.7	0.1	-38.9
Sulphonamides (plain or in combination)	4.4	0.0	0.07	-8.2	0.4	-7.9
Fourth-generation cephalosporins	4.2	0.0	0.07	-0.9	0.0	1.0
Other combinations	2.7	0.0	0.04	-22.3	0.0	-22.6
Monobactams	2.5	0.0	0.04	4.8	0.0	4.6
Nitrofuran derivatives	1.5	0.0	0.02	4,503.7	0.1	1,423.8
Imidazole derivatives	0.9	0.0	0.01	-18.8	0.0	-21.2
Beta-lactamase sensitive penicillins	0.4	0.0	0.01	-46.2	0.0	-48.8
Beta-lactamase resistant penicillins	0.3	0.0	0.01	-46.8	0.0	-40.5
Amphenicols	0.1	0.0	0.00	-15.4	0.0	-12.6
Other quinolones	0.0	0.0	0.00	-99.8	0.0	-99.8
Anti-HIV antivirals	**661.6**	**2.9**	**11.09**	**0.3**	**2.9**	**1.5**
Co-formulated regimens - 2 nucleoside/nucleotide reverse transcriptase inhibitors + 1 integrase inhibitor (2 NRTI + 1 INSTI)	196.4	0.9	3.29	9.2	0.4	18.4
Integrase inhibitors (INSTI)	126.3	0.5	2.12	-3.1	0.4	-3.7
Co-formulated regimens - 2 nucleoside/nucleotide reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor (2 NRTI + 1 NNRTI)	119.1	0.5	2.00	-2.7	0.3	-2.0
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)	67.9	0.3	1.14	-25.8	1.2	-6.0
Protease inhibitors (PIs)	52.9	0.2	0.89	-29.6	0.3	-0.6
Co-formulated regimens - 2 nucleoside/nucleotide reverse transcriptase inhibitors + 1 protease inhibitor (2 NRTIs + 1 PI)	50.4	0.2	0.85	45.4	0.1	45.0
Co-formulated regimens - 1 non-nucleoside reverse transcriptase inhibitor + 1 integrase inhibitor (1 NNRTI + 1 INSTI)	15.6	0.1	0.26	2,188.5	0.0	2,182.3
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	13.9	0.1	0.23	-22.3	0.1	-17.1
Co-formulated regimens - 1 nucleoside/nucleotide reverse transcriptase inhibitor + 1 integrase inhibitor (1 NRTI + 1 INSTI)	12.6	0.1	0.21	0.0	0.0	0.0
Other anti-HIV antivirals	6.5	0.0	0.11	-5.5	0.0	-4.7
Vaccines	**562.5**	**2.4**	**9.43**	**-0.4**	**1.2**	**9.0**
Pneumococcal polysaccharide conjugate vaccine	140.5	0.6	2.36	30.2	0.1	29.0
Meningococcal B vaccine	97.1	0.4	1.63	-10.0	0.1	-10.1
Influenza vaccine	92.1	0.4	1.54	10.8	0.7	23.6

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Papillomavirus vaccine	57.9	0.3	0.97	-10.8	0.0	-11.5
Hexavalent vaccine (diphtheria /tetanus/pertussis/*Haemophilus influenzae B*/ poliomyelitis/hepatitis B	40.7	0.2	0.68	-5.1	0.1	-2.7
MMRV vaccine (measles/mumps/rubella/varicella)	29.0	0.1	0.49	-10.0	0.0	-8.4
Tetravalent meningococcal conjugate vaccine	23.2	0.1	0.39	-18.3	0.0	-16.2
Rotavirus attenuated vaccine	17.7	0.1	0.30	-3.7	0.0	-1.6
Tetravalent vaccine (diphtheria /tetanus/ pertussis/poliomyelitis)	16.4	0.1	0.28	-16.3	0.0	-15.3
Live attenuated Varicella zoster virus vaccine	12.8	0.1	0.21	-30.7	0.0	-30.4
Pneumococcal 23 vaccine	8.2	0.0	0.14	64.2	0.0	64.2
DTP vaccine (diphtheria	6.9	0.0	0.12	-16.5	0.0	-13.8
Live attenuated varicella virus vaccine	5.3	0.0	0.09	-17.4	0.0	-13.8
MMR vaccine (measles/mumps/rubella)	2.7	0.0	0.05	-36.9	0.0	-37.8
Hepatitis A vaccine	2.6	0.0	0.04	-26.6	0.0	-25.2
Encephalitis vaccine	2.5	0.0	0.04	-40.2	0.0	-39.4
Hepatitis B vaccine	2.3	0.0	0.04	-23.0	0.0	-30.7
Meningococcal C conjugate vaccine	2.0	0.0	0.03	20.9	0.0	33.9
DT vaccine (diphtheria /tetanus)	0.5	0.0	0.01	-43.7	0.0	-45.5
Tetanus vaccine	0.3	0.0	0.01	-36.5	0.0	-37.7
Haemophilus influenzae B vaccine	0.3	0.0	0.01	195.9	0.0	170.5
Hepatitis A and B vaccine	0.3	0.0	0.01	-21.6	0.0	-23.6
Rabies vaccine	0.3	0.0	0.00	-22.6	0.0	-22.8
Poliomyelitis inactivated vaccine	0.2	0.0	0.00	3.7	0.0	3.3
Yellow fever vaccine	0.2	0.0	0.00	-72.0	0.0	-72.4
Typhus vaccine	0.2	0.0	0.00	-76.6	0.0	-71.0
Trivalent vaccine (diphtheria /tetanus/poliomyelitis)	0.0	0.0	0.00	-22.8	0.0	-23.4
Cholera vaccine	0.0	0.0	0.00	-97.0	0.0	-97.2
Coagulation factors	**535.2**	**2.3**	**8.97**	**3.6**	**0.1**	**1.8**
Haemophilia A (short acting-recombinant)	229.7	1.0	3.85	-9.3	0.0	-7.9
Haemophilia A (long acting-recombinant)	94.5	0.4	1.58	17.0	0.0	16.9
Haemophilia B (long acting-recombinant)	61.3	0.3	1.03	8.9	0.0	8.0
Factor VII deficiency (short acting-recombinant)	49.4	0.2	0.83	0.7	0.0	0.9
Haemophilia A (monoclonal antibodies)	45.0	0.2	0.75	>100	0.0	>100
Haemophilia A (plasma derivatives)	22.3	0.1	0.37	-7.0	0.0	-6.2
Haemophilia B (short acting-recombinant)	12.6	0.1	0.21	-17.5	0.0	-18.0
Antihemophilic prothrombin complex activated human	10.1	0.0	0.17	-6.8	0.0	-2.9

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Factor VII deficiency (plasma derivatives)	3.7	0.0	0.06	-13.3	0.0	-20.4
Combination of coagulation factors (plasma derivatives)	2.7	0.0	0.04	7.8	0.0	8.7
Other deficiencies of coagulation factors (long-acting, recombinant)	2.4	0.0	0.04	-7.6	0.0	-7.8
Haemophilia B (plasma derivatives)	0.7	0.0	0.01	-5.5	0.0	-6.9
Other deficiencies of coagulation factors (plasma derivatives)	0.5	0.0	0.01	3.7	0.0	2.6
Von Willebrand disease (plasma derivatives)	0.3	0.0	0.01	0.0	0.0	0.0
Medicines for osteoporosis	**510.5**	**2.2**	**8.56**	**-15.5**	**29.0**	**-14.3**
Vitamin D and analogues	256.4	1.1	4.30	-24.1	15.6	-21.7
Bisphosphonates plain	81.2	0.4	1.36	-2.4	6.9	-1.0
Teriparatide	71.7	0.3	1.20	-17.5	0.2	-11.1
Monoclonal antibodies for osteoporosis	67.2	0.3	1.13	13.3	3.3	7.3
Biphosphonates in combination	26.3	0.1	0.44	-6.7	2.1	-6.9
Calcium	6.8	0.0	0.11	-7.4	1.0	-35.1
SERM (selective estrogen-receptor modulators)	0.8	0.0	0.01	-1.9	0.0	-2.4
Double-acting pharmaceuticals	0.0	0.0	0.00	-82.9	0.0	-82.9
Antidepressants	**399.4**	**1.7**	**6.70**	**2.3**	**43.6**	**1.7**
SSRI antidepressants	200.2	0.9	3.36	1.4	30.6	1.4
Other antidepressants	96.7	0.4	1.62	6.7	5.1	5.4
SNRI antidepressants	93.0	0.4	1.56	1.1	6.8	1.3
1st generation antidepressants, plain or in combination	9.4	0.0	0.16	-8.8	1.0	-4.0
Pain therapy	**396.4**	**1.7**	**6.65**	**-0.9**	**7.6**	**-0.7**
Major opioids, plain or in combination	262.7	1.1	4.40	-2.0	2.7	-1.8
Drugs for neuropathic pain	94.2	0.4	1.58	5.5	3.0	6.6
Minor opioids, plain or in combination	39.6	0.2	0.66	-7.5	2.0	-8.8
Metabolic disorders	**377.5**	**1.6**	**6.33**	**5.2**	**0.0**	**15.2**
Lysosomal storage diseases – Fabry's disease - enzyme replacement therapy	85.4	0.4	1.43	-2.2	0.0	2.3
Lysosomal storage diseases – Pompe's disease - enzyme replacement therapy	72.0	0.3	1.21	0.4	0.0	-1.6
Lysosomal storage diseases - type 1 Gaucher's disease - enzyme replacement therapy	62.6	0.3	1.05	-2.4	0.0	-1.9
Lysosomal storage diseases - mucopolysaccharidosis II - enzyme replacement therapy	29.4	0.1	0.49	-7.2	0.0	-2.7
Transthyretin hereditary amyloidosis	23.8	0.1	0.40	62.8	0.0	31.1

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Lysosomal storage diseases - type 1 Gaucher's disease - chaperone therapy	21.0	0.1	0.35	11.5	0.0	17.6
Lysosomal storage diseases - Fabry's disease - chaperone therapy	19.9	0.1	0.33	57.8	0.0	57.8
Lysosomal storage diseases - mucopolysaccharidosis IV-a (Morquio's syndrome) - enzyme replacement therapy	15.3	0.1	0.26	-1.3	0.0	-1.5
Congenital metabolic and amino acid transport disorders-phenylketonuria	10.6	0.0	0.18	8.1	0.0	8.3
Lysosomal storage diseases - mucopolysaccharidosis I- enzyme therapy	10.2	0.0	0.17	1.8	0.0	1.5
Lysosomal storage diseases - mucopolysaccharidosis VI - enzyme therapy	6.9	0.0	0.12	9.8	0.0	9.7
Urea cycle disorders	4.9	0.0	0.08	3.3	0.0	12.2
Lysosomal storage diseases - liposomal acid lipase deficiency - therapy	4.5	0.0	0.08	5.2	0.0	11.5
Wilson's disease	3.5	0.0	0.06	215.2	0.0	27.4
Hypophosphatasia-enzyme replacement therapy	2.7	0.0	0.05	52.1	0.0	7.0
Congenital metabolic and amino acid transport disorders-homocystinuria	1.9	0.0	0.03	29.6	0.0	29.2
Congenital metabolic and amino acid transport disorders - type 1 hereditary tyrosinemia	1.5	0.0	0.02	-34.1	0.0	-6.7
Lipodystrophy	0.6	0.0	0.01	0.0	0.0	0.0
Congenital metabolic and amino acid transport disorders - cystinosis	0.4	0.0	0.01	5.1	0.0	3.0
Lysosomal storage diseases - alpha-mannosidosis - enzyme therapy	0.3	0.0	0.01	113.2	0.0	162.1
Medicines for eye disorders	**348.1**	**1.5**	**5.84**	**-14.3**	**21.1**	**-1.8**
Antiglaucoma preparations - beta plain or in combination	135.8	0.6	2.28	0.2	12.0	0.4
Antineovascular agents	89.4	0.4	1.50	-36.9	0.3	-28.5
Antiglaucoma preparations - analogues	76.4	0.3	1.28	-3.2	5.7	-2.2
Corticosteroids	20.6	0.1	0.35	-9.1	0.2	-13.4
Antiglaucoma preparations - carbonic anhydrase inhibitors	12.5	0.1	0.21	-7.0	1.4	-6.8

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Antiglaucoma preparations – sympathomimetic drugs	5.9	0.0	0.10	-1.6	1.5	-2.4
Other ophthalmological drugs	5.5	0.0	0.09	-1.3	0.0	18.6
Corticosteroids (intravitreal implants)	1.6	0.0	0.03	-3.7	0.0	-3.5
Antiglaucoma preparations – parasympathomimetic drugs	0.4	0.0	0.01	-32.6	0.0	-16.1
Antiglaucoma preparations - others	0.0	0.0	0.00	-13.0	0.0	-14.9
Platelet aggregation inhibitors	**326.9**	**1.4**	**5.48**	**-0.6**	**70.3**	**-0.8**
P2Y12 platelet receptor inhibitors	89.7	0.4	1.50	-1.8	12.7	-2.9
Acetylsalicylic acid plain and in combination	87.1	0.4	1.46	-1.6	54.4	-0.6
Other platelet aggregation inhibitors	61.8	0.3	1.04	-3.8	0.0	-5.4
Ticagrelor	60.8	0.3	1.02	6.9	1.1	4.5
Acetylsalicylic acid/clopidogrel	25.9	0.1	0.43	0.8	2.1	3.5
Glycoprotein IIb/IIIa inhibitors	1.7	0.0	0.03	-28.8	0.0	-19.7
Anti-epileptics	**312.7**	**1.4**	**5.24**	**4.5**	**10.9**	**1.6**
Second-generation anti-epileptics	168.0	0.7	2.82	2.1	4.6	3.1
Fisrt-generation anti-epileptics	82.6	0.4	1.39	0.9	5.8	-1.0
Third-generation anti-epileptics	62.1	0.3	1.04	17.9	0.5	20.3
Anti-HCV antivirals	**306.1**	**1.3**	**5.13**	**-67.6**	**0.1**	**-56.6**
Anti-HCV antivirals in combination	305.9	1.3	5.13	-67.6	0.1	-57.5
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.1	0.0	0.00	923.2	0.0	3.0
Other HCV antivirals	0.0	0.0	0.00	-72.0	0.0	0.0
Antipsychotics	**290.3**	**1.3**	**4.87**	**2.1**	**10.1**	**4.2**
Atypical and other antipsychotics	272.0	1.2	4.56	2.0	7.8	3.7
Typical antipsychotics	18.4	0.1	0.31	4.1	2.4	6.0
Medicines for genitourinary disorders	**269.8**	**1.2**	**4.52**	**-6.7**	**38.1**	**0.5**
Medicines for benign prostatic hypertrophy	266.0	1.2	4.46	-6.8	37.8	0.4
Pharmaceuticals for incontinence and urination disorders	3.7	0.0	0.06	7.1	0.3	9.7
Other medicines for benign prostatic hypertrophy	0.1	0.0	0.00	-4.2	0.0	-1.7
Antiparkinson pharmaceuticals	**209.8**	**0.9**	**3.52**	**0.7**	**5.9**	**-0.6**
DOPA-derivatives agonists, plain or in combination	75.9	0.3	1.27	1.9	2.4	-0.6
Dopamine-agonists	73.1	0.3	1.23	-2.9	1.2	-4.0
MAO inhibitors	47.7	0.2	0.80	3.1	1.7	1.2
COMT-inhibitors	10.3	0.0	0.17	6.7	0.1	8.1
Anticolinergics	2.8	0.0	0.05	0.4	0.5	0.4
Amantadine	0.0	0.0	0.00	22.7	0.0	1.1

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Antifungals for systemic use	**149.7**	**0.7**	**2.51**	**-9.1**	**0.7**	**-12.5**
Triazole derivatives	89.6	0.4	1.50	-8.9	0.6	-13.3
Polyenes	32.6	0.1	0.55	4.3	0.0	4.2
Echinocandins	26.4	0.1	0.44	-21.7	0.0	17.3
Imidazole derivatives	0.9	0.0	0.02	-8.9	0.0	-8.8
Pyrimidine analogues	0.1	0.0	0.00	-25.8	0.0	-27.1
Cystic fibrosis	**142.9**	**0.6**	**2.40**	**27.1**	**0.0**	**16.7**
CTFR modulators	128.6	0.6	2.16	28.8	0.0	25.4
Mucolytics with specific action	14.4	0.1	0.24	13.8	0.0	13.6
NSAIDs	**139.4**	**0.6**	**2.34**	**-6.7**	**16.9**	**-7.8**
Traditional NSAIDs	93.7	0.4	1.57	-8.5	12.3	-9.4
Coxib	38.3	0.2	0.64	-2.1	3.8	-2.0
Oxicam	7.0	0.0	0.12	-6.5	0.8	-8.3
Other non-steroidal anti-inflammatory/anti-rheumatic	0.4	0.0	0.01	-13.7	0.0	-14.9
Contrast agents	**92.0**	**0.4**	**1.54**	**-6.6**	**0.1**	**-11.8**
Radiocontrast agents	67.6	0.3	1.13	-6.7	0.1	-12.5
MRI contrast agents	21.8	0.1	0.36	-4.7	0.0	-9.3
Contrast agents for ultrasound	2.7	0.0	0.05	-15.2	0.0	-15.5
Thyroid medicines	**73.1**	**0.3**	**1.23**	**7.3**	**23.0**	**1.2**
Thyroid hormones	69.7	0.3	1.17	7.7	21.7	1.3
Antithyroid preparations	3.4	0.0	0.06	0.0	1.4	-0.5
Radiopharmaceuticals	**63.7**	**0.3**	**1.07**	**29.1**	**0.0**	**-2.7**
Radiopharmaceuticals for cancer detection	21.7	0.1	0.36	19.0	0.0	-0.9
Oncological therapeutic	18.4	0.1	0.31	191.7	0.0	73.9
Thyroid diagnostic radiopharmaceuticals	8.9	0.0	0.15	26.3	0.0	-2.9
CNS diagnostic radiopharmaceuticals	8.8	0.0	0.15	-28.3	0.0	-24.2
Radiopharmaceuticals for inflammation and infection detection	1.7	0.0	0.03	33.2	0.0	113.1
Cardiovascular system diagnostic radiopharmaceuticals	1.2	0.0	0.02	-26.8	0.0	-19.3
Iodized radiopharmaceuticals for therapeutic use	1.1	0.0	0.02	-14.5	0.0	-20.6
Respiratory system diagnostic radiopharmaceuticals	0.6	0.0	0.01	8.1	0.0	23.8
Other diagnostic radiopharmaceuticals	0.5	0.0	0.01	408.7	0.0	178.2
Hepatic and reticuloendothelial system diagnostic radiopharmaceuticals	0.4	0.0	0.01	7.5	0.0	12.4
Renal system diagnostic	0.3	0.0	0.01	271.1	0.0	30.0
Skeletal system diagnostic	0.1	0.0	0.00	28.9	0.0	-14.7
Radiopharmaceuticals with analgesic/anti-inflammatory action	0.1	0.0	0.00	-52.0	0.0	-54.0
Antimigraine medicines	**61.2**	**0.3**	**1.03**	**2.7**	**0.9**	**5.9**
Triptans	59.0	0.3	0.99	-0.9	0.8	0.2

Continued

Table 3.21. Continued

Group and subgroup	Total expenditure (*million*)	% on NHS expend.	Expenditure (per capita)	Δ % 20-19	DDD/1000 inhab. per day	Δ % 20-19
Monoclonal antibodies	2.2	0.0	0.04	2,811.1	0.1	204.5
Other antimigraine medicines	0.0	0.0	0.00	-2.5	0.0	-7.6
Ergot alkaloids	0.0	0.0	0.00	26.2	0.0	-17.8
Antidementia medicines	**26.3**	**0.1**	**0.44**	**-4.7**	**2.5**	**-3.0**
Anticholinesterases	17.7	0.1	0.30	-9.0	1.4	-7.0
Other antidementia medicines	8.6	0.0	0.14	5.4	1.1	3.0

Table 3.22. Groups of drugs used during the COVID-19 pandemic

Group and subgroup	Total expenditure (*million*)	Per capita expenditure	Δ % 20-19	Packages per 10,000 inhab.	Δ % 20-19
Medicines used in critically ill patients	**434.2**	**7.28**	**8.9**	**86.5**	**31.6**
Oxygen	251.7	4.22	1.7	71.6	40.4
Injectable corticosteroids	13.1	0.22	4.9	3.3	-0.9
Injectable cardiac stimulants	16.1	0.27	10.9	1.9	19.7
Injectable antipyretics	4.2	0.07	-15.7	1.7	-29.8
Injectable general anaesthetics	20.3	0.34	90.2	1.4	54.6
Injectable pain therapy	2.4	0.04	-9.0	1.4	-8.1
Injectable local anaesthetics	4.2	0.07	-30.9	1.3	-14.1
Injectable NSAIDs	1.8	0.03	-20.4	1.2	-21.6
Injectable hypnotics and sedatives	17.3	0.29	59.7	0.6	83.9
Injectable curares	21.5	0.36	454.0	0.5	181.2
Injectable ascorbic acid	0.6	0.01	144.7	0.5	102.7
Injectable antihemorrhagics	15.5	0.26	7.2	0.4	-9.6
Injectable antidotes	45.3	0.76	-5.3	0.2	-9.6
Injectable antiemetics	4.2	0.07	-11.0	0.2	-6.9
Injectable anxiolytics	1.8	0.03	13.0	0.2	7.5
Injectable thrombolytics	16.1	0.27	1.9	0.1	8.9
Injectable xanthines	0.0	0.00	-0.3	0.1	1.9
Injectable mucolytics	0.0	0.00	-46.5	0.0	-46.0
Group and subgroup	**Total expenditure (*million*)**	**Per capita expenditure**	**Δ % 20-19**	**DDD/1000 inhab**	**Δ % 20-19**
Medicines used in the treatment of COVID-19 patients	**701.4**	**11.76**	**23.4**	**20.7**	**8.5**
Heparins	246.8	4.14	8.6	9.8	6.2
Ruxolitinib	96.2	1.61	14.3	58.9	58.9
Tocilizumab	58.2	0.98	18.8	51.7	51.7
Canakinumab	52.2	0.87	22.9	33.2	33.2
Remdesivir	52.0	0.87	-	86.0	86.0
Azithromicyn	45.2	0.76	4.9	20.1	20.1
Baricitinib	35.9	0.60	33.9	12.0	12.0
Darunavir/Cobicistat	31.5	0.53	-21.8	7.9	7.9
Methylprednisolone	18.9	0.32	3.6	8.3	8.3
Tofacitinib	12.8	0.22	33.5	0.7	0.7
Dexamethasone	11.9	0.20	15.6	31.2	31.2
Hydroxychloroquine	10.8	0.18	16.6	7.5	7.5
Sarilumab	9.5	0.16	53.9	3.6	3.6
Hydrocortisone	8.7	0.15	-0.9	3.6	3.6
Anakinra	6.9	0.12	24.5	2.2	2.2
Lopinavir/Ritonavir	2.2	0.04	9.3	4.0	4.0
Colchicine	1.5	0.03	4.6	1.5	1.5
Prednisolone	0.0	0.00	-27.2	0.8	0.8

3.1 Antineoplastic and immunomodulating agents

Antineoplastic and immunomodulating agents were the therapeutic category with the highest public expenditure in 2020, amounting to 6,393 million euros (27.8% of overall expenditure), with a 6.2% increase compared to 2019 (Box. Main indices of expenditure, consumption and exposure).
The overall per capita expenditure for such medicines was 107.19 euros, mainly justified by the purchase by public health facilities (102.88 euros per capita), thus recording a sharp increase compared to the previous year (+6.2%). On the contrary, the contribution provided through the NHS outpatient care was lower (4.30 euros per capita) (Table 3.1).
Consumption for this category of drugs was 16.9 DDD/1000 inhabitants per day, with a 3.0% increase compared to 2019 (Table 3.2), which confirms the growing trend of the last seven years.
The analysis of the drug utilisation profile by age group and gender (including approved care regime and *per conto* 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 (4.7% compared to 3.6% in women), probably due to the increase in the incidence of prostate cancer in this population. The value of per capita expenditure for antineoplastic drugs is higher in women than in men and increases with age, reaching a greater value in men aged over 75 (24.8 euros per capita compared to 13.1 euros in women).
As regards pharmaceuticals under approved care regime, per capita expenditure was 4.30 euros, with a 2.0% increase compared to 2019. This trend was determined by an increase in consumption (+1.7%) and a slight shift towards more expensive medicines (mix effect: +0.5%); however, prices are stable (-0.1%) (Table 3.9). Under this supply regime, aromatase inhibitors are the first category both in terms of expenditure (2.18 euros per capita) and in terms of 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 0.77 euros and 0.59 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 (1.37 euros) and by consumption (1.7 DDD) (Table 3.10). It is recorded within the first 30 active ingredients by expenditure under approved care regime (Table 3.11) and it is the first active ingredient in its category ranking within the first 30 molecules with the greatest variation in expenditure under approved care regime compared to the previous year (Table 3.13). 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 3.14).
As regards the purchases by public health facilities, an increase was reported in expenditure (+6.0%) and consumption (+3.8%) compared to 2019, although a 6.6% reduction in prices was also recorded.

For this category a shift is recorded towards more expensive medicines (mix effect: +9.4%), with a consequent increase of the average DDD cost (+2.2%) (Table 3.16). Monoclonal antibodies are the first category in terms of per capita expenditure (25.71 euros), with a 2.4% decrease compared to 2019. They also record a decrease in consumption (-2.0%) and in prices (-13.7%), although a remarkable shift was recorded towards more expensive drugs (mix effect: +15.4%). Selective immunosuppressants (13.47 euros) and other immunosuppressants (9.84 euros) rank respectively second and third by expenditure. For these two categories, increases were found in terms of both expenditure and consumption compared to the previous year. Another category with high expenditure increase in 2020 was protein kinase inhibitors, namely: GFR TKI +42.7%; ALK inhibitors +30.6%; BTK TKI +29.1% and BRAF inhibitors +24.7%. In 2020 lenalidomide was the active ingredient with the highest per capita expenditure (5.40 euros), accounting for 5.3% of the expenditure for this category (Table 3.17). This active ingredient records a 23.0% expenditure increase and a 7.8% increase by average DDD cost (132.58 euros) compared to the previous year. Instead, pembrolizumab was the second active ingredient by expenditure (4.86 euros), but with a 38.6% decrease in average cost per day of therapy. Nivolumab (3.77 euros) also showed a remarkable decrease (-27.4%) in the average cost per day of therapy. Daratumumab, an anti-CD38 monoclonal antibody, authorised in monotherapy for patients with relapsed/refractory multiple myeloma or not eligible for stem cell treatment, recorded a significant increase in expenditure (+35.4%), whereas its average DDD cost was unchanged (186.5 euros).

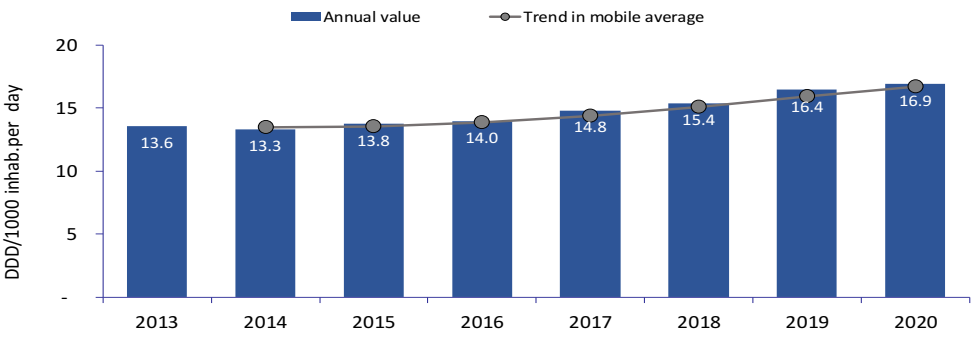
The active ingredient osimertinib, authorised for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations, records the largest increase in expenditure (>100%), and a major increase of the average DDD cost (+10.8%). Eculizumab, a drug used in the treatment of adults and children with paroxysmal nocturnal hemoglobinuria (PNH), is the most expensive active ingredient by DDD cost (774.06 euros).

Among the first 30 active ingredients purchased by public health facilities, no less than 21 belong to antineoplastic and immunomodulating agents (Table 3.18), which also represent half of the first 30 active ingredients with the greatest variation in expenditure (Table 3.20). With an aim to achieve further information on the use of medicines belonging to the same therapeutic area, analyses have been performed on the historical series of consumption by active ingredient and by region and on the efficiency in the absorption of resources according to the presence of patent-expired medicines and on a regional basis. These analyses focused on cancer medicines, immunosuppressants and immunomodulators and on drugs for multiple sclerosis (Table 3.1.1 and following).

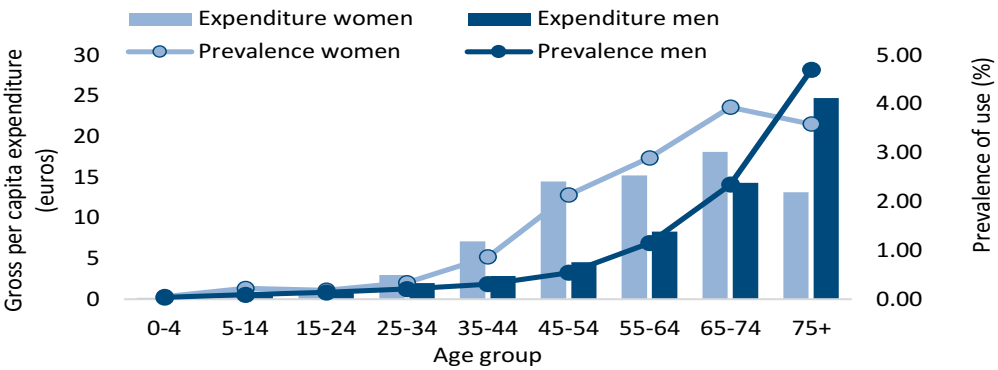
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Antineoplastic and immunomodulating agents

Public expenditure* in million euros (% over total)	**6,392.7**	**-27.8**
Δ % 2020-2019		6.2%
Regional range of gross per capita expenditure	76.0	126.5
DDD/1000 inhab. per day (% over total)	**16.9**	**-1.5**
Δ % 2020-2019		3.0%
Regional range of DDD/1000 inhab. per	13.7	20.6

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities



Distribution, by age and gender, of expenditure, prevalence of use and consumptions under approved care regime and *per conto* distribution in 2020 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0,2	0,2	0,2	0,1	0,1	0,1
5-14	0,6	1,2	0,9	0,4	1,1	0,7
15-24	1,1	1,1	1,1	0,6	0,8	0,7
25-34	2,0	3,0	2,5	0,9	1,6	1,3
35-44	2,8	7,1	5,0	1,4	6,0	3,7
45-54	4,5	14,5	9,6	2,5	16,5	9,6
55-64	8,3	15,2	11,9	5,3	18,8	12,3
65-74	14,3	18,1	16,3	10,8	24,7	18,2
75+	24,8	13,1	17,8	27,1	20,4	23,1

3.1.1 Antineoplastic medicines

National data on consumption and expenditure

In the past seven years, expenditure for antineoplastic medicines increased by about 87%, shifting from 34.8 euros in 2014 to 65.3 euros in 2020, with an 11% average annual increase. At the same time, the average DDD cost increased by 59.4%, from 10.92 to 17.41 euros (Figure 3.1.1a). Consumption shows a 2.7% average annual increase, with 10.2 DDD/1000 inhabitants per day in 2020 (Table 3.1.1a). The first three categories with the highest expenditure are monoclonal antibodies (MAbs). MAbs inhibiting immune check points rank first (10.14 euros), with a minimal expenditure decrease (-0.6%) compared to 2019 and a sharp decrease in average DDD cost (-30.3%), despite an increase in consumption (+42.2%). MAbs blocking growth factors (8.32 euros) rank second, with a decrease in all the indicators considered (expenditure -13.0%; consumption -10.0%; average DDD cost -3.6%) compared to 2019. CAR-Ts are the category with the highest change in expenditure (>100%), and record a 20% increase in the average DDD cost. Combination of antineoplastics, such as the cytarabine/daunorubicin combination, approved for the treatment of therapy-related acute myeloid leukemia or with myelodysplasia-related disorders in adults, show a significant increase in expenditure (>100%), despite a 5% decrease in average DDD cost. Individual active ingredients follow the same trend as the categories; in fact, pembrolizumab (4.86 euros) and nivolumab (3.77 euros) rank first by expenditure. The molecule with the highest average DDD cost (stable compared to the previous year) is daratumumab (186.50 euros), while bevacizumab shows the lowest cost (63.47 euros), with a 14.7% decrease, maybe due to the entry into the biosimilar drug market.
For this category, patent-covered drugs represent 94.7% of expenditure and 48.2% of consumption. Generics accounts for 37.1% of expenditure and 58.3% of the consumption of patent-expired products (Table 3.1.1c).

Figure 3.1.1a. Antineoplastic medicines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

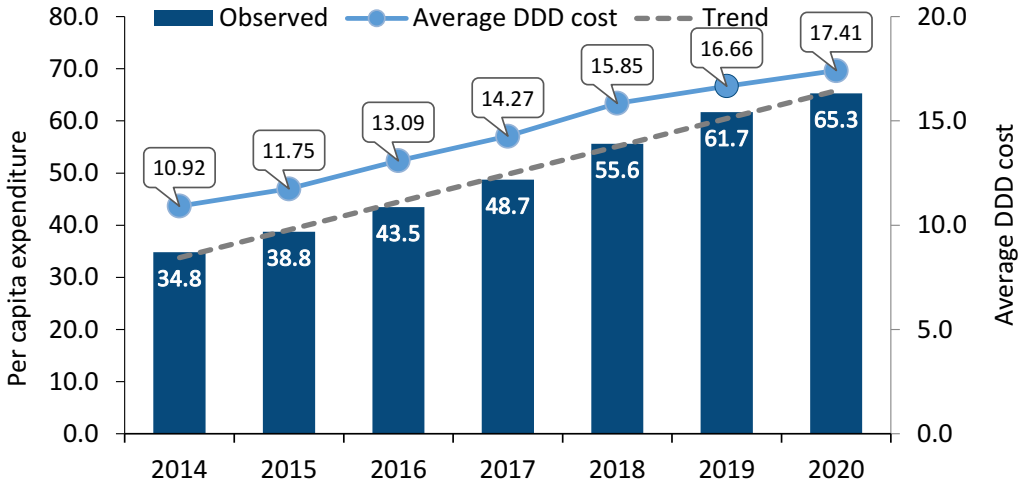


Table 3.1.1a. Antineoplastic medicines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Monoclonal antibodies inhibiting immune check points	10.14	-0.6	55.9	0.2	42.2	106.8	113.57	-30.3
Monoclonal antibodies blocking growth factors	8.32	-13.0	0.2	0.4	-10.0	6.0	62.10	-3.6
Monoclonal antibodies acting on specific targets	5.57	12.8	9.9	0.5	-10.0	4.2	29.88	24.9
Endocrine therapy - aromatase inhibitors	4.17	4.9	8.7	3.6	4.0	6.4	3.19	0.5
Cytostatic antineoplastics - other cytostatics	3.96	0.3	11.0	0.4	5.7	4.8	24.77	-5.4
VEGFR-associated multitarget tyrosin kinase inhibitors	3.83	15.4	11.1	0.1	16.6	17.2	106.34	-1.3
BRC-ABL tyrosin kinase inhibitors	3.51	-2.9	-5.3	0.2	4.0	4.1	59.02	-7.0
CDK protein kinase inhibitors	3.42	34.1	-	0.1	32.5	-	80.89	0.9
Bruton tyrosine kinase (BTK)	2.86	29.5	-	0.1	29.4	-	129.88	-0.2
Cytostatic antineoplastics – antimetabolites	2.73	-1.3	-0.3	0.7	-1.1	-4.9	11.34	-0.5
EGFR tyrosin kinase inhibitors	2.28	38.8	10.0	0.1	15.5	4.5	106.36	19.8
Endocrine therapy – antiandrogens	1.99	20.1	40.8	0.8	-10.6	-5.1	6.45	33.9
Endocrine therapy - hormones and GnRH analogues	1.95	1.1	0.0	1.1	4.7	2.2	4.65	-3.7
Monoclonal antibodies conjugated to drugs	1.69	8.1	33.3	0.0	12.6	37.7	249.53	-4.2
JAK tyrosin kinase inhibitors	1.61	16.6	129.4	0.0	15.3	134.2	109.51	0.9
ALK tyrosin kinase inhibitors	1.24	30.9	-	0.0	26.1	-	165.85	3.5
BRAF tyrosin kinase inhibitors	1.24	25.1	16.4	0.0	66.4	39.6	109.47	-25.0
Cytotoxic antineoplastics - products of natural derivation – taxanes	0.74	-10.5	5.6	0.2	-4.7	2.8	11.66	-6.4
MEK tyrosin kinase inhibitors	0.67	32.6	-	0.0	86.6	-	63.61	-29.1
Endocrine therapy - antiestrogens	0.64	-14.1	3.1	1.1	-3.8	-1.6	1.66	-11.0
Cytotoxic antineoplastics - products of natural derivation – others	0.57	-5.5	2.1	0.1	-1.3	0.5	25.36	-4.6
Cytotoxic antineoplastics - cytotoxic antibiotics -anthracyclines and related substances	0.49	4.6	-1.0	0.1	-0.7	-1.5	12.72	5.0
MTOR protein kinase inhibitors	0.49	-8.9	-12.4	0.0	3.4	-8.2	106.15	-12.2
Cytostatic antineoplastics - alkylating agents	0.36	-3.8	-11.3	0.2	-8.2	-5.0	5.62	4.4
CAR-T	0.28	1304.3	-	0.0	1066.9	-	119,133.07	20.0
Other protein kinase inhibitors	0.26	25.5	-	0.0	66.2	-	402.63	-24.7
Combination of antineoplastic agents	0.14	252.1	-	0.0	269.7	-	3803.50	-5.0
Cytostatic antineoplastics – platinum compounds	0.10	8.4	-0.9	0.2	-6.3	0.0	1.25	15.3
Cytotoxic antineoplastics – other cytotoxic antibiotics	0.02	-62.5	-20.5	0.0	-21.9	-10.1	2.18	-52.2
Antineoplastic medicines	**65.28**	**5.8**	**11.0**	**10.2**	**1.0**	**2.7**	**17.41**	**4.5**

Continued

Table 3.1.1a.
Continued

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
pembrolizumab	4.86	3.3	-	0.1	67.8	-	107.78	-38.6
nivolumab	3.77	-17.4	-	0.1	13.4	-	111.96	-27.4
daratumumab	3.54	35.4	-	0.1	35.0	-	186.50	0.0
ibrutinib	2.86	29.5	-	0.1	29.4	-	129.88	-0.2
pertuzumab	2.72	13.5	48.3	0.1	13.2	46.7	143.54	0.0
palbociclib	2.46	12.7	-	0.1	10.4	-	86.61	1.9
bevacizumab	2.35	-27.5	-3.1	0.1	-15.2	0.9	63.43	-14.7
osimertinib	1.87	126.9	-	0.0	104.2	-	146.05	10.8
abiraterone	1.84	5.5	12.1	0.1	5.2	15.2	85.36	0.0
enzalutamide	1.74	19.3	125.4	0.1	19.0	142.7	85.65	0.0

Table 3.1.1b. Antineoplastic medicines, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	33.79	35.47	39.85	43.20	51.23	55.81	58.40	4.6
Valle d'Aosta	26.10	34.09	38.78	39.23	42.12	45.05	43.77	-2.8
Lombardy	29.06	33.32	37.68	41.40	45.91	52.41	56.90	8.6
A.P. of Bolzano	37.25	39.22	41.51	52.19	58.05	69.27	71.80	3.7
A.P. of Trento	26.89	27.89	34.88	40.11	44.21	45.51	46.86	3.0
Veneto	33.43	36.14	40.73	45.22	51.97	55.57	61.51	10.7
Friuli VG	41.63	43.42	47.65	59.83	63.61	70.58	72.63	2.9
Liguria	35.62	41.03	46.40	51.35	61.61	65.86	70.93	7.7
Emilia R.	35.29	40.10	45.16	49.82	59.65	64.79	67.80	4.6
Tuscany	41.67	44.71	51.92	55.86	58.01	63.86	68.16	6.7
Umbria	37.54	43.26	50.69	54.99	63.97	71.95	78.46	9.0
Marche	40.26	45.06	51.04	55.56	62.70	69.86	75.92	8.7
Lazio	33.56	36.91	39.29	46.22	57.29	63.33	67.06	5.9
Abruzzo	42.62	46.24	51.17	54.68	63.72	66.89	70.72	5.7
Molise	30.69	33.37	39.52	48.10	53.88	61.52	66.21	7.6
Campania	40.52	46.09	51.51	57.82	66.14	75.29	78.23	3.9
Puglia	39.70	44.04	48.93	56.29	65.53	69.81	71.58	2.5
Basilicata	40.20	45.78	53.74	60.87	64.58	74.01	77.57	4.8
Calabria	31.72	38.38	43.00	48.85	56.41	63.17	63.41	0.4
Sicily	28.44	32.13	36.28	42.45	45.62	53.55	55.50	3.6
Sardinia	37.87	42.18	46.31	50.30	56.71	62.93	68.17	8.3
Italy	**34.83**	**38.76**	**43.4**	**48.73**	**55.6**	**61.68**	**65.2**	**5.8**
North	32.68	36.21	40.79	45.33	51.98	57.29	61.29	7.0
Centre	37.36	40.97	45.75	51.20	58.73	65.00	69.43	6.8
South and Islands	36.33	41.02	45.90	52.02	58.93	65.95	68.47	3.8

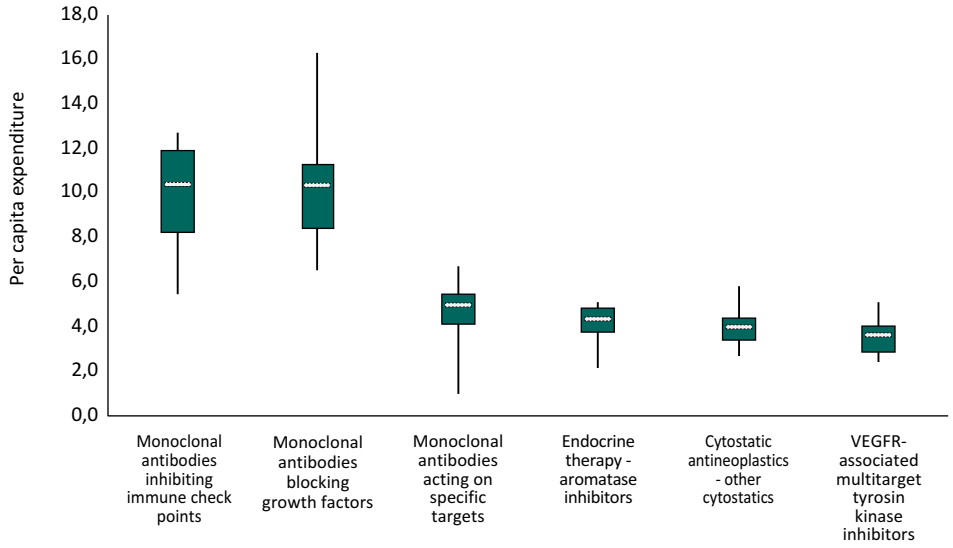
Table 3.1.1c. Prescription of antineoplastic medicines with patent expired* in 2020

Categories	Per capita	%	Δ % 20-19	DDD/1000 inhab.	%	Δ % 20-19	Average DDD cost
Patent expired	3.48	5.3	4.4	5.3	51.8	-0.1	1.79
Generic	1.29	37.1	5.7	3.1	58.3	-1.1	1.14
Ex originator	2.19	62.9	3.6	2.2	41.7	1.4	2.70
Patent covered	61.80	94.7	5.9	4.9	48.2	2.1	34.18
Antineoplastic	**65.28**	**100.0**	**5.8**	**10.2**	**100.0**	**1.0**	**17.41**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.1.1c. Antineoplastic medicines, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



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 checkpoint mechanisms. This **upward consumption trend** is likely to increase, especially in light of the presumable further extensions of indication for use, in combination with other drugs in various solid tumours, which reported positive results of therapeutic improvement. It is noteworthy that the **increase in consumption does not correspond to an increase in expenditure**, which, on the contrary, remains substantially stable due to a reduction in the cost per unit of dose.
- Another relevant phenomenon that could reasonably be confirmed in the short to medium term 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 necessary to read the 2020 consumption and expenditure data in light of the COVID-19 emergency, which has had a significant impact on patients' (including oncological patients') access to hospitals. Considering the data trend, which substantially confirm all the trends already detected in previous years, it is possible to say that **there has not been a particularly significant impact of the pandemic on cancer drug therapies**, contrary to what was recorded for surgical treatments and screening procedures. In this regard, an important aspect to evaluate will be the incidence of new treatments in 2020 compared to previous years.

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3.1.2. Immunosuppressants and immunomodulating agents

National data on consumption and expenditure

In the past seven years, expenditure for immunosuppressants and immunomodulating agents increased by about 38%, shifting from 21.5 euros per capita in 2014 to 29.7 euros in 2020, with a 5.5% average annual increase. At the same time, the average DDD cost increased by 14.2%, moving from 24.4 to 20.9 euros (figure 3.1.1a). Consumption shows an 8.2% average annual increase, with 3.9 DDD/1000 inhabitants per day in 2020 (Table 3.1.1a). In 2020, the two categories with the highest expenditure were other immunosuppressants (7.33 euros) and interleukin inhibitors (7.19 euros), which increased respectively by 18.8% and 22.7%. Particularly interesting is the increase in the average DDD cost (+6.5%) of the other immunosuppressants, probably due to the trend of lenalidomide, an authorised molecule, as well as to the treatment of multiple myeloma and mantle cell lymphoma, also for myelodysplastic syndromes associated with cytogenetic anomaly (+7.8%). TNF-α inhibitors, despite increasing in consumption (+5.8%), recorded a decrease in expenditure (-16.6%), due to the reduction in the average DDD cost (-21.4%) compared to the previous year, maybe due to the use of biosimilar drugs. The interferon subgroup also shows a reduction of all the indicators considered. Analysing the trend of the individual active ingredients, lenalidomide shows the greatest increase in terms of expenditure (+23%), followed by vedolizumab (+12.5%), used 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. Instead, adalimumab records the greatest reduction in expenditure (-20.1%), and also shows a 29.4% reduction in the average DDD cost; etanercept reports a -13.6% expenditure decrease, while its reduction in average DDD cost was -13.5%, probably due to the marketing of biosimilars.

Patent-covered immunosuppressants and immunomodulating agents account for 94.8% of expenditure and 74.7% of consumption. Within patent-expired products, use and expenditure are almost entirely attributable to ex-originators (Table 3.1.2c).

Figure 3.1.2a. Immunosuppressants and immunomodulating agents, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

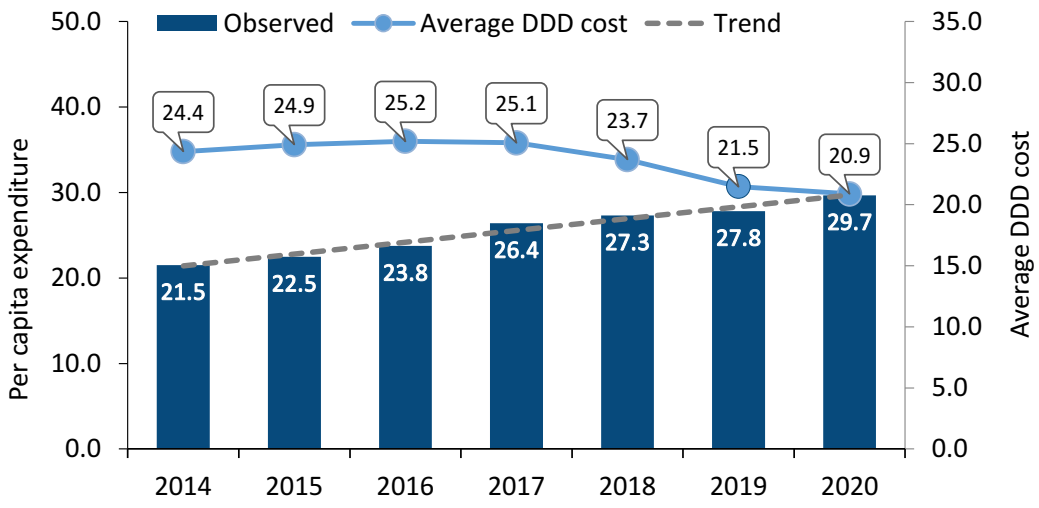


Table 3.1.2a. Immunosuppressants and immunomodulating agents, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Other immunosuppressants	7.33	18.8	17.3	0.2	11.3	17.6	117.40	6.5
Interleukin inhibitors	7.19	22.7	31.9	0.7	24.0	36.5	28.49	-1.3
Tumor necrosis factor alpha inhibitors (TNF-alpha)	5.82	-16.6	-8.9	1.4	5.8	6.8	11.69	-21.4
Immunosuppressant monoclonal antibodies	3.17	7.8	17.6	0.1	19.6	61.2	78.21	-10.1
Calcineurin inhibitors	1.51	-0.7	-2.3	0.6	1.9	0.9	6.92	-2.8
Selective T cell co-stimulation modulators	1.15	4.1	14.3	0.1	2.9	12.1	48.67	0.8
Selective immunosuppressants	1.03	3.2	11.0	0.6	6.3	6.5	4.86	-3.2
JAK tyrosin kinase inhibitors	0.82	51.0	-	0.1	45.4	-	26.07	3.6
MTOR protein kinase inhibitors	0.66	10.0	4.2	0.1	9.2	6.6	17.34	0.5
Growth factors	0.64	-15.8	-12.1	0.1	7.8	1.0	16.40	-22.1
Other immunomodulators	0.30	4.1	7.0	0.0	-11.0	6.7	160.19	16.7
Interferons	0.06	-19.8	-38.0	0.0	-19.5	-37.4	17.20	-0.6
Immunosuppressants and immunomodulating agents	**29.67**	**6.6**	**5.5**	**3.9**	**9.4**	**8.2**	**20.88**	**-2.8**
lenalidomide	5.40	23.0	14.4	0.1	13.7	17.7	132.58	7.8
eculizumab	1.98	6.1	9.1	0.0	11.6	12.6	774.06	-5.2
secukinumab	1.88	9.0	-	0.2	8.8	-	31.67	-0.1
ustekinumab	1.85	8.4	18.6	0.3	12.6	26.0	18.97	-4.0
adalimumab	1.79	-20.1	-13.0	0.5	12.9	10.3	8.93	-29.4
etanercept	1.77	-13.6	-10.9	0.3	-0.5	1.0	16.88	-13.5
abatacept	1.14	3.9	14.2	0.1	2.6	11.9	49.23	1.0
golimumab	1.06	-12.4	6.8	0.1	2.8	12.8	23.29	-15.0
vedolizumab	1.04	12.5	-	0.1	24.8	-	32.65	-10.1
pirfenidone	1.02	8.0	23.9	0.0	7.8	25.7	64.46	-0.1

Table 3.1.2b. Immunosuppressants and immunomodulating agents, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	18.77	18.98	19.75	22.14	23.19	25.05	28.67	14.4
Valle d'Aosta	12.16	13.77	16.03	13.10	12.98	16.09	20.41	26.8
Lombardy	18.66	19.40	20.16	22.58	23.01	23.27	24.86	6.8
A.P. of Bolzano	24.36	25.71	27.58	29.96	30.40	30.66	32.33	5.5
A.P. of Trento	15.14	15.61	17.41	18.67	19.52	20.50	23.00	12.2
Veneto	20.15	20.61	21.80	23.58	23.71	24.36	27.46	12.7
Friuli VG	21.76	22.41	24.24	28.55	30.86	32.20	36.27	12.6
Liguria	16.48	16.84	19.20	20.95	22.54	23.59	26.53	12.5
Emilia R.	18.45	20.23	22.43	24.55	26.02	25.57	28.32	10.8
Tuscany	25.02	26.53	29.43	30.40	26.33	27.45	31.60	15.1
Umbria	21.92	23.13	24.87	27.22	30.75	32.74	34.48	5.3
Marche	23.87	25.46	28.02	30.55	33.31	34.30	36.88	7.5
Lazio	20.50	20.91	20.58	25.54	27.34	25.03	24.76	-1.1
Abruzzo	23.32	24.49	24.79	27.76	31.71	34.48	37.50	8.8
Molise	25.28	26.54	28.72	31.54	33.27	39.91	37.72	-5.5
Campania	24.12	26.04	26.66	29.80	32.00	34.12	35.16	3.0
Puglia	29.19	29.78	31.42	33.05	35.76	35.70	34.80	-2.5
Basilicata	24.07	25.99	27.38	31.18	31.75	34.03	34.98	2.8
Calabria	26.84	27.51	28.75	31.66	34.56	37.77	38.82	2.8
Sicily	20.23	21.50	23.84	27.97	27.41	26.61	27.52	3.4
Sardinia	26.63	27.72	27.95	29.67	28.48	28.58	31.70	10.9
Italy	**21.52**	**22.48**	**23.75**	**26.41**	**27.31**	**27.83**	**29.67**	**6.6**
North	18.91	19.67	20.93	23.18	24.00	24.60	27.19	10.5
Centre	22.51	23.49	24.72	27.88	28.05	27.60	29.28	6.1
South and Islands	24.61	25.86	27.16	30.10	31.57	32.61	33.49	2.7

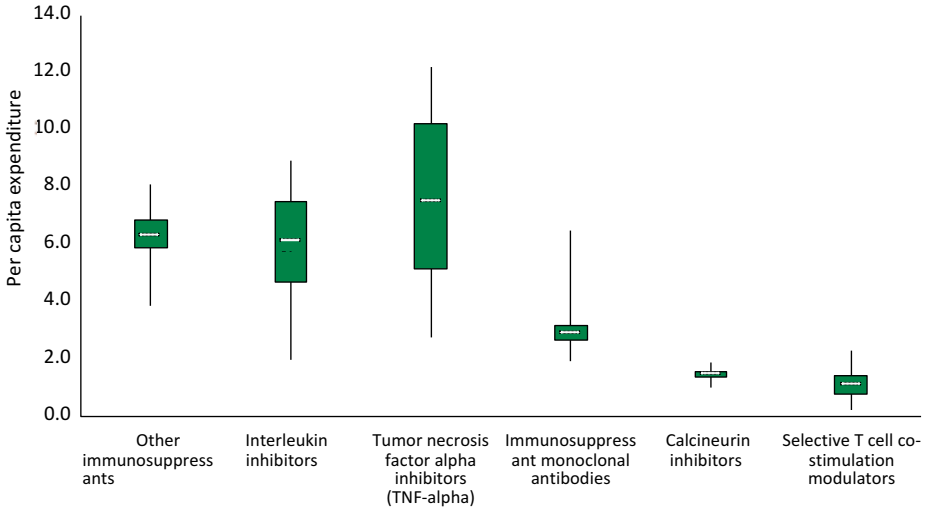
Table 3.1.2c. Prescription of immunosuppressants and immunomodulating agents with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	1.55	5.2	15.1	1.0	25.3	13.9	4.30
Generic	0.10	6.7	15.5	0.2	22.8	16.8	1.27
Ex originator	1.44	93.3	15.1	0.8	77.2	13.0	5.19
Patent covered	28.13	94.8	6.2	2.9	74.7	7.9	26.51
Immunosuppressan and immunomodulating agents	**29.67**	**100.0**	**6.6**	**3.9**	**100.0**	**9.4**	**20.88**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.1.2c. Immunosuppressants and immunomodulating agents, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- In 2020, the two categories with the highest expenditure were other immunosuppressants (7.33 euros) and interleukin inhibitors (7.19 euros), which increased compared to the previous year.
- The **TNF-α inhibitors** subgroup recorded the greatest reductions in expenditure (-16.6%), along with the greatest regional variability.
- The increase in the use of immunosuppressants and immunomodulating agents proposed since the beginning of the pandemic as a possible therapeutic option against pneumonia in the course of COVID-19 has not led to an increase in expenditure. This is maybe due to the rapid response shown by the Italian research system, whereby the pressing request for the use of such drugs in emergency conditions was turned into clinical trials with drugs provided free of charge.

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3.2 Cardiovascular system

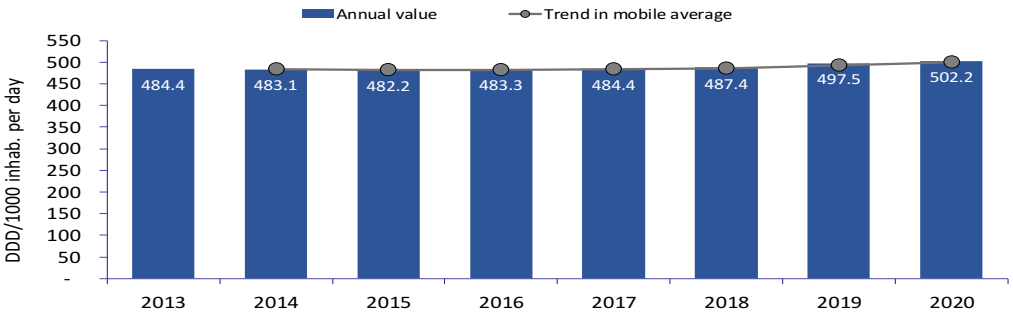
Cardiovascular diseases are the main cause of death in the world, with about 18 million deaths every year, accounting for about 30% of the total. Although death rates from cardiovascular diseases have decreased in recent years, the prevalence of these conditions is increasing in several countries, including Italy. This is partly due to the population ageing and partly to a gradually earlier onset and diagnosis of such diseases, which have increased in recent years. Between 2009 and 2018, the prevalence of arterial hypertension increased from 25.7% to 30.3%, the prevalence of ischemic heart disease from 3.9% to 4.3%, while ischemic stroke from 2.7% to 4.7% and congestive heart failure from 1% to 1.3%.
In 2020, cardiovascular drugs were the second therapeutic category with the highest public expenditure for 2020, equal to 3,276 million euros and 14.2% of overall public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was 54.92 euros, mainly due to outpatient pharmaceutical expenditure (49.05 euros per capita), reporting a +2.2% increase compared to the previous year. Instead, expenditure due to purchases by public health facilities is significantly lower (5.87 euros per capita) (Table 3.1).
Consumption for this category of drugs was 502.2 DDD/1000 inhabitants per day, with a 1.0% increase compared to 2019, so confirming the slightly growing trend of the recent years. Such figures can be attributed to the approved care regime (484.7 DDD/1000 inhabitants per day), accounting for 96.5% of the total doses of the category (Table 3.2).
Analysis of the drug use profile by age group and gender confirms the constant increase in the use of cardiovascular drugs with increasing age and for both genders, with a maximum prevalence recorded in people aged 75 and above. At the same time, the NHS per capita expenditure also increases with age, reaching 175.6 euros per capita in people aged 75 or over (187.6 euros per capita in men and 167.5 euros per capita in women).
As for the approved care regime (Table 3.9), there was an increase in expenditure, consumption and average DDD cost by respectively 1.9%, 1.3% and 0.6% compared to 2019. On the other hand, substantial stability (-0.3%) was recorded for prices, with a slight shift in prescription towards higher cost products (mix effect: +0.9%). In 2020, HMG-CoA reductase inhibitors (statins) confirm as the active ingredients with the highest per capita expenditure (8.04 euros), showing an increase in values compared to the previous year, both in terms of expenditure (+1.2%) and consumption (+3.3%), as well as a reduction in prices (-1.0%) and in the average cost per day of therapy (-2.1%), along with a shift towards lower cost products (mix effect: -1.0%). Angiotensin II receptor blockers are the second category with the highest per capita expenditure for this ATC (4.88 euros), showing an increase in almost all the indicators considered (expenditure 1.3%, DDD +0.8%, mix +0.5%, average DDD cost +0.5%). The largest expenditure changes compared to 2019 are instead attributable to other combinations of ACE inhibitors (+31%) and to combinations of various lipid modifying agents (+30.7%).
In 2020 atorvastatin confirms as the molecule with the highest per capita expenditure (4.26 euros), increasing by 4.5% compared to the previous year, also recording a 4.8% increase in consumption (Table 3.5).

This drug accounts for 9.2% of the outpatient pharmaceutical expenditure of the category, followed by the active ingredients bisoprolol and ramipril, which record per capita expenditure of 2.60 and 2.02 euros respectively.
Within the first 30 active ingredients by expenditure under approved care regime, atorvastatin records the highest figure (268.1 million), shifting from the 3rd rank in 2019 to the 1st in 2020 by per capita expenditure (Table 3.11), while ranking 2nd by consumption immediately after ramipril, with 48.8 DDD (Table 3.14) and showing a low regional variability in terms of consumption (Table 3.15). The ezetimibe/rosuvastatin combination shows the greatest variation in per capita expenditure (>100%) compared to the previous year, despite a 14.6% reduction in the average cost per day of therapy, probably attributable to the patent expiry and the consequent marketing of generic medicinal products (Table 3.13).
As for cardiovascular medicines purchased directly by public health facilities (Table 3.16), per capita expenditure was 5.87 euros, with a 13.2% increase compared to the previous year, and a 7.1% decrease in consumption. The expenditure increase compared to 2019 was therefore due to a 21.8% increase in the average DDD cost and to a shift towards more expensive medicines (mix effect +26.4%).
As for the therapeutic categories, the other cardiac preparations (ATC C01EB) (1.48 euros) exceeded the per capita expenditure recorded for drugs used in pulmonary arterial hypertension (1.47 euros).
In 2020 ranolazine is again the active ingredient with the highest per capita expenditure (1.38 euros), followed by macitentan (0.93 euros), an endothelin receptor antagonist indicated in the treatment of pulmonary arterial hypertension (Table 3.17). Significant increases in expenditure are also confirmed this year for the sacubitril/valsartan combination (+42%) and for the two PCSK9 inhibitors, evolocumab and alirocumab (respectively +31.5% and +39.9%). Overall ranolazine, macitentan and the sacubitril/valsartan combination account for 54.2% of the expenditure borne by public health facilities for cardiovascular system drugs.
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by region and on the efficiency in the absorption of resources according to the presence of patent-expired medicines and on a regional basis. 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 in the treatment of hypercholesterolemia, which provides a description of the baseline characteristics of patients undergoing treatment and their regional distribution (Section 4).

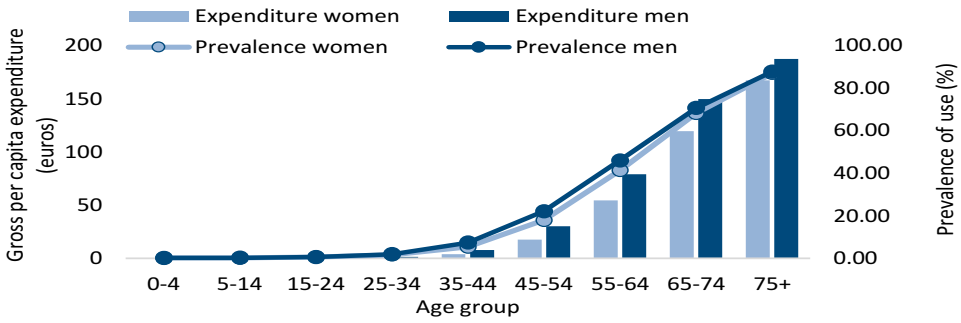
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Cardiovascular system

Public expenditure* in million euros (% over total)	**3,275.6**	**-14.2**
Δ % 2020-2019		3.3%
Regional range of gross per capita expenditure	37.4	67.8
DDD/1000 inhab. per day (% over total)	**502.2**	**-43.2**
Δ % 2020-2019		1.0%
Regional range of DDD/1000 inhab. per	374.9	615.7

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities



Distribution, by age and gender, of expenditure, prevalence of use and consumptions under approved care regime and *per conto* distribution in 2020 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab.per day		
	Men	Women	Total	Men	Women	Total
0-4	0.1	0.3	0.2	0.6	0.6	0.6
5-14	0.1	0.1	0.1	0.9	0.7	0.8
15-24	0.4	0.3	0.4	3.7	2.4	3.1
25-34	1.5	0.9	1.2	14.4	7.6	11.1
35-44	7.9	3.9	5.9	74.5	37.5	56.0
45-54	30.2	17.5	23.8	288.5	171.8	229.5
55-64	79.1	54.5	66.4	753.8	515.4	630.9
65-74	149.9	119.6	133.9	1,411.6	1,108.1	1,251.3
75+	187.6	167.5	175.6	1,840.2	1,633.3	1,716.4

3.2.1 Medicines for hypertension and heart failure

National data on consumption and expenditure

Consumption of medicines for hypertension and heart failure has been basically stable over the last seven years (CAGR +0.1%), recording a value of 378.9 DDD in 2020 and an average cost per day of therapy of 0.25 euros, with a 7.4% decrease compared to 2014 and a 1.3% decrease compared to the previous year (Figure 3.2.1a). The per capita expenditure value for these drugs was 34.22 euros, recording a 1.7% increase compared to 2019 and a 1.3% average annual reduction rate, calculated as of 2014 (Table 3.2.1a). Beta blockers are the therapeutic category with the highest per capita expenditure (5.50 euros), a 3.1% increase compared to the previous year, and an average cost per day of therapy of 0.33 euros, slightly higher than the value observed in the entire therapeutic class. The DDD/1000 inhabitants per day was 45.5, showing a 1.8% increase compared to 2019. Analysing the trend of expenditure and consumption for this subgroup over time, it is possible to note an annual increase, relating to the period 2014-2020, by 2.8% and 1.4%, respectively. The growing trend is also confirmed if compared to the previous year, with a 3.1% value for expenditure and 1.8% for consumption.

ACE inhibitors remain the category with the highest consumption (86 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 3.81 euros, albeit with a tendential reduction over time in all the values considered (CAGR expenditure -2.7%, CAGR consumption -0.9%). Bisoprolol is the substance with the highest per capita expenditure, recording a value of 2.62 euros, a 5.6% increase compared to the previous year, while ramipril recorded the highest value of DDD/1000 inhabitants per day (64.6).

Particularly interesting is the increase both in terms of expenditure (+41.9%) and consumption (+41.5%) 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.

In 2020, patent-expired drugs accounted for 86.6% of expenditure and for 93.9% of the doses (Table 3.2.1c.), with an average DDD cost of 0.23 euros, so proving stable compared to the previous year (+0.1%). The percentage of use of generic drugs was 36%, reporting a 2.6% increase compared to the previous year. However, ex-originators account for 73.7% of expenditure and for 64.0% of consumption.
Analysing the regional variability of the consumption of medicines for hypertension and heart failure, stratified by therapeutic category (Figure 3.2.1c.), it can be noted that ACE inhibitors is the category with the greatest variability. In fact, despite showing a median value of 77.6 DDD/1000 inhabitants per day, the range was found to be particularly wide (65.3-134.7 DDD/1000 inhabitants per day). On the other hand, beta blockers showed the least variability with respect to the central tendency value (median 43.5) and a less broad range (31.9-52.4 DDD/1000 inhabitants per day).

Figure 3.2.1a. Medicines for hypertension and heart failure, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

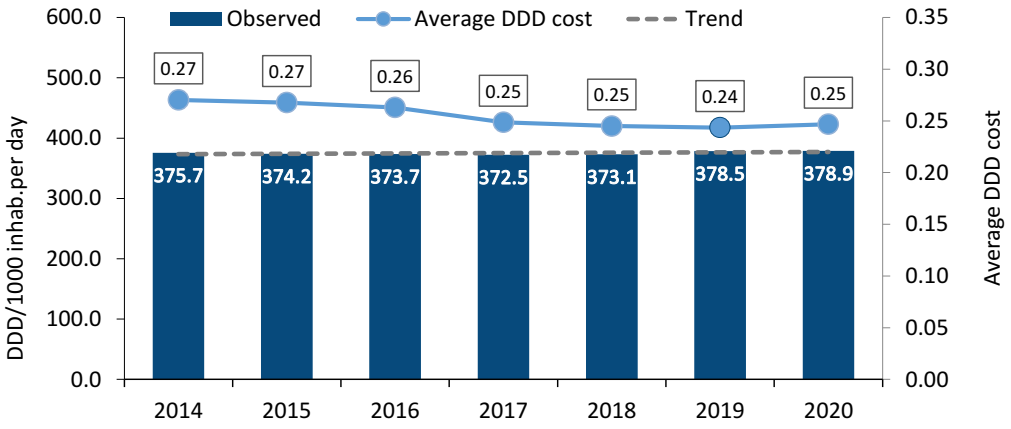


Table 3.2.1a. Medicines for hypertension and heart failure, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Beta blockers	5.50	3.1	2.8	45.5	1.8	1.4	0.33	1.0
Angiotensin II antagonists	4.89	1.6	-3.4	58.9	0.8	0.8	0.23	0.6
Calcium channel blockers	4.25	-0.2	-1.7	51.7	0.7	-0.7	0.22	-1.2
Angiotensin II receptor blockers and diuretics (combinations)	4.01	-1.6	-7.9	33.2	-1.7	-2.9	0.33	-0.2
ACE inhibitors	3.81	-2.6	-2.7	86.0	-1.7	-0.9	0.12	-1.2
ACE inhibitors and diuretics (combinations)	2.59	-3.8	-5.3	20.1	-3.4	-3.5	0.35	-0.6
ACE inhibitors and calcium channel blockers (combinations)	1.67	-3.0	5.0	12.0	0.4	10.5	0.38	-3.7
Alpha-adrenoreceptor antagonists	1.27	2.0	0.1	7.9	1.4	0.1	0.44	0.3
Angiotensin II receptor blockers and calcium channel blockers	1.21	13.8	4.1	8.3	16.5	20.0	0.40	-2.5
Angiotensin II receptor blockers and neprilysin inhibitor	1.16	41.9	-	0.7	41.5	-	4.58	0.0
High-ceiling diuretics, plain or in combination with potassium-sparing agents	1.06	-0.2	-0.1	31.2	-2.0	0.8	0.09	1.6
Beta blockers and diuretics (combinations)	0.69	1.7	0.9	7.5	1.4	2.7	0.25	0.0
Perindopril/indapamide/ amlodipine	0.62	31.7	-	3.6	31.4	-	0.47	0.0
Potassium-sparing diuretics	0.58	3.0	1.3	3.6	1.1	0.6	0.43	1.6
Calcium channel blockers (not dihydropyridines)	0.31	-6.6	-8.6	2.2	-7.3	-7.9	0.39	0.4
Thiazides and similars (including combinations)	0.24	-4.1	-3.4	4.0	-5.4	-5.3	0.16	1.1
Imidazoline receptor agonists	0.22	-3.1	-7.4	1.5	-5.7	-5.5	0.39	2.4
ACE inhibitors, other combinations	0.10	29.3	-	0.8	29.0	-	0.33	0.0
Aliskiren plain or in combination	0.05	-14.3	-17.0	0.2	-13.7	-16.8	0.89	-1.0
Alpha-2 adrenergic receptor	0.00	-52.1	-14.8	0.0	-50.1	-14.4	0.35	-4.4
Medicines for hypertension and heart failure	**34.22**	**1.7**	**-1.3**	**378.9**	**0.1**	**0.1**	**0.25**	**1.3**
bisoprolol	2.62	5.6	7.0	12.2	4.7	6.7	0.59	0.6
ramipril	2.02	-1.4	-0.4	64.6	-0.7	0.7	0.09	-0.9
olmesartan	1.65	9.2	-5.1	14.4	9.9	12.0	0.31	-0.9
amlodipine	1.63	2.6	0.2	29.0	2.6	0.4	0.15	-0.3
nebivolol	1.50	3.2	2.6	16.3	3.4	3.2	0.25	-0.4
doxazosin	1.25	1.9	0.2	7.8	1.4	0.1	0.44	0.2
olmesartan/amlodipine	1.17	12.4	3.5	7.9	14.8	19.2	0.40	-2.4
olmesartan/hydrochlorothiazide	1.16	5.9	-9.1	9.5	5.6	6.2	0.33	0.0
sacubitril/valsartan	1.16	41.9	-	0.7	41.5	-	4.58	0.0
barnidipine	0.90	2.9	1.3	4.9	3.0	1.5	0.50	-0.4

Table 3.2.1b. Medicines for hypertension and heart failure, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	365.8	362.3	364.0	361.6	359.6	365.2	363.8	-0.4
Valle d'Aosta	344.5	337.7	322.4	315.5	311.3	308.0	310.4	0.8
Lombardy	357.2	355.9	354.6	351.4	350.8	348.8	345.0	-1.1
A.P. of Bolzano	301.5	297.7	293.3	288.6	284.3	283.3	281.0	-0.8
A.P. of Trento	334.2	332.2	330.6	330.2	329.8	327.8	328.4	0.2
Veneto	386.1	382.0	375.9	370.9	369.0	371.2	368.2	-0.8
Friuli VG	384.4	377.9	375.5	376.3	376.2	378.7	383.6	1.3
Liguria	348.8	343.8	336.4	331.8	327.7	330.7	329.5	-0.4
Emilia R.	414.8	414.8	413.8	409.0	409.0	412.0	409.0	-0.7
Tuscany	373.8	370.4	367.8	367.1	367.4	376.0	380.0	1.1
Umbria	464.0	467.8	471.1	471.6	476.9	484.3	494.1	2.0
Marche	372.3	371.6	373.6	370.1	373.2	375.7	377.6	0.5
Lazio	374.2	373.4	372.2	374.9	376.5	387.3	385.3	-0.5
Abruzzo	357.5	356.1	357.7	358.5	361.4	367.6	371.0	0.9
Molise	365.6	353.4	350.4	353.4	357.5	367.6	374.0	1.7
Campania	378.4	381.0	389.2	393.0	398.1	405.6	408.9	0.8
Puglia	388.1	383.8	382.1	380.3	379.1	392.9	394.6	0.4
Basilicata	355.2	353.8	356.8	359.2	363.5	371.2	377.8	1.8
Calabria	385.2	382.4	382.9	381.9	384.4	394.9	398.9	1.0
Sicily	382.7	385.3	387.7	390.5	393.1	406.9	412.0	1.3
Sardinia	353.8	350.9	344.3	341.9	341.9	338.0	343.5	1.6
Italy	**375.7**	**374.2**	**373.7**	**372.5**	**373.1**	**378.5**	**378.9**	**0.1**
North	372.2	369.8	367.6	364.0	362.8	364.1	361.7	-0.7
Centre	380.7	379.4	378.5	379.1	380.8	389.5	390.9	0.3
South and Islands	377.7	377.3	379.4	380.6	383.0	392.5	396.3	1.0

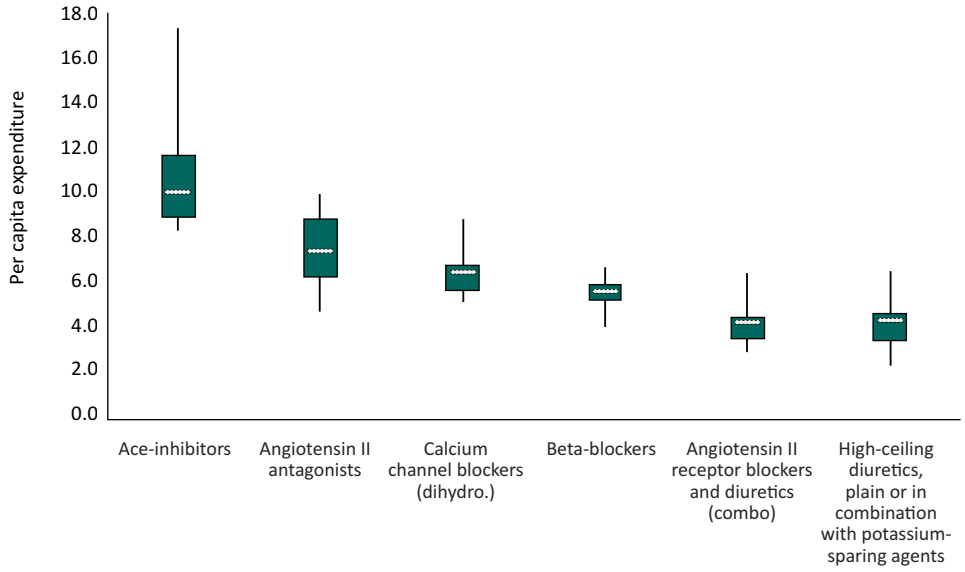
Table 3.2.1c. Prescription of medicines for hypertension and heart failure with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	29.64	86.6	0.7	355.7	93.9	0.1	0.23
Generic	7.79	26.3	3.6	128.0	36.0	2.6	0.17
Ex originator	21.85	73.7	-0.3	227.7	64.0	-1.3	0.26
Patent covered	4.58	13.4	8.6	23.2	6.1	0.4	0.54
Medicines for hypertension and heart failure	**34.22**	**100.0**	**1.7**	**378.9**	**100.0**	**0.1**	**0.25**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.1.1c. Antineoplastic medicines, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure and adherence in population

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

Exposure was higher in the +75 age groups, with men being more prevalent in the 35 to 64 age group. On the other hand, women showed greater exposure in the 75-84 age group. In 2020, 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 3.2.1d). In 2020, about a quarter of the Italian population used these drugs, with a higher prevalence in the South and the Islands (27.9%) and in the Centre (26.8%), compared to the North (24.7%) (Table 3.2.1d). Umbria was the region with the highest prevalence of use (30.4%), while the AP of Bolzano reported the lowest value (17.9%). The median age of users is 69 years and each subject receives about 10 prescriptions and 506.1 DDD in the year. Half of the exposed population is treated with a number of DDDs greater than 390, indicating the simultaneous intake of different molecules during the year, while only 6.2% of users received a single prescription.

As for adherence and persistence, the exposure data refer to a cohort of new users over 45 years old, who were followed considering the one-year follow-up. The study population includes 262,698 new users, who have a median age of 63 years (IQR 55-73), with a greater proportion of women than men (52.2% vs 47.8%).

The percentage of subjects with high and low adherence to antihypertensive treatment was 52.5% and 18.1%, respectively (Table 3.2.1e). Low adherence tends to increase with age, recording the highest value in subjects aged over 85 (25.8%) and in women compared to men (20.9% and 15.1%, respectively). Stratifying by age and geographic area, the highest percentage of low adherence was observed in users aged over 85 residing in Southern Italy (28.8%). High adherence, on the other hand, tends to decrease with increasing age, showing a greater value in the 45-54 age group (54.9%) and being higher in men than women, (57.3% and 48.1%, respectively). Users residing in Northern Italy and aged between 45 and 54 years showed the highest percentage value of high adherence (56.8%).

Analysing the persistence to medicines for hypertension and heart failure (Table 3.2.1f.), it can be highlighted that about half of the new users are found to be persistent to treatment after one year (52.3%), with a rather similar trend by geographic area (North 52.5%, Centre 52.2% and South 52.1%). Such data substantially overlap with those of 2019. Men showed higher persistence percentages than women, with values of 56.9% and 48.2% respectively.

Comparing persistence data between 2019 and 2020 (Figure 3.2.1e), no obvious differences were found and it is possible to note that, for these drugs, the median time to discontinuation is greater than 365 days.

Figure 3.2.1d. Distribution of 2020 prevalence of use and consumption of medicines for hypertension and heart failure under approved care regime and *per conto* distribution

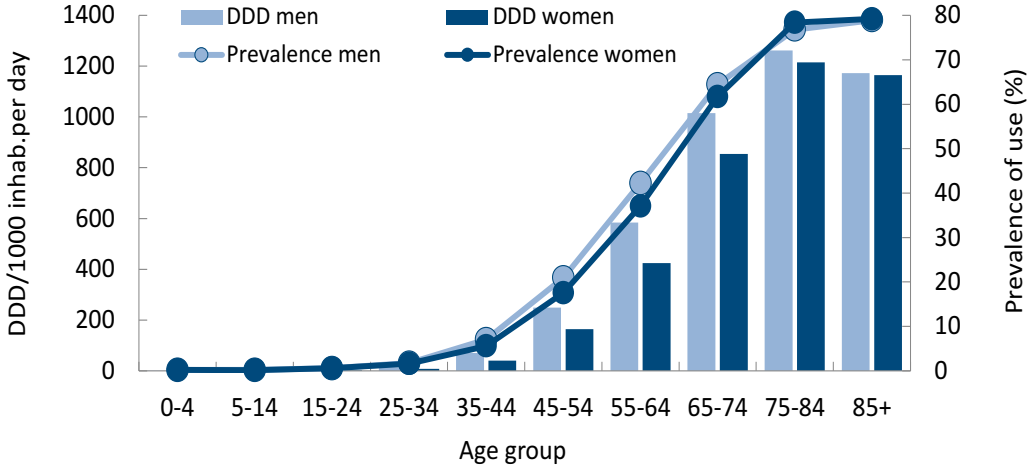


Table 3.2.1d. Exposure and duration of therapy with medicines for hypertension and heart failure by Region under NHS outpatient care and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescrip-tions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	26.9	0.93	71	9.5	480.5	364.0	6.3
Valle d'Aosta	23.2	0.93	70	8.4	475.2	362.0	6.5
Lombardy	23.5	0.96	70	8.0	522.9	392.0	6.6
A.P. of	17.9	0.95	71	8.3	502.1	378.0	6.6
A.P. of Trento	22.1	0.97	70	9.6	507.5	392.0	4.8
Veneto	24.4	0.99	70	8.6	530.4	392.0	5.7
Friuli VG	25.9	0.97	71	10.0	549.2	392.0	5.2
Liguria	27.4	0.93	72	9.2	465.8	360.0	7.1
Emilia R.	25.8	0.93	70	10.0	537.4	392.0	5.9
Tuscany	26.1	0.93	71	10.1	531.6	392.0	7.1
Umbria	30.4	0.93	70	12.3	586.0	420.0	5.0
Marche	27.5	0.93	71	9.6	465.4	357.0	5.8
Lazio	26.4	0.94	69	10.2	512.1	392.0	6.6
Abruzzo	28.4	0.91	69	10.2	471.5	364.0	5.7
Molise	30.0	0.89	69	10.0	453.2	364.0	5.6
Campania	27.3	0.93	66	10.4	496.4	392.0	5.9
Puglia	29.2	0.91	68	9.2	453.7	357.0	7.0
Basilicata	29.1	0.88	68	11.4	473.5	364.0	5.4
Calabria	28.7	0.91	68	10.5	475.2	364.0	6.4
Sicily	27.5	0.89	69	10.7	519.4	392.0	6.0
Sardinia	26.1	0.92	70	10.8	484.3	364.0	5.1
Italy	**26.2**	**0.93**	**69**	**9.7**	**506.1**	**390.0**	**6.2**
North	24.7	0.95	70	8.9	516.4	392.0	6.2
Centre	26.8	0.94	70	10.2	518.1	392.0	6.5
South and Islands	27.9	0.91	68	10.3	487.2	375.0	6.1

Table 3.2.1e. Indicators of adherence to treatment with medicines for hypertension and heart failure in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=262,698		North N=118,381		Centre N=54,135		South N=90,182	
Low adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	16.3	0	14.9	-2	16.9	2	17.6	0
55-64 years	16.5	3	15.6	4	16.7	4	17.6	1
65-74 years	18.2	3	16.7	0	19.2	10	19.7	2
75-84 years	21.1	5	19.7	5	21.5	3	23.4	5
≥85 years	25.8	3	23.3	2	27.3	6	28.8	2
Women	20.9	2	19.4	1	22.2	7	22.2	1
Men	15.1	3	14.2	3	15.1	2	16.3	3
Total	**18.1**	**2**	**16.9**	**2**	**18.8**	**5**	**19.4**	**2**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	54.9	0	56.8	0	55.9	0	52.2	0
55-64 years	54.6	-1	56.0	-1	55.7	-2	52.2	-2
65-74 years	53.0	-2	54.3	0	53.5	-4	51.1	-1
75-84 years	48.2	-3	49.5	-2	48.7	-3	45.6	-4
≥85 years	40.9	0	43.0	2	39.5	-4	38.8	-1
Women	48.1	-1	49.5	-1	48.4	-2	46.1	-1
Men	57.3	-1	58.5	0	58.2	-2	55.2	-2
Total	**52.5**	**-1**	**53.8**	**0**	**53.0**	**-2**	**50.5**	**-2**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

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

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

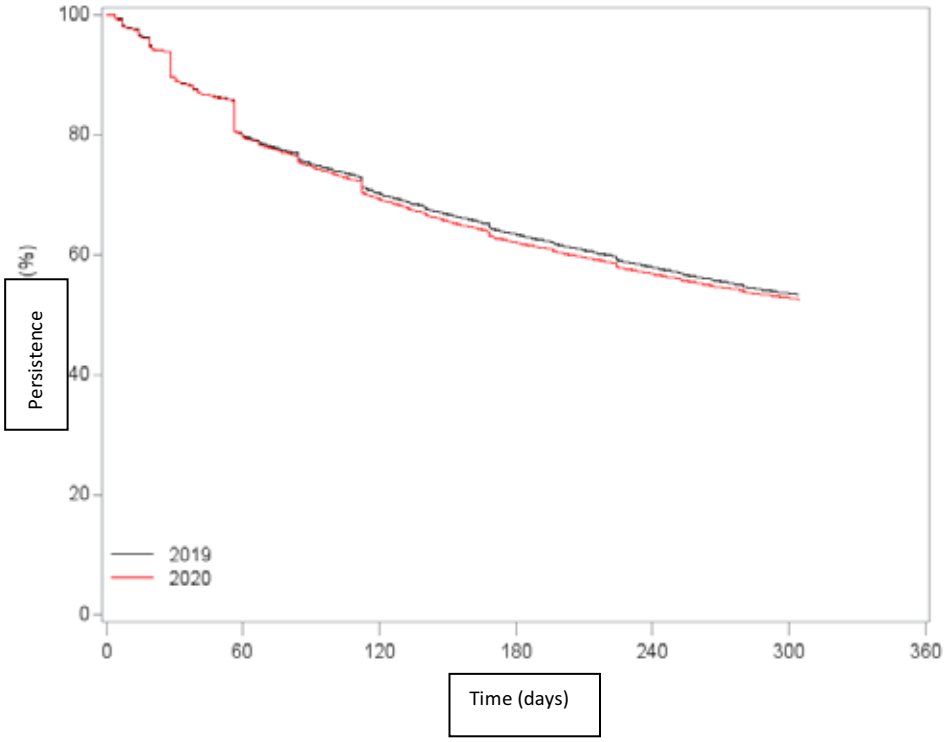
Median follow-up time (IQR): 328 (283-348)

Table 3.2.1f. Persistence after one year of treatment with medicines for hypertension and heart failure in the population aged ≥45 years in 2020 and percentage change compared to the previous year

Persistence after 12 months	Total N=262,698		North N=118,381		Centre N=54,135		South N=90,182	
	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	54.6	-1	55.4	0	54.6	-2	53.7	-1
55-64 years	54.7	-1	54.9	-1	54.9	-3	54.3	-1
65-74 years	53.0	-1	53.1	0	52.8	-3	52.9	-1
75-84 years	47.5	-3	48.0	-2	47.8	-3	46.4	-5
≥85 years	40.5	-1	41.4	1	40.0	-2	39.5	-5
Women	48.2	-2	48.4	-1	47.7	-3	48.1	-1
Men	56.9	-1	57.0	0	57.3	-2	56.4	-2
Total	**52.3**	**-1**	**52.5**	**0**	**52.2**	**-2**	**52.1**	**-2**

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

Figure 3.2.1e Time (in days) to discontinuation of treatment with medicines for hypertension and heart failure in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods). For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days)

Table 3.2.1g. Incidence of hypertension (with and without concomitant diseases^) in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Incidence (‰)						
	Hypertension	Δ % 20-19	NA hypertension*	Diabetes mellitus	CV diseases	Heart failure	Chronic kidney disease
Geographic analysis							
North	13.3	-18.6	10.3	1.5	1.5	0.2	0.5
Centre	15.5	-37.3	12.0	1.9	1.8	0.2	0.5
South and	15.6	-22.3	12.2	1.9	1.6	0.2	0.5
Analysis by gender							
Men	14.7	-24.7	10.9	2.0	1.9	0.2	0.6
Women	14.3	-22.7	11.7	1.4	1.3	0.2	0.4
Analysis by age							
≥45 years	3.2	-20.2	3.0	0.1	0.1	0.0	0.0
46-65	20.2	-20.2	17.1	1.7	1.4	0.1	0.3
66-74	42.1	-15.7	29.6	7.1	5.9	0.5	1.6
75-84	52.2	-8.7	31.2	10.0	11.7	1.6	4.1
≥85 years	41.3	-13.6	22.1	8.1	11.4	2.5	4.9
Total	**14.53**	**-23.74**	**11.3**	**1.7**	**1.5**	**0.19**	**0.49**

^The categories are not mutually exclusive

*None of the comorbidities listed below in the table CV diseases:

cardiovascular diseases

Indicators used:

Incidence of hypertension: number of patients with a "first" diagnosis of hypertension 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 hypertension and concomitant diseases: number of patients with a "first" diagnosis of hypertension
recorded during the year without concomitant pathologies (indicated in the tables as NA hypertension) or with a diagnosis of diabetes mellitus or heart failure or cardiovascular disease (coronary artery or cerebral ischemic) or chronic kidney disease [**numerators**], on the total population assisted and at risk (disease free) at the beginning of the period [**denominator**]

Table 3.2.1h. Prevalence of hypertension (with and without concomitant diseases^) in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Incidence (‰)						
	Hypertension	Δ % 20-19	NA hypertension*	Diabetes mellitus	CV diseases	Heart failure	Chronic kidney disease
Geographic analysis							
North	27.3	0.0	17.6	4.7	5.2	0.9	2.1
Centre	28.1	-0.7	17.8	5.3	5.3	0.8	2.3
South and	31.9	0.0	19.6	6.7	6.2	1.0	3.0
Analysis by gender							
Men	29.2	0.7	17.5	6.1	6.5	0.9	2.6
Women	29.2	-0.7	19.3	5.1	4.8	0.9	2.3
Analysis by age							
≥45 years	3.9	5.1	3.5	0.2	0.1	0.0	0.1
46-65	30.6	5.2	23.8	4.0	3.0	0.3	0.9
66-74	60.0	4.0	35.2	13.9	12.9	1.3	4.5
75-84	70.6	3.0	33.5	18.3	21.2	3.5	9.9
≥85 years	73.6	2.5	29.8	17.1	25.1	8.0	15.7
Total	**29.2**	**0.0**	**18.4**	**5.6**	**5.6**	**0.9**	**2.5**

^The categories are not mutually exclusive

*None of the comorbidities listed below in the table CV diseases:

cardiovascular diseases

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

Prevalence of hypertension and concomitant diseases: number of patients diagnosed with essential hypertension without concomitant diseases (indicated in the tables as NA hypertension) diagnosed with diabetes mellitus or heart failure or cardiovascular disease (coronary or ischemic cerebral) or chronic kidney disease [**numerators**], on the total population diagnosed with hypertension or the total population eligible for assistance [**denominator**]

Table 3.2.1i. Distribution of blood pressure, smoking, BMI and LDL cholesterol in patients with hypertension both on and without drug treatment

	Distribution (%)		
	NA hypertension*	On antihypertensive treatment^	Without antihypertensive treatment
Blood pressure			
<140/90 mmHg	56.5	56.6	56.0
140-159/90-99 mmHg	31.4	31.3	32.3
160-179/100-109 mmHg	9.8	9.8	9.8
≥180/110 mmHg	2.3	2.3	1.9
Smoking ^			
Yes	23.7	22.6	29.9
No	76.3	77.4	70.1
BMI ^			
Under weight	0.7	0.7	1.0
Normal weight	25.6	24.8	30.8
Over weight	40.0	40.1	39.1
Obesity	33.7	34.4	29.0
Ldl			
<100 mg/dl	40.4	41.8	26.2
100-129 mg/dl	30.6	30.4	32.7
130-159 mg/dl	19.6	19.0	25.7
160-189 mg/dl	7.1	6.7	11.8
≥190 mg/dl	2.2	2.0	3.6

BMI: Body Mass Index

^Percentages are calculated excluding patients with missing data

*None of the comorbidities listed as follows in the table Indicator used:

Distribution of the values relating to blood pressure, smoking habits, BMI and LDL cholesterol (values recorded in the last 12 months) [**numerators**] among subjects with **hypertension** with at least one value recorded in the year, divided between those on drug treatment and those without drug treatment [**denominators**].

Table 3.2.1l. Prevalence of use of antihypertensive drugs in subjects with hypertension (with and without concomitant diseases^) and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence of use (%) of antihypertensives						
	Hypertension	Δ % 20-19	NA hypertension*	Diabetes mellitus	CV diseases	Heart failure	Chronic kidney disease
Geographic analysis							
North	76.3	-0.9	71.0	85.0	87.9	91.4	87.6
Centre	80.1	-1.6	75.5	86.9	90.2	92.9	89.4
South and	78.0	-1.5	72.2	86.7	89.0	91.2	90.0
Analysis by gender							
Men	74.5	-2.2	67.7	83.8	87.1	90.0	87.2
Women	80.8	-0.5	76.4	88.8	91.0	93.1	91.0
Analysis by age							
≥45 years	39.9	-1.5	38.1	55.1	66.2	75.4	59.7
46-65	68.5	-2.2	65.9	77.2	80.5	82.4	79.2
66-74	83.9	-0.6	81.4	87.3	88.3	89.2	88.0
75-84	90.5	1.2	88.0	92.6	93.3	95.3	93.6
≥85 years	87.8	1.5	85.1	89.2	90.0	91.9	90.4
Total	**77.7**	**-1.3**	**72.3**	**86.1**	**88.8**	**91.6**	**89.1**

^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 antihypertensive drugs [**numerator**], on 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**]

Table 3.2.1m. Prevalence of use of antihypertensive drugs in subjects with hypertension (with and without concomitant diseases^): analysis by therapeutic category in 2020

Analysis by class therapeutic^	Prevalence of use (%)					
	Hypertension	NA hypertension*	Diabetes mellitus	CV diseases	Heart failure	Chronic kidney disease
ACE inhibitors	19.3	16.9	22.0	26.4	29.7	22.0
ACE inhibitors and calcium channel blockers (combinations)	4.8	4.7	5.5	5.1	2.6	4.4
ACE inhibitors and diuretics (combinations)	9.6	9.6	10.2	9.2	4.4	7.0
ACE inhibitors, other combinations	0.3	0.4	0.3	0.3	0.3	0.2
Alpha-2 adrenergic receptor agonists	-	-	-	-	-	-
Imidazoline receptor agonists	0.6	0.3	1.2	1.1	1.4	2.1
Alpha-adrenoreceptor antagonists	4.4	3.1	7.0	6.4	6.3	10.2
Aliskiren plain or in combination	0.0	0.0	0.1	0.1	0.1	0.1
Angiotensin II receptor blockers and neprilysin inhibitor	0.2	0.0	0.4	0.5	3.0	0.5
Angiotensin II antagonists	17.0	15.3	19.4	20.4	20.6	24.0
Angiotensin II receptor blockers and calcium channel blockers (combinations)	3.3	3.1	4.1	3.7	2.1	3.6
Angiotensin II receptor blockers and diuretics (combinations)	13.2	12.3	15.9	14.1	6.7	12.2
Beta blockers	29.8	23.1	38.4	48.3	64.9	43.8
Beta blockers and diuretics (combinations)	3.4	3.7	3.1	2.3	1.0	2.2
Calcium channel blockers	18.1	14.7	24.0	25.7	19.2	29.6
Calcium channel blockers (not dihydropyridines)	1.0	0.6	1.3	2.1	2.1	1.4
High-ceiling diuretics, plain or in combination with potassium-sparing agents	12.2	6.7	20.3	23.2	64.3	33.9
Potassium-sparing diuretics	3.0	1.4	5.4	6.3	27.7	7.5
Olmesartan/amlodipine/ hydrochlorothiazide	0.0	0.0	0.0	0.0	0.0	0.0
Perindopril/indapamide/ amlodipine	1.4	1.2	2.2	1.8	1.0	1.7
Thiazides and similars (including combinations)	3.5	3.2	3.8	3.8	3.3	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**], on 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**]

Table 3.2.1n. Proportion of patients adhering to treatment with antihypertensive drugs in patients with hypertension and based on the number of concomitant diseases^: stratified analysis by gender, age group, geographic area and blood pressure levels

	Therapeutic adherence (%)					
	Hypertension	1 pathology	2 pathologies	3 pathologies	4 pathologies	+4 pathologies
Geographic analysis						
North	70.0	69.1	72.3	76.1	78.3	81.0
Centre	75.5	74.6	77.1	80.3	82.9	84.5
South and Islands	70.5	68.4	71.8	75.6	78.9	79.2
Analysis by gender						
Men	73.1	72.9	75.6	78.1	80.7	79.7
Women	69.6	67.6	71.1	75.4	78.3	81.1
Analysis by age						
≥45 years	56.2	57.9	54.9	63.6	73.1	66.7
46-65	66.8	66.2	69.5	72.5	76.5	77.3
66-74	73.7	72.3	74.2	77.8	81.3	83.8
75-84	75.5	73.3	75.7	78.8	80.7	81.3
≥85 years	71.5	69.3	71.2	74.5	76.6	77.3
Blood pressure						
<140/90	73.4	71.4	74.5	77.5	80.0	81.0
140-159/90-99	75.0	74.1	76.5	81.1	83.9	85.7
160-179/100-109	73.9	71.9	78.3	81.9	86.6	89.4
≥180/110	74.9	72.7	79.1	83.1	84.0	89.5
Total	**71.3**	**69.9**	**73.0**	**76.6**	**79.4**	**80.5**

^Cardio and cerebrovascular disease, diabetes, heart failure, chronic kidney disease, COPD, asthma and osteoarthritis

Indicator used: **Proportion of patients adhering to antihypertensive treatment**: number of patients adhering (DDD/user/molecule>290/year) to treatment with antihypertensive drugs [**numerator**], on the total of hypertensive subjects in antihypertensive treatment based on the number of concomitant diseases [**denominators**].

Key message

- **Consumption of drugs for hypertension and heart failure** appears stable over the last seven years, with 378.9 DDD/1000 inhabitants per day. This trend is confirmed for all therapeutic categories of greater use, with the exception of beta-blockers which showed an increase in consumption (+1.8%) and expenditure (+2.8%), probably due to greater treatment in patients with heart failure. In particular, bisoprolol is the most used drug and has been constantly increasing since 2014 (CAGR: +6.7%). Such increase is probably attributable to the greater tolerability of the active ingredient and the possible single-dose administration, which tends to favour subjects' compliance.
- There is an **increase in regional variability** in terms of consumption. In 2020, the difference between the highest and lowest values, observed in the individual Regions, was

equal to 213 DDD/1000 inhabitants per day, a 6% increase compared to 2019 (201 DDD/1000 inhabitants per day) and a 31.1% increase compared to 2014 (162.5 DDD/1000 inhabitants per day). This variability is also observed in the prescribing pattern and cannot be explained by geographic differences in the prevalence of hypertension and heart failure that, although significantly different, does not appear significant.

- 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 subjects with low adherence to treatment equal to 16.9% in the North and 19.4% 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 24.7% vs South and Islands 27.9%), but also the different adherence shown by patients.
- The data relating to DDD per user (national average 506.1) confirms the tendency by Italian doctors to use combinations of different drugs to achieve the therapeutic target. Since antihypertensive drugs act through the inhibition of various pathophysiological mechanisms associated with the development of high blood pressure, the **combined strategy** was associated with greater efficacy in reducing cardiovascular events and allows for a reduction in the dosage of individual active ingredients, resulting in a reduction of potential adverse events.
- All the indicators confirm a reduction in consumption, exposure and adherence starting from the 75-84 age group and consolidating in the +85s. However, in this age group several guidelines suggest that antihypertensive treatment is only useful in case of grade II+ hypertension (PAS ≥160 mmHg). Furthermore, these recommendations do not consider ***fragile elderly people***, generally undergoing polytherapy and more sensitive to the risk of adverse drug reactions. Finally, considering that these drugs are used for a wide range of diseases (for example angina pectoris, atrial fibrillation, renal failure), any deprescribing strategy should be carefully evaluated and accompanied by intense monitoring of blood pressure.
- Data from General Medicine show a 77.7% **prevalence of use** in the cohort of patients diagnosed with hypertension, approximately 1.9% less than in 2019. At the same time, an increase is reported in the prevalence of use in hypertensive subjects suffering from diabetes mellitus, chronic kidney disease or with previous cardiovascular diseases, as well as an increase in adherence associated with the number of concomitant diseases and blood pressure values. These data confirm the GP's attention in particular to the most fragile patients and a therapeutic approach associated with the patient's state of health.

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3.2.2 Lipid-lowering medicines

National data on consumption and expenditure

Consumption of lipid-lowering drugs has shown a 30.6% increase over the years, from 79 DDD/1000 inhabitants per day in 2014 to 103.2 in 2020 (CAGR +4.6%). The average DDD cost, on the other hand, recorded a 31.6% decrease, from 0.57 euros in 2014 to 0.39 in 2020 (Figure 3.2.2a). The per capita expenditure value for these drugs was 14.92 euros, a 7.6% increase compared to the previous year, although the value of the CAGR, calculated for the last 7 years, shows a 1.7% reduction (Table 3.2.2a). Statins not in combination with other molecules are the therapeutic category recording the highest per capita expenditure (8.05 euros), with a 1.5% increase compared to the previous year, and an average DDD cost lower than the value calculated for the entire class of lipid-lowering drugs (0.27 euros). The trend in expenditure and consumption values for this subgroup over the last seven years shows an annual 4.5% decrease in expenditure, compared to a 3.2% increase in consumption. Ezetimibe in combination, on the other hand, is the second category with the highest expenditure, recording a value of 1.98 euros, a 30.6% increase compared to the previous year. For this class, an equally important increase was observed in terms of consumption (+35.9%), reaching a value of 8.2 DDD/1000 inhabitants per day. Particularly interesting is the decrease in the average cost per day of ezetimibe therapy, both plain and in combination, probably due to the patent expiry dates in the last two years.

