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National Report on Medicines use in Italy Year 2019

THE MEDICINES
UTILISATION
MONITORING
CENTRE

ITALIAN MEDICINES AGENCY

National Report on Medicines use in Italy Year 2019

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Dear Readers,
this is an extract/adaptation of 2019 OsMed Report.

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

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Section 1

General characteristics of pharmaceutical use in Italy

National Report
on Medicines
use in Italy
Year 2019

In 2019 the overall pharmaceutical expenditure (both public and private) amounted to €30.8 billion; 76.4% of this amount was reimbursed by the National Health System (NHS), and represented an important part of healthcare expenditure accounting for 1.7% 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 pharmacies (32.5%). The citizen pharmaceutical expenditure (out of pocket expenditure) amounted to €7.3 million. It is mainly composed of Class C prescription only medicines (POM) purchased by citizens (9.9% of the overall expenditure; Table 1.1.a). Compared to 2018, the overall pharmaceutical expenditure rose by 5.8%; it is mainly due to an increase in the consumption of medicines purchased by public health facilities (+18.3%) and of Class A medicines privately purchased by citizens (+13.5%).

Table 1.1.a Composition of pharmaceutical expenditure: 2019-2018 comparison (Table and Figure)

	Expenditure *(million)*	**%**	**Δ % 19-18**
Gross outpatient NHS expenditure^	10,034	32.5	-0.5
Oxygen	55	0.2	3.8
Class A medicines by direct and *per conto* distribution	4,481	14.5	-3.0
Local health authorities, Hospitals, Healthcare Residences and prisons*	8,980	29.1	18.3
Public expenditure	**23,550**	**76.4**	**5.3**
Private Class A	1,544	5.0	13.5
Class C with prescription	3,066	9.9	6.6
OTC medicines	2,392	7.8	5.4
Shops	259	0.9	-2.6
Private expenditure	**7,261**	**23.6**	**7.2**
Total	**30,811**	**100.0**	**5.8**

^ Including expenditure for vaccines (€24.5 million) and Class C drugs reimbursed (€18.9 million)

* Including expenditure for vaccines (€542 million) and oxygen (€248.2 million), net of direct distribution and *per conto* of Class A medicines

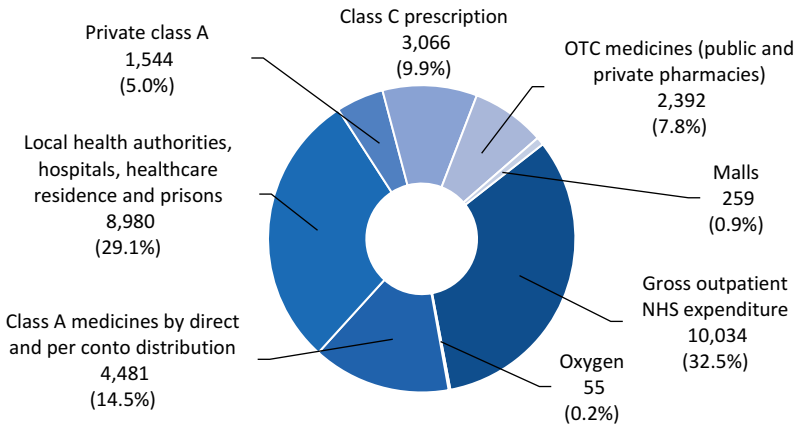
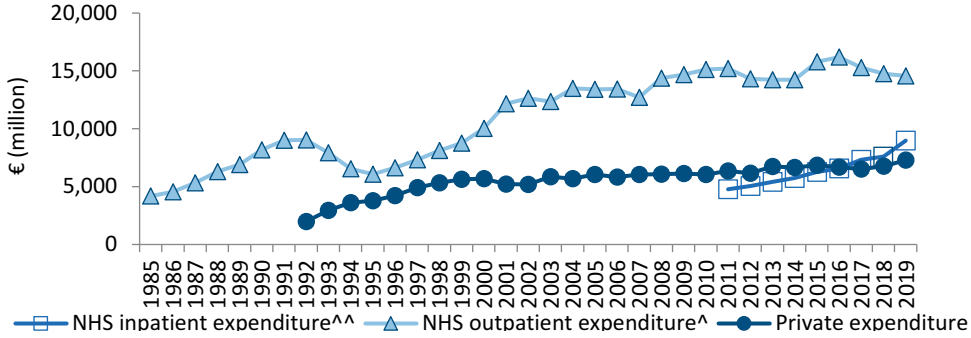


Figure 1.1.b Pharmaceutical expenditure in the period 1985 - 2019 (Figure and Table)



Years	Gross NHS outpatient expenditure* *(million)*	Direct distribution Class A *(million)*	NHS outpatient expenditure^ *(million)*	Out of pocket expenditure *(million)*	Inpatient expenditure^^ *(million)*
1994	6,539		6,539	3,625	
1995	6,087		6,087	3,785	
1996	6,638		6,638	4,216	
1997	7,321		7,321	4,919	
1998	8,113		8,113	5,332	
1999	8,760		8,760	5,640	
2000	10,041		10,041	5,684	
2001	12,154		12,154	5,232	
2002	12,644		12,644	5,204	
2003	12,354		12,354	5,849	
2004	13,491		13,491	5,694	
2005	13,408		13,408	6,046	
2006	13,440		13,440	5,814	
2007	12,712		12,712	6,046	
2008	12,724	1,651	14,375	6,088	
2009	12,928	1,767	14,695	6,122	
2010	12,985	2,144	15,129	6,046	
2011	12,387	2,832	15,219	6,346	4,774
2012	11,488	2,837	14,325	6,152	5,055
2013	11,226	3,003	14,229	6,732	5,421
2014	10,988	3,250	14,238	6,648	5,744
2015	10,863	4,921	15,784	6,859	6,282
2016	10,638	5,556	16,194	6,681	6,587
2017	10,499	4,792	15,291	6,526	7.332
2018	10,141	4,620	14,761	6,771	7,594
2019	10,089	4,481	14,570	7,261	8,980

^ inclusive of the reimbursed pharmaceutical expense (gross of the pay-back and discount) and of the direct distribution and *per conto* of the Class A, including the share paid by the citizen;
^^ expenditure on public health facilities (gross of pay-back) net of direct distribution and *per conto* of Class A;
* including expenditure for oxygen.
Source: OsMed processing of data from the Ministry of Economy and Finance and from "Traceability of medicines" flow. Processing of IMS Health data for the estimate of private expenditure for years prior to 2017

1.1 Outpatient pharmaceutical expenditure

In 2019 the overall outpatient pharmaceutical expenditure, that is composed by public and private expenses, amounted to € 21,108 million, increasing by 1.6% compared to 2018 (Table 1.1.2). The outpatient pharmaceutical expenditure covers medicines supplied according to standard distribution (7,765 million), and Class A medicines supplied through direct and *per conto* distribution channels (4,481 million) (Tables 1.1.1 and 1.1.2). This expenditure amounts to € 12,246 million (€ 202.9 per capita) and represents 58.1% of the total outpatient pharmaceutical expenditure. The pharmaceutical expenditure decreased by -1.3% compared to 2018. This decrease is due to a reduction of the expenditure for Class A medicines supplied according to direct and *per conto* distribution (-3.0%), whereas net standard distribution expenditure remained stable (-0.2%).
The citizen pharmaceutical expenditure (out of pocket expenditure) (Table 1.1.2) amounted to € 8,842 million (+5.5% compared to 2018). This change was due to an increase in expenditure for Class A medicines, going from 1,360 to 1,544 million (+13.5%), in the expenditure for Class C medicines with medical prescription (+6.6%) and in the consumption of self-medication medicines (OTC medicines) (+5.4%). On the other hand, there is a trend of decreasing expenditure in the citizen co-payment (-1.7%) and for medicinal products purchased in stores (-2.6%).
The citizen cost-sharing (Tables 1.1.1 and 1.1.2) amounted to € 1,581 million (approximately €26.2 per capita), accounting for 15.7% of the gross outpatient expenditure.
Compared to 2018, expenditure reduction was mainly determined by expenditure for the per prescription/package citizen co-payment (-4.8%) and partially by a reduction in the co-payment for the reference price system for off-patent medicines (-0.4%).
In line with data from the previous three years, the amount of packages supplied according to standard distribution showed a decrement (-1.6%) also in 2019. During 2019 (Table 1.1.3), an average of 987.7 daily doses of NHS reimbursed Class A medicines per 1,000 inhabitants (hereinafter called DDD/1000 inhabitants per day) were consumed, accounting to over 1 billion packages dispensed (18.0 packs per capita). In 2018, the amount was 978.8 DDD.
The main elements (e.g. quantity, prices and mix effect) of the change in the gross outpatient NHS expenditure in 2019, compared to the previous year (-0.8%), show a stable consumption of prescribed pharmaceuticals (+0.9% in terms of DDD), a reduction in average prices (-0.8%), related in part to an increasing use of off-patented products and in part to the strengthening of alternative retail channels and, finally, to the prescription of less expensive products (mix effect: -1.0%) (Figure 1.1.2 and Table 2.3.6).
The citizen expenditure for Class C medications with medical prescription and for Class A medicines amounted to € 116 per capita with a fair variability across Italian regions.

Table 1.1.1. NHS outpatient expenditure: comparison 2015-2019

		2015 *million*	2016 *million*	2017 *million*	2018 *million*	2019 *million*	Δ % 16/15	Δ % 17/16	Δ % 18/17	Δ % 19/18
1+2+3+4	**Gross outpatient NHS expenditure**	**10,863**	**10,638**	**10,499**	**10,141**	**10,089**	**-2.1**	**-1.3**	**-3.4**	**-0.5**
1+2	Citizen co-payment	1,521	1,540	1,549	1,608	1,581	1.2	0.6	3.8	-1.7
1	Fixed co-payment (ticket)	524	518	499	482	459	-1.2	-3.7	-3.4	-4.8
2	Reference price share	997	1,022	1,050	1,126	1,122	2.5	2.8	7.2	-0.4
3	Discount ^	865	845	830	751	743	-2.4	-1.8	-9.4	-1.1
4	**Net NHS expenditure**	**8,477**	**8,254**	**8,120**	**7,781**	**7,765**	**-2.6**	**-1.6**	**-4.2**	**-0.2**
5	Class A direct and *per conto* distribution°	4,921	5,556	4,792	4,620	4,481	12.9	-13.7	-3.6	-3.0
4+5	**Outpatient expenditure**	**13,398**	**13,810**	**12,913**	**12,402**	**12,246**	**3.1**	**-6.5**	**-4.0**	**-1.3**

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

° direct distribution and *per conto* expenditure of Class A, including - in the case of regions with missing data - the value of 40% of unconventional pharmaceutical expenditure recorded through the flow of the "Traceability of medicines", pursuant to Law 222/2007. In 2017 no Region implemented this condition.

Source: OsMed processing on NSIS data

Table 1.1.2. Comparison of public and private outpatient expenditure (2015-2019)

		2015 *million*	2016 *million*	2017 *million*	2018 *million*	2019 *million*	Δ % 16/15	Δ % 17/16	Δ % 18/17	Δ % 19/18
1	Net NHS expenditure	8,477	8,254	8,120	7,781	7,765	-2.6	-1.6	-4.2	-0.2
2	Class A medicines by direct and *per conto* distribution	4,921	5,556	4,792	4,620	4,481	12.9	-13.7	-3.6	-3.0
1+2	**Total public expenditure**	**13,398**	**13,810**	**12,913**	**12,402**	**12,246**	**3.1**	**-6.5**	**-4.0**	**-1.3**
3	Citizen co-payment	1,521	1,540	1,549	1,608	1,581	1.2	0.6	3.8	-1.7
4	Class A medicines paid by citizens	1,487	1,309	1,317	1,360	1,544	-11.9	0.6	3.2	13.5
5	Class C medicines with prescription	2,997	2,642	2,813	2,875	3,066	-11.8	6.5	2.2	6.6
6	OTC medicines	2,375	2,429	2,109	2,270	2,392	2.3	-13.2	7.6	5.4
7	Shops		301	286	266	259		-4.7	-7.0	-2.6
3+4+5+6+7	**Total private expenditure**	**8,380**	**8,220**	**8,076**	**8,379**	**8,842**	**-1.9**	**-1.8**	**3.8**	**5.5**
	Total pharmaceutical expenditure	**21,778**	**22,030**	**20,988**	**20,781**	**21,108**	**1.2**	**-4.7**	**-1.0**	**1.6**
	Share (%) borne by the NHS	61.5	62.7	61.5	59.7	58.0				

Source: OsMed processing on data from "Traceability of medicines" flow (for private expenditure data). Elaboration on IMS Health data for the estimate of private expenditure for the years prior to 2016.

Figure 1.1.1. Outpatient pharmaceutical consumption: comparison 2015-2019

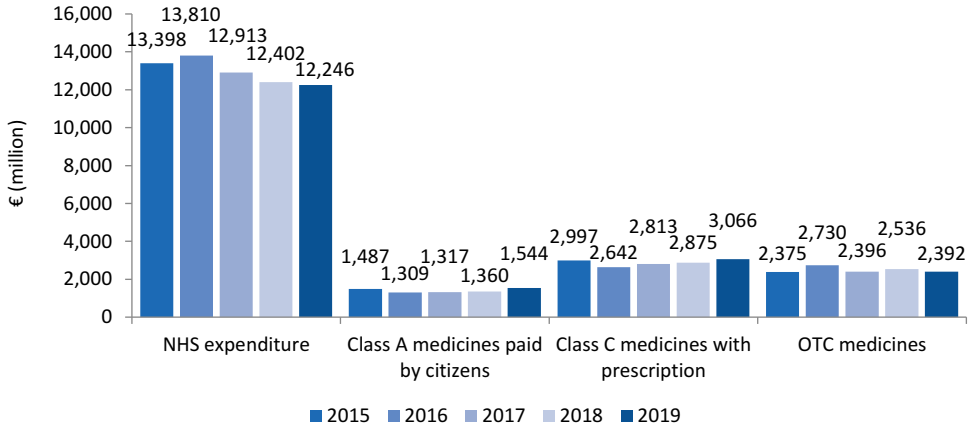


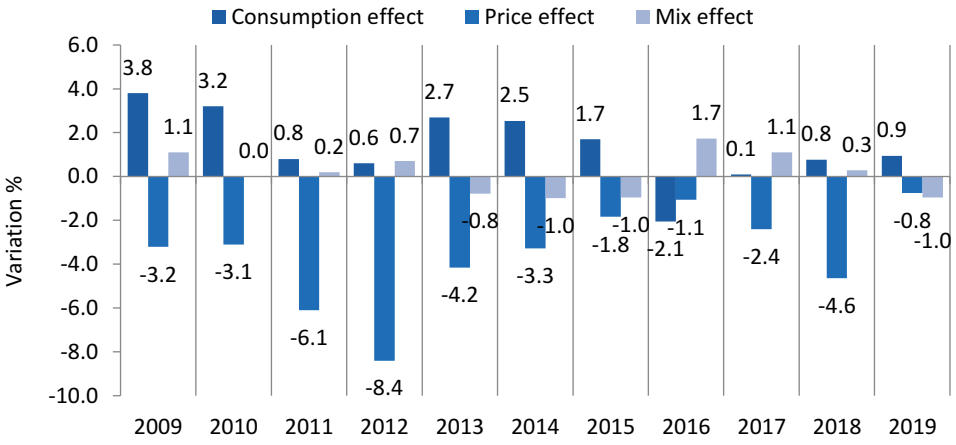
Table 1.1.3. Public and private outpatient pharmaceutical consumption: comparison 2015-2019

		2015 *million^*	**2016** *million^*	**2017** *million^*	**2018** *million^*	**2019** *million^*	**Δ % 16/15**	**Δ % 17/16**	**Δ % 18/17**	**Δ % 19/18**
	Prescriptions#	596	587	581	576	570	-1.5	-1.1	-0.8	-1.0
1	NHS consumption	1,131	1,117	1,110	1,102	1,084	-1.2	-0.7	-0.7	-1.6
2	Class A medicines paid by citizen*	225	210	216	162	190	-6.7	2.8	-24.9	17.3
3	Class A medicines by direct and *per conto* distribution	NA	86	105	105	112		21.5	0.2	6.7
1+2+3	**Total Class A medicines**	**1,356**	**1,414**	**1,430**	**1,369**	**1,386**	**4.2**	**1.2**	**-4.3**	**1.2**
4	Class C medicines with prescription	248	209	222	229	234	-15.6	6.1	3	2.2
5	OTC	280	259	231	241	242	-7.3	-10.8	4.1	0.4
6	**Malls**		**32**	**30**	**29**	**28**		**-6.2**	**-3.3**	**-3.4**
4+5+6	**Total Class C medicines**	**528**	**501**	**484**	**498**	**506**	**-5.1**	**-3.4**	**3**	**1.6**
1+2+3 +4+5	Total packages	1,884	1,915	1,914	1,867	1,862	1.6	-0.1	-2.5	-0.3
	DDD/1000 inhab. per day#	980	971.4	969.7	978.8	987.7	-0.9	-0.2	0.9	0.9

^ only the number of recipes and packages is expressed in millions of units.
# related to the consumption of Class A medicines provided under the agreed assistance scheme.
* the data relating to the private expenditure of medicines reimbursable by the NHS is obtained by the difference between total expenditure (estimated through the data from the "Traceability of medicines" flow) and the expense borne by NHS (obtained from OsMed data).
Source: OsMed processing on "Traceability of medicines" flow (for private expenditure data). Elaboration on IMS Health data for the estimate of private expenditure for the years prior to 2016.

Unless otherwise indicated, following tables report expenditure and consumption values not including oxygen

Figure 1.1.2. Trend of Class A reimbursed medicines expenditure: consumption effect, price effect and mix effect, period 2009-2019



Medicines purchased by public health facilities

The expenditure for medicines purchased by public health facilities (hospitals, local health units, etc.) amounted to approximately €13.5 billion (€218.94 per capita; Table 1.1.5.), with an increase of 10.9% compared to 2018. The pharmaceutical consumption, expressed as DDD, had an average value of 166.7 daily doses per 1000 inhabitants, and this value also rose if compared to the one of the previous year (+5.9%). It should be highlighted that, although DDD approach allows a useful parameterization of pharmaceutical consumption at different levels (geographical and temporal), 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 the outpatient consumption (for example in the paediatric population), it becomes even more valid in the hospital context, where the dose of a medicine can vary in function of the patient's care needs.

1.2 Pharmaceutical consumption by age and gender

The variability of pharmaceutical expenditure and consumption is primarily due to changes in epidemiological profiles over time, as well as to variety of healthcare settings and to different prescribing attitudes of physicians. In addition, pharmaceutical consumption is significantly higher in specific population groups, according to age, gender and type of disease. Data for this analysis derive from the information flow of prescriptions of medicines reimbursed by the NHS and provided through public and private pharmacies (so-called Health Card); this flow covers the whole Italian population.
Overall, in 2019 over 40 million people (55% women) received at least one pharmaceutical prescription with a prevalence of use equal to 67%, a per capita expenditure equal to 197 euros and a consumption of 1,029 DDD/1000 inhabitants per day (this suggests that on average every Italian citizen received a dose of medication every day of the year) (Table 1.2.1).
As expected, there is a slight difference in the level of exposure to medication in the population, with a prevalence of 62% in men and of 60% in women. As far as consumption is concerned, the number of doses registered are 1,028 DDD in men and 1,031 in women, whereas pharmaceutical expenditure reported €193 per capita in men and 201 in women (Table 1.2.1).
The trend of pharmaceutical expenditure and consumption increases with ageing of population. In fact, the pharmaceutical expenditure per capita was three times higher in citizens older than 64 years old compared to the national average value. Moreover, for citizens older than 64 years old, the NHS pharmaceutical expenditure was six times higher than the average value consumed by citizens belonging to younger age groups (Table 1.2.1). This result is due both to the change in the prevalence of medication use, which rises from about 50%, in children and adults up to 50 years, to over 95% in the elderly population over the age of 74, and to an increase in consumption ranging from 282 to 438 DDD/1000 inhabitants per day in the age bracket between 40 and 50 years to over 3,000 in the

population over 75 years of age (Figure 1.2.1 and Table 1.2.1). This shows that a patient over 75 years of age received at least 3 daily defined doses every day of the year.
Gender differences can be seen in the 15-64 age group, in which women showed a prevalence of medication use higher than men (Figure 1.2.1).
The population over 64 years old absorbs more than 60% of the standard distribution expenditure and about 70% of DDD (Table 1.2.1). In the paediatric population prevalence of medication use amounts to 50%, and ranges from over 60% in the 0-4 years old children to 38% in the 10-14 age group (for more details see section 5 on the use of pharmaceuticals in the paediatric population).

Table 1.2.1. Outpatient pharmaceutical expenditure and consumption by age, year 2019

Age (class)	Gross expenditure (per capita)			Total expenditure		DDD/1000 inhab. per day			total DDD	
	Men	Women	Total	%	% cum	Men	Women	Total	%	% cum
0-4	26	21	23	0.5	0.5	56	48	52	0.2	0.2
5-9	27	23	25	0.6	1.0	51	43	47	0.2	0.4
10-14	36	25	31	0.8	1.8	56	44	50	0.2	0.6
15-19	40	27	34	0.8	2.6	74	75	75	0.4	1.0
20-24	35	34	35	0.9	3.5	87	105	96	0.5	1.5
25-29	41	41	41	1.1	4.6	103	133	118	0.6	2.1
30-34	44	53	49	1.4	6.0	129	174	152	0.8	2.9
35-39	56	70	63	2.0	7.9	182	223	203	1.2	4.1
40-44	70	83	77	2.9	10.8	275	290	282	2.0	6.1
45-49	96	104	100	4.1	14.8	445	430	438	3.4	9.5
50-54	134	141	138	5.7	20.6	708	654	681	5.4	14.9
55-59	205	197	201	7.5	28.1	1,146	990	1,066	7.6	22.5
60-64	294	263	278	9.0	37.1	1,698	1,387	1,536	9.5	32.0
65-69	407	357	381	11.2	48.2	2,378	1,933	2,145	12.1	44.0
70-74	547	477	510	13.9	62.1	3,195	2,643	2,901	15.1	59.1
75-79	622	541	577	13.3	75.4	3,589	3,012	3,269	14.4	73.5
80-84	742	634	679	12.4	87.8	4,209	3,541	3,817	13.4	86.9
85+	784	620	674	12.2	100.0	4,358	3,506	3,785	13.1	100.0
Total	**193**	**201**	**197**			**1,028**	**1,031**	**1,029**		

Figure 1.2.1. Prevalence of use by age and gender in the outpatient setting, year 2019

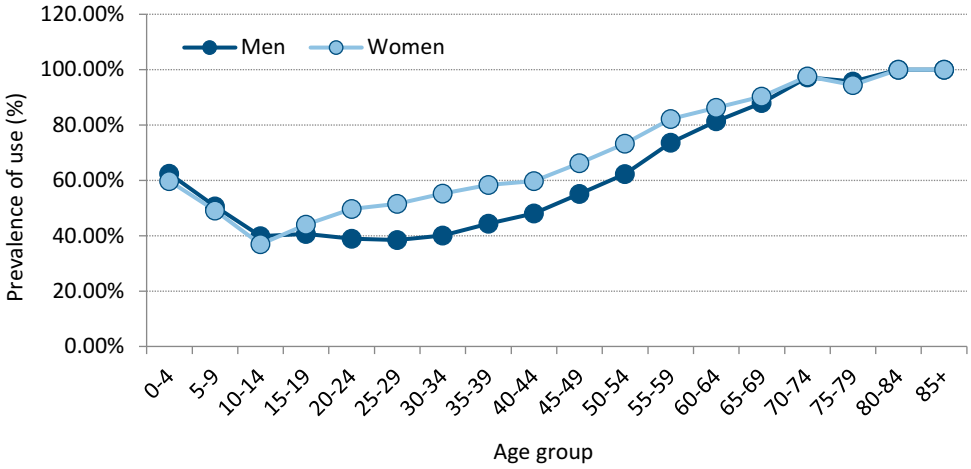
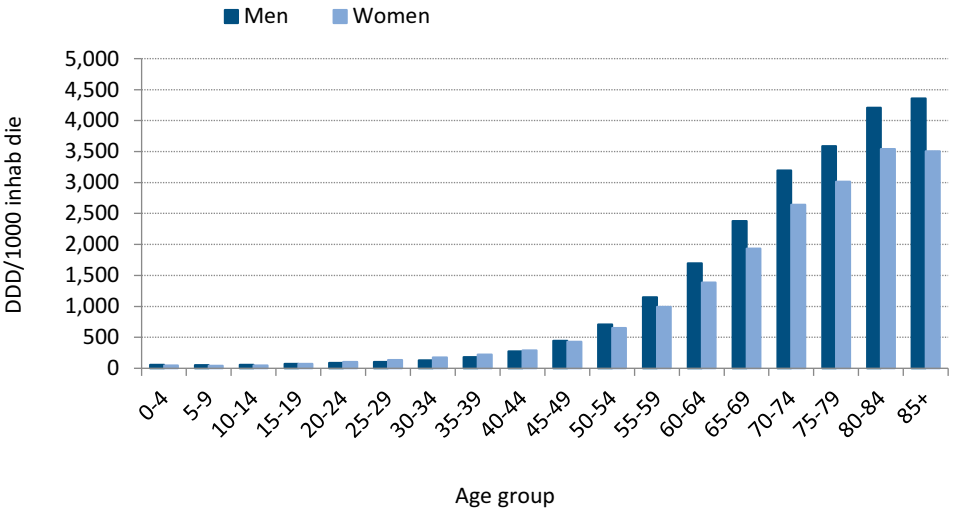


Figure 1.2.2. Outpatient consumption (DDD/1000 inhab. per day) by age and gender, year 2019



1.3 Pharmaceutical consumption on a monthly basis

Figure 1.3.1 shows consumption trend of Class A reimbursed medicines (consumption is expressed in DDD) during the period 2005-2019. Over the last fourteen years, pharmaceutical consumption has registered a persistent upward trend and has increased from 789.1 DDD/1000 inhabitants per day in 2005 up to 987.7 DDD/1000 inhabitants per day in 2019. In addition to the increased trend, pharmaceutical consumption is associated with seasonal variations as proved by peaks detectable on a monthly basis (see Figure 1.3.1). As a result of this periodicity, consumption levels registered in the first half of 2019 are higher than the annual average of 3%, in contrast to the second half of the year, when consumption is -3% lower. In particular, pharmaceutical consumptions registered in August are -14.9% lower than the average consumption of the same year. Generally, systemic antimicrobial medicines and respiratory medicines are the therapeutic categories on which consumption seasonality has the highest impact.
Figure 1.3.2 shows consumption trend of Class C prescription medicines starting from January 2005. This trend could have been affected by regulatory decisions which have determined over time the granting (or not) of the status of reimbursed medicines. Starting from 2005, a downward trend in consumption of Class C medicines was observed; indeed, the tendency varied from 231.8 DDD/1000 inhabitants per day in 2005 up to 192.4 DDD/1000 inhabitants per day in 2019 (-17% lower than the 2015 value). In 2019 the highest average consumption was recorded in September (216.6 DDD/1000 inhabitants per day) and January (205.1 DDD/1000 inhabitants per day), while the lowest levels were observed in August (157.0 DDD/1000 inhabitants per day).
Figure 1.3.3 shows consumption trend of medicines purchased by public health facilities in the period 2006-2019. In detail, an overall growing trend in consumption is recorded, increasing from 100.6 DDD/1000 inhabitants per day during 2006 up to 166.9 DDD/1000 inhabitants per day in 2019. During 2019 the lowest levels of consumption were observed in August (102.0 DDD/1000 inhabitants per day) and December (121.1 DDD/1000 inhabitants per day), whereas February (194.4 DDD/1000 inhabitants per day) and July (210.1 DDD/1000 inhabitants per day) registered the highest levels.
For a correct interpretation of monthly consumption (expressed as DDD/1000 inhabitants per day) of medicines purchased by public health facilities, it should be noted that trends of monthly consumption (unlike annual consumption trends) are influenced by purchasing procedures carried out by public health facilities themselves. Therefore, such trends cannot be strictly interpreted in terms of monthly patient consumption. This clarification is confirmed by irregularities in the volume of monthly purchases by public health facilities registered over the last six years.

Figure 1.3.1. Consumption trend of Class A medicines reimbursed by the NHS (DDD/1000 inhab. per day), years 2004-2019

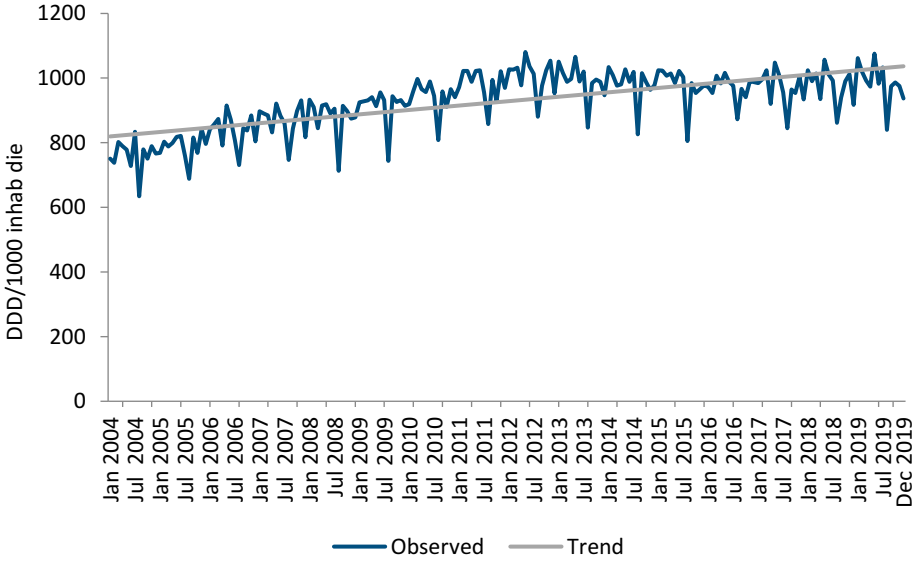


Figure 1.3.2. Consumption trend of Class C medicines requiring a medical prescription (DDD/1000 inhab. per day), years 2006-2019

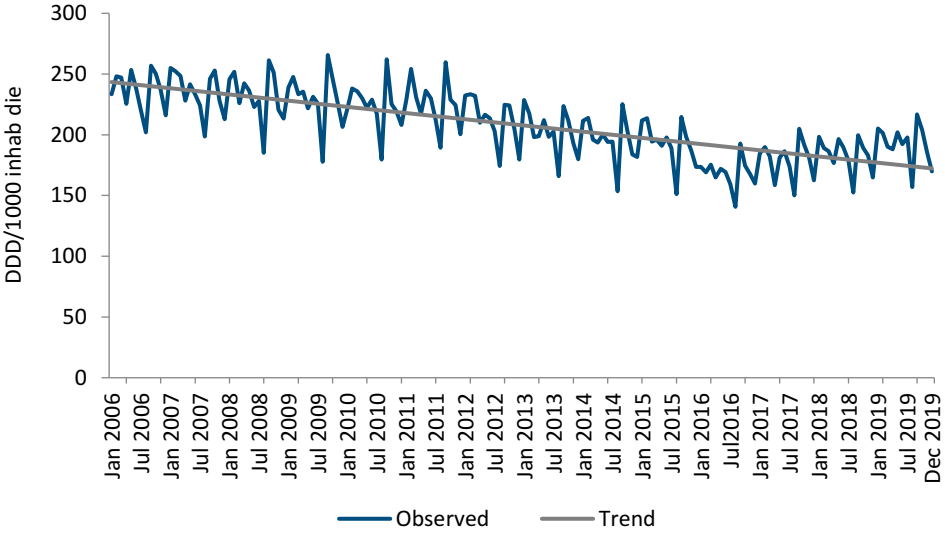
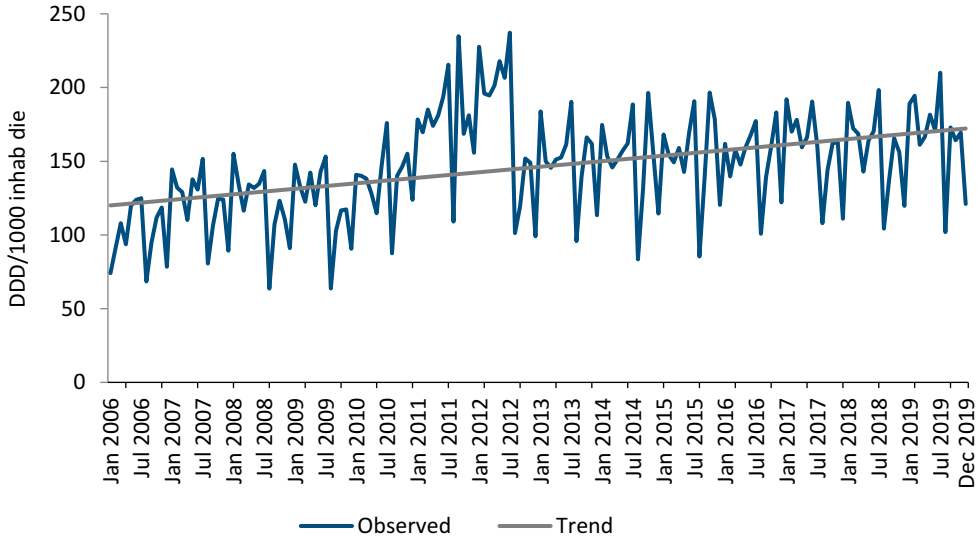


Figure 1.3.3. Consumption trend of medicines purchased by public health facilities (DDD/1000 inhab. per day), years 2006-2019



1.4. Trend of pharmaceutical prices

Data shown in Figure 1.4.1 represent the average price, weighted per package and per DDD, of Class A medicines reimbursed by the NHS in the period between January 2005 and December 2019. 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 patent expiring of pharmaceutical molecules (such as valsartan and atovastatin), by measures of price reduction implemented at national level at the beginning of 2006, and by the economic effect resulting from AIFA Resolution of 8 April 2011. These procedures resulted in a reduction of the reference prices of medicinal products included in the Transparency Lists (on the basis of a comparison carried out between prices of generic medicines in Italy and the same pharmaceutical packages marketed in Germany, UK, France and Spain.
Figure 1.4.2 shows the average price trend, weighted per package and per DDD, of Class C prescription medicines during the period between 2005 and 2019. Looking at the monthly time series data, the trend of the two indexes shows a steady growth rising from € 10.37 per package (and € 0.62 per DDD) in 2005 up to € 13.94 per package (and € 0.72 per DDD) in 2019, resulting in an increase of +26.1% and of +16.9% respectively, if compared to 2005. The year 2019 is an odd year in which pharmaceutical companies are allowed to change the price of these medicines[1], and an increase of +5.6% was recorded compared to 2018 (for further details see Section 2.8).
Figure 1.4.3 shows the average price trend, weighted per package and per DDD, of medicines purchased by public health-facilities in the period 2006-2019. Average prices increased from 2006 to 2010; they remained stable between 2011 and 2012, and increased again in the period 2013-2017. Since 2018 a slowdown in growth has been observed, probably due to the marketing of biosimilars of high-use medicines.
In this section a few categories of medicines, for which biosimilars started to be marketed in the above mentioned period, are therefore further explored with the aim of checking the time trends of the average price both for package and for DDD.
Figure 1.4.4 shows the average price trend of anti-TFN alfa medicines in the period 2016 - 2019. During such period, different biosimilars belonging to this category were marketed: infliximab in 2015, followed by etanercept in 2016 and adalimumab in 2018.
From 2016 to 2018 a steady decrease in prices was registered, with a 14% change on the price per package, and a 14.7% change on the price per DDD. However, the most significant price reduction was registered in the 2018-2019 period, with a -39.2% change on the price per package and a -38.6% change on the price per DDD. Overall, from 2016 to 2019 the price change affecting the whole class was equal to -48% both in terms of average price per package and of average price per DDD.
Figure 1.4.5. shows the average price trend, weighted per DDD, of low molecular weight eparin in respect of the following distribution channels: reimbursed by the NHS and by direct distribution. Biosimilars of enoxaparin have been marketed in Italy since 2018.
Prices of outpatient expenditure are generally three times higher than prices of direct distribution, moving from € 2.65 per DDD in 2016 to € 2.50 per DDD in 2019 (-6.0%). As far

[1] Decree law no. 87 of 27 May 2005, article 1, paragraph 3

as direct distribution is concerned, a reduction of 31.0% of price per DDD (from € 0.90 to € 0.62) is registered during the period 2016-2019.
Figures 1.4.6. and 1.4.7. show the price of rapid acting insulin as well as of slow and intermediate acting insulin in outpatient expenditure. The biosimilar for rapid acting insulin (including lispro insulin) has been marketed in Italy since 2018, therefore the average price decreased from € 1.36 per DDD in 2016 to € 1.32 in 2019, recording an overall reduction of 3.1% even if the average price per package rose by 2.2%. At the beginning of the marketing period of the biosimilar, the price per DDD decreased by 1.41% compared to 2016.
The biosimilar of slow and intermediate acting insulin (including glargine insulin) has been marketed in Italy since 2016.
Therefore, from 2016 to 2019 average prices per DDD decreased overall by 52.3% whereas average prices per package fell by 65.1%. The most significant reduction is recorded between 2016 and 2017.
During this period the average price fell from € 42.2 (€ 1.23 per DDD) to € 17.26 per package (€ 0.66 per DDD). It should be noted that much of consumption of fast acting insulin is registered in expenditure reimbursed by the NHS (about 90%), determining invariance of prices per package/DDD despite the expiration of patents.
On the contrary, the expiration of patents of intermediate long acting insulin (90% of which were purchased directly) resulted in a reduction of prices per package/DDD due to direct purchases of competing products.
As mentioned above (Section 1.3), the average price of medicines purchased by public health facilities is mainly influenced both by purchasing procedures and by the average price of mixed medicines purchased from time to time.

Figure 1.4.1. Average price trend of Class A medicines reimbursed by the NHS, years 2005-2019

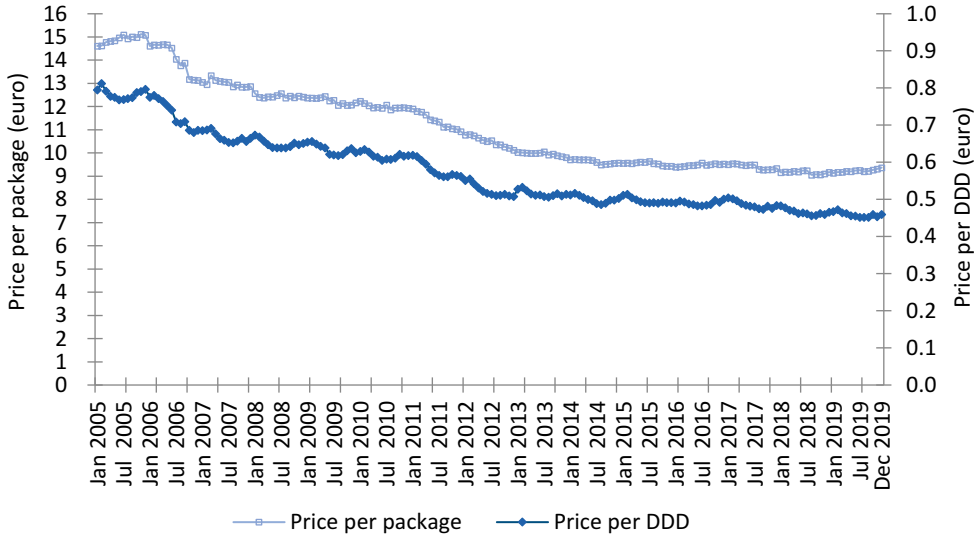


Figure 1.4.2. Average price trend of Class C medicines requiring a medical prescription, 2005-2019

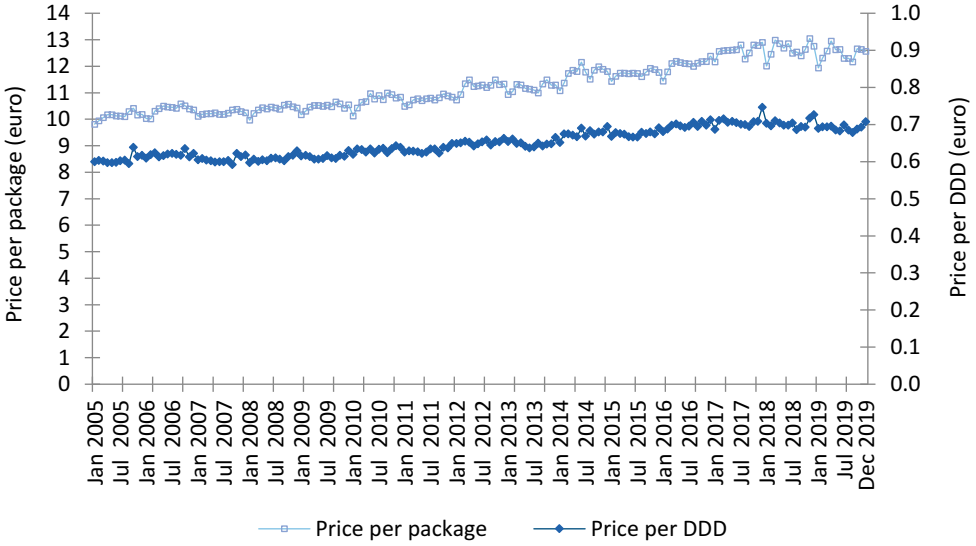


Figure 1.4.3. Average price trend of medicines purchased by public health facilities, years 2006-2019

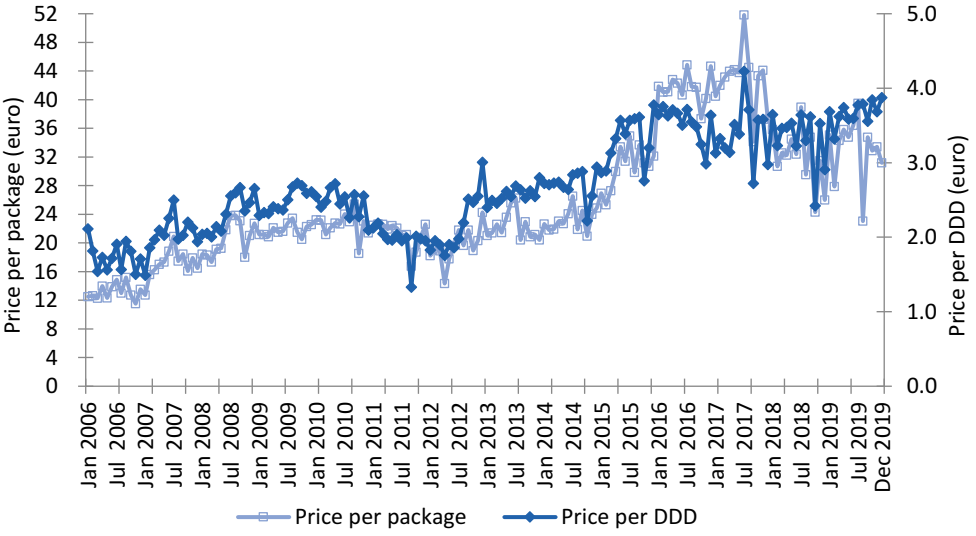


Figure 1.4.4. Average price trend of anti-TFN medicines, 2016-2019

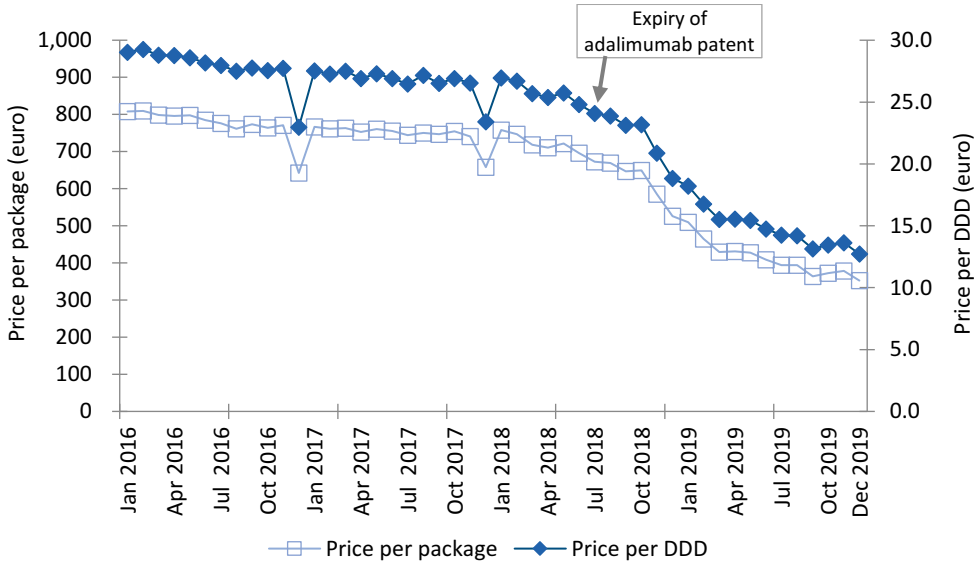


Figure 1.4.5. Average price trend of low weight molecular eparin, 2016-2019

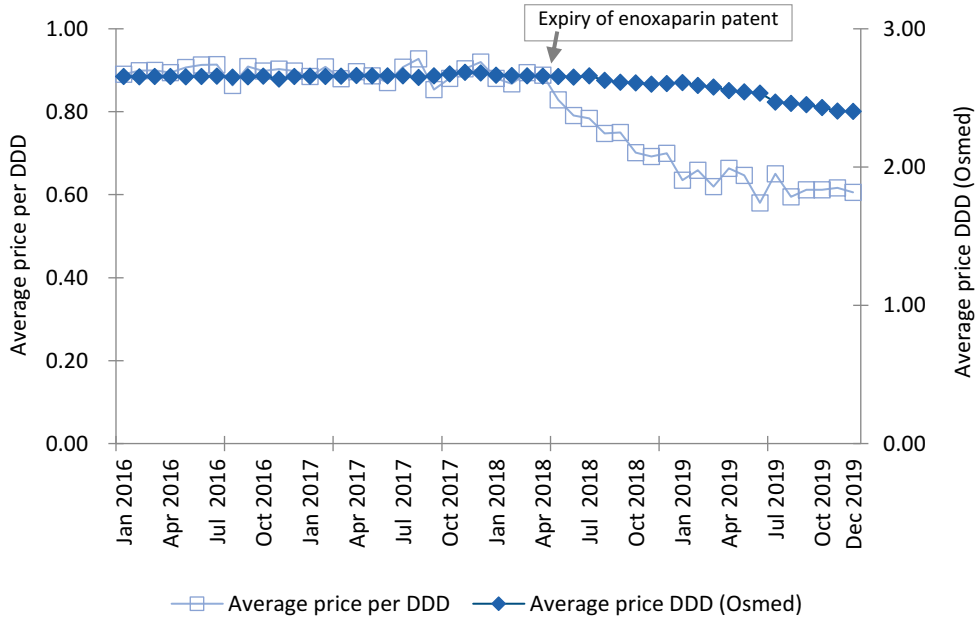
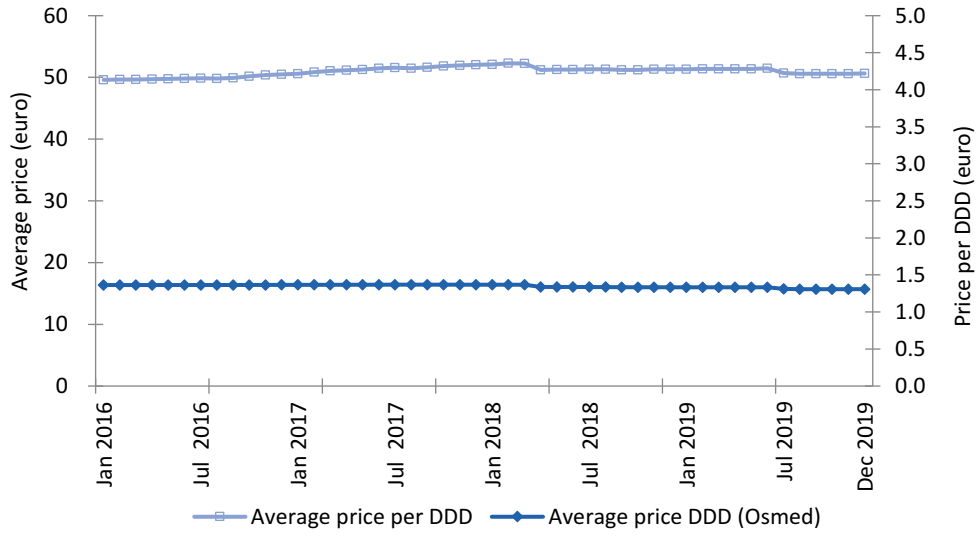
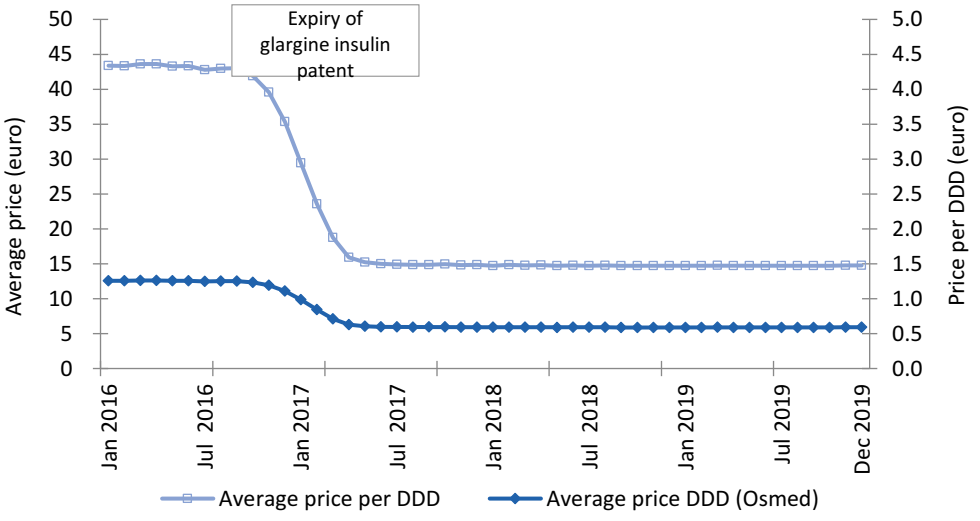


Figure 1.4.6. Average price trend of fast acting insulin*, 2016-2019 (outpatient expenditure)



* A10AB01, A10AB04, A10AB05, A10AB06

Figure 1.4.7. Average price trend of intermediate long acting insulin*, 2016-2019 (outpatient expenditure)



*A10AC01, A10AC04

1.5 International comparison

In this section, pharmaceutical expenditure per therapeutic classes, its distribution, and incidence of costs incurred for generic medicines in 2019 are compared at international level. The source of the international comparison is the IQVIA MIDAS® database. Data collected at international level for both distribution channels, outpatient and inpatient, are standardised (language, currency, name of the company, name of the product and of package). Information were obtained on patent coverage, medicinal product, biological medicinal products/biosimilars. Data of inpatient treatments include accredited private hospitals.

In addition to Italy, 9 countries were considered for the international comparison: Germany, Belgium, Austria, Spain, France, Sweden, Portugal, United Kingdom (UK) and Poland.

The overall pharmaceutical expenditure in Italy, including public and private outpatient expenditure as well as inpatient expenditure, was € 469 per capita. It was lower than expenditure recorded in Germany (€ 550.2), Belgium (€ 507) and Austria (€ 502), but higher than values of Poland (€ 183), United Kingdom (€ 344) and Portugal (€ 345) (Figure 1.5.1).

Important differences were registered in pharmaceutical expenditure distribution (outpatient and inpatient): inpatient pharmaceutical expenditure ranges from 66% (out of the total) of Spain and Italy to 29% and 31% of Poland and Sweden respectively (Figure 1.5.2).

As far as outpatient expenditure is concerned, the highest share of expenditure in Italy is represented by cardiovascular medicines, turning out to be 19.3% higher than the same expenditure recorded in other countries. In Sweden expenditure for this therapeutic class represents only 5.1% of outpatient expenditure. In UK and Spain the major part of outpatient expenditure is for central nervous system medicines (22.9%). UK (12.7%), preceded by Poland (14%), is the country with the highest expenditure for pharmacological treatments of respiratory disorders.

Medicines for gastrointestinal tract disorders account for most of the spending in Portugal (20.3%) and UK (19.4%). In Sweden (11.7%) and France (10.5%) the value of expenditure for antimicrobial medicines is the double of the same value in Italy (5.3%) (Table 1.5.1).

As for inpatient care (Table 1.5.2), the main item of expenditure in Italy is for antineoplastics (36.6%), even though higher values may be observed in nearly all the countries involved in the analysis, with the exception of Germany (34.7%). In Germany (22.9%), Italy (22.6%) and Spain (22.6%), expenditure for antimicrobials has a greater impact than in other countries. Italy is the country where expenditure for hematologic medications is the highest (13.0%) among the countries observed, followed by Sweden (12.8%) and Germany (12.6%).

If expenditure both for outpatient and inpatient medications is considered, different findings are produced in comparison with results obtained by examining the two distribution channels separately. This is due to the removing of the effect of the different distribution of medicines in separate channels. Unlike findings from the analysis on outpatient medication only, the highest incidence of spending for cardiovascular medicines is observed in Poland and Portugal (Table 1.5.3). Italy is the country with the highest incidence of spending for antimicrobials. This is partly due to the high expenditure for medicines to treat HCV infections whose incidence in Italy is higher than in other countries.

Large differences were found, both in outpatient and inpatient settings, among active substances representing the main cost items. For example, the active substance representing the main cost item in outpatient care in Italy was cholecalciferol which is placed 151th in France. Similarly, as far as inpatient care is concerned, combinations for the treatment of HCV infections, such as sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, occupy the first and second place in Italy in terms of expenditure, whereas they are placed behind 500th position in Austria and 350th position in Germany. The picture does not change if the overall pharmaceutical expenditure is considered (Tables 1.5.4, 1.5.5, 1.5.6).

Figures 1.5.3 and 1.5.4 show a comparison of the weighted average price (realizable value) for consumption in 2019. It refers to outpatient as well as inpatient medications. Figure 1.5.5 shows a comparison of prices on the overall market, including both inpatient and outpatient medications. The analysis takes into consideration medications that are identical or with a package similar to those marketed in Italy. The percentage of products in common with the country of comparison (Italy) was calculated and, on this basis, the average price was calculated as the ratio between the expenditure and the units provided in every country.

This approach makes it possible to overcome the difficulties related to different methods of delivering medications in different countries. Comparison should be made between Italy and the other countries studied, the basket analysis changes each time according to the country selected.

As far as outpatient medications are concerned, Figure 1.5.3 shows that all countries considered have average prices higher than Italy with a range varying between +11.2% of Poland and +206.3% of Germany. As for inpatient medications, the situation is totally different. Belgium, Germany, Portugal and France have lower price than Italy with differences varying between -18.4% of Belgium and -54.3% of France. Italy has lower prices than Sweden (+291%), UK (+226%), Poland (+167%), Austria (+79%), and Spain (+18%) (Figure1.5.4). When we look at the overall market, including both outpatient and inpatient medications, Italy show lower prices than Germany (+32%), Belgium (+28%) and Sweden (+17%), but it has higher prices than Spain (-3%), UK (-5%), Austria (-6%), Portugal (-35%), France (-41%) and Poland (-41%) (Figure 1.5.5).

In interpreting the results of the evaluations, the corresponding percentage of medicines between Italy and the other countries considered should be taken into consideration. On the overall market, the best correspondence is with Belgium (29%), whereas the worst one is with the UK (7.2%). A further element to be considered in interpreting results is the lack of an evaluation of the impact of conditioned reimbursement agreements, including confidential discounts, which can be applied differently in different countries.

In Italy there is a low incidence of expenditure for generics if compared to other European countries, though a substantial increase was observed in comparison with 2015 (39.6% vs 15.9%). In the countries observed, the percentage of expenditure for outpatient generics varies from 30.6% of Belgium to 66.6% of Poland (Figure 1.5.6.).