Therefore, the trend in expenditure values overall appears to be consistent with the reimbursement indications of Note 13. Inhibitors of the microsomal triglyceride transport protein (MPT), which include the active ingredient lomitapide, authorised as adjuvant therapy in adult patients suffering from homozygous familial hypercholesterolemia (HoFH), is the category showing the highest average DDD cost (863.34 euros), despite decreasing by 17.6% compared to the previous year. On the other hand, particularly interesting is the increase in expenditure and consumption of the triple combination amlodipine/atorvastatin/perindopril, which in both cases is higher than 100%, although modest in absolute terms (0.01 euros and 0.1 DDD/1000 inhabitants per day). Atorvastatin is the active ingredient with the highest per capita expenditure (4.50 euros), a 4.5% increase compared to 2019, which however showed the lowest average DDD cost, equal to 0.24 euros. The consumption value was 50.4 DDD/1000 inhabitants per day, a 3.8% 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 mean DDD values, respectively 13.12 euros and 8.91 euros. In 2020, patent-expired drugs accounted for 88% of expenditure and 97.6% of doses, with an average DDD cost of 0.36 euros (Table 3.2.2c). The percentage of use of generic drugs was 40.3%, a 7.6% increase compared to the previous year. However, the use of ex-originators was still high, with expenditure values equal to 65.7% and consumption values equal to 59.7%.

Figure 3.2.2a. Lipid-lowering medicines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

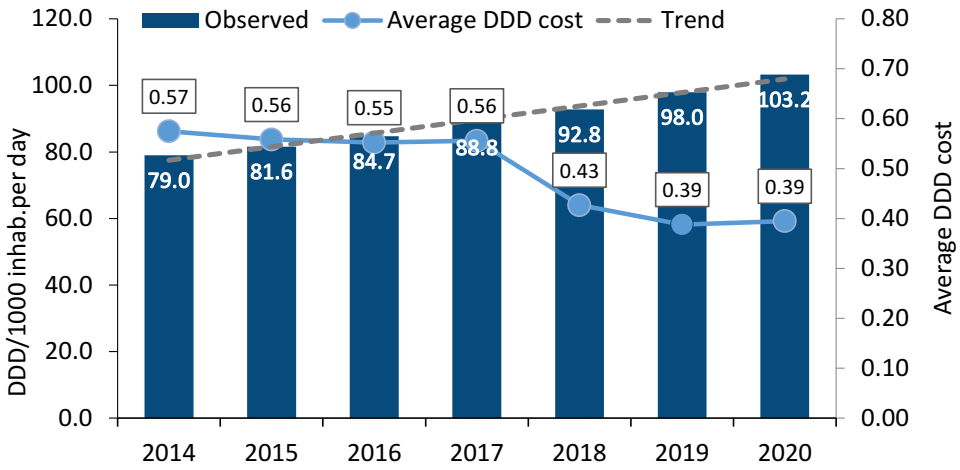


Table 3.2.2a. Lipid-lowering medicines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expendi-ture	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Statins, plain	8.05	1.5	-4.5	82.1	2.7	3.2	0.27	-1.5
Ezetimibe in combination	1.98	30.6	-4.7	8.2	35.9	15.2	0.66	-4.1
Omega 3	1.93	1.0	-0.8	4.6	1.5	4.1	1.15	-0.8
Ezetimibe	1.40	13.9	7.7	5.2	15.7	24.4	0.74	-1.8
PCSK9 inhibitors	1.04	35.2	-	0.3	54.8	-	10.81	-12.9
Fibrates	0.40	2.2	1.2	2.8	1.8	1.7	0.38	0.1
MTP inhibitor	0.12	-6.5	-	0.0	13.2	-	863.34	-17.6
Amlodipine/atorvastatin/ perindopril	0.01	2149.5	-	0.1	2137.4	-	0.43	0.3
Statins in combination	0.00	3686.0	-	0.0	4174.3	-	0.23	-11.7
Acetylsalicylic acid/atorvastatin/ramipril	0.00	-83.3	-	0.0	-83.3	-	0.57	0.0
Lipid-lowering	**14.92**	**7.6**	**-1.7**	**103.2**	**5.4**	**4.6**	**0.39**	**1.8**
atorvastatin	4.50	4.5	6.6	50.4	3.8	7.3	0.24	0.4
omega 3	1.93	1.0	-0.8	4.6	1.5	4.1	1.15	-0.8
simvastatin	1.53	-3.4	-3.1	13.0	-3.9	-3.1	0.32	0.2
ezetimibe	1.40	13.9	7.7	5.2	15.7	24.4	0.74	-1.8
rosuvastatin	1.35	6.8	-18.9	14.1	7.6	0.1	0.26	-1.0
ezetimibe/simvastatin	1.19	5.0	-12.4	4.9	5.1	5.8	0.66	-0.4
ezetimibe/rosuvastatin	0.78	107.6	-	3.3	142.6	-	0.65	-14.7
evolocumab	0.57	31.5	-	0.1	53.2	-	13.12	-14.4
alirocumab	0.47	39.9	-	0.1	56.1	-	8.91	-10.6
fenofibrate	0.37	2.5	1.9	2.6	2.2	2.4	0.38	0.0

Table 3.2.2b. Lipid-lowering medicines, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	66.2	67.8	69.7	72.7	76.3	80.8	84.4	4.5
Valle d'Aosta	57.6	58.7	57.4	60.5	63.1	64.4	66.3	3.0
Lombardy	72.7	76.2	79.5	83.7	87.7	90.8	94.7	4.3
A.P. of Bolzano	59.1	63.4	67.1	70.7	75.1	79.9	84.2	5.3
A.P. of Trento	65.1	67.2	70.2	74.6	79.2	83.7	88.9	6.3
Veneto	78.5	80.7	84.1	88.0	91.9	96.8	101.4	4.8
Friuli VG	81.5	83.5	86.3	90.7	94.4	99.8	110.7	11.0
Liguria	67.8	70.0	71.6	74.5	78.2	83.2	87.6	5.2
Emilia R.	82.4	86.3	91.2	96.1	99.3	103.8	107.6	3.7
Tuscany	71.9	74.4	77.7	81.6	84.5	88.7	94.3	6.3
Umbria	72.4	75.2	78.7	83.2	88.6	93.8	100.2	6.8
Marche	89.1	92.2	96.3	100.4	104.1	109.6	115.8	5.6
Lazio	89.4	87.8	89.1	92.9	96.8	102.6	106.5	3.8
Abruzzo	71.2	74.9	78.3	82.6	87.4	92.3	98.8	7.1
Molise	67.7	68.1	68.7	73.0	76.2	80.9	87.4	8.0
Campania	84.5	89.3	93.5	98.9	105.1	113.1	120.9	6.9
Puglia	85.9	89.4	93.0	96.6	99.4	105.8	112.1	6.0
Basilicata	74.9	78.2	81.7	87.3	92.5	98.6	104.2	5.7
Calabria	84.8	86.3	87.8	91.4	95.1	101.4	107.5	6.0
Sicily	83.2	86.2	90.0	94.5	98.9	106.5	113.0	6.1
Sardinia	96.9	100.6	101.5	104.6	107.4	111.6	119.2	6.7
Italy	**79.0**	**81.6**	**84.7**	**88.8**	**92.8**	**98.0**	**103.2**	**5.4**
North	73.9	76.7	79.9	83.9	87.7	91.8	96.2	4.8
Centre	82.4	83.1	85.6	89.5	93.2	98.4	103.3	5.0
South and Islands	84.1	87.6	90.9	95.3	99.7	106.5	113.4	6.4

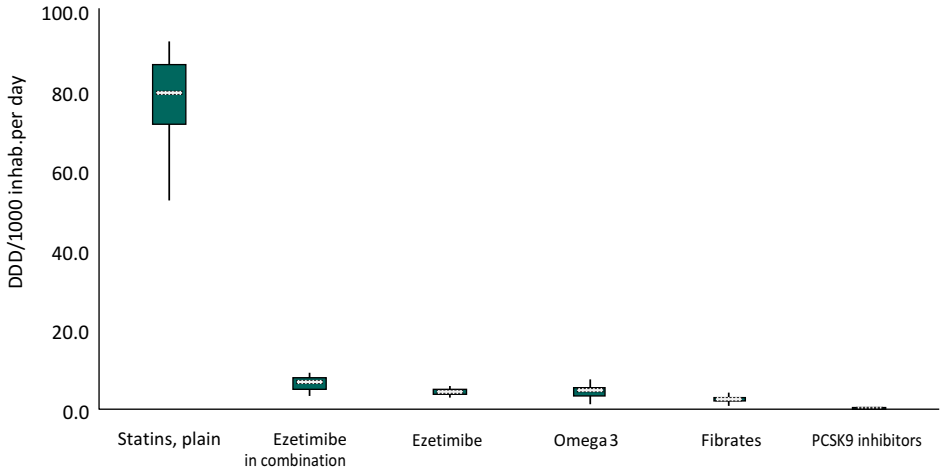
Table 3.2.2c. Prescription of lipid lowering medicines with patent expired* in 2020

Categories	Per capita expendi-ture	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	13.13	88.0	6.0	100.8	97.6	5.2	0.36
Generic	4.50	34.3	9.9	40.6	40.3	7.6	0.30
Ex originator	8.63	65.7	4.0	60.1	59.7	3.5	0.39
Patent covered	1.80	12.0	20.9	2.5	2.4	16.5	1.97
Lipid-lowering	**14.92**	**100.0**	**7.6**	**103.2**	**100.0**	**5.4**	**0.39**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.2.2c. Lipid-lowering medicines, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



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, 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 +85 group (Figure 3.2.2d). Analysing exposure by gender, it is clear that men were more exposed than women, regardless of age. Furthermore, prevalence of use tends to be higher in Southern regions (14%), compared to Central (12.8%) and Northern regions (11.3%) (Table 3.2.2d).

Analysis of the therapy duration showed that half of the users were treated for a period of at least eight months (median DDD 240), although even lower values were recorded in Southern regions (median DDD 224). About half of the observed users were 70 years old. Prevalence of use of lipid-lowering agents in the population is 12.5% and, on average, each user receives about 6 prescriptions a year and is treated for 290 days (about 10 months); in addition, 9.4% 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 subjects in primary and secondary prevention. Therefore, in order to achieve the expected benefit, in addition to choosing the most appropriate treatment, it is essential that patients take the drugs continuously. Failure to adhere to lipid-lowering treatment, in fact, leads to negative repercussions in terms of both public health (increase in the number of potentially preventable events) and health costs (cost of an ineffective therapy or cost linked to possible side effects requiring further treatment). 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 of age, and considering a one-year follow-up.

The study population included 232,349 new users, with a median age of 67 years (IQR 58-75), and a greater proportion of women than men (52.9% vs 47.1%).

The percentage of subjects with high and low adherence to treatment was 41.9% and 16%, respectively (Table 3.2.2e). As in the case of antihypertensives, low adherence tends to increase with age, recording the highest value in subjects over 85 (19.1%) and in women (18%) compared to men (13.9%). Users resident in Northern Italy and aged between 45 and 54 years have a higher percentage value of high adherence, equal to 45.9%.

Analysing persistence to lipid-lowering drugs (Table 3.2.2f), less than half of new users were found to be persistent to treatment (47.2%), with a trend similar to the national value in the Central regions (47.2%), a higher value in the Northern regions (49.4%) and a lower value in the Southern regions (45.1%). Men recorded higher persistence rates (51.3%) than women (43.6%).

Comparing persistence data between 2019 and 2020, a substantial overlap can be highlighted between the two curves (Figure 3.2.2e).

Figure 3.2.2d. Distribution of prevalence of use and consumption of lipid-lowering medicines under approved care regime and *per conto* distribution (year 2020)

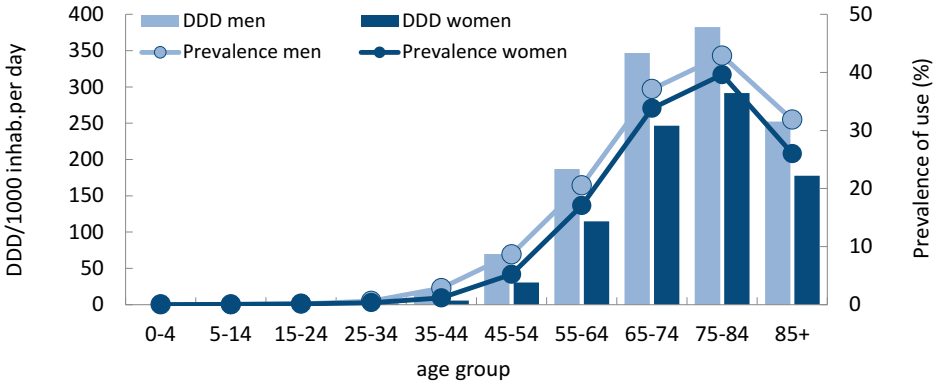


Table 3.2.2d. Exposure and duration of therapy with lipid-lowering medicines by Region under NHS outpatient care and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	DDD median	Users with 1 prescription (%)
Piedmont	11.1	1.13	71	5.6	274.4	224.0	8.6
Valle d'Aosta	8.2	1.18	71	5.5	284.6	224.0	9.8
Lombardy	11.1	1.14	71	5.2	307.0	240.0	9.6
A.P. of Bolzano	8.2	1.15	72	5.0	336.7	261.0	9.4
A.P. of Trento	10.3	1.12	71	5.8	303.9	240.0	7.4
Veneto	11.4	1.15	71	5.3	319.0	261.0	7.9
Friuli VG	11.7	1.12	72	6.0	336.8	261.0	6.8
Liguria	11.7	1.07	72	5.9	291.4	240.0	10.6
Emilia R.	12.4	1.04	71	5.6	280.4	224.0	9.2
Tuscany	12.0	1.07	72	6.1	291.1	232.0	10.1
Umbria	12.6	1.06	71	7.9	288.0	240.0	7.3
Marche	13.9	1.04	71	6.0	284.6	232.0	8.4
Lazio	13.0	1.00	70	6.3	289.6	240.0	9.7
Abruzzo	12.5	1.04	70	6.8	288.2	230.0	8.9
Molise	12.3	1.03	70	6.3	260.1	224.0	8.8
Campania	14.2	0.99	68	6.7	279.9	224.0	10.3
Puglia	14.5	0.98	69	6.1	261.8	224.0	10.6
Basilicata	13.3	0.99	69	7.9	284.2	239.0	8.1
Calabria	13.5	1.00	69	6.6	271.5	224.0	11.5
Sicily	14.0	0.97	69	6.5	280.8	240.0	9.9
Sardinia	13.8	0.91	70	7.3	319.9	246.0	6.7
Italy	**12.5**	**1.04**	**70**	**6.1**	**290.0**	**240.0**	**9.4**
North	11.3	1.11	71	5.5	300.2	240.0	9.0
Centre	12.8	1.03	71	6.3	289.3	240.0	9.5
South and Islands	14.0	0.98	69	6.6	279.2	224.0	9.9

Table 3.2.2e. Indicators of adherence to treatment with lipid-lowering medicines in the population aged ≥45 years in 2020 and percentage change compared to the previous year

Low adherence*†	Total N=232,349		North N=93,152		Centre N=46,999		South N=92,198	
	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	15.7	-3	12.9	-4	16.3	2	17.7	-4
55-64 years	15.1	-2	13.1	2	15.2	-2	16.9	-5
65-74 years	16.1	-3	14.1	-3	16.2	-2	18.0	-4
75-84 years	16.8	-3	15.0	-4	17.7	3	18.8	-6
≥85 years	19.1	1	17.3	3	19.1	1	21.1	0
Women	18.0	-2	16.1	0	18.4	-1	19.6	-5
Men	13.9	-3	11.9	-4	14.1	1	15.8	-5
Total	**16.0**	**-3**	**14.0**	**-2**	**16.4**	**0**	**17.9**	**-5**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	41.7	4	45.9	7	40.8	-2	38.6	4
55-64 years	42.2	2	45.1	1	42.8	2	39.4	3
65-74 years	41.8	4	44.7	5	41.8	2	38.8	3
75-84 years	41.9	3	43.9	2	42.0	3	39.2	5
≥85 years	41.6	2	44.4	3	42.2	-1	38.1	4
Women	37.2	4	39.5	4	37.0	2	35.0	6
Men	47.2	2	50.2	3	47.7	1	43.8	2
Total	**41.9**	**3**	**44.8**	**3**	**42.0**	**1**	**39.0**	**4**

*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 while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

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

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

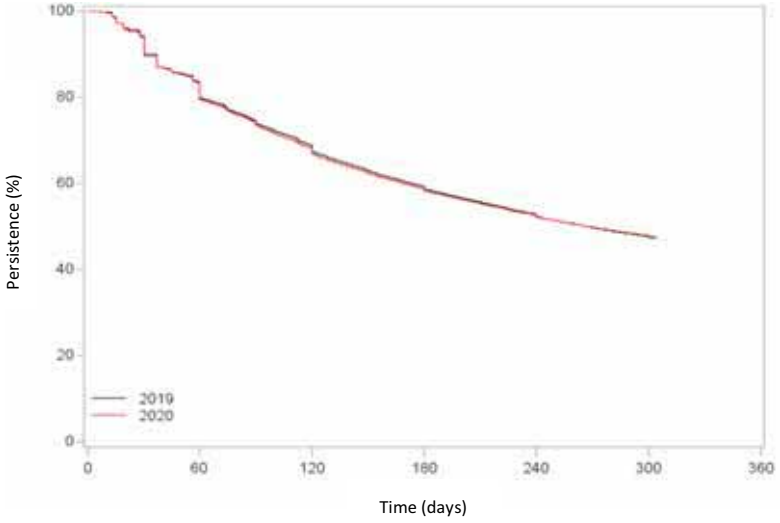
Median follow-up time (IQR): 322 (257-345)

Table 3.2.2f. Persistence after one year of treatment with lipid-lowering medicines in the population aged ≥45 years in 2020 and percentage change compared to the previous year

Persistence after 12 months	Total N=232,349		North N=93,152		Centre N=46,999		South N=92,198	
	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	46.5	1	49.7	2	46.4	-3	44.0	2
55-64 years	48.7	1	51.2	0	48.6	-2	46.5	3
65-74 years	48.0	0	50.1	1	48.2	1	45.9	0
75-84 years	45.6	-1	47.1	-1	45.5	0	43.7	-1
≥85 years	42.7	-1	45.8	2	43.0	-2	39.1	-3
Women	43.6	1	45.1	1	43.3	-1	42.3	2
Men	51.3	0	53.9	0	51.6	-1	48.4	0
Total	**47.2**	**0**	**49.4**	**1**	**47.2**	**-1**	**45.1**	**1**

Note: persistence to treatment was evaluated only for new users with at least 2 prescriptions. An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods)

Figure 3.2.2e Time (in days) to discontinuation of treatment with lipid-lowering medicines in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: an interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods). For this reason, no interruptions can be observed in the last 60 days from end of the follow-up (365 days)

Table 3.2.2g. Incidence of dyslipidemia in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Incidence (‰)					
	Dyslipidemia	Δ % 20-19	Polygenic hypercholes-terolemia	Familial dyslipidemia	Hyperlipidemias with moderate/ severe CRI *	Other dyslipidemias**
Geographic analysis						
North	8.9	-23.4	8.3	0.4	1.0	0.2
Centre	11.4	-43.9	10.6	0.5	1.4	0.4
South and Islands	10.6	-21.0	9.5	0.7	1.2	0.4
Analysis by gender						
Men	8.7	-29.9	7.9	0.4	1.1	0.4
Women	11.3	-24.2	10.5	0.6	1.1	0.2
Analysis by age						
≥45 years	2.7	-28.8	2.2	0.3	0.2	0.2
46-65	15.0	-22.8	13.8	0.8	1.4	0.5
66-74	23.9	-21.4	22.5	0.8	3.2	0.7
75-84	18.0	-18.2	17.3	0.4	3.5	0.3
≥85 years	8.4	-21.9	7.9	0.2	2.3	0.3
Total	**10.0**	**-26.9**	9.2	**0.5**	**1.1**	**0.3**

*Chronic renal failure

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

Incidence of dyslipidemia: number of patients with a "first" diagnosis of dyslipidaemia recorded during the year [**numerator**], on the total population 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 moderate and severe hyperlipidaemias and CRI or other dyslipidaemias (dysbetalipoprotheinemias, hyperchylomicronemias, hypertriglyceridaemias, drug hyperlipemia) [**numerator**], on the total population and 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 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence (%)					
	Dyslipidemia	Δ % 20-19	Polygenic hypercholes-terolemia	Familial dyslipide-mia	Hyperlipidemias with moderate/ severe CRI *	Other dyslipidemias**
Geographic analysis						
North	18.5	1.1	17.0	1.3	3.5	0.3
Centre	18.3	2.2	16.7	1.4	3.3	0.4
South and Islands	19.5	2.1	17.4	2.0	3.9	0.5
Analysis by gender						
Men	17.9	1.7	16.1	1.5	3.6	0.6
Women	19.7	1.5	18.1	1.7	3.6	0.2
Analysis by age						
≥45 years	3.7	5.4	3.0	0.6	0.3	0.2
46-65	21.4	6.1	19.2	2.2	2.7	0.5
66-74	39.0	4.4	36.1	2.9	8.3	0.7
75-84	40.3	3.5	38.0	2.3	11.6	0.5
≥85 years	32.9	3.7	31.3	1.5	11.7	0.5
Total	**18.8**	**1.6**	**17.1**	**1.6**	**3.6**	**0.4**

*Chronic renal failure

**Other dyslipidaemias: dysbetalipoproteinemias, hyperchilomicronaemias, hypertriglyceridaemias, drug-induced hyperlipemia Indicators used:

Prevalence of dyslipidemia: number of patients diagnosed with hypertension [**numerator**], on 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 with moderate and severe hyperlipidemias and CRI or other dyslipidaemias (dysbetalipoprotheinemias, hyperchylomicronemias, hypertriglyceridaemias, drug hyperlipemia) [**numerator**], on the total population eligible for assistance [**denominator**]

Table 3.2.2i. Distribution of LDL cholesterol, blood pressure, smoking, BMI in patients with dyslipidemia both on drug treatment and without drug treatment

	Distribution		
	Dyslipidemia	On lipid-lowering treatment^	Without lipid-lowering treatment^
LDL cholesterol^			
<100 mg/dl	34.6	47.5	10.7
100-129 mg/dl	27.4	27.0	28.3
130-159 mg/dl	21.6	13.8	36.2
160-189 mg/dl	11.7	7.6	19.4
≥190 mg/dl	4.6	4.2	5.5
Blood pressure^			
<140/90 mmHg	63.3	62.9	63.8
140-159/90-99 mmHg	27.8	28.2	27.4
160-179/100-109 mmHg	7.4	7.4	7.3
≥180/110 mmHg	1.5	1.5	1.5
Smoking ^			
Yes	26.6	25.2	28.4
No	73.4	74.8	71.6
BMI^			
Under weight	0.9	0.7	1.2
Normal weight	29.7	25.8	35.2
Over weight	41.0	42.4	39.0
Obesity	28.4	31.1	24.6

BMI: Body Mass Index

^Percentages are calculated excluding patients with missing data

Distribution of the values relating to blood pressure, smoking habits, BMI and LDL cholesterol (values recorded in the last 12 months) [**numerators**] among subjects with dyslipidemia with at least one value recorded in the year, divided between subjects on lipid-lowering treatment and without drug treatment [**denominators**].

Table 3.2.2l. Prevalence of use of lipid-lowering medicines in subjects with dyslipidemia (general and in its various forms) and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence of use (%)					
	Dyslipidemia	Δ % 20-19	Polygenic hypercholeste-rolemia	Familial dyslipidemia	Hyperlipidemias with moderate/ severe CRI *	Other dyslipide-mias**
Geographic analysis						
North	44.1	-1.1	44.0	51.8	53.0	27.7
Centre	47.3	-2.1	47.0	56.4	57.7	34.1
South and	51.4	-0.8	51.4	58.5	61.7	37.7
Analysis by gender						
Men	46.2	-2.2	46.5	52.0	58.0	31.9
Women	48.7	0.0	48.2	59.0	56.6	37.9
Analysis by age						
≥45 years	14.3	2.1	12.9	24.5	17.3	15.2
46-65	37.3	0.3	36.4	51.8	44.3	29.1
66-74	58.6	1.0	58.1	71.5	62.7	47.4
75-84	65.2	0.3	65.0	75.1	68.5	52.5
≥85 years	53.2	-1.1	53.1	61.6	56.0	46.4
Total	**47.5**	**-1.1**	**47.4**	**55.7**	**57.3**	**33.5**

*Chronic renal failure

**Other dyslipidaemias: dysbetalipoproteinemias, hyperchilomicronaemias, hypertriglyceridemias, drug-induced hyperlipemia Indicator 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**] on the total of patients diagnosed with dyslipidemia and polygenic hypercholesterolemia or familial dyslipidemia or with moderate and severe hyperlipidemias and CRI or other dyslipidaemias (dysbetalipoprotheinemias, hyperchylomicronemias, hypertriglyceridemias, drug hyperlipemia) [**denominators**]

Table 3.2.2m. Prevalence of use (%) of lipid-lowering medicines in patients with dyslipidemia and its different forms and by therapeutic category

Analysis by category therapeutic	Prevalence of use (%)				
	Dyslipidemia	Polygenic hypercholesterolemia	Familial dyslipidemia	Hyperlipidemias in patients with moderate or severe CRI *	Other dyslipidaemias**
amlodipine/atorvastatin/perindopril	-	-	-	-	-
ezetimibe	2.9	2.8	4.6	3.5	1.1
ezetimibe in combination	4.4	4.2	7.1	5.8	2.0
fibrates	2.3	2.1	4.6	2.6	10.4
MTP inhibitor	-	-	-	-	-
PCSK9 inhibitors	-	-	0.1	-	-
omega 3	3.3	2.9	7.4	4.6	10.4
statins, plain	39.9	40.3	42.6	48.0	16.4
statins in combination	-	-	-	-	-

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

*Chronic renal failure

**Other dyslipidaemias: dysbetalipoproteinemias, hyperchilomicronemias, hypertriglyceridemias, drug-induced hyperlipemia Indicators used:

Prevalence of use of lipid-lowering medicines in patients with dyslipidemia and its different forms: number of patients treated with a specific therapeutic category [**numerator**] on the total of patients diagnosed with dyslipidemia and polygenic hypercholesterolemia or familial dyslipidemia or with moderate and severe hyperlipidemias and CRI or other dyslipidaemias (dysbetalipoprotheinemias, hyperchylomicronemias, hypertriglyceridaemias, drug hyperlipemia) [**denominators**]

Table 3.2.2n. Proportion of patients adhering to treatment with lipid-lowering medicines in patients with dyslipidemia and based on the number of concomitant diseases ^: stratified analysis by gender, age group, geographic area, therapeutic category, cardiovascular risk, type of prevention and smoking habits

	Therapeutic adherence (%)					
	Dyslipidemia	1 pathology	2 pathologies	3 pathologies	4 pathologies	+4 pathologies
Geographic analysis						
North	40.1	39.1	45.1	51.0	56.6	58.9
Centre	40.7	37.8	45.4	50.7	57.2	61.1
South and Islands	39.4	36.1	40.5	47.6	50.1	53.5
Analysis by gender						
Men	45.3	43.8	51.0	57.0	61.5	60.3
Women	35.4	33.2	37.3	42.8	45.6	51.8
Analysis by age						
<45	29.4	33.1	37.6	62.5	71.4	0.0
46-65	39.2	39.9	46.9	54.0	60.1	60.9
66-74	41.3	38.3	44.7	50.6	58.2	61.5
75-84	41.0	36.0	41.7	48.4	52.1	55.2
≥85 years	36.6	32.7	34.6	42.0	40.6	47.8
Analysis by therapeutic category						
acetylsalicylic acid/atorvastatin/ramipril	-	-	-	-	-	-
amlodipine/atorvastatin/perindopril	74.5	83.3	66.7	80.0	80.0	100.0
ezetimibe	71.1	69.8	73.3	75.2	80.6	78.3
ezetimibe in combination	63.4	62.1	66.7	67.3	74.8	67.1
fibrates	38.9	36.3	41.4	48.4	55.6	53.3
MTP inhibitor	-	-	-	-	-	-
PCSK9 inhibitors	58.7	62.5	33.3	66.7	77.8	57.1
omega 3	65.5	63.8	69.0	73.9	76.7	73.4
statins, plain	38.7	36.3	41.7	48.6	52.2	56.0
statins in combination	15.8	33.3	33.3	-	-	-
Cardiovascular risk*						
Medium	33.4	34.5	26.8	35.9	33.3	-
Moderate	33.7	35.4	34.2	47.6	-	-
High	39.9	40.7	39.9	38.9	42.7	44.0
Very high	54.4	50.7	54.5	56.5	55.9	56.7
Type of prevention						
Primary prevention	34.3	35.0	36.5	39.6	-	40.5
Secondary prevention	57.3	54.8	58.5	59.3	-	58.4
Smoking						
Yes	42.1	40.2	44.6	52.6	58.3	54.8
No	43.3	40.3	46.3	53.1	56.1	54.4
Total	**39.9**	**37.6**	**43.1**	**49.3**	**53.2**	**55.9**

^Hypertension, cardio- and cerebrovascular disease, diabetes, heart failure, chronic kidney disease, COPD, asthma and osteoarthritis

*Indicators used pursuant to

AIFA Note 13:

Proportion of patients adhering to treatment with lipid-lowering medicines: number of patients adhering (DDD/user/molecule>290/year) to treatment with lipid-lowering medicines [**numerators**], on the total patients with dyslipidemia, on lipid lowering drug treatment and divided by number of concomitant diseases [**denominators**].

Table 3.2.2o. Proportion of patients (total and non-diabetic) using statins in primary prevention within the population aged ≥80

	Prevalence of use total population (%)	Non diabetics
Geographic analysis		
North	36.2	32.9
Centre	38.3	35.1
South and Islands	41.8	38.0
Analysis by gender		
Men	34.1	30.0
Women	42.5	39.3
Analysis by age		
80-84	55.4	52.4
85-90	49.8	47.1
90+	36.0	33.5
Total	**38.7**	**35.2**

Indicators used:

Proportion of subjects 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 subjects 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**]

Key message

- Over the years lipid-lowering drugs have experienced a **constant increase in consumption** (CAGR + 4.6%), which in 2020 was 103.2 DDD/1000 inhabitants per day. At the same time, the average cost per day of therapy appears to be decreasing, namely owing to the significant reduction observed in 2017, likely due to the patent expiry of rosuvastatin.
- The **increasing trend of PCSK9 inhibitors** continues, in terms of both expenditure and consumption. These drugs - authorised by the EMA in 2015 - showed a high efficacy profile associated with a good safety profile in patients with familial hypercholesterolemia resistant to conventional therapy. Furthermore, some recent studies confirm their efficacy even in patients at high/very high cardiovascular risk and/or in secondary prevention. The results of recent epidemiological studies estimate in more than 100,000 individuals the size of the population eligible for treatment with PCSK9, so confirming the need to carry on the activity of controlling the prescriptive appropriateness through the AIFA registries.
- The proportion of subjects with high adherence is significantly lower than the one observed for hypertension and heart failure drugs, although **extreme regional variability** is confirmed for this therapeutic category as well, with the North showing a higher adherence profile than the Central and Southern Regions and Islands. This data appears to be even more significant in light of the greater consumption of these drugs observed in the South and in the Islands, which indicates a higher figure of exposed population.

- Data from general practice indicate a more consistent use in relation to the increase in global cardiovascular risk and significantly higher in subjects in secondary prevention than in primary prevention, in accordance with the most recent guidelines. However, it should be noted that in secondary prevention over 40% of patients treated with lipid-lowering agents have suboptimal adherence, confirming the need to pursue activities **improving appropriateness**.
- Both consumption and exposure reach a peak in the 75-84 age group and subsequently decrease in the +85s, as already observed for hypertension and heart failure drugs. However, this therapeutic category does not show the same reduction in the adherence profile as occurred for antihypertensive drugs. Several meta-analyses suggest a beneficial effect of lipid-lowering drugs also for **very elderly patients**, with a reduction of the risk of cardiovascular events. Nevertheless, their efficacy in primary prevention for this age group has not yet been demonstrated, although data from General practice confirm their widespread use in both the +85s and the +90s.

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3.2.3 Acute Coronary Syndrome

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

	Incidence (‰)*	Δ % 20-19	Prevalence (%)	Δ % 20-19
Geographic analysis				
North	0.8	-33.7	1.6	0.0
Centre	1.0	-10.5	1.6	0.0
South and Islands	0.7	-30.6	1.5	0.0
Analysis by gender				
Men	1.1	-27.7	2.3	-4.4
Women	0.5	-26.9	0.8	0.0
Analysis by age				
≥45 years	0.1	12.5	0.1	0.0
46-65	0.8	-22.6	1.3	7.7
66-74	1.7	-18.4	3.6	5.6
75-84	2.0	-34.7	4.4	0.0
≥85 years	2.4	-11.7	5.1	2.0
Total	**0.8**	**-28.4**	**1.5**	**-6.7**

*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**], on the total population eligible for assistance and at risk (disease free) at the beginning of the period [**denominator**]

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

Table 3.2.3b. Prevalence of use of ACE inhibitors, sartans, beta-blockers, platelet aggregation inhibitors and lipid-lowering medicines in patients with acute coronary syndrome and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence of use (%)	Δ % 20-19
Geographic analysis		
North	88.3	0.5
Centre	88.6	-0.6
South and Islands	89.0	-1.1
Analysis by gender		
Men	87.3	-0.9
Women	92.4	1.5
Analysis by age		
≥45 years	65.3	4.4
46-65	81.4	-2.1
66-74	89.0	-0.9
75-84	96.1	2.1
≥85 years	92.2	1.7
Total	**88.6**	**-0.3**

Indicator 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 3.2.3c. Prevalence of use (%) of ACE inhibitors, sartans, beta-blockers, platelet aggregation inhibitors and lipid-lowering medicines in patients with acute coronary syndrome: analysis by therapeutic category

Analysis by therapeutic category	Prevalence of use (%)
ACE inhibitors	43.8
Sartans	25.3
Beta blockers	67.3
Platelet aggregation inhibitors	72.7
Lipid-lowering agents	77.4

Indicator 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**]

Table 3.2.3d. Distribution of LDL cholesterol, blood pressure, smoking, BMI in patients with acute coronary syndrome both on drug treatment and without drug treatment

	Distribution (%)		
	Acute Coronary Syndrome	On treatment*	Without treatment
LDL cholesterol^			
<100 mg/dl	77.2	77.7	43.3
100-129 mg/dl	14.7	14.5	25.6
130-159 mg/dl	5.4	5.1	24.4
160-189 mg/dl	1.8	1.8	5.6
≥190 mg/dl	0.8	0.8	1.1
Blood pressure^			
<140/90 mmHg	66.4	66.2	69.2
140-159/90-99 mmHg	25.1	25.2	21.6
160-179/100-109 mmHg	7.1	7.0	8.3
≥180/110 mmHg	1.5	1.5	1.0
Smoking ^			
Yes	23.3	23.3	25.0
No	76.7	76.7	75.0
BMI^			
Under weight	0.9	0.9	0.6
Normal weight	26.9	26.7	31.4
Over weight	42.6	42.3	50.3
Obesity	29.5	30.1	17.7

*At least one prescriptions of ACE inhibitors, sartans, beta-blockers, platelet aggregation inhibitors or lipidi-lowering agents

^Percentages are calculated excluding patients with missing data; Indicator

used:

Distribution of the values relating to blood pressure, smoking habits, BMI and LDL cholesterol (values recorded in the last 12 months) [**numerator**] in subjects with acute coronary syndrome with at least one value recorded in the year, divided between subjects on drug treatment and without drug treatment [**denominator**].

Table 3.2.3e. Proportion of patients adhering to treatment with ACE inhibitors, sartans, beta-blockers, platelet aggregation inhibitors and lipid-lowering medicines in patients with acute coronary syndrome: stratified analysis stratified analysis by LDL cholesterol levels, blood pressure, smoking habits, BMI and therapeutic category

	Adherence %
LDL cholesterol	
<100 mg/dl	96.8
100-129 mg/dl	93.7
130-159 mg/dl	92.6
160-189 mg/dl	88.0
≥190 mg/dl	85.1
Blood pressure	
<140/90 mmHg	92.8
140-159/90-99 mmHg	94.3
160-179/100-109 mmHg	94.3
≥180/110 mmHg	95.1
Smoking	
Yes	92.3
No	94.0
BMI	
Under weight	69.4
Normal weight	90.8
Over weight	94.7
Obesity	94.2
Analysis by therapeutic class	
ACE inhibitors	66.5
Sartans	60.8
Beta blockers	11.9
Platelet aggregation inhibitors	65.7
Lipid-lowering agents	68.7
Total	**91.4**

Indicator used:

Proportion of patients with Acute Coronary Syndrome adhering to treatment with ACE inhibitors, Sartans, Beta-blockers, Antiplatelet agents and Lipid-lowering drugs: number of patients adhering (dose unit/user> 290/year) to treatment with ACE inhibitors, Sartans, Beta-blockers, Antiplatelet agents and lipid-lowering drugs for Acute Coronary Syndrome **[numerator]** on the total number of subjects diagnosed with Acute Coronary Syndrome and on pharmacological treatment **[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 subjects 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 and the target cholesterol values to be achieved in the follow-up.
- **General practice data** suggest a predominantly appropriate use of these drugs in the management of patients with ACS. Almost 90% of patients have at least one of the above therapeutic categories; moreover, out of the total number of subjects treated, over 90% show high adherence to at least one of these therapies. It should be noted, however, that only 11% of subjects treated with beta-blockers show an optimal adherence profile. This data is supported by a consolidated scientific literature confirming the difficulty in managing adverse events associated with these drugs.

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3.3 Alimentary tract and metabolism

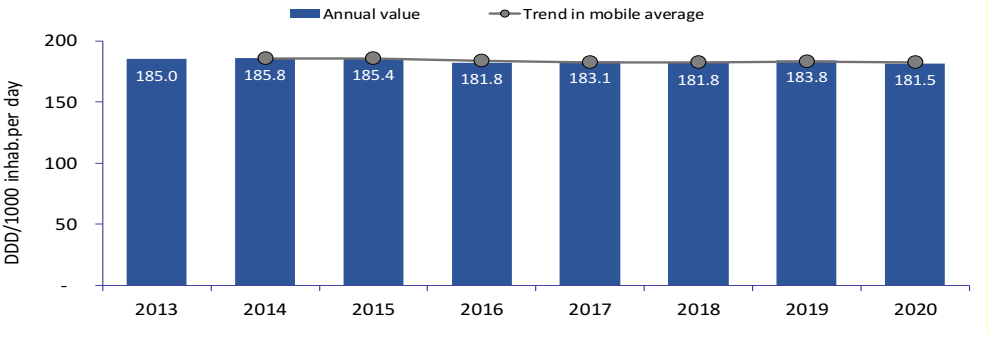
Medicines for alimentary tract and metabolism were the third therapeutic category with the highest public expenditure for 2020, equal to 2,876.7 million euros and 12.5% of overall public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was 48.23 euros, mainly due to the outpatient pharmaceutical expenditure (31.20 euros per capita), reporting a -5.1% decrease compared to the previous year. Instead, expenditure due to purchases by public health facilities is lower (17.04 euros per capita), with a 9.3% increase compared to 2019 (Table 3.1).
Consumption for this category of drugs was 181.4 DDD/1000 inhabitants per day, with a substantially stable trend in the past few years (-1.2%) (Table 3.2).
The analysis of the drug use profile by age group and gender, including outpatient pharmaceutical expenditure and *per conto* distribution shows a progressive increase in the use of drugs belonging to this category with increasing age for both genders, with a more marked trend from 45 years onwards. At the same time, the per capita expenditure borne by the NHS also presents a similar trend, reaching the maximum value of 120.8 euros in the over 75-age group and with a slightly higher expenditure for the male gender.
As regards the approved care regime, expenditure in absolute terms decreased by 5.4% compared to the previous year (Table 3.9). This trend was determined by a reduction in consumption (-2.2%) and a shift in prescription towards lower cost specialties (mix effect: -3.1%), while prices remain stable (-0.1%).
Proton pump inhibitors rank first in terms of expenditure (11.45 euros per capita) and consumption (72.7 DDD/1000 inhabitants per day), recording an increase in use (+4.7%), a decrease in expenditure (-4.9%) and a use of less expensive specialties (mix effect -9.1%). Vitamin D and analogues rank second by gross per capita expenditure (3.96 euros), despite showing a remarkable 24.6% decrease in expenditure and a 21.3% decrease in consumption due to the introduction of AIFA Note 96. A greater use of less expensive specialties was also observed for this category of drugs (mix effect -4.2%). The category calcium in combination with vitamin D and/or other drugs also recorded an important reduction in both expenditure (-24.6%) and consumption (-21.3%).
In 2020 a further increase was reported again in expenditure and consumption for analogues of the GLP-1 receptor (+66.7% and +42.8%, respectively); oral hypoglycemic agents in combination recorded a significant increase in expenditure (+35.7%), a slight reduction in consumption (-1.9%), a shift in prescriptions towards more expensive specialties (mix effect: +41.5%) and an increase in the average cost per day of therapy (+38.3%), probably due to the increase in the prescriptions of fixed glyphzine combinations with dipeptidyl-peptidase IV inhibitors.
Pantoprazole and cholecalciferol are the molecules with the highest per capita expenditure (4.26 and 3.38 euros, respectively) and together represent the main cost item of the outpatient pharmaceutical expenditure relating to medicines for the alimentary tract (24.5%) (Table 3.10). These two molecules are also confirmed in the top 30 active ingredients by outpatient expenditure (253.8 and 201.4 million euros, respectively) (Table 3.11).

Dulaglutide is in the list of the top 30 active ingredients with the greatest variation in expenditure under approved care regime, compared to the previous year (+36.1%), with a +32.8% consumption variation, followed by ursodeoxycholic acid and mesalazine (Table 3.13).
With regard to purchases by public health facilities, expenditure increased by 9.0% compared to 2019, consumption increased by 4.0% (Table 3.16), prices decreased by 1.8%, with prescriptions moving towards more expensive specialties (mix effect: +5.5%). The highest expenditure increases were recorded for the category of polyvitamins (+46.4%), for analogues of the GLP-1 receptor (+32.7%), and for various products of the alimentary tract and metabolism (+26.6%), which include some orphan drugs indicated, for example, in the treatment of Gaucher's and Fabry's disease. Enzymes such as recombinant human acid alglucosidase, agalsidase alfa, imiglucerase account for 28.5% of the expenditure, despite a very low average consumption, considering that they include medicines used in the treatment of rare diseases and which have a high average cost per DDD (Table 3.16). Insulin glargine is the active ingredient with the highest per capita expenditure (1.56 euros), a stable value compared to the previous year (-0.2%), representing 9.2% of the expenditure for drugs of this category purchased by public health facilities, with a 2.2% increase in consumption compared to the previous year (Table 3.17). This active ingredient is the only one in the category listed in the top 30 active ingredients with highest expenditure for drugs purchased by health facilities (Table 3.18).
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by region and on the efficiency in the absorption of resources according to the presence of patent-expired medicines and on a regional basis. These analyses focused on medicines for peptic ulcer and GERD and on medicines for the treatment of diabetes mellitus (Table 3.3.1 and following).

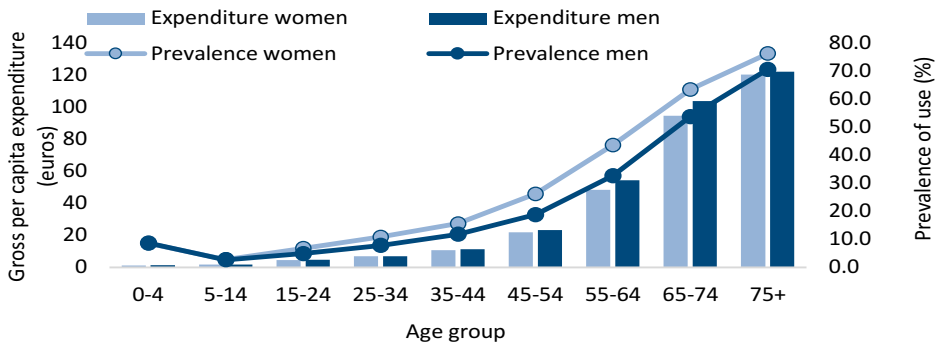
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Alimentary tract and metabolism

Public expenditure* in million euros (% over total)	**2,876.7**	**(12,5)**
Δ % 2020-2019		-0.5%
Regional range of gross per capita expenditure	28.6	65.4
DDD/1000 inhab. per day (% over total)	**181.4**	**(15,6)**
Δ % 2020-2019		-1.2%
Regional range of DDD/1000 inhab. per	122.2	233.7

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities



Distribution, by age and gender, of expenditure, prevalence of use and consumptions under approved care regime and *per conto* distribution in 2020 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab.per day		
	Men	Women	Total	Men	Women	Total
0-4	1.2	1.2	1.2	5.3	5.1	5.2
5-14	1.7	1.7	1.7	4.5	4.5	4.5
15-24	4.6	4.5	4.6	12.5	13.3	12.9
25-34	6.8	6.9	6.9	21.2	23.1	22.2
35-44	11.3	10.7	11.0	40.7	40.7	40.7
45-54	23.2	21.7	22.5	88.9	86.7	87.8
55-64	54.3	48.4	51.2	213.0	195.5	203.9
65-74	103.7	94.5	98.8	434.1	401.9	417.1
75+	121.9	120.1	120.8	564.5	555.4	559.0

3.3.1. Antidiabetics

National data on consumption and expenditure

Consumption of medicines for diabetes was stable over the period 2014-2020, from 61.8 to 64.6 DDD/1000 inhabitants per day, with an average annual variation (CAGR) of about 1%. On the contrary, the cost per day of therapy has increased on average by about 5% every year, indicating an increasing use of high-cost drugs such as GLP-1 analogues, gliptins and glyphzines (Figure and Table 3.3.1a.). In 2020, per capita expenditure was 18.36 euros, an 8.7% increase compared to the previous year, while the average DDD cost recorded a value of 0.78 euros, with a 7.5% increase compared to the previous year. Fast-acting insulins, while still representing the category with the highest expenditure, show a 1.6% decrease compared to 2019, mainly determined by the trend of insulin lispro, whose average cost decreased by 4% (Table 3.3.1a).

GLP-1 analogues, plain or in combination with insulins, show significant increases in expenditure (+40.4% and +32.7%, respectively) and consumption (+25.7% and +34.7%, respectively). Similarly, glyphzines plain or combined with metformin also show an increase in consumption by 22.8% and 21.0% respectively, with a similar increase in expenditure (+24.9% and +21.6%). In 2020, the marketing of the new ertugliflozin/metformin combination may have contributed to such increases, although the average DDD cost of glyphlozins combined with metformin remained stable compared to the previous year (+0.2%). As for consumption, less marked increases are recorded for gliptins, +8.6% plain and +3.2% in combination.

According to current guidelines, metformin, plain or in combination with other drugs, is the most used medicine for the treatment of diabetes (37.2% of doses), with a slight decrease compared to 2019. Non-combined sulfonylureas, with a consumption of 7.8 DDD, are the third most used category in the population.

In light of the most recent recommendations from scientific societies, which do not provide for the use of sulfonylureas as a first-choice drug in combination with metformin, and considering the characteristics of target population (mostly elderly, often over eighty, with pluripathology and consequent frailty), the use of sulfonylureas or repaglinide deserves careful consideration, due to an increased risk of complications including hypoglycemia.
The substances with the highest expenditure in 2020 were dulaglutide (GLP-1 analogue) with 1.91 euros (+40.3% compared to 2019) and three insulins, glargine (1.80 euros), lispro (1.68 euros) and aspart (1.64 euros). It is noteworthy that the combination between insulin degludec and liraglutide in 2020 recorded increases in expenditure and consumption higher than 30%. This drug also records the highest cost per day of therapy (4.97 euros) while metformin is at a minimum value, with 0.19 euros. The reimbursement of the combination insulin degludec/liraglutide is limited to patients inadequately controlled by the previous line of therapy with basal insulin and other hypoglycemic agents other than insulin. This association has not been studied in treatment-naïve patients, in combination with multi-injection insulin regimens and in combination with SGLT-2 inhibitors; reimbursement is therefore not recognised in such cases.
Over half of the prescribed doses (53.9%) concern patent-expired molecules (Table 3.3.1c), even if the use of generic drugs decreased by 5.1%, while the consumption of patent-covered increased by 3.9%. The average cost per day of therapy for patent-expired drugs is 0.22 euros, which rises to 1.43 euros for those still covered by a patent.

Figure 3.3.1a. Antidiabetics, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

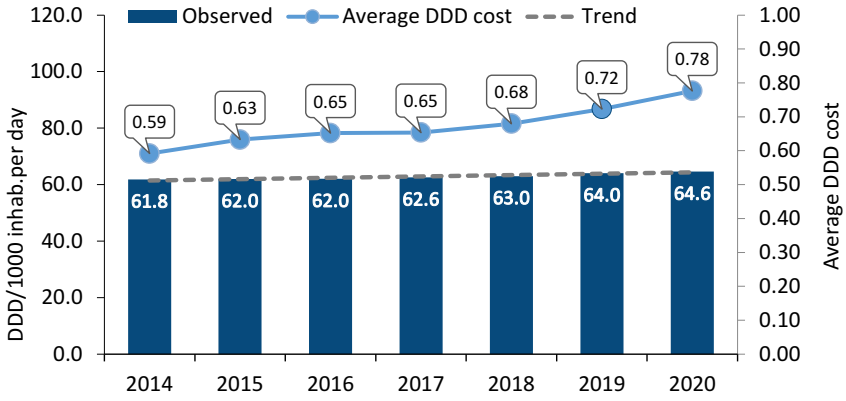


Table 3.3.1a. Antidiabetics, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Fast acting insulins	3.81	-1.6	-0.4	8.5	-0.3	0.4	1.23	-1.5
GLP-1 (glucagon-like one) analogues	3.33	40.4	27.9	2.9	25.7	30.9	3.09	11.4
Combined insulins (long/intermediate with fast)	2.95	-0.4	0.2	6.8	1.9	1.9	1.18	-2.5
Metformin plain and in combination	1.67	0.4	-0.3	24.0	-0.9	-0.7	0.19	1.0
Gliptins (DPP-4 inhibitors) plain	1.51	8.0	10.9	3.3	8.6	15.2	1.26	-0.7
Gliptins (DPP-4 inhibitors) in combination	1.36	6.7	3.7	3.2	3.2	8.2	1.15	3.1
Glifozins combined with metformin	0.84	21.6	-	1.7	21.0	-	1.33	0.2
Insulins combined with GLP-1 (glucagon-like one) analogues	0.82	32.7	-	0.5	34.7	-	4.86	-1.7
Glifozins (SGLT2 inhibitors), plain	0.81	24.9	-	1.6	22.8	-	1.35	1.4
Sulfonylureas, plain	0.51	-3.1	-1.6	7.8	-8.1	-5.8	0.18	5.1
Pioglitazone plain and in combination	0.33	-15.4	-12.0	1.7	1.7	-4.1	0.52	-17.0
Repaglinide	0.27	-12.8	-10.5	1.9	-13.4	-11.3	0.38	0.4
Acarbose	0.14	-7.8	-4.1	0.6	-6.3	-2.9	0.72	-1.9
Intermediate acting insulins	0.00	-11.7	-46.5	0.0	-7.0	-37.6	0.47	-5.4
Antidiabetics	**18.36**	**8.7**	**5.5**	**64.6**	**0.9**	**0.7**	**0.78**	**7.5**
dulaglutide	1.91	40.3	-	2.0	38.1	-	2.64	1.3
insulin glargine	1.80	0.6	-1.1	4.8	2.4	3.0	1.02	-2.1
insulin lispro	1.68	-4.0	-2.5	4.0	-0.6	-0.2	1.16	-3.7
insulin aspart	1.64	0.4	-1.9	3.3	-0.3	-1.8	1.35	0.4
metformin	1.58	2.0	2.7	22.8	0.5	1.9	0.19	1.2
insulin degludec	0.92	3.6	121.0	1.5	9.8	135.8	1.69	-5.9
insulin degludec/liraglutide	0.72	32.7	-	0.4	33.8	-	4.97	-1.1
linagliptin	0.70	10.4	39.8	1.5	10.9	44.4	1.31	-0.7
sitagliptin	0.61	10.4	3.1	1.3	10.5	7.2	1.27	-0.3
sitagliptin/metformin	0.61	2.7	0.4	1.5	2.7	4.9	1.11	-0.3

Table 3.3.1b. Antidiabetics, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	59.5	59.4	59.2	59.6	59.1	60.0	60.7	1.1
Valle d'Aosta	60.2	60.3	56.9	58.9	59.6	59.2	59.9	1.2
Lombardy	55.5	56.4	56.1	56.3	56.3	56.9	58.1	2.2
A.P. of Bolzano	43.0	42.8	40.5	40.7	40.5	41.2	40.8	-0.9
A.P. of Trento	48.6	47.9	49.3	48.5	48.8	49.1	49.5	0.9
Veneto	52.2	52.5	52.1	52.3	53.2	55.2	54.2	-1.8
Friuli VG	57.2	56.1	57.2	58.2	58.8	58.5	60.1	2.8
Liguria	51.4	50.7	50.1	49.5	49.7	50.3	49.9	-0.7
Emilia R.	58.0	58.6	59.0	60.6	61.0	61.3	62.1	1.3
Tuscany	58.1	57.6	56.5	56.7	57.2	56.4	55.9	-0.9
Umbria	57.4	57.2	57.4	57.8	58.3	59.3	61.0	2.8
Marche	50.3	52.9	54.6	55.2	55.9	57.0	59.4	4.3
Lazio	63.1	62.9	63.0	63.8	63.8	65.4	65.4	0.0
Abruzzo	63.8	63.7	63.3	64.3	65.2	65.3	67.8	3.8
Molise	64.4	63.3	63.3	64.6	65.4	66.3	68.2	2.9
Campania	68.3	69.1	70.1	71.0	71.9	74.8	74.4	-0.5
Puglia	73.4	73.0	74.0	74.6	75.2	75.5	76.8	1.8
Basilicata	69.9	70.1	71.5	74.3	74.5	75.0	77.1	2.7
Calabria	78.6	78.6	80.2	80.0	83.8	85.8	85.7	-0.2
Sicily	78.8	78.0	77.8	77.6	77.8	80.6	80.9	0.4
Sardinia	66.9	66.0	64.8	66.5	67.3	66.9	70.5	5.3
Italy	**61.8**	**62.0**	**62.0**	**62.6**	**63.0**	**64.0**	**64.6**	**0.9**
North	55.5	55.8	55.7	56.1	56.3	57.1	57.6	1.0
Centre	59.4	59.4	59.4	59.9	60.3	60.9	61.2	0.5
South and Islands	72.4	72.3	72.7	73.3	74.2	75.9	76.7	1.0

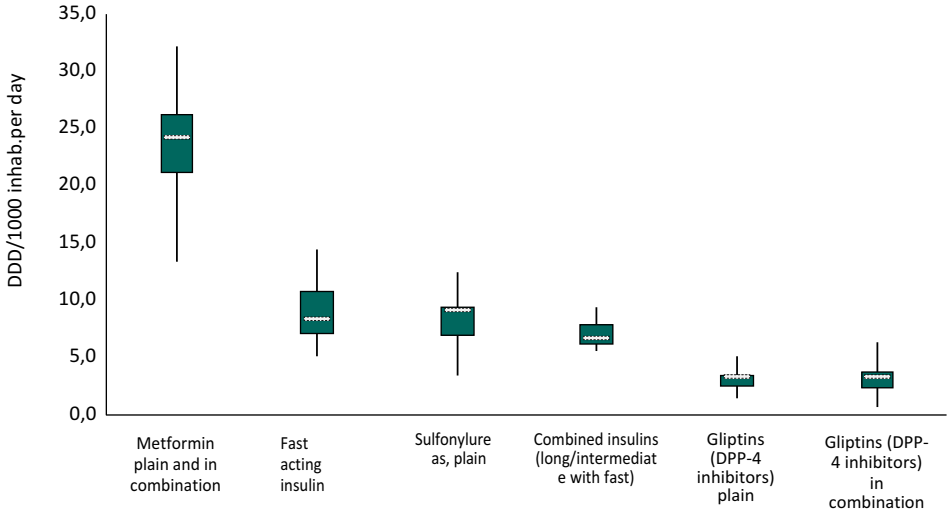
Table 3.3.1c. Prescription of antidiabetics with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	2.81	15.3	1.8	34.8	53.9	-1.5	0.22
Generic	0.92	32.8	-2.4	14.9	42.7	-5.1	0.17
Ex originator	1.89	67.2	3.9	19.9	57.3	1.4	0.26
Patent covered	15.55	84.7	10.1	29.8	46.1	3.9	1.43
Antidiabetics	**18.36**	**100.0**	**8.7**	**64.6**	**100.0**	**0.9**	**0.78**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.3.1c. Antidiabetics, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure and adherence in population

Health Card data allowed to describe the prevalence and consumption trend by age, gender and region and to calculate some indicators of intensity of use. Adherence and persistence were also estimated of chronic treatments with antidiabetic medicines.

A deeper understanding of the population shows an increasing use of diabetes drugs with increasing age, with higher prevalence (21.9%) and consumption (217.3 DDD) in men aged 75 to 84 years, in agreement with the epidemiology of the condition (Figure 3.3.1e). This difference between men and women is found in all age groups with a more marked trend from 55 to 84 years, while in the over 85 group this difference is lower. On average, the prevalence is 6%, ranging from a minimum of 5% in the North to a maximum of 7.2% in the South (Table 3.3.1d). Calabria, with a value of 8%, is the region with the greatest use of diabetes drugs, while in the AP of Bolzano the prevalence is slightly over 3%. As already highlighted, men show a higher prevalence than women (M/W ratio: 1.19); the median age of users is 70, with no particular regional differences. In line with the therapeutic regimen of a chronic condition, each user receives, on average, at least one dose of the drug per day (DDD per user: 367.3) and half of them are treated for at least 10 months a year (9 months in Central regions). The share of subjects receiving a single prescription is 7.4% with a value ranging from a minimum of 5% in Friuli Venezia Giulia and Sardinia to a maximum of 9.5% in Emilia Romagna. In reading this indicator, it should be considered that the values can be influenced both by the share of subjects who start 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, death and hospitalisation).

As for the adherence and persistence analyses, the exposure data refer to a cohort of new users over 45 years old, which were monitored considering the one-year follow-up. The study population includes 64,998 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 in both cases 28.9% (Table 3.3.1e). In particular, the highest percentages of high adherence were observed in subjects aged between 45 and 54 years (36.8% in total: 42.8% for the North, 33.4% for the Centre and 33.9% for the South), and then decrease with increasing age. The highest percentage of subjects with low adherence is in subjects resident in the South with at least 85 years of age (41.3%). In general, men have a higher adherence than women (31.6% vs 25.9%). Compared to 2019, there was an increase in subjects with low adherence (+3.4%) and the share of subjects with high adherence decreased, albeit slightly (-0.8%). The North (+7.9%) recorded the greatest increase in terms of subjects with low adherence, while the Regions of the Centre have the greatest growth of subjects with high adherence (+7.3%). The percentage of people persisting to treatment at 12 months was higher in the North (41.1%) rather than Center (36.4%) and South (39.1%). Women have a lower persistance to treatment at 12 months than men, with values of 36.1% and 42.0%, respectively (Table 3.3.1f).

The probability of being persistent decreases with increasing age: at 12 months persistent subjects vary from 44.6% to 26.9% starting from the age group of 45-54 years up to subjects aged at least 85.
If considering the median time to discontinuation of antidiabetic treatment, a 50% probability of discontinuing treatment is achieved at approximately 210 days without substantial differences compared to 2019 (Figure 3.3.1g).

Figure 3.3.1d. Distribution of 2020 prevalence of use and consumption of antidiabetic medicines under approved care regime and *per conto* distribution

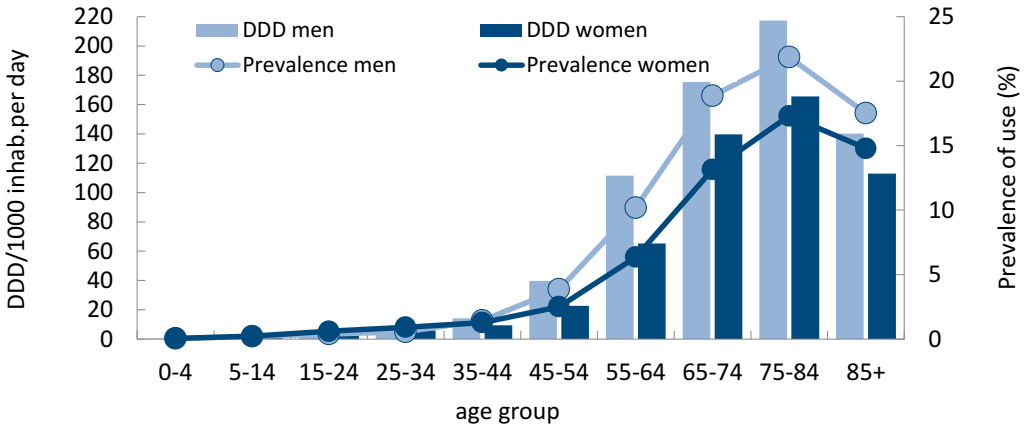


Table 3.3.1d. Exposure and duration of therapy with antidiabetic medicines by geographic area under NHS outpatient care and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	DDD median	Users with 1 prescription (%)
Piedmont	5.6	1.26	71	8.8	381.0	300.0	5.5
Valle d'Aosta	4.5	1.27	71	7.4	467.0	347.0	7.0
Lombardy	5.0	1.33	71	6.9	412.2	336.0	7.7
A.P. of	3.3	1.27	71	6.6	396.4	326.0	6.7
A.P. of Trento	4.5	1.24	71	7.5	349.6	287.0	5.4
Veneto	4.7	1.35	71	7.8	395.2	331.0	5.8
Friuli VG	5.6	1.38	72	8.2	399.9	330.0	5.0
Liguria	5.3	1.19	73	8.3	358.3	290.0	8.9
Emilia R.	4.7	1.25	71	7.0	290.0	220.0	9.5
Tuscany	6.0	1.15	71	8.5	327.1	255.0	9.1
Umbria	6.2	1.22	71	10.5	358.0	300.0	5.4
Marche	5.6	1.26	71	8.8	357.3	293.0	6.4
Lazio	6.5	1.11	70	8.5	350.0	272.0	8.8
Abruzzo	6.5	1.15	71	8.9	372.4	306.0	6.0
Molise	7.0	1.21	70	8.5	340.4	295.0	6.1
Campania	6.6	1.16	69	10.0	372.0	322.0	6.3
Puglia	7.6	1.06	70	8.3	343.5	275.0	9.5
Basilicata	7.3	1.09	70	9.6	382.3	318.0	5.4
Calabria	8.0	1.09	69	8.9	366.1	300.0	7.5
Sicily	7.6	1.12	70	9.3	369.4	300.0	6.7
Sardinia	6.3	1.20	70	10.0	397.6	337.0	5.0
Italy	**6.0**	**1.19**	**70**	**8.5**	**367.3**	**300.0**	**7.4**
North	5.0	1.30	71	7.6	380.5	300.0	7.2
Centre	6.2	1.14	71	8.7	344.6	270.0	8.3
South and Islands	7.2	1.12	70	9.3	366.4	300.0	7.0

Table 3.3.1e. Indicators of adherence to treatment with antidiabetic medicines in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=64,998		North‡ N=24,003		Centre N=14,743		South N=26,252	
Low adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	22.3	3	17.2	5	25.7	3	24.5	4
55-64 years	25.4	6	20.4	11	27.5	2	28.2	6
65-74 years	30.0	5	24.6	11	32.0	-2	33.6	5
75-84 years	34.0	-1	30.7	4	35.3	-4	37.0	-4
≥85 years	36.9	7	32.5	9	37.6	-3	41.3	12
Women	32.3	4	27.8	9	34.0	-1	35.1	4
Men	25.9	3	22.0	7	28.0	-2	28.5	3
Total	**28.9**	**3**	**24.6**	**8**	**30.9**	**-1**	**31.6**	**4**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	36.8	-3	42.8	-6	33.4	2	33.9	-3
55-64 years	32.4	0	38.9	-3	28.7	3	29.3	0
65-74 years	26.3	-3	31.0	-2	24.3	6	23.2	-8
75-84 years	24.1	3	27.2	0	22.4	11	21.5	1
≥85 years	23.9	2	26.7	-3	27.1	37	18.8	-15
Women	25.9	-2	30.3	-4	24.2	9	23.0	-4
Men	31.6	0	35.8	-1	29.2	6	28.9	-3
Total	**28.9**	**-1**	**33.4**	**-3**	**26.7**	**7**	**26.1**	**-4**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

N: refers to new users, subjects who received a first prescription in the period 01/10 / 2019- 31/12/2019, 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): 325 (273-348)

‡ Excluding Emilia Romagna.

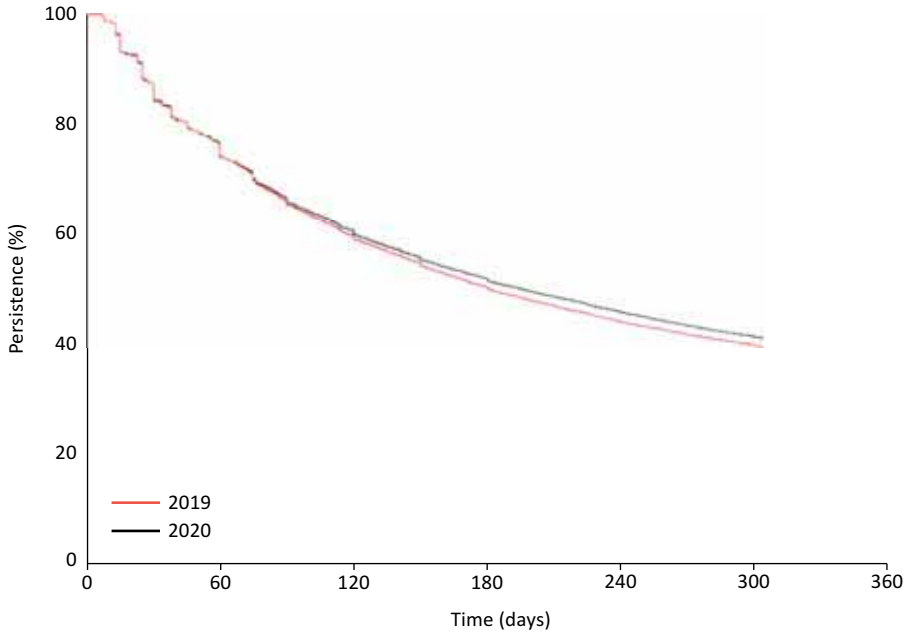
Table 3.3.1f. Persistence after one year of treatment with antidiabetic medicines in the population aged ≥45 years in 2020 and percentage change compared to the previous year

Persistence at 12 months	Total N=64,998		North‡ N=24,003		Centre N=14,743		South N=26,252	
	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	44.6	-5	48.8	-2	39.7	-9	44.1	-5
55-64 years	44.4	-2	46.7	-5	42.0	1	43.8	-2
65-74 years	39.5	-4	41.4	-2	37.6	-3	39.0	-6
75-84 years	32.5	-4	34.1	-3	29.7	-8	32.3	-4
≥85 years	26.9	-7	29.4	-7	24.7	-3	25.7	-9
Women	36.1	-4	38.4	-3	32.9	-5	36.0	-5
Men	42.0	-3	43.3	-4	39.7	-2	42.0	-3
Total	**39.2**	**-4**	**41.1**	**-3**	**36.4**	**-4**	**39.1**	**-4**

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

‡ Excluding Emilia Romagna.

Figure 3.3.1e Time (in days) to discontinuation of treatment with antidiabetic medicines in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: an interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods) For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days)

Key message

- **Over the last seven years, consumption has been stable**, with 64.6 DDD/1000 inhabitants per day in 2020. The stability in consumption is accompanied by a constant **increase in expenditure** due to the introduction of therapeutic categories with a new mechanism of action, still covered by a patent, in the last decade. Compared to 2019, the increase in consumption and expenditure is reported in particular for GLP-1 analogues (expenditure: +40.4%; consumption: +25.7%), DPP-4 inhibitors (expenditure: +8%; consumption: +8.6%) and SGLT2 inhibitors (expenditure: +24.9%; consumption: +22.8%).
- National and international guidelines recommend a step-by-step approach for diabetes, with metformin as the first choice drug and insulin added as the last choice when blood glucose is not adequately controlled by 3+ oral antidiabetic agents. In this context, there is an **ever-increasing use of the fixed combination between insulin degludec and liraglutide.** This combination exploits the efficacy of both drugs on the reduction of HbA1c and fasting and post-prandial blood glucose. Additionally, it has shown positive results also in comparison to multi-injection insulin therapy.
- 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 2020. In this case, data appears in line with the epidemiology of diabetes mellitus, which, as shown in the PASSI project, is more prevalent in Southern Regions and Islands than in the Centre-North. This is in line with the geographic distribution of major risk factors such as BMI and physical activity.
- The reduction in consumption and prevalence of use in people over 85 appears in line with the need in this age group to **simplify therapeutic regimens** to mitigate the complications related to the treatment. In this context, simplification aims to reduce the risk of hypoglycemia, which appears more frequent in this age group and can lead to cognitive impairment and neuronal damage.
- The analysis on **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 a population of elderly patients, ranging between 13% and 64% for oral hypoglycemic agents and between 19 and 46% for insulin therapy. The factors tending to reduce adherence include both clinical aspects (comorbidities, cognitive and/or sensory deficits, depression) and aspects related to the drug (polytherapy, complexity of the therapeutic regimen, adverse events) as well as the relationship with the GP (poor interaction and/or information).

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3.3.2. Medicines for peptic ulcer and GERD

National data on consumption and expenditure

In 2020, on average, the consumption of medicines for peptic ulcer and GERD was 82.7 DDD/1000 inhabitants per day, with a 6.7% decrease compared to 2014 and a 1.1% average annual change rate in the 2014-2020 period (Figure 3.3.2a). Over the last 7 years, the average DDD cost has decreased from 0.54 to 0.43 euros. The per capita expenditure value for these drugs was 13.0 euros, a 4.2% reduction compared to the previous year and a 4.8% average annual reduction in the period 2014-2020 (Table 3.3.2a). Proton pump inhibitors, with 76.4 DDD, account for over 90% of the consumption of medicines for peptic ulcer and GERD, with a 4.2% increase compared to 2019, and are confirmed as the category with the highest consumption and expenditure. In fact, they record a per capita expenditure of 11.66 euros, although the average DDD cost is the lowest (0.42 euros). The second most expensive category (0.91 euros) is represented by other drugs for peptic ulcer, including the group of alginates and sucralfate, followed by antacids (0.42 euros), consisting of magnesium and aluminum salts. Both of these categories recorded an average DDD cost of 0.58 euros. Pantoprazole is the molecule with the highest per capita expenditure (4.35 euros) and the highest consumption (26.6 DDD/1000 inhabitants per day), followed by omeprazole, lansoprazole and esomeprazole, with consumption values of 18.3, 15.2 and 14.3 DDD, respecively.

This is followed by the sodium alginate/potassium bicarbonate combination (4.1 DDD). All proton pump inhibitors, with the exception of lansoprazole (-1.0%) and rabeprazole (-2.9%), are increasing in consumption, while the average cost per day of therapy is decreasing for all molecules belonging to this category (0.42 euros average DDD cost and -7.1% compared to 2019). Despite an increase in consumption, pantoprazole recorded a decline in expenditure due to a reduction in the average cost per day of therapy.
Patent-expired medicines are about 92% of drug doses and among these, just over half are generic medicines (Table 3.3.2.c). Comparing the consumption and the average cost of the doses dispensed, it is noteworthy that most of Central and Southern Regions have a number of doses and average cost per day of therapy higher than the national average while. On the contrary, Northern regions show a lower consumption and average cost (Figure 3.3.2.b). Analysing the different categories, pump inhibitors record the greatest regional variability (Figure 3.3.2c). Most of the expenditure and consumption is attributable to patent-expired drugs, considering that patent coverage has expired for most of the molecules included in the analysis (Table 3.3.2c).

Figure 3.3.2a. Medicines for peptic ulcer and GERD, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

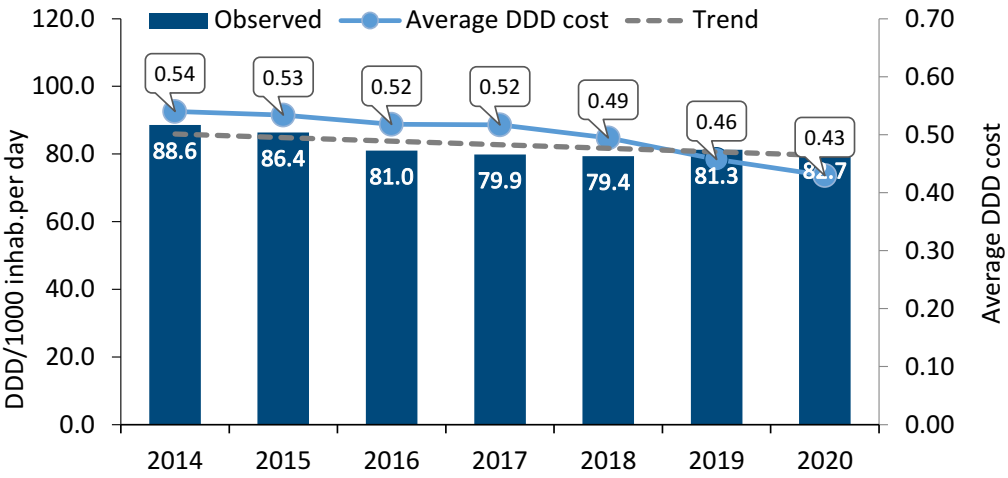


Table 3.3.2a. Medicines for peptic ulcer and GERD, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Proton pump inhibitors	11.66	-2.9	-5.0	76.4	4.2	-0.8	0.42	-7.1
Other medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	0.91	1.2	1.7	4.3	0.8	1.3	0.58	0.2
Antacids	0.42	4.6	0.8	2.0	4.1	0.3	0.58	0.2
H2 receptor antagonists	0.01	-94.7	-42.8	0.1	-97.1	-47.7	0.75	85.0
Prostaglandins	0.01	-11.1	-11.5	0.0	-9.4	-10.6	1.02	-2.1
Medicines for peptic ulcer and GERD	**13.00**	**-4.2**	**-4.8**	**82.7**	**1.8**	**-1.1**	**0.43**	**-6.1**
pantoprazole	4.35	-3.9	-2.2	26.6	8.4	3.4	0.45	-11.6
lansoprazole	2.40	-5.6	-8.8	15.2	-1.0	-5.9	0.43	-4.9
omeprazole	2.35	4.1	-6.2	18.3	4.2	-1.9	0.35	-0.4
esomeprazole	2.20	-4.3	-3.4	14.3	3.9	1.1	0.42	-8.2
sodium alginate/potassium bicarbonate	0.87	1.6	2.0	4.1	1.2	1.7	0.59	0.1
magaldrate	0.41	4.9	0.8	1.8	4.0	0.4	0.61	0.6
rabeprazole	0.34	-4.9	-6.0	1.9	-2.9	-5.3	0.49	-2.3
sucralfate	0.04	-6.8	-4.1	0.2	-7.2	-4.8	0.47	0.2
famotidine	0.02	244.1	27.3	0.1	244.7	28.7	0.73	-0.4
misoprostole	0.01	-11.1	-11.5	0.0	-9.4	-10.6	1.02	-2.1

Table 3.3.2b. Medicines for peptic ulcer and GERD, regional trend of weighted DDD/1000 inhab. per day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	83.2	79.3	70.8	68.7	68.7	69.6	69.4	-0.4
Valle d'Aosta	78.4	74.9	65.5	64.3	67.3	70.7	71.5	1.2
Lombardy	70.8	73.8	74.3	74.7	77.2	78.3	79.5	1.5
A.P. of Bolzano	43.2	44.1	44.5	45.2	46.9	47.0	46.4	-1.4
A.P. of Trento	71.2	74.3	78.0	82.8	84.9	86.4	83.9	-3.0
Veneto	80.8	76.3	68.9	64.8	64.7	66.1	66.8	1.2
Friuli VG	74.7	73.3	73.1	72.7	70.6	70.3	64.1	-8.9
Liguria	95.7	94.5	90.2	89.9	91.8	94.8	95.7	1.0
Emilia R.	77.4	76.6	68.1	65.4	66.4	66.6	67.2	0.9
Tuscany	71.0	70.0	68.0	67.3	64.4	61.5	60.8	-1.1
Umbria	87.9	89.1	85.7	86.6	88.6	84.3	84.1	-0.2
Marche	81.9	82.6	81.1	79.0	69.4	66.8	63.9	-4.3
Lazio	103.2	96.0	84.4	84.6	86.2	89.7	90.1	0.5
Abruzzo	83.2	85.0	75.8	76.4	78.6	82.4	84.6	2.6
Molise	90.6	88.8	65.5	69.8	75.5	80.8	85.5	5.7
Campania	99.7	105.1	104.1	106.6	110.9	117.0	121.9	4.2
Puglia	109.8	95.0	90.0	87.4	81.2	84.7	87.3	3.1
Basilicata	83.4	84.8	77.6	79.6	82.2	86.8	91.0	4.8
Calabria	117.8	103.4	89.9	90.4	91.3	94.2	97.7	3.7
Sicily	110.5	105.6	100.2	94.7	85.6	90.6	96.2	6.2
Sardinia	108.5	110.3	94.4	87.2	83.6	84.6	89.4	5.7
Italy	**88.6**	**86.4**	**81.0**	**79.9**	**79.4**	**81.3**	**82.7**	**1.8**
North	76.9	76.4	72.2	70.9	72.0	73.1	73.4	0.4
Centre	88.8	85.3	78.8	78.5	77.2	77.2	76.8	-0.5
South and Islands	105.1	101.3	94.9	93.4	91.1	95.5	99.8	4.5

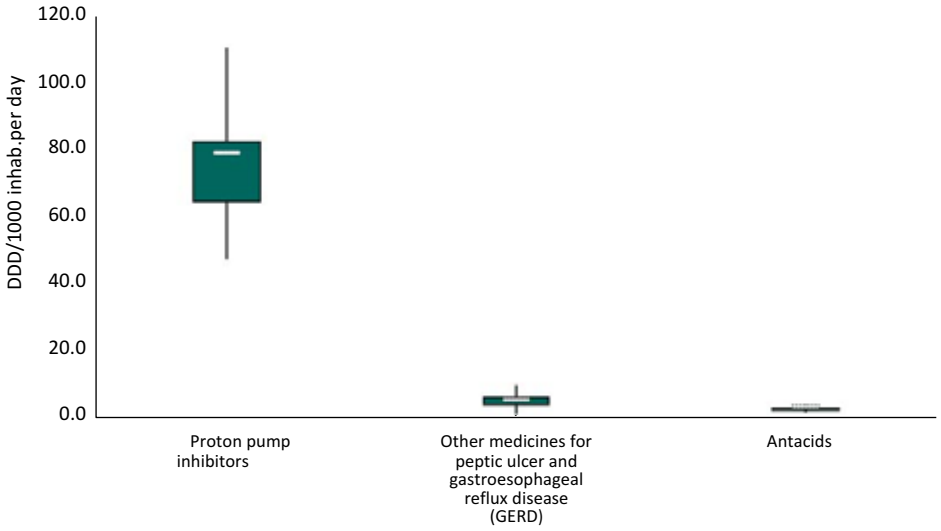
Table 3.3.2c. Prescription of medicines for peptic ulcer and GERD with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	11.49	88.4	-4.9	76.0	91.9	1.9	0.41
Generic	5.93	51.6	-1.0	41.4	54.4	-0.5	0.39
Ex originator	5.56	48.4	-8.7	34.7	45.6	5.0	0.44
Patent covered	1.51	11.6	1.6	6.7	8.1	0.2	0.62
Medicines for pept ulcer and GERD	**13.00**	**100.0**	**-4.2**	**82.7**	**100.0**	**1.8**	**0.43**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.3.2c. Medicines for peptic ulcer and GERD, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure in the general population to medicines for peptic ulcer and GERD provided under approved care regime and per conto distribution.

An analysis of prescription in the population shows an increasing use with age without substantial differences between men and women (Figure 3.3.2d). The prevalence reaches over 50% in the ≥75 age group and 19% in the general population (Table 3.3.2d). The use tends to be higher in women than in men (M/W ratio 0.82). Analysing the regional variability, the prevalence of use is reportedly higher in the Southern regions (23.2%), compared to those of the Centre (18.9%) and of the North (15.9%). One in four patients receives only one prescription during the year and on average, each user receives 5.4 prescriptions with a median treatment duration of almost 4 months.

Figure 3.3.2d. Distribution of 2020 prevalence of use and consumption of medicines for peptic ulcer and GERD under NHS outpatient care and *per conto* distribution

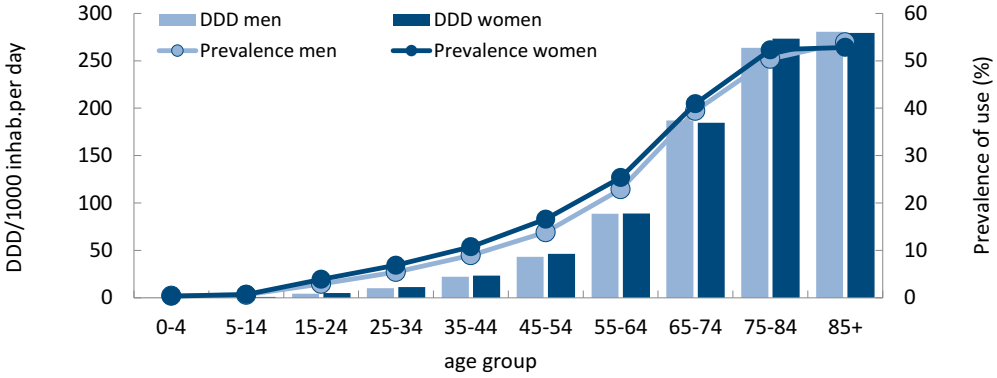


Table 3.3.2d. Exposure and duration of therapy with medicines for peptic ulcer and GERD by Region under NHS outpatient care and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescrip-tions per user	DDD per user	DDD median	Users with 1 prescription (%)
Piedmont	17.0	0.81	69	4.7	138.8	112.0	26.8
Valle d'Aosta	16.1	0.82	69	4.8	152.0	112.0	29.1
Lombardy	16.3	0.82	68	4.9	171.3	136.0	26.4
A.P. of Bolzano	9.3	0.85	70	5.1	142.2	98.0	29.5
A.P. of Trento	16.0	0.83	67	5.3	172.5	130.0	26.6
Veneto	13.2	0.83	69	5.0	165.3	112.0	27.3
Friuli VG	16.1	0.81	69	5.4	154.6	112.0	25.3
Liguria	21.5	0.80	71	5.6	167.9	140.0	23.3
Emilia R.	15.5	0.80	68	4.9	137.5	84.0	28.7
Tuscany	15.9	0.82	71	5.0	135.5	86.0	28.7
Umbria	20.9	0.82	69	6.2	143.0	106.0	24.6
Marche	16.5	0.87	71	5.0	127.5	98.0	26.7
Lazio	21.2	0.80	67	5.3	148.8	108.0	27.3
Abruzzo	21.7	0.82	67	5.6	138.9	98.0	26.4
Molise	20.8	0.83	69	5.5	147.2	112.0	25.0
Campania	26.6	0.83	63	5.8	151.0	112.0	25.4
Puglia	21.1	0.86	67	5.3	138.9	98.0	26.8
Basilicata	23.8	0.83	66	6.3	135.8	98.0	25.3
Calabria	23.3	0.85	68	6.2	143.1	112.0	23.2
Sicily	22.3	0.80	68	6.0	148.0	104.0	24.4
Sardinia	21.2	0.78	66	5.5	153.4	112.0	26.3
Italy	**19.0**	**0.82**	**68**	**5.4**	**150.2**	**112.0**	**26.3**
North	15.9	0.82	69	5.0	158.3	112.0	26.7
Centre	18.9	0.82	68	5.2	142.5	98.0	27.4
South and Islands	23.2	0.83	66	5.8	146.4	109.0	25.4

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

	Distribution (%)				
	Antacid/ antisecretory/ gastroprotective medicines	**PPI**	**Antacids**	**Anti H2**	**Others**
Reported indication*					
GERD	39.7	37.7	44.9	52.7	54.0
Gastritis	12.0	11.3	19.8	16.0	14.6
Gastro-duodenal peptic ulcer	3.6	3.7	3.0	8.3	2.5
HP eradication	1.4	1.3	1.5	1.5	1.7
Other gastrointestinal disorders	11.5	11.3	13.8	12.3	12.4
Protective therapy in case of treatments for					
Cardiometabolic disorders	19.0	21.6	4.6	1.3	4.2
Pain	9.5	9.8	10.2	8.8	7.2
Respiratory disorders	2.3	2.2	2.9	2.2	3.2
Other	14.6	14.7	15.9	15.1	12.7

*Not mutually exclusive

Indicator used:

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

Table 3.3.2f. Prevalence of use of antacid/antisecretory/gastroprotective drugs in patients on chronic therapy with gastric-damaging drugs*

	Prevalence of use (%)			
	NSAIDs/ Coxib	Platelet aggregation inhibitors (low dose ASA, ticlopidine, prasugrel, etc.)	Corticosteroids	Anticoagulants (AVK, NAO, etc.)
Geographic analysis				
North	53.4	59.8	66.7	49.7
Centre	56.1	64.8	62.7	51.9
South and Islands	66.4	73.8	71.0	62.8
Analysis by gender				
Men	56.4	64.7	64.4	51.0
Women	63.6	70.0	69.8	59.0
Analysis by age				
≥45 years	43.9	48.2	46.0	22.6
46-65	52.4	56.1	59.6	42.5
66-74	65.4	65.9	70.2	52.9
75-84	70.1	70.9	77.6	58.8
≥85 years	71.1	73.2	75.5	58.9
Total	**61.2**	**67.1**	**67.7**	**54.9**

*At least 4 prescriptions in the previous 12 months

Indicator used:

Prevalence of use of **antacid/antisecretory/gastroprotective drugs in patients on chronic therapy with gastrically damaging drugs (NSAIDs/Coxib, antiplatelet drugs, corticosteroids and anticoagulants)**: number of patients treated with antacid/antisecretory/gastroprotective drugs [**numerator**], on the total subjects with chronic therapy (at least 4 prescriptions in the previous 12 months) with NSAIDs/Coxib, antiplatelet drugs, corticosteroids and anticoagulants [**denominators**]

Key message

- **The consumption trend appears to be slightly decreasing** and in 2020 stands at 82.7 DDD/1000 inhabitants per day. This trend in consumption is accompanied by a constant reduction in expenditure (CAGR 2014-2020: -4.8%) 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 drugs. However, it is important to note that the other major drug categories, such as antacids and H2 receptor antagonists, are predominantly over-the-counter drugs; consequently, a large share of use of these drugs is not considered in this analysis since they are purchased privately.
- As with most of the main therapeutic categories, in 2020 **a large and growing regional variability is confirmed in terms of consumption and prevalence of use**. As already noted, the use of these drugs in Campania (consumption: 121.9 DDD/1000 inhabitants per day; prevalence of use: 26.6%) is more than twice than the one reported in the A.P. of Bolzano (consumption: 46.4 DDD/1000 inhabitants per day; prevalence of use: 9.3%). This data, in line with what has been observed in many therapeutic categories, in addition to differences in GPs' prescription behaviour, could be attributed to the private purchase of both OTC and SOP drugs, and class A drugs. Indeed, private purchasing data suggest a high consumption of PPIs, in particular in the regions of Northern Italy.
- Unlike many therapeutic categories, **consumption and prevalence of use of medicines for peptic ulcer and GERD do not decrease in the over 85s**. This data confirms in this age group both the greater use of potentially gastric-damaging drugs and the possible high prevalence of gastrointestinal symptoms such as dyspepsia, reflux symptoms and epigastric burning and a corresponding treatment for the relief of these symptoms. Although the 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 formulating some hypotheses:
  - **PPIs are recommended as first line for the treatment of gastroduodenal ulcers and GERD**, diseases requiring treatments of at least 4-8 weeks. Data available indicate a national estimate of 150 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 drugs 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 drugs do not lead to immediate relief of burning symptoms and may require intake for 2-3 consecutive days to achieve symptom improvement. Furthermore, their continued use is linked with an increased risk of intestinal and lung infections in the short term and of bone fracture after one year of use.
  - The still high use of non-PPI antacid drugs has no valid counterparts in the pathophysiology of upper digestive tract disorders except in a small percentage of patients. Their potentially improper use can expose the patient to lower absorption of nutrients and other drugs.

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3.3.3. Metabolic disorders

National data on consumption and expenditure

Over the last few years, the category of medicines for the treatment of diseases due to impaired cellular metabolism has recorded negligible consumption, but with an increase in per capita expenditure owing to the marketing of drugs for the treatment of diseases that in many cases were orphans of therapy. In 2020, the expenditure for these drugs reached a total of 6.33 euros per capita, with an average cost per DDD of 412.8 euros, although the previous year saw a reduction of 8.9% (Table and Figure 3.3.a).

Overall, the drugs indicated in the treatment of lysosomal storage diseases record the highest per capita expenditure (5.49 euros per capita) within the category, followed by drugs for the treatment of congenital defects of metabolism and transport of amino acids (0.24 euros).

The highest per capita expenditure is for Fabry's disease, equal to 1.43 euros for enzyme replacement therapy (average cost per DDD 811.60) and 0.33 euros for chaperone therapy (average cost per DDD 465.68).

In descending order of expenditure, drugs for the treatment of type 1 Gaucher's disease follow in second rank, with a cost of 1.05 euros for enzyme replacement therapy (average cost per DDD of 1078.08 euros) and 0.35 euros for chaperone therapy (average cost per DDD 354.68). Pompe's disease ranks third, for which only an enzyme therapy is available, represented by recombinant human acid alglucosidase, which in 2020 recorded a per capita expenditure of 1.21 euros and an average cost per DDD of 1,062.24 euros. This active ingredient is also the first among those with the highest expenditure within the category, followed by agalsidase alfa (0.83 euros per capita), which, together with agalsidase beta (0.60 euros), is used in the treatment of Fabry's disease. The third most expensive active ingredient is imiglucerase (0.78 euros), indicated in the treatment of type 1 Gaucher's disease.

Almost all of the doses dispensed (94.9%) concerned drugs covered by patents, probably because most of the drugs in this category have been marketed recently (Table 3.3.3c).

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

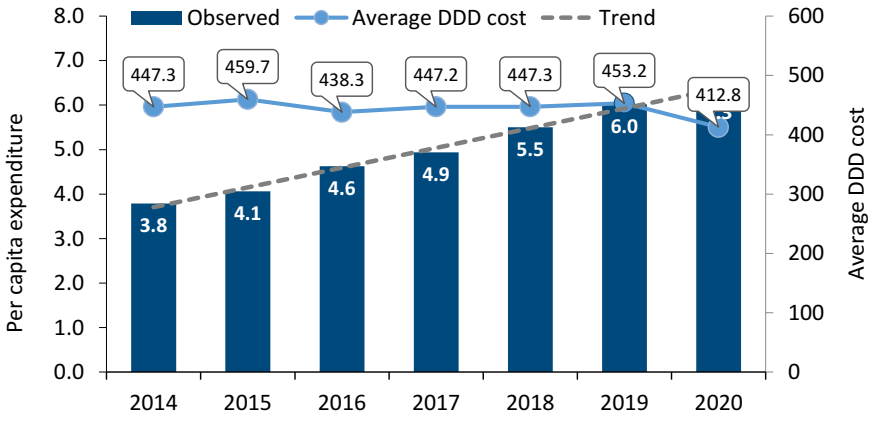


Table 3.3.3a. Metabolic disorders, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Lysosomal storage diseases - Fabry's disease - enzyme replacement therapy	1.43	-2.2	6.9	0.0	2.3	10.4	811.60	-4.6
Lysosomal storage diseases - Pompe's disease - enzyme replacement therapy	1.21	0.4	6.4	0.0	-1.6	7.1	1062.24	1.7
Lysosomal storage diseases - type 1 Gaucher's disease - enzyme therapy	1.05	-2.4	2.8	0.0	-1.9	2.8	1078.08	-0.8
Lysosomal storage diseases - mucopolysaccharidosis II - enzyme therapy	0.49	-7.2	1.7	0.0	-2.7	2.4	2715.01	-4.9
Transthyretin hereditary amyloidosis	0.40	62.8	18.5	0.0	31.1	23.1	340.56	23.9
Lysosomal storage diseases - type 1 Gaucher's disease - chaperone therapy	0.35	11.5	20.9	0.0	17.6	13.3	354.68	-5.4
Lysosomal storage diseases - Fabry's disease - chaperone therapy	0.33	57.8	-	0.0	57.8	-	465.68	-0.2
Lysosomal storage diseases - mucopolysaccharidosis IV-a (Morquio's syndrome) - enzyme replacement therapy	0.26	-1.3	-	0.0	-1.5	-	2992.00	0.0
Congenital metabolic and amino acid transport disorders - phenylketonuria	0.18	8.1	8.4	0.0	8.3	9.5	158.15	-0.4
Lysosomal storage diseases - mucopolysaccharidosis I - enzyme therapy	0.17	1.8	6.8	0.0	1.5	6.7	1433.74	0.1
Lysosomal storage diseases - mucopolysaccharidosis VI - enzyme therapy	0.12	9.8	7.0	0.0	9.7	5.2	2869.64	-0.2
Urea cycle disorders	0.08	3.3	13.5	0.0	12.2	18.7	61.69	-8.2
Lysosomal storage diseases - liposomal acid lipase deficiency - enzyme therapy	0.08	5.2	-	0.0	11.5	-	1215.68	-5.9
Wilson's disease		215.2	41.3	0.0	27.4	6.0	22.87	146.6
Hypophosphatasia-enzyme replacement therapy	0.05	52.1	-	0.0	7.0	-	2878.06	41.8
Congenital metabolic and amino acid transport disorders - homocystinuria	0.03	29.6	6.8	0.0	29.2	8.7	13.34	0.0
Congenital metabolic and amino acid transport disorders - type 1 hereditary tyrosinemia	0.02	-34.1	-1.5	0.0	-6.7	6.0	71.86	-29.6
Lipodystrophy	0.01	-	-	0.0	-	-	1094.27	-
Congenital metabolic and amino acid transport disorders - cystinosis	0.01	5.1	7.4	0.0	3.0	4.1	24.69	1.7
Lysosomal storage diseases - alpha-mannosidosis - enzyme replacement therapy	0.01	113.2	-	0.0	162.1	-	815.77	-18.9

Continued

Table 3.3.3a. Continued

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Medicines for metabolic disorders	**6.33**	**5.2**	**8.9**	**0.0**	**15.2**	**10.4**	**412.79**	**-8.9**
recombinant human acid alglucosidase	1.21	0.4	6.4	0.0	-1.6	7.1	1062.24	1.7
agalsidase alfa	0.83	-7.1	3.2	0.0	-2.7	4.1	1585.24	-4.8
imiglucerase	0.78	-3.8	1.7	0.0	-4.6	1.6	1095.92	0.6
agalsidase beta	0.60	5.5	14.2	0.0	4.5	14.1	484.37	0.6
idursulfase	0.49	-7.2	1.7	0.0	-2.7	2.4	2715.01	-4.9
migalastat	0.33	57.8	-	0.0	57.8	-	465.68	-0.2
eliglustat	0.28	41.0	-	0.0	40.6	-	622.68	0.0
velaglucerase alfa	0.27	1.9	6.8	0.0	6.4	6.7	1028.89	-4.5
elosulfase alfa	0.26	-1.3	-	0.0	-1.5	-	2992.00	0.0
tafamidis	0.22	-8.5	7.7	0.0	-8.6	15.9	274.49	-0.1

Table 3.3.3b. Metabolic disorders, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	3.47	3.56	3.96	4.04	4.43	4.76	5.05	6.0
Valle d'Aosta	0.02	0.01	0.16	1.36	2.87	3.45	2.93	-15.0
Lombardy	3.46	3.75	4.27	4.44	4.87	5.49	5.55	1.2
A.P. of Bolzano	2.24	2.39	2.83	3.23	2.86	3.03	2.44	-19.4
A.P. of Trento	4.59	5.32	6.80	7.57	7.73	8.31	7.72	-7.1
Veneto	3.48	3.64	4.22	4.56	5.48	5.56	5.54	-0.5
Friuli VG	2.60	2.78	3.54	4.32	4.34	4.66	5.16	10.6
Liguria	2.66	2.71	2.64	3.15	3.14	3.60	3.92	8.9
Emilia R.	4.42	5.04	5.61	6.03	6.99	7.30	7.18	-1.7
Tuscany	3.17	3.09	3.78	4.14	4.79	5.62	6.57	17.0
Umbria	4.14	4.46	5.70	5.83	5.80	6.08	6.81	12.1
Marche	4.84	4.97	5.81	5.86	6.01	5.64	5.48	-2.9
Lazio	2.87	3.31	3.84	4.28	5.24	5.90	6.25	6.0
Abruzzo	4.23	4.41	4.57	5.16	5.64	5.95	6.17	3.7
Molise	2.24	1.99	1.93	2.62	3.19	3.39	3.77	11.1
Campania	5.64	6.05	6.92	7.41	8.13	9.29	9.06	-2.4
Puglia	3.10	3.25	3.67	4.19	4.90	5.62	6.45	14.7
Basilicata	3.43	3.68	4.14	4.98	5.70	6.13	6.32	3.1
Calabria	5.43	5.85	6.72	6.56	6.87	7.30	8.67	18.9
Sicily	4.88	5.35	5.90	6.11	6.41	6.54	7.29	11.4
Sardinia	2.53	2.59	2.86	2.57	3.09	4.11	5.44	32.4
Italy	**3.79**	**4.06**	**4.63**	**4.94**	**5.50**	**6.02**	**6.33**	**5.2**
North	3.51	3.79	4.30	4.59	5.12	5.53	5.59	1.1
Centre	3.32	3.54	4.22	4.56	5.24	5.79	6.30	8.8
South and Islands	4.46	4.77	5.35	5.67	6.21	6.86	7.41	8.1

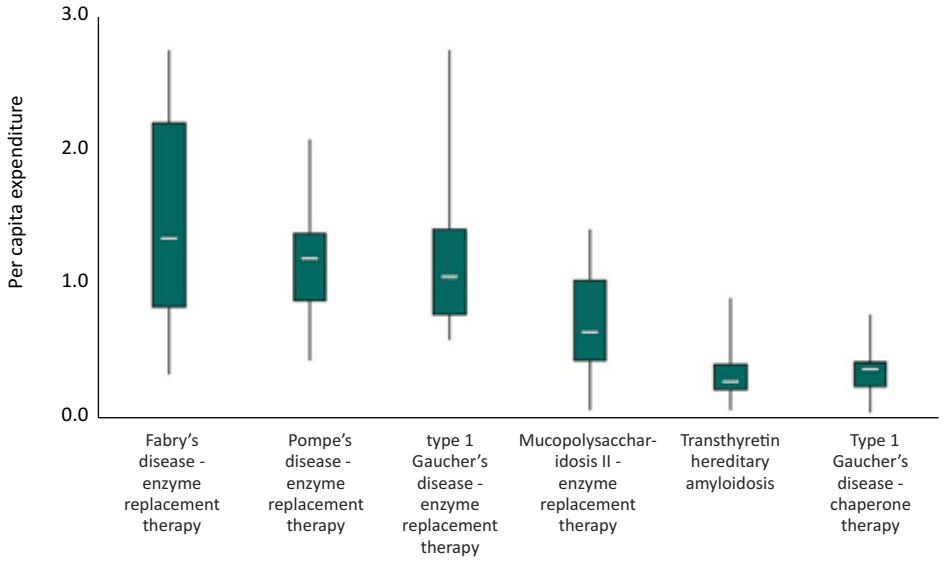
Table 3.3.3c. Prescription of medicines for metabolic disorders with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	0.09	1.4	2001.0	0.0	5.1	3477.3	109.04
Generic	0.01	15.7	13985.5	0.0	23.1	10267.8	74.12
Ex originator	0.07	84.3	1713.0	0.0	76.9	2888.0	119.55
Patent covered	6.24	98.6	3.8	0.0	94.9	9.4	429.26
Metabolic disorders	**6.33**	**100.0**	**5.2**	**0.0**	**100.0**	**15.2**	**412.79**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.3.3c. Metabolic disorders, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- Although the category of drugs for metabolic disorders has recorded negligible consumption over the years, a **progressive increase in per capita expenditure** was reported, due to the marketing of drugs for the treatment of diseases that in many cases were orphans of therapy.
- Drugs for the **treatment of lysosomal storage diseases** account for 87% of the expenditure for the entire category, with drugs for Fabry's disease ranking first for expenditure. **Recombinant human acid alglucosidase**, enzyme replacement therapy for the treatment of Pompe's disease, is instead the active ingredient with the highest expenditure.
- At regional level, **expenditure shows a high variability**, with Calabria recording a per capita expenditure three times as large as Valle d'Aosta.
- Since most of the drugs have recently been marketed, **almost all of the doses delivered concerned drugs covered by patents**.

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3.4 General antimicrobials for systemic use

General antimicrobials for systemic use were the fourth therapeutic category with the highest public expenditure in 2020, equal to 2,666.4 million euros and 11.6% of overall public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was 44.71 euros, mainly due to the expenditure borne by public health facilities for the purchase of these medicines (34.77 euros per capita). Conversely, the contribution provided by the approved care regime was lower (9.94 euros per capita). Both the expenditure under approved care regime and the expenditure due to the purchase of these medicines by public health structures recorded a significant reduction compared to 2019, by -21.3% and -21.2%, respectively (Table 3.1).
Consumption for this category of drugs was 19.2 DDD/1000 inhabitants per day, with a -16.8% decrease compared to 2019 (Table 3.2). Contrary to expenditure, the greatest contribution is due to the approved care regime; in fact, almost 70% of the doses are dispensed through this distribution channel.
The analysis of the drug profile use by age group and gender, including pharmaceutical expenditure under approved care regime and *per conto* distribution, indicates a consumption of antimicrobials for systemic use that increases with the patients' age, reaching a maximum value after 75 years, higher in men (24.5 DDD/1000 inhabitants per day) than in women (21.1 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 patients' age, reaching the maximum level of 21.9 euros and 19.2 euros per capita in men and women respectively, in subjects over 75 years of age.
As for expenditure under approved care regime, per capita expenditure was 9.94 euros, with a 21.5% decrease compared to 2019. This change is due to a decrease in consumption (-22.9%); prices are substantially stable, while the mix effect records a value of +1.8% (Table 3.9).
Within this distribution channel, penicillin combinations, including beta-lactamase inhibitors, are the category with the highest expenditure (2.26 euros), recording a reduction in expenditure and consumption (respectively by -25.4% and -25.5%), overcoming third generation cephalosporins showing an expenditure of 2.16 euros per capita, with a reduction by over 30% (Table 3.9). Triazole derivatives, a sub-category of antifungals, rank fifth with an expenditure of 0.87 euros per capita, albeit in sharp decline compared to 2019 (-13.3%), as a result of a reduction in consumption (-14.3%).
Amoxicillin in combination with clavulanic acid is the first active ingredient in the category by per capita expenditure (2.15 euros) and consumption (4.3 DDD) (Table 3.10), as well as being the only active ingredient in this category listed within the top 30 molecules with the greatest impact on outpatient expenditure (Table 3.11).
As for purchases by public health facilities, a significant reduction was recorded in expenditure (-21.4%) compared to 2019, against a slight reduction in consumption (-0.7%), an important price reduction (-11.8%) and a negative mix effect (-10.3%) (Table 3.16).

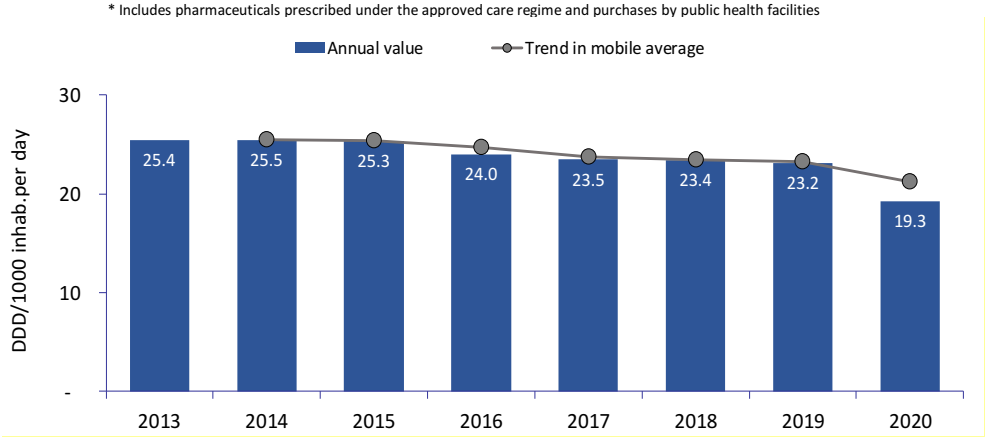
With regard to direct purchases, antivirals for the treatment of HIV infections in combination (ATC IV level) are the sub-category with the highest expenditure (8.05 euros per capita), followed by antivirals for the treatment of HCV infections (5.13 euro per capita), although the latter is significantly decreasing, compared to the previous year (-67.7%). Within antimicrobials, the first active ingredients by expenditure are the sofosbuvir/velpatasvir combination (3.92 euros per capita) and the 13-valent pneumococcal vaccine (2.10 euros per capita; Table 3.17). These active ingredients are also included in the top thirty active ingredients for pharmaceutical expenditure by public health facilities, together with an HIV antiviral (emtricitabine/rilpivirine/tenofovir alafenamide) and a vaccine (meningococcal group B) (Table 3.18). In addition, five active ingredients are also present in the ranking of the top 30 active ingredients with the greatest variation in expenditure compared to the previous year: bictegravir/emtricitabine/tenofovir alafenamide (>100%), cobicistat/darunavir/ emtricitabine/tenofovir alafenamide (+45.4%), split inactivated tetravalent influenza virus vaccine (+27.1%), 13-valent pneumococcal vaccine (+26.1%) and human immunoglobulin for intravenous use (+17.5%) (Table 3.20).
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 patent-expired medicines and on a regional basis. These analyses focused on antibiotic, antifungal, anti-HIV, anti-HCV antiviral drugs and vaccines (Table 3.4.1 and following).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

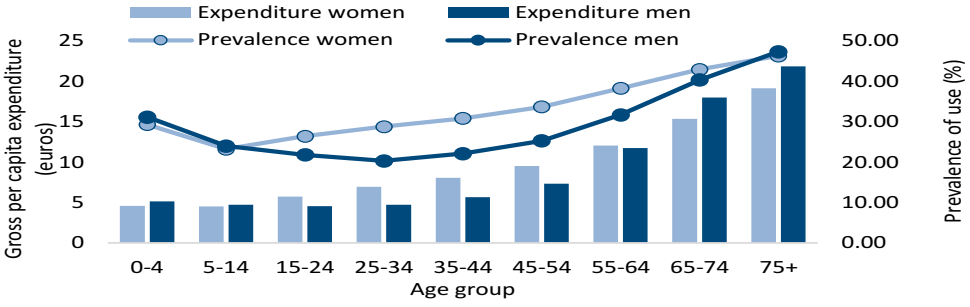
Antimicrobials for systemic use

Public expenditure* in million euros (% over total)	**2,666.4**	**(11,6)**
Δ % 2020-2019		-21.2%
Regional range of gross per capita expenditure	30.3	51.3
DDD/1000 inhab. per day (% over total)	**19.2**	**(1,7)**
Δ % 2020-2019		-16.8%
Regional range of DDD/1000 inhab. per	11.8	24.0

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities



Distribution, by age and gender, of expenditure, prevalence of use and consumptions under approved care regime and *per conto* distribution in 2020 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab.per day		
	Men	Women	Total	Men	Women	Total
0-4	5.1	4.6	4.9	7.3	6.5	6.9
5-14	4.7	4.5	4.6	7.1	6.7	6.9
15-24	4.6	5.7	5.1	7.6	8.8	8.2
25-34	4.7	6.9	5.8	7.2	10.0	8.5
35-44	5.7	8.1	6.9	8.4	11.4	9.9
45-54	7.3	9.5	8.5	10.3	13.2	11.8
55-64	11.8	12.1	11.9	14.4	16.0	15.2
65-74	18.0	15.4	16.6	20.5	19.3	19.9
75+	21.9	19.2	20.3	24.5	21.1	22.4

3.4.1. Antibiotics for systemic use

National data on consumption and expenditure

The last seven years have seen a steady decrease in the consumption of antibiotics (CAGR -5.7%), with values shifting from 19.7 DDD in 2014 to 13.9 DDD in 2020; the most important decrease was recorded in 2020 compared to 2019 (-21.7%; Figure 3.4.1a and Table 3.4.1a).
The penicillin combinations, almost entirely represented by amoxicillin+clavulanic acid, remain the category of antibiotics with the highest prescription (4.8 DDD), which in 2020 show an expenditure of 2.90 euros per capita (-25.0% and -21.1% compared to 2019 for consumption and expenditure, respectively). Macrolides and lincosamides follow in consumption (3.1 DDD); regarding expenditure, as in 2019, the second category is 3rd generation cephalosporins (2.75 euros per capita). Most of the subgroups of antibiotics recorded a reduction in consumption compared to the previous year; important changes were observed for 3rd generation cephalosporins, penicillin combinations (including beta-lactamase inhibitors) and fluoroquinolones.
The subgroup with the greatest increase, both in terms of expenditure and consumption, is other cephalosporins and penems, which includes recently marketed active ingredients (ceftolozane/tazobactam, ceftobiprole, ceftaroline) and with the highest average cost per DDD in its category (170.92 euros per dose). Amoxicillin+clavulanic acid, a broad spectrum drug widely used in paediatrics, is confirmed as the most used molecule with 4.7 DDD, followed by azithromycin and clarithromycin. Azithromycin recorded an 11.5% increase compared to 2019, while clarithromycin showed a reduction by more than 30%. The increase in azithromycin consumption could be explained by the treatment of bacterial superinfections in patients with COVID-19. Further increases were highlighted in per capita expenditure of piperacillin/tazobactam, a combination of a broad-spectrum penicillin with a beta-lactamase inhibitor (+4.1%), and avibactam/ceftazidime, a combination of a 3rd generation cephalosporin with a beta-lactamase inhibitor (+47.8%). These two combinations, together with the macrolide azithromycin, are the only active ingredients among the top ten reporting an increase in expenditure in 2020. Fosfomycin recorded a slight increase in expenditure (+0.9%), despite the consumption decrease (-4.2%), due to an increase in the cost per DDD (+5.1%).
86.5% of the doses dispensed concerned patent-expired molecules, however only 24.9% referred to generic drugs (Table 3.4.1c). Wide variability is observed in consumption of combinations of penicillins, fluoroquinolones and macrolides (Figure 3.4.1c).

Figure 3.4.1a. Antibiotics for systemic use, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

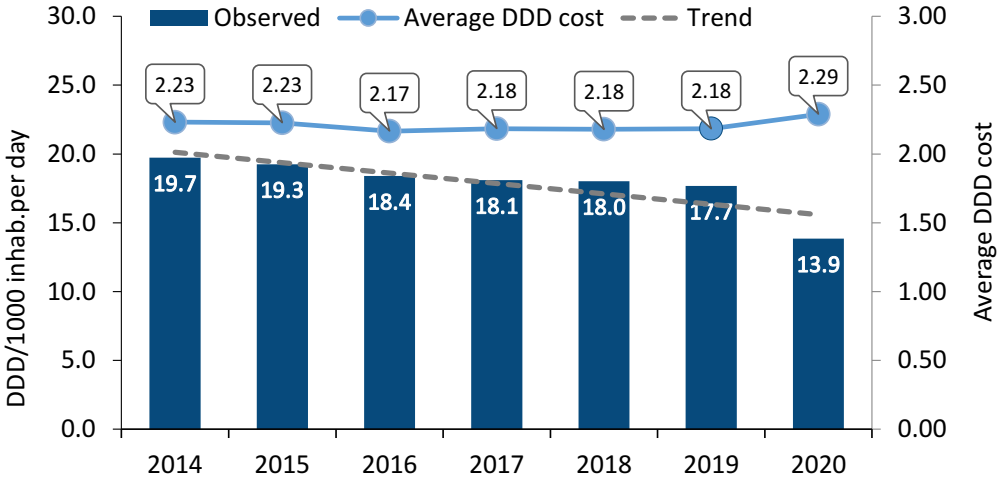


Table 3.4.1a. Antibiotics for systemic use, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Combinations of penicillins (including beta lactamase inhibitors)	2.90	-21.1	-3.3	4.8	-25.0	-4.9	1.65	4.8
Third-generation cephalosporins	2.75	-24.0	-3.6	1.7	-26.3	-3.4	4.46	2.8
Macrolides and lincosamides	1.35	-15.9	-5.7	3.1	-16.7	-5.0	1.18	0.7
Fluroquinolones	1.26	-20.0	-11.3	1.7	-22.8	-11.6	2.04	3.2
Other antibacterials	1.08	-9.7	-5.7	0.4	-2.7	2.2	6.64	-7.5
Other cephalosporins and penems	0.42	65.4	147.6	0.0	74.6	125.9	170.92	-5.5
Glycopeptides	0.37	-13.6	-12.5	0.1	-6.0	-4.3	19.68	-8.3
Carbapenems	0.25	2.4	-10.8	0.1	15.5	-3.2	11.65	-11.6
Broad-spectrum penicillins	0.23	-24.6	-6.3	0.8	-32.8	-10.3	0.78	11.9
Polymyxin	0.22	8.2	1.6	0.0	9.0	1.9	36.02	-1.0
Tetracyclines	0.17	-23.8	-14.8	0.3	-2.9	0.0	1.34	-21.8
Aminoglycosides	0.14	-30.6	-6.6	0.0	-6.9	-7.2	8.20	-25.7
First-generation cephalosporins	0.10	-20.5	-1.7	0.1	-20.2	-2.9	3.03	-0.7
Second-generation cephalosporins	0.08	-39.7	-14.4	0.1	-38.9	-13.4	1.78	-1.5
Sulphonamides (plain or in combination)	0.07	-8.2	1.8	0.4	-7.9	1.8	0.53	-0.6
Fourth-generation cephalosporins	0.07	-0.9	-0.9	0.0	1.0	2.2	22.15	-2.1
Other combinations	0.04	-22.3	-	0.0	-22.6	-	6.71	0.1
Monobactams	0.04	4.8	-0.6	0.0	4.6	-0.6	88.12	0.0
Nitrofuran derivatives	0.02	4503.7	86.7	0.1	1423.8	53.8	0.91	201.3
Imidazole derivatives	0.01	-18.8	-1.0	0.0	-21.2	0.5	1.01	2.7
Beta-lactamase sensitive penicillins	0.01	-46.2	-7.1	0.0	-48.8	-7.6	54.29	4.8
Beta-lactamase resistant penicillins	0.01	-46.8	-15.6	0.0	-40.5	-10.1	1.81	-10.8
Amphenicols	0.00	-15.4	-1.5	0.0	-12.6	-3.6	6.41	-3.4
Other quinolones	0.00	-99.8	-76.2	0.0	-99.8	-76.0	0.76	11.3
Antibiotics	**11.60**	**-17.6**	**-5.3**	**13.9**	**-21.7**	**-5.7**	**2.29**	**4.9**
amoxicillin/clavulanic acid	2.24	-26.2	-5.2	4.7	-25.6	-5.1	1.31	-1.1
ceftriaxone	1.02	-25.8	-7.2	0.5	-14.1	-2.5	6.05	-13.8
fosfomycin	0.76	0.9	4.2	0.4	-4.2	1.2	5.37	5.1
azithromicyn	0.76	5.1	0.9	1.5	11.5	2.1	1.34	-5.9
cefixime	0.70	-28.3	-3.7	0.8	-27.9	-3.3	2.26	-0.9
piperacillin/tazobactam	0.63	4.1	9.7	0.1	7.5	8.0	12.26	-3.4
ciprofloxacin	0.59	-14.3	-10.0	0.7	-14.5	-9.1	2.37	0.0
clarithromycin	0.50	-33.2	-10.7	1.5	-33.3	-9.2	0.91	-0.2
levofloxacin	0.50	-23.5	-10.5	0.9	-27.7	-12.4	1.60	5.5
avibactam/ceftazidime	0.43	47.8	-	0.0	49.8	-	240.35	-1.6

Table 3.4.1b. Antibiotics for systemic use, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	16.4	16.1	15.1	14.9	15.1	14.7	11.7	-20.1
Valle d'Aosta	16.9	16.8	14.7	14.8	15.3	14.7	11.6	-20.7
Lombardy	16.1	16.0	15.2	15.1	15.1	14.6	11.5	-21.1
A.P. of Bolzano	12.2	12.0	11.1	10.9	11.2	10.6	8.0	-24.6
A.P. of Trento	16.4	16.2	15.1	15.7	15.6	15.1	11.9	-20.7
Veneto	15.8	15.0	14.2	14.3	14.3	14.2	11.1	-21.6
Friuli VG	14.9	14.8	13.8	14.5	14.3	14.1	10.7	-24.1
Liguria	14.4	14.2	13.1	13.5	13.7	13.4	10.7	-20.2
Emilia R.	17.7	17.0	16.2	15.9	16.2	16.0	12.3	-23.5
Tuscany	18.9	18.9	17.9	17.4	17.0	16.6	12.5	-24.7
Umbria	22.2	21.5	20.7	20.6	20.5	20.7	15.9	-23.0
Marche	21.3	20.5	20.1	19.6	19.8	19.5	14.7	-24.5
Lazio	21.3	20.8	19.7	19.5	19.4	19.8	15.1	-23.7
Abruzzo	22.8	22.3	22.0	21.5	22.3	22.2	16.9	-23.8
Molise	22.2	21.3	19.8	19.0	19.5	19.4	14.9	-23.0
Campania	27.1	26.6	26.0	24.7	24.7	23.3	19.4	-17.0
Puglia	26.1	25.3	24.5	22.8	21.9	21.9	17.0	-22.2
Basilicata	23.1	21.9	20.8	20.9	20.6	20.6	16.0	-22.5
Calabria	24.3	23.6	22.6	22.6	21.9	21.9	16.9	-22.6
Sicily	22.6	21.7	21.0	21.1	21.0	20.8	16.4	-20.8
Sardinia	18.1	17.8	16.3	16.7	16.5	15.7	12.3	-21.4
Italy	**19.7**	**19.3**	**18.4**	**18.1**	**18.0**	**17.7**	**13.9**	**-21.7**
North	16.1	15.8	14.9	14.9	15.0	14.6	11.5	-21.6
Centre	20.6	20.2	19.3	18.9	18.8	18.8	14.3	-24.0
South and Islands	24.3	23.6	22.8	22.2	21.9	21.4	17.0	-20.5

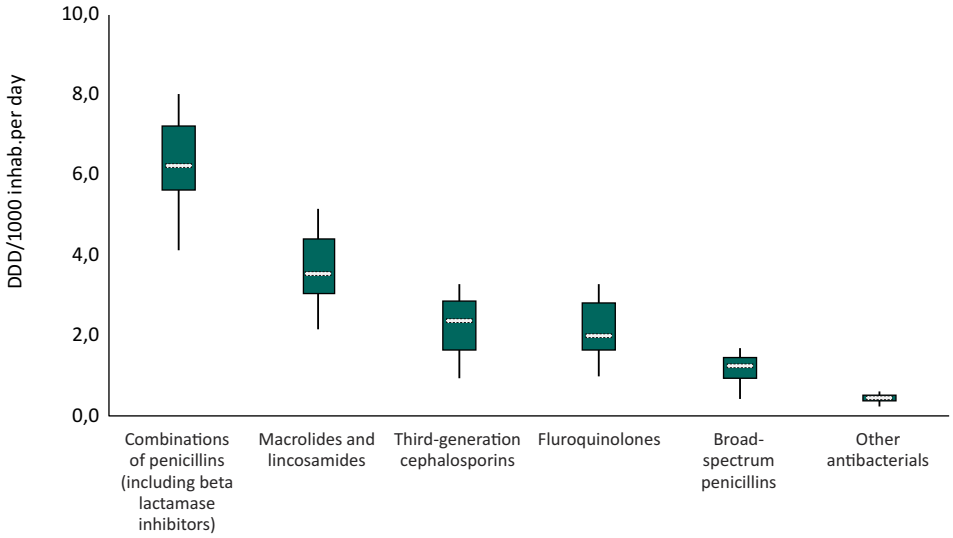
Table 3.4.1c. Prescription of antibiotics for systemic use with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	7.51	64.7	-23.0	12.0	86.5	-23.2	1.71
Generic	1.64	21.8	-21.7	3.0	24.9	-22.3	1.50
Ex originator	5.87	78.2	-23.4	9.0	75.1	-23.5	1.78
Patent covered	4.10	35.3	-5.5	1.9	13.5	-10.1	6.00
Antibiotics	**11.60**	**100.0**	**-17.6**	**13.9**	**100.0**	**-21.7**	**2.29**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.4.1c. Antibiotics for systemic use, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to antibiotics in the general population in 2020. 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, albeit in sharp decline compared to the previous year, and in people over 75 years old; almost 60% of users receive only one prescription per year. Users receive an average of 2 prescriptions per year, with a total of about 14 doses.

Similarly to consumption, a greater prevalence of use is reported in the Regions of Southern (37.5%) and Central Italy (31.8%) compared to those of the North (24.5%), where there is also a higher share of subjects with a single prescription (56.7% in the Centre and 52.6% in the South compared to 62.1% in the North; Table 3.4.1d).

Figure 3.4.1d. Distribution of prevalence of use and consumption of antibiotics for systemic use under NHS outpatient care and *per conto* distribution (year 2020)

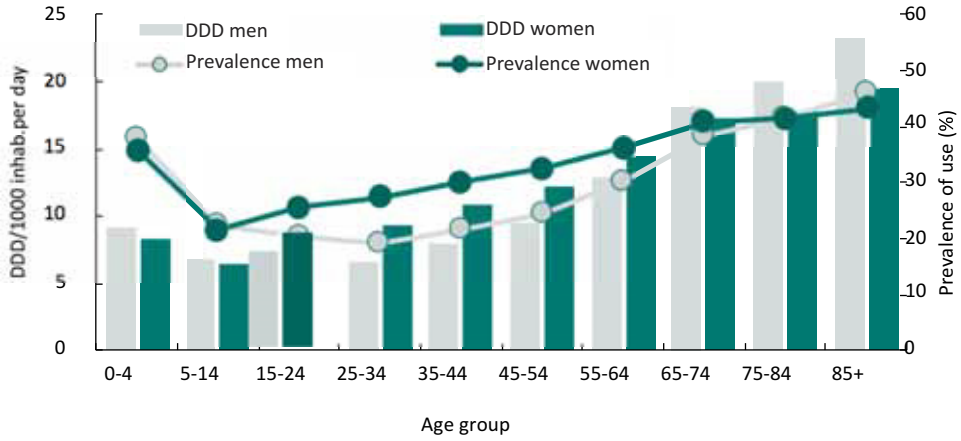


Table 3.4.1d. Exposure and duration of therapy with antibiotics for systemic use by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescrip-tions per user	DDD per user	DDD median	Users with 1 prescription (%)
Piedmont	25.2	0.81	54	1.8	13.3	10.0	61.7
Valle d'Aosta	23.9	0.81	53	1.7	14.1	10.0	63.8
Lombardy	25.0	0.85	50	1.8	14.3	10.0	62.2
A.P. of Bolzano	16.6	0.79	48	1.5	12.0	8.0	69.2
A.P. of Trento	25.3	0.81	50	1.8	13.9	10.0	60.6
Veneto	22.9	0.81	52	1.8	13.6	10.0	62.5
Friuli VG	22.1	0.78	53	1.8	15.2	12.0	62.0
Liguria	25.3	0.82	57	1.8	13.3	10.0	61.3
Emilia R.	25.5	0.82	51	1.8	13.1	9.0	61.7
Tuscany	29.1	0.83	55	1.9	13.5	8.0	58.4
Umbria	34.5	0.83	54	2.0	14.6	10.0	54.7
Marche	31.5	0.84	53	1.9	13.3	9.0	57.2
Lazio	33.2	0.82	53	2.0	14.8	10.0	55.8
Abruzzo	39.2	0.84	52	2.1	14.0	10.0	53.1
Molise	36.5	0.84	54	2.0	13.7	9.0	55.0
Campania	39.7	0.85	51	2.3	15.2	10.0	50.5
Puglia	37.9	0.84	52	2.0	13.8	10.0	54.5
Basilicata	37.2	0.83	53	2.1	14.2	10.0	54.2
Calabria	36.0	0.87	55	2.3	15.1	10.0	49.8
Sicily	37.1	0.85	54	2.1	14.0	9.0	52.6
Sardinia	29.8	0.79	52	1.9	13.6	10.0	58.6
Italy	**30.3**	**0.83**	**53**	**2.0**	**14.1**	**10.0**	**57.0**
North	24.5	0.82	52	1.8	13.8	10.0	62.1
Centre	31.8	0.82	54	2.0	14.2	10.0	56.7
South and	37.5	0.84	53	2.1	14.4	10.0	52.6

Key message

- A **downward trend in consumption** is observed in all Regions, with the most important variations in Tuscany (-24.7%), AP of Bolzano (-24.6%) and Marche (24.5%). At national level, consumption recorded a -21.7% decrease. Considering that most of the antibiotics consumed are due to the provision in the local area, it can be inferred that **the PNCAR objective of reducing consumption in the local area has been achieved.** This trend could be attributed to the change in organisational models (access to General Practitioners' and Free Choice Pediatricians' practices, adoption of the electronic prescription) and to the spread of personal protective equipment which may have reduced the transmission of bacterial infections. However, it would be necessary to assess whether these reductions were also accompanied by an improvement in prescriptive appropriateness, by applying prescription quality indicators. 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 this healthcare context.

- Despite the information sheet published by AIFA on 9 April 2020 in the context of COVID-19, which established the use of azithromycin outside the indications registered exclusively in randomised clinical trials or in case of bacterial superinfections, it was reported **an increase in the consumption of this antibiotic** (+11.5%).
- The **increase in carbapenem consumption** is confirmed, which could be partly explained by the need to use these antibiotics for the treatment of infections caused by multi-drug-resistant microorganisms (MDR). These data raise concern, given the impact of the use of these antibiotics on the further spread of resistance.
- There continues to be an increase in the use of **third generation cephalosporin ceftadime/avibactam**, other **cephalosporins** and **penems** and **polymyxin**, indicated for the treatment of infections caused by MDR microorganisms. These antibiotics belong to the *Reserve* group, according to the WHO AWaRe classification, therefore they should be used as a last resort and only in the most severe cases.
- 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.

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3.4.2. Anti-HIV antivirals

National data on consumption and expenditure

In 2020, per capita expenditure of anti-HIV antiviral drugs was 11.09 euros, remaining almost stable (+0.3%) compared to the previous year: this trend was determined by a slight reduction (-1.4%) in the average cost per DDD compared to a slight increase (+1.5%) in doses (Table and Figure 3.4.2a). In general, compared to 2014, the expenditure for this category of drugs recorded an 8.0% reduction and a 1.4% average annual decrease rate (CAGR).

The overall consumption for this category of medicines was 2.9 DDD/1000 inhabitants per day, a 1.5% increase compared to the previous year, with a 2.2% average annual growth rate (CAGR) in the period 2014-2020.

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 drugs (+9.2% compared to 2019) and for an average annual growth rate (CAGR) of over 100% compared to 2014, despite the fact that the average cost per DDD of these drugs has decreased by 8% in the last year.

Considering the consumption trend, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are the drugs with the highest value, equal to 1.2 DDD/1000 inhabitants per day, despite a 6% reduction compared to the previous year, which corresponds to a per capita expenditure of 1.14 euros, accounting for 10% of the expenditure for the category.

The combination emtricitabine/rilpivirine/tenofovir alafenamide with 1.74 euros per capita and a 0.4% increase ranks first among the active substances in the category with the highest expenditure (Table 3.4.2a). Dolutegravir ranks second for expenditure (1.52 euros, -0.2% compared to 2019), also recording the highest consumption in 2020 (0.3 DDD/1000 inhabitants per day), followed by dolutegravir/abacavir/lamivudine (1.37 euros, -4.8% compared to 2019).

Patent-covered drugs represent a significant share of consumption (83.8%) and expenditure (98.4%) of this category of drugs (Table 3.4.2c).

Co-formulated regimens with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) show the largest regional variability in per capita expenditure, while co-formulated regimens with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and 1 integrase inhibitor (INSTI) have the widest expenditure range (Figure 3.4.2c).

Figure 3.4.2a. Anti-HIV antivirals, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

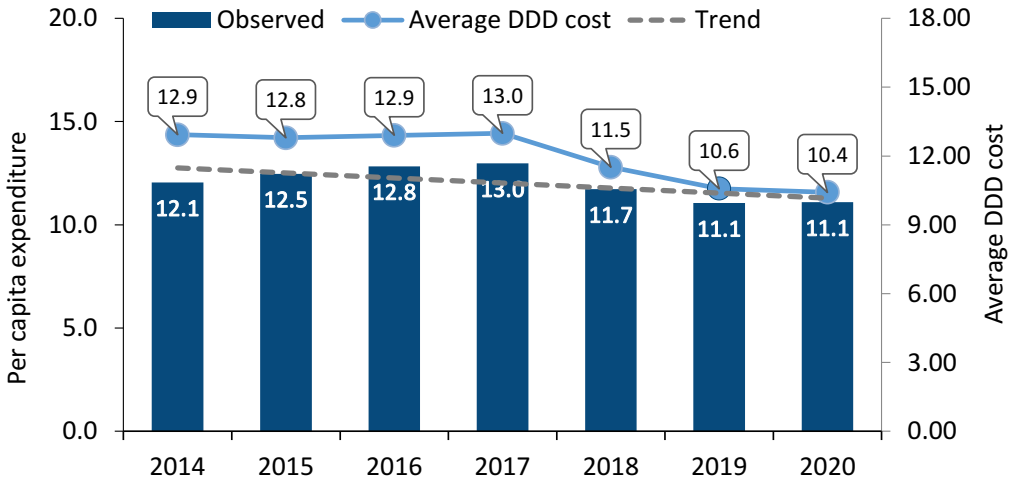


Table 3.4.2a. Anti-HIV antivirals, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Co-formulated regimens - (2 NRTI + 1 INSTI)	3.29	9.2	103.2	0.4	18.4	110.4	21.55	-8.0
INSTI	2.12	-3.1	14.9	0.4	-3.7	17.4	13.66	0.3
Co-formulated regimens - (2 NRTI + 1 NNRTI)	2.00	-2.7	-0.1	0.3	-2.0	2.3	18.55	-1.0
NRTI	1.14	-25.8	-22.7	1.2	-6.0	-1.5	2.67	-21.2
PI	0.89	-29.6	-17.8	0.3	-0.6	-11.4	8.35	-29.3
Co-formulated regimens - (2NRTI + 1 PI)	0.85	45.4	-	0.1	45.0	-	21.85	0.0
Co-formulated regimens - (1 NRTI + 1 INSTI)	0.26	2188.5	-	0.0	2182.3	-	18.31	0.0
NNRTI	0.23	-22.3	-14.2	0.1	-17.1	-9.6	4.83	-6.5
Co-formulated regimens - (1 NRTI + 1 INSTI)	0.21	-	-	0.0	-	-	16.60	-
Other anti-HIV antivirals	0.11	-5.5	-13.6	0.0	-4.7	-10.2	33.95	-1.1
Anti-HIV antivirals	**11.09**	**0.3**	**-1.4**	**2.9**	**1.5**	**2.2**	**10.4**	**-1.4**
emtricitabine/rilpivirine/ tenofovir alafenamide	1.74	0.4	-	0.2	0.1	-	19.96	0.0
dolutegravir	1.52	-0.2	135.9	0.3	-0.4	136.0	16.42	0.0
dolutegravir/abacavir/ lamivudine	1.37	-4.8	-	0.2	-5.0	-	21.48	0.0
bictegravir/emtricitabine/ tenofovir alafenamide	1.34	606.1	-	0.2	604.2	-	19.96	0.0
cobicistat/darunavir/ emtricitabine/tenofovir alafenamide	0.85	45.4	-	0.1	45.0	-	21.85	0.0
emtricitabine/tenofovir alafenamide	0.68	-25.2	-	0.2	-23.9	-	11.29	-1.9
raltegravir	0.60	-9.8	-6.9	0.2	-8.1	1.0	9.55	-2.1
elvitegravir/cobicistat/emtricitabina/tenofovir alafenamide	0.57	-58.1	-	0.1	-58.2	-	26.55	0.0
darunavir/cobicistat	0.53	-17.9	-	0.1	-18.1	-	12.25	0.0
dolutegravir/rilpivirine	0.26	2188.5	-	0.0	2182.3	-	18.31	0.0

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)

INSTI: integrase inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Protease inhibitors

Table 3.4.2b. Anti-HIV antivirals, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	11.11	11.52	12.21	12.37	10.92	10.57	11.61	9.8
Valle d'Aosta	5.52	6.04	6.54	7.50	5.62	6.02	6.34	5.3
Lombardy	19.74	20.16	20.52	20.32	19.08	19.02	17.69	-7.0
A.P. of Bolzano	7.56	8.97	6.72	7.43	7.73	8.31	8.42	1.4
A.P. of Trento	7.98	9.05	8.61	9.22	8.45	7.84	8.67	10.7
Veneto	10.49	10.34	10.36	10.81	8.98	8.79	9.39	6.9
Friuli VG	7.36	7.16	8.47	8.95	7.39	7.24	7.62	5.3
Liguria	11.78	12.19	12.36	12.51	12.07	11.84	10.96	-7.4
Emilia R.	16.29	16.67	16.66	16.53	14.58	12.77	12.50	-2.1
Tuscany	12.61	14.23	14.74	15.00	12.96	12.18	13.49	10.8
Umbria	10.25	10.21	11.08	11.48	11.98	11.07	10.47	-5.5
Marche	10.87	11.13	11.59	11.68	10.82	10.82	10.85	0.3
Lazio	15.16	15.47	15.86	16.30	15.09	13.99	14.04	0.3
Abruzzo	6.99	7.78	7.80	8.21	8.79	7.80	8.03	2.9
Molise	3.29	3.38	3.77	4.13	4.37	4.05	3.29	-18.7
Campania	7.36	7.88	8.32	8.39	6.80	5.48	6.51	18.8
Puglia	9.12	9.29	9.64	9.44	8.50	7.61	7.18	-5.7
Basilicata	4.18	4.40	4.76	4.95	4.81	4.76	4.91	3.1
Calabria	4.41	4.41	4.93	5.57	4.48	3.86	3.80	-1.4
Sicily	6.74	7.12	7.80	8.06	7.60	6.98	7.05	1.0
Sardinia	13.62	14.59	14.54	14.07	11.79	9.81	10.06	2.5
Italy	**12.05**	**12.47**	**12.84**	**12.98**	**11.73**	**11.05**	**11.09**	**0.3**
North	14.59	14.91	15.18	15.26	13.84	13.42	13.17	-1.9
Centre	13.40	14.10	14.58	14.92	13.62	12.77	13.18	3.1
South and Islands	7.61	8.03	8.45	8.55	7.57	6.59	6.83	3.5

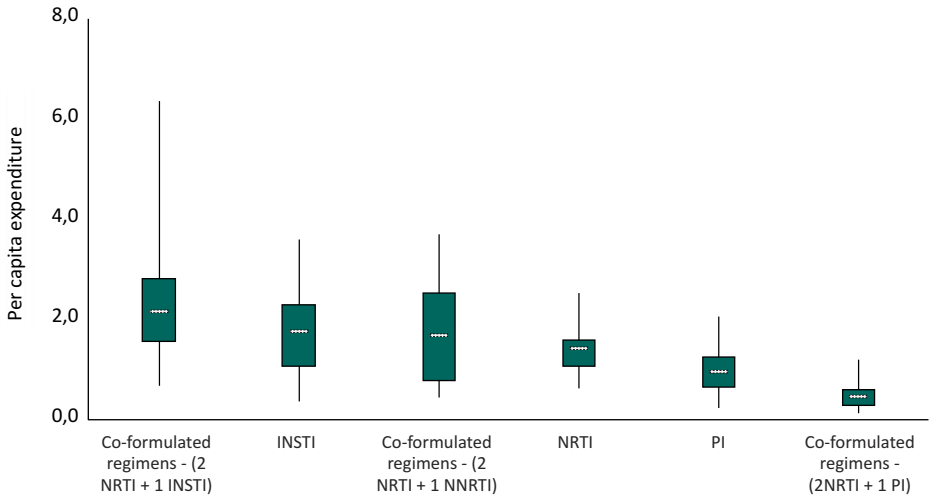
Table 3.4.2c. Prescription of anti-HIV antivirals with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	0.18	1.6	-24.4	0.5	16.2	-0.3	1.04
Generic	0.10	55.2	5.3	0.4	82.2	12.2	0.70
Ex originator	0.08	44.8	-43.9	0.1	17.8	-34.2	2.61
Patent covered	10.91	98.4	0.9	2.4	83.8	1.9	12.24
Anti-HIV antivirals	**11.09**	**100.0**	**0.3**	**2.9**	**100.0**	**1.5**	**10.42**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.4.2c. Anti-HIV antivirals, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- The use of **co-formulated antiretroviral regimens** represents the main item of expenditure and consumption within the class of antiretrovirals with a confirmed upward trend. This data confirms the need for these therapies to combine efficacy and tolerability with the need for treatment simplification.
- Anti-HIV medicines are a market with **low penetration of generic drugs**, both due to the availability of new molecules and the tendency to co-formulate patent-expired molecules.
- **Regional per capita expenditure records a wide variability in 2020**, ranging from a minimum value of 3.29 euros in Molise to a maximum of 17.69 euros in Lombardy; the latter, together with Lazio and Tuscany, is the Region with number of doses and cost above the national average. This trend could reflect the different epidemiology of the disease among the Italian regions.
- Co-formulated regimens with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and 1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) have the **largest regional variability in per capita expenditure**, while co-formulated regimens with 2 nucleoside reverse transcriptase inhibitors/nucleotides (NRTIs) and 1 integrase inhibitor (INSTI) have the **widest expenditure range**.

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3.4.3. Vaccines

National data on consumption and expenditure

Vaccine expenditure doubled from 2014 to 2020, shifting from 4.8 euros to 9.4 euros per capita. At the same time, the average DDD cost was 21 euros in 2020, down by 2 euros compared to 2019 (Figure 3.4.3a).

The polysaccharide conjugate anti-pneumococcal vaccine is the first item of expenditure in this category, accounting for 25% of the total, reaching 2.36 euros per capita in 2020, a 30.2% increase compared to the previous year, and a 9.5% average annual increase (CAGR) in the period 2014-2020. This trend was mainly determined by the expansion of the categories to which vaccination was offered free of charge. Almost all of the cost of pneumococcal vaccines (2.32 euros per capita) is due to the 13-valent conjugate vaccine (PCV13) indicated for infants and children up to 5 years and effective against the 13 strains responsible for the majority 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. This is followed by the meningococcal B vaccine with 1.63 euros per capita and the influenza vaccines with 1.54 euros per capita (Table 3.4.3a). While the formers show a 10% decrease in expenditure, influenza vaccines have increased by 10.8%; in terms of doses, the increase is 23.6%. 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 (National plan for vaccination prevention). 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 cycle of administration as soon as possible.

Among the categories with the highest expenditure, a decrease was recorded in vaccines for papilloma virus (-10.8%), the hexavalent accine (-5.1%), the MPRV vaccine (-10%), the tetravalent meningococcal vaccine (-18.3%), the rotavirus vaccine (-3.7%) and the tetravalent vaccine (-16.3%). The reasons for this trend could be attributed to the impact of the COVID-19 pandemic, which caused a slowdown in the activity of vaccination centres. An exception, together with the vaccines for meningococcus C, is the vaccine for Haemophilus influenzae B that records an expenditure increase by about 200%. This bacterium causes purulent meningitis or inflammation of the epiglottis in infants and young children, which may provoke rapid suffocation.

Figure 3.4.3a. Vaccines, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

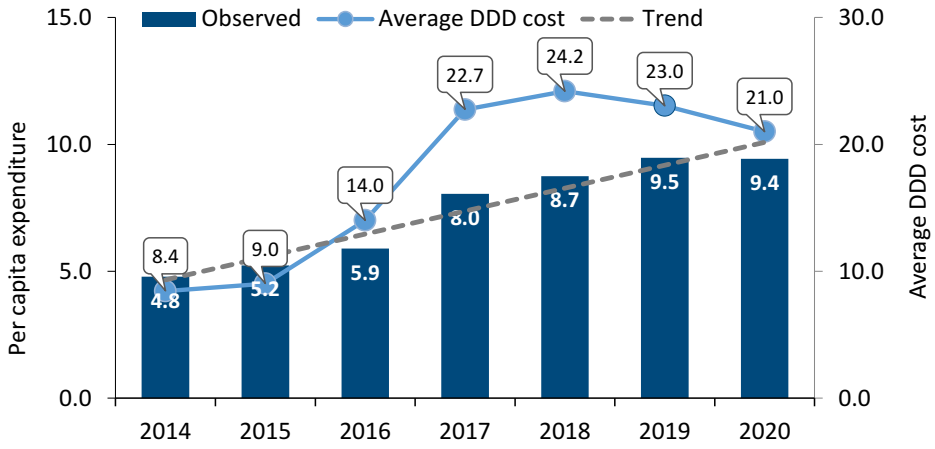


Table 3.4.3a. Vaccines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Pneumococcal polysaccharide conjugate vaccine (PCV13)	2.36	30.2	9.5	0.1	29.0	7.9	50.59	0.7
Meningococcal B vaccine	1.63	-10.0	68.5	0.1	-10.1	68.3	62.71	-0.2
Influenza vaccine	1.54	10.8	15.7	0.7	23.6	-8.6	6.10	-10.6
Papillomavirus vaccine	0.97	-10.8	16.9	0.0	-11.5	7.7	69.43	0.6
Hexavalent vaccine (diphtheria/tetanus/pertussis/ haemophilus influenzae B/poliomyelitis/hepatitis B)	0.68	-5.1	-9.4	0.1	-2.7	-1.7	32.57	-2.7
MMRV vaccine (measles/mumps/rubella/varicella)	0.49	-10.0	17.8	0.0	-8.4	20.9	45.70	-2.1
Tetravalent meningococcal conjugate vaccine	0.39	-18.3	38.8	0.0	-16.2	43.1	30.80	-2.9
Rotavirus attenuated vaccine	0.30	-3.7	32.9	0.0	-1.6	40.5	26.20	-2.4
Tetravalent vaccine (diphtheria/tetanus/pertussis/polio myelitis)	0.28	-16.3	10.3	0.0	-15.3	9.2	19.28	-1.4
Live attenuated Varicella zoster virus vaccine	0.21	-30.7	219.5	0.0	-30.4	214.6	95.70	-0.7
Pneumococcal 23 vaccine	0.14	64.2	42.6	0.0	64.2	34.9	22.33	-0.3
DTP vaccine (diphtheria/tetanus/pertussis)	0.12	-16.5	2.4	0.0	-13.8	2.6	13.71	-3.4
Live attenuated varicella virus vaccine	0.09	-17.4	-4.3	0.0	-13.8	-2.8	32.77	-4.5

Continued

Table 3.4.3a. Continued

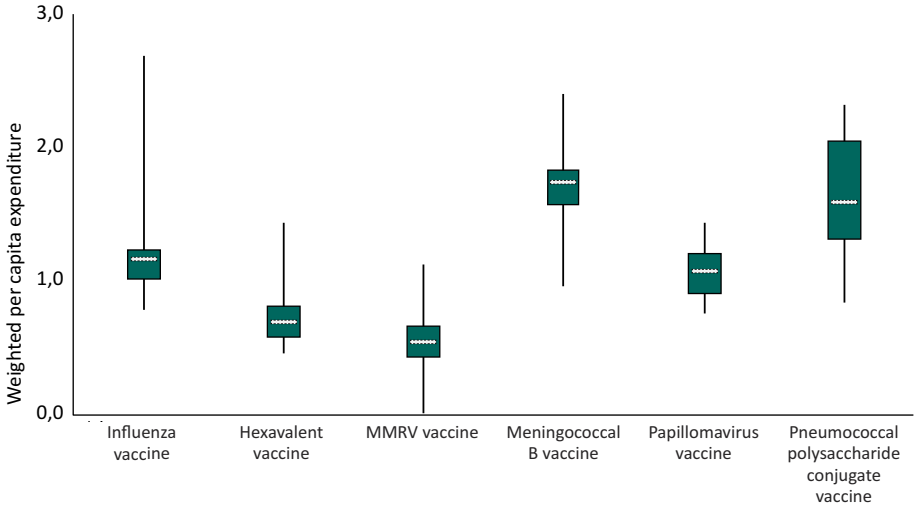
Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
MMR vaccine (measles/mumps/rubella)	0.05	-36.9	-16.7	0.0	-37.8	-15.9	9.43	1.2
Hepatitis A vaccine	0.04	-26.6	-4.0	0.0	-25.2	-1.6	17.55	-2.2
Encephalitis vaccine	0.04	-40.2	33.8	0.0	-39.4	34.4	37.60	-1.7
Hepatitis B vaccine	0.04	-23.0	-2.1	0.0	-30.7	-4.0	18.26	10.8
Meningococcal C conjugate vaccine	0.03	20.9	-16.9	0.0	33.9	-16.9	9.95	-9.9
DT vaccine (diphtheria /tetanus)	0.01	-43.7	-8.5	0.0	-45.5	-16.5	4.26	3.0
Tetanus vaccine	0.01	-36.5	-11.8	0.0	-37.7	-19.5	3.99	1.6
Haemophilus influenzae B vaccine	0.01	195.9	18.5	0.0	170.5	14.6	14.32	9.1
Hepatitis A and B vaccine	0.01	-21.6	-5.2	0.0	-23.6	15.6	31.25	2.4
Rabies vaccine	0.00	-22.6	3.9	0.0	-22.8	-7.3	50.27	0.0
Poliomyelitis inactivated vaccine	0.00	3.7	-5.4	0.0	3.3	-8.7	7.59	0.1
Yellow fever vaccine	0.00	-72.0	-14.3	0.0	-72.4	-18.2	17.09	1.1
Typhus vaccine	0.00	-76.6	-16.2	0.0	-71.0	-14.6	3.30	-19.6
Trivalent vaccine (diphtheria/tetanus/poliomyelitis)	0.00	-22.8	-21.6	0.0	-23.4	-24.6	12.85	0.5
Cholera vaccine	0.00	-97.0	-43.8	0.0	-97.2	-46.0	25.28	8.6
Vaccines	**9.43**	**-0.4**	**12.0**	**1.2**	**9.0**	**-3.9**	**21.01**	**-8.8**
thirteen-valent pneumococcal vaccine	2.32	31.1	9.2	0.1	30.6	7.4	51.22	0.1
B group meningococcal vaccine	1.63	-10.0	68.5	0.1	-10.1	68.3	62.71	-0.2
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	0.97	-10.3	-	0.0	-10.6	-	69.43	0.1
inactivated, split virus tetravalent influenza vaccine	0.89	-10.7	138.9	0.4	9.3	152.9	6.22	-18.5
diphtheria/recombinant hepatitis b/*Haemophilus influenzae* B conjugate and adjuvanted/acellular pertussis/inactivated poliomyelitis/tetanus vaccine	0.68	-5.1	-9.4	0.1	-2.7	-1.7	32.57	-2.7
measles mumps rubella and varicella vaccine	0.49	-10.0	17.8	0.0	-8.4	20.9	45.70	-2.1
inactivated virus, surface antigen, adjuvanted influenza vaccine	0.41	46.6	6.3	0.2	44.9	8.3	5.26	0.9
ACWY meningococcal vaccine conjugated to tetanus toxoid	0.29	-14.5	45.3	0.0	-12.5	49.9	30.43	-2.5
diphtheria/pertussis/poliomyelitis/ tetanus vaccine	0.28	-16.3	10.3	0.0	-15.3	9.2	19.28	-1.4
live attenuated monovalent rotavirus vaccine	0.24	-3.8	27.9	0.0	-2.1	33.1	28.90	-2.0

Table 3.4.3b. Vaccines, regional trend of weighted per capita expenditure: comparison 2014- 2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	3.75	3.45	3.45	5.37	6.04	6.84	6.87	0.4
Valle d'Aosta	4.18	3.30	3.98	5.18	5.75	7.18	6.12	-14.7
Lombardy	4.08	3.96	4.10	5.82	7.71	10.53	9.89	-6.1
A.P. of Bolzano	5.30	5.68	5.79	9.39	11.56	13.54	9.52	-29.7
A.P. of Trento	5.22	4.73	6.31	9.84	13.10	11.78	11.21	-4.8
Veneto	5.23	5.60	7.31	9.55	9.17	10.09	10.19	1.0
Friuli VG	5.46	5.39	7.51	10.71	11.25	10.89	8.41	-22.8
Liguria	4.10	4.87	5.97	7.14	7.65	7.12	7.45	4.6
Emilia R.	4.58	4.60	5.38	9.94	10.50	10.32	9.49	-8.1
Tuscany	3.23	8.88	8.57	7.34	8.02	8.43	9.68	14.9
Umbria	4.56	4.36	5.01	6.38	7.25	7.54	7.99	5.9
Marche	4.07	4.06	4.48	7.64	7.31	8.47	8.16	-3.7
Lazio	4.44	4.86	6.18	8.91	8.43	9.61	11.27	17.3
Abruzzo	4.27	4.13	4.40	6.91	7.37	7.66	7.77	1.4
Molise	5.08	5.27	4.65	6.43	8.22	7.13	7.58	6.4
Campania	4.73	4.87	5.12	7.63	8.29	9.39	9.60	2.3
Puglia	7.68	7.71	8.21	11.40	11.96	10.44	10.93	4.6
Basilicata	5.78	6.80	6.21	6.74	8.30	7.58	7.55	-0.4
Calabria	4.72	5.27	7.21	9.46	9.00	8.39	8.44	0.6
Sicily	6.86	6.69	7.77	9.46	10.52	10.67	10.04	-5.9
Sardinia	4.27	4.41	5.20	6.65	8.43	7.94	6.47	-18.6
Italy	**4.79**	**5.23**	**5.89**	**8.05**	**8.75**	**9.47**	**9.43**	**-0.4**
North	4.41	4.43	5.10	7.50	8.46	9.69	9.18	-5.3
Centre	4.01	6.01	6.64	8.05	8.06	8.92	10.10	13.3
South and Islands	5.80	5.89	6.56	8.82	9.57	9.48	9.38	-1.1

Figure 3.4.3c. Vaccines, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- The **polysaccharide conjugate anti-pneumococcal vaccine is the first item of expenditure** in this category, accounting for 25% of the total and with a 30.2% increase compared to the previous year. The effect could be attributed to the measures provided for by Ministry of Health letter no. 19214 of 4 June 2020 that anticipated the availability of the vaccine in October, expanding the categories for which it is recommended and offered free of charge. Pneumococcal vaccination is of particular importance in terms of prevention of a possible concomitant disease, pneumococcal pneumonia, characterised by a high hospitalisation rate and a high risk of antibiotic resistance.
- **Consumption of anti-influenza vaccine have increased** (+23.6%), owing to an increase in participation in the vaccination campaign during the pandemic period, allowing for a simplification of the diagnosis and management of suspected cases due to the symptoms that can overlap with COVID-19.
- **Most other vaccinations in Italy have decreased**, such as the vaccination against papilloma virus (-10.8%), the hexavalent vaccine (-5.1%), the MMRV vaccine (-10%), the tetravalent meningococcus (-18.3%), the rotavirus vaccine (-3.7%) and the tetravalent vaccine (-16.3%). The reasons for this trend can be attributed to the impact of the COVID-19 pandemic that caused a slowdown in the activity of vaccination centres.

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3.4.4 Anti-HCV antivirals

National data on consumption and expenditure

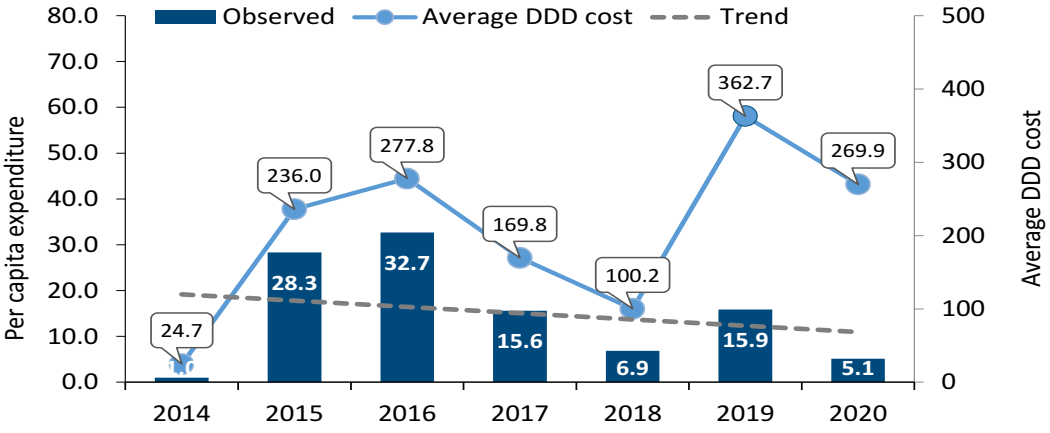
In 2020, the use of anti-HCV antiviral drugs significantly decreased: per capita expenditure for this category of drugs was 5.13 euros (-67.6% compared to 2019), while consumption was 0.1 DDD/1000 inhabitants per day (-56.6% compared to 2019), with a corresponding average cost per DDD of about 270 euros, a 25.6% decrease compared to the previous year (Figure and Table 3.4.4a). In general, between 2014 and 2020 this category of drugs recorded an average annual growth rate (CAGR) in expenditure of 31.6% and a decrease in consumption of 11.7%.

The sofosbuvir/velpatasvir combination, an antiviral acting on all genotypes of the virus by blocking the replication process ("pangenotypic" action), is the drug with the highest per capita expenditure (3.92 euros), although it has remarkably decreased (-68.8%) compared to the previous year, a trend that is also observed for all the other drugs in the category.

Drugs still covered by a patent represent the total consumption and expenditure of this category (Table 3.4.4c).

Per capita expenditure for anti-HCV antivirals in combination shows a wide regional variability ranging from a minimum value of 6.6 euros to a maximum of 20.7 euros (Figure 3.4.4c.).

Figure 3.4.4a. Anti-HCV antivirals, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)



Note: in 2018 expenditure data is net of the credit notes issued for sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/ voxilaprevir

Table 3.4.4a. Anti-HCV antivirals, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Anti-HCV antivirals in combination	5.13	-67.6	-	0.1	-57.5	-	279.56	-24.0
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.00	>100	-45.8	0.0	3.0	-48.4	3.76	890.9
Other HCV antivirals	0.00	-72.0	-49.6	0.0	-	-19.7	28.79	-125.9
Anti-HCV antivirals	**5.13**	**-67.6**	**31.6**	**0.1**	**-56.6**	**-11.7**	**269.92**	**-25.6**
sofosbuvir/velpatasvir	3.92	-68.8	-	0.0	-53.1	-	433.94	-33.7
glecaprevir/pibrentasvir	0.84	-59.7	-	0.0	-57.7	-	113.59	-5.0
sofosbuvir/velpatasvir/ voxilaprevir	0.28	-65.0	-	0.0	-49.5	-	448.48	-30.9
elbasvir/grazoprevir	0.10	-75.7	-	0.0	-75.4	-	77.30	-1.3
ribavirine	0.00	>100	-45.8	0.0	3.0	-48.4	3.76	890.9
sofosbuvir	0.00	-71.5	-48.2	0.0	61.3	-17.0	27.76	-82.4
ledipasvir/sofosbuvir	0.00	-97.8	-	0.0	-60.8	-	0.04	-94.4

Table 3.4.4b. Anti-HCV antivirals, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	0.73	16.82	28.38	16.60	7.11	19.21	6.40	-66.7
Valle d'Aosta	0.84	21.20	17.35	6.25	5.15	10.55	4.82	-54.3
Lombardy	0.74	31.75	34.99	18.37	8.46	18.66	5.59	-70.0
A.P. of Bolzano	0.27	16.91	20.81	7.01	3.50	7.49	1.99	-73.4
A.P. of Trento	0.21	13.99	18.92	7.37	5.11	13.07	7.14	-45.3
Veneto	0.87	20.38	25.01	12.41	5.42	12.55	4.59	-63.4
Friuli VG	0.58	20.17	11.34	9.95	5.28	16.92	6.70	-60.4
Liguria	0.69	25.37	25.98	14.79	6.51	12.61	4.40	-65.1
Emilia R.	1.45	28.57	30.98	14.92	8.40	16.73	3.95	-76.4
Tuscany	0.90	37.43	35.87	12.71	8.89	17.93	6.84	-61.8
Umbria	0.61	13.88	25.65	10.63	6.36	14.23	4.91	-65.5
Marche	0.79	20.35	19.23	9.98	5.28	12.36	4.59	-62.9
Lazio	0.63	24.96	30.15	11.36	5.29	12.36	3.85	-68.9
Abruzzo	0.78	21.47	18.51	9.94	3.88	6.62	2.79	-57.9
Molise	0.43	20.44	25.79	10.64	4.37	11.61	3.98	-65.7
Campania	1.88	40.77	53.24	26.71	9.36	20.71	7.52	-63.7
Puglia	1.27	37.26	37.28	16.87	6.17	15.42	4.54	-70.5
Basilicata	0.99	30.00	32.70	15.40	6.32	12.91	3.84	-70.2
Calabria	1.01	30.88	32.91	15.68	3.04	10.35	3.26	-68.5
Sicily	1.41	26.57	34.42	14.46	5.19	15.50	4.15	-73.2
Sardinia	0.80	33.91	40.50	18.96	8.00	16.77	5.79	-65.5
Italy	**0.99**	**28.32**	**32.7**	**15.61**	**6.85**	**15.86**	**5.13**	**-67.6**
North	0.85	25.24	29.25	15.42	7.27	16.58	5.22	-68.5
Centre	0.74	27.53	30.23	11.56	6.53	14.29	4.99	-65.1
South and Islands	1.35	33.16	39.13	18.37	6.47	15.77	5.09	-67.7

Table 3.4.4c. Prescription of anti-HCV antivirals with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	0.00	0.0	271.9	0.0	3.4	1.9	3.63
Generic	0.00	6.9	-35.5	0.0	23.9	-24.0	1.06
Ex originator	0.00	93.1	476.5	0.0	76.1	14.1	4.44
Patent covered	5.13	100.0	-67.6	0.1	96.6	-57.5	279.19
Anti-HCV antivirals	**5.13**	**100.0**	**-67.6**	**0.1**	**100.0**	**-56.6**	**269.92**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Key message

- **In 2020, the use of anti-HCV antivirals significantly decreased**, with a decline in per capita expenditure by almost 70% compared to 2019, due to a reduction both in the average cost per DDD and in the 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 in many clinical situations it has caused a reconversion of the hospital wards used for liver diseases into wards used only for COVID-19 patients and a greater difficulty in identifying HCV asymptomatic patients or 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; for Campania and the AP of Trento, consumption is about 30% higher than the national average, while for the AP of Bolzano and Abruzzo, use levels are lower than the national average, 48% and 31%, respectively.

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3.4.5 Antifungals for systemic use

National data on consumption and expenditure

The last seven years have seen an average annual decrease (CAGR -4.8%) in the expenditure for antifungals, with values shifting from 3.4 euros in 2014 to 2.5 euros in 2020. A remarkable 9.1% decrease was recorded compared to 2019 (Figure 3.4.5a and Table 3.4.5a). Consumption recorded a 12.5% decrease compared to 2019, while in the 2014-2020 period the average annual change was 4.9%. 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, recording a value of 1.50 euros per capita in 2020. This category showed a reduction in both consumption (-13.3%) and expenditure (-8.9%) compared to 2019. Polyenes (0.55 euros per capita) follow, with a slight increase by 4.3% compared to the previous year.
Echinocandins is the subgroup with the greatest increase in consumption (+ 17.3%), mainly driven by the increase in the consumption of caspofungin and anidulafungin.
Fluconazole is the molecule with both the highest consumption (0.4 DDD) and the highest expenditure (0.71 euros per capita), followed in consumption by itraconazole (0.2 DDD) and in expenditure by amphotericin B (0.55 euros per capita).
The molecules with the highest increases in consumption are isavuconazole and caspofungin, both indicated for the treatment of a rare disease as invasive aspergillosis. Isavuconazole is the only drug in the top ten by expenditure still covered by a patent and is included in the 2020 list of orphan drugs published by AIFA.
40.7% of the expenditure for antifungal drugs is made up of patent-expired molecules, although most refer to ex-originators (Table 3.4.5c).

Figure 3.4.5a. Antifungals for systemic use, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

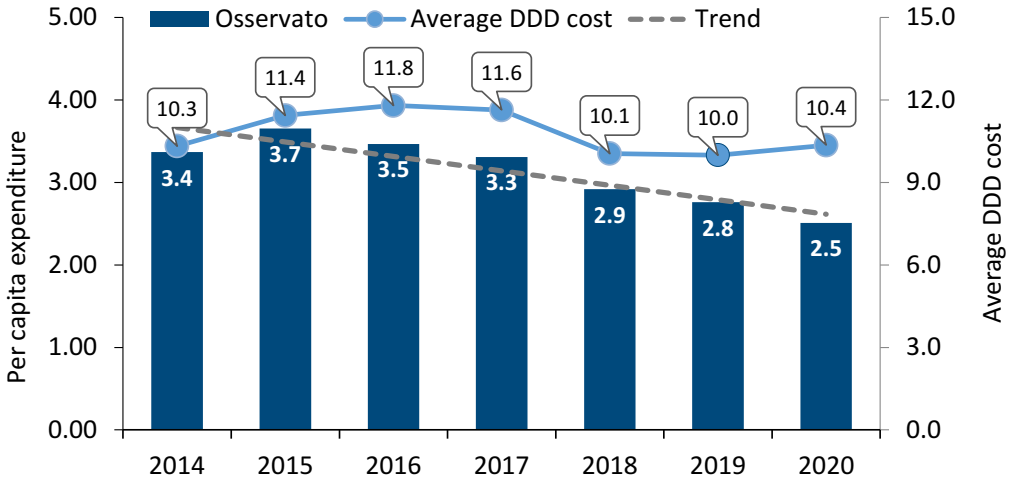


Table 3.4.5a. Antifungals for systemic use, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Triazole derivatives	1.50	-8.9	-3.4	0.6	-13.3	-5.3	6.53	4.8
Polyenes	0.55	4.3	2.9	0.0	4.2	1.3	98.78	-0.1
Echinocandins	0.44	-21.7	-13.5	0.0	17.3	9.7	91.52	-33.5
Imidazole derivatives	0.02	-8.9	101.0	0.0	-8.8	71.3	9.46	-0.3
Pyrimidine analogues	0.00	-25.8	-9.8	0.0	-27.1	-9.6	144.39	1.6
Antifungals	**2.51**	**-9.1**	**-4.8**	**0.7**	**-12.5**	**-4.9**	**10.36**	**3.7**
fluconazole	0.71	-13.0	-5.0	0.4	-13.0	-4.2	4.77	-0.2
amphotericin B	0.55	4.3	2.9	0.0	4.2	1.3	98.78	-0.1
posaconazole	0.35	-12.5	10.0	0.0	0.7	2.6	60.04	-13.3
isavuconazole	0.23	24.3	-	0.0	22.3	-	107.33	1.4
caspofungin	0.22	-26.0	-17.3	0.0	21.7	13.3	59.78	-39.4
itraconazole	0.18	-13.6	-8.2	0.2	-16.1	-8.4	2.61	2.7
micafungin	0.15	-9.0	0.5	0.0	-9.2	-1.0	392.41	0.0
anidulafungin	0.08	-29.0	-16.3	0.0	13.8	3.6	97.68	-37.7
voriconazole	0.04	-19.9	-32.8	0.0	-3.1	2.1	9.37	-17.6
ketoconazole	0.02	-8.8	-	0.0	-8.7	-	9.46	-0.4

Table 3.4.5b. Antifungals for systemic use, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	3.22	5.06	3.12	2.90	2.59	2.33	2.18	-6.6
Valle d'Aosta	1.41	2.35	1.54	1.13	0.98	1.21	0.98	-19.3
Lombardy	2.65	3.01	2.81	2.68	2.44	2.26	2.03	-10.3
A.P. of Bolzano	2.77	3.26	2.41	3.02	2.41	1.79	2.28	27.0
A.P. of Trento	2.17	2.24	1.66	1.92	1.86	1.59	1.37	-13.4
Veneto	3.49	3.39	3.52	3.59	2.57	2.82	2.68	-5.1
Friuli VG	3.04	3.38	3.47	3.57	2.66	2.44	2.89	18.5
Liguria	4.33	4.58	4.85	4.41	4.22	3.02	3.68	21.6
Emilia R.	2.84	2.98	2.98	3.09	2.91	2.83	2.80	-1.1
Tuscany	3.23	3.16	3.27	2.74	1.95	2.03	2.01	-0.8
Umbria	5.56	5.04	4.65	5.44	4.71	3.80	3.49	-8.0
Marche	2.91	3.02	3.41	3.48	2.99	2.87	2.30	-20.0
Lazio	3.71	3.80	3.67	3.42	3.07	2.80	2.41	-13.8
Abruzzo	2.95	3.50	3.56	3.30	3.54	3.50	2.78	-20.4
Molise	2.85	2.30	2.78	2.12	2.22	1.92	1.44	-25.1
Campania	3.59	3.61	3.73	3.55	3.46	2.94	2.77	-5.9
Puglia	4.15	4.37	4.08	3.79	3.07	2.97	2.56	-13.8
Basilicata	3.13	3.63	2.77	2.88	2.68	2.64	2.05	-22.3
Calabria	4.34	4.68	4.82	4.28	4.13	4.19	3.80	-9.3
Sicily	3.59	3.75	3.77	3.69	3.26	3.39	2.55	-24.6
Sardinia	3.63	4.00	3.78	3.26	3.14	3.41	2.92	-14.4
Italy	**3.37**	**3.65**	**3.47**	**3.31**	**2.92**	**2.76**	**2.51**	**-9.1**
North	3.03	3.51	3.14	3.07	2.66	2.49	2.41	-3.0
Centre	3.59	3.59	3.58	3.36	2.83	2.64	2.35	-10.8
South and Islands	3.71	3.90	3.86	3.62	3.33	3.22	2.74	-14.9

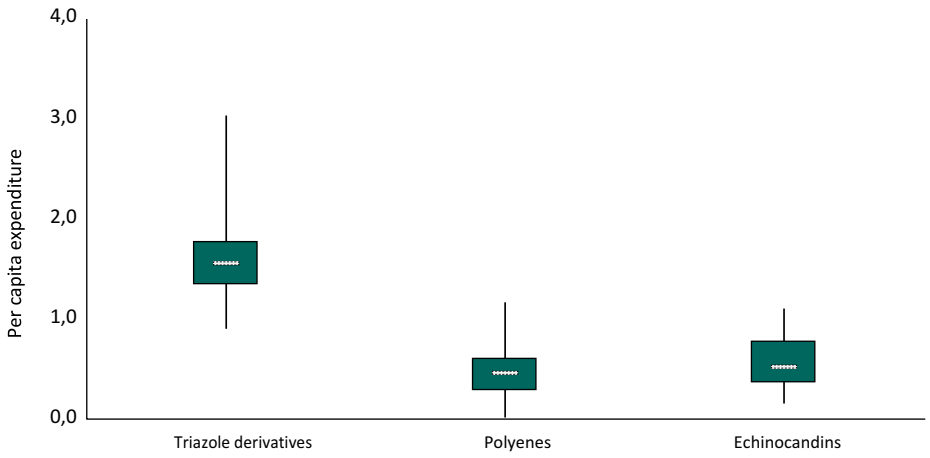
Table 3.4.5c. Prescription of antifungals for systemic use with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	1.02	40.7	11.9	0.5	83.0	-13.0	5.08
Generic	0.32	31.5	0.6	0.2	37.5	-12.6	4.26
Ex originator	0.70	68.5	17.9	0.3	62.5	-13.2	5.57
Patent covered	1.49	59.3	-19.4	0.1	17.0	-10.2	36.18
Antifungals	**2.51**	**100.0**	**-9.1**	**0.7**	**100.0**	**-12.5**	**10.36**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.4.5c. Antifungals for systemic use, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- Overall, **expenditure and consumption of antifungals decreased compared to 2019**, by -9.1% and -12.5%, respectively. Expenditure also decreased by -26% in the 2014-2020 period, with an average annual variation of 4.8%.
- **The greatest increases in consumption are recorded for isavuconazole and caspofungin**, a triazole derivative and an echinocandin, indicated for the treatment, among others, of a rare disease such as invasive aspergillosis. Isavuconazole is the only drug in the top ten by expenditure still covered by a patent and is included in the 2020 list of orphan drugs published by AIFA.
- Compared to 2019, almost all the Regions recorded a **reduction in expenditure**, with the exception of the AP of Bolzano, Liguria and Friuli Venezia Giulia. A **wide variability remains in per capita expenditure** ranging between 0.98 euros in Valle d'Aosta and 3.80 euros in Calabria.

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3.5 Blood and blood-forming organs

Medicines for blood and blood-forming organs are the fifth therapeutic category with the highest public expenditure in 2020, equal to 2,304.3 million euros and 10% of overall public expenditure (Box. Main indices of expenditure, consumption and exposure). The overall per capita expenditure for such medicines was 38.64 euros, mainly due to the purchase by public health facilities (30.78 euros per capita), thus recording a sharp increase compared to the previous year (+8.1%). On the contrary, expenditure under approved care regime was lower (7.86 euros per capita) (Table 3.1).
Contrary to the increasing trend of the past few years, the overall consumption by the NHS for this category of drugs was 136.7 DDD/1000 inhabitants per day (11.7% of the total), remaining almost stable 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 *per conto* distribution shows a progressive increase in the use of these drugs with increasing age, with a more marked increase in men starting from the 45-54 age range, probably due to the different prevalence of cardio-cerebrovascular diseases. In the younger age groups, the prevalence is higher in women than in men, probably due to a greater use of anti-anaemic preparations. At the same time, per capita expenditure borne by the NHS also shows a similar trend, reaching the maximum value of 95.2 euros per capita in the over 75 age group (107.5 euros in men and 87.0 euros in women).
As regards the approved care regime, in 2020 expenditure recorded a -1.6% decrease compared to the previous year, together with a reduction in consumption (-1.5%), with a shift in the prescription towards more expensive specialties (mix effect: +0.4%) (Table 3.9). The therapeutic categories with the greatest impact on expenditure are platelet aggregation inhibitors (3.07 euros per capita) and heparinics (2.23 euros per capita). It should be noted that, compared to the previous year, factor Xa inhibitors continue to record a high increase in expenditure (+14.0%) and consumption (+14.8%), although with a marginal expenditure value compared to the one recorded for purchases by public health facilities (0.74 euros per capita) (Table 3.9). Enoxaparin is the only active ingredient in the category of medicines for blood and blood forming organs in the top 30 with the greatest impact on pharmaceutical expenditure under approved care regime, accounting for 24.2% of the total expenditure for this category (Table 3.10 and 3.11). However, among the first 30 molecules with the greatest impact on consumption, one can find acetylsalicylic acid (ASA), used in low doses as an antiplatelet agent, and cyanocobalamin (Table 3.14). In terms of purchases by public health facilities, compared to 2019, there was an increase in both expenditure (+7.8%) and consumption (+2.5%) and a shift towards more expensive specialties (mix effect +8.2%) (Table 3.16). The therapeutic category with the highest expenditure impact is represented by coagulation factors, with a per capita expenditure of 8.18 euros, followed by factor Xa inhibitors (7.09 euros per capita). Among the most frequently used therapeutic categories it is possible to find inhibitors of direct factor Xa (10.8 DDD) and platelet aggregation inhibitors, excluding heparin (9.3 DDD). Rivaroxaban is the active ingredient ranking first in terms of per capita expenditure (3.09 euros), with an increase by 19.0% in expenditure and by 21.8% in consumption in 2020 (Table 3.17). This active ingredient also ranks among the top 30 most expensive active ingredients, immediately followed by the oral anticoagulant apixaban and the short-acting recombinant coagulation factor VIII for haemophilia A octocog alfa (Table 3.18).

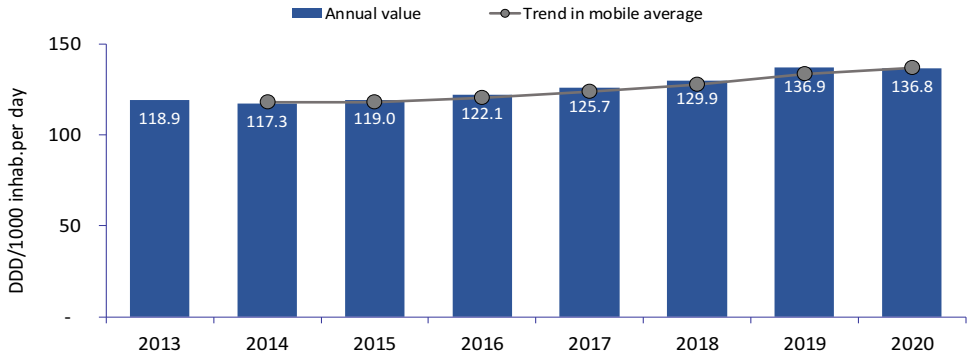
For further information on the use of medicines belonging to the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region and on the efficiency in the absorption of resources according to the presence of patent-expired medicines and on a regional basis. These analyses focused on anticoagulant medicines, coagulation factors and platelet aggregation inhibitors (Table 3.5.1a and following). Furthermore, in the section dedicated to monitoring registries, a focus is dedicated to new oral anticoagulants (NAOs) used in the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), which provides the description of baseline characteristics of treatment-initiated patients and their regional distribution (Section 4).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

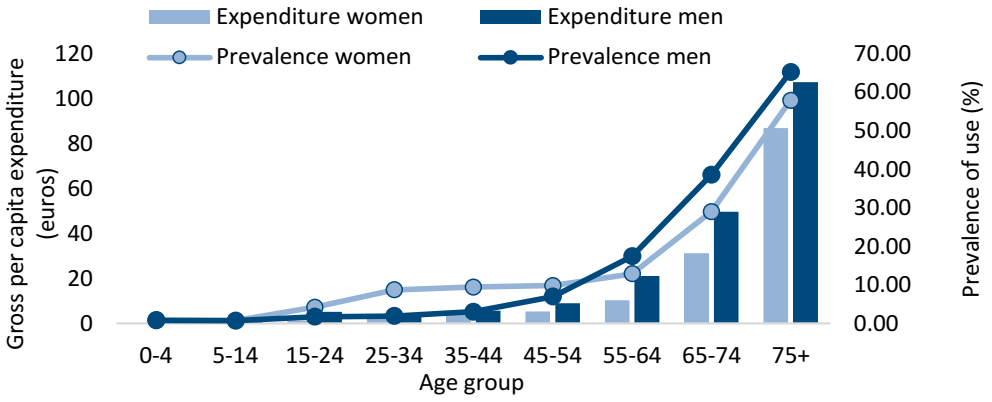
Blood and blood forming organs

Public expenditure* in million euros (% over total)	**2,304.3**	**(10,0)**
Δ % 2020-2019		6.1%
Regional range of gross per capita expenditure	28.2	48.0
DDD/1000 inhab. per day (% over total)	**136.7**	**(11,7)**
Δ % 2020-2019		-0.1%
Regional range of DDD/1000 inhab. per day	91.3	188.0

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities



Distribution, by age and gender, of expenditure, prevalence of use and consumptions under approved care regime and *per conto* distribution in 2020 (Figure and Table)



Age group	Gross expenditure (per capita)			DDD/1000 inhab.per day		
	Men	Women	Total	Men	Women	Total
0-4	1.2	0.1	0.7	1.5	1.1	1.3
5-14	2.5	0.4	1.4	1.1	1.1	1.1
15-24	5.2	1.2	3.3	3.2	7.8	5.4
25-34	4.0	3.1	3.6	4.8	21.8	13.2
35-44	5.7	4.4	5.0	11.0	25.7	18.4
45-54	9.0	5.4	7.2	37.7	31.9	34.8
55-64	21.1	10.4	15.6	121.1	68.2	93.8
65-74	49.7	31.3	40.0	312.5	202.5	254.4
75+	107.5	87.0	95.2	550.4	451.8	491.4

3.5.1. Anticoagulants

National data on consumption and expenditure

From 2014 to 2020, consumption of anticoagulants increased by 47.9%, going from 18.8 to 27.8 DDD (CAGR: +6.7%). At the same time, the average cost per day of therapy increased by 16%, from 1.22 to 1.42 euros (Figure 3.5.1a). Per capita expenditure for these drugs was 14.44 euros, a 12.7% increase compared to the previous year, which confirms the growing trend highlighted by the CAGR for the years 2014-2020 (Table 3.5. 1a).

In 2020, new oral anticoagulants (NOACs) were the category with the highest use (13.9 DDD) and per capita expenditure (9.33 euros), with both values increasing compared to the previous year (+17.5% and +14.0%, respectively), followed by low molecular weight heparins (LMWH), which recorded a consumption of 9.4 DDD (+6.6% compared to 2019) and a per capita expenditure of 3.94 euros (+9.6%). This last category of drugs also shows the greatest variability in consumption between the different regions, reporting the broadest range (7.9-15.6 DDD/1000 inhabitants per day) (Figure 3.5.1c).

Enoxaparin is the most expensive molecule (3.42 euros per capita), with a 21.1% increase compared to 2019, followed by four oral anticoagulants, namely rivaroxaban (3.15 euros), apixaban (2.88 euros), edoxaban (1.80 euros), dabigatran (1.50 euros). Edoxaban is the active ingredient with the greatest increase (+29.3%) compared to the previous year and with the highest average cost per day of therapy (2.3 euros), while the average cost of NOACs is 1.84 euros. Caplacizumab, a monoclonal antibody authorised in 2020 for episodes of acquired thrombocytopenic purpura (TTP), in combinaiton with plasmapheresis and immunosuppression, is the tenth active ingredient in the category, recording a per capita expenditure of 0.15 euros. Almost all of the consumption and expenditure for anticoagulants relates to active ingredients still covered by a patent (99.8%) (Table 3.5.1c).

Figure 3.5.1a. Anticoagulants, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

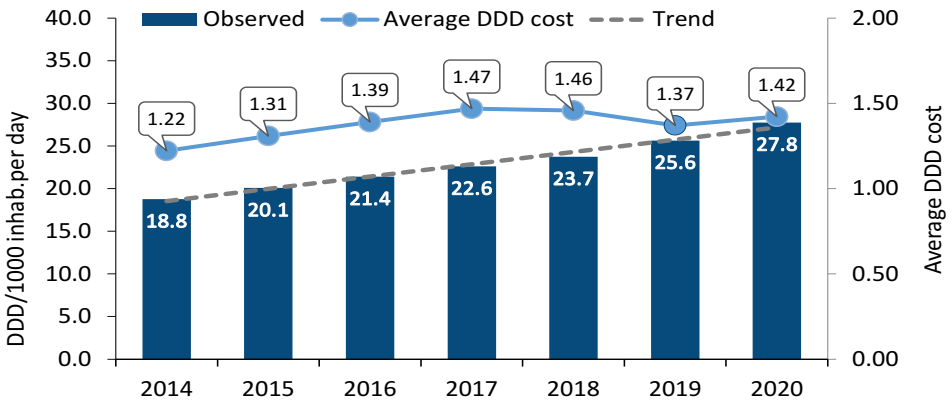


Table 3.5.1a. Anticoagulants, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
NOACs	9.33	14.0	35.6	13.9	17.5	43.4	1.84	-3.3
LMWH	3.94	9.6	-5.8	9.4	6.6	-0.6	1.15	2.5
Antithrombotic enzymes	0.27	1.9	2.0	0.0	4.1	4.3	793.65	-2.3
Fondaparinux	0.26	-6.3	0.0	0.5	-5.8	6.2	1.54	-0.7
Heparin and heparinoids	0.20	5.1	-10.9	0.4	1.6	-6.1	1.35	3.2
Monoclonal antibody	0.15	-	-	0.0	-	-	3233.51	-
Vitamin K antagonists	0.15	-12.0	-9.5	3.7	-12.0	-9.3	0.11	-0.2
Other antithrombotics	0.13	6.1	-	0.0	6.4	-	4048.3	-0.5
Antithrombotics - direct thrombin inhibitors	0.02	78.1	-18.1	0.0	313.1	-1.4	96.17	-57.0
Anticoagulants	**14.44**	**12.7**	**9.5**	**27.8**	**8.3**	**6.7**	**1.42**	**3.8**
enoxaparin	3.42	21.1	-2.4	8.5	11.3	2.2	1.10	8.5
rivaroxaban	3.15	19.6	34.2	5.1	22.1	42.1	1.69	-2.3
apixaban	2.88	6.1	53.1	4.1	11.1	63.7	1.93	-4.8
edoxaban	1.80	29.3	-	2.1	36.5	-	2.30	-5.6
dabigatran	1.50	3.9	12.6	2.6	6.9	22.4	1.60	-3.1
calcium nadroparin	0.39	-33.1	-16.8	0.6	-29.4	-14.4	1.87	-5.5
fondaparinux	0.26	-6.3	0.0	0.5	-5.8	6.2	1.54	-0.7
heparin	0.16	7.5	-7.5	0.4	2.1	-6.1	1.14	5.0
alteplase	0.16	-1.2	12.7	0.0	-0.8	12.7	817.92	-0.6
caplacizumab	0.15	-	-	0.0	-	-	3233.51	-

Table 3.5.1b. Anticoagulants, regional trend of weighted DDD/1000 inhab. per day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	16.8	17.8	18.7	20.6	21.8	23.9	28.6	19.7
Valle d'Aosta	18.6	19.7	20.8	21.1	22.6	24.7	28.3	14.3
Lombardy	16.9	18.5	20.0	20.8	22.4	24.1	27.2	12.8
A.P. of Bolzano	20.5	21.9	22.2	28.0	23.8	25.0	27.1	8.3
A.P. of Trento	22.9	22.0	24.4	25.0	28.1	31.0	36.3	17.3
Veneto	23.6	24.2	25.1	25.9	27.4	29.8	26.7	-10.6
Friuli VG	22.8	22.5	22.8	23.6	25.1	29.9	33.2	11.2
Liguria	22.7	23.9	25.0	26.2	28.0	29.5	32.8	11.3
Emilia R.	24.1	25.1	26.9	28.9	30.8	31.5	34.1	8.2
Tuscany	24.3	27.6	28.6	27.6	28.7	30.1	32.2	7.0
Umbria	23.6	25.7	27.5	29.2	31.5	32.5	34.4	5.9
Marche	16.0	19.8	25.4	27.9	25.7	29.8	34.2	14.6
Lazio	17.1	18.2	19.4	21.3	22.0	24.1	26.0	8.0
Abruzzo	17.5	18.6	19.7	21.2	22.8	24.1	28.5	18.3
Molise	16.1	17.1	17.5	19.0	20.3	21.3	24.7	15.8
Campania	14.4	15.9	17.0	18.1	19.1	21.5	23.8	10.8
Puglia	17.9	19.4	21.0	21.7	23.3	23.7	26.0	9.6
Basilicata	18.1	19.0	19.9	22.8	23.0	24.0	24.9	3.7
Calabria	17.9	19.4	20.1	21.5	21.1	23.0	23.1	0.5
Sicily	14.5	14.9	15.8	17.5	17.6	20.3	21.1	4.0
Sardinia	20.9	21.7	23.2	24.0	26.5	27.6	29.9	8.4
Italy	**18.8**	**20.1**	**21.4**	**22.6**	**23.7**	**25.6**	**27.8**	**8.3**
North	20.1	21.1	22.4	23.6	25.1	27.0	29.3	8.3
Centre	19.8	22.0	23.8	24.8	25.3	27.4	29.7	8.4
South and Islands	16.3	17.5	18.6	19.8	20.8	22.5	24.4	8.2

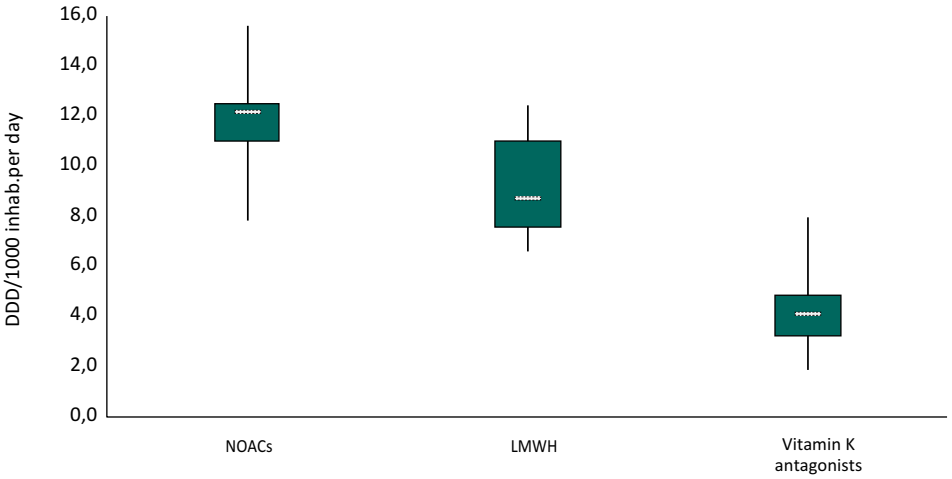
Table 3.5.1c. Prescription of anticoagulants with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	0.03	0.2	44.1	0.1	0.2	51.0	1.54
Generic	0.02	60.7	137.3	0.0	64.4	123.9	1.45
Ex originator	0.01	39.3	-10.4	0.0	35.6	-5.0	1.70
Patent covered	14.41	99.8	12.7	27.7	99.8	8.2	1.42
Anticoagulants	**14.44**	**100.0**	**12.7**	**27.8**	**100.0**	**8.3**	**1.42**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.5.1c. Anticoagulants, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure and adherence in population

Health Card data allowed to describe the trend in prevalence and consumption of anticoagulants by age class, gender and region and to calculate some indicators of intensity of use. The adherence and persistence of treatment were also estimated.

In 2020, exposure to anticoagulant drugs in the general population tends to increase with the age of patients for both genders, reaching a prevalence of use of almost 30% in men over 85, with higher use in men than in women for all age groups (Figure 3.5.1d).

The prevalence of use at the national level was 5.4%, with slightly higher values in the Regions of Central Italy (6.1%), compared to those of the South and North (5.3%) (Table 3.5.1d). The Veneto Region records the lowest prevalence values (4.5%), while Regions such as Liguria and Marche have the highest (6.8%); the median age of users is 73 years and each subject receives an average of 4.4 prescriptions and about 144 DDD of drug per year. Half of the exposed population is treated with a DDD value of 84, while 29.4% of users received only one prescription.

As regards the analysis of adherence and persistence to treatment with anticoagulant drugs, data refer to a cohort of new users of at least 45 years, who were monitored considering a one-year follow-up.

The study population includes 63,704 new users of anticoagulant drugs. The median age is 77 years (IQR 69-83), with a slightly higher proportion of men than women (51% vs 49%) (Table 3.5.1e). The percentage of subjects with high and low adherence to treatment with anticoagulants was 52% and 8.3%, respectively.

Low adherence increases with age, with the greatest percentage increase in subjects aged 75-84 and those aged 85 or older (8.2% vs 14.2%) and a higher percentage variation for subjects residing in the Regions of the Centre (Δ%= +80%). Similarly, the percentage of subjects with a coverage higher than 80% of the period considered (subjects with high adherence) increases up to 74 years of age, reaching 67.2%, and then decreases in subsequent age groups, settling on a value of 25.9% in subjects aged 85 years and over. In general, the percentage of subjects with high adherence is higher in men than in women (55.8% vs 47.9%) and this difference is more marked in the Northern Regions.

From a comparison of the 2020 adherence data compared to 2019 at national level, the percentage of subjects with low adherence decreased by -12%, while the percentage of subjects with high adherence increased by +5%; in both cases the most significant variations were observed in the Northern and Central Regions for all age groups, while in the South and in the Islands the variations are lower, with the exception of the extreme age groups.

Taking into account the persistence of treatment with anticoagulants (Table 3.5.1f), 63.1% of new users are still being treated 12 months after start of therapy. This means that one year after the start of treatment, 38% of subjects experience an interruption of at least 60 days. Higher probabilities of persistence after one year of treatment are observed for subjects aged between 65 and 74 years, in all the geographic areas considered. Minimal differences were found by gender, with men slightly more persistent than women (63.8% vs 62.3%). Taking into account the median time to discontinuation of treatment, 50% of subjects discontinue anticoagulant therapy after 273 days.

Comparing the persistence data between 2019 and 2020, it is possible to observe an increase in the percentage of persistent subjects at 12 months both in the Northern regions (+6%) and in the Centre (+4), while conversely the South recorded a decrease (-3%).

Figure 3.5.1d. Distribution of prevalence of use and consumption of anticoagulants under NHS outpatient care and per conto distribution (year 2020)

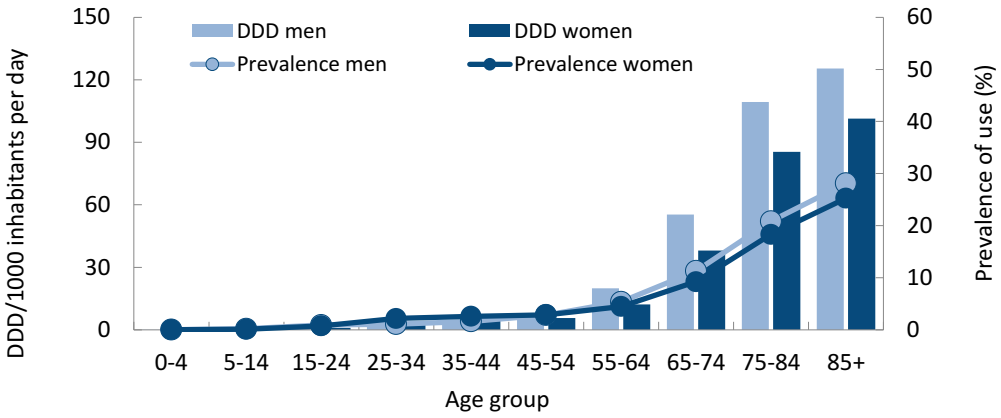


Table 3.5.1d. Exposure and duration of therapy with anticoagulants by Region under approved care regime and per conto distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	5.0	0.97	75	4.1	151.4	120.0	27.8
Valle d'Aosta	5.4	1.03	73	3.7	146.6	90.0	29.0
Lombardy	5.6	0.95	72	3.8	144.9	80.0	32.2
A.P. of Bolzano	4.8	1.06	74	3.7	153.8	120.0	26.3
A.P. of Trento	5.7	1.02	71	3.9	136.9	80.0	30.9
Veneto	4.5	1.07	76	4.3	173.1	153.0	23.0
Friuli VG	5.3	1.03	76	4.6	183.8	162.0	19.5
Liguria	6.8	0.91	76	4.4	146.8	84.0	29.3
Emilia R.	5.0	0.97	75	3.9	150.7	112.0	30.2
Tuscany	6.1	0.89	75	4.3	129.1	72.0	29.5
Umbria	6.7	0.91	76	6.0	165.2	120.0	21.9
Marche	6.8	0.87	75	4.6	140.0	80.0	30.9
Lazio	5.7	0.87	72	5.2	140.4	80.0	30.3
Abruzzo	6.1	0.88	73	4.2	136.0	72.0	31.0
Molise	5.4	0.83	74	4.2	134.0	80.0	26.9
Campania	5.6	0.78	69	4.8	122.5	60.0	33.2
Puglia	5.0	0.86	74	4.6	150.1	112.0	26.3
Basilicata	6.1	0.77	73	5.3	143.0	80.0	25.3
Calabria	5.3	0.82	72	4.6	133.3	72.0	29.9
Sicily	4.6	0.85	73	3.7	131.8	64.0	32.8
Sardinia	5.6	0.91	73	5.8	161.1	112.0	22.6
Italy	**5.4**	**0.91**	**73**	**4.4**	**144.1**	**84.0**	**29.4**
North	5.3	0.98	74	4.0	152.9	110.0	28.9
Centre	6.1	0.88	74	4.9	138.8	80.0	29.4
South and Islands	5.3	0.83	72	4.6	135.7	72.0	30.1

Table 3.5.1e. Indicators of adherence to treatment with anticoagulants in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=63,704		North‡ N=29,050		Centre N=14,169		South N=20,485	
Low adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	5.1	-24	4.0	-1	7.4	-31	5.2	-32
55-64 years	5.5	-11	4.3	-16	6.4	-27	6.6	7
65-74 years	5.4	-19	4.2	-31	6.2	-22	6.2	-4
75-84 years	8.2	-10	7.6	-18	8.6	-17	9.1	6
≥85 years	14.2	-10	13.5	-13	15.5	-14	14.3	-1
Women	9.1	-14	8.3	-20	10.5	-21	9.3	-1
Men	7.5	-10	6.6	-17	8.1	-14	8.3	1
Total	**8.3**	**-12**	**7.4**	**-18**	**9.3**	**-18**	**8.8**	**0**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	62.7	0	63.5	-4	60.8	8	62.6	1
55-64 years	66.1	2	66.1	1	64.2	5	67.2	1
65-74 years	67.2	5	68.3	8	65.4	9	66.9	0
75-84 years	50.1	7	51.9	10	48.8	8	48.1	1
≥85 years	25.9	2	27.9	6	25.4	11	23.3	-11
Women	47.9	4	48.4	7	46.1	9	48.6	-1
Men	55.8	5	57.5	8	53.4	8	55.0	0
Total	**52.0**	**5**	**53.2**	**7**	**49.8**	**8**	**51.8**	**0**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

N: refers to new users, subjects who received a first prescription in the period 01/10/2019- 31/12/2019, 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): 334 (298-351)

‡ Excluding Emilia Romagna.

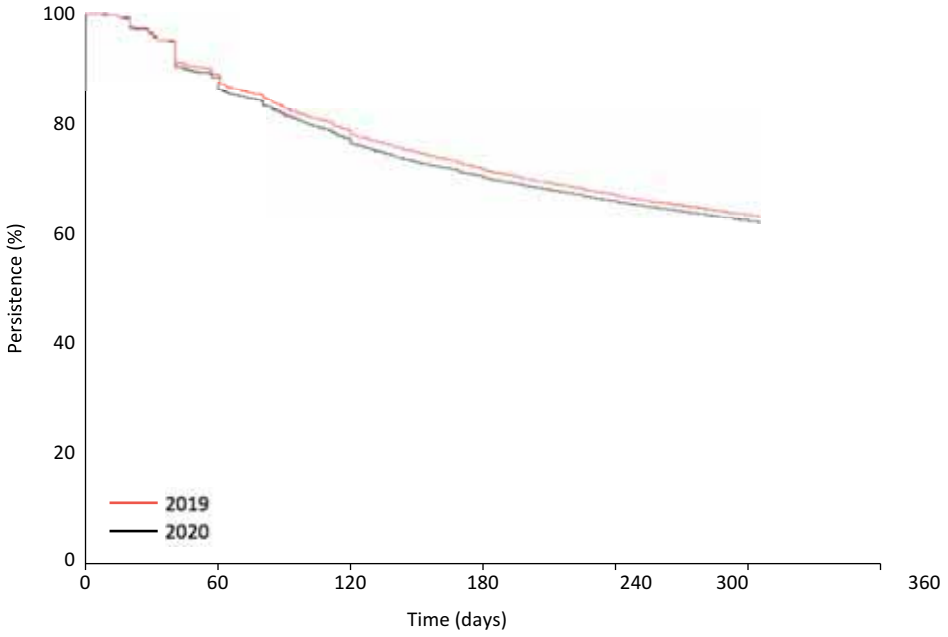
Table 3.5.1f. Persistence after one year of treatment with anticoagulants in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=63,704		North‡ N=29,050		Centre N=14,169		South N=20,485	
Persistence at 12 months	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	56.1	0	54.7	-2	56.7	20	57.8	-5
55-64 years	62.6	1	60.8	4	59.9	4	66.4	-2
65-74 years	68.8	3	68.6	6	64.6	5	71.7	-2
75-84 years	64.9	2	64.0	8	61.2	2	68.9	-3
≥85 years	53.8	0	52.3	7	51.8	3	57.6	-8
Women	62.3	2	60.7	6	58.6	4	66.7	-3
Men	63.8	2	63.2	6	60.7	3	66.9	-4
Total	**63.1**	**2**	**62.0**	**6**	**59.7**	**4**	**66.8**	**-3**

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

‡ Excluding Emilia Romagna.

Figure 3.5.1e. Time (in days) to discontinuation of treatment with anticoagulants in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods) For this reason, no interruptions can be observed in the last 60 days from the end of follow-up (365 days)

Key message

- Starting from 2014, Italy has seen **a significant increase in the consumption of anticoagulants** (CAGR: + 6.7%), reaching 27.8 DDD/1000 inhabitants per day in 2020. At the same time, per capita expenditure increased by +12.7% compared to 2019, also considering that none of the drugs with the highest consumption and expenditure (NOACs) are yet patent-expired. Among the NOACs, the greatest increase in expenditure and consumption is observed for those administered as a single daily dose, i.e. rivaroxaban and epixaban.
- In 2020, **the difference between the region with the highest consumption compared to the one with the lowest consumption** was 15.2 DDD/1000 inhabitants per day, +24% compared to 2019 (12.2 DDD/1000 inhabitants per day) and +53.5% compared to 2014 (9.9 DDD/1000 inhabitants per day). This variability is also found in the prescribing pattern and cannot be explained by geographic differences in the prevalence of clinical indications associated with these drugs, but rather in the variability of the proportion of under/overuse of anticoagulants in stroke prevention in patients with atrial fibrillation.
- 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, in the over 85s, only 25.9% showed high adherence. This data is comparable to the **persistence** analysis of the treatment where the same trend is observed.
- It is likely that the adherence analysis is strongly conditioned by the **different clinical indications** and that the adherence observed in the over 85s is due to a higher prevalence of indications other than stroke prevention in atrial fibrillation. In fact, the recommendations for the continued use of anticoagulants mainly concern the prevention of ischemic stroke in patients with atrial fibrillation. Conversely, oral anticoagulants or low molecular weight heparins are recommended in the prophylaxis of non-surgical patients at increased risk of venous thromboembolism for a treatment period generally not exceeding six months as well as in post-surgical prophylaxis for a period not exceeding 28 days.

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3.5.2. Coagulation factors

National data on consumption and expenditure

In 2020, expenditure for coagulation factors reached 9 euros per capita, with a 3.6% increase compared to 2019 and a 21% increase if compared to 2014, corresponding to a 3.2% average annual growth rate (CAGR). The average cost per day of therapy also increased in the same period (+21.6%), shifting from 415.5 euros to 433.0 euros in 2020 (Figure and Table 3.5.2a). Short acting recombinant drugs for the treatment of haemophilia A are the most expensive category, with a per capita value of 3.85 euros, a 9.3% decrease, and an average cost of 339.36 euros, which decreased by 1.8% compared to the previous year. Even plasma-derived drugs for haemophilia A have recorded a clear decrease in expenditure by 7% and a 1.1% reduction in the average cost per DDD. On the other hand, a 17.0% increase was recorded in expenditure for long-acting recombinant drugs for haemophilia A, which in 2020 reported a value of 1.58 euros per capita. This increase seems to be linked to an increase in consumption (+16.9%), with a substantial stability of the average cost per DDD (342.23 euros, -0.2% compared to 2019).
In 2020 the monoclonal antibody emicizumab reported an increase by over 100% compared to the previous year, both in expenditure (0.75 euros per capita in 2020) and in consumption, although there was a decrease by about 25% in the average cost per DDD (784.9 euros in 2020). 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.
Within the coagulation factors for the treatment of haemophilia B, long-acting recombinant drugs record the highest per capita expenditure, with 1.03 euros, a +8.9% increase compared to 2019, thus ranking third for expenditure in the category of coagulation factors. Particularly interesting is the expenditure reduction recorded for short-acting recombinant factors used in the treatment of both haemophilia A and haemophilia B.
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, with 2.37 euros, is the molecule with the highest expenditure, although with a 13.8% decrease compared to the previous year, and efmorocotog alfa, with a per capita expenditure of 1.04 euros and a 9.3% increase.
Short-acting recombinant coagulation factors for the treatment of haemophilia A, in addition to recording the highest expenditure, are the group of drugs recording the largest regional variability of per capita expenditure, highlighted by the wide range of values found in the different Italian regions (1.26-7.80 euros) (Figure 3.5.2c).