Figure 1.5.1. International comparison of the overall inpatient and outpatient per capita expenditure, year 2019

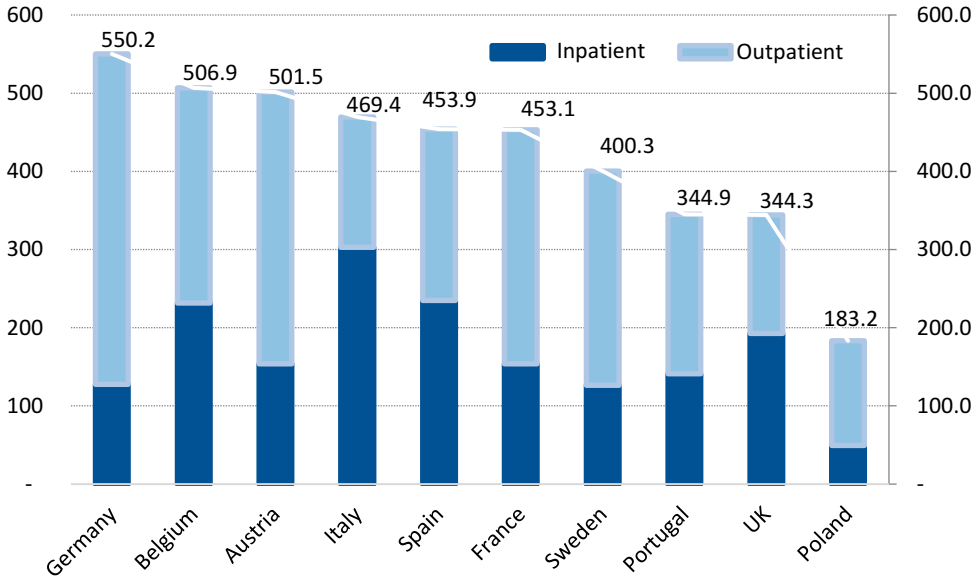


Figure 1.5.2. International comparison of the proportion of pharmaceutical expenditure 2019, inpatient vs outpatient

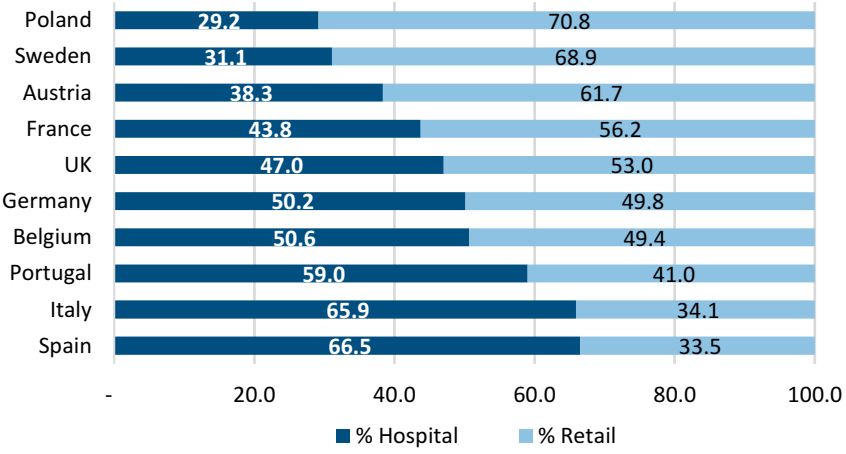


Table 1.5.1 International comparison of the proportion of outpatient pharmaceutical expenditure 2019, on the basis of the 1st level of the ATC classification

1st level ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
C - Cardiovascular	19.3	11.4	11.4	8.8	7.6	17.1	18.1	15.0	5.1	11.6
N - CNS	18.3	15.1	18.2	14.6	15.4	15.0	18.8	22.9	18.0	22.9
A - Gastrointestinal	17.7	10.5	13.5	11.8	12.0	17.4	20.3	19.1	12.3	19.4
R - Respiratory	11.6	8.3	10.6	8.1	7.9	14.0	9.3	10.5	8.6	12.7
G - Genito-urinary and sexual hormones	7.1	2.5	4.8	3.9	2.9	6.1	5.9	6.4	4.4	6.1
M - Musculo-skeletal	5.7	5.2	4.5	3.0	4.1	5.0	5.9	4.3	3.6	2.8
J - Antimicrobials	5.3	7.5	9.4	10.5	8.3	4.8	4.6	3.4	11.7	3.2
D - Dermatological	4.1	3.1	3.3	2.6	3.1	3.6	2.9	2.8	3.0	3.9
S - Sense organs	3.5	0.8	1.1	5.4	3.2	2.0	2.0	2.2	2.0	2.9
B - Hematologic	3.4	7.9	9.6	8.0	8.0	10.8	9.4	7.1	8.2	8.4
H - Systemic hormones	2.1	2.0	2.4	2.9	2.2	1.5	1.0	2.2	2.5	2.7
L - Antineoplastic	1.4	24.2	10.7	19.5	22.7	1.8	0.5	3.6	20.1	2.8
V - Various	0.3	1.3	0.2	0.6	2.2	0.7	1.1	0.5	0.4	0.3
P - Antiparasitic	0.1	0.2	0.2	0.3	0.3	0.2	0.3	0.1	0.1	0.2

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

Table 1.5.2. International comparison of the proportion of pharmaceutical expenditure 2019 on the basis of the 1st level of ATC classification

1st level ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
L - Antineoplastic	36.6	49.8	54.7	43.4	34.7	43.7	43.2	46.1	39.5	44.8
J - Antimicrobials	22.6	16.6	10.9	13.6	22.9	19.4	21.3	22.6	12.6	18.8
B - Hematologic	13.0	10.5	9.7	11.1	12.6	5.2	6.1	6.0	12.8	5.7
N - CNS	9.6	7.5	6.8	13.2	13.0	16.2	11.1	9.0	10.4	7.5
A - Gastrointestinal	6.7	5.1	6.0	6.4	5.2	1.7	7.2	4.0	6.0	4.7
C - Cardiovascular	2.3	2.4	1.7	3.0	2.2	3.7	1.7	2.1	2.0	1.6
R - Respiratory	2.3	1.3	2.4	2.3	1.2	2.0	2.3	3.3	1.8	3.4
H - Systemic hormones	1.8	0.8	0.8	1.0	0.9	3.2	1.8	1.5	1.0	1.3
M - Musculo-skeletal	1.6	1.9	1.8	2.4	2.1	1.5	1.6	1.7	4.3	3.4
S - Sense organs	1.4	1.6	3.6	0.8	1.8	2.3	1.6	2.3	8.0	6.5
V - Various	0.8	1.0	0.6	0.7	1.2	0.3	0.6	0.1	0.8	0.6
D - Dermatologic	0.7	0.7	0.3	1.6	1.8	0.4	1.0	0.9	0.5	0.9
G - Genito-urinary and sexual hormones	0.6	0.8	0.6	0.5	0.3	0.3	0.3	0.4	0.4	0.8
P - Antiparasitic	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0

Table 1.5.3. International comparison of the proportion of outpatient and inpatient pharmaceutical expenditure 2019 on the basis of the 1st level of ATC classification

1st level ATC	Italy	Austria	Belgium	France	Germany	Poland	Portugal	Spain	Sweden	UK
L - Antineoplastic	24.1	32.1	30.8	27.6	25.5	13.1	18.0	25.6	26.2	26.3
J - Antimicrobial	16.5	10.3	10.1	11.6	11.7	8.8	11.4	13.4	12.0	11.9
N - CNS	12.7	12.7	13.0	14.1	14.9	15.3	15.7	15.7	15.6	14.3
A - Gastrointestinal	10.6	8.9	10.1	10.0	10.4	13.2	14.9	11.3	10.3	11.2
B - Hematologic	9.6	8.7	9.7	9.0	9.0	9.3	8.1	6.5	9.7	6.9
C - Cardiovascular	8.3	8.6	7.0	6.8	6.4	13.5	11.4	8.3	4.1	6.0
R - Respiratory	5.6	6.2	6.9	6.1	6.3	10.8	6.4	6.8	6.4	7.5
M - Musculo-skeletal	3.1	4.2	3.2	2.8	3.7	4.1	4.1	2.9	3.8	3.1
G - Genito-urinary and sexual hormones	2.9	2.0	2.9	2.7	2.3	4.6	3.6	3.3	3.1	3.2
S - Sense organs	2.2	1.0	2.2	3.8	2.9	2.1	1.8	2.3	3.9	4.9
D - Dermatologic	1.9	2.4	2.0	2.2	2.8	2.7	2.1	1.8	2.2	2.2
H - Systemic hormones	1.9	1.6	1.7	2.3	1.9	1.9	1.3	1.8	2.0	1.9
V - Various	0.6	1.2	0.4	0.6	2.0	0.6	0.9	0.3	0.5	0.4
P - Antiparasitic	0.0	0.2	0.1	0.2	0.2	0.1	0.2	0.1	0.1	0.1

Table 1.5.4. International comparison of the first ten active substances in Italy: outpatient expenditure 2019*

Active substance	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK
colecalciferol	1	77	151	86	37	94	83	95	93	42
pantoprazol	2	34	55	26	4	15	35	33	481	399
paracetamol	3	197	2	296	5	37	11	12	11	24
atorvastatin	4	27	31	110	16	7	8	1	104	1
diclofenac	5	15	46	30	11	4	13	55	34	81
amoxicillin/clavulanic acid	6	73	58	126	53	29	21	60	552	344
ibuprofen	7	35	45	24	18	3	5	14	41	111
lansoprazole	8	229	155	1.102	419	657	126	88	447	60
omeprazole	9	269	67	143	12	24	33	11	58	29
esomeprazole	10	124	19	262	117	134	17	32	99	80

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

Table 1.5.5. International comparison of the first ten active substances in Italy: inpatient expenditure 2019

Active substance	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK
sofosbuvir/velpatasvir	1	591	112	356	33	10	40	2	55	7
glecaprevir/pibrentasvir	2	533	64	399	24	2	43	6	213	58
pembrolizumab	3	1	1	2	1	6	3	5	6	3
lenalidomide	4	159	3	225	4	9	5	3	111	8
nivolumab	5	2	5	5	2	3	13	11	4	16
adalimumab	6	161	338	72	273	20	7	1	79	1
immunoglobulin	7	7	2	1	5	25	2	4	3	4
epoetin alfa	8	164	116	157	64	128	257	75	484	91
trastuzumab	9	4	9	14	7	5	6	13	7	11
rivaroxaban	10	123	196	130	226	116	608	404	248	175

Table 1.5.6. International comparison of the first ten active substances in Italy: overall expenditure 2019

Active substance	Italy	Austria	France	Germany	Belgium	Poland	Portugal	Spain	Sweden	UK
sofosbuvir/velpatasvir	1	60	42	182	66	22	88	2	8	10
glecaprevir/pibrentasvir	2	33	33	89	47	4	90	6	164	65
pembrolizumab	3	1	2	7	1	11	7	5	11	5
lenalidomide	4	2	8	5	4	20	9	3	7	13
nivolumab	5	3	11	15	2	8	20	12	9	24
adalimumab	6	4	3	1	6	72	11	1	2	1
immunoglobulin	7	7	4	2	5	85	6	4	4	6
epoetin alfa	8	200	84	133	167	571	704	158	838	173
enoxaparin sodium	9	10	13	9	30	5	26	18	351	46
trastuzumab	10	11	18	43	11	10	10	15	18	17

Figure 1.5.3. International comparison of pharmaceutical prices (realizable prices) in 2019: outpatient care

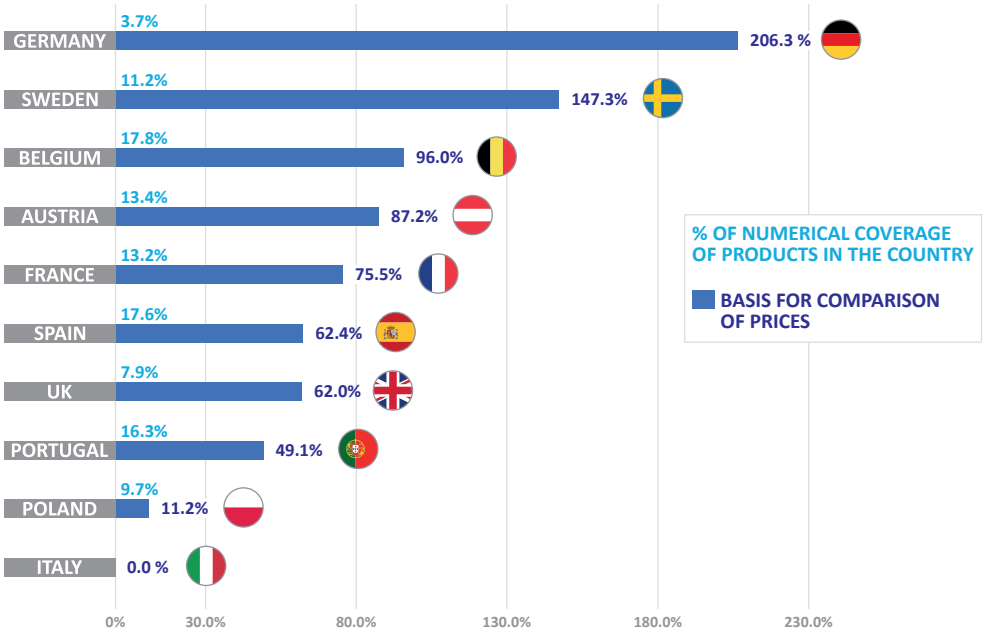


Figure 1.5.4. International comparison of pharmaceutical prices (realizable prices) in 2019: inpatient care

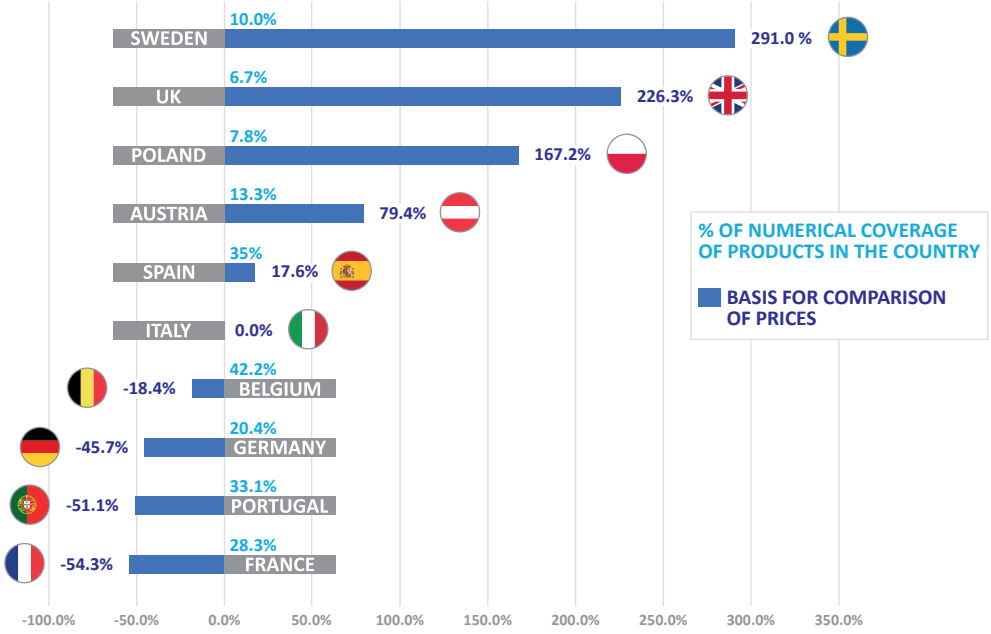


Figure 1.5.5. International comparison of pharmaceutical prices (realizable prices) in 2019: outpatient and inpatient care

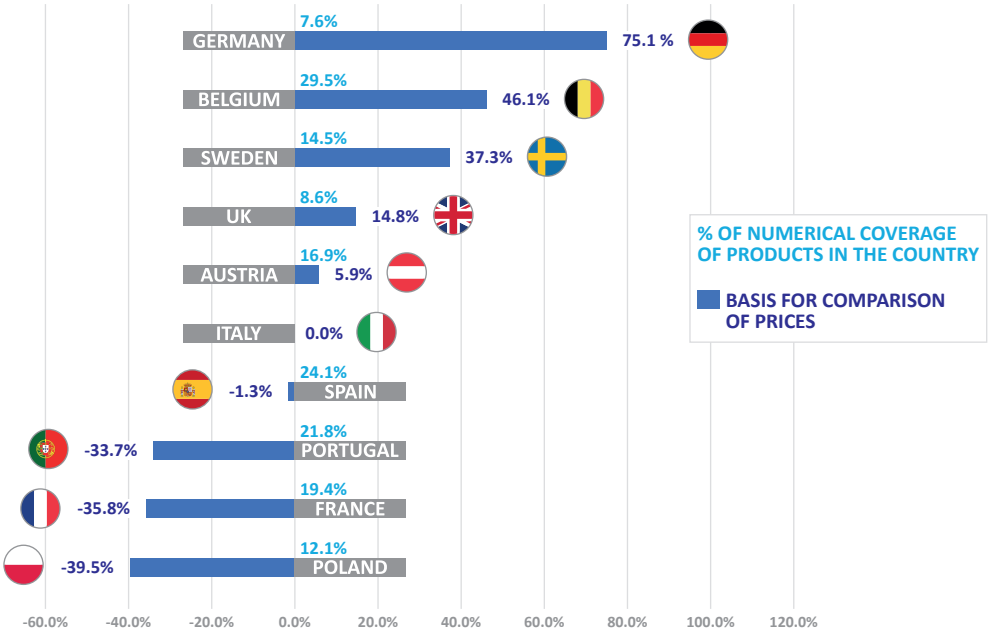
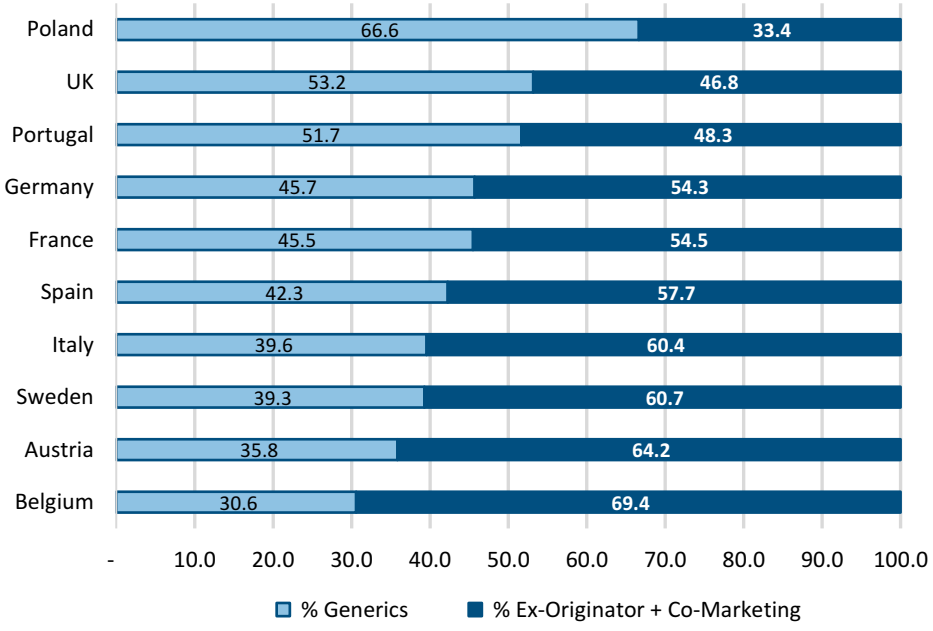


Figure 1.5.6. International comparison of the proportion of outpatient expenditure in 2019 for medicines whose patent has expired



Section 2

Detailed analysis of pharmaceutical expenditure and consumption*

* Not all sections of the Italian volume have been translated into the English version. In particular, the part relating to the analysis of regional data has been omitted

2.1 Patent-expired pharmaceuticals and biosimilars

Patent-expired pharmaceuticals within NHS outpatient expenditure

In 2019 patent-expired pharmaceuticals accounted for 67.3% of expenditure and 83.7% of consumption under Class A - NHS outpatient care regime. Generic pharmaceuticals, i.e. medicinal products based on patent-expired active ingredients, with the exception of those provided with patent coverage, represented 20.3% of the expenditure and 30.6% of the consumption of Class A medicines, respectively (Figures 2.1.1 and 2.1.2).
The three therapeutic areas recording the greatest expenditure were cardiovascular pharmaceuticals (91.2%), antimicrobials for systemic use (85.2%), antineoplastics and immunomodulators (85%). These three categories also showed the greatest incidence in terms of consumption, with 94.9%, 92.6% and 87.1% respectively (Table 2.1.1). In general, the upward trend in both expenditure and consumption of patent-expired pharmaceuticals was confirmed. Consumption and expenditure of generic medicines also displayed an increasing trend (Figures 2.1.3 and 2.1.4).
Half of the top twenty patent-expired active ingredients belonged to the cardiovascular category, followed by gastrointestinal system and metabolism pharmaceuticals.
Cholecalciferol was the active ingredient with the greatest expenditure in absolute terms, with € 277.3 million and a +3.2% increase compared to the previous year. Among the active ingredients with the highest cost and consumption under NHS outpatient care regime, four are proton pump inhibitors: pantoprazole (€ 265 million, second most used molecule), lansoprazole (€ 152.1 million), omeprazole (€ 142.3 million) and esomeprazole (€ 135.7 million), which however recorded a decrease compared to 2018. The first active ingredient with the greatest expenditure pertaining to the cardiovascular system category is atorvastatin with € 257.2 million and a +3.6% increase.
Olmesartan recorded the greatest increase in expenditure from 2018 to 2019 (+23.4%), with a total expenditure of € 90.5 million.
With regard to consumption (Table 2.1.2), the first three active principles belonged to the cardiovascular system category, with ramipril ranking first (62.5 DDD/1000 inhabitants per day), followed by atorvastatin (46.1 DDD) and amlodipine (27 DDD).
At regional level, Southern regions and Islands had the highest incidence of expenditure for patent-expired medicines belonging to Class A – NHS outpatient pharmaceutical expenditure (69.1%), followed by Central regions (67.8%) and Northern regions (65.5%).
Emilia-Romagna recorded the highest incidence of expenditure (72%), followed by Molise (71.3%) and by the Autonomous Province of Trento (70.7%). On the other hand, Lombardy (60.7%), Valle d'Aosta (65.6%) and Tuscany (66%) were the regions recording the lowest level (Table 2.1.3).
In 2019, the regions with the highest incidence of consumption were Umbria and the Autonomous Province of Trento (both with 85.1%), Emilia-Romagna (84.9%) and Friuli-Venezia Giulia (84.8%), while Tuscany (81.7%), Sardinia and Valle d'Aosta (both with 82.9%), Lombardy and Basilicata (both with 83%) were the regions showing the lowest value (Table 2.1.4).
Basilicata, Calabria and Campania were the regions with the highest spending percentages in 2019 for ex-originator medicines (80.7%, 80.7% and 80.2%, respectively), while the

Autonomous Province of Trento, Lombardy and Friuli-Venezia Giulia recorded the highest incidence of expenditure for generic medicines (43.2%, 41.8% and 38%, respectively; see Table 2.1.3 and Figure 2.1.5).

Figure 2.1.1. NHS A-Class outpatient pharmaceutical expenditure by patent coverage in 2019

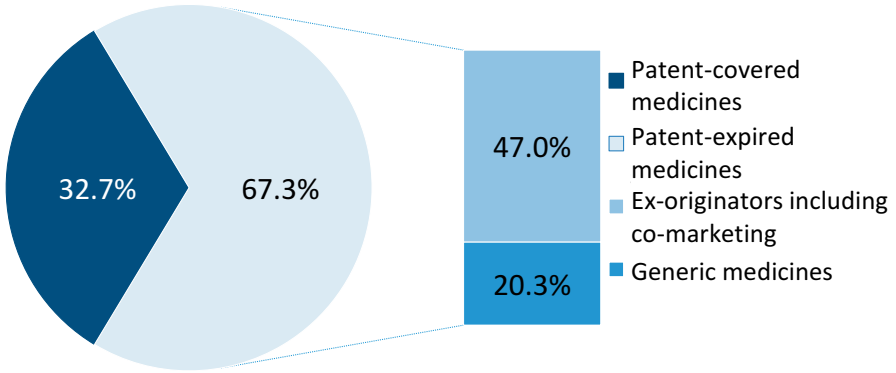
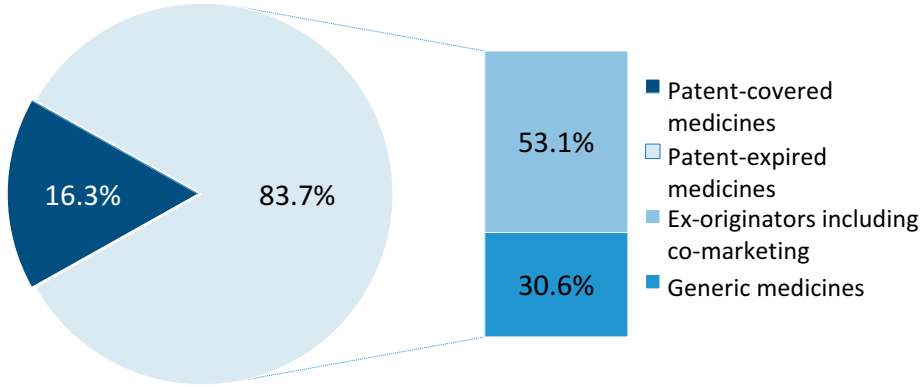


Figure 2.1.2. NHS A-Class outpatient pharmaceutical consumption by patent coverage in 2019



Generic medicines are pharmaceuticals based on active ingredients with an expired patent, with the exclusion of those provided with patent coverage, pursuant to art. 1bis, of Law Decree no. 87 of 27 May 2005, converted with amendments into Law no. 149 of 26 July 2005.

Table 2.1.1. Incidence of NHS A-Class pharmaceutical expenditure and consumption of patent-expired medicines under NHS outpatient care regime by ATC I level in 2019

Level I ATC	NHS outpatient expenditure		Outpatient consumption (DDD)	
	% Patent expired by therapeutic category	% Generic medicine by therapeutic category	% Patent expired by therapeutic category	% Generic medicine by therapeutic category
A	67.7	25.7	82.4	39.6
B	41.0	11.4	65.5	15.9
C	91.2	25.9	94.9	35.8
D	21.2	7.1	21.5	4.4
G	71.1	19.2	77.6	24.1
H	38.2	2.6	77.8	4.3
J	85.2	20.6	92.6	24.3
L	85.0	31.4	87.1	40.2
M	79.8	14.6	86.4	25.3
N	56.8	22.4	76.3	35.8
P	5.2	0.1	3.6	0.3
R	23.2	3.8	46.4	11.0
S	29.3	3.8	41.3	8.2
V	40.1	33.1	25.5	23.4

Table 2.1.2. NHS A-Class outpatient pharmaceutical expenditure, first twenty patent-expired* active ingredients with highest expenditure: comparison 2019-2018

ATC	Active ingredient	Expenditure *(million)*	Δ % 19-18	% Generic medicine**	DDD/1000 inhab. day	DDD average cost
A	cholecalciferol	277.3	3.2	16.1	10.2	1.23
A	pantoprazole	265.0	-2.6	53.6	23.0	0.52
C	atorvastatin	257.2	3.6	37.4	46.1	0.25
J	amoxicillin and enzyme inhibitors	172.5	-0.2	18.3	5.8	1.36
A	lansoprazole	152.1	-7.3	68.1	14.0	0.49
C	bisoprolol	147.3	5.8	30.9	11.2	0.6
A	omeprazole	142.3	-6.1	39.2	16.4	0.39
A	esomeprazole	135.7	-4.6	38.3	13.5	0.46
C	ramipril	122.4	-0.2	38.2	62.5	0.09
C	omega-3-triglycerides	114.4	1.5	34.8	4.4	1.19
C	amlodipine	94.8	1.0	31.7	27.0	0.16
C	simvastatin	94.7	-5.2	51.3	13.2	0.33
A	metformin	91.9	1.2	36.1	22.0	0.19
N	levetiracetam	91.3	5.8	38.8	2.0	2.04
C	olmesartan	90.5	23.4	11.9	13.0	0.32
C	nebivolol	86.9	2.6	23.1	15.5	0.26
J	ceftriaxone	77.0	-0.8	20.5	0.3	11.78
L	letrozole	75.7	9.3	44.2	1.5	2.27
C	rosuvastatin	75.4	-2.6	21.1	12.9	0.27
C	doxazosin	75.1	2.8	29.9	7.6	0.45

* source: monthly transparency lists published by the Italian Medicines Agency in 2018-2019
** calculated on the total expenditure for patent-expired medicinal products

Figure 2.1.3. Incidence trend of patent-expired and generic drug expenditure on the overall NHS-A Class expenditure: comparison 2011-2019

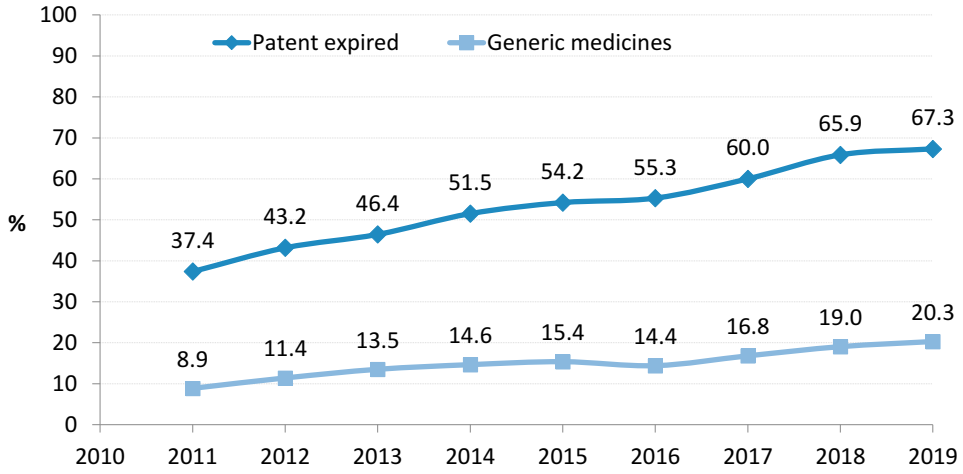


Table 2.1.3. Regional expenditure for NHS A-Class patent-expired* outpatient pharmaceuticals: comparison 2019-2018

Regions	Weighted per capita expenditure (euro)		% on total expenditure		% generic medicine expenditure**	
	2018	2019	2018	2019	2018	2019
Piedmont	95.3	95.9	65.8	66.9	35.3	37.0
Valle d'Aosta	87.9	88.9	64.5	65.6	35.8	36.9
Lombardy	105.9	106.4	60.7	60.7	40.7	41.8
A.P. of Bolzano	78.2	78.3	65.1	66.5	35.5	36.4
A.P. of Trento	96.8	98.8	69.2	70.7	42.3	43.2
Veneto	91.8	92.8	67.1	68.9	34.8	35.8
Friuli Venezia Giulia	99.2	99.8	66.2	67.5	36.7	38.0
Liguria	98.5	100.3	66.6	68.3	33.2	34.8
Emilia Romagna	90.1	91.4	70.8	72.0	35.7	37.0
Tuscany	91.9	90.7	65.6	66.0	35.2	36.5
Umbria	116.2	117.8	69.7	70.5	27.4	28.0
Marche	112.9	114.2	67.5	69.4	24.3	25.2
Lazio	124.5	127.0	66.4	67.9	22.8	23.9
Abruzzo	124.4	125.3	64.8	69.3	25.8	26.5
Molise	113.8	118.5	69.1	71.3	23.7	24.9
Campania	136.3	139.8	67.8	69.9	19.3	19.8
Puglia	127.6	130.9	66.9	69.3	23.4	24.4
Basilicata	118.8	122.8	66.2	67.5	19.2	19.3
Calabria	128.2	134.6	67.3	70.2	18.3	19.3
Sicily	117.2	120.7	66.9	68.5	20.2	21.0
Sardinia	111.2	110.9	64.6	66.3	29.2	30.7
Italy	**109.7**	**111.4**	**65.9**	**67.3**	**29.2**	**30.1**
North	97.6	98.5	64.7	65.5	37.4	38.6
Centre	111.9	113.0	66.6	67.8	26.6	27.6
South and Islands	125.4	128.7	66.9	69.1	21.5	22.3

* source: monthly transparency lists published by the Italian Medicines Agency in 2018-2019
** calculated on the total expenditure for patent-expired medicinal products

Figure 2.1.4. Trend of consumption incidence (doses) of patent-expired and generic medicines on the overall consumption of NHS A-Class pharmaceuticals: comparison 2011-2019

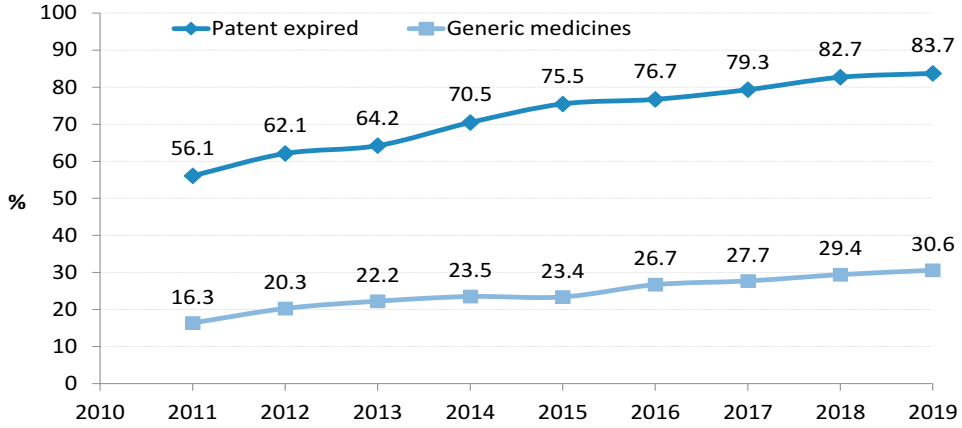
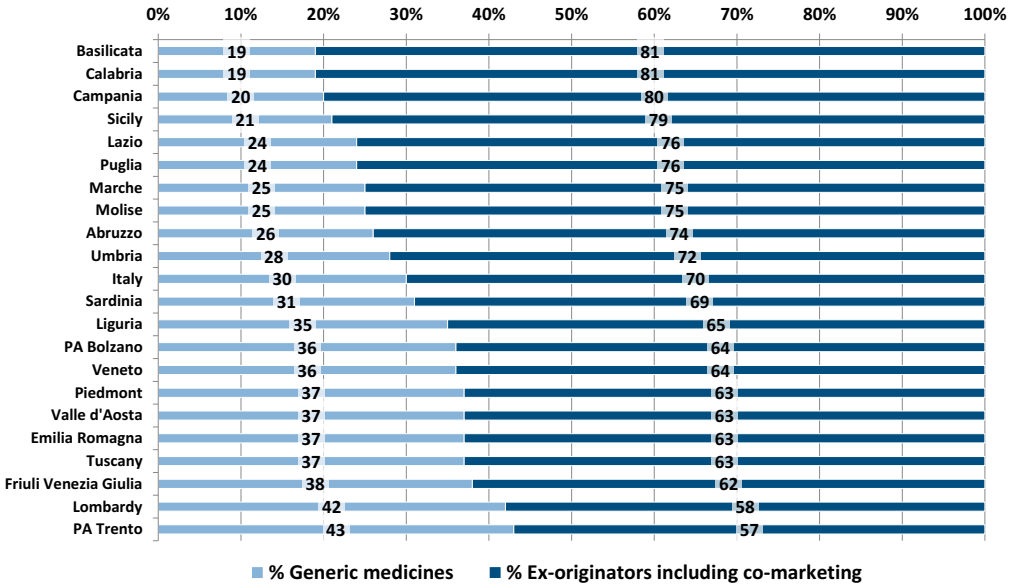


Table 2.1.4. Consumption of NHS A-Class patent-expired* medicines within regional outpatient expenditure: comparison 2019-2018

Region	Weighted DDD/1000 inhab. per day		% on total DDD		% generic medicines expenditure**	
	2018	2019	2018	2019	2018	2019
Piedmont	752.6	767.8	82.3	83.2	43.3	44.6
Valle d'Aosta	669.7	683.5	81.8	82.9	43.8	44.7
Lombardy	759.1	766.7	82.1	83.0	47.9	48.5
A.P. of Bolzano	601.4	608.0	83.3	84.4	43.4	43.6
A.P. of Trento	760.6	776.0	84.0	85.1	50.9	51.1
Veneto	725.5	738.8	82.7	83.9	43.1	43.7
Friuli Venezia Giulia	796.2	810.8	83.8	84.8	44.1	45.1
Liguria	705.2	722.5	82.2	83.3	40.6	41.7
Emilia Romagna	780.3	794.6	84.2	84.9	44.0	44.5
Tuscany	777.0	786.5	81.1	81.7	43.8	44.9
Umbria	925.9	941.5	84.3	85.1	33.6	33.9
Marche	831.3	848.6	82.6	83.8	29.9	30.6
Lazio	877.6	899.2	83.1	84.2	28.2	28.9
Abruzzo	841.4	861.5	81.6	83.6	30.5	30.9
Molise	805.7	840.1	83.0	84.4	26.2	27.1
Campania	897.6	926.6	82.8	84.1	24.4	24.7
Puglia	886.9	917.7	82.5	83.9	27.7	28.5
Basilicata	831.6	861.5	81.8	83.0	22.9	23.2
Calabria	875.9	908.9	82.2	83.7	22.2	22.8
Sicily	859.4	887.2	83.2	84.3	24.8	25.6
Sardinia	823.3	825.0	82.0	82.9	35.0	36.2
Italy	**809.0**	**826.7**	**82.6**	**83.7**	**35.9**	**36.6**
North	750.8	762.8	82.7	83.7	45.0	45.8
Centre	842.9	859.7	82.5	83.4	33.5	34.2
South and Islands	870.8	897.4	82.6	83.9	26.2	26.8

* source: monthly transparency lists published by the Italian Medicines Agency in 2018-2019
** calculated on the total expenditure for patent-expired medicinal products

Figure 2.1.5. Composition by Region of NHS A-Class patent-expired outpatient pharmaceutical expenditure in 2019



Expenditure for citizen co-payment on reference price of patent-expired medicines

In 2019 the expenditure for co-payment relating to the share exceeding the reference price of patent-expired medicines (hereinafter co-payment) was equal to € 18.6 per capita (€ 1.1 billion), accounting for 71% of overall citizen co-payment (including the ticket for prescription and/or package).
The highest per capita expenditure for co-payment was recorded in the South and in the Islands (€ 23.5), while the lowest was recorded in the North with € 14.3 (Table 2.1.5).
Within the Southern regions, Calabria and Campania showed the highest expenditure values (€ 25.5 and € 25.3 per capita, respectively). The lowest value was observed in the Autonomous Province of Bolzano (€ 12.2 per capita) and in the Autonomous Province of Trento (€ 13 per capita).
The results of a correlation analysis between co-payment expenditure and regional per capita income highlighted that the regions with the lowest income displayed the greatest co-payment. In particular, in Calabria and Sicily, which have a per capita income of less than € 10,000, a higher co-payment was found than the national average (> € 24) (Figure 2.1.6).
The first three therapeutic categories with the highest co-payment expenditure were cardiovascular system medicines, in particular lipid modifying substances (8.7%), beta-blockers (6.8%) and angiotensin II antagonists, in combination with other medicines (5.9%). These three categories represented 21.4% of the total expenditure (Table 2.1.6).
As regards the first thirty active ingredients with the greatest expenditure impact on the reference price, half of them belonged to cardiovascular system medicines; in particular, bisoprolol and atorvastatin cover 11.1% (Table 2.1.7).
Considering the first ten therapeutic categories (ATC III) with the greatest co-payment expenditure share on the reference price, the distribution of subjects who use generic medicines was assessed by geographical area, gender and age (Table 2.1.8). The results showed that, for most of the therapeutic categories, the largest users were distributed in the North and that women represented the largest share, with the exception of medicines for benign prostatic hypertrophy (ATC G04C). Overall, no differences were observed in the use of generic drugs for the pharmaceutical categories considered.
On the other hand, when considering the average difference between the retail price and the reference price and the expenditure share with respect to the distribution channel (Table 2.1.9), most of the products with an average difference of less than € 3 were distributed under NHS outpatient care regime (73.2%).
Therefore, whereas the expenditure for tickets per package and/or prescription showed that the regional variability is due to different implementations of such ticket, for co-payment on the reference price of patent-expired medicines, the regional differences were essentially attributable to the different use of generic medicines. This highlights the need to carry out further information/training actions both at national and regional level in order to promote a wider use of generic medicines.

Table 2.1.5. Co-payment distribution share on reference price by region (Table and Figure) (year 2019)

Region	Weighted per capita expenditure	Δ % national average
Piedmont	14.50	-22.1
Valle d'Aosta	13.20	-28.8
Lombardy	14.30	-23.2
A.P. of Bolzano	12.20	-34.5
A.P. of Trento	13.00	-30.1
Veneto	14.10	-24.0
Friuli Venezia Giulia	14.90	-19.6
Liguria	15.30	-17.6
Emilia Romagna	14.30	-23.1
Tuscany	13.70	-26.5
Umbria	19.90	7.0
Marche	19.60	5.5
Lazio	25.30	36.2
Abruzzo	21.10	13.3
Molise	21.80	17.4
Campania	25.30	36.1
Puglia	22.40	20.6
Basilicata	22.40	20.7
Calabria	25.50	37.0
Sicily	24.80	33.5
Sardinia	17.40	-6.7
Italy	**18.60**	-
North	14.30	-23.0
Centre	20.40	9.9
South and Islands	23.50	26.6

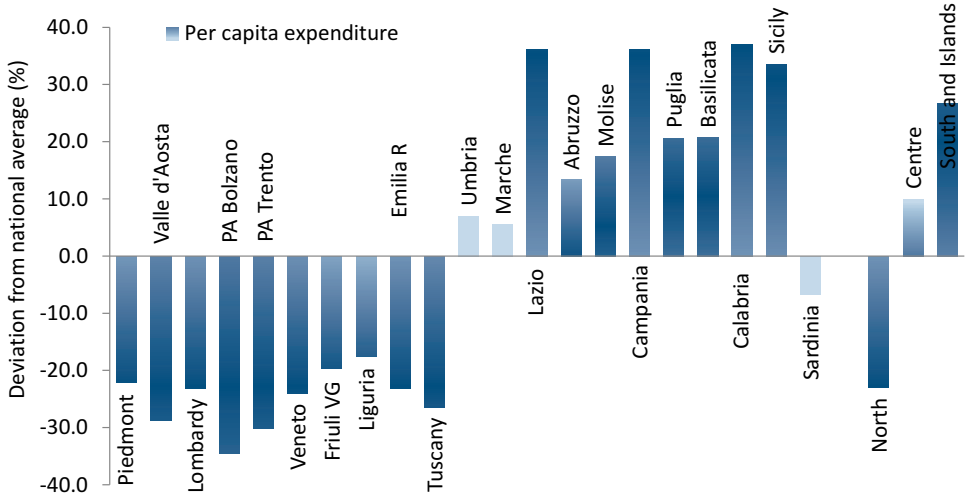


Figure 2.1.6. Correlation analysis between co-payment expenditure and per capita income

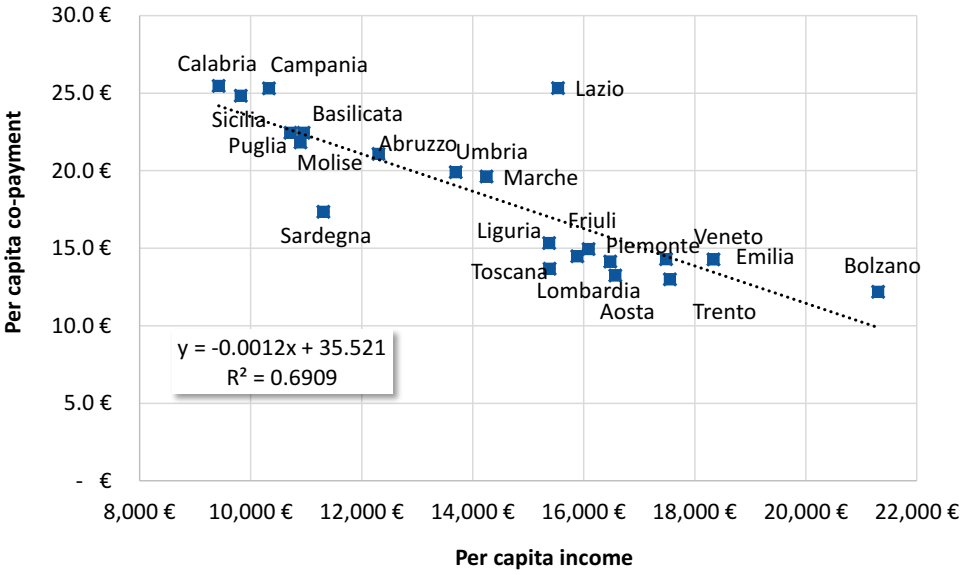


Table 2.1.6. Top 20 therapeutic categories with higher expenditure share on reference price (year 2019)

ATC III	Description	Total expenditure	Δ% 19-18	%*	% cum.
C10A	Lipid-modifying agents, plain	96,452,629	-2.8	8.7	8.7
C07A	Beta-blockers	76,202,232	1.7	6.8	15.5
C09D	Angiotensin II antagonists, in combination	65,736,057	9.5	5.9	21.4
A02B	Anti-peptic ulcer drugs	64,878,588	-18.3	5.8	27.2
C09C	Angiotensin II antagonists	56,513,083	7.3	5.1	32.3
C09B	Angiotensin converting enzyme (ACE) inhibitors, in combination	54,866,921	-0.4	4.9	37.2
C09A	Angiotensin converting enzyme (ACE) inhibitors, plain	51,067,376	-2.3	4.6	41.8
N06A	Antidepressants	50,688,819	0.6	4.6	46.4
B01A	Antithrombotic drugs	40,955,400	4.1	3.7	50.1
G04C	Drugs used in benign prostatic hypertrophy	38,909,175	-1.7	3.5	53.6
M01A	Anti-inflammatory and anti-rheumatic drugs, non-steroidal	38,270,214	-2.0	3.4	57.0
A11C	Vitamins A and D, including their combinations	37,923,291	-3.3	3.4	60.4
C08C	Selective calcium channel blockers with prevailing vascular effect	35,995,501	-2.3	3.2	63.6
A10B	Oral hypoglycaemic agents	29,960,548	-5.4	2.7	66.3
N03A	Antiepileptics	29,805,493	1.5	2.7	69.0
J01C	Beta-lactam antibiotics, penicillins	24,839,193	0.9	2.2	71.2
J01D	Other beta-lactam antibiotics	24,227,814	2.1	2.2	73.4
S01E	Antiglaucoma preparations and miotic agents	18,111,824	-1.3	1.6	75.0
R06A	Antihistamines for systemic use	15,326,497	1.5	1.4	76.4
J01F	Macrolides and lincosamides	14,888,557	6.1	1.3	77.7

*calculated on total co-payment

Table 2.1.7. Top 30 active ingredients with higher expenditure share on reference price (year 2019)

ATC V	Active ingredient	Total expenditure	Δ% 19-18	%*	% cum.
C07AB07	bisoprolol	49,420,085	3.7	4.4	4.4
C10AA05	atorvastatin	39,280,556	1.8	3.5	7.9
A11CC05	cholecalciferol	35,191,780	-3.6	3.2	11.1
C09AA05	ramipril	27,741,908	0.4	2.5	13.6
A02BC02	pantoprazole	25,836,241	-18.6	2.3	15.9
B01AC06	acetyl salicylic acid	23,869,286	-0.9	2.1	18.0
J01CR02	amoxicillin/clavulanic acid	21,376,064	1.4	1.9	19.9
C08CA01	amlodipine	20,542,422	-0.2	1.8	21.7
C10AX06	omega 3	16,663,008	-11.2	1.5	23.2
A10BA02	metformin	16,485,480	-3.3	1.5	24.7
C09CA08	olmesartan medoxomil	15,489,302	18.3	1.4	26.1
B01AC04	clopidogrel	15,466,771	15.5	1.4	27.5
G04CA02	tamsulosin	15,034,542	1.1	1.4	28.9
A02BC03	lansoprazole	14,556,507	-13.7	1.3	30.2
C09DA08	olmesartan medoxomil/hydrochlorothiazide	14,087,354	6.1	1.3	31.5
C09BB04	perindopril/amlodipine	13,950,654	-2.2	1.3	32.8
G04CB02	dutasteride	12,899,823	-4.2	1.2	34.0
C10AA07	rosuvastatin	12,852,292	-4.5	1.2	35.2
C07AB12	nebivolol	12,656,224	-0.3	1.1	36.3
M01AB05	diclofenac	12,546,447	4.6	1.1	37.4
C10AA01	simvastatin	12,319,656	-6.3	1.1	38.5
J01DD04	ceftriaxone	12,099,958	1.1	1.1	39.6
C09DB02	olmesartan medoxomil/amlodipine	11,930,030	243.9	1.1	40.7
N06AB10	escitalopram	11,653,558	-2.8	1.0	41.7
G04C	doxazosin	11,612,878	0.7	1.0	42.7
C09DA03	valsartan/hydrochlorothiazide	11,272,237	-9.5	1.0	43.7
C09BA05	ramipril/hydrochlorothiazide	11,136,371	-10.1	1.0	44.7
H03AA01	levothyroxine	10,931,683	1.6	1.0	45.7
J01XX01	fosfomycin	10,903,241	7.9	1.0	46.7
C09CA07	telmisartan	10,790,698	7.0	1.0	47.7

* calculated on total co-payment

Table 2.1.8. Distribution by geographic area, gender and age of subjects using generic drugs for the first 10 therapeutic categories (ATC III) with higher expenditure on reference price (year 2019)

	C10A %	C07A %	C09D %	A02B %	C09C %	C09B %	C09A %	N06A %	B01A %	G04C %
Geographic area										
North	42.0	44.8	40.1	39.0	39.5	42.6	47.3	47.2	41.1	42.5
Centre	20.3	19.6	18.8	20.3	21.4	20.1	21.3	23.1	22.3	21.6
South and islands	37.7	35.6	41.1	40.8	39.1	37.3	31.4	29.8	36.6	35.9
Gender										
Men	49.7	44.8	44.7	43.6	47.1	48.8	52.8	31.6	49.2	98.6
Women	50.3	55.2	55.3	56.4	52.9	51.2	47.2	68.4	50.8	1.4
Age group										
<50	5.9	7.8	6.1	18.9	7.8	8.1	8.9	21.9	8.4	3.6
50-60	15.1	15.1	15.9	15.5	17.0	18.0	17.2	17.3	10.1	10.1
60-70	27.1	23.7	25.8	20.5	25.1	25.3	24.1	17.7	20.0	24.8
70-80	32.2	29.3	31.0	24.7	28.5	28.6	27.4	21.2	31.1	35.7
>80	19.6	24.1	21.1	20.5	21.6	19.9	22.4	21.9	30.4	25.8

Note: for ATC III level descriptions see Table 2.1.7

Table 2.1.9. Average difference between retail and reference price and expenditure share under outpatient care regime, direct and *per conto* distribution (year 2019)

Average difference between retail and reference price €	% expenditure- outpatient care regime	% expenditure direct and *per conto* distribution
<1	10.61	2.59
1-2	31.68	3.63
2-3	30.88	3.16
3-5	17.89	6.75
5-20	8.22	12.13
>20	0.72	71.74

Biosimilars

The 2019 data on consumption of biosimilars supplied through public health facilities confirmed the increase compared to the previous year for those drugs whose biosimilar product has been commercially available for several years such as, for example, follitropin (+ 67.0%), epoetins (+ 21.5%), somatropin (+ 14.7%) and pegfilgrastim (+ 9.9%). This trend contributed to a reduction in expenditure by 0.4%, 8.0%, 2.7% and 10.8%, respectively (Table 2.1.10).
As regards the use of more recently marketed biosimilars, a positive trend was recorded in the consumption of rituximab in the intravenous formulation (+ 83.2%), etanercept (+ 52.7%) and insulin glargine (+17.8%).
Within the biosimilars first marketed in 2018, a major increase was registered in the consumption of adalimumab, trastuzumab in intravenous formulation, enoxaparin and insulin lispro. As for patent-expired teriparatide, marketed in the second half of 2019, a low market penetration was recorded, with an incidence equal to 0.5% compared to the originator (Table 2.1.11).
Finally, 2019 also showed a wide regional variability in the use of biosimilar medicines. In particular, compared to the national average, the regions with the highest consumption of biosimilars and the lowest consumption of originators were Tuscany, Marche, Emilia-Romagna and Piedmont (Figure 2.1.9). Conversely, the regions that display the highest consumption of originators and the lowest consumption of biosimilars were Lombardy, Autonomous Provinces of Bolzano and Trento, Liguria, Umbria, Molise, Puglia and Calabria.
The analysis of the regional variability in the expenditure incidence for the different molecules showed that Emilia-Romagna had the highest percentage for epoietin (Figure 2.1.10), Tuscany for filgrastim and Molise for pegfilgrastim (Figure 2.1.11), Piedmont for somatotropin (Figure 2.1.12), Abruzzo for follitropin (Figure 2.1.13). The most virtuous regions in the incidence of biosimilar expenditure are: Piedmont for insulin glargine (Figure 2.1.14), Sardinia for etanercept and the Autonomous Province of Trento for infliximab and rituximab (Figures 2.1.15 and 2.1.16), Tuscany for trastuzumab (Figure 2.1.17), Emilia-Romagna for low molecular weight heparins and for insulin lispro (Figures 2.1.18 and 2.1.19).

Table 2.1.10. Biosimilars, inpatient and outpatient NHS supply in 2019

Group Subgroup	Per capita expenditure	Inc %	Δ% 19-18	DDD/1000 inhab. day	Inc %	Δ% 19-18
Fast acting insulin (A10AB)	**3.91**		**-4.5**	**8.6**		**-2.4**
Originator insulin lispro[1]	1.65	42.3	-10.2	3.6	42.4	-7.7
Biosimilar insulin lispro[2]	0.08	2.1	>100	0.3	3.6	>100
Other fast acting insulins[3]	2.18	55.6	-2.3	4.6	54.0	-2.4
Long acting insulin (A10AD)	**2.79**		**-1.8**	**6.3**		**0.3**
Originator insulin glargine[4]	0.94	33.8	-18.9	2.4	38.2	-17.6
Biosimilar insulin glargine[5]	0.28	10.1	14.9	0.8	13.1	17.8
Other insulin glargine[6]	0.55	19.7	47.4	1.4	22.5	48.8
Other long acting insulin[7]	1.02	36.4	-4.1	1.7	26.2	-3.3
Low Molecular Weight Heparins (B01AB)	**3.15**		**-16.0**	**7.8**		**1.3**
Originator[8]	1.36	43.1	-34.2	2.9	37.6	-30.7
Biosimilar[9]	0.75	24.0	>100	3.3	41.9	>100
Other low molecular weight heparins[10]	1.04	32.9	-27.0	1.6	20.6	-27.2
Epoetin (B03XA)	**3.06**		**-8.0**	**3.5**		**6.2**
Originator[11]	0.52	16.9	-27.9	0.4	11.8	-22.5
Biosimilar[12]	1.36	44.3	10.2	2.5	71.5	21.5
Other epoetins[13]	1.19	38.8	-13.9	0.6	16.6	-16.8
Follitropin alfa (G03GA)	**1.01**		**-0.4**	**0.1**		**-1.6**
Originator[14]	0.29	28.7	-24.4	0.0	26.7	-22.1
Biosimilar[15]	0.13	13.0	53.0	0.0	14.6	67.0
Other follitropin[16]	0.59	58.3	8.0	0.1	58.7	0.2
Somatropin (H01AC)	**1.46**		**-2.7**	**0.3**		**1.3**
Originator[17]	0.24	16.1	-8.6	0.0	13.7	-7.6
Biosimilar[18]	0.27	18.4	10.5	0.1	24.4	14.7
Other somatropin[19]	0.95	65.5	-4.4	0.2	61.9	-1.1
Teriparatide (H05AA)	**1.44**		**1.2**	**0.2**		**3.5**
Originator[20]	1.44	99.5	0.7	0.2	99.2	2.6
Biosimilar[21]	0.01	0.5	-	0.0	0.8	-
Rituximab (L01XC02)	**1.73**		**-20.5**	**0.5**		**1.3**
Originator SC[22]	0.45	26.2	-25.9	0.2	33.5	-18.7
Originator IV[23]	0.18	10.4	-78.4	0.0	6.2	-74.6
Biosimilar IV[24]	1.10	63.4	49.9	0.3	60.2	83.2
Trastuzumab (L01XC03)	**2.20**		**-45.7**	**0.2**		**-3.0**
Originator SC[25]	1.06	48.1	-45.3	0.1	46.8	-26.0
Originator IV[26]	0.44	20.1	-78.1	0.0	9.8	-72.7
Biosimilar IV[27]	0.70	31.8	>100	0.1	43.3	>100
Bevacizumab (L01XC07)	**3.21**		**-0.7**	**0.1**		**-0.8**
Originator[28]	3.21	100.0	-0.7	0.1	100.0	-0.8
Biosimilar[29]	0.00	0.0	-	-	-	-
Growth factors (L03AA)	**0.76**		**-10.8**	**0.1**		**8.3**
Originator filgrastim[30]	0.04	5.4	-2.8	0.0	1.3	-7.7
Biosimilar filgrastim[31]	0.15	19.3	1.0	0.0	45.5	9.9
Originator pegfilgrastim[32]	0.30	39.9	-29.3	0.0	27.0	-24.7
Biosimilar pegfilgrastim[33]	0.05	6.0	-	0.0	12.3	-
Other growth factors[34]	0.22	29.5	-5.2	0.0	13.9	1.3

continued

continued Table 2.1.11

Group Subgroup	Per capita expenditure	Inc %	Δ% 19-18	DDD/1000 inhab. day	Inc %	Δ% 19-18
Anti-TNF alfa (L04AB)	**6.91**		**-34.3**	**1.3**		**6.9**
Originator etanercept[35]	1.22	17.7	-36.1	0.1	9.7	-30.4
Biosimilars etanercept[36]	0.81	11.8	5.1	0.2	12.7	52.7
Originator infliximab[37]	0.22	3.2	-59.4	0.0	3.8	-42.5
Biosimilars infliximab[38]	0.62	9.0	-12.2	0.3	21.5	19.5
Originator adalimumab[39]	1.75	25.3	-63.1	0.3	22.0	-32.3
Biosimilars adalimumab[40]	0.47	6.7	>100	0.2	15.7	>100
Other AntiTNFalfa[41]	1.82	26.3	0.7	0.2	14.5	7.8

[1] Humalog®; [2] Insulin Lispro Sanofi®; [3]Humulin®, Insuman®, Novarapid®, Actrapid®, Apidra®, Fiasp®; [4] Lantus®; [5] Abasaglar®, Semglee®; [6] Toujeo®; [7] Tresiba®, Levemir®; [8] Clexane®; [9] Inhixa®, Enoxaparina Rovi®; [10] Fragmin®, Fraxiparina®, Seledie®, Seleparina®, Fluxum®, Clivarina®, Ivor®, Arixtra®; [11] Eprex®; [12] Binocrit®, Retacrit®; [13] Aranesp®, Eporatio®, Mircera®, Neorecormon®; [14] Gonal-F®; [15] Ovaleap®, Bemfola®;[16] Meriofert®, Puregon®, Elonva®, Pergoveris®, Fostimon®, Rekovelle®, Meropur®; [17] Genotropin®; [18] Omnitrope®; [19] Humatrope®, Norditropin®, Nutropinaq®, Saizen®, Zomacton®; [20] Forsteo®; [21] Terrosa®, Movymia®; [22] Mabthera SC®; [23] Mabthera IV®; [24] Truxima®, Rixathon, Riximyo, Ritemvia, Blitzima; [25] Herceptin SC®; [26] Herceptin IV®; [27] Ontruzant®, Herzuma®, Kanjinti®, Trazimera®, Ogivri®; [28] Avastin®; [29] Zirabev®, Mvasi®; [30]Granulokine®, Neupogen®; [31]Accofil®, Ratiograstim®, Nivestim®, Tevagrastim®, Zarzio®; [32] Neulasta®; [33] Pegfilgrastim Mundipharma®, Grasustek®, Ziextenzo®, Fulphila®, Pelmeg®; Udenyca®; Pelgraz®; [34]Myelostim®, Lonquex®, Granocyte®; [35]Enbrel®; [36]Benepali®, Erelzi®; [37] Remicade®; [38] Inflectra®, Remsina®; Flixabi®, Zessly®; [39] Humira®; [40]Amgevita®, Imraldi®, Hefiya®, Halimatoz®, Hyrimoz®, Hulio®, Idacio®, Kromeya®, Cyltezo®; [41] Cimzia®, Simponi®.
Biosimilars of teriparatide were marketed in Italy as of 2019.

Figure 2.1.7. Incidence (%) of biosimilars on expenditure for biosimilar pharmaceuticals and originator medicine: 2015-2019

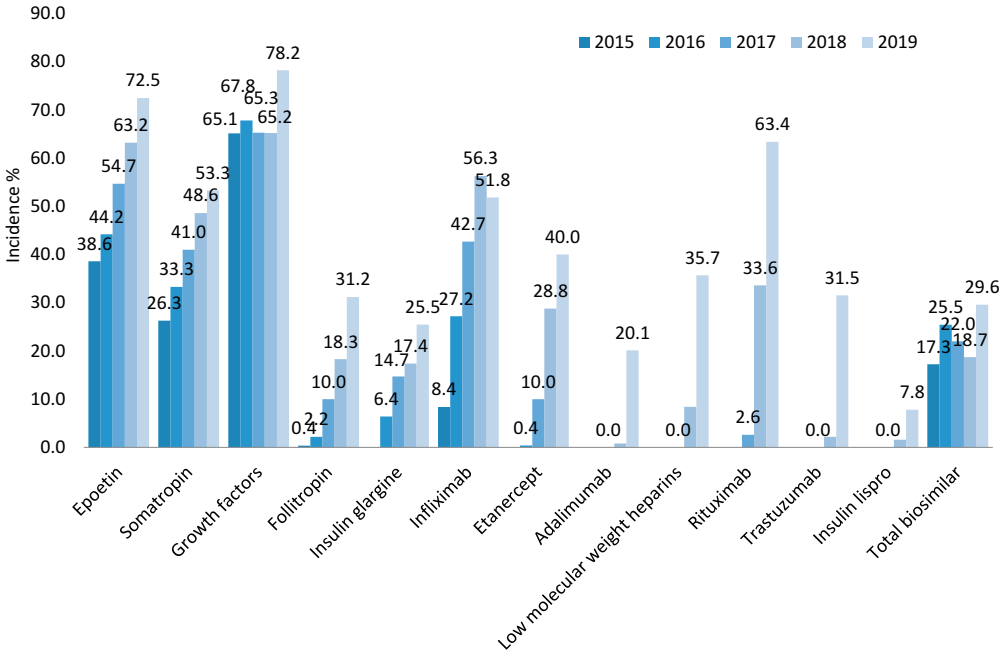


Figure 2.1.8. Incidence (%) of biosimilars on consumption of biosimilar pharmaceuticals and originator drug: 2015-2019

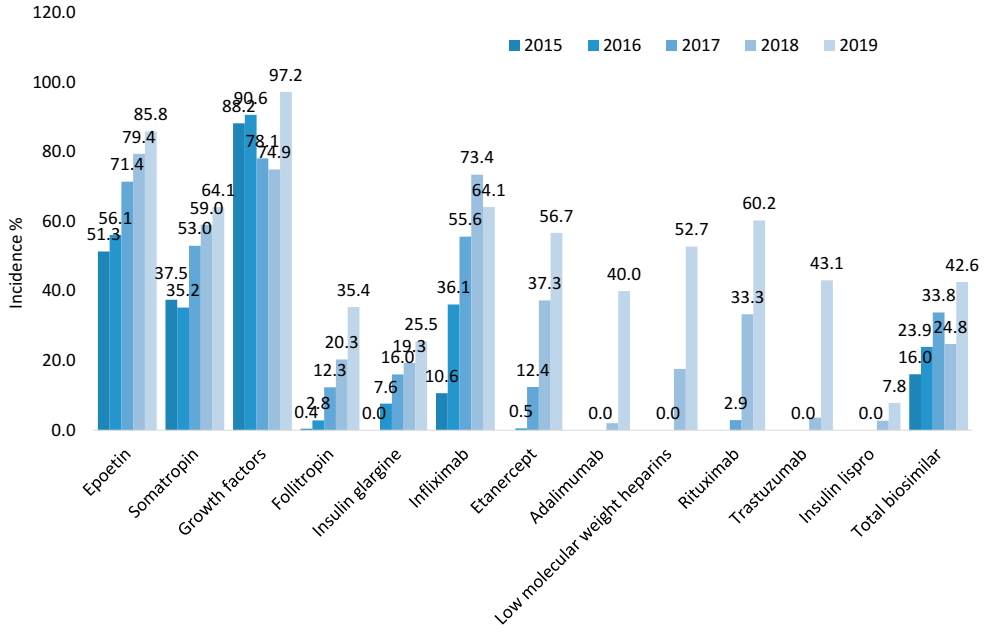


Figure 2.1.9. Consumption (DDD/1000 inhab. day) of biosimilar pharmaceuticals vs originator drug with reference to national average

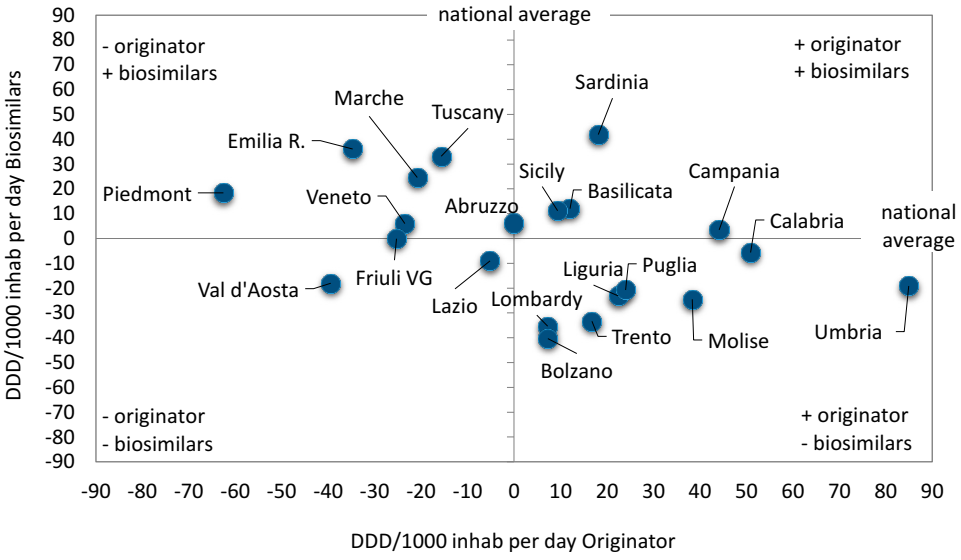


Table 2.1.11. Biosimilars, inpatient and outpatient NHS supply in 2019: comparison biosimilar vs originator drug

Group Subgroup	Per capita expenditure	Inc %	Δ% 19-18	DDD/1000 inhab. day	Inc %	Δ% 19-18
Insulin lispro	**1.73**		**-7.3**	**3.9**		**-2.5**
Originator[1]	1.65	95.4	-10.2	3.6	92.2	-7.7
Biosimilar[2]	0.08	4.6	>100	0.3	7.8	>100
Insulin glargine	**1.23**		**-13.0**	**3.2**		**-10.8**
Originator[3]	0.94	77.0	-18.9	2.4	74.5	-17.6
Biosimilar[4]	0.28	23.0	14.9	0.8	25.5	17.8
Low Molecular Weight Heparins	**2.11**		**-9.2**	**6.2**		**12.7**
Originator[5]	1.36	64.3	-34.2	2.9	47.3	-30.7
Biosimilar[6]	0.75	35.7	>100	3.3	52.7	>100
Epoetin	**1.87**		**-3.8**	**2.9**		**12.4**
Originator[7]	0.52	27.5	-27.9	0.4	14.2	-22.5
Biosimilar[8]	1.36	72.5	10.2	2.5	85.8	21.5
Follitropin alfa	**0.42**		**-10.2**	**0.1**		**-4.0**
Originator[9]	0.29	68.8	-24.4	0.0	64.6	-22.1
Biosimilar[10]	0.13	31.2	53.0	0.0	35.4	67.0
Somatropin	**0.50**		**0.7**	**0.1**		**5.5**
Originator[11]	0.24	46.7	-8.6	0.0	35.9	-7.6
Biosimilar[12]	0.27	53.3	10.5	0.1	64.1	14.7
Teriparatide	**1.44**		**1.2**	**0.2**		**3.5**
Biosimilar [13]	0.01	0.5	-	0.0	0.8	
Originator [14]	1.44	99.5	0.7	0.2	99.2	2.6
Rituximab	**1.73**		**-20.5**	**0.5**		**1.3**
Originator IV[15]	0.18	10.4	-78.4	0.0	6.2	-74.6
Originator SC[16]	0.45	26.2	-25.9	0.2	33.5	-18.7
Biosimilar IV[17]	1.10	63.4	49.9	0.3	60.2	83.2
Trastuzumab	**2.20**		**-45.9**	**0.2**		**-3.5**
Originator IV[18]	0.44	20.2	-78.1	0.0	9.9	-72.7
Originator SC[19]	1.06	48.3	-45.3	0.1	47.1	-26.0
Biosimilar IV[20]	0.69	31.5	>100	0.1	43.1	>100
Bevacizumab	**3.21**		**-0.7**	**0.1**		**-0.8**
Biosimilar [21]	0.00	0.0	-	-	-	-
Originator [22]	3.21	100.0	-0.7	0.1	100.0	-0.8
Growth factors	**0.19**		**0.1**	**0.0**		**9.3**
Biosimilar[23]	0.15	78.2	1.0	0.0	97.2	9.9
Originator[24]	0.04	21.8	-2.8	0.0	2.8	-7.7
Etanercept	**2.04**		**-24.2**	**0.3**		**0.6**
Originator[25]	1.22	60.0	-36.1	0.1	43.3	-30.4
Biosimilar[26]	0.81	40.0	5.1	0.2	56.7	52.7
Infliximab	**0.46**		**-45.3**	**0.1**		**-22.1**
Originator[27]	0.22	48.2	-59.4	0.0	35.9	-42.5
Biosimilar[28]	0.24	51.8	-19.1	0.1	64.1	-2.7
Adalimumab	**2.19**		**-54.2**	**0.5**		**10.5**
Originator[29]	1.75	79.9	-63.1	0.3	60.0	-32.3
Biosimilar[30]	0.44	20.1	>100	0.2	40.0	>100

[1] Humalog®,[2] Insulin Lispro Sanofi®; [3] Lantus®; [4] Abasaglar®, Semglee®; [5] Clexane®; [6] Inhixa®, Enoxaparina Rovi®; [7]Eprex®; [8]Binocrit®, Retacrit®; [9] Gonal-F®; [10]Ovaleap®, Bemfola®;[11]Genotropin®; [12] Omnitrope®; [13] Forsteo®; [14] Terrosa®, Movymia®;
[15] Mabthera SC®; [16] Mabthera IV®; [17] Truxima®, Rixathon, Riximyo, Ritemvia, Blitzima;[18] Herceptin SC®; [19] Herceptin IV®; [20]Ontruzant®, Herzuma®, Kanjinti®, Trazimera®; Ogivri®; [21] Avastin®,[22] Zirabev®, Mvasi®; [23]Granulokine®; Neupogen®, Neulasta®; [24]Accofil®, Ratiograstim®, Nivestim®, Tevagrastim®, Zarzio®; Pegfilgrastim Mundipharma®, Grasustek®, Ziextenzo®, Fulphila®, Pelmeg®; Udenyca®; Pelgraz®;[25]Enbrel®; [26]Benepali®, Erelzi®; [27] Remicade®; [28] Inflectra®, Remsina®; Flixabi®; Zessly®;[29] Humira®, [30]Amgevita®, Imraldi®; Hefiya®, Halimatoz®; Hyrimoz®, Hulio ®.
Biosimilars of teriparatide were marketed in Italy as of 2019.