Figure 3.5.2a. Coagulation factors, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

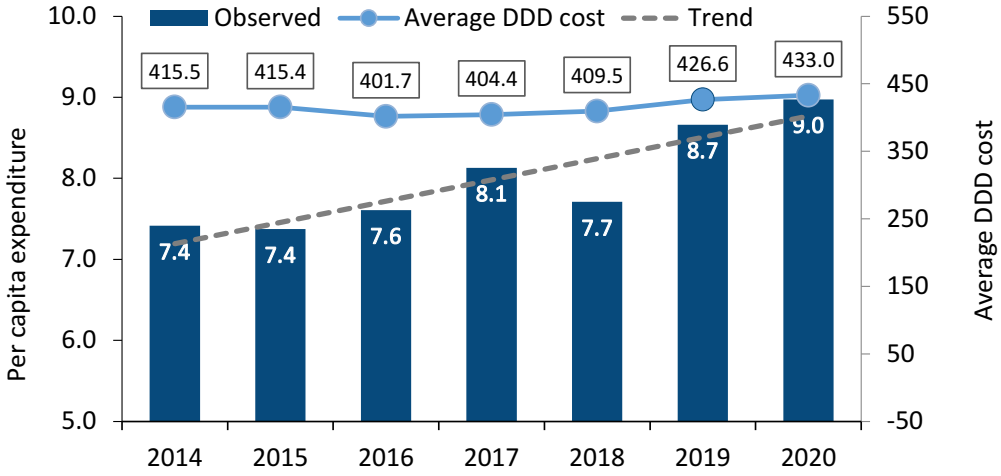


Table 3.5.2a. Coagulation factors, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

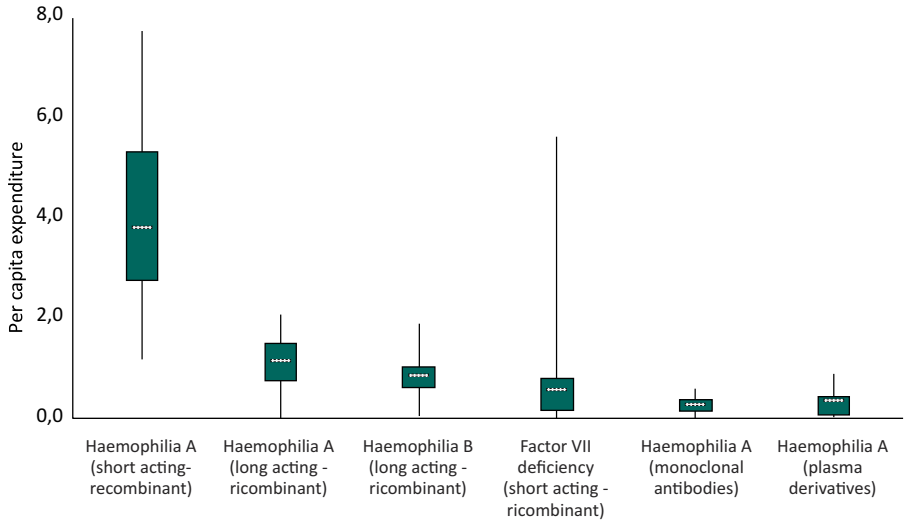
Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Haemophilia A (short acting-recombinant)	3.85	-9.3	-3.2	0.03	-7.9	-2.2	339.36	-1.8
Haemophilia A (long acting-recombinant)	1.58	17.0	-	0.01	16.9	-	342.23	-0.2
Haemophilia B (long acting-recombinant)	1.03	8.9	-	<0,05	8.0	-	884.17	0.5
Factor VII deficiency (short acting-recombinant)	0.83	0.7	-2.9	<0,05	0.9	-1.4	4077.83	-0.5
Haemophilia A (monoclonal antibodies)	0.75	>100	-	<0,05	>100	-	784.88	-25.0
Haemophilia A (plasma derivatives)	0.37	-7.0	-7.4	<0,05	-6.2	-6.8	256.99	-1.1
Haemophilia B (short acting-recombinant)	0.21	-17.5	-15.8	<0,05	-18.0	-16.1	378.82	0.4
Activated human antihemophilic prothrombin complex	0.17	-6.8	-14.0	<0,05	-2.9	-14.0	11053.48	-4.3
Factor VII deficiency (plasma derivatives)	0.06	-13.3	5.8	<0,05	-20.4	4.5	386.67	8.5
Combination of coagulation factors (plasma derivatives)	0.04	7.8	7.6	<0,05	8.7	7.0	106.56	-1.0
Other deficiencies of coagulation factors (long-acting, recombinant)	0.04	-7.6	42.8	<0,05	-7.8	38.5	15524.20	0.0
Haemophilia B (plasma derivatives)	0.01	-5.5	-10.6	<0,05	-6.9	-13.4	231.04	1.3
Other deficiencies of coagulation factors (plasma derivatives)	0.01	3.7	-	<0,05	2.6	-	5488.41	0.8
Von Willebrand's disease (plasma derivatives)	0.01	-	-29.7	<0,05	-	-29.7	71.83	-
Coagulation factors	**8.97**	**3.6**	**3.2**	**0.06**	**1.8**	**2.5**	**432.97**	**1.5**
octocog alfa	2.37	-13.8	-6.9	0.02	-12.7	-5.7	335.18	-1.5
efmorocotog alfa	1.04	9.3	-7.4	0.01	7.4	-7.4	356.62	1.5
activated heptacog alfa (recombinant DNA coagulation factor VII)	0.83	0.7	-2.9	<0,05	0.9	-1.4	4077.83	-0.5
moroctocog alfa	0.77	-4.0	-4.9	0.01	-2.8	-3.9	343.76	-1.5
emicizumab	0.75	>100	-7.4	<0,05	>100	-7.4	784.88	-25.0
albutrepenonacog alfa	0.73	9.1	-7.4	<0,05	8.9	-7.4	1088.43	0.0
turoctocog alfa	0.43	-4.1	-7.4	<0,05	-0.2	-7.4	334.25	-4.2
lonoctogoc alfa	0.40	-0.5	-7.4	<0,05	-0.3	-7.4	324.15	-0.6
factor VIII/von Willebrand's factor	0.37	-7.2	-6.6	<0,05	-6.4	-5.9	258.01	-1.1
eftrenonacog alfa	0.28	10.8	-7.4	<0,05	11.2	-7.4	667.15	-0.6

Table 3.5.2b. Coagulation factors, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	7.9	7.1	6.7	8.0	7.2	7.1	7.4	3.3
Valle d'Aosta	3.3	2.4	2.9	5.5	4.6	4.6	3.7	-19.5
Lombardy	5.5	5.6	5.7	5.8	6.3	7.0	7.9	12.0
A.P. of Bolzano	5.8	3.9	4.7	4.6	3.7	4.1	6.0	45.1
A.P. of Trento	4.5	4.5	4.8	4.2	4.6	4.9	4.5	-7.4
Veneto	4.7	4.5	4.7	5.9	4.8	6.4	6.6	3.0
Friuli VG	9.0	11.5	12.8	13.0	6.7	8.7	7.9	-9.0
Liguria	4.9	5.1	5.1	5.4	5.5	6.8	7.8	14.3
Emilia R.	6.0	5.6	6.5	7.0	6.3	7.6	7.5	-1.6
Tuscany	7.2	6.7	6.7	6.7	5.9	7.0	9.0	29.5
Umbria	3.5	4.0	4.5	5.4	5.6	5.8	6.2	5.9
Marche	6.5	5.6	5.0	5.9	5.3	5.8	5.7	-1.4
Lazio	9.4	9.7	10.2	10.5	10.3	11.9	11.4	-4.4
Abruzzo	8.1	8.0	7.8	9.9	9.4	12.0	11.2	-7.0
Molise	5.6	7.5	5.1	6.3	7.1	6.0	5.4	-10.0
Campania	11.5	11.7	11.1	11.9	11.2	12.6	13.8	9.5
Puglia	9.8	9.7	10.3	10.7	10.7	11.3	11.5	1.5
Basilicata	6.1	6.5	6.4	6.2	7.6	9.7	7.7	-21.2
Calabria	9.1	9.5	11.3	12.4	13.4	14.1	11.2	-20.7
Sicily	8.4	8.3	9.2	9.2	8.9	9.4	9.9	5.0
Sardinia	5.7	6.0	5.4	5.4	4.8	5.0	5.7	12.3
Italy	**7.4**	**7.4**	**7.6**	**8.1**	**7.7**	**8.7**	**9.0**	**3.6**
North	6.0	5.8	6.1	6.6	6.1	7.0	7.4	5.7
Centre	7.9	7.8	8.0	8.3	7.9	9.0	9.5	4.8
South and Islands	9.2	9.3	9.6	10.1	9.9	10.8	11.0	1.1

Figure 3.5.2c. Coagulation factors, regional trend of 2020 weighted per capita expenditure by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- In 2020 coagulation factors recorded an **increase in overall per capita expenditure** (+3.6%), corresponding to a modest increase in consumption (+1.8%).
- **Short-acting recombinant drugs** for both the treatment of haemophilia A and haemophilia B have recorded a reduction in consumption; on the other hand, the consumption has increased of **long-acting recombinant factors**, which, through a better pharmacokinetic profile compared to short-acting formulations, allow to lenghten the interval between infusions with greater safety margins against haemorrhagic episodes, thus improving adherence to prophylaxis and the quality of life of patients.
- No reduction in consumption was observed for all **anti-haemophilic coagulation factors** (factor VIII and factor IX, including the monoclonal antibody emicizumab), as it could be expected due to the COVID-19 epidemiological emergency. Probably, the extension of the validity period of the AIFA therapeutic plans has allowed patients to continue the therapy even though they could not go to hospitals, where the treatment plans are provided.
- The **regional variability** is wide, but the pattern is in line with current knowledge on consumption of these drugs in Italy. The Regions of the South and Islands spend more than the Regions of the Centre and the North. Regions such as Lazio and Campania confirm in the first ranks for the expenditure of these drugs.

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3.5.3. Platelet aggregation inhibitors

National data on consumption and expenditure

Consumption of antiplatelet agents has been almost stable over the last seven years, reaching 70.3 DDD/1000 inhabitants per day in 2020 (CAGR 2014-2020: +0.5%). In the same period, the average cost per DDD was between 0.20 euros and 0.21 euros (Figure 3.5.3a). Overall, per capita expenditure was 5.48 euros in 2020, a slight decrease compared to the previous year (-0.6% and CAGR 2014-2020 +2.0%). P2Y12 platelet receptor inhibitors have the highest per capita expenditure, equal to 1.50 euros (-1.8% compared to 2019), mostly attributable to clopidrogrel (1.27 euros, + 0.5% compared to 2019), while the subgroup of acetylsalicylic acid plain or in combination has the highest consumption, reaching 54.4 DDD per 1000 inhabitants per day, mainly attributable to acetylsalicylic acid plain (45.8 DDD) (Table 3.5.3a). For this group of medicines, we may find the greatest regional variability in consumption, highlighted by the wide range of values (35.78-76.48 DDD/1000 inhabitants per day), probably due to the different share of private purchases of these drugs in the different Regions (Figure 3.5.3c).

The combination acetylsalicylic acid/clopidrogrel ranks fifth in the most consumed drugs, reaching 2.1 DDD in 2020 (+3.8% compared to 2019), with an average cost per day of therapy of 0.56 euros.

Ticagrelor, another P2Y12 platelet receptor inhibitor used in combination with acetylsalicylic acid for the prevention of athero-thrombotic events in patients at risk, ranks third for expenditure (1.02 euros per capita) and consumption (1.1 DDD), recording the highest average annual growth rate (CAGR) compared to 2014, both in terms of expenditure (+ 12.1%) and consumption (14.1%).

Patent-expired drugs represent almost 84% of doses and about 47% of the category expenditure, 19.5% of which refers to generic products (Table 3.5.3c).

Figure 3.5.3a. Platelet aggregation inhibitors, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

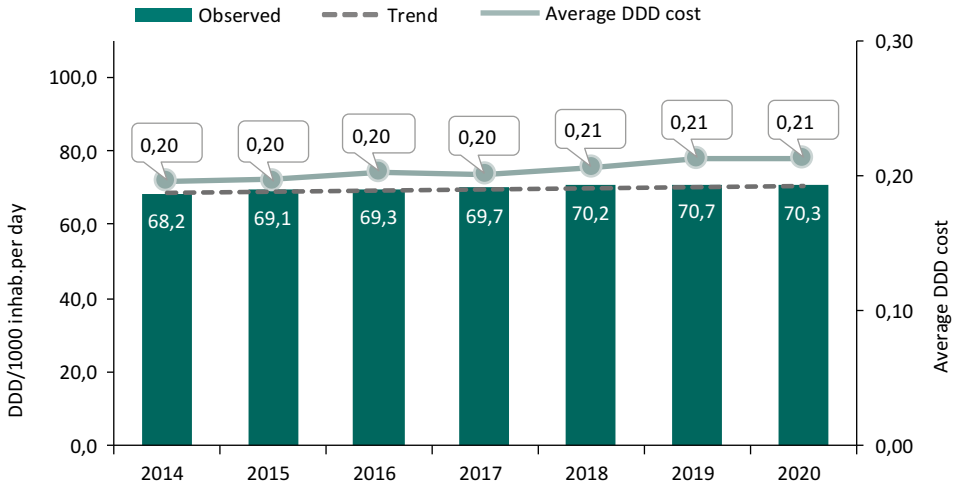


Table 3.5.3a. Platelet aggregation inhibitors, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
P2Y12 platelet receptor inhibitors	1.50	-1.8	-0.9	12.7	-2.7	0.9	0.32	0.9
Acetylsalicylic acid plain and in combination	1.46	-1.6	-0.4	54.4	-0.3	0.0	0.07	-1.3
Other platelet aggregation	1.04	-3.8	4.1	0.0	-5.1	-1.7	152.94	1.4
Ticagrelor	1.02	6.9	12.1	1.1	4.8	14.1	2.45	2.0
Acetylsalicylic acid/clopidogrel	0.43	0.8	6.2	2.1	3.8	8.8	0.56	-2.9
Glycoprotein IIb/IIIa inhibitors	0.03	-28.8	-25.2	0.0	-19.5	-6.7	88.55	-11.6
Platelet aggregation inhibitors	**5.48**	**-0.6**	**2.0**	**70.3**	**-0.6**	**0.5**	**0.21**	**0.0**
clopidogrel	1.27	0.5	4.1	10.7	-0.6	7.1	0.33	1.1
acetylsalicylic acid	1.18	0.7	1.5	45.8	0.3	0.8	0.07	0.4
ticagrelor	1.02	6.9	12.1	1.1	4.8	14.1	2.45	2.0
treprostinil	0.62	-2.1	4.2	0.0	5.9	6.1	556.21	-7.6
clopidogrel/acetylsalicylic acid	0.43	0.8	6.2	2.1	3.8	8.8	0.56	-2.9
acetylsalicylate lysine	0.22	-1.9	-2.4	7.1	-1.5	-1.8	0.08	-0.4
selexipag	0.20	36.5	-	0.0	71.0	-	118.90	-20.1
ticlopidine	0.17	-13.1	-13.7	1.9	-13.4	-13.9	0.25	0.3
iloprost	0.17	-30.6	-7.0	0.0	-30.4	-6.6	102.96	-0.3
acetylsalicylic acid/magnesium hydroxide/algeldrate	0.06	-9.4	-9.2	1.5	-9.5	-9.3	0.11	0.0

Table 3.5.3b. Platelet aggregation inhibitors, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	73.1	72.5	72.9	72.9	73.1	73.2	67.9	-7.2
Valle d'Aosta	75.7	75.5	57.4	60.2	59.5	61.4	58.0	-5.5
Lombardy	48.6	49.6	49.5	49.3	49.0	49.1	48.4	-1.4
A.P. of Bolzano	50.3	49.0	47.7	47.1	47.1	45.9	45.1	-1.7
A.P. of Trento	75.7	76.9	76.3	77.7	77.2	76.2	75.7	-0.7
Veneto	43.9	47.1	49.5	49.3	50.0	49.5	48.0	-3.0
Friuli VG	77.1	76.3	74.9	74.4	74.9	72.9	61.8	-15.1
Liguria	61.4	60.1	58.0	58.5	58.1	58.5	56.7	-3.0
Emilia R.	87.0	86.1	83.1	85.4	85.0	84.2	83.8	-0.4
Tuscany	79.4	77.9	76.9	74.4	74.4	73.7	74.4	1.0
Umbria	76.7	77.0	76.9	76.5	75.8	76.1	76.5	0.5
Marche	78.9	81.5	83.9	84.6	84.8	85.2	86.2	1.2
Lazio	73.6	76.0	76.9	78.1	78.9	80.8	80.7	-0.1
Abruzzo	85.5	86.6	87.8	88.4	89.8	90.7	92.1	1.5
Molise	87.8	86.8	87.2	89.1	90.5	92.0	89.4	-2.8
Campania	61.2	63.5	64.8	66.3	69.5	71.7	72.3	0.8
Puglia	81.3	83.5	84.1	85.0	85.8	88.1	89.0	1.1
Basilicata	77.6	77.3	77.4	78.2	79.1	80.9	83.9	3.7
Calabria	81.4	81.6	83.4	82.8	85.3	88.2	89.2	1.1
Sicily	71.5	73.2	74.5	75.7	76.7	80.0	81.4	1.8
Sardinia	77.8	77.1	75.3	75.1	74.5	73.3	74.1	1.1
Italy	**68.2**	**69.1**	**69.3**	**69.7**	**70.2**	**70.9**	**70.3**	**-0.8**
North	60.8	61.3	61.0	61.2	61.2	60.9	58.8	-3.4
Centre	76.4	77.4	77.8	77.6	78.0	78.7	79.1	0.4
South and Islands	73.5	75.0	75.9	76.8	78.4	80.5	81.5	1.2

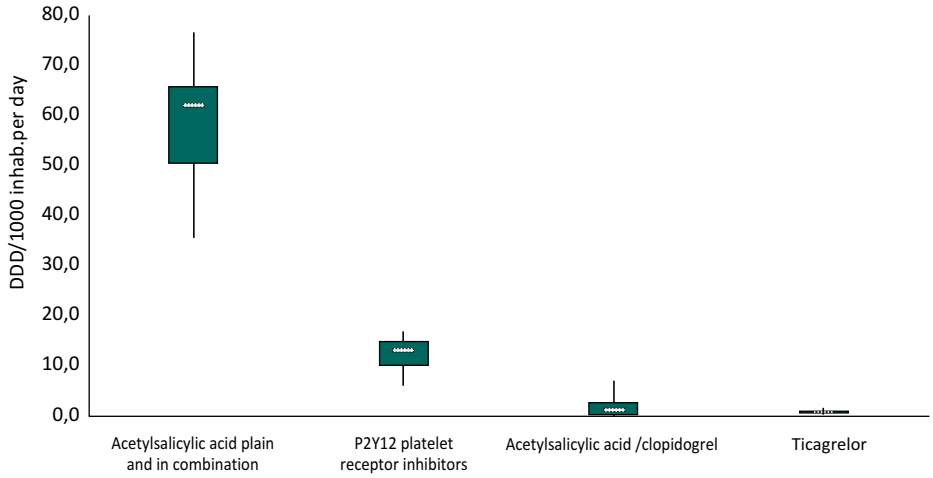
Table 3.5.3c. Prescription of platelet aggregation inhibitors with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	2.71	49.4	2.0	58.8	83.6	0.0	0.13
Generic	0.68	25.2	-3.8	18.3	31.2	-4.5	0.10
Ex originator	2.03	74.8	4.0	40.5	68.8	2.2	0.14
Patent covered	2.77	50.6	-3.0	11.5	16.4	-5.1	0.66
Platelet aggregation inhibitors	**5.48**	**100.0**	**-0.6**	**70.3**	**100.0**	**-0.8**	**0.21**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.5.3c. Platelet aggregation inhibitors, regional variability of 2020 consumption (weighted DDD/1000 inhab. per day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure and adherence in population

Health Card data allowed to describe the trend in prevalence and consumption of platelet aggregation inhibitors by age group, gender and region and to calculate some indicators of intensity of use. The adherence and persistence of treatment were also estimated.

In 2020, exposure to platelet aggregation inhibitors in the general population tends to increase with the age of patients for both genders, reaching a higher prevalence of use in men aged between 75 and 84 years; men also consume more doses than women (Figure 3.5.3d). The prevalence of use nationwide was 9.1%, with higher values in the South and the Islands (10.6%) and in the Centre (10.3%), compared to the North (7.5%) (Table 3.5.3d). The A.P. of Bolzano records the lowest prevalence values (5.1%), Molise the highest (12.7%); the median age of users is 74 years and each subject receives an average of 5.5 prescriptions and 270.0 DDD of drug. Half of the exposed population is treated with a DDD value of 300.0, while 10.7% of users received only one prescription.

As for the adherence and persistence analyses, the exposure data refer to a cohort of new users aged at least 45 years, who were monitored considering a one-year follow-up.

The study population includes 163,285 new users, with a median age of 71 years (IQR 63-79) and a greater proportion of women than men (8.4% vs 6.9%).

The percentage of subjects with high and low adherence to antiplatelet treatment was 59.7% and 7.7%, respectively (Table 3.5.3e). The percentage of subjects with low adherence tends to increase with age, recording the highest value in the over 85-age group (8.3%) and in women rather than men (8.4% vs 6.3%). Stratifying by age and geographic area, the highest percentage of subjects with low adherence is observed in the over 85-age group and in the regions of Southern Italy (10.6%). On the contrary, high adherence tends to decrease with increasing age, with a higher value in the 45-54 age group (62.8%) and more in men than in women (62.5% vs 56.8%). Users residing in Northern Italy and aged between 45 and 54 have the highest adherence (69.9%).

From a comparison of the 2020 adherence data compared to 2019, Southern regions show an increase in the percentage of subjects with high adherence (+2%) and a reduction in the percentage of subjects with low adherence (-5%), both above the national average (+1% and -3%, respectively).

Analysing the persistence to treatment with platelet aggregation inhibitors (Table 3.5.3f.), about half of the new users are found to be persistent to treatment after one year (52%), with higher percentages in the Northern regions (55%) compared to those in the Centre (51%) and the South (49%). These data, that are substantially comparable to those of 2019, indicate that one year after start of treatment, about 49% of users stop therapy for at least 60 days. Men showed higher persistence rates than women (55% vs 48%).

Comparing the persistence data between 2019 and 2020, no obvious differences are found and it is possible to note that, for these drugs, the median time to discontinuation of treatment is higher than 365 days.

Figure 3.5.3d. Distribution of prevalence of use and consumption of platelet aggregation inhibitors under approved care regime and per conto distribution (year 2020)

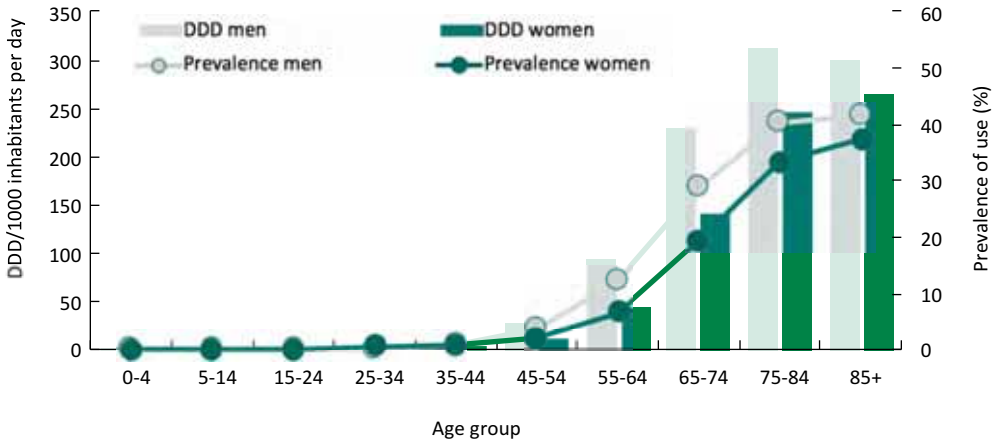


Table 3.5.3d. Exposure and duration of therapy with platelet aggregation inhibitors by Region under approved care regime and per conto distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	DDD median	Users with 1 prescription (%)
Piedmont	9.5	1.22	74	5.1	268.1	300.0	9.9
Valle d'Aosta	7.9	1.07	76	4.7	274.7	300.0	11.7
Lombardy	6.2	1.28	75	4.7	281.1	300.0	12.2
A.P. of Bolzano	5.1	1.13	76	4.6	275.8	300.0	11.3
A.P. of Trento	8.7	1.12	74	5.2	295.3	300.0	7.6
Veneto	5.7	1.42	74	4.9	284.8	300.0	9.6
Friuli VG	9.1	1.16	75	5.2	289.1	300.0	8.3
Liguria	8.5	0.99	78	5.2	251.2	270.0	12.4
Emilia R.	9.9	1.12	74	5.1	276.7	300.0	9.5
Tuscany	10.0	1.10	76	5.4	263.3	300.0	12.2
Umbria	10.0	1.18	76	7.4	279.3	300.0	7.1
Marche	11.1	1.17	75	5.4	262.6	290.0	8.6
Lazio	10.3	1.08	74	5.4	276.5	300.0	10.8
Abruzzo	12.2	1.10	74	5.9	276.2	300.0	8.6
Molise	12.7	1.07	73	5.6	265.6	300.0	9.1
Campania	9.7	1.08	72	6.4	247.3	270.0	13.2
Puglia	11.5	1.12	73	5.4	263.7	300.0	11.4
Basilicata	11.5	1.06	73	7.0	264.5	300.0	9.5
Calabria	11.5	1.02	73	6.1	267.0	300.0	10.8
Sicily	10.3	1.02	74	5.8	266.9	300.0	10.4
Sardinia	9.5	1.05	74	6.5	286.0	300.0	7.5
Italy	**9.1**	**1.13**	**74**	**5.5**	**270.0**	**300.0**	**10.7**
North	7.5	1.21	75	5.0	276.9	300.0	10.5
Centre	10.3	1.11	75	5.6	270.8	300.0	10.6
South and Islands	10.6	1.06	73	6.0	263.1	300.0	11.0

Table 3.5.3e. Indicators of adherence to treatment with platelet aggregation inhibitors in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=163,285		North N=62,929		Centre N=34,941		South N=65,415	
Low adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	7.3	-5	4.5	8	7.3	2	9.5	-10
55-64 years	7.4	2	4.7	5	6.9	4	9.9	1
65-74 years	7.4	-6	5.0	-9	7.5	-2	9.3	-5
75-84 years	8.0	0	6.0	5	8.3	6	10.3	-5
≥85 years	8.3	-9	5.9	-13	9.5	-2	10.6	-8
Women	8.4	-4	6.0	-4	8.4	-2	10.7	-5
Men	6.9	-2	4.7	1	7.3	5	9.0	-4
Total	**7.7**	**-3**	**5.3**	**-1**	**7.8**	**1**	**9.8**	**-5**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	62.8	1	69.9	0	61.3	-4	57.7	4
55-64 years	61.8	0	68.9	1	61.3	-1	56.2	1
65-74 years	60.1	1	65.5	0	60.1	1	55.6	1
75-84 years	58.2	0	62.3	-1	56.9	0	54.1	2
≥85 years	56.4	2	60.8	1	54.3	1	52.0	3
Women	56.8	1	61.8	0	56.2	-1	52.5	2
Men	62.5	0	67.7	0	61.6	1	57.9	1
Total	**59.7**	**1**	**64.9**	**0**	**58.9**	**0**	**55.2**	**2**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

N: refers to new users, subjects who received a first prescription in the period 01/10/2019- 31/12/2019, 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): 321 (259-345)

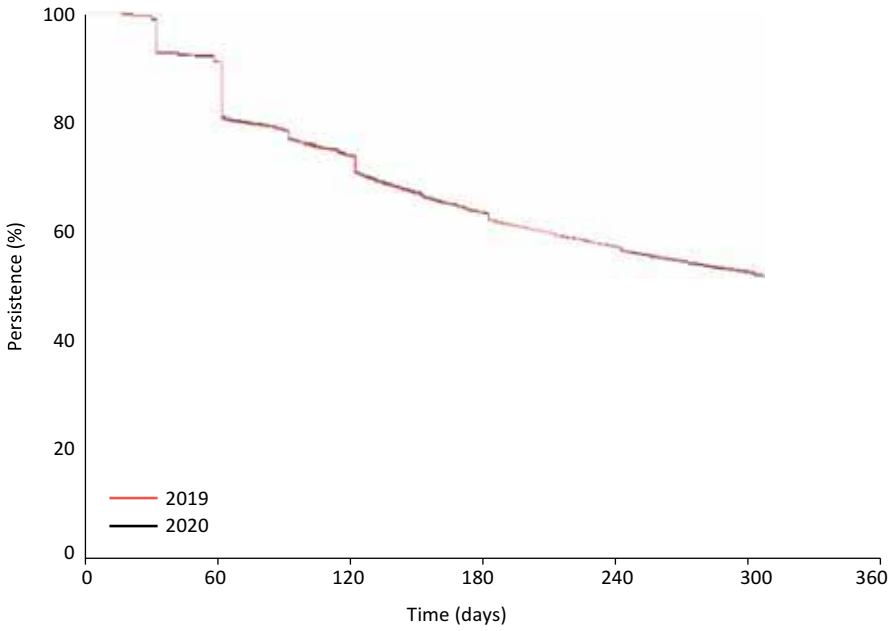
Table 3.5.3f. Persistence after one year of treatment with platelet aggregation inhibitors in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=163,285		North N=62,929		Centre N=34,941		South N=65,415	
Persistence at 12 months	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	54	2	60	1	52	-3	50	5
55-64 years	55	2	61	2	54	1	50	3
65-74 years	53	0	57	0	52	-1	50	1
75-84 years	50	-1	52	-2	49	-1	47	1
≥85 years	47	1	50	2	44	-2	45	2
Women	48	1	52	0	47	-1	46	2
Men	55	1	59	0	54	0	52	2
Total	**52**	**1**	**55**	**0**	**51**	**-1**	**49**	**2**

Note: persistence to treatment was evaluated only for new users with at least 2 prescriptions. An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods)

‡ Excluding Emilia Romagna.

Figure 3.5.3e. Figure 3.3.1e Time (in days) to discontinuation of treatment with platelet aggregation inhibitors in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details refer to statistical methods) For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days)

Key message

- **Consumption of platelet aggregation inhibitors** appears rather stable over the years considered (2014-2020), with 70.3 DDD/1000 inhabitants per day in 2020. However, compared to 2019, within the category a slight reduction is observed in expenditure and consumption of P2Y12 platelet receptor inhibitors (expenditure: -1.8%; consumption: -2.7%) and of acetylsalicylic acid plain or in combination (expenditure: -1.6%; consumption: - 0.3%), offset by a marked increase of ticagrelor.
- **Ticagrelor** is the platelet aggregation inhibitor with the greatest increase in expenditure (CAGR: +12.1%) and consumption (CAGR: +14.1%) in the 2014-2020 period. It is used in co-administration with ASA in the prevention of atherothrombotic events in patients with acute coronary syndrome. Ticagrelor requires two daily administrations and has a higher cost than other drugs of the same class.
- The analysis of the consumption of platelet aggregation inhibitors indicates a **preferential use of monotherapy or concomitant therapy based on clopidogrel and/or 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 the measures chosen by the doctor to minimise the risk of bleeding include the flexible use of dual therapy with the possibility of modulating the dose and duration of treatment of the individual molecules.
- 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 (Abruzzo: 92.1 DDD/1000 inhabitants per day vs AP of Bolzano: 45.1 DDD/1000 inhabitants per day). As regards the prevalence of use, the highest value was recorded in Molise (12.7%) and the lowest in the AP of Bolzano (5.1%). As already observed for anticoagulants, this variability is attributable to the different proportion of under/overuse of these drugs both in secondary prevention in patients with ACS and in primary prevention in patients with high cardiovascular risk.
- Despite significant geographic differences (North: 64.9% vs South and Islands: 55.2%), there is a proportion of subjects with optimal adherence around 60%. Unlike other therapeutic categories, **no significant reductions are observed with increasing age.** In fact, in the over 85s the proportion of subjects with high adherence remains above 50%. There is no supporting data, but it is possible that this result is associated with good adherence to the recommendations relating to secondary cardiovascular prevention.

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3.6. Central Nervous System

In 2020, medicines acting on the central nervous system (CNS) rank sixth within the categories with the highest public expenditure, with 1,876.7 million euros, equal to 8.2% of total public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure for these drugs was 31.47 euros, mainly relating to expenditure under approved care regime (23.65 euros per capita), with a slight increase compared to 2019 (+1.1%). The expenditure relating to the purchase by public health facilities is of lesser importance (7.81 euros per capita); however, it recorded a 6% 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 94.5 DDD/1000 inhabitants per day, a slight increase compared to the year 2019 (+ 1.9%). Also in this case, the highest consumption is recorded in the context of approved care with 67.8 DDD/1000 inhabitants per day (Table 3.2).

The analysis of 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 35 years of age, consistent with gender differences in the frequency of neurological and psychiatric diseases. Men and women in the +75 age group reach the highest level of prevalence (43% and 31.9%, respectively) and expenditure (78.35 and 61.16 euros per capita, respectively).

As for approved care, per capita expenditure for central nervous system drugs was 23.65 euros. The slight change in expenditure compared to 2019 was due to an increase in consumption (+1.4%), to a minimal decrease in prices (-0.2%), and to the use of less expensive drugs (mix effect -0.4%). This did not significantly change the average cost per day of therapy, which remains almost stable compared to the previous year (-0.6%) (Table 3.9). Analysing in detail the individual sub-categories, other antiepileptics and serotonin reuptake inhibitors (SSRIs) have a greater impact on expenditure, with 4.60 euros and 3.33 euros respectively. However, in terms of consumption, SSRIs rank first with 29.3 DDD/1000 inhabitants per day, about half of the entire category, followed by other antidepressants with 11.3 DDD/1000 inhabitants per day (Table 3.9). All three sub-categories show increases compared to 2019 both in terms of expenditure and consumption and only SSRIs report a trend towards purchase of less expensive drugs (mix effect -0.7%), resulting in a slight decrease in the average cost per day of therapy for these drugs (-0.7%).

The molecules with the greatest impact on per capita expenditure in the category are levetiracetam, fentanyl and pregabalin (Table 3.10). In particular, levetiracetam and fentanyl are among the top thirty most expensive active ingredients in 2020, ranking eighteenth and twenty-seventh respectively (Tables 3.11 and 3.12). Sertraline, on the other hand, records the highest consumption and with 8.3 DDD/1000 inhabitants per day is also the only molecule in the category falling within the first thirty most consumed active ingredients (Tables 3.10 and 3.14). Five molecules, lacosamide, vortioxetine, pregabalin, quetiapine and sertraline, show the greatest variation in expenditure between 2019 and 2020 (Table 3.13).

As regards purchases by public health facilities, there was an increase by 5.7% in expenditure and by 3.1% in consumption and, despite a reduction in prices compared to 2019 (-2.1%), a higher trend is reported to use more expensive drugs (mix effect +4.9%). Such factors led to 2.6% 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, slightly increasing compared to 2019 (+2.3%), while diazepines, oxazepines, thiazepines and oxepines (3.6 DDD/1000 inhabitants per day) and the medicines used in opioid addiction (3.3 DDD/1000 inhabitants per day) show the highest consumption in the entire category. Compared to 2019, both recorded decreases in terms of expenditure (-7.5% and -7.3%, respectively) and average cost per day of therapy (-10.4% and -7.6%). For the sub-category of medicines used in opioid addiction this is mainly due to the decrease in prices (-7.4%), while for diazepines, oxazepines, thiazepines and oxepines, this is due to the greater use of less expensive drugs (mix effect -9.3%). Other central nervous system drugs rank second in the category in terms of expenditure (0.54 euros): these drugs record a 45.3% expenditure increase owing to the greater use of more expensive drugs (mix effect +46.1%) compared to 2019 (Table 3.16).

The active ingredient with the highest incidence of expenditure (19%) is paliperidone with a unit cost per day of therapy of 1.49 euros (Table 3.17), which, however, is not among the highest in the category. Tafamidis and patisiran are the most expensive drugs in terms of average cost per DDD (274.49 and 516.03 euros, respectively). On the contrary, midazolam and lidocaine are the active ingredients of the category with the lowest incidence of expenditure (about 1%).

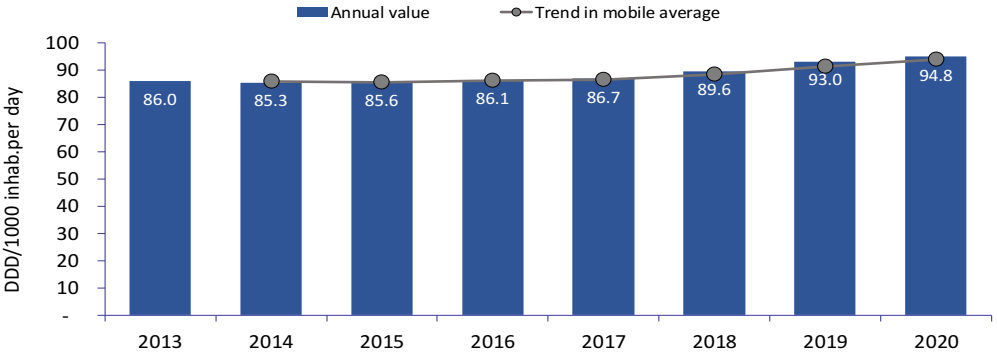
No active ingredient belonging to this category of drugs is listed in the top 30 with the highest incidence of expenditure for drugs purchased by public facilities, nor in the top 30 with the greatest variation in expenditure compared to the previous year (Tables 3.18 and 3.20).

For further information on the use of medicines belonging to the same therapeutic area, analyses have been carried out on the historical series of consumption by active ingredient and by Region and on the efficiency in the absorption of resources according to the presence of patent-expired medicines and on a regional basis. These analyses focused on medicines for multiple sclerosis, antidepressants, medicines for pain therapy, antiepileptics, antipsychotics, antiparkinsonian drugs, anti-migraine and anti-dementia drugs.

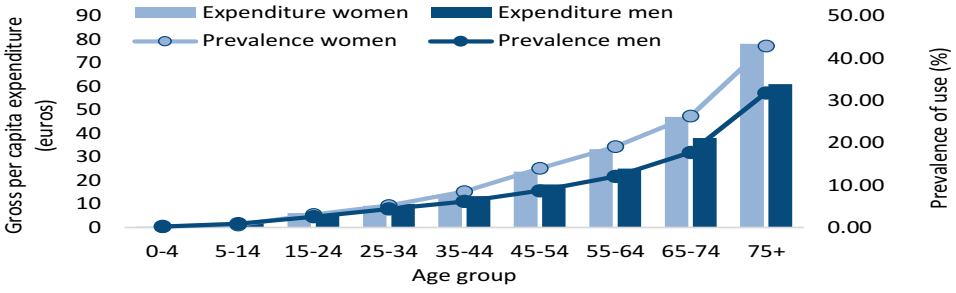
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Central nervous system

Public expenditure* in million euros (% over total)	**1,876.7**	**(8,2)**
Δ % 2020-2019		2.3%
Regional range of gross per capita expenditure	26.6	38.0
DDD/1000 inhab. per day (% over total)	**94.5**	**(8,1)**
Δ % 2020-2019		1.9%
Regional range of DDD/1000 inhab. per day	79.8	120.1

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities



Distribution, by age and gender, of expenditure, prevalence of use and consumptions under approved care regime and *per conto* distribution in 2020 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab.per day		
	Men	Women	Total	Men	Women	Total
0-4	0.4	0.4	0.4	0.7	0.6	0.6
5-14	2.3	1.7	2.0	4.1	2.8	3.5
15-24	6.3	6.2	6.3	16.1	16.3	16.2
25-34	10.1	9.2	9.7	29.7	26.8	28.3
35-44	13.4	14.0	13.7	40.4	44.1	42.2
45-54	18.4	23.8	21.2	55.3	77.0	66.3
55-64	25.1	33.4	29.4	71.0	112.0	92.1
65-74	38.1	47.2	42.9	98.7	152.0	126.9
75+	61.2	78.4	71.5	164.1	233.0	205.3

3.6.1. Medicines for multiple sclerosis

National data on consumption and expenditure

In recent years, consumption of medicines for multiple sclerosis has progressively increased with an average annual rate of 4.6%, moving from 2.2 DDD/1000 inhabitants per day in 2014 to 2.8 DDD in 2020 (Figure 3.6.1a and Table 3.6.1a). Over the past four years, the average cost per day of therapy has remained almost stable, with 11.87 euros last year. Immunosuppressive drugs account for about 70% of consumption for the entire category (1.9 DDD/1000 inhabitants per day). Despite the average cost per day of therapy being the lowest among the other sub-categories, this has an impact on per capita expenditure, which is more than a third of the entire category (3.66 out of 12.23 euros), with an increasing trend in the 2014-2020 period (CAGR: 40.7%). Monoclonal antibodies also have a significant impact on per capita expenditure (2.98 euros), however this is mainly due to the average cost per day of therapy (53.64 euros) rather than to high levels of consumption (0.2 DDD/1000 inhabitants per day). The same can be said for fingolimod with a per capita expenditure of 2.40 euros against 0.1 DDD (average DDD cost: 54.80 euros). The only two sub-categories having decreased in terms of expenditure and consumption over the years are interferons and glatiramer. However, despite comparable costs per day of therapy, they show a different impact on per capita expenditure, which is much higher for interferons (1.88 euros) rather than for glatiramer (0.39 euros), due to a different level of consumption (0.4 vs 0.1 DDD). 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 (1.36 euros). In addition to fingolimod, the most expensive drugs per day of therapy are cladribine (49.88 euros) and monoclonal antibodies, including natalizumab (56.38 euros) and ocrelizumab (48.24 euros). The last two drugs 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.

Patent-expired drugs are over 50% of the total doses, but only 9.5% of per capita expenditure and ex-originator drugs are in any case preferred over their generics (Table 3.6.1c). Overall, consumption shows slight differences between patent-expired and patent-covered drugs, with 52.7% and 47.3% of total DDD, respectively. However, the high average cost per day of therapy (22.71 euros) of the patent-covered clearly has an impact on per capita expenditure (11.07 vs 1.16). Stratifying the consumption data by therapeutic subcategory, a high regional variability is observed for the consumption of immunosuppressants, shifting from a minimum of 1.61 DDD to a maximum of 3.02 DDD, while minor interregional differences are reported for interferons (Figure 3.6.1c).

Figure 3.6.1a. Medicines for multiple sclerosis, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

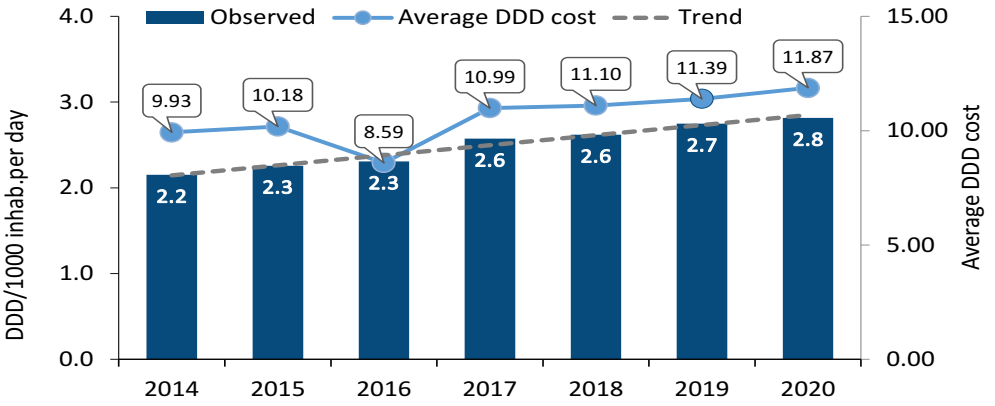


Table 3.6.1a. Medicines for multiple sclerosis, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expendi-ture	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Immunosuppressants	3.66	15.7	40.7	1.9	2.5	9.1	5.14	12.6
Monoclonal antibodies	2.98	16.5	16.7	0.2	25.1	17.9	53.64	-7.1
Fingolimod (S1P receptor modulators)	2.40	1.2	7.0	0.1	0.9	9.1	54.80	0.0
Interferons	1.88	-2.8	-9.6	0.4	-3.9	-9.6	12.41	0.9
Pyrimidine synthesis inhibitors	0.92	13.4	97.8	0.1	12.4	98.4	27.33	0.6
Glatiramer	0.39	-32.9	-15.6	0.1	-4.7	-2.9	11.22	-29.8
Medicines for multiple sclerosis	**12.23**	**7.1**	**7.8**	**2.8**	**2.4**	**4.6**	**11.87**	**4.2**
dimethyl fumarate	2.49	11.3	-	0.2	11.9	-	32.85	-0.8
fingolimod	2.40	1.2	7.0	0.1	0.9	9.1	54.80	0.0
natalizumab	1.69	8.7	6.2	0.1	9.5	6.4	56.38	-1.0
interferon beta 1a	1.36	-4.7	-12.7	0.4	-4.6	-10.7	10.57	-0.4
ocrelizumab	1.23	46.0	-	0.1	50.3	-	48.24	-3.1
teriflunomide	0.92	13.4	97.8	0.1	12.4	98.4	27.33	0.6
methotrexate	0.69	3.9	11.7	1.4	2.2	10.2	1.36	1.4
peginterferon beta-1	0.41	3.7	-	0.0	3.6	-	29.71	-0.2
glatiramer	0.39	-32.9	-15.6	0.1	-4.7	-2.9	11.22	-29.8
cladribine	0.38	142.4	-	0.0	143.4	-	49.88	-0.7

Table 3.6.1b. Medicines for multiple sclerosis, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	2.1	2.2	2.2	2.5	2.6	2.7	2.9	4.7
Valle d'Aosta	1.8	2.1	1.9	2.1	2.1	2.3	2.3	3.2
Lombardy	2.0	2.1	2.2	2.4	2.5	2.5	2.6	1.0
A.P. of Bolzano	2.9	3.0	3.0	3.3	3.4	3.6	3.6	0.7
A.P. of Trento	2.5	2.6	2.8	3.1	3.1	3.3	3.4	3.8
Veneto	2.1	2.2	2.3	2.6	2.6	2.8	2.8	1.9
Friuli VG	3.1	3.2	3.2	3.6	3.5	3.7	3.5	-4.2
Liguria	1.9	2.0	2.1	2.3	2.4	2.5	2.6	0.8
Emilia R.	1.8	2.0	2.0	2.2	2.3	2.4	2.4	-0.1
Tuscany	1.8	2.1	2.0	2.3	2.2	2.5	2.5	2.0
Umbria	2.4	2.5	2.5	2.7	2.7	2.8	2.9	3.7
Marche	2.2	2.3	2.3	2.4	2.5	2.6	2.7	4.0
Lazio	2.0	2.0	2.1	2.4	2.4	2.5	2.6	4.6
Abruzzo	2.3	2.4	2.5	2.8	2.8	3.0	3.1	4.1
Molise	2.0	1.9	2.0	2.3	2.3	2.7	3.0	10.5
Campania	2.0	2.0	2.1	2.4	2.4	2.5	2.6	2.7
Puglia	2.5	2.6	2.7	3.0	3.0	3.2	3.2	0.4
Basilicata	2.1	2.3	2.4	2.8	2.8	3.0	3.1	1.7
Calabria	2.1	2.2	2.3	2.6	2.7	2.7	2.9	6.7
Sicily	2.2	2.2	2.3	2.6	2.7	2.8	2.9	2.6
Sardinia	4.3	4.4	4.2	4.6	4.8	4.9	5.2	6.5
Italy	**2.2**	**2.3**	**2.3**	**2.6**	**2.6**	**2.7**	**2.8**	**2.4**
North	2.1	2.2	2.3	2.5	2.6	2.7	2.7	1.3
Centre	2.0	2.1	2.1	2.4	2.4	2.5	2.6	3.6
South and Islands	2.4	2.4	2.5	2.8	2.9	3.0	3.1	3.3

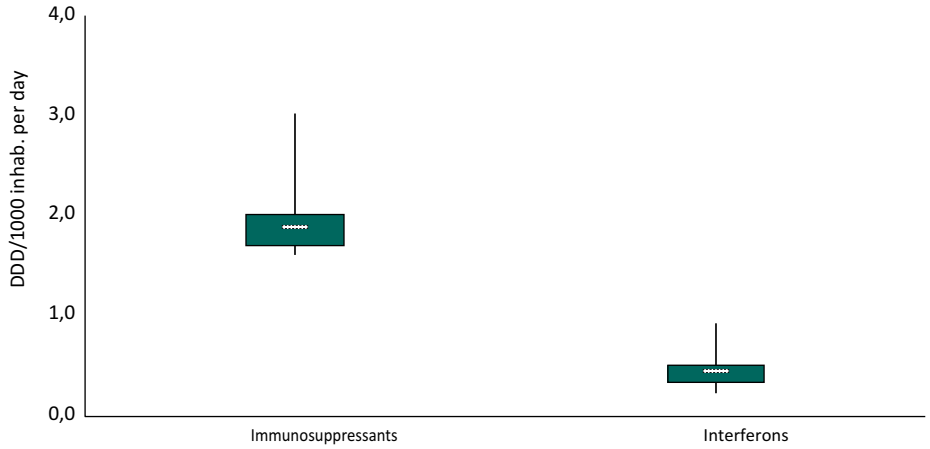
Table 3.6.1c. Prescription of medicines for multiple sclerosis with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	1.16	9.5	-3.0	1.5	52.7	2.0	2.14
Generic	0.11	9.7	1.8	0.3	22.7	-1.9	0.91
Ex originator	1.05	90.3	-3.5	1.1	77.3	3.2	2.50
Patent covered	11.07	90.5	8.2	1.3	47.3	3.0	22.71
Medicines for multiple sclerosis	**12.23**	**100.0**	**7.1**	**2.8**	**100.0**	**2.4**	**11.87**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.6.1c. Medicines for multiple sclerosis, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- Between 2014 and 2020, consumption of medicines for multiple sclerosis shows an increasing trend of those used mainly as a second line, such as **monocolonal antibodies** and **immunosuppressants** (dimethyl fumarate, methotrexate, cladibrine), against a decrease in the category of interferons.
- The wide availability of drugs in the treatment of MS has led to a **high level of personalisation of therapy** based on the benefit-risk profile of the drug and the in-depth knowledge of the mechanisms of action of the molecules as recalled by the European guidelines. In this specific context, it would be desirable, from a public health perspective, to promote and conduct a greater number of studies on the use of drugs for MS in the real world in order to typify the different prescribing patterns in relation to the numerous clinical phenotypes of the disease.

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3.6.2. Antidepressants

National data on consumption and expenditure

In the last seven years, the consumption of antidepressants has increased by more than 10%, from 39.2 DDD in 2014 to 43.6 DDD in 2020. In the same period, the cost per day of therapy fell from 0.53 to 0.42 euros due to the patent expiry of important active ingredients, such as escitalopram (2014), duloxetine (2015) and bupropion (2016) (Figure 3.6.2a).
In 2020, consumption of antidepressants was 3.7% of the total consumption of drugs in Italy, with a 1.7% increase compared to 2019. Similarly, per capita expenditure shows a 2.3% increase, reaching 6.7 euros per capita in 2020 (Table 3.6.2a). SSRIs account for 70% (30.6 DDD) of consumption and 50% (3.36 euros per capita) of expenditure for the entire category. Both indicators show a 1.4% increase compared to 2019; greater variations are seen for other antidepressants, albeit with much lower levels of use (DDD: +5.4%, expenditure: +6.7%). This trend is mainly determined by vortioxetine, a drug marketed in 2016 and indicated in the treatment of major depressive episodes in adults, which does not seem to show a superiority over other antidepressants, despite showing an effect on the cognitive system of elderly people. 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 1.01 euros per capita, is stable compared to 2019 and is confirmed as the most expensive molecule, while sertraline is the most consumed one (8.9 DDD; +3%).
Patent-expired medicines represent 90% of doses and half of these are generic, even if in 2020 the greatest increase is observed for ex-originator drugs (+5.0% compared to +1.7% of generics), even if the cost per day of therapy remains much higher (0.43 vs 0.29, Table 3.6.2c).

Figure 3.6.2a. Antidepressants, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

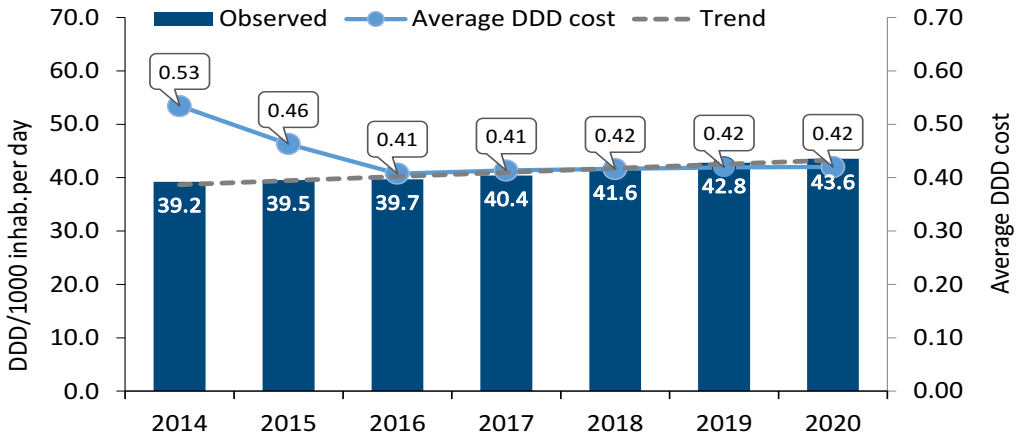


Table 3.6.2a. Antidepressants, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
SSRI antidepressants	3.36	1.4	-3.3	30.6	1.4	0.8	0.30	-0.4
Other antidepressants	1.62	6.7	12.4	5.1	5.4	10.7	0.88	0.9
SNRI antidepressants	1.56	1.1	-7.8	6.8	1.3	1.9	0.62	-0.5
1st generation antidepressants, plain or in combination	0.16	-8.8	-2.8	1.0	-4.0	-1.9	0.42	-5.2
Antidepressants	**6.7**	**2.3**	**-2.2**	**43.6**	**1.7**	**1.8**	**0.4**	**0.3**
paroxetine	1.01	-0.2	-3.2	8.1	1.4	0.2	0.34	-1.9
escitalopram	0.96	1.0	-7.7	7.5	1.0	0.7	0.35	-0.3
venlafaxine	0.80	1.6	0.9	3.7	1.9	1.2	0.59	-0.6
duloxetine	0.77	1.9	-13.0	3.2	2.1	3.0	0.67	-0.5
sertraline	0.77	4.3	3.0	8.9	3.0	3.5	0.24	0.9
vortioxetine	0.65	12.6	-	1.6	12.2	-	1.13	0.0
trazodone	0.43	2.6	6.8	1.3	3.0	7.8	0.91	-0.7
citalopram	0.41	-1.0	-2.6	4.2	-1.5	-2.3	0.27	0.3
mirtazapine	0.35	3.3	2.5	1.9	2.1	3.0	0.51	0.9
bupropione	0.18	3.7	-0.7	0.3	3.4	1.1	1.75	0.0

Table 3.6.2b. Antidepressants, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	44.3	44.6	45.2	46.0	47.3	48.8	49.2	0.8
Valle d'Aosta	38.8	38.5	38.1	38.5	40.0	41.5	42.1	1.6
Lombardy	36.6	37.1	37.6	38.3	39.5	40.0	40.7	1.6
A.P. of Bolzano	52.1	53.0	53.5	53.6	54.5	56.0	56.1	0.2
A.P. of Trento	38.1	38.4	38.9	39.6	41.5	42.4	43.2	2.0
Veneto	37.3	37.9	37.8	38.7	40.3	41.4	42.2	2.0
Friuli VG	34.1	34.0	33.6	34.4	35.7	36.5	35.3	-3.4
Liguria	53.3	53.4	52.9	54.2	55.2	56.9	57.9	1.7
Emilia R.	50.1	50.3	49.0	49.9	52.1	53.3	53.6	0.6
Tuscany	60.7	60.7	60.7	61.5	62.2	63.6	65.2	2.5
Umbria	50.5	51.0	51.9	52.5	53.9	55.1	57.1	3.7
Marche	41.3	41.7	42.2	42.7	43.6	45.0	45.6	1.3
Lazio	34.5	34.9	35.1	35.7	36.7	38.3	38.7	1.1
Abruzzo	36.8	37.2	37.8	38.7	40.1	41.6	42.9	3.0
Molise	33.1	32.1	31.8	32.9	34.4	35.7	36.8	3.2
Campania	29.3	29.9	30.5	31.0	32.1	33.3	34.2	2.7
Puglia	30.8	31.0	31.1	31.7	32.6	34.2	35.2	3.0
Basilicata	30.5	30.9	31.2	31.5	31.9	33.2	34.1	2.7
Calabria	36.6	37.0	37.4	37.8	38.8	40.2	41.3	2.7
Sicily	30.7	31.0	31.4	32.0	33.0	34.4	35.2	2.2
Sardinia	43.9	44.1	43.9	44.4	45.1	45.6	47.1	3.3
Italy	**39.2**	**39.5**	**39.7**	**40.4**	**41.6**	**42.8**	**43.6**	**1.7**
North	41.4	41.8	41.8	42.6	44.0	45.0	45.5	1.1
Centre	45.1	45.3	45.5	46.2	47.1	48.6	49.5	1.9
South and Islands	32.5	32.8	33.2	33.7	34.7	36.1	37.0	2.7

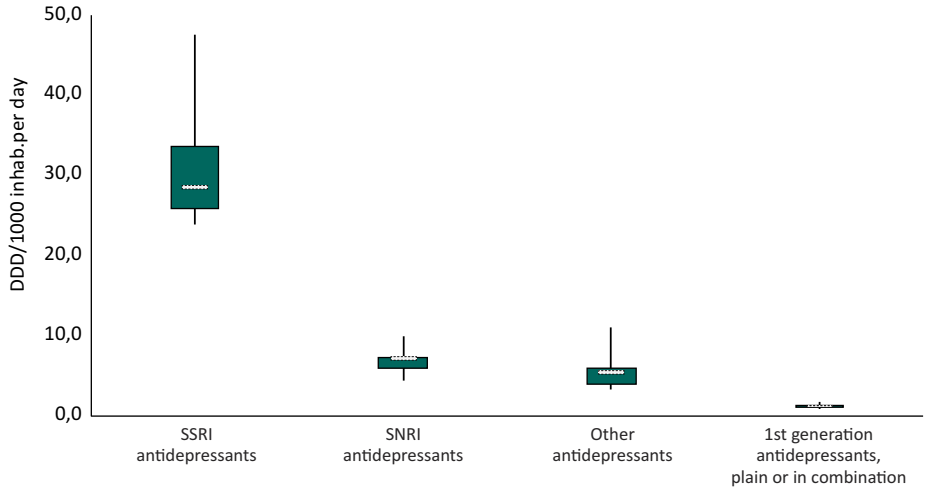
Table 3.6.2c. Prescription of antidepressants with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	5.24	78.3	4.0	39.3	90.3	3.3	0.36
Generic	2.12	40.4	2.5	19.7	50.0	1.7	0.29
Ex originator	3.12	59.6	5.1	19.7	50.0	5.0	0.43
Patent covered	1.45	21.7	-3.6	4.2	9.7	-11.2	0.94
Antidepressants	**6.70**	**100.0**	**2.3**	**43.6**	**100.0**	**1.7**	**0.42**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.6.2c. Antidepressants, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure and adherence in population

Health Card data allowed to describe the trend in prevalence and consumption by age group, gender and region and to calculate some indicators of intensity of use. Adherence and persistence of chronic treatments with antidepressants was also estimated.

6.5% of the Italian population used antidepressant drugs in 2020: while in Tuscany and Liguria this percentage reaches 10%, in the Southern Regions the prevalence drops to 5.7% compared to 7.6% in the Centre and 6.6% in the North (Table 3.6.2d). Consumption increases in relation to age, reaching a 23% prevalence 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 (Figure 3.6.2d).

Half of the users are over the age of 66 and each subject remains on treatment for about 8 months on average, although half of them uses antidepressants for less than 6 months and one in five receives only one prescription. This shows how often these drugs are prescribed for clinical conditions not related to depressive pathologies, but which could be treated with non-pharmacological approaches (Table 3.6.2d).

The study on adherence and persistence to treatment was conducted on a cohort of 124,390 new users of antidepressant drugs, aged at least 45 years, considering a one-year follow-up. The median age of the cohort is 70 years (interquartile range [IQR]: 5880); women represent about 70% of the total and a quarter belong to the age group between 75 and 84 years.

The percentage of subjects with high and low adherence to antidepressant treatment was 37.2% and 27.6%, respectively. While the former decreased by 1% compared to 2019, the proportion of low adherence increased by 2%. In particular, the percentages of high adherence decrease with age, moving from 42.6% in subjects aged between 45 and 54 years (42.6%) to 25% in the over 85s, and by geographic area with a maximum of 38.9% in the North and a minimum of 35.3% in the South. This difference between geographic areas was observed both by age group and by gender. Men have shown higher adherence than women (39.0% vs 36.4%), while in women low adherence approaches 30%. For this indicator, there are no differences between geographic areas, on the contrary there is a gradient by age with a maximum value of about 45% in the +85 age group (Table 3.6.2e).

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 (32%) remained persistent and no marked differences were reported by gender and between geographic areas. On the contrary, there is a reduction in persistence with increasing age, shifting from 36% of the 45-54 age group to 26% of subjects aged at least 85. This gradient is found in every geographic area, even if the percentage variation is less marked for the South and the Islands (Δ% =- 8%) compared to the North (Δ% =-11%) (Table 3.6.2f).

Considering the median time to discontinuation of antidepressant treatment, a 50% probability of discontinuing treatment is achieved at approximately 134 days, in line with 2019 and with values between geographic areas ranging from 140 days in the North, 133 days in the Centre and 124 days in the South and the Islands (Figure 3.6.2e).

Figure 3.6.2d. Distribution of prevalence of use and consumption of antidepressants under approved care regime and *per conto* distribution (year 2020)

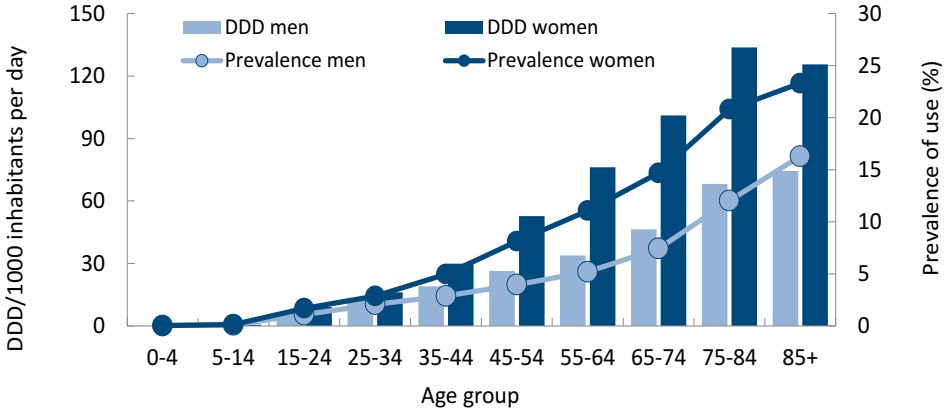


Table 3.6.2d. Exposure and duration of therapy with antidepressants by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescrip-tions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	7.5	0.49	67	5.3	227.5	180.0	19.4
Valle d'Aosta	6.3	0.46	68	5.0	226.3	180.0	20.7
Lombardy	6.0	0.48	66	5.2	242.8	196.0	19.1
A.P. of Bolzano	6.5	0.51	66	5.5	261.2	224.0	17.9
A.P. of Trento	5.9	0.47	65	5.6	245.7	196.0	17.8
Veneto	5.9	0.47	66	5.5	241.6	195.0	18.0
Friuli VG	5.6	0.43	67	5.2	224.6	180.0	19.1
Liguria	9.6	0.47	70	5.6	222.4	180.0	20.5
Emilia R.	7.3	0.47	68	5.4	230.3	180.0	18.7
Tuscany	10.0	0.48	68	5.8	234.3	180.0	19.4
Umbria	8.3	0.46	69	6.8	229.8	196.0	16.0
Marche	7.2	0.51	68	5.6	215.2	180.0	17.9
Lazio	6.0	0.48	65	5.4	229.5	180.0	20.6
Abruzzo	6.6	0.48	65	6.0	235.6	196.0	17.9
Molise	5.8	0.49	67	5.7	232.3	180.0	17.9
Campania	5.1	0.53	64	5.7	222.5	168.0	21.9
Puglia	5.7	0.54	65	5.3	209.6	168.0	23.6
Basilicata	5.6	0.50	65	6.6	222.0	174.0	18.7
Calabria	6.4	0.53	65	5.8	221.0	168.0	22.1
Sicily	5.6	0.50	66	5.8	220.9	168.0	20.8
Sardinia	6.8	0.41	65	6.5	256.4	224.0	15.8
Italy	**6.5**	**0.49**	**66**	**5.5**	**230.7**	**180.0**	**19.7**
North	6.6	0.48	67	5.3	235.7	182.0	19.0
Centre	7.6	0.48	67	5.7	229.7	180.0	19.4
South and Islands	5.7	0.51	65	5.8	223.8	178.0	21.0

Table 3.6.2e. Indicators of adherence to treatment with antidepressants in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=124,390		North N=57,338		Centre N=28,697		South N=38,355	
Low adherence to antidepressants*	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	21.9	-2	20.5	-3	22.1	2	23.8	-2
55-64 years	22.2	0	21.3	5	22.1	0	23.6	-4
65-74 years	24.6	1	23.3	4	23.9	-3	26.7	0
75-84 years	30.4	3	29.6	5	29.9	3	32.3	1
≥85 years	44.6	3	45.5	7	43.4	0	44.2	1
Women	28.0	2	27.5	4	27.5	-1	29.3	1
Men	26.9	2	25.8	4	27.4	3	28.0	-2
Total	**27.6**	**2**	**27.0**	**4**	**27.4**	**0**	**28.9**	**0**
High adherence to antidepressants*	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	42.6	1	45.1	3	40.9	-3	39.8	1
55-64 years	41.6	-1	44.1	0	39.6	-6	39.5	0
65-74 years	39.3	0	41.0	-1	39.2	-1	37.1	2
75-84 years	34.3	-1	35.8	-2	34.6	-2	31.6	0
≥85 years	25.0	-3	25.2	-5	25.2	-1	24.4	-1
Women	36.4	0	38.0	1	35.7	-2	34.4	0
Men	39.0	-2	40.7	-3	38.0	-3	37.1	1
Total	**37.2**	**-1**	**38.9**	**-1**	**36.5**	**-3**	**35.3**	**0**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

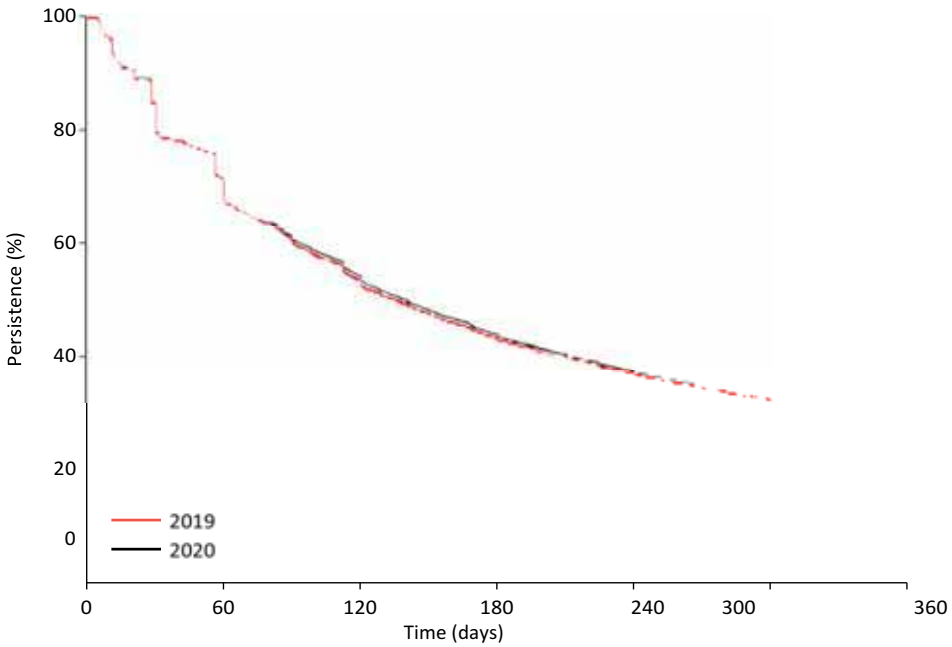
N: refers to new users, subjects who received a first prescription in the period 01/10/2020- 31/12/2020, not treated in the previous months starting from 01/01/2020; Percentages of subjects with low/high adherence relating to the specific category Median follow-up time (IQR): 307 (191-342)

Table 3.6.2f. Persistence after one year of treatment with antidepressants in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=124,390		North N=57,338		Centre N=28,697		South N=38,355	
Persistence at 12 months	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	36	3	37	2	35	4	34	6
55-64 years	34	1	36	0	33	-1	32	2
65-74 years	32	-1	33	-1	33	0	31	-1
75-84 years	31	-1	32	-2	32	2	30	-2
≥85 years	26	-3	26	-8	27	7	26	-1
Women	32	1	33	-1	32	4	31	0
Men	32	-1	34	-2	32	-2	31	1
Total	**32**	**0**	**33**	**-1**	**32**	**2**	**31**	**1**

Note: persistence to treatment was evaluated only for new users with at least 2 prescriptions. An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods)

Figure 3.6.2e. Time (in days) to discontinuation of treatment with antidepressants in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: an interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods) For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days)

Table 3.6.2g. Prevalence and incidence of depression in the population eligible for care and comparison 2020-2019

	Prevalence (%)	Δ % 20-19	Incidence (‰)	Δ % 20-19
Geographic analysis				
North	13.0	0.0	4.9	-16.2
Centre	13.6	0.7	6.2	-32.2
South and Islands	13.1	0.0	4.9	-21.9
Analysis by gender				
Men	8.6	0.0	3.9	-17.7
Women	17.5	0.0	6.4	-23.8
Analysis by age				
≥45 years	5.9	1.7	2.9	-28.6
46-65	15.3	2.0	5.0	-22.1
66-74	19.2	2.6	6.9	-16.1
75-84	22.3	3.6	11.1	-6.7
≥85 years	25.1	2.0	10.2	-16.7
Total	**13.1**	**-0.8**	**5.2**	**-21.8**

Indicators used: **Prevalence of depression:** number of patients diagnosed with depression [**numerator**], on the total population eligible for assistance [**denominator**] **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 3.6.2h. Prevalence of use of antidepressants in subjects affected by depression and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence of use (%)	% 20-19
Geographic analysis		
North	33.8	-3.3
Centre	37.3	-2.4
South and Islands	29.1	-4.1
Analysis by gender		
Men	27.9	-4.3
Women	35.0	-3.1
Analysis by age		
≥45 years	19.6	-4.1
46-65	27.7	-3.6
66-74	37.8	-0.3
75-84	47.6	-0.2
≥85 years	47.4	-1.5
Total	**32.7**	**-3.4**

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: analysis by therapeutic category

Analysis by therapeutic category	Prevalence of use (%)
1st generation antidepressants, plain or in combination	2.4
SNRI	5.9
SSRI	23.7
Other antidepressants	5.8
Total	**32.7**

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 2020 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 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 areas as well as a possible different role of general practice in different regions of the country during the pandemic.
- The data on **exposure and adherence to treatment** in the population show a great level of inadequacy of these drugs compared with their under-use, if considering the indicators on the disease frequency. For many years now, this framework has been a great challenge for public health, which, in pursuing appropriateness, must necessarily outline a new relationship between specialist medicine and general practice.

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3.6.3 Medicines for pain therapy*

National data on consumption and expenditure

The use of drugs for pain therapy has progressively increased over the years with a 1.7% average annual variation (CAGR), moving from 6.9 DDD/1000 inhabitants per day in 2014 to 7.6 DDD in 2020 (Figure 3.6.3a). The average cost per day of therapy instead slightly decreased over the years, almost stabilising at 2.39 euros between 2018 and 2020. Major opioids plain or in combination are the sub-category accounting for about 70% of the expenditure of the entire category with 4.40 euros per capita, mainly due to the high cost per day of therapy (4.47 euros), approximately twice the total of the category (Table 3.6.3a). On the other hand, minor opioids plain or in combination are the sub-category recording the greatest reductions both in terms of expenditure and consumption, compared to 2019. Analysing in detail the individual active ingredients, fentanyl, tapentadol and pregabalin (with 1.39 and 1.24 euros per capita, respectively) are the drugs with the greatest impact on expenditure. For fentanyl and tapentadol, this is due to the high costs per day of therapy (4.79 and 6.23 euros, respectively), and for pregabalin to the high levels of consumption (2.4 DDD/1000 inhabitants per day).

Prescription of patent-expired drugs (Table 3.6.3c) represents 53% of consumption, with ex originators being more than double compared to generics (2.7 vs 1.3 DDD), while the remainder (47%) relates to patented drugs that affect almost all per capita expenditure (4.80 euros out of a total of 6.65 euros). This is due to the high average cost per day of therapy (3.67 euros compared to 1.25 for patent-expired drugs).

*It includes prescription of pregabalin and gabapentin for all authorised indications

Figure 3.6.3a. Pain therapy, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

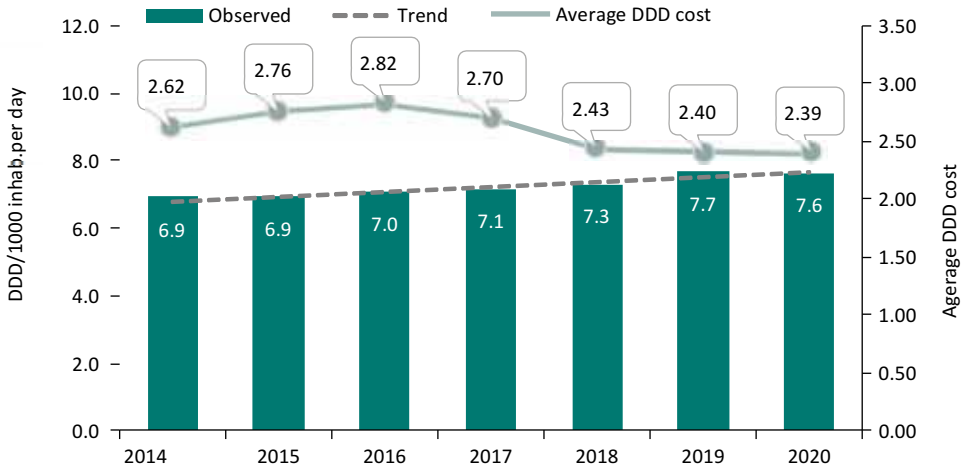


Table 3.6.3a. Pain therapy, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Major opioids, plain or in combination	4.40	-2.0	5.5	2.7	-1.8	3.4	4.47	-0.5
Medicines for neuropathic pain	1.58	5.5	-7.5	3.0	6.6	5.1	1.46	-1.3
Minor opioids, plain or in combination	0.66	-7.5	-4.6	2.0	-8.8	-4.0	0.93	1.1
Medicines for pain therapy	**6.65**	**-0.9**	**0.2%**	**7.6**	**-0.7**	**1.7**	**2.39**	**-0.5**
fentanyl	1.39	-0.2	3.4	0.8	-1.7	2.6	4.79	1.2
tapentadol	1.24	0.6	13.5	0.5	0.2	13.6	6.23	0.1
pregabalin	1.24	7.1	-9.1	2.4	7.4	6.1	1.40	-0.5
naloxone/oxycodone	0.96	-9.8	5.2	0.4	-4.4	7.1	6.39	-6.0
gabapentin	0.34	0.0	1.1	0.5	3.4	1.6	1.72	-3.5
paracetamol/codeine	0.31	-7.8	-6.4	1.2	-8.3	-5.2	0.73	0.3
tramadol	0.27	-5.4	-4.4	0.6	-7.0	-3.6	1.15	1.4
paracetamol/oxycodone	0.26	-4.0	0.4	0.3	-4.4	0.5	2.14	0.1
buprenorphine	0.25	12.7	9.6	0.2	5.6	3.7	4.01	6.4
oxycodone	0.16	0.3	-3.3	0.1	-0.4	-0.6	3.06	0.4

Table 3.6.3b. Pain therapy, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	8.5	8.4	8.6	9.0	9.1	9.6	9.3	-3.0
Valle d'Aosta	9.4	9.5	9.1	9.2	9.2	10.0	10.0	0.4
Lombardy	7.7	7.9	8.1	8.1	8.3	8.8	8.8	0.0
A.P. of Bolzano	7.2	7.3	7.5	7.6	7.7	7.9	7.8	-1.9
A.P. of Trento	7.2	7.4	7.5	7.6	7.9	8.2	8.2	0.2
Veneto	6.9	6.8	7.0	7.1	7.3	7.8	7.7	-1.0
Friuli VG	9.2	9.5	9.8	10.0	9.9	10.0	10.0	0.2
Liguria	8.4	8.4	8.3	8.6	8.8	9.2	9.2	-0.5
Emilia R.	8.6	8.6	8.7	8.9	9.0	9.2	9.0	-2.1
Tuscany	9.2	9.1	8.9	8.6	8.6	8.7	8.6	-1.3
Umbria	6.5	6.7	6.9	7.0	7.5	7.8	8.0	2.3
Marche	6.4	6.4	6.4	6.5	6.5	6.6	6.5	-1.4
Lazio	6.4	6.5	6.5	6.7	6.9	7.3	7.4	0.4
Abruzzo	5.4	5.5	5.6	5.7	5.8	6.1	6.1	1.5
Molise	4.8	5.0	5.2	5.1	5.3	5.4	5.4	-1.0
Campania	4.4	4.4	4.5	4.5	4.8	5.1	5.1	-1.0
Puglia	5.6	5.6	5.7	5.8	6.0	6.5	6.5	0.0
Basilicata	5.0	5.0	4.9	5.0	5.2	5.6	5.6	0.6
Calabria	4.7	4.8	4.9	4.9	5.0	5.3	5.2	-1.6
Sicily	5.1	5.1	5.2	5.3	5.3	5.8	5.7	-0.3
Sardinia	6.8	7.0	7.0	7.1	7.3	7.7	7.8	1.2
Italy	**6.9**	**6.9**	**7.0**	**7.1**	**7.3**	**7.7**	**7.6**	**-0.7**
North	7.9	8.0	8.2	8.3	8.5	8.9	8.8	-1.1
Centre	7.3	7.3	7.3	7.3	7.5	7.7	7.7	-0.3
South and Islands	5.1	5.2	5.2	5.3	5.5	5.9	5.9	-0.2

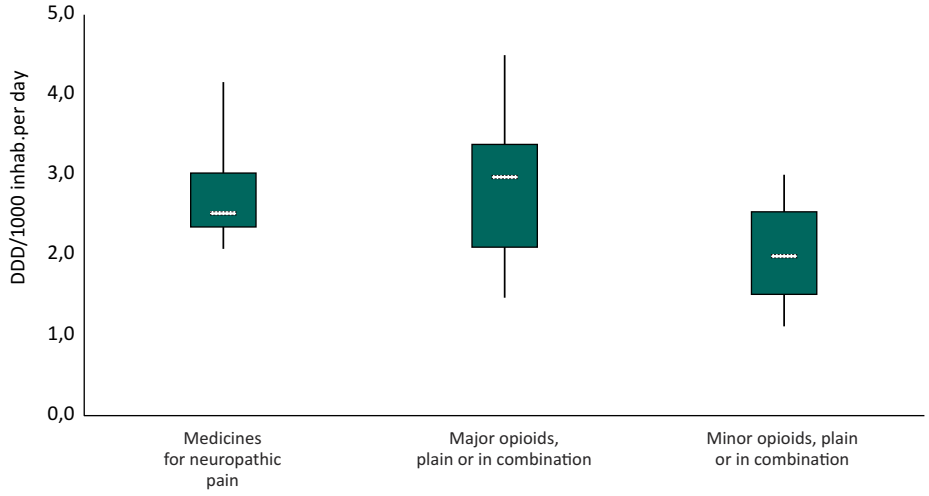
Table 3.6.3c. Prescription of medicines for pain therapy with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	1.85	27.8	3.5	4.0	53.0	2.3	1.25
Generic	0.67	36.0	5.8	1.3	31.8	7.3	1.42
Ex originator	1.18	64.0	2.2	2.7	68.2	0.1	1.17
Patent covered	4.80	72.2	-2.5	3.6	47.0	-3.9	3.67
Pain therapy	**6.65**	**100.0**	**-0.9**	**7.6**	**100.0**	**-0.7**	**2.39**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.6.3c. Pain therapy, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to medicines used for pain therapy in the general population.
Exposure data indicate a prevalence of use that progressively increases with advancing age, reaching the highest values in the age groups between 75 and 84 and in the over 85s (Figure 3.6.3d). Advancing age also highlights gender differences in terms of both prevalence and consumption. In fact, a higher prevalence can be noted in women that exceeds men by almost five percentage points, especially in the extreme age groups. In particular, in the over 85s age group, one in 5 women has received at least one prescription, while this percentage drops in men to 14.3%. The same applies to consumption, where significant differences begin to appear already in the 65-74 age group. At national level, prevalence data do not show marked differences between macro-areas, with the Centre recording the highest percentages, compared to the national average (5.3% vs 5.1%), while the South shows a lower prevalence (4.8%) (Table 3.6.3d). In detail, Tuscany is the Region with the highest level of prevalence (6.5%), while the AP of Bolzano records the lowest level (3.5%).
The median age of users of drugs for pain therapy is 70 years with a greater share of women and, on average, each user received 4.7 prescriptions during the year with Friuli Venezia Giulia and Umbria reporting the highest value compared to the national average of 5.7 prescriptions, while Puglia and Campania, respectively with 4.0 and 4.1, are the Regions recording the lowest share. Each main user received at least one dose of the drug per day for just over 1 month of therapy. In detail, the Northern Regions have an average annual coverage that is approximately 7 days higher than the Central Regions and 13 days higher than the South. 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, there is a non-negligible share (43.4%) of subjects who received a single prescription during the year, with Southern Regions reporting the highest levels of sporadic users (45.6%). Campania is the region with the highest percentage (47.4%) of sporadic users while Umbria records the lowest share of 39.6%

Figure 3.6.3d. Distribution of prevalence of use and consumption of medicines for pain therapy under approved care regime and *per conto* distribution (year 2020)

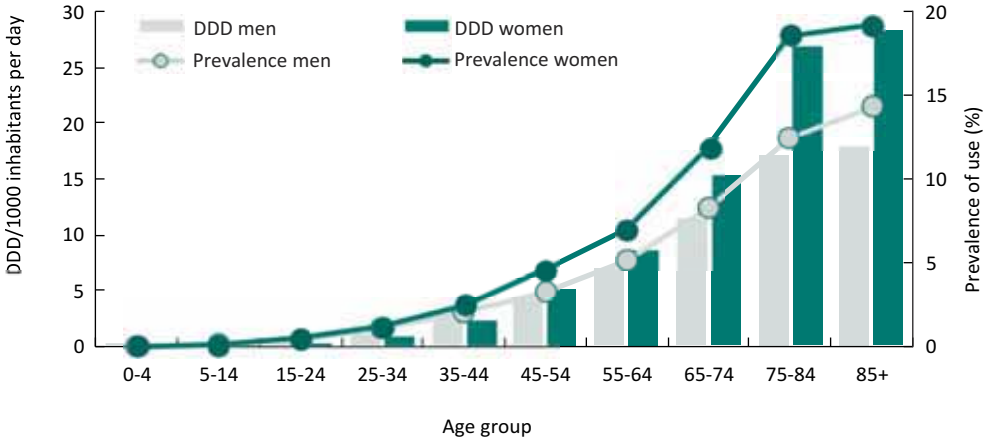


Table 3.6.3d. Exposure and duration of medicines for pain therapy by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	6.2	0.65	70	4.6	47.3	11.0	43.7
Valle d'Aosta	5.3	0.66	70	5.0	58.0	15.0	41.2
Lombardy	4.9	0.64	71	4.9	58.4	15.0	41.3
A.P. of Bolzano	3.5	0.64	73	5.1	60.3	15.0	41.2
A.P. of Trento	4.9	0.65	70	5.1	50.6	11.0	44.4
Veneto	3.8	0.61	72	5.3	59.8	15.0	40.6
Friuli VG	5.4	0.61	71	5.7	60.1	15.0	39.6
Liguria	6.3	0.64	72	4.8	49.0	14.0	42.7
Emilia R.	5.6	0.62	70	4.7	46.8	10.0	44.3
Tuscany	6.5	0.62	71	4.7	41.2	10.0	44.6
Umbria	5.4	0.63	71	5.7	46.9	11.0	39.2
Marche	4.9	0.64	71	4.5	42.5	10.0	45.5
Lazio	4.7	0.61	69	5.2	51.8	14.0	40.4
Abruzzo	4.7	0.63	69	4.9	44.6	10.0	44.0
Molise	4.1	0.62	71	4.7	45.5	10.0	44.4
Campania	4.4	0.60	67	4.1	37.6	10.0	47.4
Puglia	5.8	0.63	69	4.0	36.8	10.0	47.3
Basilicata	5.2	0.60	69	4.3	37.4	10.0	45.9
Calabria	4.6	0.64	70	4.1	37.9	10.0	46.4
Sicily	4.5	0.63	70	4.6	43.1	10.0	43.9
Sardinia	5.0	0.61	69	5.6	55.0	14.0	39.8
Italy	**5.0**	**0.63**	**70**	**4.7**	**48.0**	**12.0**	**43.4**
North	5.1	0.63	71	4.9	53.7	14.0	42.3
Centre	5.3	0.62	70	5.0	46.3	12.0	42.5
South and Islands	4.8	0.62	69	4.4	40.7	10.0	45.6

Key message

- The combination of a decrease in the consumption of minor opioids and a marked regional variability in the consumption of major opioids indicates, on the one hand, probable higher attention in prescribing these drugs for the treatment of chronic pain only, and on the other hand the presence of an urgent need to guarantee access to palliative care and pain therapy in all areas in accordance with the provisions of Law no. 38 of 15 March 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 that 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.

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3.6.4. Antiepileptics*

National data on consumption and expenditure

In 2020, the consumption of antiepileptics stood at 10.9 DDD/1000 inhabitants per day, with an increase of 1.6% compared to the previous year, while an even greater increase was recorded for expenditure (+4.5%), equal to a value of 5.24 euros per capita (Table 3.6.4a).
Expanding the time comparison to the last seven years, a certain stability of use is noted, which goes from 10 DDD in 2014 to 10.9 DDD in 2020; at the same time, the average cost per day of therapy showed a constant growth from 1.11 euros in 2014 to 1.31 euros in 2020 (+18%) (Figure 3.6.4a).
Second generation antiepileptics are, with 2.82 euros per capita, the category with the highest expenditure, up 2.7% compared to 2019. These medicines represent more than half of the expenditure of antiepileptics and the category with the lowest variability in consumption at the regional level (IQR: 4.1-4.7) (Tables 3.6.4.a and Figure 3.6.4c). Second generation antiepileptics are the most used category in the population (5.8 DDD), even if they record a 1% contraction compared to 2019. Although with much lower expenditure values (1.04 euros) and doses (0.5 DDD), the third generation antiepiletic medicines show an increase of more than 20% compared to the previous year (Table 3.6.4a).
Levetiracetam and valproic acid, both with 2.6 DDD, are confirmed as the most used molecules with an increase, compared to 2019, of 4.2% and 1.3% respectively. The use of lacosamide continues to increase, with values for expenditure and consumption rising by around 20% in 2020 (Table 3.6.4a).
A similar trend is observed for perampanel, a latest generation drug indicated for the adjunctive treatment of partial epileptic seizures, with or without secondary generalisation, in patients with epilepsy aged 12 years or more, with a safety profile, particularly cardiac, to be further investigated.
Stratifying the consumption data by subcategory, a high regional variability is observed for the consumption of first generation antiepileptics, with values ranging from a minimum of 4.52 to a maximum of 7.39 DDD per 1000 inhabitants per day, while no differences were observed for 3rd generation antiepileptics (Figure 3.6.4d).

*It does not include prescription of pregabalin and gabapentin

Figure 3.6.4a. Antiepileptics, temporal trend of consumption and average cost per day of therapy (2014-2020)

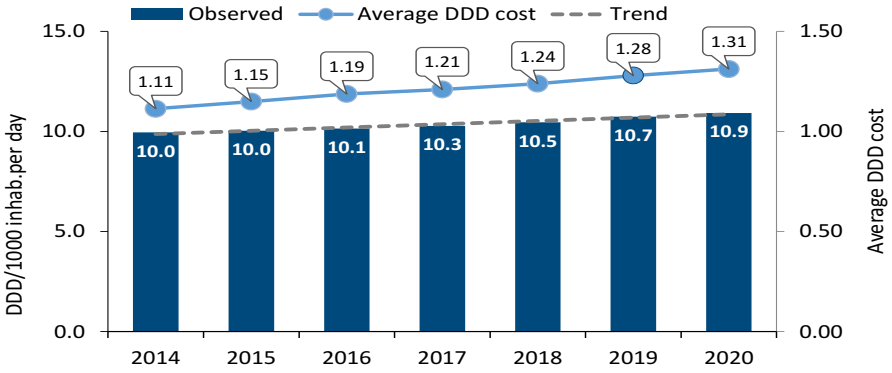


Table 3.6.4a. Antiepileptics, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Second-generation antiepileptics	2.82	2.1	2.7	4.6	3.1	4.2	1.68	-1.3
Fisrt-generation antiepileptics	1.39	0.9	0.9	5.8	-1.0	-1.2	0.65	1.6
Third-generation antiepileptics	1.04	17.9	20.7	0.5	20.3	24.0	5.21	-2.3
Antiepileptic medicines	**5.24**	**4.5**	**4.4**	**10.9**	**1.6**	**1.6**	**1.31**	**2.6**
levetiracetam	1.77	2.7	4.8	2.6	4.2	7.0	1.86	-1.7
valproic acid	1.00	1.4	1.8	2.6	1.3	1.4	1.06	-0.2
lacosamide	0.76	19.3	18.6	0.4	20.7	19.3	5.50	-1.4
lamotrigin	0.46	3.7	4.4	0.8	5.6	5.4	1.55	-2.1
topiramate	0.29	-1.4	-1.4	0.4	0.3	-0.1	2.14	-1.9
carbamazepine	0.25	-0.9	-1.2	1.3	-1.4	-1.5	0.53	0.3
oxcarbazepine	0.19	-0.7	-3.7	0.6	-1.0	-1.9	0.82	0.0
perampanel	0.12	18.1	-	0.1	17.6	-	5.32	0.2
rufinamide	0.07	0.8	2.7	0.0	0.9	3.2	9.75	-0.4
clonazepam	0.07	0.3	-0.1	0.4	0.1	-0.1	0.45	0.0

Table 3.6.4b. Antiepileptics, regional trend of weighted DDD/1000 inhab.per day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	9.7	9.7	9.9	10.2	10.3	10.6	10.8	1.5
Valle d'Aosta	9.3	9.3	8.7	8.9	8.8	8.9	9.3	3.7
Lombardy	8.1	8.2	8.3	8.4	8.5	8.7	8.8	2.1
A.P. of Bolzano	9.3	9.5	9.8	10.0	10.0	10.1	10.3	1.5
A.P. of Trento	10.6	10.6	10.5	10.8	10.7	10.7	10.9	1.2
Veneto	9.2	9.3	9.4	9.5	9.6	9.8	9.8	0.2
Friuli VG	9.4	9.3	9.5	9.6	9.8	10.1	10.5	4.4
Liguria	10.4	10.6	10.5	10.6	10.8	11.0	11.1	0.8
Emilia R.	9.8	9.9	9.9	10.0	10.2	10.3	10.2	-0.3
Tuscany	11.1	11.6	11.6	11.6	11.7	11.9	11.2	-6.5
Umbria	11.4	11.5	11.6	11.6	11.8	12.1	12.5	4.0
Marche	11.4	11.3	11.5	11.5	11.7	11.8	11.9	0.9
Lazio	10.4	10.5	10.7	10.9	11.0	11.5	11.6	0.5
Abruzzo	11.5	11.5	11.5	11.5	11.8	12.2	12.4	1.6
Molise	10.5	10.4	10.5	10.7	10.9	11.2	11.2	0.0
Campania	10.7	10.6	10.7	10.9	11.2	11.6	12.8	9.5
Puglia	10.3	10.4	10.5	10.6	10.8	11.3	11.5	2.3
Basilicata	11.1	11.4	11.5	11.6	11.7	12.0	12.1	0.9
Calabria	11.1	11.1	11.3	11.5	11.8	12.3	12.5	1.8
Sicily	10.1	10.2	10.5	10.7	10.9	11.4	11.6	1.9
Sardinia	11.2	11.2	11.1	11.3	11.4	11.5	11.8	2.7
Italy	**10.0**	**10.0**	**10.1**	**10.3**	**10.5**	**10.7**	**10.9**	**1.6**
North	9.1	9.2	9.3	9.4	9.6	9.7	9.8	1.2
Centre	10.8	11.0	11.1	11.2	11.4	11.7	11.6	-1.4
South and Islands	10.6	10.6	10.8	11.0	11.2	11.6	12.1	4.0

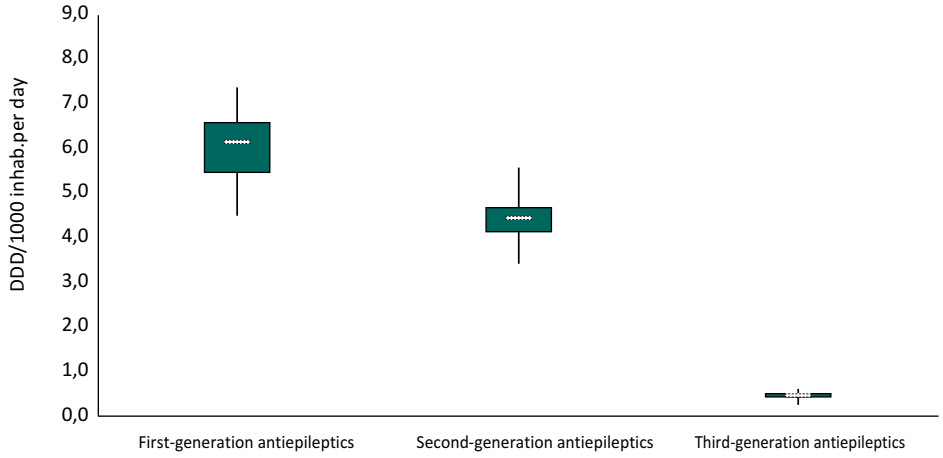
Table 3.6.4c. Prescription of antiepileptics with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	3.06	58.4	2.2	6.1	56.2	2.4	1.36
Generic	0.92	30.2	3.2	1.8	28.8	4.2	1.43
Ex originator	2.14	69.8	1.8	4.4	71.2	1.7	1.34
Patent covered	2.18	41.6	7.9	4.8	43.8	0.6	1.25
Antiepileptics	**5.24**	**100.0**	**4.5**	**10.9**	**100.0**	**1.6**	**1.31**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.6.4c. Antiepileptics, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

As expected from the epidemiology of the condition, consumption increases with age and reaches a prevalence of 4% in the over 85 population and 2% in the general population. There are no marked gender differences, with the exception of the 25-54 age group, in which men use about 30% more antiepileptics than women, with a similar prevalence level (Figure 3.6.4d).

All central and southern regions have a prevalence of more than 2%, with values ranging from a minimum of 1.3% in the Autonomous Province of Bolzano and Veneto to a maximum of 2.5% in Tuscany. The median age of users is 58 years and each subject is treated for 6 months although half of the users are treated for less than 4 months and 16% receive only one prescription in a year, probably indicating a prescription not in line with the main national and international guidelines on treatment of epilepsy (Table 3.6.4d).

Figure 3.6.4d. Distribution of prevalence of use and consumption of antiepileptics under approved care regime and *per conto* distribution (year 2020)

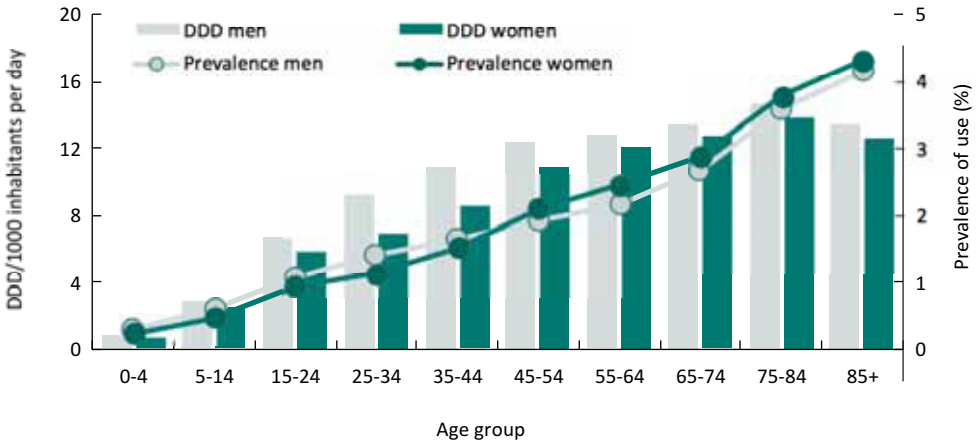


Table 3.6.4d. Exposure and duration of therapy with antiepileptics by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	1.8	0.91	60	8.7	201.7	132.0	13.8
Valle d'Aosta	1.5	1.02	57	8.3	209.8	140.0	14.6
Lombardy	1.5	0.92	58	8.1	203.4	132.0	14.3
A.P. of Bolzano	1.3	1.00	57	7.9	229.6	149.0	12.2
A.P. of Trento	1.7	0.92	60	9.1	206.7	132.0	13.4
Veneto	1.3	0.97	57	8.9	235.7	160.0	10.7
Friuli VG	1.4	0.89	60	9.0	251.8	180.0	11.5
Liguria	2.2	0.85	61	7.8	169.6	106.0	16.5
Emilia R.	1.6	0.85	60	7.7	166.2	100.0	16.9
Tuscany	2.5	0.87	60	7.7	149.0	80.0	19.0
Umbria	2.0	0.89	63	9.6	198.2	120.0	13.1
Marche	2.1	0.93	60	8.3	182.4	120.0	13.9
Lazio	2.4	0.87	58	8.3	166.9	90.0	17.3
Abruzzo	2.3	0.95	60	8.8	190.6	120.0	15.0
Molise	2.2	0.92	59	9.3	180.5	112.0	13.3
Campania	2.0	0.94	55	9.0	197.6	120.0	14.9
Puglia	2.2	0.95	59	7.7	175.8	100.0	19.9
Basilicata	2.3	0.94	59	9.6	188.2	120.0	13.5
Calabria	2.3	0.92	59	8.6	181.7	105.0	16.9
Sicily	2.2	0.96	59	8.8	179.9	110.0	14.8
Sardinia	2.4	0.84	58	9.8	176.3	112.0	13.3
Italy	**1.9**	**0.91**	**58**	**8.4**	**185.9**	**119.0**	**15.6**
North	1.6	0.91	59	8.3	201.4	130.0	14.1
Centre	2.4	0.88	59	8.2	164.6	93.0	17.2
South and	2.2	0.94	58	8.7	184.5	112.0	15.9

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.
- 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.

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3.6.5 Antipsychotics

National data on consumption and expenditure

From 2014 to 2020, the consumption of antipsychotic drugs increased by more than 20% from 8.3 in 2014 to 10.1 DDD in 2020. In terms of average annual variation (CAGR) there was an increase of 3.3%. In the same period, the cost per day of therapy remained almost stable, at 1.31 euros (Figure 3.6.5a). On average, for each citizen, the expenditure was equal to 4.87 euros with an increase of 2.1% compared to 2019 (+4.2% in terms of doses). The difference in the annual change was determined by a 2.3% reduction in the average cost per day of therapy (Table 3.6.5a).

Atypical and other antipsychotics are the category with the highest expenditure (4.56 euros per capita equal to about 94% of the total) and the highest consumption (7.8 DDD equal to 78% of the total), with an increase compared to 2019 of 2% and 3.7%, respectively (Table 3.6.5a). Although representing a smaller share of consumption, typical antipsychotics show the most consistent increases (+2.8% of expenditure and +3.7% of doses). For the subcategory of atypical antipsychotics there are marked differences in consumption between the Regions with almost double variations between minimum and maximum values (Figure 3.6.5c).

Also in 2020 paliperidone and aripiprazole are in the first two places in terms of expenditure (1.53 and 1.11 euros, respectively), with an increase compared to the previous year of 2.2% and 7.4%. Despite a reduced consumption in terms of prescribed doses, from 0.8 to 1.3 DDD, the high cost of both is determined by a cost per day of therapy which for paliperidone is 5.03 euros and for aripiprazole is 2.41 euros (Table 3.6.5a).

Haloperidol and lithium are the only typical antipsychotics present in the top ten with the highest cost, with an increase of 6.2% and 7.1%. 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. Although with an efficacy and safety profile comparable to other atypical antipsychotics, in the last year this molecule has shown an increase of 33% in terms of doses and 24.2% in terms of expenditure, with a cost per day of therapy equal to 2.30 euros compared to an average of 1.60 euros for atypical antipsychotics.

Patent-expired medicines account for 70.5% of antipsychotic doses and, of these, approximately 85% are generic products. Medicines covered by a patent, although with half the number of doses compared to those with an expired patent (3.0 vs 7.2), have an increase almost double that of the previous year (+6.3% vs 3.4%) (Table 3.6.5c).

Figure 3.6.5a. Antipsychotics, temporal trend of consumption and average cost per day of therapy (2014-2020)

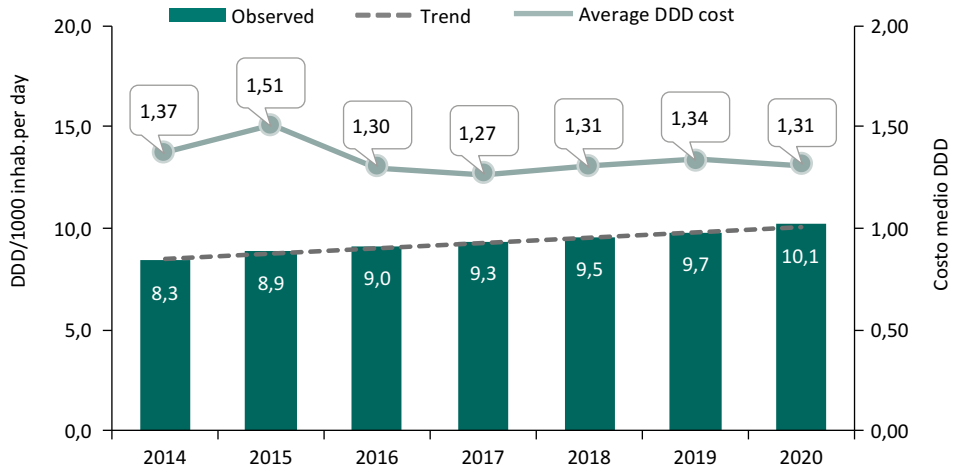


Table 3.6.5a. Antipsychotics, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Atypical and other antipsychotics	4.56	2.0	2.8	7.8	3.7	5.3	1.60	-1.9
Typical antipsychotics	0.31	4.1	-0.2	2.4	6.0	-1.7	0.35	-2.0
Antipsychotic medicines	**4.87**	**2.1**	**2.6**	**10.1**	**4.2**	**3.3**	**1.31**	**-2.3**
paliperidone	1.53	2.2	11.4	0.8	8.9	12.4	5.03	-6.5
aripiprazole	1.11	7.4	13.4	1.3	5.0	29.2	2.41	2.0
quetiapine	0.76	1.1	-4.6	2.0	2.1	2.8	1.05	-1.2
risperidone	0.43	-8.5	-7.2	0.9	-1.9	-0.2	1.38	-6.9
olanzapine	0.34	-1.7	-2.2	2.1	4.2	1.9	0.45	-5.9
clozapine	0.15	-0.5	0.4	0.5	1.1	2.3	0.88	-1.8
lurasidone	0.09	24.2	-	0.1	33.0	-	2.30	-6.9
haloperidol	0.08	6.2	0.9	1.2	6.1	0.8	0.19	-0.2
lithium	0.07	7.1	0.5	0.4	6.7	1.9	0.48	0.0
amisulpride	0.07	-1.1	-2.8	0.1	-1.1	-2.6	1.63	-0.3

Table 3.6.3b. Pain therapy, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	8.5	8.4	8.6	9.0	9.1	9.6	9.3	-3.0
Valle d'Aosta	9.4	9.5	9.1	9.2	9.2	10.0	10.0	0.4
Lombardy	7.7	7.9	8.1	8.1	8.3	8.8	8.8	0.0
A.P. of Bolzano	7.2	7.3	7.5	7.6	7.7	7.9	7.8	-1.9
A.P. of Trento	7.2	7.4	7.5	7.6	7.9	8.2	8.2	0.2
Veneto	6.9	6.8	7.0	7.1	7.3	7.8	7.7	-1.0
Friuli VG	9.2	9.5	9.8	10.0	9.9	10.0	10.0	0.2
Liguria	8.4	8.4	8.3	8.6	8.8	9.2	9.2	-0.5
Emilia R.	8.6	8.6	8.7	8.9	9.0	9.2	9.0	-2.1
Tuscany	9.2	9.1	8.9	8.6	8.6	8.7	8.6	-1.3
Umbria	6.5	6.7	6.9	7.0	7.5	7.8	8.0	2.3
Marche	6.4	6.4	6.4	6.5	6.5	6.6	6.5	-1.4
Lazio	6.4	6.5	6.5	6.7	6.9	7.3	7.4	0.4
Abruzzo	5.4	5.5	5.6	5.7	5.8	6.1	6.1	1.5
Molise	4.8	5.0	5.2	5.1	5.3	5.4	5.4	-1.0
Campania	4.4	4.4	4.5	4.5	4.8	5.1	5.1	-1.0
Puglia	5.6	5.6	5.7	5.8	6.0	6.5	6.5	0.0
Basilicata	5.0	5.0	4.9	5.0	5.2	5.6	5.6	0.6
Calabria	4.7	4.8	4.9	4.9	5.0	5.3	5.2	-1.6
Sicily	5.1	5.1	5.2	5.3	5.3	5.8	5.7	-0.3
Sardinia	6.8	7.0	7.0	7.1	7.3	7.7	7.8	1.2
Italy	**6.9**	**6.9**	**7.0**	**7.1**	**7.3**	**7.7**	**7.6**	**-0.7**
North	7.9	8.0	8.2	8.3	8.5	8.9	8.8	-1.1
Centre	7.3	7.3	7.3	7.3	7.5	7.7	7.7	-0.3
South and Islands	5.1	5.2	5.2	5.3	5.5	5.9	5.9	-0.2

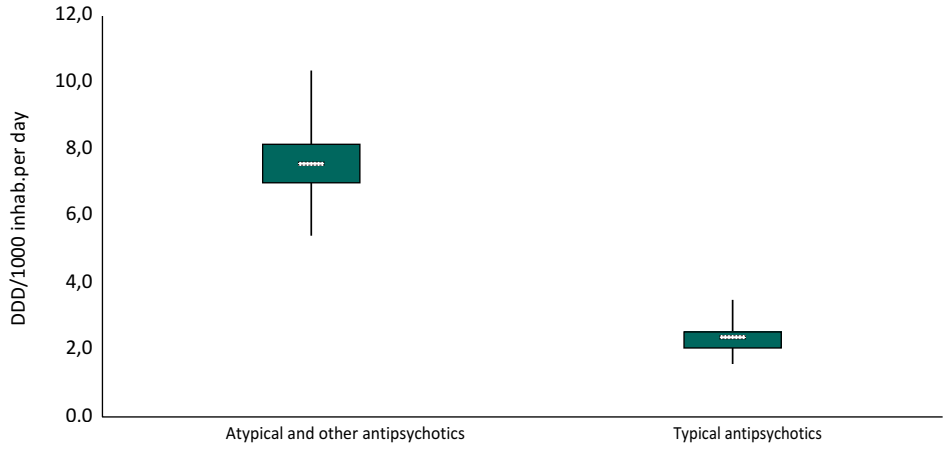
Table 3.6.3c. Prescription of medicines for pain therapy with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	1.85	27.8	3.5	4.0	53.0	2.3	1.25
Generic	0.67	36.0	5.8	1.3	31.8	7.3	1.42
Ex originator	1.18	64.0	2.2	2.7	68.2	0.1	1.17
Patent covered	4.80	72.2	-2.5	3.6	47.0	-3.9	3.67
Pain therapy	**6.65**	**100.0**	**-0.9**	**7.6**	**100.0**	**-0.7**	**2.39**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.6.5c. Antipsychotics, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to antipsychotics in the general population.

In line with the epidemiology of the clinical conditions in which antipsychotics are used, the prevalence of use increases with age up to 10% in women and 8% in men in the age group ≥85 years. Up to the age of 54, on average, men use more doses than women, despite an overlapping prevalence of use (Figure 3.6.5a). In Italy, the prevalence of use of antipsychotic medicines reached a value of 1.7% in 2020, with a minimum of 1.1% in the Veneto Region and a maximum of 2% in Sardinia. The Centre shows greater exposure than the North (2.0% vs 1.5%). The population using antipsychotic medicines is predominantly female (M/W ratio: 0.84), with a median age of 66 years (North: 67 years, Centre: 68 years and South: 64 years), receives about 7 prescriptions during the year and even if on average each user is treated for over 4 months (DDD per user: 131.4), half of the users remain on treatment for less than two months (median DDD: 56 days) and one fifth receives only one prescription during the year (Table 3.6.5d). These data may indicate that a large proportion of patients may experience significant side effects, particularly related to ideation and extrapyramidal disorders (e.g. dystonia, tremor, tardive dyskinesia), or that patients with schizophrenia do not respond to conventional antipsychotics.

Figure 3.6.5d. Distribution of prevalence of use and consumption of antipsychotic medicines under approved care regime and per conto distribution (year 2020)

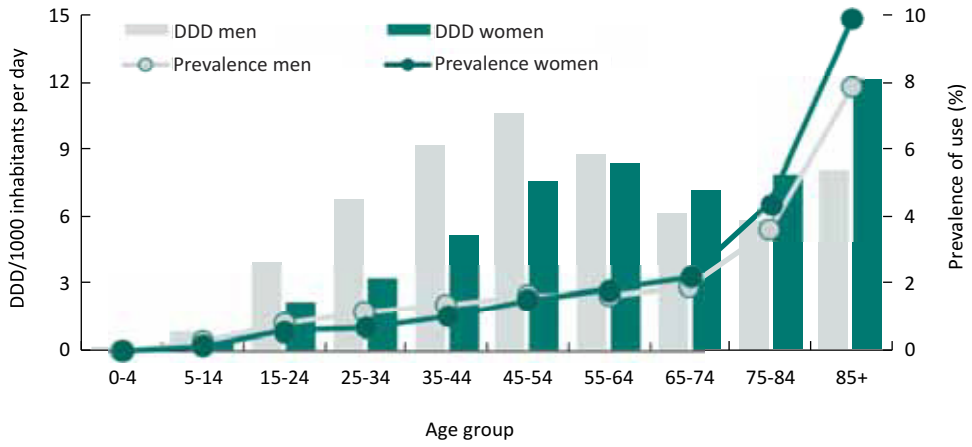


Table 3.6.5d. Exposure and duration of therapy with antipsychotics by Region under approved care regime per conto distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescrip-tions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	1.6	0.81	69	6.3	119.0	46.0	22.6
Valle d'Aosta	1.4	0.76	66	5.7	122.9	52.0	24.7
Lombardy	1.7	0.82	67	6.2	127.5	56.0	19.3
A.P. of Bolzano	1.3	0.81	63	4.7	106.3	51.0	24.7
A.P. of Trento	1.4	0.85	63	6.5	128.8	58.0	19.0
Veneto	1.1	0.84	62	6.1	132.1	60.0	20.1
Friuli VG	1.3	0.68	77	5.7	81.4	33.0	23.2
Liguria	2.0	0.75	73	6.7	99.2	40.0	22.9
Emilia R.	1.2	0.76	67	5.5	102.5	45.0	24.6
Tuscany	2.0	0.77	70	6.3	100.2	42.0	23.7
Umbria	2.1	0.72	79	7.4	82.5	37.0	19.0
Marche	1.9	0.81	68	6.3	116.8	55.0	19.9
Lazio	2.0	0.82	65	7.2	133.5	56.0	19.4
Abruzzo	2.2	0.83	70	7.4	128.5	55.0	17.3
Molise	2.1	0.81	68	7.4	135.5	60.0	17.0
Campania	1.5	0.95	62	8.4	157.4	66.0	17.0
Puglia	2.0	0.92	65	7.1	148.5	61.0	20.4
Basilicata	2.0	0.88	64	8.6	155.4	75.0	15.2
Calabria	1.8	0.95	62	7.5	162.0	75.0	18.1
Sicily	2.0	0.91	64	7.4	159.3	71.0	17.1
Sardinia	2.7	0.78	65	8.7	148.1	60.0	15.3
Italy	**1.7**	**0.84**	**66**	**6.9**	**131.4**	**56.0**	**19.7**
North	1.5	0.80	67	6.1	119.2	49.0	21.2
Centre	2.0	0.80	68	6.8	117.4	48.0	20.8
South and Islands	1.9	0.90	64	7.7	152.8	66.0	17.6

Key message

- The data document an increase in the use of antipsychotics in 2020 compared to 2019, more marked for the typical antipsychotics than for the atypical ones. This is probably related to the effect of lockdown policies to control the COVID-19 pandemic on the extremely fragile category of patients, which includes not only psychiatric patients but also those with dementia for whom off-label use of these drugs is widely described.
- 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.

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3.6.6. Antiparkinsonians

National data on consumption and expenditure

In 2020, the consumption of antiparkinsonian medicines reached 5.9 DDD/1000 inhabitants per day, down by 0.6% compared to 2019 and with an average annual increase of 1.4% between 2014 and 2020 (Figure 3.6. 6a). On average, each day of therapy costs 1.64 euros (-8.4% compared to 2014), with values ranging between 1.31 euros for MAO inhibitors and 4.11 euros 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 2020 with 2.4 DDD (equal to 41% of the total antiparkinsonians) and an expenditure of 1.27 euros per capita (-0.6% and +0.9% respectively compared to 2019), followed by dopamine agonists, down 4% in terms of doses and 2.9% 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 (+8.1%) and expenditure (+6.7%), with values exceeding 20% increase when compared to 2014 (Table 3.6.6a).

Associations of levodopa with benserazide and carbidopa are the most used molecules in the population with 1.1 and 0.9 DDD respectively, while opicapone and safinamide have the highest increase (+14.8% and +9.6%). The latter substance is indicated for the treatment of patients with moderate or advanced Parkinson's disease plain or in combination with other medicines. Opicapone, the last marketed molecule in the class of COMT inhibitors, can be administered once daily due to its prolonged action.

Expired patent medicines represent about half of the doses and about 35% of the expenditure, with a limited use of equivalent products (23% of the total) and even if compared to 2019 they show an increase of 9.2%, a trend similar is present for products still covered by patents (+6.4%). The average cost per day of therapy for patent-expired medicines is 42% lower than that of medicines covered by patents (1.19 vs 2.05 euros) (Table 3.6.6c).

Stratifying the consumption data by therapeutic subcategory, a high regional variability is observed for the consumption of MAO inhibitors, with values ranging from a minimum of 0.35 to a maximum of 2.43 DDD per 1000 inhabitants per day, while for dopamine-agonists there are the least interregional differences (Figure 3.6.6c).

Figure 3.6.6a. Antiparkinsonians, temporal trend of consumption and average cost per day of therapy (2014-2020)

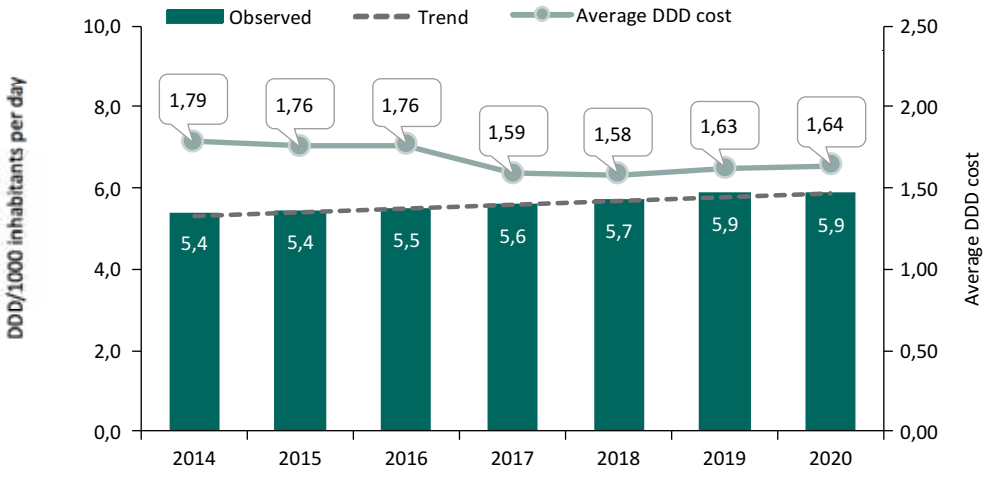


Table 3.6.6a. Antiparkinsonians, per capita expenditure and consumption (DDD/1000 inhab.per day) by therapeutic category and by substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
DOPA-derivatives agonists, plain or in combination	1.27	1.9	0.9	2.4	-0.6	1.2	1.45	2.3
Dopamine-agonists	1.23	-2.9	-1.8	1.2	-4.0	-3.4	2.82	0.9
MAO inhibitors	0.80	3.1	-1.0	1.7	1.2	6.7	1.31	1.7
COMT inhibitors	0.17	6.7	24.3	0.1	8.1	26.1	4.11	-1.6
Anticolinergics	0.05	0.4	-1.3	0.5	0.4	-1.3	0.26	-0.2
Amantadine	0.00	22.7	-10.4	0.0	1.1	-17.9	0.67	21.0
Antiparkinsonian medicines	**3.52**	**0.7**	**0.0**	**5.9**	**-0.6**	**1.4**	**1.64**	**1.0**
rotigotine	0.72	-2.0	1.8	0.4	-2.1	1.9	5.26	-0.1
levodopa/carbidopa	0.69	6.0	5.8	0.9	0.3	1.2	2.06	5.3
safinamide	0.40	7.5	-	0.3	9.6	-	4.33	-2.2
pramipexole	0.38	-2.1	-4.7	0.5	-3.4	-3.1	2.15	1.1
levodopa/benserazide	0.36	0.6	4.0	1.1	0.2	3.6	0.90	0.1
rasagiline	0.28	-0.8	-15.3	0.4	-0.5	-2.1	2.03	-0.5
melevodopa/carbidopa	0.16	-1.4	3.0	0.2	-1.1	1.7	1.82	-0.5
opicapone	0.15	10.7	-	0.1	14.8	-	4.04	-3.9
selegiline	0.12	-1.2	4.8	1.0	-0.1	6.7	0.31	-1.4
ropinirole	0.11	-9.9	-8.9	0.3	-6.6	-8.1	0.95	-3.8

Table 3.6.6b. Antiparkinsonians, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	5.9	5.9	5.9	6.0	6.1	6.3	6.2	-1.3
Valle d'Aosta	5.1	5.0	5.1	5.3	5.6	5.8	6.0	3.7
Lombardy	4.5	4.5	4.6	4.7	4.8	4.9	4.9	-0.7
A.P. of Bolzano	4.4	4.3	4.0	3.9	4.0	4.1	4.1	-0.2
A.P. of Trento	5.0	5.0	4.9	5.0	5.0	4.9	4.7	-4.7
Veneto	5.5	5.5	5.5	5.6	5.7	5.9	5.8	-1.1
Friuli VG	5.0	4.7	4.8	5.3	5.4	5.6	5.1	-9.0
Liguria	6.3	6.3	6.4	6.5	6.7	6.7	6.7	-0.2
Emilia R.	5.3	5.3	5.4	5.3	5.3	5.4	5.3	-2.0
Tuscany	5.6	5.8	5.8	5.8	5.7	5.9	5.9	-1.0
Umbria	6.0	6.0	6.2	6.2	6.4	6.6	6.6	1.1
Marche	6.6	6.6	6.6	6.7	6.8	6.8	6.8	0.0
Lazio	5.7	5.8	5.9	6.0	6.3	6.6	6.6	-0.7
Abruzzo	5.8	6.0	6.2	6.4	6.7	7.0	7.0	0.2
Molise	5.4	5.3	5.5	5.5	5.6	5.8	5.9	1.0
Campania	4.9	5.0	5.1	5.2	5.5	5.7	5.8	0.9
Puglia	5.8	5.8	5.8	5.8	5.9	6.1	6.2	0.5
Basilicata	5.5	5.4	5.6	5.8	6.1	6.3	6.3	-0.1
Calabria	5.6	5.6	5.6	5.6	5.7	5.9	5.9	-0.4
Sicily	5.7	5.7	5.8	6.0	6.2	6.4	6.5	0.7
Sardinia	4.9	5.0	4.8	5.1	5.2	5.4	5.5	2.0
Italy	**5.4**	**5.4**	**5.5**	**5.6**	**5.7**	**5.9**	**5.9**	**-0.6**
North	5.2	5.2	5.2	5.3	5.4	5.5	5.4	-1.5
Centre	5.8	5.9	6.0	6.0	6.2	6.4	6.4	-0.5
South and Islands	5.4	5.5	5.5	5.7	5.8	6.1	6.1	0.6

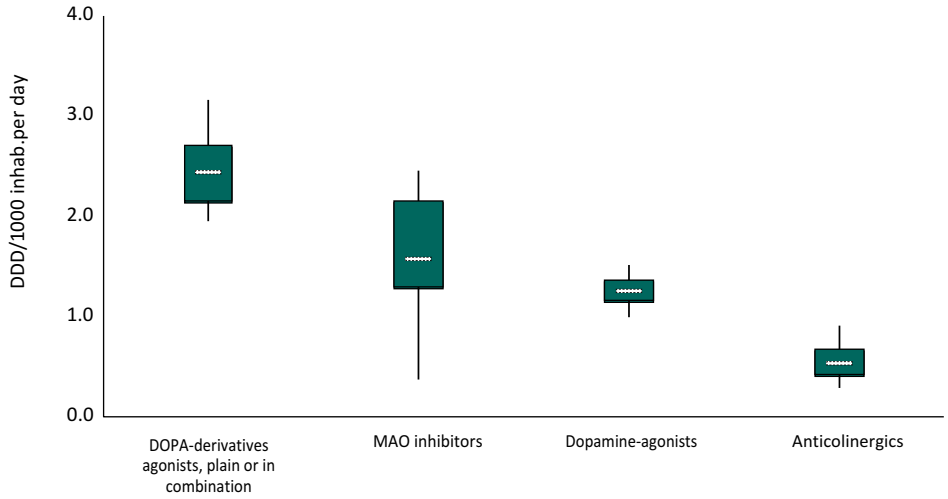
Table 3.6.6c. Prescription of antiparkinsonians with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	1.21	34.4	-3.4	2.8	47.5	-3.1	1.19
Generic	0.27	22.5	-6.2	0.6	23.1	-4.4	1.16
Ex originator	0.94	77.5	-2.6	2.1	76.9	-2.7	1.20
Patent covered	2.31	65.6	3.0	3.1	52.5	1.8	2.05
Antiparkinsonians	**3.52**	**100.0**	**0.7**	**5.9**	**100.0**	**-0.6**	**1.64**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.6.6c. Antiparkinsonians, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to antiparkinsonian medicines 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 4.6% in the age range of 85 and over, in line with the epidemiology of the condition men have a greater use in all age groups with differences compared to women ranging from 50% to 70%. For example, in the over 85 age group there is a 1% higher prevalence (4.6% vs 3.6%) and a 50% higher consumption (25.5 vs 17.1 DDD) (Figure 3.6.6d).

In Italy, about one in 100 people was treated with antiparkinsonian medicines in 2020, with a regional variability ranging from 0.5% in the A.P. of Trento to 1% in Liguria. Half of the users are older than 76 years and, on average, each subject has been in treatment for over 8 months. It should be noted, however, that half of the subjects were treated for less than 4 months and 15.6% received only one prescription during the year (Table 3.6.6d).

Figure 3.6.6d. Distribution of prevalence of use and consumption of antiparkinsonian medicines under approved care regime and *per conto* distribution (year 2020)

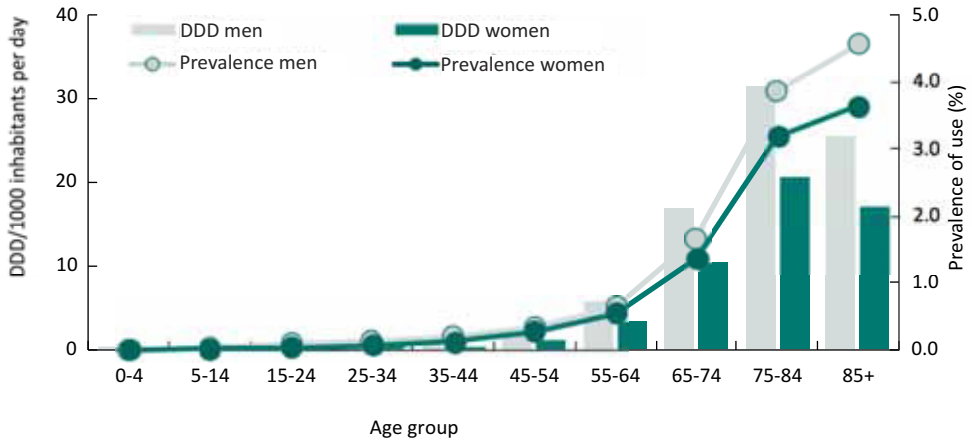


Table 3.6.6d. Exposure and duration of therapy with antiparkinsonian medicines by Region under approved care regime and per conto distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	0.8	1.02	77	10.0	253.5	122.0	13.3
Valle d'Aosta	0.7	0.91	75	9.1	285.8	135.0	15.3
Lombardy	0.6	1.03	77	9.2	279.9	144.0	12.8
A.P. of Bolzano	0.6	0.86	76	8.5	189.0	83.0	15.1
A.P. of Trento	0.5	1.01	73	10.8	271.2	141.0	10.9
Veneto	0.7	0.98	75	9.7	281.3	140.0	11.5
Friuli VG	0.6	0.93	77	10.5	291.4	149.0	12.1
Liguria	1.0	0.94	79	9.5	251.5	124.0	14.8
Emilia R.	0.7	0.98	78	9.0	198.6	108.0	13.9
Tuscany	0.9	0.95	78	10.0	228.2	103.0	17.6
Umbria	1.0	0.97	79	12.3	233.3	120.0	11.6
Marche	0.9	0.94	78	9.4	235.3	120.0	14.0
Lazio	0.8	1.02	77	10.6	287.3	144.0	14.5
Abruzzo	0.9	0.97	77	11.1	259.1	133.0	12.1
Molise	0.8	1.02	76	9.9	258.0	149.0	13.6
Campania	0.7	1.02	76	10.2	256.5	132.0	15.4
Puglia	0.9	0.99	75	8.7	226.2	116.0	18.8
Basilicata	0.8	1.05	76	11.2	276.0	140.0	11.9
Calabria	0.8	1.07	73	9.6	247.4	120.0	15.7
Sicily	0.9	1.03	75	9.1	249.3	135.0	14.2
Sardinia	0.8	0.99	72	10.9	260.0	140.0	11.5
Italy	**0.8**	**1.00**	**76**	**9.7**	**254.5**	**130.0**	**14.3**
North	0.7	1.00	77	9.5	258.8	133.0	13.0
Centre	0.9	0.98	78	10.4	256.6	124.0	15.2
South and Islands	0.8	1.02	75	9.7	248.3	126.0	15.2

Key message

- The **wide regional variability** in the use of antiparkinsonians and some specific categories (MAO inhibitors and dopa-derived agonists plain or in combination) as well as the fact that half of the subjects are treated for less than 4 months and 15,6% received only one prescription during the year highlight the **need to further disseminate and implement 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.

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3.6.7 Antimigraine medicines

National data on consumption and expenditure

In the last seven years, the consumption in terms of DDD/1000 inhabitants per day of medicines for the treatment of migraine is almost stable with slight average annual variations (CAGR 1.2%), while as regards the total per capita expenditure there is a more marked average annual variation (CAGR -4.2%), with an average cost per day of therapy which, compared to 2019, underwent a decline of 3.3% (Figure 3.6.7a and Table 3.6.7a). In detail, triptans occupy almost all of the expenditure of the entire category (0.99 out of 1.03 euros per capita) and consumption with 0.8 DDD/1000 inhabitants per day. The average cost per day of therapy is also the highest (3.22 euros) compared to the total for the category (3.07 euros). Monoclonal antibodies are a subgroup of which a historical series is not yet available either in terms of expenditure or consumption as they have been approved for the treatment of migraine (through a centralised procedure) and, therefore, placed on the market, in fairly recent times (February 2019). However, as can be seen in the detail of the individual active ingredients such as erenumab, galcanezumab and fremanezumab, their impact on expenditure and on the quantities used, although still small, is showing a significant increase compared to 2019. These medicines have been approved not for the treatment of migraines but for prophylaxis in patients who have recurrent migraine episodes and attacks (at least 4 migraine days per month).

In interpreting the expenditure and consumption indicators calculated for the different subgroups, in particular monoclonal antibodies and triptans, the different setting of use, respectively prophylaxis and acute treatment, must be taken into account.

Patent-expired medicines in 2020 represent more than 90% of the consumption of the entire category (0.8 DDD) and more than 95% of expenditure (0.98 euros) with increases, compared to 2019, of more than 1% for both measures considered. In particular, however, it is the former originators that are most widely used, accounting for about two thirds of consumption for patent-expired medicines. With regard to generic medicines, consumption, and consequently expenditure, has increased significantly compared to 2019 (+ 6.1% and + 7%, respectively), there is no particular difference in the average cost per day of therapy compared to ex originator. Medicines covered by patents, on the other hand, cover a minimal share of consumption and expenditure, however even in this case there are increases compared to the previous year.

Figure 3.6.7a. Antimigraine medicines, temporal trend of consumption and average cost per day of therapy (2014-2020)

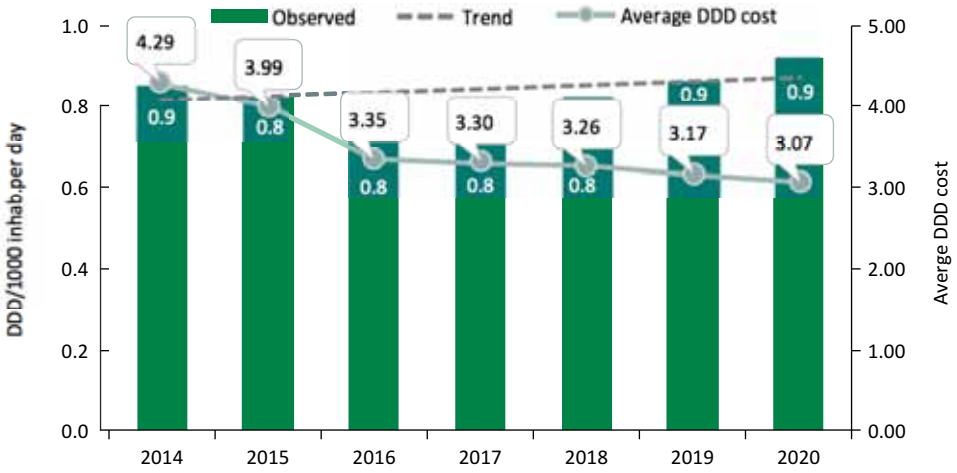

Table 3.6.7a. Antimigraine medicines, per capita expenditure and consumption (DDD/1000 ab day) by therapeutic category and by substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Triptans	0.99	-0.9	-4.8	0.8	0.2	0.5	3.22	-1.3
Monoclonal antibodies	0.04	2811.1	-	0.1	204.5	-	1.38	853.5
Other antimigraine medicines	0.00	-2.5	-29.2	0.0	-7.6	-42.2	1.17	5.2
Ergot alkaloids	0.00	26.2	-52.0	0.0	-17.8	-53.8	0.40	53.2
Antimigraine medicines	**1.03**	**2.7**	**-4.2**	**0.9**	**5.9**	**1.2**	**3.07**	**-3.3**
rizatriptan	0.22	3.0	0.7	0.2	2.1	1.6	2.86	0.6
sumatriptan	0.21	-1.2	-2.7	0.2	-2.0	-1.6	3.55	0.5
almotriptan	0.18	-0.6	-8.7	0.2	-0.8	0.0	3.21	-0.1
eletriptan	0.16	-2.5	-4.8	0.1	3.6	4.4	3.50	-6.2
frovatriptan	0.14	-1.1	-9.2	0.1	-1.3	-0.7	3.20	-0.1
zolmitriptan	0.06	-8.2	-1.5	0.1	-2.4	-0.4	3.02	-6.3
erenumab	0.02	2719.5	-	0.1	173.3	-	1.05	928.8
galcanezumab	0.01	1963.1	-	0.0	1001.9	-	2.89	86.7
fremanezumab	0.00	-	-	0.0	-	-	7.18	-
indomethacin/caffeine/ prochlorperazine	0.00	-1.0	1.2	0.0	-2.4	1.5	1.18	1.2

Table 3.6.7b. Antimigraine medicines, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.6
Valle d'Aosta	1.2	1.1	1.0	1.0	1.0	1.2	1.2	0.7
Lombardy	0.9	0.8	0.8	0.8	0.8	0.9	0.9	1.9
A.P. of Bolzano	0.8	0.8	0.8	0.7	0.7	0.8	0.9	17.8
A.P. of Trento	1.1	1.0	1.0	1.0	1.0	1.0	1.1	4.2
Veneto	1.0	1.0	1.0	1.0	1.0	1.0	1.1	5.7
Friuli VG	1.0	1.0	1.0	1.0	1.0	1.1	1.2	9.4
Liguria	0.8	0.8	0.8	0.7	0.7	0.8	0.8	6.7
Emilia R.	1.0	1.0	1.0	1.0	1.0	1.1	1.2	7.6
Tuscany	0.7	0.7	0.7	0.7	0.6	0.7	0.7	7.6
Umbria	0.6	0.5	0.5	0.5	0.5	0.6	0.6	-2.8
Marche	0.8	0.8	0.8	0.8	0.8	0.8	0.9	6.1
Lazio	0.8	0.8	0.8	0.8	0.8	0.9	1.0	11.9
Abruzzo	0.8	0.7	0.7	0.7	0.7	0.8	0.9	7.2
Molise	0.6	0.5	0.5	0.5	0.6	0.6	0.6	4.9
Campania	0.6	0.6	0.6	0.6	0.6	0.6	0.7	8.3
Puglia	0.9	0.8	0.8	0.8	0.8	0.9	0.9	6.9
Basilicata	0.6	0.6	0.6	0.6	0.5	0.6	0.6	15.8
Calabria	0.7	0.7	0.6	0.6	0.7	0.7	0.8	11.4
Sicily	0.8	0.8	0.8	0.8	0.8	0.8	0.8	4.0
Sardinia	1.1	1.1	1.1	1.1	1.1	1.1	1.1	4.0
Italy	**0.9**	**0.8**	**0.8**	**0.8**	**0.8**	**0.9**	**0.9**	**5.9**
North	1.0	0.9	0.9	0.9	0.9	1.0	1.0	4.3
Centre	0.8	0.7	0.7	0.7	0.7	0.8	0.9	9.1
South and Islands	0.8	0.7	0.7	0.7	0.7	0.8	0.8	6.7

Table 3.6.7c. Prescription of antimigraine medicines with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	0.98	95.2	1.7	0.8	91.5	1.3	3.19
Generic	0.35	36.1	7.0	0.3	36.8	6.1	3.13
Ex originator	0.62	63.9	-1.0	0.5	63.2	-1.4	3.23
Patent covered	0.05	4.8	26.6	0.1	8.5	108.5	1.73
Medicines antimigraine medicines	**1.03**	**100.0**	**2.7**	**0.9**	**100.0**	**5.9**	**3.07**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to antimigraine medicines in the general population.

In line with the prevalence data relating to migraine disorders available in literature, clear differences are observed between men and women, which are consequently also reflected in the levels of consumption (Figure 3.6.7c). In detail, starting from the 15-24 age group there is a progressive increase in the prevalence in women which reaches about 20% 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 for prevalence. A similar, but significantly less pronounced trend is seen in men, with higher prevalence (4.8%) and consumption (0.7 DDD) in the 45-54 age group. A higher prevalence in women is also confirmed by the male/female ratio of 0.29, with greater differences in the northern areas (Table 3.6.7d). On average, each user received about 4.9 prescriptions per year, rising to 5.1 in the North compared with the Centre, which has values closer to the national average. In the South, on the other hand, lower prescription data are found compared with the national average, despite Sardinia being the Region in which the greatest number of prescriptions is found as compared with the national territory, while Calabria, followed by Campania, reports lower values (4.1 and 4.4 respectively). Each user received, on average during the year, at least one dose of medicines for the treatment of migraine for about 50 days. Also for this indicator, the Northern Regions have the highest levels of intensity of use with 52 days per user, with the maximum level reached in the Veneto (54 days), while the South shows the lowest intensity of use with about 45 days per user, with Campania recording the lowest value (41 days) and Sardinia the highest value (58 days).

Since this indicator could be affected by extreme values due for example to the inclusion of subjects who receive a prescription towards the end of the year or those who stop treatment early, the median DDD indicator was also considered so as to detect, where present, any distortion that could lead to an overestimation or underestimation of the average days of therapy calculated for each user. In fact, the results show that the median duration of treatment at national level drops from about 49 to 24 days. This difference is observed to a greater or lesser extent also in each individual Region. Approximately 35% of subjects received a single prescription for migraine medicines in 2020, with Southern Regions registering the largest proportion (37.5%), while Sardinia is the only Region to register values below 30% (Table 3.6.7d).

Figure 3.6.7c. Distribution of prevalence of use and consumption of antimigraine medicines under approved care regime and *per conto* distribution (year 2020)

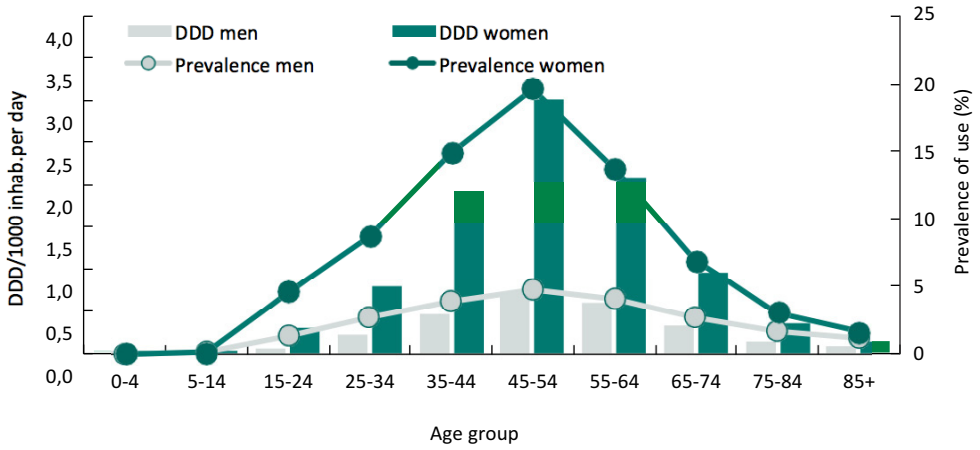

Table 3.6.7d. Exposure and duration of therapy with antimigraine medicines by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	0.7	0.27	49	5.0	51.2	24.0	32.2
Valle d'Aosta	0.7	0.22	49	4.8	49.7	24.0	33.1
Lombardy	0.6	0.27	49	4.9	50.9	24.0	33.7
A.P. of Bolzano	0.6	0.24	48	4.2	42.6	24.0	35.2
A.P. of Trento	0.7	0.30	49	5.2	53.4	24.0	32.7
Veneto	0.7	0.26	49	5.3	54.4	27.0	31.5
Friuli VG	0.7	0.25	49	5.3	54.1	24.0	30.8
Liguria	0.6	0.29	51	4.7	47.3	24.0	35.2
Emilia R.	0.7	0.27	48	5.3	53.9	24.0	31.7
Tuscany	0.5	0.28	50	4.8	45.8	24.0	35.3
Umbria	0.5	0.27	50	5.3	47.7	24.0	31.3
Marche	0.6	0.29	49	4.4	43.5	24.0	34.7
Lazio	0.6	0.30	50	4.8	48.6	24.0	35.3
Abruzzo	0.6	0.29	50	4.9	47.6	24.0	35.2
Molise	0.5	0.31	50	4.8	46.2	24.0	35.2
Campania	0.5	0.34	49	4.4	41.4	18.0	40.4
Puglia	0.7	0.35	50	4.5	45.2	18.0	39.7
Basilicata	0.5	0.33	50	4.6	42.3	18.0	39.3
Calabria	0.6	0.36	51	4.1	38.1	12.0	43.9
Sicily	0.6	0.33	50	4.7	45.1	18.0	37.5
Sardinia	0.7	0.23	49	5.9	58.3	30.0	28.7
Italy	**0.6**	**0.29**	**49**	**4.9**	**48.7**	**24.0**	**34.9**
North	0.7	0.27	49	5.1	52.0	24.0	32.6
Centre	0.6	0.29	50	4.8	47.1	24.0	35.0
South and	0.6	0.33	50	4.7	44.9	18.0	38.3

Key message

- 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.
- 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.

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3.6.8 Antidementia medicines

National data on consumption and expenditure

In 2020 medicines used in dementia recorded a slight reduction in consumption compared to 2019 (-3%). However, they reached 2.5 DDD/1000 inhabitants per day, with an average annual variation (CAGR) in the 2014-2020 period of +1.3% of consumption and -11.6% of expenditure, which stood at 0.44 euros per capita in 2020. In the same period, the average cost per day of therapy more than halved, going from 1.19 to 0.49 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 medicines recorded cost reductions. Rivastigmine is the active ingredient that represents half of the expenditure of the entire category with 0.22 euros per capita, with an average cost per day of therapy more than double compared to the category average. Galantamine is the molecule that has the smallest impact on expenditure with 0.01 euro per capita, due to low consumption. Memantine is the only active ingredient that, compared to 2019, records increases both in terms of expenditure (+5.4%; 0.14 euros per capita), and consumption (+3%; up to 1.1 DDD) (Table 3.6.8a).

As already mentioned, recent years have seen the patent expiry of all molecules used in dementia. Patent-expired medicines represent, in detail, not only almost all per capita expenditure (86.2%) with an average cost per day of therapy of 0.47 euros, but also in terms of consumption (89.1%), of which more than 2/3 relate to generic medicines that have a cost per day of therapy 32% lower than that of the ex originators (0.42 euros vs 0.62 euros) (Table 3.6.8c).

Finally, despite having a cost per day of therapy that is higher than the average for the group, patent-covered medicines have a lower impact on per capita expenditure (0.06 euros) due to reduced levels of consumption, which is also 21.5% lower than in 2019.

Figure 3.6.8a. Antidementia medicines, temporal trend of consumption and average cost per day of therapy (2014-2020)

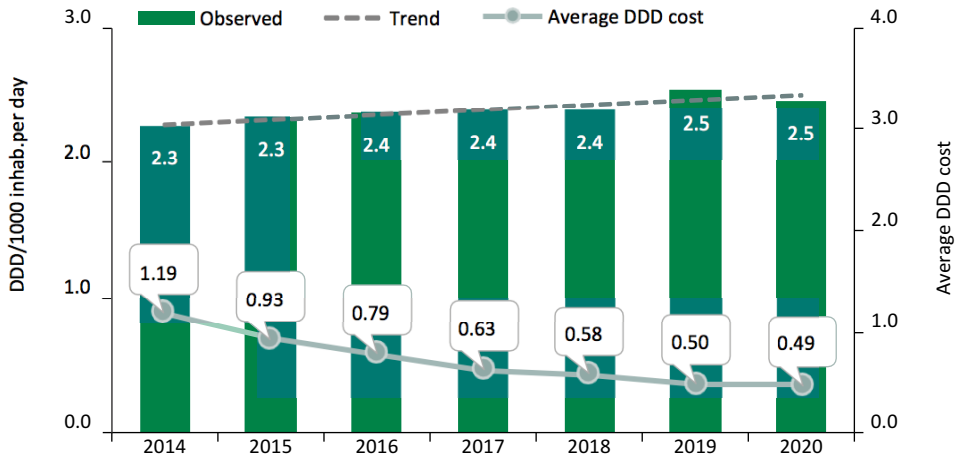


Table 3.6.8a. Antidementia medicines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Anticholinesterases	0.30	-9.0	-13.1	1.4	-7.0	-1.1	0.58	-2.4
Other antidementia medicines	0.14	5.4	-11.4	1.1	3.0	5.3	0.37	2.1
Antidementia medicines	**0.44**	**-4.7**	**-12.6**	**2.5**	**-3.0**	**1.3**	**0.49**	**-2.1**
rivastigmine	0.22	-8.6	-14.9	0.5	-6.2	-3.4	1.11	-2.9
memantine	0.14	5.4	-11.4	1.1	3.0	5.3	0.37	2.1
donepezil	0.07	-9.0	-4.9	0.8	-7.1	1.4	0.22	-2.3
galantamine	0.01	-13.7	-12.5	0.0	-15.4	-12.8	1.01	1.8
indomethacin/caffeine/ prochlorperazine	0.00	-1.0	1.2	0.0	-2.4	1.5	1.18	1.2

Table 3.6.8b. Antidementia medicines, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	2.2	2.2	2.1	2.1	2.0	2.2	2.1	-2.9
Valle d'Aosta	2.0	1.4	1.8	1.8	2.0	2.1	2.0	-2.8
Lombardy	2.0	2.2	2.2	2.2	2.3	2.3	2.2	-3.4
A.P. of Bolzano	3.5	4.2	4.6	4.1	4.7	4.7	4.5	-5.3
A.P. of Trento	1.3	1.2	1.2	1.1	1.2	1.2	1.1	-10.3
Veneto	2.4	2.5	2.6	2.6	2.8	2.9	2.6	-9.8
Friuli VG	2.0	1.5	1.6	2.2	2.1	2.1	1.7	-21.2
Liguria	3.6	3.5	3.3	3.8	3.2	3.8	4.0	5.2
Emilia R.	1.9	1.8	1.9	1.9	1.9	2.0	1.9	-3.0
Tuscany	3.1	3.5	3.7	3.2	3.5	3.4	3.5	1.4
Umbria	3.3	3.4	3.7	3.7	4.0	4.2	4.3	0.4
Marche	2.5	2.2	1.5	1.6	2.4	3.7	2.8	-24.3
Lazio	2.4	2.3	2.4	2.7	2.6	2.6	2.8	7.6
Abruzzo	3.7	3.8	3.7	3.7	4.0	3.8	3.9	2.0
Molise	1.7	1.8	2.0	2.3	2.3	2.5	2.6	2.6
Campania	2.1	2.3	2.4	2.5	2.1	2.6	2.6	0.8
Puglia	2.1	2.2	2.2	2.2	2.2	2.3	2.3	2.5
Basilicata	1.7	1.8	1.8	2.3	2.1	2.4	1.8	-23.7
Calabria	2.2	2.1	2.2	1.9	2.1	2.1	1.9	-10.8
Sicily	1.8	1.7	1.7	1.6	1.7	1.7	1.5	-12.0
Sardinia	2.3	2.1	2.2	2.1	1.5	2.2	2.2	1.2
Italy	**2.3**	**2.3**	**2.4**	**2.4**	**2.4**	**2.5**	**2.5**	**-3.0**
North	2.2	2.3	2.3	2.3	2.3	2.4	2.3	-4.7
Centre	2.7	2.8	2.8	2.8	3.0	3.1	3.1	-0.2
South and Islands	2.1	2.2	2.2	2.2	2.1	2.3	2.2	-2.6

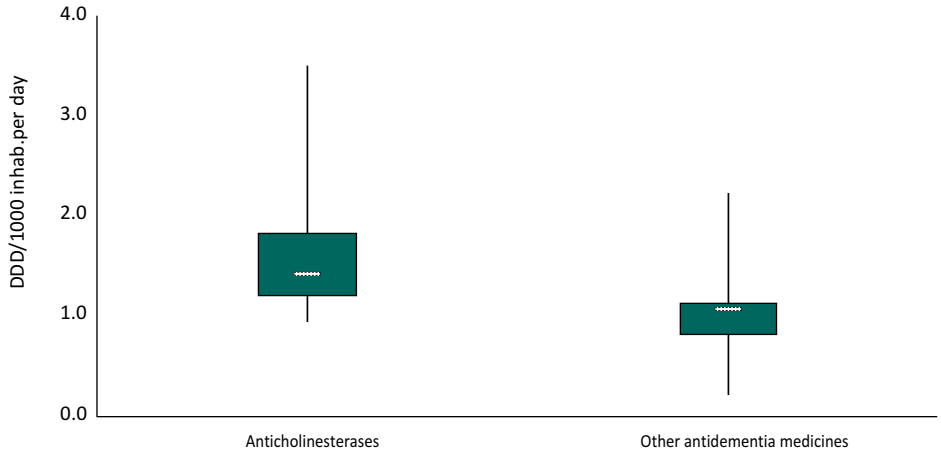
Table 3.6.8c. Prescription of antidementia medicines with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	0.38	86.2	1.8	2.2	89.1	-0.1	0.47
Generic	0.25	64.7	-0.4	1.6	72.8	-1.9	0.42
Ex originator	0.13	35.3	6.3	0.6	27.2	5.1	0.62
Patent covered	0.06	13.8	-31.9	0.3	10.9	-21.5	0.62
Antidementia medicines	**0.44**	**100.0**	**-4.7**	**2.5**	**100.0**	**-3.0**	**0.49**

*source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.6.8c. Antidementia medicines, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



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% in the more extreme ranges (85+ years). There are differences between men and women which tend to be greater both in terms of prevalence and consumption, especially in the over 75 years of age. In this age group, women have a 35% higher consumption and a higher prevalence (2.3% vs 1.7%) than men (Figure 3.6.8d).

National data show a prevalence of 0.3% with some interregional differences; in the A.P. of Trento, Emilia Romagna and Sicily, exposure to medicines is lower, while Umbria, Abruzzo and Liguria report levels above the national average (Table 3.6.d). The M/W ratio shows slight differences among Regions with Valle d'Aosta, Marche and Sardinia which report the lowest values compared to the national average (0.53 vs 0.60). As expected, the median age of users is 81 years and, even in this case, there are no differences among each individual Region. As regards prescriptions per user (6.1 on average), the North has lower values (5.4 prescriptions per user), while the Centre and even more markedly the South and Islands have 6.5 and 6.8 prescriptions per user, respectively, with Umbria having the highest intensity of use with 8.4 prescriptions. At national level, each user in 2020 took at least one dose of the medicine for about 8.5 months of therapy, with the central Regions instead recording lower consumption up to covering just over 8 months of therapy. Half of the 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 values range from the lowest in Molise (186 days) and Emilia Romagna (196 days) to the highest in Friuli Venezia Giulia (280 days) and the Autonomous Province of Bolzano (300 days). Finally, the Regions with the highest proportion of users with only one prescription are Molise, Tuscany and Emilia Romagna (between 15 and 16%) compared to Umbria and Campania where the lowest proportion is recorded (8.9%). With regard to the calculation of the latter indicator, it must be borne in mind that subjects who receive a first prescription towards the end of the year or subjects who, following the onset of undesirable effects, discontinue treatment during the year (outliers) also tend to be included.

Figure 3.6.8d. Distribution of 2020 prevalence of use and consumption of antidementia medicines under approved care regime and *per conto* distribution

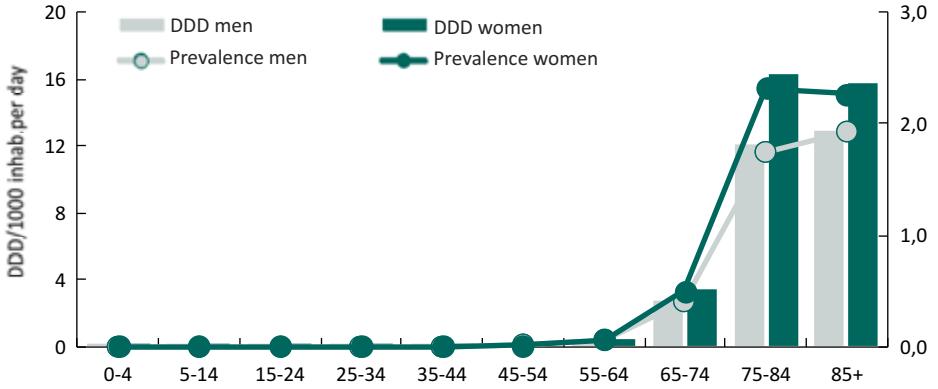


Table 3.6.8d. Exposure and duration of therapy with antidementia medicines by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	0.3	0.61	80	5.6	248.1	224.0	11.4
Valle d'Aosta	0.3	0.53	80	4.9	238.3	223.0	14.9
Lombardy	0.3	0.57	81	5.2	268.3	224.0	12.9
A.P. of Bolzano	0.3	0.53	83	5.0	312.9	300.0	12.8
A.P. of Trento	0.1	0.66	80	4.8	249.0	224.0	14.3
Veneto	0.3	0.59	81	5.4	265.9	224.0	11.4
Friuli VG	0.3	0.58	81	5.5	284.8	280.0	10.1
Liguria	0.5	0.60	82	6.9	263.9	224.0	13.1
Emilia R.	0.2	0.61	81	4.5	213.2	196.0	16.0
Tuscany	0.4	0.60	82	5.6	242.3	203.0	15.4
Umbria	0.6	0.55	82	8.4	271.7	252.0	8.9
Marche	0.4	0.53	81	5.7	236.4	224.0	11.7
Lazio	0.4	0.64	80	6.8	244.2	205.0	14.2
Abruzzo	0.5	0.59	81	6.4	272.1	242.0	11.1
Molise	0.4	0.61	81	5.9	235.9	186.0	15.5
Campania	0.3	0.62	79	8.0	243.8	242.0	8.9
Puglia	0.3	0.59	79	6.0	234.7	204.0	15.8
Basilicata	0.3	0.55	81	7.5	270.4	280.0	10.5
Calabria	0.3	0.62	80	6.6	250.6	224.0	12.7
Sicily	0.2	0.61	79	5.3	273.9	252.0	12.1
Sardinia	0.3	0.53	81	7.3	253.6	224.0	12.1
Italy	**0.3**	**0.60**	**81**	**6.1**	**253.5**	**224.0**	**12.6**
North	0.3	0.59	81	5.4	259.9	224.0	12.7
Centre	0.4	0.60	81	6.5	245.6	223.0	13.7
South and Islands	0.3	0.60	80	6.8	251.5	224.0	11.9

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 people. These two phenomena are likely to have had an effect on the **overall reduction in drug consumption**.
- 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.
- 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.

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3.7. Respiratory system

Medicines for respiratory system are confirmed as the seventh therapeutic category with the highest public expenditure, amounting to 1305.6 million euros and 5.7% of total public expenditure. (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure on these medicines was 21.89 euros, mainly resulting from the approved care regime (17.13 euros per capita), and increasing over the previous year (+1.6%). Instead, expenditure due to purchases by public health facilities is lower (4.76 euros per capita), with a +21.8% increase compared to 2019 (Table 3.1).
Consumption for this category of drugs was 44.0 DDD/1000 inhabitants per day, with a -16.8% decrease compared to 2019 (Table 3.2).
Analysis of the drug use profile by age and gender, including pharmaceuticals under approved care regime and *per conto* distribution, shows that children under the age of 5 and subjects over 75 years of age are those with the highest prevalence of use. The analysis of consumption shows that DDDs tend to grow with age and the highest value is reached in the age group over 75 years (106.5 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 52.2 euros per capita in the age group over 75 years, with a different contribution from the two genders (69.5 euros in men and 40.6 euros in women).
As regards the approved care regime, per capita expenditure was equal to 17.13 euros, with an increase of 1.3% compared to 2019. This trend was determined by a decrease in consumption (-0.8%) and prices (-0.5%), and a shift towards more expensive medicines (mix effect: +2.6%) (Table 3.9). There is also an increase in the average cost per day of therapy (+2.1%). Within this channel, beta-adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics, represent the most expensive and consumed category, with 8.45euros per capita and 13.3 DDD/1000 inhabitants per day respectively. The combination beclomethasone/formoterol is the most expensive drug (14.7%), followed by vilanterol/fluticasone furoate (13.8%) (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 150.3 and 141.1 million euros respectively (Table 3.11), and in the list of the top 30 active substances with the highest variation in pharmaceutical expenditure compared to 2019 (Table 3.13). The same list includes umeclidinium, an anticholinergic bronchodilator used for COPD, with a change in spending of +24.8%, mainly due to an increase in consumption (+21.5%), the budesonide/formoterol combination and montelukast, indicated in the treatment of asthma, with an increase in spending of 7.6% and 3.8% respectively (Table 3.13).
In terms of purchases by public health facilities, compared to 2019, there was an increase in expenditure (+21.4%), faced with a reduction in consumption (-17.2%), constant prices (-0.5%) and a shift in the purchase of pharmaceuticals towards more expensive specialties (mix effect: +47.3%; Table 3.16).

The medication that has the greatestimpact on spending is the lumacaftor/ivacaftor combination, used in cystic fibrosis, which accounts for 29.2% of spending, followed by omalizumab, used in allergic (IgE-mediated) asthma and ivacaftor indicated as monotherapy in cystic fibrosis (Table 3.17). Moreover, ivacaftor, both as monotherapy and in combination with lumacaftor, is (compared to 2019) on the list of the top 30 active ingredients involving changes in spending on medicines purchased by public health facilities, with increases of 40.0% and 19.1% respectively (Table 3.20).

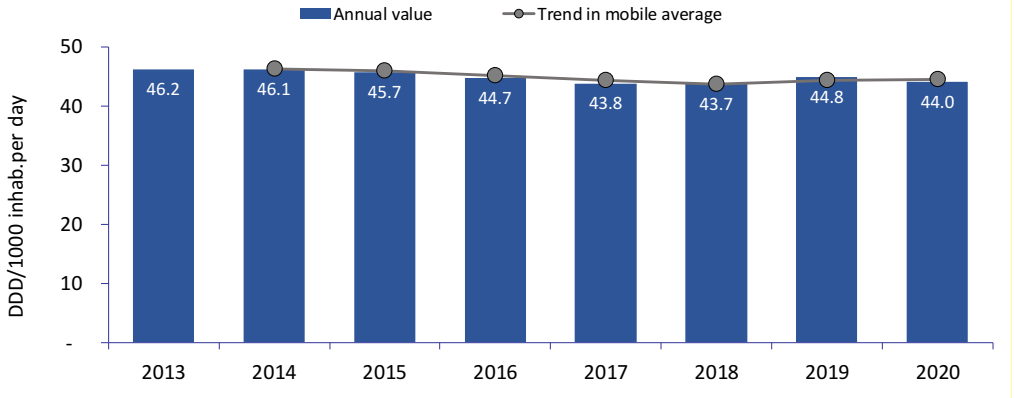
With an aim to achieve further information on the use of medicines belonging to the same therapeutic area, analyses have been performed on the historical series of consumption by active ingredient and by Region, and on the efficiency in the absorption of resources according to the presence of expired patent medicines. These analyses focused on medicines for asthma and COPD and on medicines for the treatment of cystic fibrosis (Table 3.7.1 and following).

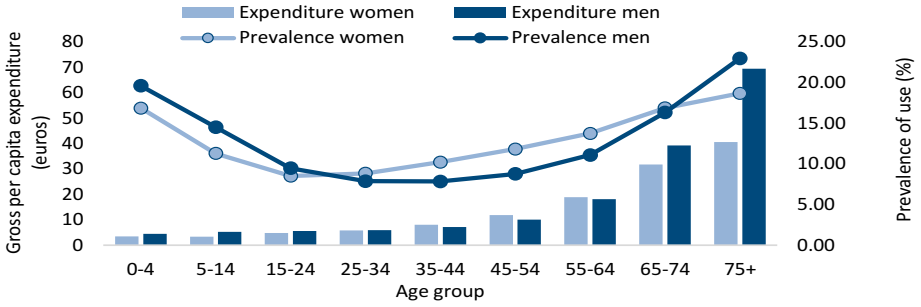
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

Respiratory system

Public expenditure* in million euros (% over total)	**1,305.6**	**(5,7)**
Δ % 2020-2019		5.4%
Regional range of gross per capita expenditure	16.8	28.8
DDD/1000 inhab. per day (% over total)	**44.0**	**(3,8)**
Δ % 2020-2019		-1.7%
Regional range of DDD/1000 inhab. per day	32.2	62.0

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities





Age group	Gross per capita expenditure			DDD/1000 inhab.per day		
	Men	Women	Total	Men	Women	Total
0-4	4.5	3.5	4.0	13.6	10.5	12.1
5-14	5.3	3.4	4.4	19.2	12.3	15.8
15-24	5.7	4.8	5.3	22.3	18.4	20.4
25-34	5.9	5.9	5.9	19.9	19.9	19.9
35-44	7.2	8.1	7.6	21.0	24.7	22.9
45-54	10.1	11.9	11.0	26.8	34.2	30.5
55-64	18.1	18.9	18.5	41.0	47.1	44.1
65-74	39.3	31.8	35.4	78.3	70.5	74.2
75+	69.5	40.6	52.2	134.5	87.6	106.5

3.7.1 Medicines for asthma and COPD

National data on consumption and expenditure

Over the past seven years, there has been a decrease in the consumption of asthma and COPD medications, by 4.6% in 2020 compared to 2014 and with an average annual change of -0.8%. In 2020, consumption was 33.1 DDD, down by 3.8% from 2019. Spending reached 18.18 euros per capita with a change of +3.0% in 2019 and an average annual change of +1.5% over the 2014-2020 period. A day of therapy with these medicines cost 1.50 euros, increasing by 6.8% compared to the previous year (Figure and Table 3.7.1a).

Combined long-term beta2-agonists and inhaling corticosteroids (LABAs+ICS) remain the most prescribed category in 2020, with consumption values of DDD 9.5/1000 inhabitants per day and expenditure per capita of 6.04 euros, up by 2.5% and 3.9% respectively compared to 2019, followed by long-term anticholinergics/antimuscarinics (LAMAs), with 5.9 DDD, and ultra-LABA+ICS (3.8 DDD and + 9.4% compared to 2019). Compared to 2019, the growth trend in consumption is confirmed for both monoclonal antibodies (+26.3%), used in severe asthma not controlled with other therapies, and for the triple therapy LAMAs+LABAs+ICS (>100%) which also recorded a strong increase in expenditure (>100%). On the other hand, the consumption of LABAs+LAMAs (-1.4%) is slightly decreasing. The top 3 substances prescribed are confirmed as beclomethasone+formoterol, fluticasone+vilanterol and salmeterol+fluticasone, increasing by 9.5% and 9.4% in the case of the first two combinations; as for salmeterol+fluticasone, a decrease of 4.5% is recorded, compared to 2019.

Expired patent medicines account for 29% of the doses used, down from 2019 (-14.9%); on the contrary, consumption of medicines covered by patents shows an increase (+1.6%); the use of equivalent medicines remains very limited (14.6%; Table 3.7.1c). Inhaled corticosteroids (ICS) are the category with the greatest regional variability in terms of consumption, both by range (3.5-9.1 DDD/1000 population days) and median value (4.7 DDD) (Figure 3.7.1c).

Figure 3.7.1a. Therapies for asthma and COPD, temporal trend of consumption and average cost per day of therapy (2014-2020)

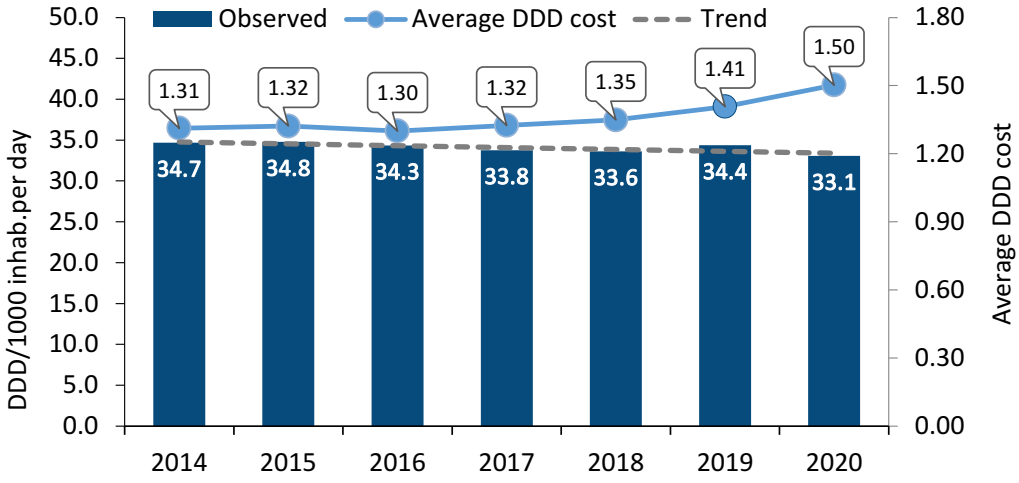


Table 3.7.1a. Therapies for asthma and COPD, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
LABAs+ICS	6.04	2.5	-4.4	9.53	3.9	-1.6	1.73	-1.6
LAMAs	3.30	2.4	-0.2	5.88	0.5	0.8	1.53	1.6
Ultra-LABAs+ICS	2.39	9.8	-	3.78	9.4	-	1.72	0.1
Monoclonal antibodies	1.93	25.0	32.8	0.19	26.3	35.6	28.29	-1.3
ICS	1.40	-27.1	-10.0	3.96	-26.9	-9.5	0.97	-0.5
LABAs+LAMAs	0.91	-1.0	445.5	1.20	-1.4	239.7	2.09	0.1
LAMAs+LABAs+ICS	0.76	>100	-	0.73	>100	-	2.84	2.7
Antileukotrienes (LTRAs)	0.49	3.8	-1.4	2.17	5.7	0.2	0.62	-2.1
LABAs	0.23	-10.2	-11.6	0.65	-10.3	-11.6	0.98	-0.1
Ultra-LABAs	0.19	-9.3	-13.0	0.48	-9.8	-13.3	1.06	0.3
SABAs	0.18	-19.2	-7.5	2.59	-11.8	-5.0	0.19	-8.7
SABAs+SAMAs	0.13	-30.5	-7.8	0.55	-30.1	-7.5	0.63	-0.8
SABAs+ICS	0.11	-11.0	-7.7	0.26	-11.8	-7.5	1.20	0.6
Theophylline-based	0.06	-11.2	-9.7	0.44	-11.2	-12.0	0.34	-0.3
SAMAs	0.05	-27.3	-11.0	0.63	-31.0	-3.7	0.24	5.0
PDE-4 inhibitors	0.01	-11.9	-13.8	0.01	-11.7	-12.8	1.50	-0.5
Chromones	0.00	43.6	-28.0	0.02	45.3	-26.5	0.63	-1.5
Medicines for asthma and COPD	**18.18**	**3.0**	**1.5**	**33.06**	**-3.8**	**-0.8**	**1.50**	**6.8**
beclomethasone/formoterol	2.55	6.4	6.2	4.06	9.5	6.7	1.72	-3.1
fluticasone furoate/vilanterol	2.39	9.8	-	3.78	9.4	-	1.72	0.1
salmeterol/fluticasone	1.76	-5.5	-15.3	2.83	-4.5	-11.5	1.70	-1.3
budesonide/formoterol	1.46	7.5	3.6	2.12	7.5	5.9	1.88	-0.3
tiotropium	1.33	-3.2	-10.0	2.46	-5.1	-8.3	1.48	1.7
omalizumab	0.90	8.5	16.9	0.10	8.2	21.3	25.75	0.0
humeclidinium	0.80	24.3	-	1.38	20.8	-	1.59	2.6
aclidinium	0.67	-1.5	11.0	1.15	-2.1	10.3	1.59	0.3
mepolizumab	0.64	15.0	-	0.05	20.8	-	33.10	-5.1
beclomethasone	0.53	-27.6	-15.3	1.55	-28.3	-14.0	0.93	0.8

Table 3.7.1b. Medicines for asthma and COPD, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	31.5	31.2	30.6	29.9	29.8	30.3	29.7	-1.8
Valle d'Aosta	39.8	38.3	35.1	34.3	34.5	33.9	32.9	-3.0
Lombardy	31.1	31.4	31.5	31.1	31.9	31.7	30.8	-2.9
A.P. of Bolzano	26.6	27.1	27.0	26.3	26.7	26.0	25.4	-2.3
A.P. of Trento	31.7	31.6	31.3	30.8	31.3	30.9	30.5	-1.4
Veneto	29.3	29.2	29.2	29.0	28.9	29.3	28.4	-3.1
Friuli VG	30.3	30.6	30.7	30.9	30.5	31.1	31.8	2.0
Liguria	33.3	33.8	33.3	33.3	33.5	34.2	33.3	-2.5
Emilia R.	33.5	33.8	33.9	33.2	33.2	33.6	30.7	-8.7
Tuscany	34.5	35.4	35.0	34.7	34.4	34.6	33.9	-1.9
Umbria	31.9	31.7	31.7	31.4	32.0	32.5	31.7	-2.6
Marche	31.3	30.7	31.0	30.4	29.8	30.5	29.2	-4.2
Lazio	39.4	39.5	38.3	38.0	38.2	39.6	36.7	-7.4
Abruzzo	29.7	29.6	29.8	29.5	29.9	31.0	29.9	-3.7
Molise	28.1	27.3	26.1	25.4	24.7	25.7	25.2	-1.8
Campania	43.8	44.1	43.7	42.6	43.7	45.0	43.0	-4.3
Puglia	40.8	41.1	40.3	38.1	34.8	36.3	35.3	-3.0
Basilicata	38.7	37.9	37.2	36.8	35.1	36.6	35.6	-2.7
Calabria	34.5	34.4	34.1	33.4	32.7	34.4	32.8	-4.4
Sicily	34.8	34.5	33.5	33.0	32.2	34.3	33.3	-3.0
Sardinia	40.3	40.2	37.5	37.0	36.1	36.2	35.8	-1.1
Italy	**34.7**	**34.8**	**34.3**	**33.8**	**33.6**	**34.4**	**33.1**	**-3.8**
North	31.3	31.5	31.3	30.9	31.2	31.4	30.3	-3.5
Centre	36.2	36.4	35.8	35.4	35.4	36.3	34.5	-5.0
South and Islands	38.5	38.5	37.7	36.7	36.0	37.5	36.2	-3.4

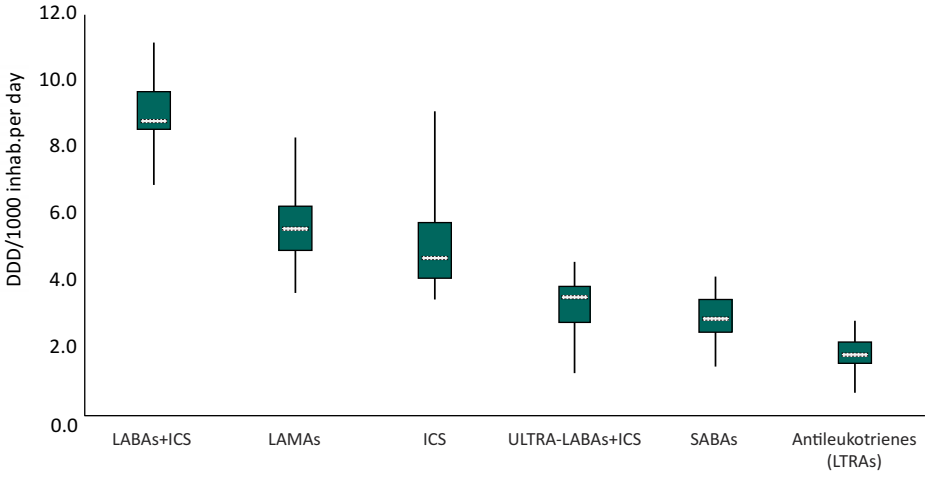
Table 3.7.1c. Prescription of medicines for asthma and COPD with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	2.51	13.8	-17.2	9.6	29.0	-14.9	0.7
Generics	0.26	10.6	-1.5	1.4	14.6	-1.6	0.5
Former originators	2.24	89.4	-18.7	8.2	85.4	-16.8	0.7
Patent covered	15.67	86.2	7.2	23.5	71.0	1.6	1.8
Medicines for asthma and COPD	**18.18**	**100.0**	**3.0**	**33.1**	**100.0**	**-3.8**	**1.5**

*Source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.7.1c. Medicines for asthma and COPD, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure and adherence in population

The prevalence of drug use for asthma and COPD was 9.2% at national level in 2020. 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 22.3% and 19.1%, in men and women respectively, and in the age group equal to or greater than 85 years of age with a percentage of 20.5% and 14.2%, in men and women respectively (Figure 3.7.1d). 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 (10.8%), compared to the Centre (9.6 %) and the North of Italy (7.9 %). The median age of users was 54 years, and an average of 123 DDDs were dispensed per user, in the face of 3.3 prescriptions. Half of the users, with no differences across geographic areas, received only one prescription in the year (Table 3.7.1d).

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 165,802 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 (56.7% vs 43.3 %).

The percentage of subjects with high and low adherence to the treatment was 23.2% and 44.0% respectively, showing an increase in subjects with high adherence (+16.5%) and a decrease in subjects with low adherence (-11.8%), compared to 2019. 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 (24.7% vs 22.0%). The proportion of subjects with high adherence to treatment was higher in the North (24.2%) and the Centre (23.4%) compared to the South and the Islands (19.9%) (Table 3.7.1e).

Taking into consideration persistence to treatment with treatments for obstructive airway diseases, at 12 months persistent subjects ranged from 6.5% to 10.8% 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 (12.3%). Men recorded higher persistence rates than women (12,6% vs 8,2%) (Tabella 3.7.1f).

If considering the median time to discontinuation of treatment, a 50% probability of discontinuing treatment is achieved at approximately 60 days in 2019 and 65 days in 2020 (Figure 3.7.1e).

Figure 3.7.1d. Distribution of 2020 prevalence of use and consumption of medicines for asthma and COPD under approved care regime and *per conto* distribution (year 2020)

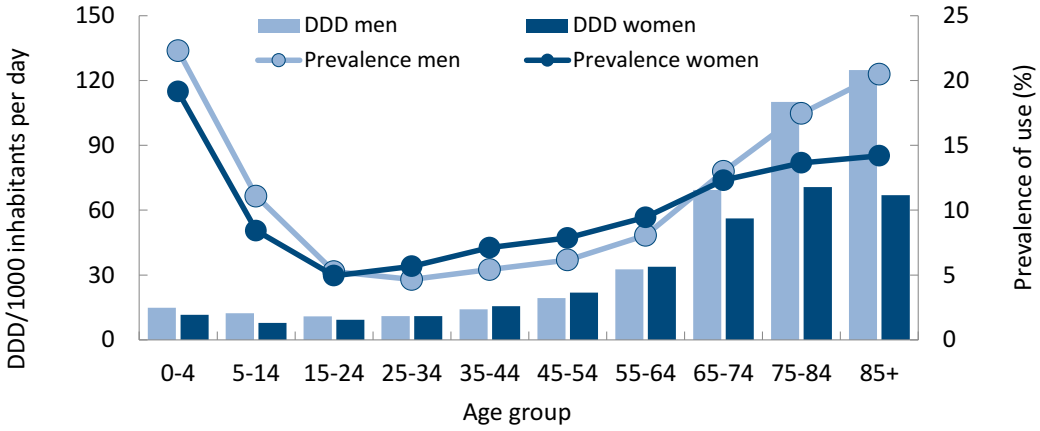


Table 3.7.1d. Exposure and duration of therapy with antidementia medicines by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	6.7	1.00	58	3.7	153.7	60	43.8
Valle d'Aosta	8.5	0.98	52	2.9	128.2	42	52.5
Lombardy	8.2	0.99	51	2.9	131.5	50	51.5
A.P. of Bolzano	6.6	1.08	48	2.7	120.8	32	55.6
A.P. of Trento	9.5	1.04	46	2.7	108.6	30	55.0
Veneto	7.5	1.04	50	3.0	129.1	40	50.4
Friuli VG	7.6	1.02	56	3.3	142.1	50	49.9
Liguria	9.2	0.99	57	3.5	138.4	54	46.2
Emilia R.	8.6	0.99	50	2.9	110.7	30	52.7
Tuscany	8.0	0.98	58	3.8	150.0	60	44.6
Umbria	8.8	1.00	58	3.9	126.7	30	49.7
Marche	7.1	1.06	57	3.5	134.7	50	47.8
Lazio	11.3	0.91	54	3.1	113.6	30	53.2
Abruzzo	9.3	0.99	53	3.3	115.4	30	53.4
Molise	8.2	1.01	59	3.3	112.0	30	53.0
Campania	13.6	0.93	51	3.2	104.1	30	51.8
Puglia	9.1	1.05	58	3.5	127.5	50	49.5
Basilicata	9.5	0.99	59	4.0	133.7	43	48.2
Calabria	9.7	0.99	59	3.4	114.1	31	51.7
Sicily	9.9	0.99	57	3.4	114.8	35	50.2
Sardinia	10.5	0.90	54	3.5	124.7	35	50.3
Italy	**9.2**	**0.98**	**54**	**3.3**	**123.1**	**39**	**50.5**
North	7.9	1.01	52	3.1	130.5	50	50.3
Centre	9.6	0.95	55	3.4	126.0	39	50.2
South and Islands	10.8	0.97	55	3.4	114.2	32	50.9

Table 3.7.1e. Indicators of adherence to treatment with medicines for asthma and COPD in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=165,802		North‡ N=50,128		Centre N=39,006		South N=76,668	
Low adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	49.7	-9.7	45.5	-12.0	49.7	-9.2	52.4	-8.6
55-64 years	44.7	-13.8	40.7	-18.0	44.3	-15.1	47.2	-10.8
65-74 years	42.8	-12.3	39.4	-14.9	40.9	-14.5	45.7	-9.8
75-84 years	41.1	-11.0	38.2	-14.1	39.9	-10.5	43.8	-9.0
≥85 years	43.2	-11.6	41.2	-15.2	41.2	-11.5	45.9	-9.1
Women	45.4	-12.6	42.1	-15.8	43.7	-13.5	48.5	-10.0
Men	42.2	-10.5	38.7	-13.3	41.8	-10.9	44.7	-8.7
Total	**44.0**	**-11.8**	**40.6**	**-14.9**	**42.9**	**-12.6**	**46.8**	**-9.5**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	18.0	14.2	19.1	10.1	18.9	16.2	16.9	16.4
55-64 years	22.1	18.3	25.1	23.0	22.5	19.0	20.0	14.8
65-74 years	24.2	16.0	26.9	18.5	25.7	16.7	21.9	13.7
75-84 years	25.9	16.2	28.2	15.9	27.6	20.3	23.4	13.6
≥85 years	25.3	18.3	27.5	21.3	26.4	11.2	23.1	20.9
Women	22.0	18.7	24.2	21.8	23.4	17.3	19.9	17.4
Men	24.7	13.8	27.3	13.3	25.8	17.3	22.5	11.9
Total	**23.2**	**16.5**	**25.6**	**17.9**	**24.4**	**17.5**	**21.0**	**14.9**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

N: refers to new users, subjects who received a first prescription in the period 01/10/2020- 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): 199 (84-325)

‡ Excluding Emilia Romagna.

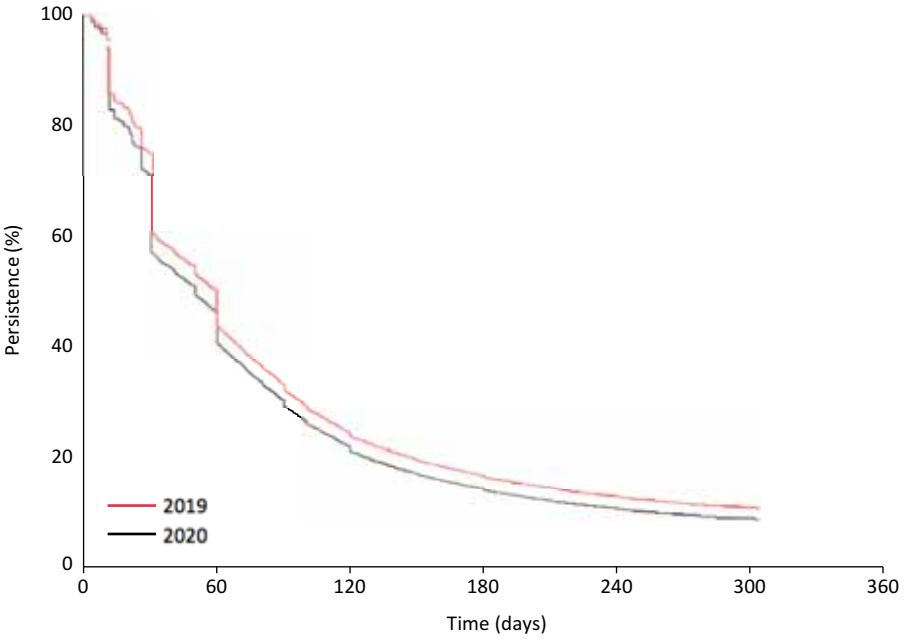
Table 3.7.1f. Persistence after one year of treatment with antidepressants in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=165,802		North‡ N=50,128		Centre N=39,006		South N=76,668	
Persistence at 12 months	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	6.5	24.5	8.0	22.7	6.2	12.9	5.6	33.7
55-64 years	9.2	34.1	11.3	29.9	9.1	47.4	8.0	30.9
65-74 years	11.0	23.2	13.3	21.6	11.8	32.0	9.2	19.4
75-84 years	12.3	21.1	14.3	20.0	12.6	28.3	10.7	17.1
≥85 years	10.8	13.7	11.3	15.4	10.7	6.2	10.5	17.3
Women	8.2	26.8	9.8	24.5	8.6	27.2	7.0	28.5
Men	12.6	20.2	14.9	19.5	12.8	27.7	10.9	16.5
Total	**10.1**	**23.6**	**12.0**	**22.2**	**10.3**	**28.1**	**8.7**	**22.0**

Note: persistence to treatment was evaluated only for new users with at least 2 prescriptions. An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods)

‡ Excluding Emilia Romagna.

Figure 3.7.1e. Time (in days) to discontinuation of treatment for asthma and COPD in the population aged ≥45 years stratified by year (2019-2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods) For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days)

Table 3.7.1g. Incidence of asthma and COPD in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Incidence (‰)	Δ % 20-19	Incidence (‰)	Δ % 20-19
Geographic analysis				
North	2.0	-57.2	0.9	-71.9
Centre	2.2	-94.9	1.5	-74.5
South and Islands	4.0	-57.4	1.7	-54.8
Analysis by gender				
Men	2.4	-50.4	1.4	-68.5
Women	3.1	-71.0	1.2	-57.8
Analysis by age				
≥45 years	2.7	-53.0	0.1	-18.2
46-65	2.8	-62.1	1.0	-63.9
66-74	2.9	-86.3	3.1	-59.4
75-84	3.0	-65.8	4.3	-50.1
≥85	2.9	-55.0	5.0	-38.0
Total	**2.8**	**-62.5**	**1.3**	**-63.6**

Indicators used:

Incidence of asthma: number of patients with a "first" diagnosis of asthma recorded during the year [**numerator**], out of the total population and at risk (disease-free) at the beginning of the period [**denominator**] **Incidence of different forms of asthma**: number of patients with a "first" diagnosis of COPD during the year [**numerator**], on the total population and at risk (disease-free) at the beginning of the period [**denominator**]

Table 3.7.1h. Incidence of asthma and COPD in the population eligible for assistance by General Practitioners participating in the Health Search network and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence (%) asthma	Δ % 20-19	Incidence (‰)	Δ % 20-19
Geographic analysis				
North	7.3	2.7	2.2	-4.6
Centre	7.3	1.4	3.1	-3.2
South and Islands	11.0	2.7	3.6	-2.8
Analysis by gender				
Men	7.9	2.5	3.4	-2.9
Women	9.4	3.2	2.4	-4.2
Analysis by age				
≥45 years	9.0	2.2	0.2	0.0
46-65	8.5	2.4	1.9	5.3
66-74	8.6	3.5	6.3	4.8
75-84	8.4	3.6	9.8	2.0
≥85	7.6	2.6	11.8	0.9
Total	**8.6**	**2.3**	**2.9**	**-3.5**

Indicator used: **Prevalence of asthma and COPD:** number of patients diagnosed with asthma and COPD [**numerator**], on the total population eligible for assistance [**denominator**]

Table 3.7.1i. Request for spirometry and flu vaccine for patients with asthma and COPD both on and without drug treatment

	Distribution (%)					
	Asthma	On pharmaceutical treatment	Without pharmaceutical treatment	COPD	On pharmaceutical treatment	Without pharmaceutical treatment
Spirometry						
Yes	3.9	9.9	1.0	9.6	15.8	3.1
No	96.1	90.1	99.0	90.4	84.2	96.9
Flu vaccine						
Yes	18.2	26.9	14.0	38.8	46.0	31.3
No	81.8	73.1	86.0	61.2	54.0	68.7

Prevalence of the demand for spirometry and flu vaccine: number of patients with asthma or COPD and at least a request for spirometry and/or flu vaccine in the last 12 months [**numerator**] out of total subjects with asthma and COPD, subdivided into those undergoing pharmacological treatment and those without pharmacological treatment [**denominator**].

Table 3.7.1j. Distribution of values on smoking habit and BMI among patients with asthma and COPD both on drug treatment and without drug treatment

	Distribution (%)					
	Asthma	On pharmaceutical treatment	Without pharmaceutical treatment	COPD	On pharmaceutical treatment	Without pharmaceutical treatment
Smoking*						
Yes	29.8	28.0	31.1	40.6	36.6	46.0
No	70.2	72.0	68.9	59.4	63.4	54.0
BMI*						
Under weight	1.5	1.6	1.5	1.9	2.2	1.3
Normal weight	31.7	29.9	33.1	27.7	27.6	28.0
Over weight	34.8	35.2	34.6	36.7	35.9	37.7
Obesity	31.9	33.3	30.9	33.7	34.2	33.0

BMI: Body Mass Index

^Percentages are calculated excluding patients with missing data

Distribution of the values relating to smoking habits and BMI (last available value in the year preceding that of observation) [**numerator**] among subjects with asthma and COPD with at least one value recorded in the year, subdivided into subjects on drug treatment and without drug treatment [**denominator**].

Table 3.7.1k. Prevalence of use of medicines for asthma and COPD in patients with these conditions and comparison 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence of use (%) asthma	Δ % 20-19	Prevalence of use (%) COPD	Δ % 20-19
Geographic analysis				
North	34.0	-10.3	53.4	-6.0
Centre	34.1	-12.9	50.7	-5.7
South and Islands	31.1	-14.2	49.6	-6.5
Analysis by gender				
Men	30.5	-11.5	50.6	-6.7
Women	34.4	-13.1	51.8	-5.4
Analysis by age				
≥45 years	24.3	-12.8	23.9	-10.5
46-65	34.9	-10.6	40.0	-8.5
66-74	42.9	-12.4	52.6	-7.0
75-84	45.2	-10.4	59.2	-3.6
≥85	39.5	-11.7	54.2	-3.3
Total	**32.6**	**-12.6**	**51.1**	**-6.1**

Indicator used:

Prevalence of use of medicines for asthma and COPD: number of patients treated with medicines for asthma and COPD [**numerator**] on the total number of patients diagnosed with asthma and COPD [**denominator**]

Table 3.7.1l. Prevalence of use of medicines for asthma and COPD in patients with these conditions: analysis by therapeutic category

	Prevalence of use (%)	
	Asthma	COPD
Monoclonal antibodies	0.1	0.1
Antileukotrienes (LTRAs)	3.5	1.7
Theophylline-based bronchodilators	0.7	2.7
Chromones	NA	NA
ICS	8.6	11.1
PDE-4 inhibitors	NA	NA
LABAs	0.7	1.7
LABAs+ICS	15.9	17.6
LABAs+LAMAs	0.3	4.4
LAMAs	3.0	22.3
LAMAs+LABAs+ICS	0.3	3.0
SABAs	7.7	5.5
SABAs+ICS	0.8	0.7
SABAs+SAMAs	1.8	3.9
SAMAs	0.5	1.7
ULTRA-LABAs	0.1	1.8
ULTRA-LABAs+ICS	4.8	9.1

Prevalence of use of medicines for asthma and COPD: number of patients treated with a specific therapeutic category [**numerator**] on the total number of patients diagnosed with asthma and COPD [**denominator**]

Table 3.7.1m. Proportion of patients adhering to treatment with medicines for asthma and COPD in subjects affected by this disease: stratified analysis by gender, age group, geographical area, therapeutic category, and number of risk factors

	Therapeutic adherence (%)	
	Asthma	COPD
Geographic analysis		
North	25.4	51.1
Centre	25.1	50.9
South and Islands	19.8	45.0
Analysis by gender		
Men	23.3	51.4
Women	22.6	44.3
Analysis by age		
≥45 years	12.4	20.6
46-65	22.1	39.6
66-74	30.8	49.8
75-84	34.6	51.9
≥85	34.9	49.6
Analysis by therapeutic class		
Monoclonal antibodies	32.6	20.0
Antileukotrienes (LTRAs)	29.6	42.2
Theophylline-based bronchodilators	5.1	8.3
Chromones	0.0	0.0
ICS	2.9	5.7
PDE-4 inhibitors	25.0	66.7
LABAs	25.9	38.7
LABAs+ICS	14.5	26.1
LABAs+LAMAs	51.7	55.8
LAMAs	31.4	41.1
LAMAs+LABAs+ICS	45.2	45.3
SABAs	2.2	4.7
SABAs+ICS	10.4	12.8
SABAs+SAMAs	1.1	3.0
SAMAs	5.2	12.2
ULTRA-LABAs	50.4	58.3
ULTRA-LABAs+ICS	27.5	40.1
Existence of risk factors*		
1 risk factor	19.7	46.6
2 risk factors	24.1	48.3
3 risk factors	28.1	47.8
4 risk factors	30.2	48.5
More than 4 risk factors	35.0	49.8
Total	**22.9**	**48.3**

*Moderate exacerbations, severe exacerbations, asthma, COPD, smoking, alcohol abuse and related diseases, obesity, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, arrhythmias, other chronic lung disease, peptic ulcer disease, mild liver disease, severe liver disease, diabetes without complications, diabetes with complications, hemiplegia, chronic renal failure, cancer, metastatic cancer, depression, dementia, AIDS

Indicator used:

Proportion of patients adhering to treatment with medicines for asthma and COPD: number of patients adhering (DDD/user/molecule>290/year, 168/year in case of ICS) to treatment with medicines for asthma and COPD [**numerators**], out of the total patients with asthma and COPD treated with therapies for these diseases [**denominators**].

Key messages

- For the past seven years, in the face of decreasing consumption, there has been an average annual increase of 1.5% in asthma and COPD drug spending with a change of +6.8% in average cost per day of therapy in 2020, compared to 2019.
- Expired patent medicines account for 29% of the doses used, down from 2019 (-14.9%); on the contrary, consumption of medicines covered by patents shows an increase (+1.6%), due to increased consumption and spending on monoclonal antibodies and triple therapy.
- Adherence and persistence analysis performed using Health Card and General Practice data still show inadequate levels of treatment adherence, although an improvement is noted in 2020 over 2019. It is recognized that adequate levels of therapy adherence produce several effects on patient quality of life, such as increased symptom control and decreased exacerbations and health care use.
- General practice data showed a sharp decline in both asthma and COPD diagnoses, partly due to the impact of the COVID-19 pandemic.

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3.7.2 Medicines for cystic fibrosis

National data on consumption and expenditure

Per capita spending on cystic fibrosis drugs has increased significantly for the past seven years, reaching 2.40 euros in 2020 (+27% compared to 2019 and CAGR 20142020 +62.4%). The cost per DDD also showed a major increase from 21.4 euros in 2014 to 151.2 euros in 2020, a growth of 8.6% over 2019 (Figure and Table 3.7.2a).

The largest expenditure category is represented by CFTR modulator therapies (2.16 euros per capita), which are mainly affected by the association lumacaftor/ivacaftor (1.39 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 2020 it recorded an increase in both expenditure (+13.8%) and consumption (+13.6%).

Treatment with ivacaftor/tezacaftor, followed by ivacaftor as monotherapy, had the largest increase in 2020, compared to 2019, in both per capita spending and consumption (Table 3.7.2a).

Figure 3.7.2a. Medications for cystic fibrosis, temporal trend of expenditure and average cost per day of therapy (2014-2020)

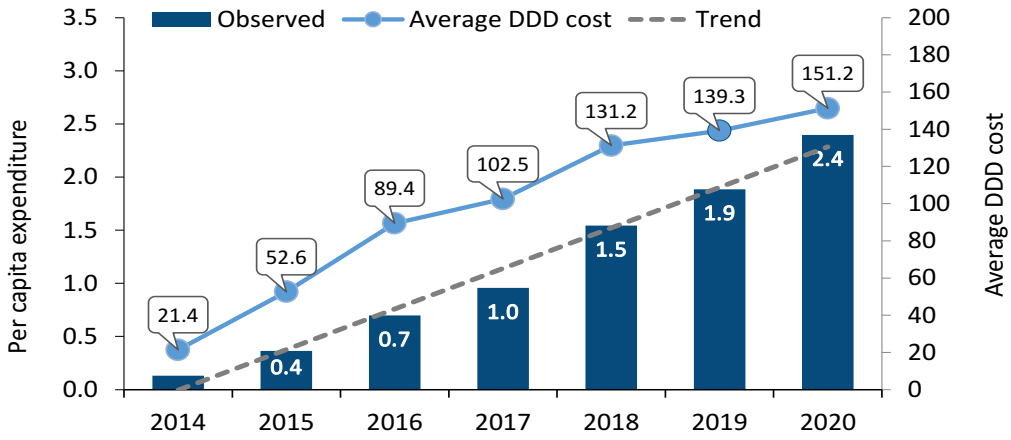

Table 3.7.2a. Medicines for multiple sclerosis, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
CFTR modulator therapies	2.16	28.8	-	0.01	25.4	-	475.18	2.4
Mucolytics with specific action	0.24	13.8	10.7	0.03	13.6	10.8	21.30	0.0
Medicines for cystic fibrosis	**2.40**	**27.1**	**62.4**	**0.04**	**16.7**	**17.2**	**151.24**	**8.6**
lumacaftor/ivacaftor	1.39	19.1	-	0.01	16.2	-	426.32	2.2
ivacaftor	0.70	40.0	-	0.00	32.3	-	676.64	5.5
DNAse	0.24	13.8	10.7	0.03	13.6	10.8	21.30	0.0
ivacaftor/tezacaftor	0.07	>100	-	0.00	>100	-	277.16	-0.6

Table 3.7.2b. Medicines for cystic fibrosis, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	0.2	0.3	0.5	0.8	1.5	1.7	1.9	10.2
Valle d'Aosta	0.1	0.2	1.7	2.1	2.6	1.2	1.4	16.1
Lombardy	0.1	0.2	0.3	0.5	1.1	1.5	2.0	35.1
A.P. of Bolzano	0.4	0.8	0.9	1.0	2.2	2.7	3.9	46.7
A.P. of Trento	0.2	0.2	0.2	0.4	1.8	1.7	3.1	79.7
Veneto	0.2	0.2	0.3	0.5	0.9	1.3	1.6	23.2
Friuli VG	0.1	0.2	0.3	0.6	1.3	1.7	2.0	19.0
Liguria	0.2	0.2	0.4	0.8	1.3	1.7	1.9	12.5
Emilia R.	0.1	0.1	0.3	0.8	1.4	1.7	2.2	23.9
Tuscany	0.1	0.4	0.7	0.6	1.2	1.5	1.8	20.5
Umbria	0.2	0.3	1.0	1.5	2.2	2.3	2.9	22.8
Marche	0.2	0.3	0.4	0.8	1.4	1.9	2.3	20.2
Lazio	0.2	0.7	1.2	1.3	1.5	1.6	2.0	25.6
Abruzzo	0.1	0.2	0.4	0.7	1.4	1.6	2.1	27.8
Molise	0.2	0.2	0.2	0.2	0.7	1.1	1.0	-10.3
Campania	0.1	0.5	0.9	1.4	2.0	2.3	2.7	18.4
Puglia	0.1	0.6	1.1	1.7	2.2	2.5	3.5	42.0
Basilicata	0.4	1.0	3.1	3.7	4.1	4.7	4.8	3.5
Calabria	0.1	1.1	2.1	2.5	2.9	3.2	4.4	36.8
Sicily	0.1	0.4	1.1	1.0	2.1	2.8	3.8	36.4
Sardinia	0.1	0.2	0.2	0.2	1.0	1.4	1.7	20.2
Italy	**0.1**	**0.4**	**0.7**	**1.0**	**1.5**	**1.9**	**2.4**	**27.1**
North	0.1	0.2	0.4	0.6	1.2	1.6	2.0	26.1
Centre	0.2	0.5	0.9	1.0	1.4	1.6	2.0	23.0
South and Islands	0.1	0.5	1.1	1.4	2.1	2.5	3.2	29.8

Key message

- Per capita spending on cystic fibrosis drugs has increased significantly over the past seven years, similar to the cost per day of therapy.
- The introduction of new CFTR modulator therapies has largely driven this increase in spending, which is also related to the increased life expectancy of patients.
- 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.

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3.8 Musculo-skeletal system

Medications for the musculoskeletal system represent the eighth largest category by public expenditure in 2020, amounting to more than 520 million euros, and 2.3% of public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was 8.73 euros, mainly due to the pharmaceutical expenditure under approved care regime (5.02 euros per capita), reporting a -8.4% decrease compared to the previous year. Expenditure due to purchases by public health facilities is lower (3.71 euros), though with an increase compared to the previous year (+5.9%) (Table 3.1).
Consumption for this category of drugs was 41.6 DDD/1000 inhabitants per day, with a 2.6% decrease compared to 2019. Even in terms of utilization, it is possible to highlight a large difference between drug utilization under approved care regime (36.4 DDD/1000 inhabitants per day) and public facilities drug utilization (5.2 DDD/1000 inhabitants per day).
Although not classified in category M, vitamin D was considered by therapeutic analogy along with osteoporosis drugs, and the relevance by gross per capita expenditure and volume of use dictates, when evaluating this category, an analysis extended to cholecalciferol and its analogs.
The analysis of the drug use profile by age group and gender, including approved care regime and per conto distribution, confirms the constant increase in the use of these drugs with increasing age, for both genders, with a higher prevalence of use in women than in men. The highest consumption values are reached in the age group over 75 years (women 148.5 and men 106.9 DDD/inhabitants per day). At the same time, per capita expenditure borne by the NHS also varies with the age of patients, reaching the maximum value of 19.5 euros in the age group over 75 years, with a different contribution from the two genders (24.6 euros in women and 11.9 euros in men). This difference is likely due to the higher use of osteoporosis medications among women.
As regards the approved care regime, per capita expenditure was equal to 5.02 euros, with an increase of 8.4% compared to 2019. This trend was determined by a reduction in prices (-4%) and a shift in prescription towards lower cost products (mix effect: -1.3%), as well as by a reduction in consumption (-3.5%). The average DDD cost also decreased by 5.3% from the previous year (Table 3.9). Within the regimen of this distributing channel, bisphosphonates had the greatest impact on spending (1.33 euros per capita), with a reduction of 1.5%. However, this must be read in the broader context of medications for osteoporosis, where cholecalciferol plays a fundamental role (3.38 euros per capita for 201.4 million euros), despite the 28.2% reduction. These are followed by preparations inhibiting uric acid production, with expenditure per capita of 0.83 euros, in sharp decrease compared to the previous year (-22.5%). However, for these drugs the highest consumption is noted (10.2 DDD/inhabitants per day), up from the previous year (+1.3%). Among bisphosphonates, alendronic acid is the active ingredient with the greatest impact on spending (0.76 euros per capita, or 15.6% of the category) with a 1.2% increase over 2019 while allopurinol is the one with the highest consumption (8.2 DDD/inhabitants per day and +22.7%). Diclofenac is the second active ingredient with the highest per capita expenditure (0.57 euros) and alone accounts for 11.3% of the expenditure for the category (Table 3.10).

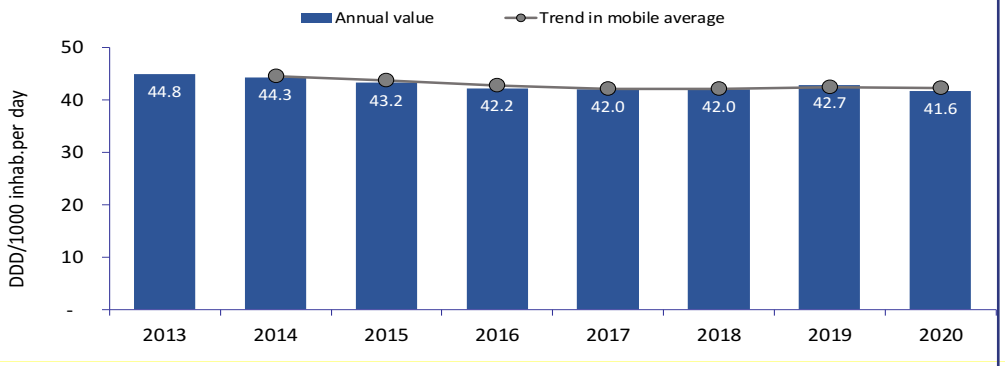
Particularly interesting is the reduction in spending on the active substance febuxostat (-34.3%), licensed for the treatment of chronic hyperuricemia with urate deposition. This may be due to a reduction in consumption (-6.7%), and in the average cost of DDDs (-29.7%) determined by patent expiration in 2019.
No active substance belonging to the ATC code M is included among the first 30 active ingredients of class A-NHS expenditure under approved care regime or with the greatest variation in expenditure (Tables 3.11 and 3.13), whereas allopurinol is the 30th active substance by consumption under approved care regime (Table 3.14).
As for public health facilities, there is evidence of an increase in spending, consumption, prices, and average cost per day of therapy with quaternary ammonium compounds, a category including active substances such as pancuronium, vecuronium, rocuronium, and atracurium (Table 3.16). 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 (1.56 euros) and alone accounts for 42% of the category's expenditure, although a 9% reduction is observed (Table 3.17). This active ingredient is also in the top 30 substances by expenditure of medications purchased by public health facilities (Table 3.18), where a shift in rank from 25th to 30th is observed, compared to 2019. Denosumab and ataluren, approved for the treatment of osteoporosis/bone loss and Duchenne muscular dystrophy (nmDMD), respectively, are the second and third active ingredients by expenditure (Table 3.17).
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 expired-patent medicines and on a regional basis. These analyses focused on osteoporosis medications and nonsteroidal anti-inflammatory drugs (Table 3.8.1 and following).