Figure 2.1.10. Regional incidence variability (%) of expenditure for epoetin biosimilars: year 2019

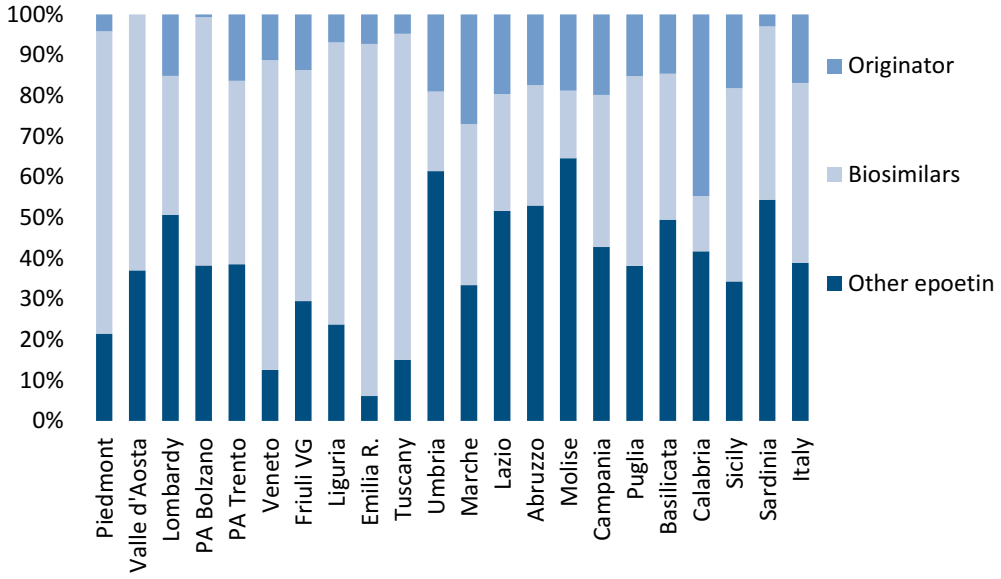


Figure 2.1.11. Regional incidence variability (%) of expenditure for growth factors biosimilars: year 2019

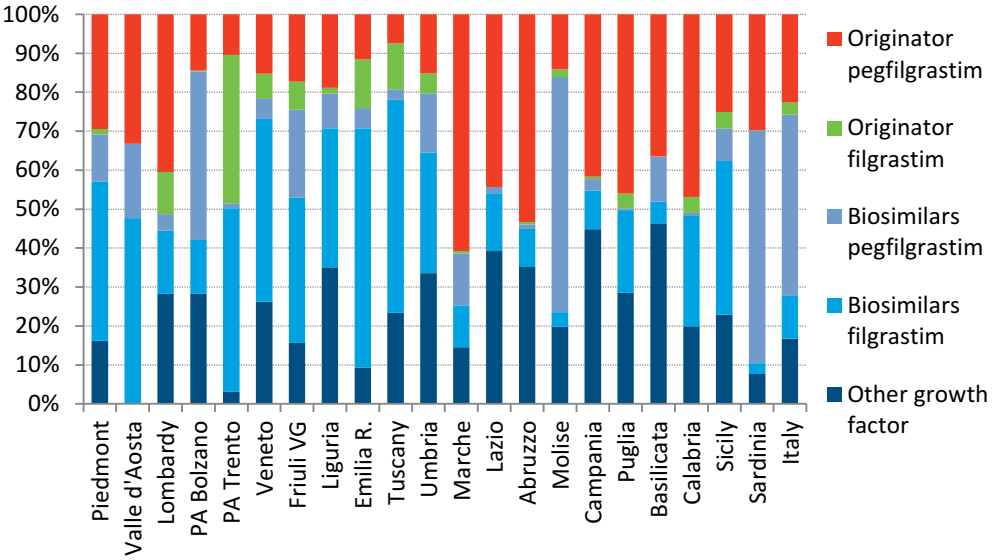


Figure 2.1.12. Regional incidence variability (%) of expenditure for somatotropin biosimilars: year 2019

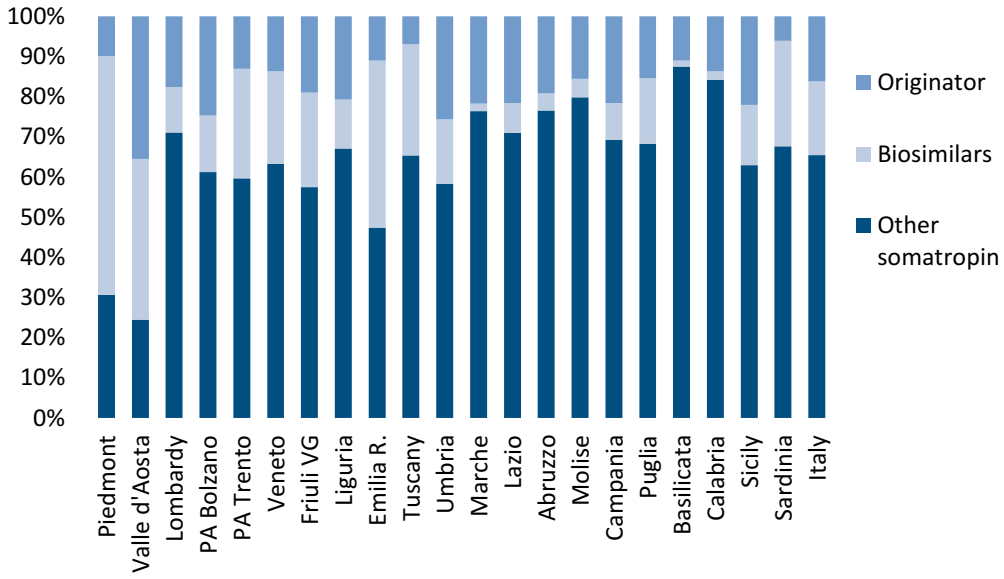


Figure 2.1.13. Regional incidence variability (%) of expenditure for follitropin alfa biosimilars: year 2019

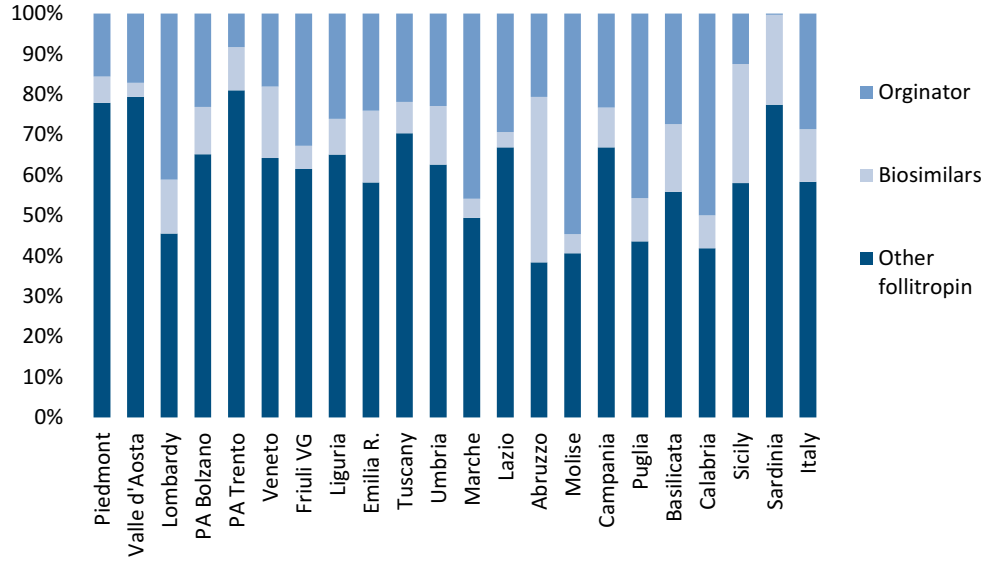


Figure 2.1.14. Regional incidence variability (%) of expenditure for insulin glargine biosimilars: year 2019

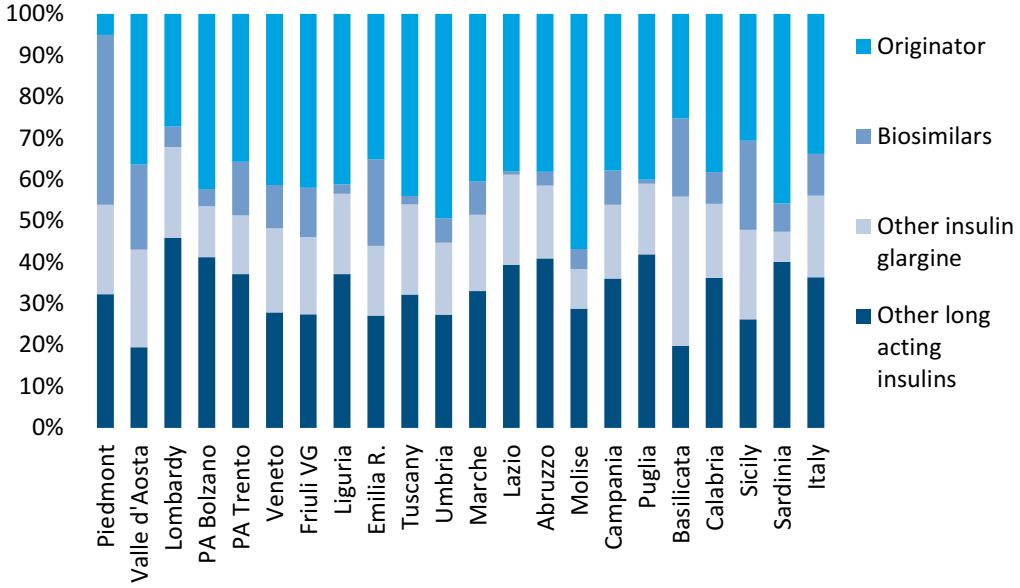


Figure 2.1.15. Regional incidence variability (%) of expenditure for biosimilars of infliximab, etanercept and adalimumab: year 2019

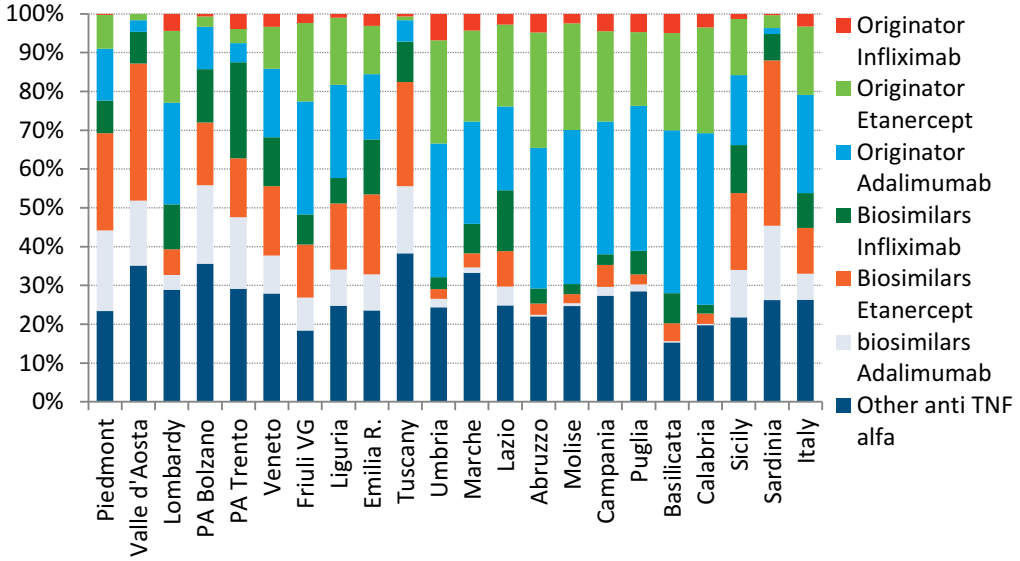


Figure 2.1.16. Regional incidence variability (%) of expenditure for rituximab biosimilars: year 2019

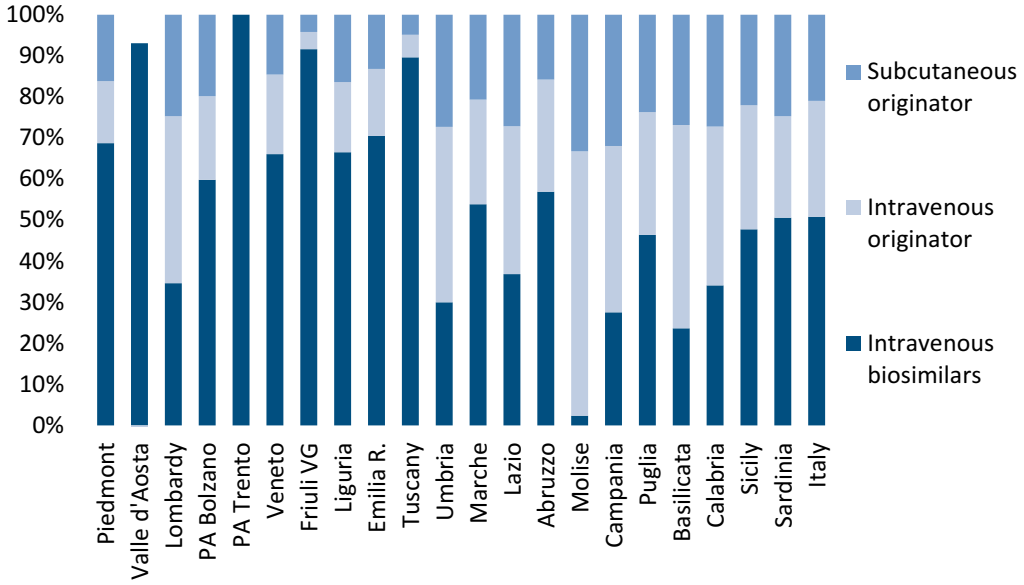


Figure 2.1.17. Regional incidence variability (%) of expenditure for trastuzumab biosimilars: year 2019

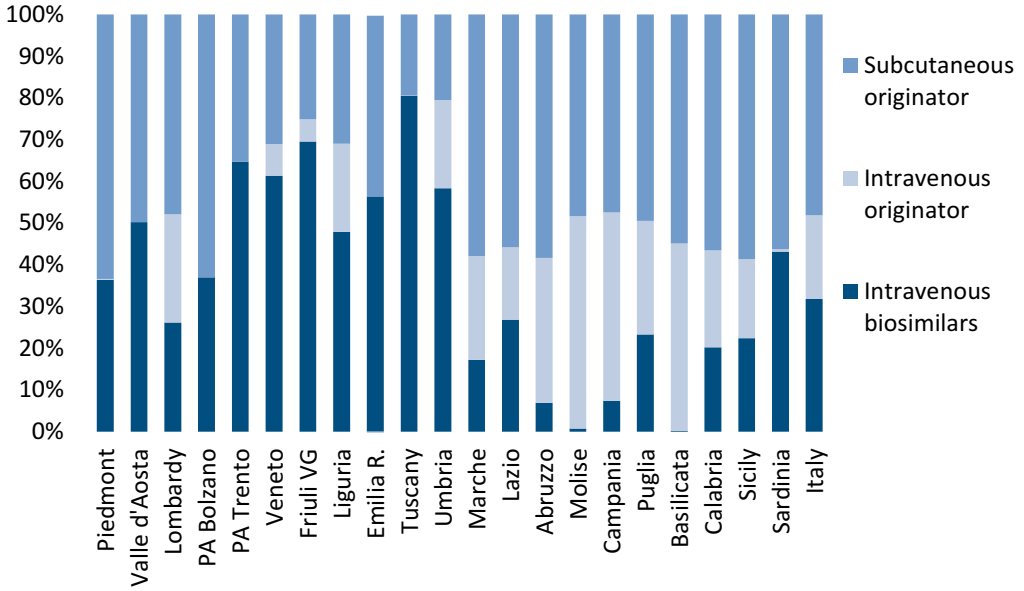


Figure 2.1.18. Regional incidence variability (%) of expenditure for biosimilars of low molecular weight heparins: year 2019

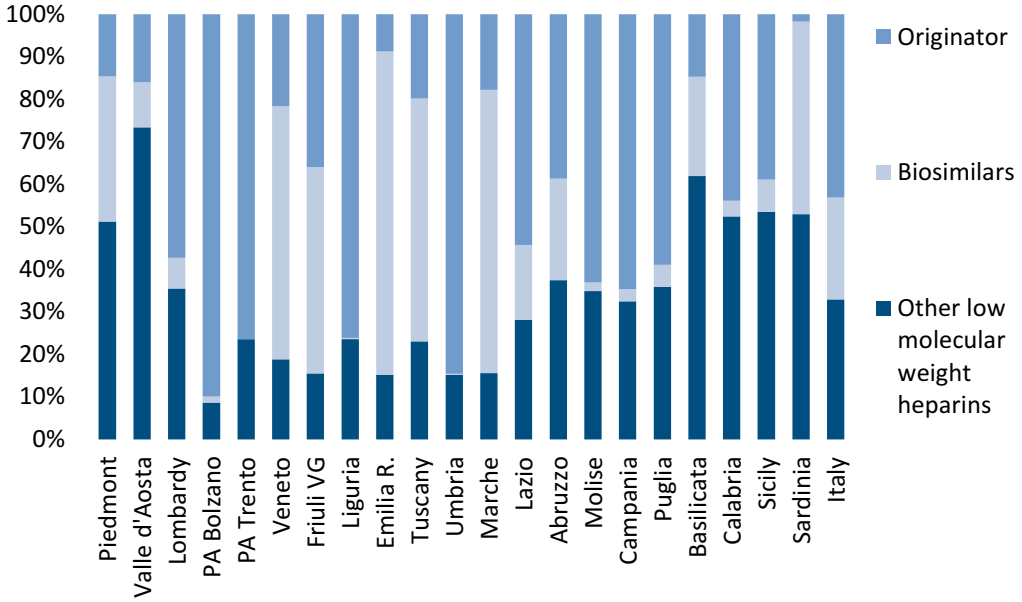
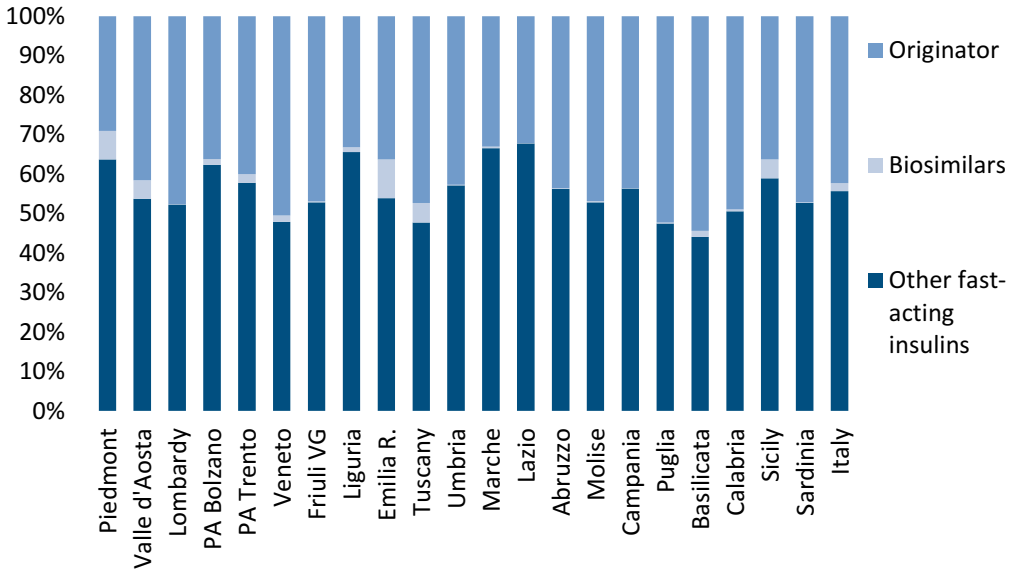


Figure 2.1.19. Regional incidence variability (%) of expenditure for insulin lispro biosimilars: year 2019



2.7 Consumption of medicinal products directly purchased by citizens

In 2019 the expenditure for Class C medicines amounted to over €5.7 billion, of which 53.6% (€3 billion) is due to medicinal products with prescription and 46.4% (€2.7 billion) to self-medication medicines (SOP and OTC), including those supplied by shops.
The 6.6% increase in expenditure of Class C medicinal products with prescription compared to the previous year was mainly due to an increase in prices (+4.4%), an increase in quantities (+2.8%) and by a stable mix effect (Figure 2.7.1).
At regional level there is a marked variability in expenditure and consumption which can be explained both by a different attitude of physicians and patients in the use of these medicines and by interregional differences in income. For example, per capita expenditure for Class C medicines in Liguria is more than double compared to Umbria (€ 68.1 vs € 31.3) and expenditure in the North is almost 15% higher than in the South. The largest increases in consumption were recorded in Marche (+16.9%), Lazio (+9.2%) and Abruzzo (+8.8%), while Sicily (-1.8%), Umbria and the Autonomous Province of Bolzano showed the largest reductions (-1.7%; Table and Figure 2.7.4).
Benzodiazepines are the most purchased category, accounting for 18.2% of the expenditure and 26% of DDD of Class C with prescription (Table 2.7.1). Consumption in the last four years increased slightly, with 49.8 DDD in 2019. Benzodiazepines with an anxiolytic effect and those with a hypnotic effect represent more than 90% of consumption of the category and rank first and fifth, respectively, in terms of expenditure within the Class C categories (the former increasing by 2.5% compared to 2018 and the latter by 7%).
Paracetamol, with €188 million, is the active ingredient with the highest expenditure, accounting for 6.1% of the total. This medicinal product, which is predominantly used in paediatrics due to its analgesic and antipyretic action, showed a 17.8% increase compared to the previous year.
Alprazolam, lorazepam and tadalafil are the other active ingredients which recorded an expenditure exceeding €100 million, with a variation compared with 2018 of 5.5%, -0.8% and +2.6% respectively (Table 2.7.2).
Lormetazepam (13.8 DDD), lorazepam (9.9 DDD) and alprazolam (9.2 DDD) are the three most prescribed active ingredients, while zolpidem is confirmed as the one with the highest increase compared to 2018 (+7%) (Tables 2.7.9a and 2.7.9c). Furthermore, among the top twenty most expensive Class C medicines with prescription (Table 2.7.2), numerous active ingredients belong to this class: alprazolam, lorazepam, zolpidem, bromazepam, delorazepam, triazolam.
Looking at the regional consumption data, a marked variability can be noted in the consumed quantities of benzodiazepines, which vary from a maximum of 78.6 DDD in Liguria to 27.2 DDD in Basilicata. Furthermore, Southern regions, with the exception of Sardinia, show a benzodiazepine consumption lower than the national average, while Marche, Lazio, Abruzzo and Puglia are the regions with the highest increase compared to the previous year (Table 2.7.9b and Figure 2.7.9c).
With an expenditure of €256 million, oral contraceptives rank second, with a stable increase in consumption over the past five years. Estro-progestin fixed combinations represent

almost 70% of the category doses. Increases in consumption can be observed for emergency contraceptives (+13.8%) and progestins (+12.6%).

The first active ingredients with the highest per capita expenditure are the fixed estro-progestin combinations: drospirenone/ethinyl estradiol (€2.27 per capita; -0.1% compared to 2018); dienogest/ethinyl estradiol (€1.12; +17.6% compared to 2018); dienogest/estradiol (€1.04; +15.9% compared to 2018); gestodene/ethinyl estradiol (€1.04; -5.1% compared to 2018). Ethinyl estra/etonogestrel, formulated as intrauterine device, ranks second. There is a high variability at regional level, with Southern regions showing an average consumption lower than the national average, with the exception of Sardinia (Table 2.7.10a and following).

With a €231 million consumption, medicinal products for the treatment of erectile dysfunction are the third largest category, increasing from 2.9 DDD in 2014 to 3.7 DDD in 2019 (Table 2.7.11a). Tadalafil, marketed subsequently to sildenafil, was the most expensive substance in 2019 (€3.73 per capita), followed by sildenafil, with €3.12 (Table 2.7.11c). Basilicata, with 2.1 DDD, is the Region with the lowest consumption, while Liguria and Tuscany show the highest (4.9 DDD). Marche, Abruzzo and Molise record the highest increases in consumption, ranging between 34.9% and 16.7% (Table 2.7.11b).

The class including non-steroidal anti-inflammatory medicines (NSAIDs) and antipyretics (Table and Figure 2.7.12a) registers a substantially stable consumption trend in the period 2014-2019, with 18.4 DDD/1000 inhab. per day in the last year, equal to a 5.2% decrease compared to the previous year.

The molecule with the highest per capita expenditure and the highest consumption is paracetamol, with values amounting to €4.88 and 7.9 DDD/1000 inhabitants per day respectively, followed by ibuprofen with a per capita expenditure of €2.32 and a consumption of 2.4 DDD/1000 inhabitants per day (Table 2.7.12c). The regional analysis reveals the highest consumption in Valle d'Aosta (26.2 DDD), Liguria (21.3 DDD) and Veneto (21.2 DDD), while Marche (11.5 DDD), Sicily (12.2 DDD) and Molise (13.6 DDD) record the lowest (Table 2.7.12c and Figures 2.7.12c and 2.7.12d).

Among self-medication medicines, diclofenac (increasing by 8.9% compared to 2018) is the first active ingredient in terms of expenditure, followed by another non-steroidal anti-inflammatory medicine (ibuprofen with € 160.6 million) (Table 2.7.3). For SOP and OTC medicines, Umbria and Marche (€ 24.4 and € 26.2 per capita) are the regions with the lowest expenditure, while Valle d'Aosta and Liguria record the highest values (€51.1 and €49.9, respectively; Table 2.7.4).

Among the Class A medicinal products purchased privately by citizens, amoxicillin in association with clavulanic acid and pantoprazole are those with the highest expenditure (€49.4 and €48.8 million, respectively), followed by ketoprofen, a non-steroidal anti-inflammatory medicine (€47.2 million). Moreover, among the first twenty highest-cost pharmaceuticals, there are three proton-pump inhibitors: lansoprazole, omeprazole and esomeprazole (Table 2.7.6). An analysis of the consumption breakdown of Class A medicines by price range shows that most of the private purchase concentrates on medicines with a price between €3 and €6 (33.7%) and between €6 and €10 (20.8%). A wide regional variability in the distribution of consumption can be observed, especially for the price range higher than €30, with a maximum percentage in Friuli Venezia Giulia (12.8%) and a minimum in Sicily (0.9%) (Table 2.7.7).

In 2019 expenditure for self-medication pharmaceuticals supplied by shops amounted to €259.4 million, with a reduction by 2.6% compared to 2018. The highest expenditure was recorded in Sardinia (€8.3 per capita) and in Emilia Romagna (€6.8 per capita), while the Autonomous Province of Bolzano and Friuli Venezia Giulia showed the lowest values (€0.5 and €2.8 per capita). Medicines most often supplied by shops in terms of consumption are diclofenac (€0.38 per capita), ibuprofen (€0.30 per capita) and paracetamol (€0.23 per capita) (Tables 2.7.8a and 2.7.8).

Figure 2.7.1. Outpatient expenditure trend for Class C medicines with prescription in the period 2012-2019: consumption, price and mix effects

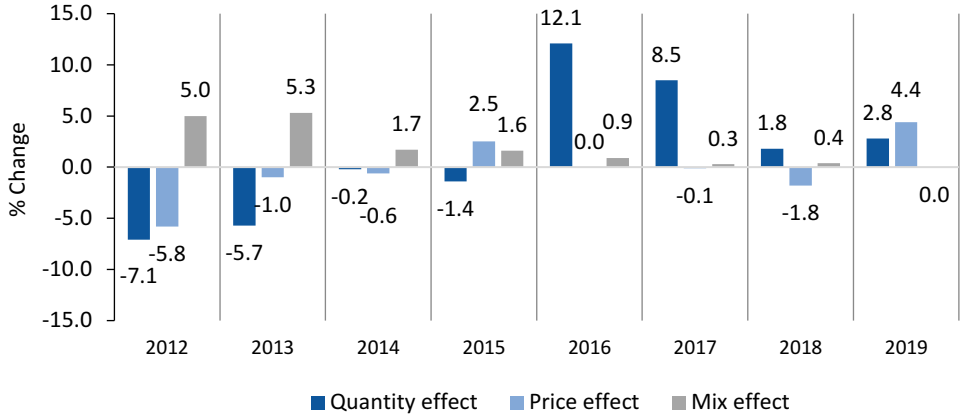


Table 2.7.1. First twenty highest-expenditure therapeutic categories of Class C medicines with prescription in 2019

ATC	Subgroup	DDD/1000 inhab per day	Expenditure *(million)*	%*	Δ% 19-18
N	Benzodiazepine derivatives (anxiolytics)	25.3	366.1	11.9	2.3
G	Medicines used in erectile dysfunction	1.8	231.1	7.5	5.5
G	Estro-progestin fixed combinations	19.4	203.0	6.6	7.4
N	Anilides	5.8	197.4	6.4	17.6
N	Benzodiazepine derivatives	19.6	130.7	4.3	7.0
D	Active corticosteroids, combination with antibiotics	4.5	85.2	2.8	8.7
S	Antimicrobial corticosteroids in combination	3.2	73.9	2.4	14.8
R	Corticosteroids	4.8	65.8	2.1	8.6
M	Other centrally-acting muscle relaxants	1.1	62.2	2.0	8.2
R	Mucolytics	5.6	61.3	2.0	5.7
N	Benzodiazepine analogues	4.9	60.6	2.0	9.0
A	Laxatives with osmotic action	1.7	58.9	1.9	6.9
N	Other psychostimulants and nootropics	1.2	55.3	1.8	10.6
N	Antivertigo preparations	2.7	48.0	1.6	2.6
M	Bisphosphonates	0.0	47.2	1.5	4.0
B	Heparins	2.0	45.2	1.5	2.5
M	Other peripheral muscle relaxants	0.0	39.1	1.3	2.6
G	Estro-progestin sequential preparations	3.4	39.0	1.3	13.0
S	Antibiotics	2.5	36.8	1.2	16.5
D	Other antibiotics for topical use	3.2	36.2	1.2	5.5

* calculated on total expenditure

Table 2.7.2. First twenty highest-expenditure Class C active ingredients with prescription in 2019

ATC	Active ingredient	DDD/1000 inhab. per day	Expenditure *(million)*	%*	Δ% 19-18
N	paracetamol	5.5	188.0	6.1	17.8
N	alprazolam	9.2	116.8	3.8	5.5
N	lorazepam	9.9	110.2	3.6	-0.8
G	tadalafil	0.9	109.7	3.6	2.6
G	sildenafil	0.7	92.4	3.0	21.1
D	gentamicin/betamethasone	3.9	72.0	2.3	7.3
N	lormetazepam	13.8	58.2	1.9	9.6
N	zolpidem	4.7	58.0	1.9	9.4
N	bromazepam	1.4	50.1	1.6	5.3
R	acetylcysteine	4.6	49.8	1.6	5.5
N	delorazepam	2.3	42.7	1.4	-1.4
M	thiocolchicoside	0.5	42.4	1.4	9.6
M	clodronic acid/lidocaine	0.0	41.5	1.4	68.7
N	triazolam	3.4	41.1	1.3	6.8
N	levoacetilcarnitin	0.8	39.9	1.3	13.0
A	macrogol 3350/potassium chloride/sodium chloride	1.2	37.3	1.2	617.3
G	drospirenone/ethinyl estradiol	2.9	36.8	1.2	-45.4
S	dexamethasone/tobramycin	1.6	35.3	1.2	7.0
G	ethynil estradiol/etonogestrel	2.4	34.7	1.1	5.2
G	dienogest/etinilestradiol	3.1	34.6	1.1	18.1

* calculated on total expenditure

Table 2.7.3. First twenty highest-expenditure self-medication (SOP and OTC) active ingredients in 2019

ATC	Active ingredient	DDD/1000 inhab. per day	Expenditure *(million)*	%*	Δ % 19-18	% SOP	% OTC
M	diclofenac	12.3	213.0	8.9	11.5	4.3	95.7
M	ibuprofen	4.0	160.6	6.7	-5.4	17.6	82.4
G	probiotic	2.8	142.2	5.9	-4.2	8.5	91.5
N	paracetamol	2.5	106.7	4.5	-12.6	92.0	8.0
R	flurbiprofen	3.9	100.3	4.2	-3.4	0.0	100
M	ketoprofen	1.6	60.6	2.5	4.5	0.0	100
C	diosmin/hesperidin	2.8	57.3	2.4	-	100	0.0
S	naphazoline	11.6	55.3	2.3	-4.2	2.9	97.1
N	acetylsalicylic acid/ascorbic acid	1.1	46.1	1.9	-1.7	0.1	99.9
R	ambroxol	0.6	45.3	1.9	-1.5	71.5	28.5
A	glycerol	5.2	45.1	1.9	-14.7	1.6	98.4
A	loperamide	0.4	36.3	1.5	-3.2	16.5	83.5
R	carbocysteine	2.1	35.9	1.5	-6.0	10.4	89.6
G	clotrimazole	0.9	31.8	1.3	1.3	7.3	92.7
N	paracetamol/ascorbic acid/phenilephrine	0.6	28.7	1.2	-7.4	0.0	100
R	iodopovidone	1.8	23.5	1.0	9.8	0.4	99.6
R	dextromethorphan/guaiafenesine	0.5	22.0	0.9	-0.9	0.0	100
R	benzydamine	0.6	20.9	0.9	-14.0	0.4	99.6
M	naproxen	1.0	20.8	0.9	-6.3	7.6	92.4
S	acetylcysteine	1.0	20.7	0.9	2.5	3.5	96.5

* calculated on total expenditure

Table 2.7.4. Territorial pharmaceutical prescription of Class C medicines with prescription and self-medication medicines (Table) and % deviation of gross expenditure from national average (Figure)

Region	Class C with prescription				Self-medication (SOP and OTC)			
	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18
Piedmont	55.3	2.0	220.3	-1.6	41.9	-9.9	128.8	-16.8
Valle d'Aosta	55.4	3.2	257.7	5.1	51.1	-8.9	147.5	-14.9
Lombardy	54.7	4.2	212.3	2.7	44.1	-5.8	128.9	-11.0
A.P. of Bolzano	40.3	2.3	150.3	-1.7	47.9	0.6	134.1	-5.9
A.P. of Trento	45.1	2.5	178.5	-0.4	46.2	-5.7	133.9	-11.0
Veneto	51.2	4.9	200.3	2.6	43.7	-5.6	128.5	-10.1
Friuli VG	45.4	4.6	180.6	1.2	40.1	-5.4	121.1	-11.0
Liguria	68.1	8.1	271.6	2.3	49.9	-8.8	156.1	-13.9
Emilia R.	53.5	9.6	205.9	7.4	42.0	-7.7	123.7	-15.7
Tuscany	53.1	3.3	229.3	0.6	42.1	-7.5	129.3	-13.2
Umbria	31.3	2.0	104.1	-1.7	24.4	-11.6	71.4	-16.4
Marche	32.1	21.6	113.7	16.9	26.2	-8.7	78.8	-15.8
Lazio	55.6	13.0	194.2	9.2	43.9	2.1	133.3	-4.2
Abruzzo	46.9	13.0	156.9	8.8	35.7	-4.5	105.9	-12.0
Molise	39.6	9.7	157.0	0.9	28.5	-6.6	87.0	-11.8
Campania	54.5	11.7	183.1	1.1	38.9	-0.8	119.5	-8.3
Puglia	46.6	12.6	168.4	7.7	34.0	-2.0	98.6	-7.9
Basilicata	40.4	6.9	154.1	3.7	27.8	-11.7	81.7	-16.1
Calabria	43.5	5.3	181.9	-0.3	30.9	-9.9	91.7	-16.7
Sicily	39.1	1.3	133.0	-1.8	30.0	-5.4	90.6	-11.8
Sardinia	52.5	5.2	223.3	2.0	34.5	-14.6	98.5	-19.4
Italy	**50.8**	**6.9**	**192.4**	**3.0**	**39.6**	**-5.5**	**118.4**	**-11.6**
Northern	53.9	4.9	211.1	2.4	43.7	-6.6	129.5	-12.8
Central	49.9	9.7	188.2	5.7	39.6	-2.9	120.3	-9.1
Southern and Insular	46.8	8.1	168.3	2.2	33.9	-5.0	101.4	-11.3

* medicinal products classified as "C- without negotiation" are included

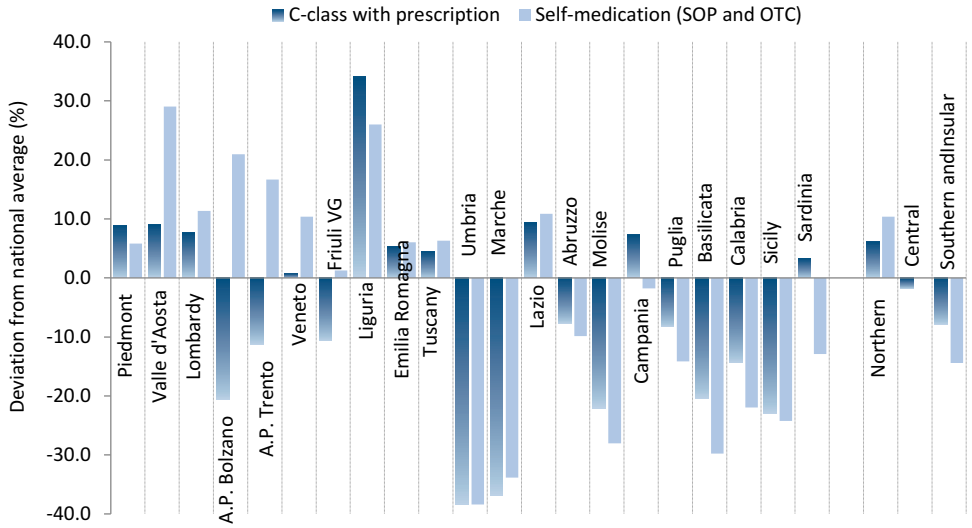


Table 2.7.5. Consumption and expenditure of Class A medicines privately purchased by citizens (Table) and % deviation of gross expenditure from national average (Figure)

Region	Per capita expenditure	Δ % 19-18	DDD/1000 inhab die	Δ % 19-18
Piedmont	49.6	-22.3	192.6	-3.4
Valle d'Aosta	28.2	-67.9	196.8	-22.3
Lombardy	29.3	39.5	207.3	33.8
A.P. of Bolzano	18.8	2.2	132.1	0.5
A.P. of Trento	11.8	-2.5	71.7	-3.6
Veneto	26.5	13.2	186.6	14.9
Friuli VG	45.9	15.6	118.8	18.8
Liguria	31.0	-37.6	237.7	2.6
Emilia R.	17.9	32.6	100.4	44.3
Tuscany	20.0	-2.4	127.3	-3.2
Umbria	5.0	13.6	12.7	-0.8
Marche	8.1	47.3	20.4	23.6
Lazio	22.0	73.2	130.7	79.0
Abruzzo	15.8	83.7	91.6	82.5
Molise	22.3	-3.9	113.0	11.2
Campania	22.8	10.7	159.7	8.7
Puglia	35.2	95.6	121.1	88.3
Basilicata	16.8	35.5	117.4	26.8
Calabria	13.4	30.1	77.4	9.5
Sicily	21.4	5.9	45.3	-8.1
Sardinia	17.0	27.8	103.3	22.7
Italy	**25.6**	**13.8**	**139.5**	**21.5**
Northern	30.6	2.3	177.9	18.3
Central	18.3	34.6	106.4	33.2
Southern and insular	22.9	31.6	105.3	23.0

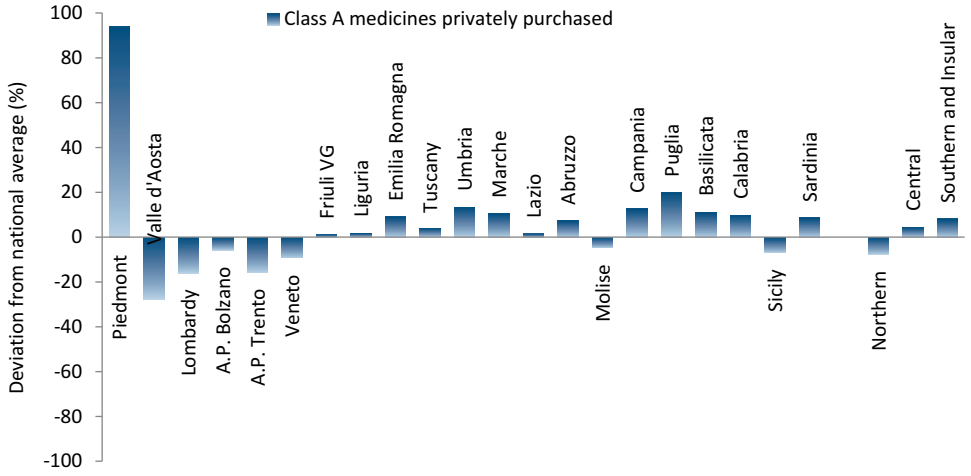


Table 2.7.6. First twenty Class A active ingredients privately purchased by citizens in decreasing order of expenditure in 2019

ATC I	Active ingredient	DDD/1000 inhab. per day	Expenditure *(million)*	%*	% private purchase**
J	amoxicillin/clavulanic acid	1.6	49.4	3.4	21.4
A	pantoprazole	4.5	48.8	3.3	15.3
M	ketoprofen	8.1	47.2	3.2	71.0
A	lansoprazole	2.8	29.8	2.0	16.3
A	omeprazole	3.3	28.7	2.0	17.5
A	esomeprazole	2.6	25.8	1.8	15.8
M	ibuprofen	2.7	25.6	1.7	59.0
B	acetylsalicylic acid	13.5	22.5	1.5	97.5
M	diclofenac	2.4	21.5	1.5	37.8
R	beclomethasone	1.0	20.6	1.4	32.2
A	cholecalciferol	1.8	20.0	1.4	6.6
B	Rivaroxaban	0.2	18.1	1.2	10.3
B	apixaban	0.2	17.8	1.2	9.9
R	betamethasone	1.8	16.7	1.1	45.0
R	cetirizine	2.5	16.2	1.1	50.3
H	levothyroxine	6.6	15.4	1.1	19.7
A	insulin glargine	0.3	14.6	1.0	12.0
C	rosuvastatin	2.4	14.6	1.0	16.2
C	Omega 3	0.5	14.2	1.0	11.0

* calculated on total expenditure of Class A medicinal products privately purchased by citizens
**calculated on total expenditure of the active ingredient (reimbursed by the NHS, privately purchased by citizens and purchased by public health structures)

Table 2.7.7. Consumption breakdown of Class A medicines privately purchased by citizens, by price range in 2019

Region	<2 € %	2-3 € %	3-6 € %	6-10 € %	10-30 € %	>30 € %
Piedmont	7.5	11.3	31.2	28.0	14.8	7.2
Valle d'Aosta	9.9	19.8	31.4	23.2	14.6	1.1
Lombardy	11.3	21.2	32.4	21.1	12.1	1.9
A.P. of Bolzano	8.3	17.7	35.3	24.4	12.6	1.7
A.P. of Trento	12.6	10.5	35.2	24.9	15.0	1.9
Veneto	11.8	21.9	32.0	20.6	11.5	2.1
Friuli VG	5.7	9.2	32.0	26.7	13.7	12.8
Liguria	11.7	20.3	33.4	21.3	12.3	0.9
Emilia R.	8.6	10.8	38.5	25.1	14.6	2.4
Tuscany	12.0	18.0	36.9	19.1	12.0	2.0
Umbria	16.9	5.3	45.9	18.2	7.7	5.9
Marche	11.3	2.4	38.3	23.3	12.8	11.9
Lazio	10.9	16.6	34.6	21.8	13.9	2.2
Abruzzo	13.2	13.7	37.9	21.9	11.4	1.9
Molise	9.5	13.2	36.2	23.3	14.1	3.7
Campania	12.9	27.5	33.1	16.2	8.2	2.1
Puglia	11.6	14.4	35.7	18.8	12.4	7.2
Basilicata	9.8	21.9	36.5	19.8	11.0	1.0
Calabria	10.0	25.8	40.6	14.5	7.0	2.2
Sicily	9.3	17.3	30.4	10.3	31.8	0.9
Sardinia	12.7	14.2	33.7	22.5	15.1	1.8
Italy	**10.9**	**18.5**	**33.7**	**20.8**	**13.1**	**3.0**

Table 2.7.8a. Expenditure and consumption of self-medication medicines supplied by shops in 2019 by Region and % deviation from national average (Figure)

Region	Expenditure *(million)*	Per capita expenditure	DDD/1000 inhab per day
Piedmont	19.6	4.3	13.4
Valle d'Aosta	0.6	4.4	12.1
Lombardy	38.3	3.8	11.7
A.P. of Bolzano	0.3	0.5	1.5
A.P. of Trento	1.9	3.6	10.2
Veneto	19.9	4.0	12.1
Friuli VG	3.6	2.8	8.4
Liguria	10.1	5.9	19.6
Emilia R.	30.8	6.8	21.5
Tuscany	18.7	4.8	14.7
Umbria	3.9	4.2	13.4
Marche	7.6	4.8	15.5
Lazio	19.8	3.4	10.8
Abruzzo	7.8	5.9	18.1
Molise	1.2	3.7	11.9
Campania	16.0	3.0	9.5
Puglia	18.7	4.7	14.9
Basilicata	3.4	6.0	17.8
Calabria	9.6	5.1	15.1
Sicily	13.7	2.8	9.6
Sardinia	14.0	8.3	23.9
Italy	**259.4**	**4.3**	**13.4**

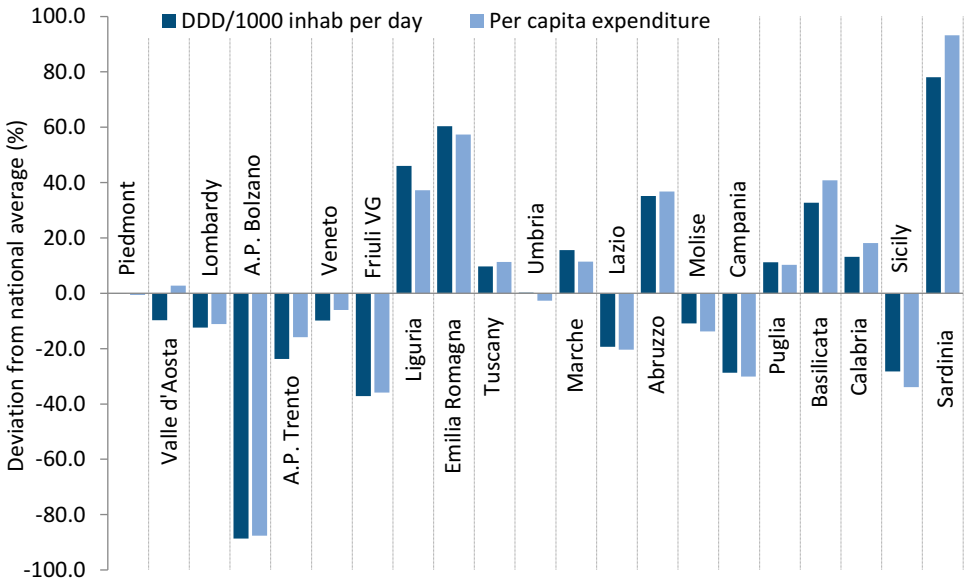


Table 2.7.8b. First twenty self-medication active ingredients supplied by shops in decreasing order of expenditure in 2019

Active ingredient	Per capita expenditure	Inc %	Cum. %	DDD/1000 inhab per day
diclofenac	0.38	9.0	9.0	1.4
ibuprofen	0.30	7.0	15.9	0.5
paracetamol	0.23	5.3	21.2	0.4
probiotic	0.20	4.7	25.9	0.2
flurbiprofen	0.18	4.3	30.1	0.4
naphazoline	0.15	3.4	33.5	1.8
glycerol	0.14	3.3	36.9	0.9
ketoprofen	0.14	3.3	40.2	0.2
diosmin/hesperidin	0.10	2.4	42.6	0.3
acetylsalicylic acid/ascorbic acid	0.08	1.9	44.4	0.1
loperamide	0.06	1.4	45.8	0.0
oximetazoline	0.05	1.3	47.0	0.3
escin	0.05	1.2	48.2	0.1
bisacodyl	0.05	1.2	49.4	0.3
paracetamol/ascorbic acid/phenylephrine	0.05	1.2	50.6	0.1
dextromethorphan/guaifenesin	0.05	1.1	51.6	0.1
carbocysteine	0.04	1.0	52.7	0.2
benzydamine	0.04	1.0	53.7	0.1
Nicotine	0.04	1.0	54.7	0.0
clotrimazole	0.04	1.0	55.7	0.1

Figure 2.7.9a. Benzodiazepines, temporal trend of territorial consumption (2014-2019)

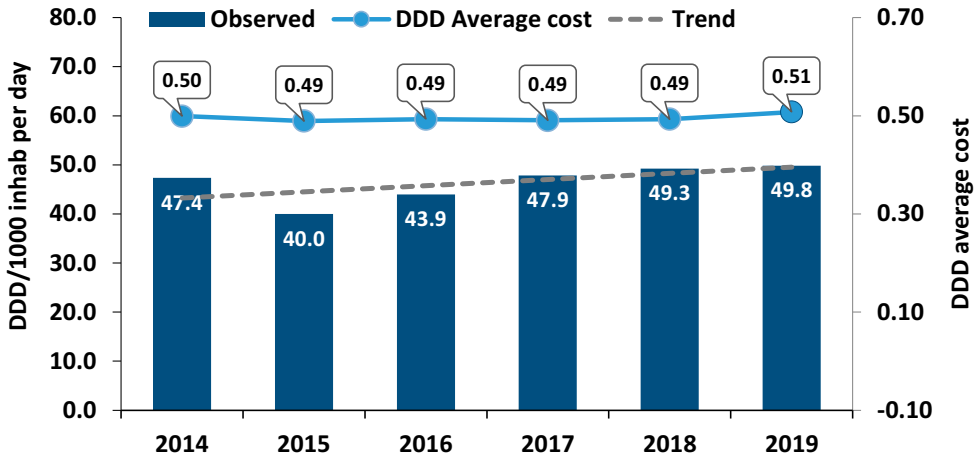


Table 2.7.9a. Benzodiazepines, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Anxiolytics	25.2	21.2	23.3	25.0	25.7	25.3	-1.4
Hypnotics	18.5	15.6	17.0	18.6	19.0	19.6	3.3
Sedatives	3.7	3.1	3.6	4.3	4.6	4.9	6.7
Benzodiazepines	**47.4**	**40.0**	**43.9**	**47.9**	**49.3**	**49.8**	**1.2**
alprazolam	8.1	7.0	8.0	8.7	9.2	9.2	0.8
lorazepam	10.8	9.2	9.7	10.2	10.3	9.9	-3.3
lormetazepam	13.1	11.1	11.9	13.0	13.2	13.8	5.2
zolpidem	3.5	3.0	3.5	4.1	4.4	4.7	7.0
bromazepam	1.5	1.2	1.3	1.4	1.4	1.4	0.5
delorazepam	2.2	1.9	2.0	2.3	2.4	2.3	-3.3
triazolam	3.1	2.7	3.0	3.3	3.4	3.4	0.3
diazepam	1.3	1.0	1.1	1.2	1.2	1.2	0.6
brotizolam	1.4	1.1	1.2	1.4	1.4	1.4	-1.0
flurazepam	0.6	0.5	0.6	0.6	0.7	0.6	-1.4

Table 2.7.9b. Benzodiazepines, weighted regional trend of territorial DDD/1000 inhab. per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	67.6	54.5	66.8	66.6	70.2	69.3	-1.2
Valle d'Aosta	68.7	53.9	66.6	67.3	72.5	73.3	1.1
Lombardy	48.8	42.7	45.5	55.6	57.8	59.0	2.2
A.P. of Bolzano	37.9	34.9	35.7	35.5	35.8	34.1	-5.0
A.P. of Trento	62.2	59.4	59.5	59.1	60.2	58.4	-3.0
Veneto	61.9	57.1	56.0	69.9	68.8	70.7	2.8
Friuli VG	60.9	47.6	56.5	60.9	60.7	61.0	0.4
Liguria	82.3	63.7	75.8	74.9	79.1	78.6	-0.6
Emilia R.	51.4	48.2	53.1	55.4	52.8	54.8	3.6
Tuscany	45.7	40.6	42.3	44.8	48.3	46.6	-3.5
Umbria	52.2	28.2	31.0	31.3	31.4	29.3	-6.4
Marche	54.4	26.8	29.7	29.9	28.1	31.2	11.2
Lazio	42.9	33.4	36.2	41.0	45.1	48.4	7.4
Abruzzo	39.0	36.1	37.8	37.5	36.6	38.8	5.9
Molise	29.0	24.9	29.7	29.7	30.7	29.5	-3.7
Campania	35.3	31.8	33.8	35.0	35.8	34.9	-2.5
Puglia	28.2	25.0	27.0	27.0	28.7	30.1	5.1
Basilicata	22.6	20.7	26.3	26.5	27.2	27.2	0.3
Calabria	34.6	25.4	31.2	32.1	33.3	32.7	-1.9
Sicily	28.8	24.4	28.0	30.1	30.8	28.9	-6.1
Sardinia	57.8	50.6	61.5	60.7	62.7	63.2	0.7
Italy	**47.4**	**40.0**	**43.9**	**47.9**	**49.3**	**49.8**	**1.2**

Table 2.7.9c. Benzodiazepines, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 ab die	Δ % 19-18	DDD Average cost
Anxiolytics	6.07	2.5	25.3	-1.4	0.66
Hypnotics	2.17	7.0	19.6	3.3	0.30
Sedatives	1.00	9.0	4.9	6.7	0.56
Benzodiazepines	**9.24**	**4.2**	**49.8**	**1.2**	**0.51**
alprazolam	1.93	5.5	9.2	0.8	0.57
lorazepam	1.83	-0.6	9.9	-3.3	0.50
lormetazepam	0.96	9.6	13.8	5.2	0.19
zolpidem	0.96	9.4	4.7	7.0	0.56
bromazepam	0.83	5.3	1.4	0.5	1.58
delorazepam	0.71	-1.4	2.3	-3.3	0.85
triazolam	0.68	6.6	3.4	0.3	0.54
diazepam	0.35	4.6	1.2	0.6	0.77
brotizolam	0.31	6.3	1.4	-1.0	0.60
flurazepam	0.14	4.9	0.6	-1.4	0.60

Figure 2.7.9c. Benzodiazepines, distribution in quartiles of 2019 territorial consumption (weighted DDD/1000 inhab. per day)

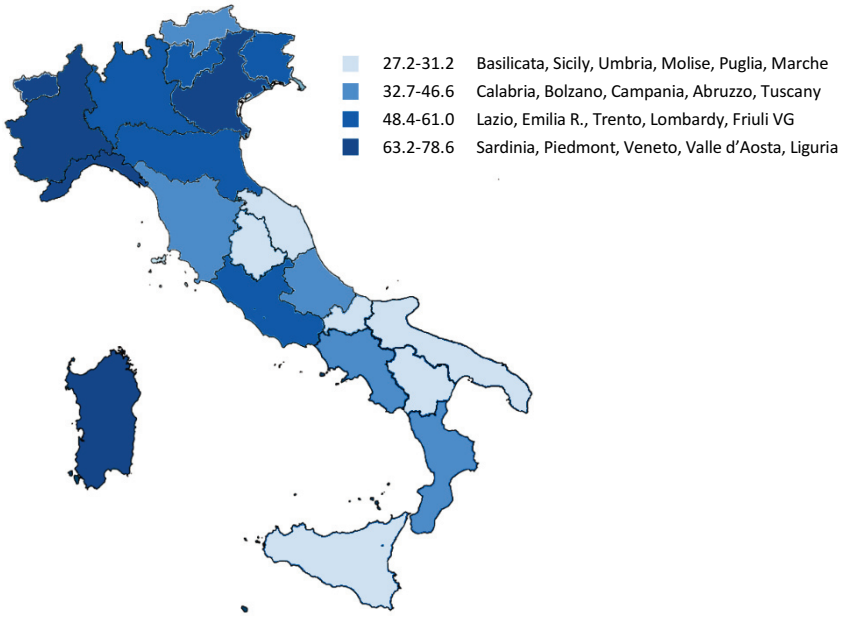
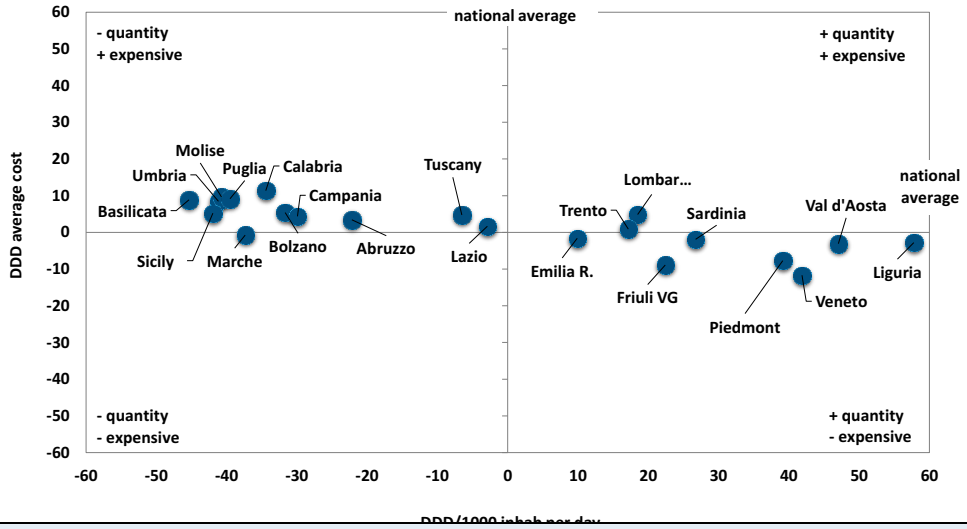


Figure 2.7.9d. Benzodiazepines, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviation from national average)



All indicators presented in this section are calculated on the female population

Figure 2.7.10a. Contraceptives, temporal trend of territorial consumption (2014-2019)

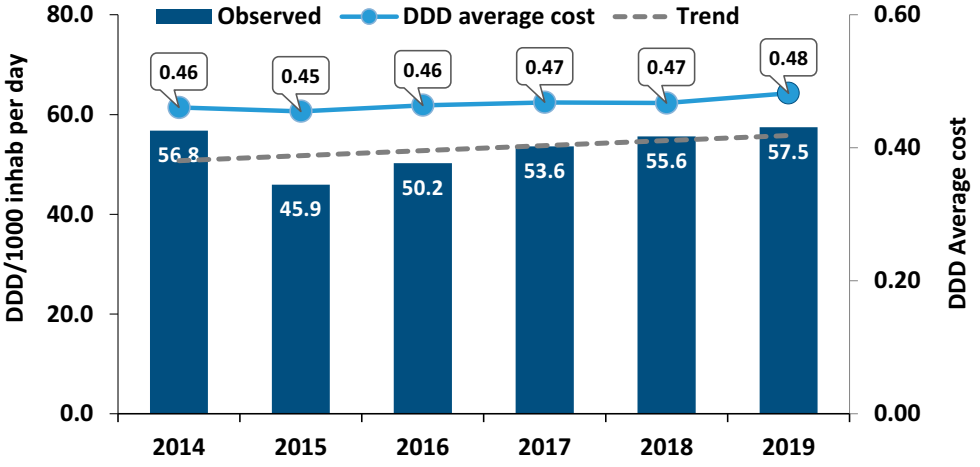


Table 2.7.10a. Contraceptives, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Estro-progestin fixed combinations	42.4	33.2	36.0	37.9	37.8	37.7	-0.2
Emergency contraceptives	6.1	6.0	6.8	7.4	8.6	9.8	13.8
Estro-progestin sequential preparations	6.4	5.1	5.4	5.7	6.2	6.6	6.1
Progestogens	1.8	1.7	2.1	2.6	3.0	3.4	12.6
Contraceptives	**56.8**	**45.9**	**50.2**	**53.6**	**55.6**	**57.5**	**3.3**
drospirenone/ethinyl estradiol	16.3	12.1	12.0	11.8	11.5	11.2	-2.6
ethinyl estradiol/etonogestrel	3.7	3.2	3.7	4.1	4.3	4.7	8.0
Dienogest/ethinyl estradiol	1.7	2.2	3.3	4.3	5.2	6.0	15.3
Dienogest/estradiol	2.7	2.4	2.8	3.4	4.0	4.5	13.5
gestodene/ethinyl estradiol	16.1	11.9	12.5	12.1	11.2	10.1	-10.2
levonorgestrel/ethinyl estradiol	4.2	3.7	4.5	5.1	5.2	5.4	3.8
oestradiol/nomegestrol	1.6	1.5	1.9	2.4	2.4	2.8	15.2
desogestrel	1.7	1.6	1.9	2.4	2.8	3.1	13.0
levonorgestrel	2.4	2.7	3.0	3.3	4.2	5.0	19.6
ethinyl estradiol/norelgestromin	1.5	1.1	1.2	1.4	1.4	1.3	-3.1

Table 2.7.10b. Contraceptives, weighted regional trend of territorial DDD/1000 inhab. per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	78.0	59.1	72.5	73.0	76.9	78.0	1.4
Valle d'Aosta	95.1	72.1	92.8	96.3	94.8	91.5	-3.4
Lombardy	67.6	55.5	59.9	73.2	80.0	83.1	3.9
A.P. of Bolzano	111.8	106.9	101.1	95.3	94.0	88.9	-5.4
A.P. of Trento	73.1	71.8	69.3	70.8	74.1	76.3	2.9
Veneto	60.8	54.5	51.9	65.2	67.3	69.3	3.1
Friuli VG	61.9	46.7	54.7	60.1	62.0	61.8	-0.3
Liguria	80.3	58.8	73.3	73.8	76.1	78.5	3.1
Emilia R.	66.4	60.7	66.0	70.2	66.5	69.8	4.9
Tuscany	62.5	53.8	54.8	59.0	64.3	65.1	1.3
Umbria	54.4	27.6	28.8	27.8	27.9	28.0	0.5
Marche	50.9	23.9	23.6	21.5	20.0	24.6	22.7
Lazio	49.2	35.2	36.0	41.5	46.8	51.5	10.0
Abruzzo	45.2	41.1	41.0	39.4	37.1	40.2	8.5
Molise	33.3	24.4	28.1	27.0	25.7	25.2	-2.0
Campania	31.9	26.7	34.8	25.7	23.8	24.4	2.5
Puglia	38.6	33.0	32.7	31.9	33.0	35.1	6.5
Basilicata	23.7	21.0	26.4	25.7	25.4	25.6	0.7
Calabria	33.0	21.8	27.7	26.3	26.2	26.1	-0.3
Sicily	33.2	25.7	28.3	28.9	28.1	27.0	-3.9
Sardinia	126.1	104.8	123.0	120.2	118.9	118.2	-0.6
Italy	**56.8**	**45.9**	**50.2**	**53.6**	**55.6**	**57.5**	**3.3**

Table 2.7.10c. Contraceptives, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 ab die	Δ % 19-18	DDD Average Cost
Estro-progestin fixed combinations	6.55	4.9	37.7	-0.2	0.48
Emergency contraceptives	1.79	6.5	9.8	13.8	0.50
Estroprogestin sequential preparations	1.26	13.2	6.6	6.1	0.53
Progestogens	0.51	12.5	3.4	12.6	0.41
Contraceptives	**10.10**	**6.5**	**57.5**	**3.3**	**0.48**
drospirenone/ethinyl estradiol	2.27	-0.1	11.2	-2.6	0.56
ethinyl estradiol/etonogestrel	1.12	4.2	4.7	8.0	0.66
Dienogest/ethinyl estradiol	1.12	17.6	6.0	15.3	0.51
Dienogest/estradiol	1.04	15.9	4.5	13.5	0.63
gestodene/ethinyl estradiol	1.04	-5.1	10.1	-10.2	0.28
levonorgestrel/ethinyl estradiol	0.93	11.6	5.4	3.8	0.47
oestradiol/nomegestrol	0.63	20.8	2.8	15.2	0.62
desogestrel	0.49	12.7	3.1	13.0	0.43
levonorgestrel	0.45	18.6	5.0	19.6	0.24
ethinyl estradiol/norelgestromin	0.28	0.9	1.3	-3.1	0.59

Figure 2.7.10c. Contraceptives, distribution in quartiles of 2019 territorial consumption (weighted DDD/1000 inhab. per day)

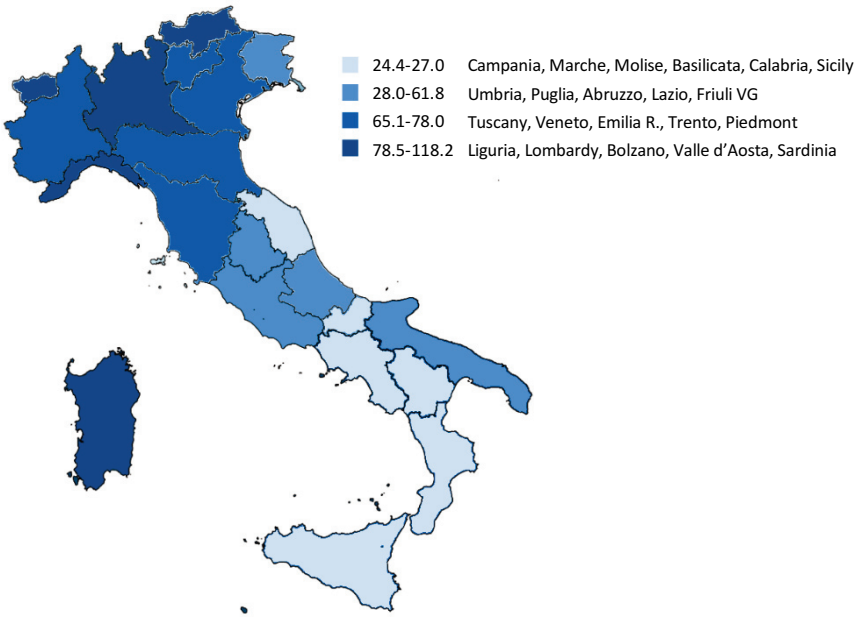
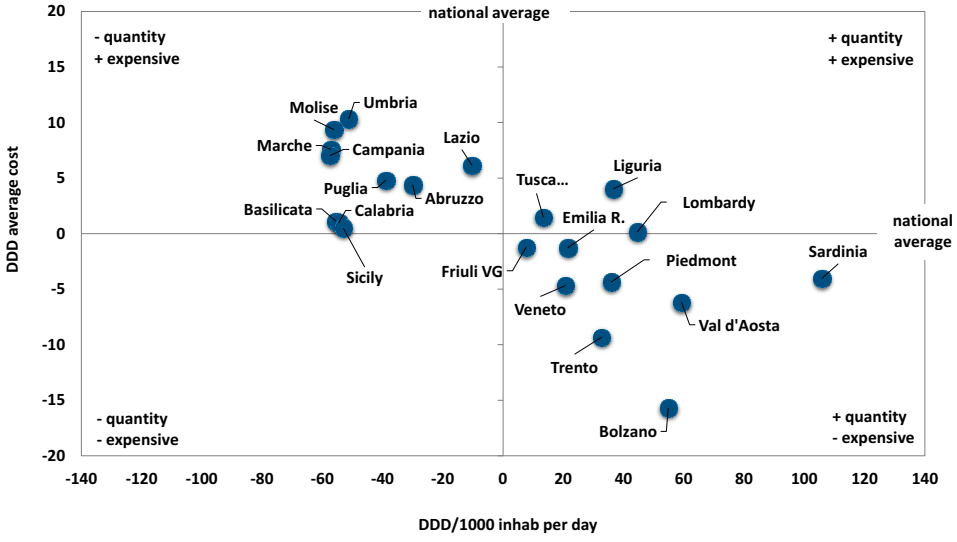