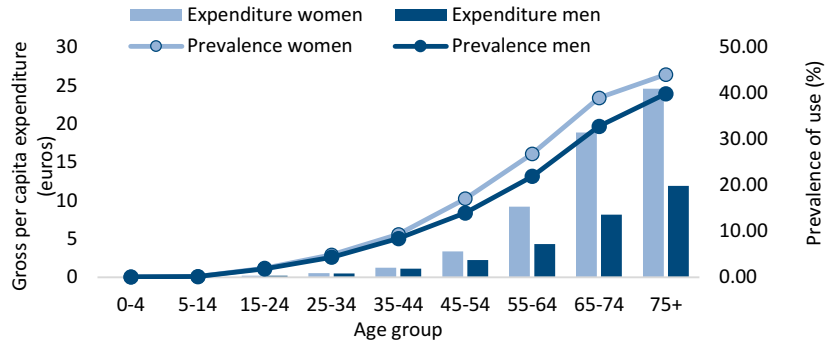
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

Musculo-skeletal system

Public expenditure* in million euros (% over total)	**520.5**	**(2,3)**
Δ % 2020-2019		-2.8%
Regional range of gross per capita expenditure	5.3	11.2
DDD/1000 inhab. per day (% over total)	**41.6**	**(3,6)**
Δ % 2020-2019		-2.6%
Regional range of DDD/1000 inhab. per	30.7	57.9

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities





	Gross per capita expenditure			DDD/1000 inhab.per day		
Age group	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
0-4	0.0	0.0	0.0	0.1	0.1	0
5-14	0.0	0.0	0.0	0.2	0.2	0
15-24	0.2	0.2	0.2	1.5	1.4	1
25-34	0.5	0.5	0.5	3.7	3.8	3.7
35-44	1.1	1.2	1.2	8.4	8.7	8.6
45-54	2.2	3.4	2.8	17.6	22.1	19.9
55-64	4.3	9.2	6.8	36.2	54.7	45.7
65-74	8.2	18.9	13.8	72.1	109.8	92.0
75+	11.9	24.6	19.5	106.9	148.5	131.8

3.8.1 Medicines for osteoporosis

National data on consumption and expenditure

The trend in osteoporosis drug consumption shows a 28.9% increase between 2014 and 2019 with a 14.3% decrease in the last 2 years, bringing the overall annual rate of change to 1.7% (Figure and Table 3.8.1a). Per capita expenditure on these drugs was 8.56 euros, decreasing of 15.5% compared to the previous year, whereas the average DDD cost (0.81 euros) shows a reduction of 1.6% compared to 2019. Vitamin D and analogues are still the therapeutic category with the highest per capita expenditure (4.30 euros), although a significant reduction of -24.1% and -21.7%, respectively, was recorded in both expenditure and consumption. This is probably due to the effects of Note 96 Even teriparatide, a biological drug with expired patent, 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 (-17.5%) and consumption (-11.1%). Monoclonal antibodies, represented by antiresorptive denosumab, on the other hand, show significant increases in expenditure (+13.3%) and consumption (+7.3%). Analyzing the individual active ingredients, cholecalciferol represents the molecule with the highest expenditure per capita (3.39 euros) and consumption (9.9 DDD/1000 inhabitants per day), followed by teriparatide, which, despite the availability of biosimilar drugs, records the highest cost per day of therapy of the entire category (15.44 euros). The trend in expenditure and consumption of the individual active ingredients perfectly reflects the trend of the individual therapeutic categories.

Figure 3.8.1a. Osteoporosis medications, temporal trend of consumption and average cost per day of therapy (2014-2020)

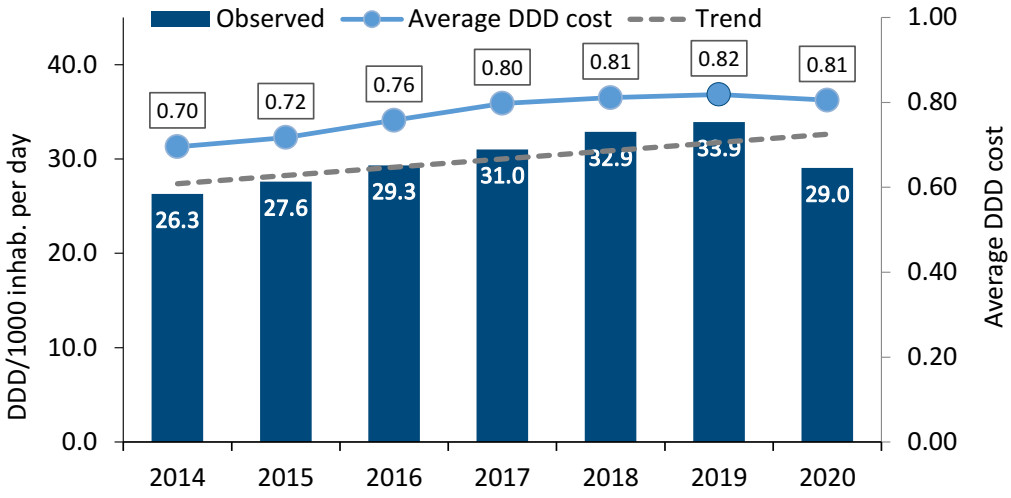


Table 3.8.1a. Osteoporosis medications, per capita expenditure and consumption (DDD/1000 ab day) by therapeutic category and by substance: comparison 2014-2020

Subgroups and substances	Per capita expendi-ture	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Vitamin D and analogues	4.30	-24.1	9.1	15.6	-21.7	3.1	0.75	-3.4
Bisphosphonates plain	1.36	-2.4	-2.7	6.9	-1.0	-0.1	0.54	-1.7
Teriparatide	1.20	-17.5	5.6	0.2	-11.1	5.1	15.44	-7.5
Monoclonal antibodies for osteoporosis	1.13	13.3	22.8	3.3	7.3	21.7	0.93	5.3
Biphosphonates, combinations	0.44	-6.7	-14.7	2.1	-6.9	-8.2	0.58	0.0
Calcium	0.11	-7.4	-1.4	1.0	-35.1	-8.4	0.33	42.3
SERM (selective estrogen-receptor modulators)	0.01	-1.9	-6.9	0.0	-2.4	-6.6	0.75	0.2
Double-acting pharmaceuticals	0.00	-82.9	-75.0	0.0	-82.9	-74.9	1.45	0.0
Medicines for osteoporosis	**8.56**	**-15.5**	**4.2**	**29.0**	**-14.3**	**1.7**	**0.81**	**-1.6**
cholecalciferol	3.39	-28.2	12.7	9.9	-26.7	9.8	0.94	-2.3
teriparatide	1.20	-17.5	5.6	0.2	-11.1	5.1	15.44	-7.5
denosumab	1.03	4.4	21.0	3.3	7.2	21.6	0.85	-2.9
alendronic acid	0.76	-0.1	3.8	4.0	1.5	5.6	0.52	-1.9
alendronic acid/ cholecalciferol	0.44	-6.7	-14.7	2.1	-6.9	-8.2	0.58	0.0
risendronic acid	0.38	-3.8	-6.4	2.1	-3.6	-4.4	0.48	-0.5
calcium/cholecalciferol	0.32	-21.6	-7.9	3.4	-22.1	-8.5	0.26	0.3
calcitriol	0.22	-1.3	0.6	1.0	-2.7	-0.3	0.60	1.1
alfacalcidol	0.19	27.9	14.9	1.2	28.0	15.2	0.45	-0.4
calcifediol	0.18	3.7	14.2	0.1	3.4	14.1	3.62	0.0

Table 3.8.1b. Osteoporosis medications, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	24.2	25.6	26.7	28.4	29.8	30.6	26.1	-14.8
Valle d'Aosta	18.8	20.1	19.5	20.6	22.6	26.1	22.8	-12.6
Lombardy	24.6	26.4	27.7	29.8	32.1	33.8	29.8	-11.6
A.P. of Bolzano	30.0	33.1	35.4	37.2	38.2	35.7	28.8	-19.5
A.P. of Trento	23.4	24.1	25.9	28.4	30.5	32.3	25.8	-20.0
Veneto	35.0	36.9	38.1	36.8	37.5	37.2	27.8	-25.2
Friuli VG	22.8	23.8	25.3	27.1	28.4	31.2	27.1	-13.1
Liguria	22.5	23.8	25.4	26.7	28.2	29.9	25.6	-14.5
Emilia R.	25.0	26.0	26.9	27.7	28.3	28.6	24.7	-13.5
Tuscany	26.1	27.3	31.6	31.3	33.2	32.2	23.5	-27.1
Umbria	20.9	21.7	23.1	25.7	27.5	27.2	23.6	-13.2
Marche	24.1	25.9	28.1	31.0	32.6	33.5	27.0	-19.2
Lazio	27.7	29.3	31.2	33.4	35.3	36.2	31.8	-11.9
Abruzzo	28.9	30.9	32.8	35.9	39.0	38.8	33.0	-15.0
Molise	24.1	26.5	28.8	32.5	32.4	32.7	30.0	-8.3
Campania	19.0	20.8	23.3	27.0	30.5	33.7	31.7	-6.1
Puglia	31.7	33.6	35.9	38.1	40.0	41.0	34.0	-16.9
Basilicata	28.4	30.4	31.5	34.4	36.0	37.6	33.5	-10.9
Calabria	25.0	25.9	27.7	30.1	32.7	33.7	29.3	-13.1
Sicily	28.0	25.9	26.1	27.8	30.0	32.2	29.3	-8.7
Sardinia	33.2	35.5	38.5	40.0	40.5	39.9	36.8	-8.0
Italy	**26.3**	**27.6**	**29.3**	**31.0**	**32.9**	**33.9**	**29.0**	**-14.3**
North	26.2	27.8	29.0	30.2	31.7	32.6	27.6	-15.6
Centre	26.2	27.6	30.3	31.8	33.7	33.9	27.9	-17.6
South and Islands	26.5	27.3	29.1	31.7	34.1	35.7	31.9	-10.8

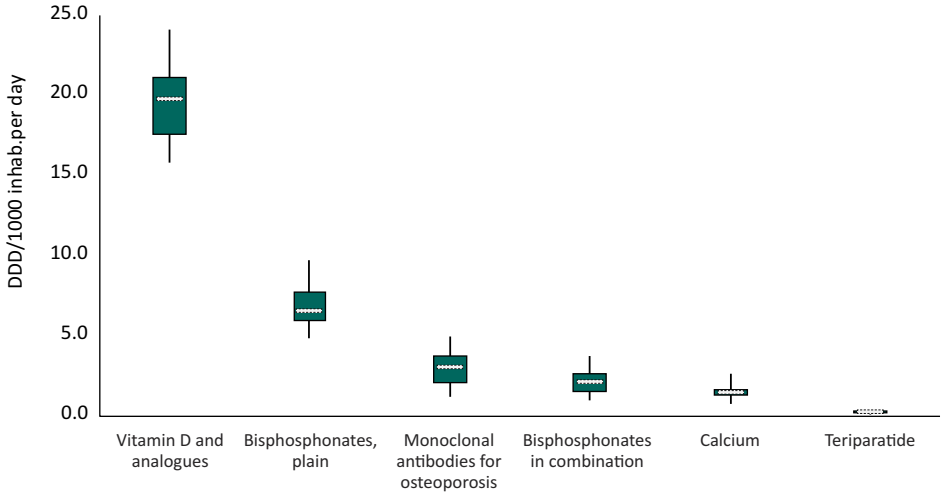
Table 3.8.1c. Prescription of osteoporosis medications with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	5.37	62.8	-21.0	20.5	70.4	-16.3	0.72
Generics	1.14	21.2	-16.1	6.0	29.2	-16.9	0.52
Former originators	4.23	78.8	-22.2	14.5	70.8	-16.0	0.80
Patent covered	3.18	37.2	-4.1	8.6	29.6	-9.4	1.01
Medicines per osteoporosis	**8.56**	**100.0**	**-15.5**	**29.0**	**100.0**	**-14.3**	**0.81**

*Source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.8.1c. Osteoporosis medications, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure and adherence in population

Health Card data were collected to perform an analysis aimed at estimating exposure to osteoporosis medications in the general population, as well as adherence and persistence to treatment.

Exposure was significantly higher for women than men in all age groups, reaching a maximum value of 41.5% for women in the 75-84 age group and 15.5% for men aged 85 years and over (Figure 3.8.1d). Analyzing the trend in prevalence of use by geographic area (Table 3.8.1d), Regions in the South show a higher value (12%), compared to the Italian average (10.5%), as well as to Regions in the North and the Center (9.7%). However, Abruzzo recorded the highest value (13.6%). The average age of patients was 68 years, and in a year each user received 3.7 prescriptions, counting for 92.2 DDDs. Half of users were treated for less than 40 days and 32% received only one prescription.

As for the adherence and persistence analyses, the exposure data refer to a cohort of new users over 45 years old, which were followed considering the one-year follow-up. The study population includes a total of 44,795 new users, with a median age of 70 years (IQR 62-78) and a greater proportion of women than men (91.4% vs 8.6%). The percentage of subjects with high and low adherence to osteoporosis treatments was respectively 67.7% and 6.8% (Table 3.2.1e). Low adherence tends to increase with age, rising from 7% for the 45-54 age group to 8.1% in people aged over 85, although there is a reduction of about 4% compared to 2019. Patients older than 85 years resident in Central Italy had the highest value of low adherence, 9.2%. High adherence, on the other hand, registered a 1% increase and was higher in subjects aged 45-54 years resident in the North (73.2%).

Analysing the persistence to medicines for osteoporosis (Table 3.8.1f.), it can be highlighted that about half of the new users are found to be persistent to treatment after one year (50.9%), with a better trend in the North (55.9%) and in the Centre (51.7%), 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 (45.4%). Women were more persistent than men (51.2% and 47.1%), although the latter showed an increase of 8% in the number of persistent individuals compared to the previous year.

Comparing the persistence data between 2019 and 2020 (Figure 3.8.1f), no obvious differences were found and it is possible to note that, for these drugs, the median time to discontinuation is 314 days.

Figure 3.8.1d. Distribution of prevalence of use and consumption of osteoporosis medications under approved care regime and *per conto* distribution (year 2020)

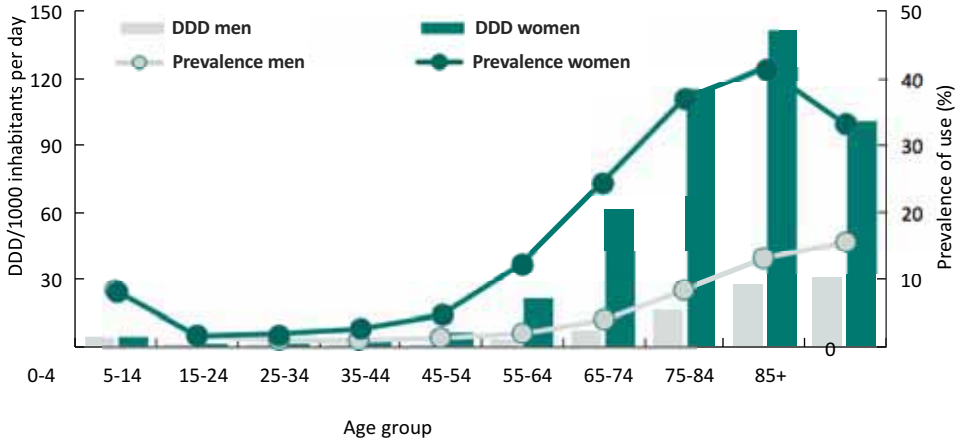


Table 3.8.1d. Distribution of prevalence of use and consumption of osteoporosis medications under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescrip-tions per user	DDD per user	DDD median	Users with 1 prescription (%)
Piedmont	9.2	0.25	69	3.5	95.3	40.0	31.8
Valle d'Aosta	8.8	0.26	68	3.4	88.8	40.0	30.4
Lombardy	10.5	0.26	68	3.5	97.9	40.0	30.1
A.P. of Bolzano	7.0	0.27	70	3.2	108.0	60.0	36.7
A.P. of Trento	9.9	0.29	66	3.4	85.1	40.0	31.9
Veneto	8.7	0.27	68	3.1	108.0	60.0	38.4
Friuli VG	10.5	0.27	68	3.7	95.4	40.0	29.9
Liguria	10.3	0.22	72	3.9	92.7	40.0	28.2
Emilia R.	9.7	0.24	67	3.2	80.1	40.0	35.7
Tuscany	8.5	0.25	69	3.3	96.1	59.0	40.1
Umbria	10.1	0.21	69	4.3	85.0	30.0	29.1
Marche	8.9	0.22	70	3.7	85.6	30.0	32.6
Lazio	10.6	0.22	68	3.8	103.6	40.0	31.1
Abruzzo	13.6	0.26	67	3.6	85.5	30.0	34.6
Molise	12.1	0.22	68	3.6	82.0	30.0	32.1
Campania	13.0	0.25	65	3.9	74.5	40.0	28.1
Puglia	12.7	0.24	68	3.5	85.7	38.0	34.5
Basilicata	12.7	0.21	66	4.6	92.6	40.0	27.1
Calabria	11.0	0.24	67	3.9	86.6	32.0	31.6
Sicily	10.4	0.21	69	4.2	89.7	40.0	27.7
Sardinia	11.1	0.20	68	4.0	115.8	60.0	33.2
Italy	**10.5**	**0.24**	**68**	**3.7**	**92.2**	**40.0**	**32.0**
North	9.7	0.26	68	3.4	95.6	40.0	32.6
Centre	9.7	0.22	68	3.7	98.0	40.0	33.6
South and Islands	12.0	0.23	67	3.9	85.5	40.0	30.5

Table 3.8.1e. Indicators of adherence to treatment with osteoporosis medications in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=44.795		North N=17.761		Centre N=9.199		South N=90,182	
Low adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	7.0	-3	4.9	6	6.6	-3	9.1	5
55-64 years	6.1	-1	5.3	7	6.5	1	6.8	2
65-74 years	6.5	-3	5.1	-5	6.5	4	7.9	2
75-84 years	7.2	-3	5.9	2	7.5	5	8.6	0
≥85 years	8.1	-17	6.8	-22	9.2	5	9.0	-19
Women	6.5	-3	5.3	-3	6.7	2	7.6	1
Men	9.4	-11	6.7	1	10.5	12	12.6	-12
Total	**6.8**	**-4**	**5.5**	**-2**	**7.0**	**3**	**7.9**	**0**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	68.5	6	73.2	1	69.2	4	63.7	6
55-64 years	68.7	1	71.5	0	69.6	2	65.6	0
65-74 years	68.0	0	72.0	-1	68.2	0	64.4	-2
75-84 years	67.2	0	70.6	1	66.9	-3	63.4	-2
≥85 years	64.7	4	67.4	4	63.0	-4	62.5	5
Women	67.7	1	71.1	0	67.9	-1	64.4	-1
Men	67.8	3	71.9	-2	67.6	2	62.5	2
Total	**67.7**	**1**	**71.2**	**0**	**67.9**	**0**	**64.2**	**-1**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

N: refers to new users, subjects who received a first prescription in the period 01/10/2020- 31/12/2020, not treated in the previous months starting from 01/01/2020

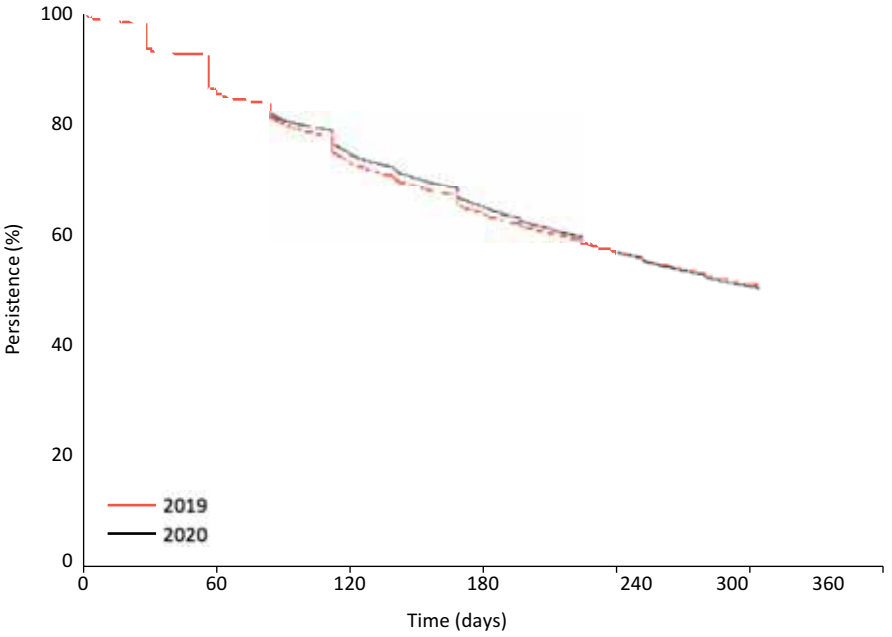
†Percentages of subjects with low/high adherence relating to the specific category. Median follow-up time (IQR): 314 (196-343)

Table 3.8.1f. Persistence after one year of treatment with osteoporosis medications in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=44.795		North N=17.761		Centre N=9.199		South N=17.835	
Persistence at 12 months	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19	%	Δ % 20-19
45-54 years	54.7	7	59.6	1	58.9	9	47.8	4
55-64 years	54.1	4	59.0	2	56.4	1	48.3	2
65-74 years	51.3	3	57.3	0	53.0	5	44.9	-2
75-84 years	48.7	2	53.2	-2	46.9	-4	44.3	1
≥85 years	43.7	5	48.9	10	41.1	-7	39.1	4
Women	51.2	3	56.2	0	52.4	1	45.8	0
Men	47.1	8	53.8	2	44.0	2	39.7	6
Total	**50.9**	**3**	**55.9**	**1**	**51.7**	**2**	**45.4**	**1**

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

Figure 3.8.1e. Time (in days) to discontinuation of treatment with osteoporosis medications in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods) For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days)

Table 3.8.1g. 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 2020-2019: stratified analysis by gender, age group and geographic area

	Incidence (‰)			
	Osteoporosis	Δ % 20-19	Without previous vertebral or femur fracture	With previous vertebral or femur fracture
Geographic analysis				
North	4.1	-40.6	1.7	2.3
Centre	4.9	-41.4	2.1	2.8
South and Islands	5.5	-53.2	1.4	4.2
Analysis by gender				
Men	2.1	-25.4	1.3	0.7
Women	7.8	-50.5	2.1	5.7
Analysis by age				
≥45 years	0.5	-37.8	0.3	0.2
46-65	4.8	-49.0	0.9	3.9
66-74	9.9	-41.8	2.7	7.2
75-84	16.0	-25.1	7.5	8.5
≥85	25.7	-11.4	17.4	8.3
Total	**4.8**	**-45.9**	**1.7**	**3.1**

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 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 3.8.1h. 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 2020-2019: stratified analysis by gender, age group and geographic area

	Prevalence (%)			
	Osteoporosis	Δ % 20-19	Without previous vertebral or femur fracture	With previous vertebral or femur fracture
Geographic analysis				
North	7.6	-1.3	2.5	5.0
Centre	8.8	-3.4	2.9	5.9
South and Islands	11.5	-2.6	2.3	9.2
Analysis by gender				
Men	2.9	0.0	1.8	1.0
Women	15.5	-1.9	3.2	12.3
Analysis by age				
≥45 years	0.9	11.1	0.7	0.2
46-65	6.6	6.1	1.5	5.1
66-74	19.6	3.1	3.5	16.0
75-84	29.1	4.1	7.6	21.5
≥85	37.7	2.1	14.8	23.0
Total	**9.3**	**-2.2**	**2.5**	**6.8**

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 [**denominator**] **Incidence of osteoporosis in patients with or without previous vertebral or femur structure**: number of patients diagnosed with osteoporosis with or without previous vertebral or femur fracture [**numerator**], out of the total patient population [**denominator**].

Table 3.8.1i. Prevalence of use of drugs for the treatment of osteoporosis in the population with osteoporosis, with or without previous vertebral or femur fracture, and comparison 2020-2019: stratified analysis by gender, age groups and geographical area

	Prevalence of use (%)	Δ % 20-19	Without previous vertebral or femur fracture	With previous vertebral or femur fracture
Geographic analysis				
North	51.0	-8.6	37.0	58.0
Centre	49.4	-10.3	38.7	54.6
South and Islands	50.0	-19.0	40.1	52.5
Analysis by gender				
Men	23.8	-17.2	15.2	38.7
Women	55.0	-13.1	51.2	56.0
Analysis by age				
≥45 years	10.8	-15.7	3.4	39.1
46-65	44.0	-19.6	23.1	50.0
66-74	56.6	-13.6	46.7	58.7
75-84	57.1	-10.7	53.4	58.4
≥85	47.0	-9.8	44.3	48.8
Total	**50.2**	**-13.8**	**38.4**	**54.6**

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 3.8.1j. Prevalence of use of drugs for the treatment of osteoporosis in the population with osteoporosis, with or without previous vertebral or femur fracture: analysis by therapeutic category

	Prevalence of use (%)		
	Osteoporosis	Without previous vertebral or femur fracture	With previous vertebral or femur fracture
Analysis by therapeutic class			
Bisphosphonates alone	10.3	8.4	11.0
Biphosphonates, combinations	2.9	2.5	3.1
Monoclonal antibody	2.0	2.5	1.8
SERM (selective estrogen-receptor modulators)	0.1	0.0	0.1
Anabolic drugs	0.3	0.6	0.2
Double-acting pharmaceuticals	0.0	0.0	0.0
Vitamin D and analogues	44.9	33.4	49
Calcium	2.0	1.7	2.1

Indicators used:

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 [**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**]

Key message

- The most relevant data in the overall analysis of osteoporosis therapy is a **decrease in the use of drugs**, more than 14%, after years of almost uninterrupted growth (+28.9% from 2014 to 2019).
- Within the approved care regime, **consumption and expenditure for vitamin D and similar products** registered an overall reduction of 21.3% and 24.6%, respectively, after a decade of increases of 9.1% per year. This decrease may be due to the effects of the implementation of Note 96 designed to promote the appropriate use of these medications. Cholecalciferol, however, is third in terms of reduced expenditure under approved care regime 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 decline involving both the use (-21.7%) and induced expenditure (-24.1%), cannot disregard the **evaluation of trends** of other drugs 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 drug prescription trends by individual regions shows greater drug consumption in Southern regions.
- 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.

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3.8.2 Nonsteroidal anti-inflammatory drugs (NSAIDs)

National data on consumption and expenditure

2020 confirms the downward trend in NSAID consumption (Figure and Table 3.8.2a) amounting to 25.9% since 2014, and switching from 22.8 to 16.9 DDD/1000 inhabitants per day with an average annual change of -4.9%. Similarly, the average DDD cost recorded a 17.8% decrease, switching from 0.46 euros in 2014 to 0.38 in 2020 (Figure 3.2.2a). Per capita expenditure was equal to 2.34 euros, with a 6.7% increase compared to 2019. Traditional NSAIDs represent the category with the highest per capita expenditure (1.57 euros) and consumption (12.3 DDD), down 8.5% and 9.4%, respectively, although the average DDD cost increased by 0.8%. The second category with the highest expenditure is represented by Coxibs, which record a per capita expenditure of 0.64 euros (-2.1%) and a consumption of 3.8 DDD/1000 inhabitants per day (-2%). For this category, there was substantial stability in the average DDD cost (-0.4%). 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 (0.58 euros), followed by etoricoxib (0.53 euros), ketoprofen (0.28 euros) and ibuprofen (0.26 euros). Ketorolac, approved only for the short-term treatment of moderate-to-severe postoperative pain, is the molecule with the highest DDD cost (0.57 euros), up 12.1% from 2019. In the case of NSAIDs, 88.7% of the expenditure relates to patent expired drugs and the percentage reaches 90.1% when considering consumption (Table 3.8.2c). However, ex-originators account for 85% of expenditure and for 78.2% of consumption. It is always traditional NSAIDs that present the greatest variability, recording a very wide range (7.6-22.4 DDD/1000 inhabitants per day) and values widely dispersed with respect to the median (Figure 3.8.2c).

Figure 3.8.2a. Nonsteroidal anti-inflammatory drugs (NSAIDs), temporal trend of consumption and average cost per day of therapy (2014-2020)

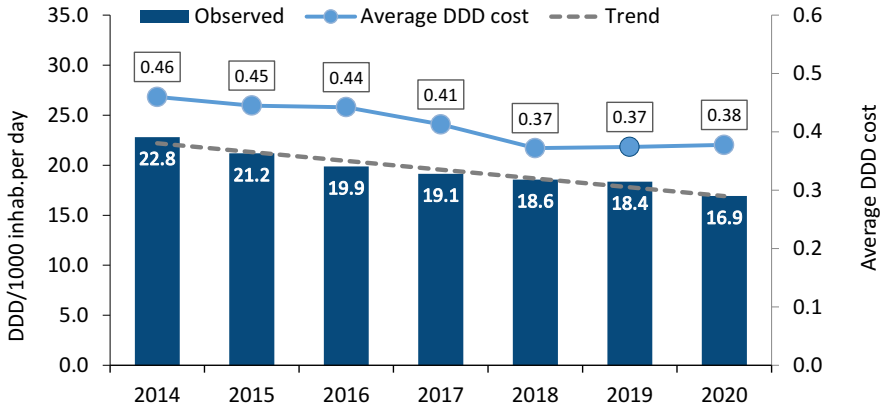


Table 3.8.2a. Nonsteroidal anti-inflammatory drugs (NSAIDs), per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Traditional NSAIDs	1.57	-8.5	-4.9	12.3	-9.4	-5.0	0.35	0.8
Coxibs	0.64	-2.1	-13.3	3.8	-2.0	-3.7	0.47	-0.4
Oxicam	0.12	-6.5	-6.4	0.8	-8.3	-7.2	0.38	1.8
Other non-steroidal anti-inflammatory/anti-rheumatic pharmaceuticals	0.01	-13.7	-14.7	0.0	-14.9	-17.8	0.63	1.1
Nonsteroidal anti-inflammatory drugs (NSAIDs)	**2.34**	**-6.7**	**-7.9**	**16.9**	**-7.8**	**-4.9**	**0.38**	**0.9**
diclofenac	0.58	-2.6	-0.8	4.0	-3.2	-0.9	0.40	0.4
etoricoxib	0.53	-1.7	-12.6	3.1	-1.6	-3.0	0.46	-0.4
ketoprofen	0.28	-14.6	-8.0	2.7	-13.8	-7.2	0.28	-1.2
ibuprofen	0.26	-13.1	-4.4	1.8	-14.1	-3.6	0.39	0.9
nimesulide	0.15	-5.5	-7.0	1.8	-6.8	-7.3	0.22	1.1
celecoxib	0.11	-3.7	-15.3	0.6	-4.0	-6.8	0.47	0.0
ketorolac	0.10	-3.3	-5.2	0.5	-14.0	-5.5	0.57	12.1
piroxicam	0.08	-2.3	-4.1	0.5	-3.1	-4.8	0.45	0.5
aceclofenac	0.07	-13.8	-11.7	0.4	-11.8	-10.4	0.50	-2.5
naproxen	0.05	-6.3	-5.6	0.6	-8.3	-6.3	0.25	1.9

Table 3.8.2b. Nonsteroidal anti-inflammatory drugs (NSAIDs), regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	18.3	16.8	15.9	15.4	15.0	14.9	13.5	-9.8
Valle d'Aosta	22.3	20.9	18.3	17.3	17.2	17.1	15.2	-11.4
Lombardy	13.4	12.9	12.3	11.9	11.6	11.4	10.4	-8.8
A.P. of Bolzano	15.9	15.3	14.4	13.3	12.6	12.0	10.8	-10.2
A.P. of Trento	16.6	16.0	15.9	15.8	16.1	15.7	14.9	-5.3
Veneto	15.9	14.5	13.6	12.7	12.1	11.8	11.1	-6.1
Friuli VG	20.9	20.0	19.5	18.8	18.4	18.4	17.9	-3.0
Liguria	16.0	14.5	13.8	13.5	13.0	13.2	11.8	-11.1
Emilia R.	14.0	12.8	11.9	11.4	11.2	10.9	10.1	-7.2
Tuscany	18.3	16.7	16.0	15.5	14.7	13.9	12.6	-9.9
Umbria	17.0	15.4	14.7	14.1	14.3	14.3	13.0	-8.6
Marche	18.4	17.3	16.6	16.3	14.8	14.2	12.5	-11.9
Lazio	29.1	26.8	24.8	24.2	23.8	23.9	21.6	-9.5
Abruzzo	23.0	22.0	20.9	20.3	20.1	20.1	18.5	-8.3
Molise	28.3	26.7	23.4	22.5	22.3	22.7	21.6	-4.9
Campania	32.7	30.8	28.4	27.9	28.4	28.3	26.3	-7.2
Puglia	39.2	36.5	34.9	32.6	29.0	28.5	26.1	-8.6
Basilicata	28.1	25.7	23.4	23.0	23.0	22.9	22.2	-2.9
Calabria	36.3	33.2	31.1	30.1	29.4	29.5	27.9	-5.6
Sicily	30.2	27.0	25.4	24.7	24.5	24.7	23.0	-7.0
Sardinia	35.5	34.2	30.0	27.5	25.7	25.5	24.9	-2.3
Italy	**22.8**	**21.2**	**19.9**	**19.1**	**18.6**	**18.4**	**16.9**	**-7.8**
North	15.4	14.4	13.6	13.1	12.7	12.5	11.5	-8.1
Centre	23.3	21.4	20.1	19.6	19.0	18.7	16.9	-9.8
South and Islands	33.1	30.7	28.6	27.5	26.6	26.6	24.8	-6.8

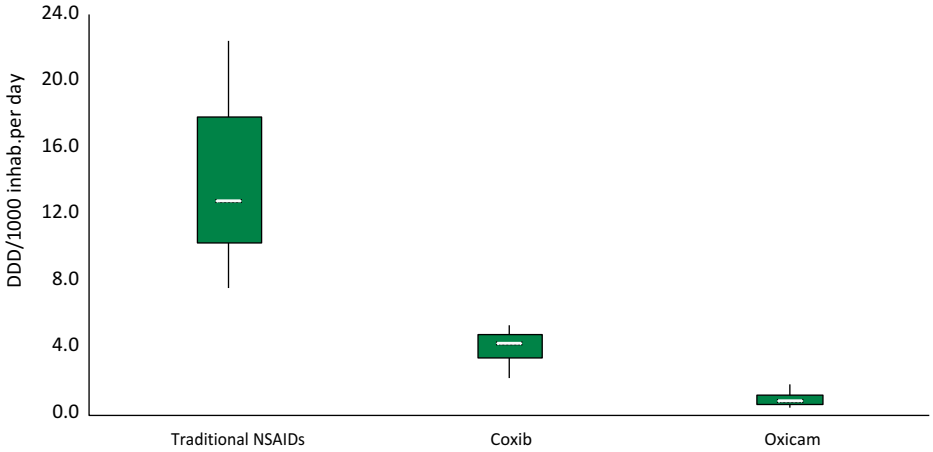
Table 3.8.2c. Prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	2.07	88.7	-5.7	15.2	90.1	-7.0	0.37
Generics	0.31	15.0	-8.8	3.3	21.8	-10.7	0.26
Former originators	1.76	85.0	-5.1	11.9	78.2	-5.9	0.40
Patent covered	0.27	11.3	-14.4	1.7	9.9	-15.0	0.43
NSAIDs	**2.34**	**100.0**	**-6.7**	**16.9**	**100.0**	**-7.8**	**0.38**

*Source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.8.2c. Nonsteroidal anti-inflammatory drugs (NSAIDs), regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to NSAIDs in the general population.

Considering all age groups, exposure was greater in women than men, with an M/F ratio of 0.75 and an increase in prevalence as age increased (Figure and Table 3.8.2d). The highest values, however, are recorded for women in the 75-84 age group (32.2%), and for men in the 65-74 age group (25.4%). The prevalence value in the general population was 14% and the median age was 63 years. The regional variability is highlighted by the prevalence values found in the North (9.5%), compared to the Center (15.2%) and the South (19.5%), with a maximum level of 21.8% in Puglia and a minimum of 5.7% in the A.P. of Bolzano. Analysis by intensity of use indicates an average treatment per user of 1.5 months and half of users on NSAIDs of less than 1 month per year. Confirming this finding, more than half of users receive only one prescription, highlighting the as-needed use of these medications.

Figure 3.8.2d. Distribution of prevalence of use and consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) under approved care regime and *per conto* distribution (year 2020)

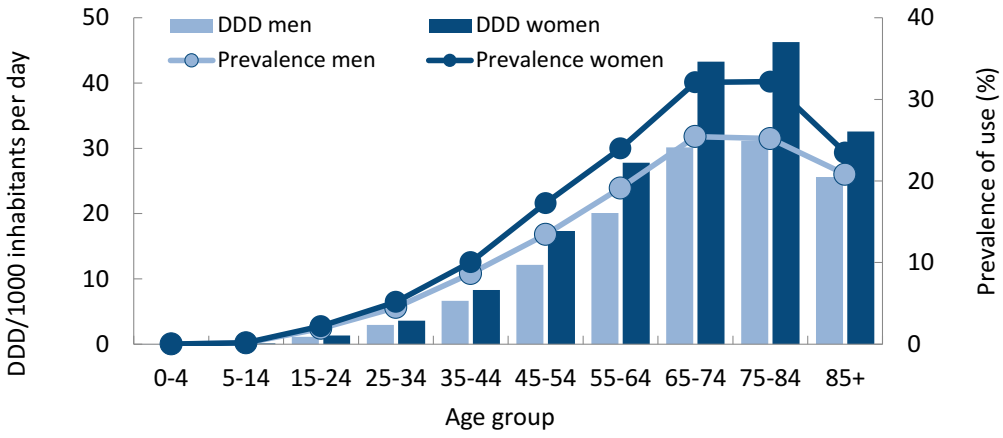


Table 3.8.2d. Exposure and duration of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	11.5	0.73	64	2.0	41.0	23.0	58.8
Valle d'Aosta	11.4	0.72	63	1.9	45.8	30.0	61.0
Lombardy	8.3	0.69	63	1.8	42.2	29.0	63.3
A.P. of Bolzano	5.7	0.70	67	2.0	55.4	30.0	60.8
A.P. of Trento	12.0	0.76	60	1.9	41.8	26.0	59.6
Veneto	8.4	0.69	63	2.0	44.3	30.0	60.7
Friuli VG	13.4	0.73	63	2.1	46.1	30.0	56.7
Liguria	11.5	0.73	67	2.0	38.3	20.0	60.9
Emilia R.	9.9	0.74	62	1.9	33.2	20.0	61.9
Tuscany	12.2	0.74	64	2.0	36.4	20.0	59.6
Umbria	13.3	0.79	63	2.0	34.8	20.0	59.2
Marche	12.1	0.80	64	1.9	33.8	20.0	61.4
Lazio	18.1	0.76	62	2.2	41.5	29.0	53.6
Abruzzo	18.3	0.79	63	2.2	35.5	20.0	54.1
Molise	19.5	0.79	64	2.2	39.3	21.0	53.3
Campania	19.8	0.74	60	2.3	43.2	30.0	51.2
Puglia	21.8	0.80	62	2.2	39.5	28.0	51.1
Basilicata	19.1	0.75	62	2.2	40.9	27.0	54.2
Calabria	19.1	0.76	66	2.7	48.9	30.0	45.6
Sicily	17.3	0.77	66	2.5	45.1	30.0	48.2
Sardinia	21.0	0.77	63	2.4	42.9	30.0	49.9
Italy	**14.0**	**0.75**	**63**	**2.2**	**41.4**	**29.0**	**54.9**
North	9.5	0.71	63	1.9	40.9	23.0	61.1
Centre	15.2	0.76	63	2.1	39.0	22.0	56.3
South and	19.5	0.77	63	2.4	42.7	30.0	50.2

Key message

- Year 2020 confirms the **downward trend in NSAID consumption**, switching from a value of 22.8 DDD/1000 inhabitants per day in 2014 to one of 16.9 in 2020 (-25.9%), and recording an average annual reduction of 4.9%.
- All therapeutic categories show a **reduction in spending and consumption compared to 2019**, although the trend of the average DDD cost is increasing, with the only exception of Coxibs.
- The category with the highest per capita expenditure and consumption is represented by **traditional NSAIDs**, for which expenditure per capita of 1.57 euros and consumption of 12.3 DDD/1000 inhabitants per day are observed.
- In particular, the active ingredient with the highest expenditure is represented by **diclofenac** (0.58 euros), followed by etoricoxib (0.53 euros), ketoprofen (0.28 euros) and ibuprofen (0.26 euros).

- **Exposure** was greater in women than men, with an M/F ratio of 0.75 and an **increase in prevalence as age increased** (Figure and Table 3.8.2d).
- 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.

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3.9 Systemic hormonal preparations, excluding sex hormones and insulins

The most common endocrine disorders, besides type 2 diabetes mellitus, mainly concern thyroid diseases, which represent a heterogeneous group of very frequent conditions affecting all stages of life and having a high socio-health impact. These diseases stem from thyroid dysfunction, an endocrine gland placed at the base of the neck, which produces hormones, in the form of thyroxine (T4) and triiodothyronine (T3). Thyroid hormone regulates several metabolic functions, including central nervous system development and body growth. The production of an adequate amount of thyroid hormones is therefore essential for normal body growth and the development and maturation of the various systems. In adulthood, women are much more prone to thyroid disease than men. In fact, over the course of her lifetime, a woman is 20% more likely to develop thyroid problems.
Within systemic hormonal preparations, glucocorticoids are also a widely used category of drugs. Their prescription, however, unlike that of thyroid hormones, is directed in small percentage to productive deficiencies of the organism (the replacement therapy is limited to less than 4% of patients treated) and takes place mostly at pharmacological doses with anti-inflammatory purposes to be used in rheumatological or respiratory obstructive problems.
In 2020, the therapeutic category of systemic hormone preparations, excluding sex hormones and insulins (H), ranks ninth in terms of public spending, accounting for 519.9 million euros and 2.3% of total public spending (Box. Main indices of expenditure, consumption and exposure). The overall per capita expenditure for such medicines was 8.72 euros, mainly due to the purchase by public health facilities (4.79 euros per capita). On the contrary, the contribution provided through the approved care regime was lower (3.93 euros per capita) with a decrease of 5.1% compared to the previous year (Table 3.1).
Consumption for this category of drugs was 41.4 DDD/1000 inhabitants per day, with a 0.7% increase compared to 2019 (Table 3.2), which confirms the growing trend of the last seven years, this category ranks eighth in terms of consumption levels (Table 3.2). The analysis of the drug use profile by age group and gender, including pharmaceutical expenditure under approved care regime and *per conto* distribution, shows a progressive increase in the use of drugs 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 24, 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 13.9 euros per capita (16.7 in women and 9.6 in men) in subjects over 75 years of age.
As for expenditure under approved care regime, per capita expenditure was 3.93 euros, with a 5.4% decrease compared to 2019. While consumption tends to remain stable, it is noted a use of less expensive specialties (mix effect -4.8%) and average cost per day decreasing of 5.7% compared to 2019 (Table 3.9).

Categories having the greatest impact on the cost of pharmaceuticals under approved care regime are glucocorticoids (1.37 euros per capita), followed by thyroid hormones (1.16 euros per capita). Glucocorticoids are decreasing in terms of expenditure and consumption (-2.7% and -1.1%, respectively) compared to the previous year with a shift towards less expensive specialties (mix effect -1.6%). On the contrary, thyroid hormones, which have the highest consumption in the whole group of systemic hormonal preparations, show increases in both spending and consumption compared to 2019, with a higher propensity to use more expensive drugs (mix effect + 5.9 %). Parathyroid hormones are the category with the greatest contraction in terms of expenditure and consumption compared to the previous year, moreover they represent the only case with a reduction in prices (-3%), probably due to the patent expiry of teriparatide showing the highest level of consumption and expenditure in this category. The increased use of cheaper drugs (mix effect -4.2 %) contributes to the highest decrease in average cost per DDD of the whole group of systemic hormonal preparations (-7.1 %). The most expensive active substance is levothyroxine (1.13 euros), followed by teriparatide (1.06 euros) (Table 3.10): both molecules are the most prescribed molecules within the respective category; in particular, levothyroxine consumption (21.3 DDD) accounts for almost the whole group of systemic hormonal preparations (35.9 DDD). Levothyroxine also ranks 14th among the 30 active ingredients with the highest variation in expenditure under approved care regime compared to 2019 (+7.8 %) (Table 3.13) and 8th among the active ingredients with the greatest consumption (Table 3.14).
This result is probably due to the overlapping of two different events: on the one hand, the presence on the market of medicinal products with a pharmaceutical form different from tablets, which have a cost per dose unit 3-4 times higher and which may have led to an increase of 5.9% in the mix effect for the category and, on the other hand, the growing conviction, not adequately supported by scientific evidence, that the absorption of these formulations could allow the meal to be taken immediately after the drug.
As for purchases by public health facilities, a slight reduction was recorded in expenditure (-0.3%) compared to 2019, against an increase in consumption (+3.5%). The trend in expenditure was thus determined by a decrease in the average cost per day of therapy (-3.7%) and in prices (-3.2%), in addition to a higher use of cheaper medicinal products (mix effect -0.5%) (Table 3.16). The category with the greatest impact on expenditure, up by +5.3% compared to 2019, is somatostatin and analogues (1.64 euros per capita), which accounts for 34.2% of the expenditure of the whole class, followed by somatotropin and analogues (1.36 euros per capita). Compared to 2019, there was an increase in consumption for both subcategories, though for somatotropin and analogues there was a more marked decrease in prices (-4.6 % vs -0.6 %) and in average cost per day of therapy (-4.8 % vs -0.4 %).
Somatropin is the active substance that ranks first in this category of drugs both in terms of consumption (0.3 DDD per 1000 inhabitants per day) and per capita expenditure (1.35 euros, -0.5% compared to 2019), whereas lanreotide, a somatostatin analogue peptide, is the active substance with the highest increase in per capita expenditure compared to 2019 (+11%) and the highest average cost per day of therapy (19.23 euros) (Table 3.17).

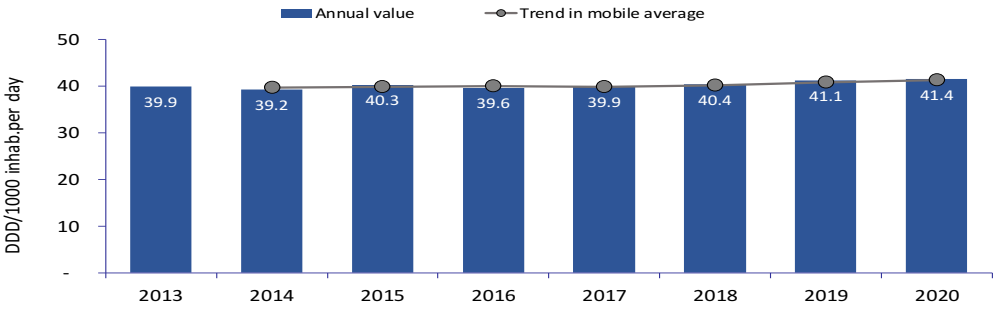
For further information on the use of medicines belonging to the same therapeutic area, analyses were performed on the historical series of consumption by active ingredient and by region and on the efficiency in the absorption of resources according to the presence of expired-patent medicines and on a regional basis. Such analyses focused on medicines for thyroid drugs (Tables 3.9.1 and following).

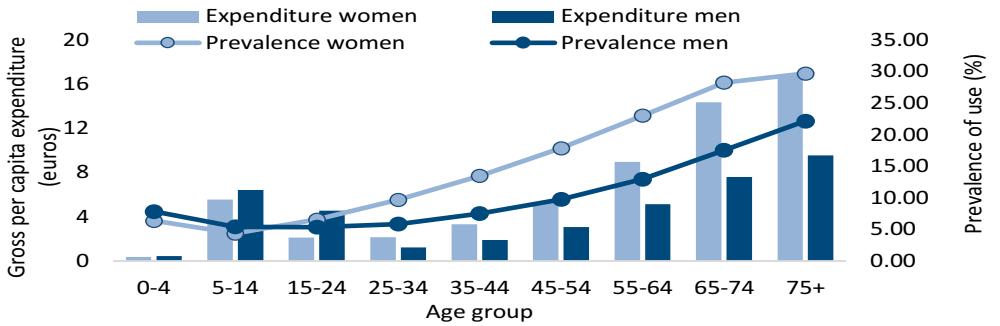
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

Systemic hormonal preparations, excluding sex hormones and insulins

Public expenditure* in million euros (% over total)	**519.9**	**(2,3)**
Δ % 2020-2019		-2.4%
Regional range of gross per capita expenditure	7.3	11.2
DDD/1000 inhab. per day (% over total)	**41.4**	**(3,6)**
Δ % 2020-2019		0.7%
Regional range of DDD/1000 inhab. per day	28.5	50.9

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities





	Gross per capita expenditure			DDD/1000 inhab.per day		
Age group	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
0-4	0.4	0.4	0.4	1.8	1.5	1.7
5-14	6.4	5.6	6.0	3.7	3.2	3.5
15-24	4.6	2.1	3.4	5.6	7.9	6.7
25-34	1.2	2.1	1.7	7.6	18.1	12.7
35-44	1.9	3.3	2.6	11.5	31.2	21.3
45-54	3.1	5.3	4.2	18.2	48.9	33.7
55-64	5.1	9.0	7.1	29.3	72.5	51.6
65-74	7.6	14.4	11.2	44.8	96.3	72.0
75+	9.6	16.7	13.9	58.4	96.6	81.3

3.9.1 Thyroid medicines

National data on consumption and expenditure

Over the past 7 years, thyroid medication consumption has remained stable with slight mean annual variations (CAGR: +1.6%) (Figure 3.9.1.a). A slightly higher increase has been recorded since 2018 (22.1 DDD/1000 inhabitants per day) to reach 23.0 DDD/1000 inhabitants per day in 2020, an increase of 1.2% compared to 2019. In recent years there has been also the greatest variation in terms of the average cost per day of therapy, which varies overall by 17%, from 0.12 euros in 2017 to 0.15 euros in 2020, due to a likely use of more expensive medicines.

Out of a per capita expenditure of 1.23 euros and consumption levels of 23 DDD/1000 inhabitants per day, thyroid hormones account for almost the whole category with 1.17 euros and 21.7 DDD respectively. In particular, over the past seven years, greater variations have been observed in expenditure (CAGR: +6.5%) in comparison with a slight increase in consumption (CAGR: +1.6%)

representing an increase of 7.3% compared to 2019 (Table 3.9.1a).

Findings for the subgroup are also observed in the analysis of the individual active substances. It appears that levothyroxine, a drug authorised for hypothyroidism and non-toxic thyroid hyperplasia or in the prevention of recurrence after partial removal of thyroid tissue, is representative of the entire thyroid hormone subgroup, with a spending of 1.13 euros per capita in 2020 increasing constantly and progressively over the years (CAGR: +7% and 20-19%: +7.8%), and consumption levels of 21.6 DDD/1000 inhabitants per day. On the contrary, over the years the use of antithyroid preparations has decreased slightly with mean annual decreases of 1.1% and a level of 1.4 DDD/1000 inhabitants per day in 2020, while expenditure has remained almost stable at 0.06 euros per capita in 2020.

It should be emphasized that 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.

The incidence of consumption of patent-expired drugs reached about 85% of doses and about 55% of spending in 2020, and within these, almost all use is represented by former originators (Table 3.9.1c). This is also confirmed by the low levels of consumption of equivalent drugs (0.6 DDD) compared to 18.9 DDD of former originators. Drugs covered by patent also determine a significant share of consumption (3.5 DDD), exceeding even the consumption of equivalent drugs. Even less negligible is that these drugs represent 45.4 % of per capita expenditure of the whole category with an average cost per day of therapy of 0.44 euros and with a per capita expenditure of 0.56 euros.

Figure 3.9.1a. Thyroid medicines, temporal trend of per capita expenditure and average cost per day of therapy

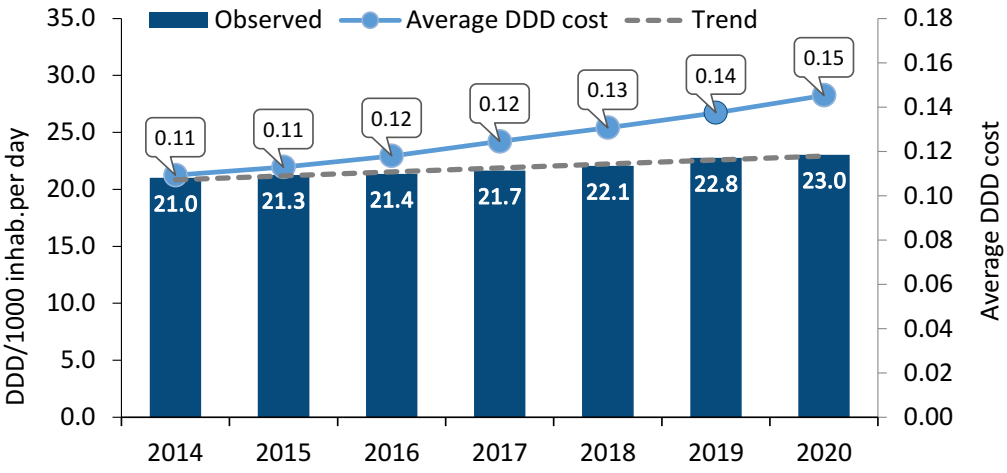


Table 3.9.1a. Thyroid medicines, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expendi-ture	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Thyroid hormones	1.17	7.7	6.9	21.7	1.3	1.7	0.15	6.0
Antithyroid preparations	0.06	0.0	0.6	1.4	-0.5	-1.1	0.11	0.2
Thyroid medicines	**1.23**	**7.3**	**6.5**	**23.0**	**1.2**	**1.6**	**0.15**	**5.7**
levothyroxine	1.13	7.8	7.0	21.6	1.3	1.7	0.14	6.1
thiamazole	0.06	0.0	0.6	1.4	-0.5	-1.1	0.11	0.2
liothyronine	0.04	3.2	3.2	0.0	2.9	3.1	2.07	0.0

Table 3.9.1b. Medicines for thyroid, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	19.6	20.1	20.5	20.9	21.5	22.3	22.3	0.0
Valle d'Aosta	24.7	25.3	17.9	18.0	18.9	19.5	19.7	1.1
Lombardy	13.8	14.2	14.3	14.7	15.2	15.6	15.8	1.4
A.P. of Bolzano	21.2	21.2	21.3	21.4	21.6	22.0	22.1	0.2
A.P. of Trento	25.3	26.1	26.5	27.3	28.2	29.0	29.5	1.6
Veneto	17.7	18.0	18.4	18.8	19.3	20.0	20.1	0.7
Friuli VG	22.4	23.1	23.7	23.9	24.6	25.4	26.5	4.4
Liguria	11.7	11.6	11.0	10.9	10.9	11.1	11.2	0.3
Emilia R.	27.8	28.2	28.0	28.1	28.5	29.2	29.4	0.9
Tuscany	22.3	22.1	22.0	22.2	22.3	22.8	23.8	4.6
Umbria	25.0	25.7	26.5	27.0	28.0	29.2	30.1	3.3
Marche	23.5	24.0	24.5	24.7	25.1	25.8	26.0	0.8
Lazio	30.0	29.9	30.0	30.2	30.5	31.5	31.2	-0.9
Abruzzo	21.3	22.0	22.4	23.0	23.8	24.9	25.2	1.3
Molise	30.0	29.3	28.5	29.0	29.7	30.4	30.9	1.5
Campania	17.4	17.4	17.3	17.5	17.8	18.4	18.7	1.4
Puglia	24.5	25.1	25.4	26.0	26.5	27.8	28.4	1.9
Basilicata	26.0	26.0	25.9	26.5	26.9	28.1	29.0	3.2
Calabria	22.8	22.4	22.4	22.5	22.8	23.7	23.9	1.1
Sicily	19.8	20.0	20.1	20.5	20.9	21.8	22.2	1.6
Sardinia	29.2	29.6	28.9	28.7	28.5	28.4	28.9	1.5
Italy	**21.0**	**21.3**	**21.4**	**21.7**	**22.1**	**22.8**	**23.0**	**1.2**
North	18.3	18.7	18.8	19.1	19.6	20.2	20.4	1.0
Centre	26.3	26.3	26.5	26.7	27.0	27.8	28.1	1.1
South and Islands	21.6	21.8	21.8	22.1	22.5	23.4	23.7	1.6

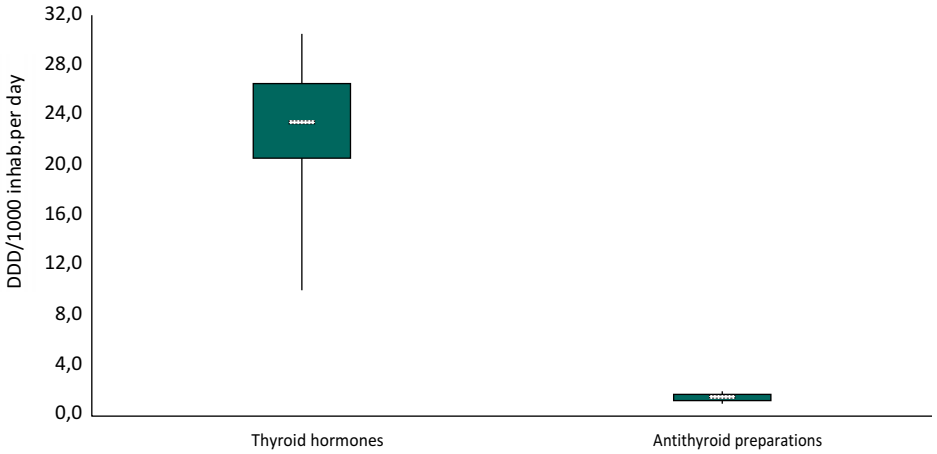
Table 3.9.1c. Prescription of medicines for thyroid with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	0.67	54.6	-0.1	19.6	84.9	-0.4	0.09
Generics	0.01	2.2	8.7	0.6	3.2	4.7	0.06
Former originators	0.65	97.8	-0.3	18.9	96.8	-0.5	0.09
Patent covered	0.56	45.4	17.9	3.5	15.1	11.4	0.44
Medicines to treat thyroid	**1.23**	**100.0**	**7.3**	**23.0**	**100.0**	**1.2**	**0.15**

*Source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.9.1c. Medicines to treat thyroid, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Exposure in population

Health Card data were collected to perform an analysis aimed at estimating exposure to antimigraine medicines in the general population.

As expected, based on epidemiological evidence of the condition, women use more drugs than men. Consumption levels increase progressively with age, reaching the highest values in the 65-74 age group for women (69.2 DDD) and in the 75-84 age group for men (22.6 DDD). The trend of prevalence follows that of consumption and for women, in the 65-74 and 75-84 age groups, the highest percentage values (almost 15%) are recorded, more than 3 times higher than for men in the same age groups; the greatest differences between men and women, however, are observed in the 55-64 age group (11.8% vs 2.5%) (Figure 3.9.1c).

The prevalence of use in the Italian population is about 5% with a median age of 63 years and a male to female ratio of 1:4. On average, each user receives 4 prescriptions and is treated for approximately 5.5 months, although half of patients remain in therapy for less than 5 months with no major differences between geographic areas. On average, 13.9% of users receive only one prescription in the year, with variability in the various Regions: this value reaches almost 20% in Campania (Table 3.9.1d).

Thyroid hormones are the category with the highest regional variability ranging from a minimum consumption value of 10 DDD/1000 inhabitants per day to a maximum of 30.6.

Figure 3.9.1d. Distribution of prevalence of use and consumption of osteoporosis medications under approved care regime and *per conto* distribution (year 2020)

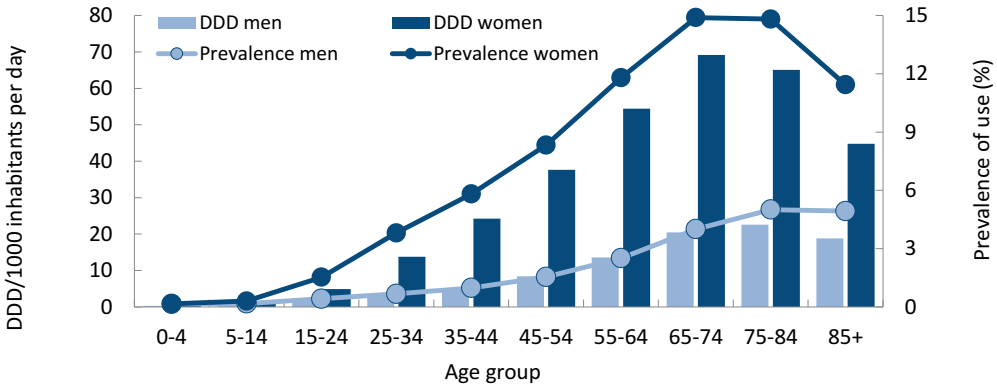


Table 3.9.1d. Exposure and duration of therapy with antidementia medicines by Region under approved care regime and *per conto* distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	5.3	0.22	65	3.9	151.4	133.0	12.3
Valle d'Aosta	4.5	0.21	66	3.2	155.9	133.0	17.1
Lombardy	3.4	0.23	63	3.2	167.5	150.0	17.6
A.P. of Bolzano	4.3	0.23	66	3.1	163.5	150.0	16.0
A.P. of Trento	6.1	0.22	60	3.7	166.6	150.0	8.9
Veneto	4.1	0.22	61	3.6	172.3	150.0	13.2
Friuli VG	5.8	0.21	64	3.9	168.0	150.0	9.7
Liguria	2.9	0.23	74	4.2	147.1	133.0	16.3
Emilia R.	6.2	0.23	63	3.8	166.4	150.0	10.8
Tuscany	5.6	0.24	65	3.9	155.8	133.0	16.0
Umbria	6.7	0.24	63	5.1	165.0	150.0	9.3
Marche	5.9	0.24	64	4.1	152.5	133.0	11.5
Lazio	6.4	0.22	63	3.9	172.2	150.0	13.2
Abruzzo	5.4	0.24	62	4.4	170.7	150.0	10.8
Molise	6.8	0.23	62	4.0	166.8	150.0	11.7
Campania	4.0	0.24	60	3.7	154.2	133.0	19.4
Puglia	6.2	0.24	61	3.7	156.2	133.0	14.9
Basilicata	6.1	0.24	61	4.4	174.7	166.0	12.0
Calabria	4.9	0.25	64	4.1	167.4	150.0	15.0
Sicily	4.5	0.22	64	4.2	173.0	160.0	13.5
Sardinia	5.8	0.20	63	4.7	185.7	175.0	8.6
Italy	**4.9**	**0.23**	**63**	**3.9**	**164.5**	**150.0**	**13.9**
North	4.4	0.22	64	3.6	164.2	150.0	13.6
Centre	6.1	0.23	64	4.0	164.5	150.0	13.5
South and Islands	5.0	0.23	62	4.0	165.0	150.0	14.6

Key message

- Thyroid hormones are the category under approved care regime that registers the highest consumption (21.3 DDD/1000 inhabitants per day) with an increase of 1.3% in prescription and of 5.9% in the average cost per day of therapy, compared to the previous year.
- An analysis of the category of thyroid drugs shows an increase in the average DDD cost, which rose from 0.11 to 0.15 euros, despite substantial stability in consumption (1.2%). According to prevalence data in literature, regions of the Centre show the highest levels of consumption (28.1 DDD/1000 inhabitants per day), compared to the South (23.7) and the North (20.4).
- Out of a per capita expenditure of 1.23 euros and consumption levels of 23 DDD/1000 inhabitants per day, thyroid hormones account for almost total expenditure and consumption of the whole category with 1.13 euros and 21.6 DDD/1000 inhabitants per day respectively. The 7.4% increase in per capita expenditure is due, rather than to an increase in consumption (+1.3%), to a shift towards more expensive medicinal products (mix effect +5.9%). These hormones are also the category with the greatest regional variability, showing a particularly wide range of values (10.1-30.6 DDD/1000 inhabitants per day).
- 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 expenditure under approved care regime compared to 2019 (+7.8%) and 8th among the active ingredients with the highest consumption. If the consumption of this molecule is slightly increasing (+1.3%), the significant growth of the average cost of DDD (+6.1%) is particularly evident. For this active ingredient it should be emphasised the presence on the market of medicinal products with dosage forms different from tablets which are more expensive and still covered by a patent. They might be co-responsible for the very low consumption of generic medicines in the category (0.6 DDD vs 18.9 DDD of originators) that seems unjustified.

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3.10 Genito-urinary system and sex hormones

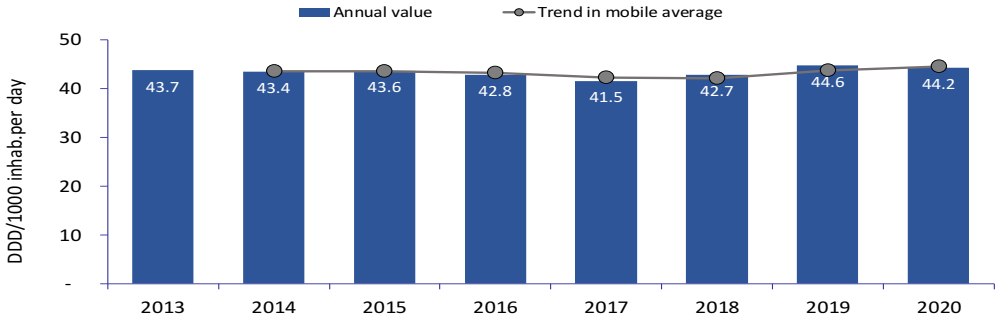
In 2020, drugs affecting the genito-urinary system and sex hormones were the 10th therapeutic category with the highest public expenditure, equal to 395.3 million euros and 1.7% of overall public expenditure (Box. Main indices of expenditure, consumption and exposure). The total per capita expenditure for these drugs was 6.63 euros, mainly relating to pharmaceutical expenditure under approved care regime (5.42 euros per capita), with a decrease compared to 2019 (-6.9%). The expenditure relating to the purchase by public health facilities is of lesser importance (1.21 euros per capita), however it recorded a 21.7% decrease compared to the previous year (Table 3.1).
On the other hand, this category of medicines ranks fifth in terms of NHS consumption with 44.2 DDD/1000 inhabitants per day, slightly down compared to 2019 (-1%), with a rather steady trend in recent years (Table 3.2).
The analysis of the drug use profile by age group and gender, including pharmaceutical expenditure under approved care regime and *per conto* distribution, confirms an almost exclusive use of this class of drugs in men aged 55 and over, essentially due to the treatment of prostatic hypertrophy. The prevalence of use of these drugs 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 25-44 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 8.9 euros per capita.
As for the approved care regime, per capita expenditure for drugs affecting the genito-urinary system and sex hormones is 5.42 euros decreasing compared to 2019. This trend was determined by a slight decrease in consumption (-0.5%), a more marked decrease in prices (-5.7%) and the use of cheaper medicinal products (mix effect -1.1%), all of which led to a 6.7 % reduction in the average cost per day of therapy (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 2.84 euros per capita expenditure and 26.4 DDD/1000 inhabitants per day, followed by testosterone-5-alpha reductase inhibitors, with 1.61 euros and DDD 10.9 (Table 3.9). While testosterone-5-alpha reductase enzyme inhibitor drugs show slight increases in spending and consumption compared to 2019, albeit with greater use of less expensive medicinal products (mix effect -1.0%), alpha-adrenergic receptor antagonists show important contractions especially in terms of spending (-10, 7%) mainly determined by reduction in prices (-10.1%) and prescription of less expensive preparations (mix effect -1.3%), with a reduction of 11.3% in the average cost per day of therapy compared to the previous year. The molecules with the greatest impact on per capita expenditure in the category are tamsulosin and dutasteride (Table 3.10). Alfuzosin (0.86 euros per capita), in particular, is the only active ingredient belonging to this category of pharmaceuticals that is included among the first 30 with the greatest variation in pharmaceutical expenditure under approved care regime compared to the previous year (+5%) (Table 3.13). A similar variation is seen in consumption (+4.7%) which, with 9.1 DDD, places it in 23rd place among the top 30 active ingredients with the highest consumption (Table 3.14 and 3.15).

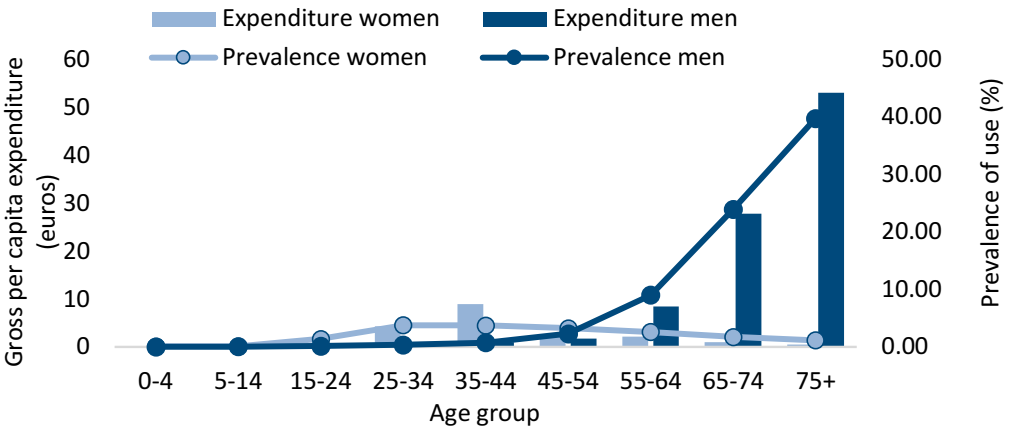
In terms of purchases by public health facilities, there was a reduction in both per capita spending (-22%) and consumption (-9.7%) and an increase in the use of cheaper drugs (mix effect -11.2%), with a consequent reduction of 13.5% in the average cost per day of therapy (Table 3.16). The gonadotropin subcategory has the highest per capita spending, however, it is also the one where the largest decreases are noted compared to 2019 (-24.3% spending and -20.7 DDDs). These drugs 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 (Table 3.16).
The active ingredient with the highest incidence of expenditure (23.6%) is represented by recombinant follitropin alfa with a cost per day of therapy equal to 19.0 euros. However, its consumption levels represent a little less than 2% of the whole category, 20% down compared to the previous year (Table 3.17). Similarly, the expenditure of menotropin and follitropin alfa/lutropin alfa combination decreased (-15.6% and -25.1%, respectively).
No active ingredient belonging to this category of drugs is listed in the top 30 with the highest incidence of expenditure for 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).
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 expired-patent medicines and on a regional basis. These analyses focused on genitourinary tract agents (Table 3.10.1 and following).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Genito-urinary system and sex hormones

Public expenditure* in million euros (% over total)	**395.3**	**(1,7)**
Δ % 2020-2019		-10.0%
Regional range of gross per capita expenditure	4.7	7.7
DDD/1000 inhab. per day (% over total)	**44.2**	**(3,8)**
Δ % 2020-2019		-1.0%
Regional range of DDD/1000 inhab. per	30.3	52.0

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities





	Gross per capita expenditure			DDD/1000 inhab.per day		
Age group	**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	0.1
15-24	0.2	0.6	0.4	0.4	3.9	2.1
25-34	0.6	4.3	2.4	1.1	9.7	5.3
35-44	1.0	8.9	4.9	2.4	11.8	7.1
45-54	1.8	2.5	2.1	11.2	13.7	12.4
55-64	8.4	2.2	5.2	66.9	14.9	40.1
65-74	27.8	1.0	13.6	227.7	8.2	111.7
75+	53.1	0.5	21.6	422.4	3.9	171.9

3.10.1 Medicines for genitourinary disorders

National data on consumption and expenditure

Between 2014 and 2020, consumption of medications for genito-urinary disorders increased from 31.8 to 38.1 DDD/1000 inhabitants per day, representing a mean annual increase (CAGR) of 3.1% (Figure and Table 3.10.1a). In terms of per capita spending (4.52 euros), there is a 6.7% decrease compared to 2019 with an annual reduction of 3.2% since 2014. The average cost per day of therapy decreased slightly from 0.35 euros in 2019 to 0.32 euros in 2020 (Table 3.10.1a), with the largest decrease in average cost occurring in 2017-2018 (-26.3%) due to the patent expiration of dutasteride (which occurred in the second half of 2017).

Medications for BPH account both for almost total consumption of drugs for genitourinary disorders (37.8 DDD), slightly up compared to 2019, and for total per capita spending (4.46 euros) of the category, whereas the use of treatments for urinary incontinence is low (0.3 DDD), with mean annual increases of 8.1% from 2014 to 2020 (+9.7% compared to 2019). It is recalled that these drugs are prescribed under approved care regime with Note 87 only to patients suffering from urgency urinary incontinence, in cases where the urination disorder is related to diseases of the central nervous system (eg, stroke, Parkinson's disease, trauma, cancer, spina bifida, multiple sclerosis).

Similar to the year 2019, the most prescribed drugs for 2020 are tamsulosin, dutasteride, alfuzosin, and silodosin with year-over-year increases ranging from 1.7% for tamsulosin and dutasteride to 3.6% for alfuzosin, while silodosin shows a 6.7% decrease.

Although these are the drugs with the highest consumption, they record the lowest average cost per day of therapy of the category, ranging between 0.26 euros (alfuzosin) and 0.35 euros (silodosin), compared to other medications such as tolterodine, a drug 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 with 0.66 euros, about twice as much.

As for expenditure, silodosin is the drug for which the largest reduction in per capita expenditure is observed (-35.2%) compared to the previous year, corresponding to a reduction in the average cost per DDD of 30.7%, due to the patent expiry of the drug in November 2018, for which generic products are currently available. Although still small, tolterodine use has increased of 16.2% since the previous year, with an average annual increase of 58.8%. This drug is included in Note AIFA 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).

Expired patent medicines account for more than 98% of doses and 97% of expenditure per capita, of which only one third is represented by generic products showing a reduction of more than 3% in terms of both expenditure and consumption compared to 2019. Drugs covered by patents have a cost per day of therapy about twice as much as medicines with expired patents, but they account for a small part of consumption and expenditure, which shows a decrease of 87.5% compared to 2019 (Table 3.10.1c).
For drugs for genito-urinary disorders, there is no regional variability in consumption by quantity and average cost per day of therapy, in fact all regions, regardless of consumption, have an average cost per day of therapy aligned with the national average (Figure 3-10.1b).

Figure 3.10.1a. Medicines for genitourinary disorders, temporal trend of consumption and average cost per day of therapy (2014-2020)

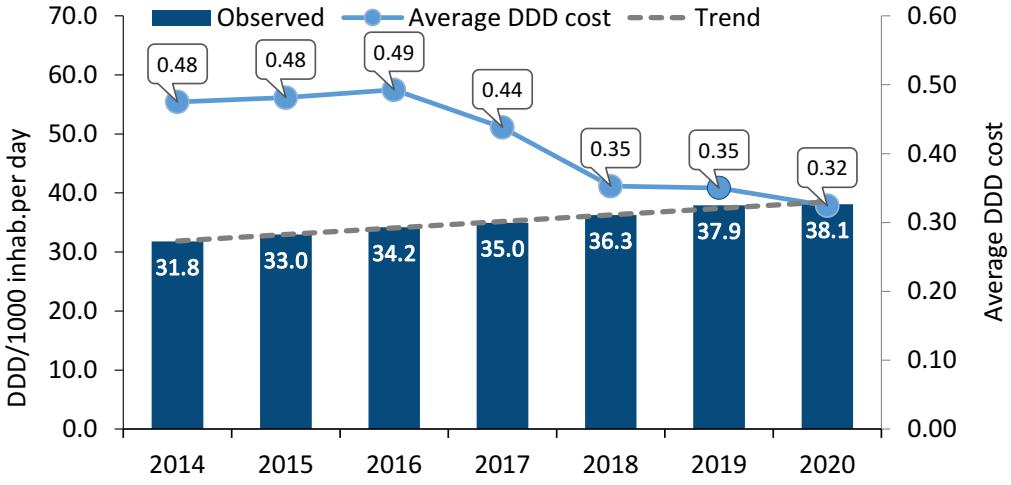


Table 3.10.1a. Medicines for genitourinary disorders, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Medicines for benign prostatic hypertrophy	4.46	-6.8	-3.3	37.8	0.4	3.0	0.32	-7.5
Pharmaceuticals for incontinence and urination disorders	0.06	7.1	7.0	0.3	9.7	8.1	0.63	-2.6
Other medicines for benign prostatic hypertrophy	0.00	-4.2	-1.7	0.0	-1.7	-3.2	1.14	-2.8
Medicines for genitourinary disorders	**4.52**	**-6.7**	**-3.2**	**38.1**	**0.5**	**3.1**	**0.32**	**-7.4**
tamsulosin	1.10	1.3	2.0	10.8	1.7	2.3	0.28	-0.7
dutasteride	1.06	1.1	-12.1	8.4	1.7	4.6	0.34	-0.9
alfuzosin	0.87	5.0	3.1	9.2	3.6	3.0	0.26	1.1
silodosin	0.70	-35.2	1.8	5.4	-6.7	8.2	0.35	-30.7
finasteride	0.55	-0.7	-0.9	2.6	-1.2	-0.7	0.58	0.2
terazosin	0.15	-5.2	-5.4	1.3	-5.0	-5.2	0.33	-0.4
oxybutynin	0.05	3.4	4.7	0.2	2.4	4.7	0.61	0.7
doxazosin	0.03	-6.4	-7.6	0.2	-6.7	-7.7	0.42	0.0
tolterodine	0.01	12.9	33.2	0.0	16.2	58.8	0.66	-3.1
solifenacin	0.00	74.5	8.0	0.0	269.4	22.3	0.55	-52.9

Table 3.10.1b. Medicines for genitourinary disorders, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	31.6	32.4	33.5	34.1	35.0	36.4	35.4	-2.7
Valle d'Aosta	28.5	29.3	29.5	29.6	30.7	31.3	30.3	-3.0
Lombardy	28.5	29.7	30.8	31.6	32.9	33.8	33.5	-0.7
A.P. of Bolzano	21.5	21.9	22.1	22.6	22.8	23.3	23.2	-0.2
A.P. of Trento	28.8	29.8	30.5	31.5	33.0	33.9	33.7	-0.6
Veneto	27.9	28.8	30.0	30.6	31.8	33.3	33.5	0.6
Friuli VG	28.3	29.2	30.1	30.5	31.5	32.9	31.4	-4.4
Liguria	33.6	34.6	35.7	36.3	37.4	39.2	38.8	-0.8
Emilia R.	33.2	35.0	36.2	36.8	37.6	39.0	39.0	-0.1
Tuscany	31.6	32.4	33.4	34.2	35.3	36.8	37.1	0.8
Umbria	36.7	37.9	39.3	40.1	41.8	43.7	44.9	2.8
Marche	39.5	40.9	42.7	43.3	45.1	46.9	46.7	-0.4
Lazio	34.4	35.4	36.3	36.9	38.0	39.9	39.8	-0.2
Abruzzo	32.2	33.3	34.7	35.6	37.4	39.1	39.9	2.0
Molise	30.2	30.6	31.7	32.8	34.3	35.9	36.9	2.7
Campania	31.4	33.1	34.9	36.2	38.3	40.6	41.5	2.5
Puglia	33.5	34.9	36.6	37.9	39.5	42.1	43.1	2.3
Basilicata	34.5	36.6	38.5	39.8	41.9	44.1	45.8	3.9
Calabria	34.1	34.9	36.4	37.1	38.4	40.2	40.8	1.5
Sicily	34.3	35.4	36.5	37.3	38.8	41.2	42.1	2.2
Sardinia	31.4	32.9	34.0	35.0	36.6	38.0	38.8	1.9
Italy	**31.8**	**33.0**	**34.2**	**35.0**	**36.3**	**37.9**	**38.1**	**0.5**
North	29.9	31.0	32.1	32.7	33.8	35.0	34.7	-0.9
Centre	34.4	35.4	36.4	37.1	38.3	40.1	40.2	0.3
South and Islands	32.9	34.3	35.7	36.8	38.5	40.7	41.6	2.3

Table 3.10.1c. Prescription of medicines for genitourinary disorders with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/ 1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	4.38	96.9	17.9	37.4	98.3	17.5	0.32
Generics	1.21	27.5	-3.3	12.0	32.2	-3.9	0.27
Former originators	3.18	72.5	28.7	25.4	67.8	31.4	0.34
Patent covered	0.14	3.1	-87.5	0.6	1.7	-89.3	0.59
Medicines per disorders genitourinary	**4.52**	**100.0**	**-6.7**	**38.1**	**100.0**	**0.5**	**0.32**

*Source: monthly transparency lists published by the Italian Medicines Agency in 2020

Exposure and adherence in population

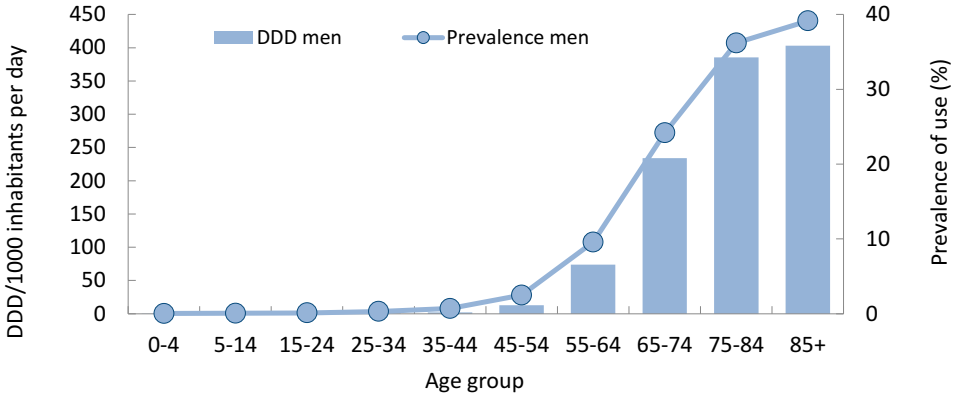
Owing to Health Card data it was possible to describe the trend of prevalence and consumption by age group and region and calculate some indicators of intensity of use of drugs for genito-urinary disorders, represented for 99% by drugs for the treatment of BPH. In addition, patient adherence and persistence 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 drugs is insignificant and therefore it has not been represented graphically) it is noted the growing use of drugs for genito-urinary disorders with increasing age, with higher values of prevalence (49.1%) and consumption (403.2 DDD/1000 inhabitants per day) in men over 80, in accordance with literature epidemiology. In the 75-84 age group, prevalence and consumption values are similar to those in the following age group. In younger ages prevalence is observed, but it decreases by 12% in the 65-74 age group and by almost 15% in the 54-45 age group (Figure 3.10.1c). At national level, prevalence is around 8%, ranging from a minimum of 7.5% in Northern areas to a maximum of 8.8% in Central regions (8.7% in the South). The highest prevalence value is recorded in the Marche region (9.8%), while the A.P. of Bolzano, with a prevalence of 4.9%, shows the lowest value. The median age of users is 73 years evenly distributed in all Regions (Table 3.10.1d)

In accordance with guidelines on the treatment of a condition that has now become chronic, each user has received on average at least one dose of drug per day for about 11 months of therapy: in detail, regions of the North and South have an average annual coverage of about 15 days more than regions of the Center. 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 330) made it possible to confirm the data obtained previously. As it can be noted with the last indicator "users with 1 prescription", there is a signinficant percentage (13%) of subjects who received only one prescription during the year, with Puglia having the highest percentage (15.7%) of sporadic users and Umbria and Friuli Venezia Giulia having, on the contrary, the lowest percentage (10.3%). Therefore, as above, the same considerations should be made for the reading of this indicator.
As for the adherence and persistence analyses, the exposure data refer to a cohort of new users over 45 years old, which were followed considering the one-year follow-up. Therefore, as above, the same considerations should be made for the reading of this indicator. The percentage of subjects with high adherence is 62.8% and follows a normal distribution in which it tends to increase progressively from the age of 45 until the age of 65-74 (64.4%), then it decreases again in the following age groups (60% in the over 85s)) (Table 3.10.1e). Users residing in Central Italy and aged between 65 and 74 years showed the highest percentage value of high adherence (65%). For low adherence to treatment (10.3% 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 (13.9% and 11% respectively), while the 65-74 age group is the one that records the lowest percentage of users with low adherence (9%). 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, with the exception of the over-80s, who are more concentrated in the Centre (11.8% vs 12.4%).
An analysis of persistence data shows that about half of users (49.9%) sustained drug therapy almost continuously over a period of 1 year. These data are almost overlapping with those of 2019 and show that at one year after starting treatment half of users discontinue therapy for at least 60 days thus resulting in non-persistent. In detail, while in Northern regions there are more persistent medication users, in the South there are the lowest rates, 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 3.10.1f). Comparing persistence data between 2019 and 2020 (Figure 3.10.1d) there are no substantial differences confirming that the median time to discontinuation is about 300 days with Northern Regions also exceeding 365 days.

Figure 3.10.1c. Distribution of 2020 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 3.10.1d. Exposure and duration of therapy with medicines for genitourinary disorders by Region under approved care regime and per conto distribution (year 2020)

Region	Prevalence of use (%)	Ratio M/W	Median age	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription (%)
Piedmont	8.3	74	7.4	320.9	320.0	11.6	12.3
Valle d'Aosta	7.6	73	6.7	296.9	300.0	14.5	17.1
Lombardy	7.1	73	7.2	347.7	336.0	12.6	17.6
A.P. of Bolzano	4.9	75	6.9	300.1	300.0	15.6	16.0
A.P. of Trento	6.7	74	7.7	354.8	360.0	12.3	8.9
Veneto	6.9	73	7.5	355.6	360.0	11.4	13.2
Friuli VG	7.3	74	8.1	353.4	355.0	10.3	9.7
Liguria	9.5	75	7.5	335.5	320.0	13.3	16.3
Emilia R.	8.1	74	7.8	337.9	330.0	12.0	10.8
Tuscany	8.8	74	7.6	319.4	320.0	15.2	16.0
Umbria	9.7	74	9.2	350.2	340.0	10.3	9.3
Marche	9.8	73	7.4	338.5	320.0	12.6	11.5
Lazio	8.5	72	7.1	342.2	330.0	13.9	13.2
Abruzzo	8.5	73	7.7	349.2	350.0	12.7	10.8
Molise	8.4	73	7.4	327.4	320.0	13.0	11.7
Campania	8.8	71	7.3	322.8	320.0	13.4	19.4
Puglia	8.9	72	7.0	327.8	320.0	15.7	14.9
Basilicata	9.4	72	8.9	356.1	360.0	11.4	12.0
Calabria	8.6	72	7.6	331.3	320.0	13.2	15.0
Sicily	8.7	72	7.7	347.5	360.0	12.4	13.5
Sardinia	8.6	72	7.9	342.9	340.0	12.5	8.6
Italy	**8.2**	**73**	**7.5**	**337.6**	**330.0**	**13.0**	**13.9**
North	7.5	73	7.5	341.3	330.0	12.1	13.6
Centre	8.8	73	7.4	335.2	320.0	13.8	13.5
South and Islands	8.7	72	7.5	334.8	330.0	13.4	14.6

Table 3.10.1e. Indicators of adherence to treatment with medications for benign prostatic hypertrophy in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=93.875		North N=38.226		Centre N=19.874		South N=35.775	
Low adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	13.9	-3	12.1	-6	12.9	-4	15.7	-1
55-64 years	10.5	3	9.4	2	10.4	2	11.6	4
65-74 years	9.4	1	8.9	5	9.1	-7	10.2	0
75-84 years	10.3	3	9.2	1	10.7	6	11.5	2
≥85 years	11.0	-5	9.8	-5	12.4	-1	11.8	-7
Total	**10.3**	**1**	**9.3**	**2**	**10.3**	**-1**	**11.4**	**1**
High adherence*†	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	58.2	2	58.0	2	60.8	4	57.0	2
55-64 years	62.9	0	63.9	2	62.3	-3	62.3	0
65-74 years	64.4	0	64.8	-1	65.0	1	63.7	1
75-84 years	62.3	-1	63.5	-1	61.7	-2	61.0	-1
≥85 years	60.0	0	61.6	-1	58.9	0	58.6	0
Total	**62.8**	**0**	**63.6**	**0**	**62.8**	**0**	**61.9**	**0**

*Adherence to treatment was assessed in the 365 days following the date of the first prescription (index date) only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) <40% of the observation period while high adherence was defined as therapeutic coverage ≥80% of the observation period (for further details please refer to statistical methods)

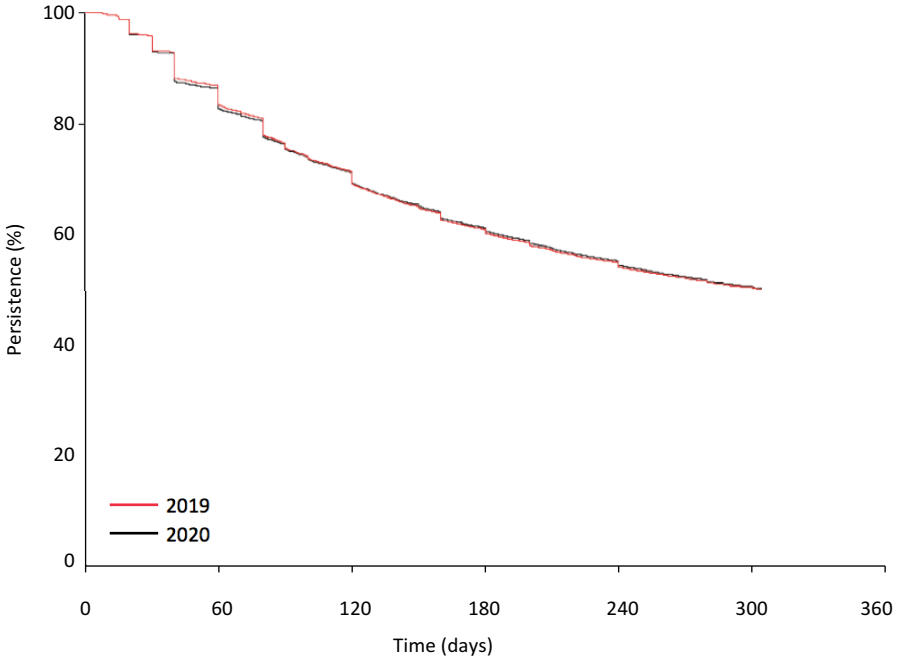
N: refers to new users, subjects who received a first prescription in the period 01/10/2019- 31/12/2019, not treated in the previous months starting from 01/01/2019; Percentages of subjects with low/high adherence relating to the specific category Median follow-up time (IQR): 322 (217-346)

Table 3.10.1f. Persistence after one year of treatment with medicines for benign prostatic hypertrophy in the population aged ≥45 years in 2020 and percentage change compared to the previous year

	Total N=93.875		North N=38.226		Centre N=19.874		South N=35.775	
Persistence after 12 months	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**	**%**	**Δ % 20-19**
45-54 years	41.5	4	42.7	5	41.8	-1	40.5	7
55-64 years	49.0	-1	50.8	2	48.3	-2	47.5	-2
65-74 years	51.6	0	52.8	0	52.2	0	50.1	1
75-84 years	50.9	-2	52.7	-1	50.3	-2	48.8	-3
≥85 years	49.6	-1	51.0	-3	48.5	0	47.4	0
Total	**49.9**	**0**	**51.6**	**0**	**49.8**	**-1**	**48.2**	**0**

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

Figure 3.10.1d. Time (in days) to discontinuation of treatment with osteoporosis medications in the population aged ≥45 years stratified by year (2019 and 2020); the curves are adjusted for gender and age (the Cox model was used to estimate the persistence curves)



Note: An interruption to treatment occurs if the subject does not receive a prescription within 60 days (for more details please refer to statistical methods) For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days)

Key message

- In the field of drugs for genitourinary disorders, reference is mainly made to drugs 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 this disorder by the clinician and increased awareness of need for treatment by patient.
- In the male population, consumption increases progressively with age in accordance with epidemiological data in literature. Each main user received at least one dose of the drug per day for just over 11 month of therapy, with slight interregional variations with respect to the national average.
- Faced with an increase in consumption, per capita expenditure of these drugs which mainly affects expenditure under approved care regime has fallen in recent years, as the average cost per day of therapy. This trend is probably due to the patent expiry of some drugs in the category.

- Although there is variability in consumption at regional level, with regions of the South consuming on average more doses than those of the North, there is no regional variability in the average cost per day of therapy. In fact, all regions, regardless of consumption, have an average cost per day of therapy in line with the national average.
- Adherence and persistence to treatment with drugs 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.

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3.11 Sensory organs

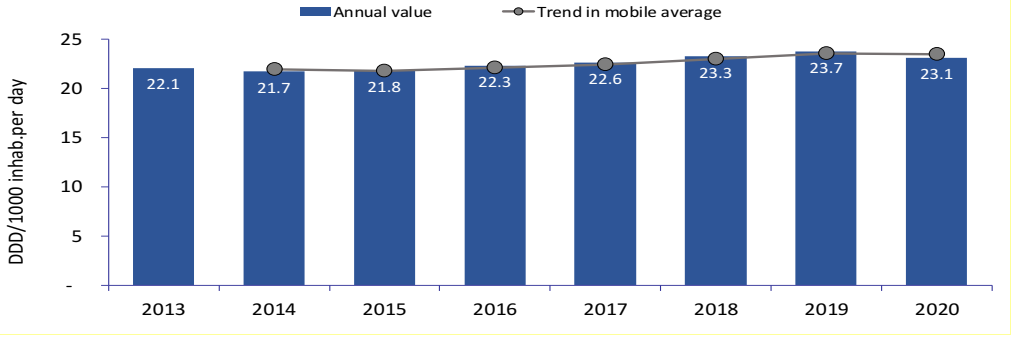
In 2020, drugs for sense organs are confirmed in 11th place in terms of public spending, amounting to about 359 million euros (1.6% of total spending; Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure for these drugs was 6.0 euros, mainly due to the expenditure under approved care regime (3.89 euros per capita), reporting a -8.4% decrease compared to the previous year. Expenditure due to purchases by public health facilities is lower (2.14 euros per capita), with a -31.8% increase compared to 2019 (Table 3.1).
Consumption for this category of drugs was 23.1 DDD/1000 inhabitants per day, with a 2.7% decrease compared to 2019.
The analysis of the drug use profile by age group and gender, including pharmaceutical expenditure under approved care regime and *per conto* distribution, confirms an almost exclusive use of this class of drugs in subjects aged up to 55 years old. Consumption remains slightly higher in women than in men, until the trend is after the age of 75 (96.1 DDD for men versus 84.0 DDD for women). At the same time, NHS per capita expenditure also increases with the age of patients, reaching the maximum level of 16.5 euros per capita (18.0 in women and 15.5 in men) in subjects over 75 years of age.
As for the approved care regime, a significant reduction was recorded in expenditure (-1.3%) compared to 2019, against a slight reduction in consumption (-0.4%), an important price reduction (-11.8%) and a negative mix effect (-0.9%) (Table 3.9). Within this distribution channel, beta-blockers are the subcategory with the highest expenditure (2.26 euros) and consumption (11.8 DDD), the only one to register an increase, albeit slight, in consumption in 2020 (+0.3%). Prostaglandin analogues followed, with values of 1.28 and 5.7 DDD, respectively (Table 3.9). Timolol alone or in combination with other active ingredients accounts for about 45% of the expenditure of the entire category (Table 3.10).
In terms of purchases by public health facilities, marked decreases were recorded in terms of per capita expenditure (-32.0%), consumption (-19.9%), prices (-13.3%) and average DDD cost (-15.1%), with a greater preference for less expensive medicines (mix effect: -2.1%). The therapeutic category with the greatest impact on spending is antineovascular agents, which account for 70% of expenditure, such as drugs 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 2019 (Table 3.16). Within this subgroup, aflibercept is the highest-spending active ingredient, accounting for approximately 40% of category expenditure, followed by ranibizumab (30%) (Table 3.17).
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 expired-patent medicines and on a regional basis. These analyses focused on medicines for eye disorders (Table 3.11.1a and following).
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).

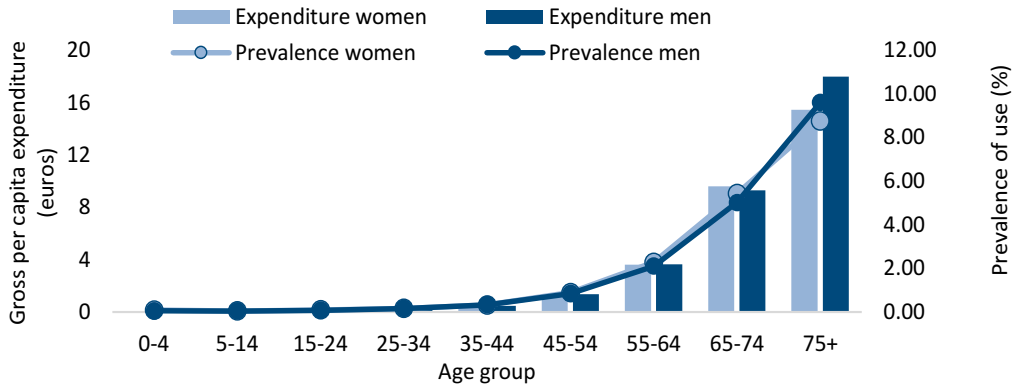
MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

Sensory organs

Public expenditure* in million euros (% over total)	**359.3**	**(1,6)**
Δ % 2020-2019		-14.7%
Regional range of gross per capita expenditure	4.4	8.1
DDD/1000 inhab. per day (% over total)	**23.1**	**(2,0)**
Δ % 2020-2019		-2.7%
Regional range of DDD/1000 inhab. per	18.1	32.1

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities





	Gross per capita expenditure			DDD/1000 inhab.per day		
Age group	**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	0.2	0.2	0.2
15-24	0.1	0.1	0.1	0.5	0.5	0.5
25-34	0.2	0.2	0.2	1.1	0.9	1.0
35-44	0.5	0.4	0.4	2.6	2.0	2.3
45-54	1.4	1.2	1.3	7.4	6.6	7.0
55-64	3.7	3.6	3.6	19.5	19.6	19.6
65-74	9.3	9.6	9.5	49.4	51.3	50.4
75+	18.0	15.5	16.5	96.1	84.0	88.9

3.11.1 Medicines for eye disorders

National data on consumption and expenditure

Over the past seven years, consumption of drugs used for eye disorders has remained nearly stable, increasing from 19.9 DDD in 2014 to 21.1 DDD in 2020, with a mean annual variation of 1% (Figure and Table 3.11.1a). By analysing variation between 2019 and 2020 it is noted a slight decrease in consumption of 1.8%. Over the same period, the average cost per therapy day decreased by 13.0%, reaching 0.76 euros in 2020 (0.87 euros in 2019). Similar to 2019, also for 2020, the highest consumption is represented by antiglaucoma preparations, which in detail concern more antiglaucoma/beta-blockers alone or in combination (12.0 DDD/1000 inhabitants per day) and antiglaucoma/prostanglandin analogues (5.7 DDD). This aspect is also reflected in per capita spending, which for the former is 2.28 euros and for the latter 1.28 euros. Neovascularizing agents, at 1.50 euros, show a significant decrease in per capita spending compared to 2019 (-36.9%), although they remain the drugs with the highest average cost per day of therapy of the whole category (13.74 euros). Timolol alone or in combination represents the active ingredient with the highest expenditure (1.75 euros per capita) and consumption (9.1 DDD). They are followed in spending by aflibercept (0.85 euros) and ranibizumab (0.64 euros), drugs indicated in the treatment of neovascular (exudative) age-related macular degeneration (AMD), which however show an important decrease compared to 2019 (-28.7% and -45.3%, 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 drugs, see Section 4 on Monitoring Registries (“Anti-neovascular Drugs for Intravitreal Use”) (Table 3.11.1a). Steroids, in particular dexamethasone, and corticosteroids (intravitreal implants) record the highest average costs per day of therapy (4.45 euros and 6,646.83 euros, respectively); however, low levels of consumption do not affect per capita spending (0.35 euros and 0.03 euros, respectively).

In 2020, expired-patent drugs accounted for 48.2% of doses and for 26.0% of expenditure, with a limited use of equivalent medicines, though increasing compared to the previous year (+9.4%) (Table 3.11.1c). Antiglaucoma preparations, represented by beta-blockers alone and in combination, are the drugs with the greatest regional variability in terms of consumption, presenting a wide range of values (8.0-17.3 DDD/1000 inhabitants per day) (Figure 3.11.1c).