Figure 2.7.10d. Contraceptives, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviation from national average)



All indicators presented in this section are calculated on the male population

Figure 2.7.11a. Medicines for erectile dysfunction, temporal consumption trend (2014-2019)

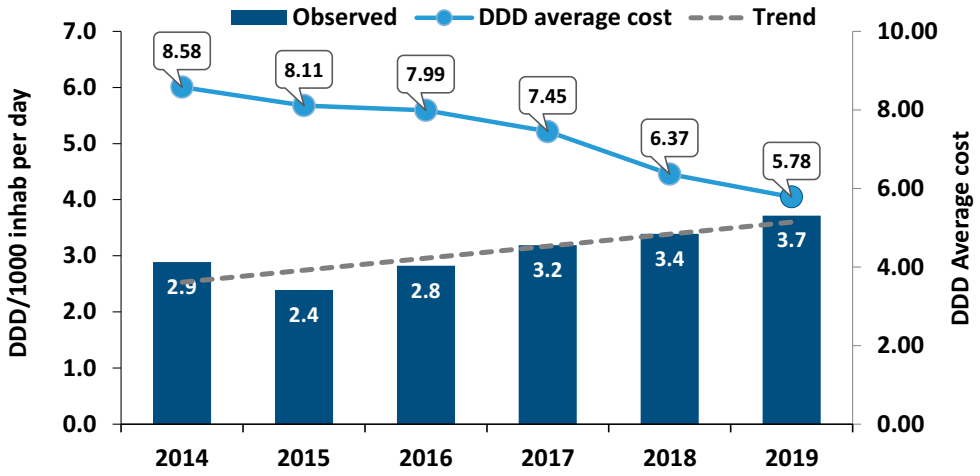


Table 2.7.11a. Medicines for erectile dysfunction, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Medicines for erectile dysfunction	**2.9**	**2.4**	**2.8**	**3.2**	**3.4**	**3.7**	**9.7**
tadalafil	0.6	0.5	0.5	0.6	0.8	0.9	13.3
sildenafil	0.5	0.5	0.6	0.7	0.7	0.7	10.4
vardenafil	0.2	0.2	0.2	0.2	0.1	0.1	-6.3
avanafil	0.0	0.1	0.1	0.1	0.1	0.1	-12.9
alprostadil	0.0	0.0	0.0	0.0	0.0	0.0	2.1

Table 2.7.11b. Medicines for erectile dysfunction, weighted regional trend of DDD/1000 inhab. per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	3.3	2.6	3.3	3.3	3.6	3.8	7.0
Valle d'Aosta	2.7	2.1	3.0	2.9	3.3	3.4	2.8
Lombardy	2.6	2.1	2.5	3.1	3.4	3.5	3.7
A.P. of Bolzano	2.5	2.4	2.5	2.4	2.6	2.6	3.2
A.P. of Trento	2.1	2.1	2.1	2.1	2.3	2.4	2.6
Veneto	2.3	2.1	2.2	2.9	3.0	3.3	10.5
Friuli VG	2.4	1.8	2.3	2.6	2.6	2.9	11.3
Liguria	4.4	3.3	4.2	4.5	4.8	4.9	1.8
Emilia R.	3.6	3.3	3.8	4.2	4.1	4.5	9.9
Tuscany	4.1	3.5	3.9	4.5	4.8	4.9	2.1
Umbria	3.7	1.9	2.4	2.6	2.6	2.8	6.4
Marche	3.4	1.9	2.2	2.3	2.1	2.8	34.9
Lazio	3.5	2.6	3.0	3.4	4.0	4.5	13.4
Abruzzo	3.1	2.9	3.2	3.4	3.4	4.0	20.4
Molise	2.2	2.1	2.4	2.6	2.7	3.1	16.7
Campania	3.2	2.8	3.4	3.5	3.8	4.3	13.5
Puglia	2.4	2.2	2.5	2.7	2.9	3.4	16.4
Basilicata	1.3	1.4	1.7	1.8	1.9	2.1	12.0
Calabria	1.9	1.4	1.9	2.1	2.1	2.4	14.4
Sicily	1.9	1.6	2.0	2.5	2.6	2.9	11.9
Sardinia	2.3	1.9	2.6	2.7	2.8	3.1	10.6
Italy	**2.9**	**2.4**	**2.8**	**3.2**	**3.4**	**3.7**	**9.7**

Table 2.7.11c. Medicines for erectile dysfunction, prescription by therapeutic category and substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	DDD Average Cost
Medicines for erectile dysfunction	**7.89**	**0.1**	**3.7**	**9.7**	**5.78**
tadalafil	3.73	-1.7	0.9	13.3	5.48
sildenafil	3.12	10.0	0.7	10.4	5.70
vardenafil	0.62	-26.1	0.1	-6.3	7.64
avanafil	0.23	-12.9	0.1	-12.9	5.54
alprostadil	0.14	-3.7	0.0	2.1	24.11

Figure 2.7.11c. Medicines for erectile dysfunction, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

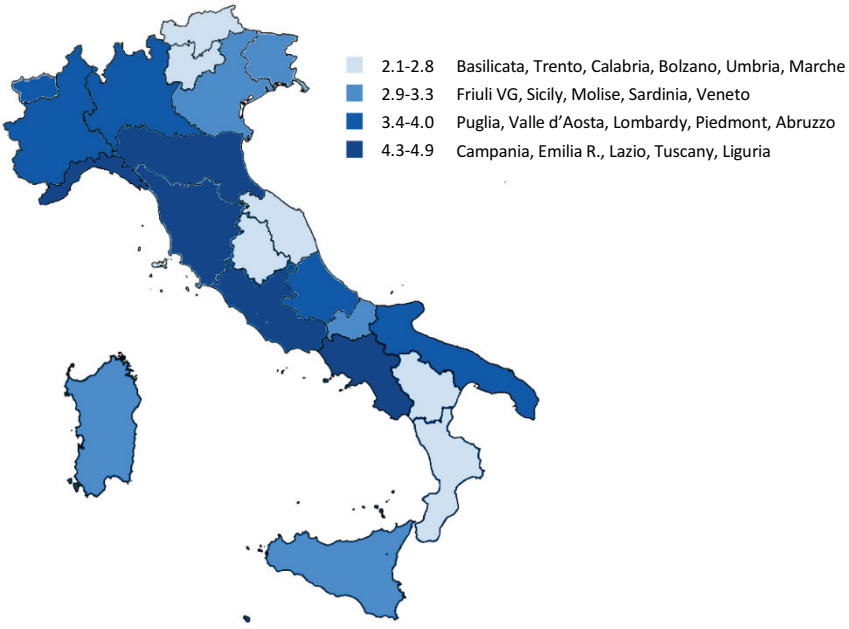


Figure 2.7.11d. Medicines for erectile dysfunction, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviation from national average)

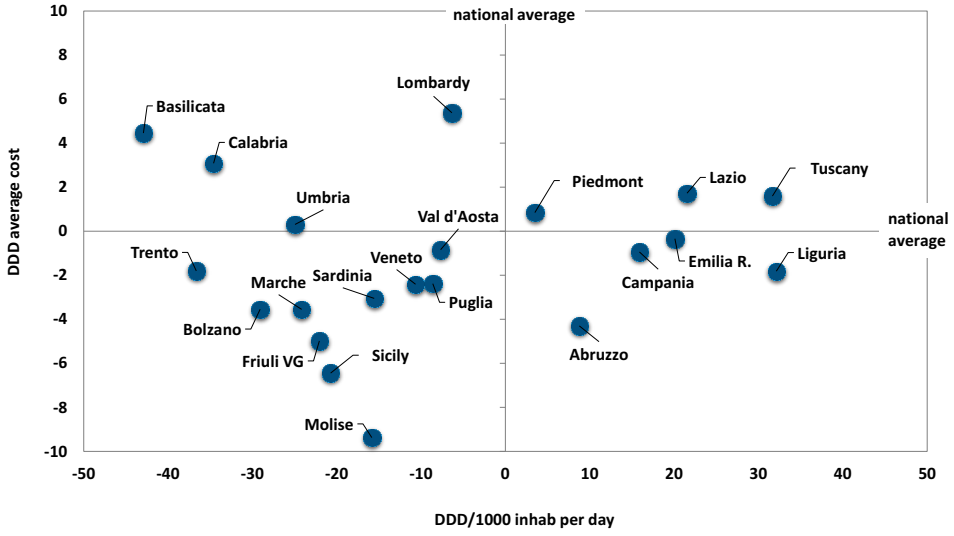


Figure 2.7.12a. NSAIDS and antipyretics, temporal consumption trend (2014-2019)

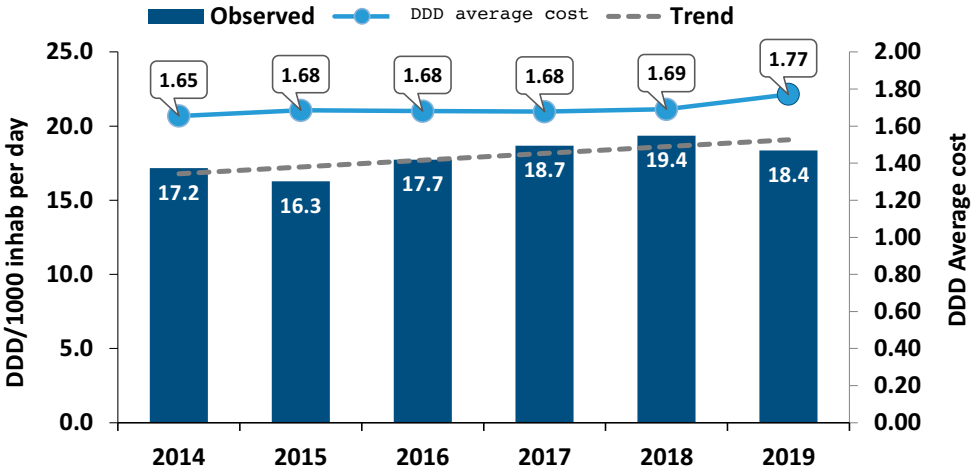


Table 2.7.12a. NSAIDs and antipyretics, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Other antipyretics - anilides	8.2	7.9	8.8	9.3	10.1	9.9	-1.7
Traditional NSAIDs	6.5	6.1	6.8	7.2	7.2	6.5	-9.9
Other antipyretics - salicylic acid and derivatives	1.7	1.7	1.6	1.5	1.4	1.3	-7.8
Other antipyretics - pyrazolones	0.4	0.3	0.3	0.4	0.3	0.3	-7.2
Other NSAIDs	0.3	0.2	0.2	0.2	0.2	0.3	11.9
Coxib	0.0	0.0	0.0	0.0	0.0	0.0	3.4
Oxicam	0.1	0.0	0.0	0.0	0.0	0.0	-15.2
Other analgesics and antipyretics	0.0	0.0	0.0	0.0	0.0	0.0	-99.5
NSAIDS and antipyretics	**17.2**	**16.3**	**17.7**	**18.7**	**19.4**	**18.4**	**-5.2**
paracetamol	6.2	6.1	6.8	7.4	8.0	7.9	-0.7
ibuprofen	2.3	2.2	2.4	2.5	2.6	2.4	-7.9
ketoprofen	0.7	0.8	0.9	1.2	1.2	1.2	-2.9
acetylsalicylic acid/ascorbic acid	1.4	1.4	1.3	1.3	1.2	1.1	-6.5
paracetamol/ascorbic acid/phenylephrine	0.5	0.6	0.6	0.6	0.6	0.6	-13.1
diclofenac	0.4	0.5	0.6	0.7	0.6	0.6	-15.0
naproxen	0.5	0.6	0.8	0.8	0.8	0.7	-12.4
paracetamol/pseudoephedrine/diphenhydramine	0.0	0.0	0.0	0.0	0.2	0.2	19.0
ketorolac	0.2	0.2	0.2	0.2	0.2	0.2	2.9
paracetamol/caffeine/chlorphenamine /isopropamide	0.5	0.5	0.5	0.5	0.5	0.4	-11.8

Table 2.7.12b. NSAIDs and antipyretics, weighted regional trend of DDD/1000 inhab. per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	20.3	18.8	21.8	22.4	23.3	20.8	-10.7
Valle d'Aosta	26.1	23.5	27.7	28.9	29.4	26.2	-10.8
Lombardy	17.8	17.2	19.1	21.7	22.2	21.0	-5.5
A.P. of Bolzano	20.0	20.6	20.5	20.8	21.3	20.8	-2.3
A.P. of Trento	20.6	21.1	21.3	21.8	22.7	20.4	-9.9
Veneto	20.1	19.8	20.6	23.3	23.6	21.2	-10.2
Friuli VG	19.3	18.3	20.2	21.8	22.2	20.9	-6.1
Liguria	21.1	18.3	21.6	22.0	23.0	21.3	-7.3
Emilia R.	19.5	20.2	20.9	21.5	21.3	20.1	-5.8
Tuscany	15.4	15.3	16.1	16.6	17.4	16.3	-6.4
Umbria	20.8	15.3	15.8	15.5	15.6	13.8	-11.4
Marche	17.0	11.8	12.8	12.2	12.6	11.5	-8.3
Lazio	16.9	15.2	16.1	17.5	19.1	19.6	2.7
Abruzzo	15.3	15.5	15.9	15.9	16.6	16.2	-2.6
Molise	12.6	11.8	13.4	13.5	14.3	13.6	-4.9
Campania	17.1	16.3	17.5	16.8	17.6	18.1	2.5
Puglia	15.4	15.0	16.3	15.9	16.7	16.7	0.3
Basilicata	13.9	13.9	16.0	16.0	16.4	15.5	-5.4
Calabria	13.1	11.9	13.8	14.2	14.8	13.7	-8.0
Sicily	10.6	10.2	11.4	12.1	12.9	12.2	-5.4
Sardinia	15.8	14.9	17.6	18.1	18.9	16.6	-12.3
Italy	**17.2**	**16.3**	**17.7**	**18.7**	**19.4**	**18.4**	**-5.2**

Table 2.7.12c. NSAIDs and antipyretics, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	DDD average cost
Other antipyretics - anilides	6.18	3.5	9.9	-1.7	1.70
Traditional NSAIDs	4.40	-5.5	6.5	-9.9	1.86
Other antipyretics - salicylic acid and derivatives	0.93	-4.4	1.3	-7.8	1.90
Other antipyretics - pyrazolones	0.25	0.1	0.3	-7.2	2.09
Other NSAIDs	0.10	13.4	0.3	11.9	1.03
Coxib	0.01	6.5	0.0	3.4	1.10
Oxicam	0.00	-20.4	0.0	-15.2	0.90
Other analgesics and antipyretics	0.00	-97.9	0.0	-99.5	17.15
NSAIDS and antipyretics	**11.86**	**-0.7**	**18.4**	**-5.2**	**1.77**
paracetamol	4.88	4.7	7.9	-0.7	1.69
ibuprofen	2.32	-6.7	2.4	-7.9	2.69
ketoprofen	0.84	2.9	1.2	-2.9	1.92
acetylsalicylic acid/ascorbic acid	0.76	-2.8	1.1	-6.5	1.83
paracetamol/ascorbic acid/phenylephrine	0.48	-10.3	0.6	-13.1	2.31
diclofenac	0.37	-9.4	0.6	-15.0	1.85
naproxen	0.31	-6.6	0.7	-12.4	1.14
paracetamol/pseudoephedrine/diphenhydramine	0.19	30.2	0.2	19.0	2.86
ketorolac	0.19	5.0	0.2	2.9	2.40
paracetamol/caffeine/chlorphenamine /isopropamide	0.16	-10.3	0.4	-11.8	1.00

Figure 2.7.12c. NSAIDs and antipyretics, distribution in quartiles of 2019 territorial consumption (weighted DDD/1000 inhab. per day)

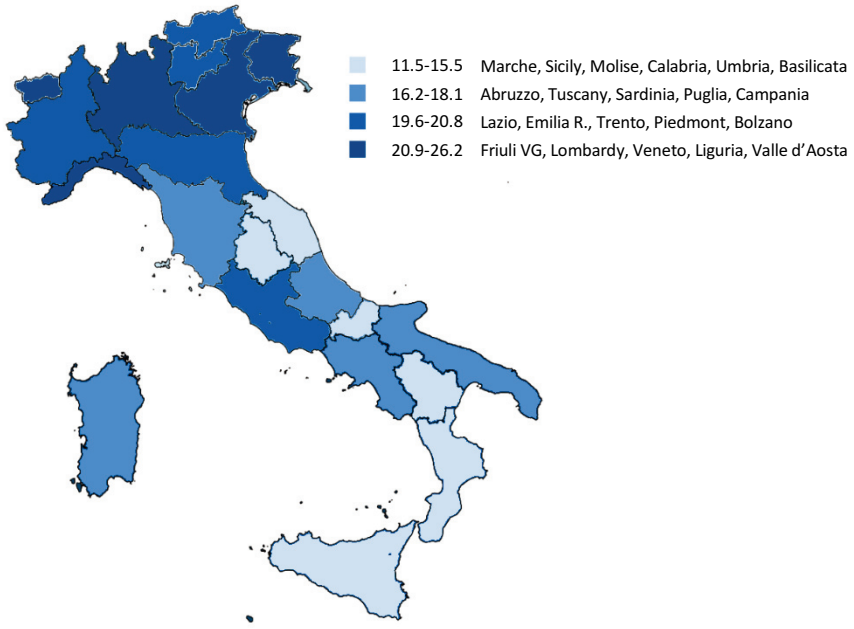
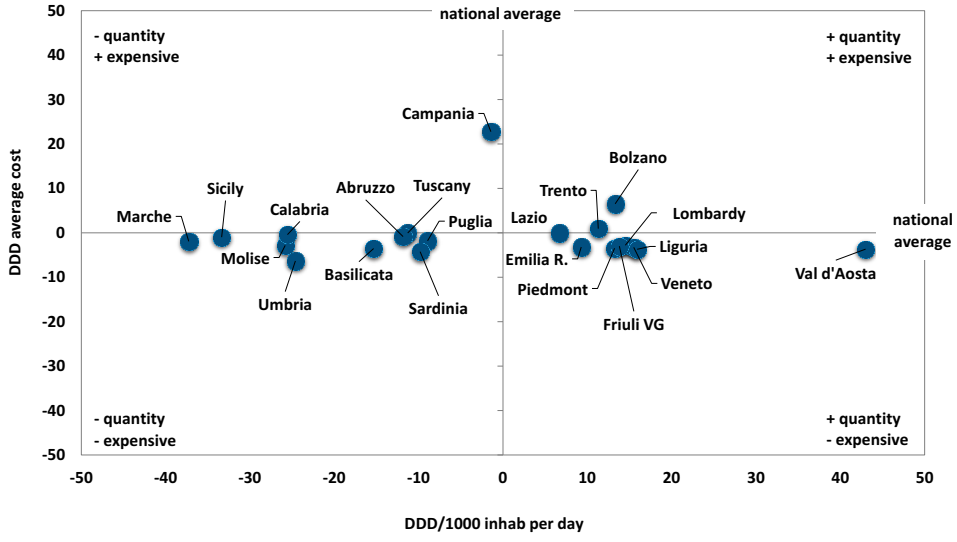


Figure 2.7.12d. NSAIDs and antipyretics, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviation from national average)



Section 3

Consumption and expenditure by therapeutic class

This section analyses the trend of public pharmaceutical expenditure (including gross NHS outpatient pharmaceutical expenditure and the expenditure of medicines directly purchased by public health facilities) by level I ATC, by individual therapeutic categories and by active ingredient.

Tables 3.1 and 3.2 respectively show the NHS outpatient expenditure and consumption according to level I ATC. In 2019, the overall per capita pharmaceutical expenditure was € 384.43, with an increase of 5.6% compared to 2018, mainly due to the increase in the expenditure for medicines directly purchased by public health facilities (+10.9%). The therapeutic class with the highest per capita expenditure in the NHS outpatient category is represented by cardiovascular medicinal products (€ 47.58), followed by gastrointestinal pharmaceuticals (€ 32.58). Both categories show a reduction compared to the previous year (-2.9% and -1.2% respectively). As regards the pharmaceuticals supplied by public health facilities, per capita expenditure is higher for oncological and immunosuppressive pharmaceuticals (€ 95.86). As for consumption, on the whole, 1,154.4 doses were dispensed every day, with an increase of 1.6% due to a slight increase in NHS outpatient expenditure medicine (+0.9%) and to a more significant increase in those directly purchased by public health facilities (+5.9%).

Analysing the composition of public and private pharmaceutical expenditure by level I ATC (Table 3.3), antineoplastics and immunomodulators represent the pharmaceutical category with the highest expenditure and account for 20% of overall pharmaceutical expenditure. As expected, for Class A (NHS-reimbursed), cardiovascular pharmaceuticals show the highest expenditure (€ 2.9 billion), followed by gastrointestinal pharmaceuticals (around € 2 billion), while antineoplastic and antimicrobial medicines (€ 5.8 billion and € 2.6 billion respectively) represent the two categories with the highest distribution through public facilities. CNS medicines show the highest expenditure among Class C medicines with prescription (over € 1 billion), whereas, as for SOP and OTC the group of pharmaceuticals for gastrointestinal system and metabolism shows the highest expenditure, with € 647 million.

Table 3.4 shows the composition of the consumption of medicines, distinguished between medicines reimbursed by the NHS and medicines purchased by citizens, differentiated by reimbursement class. Overall, in Italy more than 1,604 doses per 1,000 inhabitants were consumed every day, of which 72% supplied by the NHS and 28% privately purchased by citizens (mainly Class C medicines with prescription). Deepening the analysis by therapeutic group and reimbursement class, a higher number of doses of the cardiovascular group (32.8 DDD) is observed within the privately purchased medicines of Class A, whereas as regards SOP and OTC medicines, the highest consumption was reported for gastrointestinal and respiratory medicines (respectively 31.4 and 22.3 DDD).

Antineoplastics, immunomodulators (€ 101.1 per capita) and pharmaceuticals for the gastrointestinal system and metabolism (€ 67.5) record the highest total expenditure values (Figure 3.1), while the lowest values are observed for antiparasitic (P), with € 0.4 and for medicines of the category “miscellaneous” (V) with € 7.7.

Table 3.1 NHS per capita expenditure by level I ATC in descending order of expenditure: comparison 2019-2018

Level I ATC	Per capita expenditure Class A – outpatient (a)	Δ% 19-18	Per capita expenditure – public health facilities (b)	Δ% 19-18	NHS expenditure (a+b)	Δ% 19-18
L	4.17	1.7	95.86	7.1	100.03	6.9
J	12.51	-4.3	43.72	24.4	56.23	16.7
C	47.58	-2.9	5.12	11.6	52.71	-1.6
A	32.58	-1.2	15.45	11.3	48.03	2.5
B	7.89	-0.2	28.20	6.4	36.09	4.8
N	23.18	2.9	7.30	5.3	30.49	3.5
R	16.71	3.0	3.87	27.1	20.58	6.8
M	5.43	-4.9	3.47	11.7	8.90	0.9
H	4.11	3.2	4.75	2.7	8.85	2.9
G	5.77	2.3	1.53	-2.7	7.30	1.2
S	3.89	2.3	3.10	10.3	7.00	5.7
V	0.15	-1.1	5.70	6.2	5.84	6.1
D	1.29	14.5	0.84	113.7	2.13	40.0
P	0.23	3.2	0.03	22.4	0.26	5.2
Total	**165.49**	**-0.6**	**218.94**	**10.9**	**384.43**	**5.6**

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

Table 3.2 Consumption (DDD/1000 inhab. day) NHS by level I ATC in descending consumption order: comparison 2019-2018

Level I ATC	DDD/1000 inhab. day NHS outpatient (a)	Δ% 19-18	DDD/1000 inhab. day public health facilities (b)	Δ% 19-18	DDD/1000 inhab. day NHS (a+b)	Δ% 19-18
C	474.3	0.8	18.6	10.2	492.9	1.1
A	153.1	0.3	29.2	0.0	182.2	0.3
B	88.2	1.2	47.4	10.9	135.6	4.4
N	66.5	2.1	25.7	5.9	92.1	3.1
R	41.9	1.7	2.6	4.1	44.4	1.8
G	41.8	2.5	2.4	23.6	44.2	3.5
M	37.4	0.0	4.9	6.7	42.3	0.7
H	35.4	0.8	5.3	1.4	40.7	0.9
S	20.7	1.2	2.8	0.2	23.5	1.1
J	16.6	-3.1	6.3	0.5	22.9	-2.1
L	6.2	2.3	10.3	8.3	16.5	5.9
D	4.6	6.2	8.2	-3.1	12.7	0
V	0.1	-0.7	3.2	1.8	3.3	1.7
P	0.9	2.5	0.0	5.9	1.0	2.6
Total	**987.7**	**0.9**	**166.7**	**5.9**	**1154.4**	**1.6**

Table 3.3. Composition of 2019 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 facilities§		Tot
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°
L	252	4.1	49	0.8	19	0.3	-	-	5,786	94.8	6,106
A	1,967	48.2	305	7.5	226	5.5	647	15.9	932	22.9	4,077
J	755	20.9	143	4.0	78	2.2	-	-	2,639	73.0	3,615
C	2,872	81.1	186	5.3	41	1.2	134	3.8	309	8.7	3,542
N	1,399	42.2	168	5.1	1,049	31.7	257	7.8	441	13.3	3,314
B	476	19.6	163	6.7	81	3.3	4	0.2	1,702	70.2	2,426
R	1,008	51.4	135	6.9	164	8.4	420	21.4	234	11.9	1,961
M	328	23.4	157	11.2	209	14.9	499	35.6	209	14.9	1,402
G	348	29.3	40	3.4	640	53.9	68	5.7	92	7.7	1,188
S	235	31.6	14	1.9	223	30.0	84	11.3	187	25.2	743
D	78	11.3	26	3.8	263	38.0	275	39.7	50	7.2	692
H	248	38.3	72	11.1	42	6.5	-	-	286	44.1	648
V	9	1.9	83	17.8	29	6.2	-	-	344	74.0	465
P	14	53.8	4	15.4	3	11.5	3	11.5	2	7.7	26
Total	**9,989**	**33.1**	**1,544**	**5.1**	**3,066**	**10.2**	**2,392**	**7.9**	**13,215**	**43.7**	**30,206**

^ Expenditure for Class A net of Class C reimbursed (18,9 millions); § Excluding oxygen; ° Gross in millions euros;
* Calculated on the category
Source: OsMed, Traceability of medicinal products

Table 3.4. Composition of 2019 consumption (in terms of DDD/1000 inhabitants 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 facilities		Total
	N.	%*	N.	%*	N.	%*	N.	%*	N.	%*	units
C	474.3	88.6	32.8	6.1	1.5	0.3	7.9	1.5	18.6	3.5	535.1
A	153.1	62.7	23.3	9.6	7.1	2.9	31.4	12.9	29.2	11.9	244.0
B	88.2	46.4	20.0	10.5	34.4	18.1	0.1	0.1	47.4	24.9	190.2
N	66.5	39.2	6.9	4.1	64.2	37.9	6.3	3.7	25.7	15.1	169.6
R	41.9	46.8	10.3	11.5	12.5	13.9	22.3	24.9	2.6	2.9	89.5
M	37.4	42.5	21.5	24.4	3.2	3.6	21.0	23.8	4.9	5.6	87.9
G	41.8	49.7	3.5	4.2	34.3	40.7	2.1	2.5	2.4	2.8	84.1
H	35.4	66.2	11.0	20.5	1.8	3.4	-	-	5.3	9.9	53.6
D	4.6	9.0	3.4	6.7	17.3	34.4	17.0	33.7	8.2	16.2	50.5
S	20.7	43.4	1.8	3.7	12.4	26.0	10.1	21.1	2.8	5.8	47.7
J	16.6	55.9	4.1	13.8	2.7	9.1	-	-	6.3	21.2	29.7
L	6.2	36.1	0.5	3.1	0.1	0.7	-	-	10.3	60.1	17.1
V	0.1	2.4	0.1	2.7	0.9	20.5	0.0	1.0	3.2	73.4	4.3
P	0.9	78.5	0.2	15.6	0.0	2.3	0.0	1.1	0.0	2.5	1.2
Total	**987.7**	**61.6**	**139.5**	**8.7**	**192.4**	**12.0**	**118.2**	**7.4**	**166.7**	**10.4**	**1604.5**

* Calculated on the category

Source: OsMed, Traceability of medicinal products

Figure 3.1. 2019 total per capita pharmaceutical expenditure by level I ATC

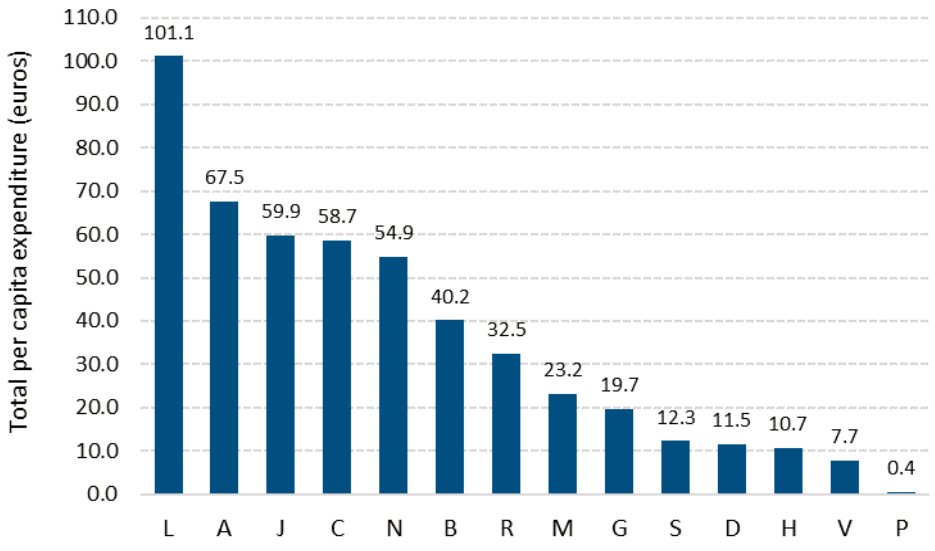


Table 3.5 shows, for each level I ATC category, the substances accounting for 75% of the NHS outpatient expenditure, sorted by per capita expenditure. Information is also provided on the prescribed doses and on the average cost per day of therapy. The variation from the previous year is calculated for all indicators.
Ramipril is the pharmaceutical showing the highest prescription (62.5 DDD) while cholecalciferol is the one with the highest expenditure (€ 4.66 per capita); high levels of consumption are also observed for atorvastatin (46.1 DDD), acetylsalicylic acid (indicated as antiplatelet agent: 43.8 DDD), amlodipine (27 DDD), furosemide (24.5 DDD) and pantoprazole (23 DDD). With the exception of human hepatitis B immunoglobulin (€ 310.27), human albumin (€ 52.22), parathyroid hormone (€ 18.03) and ceftriaxone (€ 11.78), a high average cost per day of therapy is reported with reference to medicines for pain therapy: naloxone/oxycodone (€ 7.03), tapentadol (€ 6.31) and fentanyl (€ 5.72).
Within cardiovascular pharmaceuticals, olmesartan plain or in combination with hydrochlorothiazide or amlodipine, has increased its prescription from 2018 to 2019 respectively by 27.5%, 9.3% and 24.3%, while, always within angiotensin II inhibitors, the consumption has decreased of valsartan plain (-24.5%) and in combination with hydrochlorothiazide (-24.7%).
The constant increase in cholecalciferol (+ 6.2%) continues, although it is not yet possible to assess the impact of AIFA Note 96 issued at the end of October 2019; within proton pump inhibitors, the use of omeprazole proves stable, lansoprazole decreases (-3.4%) while pantoprazole (+ 7%) and esomeprazole (+ 6.8%) increase.
Four proton pump inhibitors (pantoprazole, lansoprazole, omeprazole and esomeprazole) rank among the top five most expensive gastrointestinal pharmaceuticals, with a reduction in expenditure, due to a price drop of generic pharmaceuticals and to an increase in consumption. As in 2018, cholecalciferol ranks first, representing 14.3% of the expenditure and 8.5% of the doses of the category. Mesalazine, used in patients with chronic inflammatory bowel disease (Crohn's disease and ulcerative colitis) for its anti-inflammatory effect on the intestinal mucosa affected by the lesions, shows in 2019 an increase by over 5% in both expenditure and doses and a stable average cost compared to the previous year.
Within pharmaceuticals for diabetes, an increase in metformin (+1.8% of doses) is reported, while as for insulins, lyspro decreases (-1.8%) and aspart shows a growing trend (+ 1%).
As regards CNS medicines, significant increases are detected for vortioxetine (+25.2%), an antidepressant used in adults that has been marketed for a few years, whose cost is almost double compared to duloxetine (€ 1.14 vs 0.68) and significantly higher than sertraline (€ 0.25); other increases concern the antiepileptic lacosamide (+24.7%) and safinamide, indicated in the treatment of patients with Parkinson's disease in medium-advanced stage.
Analysing the first 30 active ingredients by expenditure, provided according to standard distribution (Table 3.6), as many as 19 out of 30 belong to the categories of the cardiovascular system and gastrointestinal system pharmaceuticals. The same medicines of 2018 rank in the first five places, with the highest expenditure in absolute terms for cholecalciferol (€ 281.3 million), pantoprazole (265 million), atorvastatin (257.3 million), amoxicillin/clavulanic acid (173.3 million) and lansoprazole (152.1 million). Overall, the top 30 active ingredients represent around 37% of Class A/NHS outpatient expenditure. The active ingredients showing the greatest variation in expenditure (Table 3.7) are 9 cardiovascular system pharmaceuticals and 6 CNS pharmaceuticals. In particular, the active

ingredient with the greatest variation in expenditure is humeclidinium (+72.9%), indicated as a maintenance treatment bronchodilator to relieve symptoms in adult patients with COPD, attributable exclusively to an increase in consumption (+74.9%), while the DDD average cost decreased by 1.2%, followed by calcipotriol associated with betamethasone (+33.2%), whose increase in expenditure is once again credited to a significant increase in consumption (+28.7%). Considering instead the first 30 active ingredients for consumption, representing 51.5% of Class A-NHS doses (Table 3.8), as many as 17 are cardiovascular and 6 are gastrointestinal pharmaceuticals. Ramipril with 62.5 DDD, equal to 6.3% of the total, is the most widely used medicine, followed by atorvastatin (46.1 DDD) and acetylsalicylic acid (3.8 DDD).

Table 3.5. 2019 NHS outpatient consumption and expenditure: most frequently prescribed active ingredients by level I ATC (up to 75% of expenditure within the therapeutic category

Therapeutic category	Gross per capita expenditure	%*	Δ % 19-18	DDD/1000 inhab. day	%*	Δ % 19-18	Average cost DDD	Δ % 19-18
C – Cardiovascular	**47.58**		**-2.9**	**474.3**		**0.8**	**0.27**	**-3.6**
atorvastatin	4.26	9.0	3.8	46.1	9.7	4.5	0.25	-0.7
bisoprolol	2.44	5.1	6.0	11.1	2.3	5.9	0.60	0.1
ramipril	2.03	4.3	-0.1	62.5	13.2	1.0	0.09	-1.1
omega 3	1.90	4.0	1.7	4.3	0.9	4.5	1.19	-2.6
amlodipine	1.57	3.3	1.2	27.0	5.7	1.7	0.16	-0.5
simvastatin	1.57	3.3	-5.0	13.2	2.8	-4.9	0.33	-0.1
olmesartan	1.50	3.2	23.7	13.0	2.7	27.5	0.32	-3.0
nebivolol	1.44	3.0	2.8	15.5	3.3	3.2	0.26	-0.5
rosuvastatin	1.25	2.6	-2.4	12.9	2.7	5.5	0.27	-7.5
doxazosin	1.22	2.6	0.9	7.4	1.6	0.8	0.45	0.1
ezetimibe	1.20	2.5	-12.3	4.4	0.9	19.5	0.76	-26.6
ezetimibe/simvastatin	1.11	2.3	-51.6	4.5	1.0	6.4	0.67	-54.5
olmesartan/hydrochlorotiazide	1.08	2.3	8.6	8.9	1.9	9.3	0.33	-0.6
olmesartan/amlodipine	1.03	2.2	-30.8	6.8	1.4	24.3	0.41	-44.3
barnidipine	0.86	1.8	0.3	4.7	1.0	0.7	0.50	-0.4
perindopril/amlodipine	0.84	1.8	3.5	5.3	1.1	5.9	0.43	-2.2
flecainide acetate	0.81	1.7	7.3	2.7	0.6	8.4	0.83	-1.0
losartan	0.80	1.7	1.2	7.6	1.6	2.0	0.29	-0.8
lercanidipine	0.77	1.6	1.1	9.4	2.0	1.2	0.22	-0.1
valsartan/hydrochlorotiazide	0.75	1.6	-22.4	6.8	1.4	-24.7	0.30	3.0
furosemide	0.73	1.5	0.3	24.5	5.2	0.1	0.08	0.2
irbesartan	0.71	1.5	5.7	8.7	1.8	5.9	0.22	-0.2
valsartan	0.69	1.5	-18.8	10.0	2.1	-24.5	0.19	7.5
zofenopril	0.66	1.4	8.0	4.5	0.9	7.5	0.41	0.4
zofenopril/hydrochlorotiazide	0.64	1.4	-1.1	4.1	0.9	-1.0	0.43	0.0
irbesartan/hydrochlorotiazide	0.64	1.3	-5.4	5.5	1.2	-5.1	0.32	-0.4
A – Gastrointestinal and metabolism	**32.58**		**-1.3**	**153.1**		**0.3**	**0.58**	**-1.5**
cholecalciferol	4.66	14.3	3.3	13.0	8.5	6.2	0.98	-2.7
pantoprazole	4.39	13.5	-2.5	23.0	15.0	7.0	0.52	-8.9
lansoprazole	2.52	7.7	-7.1	14.0	9.2	-3.4	0.49	-3.9
omeprazole	2.36	7.2	-5.9	16.4	10.7	-0.1	0.39	-5.8
esomeprazole	2.27	7.0	-4.4	13.5	8.8	6.8	0.46	-10.4

continued

Table 3.5 (continued)

Therapeutic category	Gross per capita expenditure	%*	Δ % 19-18	DDD/1000 inhab. day	%*	Δ % 19-18	Average cost DDD	Δ % 19-18
mesalazine	1.88	5.8	5.2	4.7	3.1	5.5	1.09	-0.3
insulin lyspro	1.59	4.9	-5.6	3.4	2.2	-1.8	1.29	-3.9
metformin	1.52	4.7	1.4	22.0	14.4	1.8	0.19	-0.5
insulin aspart	1.46	4.5	0.5	2.9	1.9	1.0	1.39	-0.5
rifaximin	1.40	4.3	0.7	1.8	1.2	0.8	2.08	0.0
sodium alginate/potassium bicarbonate	0.85	2.6	3.1	4.0	2.6	2.9	0.59	0.2
N – Nervous system	**23.18**		**2.9**	**66.5**		**2.1**	**0.96**	**0.8**
levetiracetam	1.55	6.7	3.3	2.1	3.1	5.0	2.04	-1.7
fentanyl	1.35	5.8	3.3	0.6	1.0	2.0	5.72	1.3
tapentadol	1.20	5.2	5.8	0.5	0.8	5.7	6.31	0.1
pregabalin	1.13	4.9	7.8	2.0	3.0	7.9	1.53	-0.1
naloxone/oxycodone	1.01	4.3	-5.7	0.4	0.6	-3.4	7.03	-2.4
paroxetine	1.00	4.3	-2.6	7.7	11.5	-0.6	0.36	-2.0
escitalopram	0.94	4.0	0.2	7.3	11.0	0.9	0.35	-0.7
valproic acid	0.92	4.0	1.2	2.2	3.3	0.3	1.16	0.9
venlafaxine	0.78	3.3	1.3	3.4	5.1	1.7	0.62	-0.5
duloxetine	0.75	3.2	4.2	3.0	4.5	5.2	0.68	-1.0
sertraline	0.73	3.1	3.2	7.9	11.9	3.6	0.25	-0.4
rotigotine	0.70	3.0	-1.9	0.4	0.5	-1.9	5.39	0.0
vortioxetine	0.57	2.4	25.3	1.4	2.1	25.2	1.14	0.0
quetiapine	0.53	2.3	5.7	0.4	0.6	2.8	3.42	2.8
lacosamide	0.53	2.3	21.6	0.3	0.4	24.7	5.38	-2.5
lamotrigine	0.43	1.9	4.9	0.7	1.0	4.8	1.77	0.1
citalopram	0.41	1.7	-2.2	3.9	5.9	-1.9	0.28	-0.3
trazodone	0.38	1.7	3.7	1.1	1.6	3.4	0.99	0.3
pramipexol	0.38	1.6	-1.5	0.5	0.7	-1.9	2.27	0.4
lidocaine	0.37	1.6	3.9	0.3	0.4	3.9	3.61	0.0
safinamide	0.36	1.5	11.7	0.2	0.3	16.1	4.54	-3.8
levodopa/benserazide	0.34	1.5	9.6	1.0	1.5	9.9	0.93	-0.3
mirtazapine	0.33	1.4	4.2	1.6	2.4	3.7	0.57	0.5
gabapentin	0.33	1.4	3.0	0.4	0.6	2.8	2.14	0.2
paracetamol/codeine	0.29	1.2	-2.4	1.1	1.7	-2.4	0.71	0.0
topiramate	0.28	1.2	-1.1	0.3	0.5	-0.8	2.41	-0.3
R - Respiratory	**16.71**		**2.9**	**41.9**		**1.7**	**1.09**	**1.3**
beclomethasone/formoterol	2.34	14.0	4.6	3.6	8.6	4.7	1.79	0.0
fluticasone/vilanterol	2.13	12.8	13.4	3.4	8.0	13.4	1.74	0.0
salmeterol/fluticasone	1.81	10.8	-15.2	2.8	6.7	-11.6	1.77	-4.1
budesonide/formoterol	1.34	8.0	11.6	1.9	4.6	13.4	1.92	-1.6
tiotropium	1.32	7.9	-8.3	2.4	5.7	-8.9	1.52	0.7
beclomethasone	0.68	4.1	-8.9	1.9	4.5	-8.4	1.00	-0.5
aclidinium	0.67	4.0	-2.3	1.1	2.7	-2.3	1.61	0.0
umeclidinium	0.63	3.8	72.9	1.1	2.7	74.9	1.56	-1.2
glycopyrrolate	0.50	3.0	-8.9	0.9	2.2	-8.9	1.51	0.0
montelukast	0.47	2.8	0.8	2.0	4.8	2.2	0.64	-1.3
flunisolide	0.40	2.4	12.2	1.5	3.6	11.4	0.73	0.7
fluticasone	0.39	2.3	-7.7	0.9	2.1	-6.6	1.24	-1.1
J - Antimicrobials	**12.51**		**-4.3**	**16.6**		**-3.1**	**2.06**	**-1.2**
amoxicillin/clavulanic acid	2.87	23.0	0.0	5.8	34.7	-0.1	1.36	0.1
ceftriaxone	1.28	10.2	-0.6	0.3	1.8	-0.9	11.78	0.3

continued

Table 3.5 (continued)

Therapeutic category	Gross per capita expenditure	%*	Δ % 19-18	DDD/1000 inhab. day	%*	Δ % 19-18	Average cost DDD	Δ % 19-18
cefixime	0.96	7.6	7.9	1.1	6.7	8.2	2.33	-0.2
fluconazole	0.79	6.3	-4.6	0.4	2.3	-4.4	5.56	-0.3
clarithromycin	0.72	5.7	-1.2	2.1	12.9	0.7	0.92	-1.9
azithromycin	0.68	5.5	1.8	1.3	7.6	1.8	1.47	0.0
ciprofloxacin	0.67	5.3	-23.5	0.7	4.3	-22.6	2.58	-1.2
fosfomycin	0.64	5.1	6.8	0.4	2.3	6.5	4.59	0.3
levofloxacin	0.55	4.4	-29.6	1.0	6.1	-29.8	1.48	0.3
human immunoglobulin antihepatitis B	0.36	2.8	-34.1	0.0	0.0	-32.5	310.27	-2.3
B – Blood and blood-forming organs	**7.89**		**-0.2**	**88.2**		**1.2**	**0.25**	**-1.5**
enoxaparin	1.77	22.4	-0.3	2.0	2.3	4.9	2.39	-5.0
acetylsalicylic acid	1.15	14.5	0.0	43.8	49.7	0.3	0.07	-0.4
clopidogrel	1.14	14.5	11.8	5.5	6.2	11.6	0.57	0.2
folic acid	0.48	6.1	3.3	6.0	6.9	5.4	0.22	-2.0
edoxaban	0.44	5.6	44.4	0.3	0.3	49.0	4.53	-3.1
nadroparin calcium	0.38	4.9	-30.0	0.4	0.4	-30.0	2.92	0.0
ferrous sulphate	0.25	3.2	0.7	2.2	2.5	0.7	0.31	0.0
clopidogrel/acetylsalicylic acid	0.24	3.0	0.3	0.8	0.9	0.3	0.86	0.0
human albumin	0.23	2.9	2.6	0.0	0.0	1.4	52.22	1.2
G - Genito-urinary and sex hormones	**5.77**		**2.3**	**41.8**		**2.5**	**0.38**	**-0.3**
tamsulosin	1.07	18.6	2.5	10.2	24.5	2.9	0.29	-0.4
silodosin	1.07	18.5	7.3	5.7	13.6	7.3	0.51	0.0
dutasteride	1.04	18.0	2.1	8.1	19.5	4.4	0.35	-2.2
alfuzosin	0.82	14.1	3.9	8.6	20.6	4.1	0.26	-0.2
finasteride	0.55	9.5	-2.1	2.5	6.0	-1.6	0.59	-0.5
M - Musculo-skeletal	**5.43**		**-4.9**	**37.4**		**0.0**	**0.40**	**-4.9**
alendronic acid	0.75	13.8	4.2	3.8	10.2	5.2	0.54	-1.0
febuxostat	0.73	13.4	-24.8	2.1	5.6	4.2	0.95	-27.8
diclofenac	0.58	10.6	1.6	3.9	10.5	1.1	0.40	0.4
etoricoxib	0.54	9.9	2.0	3.1	8.4	3.3	0.47	-1.2
alendronic acid/cholecalciferol	0.47	8.6	-8.7	2.2	5.9	-8.4	0.58	-0.3
risedronate	0.39	7.2	-2.6	2.2	5.9	-1.4	0.49	-1.2
Allopurinol	0.33	6.1	4.5	7.9	21.1	4.1	0.12	0.3
ketoprofen	0.31	5.7	-5.5	3.0	8.0	-5.4	0.28	-0.2
L - Antineoplastics and immunomodulators	**4.17**		**1.7**	**6.2**		**2.3**	**1.85**	**-0.6**
letrozole	1.25	30.1	9.6	1.5	24.5	10.0	2.27	-0.4
methotrexate	0.64	15.3	6.2	1.3	20.3	4.8	1.39	1.4
cyclosporine	0.57	13.6	-7.6	0.2	3.0	-6.7	8.22	-0.9
anastrozole	0.40	9.7	-1.9	0.8	13.0	-0.9	1.38	-1.0
exemestane	0.37	9.0	12.7	0.5	7.4	13.2	2.24	-0.5
H – Systemic hormones	**4.11**		**3.2**	**35.4**		**0.8**	**0.32**	**2.3**
teriparatide	1.23	29.9	3.0	0.2	0.5	5.4	18.03	-2.3
levothyroxine	1.04	25.2	7.4	20.8	58.7	2.7	0.14	4.6
prednisone	0.65	15.9	2.5	6.4	18.0	4.9	0.28	-2.3
betamethasone	0.32	7.8	0.2	2.1	5.9	0.4	0.42	-0.2
methylprednisolone	0.19	4.6	-13.8	2.9	8.2	-17.1	0.18	4.0
S - Sensory organs	**3.89**		**2.3**	**20.7**		**1.2**	**0.51**	**1.0**
bimatoprost	0.46	11.8	0.3	1.9	9.1	1.1	0.67	-0.9

continued

Table 3.5 (continued)

Therapeutic category	Gross per capita expenditure	%*	Δ % 19-18	DDD/1000 inhab. day	%*	Δ % 19-18	Average cost DDD	Δ % 19-18
timolol/bimatoprost	0.45	11.4	1.0	1.4	6.9	1.5	0.85	-0.5
tafluprost	0.44	11.4	10.4	1.4	6.8	10.4	0.86	0.0
brinzolamide/timolol	0.43	11.0	4.4	1.7	8.4	4.4	0.68	0.0
timolol	0.34	8.7	4.6	3.1	14.8	1.2	0.31	3.4
dorzolamide/timolol	0.29	7.4	4.5	2.1	9.9	5.8	0.39	-1.3
travoprost	0.21	5.4	5.0	1.0	5.0	3.9	0.56	1.0
tafluprost/timolol	0.19	4.9	40.3	0.5	2.6	40.3	0.96	0.0
timolol/travoprost	0.19	4.8	-15.3	0.7	3.4	-9.9	0.73	-6.0
D - Dermatological	**1.29**		**14.5**	**4.6**		**6.2**	**0.78**	**7.8**
calcipotriol/betamethasone	0.80	61.8	33.2	2.4	52.0	28.7	0.92	3.5
diclofenac	0.08	6.2	-1.3	0.1	1.8	0.8	2.60	-2.1
isotretinoin	0.07	5.8	2.4	0.1	3.2	3.2	1.41	-0.8
terbinafine	0.06	4.6	-0.6	0.1	2.5	0.0	1.41	-0.6
clobetasol	0.06	4.4	-7.1	0.6	12.6	-31.8	0.27	36.3
P – Antiparasitic products	**0.23**		**3.2**	**0.9**		**2.5**	**0.67**	**0.6**
hydroxychloroquine	0.15	65.6	6.0	0.8	84.2	6.0	0.52	0.0
mefloquine	0.03	13.1	-2.3	0.0	0.7	-2.3	13.27	0.0
mebendazole	0.02	9.4	2.3	0.1	9.8	0.4	0.65	2.0
metronidazole	0.01	5.1	6.3	0.0	3.3	6.3	1.03	0.0
tinidazole	0.01	2.6	-0.8	0.0	0.7	-0.8	2.71	0.0
V – Miscellaneous	**0.15**		**-1.1**	**0.1**		**-0.7**	**3.78**	**-0.3**
sevelamer	0.05	35.1	4.5	0.0	24.5	4.3	5.42	0.2
sodium polystyrene sulphonate	0.03	20.8	0.1	0.0	27.3	0.1	2.88	0.0
sucroferric oxidroxide	0.02	12.5	3.8	0.0	5.6	9.3	8.44	-5.0
calcium polystyrene sulphonate	0.01	9.8	7.5	0.0	14.2	7.5	2.62	0.0
deferoxamine	0.01	5.0	2.0	0.0	1.0	20.7	19.64	-15.5

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

Table 3.6. First thirty active ingredients in terms of NHS outpatient expenditure (Class A-NHS): comparison 2019-2018

ATC	Active ingredient	Exp. *(million)*	%*	Gross per capita expenditure	Rank 2019	Rank 2018	Average cost DDD	Δ % 19-18
A	cholecalciferol	281.3	2.8	4.66	1	1	0.98	-2.7
A	pantoprazole	265.0	2.7	4.39	2	2	0.52	-8.9
C	atorvastatin	257.3	2.6	4.26	3	3	0.25	-0.7
J	amoxicillin/clavulanic acid	173.3	1.7	2.87	4	4	1.36	0.1
A	lansoprazole	152.1	1.5	2.52	5	5	0.49	-3.9
C	bisoprolol	147.3	1.5	2.44	6	8	0.60	0.1
A	omeprazole	142.3	1.4	2.36	7	6	0.39	-5.8
R	beclomethasone/formoterol	141.2	1.4	2.34	8	10	1.79	0.0
A	exomeprazole	136.9	1.4	2.27	9	7	0.46	-10.4
R	fluticasone furoate/vilanterol	128.7	1.3	2.13	10	13	1.74	0.0
C	ramipril	122.4	1.2	2.03	11	12	0.09	-1.1
C	omega 3	114.4	1.1	1.90	12	14	1.19	-2.6
A	mesalazine	113.7	1.1	1.88	13	15	1.09	-0.3
R	salmeterol/fluticasone	109.3	1.1	1.81	14	11	1.77	-4.1
B	enoxaparin	106.8	1.1	1.77	15	16	2.39	-5.0
A	insulin lyspro	96.1	1.0	1.59	16	17	1.29	-3.9
C	amlodipine	94.8	0.9	1.57	17	19	0.16	-0.5
C	simvastatin	94.7	0.9	1.57	18	18	0.33	-0.1
N	levetiracetam	93.6	0.9	1.55	19	21	2.04	-1.7
A	metformin	91.9	0.9	1.52	20	20	0.19	-0.5
C	olmesartan	90.5	0.9	1.50	21	31	0.32	-3.0
A	insulin aspart	88.2	0.9	1.46	22	23	1.39	-0.5
C	nebivolol	86.9	0.9	1.44	23	25	0.26	-0.5
A	rifaximin	84.7	0.8	1.40	24	26	2.08	0.0
N	fentanyl	81.6	0.8	1.35	25	28	5.72	1.3
R	budesonide/formoterol	81.2	0.8	1.34	26	33	1.92	-1.6
R	tiotropium	79.5	0.8	1.32	27	24	1.52	0.7
J	ceftriaxone	77.0	0.8	1.28	28	29	11.78	0.3
L	letrozole	75.7	0.8	1.25	29	36	2.27	-0.4
C	rosuvastatin	75.4	0.8	1.25	30	30	0.27	-7.5
	Total	**3,684.0**	**36.9**					
	Total expenditure Class A-NHS	**9,988.9**						

* Calculated on overall NHS outpatient expenditure

Table 3.7. First thirty active ingredients* with higher variation in NHS outpatient expenditure compared to the previous year: comparison 2019-2018

ATC	Active ingredient	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. day	Δ % 19-18	DDD Average cost	Δ % 19-18
R	humeclidinium	0.63	72.9	1.1	74.9	1.56	-1.2
D	calcipotriol/betamethasone	0.80	33.2	2.4	28.7	0.92	3.5
N	vortioxetine	0.57	25.3	1.4	25.2	1.14	0.0
C	olmesartan	1.50	23.7	13.0	27.5	0.32	-3.0
N	lacosamide	0.53	21.6	0.3	24.7	5.38	-2.5
R	fluticasone/vilanterol	2.13	13.4	3.4	13.4	1.74	0.0
B	clopidogrel	1.14	11.8	5.5	11.6	0.57	0.2
R	budesonide/formoterol	1.34	11.6	1.9	13.4	1.92	-1.6
L	letrozole	1.25	9.6	1.5	10.0	2.27	-0.4
C	olmesartan/hydrochlorothiazide	1.08	8.6	8.9	9.3	0.33	-0.6
C	zofenopril	0.66	8.0	4.5	7.5	0.41	0.4
J	cefixime	0.96	7.9	1.1	8.2	2.33	-0.2
N	pregabalin	1.13	7.8	2.0	7.9	1.53	-0.1
H	levothyroxine	1.04	7.4	20.8	2.7	0.14	4.6
C	flecainide acetate	0.81	7.3	2.7	8.4	0.83	-1.0
G	silodosin	1.07	7.3	5.7	7.3	0.51	0.0
J	fosfomycin	0.64	6.8	0.4	6.5	4.59	0.3
L	methotrexate	0.64	6.2	1.3	4.8	1.39	1.4
C	bisoprolol	2.44	6.0	11.1	5.9	0.60	0.1
C	telmisartan	0.55	5.9	9.1	4.7	0.17	1.1
N	tapentadol	1.20	5.8	0.5	5.7	6.31	0.1
C	candesartan	0.48	5.7	8.8	6.9	0.15	-1.1
N	quetiapine	0.53	5.7	0.4	2.8	3.42	2.8
C	irbesartan	0.71	5.7	8.7	5.9	0.22	-0.2
A	mesalazine	1.88	5.2	4.7	5.5	1.09	-0.3
R	beclomethasone/formoterol	2.34	4.6	3.6	4.7	1.79	0.0
M	alendronic acid	0.75	4.2	3.8	5.2	0.54	-1.0
N	duloxetine	0.75	4.2	3.0	5.2	0.68	-1.0
G	alfuzosin	0.82	3.9	8.6	4.1	0.26	-0.2
C	atorvastatin	4.26	3.8	46.1	4.5	0.25	-0.7

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

Table 3.8. First thirty active ingredients in terms of NHS outpatient consumption (Class A-NHS): comparison 2019-2018

ATC	Active ingredient	DDD/1000 inhab. day	%*	Rank 2019	Rank 2018	DDD Average cost	Δ % 19-18
C	ramipril	62.5	6.3	1	1	0.09	-1.1
C	atorvastatin	46.1	4.7	2	2	0.25	-0.7
B	acetylsalicylic acid	43.8	4.4	3	3	0.07	-0.4
C	amlodipine	27.0	2.7	4	4	0.16	-0.5
C	furosemide	24.5	2.5	5	5	0.08	0.2
A	pantoprazole	23.0	2.3	6	7	0.52	-8.9
A	metformin	22.0	2.2	7	6	0.19	-0.5
H	levothyroxine	20.8	2.1	8	8	0.14	4.6
A	omeprazole	16.4	1.7	9	9	0.39	-5.8
C	nebivolol	15.5	1.6	10	10	0.26	-0.5
A	lansoprazole	14.0	1.4	11	11	0.49	-3.9
A	exomeprazole	13.5	1.4	12	14	0.46	-10.4
C	simvastatin	13.2	1.3	13	12	0.33	-0.1
A	cholecalciferol	13.0	1.3	14	15	0.98	-2.7
C	olmesartan	13.0	1.3	15	18	0.32	-3.0
C	rosuvastatin	12.9	1.3	16	16	0.27	-7.5
C	bisoprolol	11.1	1.1	17	17	0.60	0.1
G	tamsulosin	10.2	1.0	18	19	0.29	-0.4
C	valsartan	10.0	1.0	19	13	0.19	7.5
B	cyanocobalamin	9.5	1.0	20	25	0.02	-0.1
C	lercanidipine	9.4	0.9	21	21	0.22	-0.1
C	telmisartan	9.1	0.9	22	23	0.17	1.1
C	olmesartan/hydrochlorothiazide	8.9	0.9	23	29	0.33	-0.6
C	enalapril	8.8	0.9	24	20	0.15	-1.4
C	candesartan	8.8	0.9	25	27	0.15	-1.1
C	irbesartan	8.7	0.9	26	28	0.22	-0.2
G	alfuzosin	8.6	0.9	27	26	0.26	-0.2
G	dutasteride	8.1	0.8	28	30	0.35	-2.2
C	atenolol	8.0	0.8	29	24	0.13	0.4
N	sertraline	7.9	0.8	30	32	0.25	-0.4
	Total	**508.5**	**51.5**				
	Total DDD Class A-NHS	**987.7**					

* calculated on overall NHS outpatient expenditure

Within the most used NHS outpatient care categories, CNS pharmaceuticals show an increase in quantities by 1.9%, genitourinary system pharmaceuticals increase by 2.3%, dermatologicals by 5.9%, while antimicrobial medicines show the largest reductions (-3.1%). On average, prices have decreased significantly for cardiovascular medicines (-4.9%) and for musculoskeletal system pharmaceuticals (-4.3%) (Figure 3.2). The mix effect (prescription shift towards specialties with a higher average cost per day of therapy) of NHS outpatient medicines shows the greatest variation for dermatological medicines (+8.2%), for systemic hormonal preparations (+2.9%) and for respiratory system pharmaceuticals (+1.7%). The greatest reduction is represented by gastrointestinal and metabolism medicines (-1.3%) as well as by blood and blood-forming organs pharmaceuticals (-1.1%).
As for the therapeutic category, the slight reduction in the expenditure for statins (-0.6%) was determined by a contraction in prices (-1.7%) and consequently in the mix effect (-1.1%), counterbalanced by a 2.3% increase in doses. Still relating to cardiovascular medicines, a marked decrease (-29.6%) was recorded in the expenditure for angiotensin II receptor blockers and calcium channel blockers, only attributable to the patent expiry of the olmesartan/amlodipine association, which resulted in a price reduction (-43.3%), partially offset by an increase in consumption (+26.8%). As for proton pump inhibitors, in 2019 a shift was reported towards prescription of less expensive specialties (mix effect: -7.1%) (Table 3.9). The increase in the mix (+11%) of slow-acting injectable insulins and analogues is linked to a higher use of the insulin glargine/lixisenatide and insulin degludec/liraglutide combinations which have a cost per day of therapy between € 7 and € 9 (Table 3.10).