Figure 3.11.1a. Medicines for eye disorders, temporal trend of consumption and average cost per day of therapy (2014-2020)

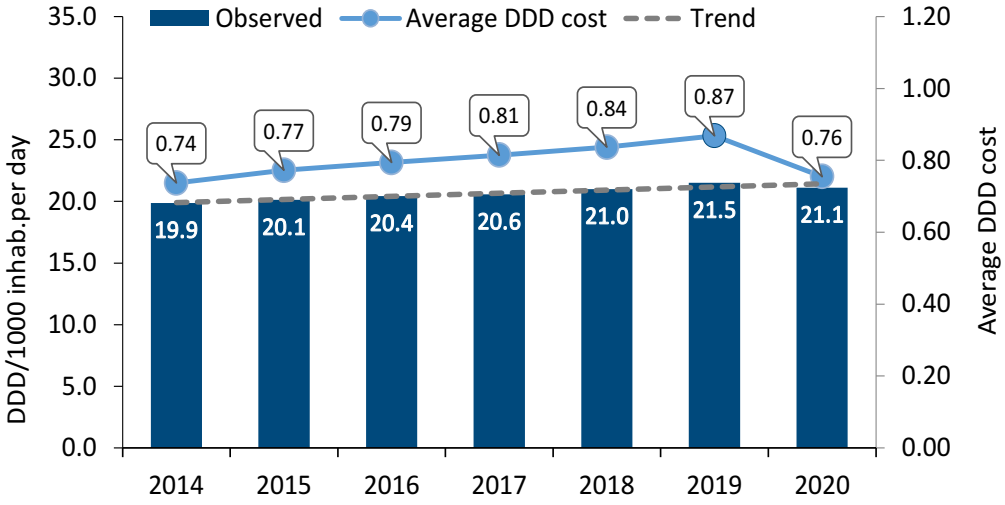


Table 3.11.1a. Medications for eye disorders, per capita expenditure and consumption (DDD/1000 ab day) by therapeutic category and by substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Antiglaucoma preparations - beta blockers plain or in combination	2.28	0.2	2.1	12.0	0.4	1.1	0.52	-0.4
Antineovascular agents	1.50	-36.9	-0.1	0.3	-28.5	7.5	13.74	-12.1
Antiglaucoma preparations - prostaglandin analogues	1.28	-3.2	-0.2	5.7	-2.2	0.4	0.61	-1.3
Corticosteroids	0.35	-9.1	13.3	0.2	-13.4	13.7	4.45	4.6
Antiglaucoma preparations - carbonic anhydrase inhibitors	0.21	-7.0	-4.2	1.4	-6.8	-1.0	0.42	-0.6
Antiglaucoma preparations – sympathomimetic drugs	0.10	-1.6	3.5	1.5	-2.4	2.8	0.18	0.5
Other ophthalmological drugs	0.09	-1.3	59.8	0.0	18.6	-6.1	143.41	-17.0
Corticosteroids (intravitreal implants)	0.03	-3.7	-	0.0	-3.5	-	6646.83	-0.4
Antiglaucoma preparations – parasympathomimetic drugs	0.01	-32.6	-4.4	0.0	-16.1	-10.5	0.75	-19.9
Antiglaucoma preparations - others	0.00	-13.0	-1.8	0.0	-14.9	-3.5	0.36	1.9
Medicines for eye disorders	**5.84**	**-14.3**	**1.5**	**21.1**	**-1.8**	**1.0**	**0.76**	**-13.0**
aflibercept	0.85	-28.7	31.0	0.2	-26.5	35.8	10.69	-3.3
ranibizumab	0.64	-45.3	-11.3	0.1	-33.4	-10.5	21.42	-18.0
tafluprost	0.48	7.1	10.2	1.5	6.8	10.1	0.86	0.0
timolol/bimatoprost	0.44	-1.8	3.6	1.4	-1.6	3.0	0.85	-0.4
bimatoprost	0.41	-13.5	-1.2	1.9	-5.6	0.2	0.60	-8.6
timolol/brinzolamide	0.40	-7.8	4.7	1.7	-4.7	6.4	0.65	-3.5
timolol	0.35	2.6	3.5	3.1	-0.3	-0.3	0.31	2.7
dexamethasone	0.34	-9.0	12.9	0.2	-13.5	14.0	4.40	4.8
dorzolamide/timolol	0.33	11.9	2.0	2.3	11.0	2.5	0.38	0.5
tafluprost/timolol	0.23	18.5	-	0.6	18.2	-	0.96	0.0

Table 3.11.1b. Medicines for eye disorders, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	21.8	22.0	22.3	22.4	23.0	23.7	23.3	-2.0
Valle d'Aosta	20.6	20.8	20.4	19.9	19.3	19.7	19.6	-0.2
Lombardy	16.1	16.5	16.8	16.9	17.3	17.4	16.9	-2.9
A.P. of Bolzano	14.2	15.0	15.5	15.9	16.5	16.9	16.3	-3.2
A.P. of Trento	15.1	15.4	16.0	16.5	17.3	17.3	17.0	-1.8
Veneto	17.7	17.8	18.2	18.5	19.2	19.4	19.2	-1.1
Friuli VG	22.6	22.9	22.9	23.6	24.1	24.5	26.9	10.0
Liguria	21.1	21.2	21.6	21.5	21.6	22.0	21.4	-2.4
Emilia R.	25.1	25.4	25.9	26.9	27.6	28.0	27.4	-2.1
Tuscany	25.8	25.8	26.4	26.4	26.7	27.2	26.6	-2.0
Umbria	22.9	23.1	23.7	23.9	24.7	25.4	25.1	-0.9
Marche	28.5	28.8	29.4	29.5	29.9	30.7	30.2	-1.4
Lazio	22.0	22.2	22.3	22.1	22.3	22.9	22.2	-3.2
Abruzzo	25.3	25.7	25.9	25.9	26.5	27.2	26.7	-1.9
Molise	15.9	15.7	16.3	16.1	16.3	17.1	16.6	-2.7
Campania	16.8	17.1	17.5	17.4	17.9	18.5	18.2	-1.6
Puglia	18.4	18.5	18.8	18.8	19.1	19.9	19.5	-2.2
Basilicata	19.1	19.5	20.1	20.0	20.7	21.2	21.0	-0.8
Calabria	18.9	19.3	19.3	19.2	19.5	20.3	20.0	-1.7
Sicily	16.1	16.3	16.6	16.8	17.3	18.1	17.9	-1.3
Sardinia	19.6	19.7	19.6	19.6	19.8	20.0	19.9	-0.5
Italy	**19.9**	**20.1**	**20.4**	**20.6**	**21.0**	**21.5**	**21.1**	**-1.8**
North	19.4	19.6	20.0	20.3	20.8	21.1	20.8	-1.6
Centre	24.1	24.3	24.7	24.6	24.9	25.5	24.9	-2.4
South and Islands	18.0	18.2	18.5	18.5	18.9	19.6	19.3	-1.6

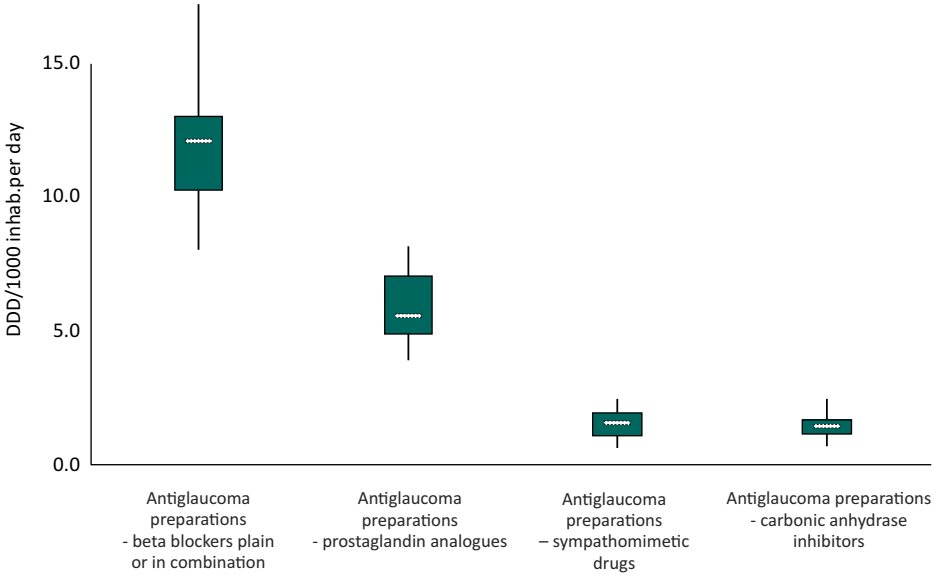
Table 3.11.1c. Prescription of medicines for eye disorders with patent expired* in 2020

Categories	Per capita expenditure	%	Δ % 20-19	DDD/1000 inhab. per day	%	Δ % 20-19	Average DDD cost
Patent expired	1.52	26.0	31.2	10.2	48.2	16.1	0.41
Generics	0.18	12.0	22.0	1.9	18.8	9.4	0.26
Former originators	1.33	88.0	32.6	8.3	81.2	17.8	0.44
Patent covered	4.32	74.0	-23.6	10.9	51.8	-14.1	1.08
Medicines for eye disorders	**5.84**	**100.0**	**-14.3**	**21.1**	**100.0**	**-1.8**	**0.76**

*Source: monthly transparency lists published by the Italian Medicines Agency in 2020

Figure 3.11.1c. Medications for eye disorders, regional variability of 2020 consumption (weighted DDD/1000 inhab. day) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- On average, from 2014 to 2020, drugs for ocular disorders **do not record particular variations in terms of consumption**, however, analysing only the biennium 2019-2020 it is noted a decrease in both consumption and average cost per day of therapy.
- Antiglaucoma preparations are also the most widely used drugs for 2020, with marked regional variability. Overall, compared to 2019, there are decreases in consumption in all regions except Friuli Venezia Giulia.
- In general, **drugs available for the treatment of ocular 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.

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World Health Organization. World report on vision. Geneva: World Health Organization, 2019. Licence: CC BY-NC-SA 3.0 IGO.

3.12. Miscellaneous

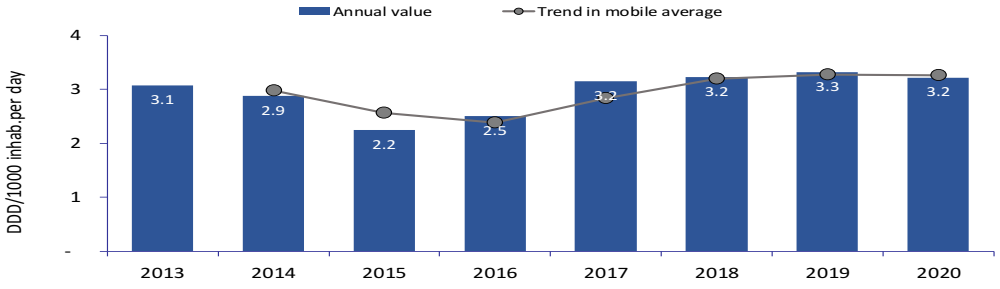
In 2020, the therapeutic category of "Miscellaneous" drugs ranks 12th in terms of public spending, accounting for 354.7 million euros and 1.5% of total public expenditure (Box. Main indices of expenditure, consumption and exposure). Total per capita expenditure on these drugs amounted to 5.95 euros, increasing of 1.5% compared to the previous year because of purchases by public health structures (5.81 euros per capita). On the contrary, the contribution provided through the approved care regime was lower (0.14 euros per capita) (Table 3.1).
Consumption for this category of drugs was 3.2 DDD/1000 inhabitants per day, with a 2.8% increase compared to 2019, interrupting the upward trend of recent years (Table 3.2).
The analysis of the drug use profile by age group and gender, including pharmaceutical expenditure under approved care regime and *per conto* distribution, shows a declining use of these drugs between 55 and 64 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 3.9% and 3.4%, respectively. At the same time, NHS per capita expenditure also increases with the age of patients, reaching the maximum level of 10.3 euros per capita in men and 7.9 in women over 75 years of age. As for the approved care regime, per capita expenditure was 0.14 euros, decreasing of 4.8% compared to 2019, and with a corresponding reduction in consumption (-3.5%), a shift in prescription towards less expensive medicinal products (mix effect: -1.3%) and substantial stability in prices (Table 3.9). Fourth ATC level includes miscellaneous drugs, 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 is sevelamer, accounting for 37.9% of total expenditure. It is licensed 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. This is followed by polystyrene sulphonate, approved for the treatment of hyperkalaemia, which has an expenditure incidence of 30.8% (Table 3.10).
Among medicines purchased by public health facilities, there was an increase in expenditure (+1.4%), average cost per day of therapy (+4.4%) and a shift to more expensive medicines (mix effect +3.4%), compared to a reduction in consumption of 2.8% (Table 3.16). The category with the greatest impact on expenditure is reconfirmed as that of iron chelating substances (1.58 euros per capita), followed by radiological, water-soluble, nephrotropic and low osmolar contrast agents (1.12 euros) and antidotes (0.76 euros).
Among iron chelators, deferasirox, has a per capita expenditure of 1.44 euros and impacts 24.8% on category expenditure (Table 3.17). 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 0.66 euros and an impact of 11.4 % on the expenditure for the category.

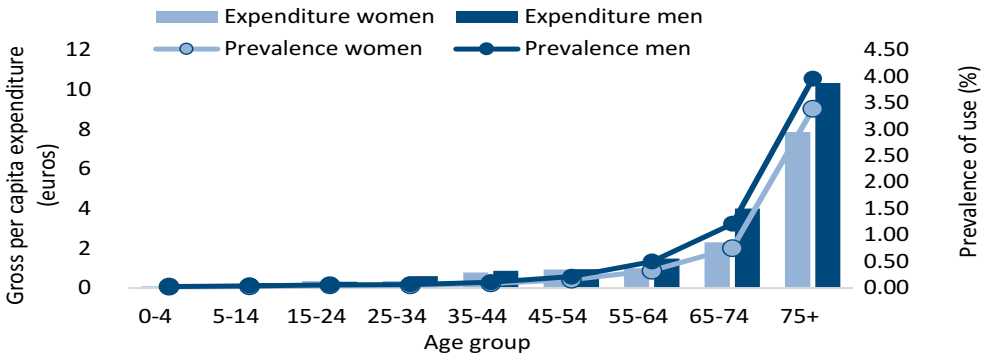
None of the active ingredients included in the category are among the 30 medicines with the highest incidence or variation in expenditure of medicines purchased by public health facilities (Tables 3.18 and 3.20).

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Miscellaneous

Public expenditure* in million euros (% over total)	**354.7**	**(1,5)**
Δ % 2020-2019		1.5%
Regional range of gross per capita expenditure	4.4	12.2
DDD/1000 inhab. per day (% over total)	**3.2**	**(0,3)**
Δ % 2020-2019		-2.8%
Regional range of DDD/1000 inhab. per	1.5	6.3

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities





	Gross per capita expenditure			DDD/1000 inhab.per day		
Age group	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
0-4	0.1	0.1	0.1	0.0	0.0	0.0
5-14	0.2	0.2	0.2	0.1	0.1	0.1
15-24	0.3	0.3	0.3	0.2	0.1	0.1
25-34	0.6	0.3	0.5	0.1	0.1	0.1
35-44	0.9	0.8	0.8	0.1	0.1	0.1
45-54	1.0	0.9	0.9	0.2	0.1	0.2
55-64	1.5	1.0	1.2	0.4	0.2	0.3
65-74	4.0	2.3	3.1	0.7	0.3	0.5
75+	10.3	7.9	8.9	0.9	0.4	0.6

3.12.1 Contrast agents

National data on consumption and expenditure

Per capita expenditure on contrast agents has remained broadly stable over the last 7 years (average annual variation in 2014-2020: +0.2%) with a value of 1.54 euros in 2020, decreasing of 6.6% compared to the previous year (Figure and Table 3.12.1a). This value was probably determined by the lower number of diagnostic tests carried out during 2020 due to the COVID-19 pandemic. At the same time, the average DDD cost increased by 13.5%, moving from 44.4 to 50.3 euros (Figure 3.1.1a). The average cost per day of therapy, on the contrary, increased by 13.5%, switching from a value of 44.4 euros in 2014 to 50.3 euros in 2020, and increasing of 5.7 % compared to 2019. In second place in terms of expenditure is RMI contrast agents, with a per capita expenditure value of 0.36 euros and a reduction of 4.7%.
The active ingredient with the highest spending is represented by iomeprol, a radiological contrast agent (iodinated, non-ionic, monomeric), with high solubility in water, low chemotoxicity, osmolality and viscosity. In second place is iodixanol, another radioactive iodine (dimeric, nonionic, iso-osmolal), characterized by diagnostic efficacy similar to that of other drugs in the same category (V08AB). The active ingredients iopromide, diagnostic iodine (used for angiography, contrast enhancement in computed tomography, urography, visualization of body cavities) and gadobutrol (drug containing gadolinium and the macrocyclic ligand butrol), used for contrast enhancement in MRI, have a per capita expenditure of 0.17 euros.

With regard to therapeutic categories, it is radiological contrast agents that show the greatest variability (Figure 3.12.1 b).

Figure 3.12.1a. Contrast agents temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

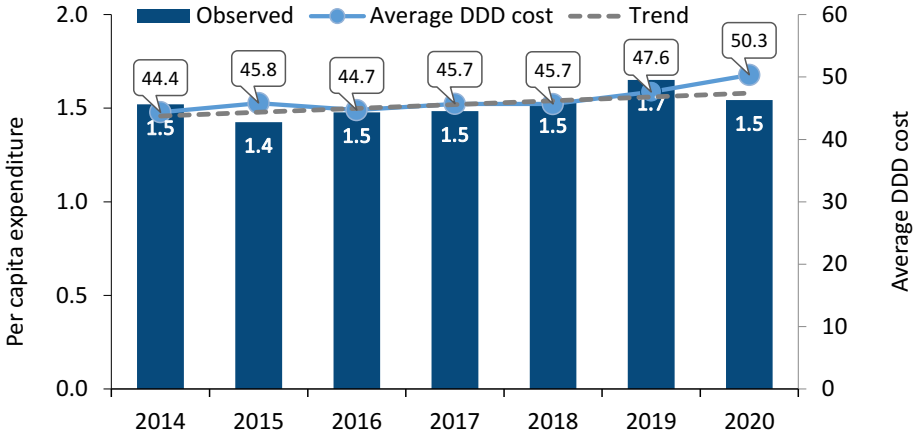


Table 3.12.1a. Contrast agents, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

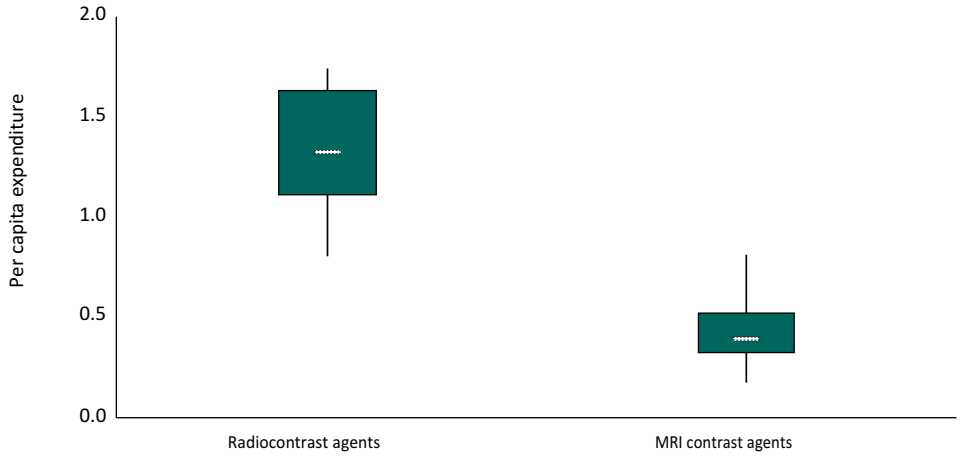
Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Radiocontrast agents	1.13	-6.7	0.0	0.1	-12.5	-2.6	50.27	6.3
MRI contrast agents	0.36	-4.7	1.2	0.0	-9.3	0.4	49.00	4.8
Contrast agents for ultrasound	0.05	-15.2	-1.6	0.0	-15.5	-1.7	67.50	0.0
Contrast agents	**1.54**	**-6.6**	**0.2**	**0.1**	**-11.8**	**-1.9**	**50.33**	**5.7**
iomeprol	0.44	-4.9	1.3	0.0	-8.7	-2.7	70.38	3.9
iodinaxol	0.22	-10.0	0.1	0.0	-10.1	-0.5	77.86	-0.1
iopromide	0.17	4.5	-3.6	0.0	-7.5	-3.8	56.99	12.7
gadobutrol	0.17	-1.8	5.0	0.0	-3.8	5.4	79.56	1.8
iobitridol	0.11	-15.8	-1.6	0.0	-20.3	-0.5	47.43	5.4
iopamidol	0.09	-5.8	3.8	0.0	-12.3	-2.1	24.47	7.1
ioexol	0.07	-2.2	7.0	0.0	1.4	8.0	31.00	-3.8
gadoxetic acid	0.07	7.6	8.3	0.0	4.8	7.0	173.64	2.4
gadoteric acid	0.06	-27.9	-1.9	0.0	-16.8	4.3	21.19	-13.6
gadoteridol	0.05	-7.4	32.4	0.0	-6.4	28.5	25.51	-1.3

Table 3.12.1b. Contrast agents, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	1.57	1.38	1.39	1.42	1.48	1.60	1.47	-8.5
Valle d'Aosta	2.71	2.46	2.45	2.51	2.38	2.48	2.29	-7.5
Lombardy	1.44	1.39	1.31	1.29	1.27	1.29	1.19	-7.9
A.P. of Bolzano	1.38	1.39	1.34	1.42	1.50	1.65	1.53	-7.1
A.P. of Trento	1.11	1.20	1.06	1.14	1.03	1.27	1.36	7.2
Veneto	1.68	1.58	1.59	1.60	1.67	1.71	1.74	2.1
Friuli VG	2.16	1.78	1.51	1.89	1.94	2.35	2.12	-9.7
Liguria	1.10	1.09	1.16	1.17	1.26	1.30	1.19	-8.3
Emilia R.	1.70	1.53	1.84	1.73	1.82	1.88	1.73	-7.7
Tuscany	1.89	1.82	1.95	1.89	1.89	2.08	1.99	-4.1
Umbria	2.19	2.21	2.17	2.20	2.24	2.17	2.10	-3.1
Marche	1.84	1.81	2.01	2.01	2.11	2.15	1.98	-8.0
Lazio	1.47	1.28	1.36	1.43	1.51	1.64	1.50	-8.5
Abruzzo	1.74	1.77	1.97	1.89	2.03	2.06	1.90	-7.7
Molise	1.38	1.42	1.20	1.25	1.27	1.36	1.42	4.2
Campania	0.80	0.70	0.82	0.82	0.92	1.03	0.99	-3.9
Puglia	1.58	1.52	1.56	1.58	1.68	1.97	1.82	-7.7
Basilicata	1.99	2.01	2.05	2.34	1.90	2.34	2.11	-9.8
Calabria	1.26	1.28	1.45	1.41	1.46	1.70	1.55	-8.9
Sicily	1.41	1.34	1.37	1.43	1.46	1.62	1.51	-6.6
Sardinia	1.98	1.95	1.92	1.76	1.86	2.07	1.80	-13.3
Italy	**1.52**	**1.43**	**1.48**	**1.48**	**1.53**	**1.65**	**1.54**	**-6.6**
North	1.56	1.44	1.46	1.46	1.49	1.57	1.47	-6.0
Centre	1.71	1.59	1.70	1.71	1.77	1.89	1.77	-6.4
South and Islands	1.35	1.30	1.37	1.38	1.44	1.62	1.50	-7.5

Figure 3.12.1b. Contrast agents, variability of 2020 consumption (weighted per capita expenditure) by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- **Contrast media** (mdc) represent a useful diagnostic tool that, thanks to the ability to modify the X-ray absorption of organs and tissues (similar in composition and/or thickness with respect to surrounding body parts), have improved the imaging of different diagnostic techniques, revolutionizing clinical practice.
- The **value of per capita expenditure** has remained substantially stable over the last 7 years, recording a value of 1.54 euros in 2020, decreasing of 6.6% compared to the previous year. Although an increase of 5.7% in average cost per therapy day is observed, decreasing in spending and consumption may be due to the lower number of diagnostic tests carried out during 2020 due to the COVID-19 pandemic. This seems to be confirmed by the trend in all categories considered (radiology contrast agents, MRI, and ultrasonology), where, compared to 2019, there are reductions in spending and consumption, accompanied by increases o by substantial stability in the average cost per day of therapy.
- Analyzing the trend of the different active ingredients, the compounds used in the radiological field record the highest values of expenditure per capita, representing, moreover, the category with the highest regional variability.

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3.12.2 Radiopharmaceuticals

National data on consumption and expenditure

In 2020, per capita spending on radiopharmaceuticals was 1.07 euros, showing a growth trend of 29.1% over the previous year, after years of substantial stability (Table and Figure 3.12.2a). The average cost per therapy day of radiopharmaceuticals has increased by 50% over the past seven years, from 299.7 euros in 2014 to 449.6 euros in 2020. Analyzing the trend over the years, however, it is noted a decrease of 12.4% in the 2014-2018 period , followed by an increase of over 70% in the last two years. The category with the highest expenditure is represented by radiodiagnostics for tumor detection (0.36 euros), followed by radiopharmaceuticals for therapeutic oncological use (0.31 euros), which show an important increase in expenditure (>100%), consumption (+73.9%) and average cost per DDD (+67.3%). Thyroid and central nervous system (CNS) radiodiagnostics show instead a per capita value of 0.15 euros, increasing of 26.3% compared to the previous year. The first active ingredient by expenditure is represented by fluorodeoxyglucose (18F), a radiodiagnostic for tumor detection that records a per capita expenditure of 0.28 euros, followed by lutetium ($_{177}$Lu) oxodotreodite (0.25 euros), indicated in adult patients for the treatment of well-differentiated, progressive, non-removable or metastatic somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (NET-GEP). Technetium($_{99m}$TC) pertechnetate and iodine ioflupane ($_{123}$I), two radiodiagnostics used respectively for the thyroid and the central nervous system, record a per capita expenditure of 0.13 and 0.12 euros respectively. For these drugs, it should be noted that the average cost per DDD may be influenced by the presence of some medicinal products in class Cnn.

Finally, radiodiagnostics for tumor detection represent the therapeutic category with the greatest variability, both in range and median value (Figure 3.12.2b).

Figure 3.12.2a. Radiopharmaceuticals, temporal trend of per capita expenditure and average cost per day of therapy (2014-2020)

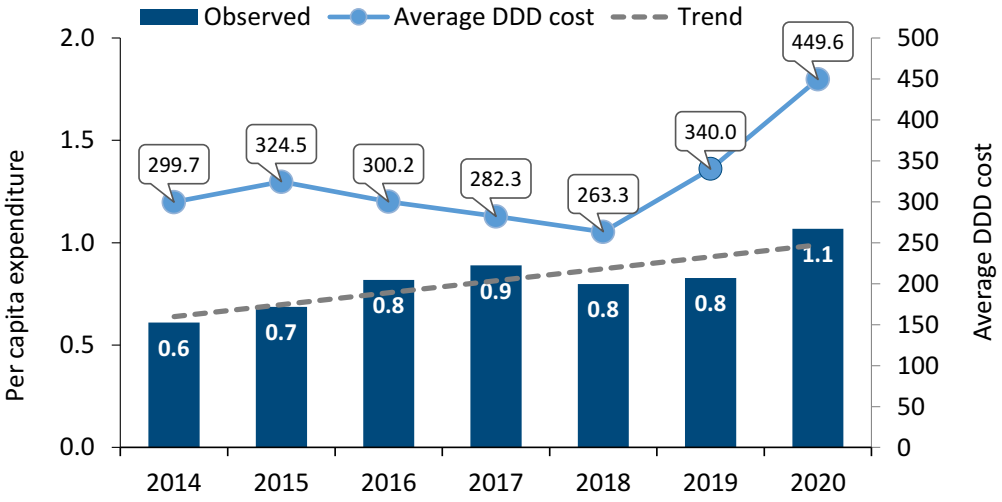


Table 3.12.2a. Radiopharmaceuticals, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

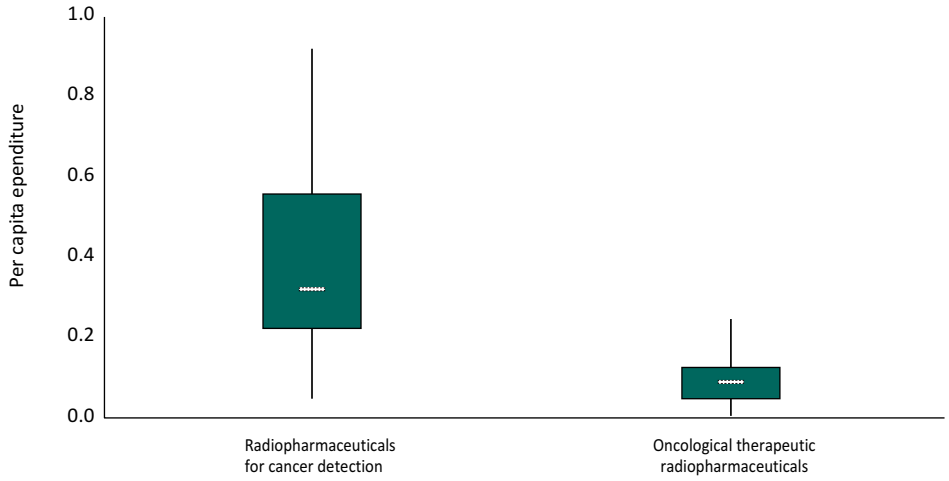
Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Radiopharmaceuticals for cancer detection	0.36	19.0	10.4	0.0	-0.9	-2.8	498.54	19.8
Oncological therapeutic radiopharmaceuticals	0.31	191.7	100.8	0.0	73.9	85.2	9449.14	67.3
Thyroid diagnostic radiopharmaceuticals	0.15	26.3	-0.1	0.0	-2.9	21.9	224.71	29.7
CNS diagnostic radiopharmaceuticals	0.15	-28.3	-1.0	0.0	-24.2	-2.4	670.30	-5.7
Radiopharmaceuticals for inflammation and infection detection	0.03	33.2	21.6	0.0	113.1	-37.0	16847.53	-37.7
Cardiovascular system diagnostic radiopharmaceuticals	0.02	-26.8	-14.0	0.0	-19.3	-9.8	136.48	-9.5
Iodized radiopharmaceuticals for therapeutic use	0.02	-14.5	33.7	0.0	-20.6	105.2	194.43	7.3
Respiratory system diagnostic radiopharmaceuticals	0.01	8.1	14.0	0.0	23.8	18.4	44.26	-12.9
Other diagnostic	0.01	408.7	-	0.0	178.2	-	625.85	82.4
Hepatic and reticuloendothelial system diagnostic radiopharmaceuticals	0.01	7.5	-19.8	0.0	12.4	-4.8	33.11	-4.5
Renal system diagnostic radiopharmaceuticals	0.01	271.1	6.2	0.0	30.0	-10.8	152.58	184.6
Skeletal system diagnostic radiopharmaceuticals	0.00	28.9	-	0.0	-14.7	-	106.65	50.7
Radiopharmaceuticals with analgesic/anti-inflammatory action	0.00	-52.0	-18.1	0.0	-54.0	-5.4	2280.65	4.0
Radiopharmaceuticals	**1.07**	**29.1**	**9.8**	**0.0**	**-2.7**	**2.6**	**449.58**	**32.2**
fluorodeoxyglucose (18F)	0.28	12.0	10.9	0.0	-1.3	-2.7	413.08	13.2
lutetium oxodotreotide (177Lu)	0.25	334.9	-	0.0	288.6	-	15971.94	11.6
tecnetium pertecnetate (99 mTc)	0.13	46.2	16.0	0.0	21.6	23.7	326.81	19.9
iodine ioflupane (123I)	0.12	-29.8	-1.5	0.0	-30.1	-1.9	868.11	0.1
radium dichloride (223Ra)	0.05	15.9	61.2	0.0	14.4	72.0	3230.92	1.1
fluoromethylcholine (18F)	0.05	72.7	-	0.0	25.0	-	2334.30	37.8
sodium chloride (123I)	0.03	-1.3	205.9	0.0	-22.5	258.7	92.78	27.1
gallium citrate (67Ga)	0.03	29.8	-	0.0	-25.0	-	53384.32	72.5
technetium tetrophosmin (99mTc)	0.02	-35.1	-9.3	0.0	-31.1	-7.5	177.74	-6.1
flutemetamol (18F)	0.01	-23.6	-	0.0	-21.5	-	1172.93	-2.9

Table 3.12.2b. Radiopharmaceuticals, regional trend of weighted per capita expenditure: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ %
Piedmont	0.65	0.64	0.76	0.84	0.84	0.74	0.91	22.1
Valle d'Aosta	1.99	2.48	2.01	1.56	1.56	1.54	1.54	0.0
Lombardy	0.55	0.64	0.72	0.71	0.68	0.76	1.12	48.0
A.P. of Bolzano	0.59	0.54	0.72	0.89	0.66	0.64	0.86	33.4
A.P. of Trento	0.53	0.67	0.94	0.96	1.12	0.85	0.87	1.7
Veneto	0.67	0.64	0.62	0.55	0.49	0.48	0.99	107.6
Friuli VG	0.63	0.98	1.15	1.55	1.56	1.36	0.90	-33.7
Liguria	0.84	0.97	0.91	0.87	0.78	0.89	1.07	20.5
Emilia R.	0.82	1.00	1.07	1.13	1.06	1.22	1.77	45.0
Tuscany	1.12	1.21	1.39	1.45	1.17	1.18	1.29	9.4
Umbria	0.67	0.68	0.89	0.91	0.91	0.73	0.60	-18.2
Marche	1.43	1.57	1.60	1.67	1.40	1.37	1.58	15.1
Lazio	0.30	0.49	0.69	0.76	0.57	0.63	0.94	48.3
Abruzzo	0.63	0.82	0.70	1.42	1.15	0.86	0.49	-42.7
Molise	0.75	0.86	0.83	0.71	0.78	0.64	0.67	4.5
Campania	0.36	0.42	0.49	0.52	0.42	0.52	0.78	49.9
Puglia	0.56	0.38	0.85	0.99	0.96	0.93	1.27	36.1
Basilicata	1.31	1.97	2.21	2.22	1.79	1.99	2.33	17.2
Calabria	0.31	0.64	1.03	1.37	1.44	1.48	1.48	-0.2
Sicily	0.24	0.27	0.45	0.57	0.49	0.60	0.70	16.1
Sardinia	0.91	0.61	0.74	0.71	0.60	0.59	0.55	-7.1
Italy	**0.61**	**0.69**	**0.82**	**0.89**	**0.80**	**0.83**	**1.07**	**29.1**
North	0.66	0.74	0.81	0.83	0.79	0.82	1.15	40.0
Centre	0.74	0.88	1.05	1.11	0.89	0.91	1.11	21.5
South and Islands	0.46	0.49	0.69	0.84	0.75	0.78	0.93	18.0

Figure 3.12.2b. Radiopharmaceuticals, regional trend of 2020 weighted per capita expenditure by subgroup

(the line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum)



Key message

- A radiopharmaceutical is any drug 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 drug.
- In 2020, per capita spending on radiopharmaceuticals was 1.07 euros, showing a growth trend of 29.1% over the previous year, after years of substantial stability. This value appears to be driven by an increase in the average cost per day of therapy, which has risen by 50% over the past seven years. For these drugs, it should be noted that the average cost per DDD may be influenced by the presence of some medicinal products in class Cnn.
- **The active ingredients fluorodeoxyglucose (^{18}F) and lutetium (^{177}Lu) oxodotreodite** present the highest values of per capita expenditure, confirming that radiodiagnostics and radiotherapeutics, used in oncology, are the categories with the highest expenditure and greater regional variability.
- The per capita expenditure values of the individual regions are particularly heterogeneous (CV 41.3%), ranging from 0.49 euros in Abruzzo to 2.33 euros in Basilicata. Regions of the North (1.15 euros) and those of the Center (1.11 euros) show greater spending than those of the South and Islands (0.93 euros) and a higher increase (+40% and +21.5%).

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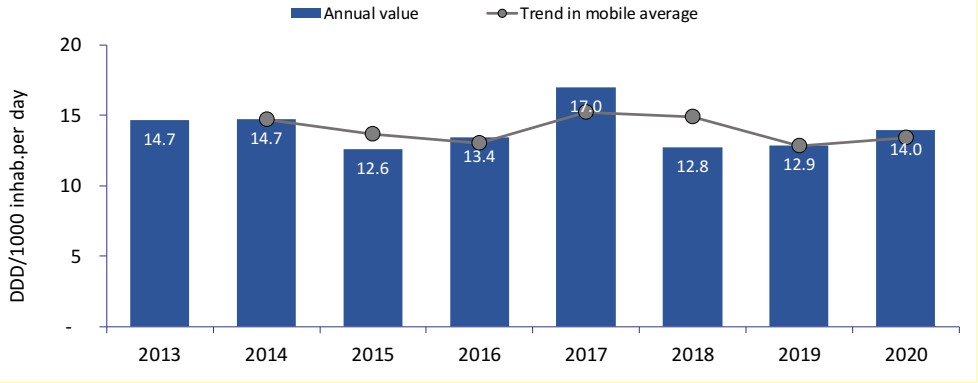
3.13 Dermatologicals

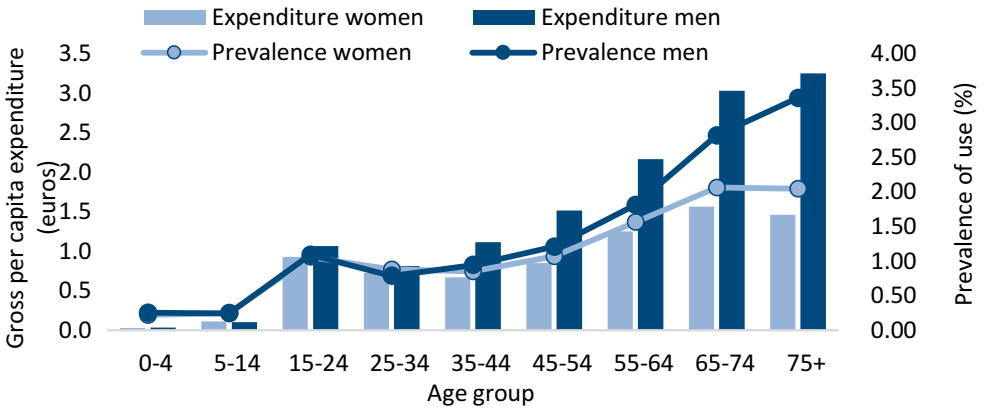
In 2020, dermatologicals were the 13th therapeutic category with the highest public expenditure, amounting to 151 million euros, and corresponding to 0.7% of total public expenditure (Box Main indexes of expenditure, consumption and exposure). The overall per capita expenditure on these drugs is 2.53 euros, a sharp increase over the previous year (+18%) and similarly distributed for the approved care regime (1.25 euros per capita) and public health facilities (1.28 euros), which show a significant increase over 2019 (+51.9%) (Table 3.1).
Consumption for this category of drugs was 13.9 DDD/1000 inhabitants per day, increasing mainly in public health facilities, compared to 2019 (Table 3.2).
The analysis of the drug use profile by age group and gender, including pharmaceutical expenditure under approved care regime and *per conto* distribution, shows an increase from the age of 15 years for both genders, particularly in men, reaching a prevalence of about 3.5% in the over 75s. 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%. Per capita expenditure borne by the NHS increases with the age of patients, reaching a maximum value of 2.2 euros per capita in the over 75s (3.3 euros in men and 1.5 euros in women).
As for the approved care regime, per capita expenditure was 1.25 euros, with a 4.3% decrease compared to 2019. A greater use of less expensive specialties was also observed for this category of drugs (mix effect -5.9%). The category that has the greatest impact on the expenditure under approved care regime is represented by other antipsoriatic drugs for topical use (0.87 euros per capita) (Table 3.9). The drug with the highest expenditure and consumption is the calcipotriol/betamethasone combination, which accounts for 65% of gross expenditure and 50% of consumption for the category (Table 3.10).
Among medicines purchased by public health facilities, there was an increase in expenditure (>50%) and consumption (+12,8%) (Table 3.16). The active ingredient with the highest expenditure is dupilumab (67% of the total for the whole category), increasing by more than 90% compared to 2019 and with an average cost of 32.50 euros, the highest in the category; sodium hypochlorite, instead, is the active ingredient with the highest levels of consumption (3.7 DDD/1000 inhabitants per day) (Table 3.17). Dupilumab is a monoclonal antibody that is on the innovative drugs list and is used for the treatment of moderate to severe atopic dermatitis in adult and adolescent patients (aged 12-17 years) eligible for systemic therapy.

MAIN INDICES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Dermatologicals

Public expenditure* in million euros (% over total)	**151.0**	**(0,7)**
Δ % 2020-2019		17.9%
Regional range of gross per capita expenditure	1.9	3.6
DDD/1000 inhab. per day (% over total)	**13.9**	**(1,2)**
Δ % 2020-2019		8.5%
Regional range of DDD/1000 inhab. per	9.4	25.3

* Includes pharmaceuticals prescribed under the approved care regime and purchases by public health facilities





	Gross per capita expenditure			DDD/1000 inhab.per day		
Age group	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
0-4	0.0	0.0	0.0	0.4	0.3	0.3
5-14	0.1	0.1	0.1	0.5	0.5	0.5
15-24	1.1	0.9	1.0	2.8	2.6	2.7
25-34	0.8	0.7	0.8	2.7	2.4	2.6
35-44	1.1	0.7	0.9	3.8	2.5	3.2
45-54	1.5	0.9	1.2	5.2	3.3	4.2
55-64	2.2	1.3	1.7	7.7	4.9	6.2
65-74	3.0	1.6	2.3	11.1	6.6	8.7
75+	3.3	1.5	2.2	12.2	6.5	8.8

3.14 Medicines used in critically ill patients

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 drugs used in intensive or sub-intensive care units during 2020, 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 drugs generally used in critically ill patients stood at 86.5 packages per 10,000 inhabitants per day in 2020, an increase of about 32% compared to the previous year and an average annual variation of 55.8% over the 2014-2020 period. Spending, on the other hand, showed a less noticeable increase, standing at 7.28 euros (increasing of 8.9% compared to 2019) and showing an average annual rate of 1.5% from 2014 to 2020. The average cost per package was 2.30 euros, decreasing of 17.5% compared to the previous year (Table 3.14a).
Northern Regions reported consumption (94.2 packages per 10,000 inhabitants per day) of 26% and 9% higher than Southern (75 packages) and Central (86.8 packages) Regions, respectively (Table 3.14b). Compared to the previous year, the greatest variations were seen in regions of the North (43%), rather than in those of the Center (23%) and the South (20%).
Analyzing the monthly trend over the past 2 years it is noted that in the months corresponding to the peak of SARS-CoV-2 infections (March-April and October-December), the difference in packages per 10,000 inhabitants per day was of 110% higher in March 2020 than in the same month of 2019 (120 vs 57), decreasing to 74% in April (104 vs 60) and then stabilizing at levels between -45% (August) and +12% (September) compared to the same period in 2019. In the last three months of the year, it went from +52% in October (85 vs 56) to +136% in November (155 vs 66) and finally to +106% in December (129 vs 63) (Figure 3.14a). 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 58% of expenditure and 83% of total consumption, an increase of 1.7% and 40.4% respectively over the previous year.
Large increases were observed in the use of several injectable medications including: curare (+181.2%), ascorbic acid (+102.7%), hypnotics and sedatives (+83.9%), and general anesthetics (+54.6%) (Table 3.14a). Other injectable products such as mucolytics (-46%), antipyretics (-29.8%), NSAIDs (-21.6%), local anesthetics (-14.1%) and antidotes (-9.6%), on the contrary, show a reduction in the number of packages. A high increase in spending (+113.7%) is observed for propofol, an anesthetic used for sedation of mechanically ventilated patients.

Figure 3.14.a. Medications used in critically ill patients, monthly trend in packs/10,000 inhabitants per day: comparison 2020-2019

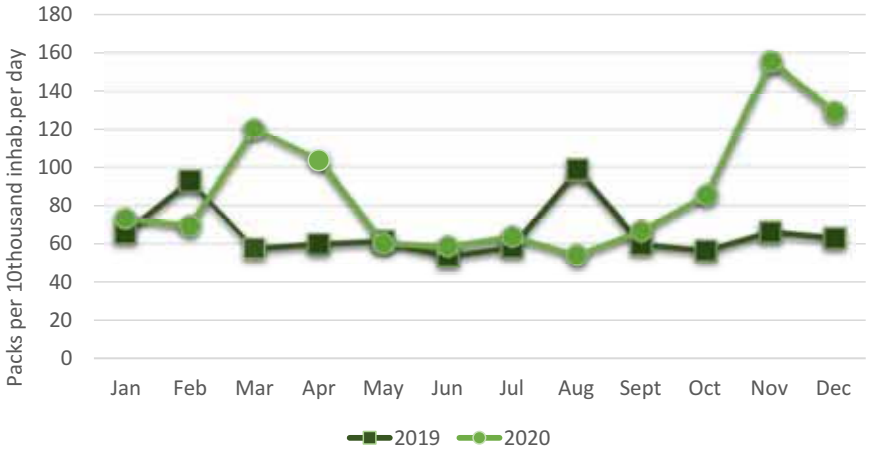


Tabella 3.14.a. Medications used in critically ill patients, per capita expenditure and consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2020

Subgroups and substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
Oxygen	4.22	1.7	-1.6	71.6	40.4	73.4	1.61	-27.7
Injectable corticosteroids	0.22	4.9	-3.2	3.3	-0.9	-14.8	1.80	5.6
Injectable cardiac stimulants	0.27	10.9	17.2	1.9	19.7	26.1	3.95	-7.6
Injectable antipyretics	0.07	-15.7	-13.2	1.7	-29.8	236.1	1.18	19.6
Injectable general anaesthetics	0.34	90.2	5.5	1.4	54.6	59.9	6.43	22.7
Injectable pain therapy	0.04	-9.0	-0.9	1.4	-8.1	-19.5	0.68	-1.3
Injectable local anaesthetics	0.07	-30.9	-17.6	1.3	-14.1	-22.9	1.42	-19.9
Injectable NSAIDs	0.03	-20.4	-12.3	1.2	-21.6	-32.5	0.68	1.2
Injectable hypnotics and sedatives	0.29	59.7	51.1	0.6	83.9	70.7	14.03	-13.4
Injectable curares	0.36	454.0	22.2	0.5	181.2	142.9	19.77	96.5
Injectable ascorbic acid	0.01	144.7	19.3	0.5	102.7	916.6	0.51	20.4
Injectable antihemorrhagics	0.26	7.2	8.6	0.4	-9.6	-41.5	17.84	18.3
Injectable antidotes	0.76	-5.3	21.7	0.2	-9.6	-24.0	86.76	4.5
Injectable antiemetics	0.07	-11.0	-12.5	0.2	-6.9	-41.8	9.50	-4.7
Injectable anxiolytics	0.03	13.0	8.8	0.2	7.5	-0.9	3.99	4.8
Injectable thrombolytics	0.27	1.9	2.0	0.1	8.9	47.9	57.04	-6.6
Injectable xanthines	0.00	-0.3	-7.7	0.1	1.9	-44.2	0.94	-2.5
Injectable mucolytics	0.00	-46.5	-21.5	0.0	-46.0	-77.0	3.57	-1.2
Critical condition medications	**7.28**	**8.9**	**1.5**	**86.5**	**31.6**	**55.8**	**2.30**	**17.5**
oxygen	4.22	1.7	-1.6	71.61	0.4	73.4	-	-
paracetamol	0.05	-22.5	-15.6	1.60	-0.3	268.5	9.20	8.8
methylprednisolone	0.12	10.6	-3.4	1.46	-0.1	-16.2	5.71	19.8
dexamethasone	0.04	36.5	-1.7	1.12	0.3	-1.5	11.04	1.3
morphine	0.02	-6.6	0.6	0.98	0.0	-29.9	1.93	0.5
ketorolac	0.01	-18.7	-8.8	0.94	-0.2	-30.9	3.00	0.0
noradrenaline	0.03	66.0	7.8	0.79	0.5	42.7	1.83	0.0
propofol	0.23	113.7	11.3	0.69	0.9	66.5	6.80	-25.2
lidocaine	0.01	-15.0	-0.8	0.63	-0.1	-21.0	5.33	0.2
adrenaline	0.04	10.4	7.0	0.53	0.0	11.4	10.55	-1.4

Figure 3.14.b. Medications used in critically ill patients, regional trend in weighted packs/10,000 inhabitants per day: comparison 2020-2019

Region	I- 2 months 20	Δ % 20-19	II- 2 months 20	Δ % 20-19	III- 2 months 20	Δ % 20-19	IV- 2 months 20	Δ % 20-19	V- 2 months 20	Δ % 20-19	VI- 2 months 20	Δ % 20-19	2020	Δ % 20-19
Piedmont	11.9	-5	21.9	147	10.4	21	10.1	-28	14.8	63	31.5	187	100.5	57
Valle d'Aosta	34.6	1	58.8	77	37.7	22	35.1	-2	43.4	30	76.3	129	285.8	42
Lombardy	11.9	-12	32.8	203	10.8	1	9.7	-17	14.0	31	26.8	137	106.1	54
A.P. of Bolzano	7.1	-11	13.9	86	5.7	-30	6.7	-2	7.9	16	17.2	159	58.5	34
A.P. of Trento	7.6	1	14.2	110	5.4	-19	5.8	-17	7.6	13	19.9	229	60.4	49
Veneto	12.3	-15	16.1	51	9.4	-15	9.0	-1	11.7	10	24.3	147	82.7	26
Friuli VG	13.0	4	12.3	4	9.2	-26	9.7	-3	11.3	8	22.1	101	77.5	14
Liguria	10.9	-10	23.1	111	10.6	-1	9.7	3	14.4	54	26.2	182	94.8	54
Emilia R.	10.9	-5	22.8	117	8.4	-14	8.7	-15	11.4	12	19.2	75	81.5	29
Tuscany	14.9	-14	19.3	51	12.6	3	14.2	-16	16.1	28	27.5	100	104.7	22
Umbria	13.6	-2	13.6	-4	11.3	-3	11.0	-4	13.4	22	21.5	86	84.5	14
Marche	16.9	-6	27.1	67	16.2	3	16.2	-17	17.7	21	29.9	87	124.0	24
Lazio	9.0	-8	10.5	45	7.8	7	8.0	-27	10.3	46	19.1	118	64.7	26
Abruzzo	12.8	-2	17.3	34	11.9	4	11.3	-5	13.6	14	25.8	111	92.7	26
Molise	12.6	95	13.5	68	10.9	-8	10.8	-10	13.2	22	25.6	117	86.7	42
Campania	9.8	6	11.1	53	8.2	10	8.9	-32	12.1	58	21.8	144	71.9	34
Puglia	13.0	-6	14.3	71	10.1	13	11.0	-42	12.5	26	24.2	107	85.1	19
Basilicata	13.9	-7	12.1	195	11.3	252	11.3	-64	13.4	86	20.0	51	82.0	10
Calabria	10.3	-12	11.8	37	10.2	22	9.7	-35	10.5	28	15.5	43	68.0	8
Sicily	11.4	-13	11.3	28	8.9	12	9.6	-42	11.2	33	19.6	91	72.1	10
Sardinia	9.1	-5	9.0	54	7.3	34	7.8	-50	7.9	19	17.9	128	59.0	16
Italy	**11.4**	**-8**	**18.7**	**91**	**9.9**	**3**	**9.9**	**-25**	**12.7**	**31**	**23.7**	**120**	**86.5**	**32**
North	11.7	-9	24.4	134	9.9	-4	9.5	-15	13.1	29	25.6	138	94.2	43
Centre	12.3	-10	15.7	46	10.7	4	11.3	-20	13.4	32	23.4	103	86.8	23
South and Islands	11.2	-4	12.2	49	9.3	16	9.7	-39	11.6	35	21.1	105	75.0	20

Key message

- Utilization of drugs generally used in critically ill patients stood at 86.5 packages per 10,000 inhabitants per day in 2020, an increase of about 32% compared to the previous year and an average annual variation of +8.9% over the 2014-2020 period.
- 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 58% of expenditure and 83% of total consumption, an increase of 1.7% and 40.4% respectively over the previous year. Large increases were observed in the use of several injectable medications including: curare, hypnotics and sedatives, and general anesthetics.
- A comparison of bimonthly consumption trends between 2019 and 2020 shows an increase in consumption during the months with the highest peaks of SARS-CoV-2 infections (March-April and October-December 2020). In the second two-month period (March-April) the greatest increases are observed in the Regions most affected by the first phase of the pandemic (Lombardy, Piedmont, Emilia Romagna and Liguria), while from the fifth two-month period (September-October) and to a greater extent in the last one (November-December) the increase in consumption is observed in all Regions. Northern Regions reported consumption of 26% and 9% higher than Southern and Central Regions, respectively.

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3.15 Medicines used in the treatment of COVID-19 patients

The objective of this section is to provide an overview of the use of the most widely used drugs at the national level in the treatment of patients with COVID-19 during the health emergency that has affected Italy since March 2020.
The drugs 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 drugs 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 drugs for home management (e.g. corticosteroids and heparins) and drugs that can be used in hospitals (e.g. remdesivir).

National data on consumption and expenditure

The drug utilization trend in the treatment of patients with COVID-19 has remained essentially stable over the past 7 years, standing at 20.7 DDD/1000 inhabitants per day in 2020, increasing of 8.5% compared to 2019. Similarly, spending, which amounted to 11.76 euros per capita, increased by 23.4% compared to the previous year, with an average annual growth rate (CAGR) of 5.3%. The average cost per therapy day increased by 13.7% in the last year, switching from €1.37 in 2019 to €1.56 in 2020 (Table 3.15a and Figure 3.15a).
Heparins accounted for almost half of the consumption of drugs used to treat COVID-19, with a value of 9.8 DDD/1000 inhabitants per day, and almost a third of expenditure (4.14 euros per capita), increasing of 6.2% and 8.6%, respectively, over 2019, though the corresponding average cost per day of therapy turns out to be very low (1.16 euros). After heparins, corticosteroids such as methylprednisolone and dexamethasone follow among the drugs with the highest consumption, corresponding to 4.0 DDD/1000 and 2.7 DDD/1000 inhabitans per day, respectively, with an increase of 3.3% and 18.8% compared to the previous year.
According to the indications of the AIFA fact sheet (updated to October 6, 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.
Consumption of hydroxychloroquine (+25.4%) and azithromycin (+10.6%) also increased, as well as the lopinavir/ritonavir combination which, despite low consumption (0.02 DDD/1000 inhabitants per day), had an increase of 59.3%. The darunavir/cobicistat combination, whose off-label use in the early stages of the epidemic had been allowed as an alternative to lopinavir/ritonavir and whose off-study authorization was subsequently suspended by AIFA, shows a 21.8% decrease in consumption compared to 2019 (Table 3.15a).

It is useful to point out that the evidence collected in 2020 on the therapeutic use of hydroxychloroquine has demonstrated a complete lack of efficacy of this drug, 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. The increased consumption of azithromycin could be explained by the treatment of bacterial overinfections in patients with COVID-19, as also recommended by the fact sheet published by AIFA on April 9, 2020.

Figure 3.15.a. Medicines used in the treatment of COVID-19 patients, temporal trend of consumption and average cost per day of therapy (2014-2020)

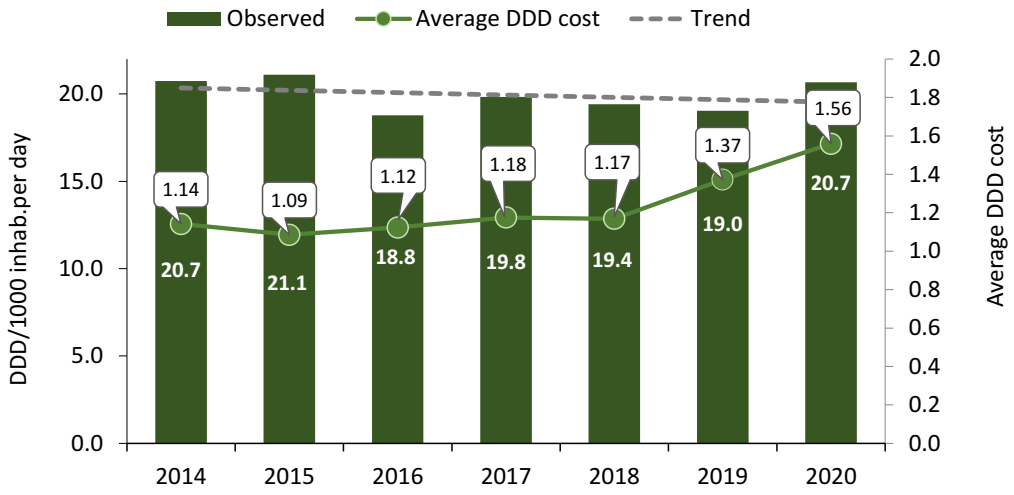

Table 3.15.a. Medicines used in the treatment of COVID-19 patients, per capita expenditure and consumption by therapeutic category and substance: comparison 2014-2020

Active substances	Per capita expenditure	Δ % 20-19	CAGR % 14-20	DDD/ 1000 inhab. per day	Δ % 20-19	CAGR % 14-20	Average DDD cost	Δ % 20-19
heparins	4.14	8.6	-6.2	9.79	6.2	-1.0	1.16	2.5
ruxolitinib	1.61	14.3		0.04	13.5		109.51	0.9
tocilizumab	0.98	18.8	12.9	0.10	22.2	21.2	25.59	-4.4
canakinumab	0.87	22.9	43.2	0.02	32.6	51.6	142.33	-14.4
remdesivir	0.87	-	-	0.01	-	-	379.50	-
azithromicyn	0.76	4.9	0.8	1.55	10.6	1.0	1.34	-6.3
baricitinib	0.60	33.9	-	0.06	30.3	-	27.57	5.2
darunavir/cobicistat	0.53	-21.8	-	0.12	-21.8	-	12.25	0.0
methylprednisolone	0.32	3.6	-3.1	4.00	3.3	-3.0	0.22	0.3
tofacitinib	0.22	33.5	-	0.03	32.7	-	23.14	1.3
dexamethasone	0.20	15.6	-1.5	2.65	18.8	3.2	0.21	-4.0
hydroxychloroquine	0.18	16.6	6.8	1.07	25.4	8.8	0.47	-11.8
sarilumab	0.16	53.9	-	0.02	54.0	-	26.47	-0.3
hydrocortisone	0.15	-0.9	18.8	0.64	-20.4	-1.7	0.62	16.3
anakinra	0.12	24.5	10.7	0.01	26.2	12.1	28.24	-2.2
lopinavir/ritonavir	0.04	9.3	-32.9	0.02	59.3	-22.9	5.13	-123.0
colchicine	0.03	4.6	5.3	0.54	1.9	3.6	0.13	2.7
prednisolone	0.00	-27.2	-4.8	0.00	-18.2	0.3	0.33	-7.7
Medicines used to treat COVID-19	**11.76**	**23.4**	**5.3**	**20.66**	**8.5**	**-0.1**	**1.56**	**13.7**

Table 3.15.b. Medicines used in the treatment of COVID-19 patients, regional trend of weighted DDD/1000 inhabitants per day: comparison 2014-2020

Region	2014	2015	2016	2017	2018	2019	2020	Δ % 20-19
Piedmont	14.8	15.0	13.3	14.5	14.4	14.5	19.1	31.9
Valle d'Aosta	16.9	22.7	11.2	13.6	13.7	14.0	17.8	27.1
Lombardy	13.7	14.0	16.2	16.6	16.3	16.3	18.3	12.5
A.P. of Bolzano	45.0	52.4	13.2	17.2	16.2	16.2	19.1	18.0
A.P. of Trento	34.7	26.2	19.3	21.1	21.0	20.6	24.7	19.7
Veneto	17.4	17.5	19.0	19.7	18.3	17.5	18.3	4.5
Friuli VG	28.2	26.0	14.8	18.7	19.0	18.4	19.1	3.8
Liguria	21.3	22.9	19.7	20.4	20.6	19.7	22.0	11.8
Emilia R.	21.6	22.0	25.2	25.9	26.8	24.8	26.4	6.5
Tuscany	29.3	32.3	35.3	31.6	32.0	29.8	32.6	9.2
Umbria	64.4	66.6	21.5	24.3	24.8	24.0	22.8	-4.8
Marche	24.0	20.5	24.5	27.7	26.2	26.0	27.4	5.6
Lazio	13.1	16.1	15.4	16.6	16.4	16.5	17.8	8.4
Abruzzo	30.9	32.2	21.6	24.3	25.0	22.7	23.1	2.1
Molise	80.9	58.0	13.7	18.0	17.8	18.9	18.5	-2.3
Campania	12.5	13.6	15.5	17.8	17.5	17.9	20.6	15.1
Puglia	19.0	21.2	19.7	20.9	20.1	19.7	19.4	-1.9
Basilicata	80.8	69.6	16.3	21.1	20.2	20.4	20.0	-2.1
Calabria	22.2	19.8	18.3	21.5	18.5	18.6	18.5	-0.4
Sicily	18.5	17.7	14.9	16.5	15.1	15.9	16.1	1.4
Sardinia	42.7	40.5	20.2	20.5	19.8	19.6	20.6	5.4
Italy	**20.7**	**21.1**	**18.8**	**19.8**	**19.4**	**19.0**	**20.7**	**8.5**
North	17.9	18.1	17.8	18.7	18.5	18.0	20.2	12.2
Centre	23.7	25.8	23.5	23.5	23.3	22.6	24.2	7.2
South and Islands	23.0	22.5	17.2	19.2	18.3	18.4	19.2	4.4

Key message

- In 2020, the consumption of drugs used for the treatment of COVID-19 disease stood at 20.7 DDD/1000 inhabitans per day (+8.5% compared to 2019), with the average cost per day of therapy increasing by 13.7%.
- Heparins accounted for almost half of the consumption of drugs used to treat COVID-19, with a value of 9.8 DDD/1000 inhabitants per day, and almost a third of expenditure (4.14 euros per capita), though the corresponding average cost per day of therapy turns out to be very low (1.16 euros).
- Corticosteroids, such as methylprednisolone and dexamethasone, which are considered standard of care in hospitalized patients with severe COVID-19 disease requiring oxygen supplementation, rank 2nd and 3rd among the most commonly used drugs, with a consumption of 4.0 DDD/1000 inhabitants per day and 2.7 DDD/1000 inhabitants per day, respectively.
- At the regional level, there is a marked variability in consumption, with the areas of the Centre (24.2 DDD) using more doses than the North (20.2 DDD) and the South (19.2 DDD); Tuscany, in particular, registered double consumption compared to Sicily (32.6 vs 16.1 DDD); Tuscany, Marche, Emilia Romagna, Liguria, Abruzzo and the Autonomous A.P. of Trento consumed more quantity at an average cost per DDD lower than the national average, while the Autonomous Provinces of Bolzano, Lazio, Lombardy, Molise, Calabria and Sicily were, on the contrary, the Regions in which lower consumption and higher costs than average were observed.

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Section 4

Monitoring Registers and coditional reimbursement agreements

4.1 Medicines Monitoring Registers

The AIFA Monitoring Registers 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 Registers 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 Registers 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 Registers 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 Registers 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 Registers 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 Registers are useful in assessing the clinical-therapeutic impact of medicines in the specific Italian healthcare context. Accordingly, the Registers 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 Registers include different types of monitoring. The first concerns the **Registers 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 Registers that, with methods substantially similar to the Registers in the strict sense, monitor medicines reimbursed by the NHS according to Law 648/96, i.e. before their actual authorisation (Registers 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 for treatment, as well as, in some cases, on the possible evaluation and re-evaluation the results of the therapy. Lastly, at the end of 2019 **Simplified Multidrug Monitoring Registers** were introduced, which are a tool for prescribing and monitoring the use of multiple medicinal products within the same therapeutic indication. This particular Register has been simplified, compared to web-based TPs or Registers 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 Registers: legal basis

Starting from 2012, the AIFA Monitoring Registers 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 Registers 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");
- support in quantifying the so-called avoidable costs in healthcare.

AIFA Registers and the Regions

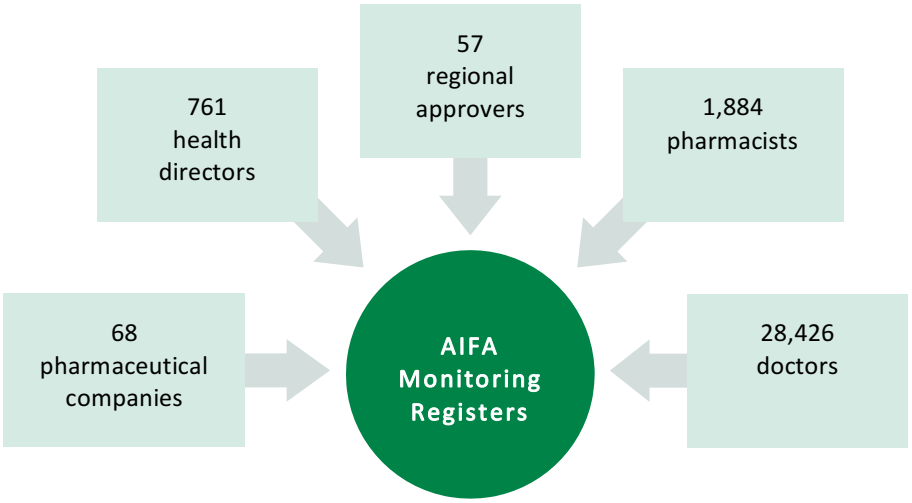
The AIFA Monitoring Registers are a support infrastructure for the Regions. Through the functions of the AIFA Registers, the Regions exercise their responsibility in coordinating health facilities and, consequently, in enabling their doctors to prescribe medicines subject to the register and the pharmacists 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 Registers.

The collaborative network of AIFA Registers

The AIFA monitoring registers constitute a collaborative network that allows the exchange of information between AIFA, Regions, health facilities, doctors, pharmacists and pharmaceutical companies. This network includes about 1,542 active health facilities (with at least one treatment started in 2020), in all 21 Italian Regions and Autonomous Provinces, 57 regional managers, 761 health directors, 28,426 doctors registered on the platform and 1,884 pharmacists (Figure 4.1.1). 68 pharmaceutical companies owning at least one monitoring register 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 registers of medicines owned by them, admitted for reimbursement with a MEA based on the register.

In this network, the Monitoring Registers Office is responsible for developing the monitoring form and the process leading to its approval, for testing the production of the register within the AIFA web platform and for interacting with all stakeholders for the management of the activities relating to the registers and the related reporting.

Figure 4.1.1. Personnel participating in the Registers network in the year 2020



Access and structure of AIFA Registers

Access to the AIFA Monitoring Registers is possible through the following web page: https://servizionline.aifa.gov.it/; the users will then have to select the link: "Registers of medicines subject to monitoring" and will thus be able to access the registers 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 prefilled 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 Registers 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 Registers and/or AP Therapeutic Plans)
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 Registers in the strict sense, the web-based TPs are active, for which the participation of specialist doctors is required, with the compilation of the following forms:

1. Patient data (unique for all Registers 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 2020, 166 Registers were available online (intended as single IT entities active during 2020). In particular, during the year 24 new registers were released online, 10 registers were modified, adding a new indication to the monitoring or with the extension of an indication already monitored, while 24 registers were closed (Table 4.1.1).
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/registri-e-piani-terapeutici 1

Data on Monitoring Registers

Table 4.1.1. Summary data of the Monitoring Registers present on the web platform: cumulative trend 2018-2020

	N.			Δ %
	2018	2019	2020	20-19
Registers*	141	166	166	0.0
web-based TPs*	12	14	13	-7.1
Treatments	2,177,819	2,730,119	3,209,838	17.6
Patients	1,858,603	2,288,704	2,655,909	16.0

*Registers intended as single active IT entities are counted (therefore all previous and inactive versions of a Register that have occurred over time are excluded from the calculation)

In 2020, the ATC categories C *"Cardiovascular system"*, V *"Various"* and D *"Dermatological"* 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 Registers (Tables 4.1.2, 4.1.3 and 4.1.4).

Table 4.1.2. Number of patients* by ATC category (I level) in the period 2018-2020

ATC code	No. of patients			Incidence %			Δ %	
	2018	2019	2020	2018	2019	2020	19-18	20-19
A	70	72	79	0	0	0	2.9	9.7
B	1,018,921	1,275,751	1,489,346	52.6	52.9	52.9	25.2	16.7
C	10,974	45,809	71,584	0.6	1.9	2.5	317.4	56.3
D	2,295	5,426	8,217	0.1	0.2	0.3	136.4	51.4
H	217	237	246	0	0	0	9.2	3.8
J	164,405	200,470	236,370	8.5	8.3	8.4	21.9	17.9
L	347,986	411,978	463,900	18	17.1	16.5	18.4	12.6
M	184,192	227,415	261,153	9.5	9.4	9.3	23.5	14.8
N	8,967	12,424	16,980	0.5	0.5	0.6	38.6	36.7
R	3,184	3,369	3,873	0.2	0.1	0.1	5.8	15.0
S	193,918	226,272	262,190	10	9.4	9.3	16.7	15.9
V	483	704	1085	0	0	0	45.8	54.1
Total	**1,935,612**	**2,409,927**	**2,815,023**	**100**	**100**	**100**	**24.5**	**16.8**

*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 for the years 2019 and 2020 do not add up to 100%

Table 4.1.3. Number of active Registers and PTs per ATC category (Level I) in the period 2018-2020

ATC code	No. of Registers			No. of TP			Total		
	2018	2019	2020	2018	2019	2020	2018	2019	2020
A	2	3	4	0	0	0	2	3	4
B	2	3	1	8	8	8	10	11	9
C	4	6	6	0	1	1	4	7	7
D	2	2	2	0	0	0	2	2	2
H	1	1	1	0	0	0	1	1	1
J	14	10	8	0	0	0	14	10	8
L	97	127	124	0	0	0	97	127	124
M	2	3	3	2	2	1	4	5	4
N	3	3	7	1	2	2	4	5	9
R	3	4	5	1	1	1	4	5	6
S	11	2	3	0	0	0	11	2	3
V	0	2	2	0	0	0	0	2	2
Total	**141**	**166**	**166**	**12**	**14**	**13**	**153**	**180**	**179**

Table 4.1.4. Number of patients* enrolled per ICD-11 category (years 2018-2020)

ICD-11	No. of patients			Incidence %			Δ %	
	2018	2019	2020	2018	2019	2020	19-18	20-19
Mental and behavioural disorders	-	1,609	3,365	0.0	0.1	0.1	Inf	109.1
Diseases of the blood and blood-forming organs	4,654	5,934	6,777	0.2	0.3	0.2	27.5	14.2
Diseases of the circulatory system	1,016,610	1,292,158	1,517,904	53.3	54.7	55.1	27.1	17.5
Diseases of the immune system	1,236	1,693	2,042	0.1	0.1	0.1	37	20.6
Diseases of the musculoskeletal system and connective tissue	160,677	200,236	230,554	8.4	8.5	8.4	24.6	15.1
Diseases of the nervous system	10,721	12,866	15,840	0.6	0.5	0.6	20	23.1
Diseases of the digestive system	3,121	3,123	3,123	0.2	0.1	0.1	0.1	0.0
Diseases of the genitourinary system	229	414	595	0.0	0.0	0.0	80.8	43.7
Diseases of the respiratory system	9,771	12,312	14,079	0.5	0.5	0.5	26	14.4
Skin diseases	2,295	5,426	8,619	0.1	0.2	0.3	136.4	58.8
Eye diseases	212,879	248,330	282,241	11.2	10.5	10.2	16.7	13.7
Diseases of the endocrine glands of nutrition and metabolism and immune disorders	9,110	15,285	21,955	0.5	0.6	0.8	67.8	43.6
Infectious and parasitic diseases	163,077	198,304	232,992	8.6	8.4	8.5	21.6	17.5
Tumors	312,900	363,594	414,391	16.4	15.4	15	16.2	14.0
Total	**1,907,280**	**2,361,284**	**2,754,477**	**100**	**100**	**100**	**23.8**	**16.7**

ICD: International Classification of Diseases

*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 Registers 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 Registers 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 Table 4.1.6, the distribution of treatments by age and gender is reported, separately by Registers and Therapeutic Plans. As for the Registers, 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 Register, while the number of patients entered in the Registers referred to ATC S begins to be relevant, up to 80,000 patients entered in the age group from 80 years upwards (Table 4.1.7).

Table 4.1.5. Number of patients by age group and gender in the Registers (year 2020)

Age class	Men		Wome	
	No. of patients	Inc. %	No. of patients	Inc. %
<40	22,779	4.2	19,443	4.0
40-49	47,795	8.9	38,506	8.0
50-59	100,033	18.6	79,575	16.4
60-69	132,087	24.6	111,818	23.1
70-79	160,186	29.9	147,323	30.4
≥80	73,709	13.7	87,301	18.0
Total	**536,589**	**100.0**	**483,966**	**100.0**

Table 4.1.6. Number of patients by age group and gender in the Therapeutic Plans (year 2020)

Age class	Men		Wome	
	No. of patients	Inc. %	No. of patients	Inc. %
<40	12,196	1.5	8,914	0.9
40-49	22,770	2.8	20,280	2.1
50-59	64,669	7.9	56,179	5.8
60-69	157,850	19.3	147,839	15.3
70-79	288,480	35.4	323,546	33.4
≥80	270,018	33.1	411,921	42.5
Total	**815,983**	**100.0**	**968,679**	**100.0**

Table 4.1.7. Number of patients* in ATC categories (level I) until 2020

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	62	11	73	2	3	5	1	0	1	0	0	0	0	0	0	0	0	0
B	8,957	7,089	16,046	20,366	11,829	32,195	57,082	26,701	83,783	143,185	90,260	233,445	267,231	244,660	511,891	254,162	357,824	611,986
C	1106	349	1455	3526	936	4,462	9,464	2,844	12,308	14,732	5,158	19,890	15,881	6,289	22,170	7,503	3,796	11,299
D	2018	1,531	3,549	739	605	1344	733	792	1,525	546	472	1018	338	221	559	137	85	222
H	20	55	75	9	62	71	12	34	46	9	24	33	2	14	16	0	5	5
J	10,793	5,498	16,291	26,720	10,104	36,824	45,292	20,646	65,938	23,740	21,607	45,347	22,775	30,622	53,397	7,891	10,682	18,573
L	5,976	8,197	14,173	12,486	20,389	32,875	34,326	41,459	75,785	70,305	59,009	129,314	87,042	64,235	151,277	31,565	28,911	60,476
M	718	2115	2,833	1,228	8,514	9,742	3,964	29,096	33,060	8,955	56,835	65,790	12,048	79,060	91,108	7,249	51,371	58,620
N	3663	1,765	5,428	1,524	2,703	4,227	1,571	2,983	4,554	889	1316	2,205	241	278	519	22	25	47
R	443	392	835	83	103	186	185	167	352	709	261	970	964	205	1,169	307	54	361
S	1,405	1,461	2,866	4,026	3,260	7,286	12,776	10,482	23,258	28,437	25,166	53,603	44,160	50,166	94,326	32,613	48,238	80,851
V	8	7	15	29	25	54	97	56	153	239	75	314	331	66	397	139	13	152
Total	**35,169**	**28,470**	**63,639**	**70,738**	**58,533**	**129,271**	**165,503**	**135,260**	**300,763**	**291,746**	**260,183**	**551,929**	**451,013**	**475,816**	**926,829**	**341,588**	**501,004**	**842,592**

*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 ≥100 mg/dl 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 2020, 19,377 treatments were started, of which 10,933 with evolocumab and 8,444 with alirocumab (Table 4.1.9).
The trend of treatments initiated per month from the start of monitoring is shown in Figure 4.1.2 which shows a significant and progressive increase in the number of new treatments for both medicines, with a constant relationship between them. In the months of March-June 2020, the significant decline is motivated by the concomitance of the SARS-CoV-2 epidemic, with a complete recovery of the previous trend as early as July. About 65% of the treatments involved male subjects, while the median age was 62 years (range 14-80) (Table 4.1.8). Consistent with the different prevalence of forms of hypercholesterolemia, most prescriptions were made in subjects diagnosed with non-familial hypercholesterolemia (51.9%), followed by those for mixed dyslipidemia (26.6%) and heterozygous familial hypercholesterolemia (20.9%) and, lastly, for homozygous familial hypercholesterolemia (0.6%). Please note that for the latter indication only evolocumab is authorised.
A marginal share of patients (n = 205, equal to 1.1% of the total) appears to be being treated with one of the two medicines after having already been treated by the NHS with the other antiPCSK9, then suspended for different reasons.
87.5% of subjects undertook treatment in secondary cardiovascular prevention while the remaining 12.5% in primary prevention. As regards the relevant comorbidities, 71.1% of the entire sample had cardiovascular disease, 63.6% arterial hypertension and 20.5% diabetes mellitus. Only 7.5% of subjects have no relevant comorbidities at baseline. Furthermore, 13.4% of subjects have a current smoking habit, while a more consistent share of 37.0% reports a previous smoking habit.
Compared to the conditions that led to the initiation of treatment with an inhibitor (PCSK9i), more than half of the patients (53.7%) have statin intolerance; the number of treatments initiated in patients intolerant to ezetimibe is, on the other hand, marginal (about 5% of all treatments).

However, it should be noted that for the latter type of patients, admission to reimbursement of treatment with PCSK9i was granted only between the end of 2019 (evolocumab) and the first months of 2020 (alirocumab); referring the number of treatments started in ezetimibe intolerant to that of the total number of treatments started since reimbursement was changed, the share of patients intolerant to ezetimibe reaches about 19%. Among patients receiving a high-potency statin at the maximum tolerated dose, there appears to be no difference in the choice between atorvastatin and rosuvastatin.

Considering the populations treated with the two medicines, evolocumab and alirocumab, the basal characteristics are similar overall; the main difference (in percentage terms on the absolute values) is found in the prevalence of arterial hypertension, greater in subjects treated with evolocumab. In relation to the type of hypercholesterolemia, a higher percentage of subjects with heterozygous familial hypercholesterolemia are treated with alirocumab and, conversely, a higher percentage of subjects with non-familial hypercholesterolemia are 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 (21.5% of the national total), followed by Lombardy (12.6%) and Lazio (9.5%). These three Regions alone represent almost half (43.6%) of all subjects treated with PCSK9 inhibitors (Table 4.1.9).

Table 4.1.8. Characteristics of patients at the start of treatment with anti PCSK9

	Alirocumab N (%)	Evolocumab N (%)	Totale N (%)
Total patients	**8,444 (43.6)**	**10,933 (56.4)**	**19,377 (100)**
Women	2,933 (34.7)	3,809 (34.8)	6,742 (34.8)
Men	5,511 (65.3)	7,124 (65.2)	12,635 (65.2)
Median age (range)	62 (18-80)	63 (14-80)	62 (14-80)
Previous anti-PCSK9 treatment	98 (1.2)	107 (1.0)	205 (1.1)
Type of hypercholesterolemia			
HoFH*	0 (0.0)	111 (1.0)	111 (0.6)
HeFH	1,886 (22.3)	2,171 (19.9)	4,057 (20.9)
noFH	4,258 (50.4)	5,794 (53.0)	10,052 (51.9)
MD	2,300 (27.2)	2,857 (26.1)	5,157 (26.6)
Use in CV prevention			
Primary prevention	1,089 (12.9)	1,341 (12.3)	2,430 (12.5)
Secondary prevention	7,355 (87.1)	9,592 (87.7)	16,947 (87.5)
Relevant co-morbidities§			
Cardiovascular disease (heart disease)	5,879 (69.6)	7,902 (72.3)	13,781 (71.1)
Cerebrovascular disease (previous stroke)	710 (8.4)	812 (7.4)	1,522 (7.8)
Peripheral arterial disease	1,547 (18.3)	1,847 (16.9)	3,394 (17.5)
Diabetes mellitus	1,802 (21.3)	2,173 (19.9)	3,975 (20.5)
Arterial hypertension	5,203 (61.6)	7119 (65.1)	12,322 (63.6)
None	724 (8.6)	734 (6.7)	1,458 (7.5)
Smoking habit			
Present	1,133 (13.2)	1,476 (13.5)	2,589 (13.4)
Previous	3,009 (35.6)	4,168 (38.1)	7,177 (37.0)
Absent	4,322 (51.2)	5,289 (48.4)	9,611 (49.6)
Previous use of statins and/or ezetimibe			
Intolerance to statins	4,450 (52.7)	5,957 (54.5)	10,407 (53.7)
Intolerance to ezetimibe	374 (4.4)	678 (6.2)	1052 (5.4)
Statin in combination, treatment with:^			
Atorvastine	1,923 (22.8)	2,442 (22.3)	4,365 (22.5)
Rosuvastatin	2,071 (24.5)	2,534 (23.2)	4,605 (23.8)

HoFH: homozygous familial hypercholesterolaemia HeFH: heterozygous familial hypercholesterolemia noFH: non-familial hypercholesterolemia MD: mixed dyslipidemia

*Only evolocumab has an indication in HoFH

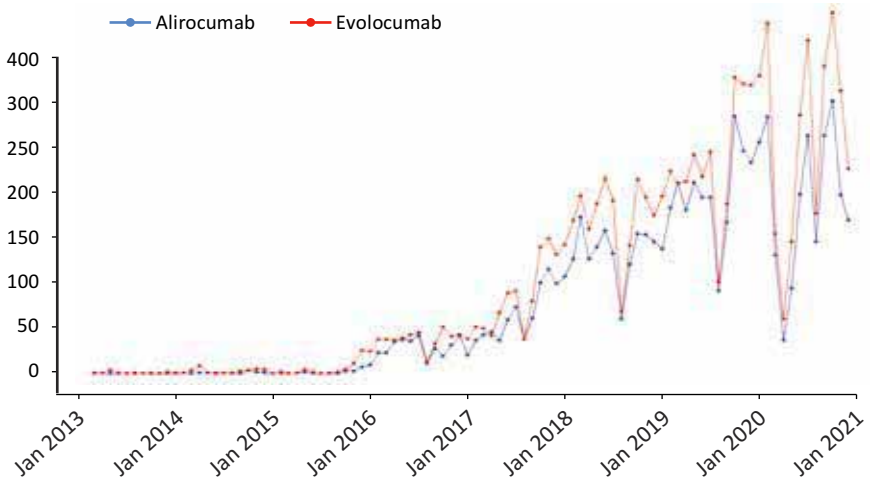
§You can select multiple items

^For 12 treatments there is no information on the statin used in combination

Table 4.1.9. Regional distribution of prescribing centers and of patients starting treatment

Region	Centers No.		Patients undergoing treatment No.		Total No. (%)
	Alirocumab	Evolocumab	Alirocumab	Evolocumab	
Abruzzo	6	6	174	240	414 (2.1)
Basilicata	5	9	144	297	441 (2.3)
Calabria	7	11	276	538	814 (4.2)
Campania	40	53	1,502	2,667	4,169 (21.5)
Emilia R.	15	14	365	528	893 (4.6)
Friuli VG	12	11	132	197	329 (1.7)
Lazio	25	24	1,045	790	1,835 (9.5)
Liguria	15	15	518	377	895 (4.6)
Lombardy	79	81	954	1,482	2,436 (12.6)
Marche	12	14	124	286	410 (2.1)
Molise	5	4	89	12	101 (0.5)
Piedmont	26	25	1,029	630	1,659 (8.6)
A.P. of Bolzan	5	3	34	28	62 (0.3)
A.P. of Trento	2	2	27	31	58 (0.3)
Puglia	9	9	405	869	1,274 (6.6)
Sardinia	6	8	201	268	469 (2.4)
Sicily	20	19	317	266	583 (3.0)
Tuscany	17	20	494	710	1,204 (6.2)
Umbria	10	8	197	169	366 (1.7)
Valle d'Aosta	1	1	15	26	41 (0.2)
Veneto	12	12	402	522	924 (4.8)
Total	**330**	**349**	**8,444**	**10,933**	**19,377 (100.0)**

Figure 4.1.2. Treatments initiated with anti-PCSK9 medicines in December 2020 (monthly trend)



Intravitreal anti-VEGF medicines

The treatment of neovascular (exudative) age-related macular degeneration (AMD) involves the use of intravitreal (IVT) anti-neovascularization agents (VEGF inhibitors). Data are referred to the medicines authorised to treat wet AMD (ranibizumab, aflibercept and pegaptanib) as well as to bevacizumab, added to the list of medicines under Law 648/96, even though it is non authorised for this indication. Since 1 January 2019, upon request of the marketing authorisation holder, the revocation of the MA for the medicinal product Macugen® (pegaptanib) became effective in Europe [*Commission implementing decision* C (2018) 9064 final, 17/12/2018]. The Register of pegaptanib was closed on 1 September 2019. Information is referred to Monitoring Registers operating for pegaptanib since 25 February 2013, for ranibizumab since 7 March 2013, for bevacizumab (respectively for the medicines Avastin and Mvasi) since 28 June 2014 and 19 Juni 2020 and for aflibercept since 15 April 2014. All these Registers, except for the aforementioned exception of the pegaptanib, were closed on 8 October 2019 and a temporary paper-form was first introduced and, since 6 February 2020, it has been substituted by a 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 registers or in paper form, so as to allow the management of monitoring in a single 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 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 indication.

Although the data reported here are prior to the introduction of Note 98, it should in any case be specified that they include both the treatments included in the old Monitoring Registers and those started directly within the simplified multi-drug form, established by 6/2/2020. It is therefore specified that, for the purposes of the analyses reported below, the treatments opened in the old Monitoring Registers and subsequently migrated to the simplified multi-drug card are considered as a single treatment. In the reference period, a total of 270,610 eyes were initiated for treatment for AMD (Table 4.1.10), 87.2% of which were treated as part of a unilateral therapy. The number of *naïve* patients (first treatment with an intravitreal IVT anti-VEGF) is 187,441. More than a third of treatments (no. of eyes) were started with ranibizumab (106,551; 39.4%), followed by aflibercept (85,348; 31.5%), bevacizumab (77,638; 28.7%) and, finally, pegaptanib (1,073; 0.4%). The baseline characteristics of *naïve* patients show a higher prevalence of use in women (56.9%) than in men (43.1%). The median age of treated patients is 78 years (range 20-105 years), the maximum age is 105 years and the largest number of patients treated falls in the age group between 75 and 84 years.

18.2% of the treatments started refer to eyes previously treated with an antineovascularizer. Specifically, 28.9% of the eyes treated with aflibercept, 23.4% of those treated with bevacizumab and 5.7% 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 (median value 4), followed by bevacizumab with 3.6 (median value 3), ranibizumab with 3.5 (median value 3) and finally pegaptanib of 2.6 (median value 2).
The trend of treatments initiated per month from the start of monitoring is shown in Figure 4.1.3.
The Figure shows how in 2020 bevacizumab was the most used anti-VEGF (with about 1,880 new eyes treated per month of which about 1,730 treated with Avastin and about 150 treated with Mvasi), followed by aflibercept with 871 new eyes/month and ranibizumab with 568 new eyes/month. This data is in clear contrast when compared with the trend up to 2018 which saw aflibercept as the most used medicine; in addition, the use of bevacizumab is confirmed to increase sharply even compared to 2019, in which an average of 1,349 new eyes/month were observed for bevacizumab (almost all of which were treated with the medicine Avastin). The distribution of the percentage of switches on active patients by year and medicine of origin is shown in Figure 4.1.4, where it is evident that the percentage of switches targeting bevacizumab has sharply increased starting from 2019, regardless of the medicine of origin.
The regional distribution shows that more than half of the treatments initiated with medicines for AMD are distributed over 5 Regions: Lombardy, Veneto, Lazio, Tuscany and Emilia Romagna. The regional distribution of prescribing centers and the treatments started are shown in Table 4.1.11, while the number of treatments started by Regions normalised on the basis of the resident population is shown in Figure 4.1.5.

Table 4.1.10. Baseline characteristics of patients at the start of anti-VEGF treatment

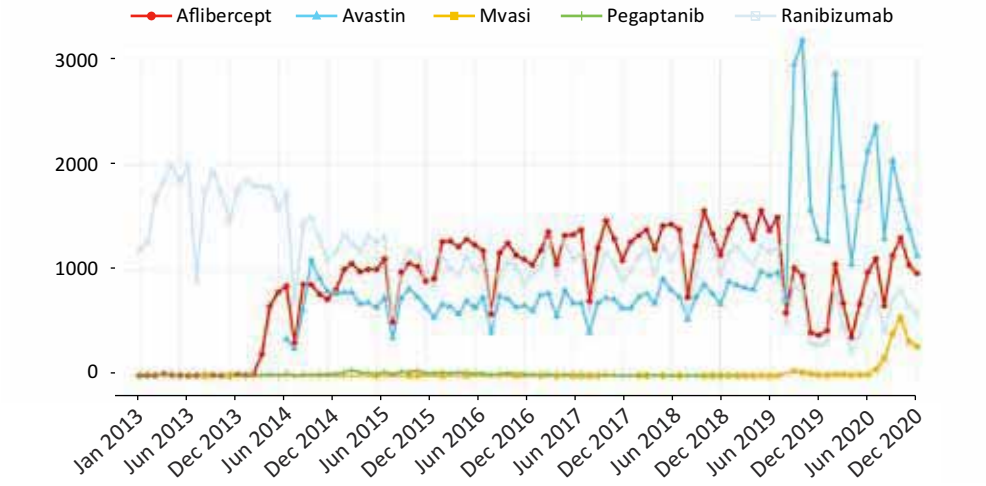
	Aflibercept		Bevacizumab (Law 648/96)/ Avastin		Bevacizumab (Law 648/96)/ biosimilar bevacizumab		Pegaptanib		Ranibizumab		Total	
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
No. of patients*	**48,484**	**25.9**	**48,718**	**26.0**	**522**	**0.3**	**720**	**0.4**	**88,997**	**47.5**	**187,441**	**100.00**
Age, yy median (range)	**78 (24–104)**		**79 (20–103)**		**79 (46–99)**		**80 (51-100)**		**78 (22–105)**		**78 (20–105)**	
≤64	5,042	10.4	3,489	7.2	40	7.7	36	5.0	9,498	10.7	18,105	9.7
65-74	13,223	27.3	11,487	23.6	137	26.2	148	20.6	23,577	26.5	48,572	25.9
75-84	21,821	45.0	23,171	47.6	243	46.6	360	50.0	39,781	44.7	85,376	45.5
≥85	8,398	17.3	10,571	21.7	102	19.5	176	24.4	16,141	18.1	35,388	18.9
Gender												
Women	27,007	55.7	28,530	58.6	301	57.7	355	49.3	50,499	56.7	106,692	56.9
Men	21,477	44.3	20,188	41.4	221	42.3	365	50.7	38,498	43.3	80,749	43.1
No. treatments (eyes)	**85,348**	**31.5**	**75,639**	**28.0**	**1,999**	**0.7**	**1,073**	**0.4**	**106,551**	**39.4**	**270,610**	**100.0**
Previous anti-VEGF IV treatment*	**24,638**	**50.0**	**16.959****	**34.4**	**1.217****	**2.5**	**304**	**0.6**	**6,117**	**12.4**	**49,235**	**100.0**
Monocular treatment	**63,868**	**85.6**	**57,445**	**86.3**	**1,787**	**94.4**	**1,059**	**99.3**	**85,211**	**88.9**	**209,370**	**87.2**
Biocular treatment	**10,740**	**14.4**	**9,097**	**13.7**	**106**	**5.6**	**7**	**0.7**	**10,670**	**11.1**	**30,620**	**12.8**
Average (median) number of treatments in the first 12 months***	**3.8 (4)**		**3.6 (3)**				**2.6 (2)**		**3.5 (3)**		**3.6 (3)**	

*The row percentages are shown

**The total of patients with previous treatment for bevacizumab in the AMD indication, regardless of the medicine used, is 17,129 equal to 35.5% of the switches observed

***Average (median) number of administrations for patients with at least one year of potential follow-up as of 31/12/2020

Figure 4.1.3. Monthly trend of treatments initiated with anti-VEGF IVT medicine from January 2013 to 2020 in Italy

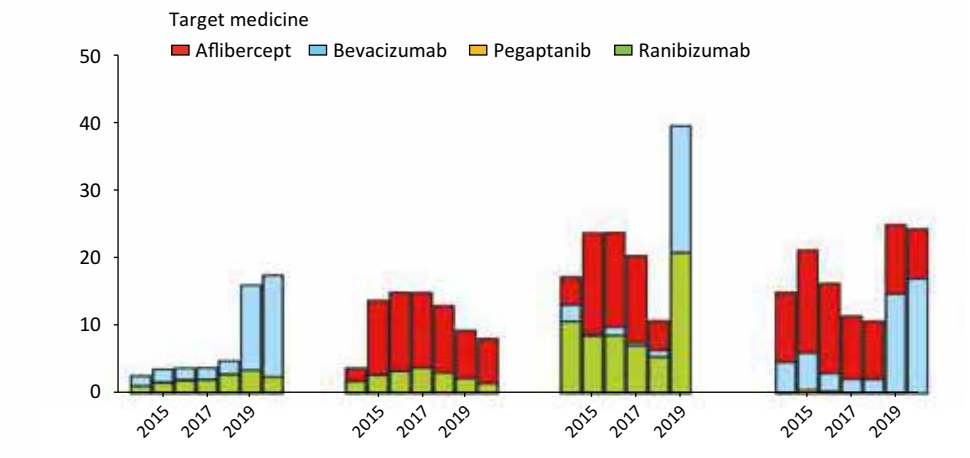


*The trends shown are net of migration from old registers to multidrug anti-VEGF form.

Table 4.1.11. Regional distribution of prescribing centers and of patients starting treatment

Region	No. of active prescribing centers					No. of Eyes				
	Aflibercept	Bevacizumab Avastin	Bevacizumab Mvasi	Pegaptanib	Ranibizumab	Aflibercept	Bevacizumab Avastin	Bevacizumab Mvasi	Pegaptanib	Ranibizumab
Abruzzo	11	4	-	4	11	2,043	200	-	16	2,954
Basilicata	4	1	-	2	5	524	14	-	8	1,049
Calabria	10	1	-	5	14	1,208	4	-	22	1,893
Campania	31	3	-	5	30	4,177	745	-	8	7,517
Emilia R.	18	20	-	7	19	4,503	11,959	-	32	4,120
Friuli VG	6	6	-	-	6	2,332	4,848	-	-	2,266
Lazio	30	17	5	10	33	9,852	4,640	109	49	9,557
Liguria	9	8	-	4	8	3,210	3,957	-	10	4,121
Lombardy	67	64	1	23	75	18,389	15,618	155	260	25,522
Marche	14	12	1	8	15	2,141	4,807	29	94	3,384
Molise	4	1	-	-	5	365	28	-	-	838
Piedmont	25	19	-	6	25	7,544	6,858	-	28	5,073
A.P. of Bolzano	3	3	1	1	3	972	1,407	4	2	815
A.P. of Trento	2	2	-	-	2	624	1,076	-	-	608
Puglia	28	6	1	25	38	6,085	339	36	296	9,548
Sardinia	8	1	-	5	8	1,885	59	-	39	3,396
Sicily	23	9	1	6	24	5,514	341	181	17	6,386
Tuscany	17	13	11	11	21	6,555	4,537	1,426	104	8,165
Umbria	7	6	1	-	7	1,427	632	1	-	2,676
Valle d'Aosta	1	1	-	1	1	219	1,071	-	5	81
Veneto	27	28	1	15	29	5,779	12,499	58	83	6,582
Total	**345**	**225**	**23**	**138**	**379**	**85,348**	**75,639**	**1,999**	**1,073**	**106,551**

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

ALK inhibitors (ALKi) for the treatment of patients with non-small cell lung cancer

As part of the therapies for the treatment of adult patients diagnosed with non-small cell lung cancer (NSCLC), reimbursed by the NHS and included in the Monitoring Registers platform, there are also four medicines based on crizotinib, ceritinib, alectinib and brigatinib with specific indication in patients whose disease has translocation of the gene ALK (Anaplastic Lymphome Kinase - Anaplastic Lymphoma Kinase).
The four medicinal products are indicated both as first line (1L) and in pre-treated patients (LS, subsequent lines), as summarised in Table 4.1.12. In particular, in pretreated patients, alectinib and ceritinib are authorised only after failure (progression and/or toxicity) to previous crizotinib treatment; brigatinib, on the other hand, is authorised after failure of a crizotinib therapy and in patients pretreated but *naïve* to ALK inhibitor (ALKi) therapy. Crizotinib, on the other hand, is not reimbursed after previous ALKi therapy.

Table 4.1.12. Details of authorised/reimbursed indications for ALK inhibitors and monitoring start date

Active ingredient (medicine)	Indication authorised/reimbursed	Line of therapy/ synthetic indication	Monitoring start date
crizotinib (Xalkori)	Treatment of pre-treated adult ALK-positive advanced NSCLC patients	LS	24/04/2013 (Law 648/1996) [Monitoring closed on 23/07/2015]
	Treatment of pre-treated adult patients for advanced ALK-positive NSCLC	LS	11/04/2015
	As monotherapy for the treatment of 1L of adult patients with ALK-positive advanced NSCLC.	1L	10/03/2017
ceritinib (Zykadia)	Treatment of adult patients with advanced ALK-positive NSCLC, previously treated with crizotinib	LS after crizotinib	06/07/2017
	Treatment in 1L of adult patients with ALK-positive NSCLC	1L	18/12/2019
alectinib (Alecensa)	As monotherapy for the treatment of adult patients with advanced ALK-positive NSCLC previously treated with crizotinib	LS after crizotinib	01/08/2018
	As monotherapy for the treatment of 1L of adult patients with ALK-positive advanced NSCLC.	1L	01/08/2018
brigatinib (Alunbrig)	As monotherapy for the treatment of adult patients with advanced ALK-positive NSCLC, previously treated with crizotinib	LS after crizotinib	27/10/2020
	As monotherapy for the treatment of adult patients with ALK-positive NSCLC in advanced stage, previously not treated with an ALK inhibitor	*Naïve* to ALKi	10/12/2020

1L: first line LS: subsequent lines

As of 31 December 2020, a total of 3,291 treatments with ALK inhibitors have been initiated, 44.2% of which with crizotinib (1,454 patients), 53.2% with alectinib (1,751 patients), 1.6% with ceritinib (54 patients) and approximately 1% with brigatinib (32 patients) (Table 4.1.13). Figure 4.1.6 shows the trends of the treatments initiated per month from the start of monitoring of each of the four ALK inhibitors. This graph shows a significant increase in new alectinib treatments at the release of the monitoring registry and a progressive decline in new crizotinib treatments. Substantial homogeneity with regard to gender is evident (51.6% of women and 48.4% of men) and a uniformity of the baseline characteristics of the populations present in the Register, in particular with regard to crizotinib and alectinib treatments.
Most of the treated patients have an adenocarcinomatous histotype (96.3%) with a clear predominance of the metastatic stage of disease (93.1%). At baseline, 63.4% of patients had lung metastases and 46.7% had localised lymph node metastatic disease. 55.4% scored 0 at the Performance status, measured by the ECOG scale.
As regards the lines of therapy, it should be noted that about 56% of patients were treated on the front line, with a preferential use of alectinib (70.0% of the total number of treatments started on the first line).
Considering the small number of treatments initiated with ceritinib and brigatinib, in relation to the total, it is still premature to carry out an adequate descriptive analysis of the corresponding populations and, above all, a comparison with the characteristics of patients treated with crizotinib and alectinib.
The population of patients treated with crizotinib through Law 648/1996 (subsequent post-chemotherapy lines - 624 treatments) is subject to a separate descriptive analysis (Table 4.1.14) as the information required at baseline is minimal even if almost overlapping, in percentage terms, to those analysed in the previous paragraph.
As regards Table 4.1.15, relating to the regional distributions of treatments initiated, it should be noted that 36.3% of the total treatments were initiated in the two Regions with the highest number of residents.