Figure 3.2. Consumption, price and mix effects on the variation of NHS outpatient pharmaceutical expenditure (Class A-NHS) by level I ATC: comparison 2019-2018

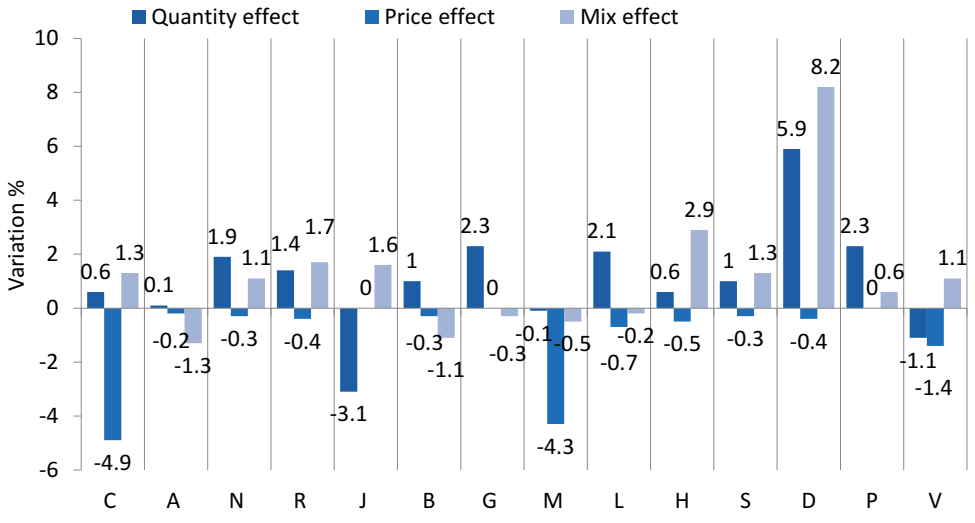


Table 3.9 Consumption, price and mix effects on the variation of NHS outpatient pharmaceutical expenditure (Class A-NHS) by level I ATC: comparison 2019-2018
(for each ATC category the therapeutic subgroups were included in descending order of expenditure, up to per capita expenditure of € 0.10)

Level I ATC Subgroups	Gross per capita expenditure	DDD/ 1000 inhab. day	Δ % 19-18				Δ % DDD Average cost
			Expenditure	DDD	Prices	Mix	
Italy	**165.49**	**987.7**	**-0.5**	**0.7**	**-1.8**	**0.5**	**-1.2**
C – Cardiovascular system	**47.58**	**474.3**	**-3.1**	**0.6**	**-4.9**	**1.3**	**-3.6**
HMG-CoA reductase inhibitors	7.86	76.9	-0.6	2.3	-1.7	-1.1	-2.8
Angiotensin II receptor blockers, plain	4.76	57.4	4.8	1.8	-0.3	3.3	3.0
Beta blockers, selective	4.50	38.7	3.6	2.0	-0.1	1.7	1.6
Dihydropyridine derivatives	4.20	49.7	-1.8	-0.2	0.0	-1.6	-1.6
Angiotensin II receptor blockers and diuretics	4.03	33.4	-6.6	-7.3	-0.2	0.8	0.7
ACE inhibitors, plain	3.87	84.3	-1.0	-0.2	-0.2	-0.7	-0.8
Other lipid modifying agents	3.10	8.7	-4.4	11.3	-10.7	-3.8	-14.1
ACE inhibitors and diuretics	2.67	20.6	-3.0	-3.6	0.0	0.7	0.7
ACE inhibitors and calcium channel blockers	1.71	11.9	3.9	6.7	-0.7	-1.9	-2.6
HMG-CoA reductase inhibitors in combination with other lipid modifying agents	1.48	5.9	-37.1	31.3	-52.1	0.1	-52.1
Alpha-adrenoreceptor blockers	1.22	7.4	0.6	0.6	0.0	0.1	0.1
Angiotensin II receptor blockers and calcium channel blockers	1.05	7.0	-29.6	26.8	-43.3	-2.1	-44.5
Antiarrhythmic agents, class Ic	1.02	4.6	3.4	0.0	0.0	3.3	3.3
Sulfonamides, plain	0.86	25.8	1.3	0.3	0.0	1.0	1.0
Organic nitrates	0.74	7.1	-14.1	-14.1	-0.5	0.4	0.0
Alpha and beta adrenoreceptor blockers	0.55	3.1	-6.1	-5.6	0.0	-0.5	-0.5
ACE inhibitors, other combinations	0.54	3.3	21.7	23.0	0.5	-1.5	-1.0
Selective beta-blockers and thiazides	0.54	5.5	-1.3	-0.4	-0.2	-0.8	-0.9
Aldosterone antagonists	0.52	3.2	3.5	1.9	0.0	1.6	1.6
Fibrates	0.38	2.7	1.0	1.3	0.0	-0.3	-0.3
Antiarrhythmic agents, class III	0.26	2.9	-1.4	-1.5	0.0	0.0	0.0
Imidazoline receptor agonists	0.21	1.5	-5.1	-8.2	0.0	3.3	3.3
Angiotensin II receptor blockers, other combinations	0.20	0.1	78.6	69.7	5.3	0.0	5.3
Other cardiac preparations	0.19	0.6	25.7	52.1	-8.9	-9.2	-17.3
Benzothiazepine derivatives	0.19	1.1	-8.0	-7.9	0.0	-0.1	-0.1
Beta-blocking agents, not selective	0.14	1.6	-1.5	-2.1	0.0	0.7	0.7
Phenylalkylamine derivatives	0.14	1.2	-9.1	-8.6	0.0	-0.5	-0.5
Sulfonamides, plain	0.13	2.0	43.4	39.2	0.2	2.9	3.0
Selective beta-blocking agents and other diuretics	0.13	1.8	-6.6	-6.7	0.0	0.1	0.1
High-ceiling diuretics in combination with potassium-sparing agents	0.12	0.6	1.9	2.1	0.0	-0.2	-0.2

continued

Table 3.9 (continued)

Level I ATC Subgroups	Gross per capita expenditure	DDD/ 1000 inhab. day	Δ % 19-18				Δ % DDD Average cost
			Expenditure	DDD	Prices	Mix	
A - Gastrointestinal system and metabolism	**32.58**	**153.1**	**-1.5**	**0.1**	**-0.2**	**-1.3**	**-1.5**
Proton-pump inhibitors	11.89	68.9	-4.9	2.3	0.0	-7.1	-7.1
Vitamin D and analogues	5.19	15.0	3.9	6.1	0.0	-2.0	-2.0
Insulins and injectable analogues, fast-acting	3.65	7.6	-3.7	-2.1	-1.4	-0.3	-1.7
Aminosalicylic acid and analogues	1.94	5.0	3.8	3.3	-0.2	0.7	0.5
Biguanides	1.52	22.0	1.2	1.6	-1.6	1.2	-0.5
Antibiotics	1.52	2.0	0.5	0.7	0.0	-0.2	-0.2
Other anti peptic ulcer and gastro-esophageal reflux disease	0.89	4.2	2.6	2.4	0.0	0.2	0.2
Insulins and injectable analogues, long-acting	0.76	0.6	15.0	2.8	0.8	11.0	11.9
Bile acids and derivatives	0.74	2.4	-0.7	3.7	1.2	-5.3	-4.2
Sulfonylureas	0.52	8.2	-5.4	-9.7	0.0	4.8	4.8
GLP-1 (glucagon-like peptide-1) receptor analogues	0.50	0.3	67.7	55.4	0.0	7.9	7.9
Calcium, combinations with vitamin D and/or other pharmaceuticals	0.40	4.2	-8.4	-8.8	0.0	0.5	0.5
Combinations between aluminium, calcium and magnesium compounds	0.38	1.7	-8.4	-8.7	0.0	0.3	0.3
Combinations of oral hypoglycemic agents	0.36	1.8	-11.0	-20.2	-2.5	14.3	11.4
Other hypoglycemic agents, excluding insulins	0.30	2.1	-15.0	-16.0	0.0	1.2	1.2
Corticosteroids for topical use	0.29	0.4	0.2	-1.6	0.0	1.8	1.8
H2 receptor antagonists	0.24	1.5	-26.3	-26.6	0.0	0.4	0.4
Enzyme preparations	0.22	0.6	4.1	4.1	0.0	0.0	0.0
Serotonin antagonists (5HT3)	0.21	0.0	-0.5	-2.1	0.0	1.6	1.6
Dipeptil Peptidase 4 Inhibitors (DPP-4)	0.19	0.2	6.2	6.5	0.0	-0.3	-0.3
Alpha Glucosidase Inhibitors	0.15	0.6	-8.1	-6.9	0.0	-1.3	-1.3
Insulins and injectable analogues, intermediate or long-acting in combination with fast-acting	0.14	0.3	-23.4	-22.2	-1.5	0.0	-1.5
Osmotic laxatives	0.13	1.1	-1.6	-1.2	-0.1	-0.3	-0.4
Calcium	0.11	1.3	-0.3	-0.7	0.0	0.4	0.4
N – Nervous system	**23.18**	**66.5**	**2.7**	**1.9**	**-0.3**	**1.1**	**0.8**
Other antiepileptics	4.36	5.9	6.3	6.1	-0.5	0.7	0.2
Selective serotonin reuptake inhibitors	3.27	28.6	-0.6	0.5	-0.2	-1.0	-1.1
Other antidepressants	2.99	10.8	6.2	5.4	0.0	0.8	0.7
Other opiates	1.47	1.1	3.6	0.1	0.0	3.5	3.5
Phenylpiperidine derivatives	1.35	0.6	3.1	1.8	-0.2	1.5	1.3
Natural opium alkaloids	1.26	0.6	-5.1	-2.8	0.0	-2.4	-2.4
Dopamine agonists	1.20	1.1	-2.5	-3.5	0.0	1.1	1.1
5HT1 Selective receptor agonists	0.98	0.8	0.7	1.3	0.0	-0.6	-0.6
Fatty acid derivatives	0.96	2.2	1.4	1.1	0.0	0.3	0.3
Diazepines, oxazepines and thiazepines	0.90	1.2	4.4	2.8	-0.2	1.8	1.6
Type B monoamine oxidase inhibitors	0.75	1.6	6.8	4.6	0.0	2.1	2.1
Dopa and derivatives	0.73	2.1	3.6	2.1	-0.2	1.6	1.5

continued

Table 3.9 (continued)

Level I ATC Subgroups	Gross per capita expenditure	DDD/ 1000 inhab. day	Δ % 19-18				Δ % DDD Average cost
			Expenditure	DDD	Prices	Mix	
Opiates in combination with non-opioidanalgesics	0.69	1.7	2.1	2.8	0.5	-1.2	-0.7
Carboxamide derivatives	0.48	1.8	-2.4	-1.9	0.0	-0.5	-0.5
Amides	0.37	0.3	3.6	3.6	0.0	0.0	0.0
Other antipsychotics	0.25	0.4	-1.4	1.3	-2.6	-0.1	-2.7
Oripavine derivatives	0.21	0.4	54.2	105.0	0.0	-24.8	-24.8
Non-selective monoamine reuptake inhibitors	0.17	1.0	-0.4	-0.1	-0.2	-0.2	-0.3
Anticholinesterases	0.16	0.4	-11.4	-5.3	-2.1	-4.5	-6.5
R – Respiratory system	**16.71**	**41.9**	**2.7**	**1.4**	**-0.4**	**1.7**	**1.3**
Adrenergics in combination with corticosteroids or others, excluding anticolinergics	8.02	12.5	1.7	2.9	-0.8	-0.3	-1.1
Anticolinergics	3.18	6.1	2.4	1.8	0.0	0.7	0.7
Glycocorticoids	1.86	5.1	-3.6	-1.3	-0.4	-2.0	-2.3
Combination adrenergics with anticholinergics including triple combination with corticosteroids	1.41	2.2	38.0	21.8	0.1	13.2	13.3
Selective agonists of beta2-adrenergic receptors	0.66	3.8	-13.1	-9.1	-0.1	-4.3	-4.4
Other antihistamines for systemic use	0.64	5.8	2.2	2.5	0.0	-0.3	-0.3
Leukotriene receptor antagonists	0.47	2.0	0.6	2.0	0.0	-1.3	-1.3
Piperazine derivatives	0.37	3.8	1.6	2.2	0.0	-0.6	-0.6
J – General antimicrobials for systemic use	**12.51**	**16.6**	**-1.5**	**-3.1**	**0.0**	**1.6**	**-1.2**
Third generation cephalosporins	3.12	2.0	3.6	7.6	0.0	-3.7	-3.7
Penicillin combinations, including betalactamase inhibitors	2.99	5.8	0.0	-0.3	0.0	0.3	0.3
Macrolides	1.49	3.5	-0.7	0.5	-0.5	-0.7	-1.2
Fluoroquinolones	1.43	1.9	-27.0	-27.2	0.0	0.3	0.3
Triazole derivatives	0.99	0.6	-4.9	-5.4	0.0	0.5	0.5
Other antibacterial agents	0.65	0.4	7.3	6.3	0.0	0.9	0.9
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.62	0.3	2.8	4.0	0.0	-1.2	-1.2
Specific immunoglobulins	0.41	0.0	-28.5	-8.1	2.2	-23.9	-22.2
Influenza vaccines	0.29	0.0	>100	>100	-81.5	>100	0.6
Broad spectrum penicillins	0.25	1.2	-1.7	-1.3	0.0	-0.5	-0.5
Second generation cephalosporins	0.11	0.2	5.1	2.7	0.0	2.3	2.3
Pneumococcal vaccines	0.11	0.0	>100	>100	0.0	-4.0	-3.9
B – Blood and blood-forming organs	**7.89**	**88.2**	**-0.4**	**1.0**	**-0.3**	**-1.1**	**-1.5**
Platelet aggregation inhibitors, excl. heparin	3.07	60.8	2.4	-0.2	-0.1	2.7	2.6
Heparins	2.33	2.6	-9.8	-5.1	-0.1	-4.8	-5.0
Direct Xa Factor inhibitors	0.65	0.4	28.2	29.8	-2.9	1.8	-1.2
Folic acid and derivatives	0.48	6.0	3.1	5.2	-0.6	-1.5	-2.0
Bivalent iron, oral preparations	0.36	2.8	0.0	0.2	0.0	-0.3	-0.3
Blood substitutes and plasma protein fractions	0.23	0.0	2.4	1.2	0.0	1.2	1.2
Vitamin K antagonists	0.16	3.9	-11.0	-10.9	0.0	-0.1	-0.1

continued

Table 3.9 (continued)

Level I ATC Subgroups	Gross per capita expenditure	DDD/ 1000 inhab day	Δ % 19-18				Δ % DDD Average cost
			Expenditure	DDD	Prices	Mix	
Solutions influencing the electrolyte balance	0.16	0.3	0.9	0.2	0.3	0.4	0.8
Acetic acid derivatives and related substances	0.78	4.8	-0.7	-0.5	0.0	-0.2	-0.2
Propionic acid derivatives	0.72	5.9	-3.7	-3.9	0.0	0.2	0.2
Coxib	0.65	3.8	-0.4	0.7	0.0	-1.0	-1.0
Biphosphonates, combinations	0.47	2.2	-8.9	-8.6	-0.2	-0.1	-0.3
Other non-steroidal anti-inflammatory /anti-rheumatic pharmaceuticals	0.16	1.9	-5.7	-6.6	0.0	0.9	0.9
Oxicam-derivatives	0.12	0.9	1.4	-2.0	0.0	3.5	3.4
L - Antineoplastic and immunomodulatory pharmaceuticals	**4.17**	**6.2**	**1.4**	**2.1**	**-0.7**	**-0.2**	**-0.6**
Aromatase inhibitors	2.03	2.8	7.4	6.9	0.0	0.5	0.5
Other immunosuppressants	0.74	1.6	4.6	2.8	0.0	1.8	1.8
Calcineurin inhibitors	0.63	0.2	-8.9	-7.4	0.0	-1.5	-1.5
Other antineoplastics	0.16	0.3	2.6	3.5	0.0	-0.8	-0.8
Antiandrogens	0.15	0.3	-5.4	-6.2	-0.6	1.3	0.8
Folic acid analogues	0.11	0.1	-5.0	-5.0	0.0	0.0	0.0
H - Systemic hormonal preparations, excluding sex hormones	**4.11**	**35.4**	**3.0**	**0.6**	**-0.5**	**2.9**	**2.3**
Glycocorticoids	1.39	12.9	-0.9	-2.2	0.0	1.3	1.3
Parathyroid hormones and analogues	1.23	0.2	2.7	5.1	-2.0	-0.3	-2.3
Thyroid hormones	1.07	20.9	7.7	2.5	0.0	5.0	5.0
Vasopressin and analogues	0.14	0.1	-0.5	-0.8	0.0	0.4	0.4
Somatropin and somatropin agonists	0.11	0.0	7.7	6.8	0.0	0.9	0.9
S – Sensory organs	**3.89**	**20.7**	**2.1**	**1.0**	**-0.3**	**1.3**	**1.0**
Beta-blockers	2.24	11.7	2.2	1.2	-0.6	1.5	0.9
Prostaglandins analogues	1.30	5.7	2.3	0.8	0.0	1.5	1.5
Carbonic anhydrase inhibitors	0.22	1.4	-0.3	-0.8	0.0	0.6	0.6
D - Dermatologicals	**1.29**	**4.6**	**14.1**	**5.9**	**-0.4**	**8.2**	**7.8**
Other antipsoriatic agents for topical use	0.87	2.6	26.7	22.4	0.0	3.5	3.5
P - Antiparasitic, insecticide and repellent pharmaceuticals	**0.23**	**0.9**	**3.0**	**2.3**	**0.0**	**0.6**	**0.6**
Aminoquinolines	0.15	0.8	4.3	2.5	0.0	1.7	1.7
V - Miscellaneous	**0.15**	**0.1**	**-1.4**	**-1.1**	**-1.4**	**1.1**	**-0.3**
Pharmaceuticals for treatment of hyperkalemia and hyperphosphatemia	0.13	0.1	0.2	0.8	-0.7	0.2	-0.5

Antineoplastic medicines are the most expensive category with € 95.86 per capita (equal to about 44% of the overall pharmaceuticals purchased by public health facilities), followed by antimicrobials with € 43.72 (+24.4% compared to 2018).
Within antineoplastics, monoclonal antibodies, tyrosine kinase inhibitors and selective immunosuppressants are the groups with the highest expenditure, accounting for about 55% of the category; within antimicrobials, HCV and HIV treatments show an expenditure of € 15.71 and € 7.48 per capita, respectively (Table 3.10).
Dermatological medicines show the highest increase in expenditure (+113.7%), along with pharmaceuticals for the respiratory system (+27.1%), whereas genitourinary pharmaceuticals is the only group recording a decrease compared to the previous year (-2.7%). As regards consumption, however, the highest increase is always reported by genitourinary system medicines (+23.3%), followed by cardiovascular system pharmaceuticals (+9.9%), while the only reductions are related to gastrointestinal (-0.2%) and dermatological medicines (-3.3%).
With regard to the average DDD cost, the highest increases are attributable to dermatological medicines (+120.5%), antimicrobials (+23.5%) and respiratory pharmaceuticals (+22.1%). Genitourinary pharmaceuticals show the highest decrease (-21.3%), to a much lesser extent than antineoplastics and immunomodulators (-1%) and CNS pharmaceuticals (-0.6%).
Table 3.11 shows the expenditure and consumption of medicines purchased directly by healthcare facilities, considering the most prescribed active ingredients for each level I ATC, which include up to 75% of the category expenditure.
Within antineoplastics, daratumumab and ocrelizumab are the molecules with the most significant increase in expenditure compared to 2018. Similarly, as for antimicrobials, the combinations sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir and cobicistat/darunavir/emtricitabine/tenofovir alafenamide show the highest increase. Although factor VIII is the most expensive substance within blood and blood-forming organs pharmaceuticals, it shows a contraction in use by over 40%. With the exception of enzymes and heptacog, ataluren, indicated in Duchenne muscular dystrophy, is the molecule with the highest cost per DDD (€ 1618.86).
Considering the top 30 most expensive active ingredients purchased directly by public health facilities (Table 3.12), 19 belong to antineoplastics and 6 to antimicrobials. The first medicine is the anti-HCV association sofosbuvir/velpatasvir with an expenditure of € 751.9 million and an average cost of € 654.84. However, it should be highlighted that credit notes (which were not present in 2018) are also included in the expenditure for such medicines, which may generate significant differentials.
Pembrolizumab and nivolumab rank in the first places, with an expenditure of respectively € 281.4 and 272.8 million and an average DDD cost of € 87.8 and 154.24. These two molecules are indicated for the treatment of some cancers, in that they stimulate the immune system to destroy cancer cells.
The molecules reporting the greatest variation in rank compared to 2018 were daratumumab (from 41st to 7th place) and eculizumab (from 47th to 19th place). The former is indicated in the treatment of multiple myeloma and the latter is used in patients with paroxysmal nocturnal haemoglobinuria with a record of previous transfusions. Overall, the top 30 active ingredients make up 36.4% of the expenditure by public health facilities.

Within the top 30 active ingredients showing the greatest variation in expenditure by public health facilities (Table 3.13), 16 belong to the group of antineoplastics and immunosuppressants, 6 to the group of antimicrobials and 5 to the group of blood and blood-forming organs pharmaceuticals. Ocelizumab (humanized monoclonal antibody used in multiple sclerosis) is the medicine with the greatest variation, mainly linked to an increase in consumption.

Table 3.10. 2019 expenditure and consumption of medicines purchased by public health facilities: therapeutic categories by level I ATC *(for each level I ATC category therapeutic subgroups were included in descending expenditure order, up to per capita expenditure of € 0.1)*

Level I ATC Subgroups	NHS per capita expendi-ture	%	Δ % 19-18	DDD/ 1000 inhab. day	%	Δ % 19-18	DDD Average cost	Δ % 19-18
L - Antineoplastic and immunomodulatory pharmaceuticals	**95.86**		**7.1**	**10.3**		**8.0**	**25.52**	**-1.0**
Monoclonal antibodies	26.02	27.1	7.9	1.2	11.9	9.9	58.33	-1.8
Tyrosine kinase inhibitors	17.75	18.5	16.2	0.5	4.9	20.5	95.69	-3.6
Selective immunosuppressants	11.94	12.5	27.8	1.1	11.0	18.7	28.83	7.7
Other immunosuppressants	8.35	8.7	19.4	0.4	4.4	12.9	50.86	5.8
Tumour necrosis factor alpha inhibitors (TNF-alpha)	6.91	7.2	-34.2	1.3	12.4	7.1	14.88	-38.6
Interleukin inhibitors	5.81	6.1	31.0	0.6	5.4	37.0	28.86	-4.4
Other antineoplastics	3.72	3.9	6.1	0.2	2.1	9.8	46.96	-3.4
Interferons	1.97	2.1	-13.4	0.4	4.2	-10.2	12.39	-3.6
Other hormonal antagonists and related agents	1.85	1.9	7.5	0.1	1.2	4.0	39.78	3.4
Gonadotropin-releasing hormone analogues	1.84	1.9	3.7	1.0	10.0	4.2	4.90	-0.5
Pyrimidine analogues	1.60	1.7	7.7	0.4	4.2	4.9	10.23	2.7
Antiandrogens	1.49	1.6	24.1	0.6	6.2	-5.4	6.41	31.3
Folic acid analogues	0.95	1.0	6.1	0.1	0.9	1.8	28.74	4.3
Calcineurin inhibitors	0.88	0.9	3.5	0.4	3.6	4.9	6.43	-1.4
Other immunostimulants	0.86	0.9	-29.5	0.1	1.0	1.4	22.51	-30.5
Taxanes	0.82	0.9	4.9	0.2	1.7	5.2	12.46	-0.2
Colony stimulation factors	0.67	0.7	-13.4	0.1	0.9	8.2	19.17	-20.0
Antiestrogens	0.66	0.7	4.3	0.3	2.7	1.9	6.43	2.3
Anthracyclines and related substances	0.46	0.5	5.5	0.1	1.0	3.4	12.10	2.0
Other plant alkaloids and natural products	0.32	0.3	2.5	0.0	0.0	2.4	245.43	0.1
Vinca alkaloids and analogues	0.26	0.3	17.8	0.0	0.4	10.0	16.20	7.0
J – General antimicrobials for systemic use	**43.72**		**24.4**	**6.3**		**0.5**	**19.04**	**23.5**
Antivirals for treatment of HCV infections	15.71	35.9	>100	0.1	1.9	-36.7	362.80	>100

continued

Table 3.10 (continued)

Level I ATC Subgroups	NHS per capita expendi-ture	%	Δ % 19-18	DDD/ 1000 inhab. day	%	Δ % 19-18	DDD Average cost	Δ % 19-18
Other antivirals	2.46	5.6	22.9	0.4	7.1	20.8	15.10	1.8
Meningococcal vaccines	2.29	5.2	-2.5	0.1	2.0	-5.7	49.97	3.4
Normal human immunoglobulin	1.78	4.1	4.0	0.0	0.3	-5.5	307.47	10.1
Pneumococcal vaccines	1.76	4.0	6.1	0.1	1.7	8.3	46.13	-2.0
Influenza vaccines	1.09	2.5	18.1	0.5	8.1	18.6	5.84	-0.4
Papillomavirus vaccines	1.08	2.5	15.9	0.0	0.7	6.1	69.02	9.2
Bacterial and viral vaccines in combination	1.04	2.4	-15.8	0.1	1.7	3.5	27.32	-18.7
Specific immunoglobulins	0.73	1.7	26.9	0.0	0.3	16.6	117.19	8.8
Penicillin combinations, including beta-lactamase inhibitors	0.65	1.5	26.1	0.6	9.1	7.0	3.10	17.8
Triazole derivatives	0.64	1.5	11.6	0.1	1.8	-11.5	15.57	26.2
Measles vaccines	0.61	1.4	-7.3	0.1	0.8	-15.3	31.62	9.4
Other antimycotics for systemic use	0.56	1.3	-29.8	0.0	0.2	10.6	138.07	-36.6
Other antibacterial agents	0.54	1.2	-1.3	0.1	1.1	19.8	21.27	-17.6
Antibiotics	0.52	1.2	7.2	0.0	0.2	5.9	98.89	1.3
Third generation cephalosporins	0.46	1.1	28.8	0.3	5.0	0.8	4.09	27.8
Nucleosides and nucleotides reverse-transcriptase inhibitors	0.46	1.1	-53.7	0.8	13.2	6.2	1.53	-56.4
Varicella zoster vaccines	0.41	0.9	44.9	0.0	0.3	6.9	65.62	35.6
Protease inhibitors	0.40	0.9	-42.6	0.1	1.5	-28.2	11.26	-20.0
Glycopeptide antibacterials	0.34	0.8	-18.6	0.1	0.9	1.5	16.12	-19.8
Rotavirus diarrhoea vaccines	0.31	0.7	8.6	0.0	0.5	21.8	26.85	-10.9
Non-nucleoside reverse-transcriptase inhibitors	0.30	0.7	-6.6	0.2	2.5	-7.3	5.17	0.8
Other cephalosporins and penems	0.25	0.6	40.6	0.0	0.1	45.7	180.94	-3.5
Carbapenems	0.24	0.6	-1.5	0.1	0.8	10.3	13.17	-10.7
Polymyxins	0.20	0.5	-2.7	0.0	0.2	-3.1	36.38	0.4
B - Blood and blood-forming organs	**28.20**		**6.4**	**47.4**		**10.6**	**1.63**	**-4.1**
Blood coagulation factors	8.25	29.2	7.6	0.1	0.1	5.9	433.78	1.7
Direct Xa Factor inhibitors	6.03	21.4	12.6	8.9	18.8	29.3	1.85	-12.9
Other antianemic preparations	3.03	10.7	-8.2	3.5	7.4	6.1	2.36	-13.5
Platelet aggregation inhibitors, excl. heparin	2.39	8.5	3.9	9.5	20.0	0.4	0.69	3.5
Heparins	1.43	5.1	-23.6	6.6	13.8	-0.9	0.60	-22.9
Direct thrombin inhibitors	1.41	5.0	-4.6	2.4	5.0	10.2	1.64	-13.4
Other haemostatic agents for systemic use	1.24	4.4	42.1	0.0	0.1	20.9	70.86	17.5
Solutions influencing the electrolyte balance	0.90	3.2	21.6	7.5	15.9	21.4	0.33	0.2
Parenteral nutritional solutions	0.70	2.5	26.8	0.7	1.5	13.1	2.66	12.2
Medicines used in hereditary angioedema	0.39	1.4	1.0	0.0	0.0	2.2	1650.39	-1.2
Other antithrombotic agents	0.37	1.3	9.5	0.5	1.0	3.3	2.15	6.0
Local haemostatic agents	0.36	1.3	71.6	0.0	0.0	>100	251.03	-14.5
Iron, parenteral preparations	0.32	1.1	37.5	0.1	0.2	37.2	8.48	0.2
Hypertonic solutions	0.29	1.0	46.5	0.1	0.2	35.5	9.28	8.1
Enzymes	0.26	0.9	-1.5	0.0	0.0	-1.5	812.38	0.0

continued

Table 3.10 (continued)

Level I ATC Subgroups	NHS per capita expendi-ture	%	Δ % 19-18	DDD/ 1000 inhab. day	%	Δ % 19-18	DDD Average cost	Δ % 19-18
Blood substitutes and plasma protein fractions	0.25	0.9	-15.5	0.0	0.1	-20.0	14.06	5.6
Protease inhibitors	0.22	0.8	37.3	0.0	0.0	0.1	55.58	37.2
A - Gastrointestinal system and metabolism	**15.45**		**11.3**	**29.2**		**-0.2**	**1.45**	**11.3**
Enzymes	4.87	31.5	4.7	0.0	0.0	6.5	1125.96	-1.7
Insulins and injectable analogues, long-acting	2.64	17.1	9.2	6.1	20.8	3.8	1.19	5.2
Oral hypoglycemic agents, combinations	1.98	12.8	6.5	5.1	17.5	8.9	1.06	-2.1
Dipeptil Peptidase 4 Inhibitors (DPP-4)	1.85	12.0	39.4	2.2	7.6	42.2	2.28	-2.0
Dipeptil Peptidase 4 Inhibitors (DPP-4)	1.20	7.8	11.2	2.8	9.4	12.6	1.19	-1.2
Various products of the gastrointestinal system and metabolism	0.80	5.2	44.8	0.0	0.0	14.2	161.02	26.8
SGLT-2 Co-transporter inhibitors (sodium-glucose type 2)	0.59	3.8	34.6	1.3	4.4	35.3	1.28	-0.5
N - Nervous system	**7.30**		**5.3**	**25.7**		**5.7**	**0.78**	**-0.6**
Other antipsychotics	2.74	37.6	5.8	2.5	9.6	9.7	3.05	-3.5
Medicines used in opiate addiction	0.53	7.2	0.0	3.3	12.8	2.0	0.44	-2.0
Dopa and derivatives	0.50	6.9	6.2	0.3	1.2	-1.2	4.64	7.5
Diazepines, oxazepines, thiazepines and oxepins	0.43	5.8	-9.1	3.5	13.5	1.2	0.34	-10.2
Other antiepileptics	0.42	5.8	13.1	1.0	3.8	7.7	1.17	5.0
Other medicines of the nervous system	0.37	5.1	20.7	0.1	0.3	8.8	13.02	10.9
Halogenated hydrocarbons	0.25	3.4	31.1	0.0	0.0	44.8	62.78	-9.5
Amides	0.20	2.8	-8.1	1.9	7.6	17.7	0.28	-21.9
V – Miscellaneous	**5.66**		**6.2**	**3.2**		**1.6**	**4.88**	**4.3**
Iron chelating substances	1.55	27.3	5.6	0.1	1.9	3.2	71.43	2.3
Water-soluble, nephrotropic, low osmolarity radiological contrast media	1.19	21.0	4.9	0.1	2.0	1.8	51.45	3.0
Antidotes	0.80	14.1	16.0	0.1	3.8	44.1	17.91	-19.5
Paramagnetic contrast media	0.38	6.7	14.3	0.0	0.7	5.9	46.76	8.0
Other diagnostic radiopharmaceuticals for cancer detection	0.30	5.3	-0.3	0.0	0.1	-3.2	412.92	3.0
Medicines for treatment of hyperkalemia and hyperphosphatemia	0.24	4.2	-9.6	0.2	7.1	3.1	2.91	-12.3
Detoxifying substances for cytostatic antineoplastic treatments	0.23	4.0	16.6	0.2	7.0	2.8	2.81	13.4
C - Cardiovascular system	**5.12**		**11.6**	**18.6**		**9.9**	**0.75**	**1.3**
Antihypertensives for pulmonary arterial hypertension	1.43	28.0	-2.5	0.1	0.4	12.1	48.65	-13.1
Other cardiac preparations	1.35	26.3	-8.9	2.2	11.9	-4.1	1.67	-5.0
Other lipid modifying substances	0.90	17.6	64.6	0.4	2.1	34.2	6.31	22.6
Angiotensin II receptor blockers, other combinations	0.61	11.8	75.9	0.4	2.2	77.9	4.08	-1.1

continued

Table 3.10 (continued)

Level I ATC Subgroups	NHS per capita expendi-ture	%	Δ % 19-18	DDD/ 1000 inhab. day	%	Δ % 19-18	DDD Average cost	Δ % 19-18
H - Systemic hormonal preparations, excluding sex hormones	**4.75**		**2.7**	**5.3**		**1.2**	**2.45**	**1.2**
Somatostatin and analogues	1.54	32.4	3.7	0.2	3.8	4.7	20.74	-0.9
Somatropin and somatotropin agonists	1.35	28.5	-3.3	0.3	5.0	1.3	13.84	-4.5
Other antiparathyroid substances	0.82	17.2	18.2	0.3	6.6	15.6	6.43	2.3
Other anterior pituitary hormones and analogues	0.42	8.8	4.3	0.0	0.3	4.5	69.35	-0.2
Glycocorticoids	0.33	7.0	-4.4	4.0	74.7	1.1	0.23	-5.5
Parathyroid hormones and analogues	0.22	4.5	-6.6	0.1	0.9	-2.1	11.73	-4.6
R – Respiratory system	**3.87**		**27.1**	**2.6**		**3.9**	**4.15**	**22.1**
Other preparations for the respiratory system	1.69	43.6	21.6	0.0	0.4	20.3	468.68	1.1
Other systemic medicines for respiratory obstructive diseases	1.53	39.6	46.5	0.2	6.1	38.3	26.90	5.9
Mucolytics	0.23	6.0	12.9	0.2	9.4	3.7	2.65	8.9
M - Musculoskeletal system	**3.47**		**11.7**	**4.9**		**6.5**	**1.92**	**4.6**
Other medicines for musculoskeletal system diseases	1.94	56.0	11.9	0.0	1.0	-1.0	106.56	13.0
Other medicines acting on bone structure and mineralisation	0.97	27.9	14.7	3.0	61.5	11.0	0.87	3.3
Other peripheral muscle relaxants	0.27	7.7	8.7	0.0	0.1	7.3	126.56	1.2
S – Sensory organs	**3.10**		**10.3**	**2.8**		**0.0**	**3.06**	**10.1**
Anti-vascularisation substances	2.36	75.9	7.7	0.4	14.9	14.0	15.63	-5.5
Corticosteroids, plain	0.40	13.0	14.2	0.2	8.7	17.5	4.60	-2.8
G - Genitourinary system and sex hormones	**1.53**		**-2.7**	**2.4**		**23.3**	**1.78**	**-21.3**
Gonadotropins	0.96	62.8	-0.4	0.1	5.6	-1.5	20.04	1.1
Medicines used in erectile dysfunctions	0.20	13.3	-28.0	0.3	10.7	14.0	2.22	-36.9
D – Dermatologicals	**0.84**		**113.7**	**8.2**		**-3.3**	**0.28**	**120.5**
Substances for dermatitis, excl. corticosteroids	0.45	53.9	>100	0.0	0.5	>100	27.81	>100

Table 3.11. 2019 expenditure and consumption for pharmaceuticals purchased by public health facilities: most frequently prescribed active ingredients by level I ATC (up to 75% of expenditure within the therapeutic category)

Level I ATC	Per capita expenditure	%*	Δ % 19-18	DDD/ 1000 inhab. day	%*	Δ % 19-18	DDD Average cost	Δ % 19-18
L - Antineoplastics and immunomodulators	**95.86**		**7.1**	**10.3**		**8.0**	**25.52**	**-1.0**
pembrolizumab	4.66	4.9	45.1	0.1	1.4	59.7	87.82	-9.1
nivolumab	4.52	4.7	2.5	0.1	0.8	15.8	154.24	-11.5
lenalidomide	4.35	4.5	22.6	0.1	0.9	19.8	122.97	2.3
bevacizumab	3.21	3.3	-0.5	0.1	1.1	-0.6	74.33	0.1
daratumumab	2.59	2.7	>100	0.0	0.4	>100	186.45	-0.6
pertuzumab	2.37	2.5	14.1	0.0	0.4	14.0	143.60	0.1
fingolimod	2.35	2.5	3.2	0.1	1.1	3.2	54.80	0.0
adalimumab	2.22	2.3	-53.6	0.5	4.7	14.0	12.65	-59.3
dimethylfumarate	2.22	2.3	13.9	0.2	1.8	15.2	33.13	-1.1
trastuzumab	2.20	2.3	-45.6	0.2	2.0	-2.8	29.54	-44.0
ibrutinib	2.19	2.3	18.6	0.0	0.4	34.3	130.10	-11.7
palbociclib	2.16	2.3	74.4	0.1	0.7	68.6	85.01	3.4
etanercept	2.04	2.1	-24.1	0.3	2.8	0.8	19.51	-24.7
eculizumab	1.85	1.9	67.2	0.0	0.1	7.1	816.51	56.1
rituximab	1.73	1.8	-20.4	0.5	5.0	1.5	9.21	-21.5
abiraterone	1.73	1.8	8.0	0.1	0.5	8.0	85.36	0.0
secukinumab	1.71	1.8	26.8	0.1	1.4	26.8	31.69	0.0
ustekinumab	1.69	1.8	17.5	0.2	2.3	39.7	19.77	-15.9
natalizumab	1.54	1.6	3.9	0.1	0.7	3.8	56.94	0.1
enzalutamide	1.44	1.5	25.9	0.0	0.4	25.8	85.64	0.1
interferon beta 1a	1.42	1.5	-14.5	0.4	3.6	-9.5	10.61	-5.5
ruxolitinib	1.37	1.4	25.6	0.0	0.3	23.9	108.52	1.4
nilotinib	1.22	1.3	5.4	0.0	0.2	5.2	131.45	0.2
golimumab	1.20	1.3	-1.9	0.1	1.2	8.3	27.41	-9.4
abatacept	1.08	1.1	3.8	0.1	0.6	2.9	48.73	0.9
dasatinib	1.08	1.1	-11.3	0.0	0.2	-2.0	117.20	-9.5
leuproreline	1.01	1.1	1.9	0.2	1.8	-1.4	14.74	3.3
azacitidine	0.94	1.0	4.9	0.0	0.1	4.9	351.43	0.0
pemetrexed	0.94	1.0	7.1	0.0	0.3	6.5	97.13	0.5
pirfenidone	0.93	1.0	21.9	0.0	0.4	21.9	64.50	0.0
vedolizumab	0.92	1.0	25.8	0.1	0.7	24.6	36.30	0.9
nintedanib	0.91	0.9	20.1	0.0	0.2	33.7	123.36	-10.2
trastuzumab emtansine	0.90	0.9	9.1	0.0	0.1	9.0	210.96	0.0
dabrafenib	0.85	0.9	14.0	0.0	0.2	14.4	146.15	-0.4
infliximab	0.84	0.9	-32.7	0.3	3.1	3.2	7.17	-34.8
ocrelizumab	0.84	0.9	>100	0.0	0.4	>100	49.80	-2.4
osimertinib	0.81	0.8	20.7	0.0	0.2	84.1	131.79	-34.4
triptorelin	0.81	0.8	6.5	0.8	8.0	6.0	2.68	0.5
teriflunomide	0.81	0.8	15.2	0.1	0.8	15.8	27.17	-0.5
tacrolimus	0.80	0.8	5.1	0.3	3.2	7.0	6.61	-1.8
tocilizumab	0.79	0.8	-2.8	0.1	0.8	2.8	26.71	-5.5
sunitinib	0.77	0.8	-12.3	0.0	0.1	-1.9	166.85	-10.6
pomalidomide	0.76	0.8	21.7	0.0	0.1	19.2	307.37	2.1
imatinib	0.75	0.8	-18.3	0.1	0.9	-0.4	21.76	-18.0
bortezomib	0.71	0.7	-26.6	0.1	1.1	7.1	17.41	-31.4

continued

Table 3.11 (continued)

Level I ATC	Per capita expenditure	%*	Δ % 19-18	DDD/ 1000 inhab. day	%*	Δ % 19-18	DDD Average cost	Δ % 19-18
J - Antimicrobials	**43.72**		**24.4**	**6.3**		**0.5**	**19.04**	**23.5**
sofosbuvir/velpatasvir	12.46	28.5	>100	0.1	0.8	-33.8	654.84	>100
glecaprevir/pibrentasvir	2.07	4.7	-42.3	0.0	0.8	-34.5	119.50	-11.8
meningococcal vaccine group b	1.79	4.1	-2.2	0.1	1.2	-4.5	62.84	2.4
emtricitabine/rilpivirine/ tenofovir alafenamide	1.72	3.9	30.7	0.2	3.8	30.7	19.96	0.0
pneumococcal saccharide conjugated vaccine, adsorbed	1.65	3.8	3.5	0.1	1.5	3.3	49.50	0.2
dolutegravir	1.51	3.5	29.0	0.3	4.0	29.5	16.42	-0.4
dolutegravir/abacavir/lamivudine	1.43	3.3	-5.4	0.2	2.9	-2.2	21.48	-3.3
elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide	1.35	3.1	-4.1	0.1	2.2	-4.1	26.55	0.0
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.07	2.5	30.1	0.0	0.7	30.1	69.33	0.0
emtricitabine/tenofovir alafenamide	0.91	2.1	-16.9	0.2	3.4	-10.5	11.51	-7.1
inactivated influenza vaccine	0.83	1.9	33.9	0.4	6.3	32.4	5.74	1.2
sofosbuvir/velpatasvir/ voxilaprevir	0.79	1.8	>100	0.0	0.1	-8.1	649.29	>100
human immunoglobulin, intravenous use	0.72	1.6	-10.2	0.0	0.1	-12.8	278.25	3.0
hexavalent vaccine	0.71	1.6	0.0	0.1	0.9	0.0	33.46	-
human immunoglobulin, intravenous use	0.71	1.6	13.8	0.0	0.1	4.3	283.54	9.1
raltegravir	0.65	1.5	-3.5	0.2	2.9	12.2	9.76	-14.0
darunavir/cobicistat	0.64	1.5	-22.0	0.1	2.3	-22.0	12.25	0.0
cobicistat/darunavir/ emtricitabine/tenofovir alafenamide	0.58	1.3	>100	0.1	1.1	>100	21.84	0.0
measles, mumps, rubella and varicella vaccine	0.54	1.2	-2.7	0.0	0.5	-0.8	46.66	-1.9
amfotericin b	0.52	1.2	7.2	0.0	0.2	5.9	98.89	1.3
piperacillin/tazobactam	0.48	1.1	27.8	0.1	2.0	25.5	10.74	1.8
B - Blood and blood-forming organs	**28.20**		**6.4**	**47.4**		**10.6**	**1.63**	**-4.1**
factor VIII	2.70	9.6	-39.7	0.0	0.0	-40.7	341.96	1.6
rivaroxaban	2.57	9.1	21.0	4.1	8.7	29.4	1.71	-6.5
apixaban	2.53	9.0	-0.1	3.5	7.4	22.5	1.97	-18.5
dabigatran	1.40	5.0	-4.7	2.4	5.0	10.2	1.63	-13.6
epoetin alpha	1.27	4.5	-12.6	1.7	3.6	1.8	2.02	-14.2
darbepoetin alpha	1.05	3.7	-9.4	0.5	1.0	-8.5	6.17	-1.0
enoxaparin	1.03	3.6	-21.9	5.6	11.7	6.3	0.51	-26.5
octocog alpha	1.02	3.6	0.0	0.0	0.0	0.0	339.55	-
efmoroctocog alpha	0.94	3.3	0.0	0.0	0.0	0.0	351.24	-
edoxaban	0.93	3.3	33.5	1.3	2.7	52.3	2.00	-12.3

continued

Table 3.11 (continued)

Level I ATC	Per capita expenditure	%*	Δ % 19-18	DDD/ 1000 inhab. day	%*	Δ % 19-18	DDD Average cost	Δ % 19-18
ticagrelor	0.91	3.2	9.0	1.1	2.2	13.0	2.35	-3.5
eptacog alpha activated (coagulation factor VII, recombinant)	0.81	2.9	28.6	0.0	0.0	29.0	32519.96	-0.3
sodium chloride	0.73	2.6	20.2	6.5	13.7	18.9	0.31	1.1
albutrepenonacog alpha	0.66	2.3	28.4	0.0	0.0	28.2	1088.67	0.1
eltrombopag olamine	0.64	2.3	9.4	0.0	0.1	22.5	56.09	-10.7
treprostinil	0.63	2.2	-0.6	0.0	0.0	2.9	601.75	-3.4
epoetin zeta	0.54	1.9	26.6	1.2	2.5	33.4	1.25	-5.1
factor VIII/Von Willebrand factor	0.44	1.6	13.5	0.0	0.0	14.5	348.80	-0.8
lonoctogoc alpha	0.40	1.4	>100	0.0	0.0	>100	324.77	-2.5
A - Gastrointestinal and metabolism	**15.45**		**11.3**	**29.2**		**-0.2**	**1.45**	**11.3**
insulin glargine	1.55	10.0	-0.2	4.3	14.9	2.0	0.98	-2.1
acid human alglucosidase, recombinant	1.19	7.7	8.3	0.0	0.0	10.0	1043.98	-1.6
dulaglutide	0.90	5.8	82.7	1.2	4.0	77.5	2.14	2.9
agalsidase alpha	0.89	5.7	2.1	0.0	0.0	3.9	1664.35	-1.7
imiglucerase	0.81	5.2	-4.4	0.0	0.0	-3.9	1089.89	-0.6
liraglutide	0.72	4.7	12.9	0.9	3.1	19.0	2.22	-5.1
insulin degludec	0.58	3.8	4.9	1.1	3.9	6.0	1.41	-1.1
sitagliptin/metformin	0.58	3.7	3.4	1.4	4.9	3.4	1.10	0.0
agalsidase beta	0.56	3.7	10.8	0.0	0.0	11.3	481.24	-0.5
sitagliptin	0.53	3.4	10.3	1.2	4.0	11.7	1.25	-1.3
idursulfase	0.53	3.4	-1.0	0.0	0.0	0.7	2854.79	-1.7
linagliptin	0.46	3.0	16.0	1.1	3.8	16.9	1.15	-0.8
insulin degludec/liraglutide	0.34	2.2	>100	0.2	0.8	>100	3.95	5.5
empagliflozin	0.30	1.9	23.1	0.7	2.2	25.7	1.24	-2.1
dapagliflozin/metformin	0.29	1.9	47.2	0.6	2.1	47.9	1.32	-0.5
vildagliptin/metformin	0.28	1.8	5.7	0.7	2.4	3.4	1.07	2.2
velaglucerase alpha	0.26	1.7	0.8	0.0	0.0	2.6	1076.92	-1.8
elosulfase alpha	0.26	1.7	9.0	0.0	0.0	9.0	2992.00	0.0
dapagliflozin	0.25	1.6	38.4	0.5	1.7	38.7	1.33	-0.2
empagliflozin/metformin	0.21	1.4	27.9	0.5	1.8	33.2	1.09	-4.0
migalastat	0.21	1.4	41.0	0.0	0.0	81.0	466.73	-22.1
N – Nervous system	**7.30**		**5.3**	**25.7**		**5.7**	**0.78**	**-0.6**
paliperidone	1.46	20.0	3.9	0.7	2.9	8.5	5.43	-4.2
aripiprazole	0.89	12.3	14.7	1.0	4.0	12.6	2.40	1.9
levodopa/carbidopa	0.46	6.3	10.6	0.1	0.5	9.3	10.84	1.1
risperidone	0.38	5.2	-6.1	0.7	2.7	4.0	1.52	-9.7
methadone	0.31	4.2	3.2	2.4	9.4	3.2	0.35	0.0
tafamidis meglumine	0.24	3.3	24.6	0.0	0.0	24.6	274.86	0.0
quetiapine	0.21	2.8	-9.1	1.5	5.8	6.0	0.38	-14.3
buprenorphine/naloxone	0.18	2.4	-8.2	0.2	0.7	-5.0	2.70	-3.4
sevoflurane	0.17	2.3	11.6	0.0	0.0	23.1	67.25	-9.4
levetiracetam	0.16	2.2	-6.2	0.4	1.6	2.8	1.09	-8.8
dexmedetomidine	0.14	2.0	7.2	0.0	0.1	18.0	11.90	-9.2
rivastigmine	0.14	1.9	-14.0	0.4	1.7	-3.6	0.86	-10.8

continued

Table 3.11 (continued)

Level I ATC	Per capita expenditure	%*	Δ % 19-18	DDD/ 1000 inhab. day	%*	Δ % 19-18	DDD Average cost	Δ % 19-18
olanzapine	0.11	1.6	-11.9	1.5	5.9	-2.6	0.20	-9.5
propofol	0.11	1.5	-0.6	0.3	1.2	-9.4	0.93	9.8
lacosamide	0.10	1.4	31.9	0.0	0.2	36.6	6.86	-3.4
delta-9-tetrahydrocannabinol/ cannabidiol	0.10	1.4	-4.1	0.0	0.1	-1.4	18.44	-2.8
sodium oxybate	0.10	1.3	-11.1	0.1	0.4	-11.2	2.62	0.0
paracetamol	0.09	1.2	1.8	2.4	9.5	21.4	0.10	-16.2
lidocaine	0.09	1.2	-1.5	1.4	5.4	16.6	0.17	-15.5
desflurane	0.08	1.1	>100	0.0	0.0	>100	55.17	-0.4
V - Miscellaneous	**5.66**		**6.2**	**3.2**		**1.6**	**4.88**	**4.3**
deferasirox	1.42	25.0	6.5	0.0	1.1	5.4	109.52	1.0
sugammadex	0.70	12.3	16.7	0.0	0.7	16.0	82.61	0.6
iomeprol	0.45	8.0	4.9	0.0	0.6	1.6	67.77	3.2
fluorodeoxyglucose (18F)	0.25	4.4	-4.4	0.0	0.1	-3.9	364.92	-0.5
iodixanol	0.24	4.2	1.0	0.0	0.3	-0.4	77.96	1.4
iodine 123	0.17	3.1	7.2	0.0	0.0	5.8	867.43	1.4
gadobutrol	0.17	3.0	24.9	0.0	0.2	16.5	78.16	7.2
iopromide	0.16	2.9	10.4	0.0	0.3	5.9	50.58	4.3
iobitridol	0.13	2.3	-3.0	0.0	0.2	-1.9	45.00	-1.1
rasburicase	0.11	2.0	9.0	0.0	0.0	7.2	774.73	1.7
lanthanum carbonate hydrated	0.11	1.9	-2.4	0.0	1.4	-0.8	6.49	-1.6
deferiprone	0.11	1.9	-1.1	0.0	0.5	-1.2	16.74	0.0
sevelamer	0.10	1.8	-20.3	0.1	4.6	3.8	1.87	-23.3
iopamidol	0.10	1.7	12.2	0.0	0.4	-2.1	22.85	14.6
thyrotropin	0.09	1.6	-6.0	0.0	0.0	-4.9	335.52	-1.2
C - Cardiovascular	**5.12**		**11.6**	**18.6**		**9.9**	**0.75**	**1.3**
ranolazine	1.24	24.1	9.5	1.2	6.3	9.6	2.88	-0.1
macitentan	0.87	17.0	10.8	0.0	0.1	14.7	89.30	-3.3
sacubitril/valsartan	0.61	11.8	75.9	0.4	2.2	77.9	4.08	-1.1
evolocumab	0.43	8.4	81.9	0.1	0.4	82.8	15.33	-0.5
alirocumab	0.33	6.5	88.1	0.1	0.5	90.7	9.96	-1.4
ambrisentan	0.27	5.3	0.8	0.0	0.1	6.9	75.92	-5.7
riociguat	0.18	3.5	26.7	0.0	0.0	29.0	59.34	-1.8
H – Systemic hormones	**4.75**		**2.7**	**5.3**		**1.2**	**2.45**	**1.2**
somatropin	1.35	28.4	-3.3	0.3	5.0	1.3	13.82	-4.5
octreotide	0.75	15.8	-1.5	0.1	2.1	-1.2	18.66	-0.3
lanreotide	0.62	13.1	12.2	0.1	1.7	13.1	19.39	-0.8
cinacalcet	0.51	10.8	-2.8	0.1	2.1	-3.0	12.59	0.2
pegvisomant	0.42	8.8	4.3	0.0	0.3	4.5	69.35	-0.2
R - Respiratory	**3.87**		**27.1**	**2.6**		**3.9**	**4.15**	**22.1**
lumacaftor/ivacaftor	1.16	29.9	32.5	0.0	0.3	24.6	416.96	6.3
omalizumab	0.82	21.1	15.2	0.1	3.4	15.7	25.66	-0.4
mepolizumab	0.55	14.2	67.0	0.0	1.7	66.9	34.87	0.0
ivacaftor	0.49	12.8	2.1	0.0	0.1	3.5	641.16	-1.4
deoxyribonuclease	0.21	5.4	11.9	0.0	1.1	11.9	21.31	0.0
M - Musculoskeletal	**3.46**		**11.5**	**4.9**		**6.5**	**1.92**	**4.6**
nusinersen	1.69	48.8	11.2	0.0	0.2	0.0	421.82	11.2
denosumab	0.96	27.7	13.9	3.0	61.5	11.0	0.87	2.6

continued

Table 3.11 (continued)

Level I ATC	Per capita expenditure	%*	Δ % 19-18	DDD/ 1000 inhab. day	%*	Δ % 19-18	DDD Average cost	Δ % 19-18
botulinum toxin by Clostridium botulinum type a	0.27	7.7	8.8	0.0	0.1	7.4	126.55	1.3
ataluren	0.23	6.6	18.5	0.0	0.0	8.8	1618.86	9.0
zoledronic acid	0.07	2.0	17.5	0.0	0.1	-12.8	53.14	34.8
S – Sensory organs	**3.10**		**10.3**	**2.8**		**0.0**	**3.06**	**10.1**
aflibercept	1.18	38.0	23.9	0.3	10.5	21.1	11.05	2.3
ranibizumab	1.15	37.1	-4.9	0.1	4.3	0.2	26.12	-5.1
dexamethasone	0.37	11.9	13.5	0.2	8.6	18.1	4.21	-3.9
cenegermin	0.07	2.2	11.1	0.0	0.0	16.5	265.26	-4.6
iodopovidone	0.04	1.2	>100	0.0	0.9	-49.3	4.24	>100
G - Genito-urinary and sex hormones	**1.53**		**-2.9**	**2.4**		**23.3**	**1.78**	**-21.3**
follitropin alpha, from recombinant dna	0.37	24.2	-10.6	0.1	2.1	-4.1	20.00	-6.8
menotropin	0.22	14.6	2.2	0.0	1.9	2.0	13.62	0.2
follitropin alpha/luteotropin alpha	0.15	9.7	64.8	0.0	0.2	64.9	79.60	-0.1
tadalafil	0.12	7.8	-21.2	0.2	7.8	17.1	1.77	-32.8
follitropin beta	0.11	6.9	-23.7	0.0	0.5	-23.4	27.00	-0.4
dinoprostone	0.10	6.4	6.2	0.1	2.1	6.1	5.34	0.1
sildenafil	0.06	3.9	-44.9	0.0	2.0	4.8	3.42	-47.5
testosterone	0.06	3.6	42.4	0.1	4.7	28.6	1.37	10.7
D - Dermatologicals	**0.83**		**113.7**	**8.2**		**-3.3**	**0.28**	**120.5**
Dupilumab	0.44	52.9	>100	0.0	0.5	>100	32.65	0.0
iodopovidone	0.06	6.7	0.0	0.7	8.9	-2.9	0.21	3.1
silver sulfadiazine	0.05	6.6	9.5	0.7	8.4	1.8	0.22	7.6
chlorhexidine/benzalkonium	0.05	6.3	14.9	1.2	14.7	-20.3	0.12	44.1
sodium hypochlorite	0.04	4.5	6.1	2.6	31.9	2.0	0.04	4.0
P - Antiparasitics	**0.03**		**22.4**	**<0.05**		**5.7**	**2.97**	**15.6**
atovaquone	0.02	51,6	16.7	0.0	10.1	16.7	15.13	0.0
permethrin	0.01	20,0	>100	0.0	5.8	>100	10.17	-5.4
atovaquone/proguanil	0.00	11,9	-2.5	0.0	5.0	10.6	7.12	-11.8
Hydroxychloroquine	0.00	4,7	6.6	0.0	40.7	5.9	0.34	0.7
pentamidine isethionate	0.00	4,3	6.2	0.0	1.2	6.1	10.53	0.1

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

Table 3.12. First thirty active ingredients* purchased by public health facilities in terms of expenditure: comparison 2019-2018

ATC	Active ingredient	Exp. *(million)*	%*	Per capita expenditure	Rank 2019	Rank 2018	DDD Average cost	Δ % 19-18
J	sofosbuvir/velpatasvir	751.9	5.7	12.46	1	12	654.84	>100
L	pembrolizumab	281.4	2.1	4.66	2	8	87.82	-9.1
L	nivolumab	272.8	2.1	4.52	3	3	154.24	-11.5
L	lenalidomide	262.8	2.0	4.35	4	6	122.97	2.3
L	bevacizumab	193.6	1.5	3.21	5	7	74.33	0.1
B	factor VIII	162.9	1.2	2.70	6	2	341.96	1.6
L	daratumumab	156.3	1.2	2.59	7	41	186.45	-0.6
B	rivaroxaban	155.1	1.2	2.57	8	14	1.71	-6.5
B	apixaban	152.7	1.2	2.53	9	10	1.97	-18.5
L	pertuzumab	143.3	1.1	2.37	10	15	143.60	0.1
L	fingolimod	142.0	1.1	2.35	11	11	54.80	0.0
L	adalimumab	133.8	1.0	2.22	12	1	12.65	-59.3
L	dimethylfumarate	133.7	1.0	2.22	13	16	33.13	-1.1
L	trastuzumab	133.1	1.0	2.20	14	4	29.54	-44.0
L	ibrutinib	132.0	1.0	2.19	15	17	130.10	-11.7
L	palbociclib	130.5	1.0	2.16	16	37	85.01	3.4
J	glecaprevir/pibrentasvir	124.7	0.9	2.07	17	5	119.50	-11.8
L	etanercept	122.8	0.9	2.04	18	9	19.51	-24.7
L	eculizumab	111.8	0.8	1.85	19	47	816.51	56.1
J	meningococcal vaccine group B	108.2	0.8	1.79	20	18	62.84	2.4
L	rituximab	104.4	0.8	1.73	21	13	9.21	-21.5
L	abiraterone	104.2	0.8	1.73	22	20	85.36	0.0
J	emtricitabine/rilpivirine/ tenofovir alafenamide	103.9	0.8	1.72	23	34	19.96	0.0
L	secukinumab	103.1	0.8	1.71	24	32	31.69	0.0
M	nusinersen	102.2	0.8	1.69	25	23	421.82	11.2
L	ustekinumab	102.2	0.8	1.69	26	28	19.77	-15.9
J	pneumococcal saccharide conjugated vaccine, adsorbed	99.6	0.8	1.65	27	21	49.50	0.2
A	insulin glargine	93.5	0.7	1.55	28	22	0.98	-2.1
L	natalizumab	93.2	0.7	1.54	29	25	56.94	0.1
J	dolutegravir	91.2	0.7	1.51	30	42	16.42	-0.4
	Total	**4,802.9**	**36.4**					
	Total expenditure public health facilities	**13,212.8**						

*calculated on the total expenditure of medicines purchased by public health facilities
Traceability data for sofosbuvir/velpatasvir combination are net of the credit notes relating to the price/volume agreement in force

Table 3.13. First thirty active ingredients* with higher variation in expenditure relating to medicines purchased by public health facilities compared to the previous year: comparison 2019-2018

ATC	Active ingredient	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. day	Δ % 19-18	DDD average cost	Δ % 19-18
L	ocrelizumab	0.84	2060.4	0.0	2113.7	49.80	-2.4
L	atezolizumab	0.67	887.2	0.0	410.6	147.88	93.3
L	alectinib	0.68	541.9	0.0	548.3	173.59	-1.0
J	sofosbuvir/velpatasvir	12.46	448.6	0.1	-33.8	654.84	728.5
J	sofosbuvir/velpatasvir/ voxilaprevir	0.79	340.6	0.0	-8.1	649.29	379.7
L	daratumumab	2.59	120.7	0.0	122.1	186.45	-0.6
A	dulaglutide	0.90	82.7	1.2	77.5	2.14	2.9
L	palbociclib	2.16	74.4	0.1	68.6	85.01	3.4
L	eculizumab	1.85	67.2	0.0	7.1	816.51	56.1
L	canakinumab	0.67	66.1	0.0	86.5	162.88	-11.0
L	pembrolizumab	4.66	45.1	0.1	59.7	87.82	-9.1
J	inactivated influenza vaccine	0.83	33.9	0.4	32.4	5.74	1.2
B	edoxaban	0.93	33.5	1.3	52.3	2.00	-12.3
R	lumacaftor/ivacaftor	1.16	32.5	0.0	24.6	416.96	6.3
J	emtricitabine/rilpivirine/ tenofovir alafenamide	1.72	30.7	0.2	30.7	19.96	0.0
J	human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.07	30.1	0.0	30.1	69.33	0.0
J	dolutegravir	1.51	29.0	0.3	29.5	16.42	-0.4
B	eptacog alpha activated (coagulation factor VII, from recombinant dna)	0.81	28.6	0.0	29.0	32519.96	-0.3
B	albutrepenonacog alpha	0.66	28.4	0.0	28.2	1088.67	0.1
L	secukinumab	1.71	26.8	0.1	26.8	31.69	0.0
L	enzalutamide	1.44	25.9	0.0	25.8	85.64	0.1
L	vedolizumab	0.92	25.8	0.1	24.6	36.30	0.9
L	ruxolitinib	1.37	25.6	0.0	23.9	108.52	1.4
S	aflibercept	1.18	23.9	0.3	21.1	11.05	2.3
L	lenalidomide	4.35	22.6	0.1	19.8	122.97	2.3
L	pirfenidone	0.93	21.9	0.0	21.9	64.50	0.0
L	pomalidomide	0.76	21.7	0.0	19.2	307.37	2.1
B	rivaroxaban	2.57	21.0	4.1	29.4	1.71	-6.5
L	osimertinib	0.81	20.7	0.0	84.1	131.79	-34.4
B	sodium chloride	0.73	20.2	6.5	18.9	0.31	1.1

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

Table 3.14 shows the data on expenditure, consumption and average cost per day of therapy of the categories which will be studied in depth in the following pages.
This analysis includes both medicines provided under NHS outpatient care and pharmaceuticals purchased by public health facilities. With reference to vaccines, data were included relating to those purchased by citizens, accounting for 8.6% of the total expenditure for vaccines. With regard to NHS outpatient care, gross expenditure was considered including partnerships and discounts.
For each category, the consumption trend is presented over the period 2014-2019; the same analysis is presented for the main therapeutic subgroups, for the 10 most expensive substances in 2019 and for all the regions. A specific framework is provided, in terms of analysis of temporal and geographical variability as well as for medicines with expired patents (generic medicines).
For some therapeutic categories, the analysis of the consumption variability in the main subgroups, the consumption and population prevalence and some indicators of intensity of use are presented.
The categories analysed are as follows:

- **Antineoplastic pharmaceuticals and immunomodulators**
  - Antineoplastic medicines
  - Immunosuppressants and immunomodulators
  - Medicines for multiple sclerosis
- **Cardiovascular system**
  - Medicines for hypertension and heart failure
  - Lipid-lowering agents
- **General antimicrobials for systemic use**
  - Antibiotics
  - Anti-HIV antivirals
  - Anti-HCV antivirals
  - Vaccines
- **Gastrointestinal system and metabolism**
  - Medicines for peptic ulcer and GERD
  - Antidiabetics
- **Blood and blood-forming organs**
  - Anticoagulants
  - Coagulation factors
  - Platelet aggregation inhibitors
- **Central Nervous System**
  - Antiparkinsonian medicines
  - Antipsychotics
  - Antidepressants
  - Antiepileptics
  - Antidementia medicines
  - Pain therapy
- **Respiratory system**
  - Medicines for per asthma and COPD
  - Medicines for cystic fibrosis
- **Musculoskeletal system**
  - Medicines for osteoporosis
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
- **Systemic hormonal preparations, excluding sex hormones**
  - Thyroid medicines
- **Genito-urinary system and sex hormones**
  - Medicines for genito-urinary disorders
- **Sensory organs**
  - Medicines for eye disorders
- **Miscellaneous**
- **Dermatological medicines**

Table 3.14. Largest prescription pharmaceutical groups in 2019

Group Subgroup	Total expenditure *(in millions)*	% on NHS exp.	Per capita exp.	Δ% 19-18	DDD/ 1000 inhab. day	Δ% 19-18
Antineoplastic medicines	**3,689.7**	**15.9**	**61.13**	**9.9**	**10.2**	**4.7**
Monoclonal antibodies	1,570.6	6.8	26.02	7.9	1.2	9.9
Tyrosin kinase inhibitors	1,071.2	4.6	17.75	16.2	0.5	20.5
Endocrine therapy - aromatase inhibitors	238.0	1.0	3.94	7.6	3.4	7.4
Cytostatic antineoplastics - cytostatic - others	236.1	1.0	3.91	6.0	0.5	6.2
Cytostatic antineoplastics -antimetabolites	165.2	0.7	2.74	5.7	0.7	2.2
Endocrine therapy - hormones and GnRH analogues	115.7	0.5	1.92	2.6	1.1	3.6
Endocrine therapy – antiandrogens	99.2	0.4	1.64	20.8	0.9	-5.6
Cytotoxic antineoplastics - products of natural derivation – taxanes	49.3	0.2	0.82	4.9	0.2	5.2
Endocrine therapy - anti-estrogens	44.7	0.2	0.74	2.9	1.1	-3.6
Cytotoxic antineoplastics - products of natural derivation – others	36.2	0.2	0.60	8.5	0.1	10.0
Cytotoxic antineoplastics – cytotoxicanthracycline antibiotics and related substances	27.9	0.1	0.46	5.4	0.1	3.4
Cytostatic antineoplastics - alkylating agents	22.7	0.1	0.38	-9.4	0.2	16.2
Cytostatic antineoplastics – platinum compounds	5.3	0.0	0.09	-3.9	0.2	6.7
Cytotoxic antineoplastics - cytotoxic antibiotics - others	3.9	0.0	0.06	-28.8	0.1	-17.3
Combination of antineoplastic agents	2.4	0.0	0.04	0.0	0.0	0.0
CAR-T	1.2	0.0	0.02	0.0	0.0	0.0
Antihypertensive medicines	**2,012.5**	**8.7**	**33.34**	**-0.1**	**375.1**	**0.6**
Beta blockers	319.2	1.4	5.29	2.9	44.3	1.5
Angiotensin II receptor blockers (ARBs)	287.7	1.2	4.77	5.0	58.0	1.9
Calcium channel blockers (dihydropyridines)	254.8	1.1	4.22	-1.5	50.9	0.1
Angiotensin II receptor blockers and diuretics (combinations)	243.6	1.0	4.04	-6.4	33.5	-7.1
ACE inhibitors	233.7	1.0	3.87	-0.8	86.7	0.0
ACE inhibitors and diuretics (combinations)	161.2	0.7	2.67	-2.8	20.7	-3.4
ACE inhibitors and calcium channel blockers (combinations)	103.2	0.4	1.71	4.1	11.9	6.9
Alpha-adrenoreceptor antagonists	74.5	0.3	1.24	0.8	7.7	0.9
High-ceiling diuretics, plain or in combination with potassium-sparing agents	63.6	0.3	1.05	2.1	31.6	4.1
Angiotensin II receptor blockers and calcium channel blockers (combinations)	63.5	0.3	1.05	-29.4	7.0	27.4
Angiotensin II receptor blockers and neprilysin inhibitor	48.7	0.2	0.81	76.6	0.5	76.6
Beta blockers and diuretics (combinations)	40.4	0.2	0.67	-2.1	7.3	-1.8
Potassium-sparing diuretics	33.6	0.1	0.56	3.2	3.6	1.8
ACE inhibitors, other combinations	32.8	0.1	0.54	22.0	3.3	23.2
Calcium channel blockers (not dihydropyridines)	19.9	0.1	0.33	-8.2	2.3	-8.0
Thiazides and similars (including combinations)	14.7	0.1	0.24	-1.3	4.2	-9.7
Imidazoline receptor agonists	13.5	0.1	0.22	-5.0	1.6	-8.0
Aliskiren plain or in combination	3.6	0.0	0.06	-16.7	0.2	-15.9
Alpha-2 adrenergic agonists	0.4	0.0	0.01	-4.6	0.0	-5.9
Pharmaceuticals acting on arteriolar muscle	0.0	0.0	0.00	-91.9	0.0	-80.9

continued

Table 3.14 (continued)

Group Subgroup	Total expenditure *(in millions)*	% on NHS exp.	Per capita exp.	Δ% 19-18	DDD/ 1000 inhab. day	Δ% 19-18
Immunosuppressants and immunomodulators	**1,664.6**	**7.2**	**27.58**	**1.0**	**3.5**	**11.4**
Tumour necrosis factor alpha (TNFα) inhibitors	417.2	1.8	6.91	-34.2	1.3	7.1
Selective immunosuppressants	369.8	1.6	6.13	33.9	0.8	13.7
Other Immunosuppressants	369.0	1.6	6.11	21.7	0.2	17.0
Interleukin inhibitors	350.5	1.5	5.81	31.0	0.6	37.0
Calcineurin inhibitors	90.8	0.4	1.50	-2.0	0.6	0.2
Growth factors	45.6	0.2	0.76	-10.6	0.1	8.5
Other immunomodulators	17.1	0.1	0.28	0.9	0.0	5.7
Interferons	4.4	0.0	0.07	-32.4	0.0	-38.0
Asthma and COPD	**1,055.5**	**4.5**	**17.49**	**5.6**	**34.2**	**1.4**
Laba+ics	352.0	1.5	5.83	-1.6	9.1	-0.1
Lama	192.7	0.8	3.19	2.2	5.8	1.7
Ultralaba+ics	129.9	0.6	2.15	13.3	3.4	13.6
Ics	115.0	0.5	1.90	-3.3	5.5	-1.0
Monoclonal antibodies	92.4	0.4	1.53	46.8	0.1	44.1
Laba+lama	55.2	0.2	0.91	7.6	1.2	7.7
Leukotriene receptor antagonist (LTRA)	28.5	0.1	0.47	0.8	2.0	2.2
Lama+laba+ics	21.1	0.1	0.35	>100	0.3	>100
Laba	15.5	0.1	0.26	-16.5	0.7	-16.6
Saba	13.5	0.1	0.22	-4.4	2.9	-4.4
Ultra-laba	12.3	0.1	0.20	-15.6	0.5	-15.7
Saba+sama	10.8	0.0	0.18	-0.8	0.8	-0.5
Saba+ics	7.7	0.0	0.13	-6.8	0.3	-6.9
Sama	4.5	0.0	0.07	-1.0	0.9	2.1
Bronchodilators - theophylline	3.8	0.0	0.06	-6.3	0.5	-9.5
PDE-4 inhibitor	0.4	0.0	0.01	-14.7	0.0	-14.8
Chromones	0.2	0.0	0.00	-77.2	0.0	-73.4
Antidiabetics	**1,010.0**	**4.4**	**16.73**	**7.1**	**63.6**	**0.7**
Insulins, fast acting	231.8	1.0	3.84	-3.9	8.4	-1.7
Combined insulins (long/intermediate with fast)	177.3	0.8	2.94	-2.9	6.6	-0.8
GLP-1 (glucagon-like one) analogues	141.9	0.6	2.35	44.7	2.5	43.6
Metformin plain and in combination	99.2	0.4	1.64	-1.0	24.0	-0.1
Gliptins (DPP-4 inhibitors) plain	83.7	0.4	1.39	10.6	3.0	12.1
Gliptins (DPP-4 inhibitors) in combination	76.3	0.3	1.26	3.0	3.1	3.5
Glifozins combined with metformin	41.5	0.2	0.69	33.9	1.4	38.4
Glifozins (SGLT2 inhibitors) plain	38.6	0.2	0.64	21.8	1.3	27.7
Combined insulins	36.9	0.2	0.61	>100	0.3	>100
Sulfonylureas, plain	31.7	0.1	0.53	-5.2	8.4	-9.5
Pioglitazone plain and in combination	23.0	0.1	0.38	-19.6	1.7	-0.9
Repaglinide	18.4	0.1	0.30	-14.9	2.2	-16.1
Acarbose	9.4	0.0	0.16	-7.9	0.6	-6.8
Intermediate acting insulins	0.3	0.0	0.00	-21.3	0.0	-19.4
Anti-HCV antivirals	**948.4**	**4.1**	**15.71**	**129.2**	**0.1**	**-36.7**
Anti-HCV antivirals in combination	948.3	4.1	15.71	>100	0.1	-36.1
Other HCV antivirals	0.1	0.0	0.00	0.0	0.0	0.0
Nucleosides and nucleotides inhibitors of reverse transcriptase	0.0	0.0	0.00	-88.4	0.0	-51.8
HCV protease inhibitors	0.0	0.0	0.00	0.0	0.0	0.0

continued

Table 3.14 (continued)

Group Subgroup	Total expenditure *(in millions)*	% on NHS exp.	Per capita exp.	Δ% 19-18	DDD/ 1000 inhab. day	Δ% 19-18
Antibiotics	**839.2**	**3.6**	**13.90**	**-2.7**	**17.5**	**-2.8**
Penicillin associations (including beta lactamase inhibitors)	219.7	0.9	3.64	4.0	6.3	0.5
III generation cephalosporins	216.5	0.9	3.59	6.5	2.3	6.8
Macrolides and lincosamides	96.2	0.4	1.59	0.1	3.7	1.4
Fluoroquinolones	93.9	0.4	1.56	-26.0	2.2	-27.4
Other antibacterial agents	71.4	0.3	1.18	3.3	0.5	8.4
Glycopeptides	25.7	0.1	0.43	-16.5	0.1	1.1
Broad-spectrum penicillins	18.5	0.1	0.31	3.2	1.2	-1.1
Other cephalosporins and penems	15.1	0.1	0.25	40.6	0.0	45.7
Carbapenems	14.6	0.1	0.24	-1.5	0.1	10.3
Tetracyclines	13.5	0.1	0.22	-50.4	0.4	4.1
Aminoglycosides	12.3	0.1	0.20	-1.9	0.1	-15.5
Polimixin	12.1	0.1	0.20	-2.7	0.0	-3.1
I generation cephalosporins	7.8	0.0	0.13	2.9	0.1	3.9
II generation cephalosporins	7.8	0.0	0.13	3.7	0.2	2.8
Sulfonamidies plain and in combination	4.8	0.0	0.08	13.0	0.4	14.2
IV generation cephalosporins	4.2	0.0	0.07	-12.5	0.0	-13.8
Monobactams	2.4	0.0	0.04	1.2	0.0	1.2
Imidazole derivatives	1.1	0.0	0.02	34.7	0.1	41.3
Penicillins sensitive to beta lactamases	0.8	0.0	0.01	11.8	0.0	8.7
Penicillins resistant to beta lactamases	0.6	0.0	0.01	-49.8	0.0	-36.4
Amphenicoles	0.1	0.0	0.00	1.2	0.0	-7.4
Other quinolones	0.0	0.0	0.00	-78.9	0.0	-79.2
Nitrofuran derivatives	0.0	0.0	0.00	1.7	0.0	2.7
Lipid lowering agents	**829.9**	**3.6**	**13.75**	**-4.9**	**97.1**	**4.7**
Statins, plain	474.7	2.0	7.86	-0.5	79.2	2.4
Ezetimibe plain or in combination	164.1	0.7	2.72	-28.1	10.5	25.6
Omega 3	114.5	0.5	1.90	1.7	4.5	4.4
PCSK9 inhibitors	46.0	0.2	0.76	84.5	0.2	87.0
Fibrates	23.1	0.1	0.38	1.3	2.7	1.6
MTP inhibitors	7.5	0.0	0.12	8.0	0.0	16.6
Statins in combination	0.0	0.0	0.00	>100	0.0	>100
Medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	**811.9**	**3.5**	**13.45**	**-6.1**	**80.5**	**1.5**
Proton pump inhibitors	717.8	3.1	11.89	-6.1	72.6	2.5
Other medicines for peptic ulcer and gastroesophageal reflux disease (GERD)	53.7	0.2	0.89	2.8	4.2	2.5
Antacids	23.9	0.1	0.40	-8.0	1.9	-8.0
H2 receptor antagonists	15.9	0.1	0.26	-25.7	1.8	-22.6
Prostaglandins	0.5	0.0	0.01	-12.6	0.0	-12.0
Anticoagulants	**766.5**	**3.3**	**12.70**	**0.5**	**25.4**	**7.0**
Nao	489.8	2.1	8.11	10.3	11.7	25.0
Ebpm	215.1	0.9	3.56	-15.9	8.7	-2.0
Antithrombotics	23.7	0.1	0.39	6.4	0.0	2.2
Fondaparinux	16.3	0.1	0.27	-0.1	0.5	2.6
Heparin and heparinoids	11.5	0.0	0.19	-7.1	0.4	-3.1
Vitamin K antagonists	10.1	0.0	0.17	-10.8	4.1	-10.6

continued

Table 3.14 (continued)

Group / Subgroup	Total expenditure *(in millions)*	% on NHS exp.	Per capita exp.	Δ% 19-18	DDD/ 1000 inhab day	Δ% 19-18
Multiple sclerosis pharmaceuticals	**674.1**	**2.9**	**11.17**	**5.2**	**2.7**	**3.6**
Immunosuppressants	179.8	0.8	2.98	11.4	1.9	4.2
Monoclonal antibodies	153.1	0.7	2.54	38.4	0.1	63.0
Fingolimod	142.0	0.6	2.35	3.2	0.1	3.2
Interferons	115.5	0.5	1.91	-12.5	0.4	-9.2
Teriflunomide	48.7	0.2	0.81	15.2	0.1	15.8
Glatiramer	35.1	0.2	0.58	-38.4	0.1	1.2
Anti-HIV antivirals	**661.2**	**2.8**	**10.96**	**-6.6**	**2.8**	**1.7**
Anti-HIV anti-virals in coformulated regimens	345.9	1.5	5.73	4.8	0.9	7.3
Integrase inhibitors	130.7	0.6	2.17	17.1	0.4	21.6
Nucleosides and nucleotides inhibitors of reverse transcriptase	84.5	0.4	1.40	-33.8	1.1	2.4
Protease inhibitors plain or in combination	75.3	0.3	1.25	-31.8	0.3	-25.6
Non-nucleoside inhibitors of reverse transcriptase	17.9	0.1	0.30	-6.6	0.2	-7.3
Other anti-HIV antivirals	6.9	0.0	0.12	-24.1	0.0	-17.6
Osteoporosis pharmaceuticals	**607.9**	**2.6**	**10.07**	**3.0**	**33.6**	**2.2**
Vitamin D and analogues	339.0	1.5	5.62	3.1	19.7	2.3
Anabolic pharmaceuticals	87.2	0.4	1.44	1.4	0.2	3.7
Bisphosphonates, plain	86.1	0.4	1.43	2.0	6.9	2.2
Monoclonal antibodies	59.1	0.3	0.98	14.6	3.1	11.4
Bisphosphonates in combination	28.3	0.1	0.47	-8.7	2.2	-8.4
Calcium	7.4	0.0	0.12	0.1	1.5	1.1
SERM (selective estrogen-receptor modulators)	0.8	0.0	0.01	-2.5	0.0	-2.9
Double-acting pharmaceuticals	0.0	0.0	0.00	-83.4	0.0	-83.4
Vaccines	**566.4**	**2.4**	**9.38**	**7.4**	**1.1**	**13.8**
Meningococcal B vaccine	108.2	0.5	1.79	-2.2	0.1	-4.5
Pneumococcal 13 vaccine	105.8	0.5	1.75	9.0	0.1	5.8
Papillomavirus vaccine	65.1	0.3	1.08	15.9	0.0	6.1
Quadrivalent influenza vaccine from inactivated split virus	64.4	0.3	1.07	63.7	0.4	37.2
Hexavalent vaccine (diphtheria /tetanus/ pertussis/haemophilus influenzae b/ poliomyelitis/hepatitis B)	43.0	0.2	0.71	-26.1	0.1	-7.1
MMRV vaccine (measles/mumps/rubella/varicella)	32.3	0.1	0.54	-2.7	0.0	-0.8
Tetravalent meningococcal conjugated vaccine	28.5	0.1	0.47	-3.9	0.0	0.8
Tetravalent vaccine (diphtheria /tetanus/ pertussis/poliomyelitis)	19.7	0.1	0.33	21.6	0.0	22.1
Live attenuated varicella zoster virus vaccine	18.5	0.1	0.31	>100	0.0	>100
Rotavirus attenuated vaccine	18.5	0.1	0.31	8.6	0.0	21.8
Influenza vaccine from inactivated virus, adjuvated	16.9	0.1	0.28	14.3	0.1	14.0
DTP vaccine (diphtheria /tetanus/pertussis)	8.2	0.0	0.14	10.2	0.0	14.3
Live attenuated varicella virus vaccine	6.5	0.0	0.11	-32.4	0.0	-30.8
Pneumococcal 23 vaccine	5.0	0.0	0.08	72.6	0.0	61.1
MMR vaccine (measles/mumps/rubella)	4.4	0.0	0.07	-31.7	0.0	-30.3
Encephalitis vaccine	4.3	0.0	0.07	28.6	0.0	22.2
Hepatitis A vaccine	3.5	0.0	0.06	-23.4	0.0	-23.0
Hepatitis B vaccine	3.1	0.0	0.05	-20.3	0.0	-27.4
Pneumococcal 10 vaccine	2.4	0.0	0.04	84.2	0.0	84.9

continued

Table 3.14 (continued)

Group Subgroup	Total expenditure *(in millions)*	% on NHS exp.	Per capita exp.	Δ% 19-18	DDD/ 1000 inhab. day	DDD/ 1000 inhab. day
Influenza vaccine (surface antigen, inactivated, produced in cell cultures)	2.1	0.0	0.03	0.0	0.0	0.0
Meningococcal C conjugated vaccine	1.6	0.0	0.03	-35.1	0.0	-39.3
DT vaccine (diphtheria /tetanus)	0.9	0.0	0.01	-0.7	0.0	-4.9
Typhus vaccine	0.8	0.0	0.01	18.0	0.0	13.1
Yellow fever vaccine	0.7	0.0	0.01	3.6	0.0	-3.9
Tetanus vaccine	0.5	0.0	0.01	-3.0	0.0	7.6
Hepatitis A and B vaccines	0.4	0.0	0.01	-53.4	0.0	-52.2
Cholera vaccine	0.4	0.0	0.01	-9.2	0.0	-17.4
Rabies vaccine	0.4	0.0	0.01	-19.7	0.0	-21.0
Poliomyelitis inactivated vaccine	0.2	0.0	0.00	-63.6	0.0	-64.7
Haemophilus influenzae B vaccine	0.1	0.0	0.00	-40.9	0.0	-40.4
Trivalent vaccine (diphtheria /tetanus/poliomyelitis	0.1	0.0	0.00	-56.5	0.0	-60.2
Coagulation factors	**515.6**	**2.2**	**8.54**	**11.4**	**0.1**	**7.4**
Haemophilia A (recombinant)	334.0	1.4	5.53	9.0	0.0	7.3
Haemophilia B (recombinant)	71.8	0.3	1.19	15.9	0.0	4.0
Haemophilia A (plasma derivatives)	34.9	0.2	0.58	-26.6	0.0	-9.7
Factor VII deficiency (recombinant)	30.1	0.1	0.50	-16.7	0.0	-16.4
Coagulation factors	20.0	0.1	0.33	>100	0.0	>100
Haemophilia A (monoclonal antibodies)	16.5	0.1	0.27	0.0	0.0	802.2
Factor VII deficiency (plasma derivatives)	4.2	0.0	0.07	4.9	0.0	4.6
Other deficiencies of coagulation factors (recombinant)	2.6	0.0	0.04	-1.0	0.0	-1.0
Haemophilia B (plasma derivatives)	0.8	0.0	0.01	55.6	0.0	36.6
Other deficiencies of coagulation factors (plasma derivatives)	0.5	0.0	0.01	2.7	0.0	0.3
Factor VIII	0.2	0.0	0.00	0.0	0.0	0.0
Von Willebrand disease (plasma derivatives)	0.0	0.0	0.00	0.0	0.0	0.0
Pharmaceuticals for eye disorders	**407.3**	**1.8**	**6.75**	**5.2**	**21.3**	**1.4**
Antineovascular agents	142.2	0.6	2.36	7.7	0.4	14.0
Antiglaucoma preparations - beta blocking agents plain or in combination	135.9	0.6	2.25	2.3	11.8	1.3
Antiglaucoma preparations - prostaglandin analogues	79.1	0.3	1.31	2.4	5.8	0.8
Corticosteroids	22.7	0.1	0.38	13.1	0.2	18.1
Antiglaucoma preparations – carbonic anhydrase inhibitors	13.5	0.1	0.22	-0.2	1.5	-1.0
Antiglaucoma preparations – sympathomimetic drugs	6.0	0.0	0.10	4.4	1.5	2.6
Other ophthalmologicals	5.6	0.0	0.09	49.0	0.0	86.5
Corticosteroids (intravitreal implants)	1.7	0.0	0.03	31.7	0.0	32.0
Antiglaucoma preparations – parasympathomimetic drugs	0.6	0.0	0.01	20.3	0.0	-11.7
Antiglaucoma preparations - others	0.0	0.0	0.00	-32.5	0.0	-32.5
Pain therapy	**399.3**	**1.7**	**6.62**	**2.7**	**7.7**	**5.2**
Major opioids plain or in combination	268.6	1.2	4.45	2.5	2.9	9.2
Drugs for neuropathic pain	89.5	0.4	1.48	6.0	2.7	6.6
Minor opioids plain or in combination	41.2	0.2	0.68	-3.2	2.0	-2.0
Antidepressants	**391.6**	**1.7**	**6.49**	**2.7**	**42.4**	**2.1**
SSRI antidepressants	198.1	0.9	3.28	-0.3	29.9	0.9

continued

Table 3.14 (continued)

Group Subgroup	Total expenditure *(in millions)*	% on NHS exp.	Per capita exp.	Δ% 19-18	DDD/ 1000 inhab. day	DDD/ 1000 inhab. day
SNRI antidepressants	92.3	0.4	1.53	2.7	6.7	3.3
Other antidepressants	45.6	0.2	0.76	3.1	3.1	2.9
SMS (serotonin modulators and stimulators)	34.6	0.1	0.57	25.6	1.4	25.7
Tricyclic antidepressants	10.3	0.0	0.17	-0.3	1.1	-0.1
Bupropion	10.2	0.0	0.17	1.7	0.3	6.2
NaRi (norepinephrine reuptake inhibitors)	0.5	0.0	0.01	-0.7	0.0	-1.4
NaSSA (agomelatoninergics)	0.0	0.0	0.00	-38.1	0.0	-35.2
Antiplatelet agents and anticoagulants	321.0	1.4	5.32	1.9	70.3	0.1
Platelet aggregation inhibitors excluding P2Y12 inhibitors	170.0	0.7	2.82	0.1	56.3	-0.2
Inhibitors of platelet receptor P2Y12	91.6	0.4	1.52	2.5	13.0	0.3
Ticagrelor	57.0	0.2	0.95	9.7	1.1	13.1
Glycoprotein IIb/IIIa inhibitors	2.4	0.0	0.04	-35.8	0.0	1.3
Antiepileptics	**300.0**	**1.3**	**4.97**	**5.1**	**10.6**	**1.8**
Other antiepileptics	199.2	0.9	3.30	7.6	4.1	6.4
Fatty acids derivatives – valproic acid and derivatives	59.3	0.3	0.98	1.7	2.5	0.9
Carboxamide derivatives	31.9	0.1	0.53	-1.1	1.9	-1.6
Benzodiazepine derivatives	4.0	0.0	0.07	0.4	0.4	-0.2
Barbiturates and derivatives	3.2	0.0	0.05	-3.3	1.4	-3.2
Fatty acids derivatives plain and in combination	1.6	0.0	0.03	-4.4	0.0	-4.1
Phenytoin plain or in combination	0.5	0.0	0.01	-5.4	0.1	-6.4
Succinimide derivatives	0.3	0.0	0.01	22.4	0.0	27.5
Pharmaceuticals for genitourinary disorders	**289.9**	**1.2**	**4.80**	**2.8**	**37.6**	**3.6**
Pharmaceuticals for benign prostatic hyperplasia	286.4	1.2	4.74	2.8	37.3	3.5
Pharmaceuticals for incontinence and urination disorders	3.4	0.0	0.06	8.5	0.2	10.2
Other pharmaceuticals for benign prostatic hyperplasia	0.1	0.0	0.00	9.9	0.0	5.4
Antipsychotics	**285.1**	**1.2**	**4.72**	**4.0**	**9.7**	**1.3**
Atypical and other antipsychotics	267.4	1.2	4.43	4.4	7.4	5.0
Typical antipsychotics	17.7	0.1	0.29	-1.5	2.2	-9.6
Antiparkinson pharmaceuticals	**206.2**	**0.9**	**3.42**	**5.4**	**5.3**	**2.8**
Dopamine-agonists	75.5	0.3	1.25	-2.7	1.2	-3.6
Dopa-derivatives agonists	74.6	0.3	1.24	4.8	2.4	1.8
MAO-inhibitors	46.4	0.2	0.77	6.4	1.6	4.8
COMT-inhibitors	9.7	0.0	0.16	>100	0.1	>100
Amantadine	0.0	0.0	0.00	69.8	0.0	120.3
NSAIDs	**149.9**	**0.6**	**2.48**	**-1.5**	**18.2**	**-2.0**
Traditional NSAIDs	102.7	0.4	1.70	-2.3	13.4	-2.9
Coxib	39.3	0.2	0.65	-0.1	3.8	0.9
Oxicam	7.5	0.0	0.12	1.6	0.9	-1.8
Other NSAIDs	0.5	0.0	0.01	13.8	0.0	12.4
Pharmaceuticals for cystic fibrosis	**100.1**	**0.4**	**1.66**	**22.3**	**0.0**	**20.4**
Thyroid pharmaceuticals	**68.3**	**0.3**	**1.13**	**7.6**	**22.6**	**2.3**
Thyroid hormones	64.9	0.3	1.08	7.8	21.2	2.5
Thyroid hormones	3.4	0.0	0.06	4.1	1.4	-1.2
Antidementia pharmaceuticals	**27.7**	**0.1**	**0.46**	**-9.8**	**2.5**	**4.9**
Anticholinesterase pharmaceuticals	19.5	0.1	0.32	-11.8	1.5	3.6
Other antidementia pharmaceuticals	8.2	0.0	0.14	-4.8	1.0	6.9

3.1 Antineoplastic and immunomodulating pharmaceuticals

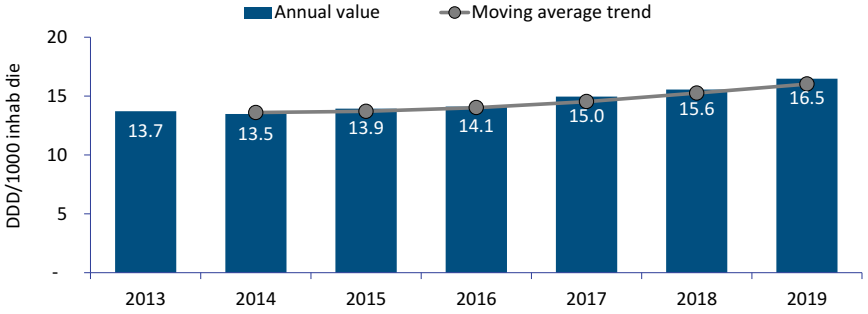
Antineoplastic and immunomodulatory pharmaceuticals were the therapeutic category with the highest public expenditure in 2019, amounting to € 6,038 million (26% of overall expenditure). The overall per capita expenditure for such medicines was € 100, mainly justified by the purchase of public health facilities (€ 95.86 per capita), thus recording a sharp increase compared to the previous year (+7.1%). On the contrary, the contribution provided through the NHS outpatient care was lower (€ 4.17 per capita) (Table 3.1).
Consumption for this category of drugs was 16.5 DDD/1000 inhabitants per day, with an increase of about 6% compared to 2018 (Table 3.2), which confirms the growing trend of the last seven years.
The analysis of the medicine utilisation profile by age group and gender (including outpatient care and *per conto* distribution) confirms a higher use of antineoplastic and immunomodulatory drugs with increasing age, with a marked increase in the prevalence of use in women compared to men from the age of 35, which is probably attributable to the prescription of medicines for breast cancer therapy and to the different gender prevalence of autoimmune diseases. However, a turnaround is recorded in the population over 75 years of age, with a greater prevalence of use in the male population (4.9% compared to 3.7% of women), probably due to the increase in the incidence of prostate cancer in this population. The value of per capita expenditure on antineoplastic drugs is higher in women than in the male population and increases with age, reaching a greater value in men aged over 75 (€ 25.7 per capita compared to 12.7 in women).
As regards the NHS outpatient care, per capita expenditure was equal to € 4.17, with a +1.4% increase compared to 2018. This trend was determined by an increase in consumption (+2.1%) and a slight drop in prices (-0.7%) (Table 3.9). Under the regime of this supply channel, aromatase inhibitors are the first category both in terms of expenditure (€ 2.03 per capita) and in terms of consumption (2.8 DDD), followed by other substances with immunosuppressive action and calcineurin inhibitors (belonging to the class of immunosuppressants), with a per capita expenditure respectively of € 0.74 and € 0.63 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 (€ 1.25) and by consumption (1.5 DDD) (Table 3.5). It is also the first active ingredient in its category ranking within the first 30 molecules with the greatest variation in spending compared to the previous year (Table 3.7) and is one of the top 30 active ingredients for NHS outpatient expenditure (Table 3.6). However, no active ingredient in this therapeutic category is included in the top 30 active ingredients with the highest consumption under outpatient assistance regime (Table 3.8).
As regards the purchases by public health facilities, an increase was reported in expenditure (+7.1%) and consumption (+8%) compared to 2018, although a 1% reduction in the average cost per DDD was also recorded (Table 3.11). Monoclonal antibodies are the first category in terms of per capita expenditure (€ 26.02), followed by tyrosine kinase inhibitors (€ 17.75) and by selective immunosuppressants (€ 11.94). For these three categories, increases were recorded both in terms of expenditure and consumption compared to the previous year. In particular, selective immunosuppressants recorded a net increase in expenditure (+27.8%) consumption (+18.7%) and average cost per DDD (+7.7%). Interleukin inhibitors showed the

greatest increase in terms of expenditure (+31%), compared to the previous year, although the average cost for DDD decreased by 4.4% (Table 3.10).
In 2019 pembrolizumab was the active ingredient with the highest per capita expenditure (€ 4.66), with an average DDD cost of € 87.82, followed by nivolumab (€ 4.52 per capita and € 154.24) and by lenalidomide (€ 4.35 per capita and € 122.97). Such increases are likely due to the indication extensions of the three active ingredients reimbursed in 2019. A significant reduction should be highlighted in adalimumab expenditure (-53.6%), mainly attributable to the net decrease in the average cost per DDD (-59.3%) and to the greater penetration of the biosimilar (Tables 3.11 and 3.12). Daratumumab, an anti-CD38 monoclonal antibody, authorised and reimbursed for patients with relapsed/refractory multiple myeloma, recorded a significant increase in expenditure and consumption, reporting a per capita value of € 2.59.
Within the top 30 active ingredients showing the greatest variation in expenditure in 2019 we recorded ocrelizumab, a humanized monoclonal antibody used in relapsing-remitting multiple sclerosis (RRMS) and in primary progressive multiple sclerosis (PPMS), atezolizumab, monoclonal antibody reimbursed in 2019 for non-small cell lung cancer, and tyrosine kinase inhibitor alectinib, indicated for the treatment of adult patients with anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC) (Table 3.13).
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 and on a regional basis. These analyses focused on cancer medicines, immunosuppressants and immunomodulators and pharmaceuticals for multiple sclerosis (Tables 3.1.1 and following).

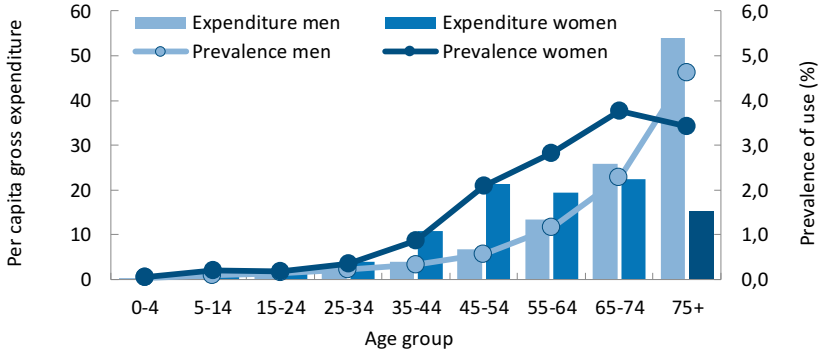
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Antineoplastic and immunomodulatory pharmaceuticals

Public expenditure* in millions € (% on total)	**6,037.7**	**(26.0)**
Δ % 2019-2018		6.7
Regional range of gross per capita expenditure:	71.8	120.2
DDD/1000 inhab. *day (% on total)**	**16.5**	**(1.4)**
Δ % 2019-2018		5.8
Regional range DDD/1000 inhab. day:	13.2	19.6

** Includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure and *per conto* distribution 2019 (Chart and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab./day		
	Men	Women	Total	Men	Women	Total
0-4	0.2	0.2	0.2	0.1	0.1	0.1
5-14	0.5	1.1	0.8	0.4	1.0	0.7
15-24	1.1	1.2	1.1	0.6	0.7	0.7
25-34	2.0	2.9	2.4	1.0	1.6	1.3
35-44	2.8	6.6	4.7	1.4	5.7	3.6
45-54	4.6	13.7	9.2	2.6	15.8	9.3
55-64	8.6	14.8	11.8	5.3	18.3	12.0
65-74	14.5	17.8	16.2	10.8	23.8	17.7
75+	25.7	12.7	17.9	27.8	19.6	22.9

3.1.1 Cancer medicines

- Between 2014 and 2019 per capita expenditure for cancer medicines shifted from € 34.8 to € 61.1 (+75%); in the same period the average cost per day of therapy increased by 53% reaching € 16.36 in 2019; this category represents about 16% of the NHS expense;
- Monoclonal antibodies and tyrosine kinase inhibitors were the two most expensive categories, with € 26.0 and € 17.7 per capita respectively, and account for 71% of cancer medicines. Both categories show an increase compared to 2018 (+7.9% and +16.2%); tisagenlecleucel, the first CAR-T authorized in Italy, recorded an expenditure of € 1.2 million;
- Significant increases in expenditure were reported for daratumumab, palbociclib and pembrolizumab (+121%, +74% and +45%). The first is indicated (plain or in combination) in the treatment of multiple myeloma and has a cost per day of therapy of € 186, while palbociclib is indicated for the treatment of locally advanced or metastatic breast cancer positive to hormonal receptors (HR) and negative to human epidermal growth factor receptor 2 (HER2);
- All regions, although with different levels, recorded an increased expenditure compared to 2018; ranging from +3.4% of the Autonomous Province of Trento to +19.1% of the Autonomous Province of Bolzano; Campania with € 74.39 per capita remains the Region with the highest expenditure also in 2019;
- As expected, 95% of the expenditure relates to patented drugs;
- Campania, Umbria, Friuli Venezia Giulia, Abruzzo and Emilia Romagna are the regions that have a consumption and cost per day of therapy above the national average, while Valle d'Aosta, Sicily, the Autonomous Province of Trento, Piedmont and Veneto are those using a lower quantity of drugs at a lower cost than the national average;
- The major differences in expenditure between the regions relate to monoclonal antibodies (coefficient of variation - CV 19%) and tyrosine kinase inhibitors (CV 16%).

Figure 3.1.1a. Cancer medicines, temporal trend of per capita expenditure (2014-2019)

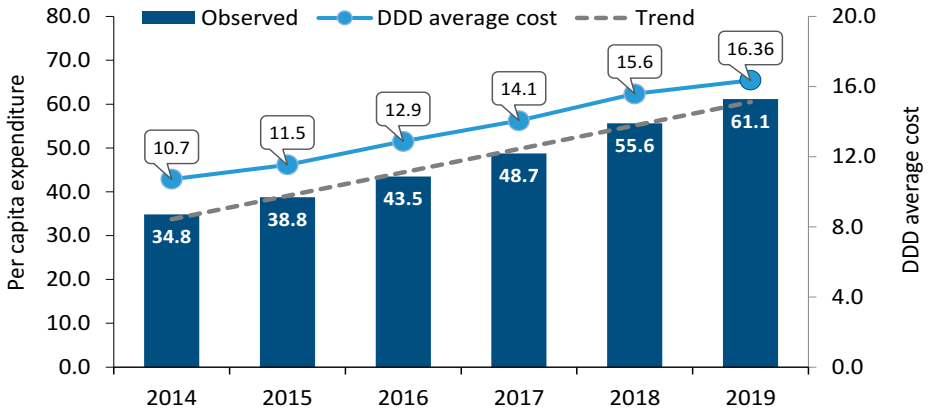


Table 3.1.1a. Cancer medicines, per capita expenditure by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Monoclonal antibodies	12.4	15.0	16.7	20.4	24.1	26.0	7.9
Tyrosin kinase inhibitors	9.8	10.1	12.2	12.9	15.3	17.7	16.2
Endocrine therapy - aromatase inhibitors	2.5	3.2	3.5	3.5	3.7	3.9	7.6
Cytostatic antineoplastics - cytostatic - others	2.1	2.2	2.6	3.4	3.7	3.9	6.0
Cytostatic antineoplastics – antimetabolites	2.8	2.7	2.6	2.5	2.6	2.7	5.7
Endocrine therapy - hormones and GnRH analogues	2.0	1.9	1.9	1.8	1.9	1.9	2.6
Endocrine therapy – antiandrogens	0.3	0.5	0.7	1.0	1.4	1.6	20.8
Cytotoxic antineoplastics - natural products-taxanes	0.5	0.6	0.7	0.7	0.8	0.8	4.9
Endocrine therapy – antiestrogens	0.5	0.5	0.6	0.7	0.7	0.7	2.9
Cytotoxic antineoplastics - natural products - others	0.5	0.5	0.6	0.6	0.6	0.6	8.5
Cytotoxic antineoplastics - cytotoxic-anthracycline antibiotics and related substances	0.5	0.5	0.5	0.5	0.4	0.5	5.4
Cytostatic antineoplastics - alkylating agents	0.7	0.8	0.7	0.6	0.4	0.4	-9.4
Cytostatic antineoplastics - platinum compounds	0.1	0.1	0.1	0.1	0.1	0.1	-3.9
Cytotoxic antineoplastics - cytotoxic antibiotics - Others	0.1	0.1	0.1	0.1	0.1	0.1	-28.8
Combination of antineoplastic agents	0.0	0.0	0.0	0.0	0.0	0.0	-
CAR-T	0.0	0.0	0.0	0.0	0.0	0.0	-
Cancer medicines	**34.8**	**38.8**	**43.5**	**48.7**	**55.6**	**61.1**	**9.9**
pembrolizumab	0.0	0.0	0.2	1.0	3.2	4.7	45.1
nivolumab	0.0	0.0	1.0	3.0	4.4	4.5	2.5
bevacizumab	2.8	3.3	3.6	3.7	3.2	3.2	-0.5
daratumumab	0.0	0.0	0.0	0.2	1.2	2.6	120.7
pertuzumab	0.3	0.9	1.3	1.7	2.1	2.4	14.1
trastuzumab	4.0	4.3	4.5	4.6	4.1	2.2	-45.6
ibrutinib	0.0	0.0	0.6	1.3	1.8	2.2	18.6
palbociclib	0.0	0.0	0.0	0.0	1.2	2.2	74.4
rituximab	3.1	3.2	3.1	3.1	2.2	1.7	-20.4
abiraterone	0.9	1.6	1.7	1.6	1.6	1.7	8.0

Table 3.1.1b. Cancer medicines, regional trend of weighted per capita expenditure: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	33.79	35.47	39.85	43.20	51.23	55.44	8.2
Valle d'Aosta	26.10	34.09	38.78	39.23	42.12	45.00	6.8
Lombardy	29.06	33.32	37.68	41.40	45.91	52.17	13.6
A.P. of Bolzano	37.25	39.22	41.51	52.19	58.05	69.15	19.1
A.P. of Trento	26.89	27.89	34.88	40.11	44.21	45.70	3.4
Veneto	33.43	36.14	40.73	45.22	51.97	55.33	6.5
Friuli VG	41.63	43.42	47.65	59.83	63.61	70.31	10.5
Liguria	35.62	41.03	46.40	51.35	61.61	65.12	5.7
Emilia R.	35.29	40.10	45.16	49.82	59.65	64.81	8.7
Tuscany	41.67	44.71	51.92	55.86	58.01	63.40	9.3
Umbria	37.54	43.26	50.69	54.99	63.97	71.25	11.4
Marche	40.26	45.06	51.04	55.56	62.70	69.64	11.1
Lazio	33.56	36.91	39.29	46.22	57.29	62.28	8.7
Abruzzo	42.62	46.24	51.17	54.68	63.72	66.31	4.1
Molise	30.69	33.37	39.52	48.10	53.88	61.10	13.4
Campania	40.52	46.09	51.51	57.82	66.14	74.39	12.5
Puglia	39.70	44.04	48.93	56.29	65.53	68.81	5.0
Basilicata	40.20	45.78	53.74	60.87	64.58	73.40	13.6
Calabria	31.72	38.38	43.00	48.85	56.41	62.00	9.9
Sicily	28.44	32.13	36.28	42.45	45.62	52.52	15.1
Sardinia	37.87	42.18	46.31	50.30	56.71	62.22	9.7
Italy	**34.83**	**38.76**	**43.48**	**48.73**	**55.63**	**61.13**	**9.9**

Table 3.1.1c. Cancer medicines, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita exp.	Δ % 19-18	DDD/1000 inhab. day	Δ % 19-18	DDD Average cost	Δ % 19-18
Monoclonal antibodies	26.02	7.9	1.2	9.9	58.33	-1.8
Tyrosin kinase inhibitors	17.75	16.2	0.5	20.5	95.69	-3.6
Endocrine therapy - aromatase inhibitors	3.94	7.6	3.4	7.4	3.17	0.2
Cytostatic antineoplastics - cytostatic - others	3.91	6.0	0.5	6.2	21.76	-0.2
Cytostatic antineoplastics – antimetabolites	2.74	5.7	0.7	2.2	11.40	3.4
Endocrine therapy - hormones and GnRh analogues	1.92	2.6	1.1	3.6	4.83	-1.0
Cytotoxic antineoplastics - natural products - taxanes	1.64	20.8	0.9	-5.6	4.82	27.9
Endocrine therapy – antiestrogens	0.82	4.9	0.2	5.2	12.46	-0.2
Cytotoxic antineoplastics - natural products - others	0.74	2.9	1.1	-3.6	1.86	6.8
Cytotoxic antineoplastics - cytotoxic antibiotics - anthracycline and related substances	0.60	8.5	0.1	10.0	23.32	-1.4
Cytostatic antineoplastics - alkylating agents	0.46	5.4	0.1	3.4	12.10	2.0
Endocrine therapy - antiandrogens	0.38	-9.4	0.2	16.2	5.31	-22.1
Cytostatic antineoplastics - platinum compounds	0.09	-3.9	0.2	6.7	1.08	-9.9
Cytotoxic antineoplastics - cytotoxic antibiotics - others	0.06	-28.8	0.1	-17.3	2.61	-14.0
Combination of antineoplastic agents	0.04	-	0.0	-	>100	-
CAR-T	0.02	-	0.0	-	>100	-
Cancer medicines	**61.13**	**9.9**	**10.2**	**4.7**	**16.36**	**4.9**
pembrolizumab	4.66	45.1	0.1	59.7	87.82	-9.1
nivolumab	4.52	2.5	0.1	15.8	154.24	-11.5
bevacizumab	3.21	-0.5	0.1	-0.6	74.33	0.1
daratumumab	2.59	>100	0.0	>100	186.45	-0.6
pertuzumab	2.37	14.1	0.0	14.0	143.60	0.1
trastuzumab	2.20	-45.6	0.2	-2.8	29.54	-44.0
ibrutinib	2.19	18.6	0.0	34.3	130.10	-11.7
palbociclib	2.16	74.4	0.1	68.6	85.01	3.4
rituximab	1.73	-20.4	0.5	1.5	9.21	-21.5
abiraterone	1.73	8.0	0.1	8.0	85.36	0.0

Table 3.1.1d. Prescription of cancer medicines with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. day	%	Δ % 19-18	DDD average cost
Patent expired	3.30	5.4	-1.6	5.3	51.4	2.2	1.72
Generic	1.21	36.7	6.5	3.1	58.8	3.4	1.07
Ex originator	2.09	63.3	-5.7	2.2	41.2	0.6	2.64
Patent covered	57.82	94.6	10.6	5.0	48.6	7.5	31.86
Cancer medicines	**61.13**	**100.0**	**9.9**	**10.2**	**100.0**	**4.7**	**16.36**

* source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.1.1b. Cancer medicines, distribution in quartiles of 2019 per capita expenditure

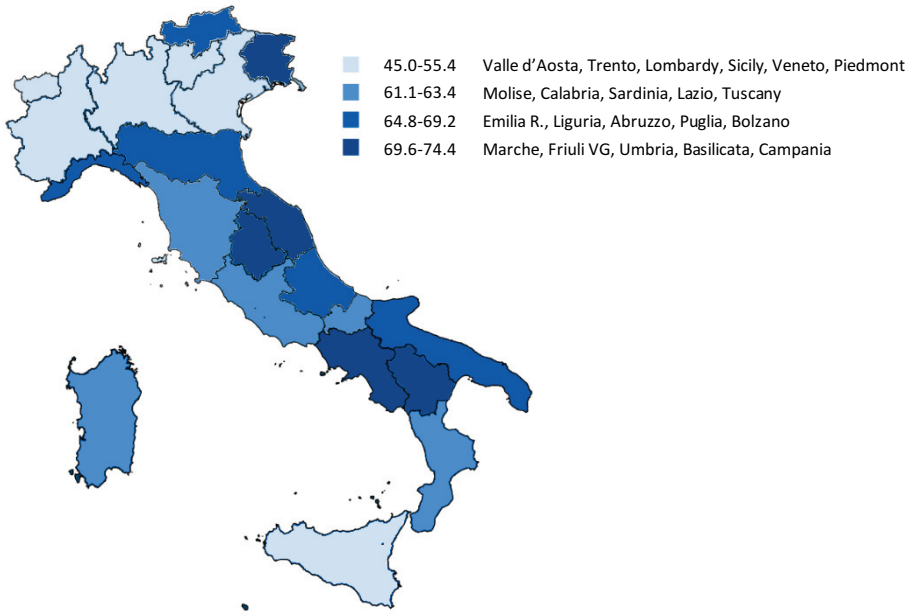


Figure 3.1.1c. Cancer medicines, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviations from national average)

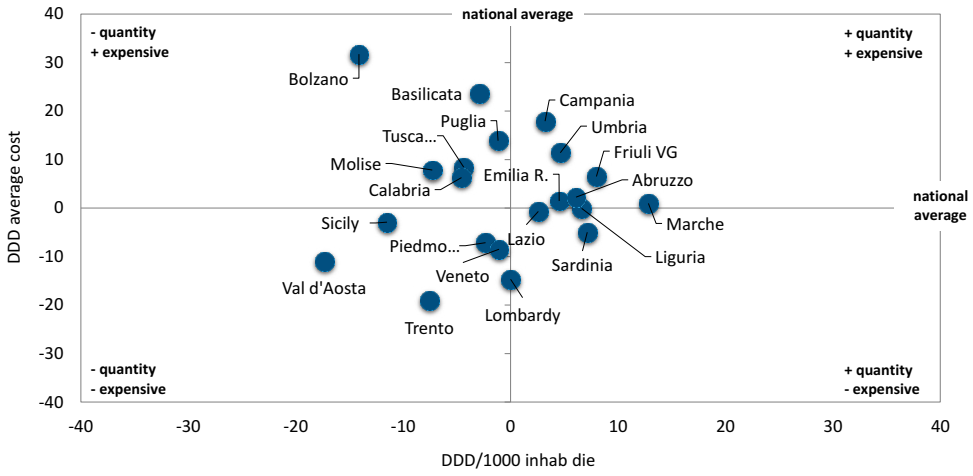
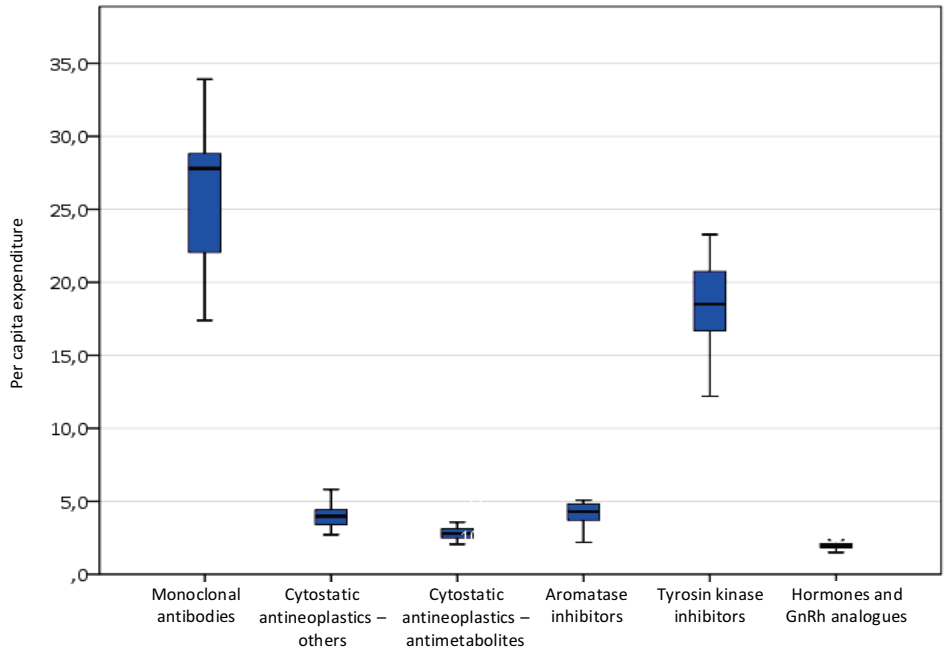


Figure 3.1.1d. Cancer medicines, variability of 2019 consumption (weighted per capita expenditure) by subgroup

(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)



3.1.2 Immunosuppressants and immunomodulators

- In 2019 the expenditure for immunosuppressants and immunomodulators reached € 27.6 per capita, equal to 7.2% of total expenditure, with a 28.2% increase compared to 2013 and 1.0% compared to 2018; due to the patent expiry of important molecules in recent years, the cost per day of therapy shifted from € 24.4 in 2014 to € 21.5 in 2019 (-12%);
- anti TNF is the category with the highest expenditure (€ 6.9 per capita) even if a 34.2% decrease was recorded compared to 2018; instead, significant increases were reported for selective immunosuppressants (+33.9%), other immunosuppressants (+21.7%) and interleukin inhibitors (+ 31%);
- lenalidomide with € 4.4 (+22.6% compared to 2018) is the molecule with the highest expenditure, followed by adalimumab (€ 2.2) and etanercept (€ 2.0), whose expenditure decreased respectively by 59.3% and 24.7%, probably due to a greater use of biosimilar drugs; eculizumab, indicated for the treatment of paroxysmal nocturnal haemoglobinuria and for atypical haemolytic uremic syndrome, is the molecule showing the greatest increase compared to the previous year (+67.2%);
- Emilia Romagna, Lazio, Sicily and Sardinia are the regions whose spending is lower than in 2018, while Valle d'Aosta and Molise recorded the highest increases (+23.8% and +19.1% respectively); the variability of expenditure ranges from a minimum of € 16.07 in Valle d'Aosta to € 39.64 in Molise; wide regional differences are also maintained in relation to the average cost per day of therapy: the Autonomous Province of Trento -22% from the national average and Molise + 49%;
- As for the category level, regional variability is fairly high for anti TNF and interleukin inhibitors with coefficient of variation values equal to 37% and 31%.

Figure 3.1.2a. Immunosuppressants and immunomodulators, temporal trend of per capita expenditure (2014-2019)

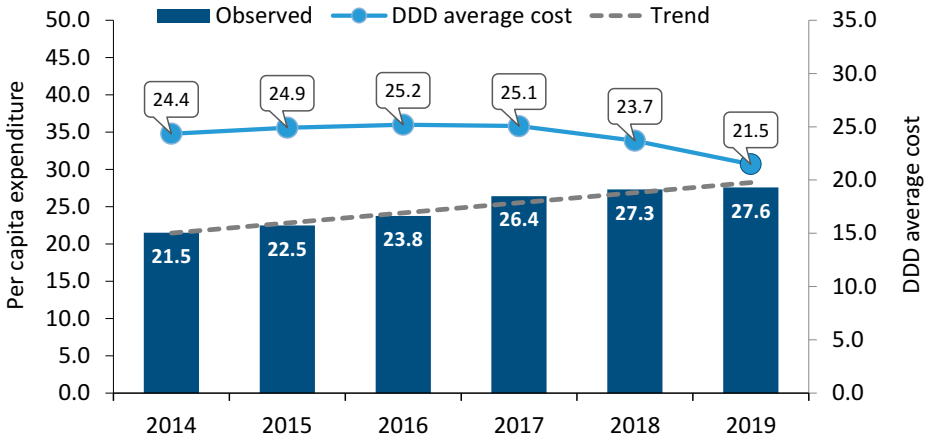


Table 3.1.2a. Immunosuppressants and immunomodulators, per capita expenditure by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Tumour necrosis factor alpha (TNFα) inhibitors	10.2	10.9	10.7	10.9	10.5	6.9	-34.2
Selective Immunosuppressants	2.8	3.0	3.6	4.4	4.6	6.1	33.9
Other immunosuppressants	2.8	3.4	4.2	4.7	5.0	6.1	21.7
Interleukin inhibitors	1.4	1.7	2.2	3.4	4.4	5.8	31.0
Calcineurin inhibitors	1.7	1.7	1.5	1.5	1.5	1.5	-2.0
Growth factors	1.4	1.2	1.0	1.0	0.8	0.8	-10.6
Other immunomodulators	0.2	0.2	0.3	0.3	0.3	0.3	0.9
Interferons	1.0	0.4	0.2	0.1	0.1	0.1	-32.4
Immunosuppressants and immunomodulators	**21.5**	**22.5**	**23.8**	**26.4**	**27.3**	**27.6**	**1.0**
lenalidomide	2.4	2.7	3.0	3.3	3.6	4.4	22.6
adalimumab	4.1	4.4	4.4	4.7	4.8	2.2	-53.6
etanercept	3.5	3.6	3.2	3.0	2.7	2.0	-24.1
eculizumab	1.2	1.3	1.5	1.7	1.1	1.9	67.2
secukinumab	0.0	0.0	0.1	0.8	1.3	1.7	26.8
ustekinumab	0.7	0.9	1.1	1.3	1.4	1.7	17.5
golimumab	0.7	1.0	1.2	1.2	1.2	1.2	-1.9
abatacept	0.5	0.7	0.8	1.0	1.0	1.1	3.8
pirfenidone	0.3	0.5	0.6	0.6	0.8	0.9	21.9
vedolizumab	0.0	0.0	0.1	0.5	0.7	0.9	25.8

Table 3.1.2b. Immunosuppressants and immunomodulators, regional trend of weighted per capita expenditure: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	18.77	18.98	19.75	22.14	23.19	24.89	7.3
Valle d'Aosta	12.16	13.77	16.03	13.10	12.98	16.07	23.8
Lombardy	18.66	19.40	20.16	22.58	23.01	23.16	0.7
A.P. of Bolzano	24.36	25.71	27.58	29.96	30.40	30.61	0.7
A.P. of Trento	15.14	15.61	17.41	18.67	19.52	20.58	5.4
Veneto	20.15	20.61	21.80	23.58	23.71	24.26	2.3
Friuli VG	21.76	22.41	24.24	28.55	30.86	32.08	4.0
Liguria	16.48	16.84	19.20	20.95	22.54	23.33	3.5
Emilia R.	18.45	20.23	22.43	24.55	26.02	25.58	-1.7
Tuscany	25.02	26.53	29.43	30.40	26.33	27.26	3.5
Umbria	21.92	23.13	24.87	27.22	30.75	32.42	5.4
Marche	23.87	25.46	28.02	30.55	33.31	34.19	2.6
Lazio	20.50	20.91	20.58	25.54	27.34	24.61	-10.0
Abruzzo	23.32	24.49	24.79	27.76	31.71	34.18	7.8
Molise	25.28	26.54	28.72	31.54	33.27	39.64	19.1
Campania	24.12	26.04	26.66	29.80	32.00	33.71	5.3
Puglia	29.19	29.78	31.42	33.05	35.76	35.18	-1.6
Basilicata	24.07	25.99	27.38	31.18	31.75	33.75	6.3
Calabria	26.84	27.51	28.75	31.66	34.56	37.07	7.3
Sicily	20.23	21.50	23.84	27.97	27.41	26.10	-4.8
Sardinia	26.63	27.72	27.95	29.67	28.48	28.26	-0.8
Italy	**21.52**	**22.48**	**23.75**	**26.41**	**27.31**	**27.58**	**1.0**

Table 3.1.2c. Immunosuppressants and immunomodulators, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita exp.	Δ % 19-18	DDD/1000 inhab. day	Δ % 19-18	DDD Average cost	Δ % 19-18
Tumor necrosis factor alpha (TNFα) inhibitors	6.91	-34.2	1.3	7.1	14.88	-38.6
Selective Immunosuppressants	6.13	33.9	0.8	13.7	19.80	17.7
Other Immunosuppressants	6.11	21.7	0.2	17.0	110.25	3.9
Interleukin inhibitors	5.81	31.0	0.6	37.0	28.86	-4.4
Calcineurin inhibitors	1.50	-2.0	0.6	0.2	7.12	-2.2
Growth factors	0.76	-10.6	0.1	8.5	21.05	-17.6
Other immunomodulators	0.28	0.9	0.0	5.7	137.22	-4.5
Interferons	0.07	-32.4	0.0	-38.0	17.31	9.1
Immunosuppressants and immunomodulators	**27.58**	**1.0**	**3.5**	**11.4**	**21.47**	**-9.4**
lenalidomide	4.35	22.6	0.1	19.8	122.97	2.3
adalimumab	2.22	-53.6	0.5	14.0	12.65	-59.3
etanercept	2.04	-24.1	0.3	0.8	19.51	-24.7
eculizumab	1.85	67.2	0.0	7.1	816.51	56.1
secukinumab	1.71	26.8	0.1	26.8	31.69	0.0
ustekinumab	1.69	17.5	0.2	39.7	19.77	-15.9
golimumab	1.20	-1.9	0.1	8.3	27.41	-9.4
abatacept	1.08	3.8	0.1	2.9	48.73	0.9
pirfenidone	0.93	21.9	0.0	21.9	64.50	0.0
vedolizumab	0.92	25.8	0.1	24.6	36.30	0.9

Figure 3.1.2b. Immunosuppressants and immunomodulators, distribution in quartiles of 2019 per capita expenditure

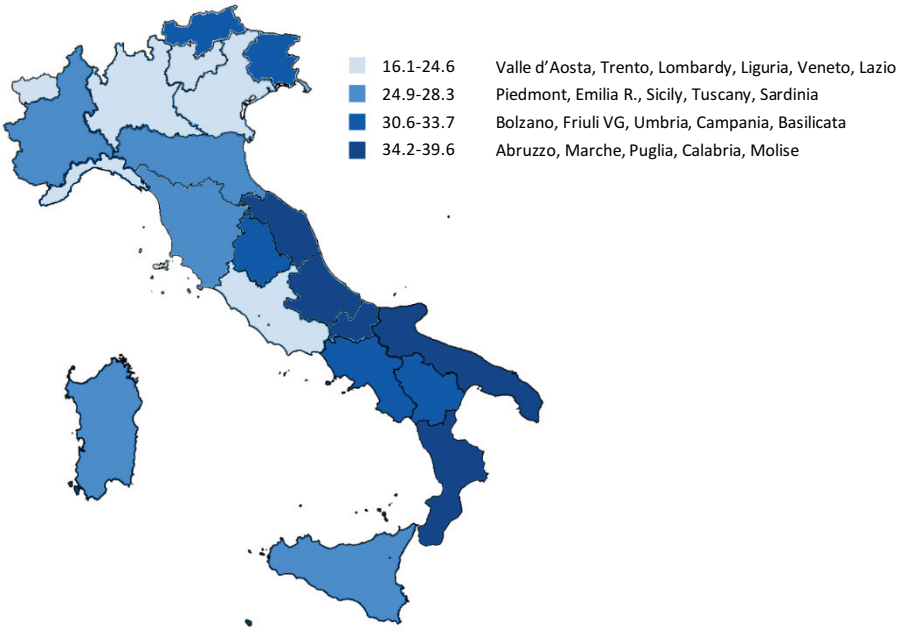


Figure 3.1.2c. Immunosuppressants and immunomodulators, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviations from national average)

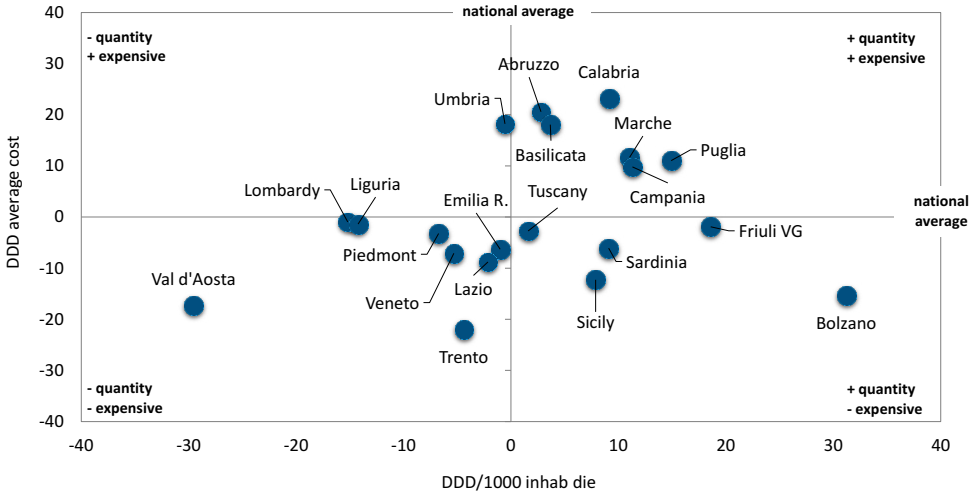
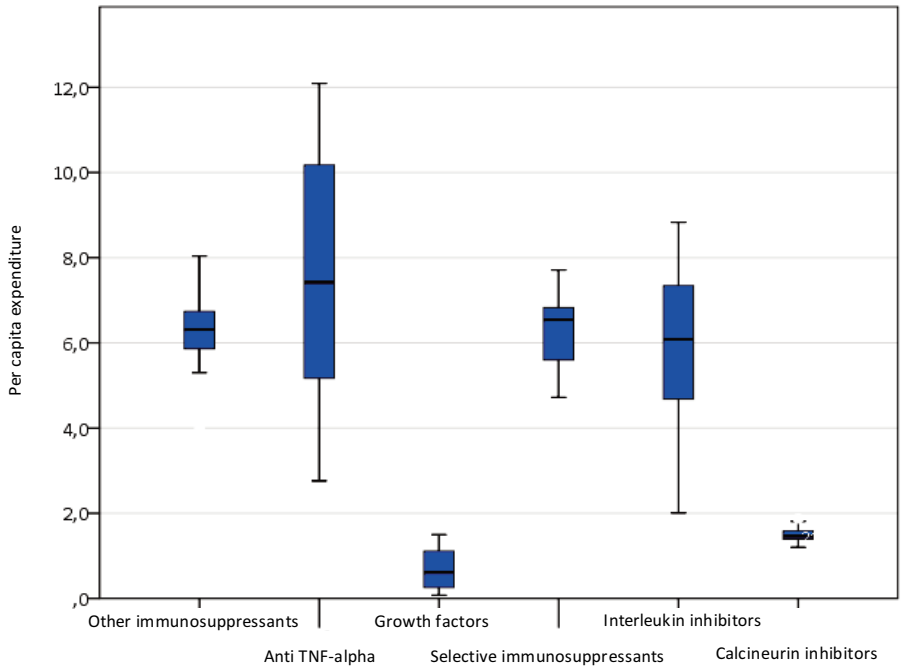


Figure 3.1.2d. Immunosuppressants and immunomodulators, variability of 2019 consumption (weighted per capita expenditure) by subgroup

(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)



3.1.3 Medicines for Multiple Sclerosis

- Multiple sclerosis (MS) is a worsening chronic degenerative autoimmune disease affecting the central nervous system, with a prevalence in Italy of 198 cases per 100,000 inhabitants (with the exception of Sardinia with 370 cases per 100,000 residents) and an estimated incidence ranging between 5.5 and 6 out of 100,000 in Italy (12 out of 100,000 in Sardinia);
- in the last six years the prescription of medicines for multiple sclerosis has shifted from 2.2 in 2014 to 2.7 DDD in 2019 (with a +26% variation); this trend was mainly due to the use of immunosuppressants, including methotrexate which accounts for over half of the consumption of the entire category (from 0.8 DDD in 2014 to 1.3 DDD in 2019); in the last three years the average cost per day of therapy has remained quite stable, reaching € 11.3 in 2019;
- fingolimod with € 2.35 per capita is the substance with the highest expenditure (+3.2% compared to 2018), followed by dimethyl fumarate (€ 2.22; +14%) and natalizumab (€ 1.54; +3.9%); the expenditure for interferons decreased by 12.5% - namely, interferon beta 1a (-14.4%) and peginterferon beta-1 (-4.6%). It should be underlined the decrease in expenditure (-38.4%) of glatiramer, an expired-patent drug, and the substantial increase of ocrelizumab, authorized in Italy in 2018, for which recent scientific evidence shows a reduction in the risk of progression of disability in relapsing MS (RMS) and in primary progressive MS (PPMS) in patients treated continuously;
- in line with the epidemiological data on prevalence of multiple sclerosis in Italy, Sardinia is the region recording the greatest use: in 2019, 4.8 DDD were prescribed per 1000 inhabitants per day; the average cost per day of therapy ranges from a minimum of € 8.3 in the Autonomous Province of Trento to € 15.8 in Molise;
- expired-patent medicines represent over half of the doses and 10.7% of the expenditure;
- with the exception of interferons (CV 40%), the other categories do not show a significant regional variability.