Figure 4.1.6. Trend of treatments initiated per month from the start of monitoring

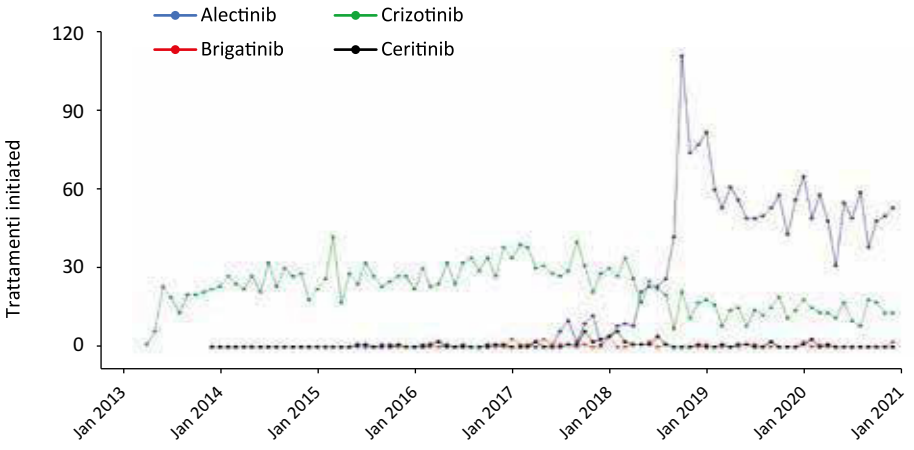


Table 4.1.13. Baseline characteristics of the populations of the Crizotinib, Alectinib, Ceritinib and Brigatinib Monitoring Registers in indications reimbursed by the NHS

	Crizotinib N (%)	Alectinib N (%)	Ceritinib N (%)	Brigatinib N (%)	TOTAL
Monitored indications register NSCLC ALK+	1) 1L 2) LS after chemo	1) 1L 2) LS after crizotinib	1) 1L 2) LS after crizotinib	1) naive ALKi 2) LS after crizotinib	
Total patients	**1.454 (44,18)**	**1.751 (53,21)**	**54 (1,64)**	**32 (0,97)**	**3.291 (100)**
Women	764 (52,54)	895 (51,11)	22 (40,74)	16 (50,00)	1.697 (51,56)
Men	690 (47,46)	856 (48,89)	32 (59,26)	16 (50,00)	1.594 (48,44)
Age group 18-39	70 (4,81)	96 (5,48)	3 (5,56)	5 (15,63)	174 (5,29)
Age group 40-54	328 (22,56)	443 (25,30)	13 (24,07)	8 (25,00)	792 (24,07)
Age group 55-64	368 (25,31)	467 (26,67)	14 (25,93)	7 (21,88)	856 (26,01)
Age group 65-74	442 (30,40)	462 (26,38)	19 (35,19)	7 (21,88)	930 (28,26)
Age group 75-84	230 (15,82)	265 (15,13)	5 (9,26)	5 (15,63)	505 (15,34)
Age group ≥85	16 (1,10)	18 (1,03)	0 (0,00)	0 (0,00)	34 (1,03)
Histological type					
Adenocarcinoma	1.398 (96,15)	1.687 (96,34)	52 (96,30)	32 (100,00)	3.169 (96,29)
Squamous cell carcinoma	15 (1,03)	26 (1,48)	0 (0,00)	0 (0,00)	41 (1,25)
Adenosquamous Carcinoma	7 (0,48)	4 (0,23)	1 (1,85)	0 (0,00)	12 (0,36)
Large cell carcinoma	10 (0,69)	6 (0,34)	0 (0,00)	0 (0,00)	16 (0,49)
Carcinoma NOS (Not Otherwise Specified)	24 (1,65)	28 (1,60)	1 (1,85)	0 (0,00)	53 (1,61)
Locally advanced	120 (8,25)	106 (6,05)	1 (1,85)	1 (3,13)	228 (6,93)
Metastatic	1.334 (91,75)	1.645 (93,95)	53 (98,15)	31 (96,88)	3.063 (93,07)
Locations of metastases					
Lung	911 (62,65)	1.122 (64,08)	35 (64,81)	18 (56,25)	2.086 (63,38)
Brain	277 (19,05)	586 (33,47)	19 (35,19)	19 (59,38)	901 (27,38)
Liver	201 (13,82)	239 (13,65)	11 (20,37)	3 (9,38)	454 (13,80)
Adrenal	123 (8,46)	143 (8,17)	5 (9,26)	0 (0,00)	271 (8,23)
Bones	401 (27,58)	516 (29,47)	11 (20,37)	5 (15,63)	933 (28,35)
Lymph nodes	670 (46,08)	837 (47,80)	20 (37,04)	11 (34,38)	1538 (46,73)
Other	232 (15,96)	284 (16,22)	8 (14,81)	5 (15,63)	529 (16,07)
Line of therapy					
1st line	545 (37,48)	1.290 (73,67)	2 (3,70)	5 (15,63)	1.842 (55,97)
2nd line	819 (56,33)	312 (17,82)	16 (29,63)	11 (34,38)	1.158 (35,19)
3rd line	59 (4,06)	121 (6,91)	31 (57,41)	12 (37,50)	223 (6,78)
Subsequent lines	31 (2,13)	28 (1,60)	5 (9,26)	4 (12,50)	68 (2,07)
Previous chemotherapy*					
Yes	0 (0,00)	211 (12,05)	29 (53,70)	15 (46,88)	255 (7,75)
No	0 (0,00)	249 (14,22)	13 (24,07)	12 (37,50)	274 (8,33)
N.D.	909 (62,52)	1 (0,06)	10 (18,52)	0 (0,00)	920 (27,96)
ECOG performance status					
0	740 (50,89)	1.028 (58,71)	31 (57,41)	23 (71,88)	1.822 (55,36)
1	637 (43,81)	663 (37,86)	19 (35,19)	8 (25,00)	1.327 (40,32)
2	74 (5,09)	60 (3,43)	4 (7,41)	1 (3,13)	139 (4,22)
3	3 (0,21)	0 (0,00)	0 (0,00)	0 (0,00)	3 (0,09)
4	0 (0,00)	0 (0,00)	0 (0,00)	0 (0,00)	0 (0,00)

Table 4.1.14. Baseline characteristics of the population of the crizotinib Monitoring Register in the indication reimbursed through Law 648/1996

	Crizotinib N (%)
Indications monitored in Register NSCLC ALK+	**LS after chemotherapy**
Total patients	**624 (100)**
Women	323 (51.76)
Men	301 (48.24)
18-39	39 (6.25)
40-54	187 (29.97)
55-64	165 (26.44)
65-74	167 (26.76)
75-84	64 (10.26)
≥85	2 (0.32)
Histological type	
Adenocarcinoma	598 (95.83)
Squamous cell carcinoma	8 (1.28)
Adenosquamous carcinoma	6 (0.96)
Large cell carcinoma	3 (0.48)
Carcinoma NOS	9 (1.44)

NOS: Not Otherwise Specified

Table 4.1.15. Regional distribution of total treatments initiated for all indications monitored through the AIFA Register (Law 648/1996 included)

Region	Centers No.				Patients undergoing treatment No.				Total No. (%)
	Crizotinib	Alectinib	Ceritinib	Brigatinib	Crizotinib	Alectinib	Ceritinib	Brigatinib	
Abruzzo	9	6	1	0	36	25	1	0	62 (1.58)
Basilicata	3	2	0	0	18	10	0	0	28 (0.72)
Calabria	10	7	1	0	18	20	1	0	39 (1.00)
Campania	20	14	2	1	155	120	12	3	290 (7.41)
Emilia R.	26	20	4	4	215	139	5	11	370 (9.45)
Friuli VG	5	3	1	1	43	49	4	5	101 (2.58)
Lazio	23	20	4	0	339	336	4	0	679 (17.34)
Liguria	7	9	1	0	46	48	1	0	95 (2.43)
Lombardy	52	46	5	2	418	309	15	2	744 (19.00)
Marche	13	10	1	0	55	39	1	0	95 (2.43)
Molise	3	3	1	0	11	5	1	0	17 (0.43)
Piedmont	21	20	1	2	130	110	1	3	244 (6.23)
A.P. of Bolzano	4	3	0	0	14	13	0	0	27 (0.69)
A.P. of Trento	1	1	0	0	5	9	0	0	14 (0.36)
Puglia	20	19	0	0	120	102	0	0	222 (5.67)
Sardinia	10	9	0	0	44	51	0	0	95 (2.43)
Sicily	22	21	2	1	102	88	2	2	194 (4.96)
Tuscany*	16	20	2	1	109	100	3	1	213 (5.44)
Umbria	7	5	0	1	46	37	0	5	88 (2.25)
Valle d'Aosta	1	1	0	0	5	6	0	0	11 (0.28)
Veneto	23	21	2	0	149	135	3	0	287 (7.33)
Total	**296**	**260**	**28**	**13**	**2,078**	**1,751**	**54**	**32**	**3,915 (100)**

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 poor.

This paragraph briefly summarises the first data from the AIFA Monitoring Registers 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 31/12/2020 (Registers analysis date), 20 centers were qualified for the administration of Yescarta and Kymriah throughout the national territory (Table 4.1.18) but there is still a lack of homogeneity in the territorial distribution, with 70% of the qualified centers found in only 4 Regions (Lazio, Lombardy, Piedmont and Tuscany).

In total, 164 patients with aggressive large cell B lymphomas were entered in the AIFA Registers and considered eligible for CAR-T treatment (Kymriah n = 97, Yescarta n = 67, Table 4.1.16). The median age of these patients is 55 years (range 20-71) with a prevalence of male subjects (M/F ratio 1.5: 1), in line with what was expected on the basis of epidemiological data.

The population of patients included in the AIFA Monitoring Registers is representative of the advanced disease setting for which these products are indicated: the median time from the diagnosis of lymphoma was 1.4 years, 42% of patients had previously undergone at least 3 lines of systemic therapy and 98% were no longer eligible for hematopoietic stem cell transplant procedures, in most cases due to failure of a previous transplant (32% post-transplant recurrence) or failure to respond to salvage therapy (78.6%)[2]. The data entered in the Monitoring Registers also confirm the high clinical risk of patients candidates for CAR-T therapy: 43.3% of patients had an IPI score ≥3, 77.5% a stage III/IV sec. Ann-Arbor and 55% a disease refractory to previous treatments.
At the time of the analysis, 137 out of 164 patients eligible for treatment (83.5%) had undergone CAR-T cell infusion, with a median time from eligibility to infusion of 63 days. The discrepancy between the number of eligible and truly infused patients (Table 4.1.19) 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, 25 patients were entered in the AIFA Registers and considered eligible for treatment with tisagenlecleucel (Table 4.1.17). The median age of the patients is 14 years (range 3-26) with a prevalence of male subjects (M/F ratio 2.4: 1). Most patients had ALL in relapse post haematopoietic stem cell transplant procedure (48%) or second or further relapse (48%), median time from diagnosis of ALL was 2.7 years, and in most of the cases there were no high-risk cytogenetic characteristics (72%). 64% of the patients included in the AIFA Register had a suboptimal PS (Karnofsky-Lansky score ≤80%), and most (72%) had already undergone anti-CD19 immunotherapy (blinatumomab monotherapy in 94% of cases).
At the time of analysis, most of the patients eligible for treatment (22 out of 25, 88%) had undergone CAR-T cell infusion, with a median time from eligibility to infusion of 69.5 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 4.1.16. Baseline characteristics for adult patients with diffuse large B cell lymphoma

Characteristics at baseline	Axicabtagen ciloleucel N (%)	Tisagenle-cleuce N. (%)	Total N. (%)
Eligible patients	**67 (100.0)**	**97 (100.0)**	**164 (100.0)**
Gender*			
F	24 (36.4)	38 (42.2)	62 (39.7)
M	42 (63.6)	52 (57.8)	94 (60.3)
Age at register entry (median years - range)	**49.4 (19,8-70,2)**	**57.5 (29,7-70,6)**	**54.8 (19,8-70,6)**
Time since first diagnosis (median years - IQR)	**1.2 (0,8-2,2)**	**1.6 (1,0-3,8)**	**1.4 (0,9-3,1)**
IPI score			
0	4 (6.0)	8 (8.2)	12 (7.3)
1	15 (22.4)	15 (15.5)	30 (18.3)
2	21 (31.3)	30 (30.9)	51 (31.1)
3	17 (25.4)	30 (30.9)	47 (28.7)
4	10 (14.9)	11 (11.3)	21 (12.8)
5	0 (0.0)	3 (3.1)	3 (1.8)
Days from insertion to infusion (median days - range)	**61.5 (40,0-120,0)**	**64 (33-131)**	**63 (33-131)**
Number of previously administered systemic lines of therapy	**(including rituximab and anthracyclines)**		
2	38 (56.7)	57 (58.8)	95 (57.9)
3	19 (28.4)	29 (29.9)	48 (29.3)
≥4	10 (14.9)	11 (11.3)	21 (12.8)
Patient candidate for ASCT			
No	66 (98.5)	95 (97.9)	161 (98.2)
Yes	1 (1.5)	2 (2.1)	3 (1.8)
Performance status (ECOG)			
0	53 (79.1)	67 (69.1)	120 (73.2)
1	14 (20.9)	30 (30.9)	44 (26.8)
Previous anti-CD19 therapy			
No	66 (98.5)	97 (100.0)	163 (99.4)
Yes	1 (1.5)	0 (0.0)	1 (0.6)
Relapse after ASCT			
No	44 (65.7)	67 (69.1)	111 (67.7)
Yes	23 (34.3)	30 (30.9)	53 (32.3)
Patient not eligible for ASCT			
Other (including transplant already performed)	13 (19.4)	21 (21.6)	34 (20.7)
Age/Comorbidity	0 (0.0)	1 (1.0)	1 (0.6)
Age/Comorbidity+failure to respond to rescue therapy	1 (1.5)	4 (4.1)	5 (3.0)
Failure to respond to rescue therapy	53 (79.1)	71 (73.2)	124 (75.6)
Stadium (Lugano mod. Ann Arbor criteria)			
I	0 (0)	1 (1.0)	1 (0.6)
I E	0 (0)	1 (1.0)	1 (0.6)
II	5 (7.5)	11 (11.3)	16 (9.8)
II bulky	8 (11.9)	4 (4.1)	12 (7.3)
II E	6 (9.0)	1 (1.0)	7 (4.3)
III	9 (13.4)	20 (20.6)	29 (17.7)
IV	39 (58.2)	59 (60.8)	98 (59.8)

Following

Table 4.1.16. Following

Characteristics at baseline	Axicabtagen ciloleucel	Tisagenle-cleuce	Total
Stage of the disease			
Recurrent DLBCL	14 (20.9)	44 (45.4)	58 (35.4)
Refractory DLBCL	37 (55.2)	53 (54.6)	90 (54.9)
Primary mediastinal DLBCL	16 (23.9)		16 (9.8)
Infusion occurred			
No	7 (10.4)	20 (20.6)	27 (16.5)
Yes	60 (89.6)	77 (79.4)	137 (83.5)
Treatments with FT card completed	**12 (17.9)**	**23 (23.7)**	**35 (21.3)**

*For 1 patient of axicabtagene ciloleucel and 7 of tisagenlecleucel no gender information is available

Table 4.1.17. 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	No. (%)
Gender*	
F	7 (42.2)
M	17 (57.8)
Age at register entry (median years - range)	**14.0 (2,9-26,0)**
Time since first diagnosis (median years - IQR)	**2.7 (1,6-5,3)**
Days from insertion to infusion (median - IQR)	**69.5 (54-90)**
Diagnosis	
Post-transplant relapsed B-cell ALL	12 (48.0)
B-cell ALL in second or further relapse	12 (48.0)
Refractory B-cell ALL	1 (4.0)
Presence of high-risk genetic characteristics	
Other	1 (4.0)
Other+rearrangement involving MLL/KMT2A	1 (4.0)
Complex karyotype	3 (12.0)
Ph+ chromosome	1 (4.0)
None	18 (72.0)
Rearrangement involving MLL/KMT2A	1 (4.0)
With failure of at least 2 lines of therapy with TKI (chromosome Ph+)	**1 (4.0)**
Number of lines of systemic therapy	
2	3 (12.0)
3	3 (12.0)
≥4	6 (24.0)
Days since alloSCT (median - IQR)	**392 (227-1089)**
Karnofsky-Lansky performance status	
70	10 (40.0)
80	6 (24.0)
90	4 (16.0)
100	5 (20.0)
Previous anti-CD19 therapy	
No	7 (28.0)
Yes	18 (72.0)
Percentage of blasts (median - IQR)	**10.0 (7,0-30,0)**
Anti-CD19 therapy	
Blinatumomab	17 (94.4)
Blinatumomab and CD19-CAR-T01 protocol	1 (5.6)
Infusion occurred	
No	3 (12.0)
Yes	22 (88.0)
Treatments with FT card completed	**1 (4.0)**

*For one patient no gender information is available

Table 4.1.18. Centers with at least one patient eligible in the CAR-T registers

Region	Tisagenlecleucel		Axicabtagene ciloleucel	Total	
	LLA	DLBCL	DLBCL	No.	%
Abruzzo	0	0	0	0	0.0
Basilicata	0	0	0	0	0.0
Calabria	0	1	0	1	5.0
Campania	0	0	0	0	0.0
Emilia R.	0	1	1	1	5.0
Friuli VG	0	0	0	0	0,0
Lazio	2	2	1	3	15.0
Liguria	0	1	0	1	5.0
Lombardy	4	4	5	6	30.0
Marche	0	0	0	0	0.0
Molise	0	0	0	0	0.0
Piedmont	1	1	0	2	10.0
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	0	1	1	5.0
Tuscany	1	1	1	3	15.0
Umbria	0	1	0	1	5.0
Valle d'Aosta	0	0	0	0	0.0
Veneto	0	1	1	1	5.0
Total	**8**	**13**	**10**	**20**	**1.0**

Table 4.1.19. Regional distribution of patients in the CAR-T registers divided by eligible and infused patients

Region	Tisagenlecleuce					Axicabtagene ciloleucel		
	DLBLC		LLA		Total infused patients	DLBLC		Total infused patients
	Eligible patients	Infused patients	Eligible patients	Infused patients		Eligible patients	Infused patients	
Abruzzo	-	-	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-	-	-
Calabria	9	6	-	-	6	-	-	-
Campania	-	-	-	-	-	-	-	-
Emilia R.	10	10	-	-	10	12	11	11
Friuli VG	-	-	-	-	-	-	-	-
Lazio	13	10	13	11	21	3	3	3
Liguria	4	2	-	-	2	-	-	-
Lombardy	46	37	9	9	46	41	37	37
Marche	-	-	-	-	-	-	-	-
Molise	-	-	-	-	-	-	-	-
Piedmont	2	-	2	1	1	-	-	-
A.P. of Bolzano	-	-	-	-	-	-	-	-
A.P. of Trento	-	-	-	-	-	-	-	-
Puglia	-	-	-	-	-	-	-	-
Sardinia	-	-	-	-	-	-	-	-
Sicily	-	-	-	-	-	1	1	1
Tuscany	1	1	1	1	2	8	6	6
Umbria	8	7	-	-	7	-	-	-
Valle d'Aosta	-	-	-	-	-	-	-	-
Veneto	4	4	-	-	4	2	2	2
Total	**97**	**77**	**25**	**22**	**99**	**67**	**60**	**60**

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 Registers (*patient level*) and at the level of the entire population (*population level*) through the flows information for monitoring expenditure and consumption by the NHS (i.e. OsMed Flow and Medicine Traceability Flow).

Conditional reimbursement agreements managed through the Registers (*patient level*)

The MEAs managed through the AIFA Registers can be classified, on the basis of an international taxonomy,[3] in two main categories:

1. outcome-based risk sharing agreements (*Performance-based Risk Sharing schemes*);
2. 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 bankruptcy is entirely borne by the pharmaceutical company that owns the medicine), *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 the Monitoring Register.

- 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. The *Capping* model provides that the pharmaceutical company pays therapy costs when the quantities established by the agreement are exceeded. By way of example, it is shown that in the negotiation with pharmaceutical companies the maximum cost of a treatment for the NHS can be fixed, providing for a flat 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 the non-response based on the evidence available from the pivotal clinical trials.

3. Garrison LP Jr et al. Value Health 2013; 16(5): 703-19

SF is useful in the case of high-cost treatments, which involve financial exposure on the part of the healthcare company, only after having achieved therapeutic success. Conceptually identical to the PbR, instead of obtaining reimbursement of the cost of bankruptcy by the pharmaceutical company, with the SF the NHS only remunerates the therapeutic success once obtained. Finally, the recently introduced PaR model for advanced therapy medicines, CAR-T, which is in fact a SF model, provides that 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 31/12/2020) excluding PaR

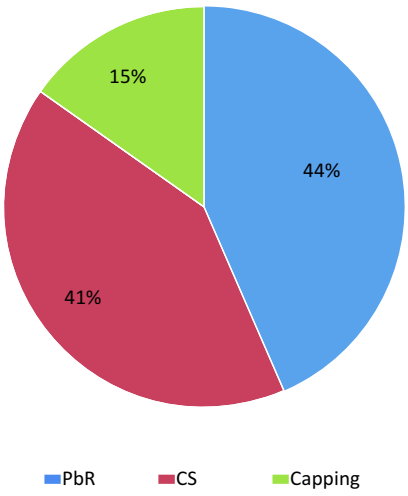


Figure 4.2.1 shows the percentage of each agreement, as of 31/12/2020. The most widely applied agreement is the *Payment by Result*, which in 2020 constitutes all the agreements based on the outcome (44% of the total agreements in force, corresponding to 20 different agreements), with the exception of the PaR agreements which are managed by the Registers platform.
There are no longer any active agreements managed through the Register, neither of *Risk Sharing* nor of *Success Fee*.
Cost Sharing financial agreements (19 agreements equal to 41%) and *Capping* agreements (7 agreements equal to 15%) follow in terms of frequency of application.
Table 4.2.1 shows the reimbursements relating to the MEAs detected by the Registers platform for the three-year period 2018-2020, divided by Region.
73.3% of the reimbursement obtained in 2020 (114,835,024) relates to financial agreements (Figure 4.2.2), with 51.4% of the reimbursement for *Cost Sharing* agreements and 21.9% for *Capping* agreements.

The risk sharing agreements, *Payment by Result* and *Risk Sharing* cover 26.7% of reimbursements, with *Risk Sharing* representing a very small percentage: 0.03%.
The reimbursement percentages by ATC level (Figure 4.2.3) are instead distributed mainly on two categories: 83.5% of the reimbursement for antineoplastic and immunomodulatory medicines (L) and 15.6% for general antimicrobials for systemic use (J). They are followed by sensory organs medicines (S): 0.6% of reimbursement 2020; medicines for the nervous system (N): 0.3%; medicines for the muscular and skeletal system (M): 0.001%.

Table 4.2.1. Reimbursement obtained (€) for MEA online years 2018-2020*

Region	Reimbursement 2018	Reimbursement 2019	Reimbursement 2020
Abruzzo	2,439,266	3,551,689	1,876,868
Basilicata	968,286	1,230,691	2,428,342
Calabria	5,710,372	2,733,155	2,658,502
Campania	15,674,460	15,570,670	12,625,291
Emilia R.	14211105.56	11,425,176	8,328,812
Friuli VG	1,824,346	2,341,654	3,544,962
Lazio	15,664,569	8,383,726	13,956,431
Liguria	5,258,173	3,261,973	3,014,634
Lombardy	19,486,107	20,938,350	16,375,366
Marche	4,118,372	3,766,917	3,270,264
Molise	1,206,557	251,825	407,513
Piedmont	11,077,759	6,346,751	6,885,198
A.P. of Bolzano	1,096,455	1,902,342	790,126
A.P. of Trento	937,169	680,717	978,416
Puglia	13,163,388	7,346,545	8,941,056
Sardinia	11,952,033	2,156,710	3,227,223
Sicily	24,488,257	9,676,137	6,004,371
Tuscany	9,917,783	8,643,847	8,877,098
Umbria	3,001,917	1,169,618	1,318,537
Valle d'Aosta	90899.29	214,841	89,952
Veneto	10,459,210	7,774,687	9,236,063
Total	**172,746,483**	**119,368,022**	**114,835,024**

*Reimbursement reported for 2018, 2019 and 2020 is obtained using data updated to May 2019, 2020 and 2021 respectively

Table 4.2.2. Reimbursements obtained by type of MEA (year 2020)

Region	Capping	Cost Sharing	Payment by Result	Risk Sharing	Total
Abruzzo	266,795	953,872	656,200		1,876,868
Basilicata	1,094,341	901,672	432,329		2,428,342
Calabria	1,175,942	1,148,854	330,884	2,822	2,658,502
Campania	3,646,094	5,725,941	3,253,256		12,625,291
Emilia R.	1,323,948	4,636,446	2,368,417		8,328,812
Friuli VG	950,921	1,309,011	1,285,030		3,544,962
Lazio	6,377,999	4,374,978	3,202,652	802	13,956,431
Liguria	227,324	1,797,988	987,386	1,936	3,014,634
Lombardy	2,151,770	9,693,512	4,528,394	1,689	16,375,366
Marche	392,161	1,866,328	1,011,775		3,270,264
Molise	119,883	238,994	48,636		407,513
Piedmont	694,565	3,667,472	2,518,497	4,665	6,885,198
Molise	109,459	476,069	204,599		790,126
A.P. of Trento	55,200	639,797	283,419		978,416
Puglia	1,847,679	4,687,036	2,381,473	24,868	8,941,056
Sardinia	1,027,169	1,409,928	789,324	802	3,227,223
Sicily	1,306,541	3,240,510	1,457,321		6,004,371
Tuscany	1,324,581	5,312,097	2,240,420		8,877,098
Umbria	241,944	919,069	157,523		1,318,537
Valle d'Aosta	10,044	74,602	5,305		89,952
Veneto	791,794	5,958,199	2,486,070		9,236,063
Total	**25,136,154**	**59,032,377**	**30,628,910**	**37,583**	**114,835,024**

Figure 4.2.2. Reimbursemnt 2020, percentages by type of agreement

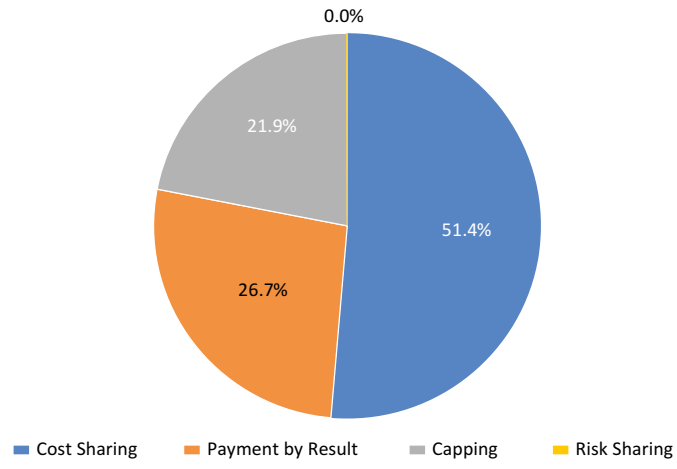
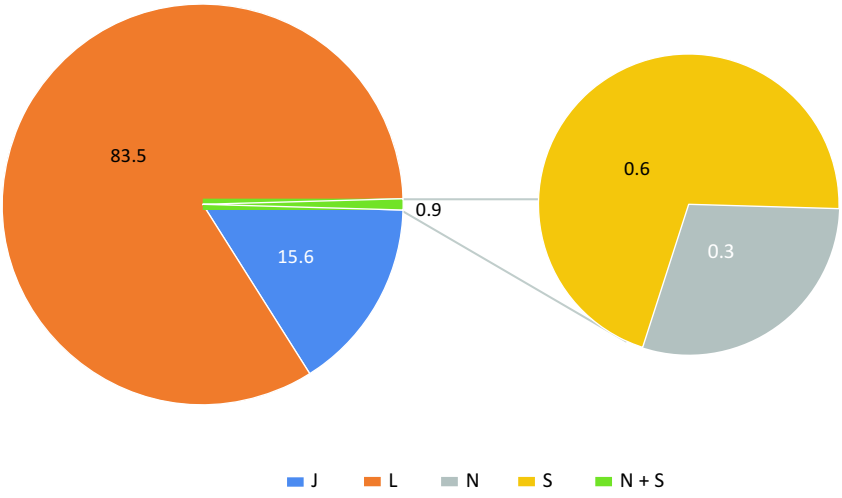


Figure 4.2.3. Reimbursemnt 2020, percentages for ATC level I



Conditional reimbursement agreements managed through information flows for monitoring expenditure and consumption (*population level)*

The agreements managed in a manner other than the Registers 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 expense of 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 on the invoice in favour of the healthcare facilities of the NHS. 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 2020 gave rise to reimbursements by companies for the application of expenditure ceilings and price/volume agreements. The medicines involved were a total of 16 (18 *payback*), for a total of 197.1 million euros (Tables 4.2.4a, 4.2.4b, 4.2.5). In particular, 56.64 million euros were paid by pharmaceutical companies for the application of the expenditure ceilings and the remaining 140.41 million for the application of price/volume agreements. Considering the reimbursement class, € 52.22 million was paid for class A products and € 144.83 million for class H products.

In addition, the *payback* percentage with respect to the expenditure ceiling has been reported in Table 4.2.4c.

Finally, Table 4.2.6 shows the measures that in 2020 gave rise to reimbursements by the companies in application of the "2015 budget law" agreements. The medicines involved were a total of 46, for a total of 31.7 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	Price/volume
Cluviat	(Italian Official Journal General Series n. 89	Expenditure ceiling
Dapagut	(Italian Official Journal General Series n. 69	Expenditure ceiling
Daparox	(Italian Official Journal General Series n. 69	Expenditure ceiling
Darzalex	(Italian Official Journal General Series n. 192 dated 01-08-2020) (Italian Official Journal	Price/volume
Firmagon	(Italian Official Journal General Series n. 130	Expenditure ceiling
Iclusig	(Italian Official Journal General Series n. 183	Expenditure ceiling
Jevtana	(Italian Official Journal General Series n. 30	Expenditure ceiling
Keytruda	(Italian Official Journal General Series n. 80	Price/volume
Luveris	(Italian Official Journal General Series n. 130	Expenditure ceiling
Opdivo	(Italian Official Journal General Series n. 172 dated 10-07-2020) (Italian Official Journal	Price/volume
Oralair	(Italian Official Journal General Series n. 125	Expenditure ceiling
Orkambi	(Italian Official Journal General Series n. 207	Expenditure ceiling
Tagrisso	(Italian Official Journal General Series n. 175	Price/volume
Xadago	(Italian Official Journal General Series n. 175	Expenditure ceiling
Xgeva	(Italian Official Journal General Series n. 112	Expenditure ceiling
Zavicefta	(Italian Official Journal General Series n. 286	Expenditure ceiling
Zerbaxa	(Italian Official Journal General Series n. 305	Expenditure ceiling

Table 4.2.4a. Amounts paid by companies to the Regions in 2020 (class A) - Expenditure ceilings

Region	Dapagu	Daparox	Firmagon	Luveri	Oralair	Orkambi	Xadago	Xgeva	Total
Piedmont	-	87,177	351,711	4,328	20,833	2,555,520	427,506	27,428	3,474,503
Valle d'Aosta	-	2,765	14,808	26	553	41,464	10,746	3	70,364
Lombardy	-	190,713	748,446	28,843	58,115	4,679,851	920,049	53,675	6,679,693
A.P. of	-	3,059	2,765	78	5,659	-	15,440	5,306	32,306
A.P. of Trento	-	8,388	66,975	100	2,388	944,984	33,543	2,220	1,058,599
Veneto	-	72,556	333,522	1,489	26,774	2,467,185	413,223	11,949	3,326,700
Friuli VG	-	22,943	75,442	63	2,836	261,731	97,150	4,024	464,189
Liguria	-	69,710	75,170	1,266	1,047	745,531	182,179	7,518	1,082,421
Emilia R.	-	101,454	87,930	7,050	22,644	2,713,675	203,863	17,106	3,153,721
Tuscany	-	133,346	376,401	5,205	8,750	1,915,535	407,555	7,068	2,853,861
Umbria	-	15,738	12,700	746	5,624	656,703	91,306	164	782,981
Marche	-	32,704	158,776	1,093	6,399	965,306	144,762	11,569	1,320,611
Lazio	-	118,584	546,202	11,996	14,947	2,330,338	840,425	25,422	3,887,914
Abruzzo	-	26,565	189,336	1,007	8,143	899,587	323,792	13,176	1,461,605
Molise	-	6,508	98,993	347	1,312	63,261	51,285	4,877	226,583
Campania	-	83,560	945,954	9,733	4,124	3,534,595	469,407	63,735	5,111,109
Puglia	-	113,463	703,526	3,432	15,187	2,959,672	468,226	42,262	4,305,768
Basilicata	-	12,518	51,690	706	4,688	766,673	61,682	3,253	901,209
Calabria	-	59,679	514,266	1,391	16,507	835,179	215,770	16,004	1,658,795
Sicily	-	74,171	857,087	3,164	6,701	2,763,005	265,992	31,029	4,001,149
Sardinia	-	24,765	338,048	1,325	33	652,770	146,969	12,501	1,176,411
Italy	**-**	**1,260,364**	**6,549,748**	**83,389**	**233,265**	**32,752,565**	**5,790,872**	**360,288**	**47,030,491**

Table 4.2.4b. Amounts paid by companies to the Regions in 2020 (class H) - Expenditure ceilings

Region	Cluviat	Iclusig	Jevtana	Zavicefta	Zerbaxa	Total
Piedmont	3,836	139,533	28,469	131,408	520,661	823,907
Valle d'Aosta	-	1,744	1,908	5,688	6,600	15,940
Lombardy	10,260	325,019	42,284	126,306	626,434	1,130,303
A.P. of Bolzano	-	42,209	3,129	1,129	32,998	79,466
A.P. of Trento	1,985	-	3,893	1,882	16,767	24,527
Veneto	14,736	124,324	36,865	99,748	433,438	709,111
Friuli VG	-	57,278	6,488	14,471	409,892	488,129
Liguria	277	6,279	11,983	60,237	344,253	423,029
Emilia R.	23,279	181,253	36,560	83,353	410,785	735,230
Tuscany	4,208	103,045	18,852	105,980	407,574	639,660
Umbria	-	36,627	3,893	68,632	224,567	333,719
Marche	2,595	60,348	9,464	43,412	132,529	248,348
Lazio	10,766	208,880	18,623	325,688	455,377	1,019,335
Abruzzo	-	65,511	7,251	20,702	94,714	188,178
Molise	-	698	1,069	2,426	14,983	19,175
Campania	-	243,206	44,421	123,880	367,620	779,127
Puglia	1,160	218,718	35,797	94,855	247,399	597,928
Basilicata	-	41,092	3,816	18,611	46,198	109,718
Calabria	-	131,231	14,807	36,470	131,458	313,966
Sicily	-	241,810	29,843	118,318	453,950	843,922
Sardinia	-	11,023	9,846	14,387	59,394	94,650
Italy	**73,102**	**2,239,827**	**369,263**	**1,497,584**	**5,437,591**	**9,617,367**

Table 4.2.4c. Comparison between the amounts paid by companies to the Regions in 2020 with respect to the negotiated expenditure ceiling

Medicine	Amont paid	Expenditure ceiling	Weight of payback on the expenditure ceiling (%)
Jevtana	369,263	15,000,000	2
Daparox Dapagut	1,260,364	10,200,000	12
Cluviat	73,102	800,000	9
Xgeva	360,288	25,000,000	1
Oralair	233,265	2,800,000	8
Firmagon	6,549,748	7,250,000	90
Luveris	83,389	1,300,000	6
Xadago	5,790,872	6,000,000	97
Iclusig	2,239,827	15,000,000	15
Orkambi	32,752,565	33,000,000	99
Zavicefta	1,497,584	25,000,000	6
Zerbaxa	5,437,591	16,000,000	34

Table 4.2.5. Amounts paid by companies to the Regions in 2020 (class A) - Price/volume agreements (class A and H)

Region	Brintellix	Darzalex	Keytruda	Opdivo	Tagrisso	Total
Piedmont	246,393	2,369,413	3,197,441	3,448,160	437,855	9,699,261
Valle d'Aosta	14,264	-	71,858	72,093	4,759	162,973
Lombardy	691,926	5,972,109	5,815,980	7,005,894	1,333,889	20,819,798
A.P. of Bolzano	43,064	361,027	456,592	483,009	62,823	1,406,515
A.P. of Trento	46,984	167,941	283,968	247,998	64,727	811,619
Veneto	247,706	3,452,217	2,230,026	2,940,792	615,855	9,486,597
Friuli VG	84,837	652,920	1,255,705	999,905	202,747	3,196,114
Liguria	207,928	1,117,950	1,756,515	1,606,809	208,458	4,897,660
Emilia R.	165,830	3,089,809	4,208,332	4,296,957	791,950	12,552,878
Tuscany	379,860	2,318,020	3,222,416	4,040,692	463,672	10,424,660
Umbria	93,495	565,662	934,903	850,753	60,934	2,505,747
Marche	139,157	537,147	1,615,054	1,100,434	212,266	3,604,058
Lazio	557,606	3,647,769	5,448,951	5,658,555	481,656	15,794,536
Abruzzo	253,147	470,114	927,391	1,091,591	158,961	2,901,204
Molise	43,708	109,363	63,009	280,299	20,941	517,320
Campania	660,528	2,833,835	3,554,728	6,707,733	397,879	14,154,702
Puglia	359,817	2,009,160	3,274,001	3,450,318	350,286	9,443,582
Basilicata	42,105	311,899	335,860	455,658	28,556	1,174,077
Calabria	253,872	596,940	777,931	1,542,345	91,379	3,262,467
Sicily	473,694	2,010,432	2,629,939	3,848,915	393,120	9,356,099
Sardinia	187,417	894,028	1,199,718	1,840,412	117,287	4,238,862
Italy	**5,193,337**	**33,487,774**	**43,260,318**	**51,969,321**	**6,500,000**	**140,410,750**

Table 4.2.6. List of medicines subject to the payback mechanism for the application of expenditure ceilings and "2015 budget law" agreements

Medicine	Italian Official Journal (IOJ)
Accuretic	IOJ General Series n. 130 of 21-5-2020 and IOJ General Series n. 311 of 16-12-2020*
Alendros	IOJ General Series n. 171 of 9-7-2020
Aprovel	IOJ General Series n. 81 of 05-04-2019
Atimos	IOJ General Series n. 81 of 05-04-2019
Bonviva	IOJ General Series n. 81 of 05-04-2019
Cedravis	IOJ General Series n. 79 of 25-3-2020
Cipralex	IOJ General Series n. 81 of 05-04-2019
Clexane	IOJ General Series n. 81 of 05-04-2019
Coaprovel	IOJ General Series n. 81 of 05-04-2019
Dumirox	IOJ General Series n. 81 of 05-04-2019
Elopram	IOJ General Series n. 79 of 25-3-2020
Enapren	IOJ General Series n. 81 of 05-04-2019
Entact	IOJ General Series n. 79 of 25-3-2020
Fevarin	IOJ General Series n. 81 of 05-04-2019
Fluxum	IOJ General Series n. 81 of 05-04-2019
Formodual	IOJ General Series n. 34 of 11-02-2020 and IOJ General Series n. 311 of 16-12-2020*
Forzaar	IOJ General Series n. 81 of 05-04-2019
Fosamax	IOJ General Series n. 81 of 05-04-2019
Foster	IOJ General Series n. 34 of 11-02-2020 and IOJ General Series n. 311 of 16-12-2020*
Goltor	IOJ General Series n. 81 of 05-04-2019
Gopten	Italian Official Journal General Series n. 81 dated 05-04-2019
Hizaar	IOJ General Series n. 81 of 05-04-2019
Inuver	IOJ General Series n. 34 of 11-02-2020 and IOJ General Series n. 311 of 16-12-2020*
Ivor	IOJ General Series n. 128 of 19-05-2020
Karvea	IOJ General Series n. 81 of 05-04-2019
Karvezide	IOJ General Series n. 81 of 05-04-2019
Liferol	IOJ General Series n. 81 of 05-04-2019
Lortaan	IOJ General Series n. 81 of 05-04-2019
Maveral	IOJ General Series n. 81 of 05-04-2019
Medeoros	IOJ General Series n. 213 of 27-8-2020
Mepral	IOJ General Series n. 32 of 8-2-2020
Micardis	IOJ General Series n. 175 of 14-7-2020
Micardisplus	IOJ General Series n. 175 of 14-7-2020
Recombinate	IOJ General Series n. 81 of 05-04-2019
Seledie	IOJ General Series n. 175 of 14-07-2020
Seleparina	IOJ General Series n. 175 of 14-07-2020
Seropram	IOJ General Series n. 79 of 25-3-2020
Sinertec	IOJ General Series n. 81 of 05-04-2019
Sinvacor	IOJ General Series n. 81 of 05-04-2019
Triatec	IOJ General Series n. 81 of 05-04-2019
Triatec hct	IOJ General Series n. 81 of 05-04-2019
Urorec	IOJ General Series n. 81 of 05-04-2019
Vasoretic	IOJ General Series n. 81 of 05-04-2019
Zinadiur	IOJ General Series n. 38 of 15-02-2020
Zinadril	IOJ General Series n. 38 of 15-02-2020
Zoton	IOJ General Series n. 130 of 21-5-2020 and IOJ General Series n. 311 of 16-12-2020*

*Determination of adjustment

Table 4.2.7. Amounts paid by companies to the Regions in 2020 for the application of the "2015 budget law" agreements

Region	Payback per 2015 budget law
Piedmont	2,254,741
Valle d'Aosta	57,755
Lombardy	5,004,070
A.P. of Bolzano	168,910
A.P. of Trento	196,939
Veneto	2,125,813
Friuli VG	552,236
Liguria	806,562
Emilia R.	1,754,482
Tuscany	2,145,928
Umbria	493,153
Marche	794,154
Lazio	3,785,986
Abruzzo	658,391
Molise	188,365
Campania	3,371,109
Puglia	2,177,104
Basilicata	353,701
Calabria	1,176,045
Sicily	2,779,624
Sardinia	916,332
Total	**31,761,401**

In 2020, the total reimbursements obtained by pharmaceutical companies following the application of the MEAs, both managed through the registers and through monitoring flows, amounted to € 343.7 million (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 (66.6%).
The *payback* paid by companies for the application of the MEAs affect the pharmaceutical expenditure of the NHS in 2020 by 1.5%; if we consider the *payback* relating to drugs purchased mainly from public health facilities, the incidence on direct purchases is 2.2%. Reimbursements have an impact of approximately 11% on the overrun of direct purchase expenditure recorded for the year 2020. In the overall evaluation of efficacy of MEAs it is important to take into consideration the impact (not easily quantifiable) of the appropriateness of use of medicines ensured by the Registers, which allow to dispense medications to patients for whom treatment efficacy was highly demonstrated during the authorisation process.
Furthermore, it is important to emphasise that as regards the evaluation of the effectiveness of the agreements based on the outcomes, it is not enough to take into account the reimbursements obtained, as the latter are linked to treatment failures. In fact, an optimisation of the definition of the eligibility form allows to reduce the failure rate detected through the Registers and therefore the amount of reimbursememt obtainable.

Table 4.2.8. Impact of MEAs on pharmaceutical expenditure and expenditure overrun in 2020

	2020
MEA reimbursements managed by the Registers	114,835,024
MEA reimbursements managed through monitoring flows	228,820,009
MEA reimbursements managed through monitoring flows of exp.under appr.care reg.	43,251,664
MEA reimbursements managed through direct purchase monitoring flows	185,568,345
Total reimbursements	**343,655,033**
Impact of MEAs managed by the Registers on NHS expenditure (%)	0.5
Impact of MEAs managed by the Registers on direct purchase expenditure (%)	0.8
Impact of MEAs managed through monitoring flows on NHS expenditure (%)	1.0
Impact of MEAs managed through monitoring flows on expend. under appr. care regime (%)	0.4
Impact of MEAs managed through monitoring flows on direct purchases (%)	1.4
Total impact of MEAs (managed by the Registers and through monitoring flows) on NHS expenditure (%)	1.5
Total impact of MEAs (managed by the Registers and through monitoring flows) on direct purchases (%)*	2.2
Inc.% on overrun	11.1

*Excluding reimbursements that are provided under approved care regime

Section 5

Orphan medicines

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.

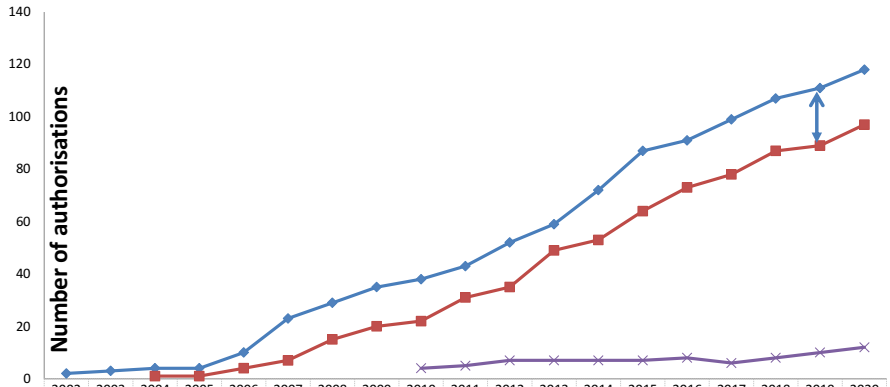
In 2020, the EMA granted authorisation for a total of 20 new orphan medicines while AIFA made 18 available. The main therapeutic areas of medicines authorised under the centralised procedure by the EMA were antineoplastic agents (pretomanid [Dovprela], obiltoxaximab [Obiltoxaximab SFL], amikacin sulphate [Arikayce liposomal] and bulevirtide [Hepcludex]), haematology (crizanlizumab [Adakveo], luspatercept [Reblozyl] and treprostinil [Trepulmix]) and finally neurology (fenfluramine [Fintepla] and atidarsagene autotemcel [Libmeldy]).

As of 31 December 2020, out of a total of 118 orphan medicines authorised by the EMA (Figure 5.2.1 and Figure 5.2.2), 97 were available in Italy of which:
• 17 (17.5%) in class A;
• 58 (59.8%) in class H;
• 12 (12.4%) in class C;
• 10 (10.3%) in class C-NN;

Of the 21 medicines not marketed in 2020:
• 5 were marketed starting from 2021;
• 12 are in the phase of definition of price and reimbursement;
• 4 were not the subject of an application by the manufacturing companies for price and reimbursement.

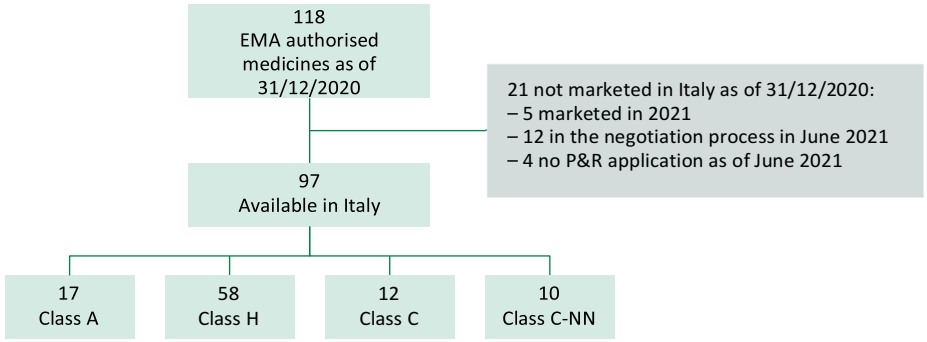
The 5 medicines marketed starting from 2021 are: Givlaari, Luxturna, Palynziq, Waylivra and Zolgensma.
Interestingly, 52% of the medicines included in AIFA's orphan list is subject to a Monitoring Register and 12% of the orphan drugs in the price and reimbursement phase have a *Managed Entry Agreement* (MEA) applied which can be either a financial agreement or an outcome-based agreement. Moreover, about 15% of medicines also obtained the innovativeness requirement (7 innovative oncological medicines and 4 innovative non-oncological medicines).

Figure 5.2.1. Comparison between medicines authorised with EMA centralised procedure and available in Italy (cumulative data 2002-2020)



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
EMA	2	3	4	4	10	23	29	35	38	43	52	59	72	87	91	99	107	111	118
AIFA			1	1	4	7	15	20	22	31	35	49	53	64	73	78	87	89	97
EMA-AIFA difference	2	3	3	3	6	16	14	15	16	12	17	10	19	23	18	21	20	22	21
AIFA - class C									4	5	7	7	7	7	8	6	8	10	12

Figure 5.2.2. Comparison between number of orphan medicines authorised with EMA and AIFA centralised procedure as of 31 December 2020



Expenditure and consumption of orphan medicines

Table 5.2.1. Expenditure and consumption trend (agreed and direct purchases) for orphan medicines, years 2013-2020 in reimbursement class A-SSN, H-SSN and C

Year	2013	2014	2015	2016	2017	2018	2019	2020
Expenditure for orphan medicines (million)	608.9	716.2	822.2	947.6	1,022.7	1,306.9	1,554.9	1,393.4
Incidence (%) of orphan medicines on pharmaceutical expenditure	6.4	7.1	6.7	4.2	4.5	5.8	6.8	6.0
Incidence (%) orphan direct purchase expenditure vs orphan total expenditure	100.0	100.0	100.0	99.7	99.6	99.7	99.9	100.0
Incidence % orphan medicines class C on orphan medicines total expenditure	2.0	0.7	0.9	0.5	0.4	0.3	0.3	0.1
Consumption (DDD) orphan medicines (million)	5.6	6.1	6.7	7.0	7.2	8.8	10.1	8.0
Incidence (%) of orphan medicines on consumption (Osmed+Traccia)	0.002	0.002	0.003	0.028	0.029	0.035	0.040	0.032
Incidence % orphan medicines class C on orphan medicines total consumption	1.2	0.1	0.1	0.8	0.6	0.9	1.3	1.4

The expenditure for orphan medicines, including the purchase by public health structures and the provision under the agreed assistance regime, was approximately 1.4 billion euros in 2020 (-10.4% compared to 2019), corresponding to 6.0% of the pharmaceutical expenditure borne by the NHS. The incidence % on the expenditure for class C orphan medicines is equal to 0.1%, showing a decrease over the years (it was 1.95% in 2013). Consumption of orphan medicines amounted to 8.0 million DDD (-2.1 million compared to the previous year), corresponding to 0.032% of the total consumption of medicines. The incidence % on the consumption of class C orphan medicines was 1.4% in 2020, showing an increase compared to 2019 when an incidence of 1.3% was recorded (Table 5.2.1).

Table 5.2.2. Consumption and expenditure (agreed and direct purchases) for orphan medicines by Region in 2020

Region	Expenditure *(million)*	DDD *thousand*	Inc.% expenditure*	% purchases direct	Per capita expenditure	Δ % 20-19	DDD/1000 inhab per day	Δ % 20-19
Piedmont	103.8	632.1	7.4	100.0	22.92	-10.3	0.4	180.8
Valle d'Aosta	1.4	9.6	0.1	100.0	11.03	-24.4	0.2	166.4
Lombardy	219.2	1141.5	15.7	99.8	21.98	-7.7	0.3	179.9
A.P. of	12.9	74.8	0.9	100.0	25.88	-11.8	0.4	183.6
A.P. of Trento	8.8	52.8	0.6	100.0	16.44	-18.9	0.3	176.5
Veneto	115.0	623.0	8.3	100.0	23.41	-10.3	0.3	177.6
Friuli VG	29.5	168.2	2.1	99.9	22.98	-17.0	0.4	173.9
Liguria	43.2	240.0	3.1	100.0	25.59	-6.0	0.4	180.6
Emilia R.	119.9	652.6	8.6	100.0	26.36	-8.7	0.4	181.0
Tuscany	98.5	554.1	7.1	100.0	25.48	-5.6	0.4	183.4
Umbria	26.3	151.4	1.9	99.9	28.85	-10.3	0.5	175.3
Marche	40.8	265.9	2.9	100.0	26.11	-13.0	0.5	179.7
Lazio	127.4	780.3	9.1	100.0	22.43	-11.8	0.4	179.0
Abruzzo	28.5	205.2	2.0	100.0	21.59	-13.6	0.4	178.9
Molise	5.7	35.8	0.4	100.0	18.27	-28.7	0.3	169.8
Campania	123.1	740.8	8.8	100.0	23.39	-10.4	0.4	176.3
Puglia	111.0	638.7	8.0	100.0	28.59	-8.1	0.5	181.1
Basilicata	12.1	78.4	0.9	100.0	21.82	-18.3	0.4	174.5
Calabria	40.9	232.4	2.9	100.0	22.22	-16.8	0.3	172.6
Sicily	90.8	546.6	6.5	100.0	19.34	-14.1	0.3	181.2
Sardinia	34.7	206.6	2.5	100.0	20.84	-1.3	0.3	183.8
Italy	**1,393.4**	**8,031.0**	**100.0**	**100.0**	**23.36**	**-10.1**	**0.4**	**179.4**
North	653.7	3594.7	46.9	99.9	23.27	-9.4	0.4	179.6
Centre	292.9	1751.7	21.0	100.0	24.37	-9.9	0.4	180.1
South and	446.7	2684.6	32.1	100.0	22.87	-11.3	0.4	178.6

* Calculated on the total expenditure of orphan medicines nationwide

In terms of DDD, in 2020 there is a greater consumption of orphan medicines in the Northern Regions, and consequently also a greater absolute expenditure. The Regions with the highest per capita expenditure are Umbria and Puglia with an expenditure, respectively, of 28.85 euros and 28.59 euros compared to the national average of 23.36 euros, while the Regions with the lowest expenditure are Valle d'Aosta and A.P. of Trento with an expenditure of 11.03 and 16.44 euros respectively (Table 5.2.2).

Also for class C orphan medicines, there is a higher consumption and consequently a higher expenditure in the Northern Regions. As regards expenditure per 100 inhabitants, overall the central and the northern Regions have higher values than the Italian average, while only the southern Regions have per capita values below the average.

As for expenditure per 100 inhabitants, the highest value is observed in Valle d'Aosta with a value of 10.94 euros compared to the national average of 3.04 euros, while Sardinia is the Region with the lowest per capita expenditure, equal to 0.72 euros (Table 5.2.3).

Table 5.2.3. Consumption and expenditure (agreed and direct purchases) for class C orphan medicines by Region in 2020

Region	DDD *thousand*	Expenditure *thousand*	Expenditure per 100 inhab	Inc. % on consumption	Inc. % on expenditure
Piedmont	10.5	126.1	2.78	0.001	0.008
Valle d'Aosta	0.9	14.0	10.94	0.002	0.037
Lombardy	24.1	487.6	4.89	0.001	0.013
A.P. of Bolzano	1.6	17.7	3.55	0.001	0.011
A.P. of Trento	1.7	18.5	3.45	0.001	0.011
Veneto	9.6	111.2	2.26	0.000	0.007
Friuli VG	1.9	22.2	1.73	0.000	0.005
Liguria	3.4	67.3	3.99	0.001	0.011
Emilia R.	11.8	148.9	3.27	0.001	0.009
Tuscany	10.0	121.0	3.13	0.001	0.008
Umbria	3.4	38.4	4.21	0.001	0.010
Marche	3.4	45.6	2.92	0.000	0.007
Lazio	19.9	241.6	4.25	0.001	0.010
Abruzzo	3.3	36.9	2.80	0.001	0.007
Campania	9.8	116.3	2.21	0.000	0.005
Puglia	6.4	77.1	1.99	0.000	0.005
Basilicata	1.8	16.8	3.03	0.001	0.007
Calabria	0.5	25.6	1.39	0.000	0.003
Sicily	6.2	70.1	1.49	0.000	0.004
Sardinia	1.1	12.0	0.72	0.000	0.002
Italy	**131.5**	**1,814.9**	**3.04**	**0.001**	**0.008**
North	65.6	1,013.5	3.61	0.001	0.010
Centre	36.8	446.6	3.72	0.001	0.009
South and Islands	29.1	354.8	1.82	0.000	0.004

Table 5.2.4. Expenditure and consumption for the first 30 orphan medicines in descending order of expenditure: comparison years 2019-2020

Rank	Active substance	Consumption (DDD *thousand*)	Δ % 20-19	Expenditure (*million*)	Δ % 20-19	Inc. % on consumption	Inc.% expenditure	% direct purchases
1	daratumumab	1,131.5	35.0	211	35.0	13.3	14.7	100.0
2	ibrutinib	1,312.5	29.3	170	29.1	15.4	11.9	100.0
3	eculizumab	152.7	11.6	118	5.8	1.8	8.2	100.0
4	nusinersen	219.5	-9.5	93	-9.3	2.6	6.5	100.0
5	nintedanib	838.8	20.4	65	22.7	9.9	4.5	100.0
6	pirfenidone	940.0	7.7	61	7.7	11.0	4.2	100.0
7	macitentan	634.5	7.9	56	6.0	7.5	3.9	100.0
8	pomalidomide	171.4	14.1	51	10.2	2.0	3.5	100.0
9	albutrepenonacog alfa	39.7	8.8	43	8.8	0.5	3.0	99.9
10	ivacaftor	61.5	32.3	42	39.6	0.7	2.9	100.0
11	carfilzomib	261.4	3.1	36	3.1	3.1	2.5	100.0
12	brentuximab vedotin	102.9	14.4	30	-1.4	1.2	2.1	100.0
13	niraparib	130.2	35.2	26	34.9	1.5	1.8	100.0
14	ponatinib	93.2	10.3	22	6.7	1.1	1.5	100.0
15	sorafenib	175.0	-0.4	21	2.4	2.1	1.5	100.0
16	migalastat	42.8	57.7	20	57.4	0.5	1.4	100.0
17	letermovir	50.0	87.7	19	73.7	0.6	1.3	100.0
18	decitabine	29.8	-3.1	18	-3.4	0.4	1.2	100.0
19	ataluren	10.9	28.1	17	24.9	0.1	1.2	100.0
20	eftrenonacog alfa	25.5	11.2	17	10.5	0.3	1.2	100.0
21	eliglustat	26.9	40.6	17	40.6	0.3	1.2	100.0
22	velaglucerasi alfa	15.4	6.3	16	1.6	0.2	1.1	100.0
23	midostaurin	29.4	25.1	16	25.1	0.3	1.1	100.0
24	elosulfase alfa	5.1	-1.6	15	-1.6	0.1	1.1	100.0
25	lutezio (177lu) oxodotreotide	0.9	>100	15	>100	0.0	1.1	100.0
26	blinatumomab	7.3	27.4	14	18.0	0.1	1.0	100.0
27	isavuconazole	127.7	22.2	14	23.9	1.5	1.0	99.8
28	tafamidis	48.8	-8.6	13	-8.8	0.6	0.9	100.0
29	obinutuzumab	203.8	78.7	13	70.7	2.4	0.9	100.0
30	tisagenlecleucel	0.1	>100	13	>100	0.0	0.9	100.0
	Total first 30	**6,889.4**	**19.2**	**1,281**	**18.4**	**81.0**	**89.2**	**100.0**

The main active ingredients with the greatest consumption and expenditure in 2020 are daratumumab and ibrutinib with an increase, respectively, of expenditure of 35.0% and 29.3% and consumption of 35.0% and 29.1%. Tisagenlecleucel, the CART-T indicated in pediatric and young adult patients up to 25 years of age with acute lymphoblastic leukemia (ALL) and in adult patients with diffuse large B-cell lymphoma (DLBCL), records the largest variance in consumption and expenditure, together with Lutetium (177lu) oxodotreotide, a radiopharmaceutical authorised for the treatment of gastroenteropancreatic neuroendocrine tumors (NET-GEP). Both medicines were marketed starting in 2019 (Table 5.2.4).

Table 5.2.5. 2020 regional rank of the first 30 orphan medicines by expenditure in class A-SSN and H-SSN

Rank Italy	Active substance	Piedmont	Valle d'Aosta	Lombardy	PA Bolzano	A.P. of Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Calabria	Sicily	Sardinia
1	daratumumab	1		1	1	2	1	2	1	1	1	2	2	1	3	2	1	1	1	3	1	1
2	ibrutinib	3	8	2	2	1	2	1	2	2	2	1	1	2	1	3	2	2	2	2	2	3
3	eculizumab	2	1	3	3	3	4	3	3	3	3	4	3	6	2	1	3	5	3	4	6	2
4	nusinersen	4		4	5	5	3	4	9	6	8	3	4	3	8	4	4	3	17	6	4	9
5	nintedanib	7	5	7	6	6	9	10	5	8	7	5	5	4	4	5	5	7	5	8	7	8
6	pirfenidone	5	2	8	13	8	18	12	7	7	5	6	6	5	5	7	6	9	7	5	5	5
7	macitentan	8	4	5	4	7	7	6	6	4	6	12	7	13	6	6	18	4	6	7	11	4
8	pomalidomide	6		10	7	18	5	7	10	5	4	14	8	8	10	13	10	10	12	11	8	6
9	albutrepenonacog alfa	14		6			8	5	4	9	9	26	10	10	7		11	6		17	19	37
10	ivacaftor	15		16	9	15	26	17	14	11	15	10	32	7	19		7	8	4	1	3	16
11	carfilzomib	9	10	11	8	20	10	18	12	12	10	18	19	20	13	20	12	11	8	9	9	7
12	brentuximab vedotin	13	19	18	14	17	6	13	11	10	19	9	13	11	12	8	8	14	14	20	13	14
13	niraparib	17	6	17	10	14	11	9	17	13	13	21	16	9	14	15	20	12	27	16	14	17
14	ponatinib	18	9	23	12	30	21	15	26	17	20	23	17	15	11	12	17	13	11	10	10	31
15	sorafenib	20	21	15	16	13	15	14	30	14	16	29	15	29	18	10	15	33	13	22	20	11
16	migalastat	12	3	14			24	27		26	14	16		14		11	9	32		13	16	15
17	letermovir	27		12	19		36	8	18	19	17	15	12	17	22	24	33	21	31	29	29	19
18	decitabine	24		31	26	22	16	11	24	24	12	31	20	33	23	23	19	19	9	15	22	22
19	ataluren	19		28			12	25	16	16	42		9	28	24		16	27	39	19	31	
20	eftrenonacog alfa	10		20			34		8	37	23	46	33	23	9		24	15	19	60	15	
21	eliglustat	16		21	20	9	14	20	36	18	21	19		16	51		39	41	20	35	18	12
22	velaglucerasi alfa	46		30	15	10	29	42	49	36	22	7	11	34			13	16		14	17	13
23	midostaurin	11		24	17	11	20	36	22	20	29	17	14	22	45		28	17	33	52	33	35
24	elosulfase alfa	22	20	29		4	51			25	11	8	18	42			21	46	10	12	21	26
25	lutezio (177lu) oxodotreotide	29		13			13		40	15	27		43	24			25	53	18		24	
26	blinatumomab	23		27	11		23	21	25	22	32	20	21	19	33		23	30		24	32	25
27	isavuconazole	25	18	19	28	29	19	23	20	35	31	13	25	18	17	17	26	45	38	26	40	41
28	tafamidis	28		26			44	46	19	21	25		30	12	21	9	30	20		34	23	36
29	obinutuzumab	26		38	31	31	22	29	33	30	26	22	23	26	15		14	26	25	25	25	27
30	tisagenlecleucel	33		9			39		31	31	34	11		31			38	37		18	41	

Analysing the first 30 orphan molecules by expense, a different behaviour is observed among the different Regions. Almost all of them have one or more molecules with higher expenditure values than the Italian average. The most significant cases concern the active ingredients eftrenonacog alfa and midostaurin which in the Calabria Region have respectively rank 60 compared to rank 20 of the Italian average and rank 52 compared to rank 23 of the Italian average, thus generating a lower expenditure (Table 5.2.5).

Table 5.2.6. 2020 regional rank of the first 30 orphan medicines by consumption in class A-SSN and H-SSN

Rank Italy	Active substance	Piedmont	Valle d'Aosta	Lombardy	A.P of Bolzano	A.P. of Trento	Veneto	Friuli VG	Liguria	Emilia R.	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Calabria	Sicily	Sardinia
1	ibrutinib	1	7	1	2	1	1	1	1	1	1	1	3	1	3	3	4	1	1	2	1	3
2	daratumumab	2		2	1	2	2	2	2	2	2	3	5	2	5	2	2	3	2	5	4	1
3	pirfenidone	3	1	3	5	3	6	7	4	4	3	4	2	4	1	1	3	4	5	1	2	2
4	nintedanib	5	4	5	4	4	4	5	3	5	4	2	1	3	2	4	5	5	4	3	5	5
5	hydrocortisone	4	6	9	14	9	5	4	6	6	7	5	6	5	4	6	1	6	3	6	3	7
6	macitentan	6	2	4	3	5	3	3	5	3	5	6	4	7	6	5	7	2	6	4	7	4
7	carfilzomib	8	9	7	6	16	8	16	8	7	6	12	13	13	8	19	8	8	7	7	6	6
8	nusinersen	13		6	11	12	7	9	19	12	14	8	7	6	19	10	11	9	23	10	10	12
9	obinutuzumab	11		15	20	26	10	12	11	13	9	7	10	10	7		6	10	14	11	8	13
10	riociguat	7		8	7	11	12	8	9	36	10	15	18	11	15	9	10	7	24	8	9	11
11	sorafenib	14	21	11	10	7	11	11	20	8	13	20	9	18	11	7	9	19	8	17	11	8
12	pomalidomide	10		14	13	22	9	14	12	9	8	17	12	14	16	18	14	11	15	14	12	9
13	eculizumab	9	5	12	8	13	17	13	10	10	11	14	11	19	10	8	12	16	9	12	16	10
14	pitolisant	15	3	13	9	8	18	21	16	14	12	11	16	8	13		17	22	10	33	18	19
15	niraparib	17	10	16	12	14	15	10	15	11	15	18	14	12	14	20	18	12	25	15	14	16
16	isavuconazole	16	18	10	17	19	14	15	18	19	16	9	19	9	9	13	13	32	30	16	32	28
17	brentuximab vedotin	19	19	20	16	20	13	19	13	15	24	13	17	16	18	11	15	17	18	20	17	14
18	ketoconazole	12		18		33	20	6	7	21	27	10	8	28	12	27	29	24		30	33	24
19	ponatinib	20	11	21	15	28	22	18	29	17	20	21	15	21	17	14	16	13	13	13	13	25
20	obeticholic acid	18	16	17	19	15	23	22	14	16	19	16	26	15	21	16	25	14	16	18	20	15
21	sapropterin	34		27	30	10	16	17	28	18	29		22	22	22	21	24	18	19	19	19	
22	ivacaftor	28		30	18	29	38	29	27	23	31	22	37	20	31		20	15	11	9	15	27
23	ixazomib	21		22	28		24	26	17	33	17	24	38	25	27	22	23	20	12	23	21	21
24	pasireotide	23	12	29	24	17	19	27	22	29	23	19	23	24	20	17	21	30	20	32	23	31
25	letermovir	29		19	21		32	20	21	24	25	32	20	23	24	24	31	27	31	26	26	22
26	tafamidis	26		26			39	41	23	20	28		30	17	23	12	26	26		31	22	36
27	migalastat	24	8	25			34	32		31	30	23		26		15	19	37		21	25	18
28	albutrepenonacog alfa	32		24			27	24	25	22	26	38	27	32	26		30	23		29	35	44
29	decitabine	30		36	33	31	28	23	34	32	22	33	29	37	33	26	27	33	17	22	31	29
30	midostaurin	22		32	25	23	33	38	30	27	35	27	24	30	45		35	31	34	55	36	41

The first active substances for consumption were ibrutinib, daratumumab and pirfenidone with moderate variability in regional ranks (Table 5.2.6). In 2020, expenditure for orphan medicines also meeting the innovation requirement amounted to 373.2 euros million, an increase compared to 2019 in which the expenditure was equal to 296.3 million euros, in line with the increase in consumption (Table 5.2.7). The number of innovative orphan medicines increased from 8 in 2018 and 9 in 2019 to 11 in 2020.
Of these innovative orphan medicines, daratumumab and nusinersen are also among the top 30 most expensive orphan medicines, ranking first and fourth respectively.

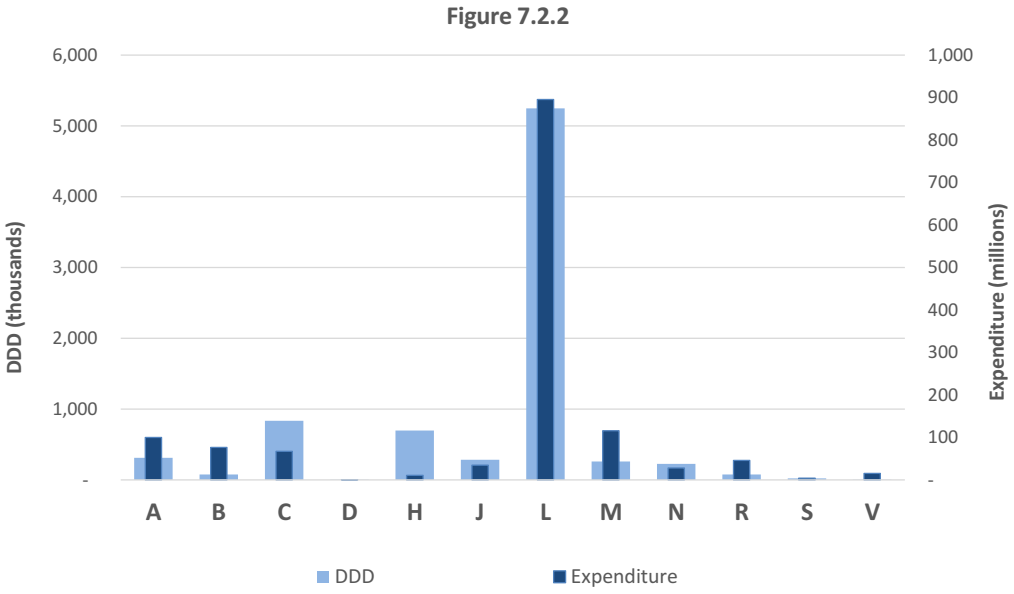
Table 5.2.7. Orphan medicines accessing the fund for oncology and non-oncology innovative medicines: expenditure and consumption, years 2018-2020 (direct purchases)

Active substance	Expend 2018	Expend 2019	Expend 2020	DDD 2018	DDD 2019	DDD 2020
axicabtagene ciloleucel	-	-	3.3	-	-	0.1
cenegermin	3.6	4.0	2.8	13.1	15.2	11.0
citarabine/daunorubicine	-	2.4	8.6	-	0.6	2.3
daratumumab	58.3	156.3	211.0	312.1	838.4	1,131.5
dinutuximab beta	-	3.2	4.8	-	0.9	1.3
ibrutinib	111.6	-	-	757.2	-	-
ivacaftor	11.1	-	-	16.5	-	-
letermovir	0.0	10.8	18.7	-	26.7	50.0
lutezio (177lu) oxodotreotide	-	3.5	15.1	-	0.2	1.0
midostaurin	1.2	12.6	15.8	2.3	23.5	29.4
nusinersen	92.1	102.2	70.2	242.9	242.4	166.3
patisiran	-	-	9.5	-	-	18.4
pomalidomide	18.6	-	-	61.9	-	-
tisagenlecleucel	-	1.2	13.2	-	<0.05	0.1
Total	**296.6**	**296.3**	**373.2**	**1,405.9**	**1,148.1**	**1,411.3**

Table 5.2.8. Orphan medicines accessing the fund for oncology and non-oncology innovative medicines: comparison expenditure and consumption, years 2019-2020

Type of medicines	Expenditure 2019 *(million)*	Expenditure 2020 *(million)*	Δ % 20-19	2019 *(thousand)*	2020 *(thousand)*	Δ % 20-19
Oncology innovative medicines	179.2	271.9	51.7	863.8	1,165.6	34.9
Non-oncology innovative medicines	117.1	101.3	-13.5	284.3	245.7	-13.6

Figure 5.2.3. Expenditure and consumption of orphan mediciness in Italy for ATC level I, year 2020



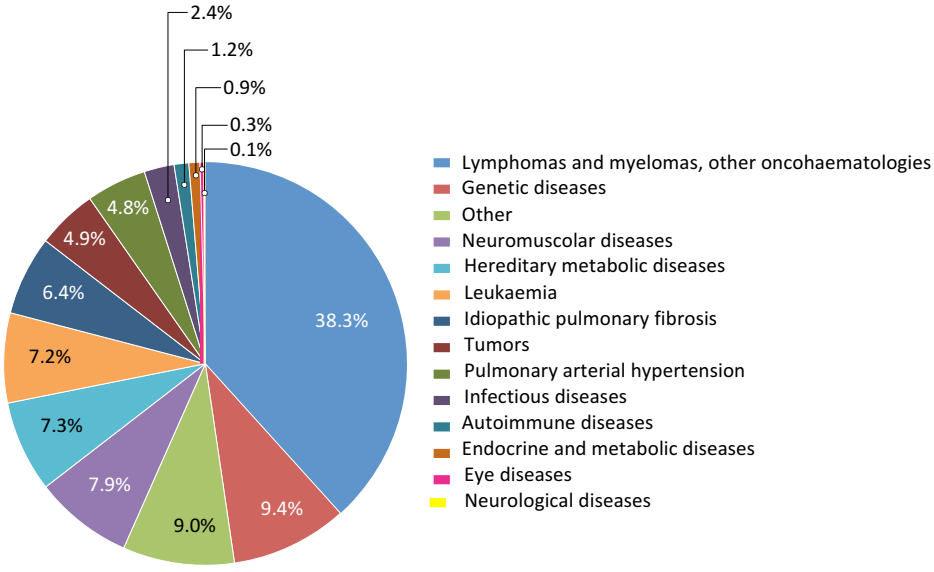
L	Antineoplastic and immunomodulating agents	V	Various
A	Gastrointestinal system and metabolism	R	Respiratory system
C	Cardiovascular system	M	Musculo-skeletal system
B	Blood and blood forming organs	G	Genito urinary system and sex hormones
N	Central nervous system	J	General antimicrobials for sistemic use
H	Systemic hormonal preparations, excl.sex hormones	D	Dermatologicals
		S	Sensory organs

As regards therapeutic classes, 64.3% of orphan medicine expenditure was covered by anti-neoplastic agents and immuno-modulators, followed by musculo-skeletal system medicines (8.3%), gastrointestinal tract and metabolism medicines (7.2%) and other (20.2%).
As regards consumption, the classes concerned are antineoplastics and immuno-modulators (65.3%), cardiovascular system medicines (10.4%) and systemic hormonal preparations, excl.sex hormones (8.7%), while the remaining 15.6% of consumption is represented by something else (Figure 5.2.3).

Table 5.2.9. Expenditure and consumption of orphan medicines in Italy by therapeutic area: year 2020 (Table and Figure)

Therapeutic Area	Expenditure *(million)*	Δ % 20-19	DDD *(thousand)*	Δ % 20-19	Per capita expenditure	DDD/1000 inhab per day	Inc.% expenditure*
Lymphomas and myelomas, other oncohaematologies	533.7	-21.4	3,053.1	-32.5	8.95	0.14	38.3
Genetic diseases	130.7	14.5	250.7	18.5	2.19	0.01	9.4
Other	124.8	7.6	169.7	14.1	2.09	0.01	9.0
Neuromuscular diseases	109.9	-5.2	230.4	-8.2	1.84	0.01	7.9
Hereditary metabolic diseases	102.3	34.8	253.8	24.0	1.71	0.01	7.3
Leukaemia	100.4	-33.3	396.0	-50.4	1.68	0.02	7.2
Idiopathic pulmonary fibrosis	88.8	-18.7	1,307.5	-16.7	1.49	0.06	6.4
Tumors	67.5	-1.6	311.0	-15.2	1.13	0.01	4.9
Pulmonary arterial hypertension	67.2	6.0	834.5	8.2	1.13	0.04	4.8
Infectious diseases	33.5	33.9	188.3	14.0	0.56	0.01	2.4
Autoimmune diseases	16.5	28.6	92.5	-45.1	0.28	<0.05	1.2
Endocrine and metabolic diseases	12.3	-26.1	792.2	-0.3	0.21	0.04	0.9
Eye diseases	4.0	-26.3	19.9	-18.6	0.07	<0.05	0.3
Neurological diseases	1.8	-10.2	131.4	-14.6	0.03	0.01	0.1
Total	**1,393.4**	**-10.4**	**8,031.0**	**-20.9**	**23.36**	**0.37**	**100.0**

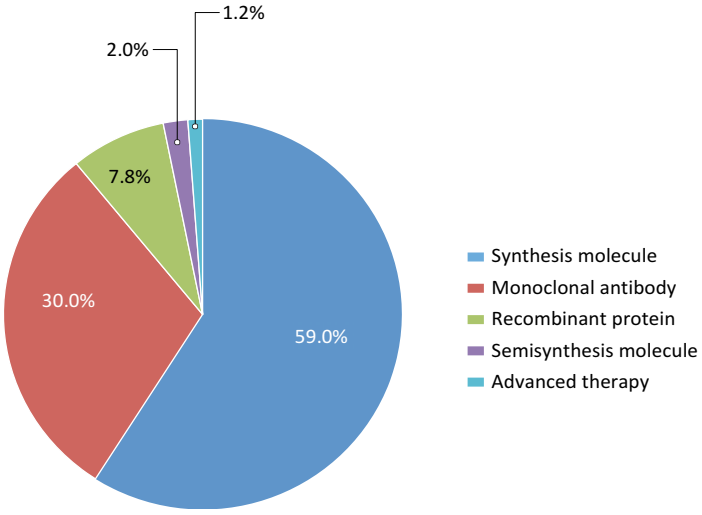
*Calculated on the total expenditure of orphan medicines nationwide



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 (38.3% and 9.4% respectively); on the consumption side, the first in the ranking are the medicines used in lymphomas, myelomas and other onco-haematologic diseases, followed at a distance by those for idiopathic pulmonary fibrosis (Table and Figure 5.2.9).
Analysis by product type shows that most orphan medicines are synthesis molecules (59.0%), followed by monoclonal antibodies (30.0%) (Table and Figure 5.2.10). Compared to 2019, there is a decrease in both the expenditure and consumption of synthetic molecules, while an increase is recorded for monoclonal antibodies.

Table 5.2.10. Expenditure and consumption of orphan medicines in Italy by type, year 2020 (Table and Figure)

Type of medicines	No. of molecules	Expenditure	Δ % 20-19	DDD thousand	Δ % 20-19	Per capita expenditure	DDD/ 1000 inhab per day	Inc.% expenditure *
Synthesis molecule	52	822.7	-23.2	6,145.4	-27.8	13.79	0.28	59.0
Monoclonal antibody	17	418.2	24.8	1,653.4	34.9	7.01	0.08	30.0
Recombinant protein	12	108.1	-2.7	168.5	-39.6	1.81	0.01	7.8
Semisynthesis molecule	8	27.8	-23.6	63.5	-54.0	0.47	<0.05	2.0
Advanced therapy	4	16.6	>100	0.1	>100	0.28	<0.05	1.2
Total	**93**	**1,393.4**	**-10.4**	**8,031.0**	**-20.9**	**23.36**	**0.37**	**100.0**



Access to medicines for rare diseases pursuant to Law 648, AIFA 5% fund and Ministerial Decree 7 September 2017

Despite notable medical advances in the diagnosis and treatment of many diseases, there are still so-called "niche" therapeutic areas which refer to unmet clinical needs and which represent a challenge and a healthcare goal for medicine.
And it is precisely in this niche position that Law n. 648/96, the National Fund and compassionate use are inserted at a regulatory level.

Law no. 648 of 1996

This rule allows the provision by the National Health Service, in the absence of a valid therapeutic alternative, of:

- innovative medicines whose marketing is authorised in other countries, but not in Italy;
- medicines not yet authorised, but undergoing clinical trials;
- medicines to be used for a therapeutic indication other than that authorszed in Italy.

In all the cases described above, the inclusion in list 648 must be supported by the results of concluded clinical studies, at least in phase II, which have demonstrated adequate efficacy with an acceptable risk profile.
With the entry into force of Law no. 79 of 2014, after AIFA's evaluation, the inclusion of medicines in the list is envisaged even in the presence of alternatives; these medicines can be used for a therapeutic indication other than that authorised, provided that this indication is known and compliant with research conducted within the national and international medical-scientific community, according to parameters of cost-effectiveness and appropriateness.
Inclusion is carried out by AIFA upon documented request by Patient Associations, Scientific Societies, Health Authorities, Universities or on the recommendation of the AIFA Scientific Technical Committee.
The list of orphan medicines and medicines for the treatment of rare diseases reimbursed pursuant to Law no. 648/96 can be downloaded from the Agency's website at the following link: https://www. aifa.gov.it/legge-648-96/

Law no. 326/2003 (AIFA 5% Fund)

Law no. 326 of 2003 provided for the establishment at AIFA of a national fund for the use of orphan medicines for the treatment of rare diseases and medicines that represent a hope of therapy, pending marketing, for particular and serious diseases.
The Fund consists of 50% of the contribution that pharmaceutical companies pay to AIFA on an annual basis. This contribution corresponds to 5% of the annual expenses that pharmaceutical companies sustain for promotional activities for healthcare professionals.

Ministerial Decree 7 September 2017

In Italy the D.M. 7 September 2017, "Discipline of the therapeutic use of medicinal products subjected to clinical trials", represents the regulatory instrument that establishes the procedures and methods of access to experimental pharmacological therapies for the treatment of serious diseases, rare diseases, rare cancers or conditions of disease that put the patient in danger of life, when, in the opinion of the doctor, there are no further valid therapeutic alternatives or in the event that the patient cannot be included in a clinical trial or, for the purposes of therapeutic continuity, for patients already treated with clinical benefit in a completed clinical trial.

Access to the experimental medicine requires authorisation for use by the Ethics Committee within whose sphere of competence this request originated, given the prior declared availability of the pharmaceutical company producing the free supply of the medicine.

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 expenditue monitoring; therefore, these data do not include the lists of medicines for consolidated use.

Table 5.2.11 lists the medicines included in list 648 in 2020, intended for the treatment of rare diseases, both without the status of orphan and with the status of orphan medicine.

Table 5.2.11. Medicines included in list 648 in 2020, intended for the treatment of rare diseases, both without the status of orphan medicine and with the status of orphan medicine.

Active ingredient	Therapeutic indication
bevacizumab (originator or biosimilar)	Treatment of type 2 neurofibromatosis
carboplatin association + paclitaxel	Treatment of thymic carcinoma
ibrutinib	Treatment of relapsed/refractory marginal zone non-Hodgkin B lymphomas after at least one line of anti-CD20 chemoimmunotherapy
infliximab (originator or biosimilar)	Treatment of patients with severe sarcoidosis and/or with life-threatening localisations who have failed the 1st and 2nd line of treatment (steroids and cytotoxic agents)
peginterferon alfa 2a	Treatment of refractory forms of Behçet's disease
lenvatinib	Treatment of cystic adenoid carcinoma
onasemnogene abeparvovec (Zolgensma)	Treatment within the first six months of life of patients with a genetic diagnosis (biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene) or clinical diagnosis of type 1 spinal muscular atrophy (SMA1)
plasminogen	Treatment of ligneous conjunctivitis
regorafenib	Treatment of relapsed glioblastoma multiforme
rituximab (originator or biosimilar)	Treatment of lymphoblastic leukemia
trastuzumab (originator or biosimilar)	Treatment of serous tumors of the metastatic endometrium, amplified HER2 in association with carboplatin and paclitaxel
venetoclax	Treatment of adult patients with newly diagnosed acute myeloid leukemia who are not candidates for intensive induction chemotherapy or with age ≥75 years, in combination with azacitidine or decitabine

Note: the medicines on the list 648 indicated for the treatment of rare diseases and which also meet the orphan medicine requirement are shown in red

Table 5.2.12. Medicines intended for the treatment of rare diseases for which a program was activated in 2020 pursuant to Ministerial Decree 7th September 2017

Active substance (trade name)	Therapeutic indication
tafamidis (Vyndaqel)	Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)
niraparib (Zejula)	Maintenance treatment of patients with advanced ovarian cancer in response after first-line treatment with platinum-based chemotherapy, which cannot be treated with authorised therapeutic alternatives
risdiplam (Evrysdi)	Treatment of spinal muscular atrophy (SMA) type 1, in patients who are not candidates for authorised therapies or who, in the opinion of the treating physician, are unable to continue the current treatment with the authorised therapy
risdiplam (Evrysdi)	Treatment of spinal muscular atrophy (SMA) type 2, in patients who are not candidates for authorised therapies or who, in the opinion of the treating physician, are unable to continue the current treatment with the authorised therapy
pemigatinib (Pemazyre)	Treatment of adult patients with metastatic or locally advanced cholangiocarcinoma
belantamab mafodotin (Blemrep)	As monotherapy for the treatment of adult patients with relapsed/refractory multiple myeloma, who have received at least four previous therapies, whose disease is refractory to at least one proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody
lumasiran (Oxlumo)	Treatment of patients with primary hyperoxaluria type 1 (PH1), without a valid therapeutic alternative
pevonedistat	First-line treatment of patients with high-risk acute myelodysplastic syndromes, or Low Blast Acute Myelogenous Leukemia
luspatercept (Reblozyl)	Treatment of transfusion-dependent anemia associated with beta-thalassemia
luspatercept (Reblozyl)	Treatment of transfusion-dependent anemia due to myelodysplastic syndrome (MDS) at very low, low and intermediate risk, in patients with ring sideroblasts with unsatisfactory response or unsuitable for erythropoietin-based therapy
elexacaftor/tezacafto/ ivacaftor (Kaftrio)	Treatment of patients aged 12 years or older with cystic fibrosis who are homozygous for the F508del mutation

During the year 2020, 11 compassionate use programs were opened for rare diseases with medicines that received the designation of orphan medicine by the COMP.
The amount of the AIFA 5% Fund in 2020 was 16,303,619 euros. Please note that the capacity of the Fund for the year 2020 is affected by a reduction due to the decrease in promotional activities by pharmaceutical companies due to the pandemic. The number of patients for whom access to the fund was requested in the year 2020 was 1,928; of these patients 1,641 were affected by rare disease, 1,293 by rare cancer.

Among patients with rare cancer, 770 had blood cancer and 605 of them had a favorable opinion on access to the fund. Of the 1,641 patients with rare disease who applied, 1,361 received positive responses while 937 were positive responses for patients with rare cancer as indicated in Table 5.2.13.

Table 5.2.13. Number of requests for access to the fund and number of actual accesses obtained in the year 2020

	Number of patients who have submitted an application for access to the AIFA fund		Number of patients who had a positive response to the request for access to the AIFA fund	
Year	With rare disease	With rare tumor	With rare disease	With rare tumor
2020	1,641	1,293	1,361	937

The above data were calculated on the base of the number of patients with rare disease and not on the number of requests; in fact, one or more renewals were often requested for the same patient to access the fund for the benefit obtained.

Table 5.2.14. Top 10 medicines by number of requests for access to the 5% fund in the year 2020

Medicine	Number of requests
venetoclax (alone or in combination)	488
nivolumab	159
pembrolizumab	157
dupilumab	132
blinatumomab	69
cannabidiol	49
ivosidenib	39
sorafenib	37
brentuximab vedotin	31
recombinant human parathyroid hormone	26

Table 5.2.15. Top 10 medicines with the greatest expenditure impact on the AIFA 5% fund for the year 2020

Medicine	Agreed expenditure
venetoclax (alone or in combination)	9.4
blinatumomab	7.6
cerliponase alfa	3.3
sebelipase alfa	3.1
volanesorsen	2.8
elexacaftor/ivacaftor/tezacaftor	2.7
givosiran	2.6
nivolumab	2.6
ivosidenib	2.3
pembrolizumab	2.0

As can be seen from Tables 5.2.14 and 5.2.15, most of the requests concern the active ingredients venetoclax, nivolumab, pembrolizumab and dupilumab. Venetoclax, which is also the active ingredient with the highest number of requests, is among the top 10 active ingredients by expense, followed by blinatumomab with a commitment of 7.6 million against 69 requests, cerliponase alfa with a commitment of expenditure of 3.3 million against a number of requests of less than 26 and sebelipase alfa with a commitment of 3.1 million against, also in this case, a number of requests of less than 26.

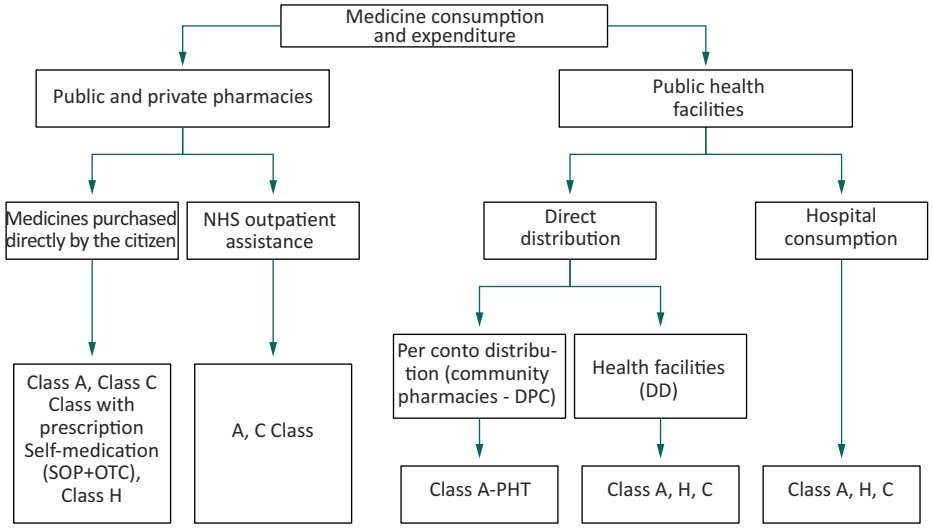
Appendix 2

Data source and methods

Medicines use in Italy
National Report
Year 2020

1. Pharmaceutical consumption and expenditure data

The 2020 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 (outpatient assistance), direct and 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.



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 Medicinals) 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 recipes 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 2020 was generally 96.2% of expenditure.

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").

The share of expenditure and missing consumption was obtained through an expansion. 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-agreed 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 to 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 per conto distribution, therefore it was 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 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 later than that of the movements, 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). The analysis of pharmaceutical consumption by the citizen is carried out using the data collected for Class C medicines 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, concerning the drugs delivered to local pharmacies. The private purchase of Class C medicines is derived by difference between what is purchased from pharmacies (Sell-in), compared to what is paid by the NHS (sell-out, i.e. the OsMed flow), considering 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 is minimised, consequent to the recomposition of the warehouse stocks of the pharmacy, which, on the contrary, could affect significantly on the single month.

- **Direct and *per conto* distribution.** The information flow of pharmaceutical services carried out directly and *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 of medicines to be paid by the NHS to the assisted person, for consumption at his/her own home, an alternative to the traditional provision of the same 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 the facilities, in home care, residential or semi-residential (i.e. direct distribution), by the affiliated pharmacies, public or private, on behalf of the Local Health Authorities (i.e. *per conto* distribution). The survey is extended to the prescriptions of all medicines authorised for marketing in Italy and identified by the MA code, regardless of the class of supply paid by the NHS and the supply regime. However, in order to have a complete picture of the consumption and expenditure of medicines directly borne by the public structures of the National Health Service, the survey also includes foreign medicines not registered in Italy, medicines prepared in pharmacies on the basis of a medical prescription for a specific patient, "magistral formulae", and medicines prepared in pharmacies according to the indications of the European Pharmacopoeia or national Pharmacopoeias in force in the Member States of the European Union, "officinal formulae", which shall be directly provided to patients served by this pharmacy. For the purposes of this Report, analyses on pharmaceutical performance in direct or *per conto* distribution have been carried out with exclusive reference to medicines provided with MA. The data of this information flow was used for the periodic monitoring of the territorial pharmaceutical expenditure performed by AIFA, as well as for the calculation of the deviation from the ceiling of territorial pharmaceutical expenditure and the allocation of budgets to pharmaceutical companies. Starting from 2017, in accordance with Law 236/2016 (Budget Law 2017), Article 1, paragraph 399, the ceiling of local pharmaceutical expenditure, renamed "agreed pharmaceutical expenditure ceiling", is calculated net of direct and *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 *per conto* distribution, the Regions and the Autonomous Provinces of Trento and Bolzano detect the delivery of medicines through the facilities not directly managed by the NHS. Such facilities provide for the purchase of medicines, subsequently reimbursed by the NHS as an excess over 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). The provision of health services (local health authorities, hospitals, scientific institutions and hospitals, university clinics, public and private pharmacies, specialist outpatient clinics and other accredited facilities) have the obligation of electronic transmission to the Ministry of Economy and Finance (MEF) of the recipes charged

to the NHS. For the purpose of monitoring health expenditure, pursuant to the aforementioned rule, the electronic transmission is requested of recipe data (and prescriptions) compliant with paragraph 2, Art. 50, commonly referred to as "red recipes", regardless of the content of the prescription and the medicine delivery method. This means that, in the case of prescription of medicines through "*per conto* distribution" mode or products related to supplementary assistance, reported on a "red recipe", the relative data are subject to the obligation of transmission, and incomplete, late or no transmission are sanctioned pursuant to Art. 50. The supply structures can also transmit recipes written on different models (white recipes, or modules not processed by the Health Card System, such as the tracing form) and recipes for the supply of pharmaceutical products in different ways: *per conto* distribution, direct distribution, additional home assistance and supplementary assistance. The data to be transmitted relate to the patient (fiscal code, Health Care Trust of residence, etc.), to the recipe (recipe identification code, Health Care Trust 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.). The transmission of recipe data by the dispensing facilities in the case of pharmaceutical prescriptions, by pharmacies open to the public, takes 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 analyses on the use of pharmaceuticals by age group and gender. 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 in question (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. 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 parametrise 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 to 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 2020.

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 the variable 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 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 (59,641,488 inhabitants in 2020). 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 2019 and 2020.7

Table 3.2. Resident population measured by ISTAT and weighted population for 2019 and 2020

Region	Resident population as of 1.1.2019	Weighted popolation 2019	Resident population as of 1.1.2020	Weighted popolation 2020	Δ % 20-19 Resident population	Δ % 20-19 Weighted population
Piedmont	4,328,565	4,552,854	4,311,217	4,526,583	-0.40	-0.58
Valle d'Aosta	125,653	128,798	125,034	128,252	-0.49	-0.42
Lombardy	10,010,833	9,977,368	10,027,602	9,973,090	0.17	-0.04
A.P. of Bolzano	530,313	496,691	532,644	497,505	0.44	0.16
A.P. of Trento	543,721	534,906	545,425	536,117	0.31	0.23
Veneto	4,884,590	4,917,763	4,879,133	4,913,136	-0.11	-0.09
Friuli VG	1,210,414	1,289,391	1,206,216	1,283,315	-0.35	-0.47
Liguria	1,532,980	1,701,425	1,524,826	1,686,057	-0.53	-0.90
Emilia R.	4,459,453	4,560,001	4,464,119	4,549,392	0.10	-0.23
Tuscany	3,701,343	3,882,065	3,692,555	3,865,341	-0.24	-0.43
Umbria	873,744	914,808	870,165	910,263	-0.41	-0.50
Marche	1,520,321	1,572,624	1,512,672	1,563,830	-0.50	-0.56
Lazio	5,773,076	5,692,069	5,755,700	5,678,841	-0.30	-0.23
Abruzzo	1,300,645	1,323,923	1,293,941	1,318,465	-0.52	-0.41
Molise	303,790	313,093	300,516	311,012	-1.08	-0.66
Campania	5,740,291	5,270,790	5,712,143	5,260,415	-0.49	-0.20
Puglia	3,975,528	3,891,756	3,953,305	3,881,368	-0.56	-0.27
Basilicata	558,587	559,909	553,254	555,673	-0.95	-0.76
Calabria	1,912,021	1,853,287	1,894,110	1,842,325	-0.94	-0.59
Sicily	4,908,548	4,716,968	4,875,290	4,696,516	-0.68	-0.43
Sardinia	1,622,257	1,666,184	1,611,621	1,663,991	-0.66	-0.13
Italy	**59,816,673**	**59,816,673**	**59,641,488**	**59,641,488**	**-0.29**	**-0.29**

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:

$$IV = \frac{S^{20}}{S_{19}} = \frac{\sum_i q_i^{20}}{\sum_i q_i^{19}} \times \frac{\sum_i p_i^{20} q_i^{19}}{\sum_i p_i^{19} q_i^{19}} \times \frac{\frac{\sum_i p_i^{20} q_i^{20}}{\sum_i q_i^{17}}}{\frac{\sum_i p_i^{20} q_i^{19}}{\sum_i q_i^{19}}}$$

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 2020 and 2019
S_{20} = pharmaceutical expenditure in 2020 S_{19} = pharmaceutical expenditure in 2019
Qi_{20} = quantity of the "i" package (expressed in DDD) sold in 2020 qi_{19} = quantity of the "i" package (expressed in DDD) sold in 2019 pi_{20} = average price in 2020 of the single DDD with the "i" package pi_{19} = average price in 2019 of the single DDD with the "i" package

This indicator consists of three factors:

- the first factor relates to variation in the quantities of pharmaceuticals consumed (quantity effect);
- the second factor concerns changes in the price of pharmaceuticals (price effect);
- the third factor describes if in the current year (considering current prices) more expensive medicinal products are consumed, compared to the previous year: if it 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 (mix effect).

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 mediciness 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_i= is the price of a DDD (or of a package) of the specialty "j" in the month "i"

q_i = is the number of DDDs (or of the packages) of the specialities "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.

Definitions 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:

$$CV = \frac{DS}{mean} \times 100$$

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.

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.

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 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)

Compound Annual Growth Rate (CAGR): is calculated through the n^{th} 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, xi represents the indicator calculated in the initial period and n represents the number of years considered.

Prescriptions per user (Pr/Ut): it is an indicator of the intensity of use of a medicine. It is calculated as the ratio between the overall number of prescriptions and the subjects who received at least one prescription during a period of time (users in the period).

Pr/Ut = (no. prescriptions / users in the period)

Mediana: 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 use: the prevalence (P) of a given condition in a population is the proportion of the population presenting the condition. The prevalence of medicine use is the ratio between the number of subjects who received at least one prescription and the reference population (potential users) in a specific period of time:

P = (no. users / population) x 100 (or x 1000 inhabitants, etc.)

The 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

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

Quartiles: values dividing the ordered distribution (expenditure, DDD, ...) into four parts of equal frequency.
The first quartile is the value including 25% of data (25th percentile);
the second quartile is the value including 50% of data (50th percentile), thus corresponding to the median;
the third quartile is the value which includes 75% of data (75th percentile).

% deviation from average: the % deviation from average of the Region i, with reference to an indicator x (per capita expenditure, DDD/1000 inhabitants per day, etc.), is constructed as:

$$\frac{x_i - Mean}{Mean} \times 100$$

where x_i represents the indicator calculated in the Region *i* and Media (Average) 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, the legal discounts and the shareholdings 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.

Indicators of adherence and persistence

The administrative database of prescriptions of Class A medicines dispensed on the national territory through public and private pharmacies, including *per conto* distribution, was employed 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 treatment 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 drugs belonging to the therapeutic category in question in the period between 01/10/2019 and 31/12/2019 and who did not receive prescriptions for medicines belonging to the same category in the previous months starting from 01/01/2019. The year 2020 was therefore used for the follow-up of the subjects enrolled in 2019, 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 Ratio (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:

$$MPR = \frac{number\ of\ therapy\ days}{\begin{array}{c}time\ interval\ between\ first\\ and\ last\ prescription\\ (plus\ days\ last\ prescription)\end{array}} \times 100$$

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. The maintenance of the treatment regime also includes 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 the start of the same 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.

Before the computation of adherence and persistence, it was necessary to carry out a series of data systematisation procedures. In particular, if a subject received multiple prescriptions, relating to different medicines, on the same date, only the prescription with the longest duration was considered. Also, 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, 84+) and geographical distribution (North: Piedmont, Valle d'Aosta, Liguria, Lombardy, A.P. of Trento and A.P. of Bolzano, Veneto, Friuli Venezia Giulia, Emilia Romagna; Centre: Tuscany, Umbria, Marche, Lazio; South and Islands: Abruzzo, Molise, Campania, Puglia, Basilicata, Calabria, Sicily, Sardinia). The results show the percentage changes in the 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 the territorial assistance regime (agreed and *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).

Medicinal products and therapeutic classes considered

1. **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)
2. **Medicines for hypertension and heart failure:**
   - Antihypertensives (ATC: C02A; C02C);
   - Diuretics (ATC: C03);
   - Beta blockers (ATC: C07);
   - Calcium channel blockers (ATC: C08);
   - Medicines for the renin-angiotensin system (ATC: C09)
3. **Antidiabetic medicines (ATC: A10*)**
4. **Anticoagulant medicines:**
   - Direct thrombin inhibitors (ATC: B01AE*);
   - Direct Xa factor inhibitors (ATC: B01AF*);
   - Vitamin K antagonists (ATC: B01AA*)
5. **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).

6. **Antidepressant medicines:**
   - Antidepressants (ATC: N06A)
7. **Medicines for asthma and COPD** (ATC: R03*)
8. **Antiosteoporosis medicines:**
   - Raloxifene (ATC: G03XC01)
   - Bazedoxifene (ATC: G03XC02)
   - Bisphosphonates alone (ATC: M05BA)
   - Bisphosphonates in combination (ATC: M05BB)
   - Teriparatide (ATC: H05AA02)
   - Strontium ranelate (ATC M05BX03)
9. **Medicines for benign prostatic hypertrophy** (ATC: G04C)

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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.

On the basis of compliance with a series of quality criteria in data recording, 800 "validated" and active GPs in 2020 were selected for the OsMed 2020 Report.[2] The data presented therefore refers to an overall population of 1,086,399 patients over the age of 14 who were found to be alive and registered in the lists of GPs in the aforementioned period.

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

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 XIII Report Health Search 2020 (Report_XIII.pdf [healthsearch.it]).

involve slight variations in the values, even with respect to the data reported in the reports and publications of previous years.

Epidemiology and prescribing profiles in General Medicine

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.

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 % 2020-2019).
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 [**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% 2020-2019).

To describe the methods of use of the medicines prescribed for the pathologies analysed, the **repeated prescriptions** were evaluated, so as to be able to estimate the share of patients adhering to the treatment, calculated considering the number of subjects with at least 80% of the days covered by the treatment relative to the potential exposure period [**numerator**], on the total of patients with at least one medicine prescription belonging to a specific therapeutic class [**denominator**]. DDDs were commonly used to estimate days of exposure. However, in the event that there was a discrepancy between the DDD and the commonly prescribed dose, such as for statins, the dosage unit (**Dosage unit/user**) was used. Furthermore, a grace period of 30 days was also considered in the evaluation of the days covered by the treatment. In this way, a patient was considered covered by the treatment if there was a gap of ≤ 30 days between the end of one prescription and the start of the next.
In the event that the treatment of a pathology required the concomitant use of two or more molecules, the adherence was assessed for each single molecule (**DDD/ user/molecule**) and the patient was associated with the highest adherence value detected in the observation period.
For various clinical pictures, the anamnestic parameters collected by the GP during the visits in the last 12 months (1 January 31 December 2020) are also reported, presented as the frequency of each single parameter [**numerator**] among the subjects affected by a given pathology [**denominator**], dividing the subjects under pharmacological treatment from those without any prescription of at least one medicine indicated for the given pathology.
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 disease (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) of the Ministry of Health, are updated as of 21 April 2021 and, therefore, do not take into account any further revisions by companies and Regions. The data of the gross agreed expenditure 2019 are updated to the January-December 2019 National and Regional Expenditure Monitoring dated 29 October 2020.