Figure 3.1.3a. Medicines for multiple sclerosis, temporal consumption trend (2014-2019)

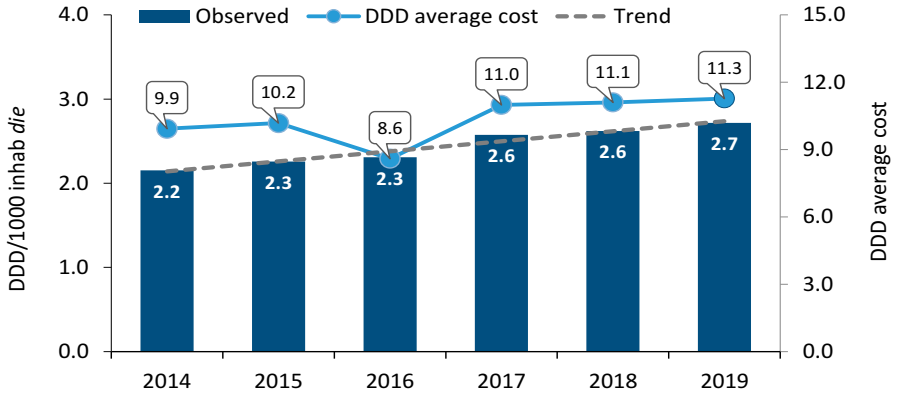


Table 3.1.3a. Medicines for multiple sclerosis, consumption (DDD/1000 inhab. day) by therapeutic category and substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Immunosuppressants	1.2	1.3	1.5	1.7	1.8	1.9	4.2
Monoclonal antibodies	0.1	0.1	0.1	0.1	0.1	0.1	63.0
Fingolimod	0.1	0.1	0.1	0.1	0.1	0.1	3.2
Interferons	0.8	0.7	0.5	0.5	0.5	0.4	-9.2
Teriflunomide	0.0	0.0	0.0	0.1	0.1	0.1	15.8
Glatiramer	0.1	0.1	0.1	0.1	0.1	0.1	1.2
Medicines for multiple sclerosis	**2.2**	**2.3**	**2.3**	**2.6**	**2.6**	**2.7**	**3.6**
fingolimod	0.1	0.1	0.1	0.1	0.1	0.1	3.2
dimethyl fumarate	0.0	0.0	0.0	0.1	0.2	0.2	15.2
natalizumab	0.1	0.1	0.1	0.1	0.1	0.1	3.8
interferon beta 1a	0.7	0.6	0.4	0.5	0.4	0.4	-9.5
ocrelizumab	0.0	0.0	0.0	0.0	0.0	0.0	>100
teriflunomide	0.0	0.0	0.0	0.1	0.1	0.1	15.8
methotrexate	0.8	0.9	1.2	1.2	1.3	1.3	5.0
glatiramer	0.1	0.1	0.1	0.1	0.1	0.1	1.2
peginterferon beta-1	0.0	0.0	0.0	0.0	0.0	0.0	-4.7
alemtuzumab	0.0	0.0	0.0	0.0	0.0	0.0	-47.3

Table 3.1.3b. Medicines for multiple sclerosis, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	2.1	2.2	2.2	2.5	2.6	2.7	4.6
Valle d'Aosta	1.8	2.1	1.9	2.1	2.1	2.3	5.8
Lombardy	2.0	2.1	2.2	2.4	2.5	2.5	0.5
A.P. of Bolzano	2.9	3.0	3.0	3.3	3.4	3.5	4.9
A.P. of Trento	2.5	2.6	2.8	3.1	3.1	3.3	3.9
Veneto	2.1	2.2	2.3	2.6	2.6	2.7	4.6
Friuli VG	3.1	3.2	3.2	3.6	3.5	3.6	3.0
Liguria	1.9	2.0	2.1	2.3	2.4	2.5	2.9
Emilia R.	1.8	2.0	2.0	2.2	2.3	2.4	6.5
Tuscany	1.8	2.1	2.0	2.3	2.2	2.4	9.9
Umbria	2.4	2.5	2.5	2.7	2.7	2.8	2.3
Marche	2.2	2.3	2.3	2.4	2.5	2.6	3.2
Lazio	2.0	2.0	2.1	2.4	2.4	2.4	3.1
Abruzzo	2.3	2.4	2.5	2.8	2.8	3.0	4.1
Molise	2.0	1.9	2.0	2.3	2.3	2.6	16.3
Campania	2.0	2.0	2.1	2.4	2.4	2.5	4.1
Puglia	2.5	2.6	2.7	3.0	3.0	3.1	4.1
Basilicata	2.1	2.3	2.4	2.8	2.8	3.0	7.5
Calabria	2.1	2.2	2.3	2.6	2.7	2.7	-0.5
Sicily	2.2	2.2	2.3	2.6	2.7	2.8	3.6
Sardinia	4.3	4.4	4.2	4.6	4.8	4.8	0.6
Italy	**2.2**	**2.3**	**2.3**	**2.6**	**2.6**	**2.7**	**3.6**

Table 3.1.3c. Medicines for multiple sclerosis, prescription by therapeutic category and substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. day	Δ % 19-18	DDD Average cost	Δ % 19-18
Immunosuppressants	2.98	11.4	1.9	4.2	4.36	6.9
Monoclonal antibodies	2.54	38.4	0.1	63.0	57.75	-15.1
Fingolimod	2.35	3.2	0.1	3.2	54.80	0.0
Interferons	1.91	-12.5	0.4	-9.2	12.31	-3.7
Teriflunomide	0.81	15.2	0.1	15.8	27.18	-0.5
Glatiramer	0.58	-38.4	0.1	1.2	15.97	-39.2
Medicines for multiple sclerosis	**11.17**	**5.2**	**2.7**	**3.6**	**11.27**	**1.5**
fingolimod	2.35	3.2	0.1	3.2	54.80	0.0
dimethyl fumarate	2.22	14.0	0.2	15.2	33.13	-1.1
natalizumab	1.54	3.9	0.1	3.8	56.94	0.1
interferon beta 1a	1.42	-14.4	0.4	-9.5	10.61	-5.5
ocrelizumab	0.84	>100	0.0	>100	49.80	-2.4
teriflunomide	0.81	15.2	0.1	15.8	27.18	-0.5
methotrexate	0.66	6.0	1.3	5.0	1.34	0.9
glatiramer	0.58	-38.4	0.1	1.2	15.97	-39.2
peginterferon beta-1	0.40	-4.6	0.0	-4.7	29.77	0.1
alemtuzumab	0.16	-49.1	0.0	-47.3	>100	-3.4

Table 3.1.3d. Prescription of medicines for multiple sclerosis with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. day	%	Δ % 19-18	DDD average cost
Patent expired	1.19	10.6	66.5	1.4	53.1	10.0	2.25
Generic	0.11	9.2	-7.6	0.3	23.6	-5.5	0.88
Ex originator	1.08	90.8	81.3	1.1	76.4	15.9	2.68
Patent covered	9.98	89.4	0.8	1.3	46.9	-2.8	21.48
Medicines for multiple sclerosis	**11.17**	**100.0**	**5.2**	**2.7**	**100.0**	**3.6**	**11.27**

* source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.1.3b. Medicines for multiple sclerosis, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. day)

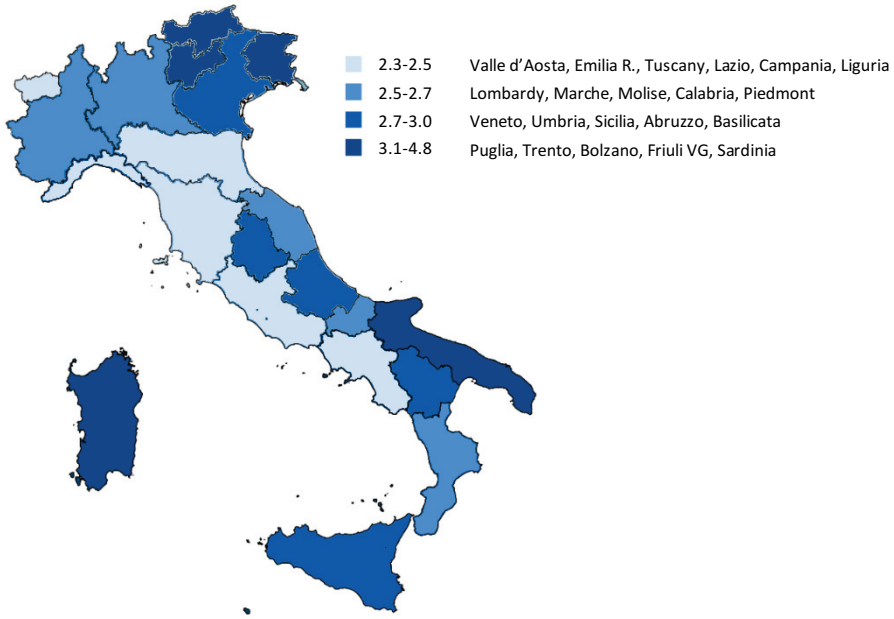


Figure 3.1.3c. Medicines for multiple sclerosis, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviations from national average)

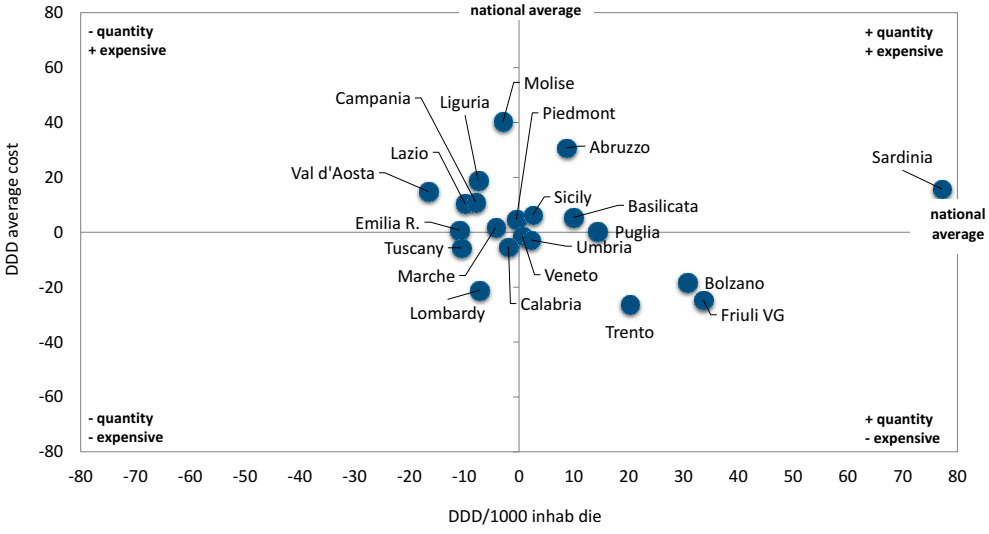
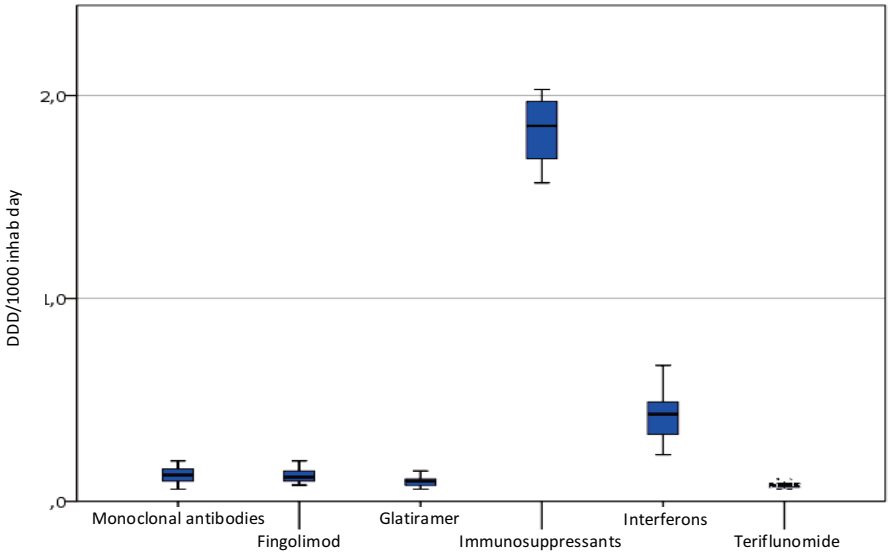


Figure 3.1.3d. Medicines for multiple sclerosis, regional variability of 2019 consumption (weighted DDD/1000 inhab. day) by subgroup

(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)



3.2 Cardiovascular system

Cardiovascular medicines were the third therapeutic category with the highest public expenditure in 2019, accounting for € 3,181 million and 13.7% of total public expenditure. The overall per capita expenditure for these drugs was approximately € 52.71, mainly attributable to NHS outpatient expenditure (€ 47.58 per capita), so recording a decrease if compared to the previous year (-1.6%). On the contrary, the contribution deriving from purchases by public health structures was significantly lower (€ 5.12 per capita) (Table 3.1). Consumption for this category of medicines was 493 DDD/1000 inhabitants per day, with a 1% increase compared to 2018 (Table 3.2), thus confirming the slight increase trend of the last seven years.
The analysis of the medicine utilisation profile by age group and gender confirms the growing use of cardiovascular drugs with increasing age for both genders, with a maximum prevalence recorded in subjects aged 75 and over. Besides, per capita expenditure borne by the NHS also increases with the age of patients, up to € 172.6 per capita in subjects aged 75 and over (€ 183.6 per capita in men and € 165.3 per capita in women).
With regard to NHS outpatient care, expenditure decreased by 3.1% compared to 2018, against a substantial stability of consumption (+0.6%) and a -4.9% drop in prices with a slight shift of prescription towards higher-cost specialties (mix effect: +1.3%; Table 3.9). In 2019 the HMG-CoA reductase inhibitors (statins) remain the active ingredients of the category with the highest per capita expenditure (€ 7.86 per capita), without variations for the plain formulations but with an important reduction in expenditure for fixed combinations with other lipid modifying substances (-37.1%), due to a significant drop in prices (-52.1%) caused by the marketing of generics. The pharmaceuticals which recorded the greatest changes in expenditure compared to 2018 include angiotensin II antagonists in combination (+78.6%), excluding combinations with diuretics and calcium antagonists, attributable to the consumption increase of the sacubitril/valsartan combination. ACE inhibitors, plain or in combination, confirm as the most used medicines (overall 120.1 DDD), followed by angiotensin II inhibitors (sartans), plain and in combination (overall 97.9 DDD), by statins, plain or in combination (overall 82.8 DDD), by dihydropyridine calcium channel blockers (49.7 DDD) and selective beta blockers (38.7 DDD) (Table 3.9). In 2019 atorvastatin confirmed to be the molecule with the highest per capita expenditure (€ 4.26), accounting for 9% of the NHS outpatient expenditure of the category; its consumption shows a 4.5% increase compared to the previous year (Table 3.5). Within the top 30 active ingredients in NHS outpatient expenditure, atorvastatin recorded the highest expenditure (257.3 million), with a 2.6% increase compared to the previous year, ranking second as for consumption, immediately after ramipril, with a value of 62.5 DDD (Tables 3.6 and 3.8). Moreover, it should be noted that in 2019 also nitroglycerin recorded a reduction in expenditure (-14.2%) and in consumption (-14.3%), in line with the previous year's data (Table 3.5). Within the top 30 active ingredients showing the greatest variation in NHS outpatient expenditure, compared to 2018, 9 belong to this category, including olmesartan, which recorded a +23.7% increase in terms of expenditure and a +27.5% increase in terms of consumption (Table 3.7).
With regard to cardiovascular medicines purchased by public health facilities, expenditure increased by 11.6% compared to 2018, with a corresponding increase in consumption by

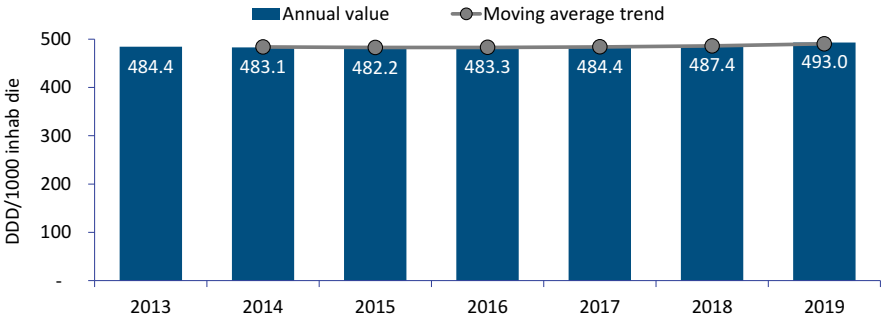
9.9% (Table 3.10). Pharmaceuticals for pulmonary arterial hypertension are the category with the highest per capita expenditure (€ 1.43) and with the highest DDD cost (€ 48.65), despite recording the lowest consumption share.
In 2019, ranolazine was the active ingredient with the highest per capita expenditure (€ 1.24), followed by macitentan, an endothelin receptor antagonist, indicated for the treatment of pulmonary arterial hypertension. Significant expenditure increases were recorded for sacubitril/valsartan (+75.9%) and for the two PCSK-9 inhibitors, evolocumab and alirocumab (+81.9% and +88.1%, respectively). These active ingredients also include other molecules indicated for the treatment of pulmonary arterial hypertension, ambrisentan and riociguat, which contribute by 5.3% and 3.5% respectively to the expenditure for the category. Overall macitentan, ambrisentan and riociguat are responsible for 25.8% of the expenditure for cardiovascular medicines by public health facilities (Table 3.11).
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 hypertension, heart failure and lipid-lowering agents (Tables 3.2.1 and following).
Furthermore, the section dedicated to monitoring registers, focuses on PCSK-9 inhibitors in the treatment of hypercholesterolemia, providing a description of the baseline characteristics of the patients and the related regional distribution (Section 6).

MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

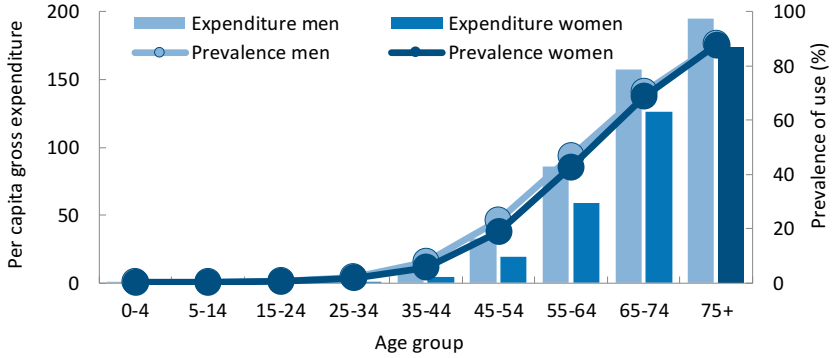
Cardiovascular system

Public expenditure * in millions € (% on total)	**3,181.3**	**(13.7)**
Δ % 2019-2018		-1.8
Regional range of gross per capita expenditure:	35.9	64.2
DDD/1000 inhab. *day (% on total)**	**492.9**	**(42.7)**
Δ % 2019-2018		1.1
Regional range DDD/1000 inhab./day:	372.6	594.7

** Includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure and *per conto* distribution 2019 (Chart and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab./day		
	Men	Women	Total	Men	Women	Total
0-4	0.1	0.2	0.2	0.6	0.6	0.6
5-14	0.1	0.1	0.1	1.0	0.7	0.8
15-24	0.4	0.3	0.3	3.7	2.4	3.1
25-34	1.5	0.8	1.2	14.6	7.6	11.1
35-44	8.0	3.9	5.9	76.5	38.1	57.3
45-54	30.3	17.7	24.0	293.9	175.0	233.8
55-64	79.3	55.1	66.8	766.6	524.4	641.5
65-74	147.2	118.7	132.1	1406.4	1105.9	1247.8
75+	183.6	165.3	172.6	1827.1	1621.8	1703.8

3.2.1 Medicines for hypertension and heart failure

- Consumption of medicines for hypertension and heart failure has remained stable in the last 6 years, reaching a value of 375.1 DDD in 2019; on average the cost per day of therapy is € 0.24, with a 10% reduction compared to 2014;
- Within the most used categories, a stability of consumption was recorded, albeit with a variability between the different geographical areas, in particular with regard to ACE inhibitors (CV 22%) and angiotensin II receptor blockers (CV 21%); as regards the substances, an increase by more than 10% is recorded for olmesartan plain or in combination, whose patent expired between 2017 and 2018;
- Beta blockers is the category with the highest expenditure (€ 5.29 per capita) while ACE inhibitors show the greatest use with 86.7 DDD and the lowest cost per day of therapy (0.12); bisoprolol and ramipril were the most expensive substances in 2019, with respectively € 2.45 and € 2.03; however, while the latter was stable compared to 2018, bisoprolol increased by 6%;
- Consumption varies significantly in the different regions, ranging from a minimum of 282.8 DDD in the Autonomous Province of Bolzano to a maximum of 479.6 DDD in Umbria. Campania, Sicily, Calabria, Puglia and Lazio are the regions recording an average cost per day of therapy and a consumption value above the national average;
- Patent-expired medicines represent 94% of doses and 87.5% of expenditure, with an average cost per day of therapy of € 0.23 compared to 0.50 of patent-covered products;
- A quarter of the Italian population used medicines for hypertension and heart failure in 2019. Use increases with age and is greater in men; in the over 75 age bracket about eight out of 10 people received at least one prescription; moreover, compared to the 35-44 age bracket, consumption was 28 times higher. Each user received on average 10 prescriptions in a year and half of the population is treated with more than 385 doses, so confirming a treatment which includes the combination of more molecules. Only 6.4% of users received a single prescription.

Figure 3.2.1a. Medicines for hypertension and heart failure, temporal consumption trend (2014-2019)

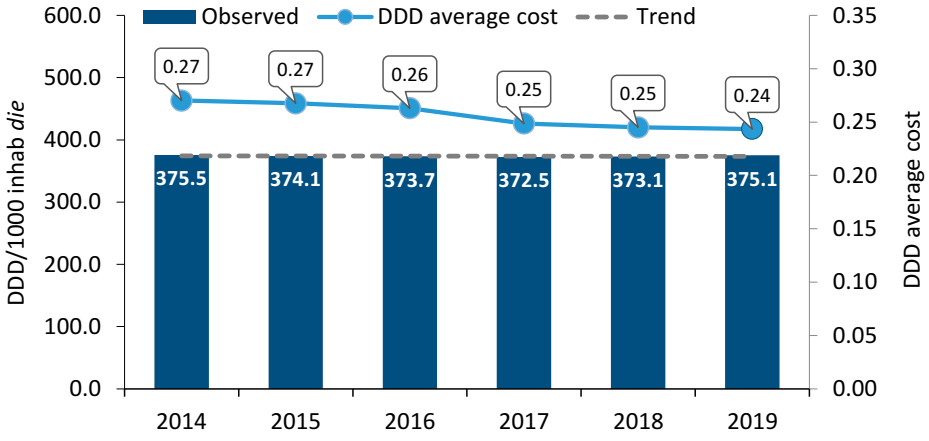


Table 3.2.1a. Medicines for hypertension and heart failure, consumption (DDD/1000 inhab. day) by therapeutic category and substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Beta blockers	41.8	42.2	42.5	43.1	43.6	44.3	1.5
Angiotensin II receptor blockers	56.3	56.2	56.3	56.4	56.9	58.0	1.9
Calcium channel blockers (dihydropyridines)	54.0	52.8	52.2	51.2	50.8	50.9	0.1
Angiotensin II receptor blockers and diuretics (combination)	39.5	38.6	37.8	36.8	36.0	33.5	-7.1
Ace inhibitors	90.4	89.2	88.6	87.4	86.7	86.7	0.0
Ace inhibitors and diuretics (combination)	25.0	23.9	23.0	22.1	21.4	20.7	-3.4
Ace inhibitors and calcium channel blockers (combination)	6.6	8.0	9.6	10.5	11.1	11.9	6.9
Alpha-blockers	7.8	7.7	7.7	7.6	7.6	7.7	0.9
High-ceiling diuretics plain or in combination with potassium-sparing agents	29.7	30.7	30.7	30.5	30.3	31.6	4.1
Angiotensin II receptor blockers and calcium channel blockers (combination)	2.8	3.6	4.2	4.8	5.5	7.0	27.4
Angiotensin II receptor blockers and neprisylin inhibitor	0.0	0.0	0.0	0.1	0.3	0.5	76.6
Beta blockers and diuretics (combination)	6.3	6.7	7.1	7.3	7.4	7.3	-1.8
Potassium-sparing diuretics	3.5	3.5	3.0	3.5	3.5	3.6	1.8
Ace inhibitors, other combinations	0.0	0.0	0.5	1.6	2.7	3.3	23.2
Calcium channel blockers (non dihydropyridines)	3.6	3.3	3.0	2.8	2.5	2.3	-8.0
Thiazide and similars (including combinations)	5.5	5.2	4.9	4.7	4.6	4.2	-9.7
Imidazole receptor agonists	2.2	2.1	2.0	1.9	1.8	1.6	-8.0
Aliskiren plain or in combination	0.5	0.4	0.3	0.3	0.2	0.2	-15.9
Alpha-2 adrenergic receptor agonists	0.1	0.1	0.1	0.1	0.0	0.0	-5.9
Pharmaceuticals acting on arteriolar muscle	0.0	0.0	0.0	0.0	0.0	0.0	-80.9
Medicines for hypertension and heart failure	**375.5**	**374.1**	**373.7**	**372.5**	**373.1**	**375.1**	**0.6**
bisoprolol	8.2	8.9	9.5	10.2	10.9	11.5	5.9
ramipril	62.1	62.7	63.6	63.6	63.9	64.5	1.0
amlodipine	28.2	27.8	27.7	27.4	27.5	28.0	1.7
Olmesartan	7.3	7.7	8.0	8.6	10.2	13.0	27.5
nebivolol	13.5	13.9	14.3	14.7	15.1	15.6	3.2
doxazosin	7.8	7.7	7.7	7.6	7.6	7.6	0.9
oolmesartan/hydrochlorothiazide	6.6	6.9	7.1	7.2	8.1	8.9	9.3
oolmesartan/amlodipine	2.8	3.6	4.2	4.8	5.5	6.8	24.3
barnidipine	4.5	4.6	4.8	4.8	4.7	4.7	0.7
pperindopril/amlodipine	3.9	4.6	4.9	5.0	5.0	5.3	5.9

Table 3.2.1b. Medicines for hypertension and heart failure, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	365.6	362.2	364.0	361.6	359.6	362.8	0.9
Valle d'Aosta	344.2	337.5	322.4	315.5	311.3	307.7	-1.1
Lombardy	357.0	355.8	354.6	351.4	350.8	347.2	-1.0
A.P. of Bolzano	301.4	297.7	293.3	288.6	284.3	282.8	-0.5
A.P. of Trento	334.1	332.1	330.6	330.2	329.8	329.2	-0.2
Veneto	386.0	382.0	375.9	370.9	369.0	369.6	0.2
Friuli VG	384.2	377.7	375.4	376.3	376.2	377.2	0.3
Liguria	348.6	343.7	336.4	331.8	327.7	327.0	-0.2
Emilia R.	414.6	414.7	413.8	409.0	409.0	412.2	0.8
Tuscany	373.6	370.3	367.8	367.1	367.4	373.4	1.6
Umbria	463.8	467.6	471.1	471.6	476.9	479.6	0.6
Marche	372.0	371.4	373.6	370.1	373.2	374.5	0.4
Lazio	374.0	373.3	372.2	374.9	376.5	380.9	1.2
Abruzzo	357.3	356.0	357.7	358.5	361.4	364.3	0.8
Molise	365.4	353.3	350.4	353.4	357.5	365.1	2.1
Campania	378.2	380.9	389.2	393.0	398.1	400.7	0.7
Puglia	388.0	383.7	382.1	380.3	379.1	387.3	2.2
Basilicata	355.0	353.7	356.8	359.2	363.5	368.1	1.3
Calabria	385.0	382.2	382.9	381.9	384.4	387.5	0.8
Sicily	382.4	385.2	387.6	390.5	393.1	399.0	1.5
Sardinia	353.6	350.7	344.3	341.9	341.9	334.2	-2.3
Italy	**375.5**	**374.1**	**373.7**	**372.5**	**373.1**	**375.1**	**0.6**

Table 3.2.1c. Medicines for hypertension and heart failure, prescription by therapeutic category and substance in 2019

Subgroups and substances	Per capita exp.	Δ % 19-18	DDD/1000 inhab. day	Δ % 19-18	DDD Average cost	Δ % 19-18
Beta blockers	5.29	2.9	44.3	1.5	0.33	1.4
Angiotensin II receptor blockers	4.77	5.0	58.0	1.9	0.23	3.0
Calcium channel blockers (dihydropyridines)	4.22	-1.5	50.9	0.1	0.23	-1.6
Angiotensin II receptor blockers and diuretics (combination)	4.04	-6.4	33.5	-7.1	0.33	0.7
Ace inhibitors	3.87	-0.8	86.7	0.0	0.12	-0.9
Ace inhibitors and diuretics (combination)	2.67	-2.8	20.7	-3.4	0.35	0.7
Ace inhibitors and calcium channel blockers (combination)	1.71	4.1	11.9	6.9	0.39	-2.6
Alpha blockers	1.24	0.8	7.7	0.9	0.44	0.0
High-ceiling diuretics plain or in combination with potassium sparing agents	1.05	2.1	31.6	4.1	0.09	-1.9
Angiotensin II receptor blockers and calcium channel blockers (combination)	1.05	-29.4	7.0	27.4	0.41	-44.6
Angiotensin II receptor blockers and neprisylin inhibitor	0.81	76.6	0.5	76.6	4.58	0.0
Beta blockers and diuretics (combination)	0.67	-2.1	7.3	-1.8	0.25	-0.3
Potassium-sparing diuretics	0.56	3.2	3.6	1.8	0.43	1.4
Ace inhibitors, other combinations	0.54	22.0	3.3	23.2	0.45	-1.0
Calcium channel blockers (non dihydropyridines)	0.33	-8.2	2.3	-8.0	0.39	-0.2
Thiazide and similars (including combinations)	0.24	-1.3	4.2	-9.7	0.16	9.3
Imidazole receptor agonists	0.22	-5.0	1.6	-8.0	0.38	3.3
Aliskiren plain or in combination	0.06	-16.7	0.2	-15.9	0.90	-1.0
Alpha-2 adrenergic receptor agonists	0.01	-4.6	0.0	-5.9	0.36	1.4
Pharmaceuticals acting on arteriolar muscle	0.00	-91.9	0.0	-80.9	0.84	-57.6
Medicines for hypertension and heart failure	**33.34**	**-0.1**	**375.1**	**0.6**	**0.24**	**-0.6**
bisoprolol	2.45	6.0	11.5	5.9	0.58	0.1
ramipril	2.03	-0.1	64.5	1.0	0.09	-1.1
amlodipine	1.57	1.2	28.0	1.7	0.15	-0.5
olmesartan	1.50	23.7	13.0	27.5	0.32	-3.0
nebivolol	1.44	2.8	15.6	3.2	0.25	-0.5
doxazosin	1.22	0.9	7.6	0.9	0.44	0.0
olmesartan/ hydrochlorothiazide	1.08	8.6	8.9	9.3	0.33	-0.6
olmesartan/amlodipine	1.03	-30.8	6.8	24.3	0.41	-44.3
barnidipine	0.86	0.3	4.7	0.7	0.50	-0.4
perindopril/amlodipine	0.84	3.5	5.3	5.9	0.43	-2.2

Table 3.2.1d. Prescription of medicines for hypertension and heart failure with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. day	%	Δ % 19-18	DDD Average cost
Patent expired	29.17	87.5	3.5	352.2	93.9	2.1	0.23
Generic	7.45	25.5	3.6	123.7	35.1	2.3	0.17
Ex originator	21.72	74.5	3.5	228.6	64.9	2.0	0.26
Patent covered	4.18	12.5	-19.5	22.9	6.1	-18.3	0.50
Medicines for hypertension and heart failure	**33.34**	**100.0**	**-0.1**	**375.1**	**100.0**	**0.6**	**0.24**

* source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.2.1b. Medicines for hypertension and heart failure, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. day)

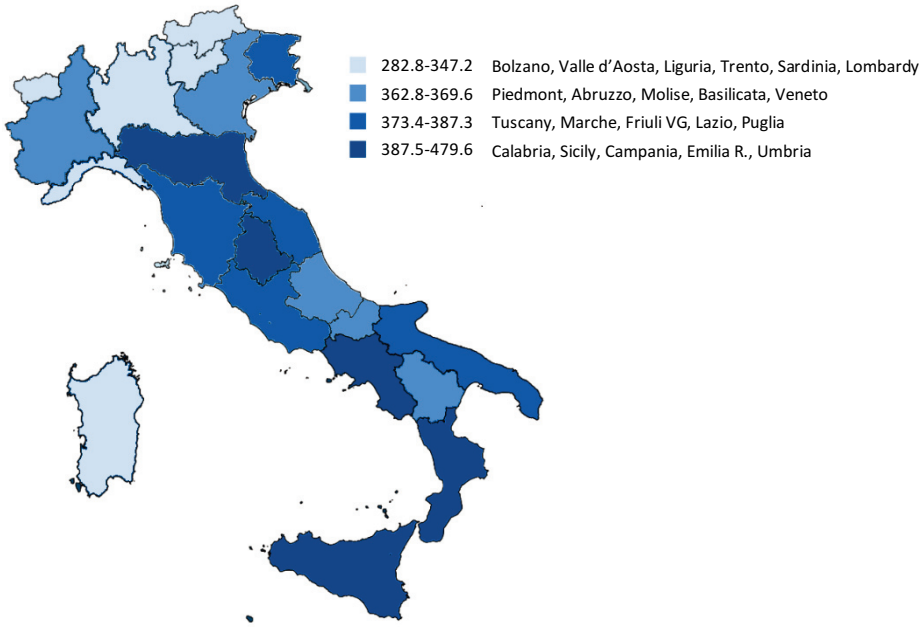


Figure 3.2.1c. Medicines for hypertension and heart failure, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviations from national average)

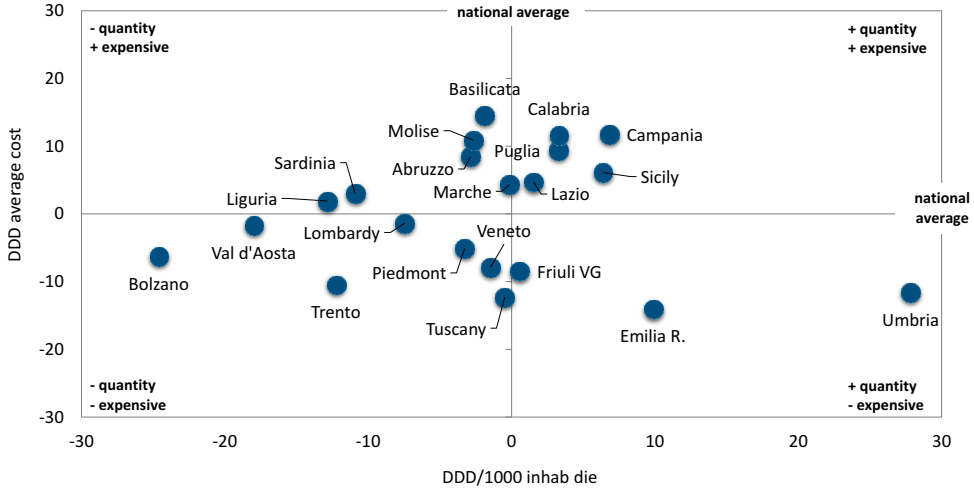


Figure 3.2.1d. Medicines for hypertension and heart failure, regional variability of 2019 consumption (weighted DDD/1000 inhab. day) by subgroup

(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)

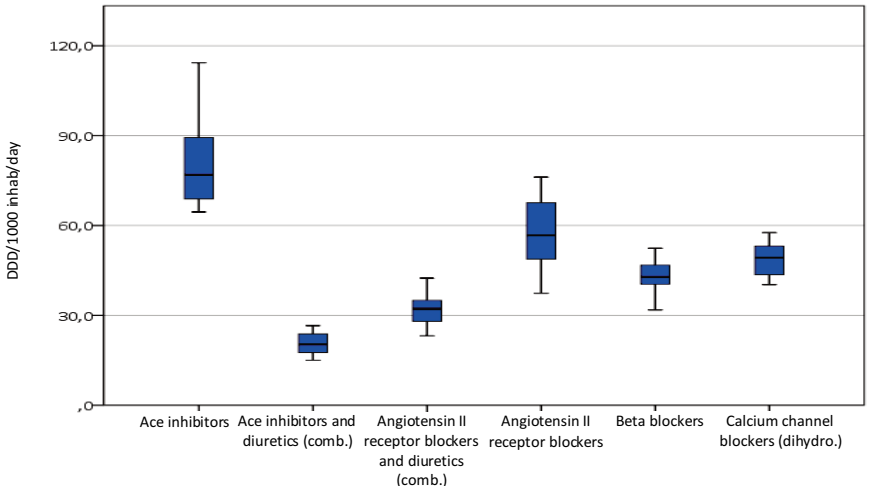


Figure 3.2.1e. Distribution of 2019 prevalence of use and consumption of medicines for hypertension and heart failure under NHS outpatient care

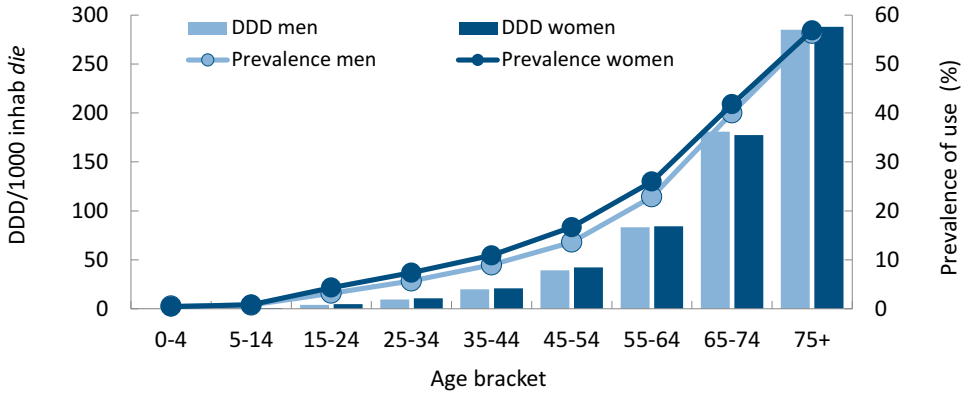


Table 3.2.1e. Duration of therapy with medicines for hypertension and heart failure by geographic area under NHS outpatient care (year 2019)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	8.7	518.3	392.0	6.3
Centre	10.3	517.4	392.0	6.8
South and Islands	10.4	485.7	366.0	6.2
Medicines for hypertension and heart failure	**9.6**	**506.4**	**385.0**	**6.4**

3.2.2 Lipid-lowering agents

- 2019 confirmed the growing trend of lipid-lowering agents with a value of 97.1 DDD (equal to 8.4% of the consumption borne by NHS), increasing by 4.7% compared to 2018 and by 23% compared to 2014; in the last two years the average cost per day of therapy has decreased from € 0.56 in 2017 to € 0.39 in 2019, due to the patent expiry of important molecules such as rosuvastatin, ezetemibe plain or in combination with simavastatin;
- approximately 82% of prescriptions for this category is represented by statins (79.2 DDD), with a 2.2% increase compared to the previous year; significant increases are also recorded for ezetimibe plain or in combination (+25.6%) and especially for PCSK9 inhibitors (+87.0%), mainly caused by evolocumab (+83% of doses); statins are also the category showing the greatest regional differences (min-max 52-91 DDD; CV 13%);
- atorvastatin with 48.1 DDD and € 4.26 per capita is the most used molecule, followed by simvastatin (13.4 DDD and € 1.57) and rosuvastatin (13 DDD and € 1.25);
- regional consumption ranges from a minimum of 64.3 DDD in Valle d'Aosta to a maximum of 111.7 DDD in Campania which, together with Lazio, Puglia, Calabria and Sardinia are the regions using more doses and with the highest average cost;
- in 2019, one out of ten citizens in Italy received at least one prescription of lipid-lowering agents with a marked age trend, reaching around 40% in the ≥75 age bracket; men show a greater level of use and exposure in all age brackets;
- expired-patent drugs represent 97.8% of the doses and 89.3% of the expenditure with an average cost per day of therapy of € 0.35 compared to € 1.90 of patent-covered medicines;
- half of the users were treated for a period of less than 7 months without particular geographical differences; moreover, one user out of 10 received only one prescription during the year. Scientific evidence indicates that, in order to prevent cardiovascular events, these medicines should be taken for long periods and without interruption. These data also show that there are still areas of improvement in clinical practice.

Figure 3.2.2a. Lipid-lowering agents, temporal consumption trend (2014-2019)

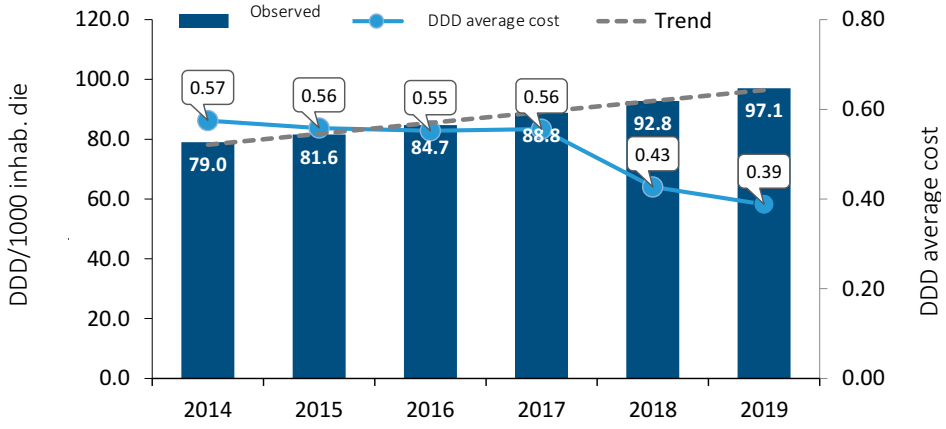


Table 3.2.2a. Lipid-lowering agents, consumption (DDD/1000 inhab. day) by therapeutic category and substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Statins (plain)	67.9	69.8	72.0	74.9	77.4	79.2	2.4
Ezetimibe plain or in combination	4.9	5.5	6.3	7.2	8.3	10.5	25.6
Omega 3	3.6	3.7	3.8	4.1	4.3	4.5	4.4
PCSK9 inhibitors	0.0	0.0	0.0	0.0	0.1	0.2	87.0
Fibrates	2.5	2.6	2.6	2.6	2.7	2.7	1.6
MTP inhibitor	0.0	0.0	0.0	0.0	0.0	0.0	16.6
Statins in combination	0.0	0.0	0.0	0.0	0.0	0.0	>100
Lipid-lowering agents	**79.0**	**81.6**	**84.7**	**88.8**	**92.8**	**97.1**	**4.7**
atorvastatin	33.0	36.2	39.5	43.1	46.0	48.1	4.5
omega 3	3.6	3.7	3.8	4.1	4.3	4.5	4.4
simvastatin	15.7	15.3	15.0	14.6	14.1	13.4	-5.0
rosuvastatin	14.0	13.1	12.5	12.1	12.3	13.0	5.5
ezetimibe	1.4	1.9	2.4	3.0	3.7	4.5	19.6
ezetimibe/simvastatin	3.5	3.7	3.9	4.2	4.4	4.7	5.9
evolocumab	0.0	0.0	0.0	0.0	0.0	0.1	82.8
ezetimibe/rosuvastatin	0.0	0.0	0.0	0.0	0.2	1.3	>100
lovastatin	0.9	1.0	1.1	1.2	1.2	1.2	0.9
fenofibrate	2.3	2.3	2.3	2.4	2.5	2.5	2.1

Table 3.2.2b. Lipid-lowering agents, regional trend of weighted DDD/1000 inhab. day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	66.2	67.8	69.7	72.7	76.3	80.2	5.1
Valle d'Aosta	57.6	58.7	57.4	60.5	63.1	64.3	1.8
Lombardy	72.7	76.2	79.5	83.7	87.7	90.4	3.1
A.P. of Bolzano	59.1	63.4	67.1	70.7	75.1	79.8	6.3
A.P. of Trento	65.1	67.2	70.2	74.6	79.2	84.0	6.1
Veneto	78.5	80.7	84.1	88.0	91.9	96.4	4.8
Friuli VG	81.5	83.5	86.3	90.7	94.4	99.4	5.2
Liguria	67.8	70.0	71.6	74.5	78.2	82.3	5.3
Emilia R.	82.4	86.3	91.2	96.1	99.3	103.8	4.5
Tuscany	71.9	74.4	77.7	81.6	84.5	88.1	4.3
Umbria	72.4	75.2	78.7	83.2	88.6	92.9	4.9
Marche	89.1	92.2	96.3	100.4	104.1	109.2	5.0
Lazio	89.4	87.8	89.1	92.9	96.8	100.9	4.2
Abruzzo	71.2	74.9	78.3	82.6	87.4	91.5	4.7
Molise	67.7	68.1	68.7	73.0	76.2	80.4	5.4
Campania	84.5	89.3	93.5	98.9	105.1	111.7	6.3
Puglia	85.9	89.4	93.0	96.6	99.4	104.3	4.9
Basilicata	74.9	78.2	81.7	87.3	92.5	97.8	5.8
Calabria	84.8	86.3	87.8	91.4	95.1	99.5	4.6
Sicily	83.2	86.2	90.0	94.5	98.9	104.5	5.6
Sardinia	96.9	100.6	101.5	104.6	107.4	110.4	2.8
Italy	**79.0**	**81.6**	**84.7**	**88.8**	**92.8**	**97.1**	**4.7**

Table 3.2.2c. Lipid-lowering agents, prescription by therapeutic category and substance in 2019

Subgroups and substances	Per capita exp.	Δ % 19-18	DDD/1000 inhab. day	Δ % 19-18	DDD Average cost	Δ % 19-18
Statins (plain)	7.86	-0.5	79.2	2.4	0.27	-2.8
Ezetimibe plain or in combination	2.72	-28.1	10.5	25.6	0.71	-42.8
Omega 3	1.90	1.7	4.5	4.4	1.16	-2.6
PCSK9 inhibitors	0.76	84.5	0.2	87.0	12.41	-1.3
Fibrates	0.38	1.3	2.7	1.6	0.38	-0.3
MTP inhibitor	0.12	8.0	0.0	16.6	1,047.91	-7.3
Statins in combination	0.00	>100	0.0	>100	0.41	-17.8
Lipid-lowering agents	**13.75**	**-4.9**	**97.1**	**4.7**	**0.39**	**-9.1**
atorvastatin	4.26	3.9	48.1	4.5	0.24	-0.6
omega 3	1.90	1.7	4.5	4.4	1.16	-2.6
simvastatin	1.57	-5.0	13.4	-5.0	0.32	0.0
rosuvastatin	1.25	-2.4	13.0	5.5	0.26	-7.5
ezetimibe	1.22	-12.4	4.5	19.6	0.75	-26.8
ezetimibe/simvastatin	1.13	-51.7	4.7	5.9	0.66	-54.4
evolocumab	0.43	81.8	0.1	82.8	15.33	-0.5
ezetimibe/rosuvastatin	0.37	>100	1.3	>100	0.76	-9.9
lovastatin	0.37	-13.7	1.2	0.9	0.82	-14.4
fenofibrate	0.35	1.8	2.5	2.1	0.38	-0.3

Table 3.2.2d. Prescription of lipid-lowering agents with patent expired* in 2019

Categories	Per capita exp.	%	Δ % 19-18	DDD/1000 inhab. day	%	Δ % 19-18	DDD Average cost
Patent expired	12.28	89.3	9.0	95.0	97.8	7.7	0.35
Generic	4.05	33.0	20.2	37.4	39.4	11.9	0.30
Ex originator	8.22	67.0	4.3	57.5	60.6	5.2	0.39
Patent covered	1.47	10.7	-53.9	2.1	2.2	-53.9	1.90
Lipid-lowering agents	**13.75**	**100.0**	**-4.9**	**97.1**	**100.0**	**4.7**	**0.39**

* source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.2.2b. Lipid-lowering agents, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. day)

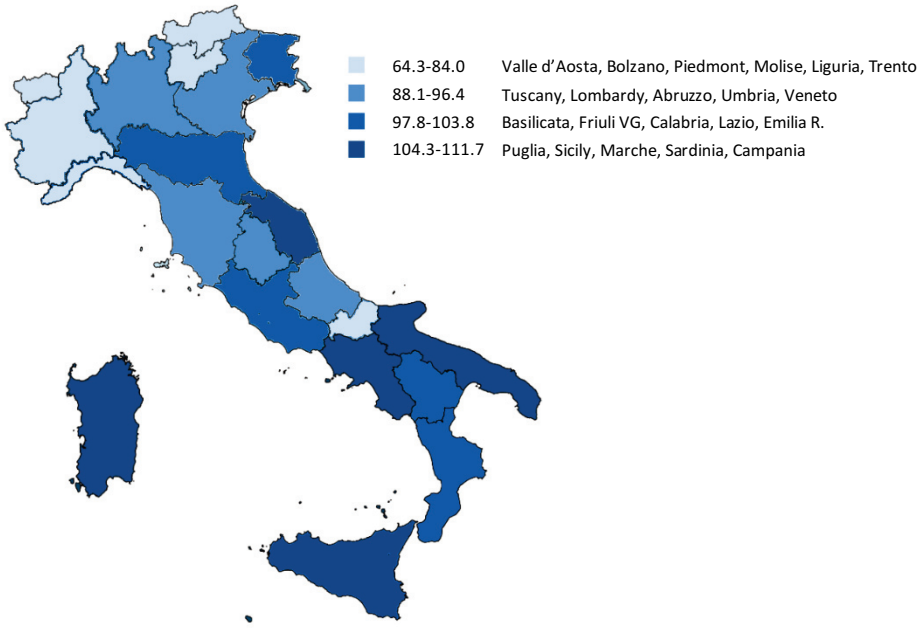


Figure 3.2.2c. Lipid-lowering agents, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviations from national average)

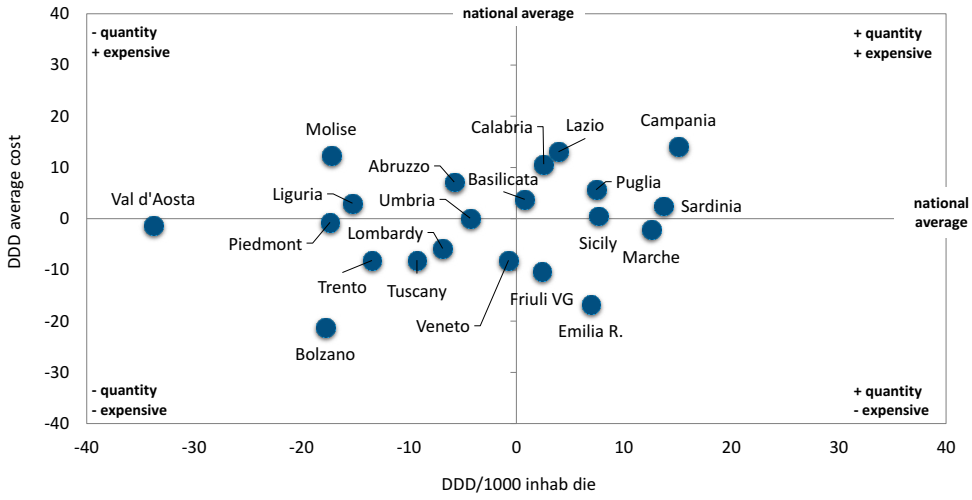


Figure 3.2.2d. Lipid-lowering agents, regional variability of 2019 consumption (weighted DDD/1000 inhab. day) by subgroup

(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)

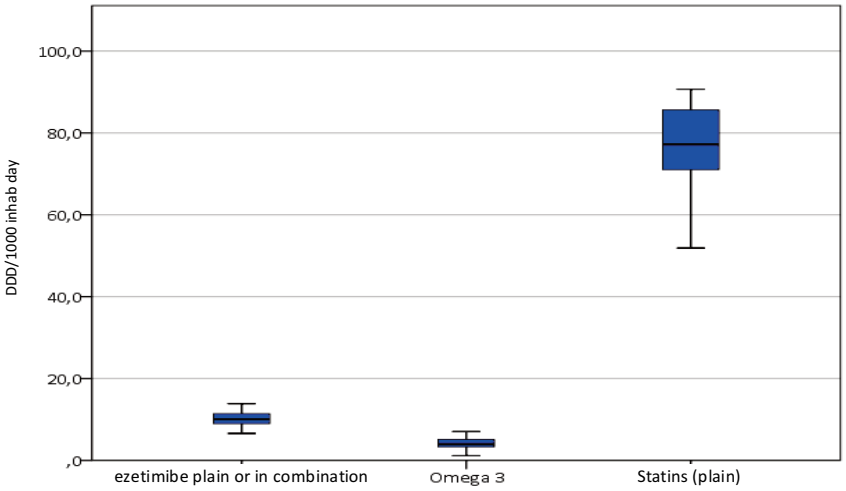


Figure 3.2.2e. Distribution of 2019 prevalence of use and consumption of lipid-lowering agents under NHS outpatient care

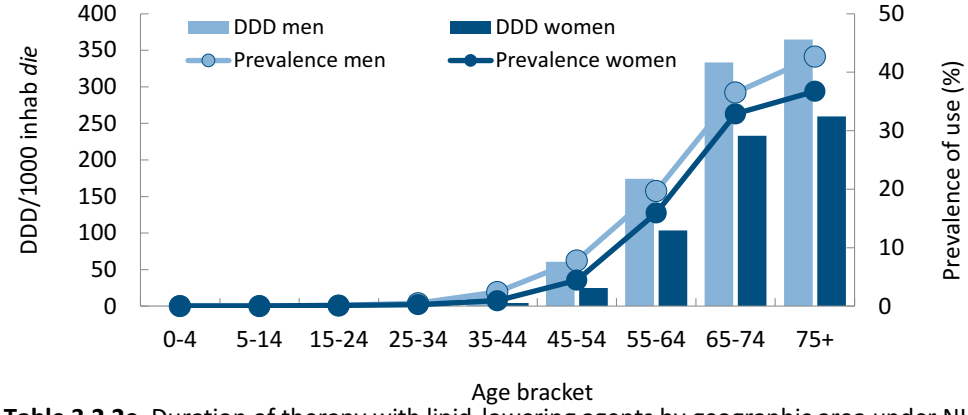


Table 3.2.2e. Duration of therapy with lipid-lowering agents by geographic area under NHS outpatient care (year 2019)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	5.4	292.3	224.0	9.3
Centre	6.3	281.6	224.0	10.0
South and Islands	6.6	271.2	224.0	10.2
Lipid-lowering agents	**6.0**	**282.2**	**224.0**	**9.7**

3.3 General antimicrobials for systemic use

General antimicrobials for systemic use are the second therapeutic category with the highest public expenditure for 2019, amounting to € 3,394 million and 14.6% of total expenditure. The total per capita expenditure for these medicines was € 56.23, mainly justified by the expenditure deriving from the purchase of these medicines by public health structures (€ 43.72 per capita), a sharp increase over the previous year (+ 24.5%). On the contrary, the amount of NHS outpatient pharmaceutical expenditure is lower (€ 12.51 per capita) (Table 3.1).
Consumption for this category of medicinal products was 23 DDD/1000 inhabitants per day, down 2.1% compared to 2018 (Table 3.2), confirming the downward trend of recent years.
The medicine utilization profile analysis by age group and gender, including NHS outpatient pharmaceuticals and *per conto* distribution, confirms a greater consumption of antimicrobials in extreme age groups, with a higher level of utilisation in the first four years of life (16.6 DDD in males and 14.9 DDD in females in the population in this age group) and in people aged over 75 (26.7 DDD in the population in this age group). A more frequent use of antimicrobials in women in the intermediate age groups is also confirmed. At the same time, the per capita NHS expenditure also increases with the age of patients, reaching the maximum level of € 26.0 and € 22.8 per capita in men and women respectively over 75 years of age.
As regards the NHS outpatient expenditure, the per capita expenditure was equal to € 12.51, with a 4.3% decrease compared to 2018. This change is due to a decrease in consumption (-3.1%); prices remain substantially stable, while the mix effect records a value of + 1.6% (Table 3.9). Within this supply method, third generation cephalosporins are the category with the highest expenditure (€ 3.12), recording an overall increase in consumption (+7.6%), immediately followed by the association of penicillins, including beta lactamases, which have a per capita expenditure of € 2.99. Amoxicillin in association with clavulanic acid appears to be the first active ingredient in the category per capita expenditure (€ 2.87) and consumption (5.8 DDD) (Table 3.5), as well as being the only active ingredient together with ceftriaxone to be among the top 30 molecules with the greatest impact on the NHS outpatient expenditure (Table 3.6). On the other hand, among the top 30 active ingredients with the greatest variation in NHS outpatient expenditure, we find cefixime with an increase in expenditure of 7.9% and fosfomycin (+ 6.8%).
Conversely, as for purchases by public health structures, there was a significant increase in spending (+24.4%) compared to 2018, against a slight increase in consumption (+0.5%) (Table 3.11). However, this figure is affected by the fact that in the calculations of the expenditure incurred by public health structures in 2019 it was not possible to take account of mechanisms for reducing expenditure through credit notes relating in particular to the medicinal specialties sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir.
For this reason, in fact, in the purchases by public health structures, the anti-HCV association sofosbuvir/velpatasvir represents the first active principle in terms of expenditure (€ 751.9 million), with a value per capita of € 12.46. The data relating to the increase in per capita expenditure (+448.6%) (Table 3.11) and average cost per DDD (+654.84%; Table 3.11) compared to the previous year cannot be interpreted as it compares the actual expenditure in 2018 calculated net of all price reduction mechanisms compared

to that in 2019 which does not consider the return via credit notes. As part of the first thirty active ingredients for expenditure on medicines purchased from public health facilities, there are also 5 other antimicrobial drugs represented by glecaprevir/pibrentasvir, two antivirals for HIV (emtricitabine/rilpivirine/tenofovir alafenamide and dolutegravir) and two vaccines (group B meningococcal and adsorbed conjugated saccharide pneumococcal) (Table 3.12).

In addition, 6 active ingredients are also present in the ranking of the top 30 active ingredients with greater variation in expenditure: sofosbuvir/velpatasvir (+448.6%), sofosbuvir/velpatasvir/voxilaprevir (+340.6%), flu vaccine inactivated (+33.9%) emtricitabine/rilpivirine/tenofovir alafenamide (+30.7%), human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58) (+30,1%), dolutegravir (+29%) (Table 3.13).

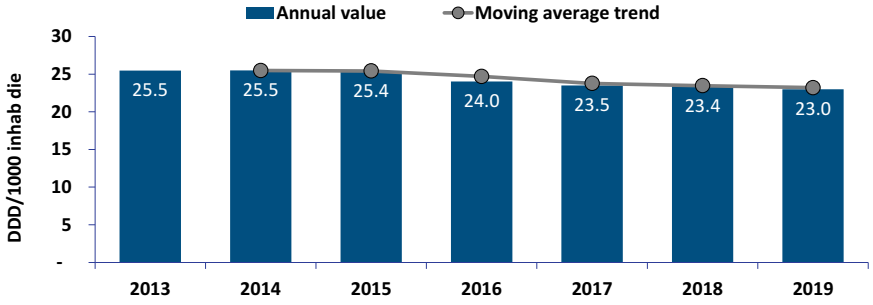
For further information on the use of medicinal products of the same therapeutic area, analyses have been developed on the historical series of consumption by active ingredient and by Region and on the efficiency in the use of resources according to the presence of patent-expired pharmaceuticals and on a regional basis. Such analyses focused on antibiotic, anti-HIV antivirals, anti-HCV medicinal products and vaccines (Table 3.3.1 and following).

MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

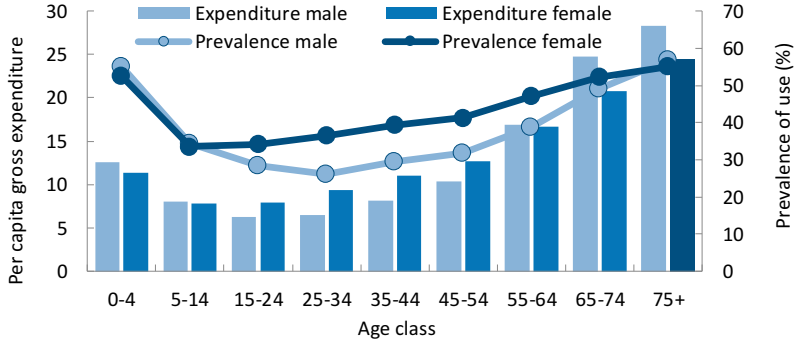
Antimicrobials for systemic use

NHS expenditure, millions €* (% on the total)	**3,394.0**	**(14.6)**
Δ % 2019-2018		16.4
Gross per capita expenditure, range among regions:	37.3	64.3
DDD/1000 inhab./day* (% on the total)	**22.9**	**(2.0)**
Δ % 2019-2018		-2.1
DDD/1000 inhab./day, range among regions:	14.8	27.5

** Includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure and *per conto* distribution 2019 (Chart and Table)



Age (group)	Gross per capita expenditure			DDD/1000 inhab./day		
	Men	Women	Total	Men	Women	Total
0-4	11.5	10.3	10.9	16.6	14.9	15.8
5-14	8.3	8.0	8.1	12.6	12.0	12.3
15-24	6.1	7.6	6.8	10.2	11.9	11.0
25-34	6.0	8.8	7.4	9.2	13.0	11.1
35-44	7.2	10.3	8.8	11.0	15.0	13.0
45-54	8.9	11.7	10.3	12.6	16.4	14.5
55-64	14.1	15.3	14.7	17.3	20.3	18.9
65-74	21.5	19.1	20.2	24.7	24.1	24.4
75+	26.0	22.8	24.1	29.0	25.2	26.7

3.3.1 Antibiotics

- Antibiotic resistance has now become a threat to public health worldwide. Both WHO and the main international and national institutions have defined intervention programs aimed at reducing the consumption of antibiotics in the human and veterinary fields;
- in the last 6 years there has been a constant decrease (CAGR: -2%) in the consumption of antibiotics, which have gone from 19.7 DDD in 2014 to 17.5 DDD in 2019;
- associations of penicillins, almost entirely represented by amoxicillin+clavulanic acid, were the category with the highest prescription and in 2019 they produced an expenditure of € 3.64 per capita and 6.3 DDD per 1000 inhabitants, followed by cephalosporins of third generation with € 3.59 and 2.3 DDD (+ 6.8% compared to 2018). It should be remembered that this category has a greater risk of inducing resistances and should be used as a second choice treatment. The prescription of fluoroquinolones, a category subject to a restriction of use by EMA in November 2018, decreased by more than 27%;
- amoxicillin+clavulanic acid, a broad-spectrum drug widely used in the paediatric field, was the molecule with the greatest use with 6.2 DDD, followed by ceftriaxone and cefixime. Phosphomycin, although little used (0.4 DDD), shows a 7.1% growth;
- consumption varies from 10.6 DDD in the PA of Bolzano to 23.0 DDD in Campania, which shows a reduction of about 7% compared to 2018. Most of the Central-South regions have a number of doses and average cost per day of therapy above the national average while, at the opposite, those in the North have a lower consumption and average cost;
- about 4 out of 10 people received at least one prescription for antibiotics during 2019, with higher use levels in children up to 4 years of age and in people over 75 years of age, where the prevalence exceeds 50%; one user out of two receives only one prescription in the year and, as expected, for a short period (15 days).

Figure 3.3.1a. Antibiotics, temporal consumption trend (2014-2019)

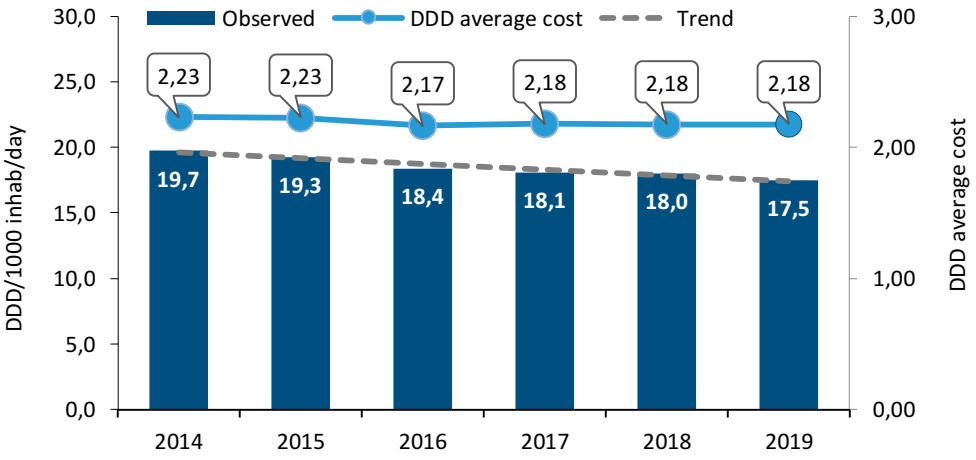


Table 3.3.1a. Antibiotics, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Penicillin associations (including beta-lactamase inhibitors)	6.5	6.4	6.3	6.3	6.3	6.3	0.5
Third generation Cephalosporins	2.1	2.1	2.0	2.0	2.1	2.3	6.8
Macrolides and Lincosamides	4.3	4.1	3.9	3.7	3.7	3.7	1.4
Fluoroquinolones	3.5	3.5	3.2	3.1	3.0	2.2	-27.4
Other antibacterials	0.4	0.4	0.4	0.4	0.4	0.5	8.4
Glycopeptides	0.1	0.1	0.1	0.1	0.1	0.1	1.1
Broad-spectrum penicillins	1.6	1.5	1.4	1.3	1.2	1.2	-1.1
Other Cephalosporins and penems	0.0	0.0	0.0	0.0	0.0	0.0	45.7
Carbapenems	0.1	0.0	0.0	0.0	0.0	0.1	10.3
Tetracyclines	0.3	0.3	0.3	0.3	0.3	0.4	4.1
Aminoglycosides	0.1	0.1	0.1	0.1	0.1	0.1	-15.5
Polymyxin	0.0	0.0	0.0	0.0	0.0	0.0	-3.1
First generation Cephalosporins	0.1	0.1	0.1	0.1	0.1	0.1	3.9
Second generation Cephalosporins	0.3	0.3	0.2	0.2	0.2	0.2	2.8
Sulfonamides alone and in association	0.3	0.3	0.3	0.3	0.4	0.4	14.2
Fourth generation Cephalosporins	0.0	0.0	0.0	0.0	0.0	0.0	-13.8
Monobactams	0.0	0.0	0.0	0.0	0.0	0.0	1.2
Imidazole derivatives	0.0	0.0	0.0	0.0	0.0	0.1	41.3
beta-lactamase sensitive Penicillins	0.0	0.0	0.0	0.0	0.0	0.0	8.7
Beta-lactamase resistant Penicillins	0.0	0.0	0.0	0.0	0.0	0.0	-36.4
Amphenicols	0.0	0.0	0.0	0.0	0.0	0.0	-7.4
Other Quinolones	0.0	0.0	0.0	0.0	0.0	0.0	-79.2
Nitrofuran derivatives	0.0	0.0	0.0	0.0	0.0	0.0	2.7
Antibiotics	**19.7**	**19.3**	**18.4**	**18.1**	**18.0**	**17.5**	**-2.8**
amoxicillin/clavulanic acid	6.4	6.3	6.1	6.2	6.2	6.2	0.1
ceftriaxone	0.5	0.5	0.5	0.5	0.5	0.5	0.0
cefixime	1.0	1.0	1.0	1.0	1.1	1.2	8.5
fosfomycin	0.4	0.4	0.4	0.4	0.4	0.4	7.1
clarithromycin	2.7	2.6	2.4	2.3	2.2	2.2	1.1
azithromycin	1.4	1.4	1.3	1.3	1.3	1.4	2.9
ciprofloxacin	1.2	1.2	1.2	1.1	1.0	0.8	-23.2
levofloxacin	1.9	1.9	1.8	1.7	1.7	1.2	-30.0
piperacillin/tazobactam	0.1	0.1	0.1	0.1	0.1	0.1	24.3
daptomycin	0.0	0.0	0.0	0.0	0.0	0.0	27.5

Table 3.3.1b. Antibiotics, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	16.4	16.1	15.1	14.8	15.1	14.6	-3.6
Valle d'Aosta	16.9	16.8	14.7	14.8	15.3	14.7	-3.9
Lombardy	16.1	16.0	15.2	15.0	15.1	14.5	-3.6
A.P. of Bolzano	12.2	12.0	11.1	10.9	11.2	10.6	-5.3
A.P. of Trento	16.4	16.2	15.1	15.6	15.5	15.1	-2.9
Veneto	15.8	15.1	14.2	14.3	14.3	14.1	-1.2
Friuli VG	14.9	14.8	13.8	14.5	14.2	14.0	-1.7
Liguria	14.4	14.2	13.1	13.5	13.7	13.3	-3.3
Emilia R.	17.7	17.0	16.2	15.9	16.1	16.0	-0.8
Tuscany	18.9	18.9	17.9	17.4	17.0	16.4	-3.3
Umbria	22.2	21.5	20.7	20.5	20.5	20.5	0.1
Marche	21.3	20.5	20.1	19.6	19.8	19.4	-1.7
Lazio	21.3	20.8	19.7	19.5	19.4	19.4	0.3
Abruzzo	22.8	22.3	21.9	21.5	22.3	22.0	-1.1
Molise	22.2	21.3	19.8	19.0	19.4	19.2	-1.3
Campania	27.1	26.6	25.9	24.7	24.7	23.0	-6.9
Puglia	26.1	25.3	24.5	22.8	21.8	21.5	-1.4
Basilicata	23.1	21.9	20.8	20.9	20.6	20.4	-0.8
Calabria	24.3	23.6	22.6	22.6	21.9	21.4	-2.2
Sicily	22.6	21.7	21.0	21.0	21.0	20.3	-3.0
Sardinia	18.1	17.8	16.3	16.6	16.5	15.5	-6.1
Italy	**19.7**	**19.3**	**18.4**	**18.1**	**18.0**	**17.5**	**-2.8**

Table 3.3.1c. Antibiotics, prescription by therapeutic category and by substance in 2019

Subgroups and substances	per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Penicillin associations (including beta-lactamase inhibitors)	3.64	4.0	6.3	0.5	1.57	3.5
Third generation Cephalosporins	3.59	6.5	2.3	6.8	4.34	-0.3
Macrolides and Lincosamides	1.59	0.1	3.7	1.4	1.17	-1.2
Fluoroquinolones	1.56	-26.0	2.2	-27.4	1.98	1.9
Other antibacterials	1.18	3.3	0.5	8.4	7.18	-4.7
Glycopeptides	0.43	-16.5	0.1	1.1	18.90	-17.4
Broad-spectrum penicillins	0.31	3.2	1.2	-1.1	0.69	4.3
Other Cephalosporins and penems	0.25	40.6	0.0	45.7	180.94	-3.5
Carbapenems	0.24	-1.5	0.1	10.3	13.17	-10.7
Tetracyclines	0.22	-50.4	0.4	4.1	1.72	-52.3
Aminoglycosides	0.20	-1.9	0.1	-15.5	11.03	16.1
Polymyxin	0.20	-2.7	0.0	-3.1	36.39	0.4
First generation Cephalosporins	0.13	2.9	0.1	3.9	3.05	-0.9
Second generation Cephalosporins	0.13	3.7	0.2	2.8	1.81	0.9
Sulfonamides alone and in association	0.08	13.0	0.4	14.2	0.54	-1.0
Fourth generation Cephalosporins	0.07	-12.5	0.0	-13.8	22.62	1.5
Monobactams	0.04	1.2	0.0	1.2	88.12	0.0
Imidazole derivatives	0.02	34.7	0.1	41.3	0.99	-4.7
beta-lactamase sensitive Penicillins	0.01	11.8	0.0	8.7	51.79	2.9
Beta-lactamase resistant Penicillins	0.01	-49.8	0.0	-36.4	2.02	-21.0
Amphenicols	0.00	1.2	0.0	-7.4	6.64	9.3
Other Quinolones	0.00	-78.9	0.0	-79.2	0.69	1.4
Nitrofuran derivatives	0.00	1.7	0.0	2.7	0.30	-0.9
Antibiotics	**13.90**	**-2.7**	**17.5**	**-2.8**	**2.18**	**0.0**
amoxicillin/clavulanic acid	3.01	0.7	6.2	0.1	1.33	0.6
ceftriaxone	1.36	-0.5	0.5	0.0	7.02	-0.5
cefixime	0.97	8.1	1.2	8.5	2.28	-0.3
fosfomycin	0.75	10.8	0.4	7.1	5.11	3.4
clarithromycin	0.75	0.0	2.2	1.1	0.91	-1.1
azithromycin	0.71	1.9	1.4	2.9	1.43	-1.0
ciprofloxacin	0.69	-23.4	0.8	-23.2	2.37	-0.3
levofloxacin	0.65	-27.5	1.2	-30.0	1.51	3.5
piperacillin/tazobactam	0.60	22.5	0.1	24.3	12.70	-1.4
daptomycin	0.36	-0.5	0.0	27.5	38.48	-22.0

Table 3.3.1d. Prescription of antibiotics with patent expired* in 2019

Categories	per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	9.66	69.5	-3.7	15.5	88.4	-3.3	1.71
Generic	2.07	21.4	-7.0	3.8	24.6	-7.4	1.49
Ex originator	7.59	78.6	-2.8	11.7	75.4	-1.9	1.78
Patent covered	4.24	30.5	-0.3	2.0	11.6	1.3	5.70
Antibiotics	**13.90**	**100.0**	**-2.7**	**17.5**	**100.0**	**-2.8**	**2.18**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.3.1b. Antibiotics, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

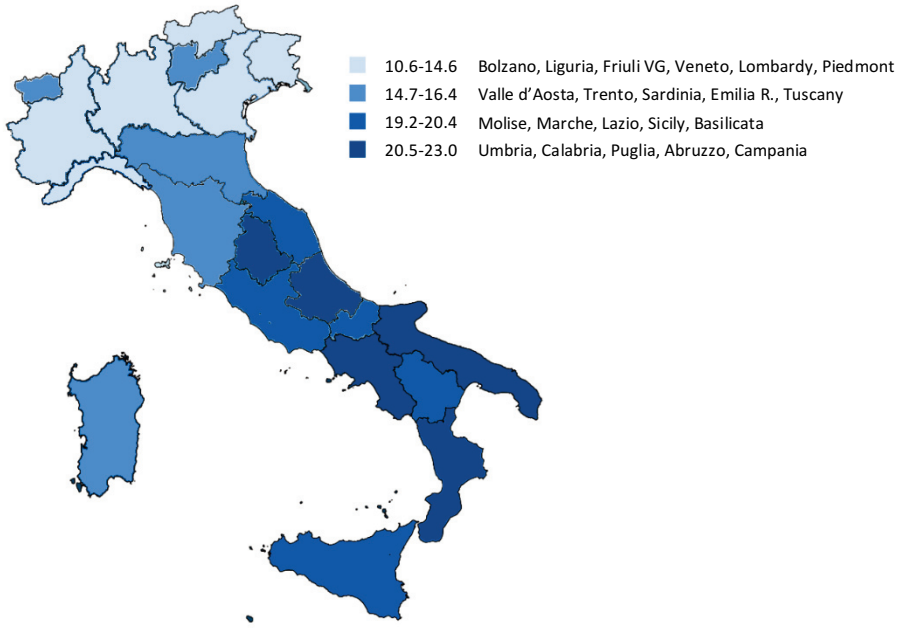


Figure 3.3.1c. Antibiotics, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

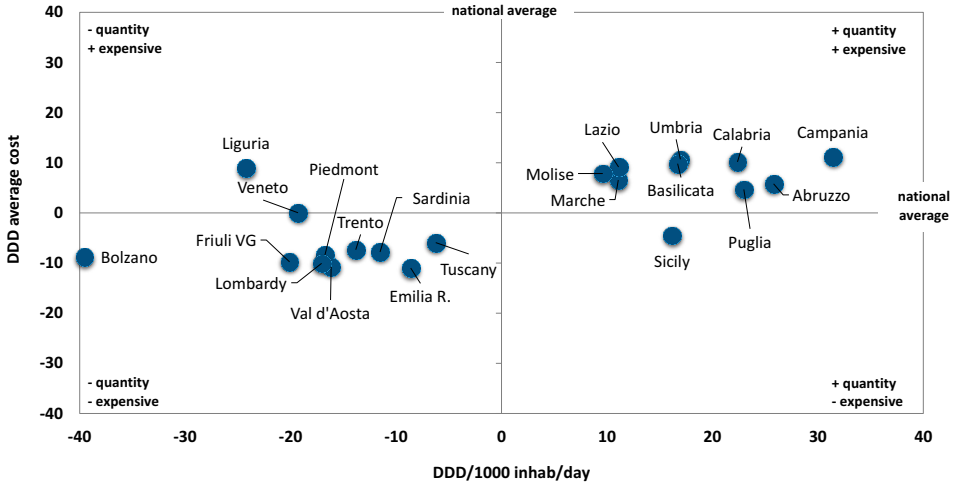


Figure 3.3.1d. Antibiotics, regional variability of consumption in 2019 (weighted DDD/1000 inhab./day) by subgroup

(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 maximum).

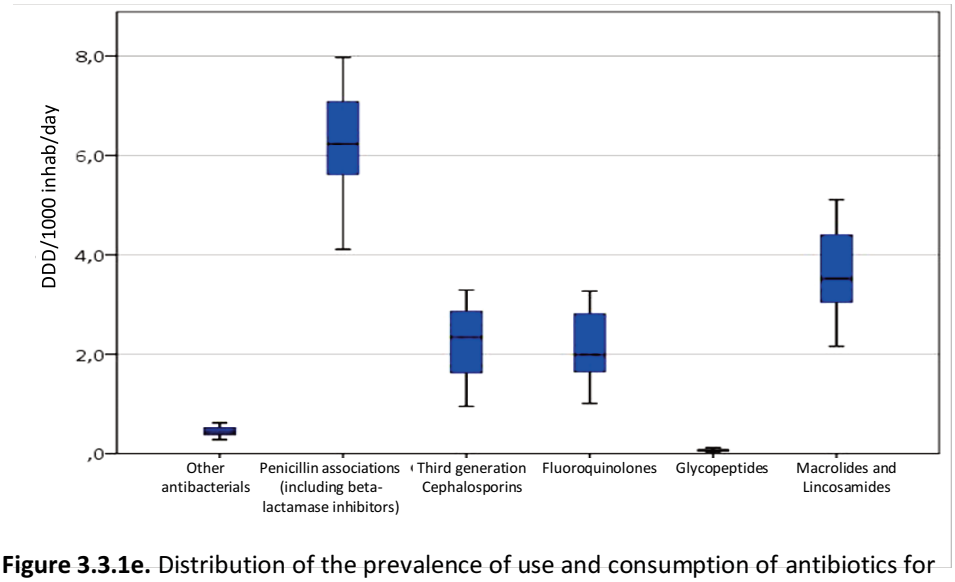


Figure 3.3.1e. Distribution of the prevalence of use and consumption of antibiotics for NHS outpatient expenditure in 2019

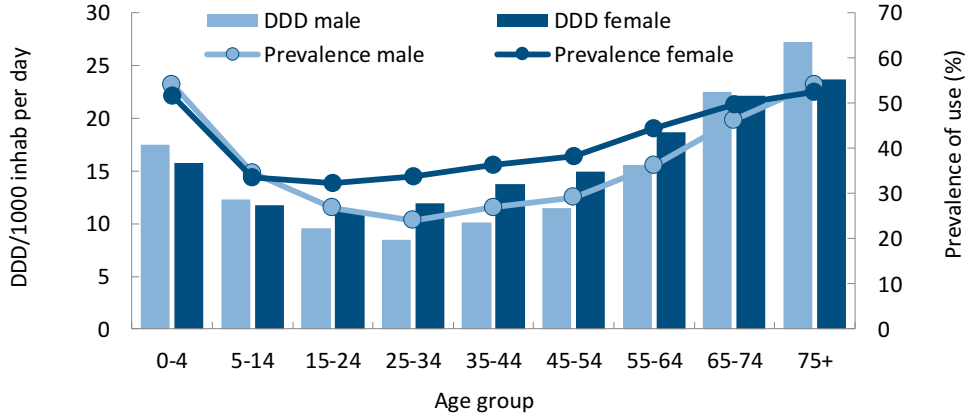


Table 3.3.1e. Duration of antibiotic therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	Users with 1 prescription
North	1.8	14.1	10.0	58.1
Centre	2.1	15.1	10.0	51.3
South and Islands	2.3	15.1	10.0	47.8
Antibiotics	**2.1**	**14.7**	**10.0**	**52.5**

3.3.2 Anti-HIV antivirals

- Acquired Immunodeficiency Syndrome represents the terminal clinical stage of the infection caused by the Human Immunodeficiency Virus (HIV), which belongs to a particular viral family, that of retroviruses, which has an absolutely unique replicative mechanism. The spread of HIV has decreased thanks to the use of drugs with powerful antiviral activity. A highly effective therapy, called HAART (Highly Active Anti-Retroviral Therapy), is currently offered to HIV-positive people. It consists of the combination of various antiretroviral drugs;
- in 2019 the expenditure of anti-HIV antiviral drugs decreased by 6.6%, this trend was mainly determined by a reduction in the average DDD cost of 8.2% against an increase in doses of 1.7 %;
- antivirals in co-formulated regimens represent 52% of the expenditure of this category with an increase of 4.8% compared to the previous year, also the integrase inhibitors show an increase of over 17% while both the nucleoside and nucleotide reverse transcriptase inhibitors as well as the protease inhibitors alone or in association are decreased by more than 30%;
- the combination emtricitabine/rilpivirine/tenofovir alafenamide with € 1.72 per capita and an increase of 30.7% ranks first; recent studies have shown the safety of the switch from emtricitabine/rilpivirine/tenofovir disoproxil or from efavirenz/emtricitabine/ tenofovir disoproxil towards this association. In second place for spending is dolutegravir (€ 1.51; +29% compared to 2018) followed by dolutegravir/abacavir /lamivudine (€ 1.43; -5.4%);
- with the exception of Valle d'Aosta (+ 7%) and the Autonomous Province of Bolzano (+7.45), in all regions there is a decrease in expenditure, with a wide variability ranging from a minimum of € 4.02 in Molise to a maximum of € 18.93 in Lombardy; the latter together with Lazio and Tuscany is the one with a number of doses and a cost which are higher than the national average;
- the medicinal products still covered by the patent represent a significant share (83.5%) of the use in this category and 97.9% of the expenditure.

Figure 3.3.2a. Anti-HIV antivirals, temporal trend of per capita expenditure (2014-2019)

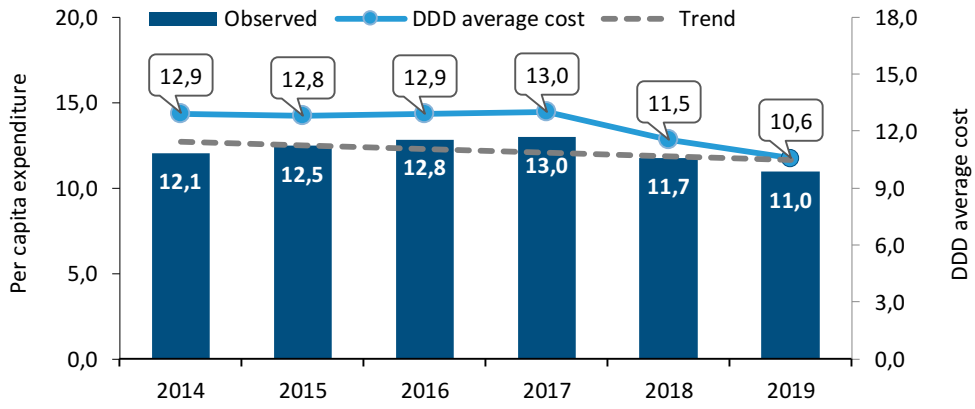


Table 3.3.4a. HIV antivirals, per capita expenditure by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Anti-HIV antivirals in co-formulated regimens	5.3	5.5	5.8	5.9	5.5	5.7	4.8
Integrase inhibitors	0.9	1.3	1.6	1.7	1.8	2.2	17.1
Nucleoside and nucleotide reverse transcriptase inhibitors	2.1	2.2	2.3	2.7	2.1	1.4	-33.8
Protease inhibitors alone and in association	2.9	2.7	2.4	2.1	1.8	1.2	-31.8
Non-nucleoside reverse transcriptase inhibitors	0.6	0.5	0.5	0.4	0.3	0.3	-6.6
Other anti-HIV antivirals	0.3	0.3	0.2	0.2	0.2	0.1	-24.1
Anti-HIV antivirals	**12.1**	**12.5**	**12.8**	**13.0**	**11.7**	**11.0**	**-6.6**
emtricitabine/rilpivirine/tenofovir alafenamide	0.0	0.0	0.0	0.2	1.3	1.7	30.7
dolutegravir	0.0	0.3	0.7	0.9	1.2	1.5	29.0
dolutegravir/abacavir/lamivudine	0.0	0.0	0.3	1.1	1.5	1.4	-5.4
elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	0.0	0.0	0.0	0.5	1.4	1.4	-4.1
emtricitabine/tenofovir alafenamide	0.0	0.0	0.0	0.4	1.1	0.9	-16.9
raltegravir	0.9	0.9	0.9	0.8	0.7	0.7	-3.5
darunavir/cobicistat	0.0	0.0	0.1	0.6	0.8	0.6	-22.0
cobicistat/darunavir/emtricitabine/tenofovir alafenamide	0.0	0.0	0.0	0.0	0.0	0.6	>100
darunavir	1.1	1.2	1.1	0.6	0.4	0.2	-44.4
emtricitabine/rilpivirine/tenofovir disoproxil	0.5	1.0	1.3	1.3	0.4	0.2	-53.9

Table 3.3.2b. Anti-HIV antivirals, weighted regional trend of per capita expenditure: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	11.11	11.52	12.21	12.37	10.92	10.51	-3.8
Valle d'Aosta	5.52	6.04	6.54	7.50	5.62	6.01	7.0
Lombardy	19.74	20.16	20.52	20.32	19.08	18.93	-0.8
A.P. of Bolzano	7.56	8.97	6.72	7.43	7.73	8.29	7.4
A.P. of Trento	7.98	9.05	8.61	9.22	8.45	7.87	-6.9
Veneto	10.49	10.34	10.36	10.81	8.98	8.75	-2.5
Friuli VG	7.36	7.16	8.47	8.95	7.39	7.22	-2.4
Liguria	11.78	12.19	12.36	12.51	12.07	11.71	-3.0
Emilia R.	16.28	16.67	16.66	16.53	14.58	12.78	-12.4
Tuscany	12.61	14.23	14.74	15.00	12.96	12.09	-6.7
Umbria	10.25	10.21	11.08	11.48	11.98	10.97	-8.5
Marche	10.87	11.13	11.59	11.68	10.82	10.79	-0.3
Lazio	15.16	15.47	15.86	16.30	15.09	13.76	-8.8
Abruzzo	6.99	7.78	7.80	8.21	8.79	7.74	-12.0
Molise	3.29	3.38	3.77	4.13	4.37	4.02	-7.9
Campania	7.36	7.88	8.32	8.39	6.80	5.42	-20.4
Puglia	9.12	9.29	9.64	9.44	8.50	7.50	-11.7
Basilicata	4.18	4.40	4.76	4.95	4.81	4.72	-1.8
Calabria	4.41	4.41	4.93	5.57	4.48	3.79	-15.5
Sicily	6.74	7.12	7.80	8.06	7.60	6.85	-9.9
Sardinia	13.62	14.59	14.54	14.07	11.79	9.70	-17.7
Italy	**12.05**	**12.47**	**12.84**	**12.98**	**11.73**	**10.96**	**-6.6**

Table 3.3.2c. Anti-HIV antivirals, prescription by therapeutic category and by substance in 2019

Subgroups and substances	per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Anti-HIV antivirals in co-formulated regimens	5.73	4.8	0.9	7.3	17.65	-2.3
Integrase inhibitors	2.17	17.1	0.4	21.6	13.61	-3.7
Nucleoside and nucleotide reverse transcriptase inhibitors	1.40	-33.8	1.1	2.4	3.63	-35.4
Protease inhibitors alone and in association	1.25	-31.8	0.3	-25.6	11.82	-8.3
Non-nucleoside reverse transcriptase inhibitors	0.30	-6.6	0.2	-7.3	5.17	0.8
Other anti-HIV antivirals	0.12	-24.1	0.0	-17.6	34.32	-7.9
Anti-HIV antivirals	**10.96**	**-6.6**	**2.8**	**1.7**	**10.57**	**-8.2**
emtricitabine/rilpivirine/tenofovir alafenamide	1.72	30.7	0.2	30.7	19.96	0.0
dolutegravir	1.51	29.0	0.3	29.5	16.42	-0.4
dolutegravir/abacavir/lamivudine	1.43	-5.4	0.2	-2.2	21.48	-3.3
elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide	1.35	-4.1	0.1	-4.1	26.55	0.0
emtricitabine/tenofovir alafenamide	0.91	-16.9	0.2	-10.5	11.51	-7.1
raltegravir	0.65	-3.5	0.2	12.2	9.76	-14.0
darunavir/cobicistat	0.64	-22.0	0.1	-22.0	12.25	0.0
cobicistat/darunavir/emtricitabine/ tenofovir alafenamide	0.58	>100	0.1	>100	21.84	0.0
darunavir	0.23	-44.4	0.1	-18.0	11.86	-32.1
emtricitabine/rilpivirine/tenofovir disoproxil	0.21	-53.9	0.0	-53.9	19.96	0.0

Table 3.3.2d. Prescription of anti-HIV antivirals with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	0.23	2.1	-61.7	0.5	16.5	6.8	1.37
Generic	0.09	39.7	49.3	0.3	73.1	98.7	0.74
Ex-originator	0.14	60.3	-74.3	0.1	26.9	-52.7	3.07
Patent covered	10.72	97.9	-3.5	2.4	83.5	0.8	12.40
Anti-HIV antivirals	**10.96**	**100.0**	**-6.6**	**2.8**	**100.0**	**1.7**	**10.57**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.3.2b. Anti-HIV antivirals, distribution in quartiles of per capita expenditure in 2019

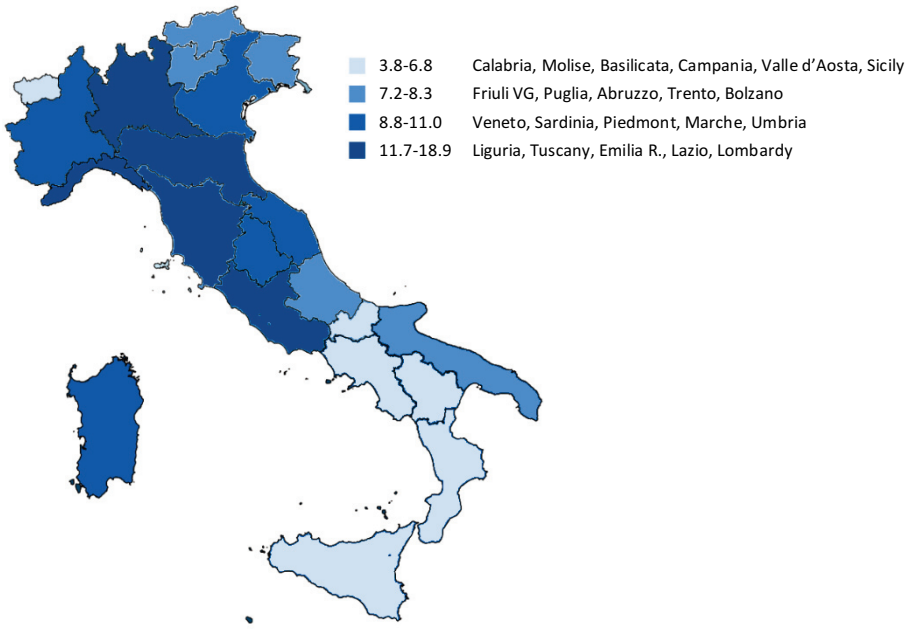
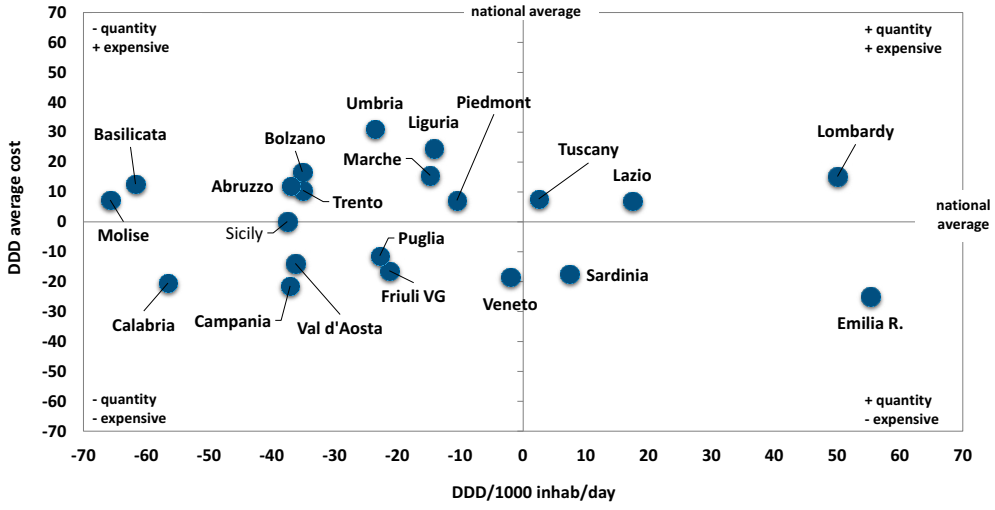


Figure 3.3.2c. Anti-HIV antivirals, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)



3.3.3 Anti-HCV antivirals

- Initial acute hepacavirus (HCV) infection is in most cases asymptomatic and anicteric. A fatal fulminant course is observed very rarely (0.1%), while a high percentage of cases, estimated up to 85%, will go into chronic condition. 20-30% of patients with chronic hepatitis C develop cirrhosis and, in about 1-4% of cases, subsequent hepatocellular carcinoma. In recent years several innovative drugs have been marketed which, in therapeutic cycles of 8, 12 or 16 weeks, allow the healing of a high percentage of patients;
- the use of anti-HCV antivirals increased by about 130% in 2019 to € 15.7 per capita, with a corresponding increase in the average DDD cost which went from € 100 in 2018 to 362.7 in 2019;
- this trend was determined entirely by the sofosbuvir/velpatasvir association (€ 12.5; +448.6%). This association acts directly against the virus, blocking the replication process, and is able to act on all virus genotypes ("pangenotypic" action). Another association with a similar mechanism of action is that between sofosbuvir/velpatasvir/voxilaprevir marketed in 2018, whose expenditure in 2019 increased by 341% to € 0.8;
- Campania, with € 20.46 per capita, is the Region with the highest expenditure followed by Piedmont with € 19.08; Abruzzo and the Autonomous Province of Bolzano are the regions with the lowest expenditure of € 6.57 and € 7.48, respectively. Always Campania and Piedmont, together with Tuscany and Friuli Venezia Giulia, have a consumption and an average cost per day of therapy above the national average.

Figure 3.3.3a. Anti-HCV antivirals, temporal trend of per capita expenditure (2014-2019)

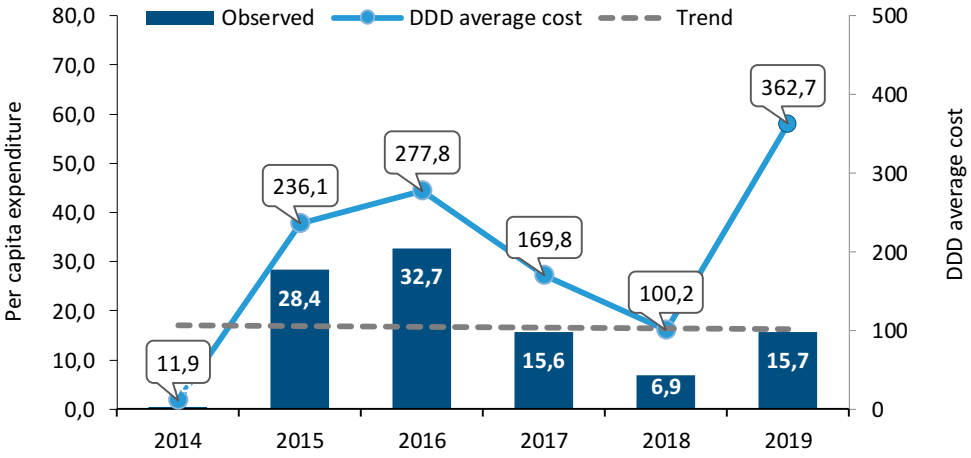


Table 3.3.3a. Anti-HCV antivirals, per capita expenditure by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Anti-HCV antivirals in combination	0.0	9.3	17.9	10.2	6.9	15.7	128.9
Other anti-HCV antivirals	0.0	16.8	14.7	5.4	0.0	0.0	-
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.1	0.1	0.0	0.0	0.0	0.0	-88.4
HCV protease inhibitors	0.3	2.2	0.1	0.0	0.0	0.0	-
Anti-HCV antivirals	**0.5**	**28.4**	**32.7**	**15.6**	**6.9**	**15.7**	**129.2**
sofosbuvir/velpatasvir	0.0	0.0	0.0	2.6	2.3	12.5	448.6
glecaprevir/pibrentasvir	0.0	0.0	0.0	0.4	3.6	2.1	-42.3
sofosbuvir/velpatasvir/voxilaprevir	0.0	0.0	0.0	0.0	0.2	0.8	340.6
elbasvir/grazoprevir	0.0	0.0	0.0	1.4	0.8	0.4	-51.0
sofosbuvir	0.0	14.7	11.4	4.3	-	-	-

Table 3.3.3b. Anti-HCV antivirals, weighted regional trend of per capita expenditure: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	0.49	16.83	28.38	16.60	7.11	19.08	168.5
Valle d'Aosta	0.56	21.20	17.35	6.25	5.15	10.53	104.4
Lombardy	0.37	31.80	34.99	18.37	8.46	18.58	119.6
A.P. of Bolzano	0.11	16.96	20.81	7.01	3.50	7.48	113.4
A.P. of Trento	0.09	13.99	18.92	7.37	5.11	13.12	156.8
Veneto	0.36	20.41	25.01	12.41	5.42	12.49	130.6
Friuli VG	0.23	20.16	11.34	9.95	5.28	16.85	219.2
Liguria	0.26	25.39	25.98	14.79	6.51	12.47	91.5
Emilia R.	0.74	28.66	30.98	14.92	8.40	16.73	99.1
Tuscany	0.37	37.45	35.87	12.71	8.89	17.80	100.1
Umbria	0.18	13.95	25.65	10.63	6.36	14.09	121.7
Marche	0.34	20.35	19.23	9.98	5.28	12.32	133.4
Lazio	0.25	24.96	30.15	11.36	5.29	12.16	129.7
Abruzzo	0.29	21.47	18.51	9.94	3.88	6.57	69.4
Molise	0.18	20.46	25.79	10.64	4.37	11.53	164.1
Campania	0.84	40.82	53.24	26.71	9.36	20.46	118.7
Puglia	0.64	37.31	37.29	16.87	6.17	15.19	146.3
Basilicata	0.37	30.00	32.70	15.40	6.32	12.80	102.5
Calabria	0.31	30.92	32.91	15.68	3.04	10.16	234.5
Sicily	0.55	26.67	34.42	14.46	5.19	15.20	192.7
Sardinia	0.40	33.94	40.50	18.96	8.00	16.58	107.3
Italy	**0.45**	**28.36**	**32.71**	**15.61**	**6.85**	**15.71**	**129.2**

Table 3.3.3c. Anti-HCV antivirals, prescription by therapeutic category and by substance in 2019

Subgroups and substances	per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18
Anti-HCV antivirals in combination	15.71	>100	0.1	-36.1
Other anti-HCV antivirals	0.00	-	0.0	-100.0
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.00	-88.4	0.0	-51.8
HCV protease inhibitors	0.00	-	0.0	-100.0
Anti-HCV antivirals	**15.71**	**129.2**	**0.1**	**-36.7**
sofosbuvir/velpatasvir	12.46	>100	0.1	-33.8
glecaprevir/pibrentasvir	2.07	-42.3	0.0	-34.5
sofosbuvir/velpatasvir/voxilaprevir	0.79	>100	0.0	-8.1
elbasvir/grazoprevir	0.40	-51.0	0.0	-48.5
sofosbuvir	0.00	-	0.0	-

Figure 3.3.3b. Anti-HCV antivirals, distribution in quartiles of per capita expenditure in 2019

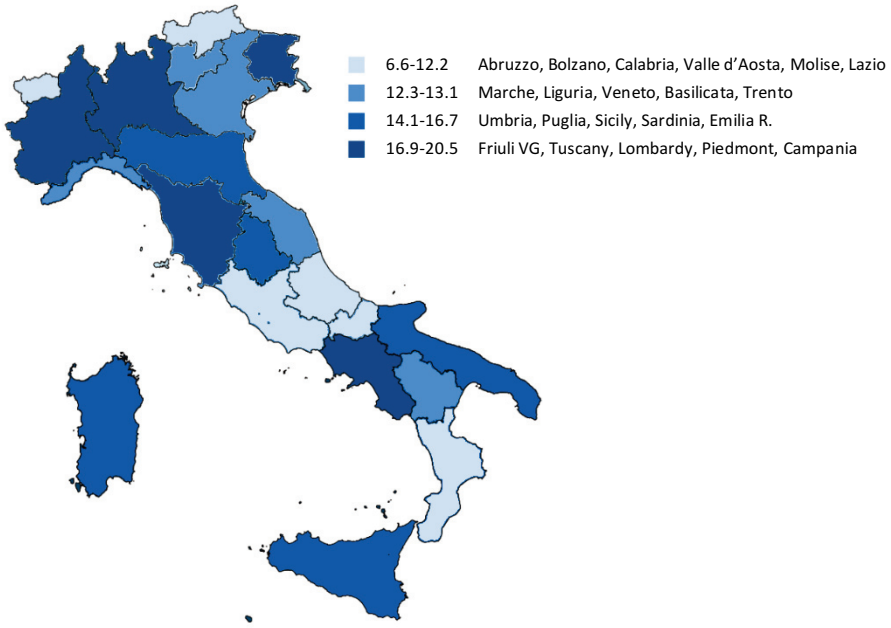
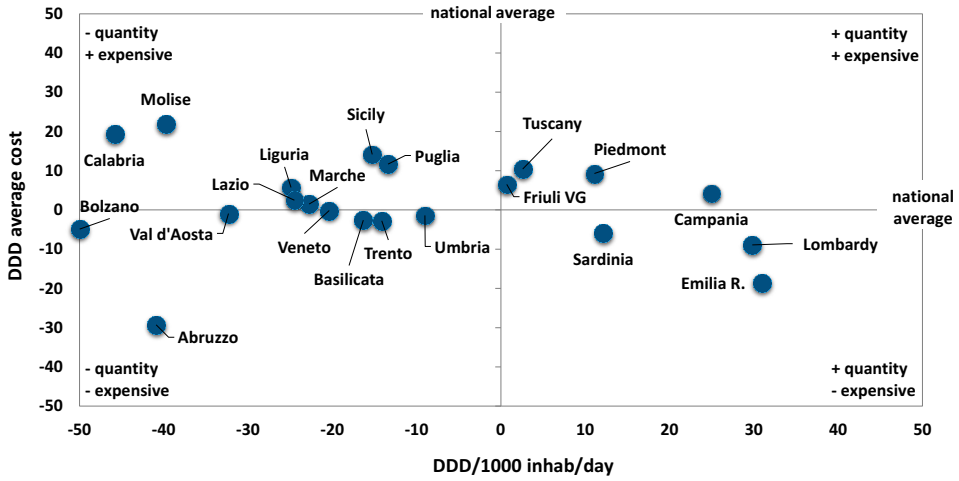


Figure 3.3.3c. Anti-HCV antivirals, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)



3.3.4 Vaccines

- The increase in vaccine spending already observed in previous years continued also in 2019; it went from € 4.5 per capita in 2014 to € 9.4 in 2019 (+7.4% compared to the previous year) with an average annual change (CAGR) of +16%. On the contrary, the average DDD cost dropped from € 24.4 in 2018 to € 23 in 2019 with a difference of - 5.7%;
- among vaccines with a per capita expenditure greater than € 1, those for the quadrivalent influenza from split inactivated virus and for the papilloma virus show the greatest variation compared to the previous year (+63.7% and +15.9% respectively). Vaccines for meningococcus B and 13-valent pneumococcus are in the first two places for spending with € 1.8 per capita, while the former decreases by 2.2%, the latter is increasing by 9%;
- the regional differences in terms of per capita expenditure are very marked, in fact the Autonomous Province of Bolzano with € 13.5 records double the level of Piedmont (€ 6.8). The highest increases compared to 2018 are borne by Lombardy (+ 36.0%), Valle d'Aosta (+ 24.6%), the Autonomous Province of Bolzano (+ 17%) and Marche (+15.6 %);
- The Autonomous Province of Bolzano and Trento, together with the Regions Puglia and Sicily, use more doses, with a higher cost per day of therapy than the national average.

Figure 3.3.4a. Vaccines, temporal trend of per capita expenditure (2014-2019)

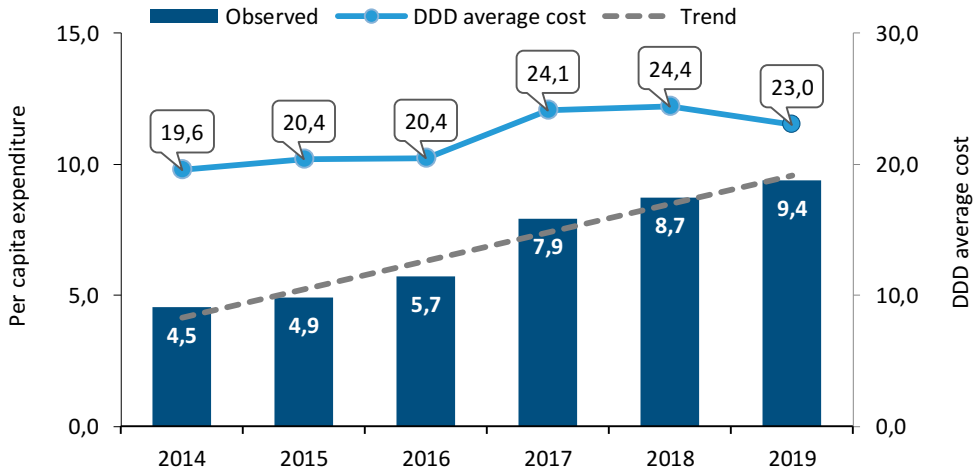


Table 3.3.4a. Vaccines, per capita expenditure by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Meningococcal group B vaccine	0.1	0.3	1.0	2.0	1.8	1.8	-2.2
Pneumococcal vaccine 13-valent	1.4	1.5	1.5	1.6	1.6	1.8	9.0
Papillomavirus vaccine	0.4	0.3	0.3	0.4	0.9	1.1	15.9
Quadrivalent Influenza Vaccine (split virion, inactivated)	0.0	0.0	0.2	0.3	0.7	1.1	63.7
Hexavalent vaccine	1.2	1.2	1.0	1.1	1.0	0.7	-26.1
MPRV vaccine (measles/mumps/rubella/varicella)	0.2	0.2	0.2	0.5	0.5	0.5	-2.7
Meningococcal tetravalent conjugate vaccine	0.1	0.2	0.2	0.7	0.5	0.5	-3.9
Tetravalent vaccine (diphtheria/tetanus/pertussis/poliomyelitis)	0.2	0.1	0.2	0.2	0.3	0.3	21.6
Live attenuated varicella zoster virus vaccine	0.0	0.0	0.0	0.1	0.1	0.3	>100
Attenuated rotavirus vaccine	0.1	0.1	0.1	0.1	0.3	0.3	8.6
Influenza vaccine (adjuvanted inactivated virus)	0.3	0.2	0.2	0.3	0.2	0.3	14.3
DTP vaccine (diphtheria/tetanus/pertussis)	0.1	0.1	0.1	0.1	0.1	0.1	10.2
Live attenuated varicella virus vaccine	0.1	0.1	0.1	0.1	0.2	0.1	-32.4
Pneumococcal Vaccine 23-valent	0.0	0.0	0.0	0.0	0.0	0.1	72.6
MMR vaccine (measles/mumps/rubella)	0.1	0.1	0.1	0.1	0.1	0.1	-31.7
Encephalitis vaccine	0.0	0.0	0.0	0.0	0.1	0.1	28.6
Hepatitis A vaccine	0.0	0.1	0.1	0.1	0.1	0.1	-23.4
Hepatitis B vaccine	0.0	0.0	0.0	0.0	0.1	0.1	-20.3
Vaccines	**4.5**	**4.9**	**5.7**	**7.9**	**8.7**	**9.4**	**7.4**
meningococcal group B vaccine	0.1	0.3	1.0	2.0	1.8	1.8	-2.2
pneumococcal saccharide conjugated vaccine, adsorbed	1.4	1.5	0.0	0.0	1.6	1.8	9.0
inactivated influenza vaccine	0.4	0.3	0.0	0.0	0.6	1.1	87.6
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	0.0	0.0	0.0	0.1	0.8	1.1	30.1
diphtheria/hepatitic B recombinant/haemofilus influenzae b conjugated and adjuvanted/pertussis acellular/polyomelitic inactivated/tetanic vaccine	1.2	1.2	0.0	0.0	0.0	0.7	-
measles/mumps/rubella/varicella vaccine	0.2	0.2	0.2	0.5	0.5	0.5	-2.7
Meningococcal ACWY vaccine	0.1	0.2	0.2	0.7	0.5	0.5	-3.9
diphtheria/pertussis/poliomyelitic/tetanus vaccine	0.2	0.1	0.2	0.2	0.3	0.3	21.6
live attenuated varicella zoster vaccine	0.0	0.0	0.0	0.1	0.1	0.3	>100
live attenuated anti-rotavirus vaccine	0.1	0.1	0.1	0.1	0.3	0.3	8.6

Table 3.3.4b. Vaccines, weighted regional trend of per capita expenditure: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	3.70	3.37	3.35	5.25	6.04	6.79	12.6
Valle d'Aosta	4.17	3.17	3.98	5.00	5.75	7.17	24.6
Lombardy	3.74	3.67	3.95	5.72	7.71	10.48	36.0
A.P. of Bolzano	5.01	5.38	5.50	9.33	11.56	13.52	17.0
A.P. of Trento	5.16	4.66	6.23	9.78	13.09	11.82	-9.7
Veneto	5.02	5.39	7.28	9.54	9.17	10.04	9.6
Friuli VG	5.12	4.99	7.30	10.62	10.25	10.85	5.9
Liguria	3.84	4.28	5.55	6.87	7.65	7.04	-8.0
Emilia R.	4.25	4.29	5.24	9.84	10.50	10.33	-1.6
Tuscany	2.90	8.86	8.55	7.31	8.25	8.37	1.4
Umbria	4.25	3.96	4.84	6.26	7.25	7.47	3.0
Marche	4.01	3.77	4.46	7.52	7.31	8.44	15.6
Lazio	4.31	4.63	6.11	8.84	8.43	9.45	12.1
Abruzzo	4.05	3.63	4.09	6.78	7.37	7.60	3.0
Molise	4.76	5.16	4.41	6.22	8.22	7.08	-13.8
Campania	4.52	4.65	4.72	7.40	8.29	9.28	11.9
Puglia	7.28	7.43	8.07	11.35	11.96	10.29	-13.9
Basilicata	5.27	6.29	5.85	6.51	8.30	7.52	-9.4
Calabria	4.48	4.89	7.12	9.39	9.00	8.23	-8.5
Sicily	6.53	5.86	7.49	9.16	10.52	10.46	-0.5
Sardinia	4.10	3.81	5.15	6.64	8.43	7.85	-6.8
Italy	**4.53**	**4.92**	**5.73**	**7.93**	**8.74**	**9.38**	**7.4**

Table 3.3.4c. Vaccines, prescription by therapeutic category and by substance in 2019

Subgroups and substances	per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Meningococcal group B vaccine	1.79	-2.2	0.1	-4.5	62.85	2.4
Pneumococcal vaccine 13-valent	1.75	9.0	0.1	5.8	51.15	3.1
Papillomavirus vaccine	1.08	15.9	0.0	6.1	69.02	9.2
Quadrivalent Influenza Vaccine (split virion, inactivated)	1.07	63.7	0.4	37.2	7.40	19.3
Hexavalent vaccine	0.71	-26.1	0.1	-7.1	33.46	-20.5
MPRV vaccine (measles/mumps/ rubella/varicella)	0.54	-2.7	0.0	-0.8	46.66	-1.9
Meningococcal tetravalent conjugate vaccine	0.47	-3.9	0.0	0.8	31.71	-4.7
Tetravalent vaccine (diphtheria/tetanus/ pertussis/poliomyelitis)	0.33	21.6	0.0	22.1	19.56	-0.4
Live attenuated varicella zoster virus vaccine	0.31	>100	0.0	>100	96.37	5.1
Attenuated rotavirus vaccine	0.31	8.6	0.0	21.8	26.85	-10.9
Influenza vaccine (adjuvanted inactivated virus)	0.28	14.3	0.1	14.0	5.21	0.3
DTP vaccine (diphtheria/tetanus/pertussis)	0.14	10.2	0.0	14.3	14.20	-3.6
Live attenuated varicella virus vaccine	0.11	-32.4	0.0	-30.8	34.29	-2.3
Pneumococcal Vaccine 23-valent	0.08	72.6	0.0	61.1	22.39	7.2
MMR vaccine (measles/mumps/rubella)	0.07	-31.7	0.0	-30.3	9.32	-2.0
Encephalitis vaccine	0.07	28.6	0.0	22.2	38.23	5.3
Hepatitis A vaccine	0.06	-23.4	0.0	-23.0	17.94	-0.5
Hepatitis B vaccine	0.05	-20.3	0.0	-27.4	16.48	9.7
Vaccines	**9.38**	**7.4**	**1.1**	**13.8**	**23.05**	**-5.7**
meningococcal group B vaccine	1.79	-2.2	0.1	-4.5	62.85	2.4
pneumococcal saccharide conjugated vaccine, adsorbed	1.75	9.0	0.1	5.8	51.15	3.1
inactivated influenza vaccine	1.12	87.6	0.4	51.6	6.99	23.7
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	1.07	30.1	0.0	30.1	69.33	0.0
diphtheria/hepatitic B recombinant/ haemofilus influenzae b conjugated and adjuvanted/pertussis acellular/ poliomyelitic inactivated/tetanic vaccine	0.71	-	0.1	-	33.46	-
measles/mumps/rubella/varicella vaccine	0.54	-2.7	0.0	-0.8	46.66	-1.9
Meningococcal ACWY vaccine	0.47	-3.9	0.0	0.8	31.71	-4.7
diphtheria/pertussis/poliomyelitic/ tetanus vaccine	0.33	21.6	0.0	22.1	19.56	-0.4
live attenuated varicella zoster vaccine	0.31	>100	0.0	>100	96.37	5.1
live attenuated anti-rotavirus vaccine	0.31	8.6	0.0	21.8	26.85	-10.9

Figure 3.3.4b. Vaccines, distribution in quartiles of weighted per capita expenditure in 2019

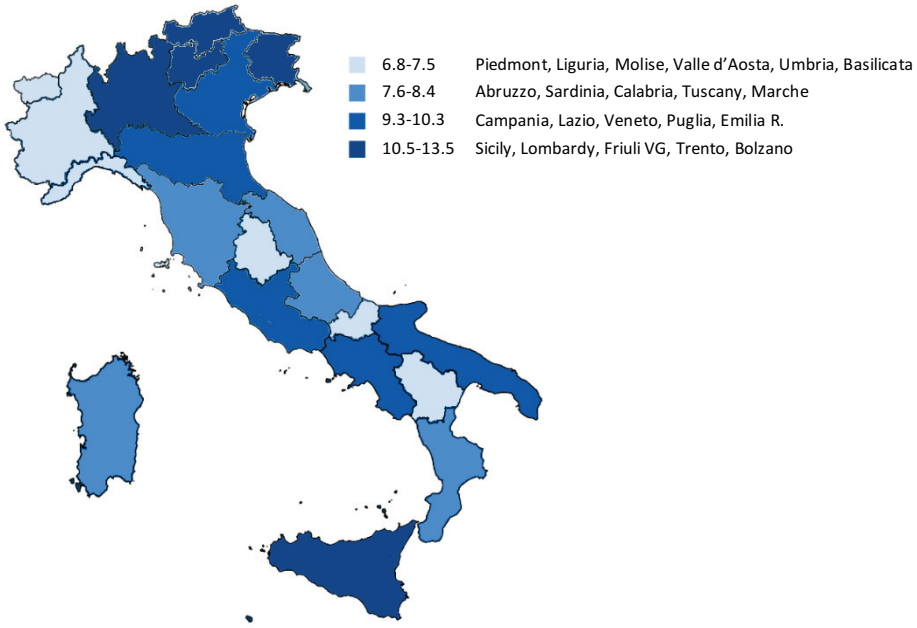
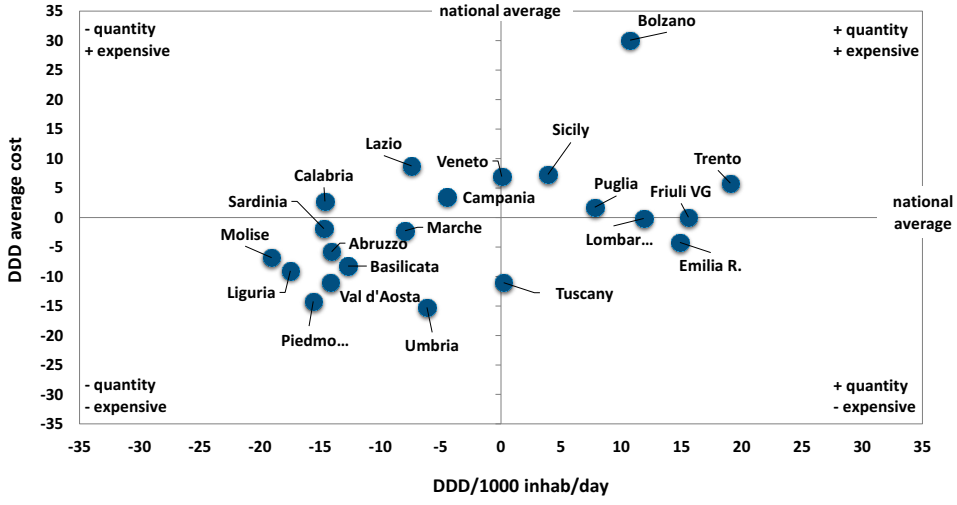


Figure 3.3.4c. Vaccines, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)



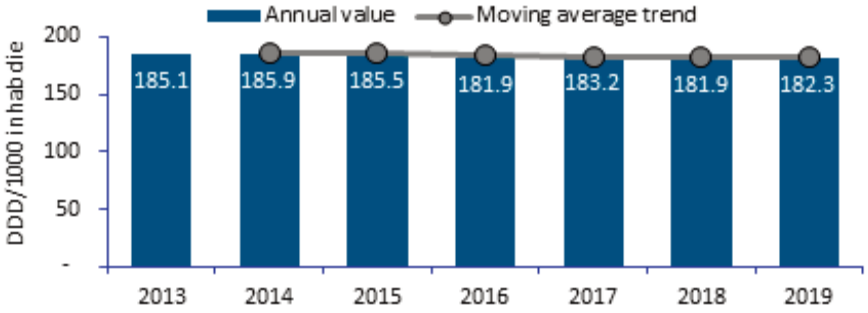
3.4 Gastrointestinal system and metabolism

Gastrointestinal and metabolism medicinal products are the fourth therapeutic category with the highest public expenditure for 2019, equal to € 2,899 million and 12.5% of total public expenditure. The overall per capita expenditure for these medicinal products was € 48.03, mainly determined by the NHS outpatient pharmaceutical expenditure (€ 32.58 per capita), down on the previous year (-1.2%). On the contrary, the purchase by the public health structures is lower (€ 15.45 per capita) (Table 3.1).
Consumption for this category of drugs was 182.2 DDD/1000 inhabitants per day, a trend that has been almost stable in recent years.
The medicine utilization profile analysis by age group and gender (including NHS outpatient pharmaceuticals and *per conto* distribution) documents a progressive increase in the use of medicinal products of this category with increasing age for both genders, with the exception of an initial deflection between 5 and 14 years of age and a more marked trend between 45 and 74 years. At the same time, the per capita expenditure incurred by the NHS also shows a similar trend, reaching the maximum value of € 124.2 per capita in the age group of subjects over 75 years of age and a slightly higher expenditure for females.
As regards the NHS expenditure, a gross per capita expenditure of € 32.58 was recorded, representing a decrease of 1.3% compared to the previous year (Table 3.1). This trend was determined by a slight reduction in prices (-0.2%) and a shift in the prescription towards lower-cost specialties (mix effect: -1.5%), while there was a slight increase in consumption (+0.3%) (Table 3.9).
Proton pump inhibitors rank first in terms of expenditure (€ 11.89 per capita) and consumption (68.9 DDD 1000 inhabitants/day), recording an increase in use (+2.3%), a decrease of expenditure (-4.9%), and the use of less expensive specialties (mix effect of -7.1%). In second place for gross expenditure per capita is vitamin D and analogues (€ 5.19), with an increase of 3.9% and a DDD value of 15 (+6.1% compared to 2018). Finally, a greater use of cheaper specialties was observed for this category of medicinal products (mix effect -2.0%).
Also in 2019 there is a further increase in spending and consumption for GLP-1 receptor analogues (+67.7% and +55.4%, respectively) and for slow-acting insulins (+15.0% and +2.8%, respectively); on the other hand, oral hypoglycaemic agents in association recorded a significant reduction in expenditure and consumption (-11% and -20.2% respectively), as did the other hypoglycaemic agents (-15% and -16%). H2 receptor antagonist represent another category for which there is a sharp reduction in spending and consumption in 2019, with a deflection of 26% and 26.6% respectively.
Cholecalciferol and pantoprazole are the molecules with the highest per capita expenditure (€ 4.66 and € 4.39 per capita, respectively) and together represent the main cost item of the NHS pharmaceutical expenditure for drugs for the gastrointestinal system (27.8%) (Table 3.5). These two molecules are also confirmed in the first places, considering the first 30 active ingredients for NHS expenditure, with € 281.3 and 265 million respectively (Table 3.6).
Only mesalazine is in the list of the top 30 active ingredients with the greatest variation in NHS spending compared to the previous year (+5.2%) and with a variation in consumption of +5.5% (Table 3.7).

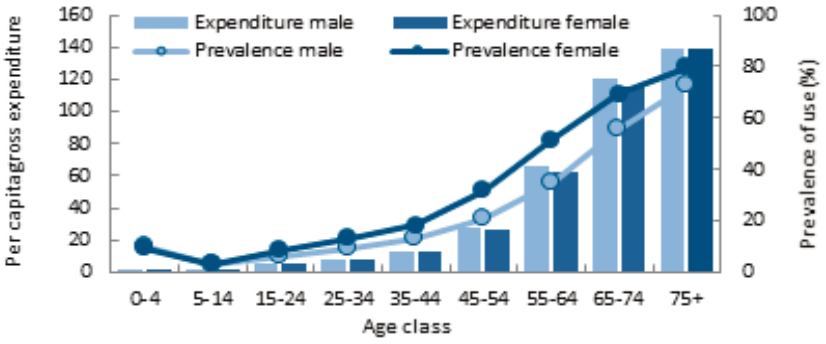
As for purchases by public health structures, there was an increase in expenditure of 11.3% compared to 2018 despite a slight decrease in consumption of 0.2% (Table 3.11). The most important increases in spending were recorded for the miscellaneous products category (+44.8%), which include some orphan drugs indicated, for example, in the treatment of Gaucher and Fabry disease; followed by the analogues of the GLP-1 receptor (+39.4%), the inhibitors of the co-transporter SGLT-2 (+34.6%) and the inhibitors of Dipeptil Peptidase 4 (DPP-4) (+11.2%). Enzymes such as, for example, recombinant human acid alglucosidase, agalsidase alfa, imiglucerase, alone account for 31.5% of expenditure, despite very low average consumption, in consideration of the fact that they include medicines used in the treatment of rare diseases and which have a high average cost per DDD (Table 3.10). Insulin glargine is the active ingredient associated with the highest per capita expenditure (€ 1.55), stable compared to the previous year (-0.2%), representing 10.0% of the expenditure on this category purchased from public health facilities, with an increase in consumption compared to the previous year of 2.0% (Table 3.9). This active ingredient is the only one in the category included in the top 30 most expensive active ingredients for medicinal products purchased from healthcare facilities (Table 3.12).
For further information on the use of medicinal products of 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 use of resources according to the presence of patent-expired pharmaceuticals and on a regional basis. Such analyses focused on drugs for peptic ulcer and GERD and drugs for the treatment of diabetes mellitus (Table 3.4.1 and following).

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

NHS expenditure, millions €* (% on the total)	**2899.1**	**(12.5)**
Δ % 2019-2018		2.3
per capita gross expenditure, range among regions:	30.5	66.2
DDD/1000 inhab./day* (% on the total)	**182.2**	**(15.8)**
Δ % 2019-2018		0.2
DDD/1000 inhab/day, range among regions:	128.0	227.3



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure and *per conto* distribution 2019 (Chart and Table)



Age (group)	Gross per capita expenditure			DDD/1000 inhab/day		
	Men	Women	Total	Men	Women	Total
0-4	1.3	1.2	1.3	5.4	5.2	5.3
5-14	1.8	1.8	1.8	4.5	4.6	4.6
15-24	4.8	4.8	4.8	12.9	14.1	13.5
25-34	7.0	7.3	7.1	21.6	24.2	22.9
35-44	11.5	11.5	11.5	41.2	42.7	41.9
45-54	23.2	24.1	23.7	89.5	93.7	91.6
55-64	54.1	53.3	53.7	216.5	212.0	214.2
65-74	101.8	100.5	101.1	433.4	420.7	426.7
75+	122.3	125.4	124.2	561.2	563.9	562.8

3.4.1 Medicinal products for peptic ulcer and GERD

- In 2019 the use of this category was slightly increasing compared to the previous year (+ 1.5%) equal to a value of 80.5 DDD/1000 inhabitants per day which represent about 7% of the NHS consumption in Italy. On average, each day of therapy has a cost of € 0.46 compared to 0.49 in 2018;
- proton pump inhibitors, with 72.6 DDD, represent 90% of the consumption of drugs for peptic ulcer and GERD, with a 2.5% increase compared to 2018; they are also the category that shows the greatest level of variability between the various Italian regions (CV 18%);
- pantoprazole, lansoprazole, omeprazole and esomeprazole are in the top four in terms of consumption (24.4; 15.2; 17.4 and 13.7 DDD respectively) followed at a distance by the association between sodium alginate and potassium bicarbonate (4.0 DDD). All pump inhibitors except lansoprazole (-3.1%) and rabeprazole (-7.3%) are growing, while the average cost per day of therapy is decreasing for all the molecules of this category, probably for a greater use of generics (€ 0.39 of average DDD cost and +55.8% compared to 2018) instead of ex originators (€ 0.51 of average DDD cost);
- patent-expired medicinal products represent about 92% of the doses of drugs for peptic ulcer and GERD;
- the use levels in Campania (115.6 DDD/1000 inhabitants per day) are more than double compared to those in the Autonomous Province of Bolzano (47 DDD); Umbria (-5.8%), Tuscany (-5.1%) and Marche (-4.1%) are the regions with the largest reduction in consumption compared to 2018;
- the analysis of the prescription in the population shows an increase in use with age without substantial differences between men and women, the prevalence reaches about 60% in the age group ≥75 years and 8% in the overall population; non-continuous use of these medicinal products is confirmed, in fact half of the users have been treated for less than 3 months and one in four patients receives only one prescription in a year.

Figure 3.4.1a. Medicinal products for peptic ulcer and GERD, temporal consumption trend (2014-2019)

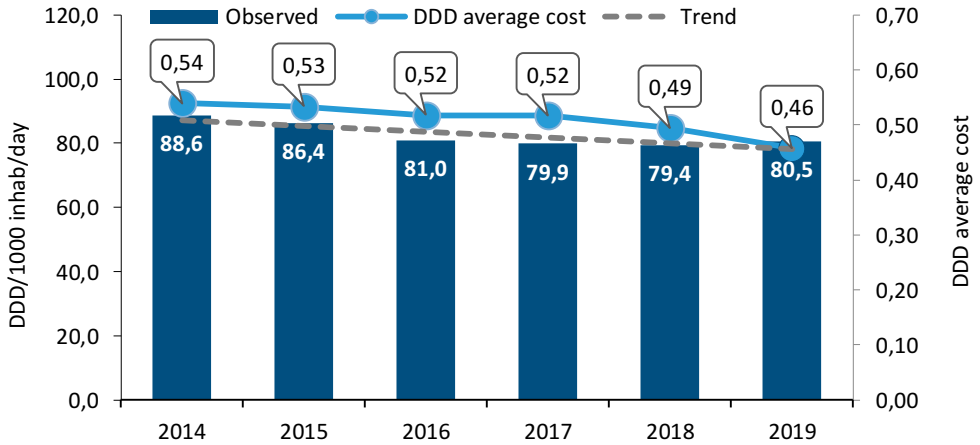


Table 3.4.1a. Medicinal products for peptic ulcer and GERD, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Proton pump inhibitors	80.1	77.9	72.6	71.5	70.9	72.6	2.5
Other drugs for peptic ulcer and GERD	4.0	4.0	4.1	4.0	4.1	4.2	2.5
Antacids	1.9	2.0	2.0	2.0	2.0	1.9	-8.0
H2 receptor antagonists	2.5	2.4	2.4	2.3	2.3	1.8	-22.6
Prostaglandins	0.0	0.0	0.0	0.0	0.0	0.0	-12.0
Drugs for peptic ulcer and GERD	**88.6**	**86.4**	**81.0**	**79.9**	**79.4**	**80.5**	**1.5**
pantoprazole	21.7	22.1	21.5	21.8	22.8	24.4	6.6
lansoprazole	21.8	20.0	17.8	16.7	15.7	15.2	-3.1
esomeprazole	13.4	13.2	12.4	12.7	12.8	13.7	6.7
omeprazole	20.5	19.8	18.5	17.9	17.4	17.4	0.2
sodium alginate/ + potassium bicarbonate	3.7	3.8	3.8	3.8	3.9	4.0	2.9
magaldrate	1.8	1.8	1.9	1.9	1.9	1.8	-8.3
rabeprazole	2.7	2.7	2.5	2.3	2.1	2.0	-7.3
ranitidine	2.5	2.4	2.4	2.3	2.3	1.8	-23.1
sucralfate	0.3	0.3	0.3	0.2	0.2	0.2	-3.4
misoprostol	0.0	0.0	0.0	0.0	0.0	0.0	-12.0

Table 3.4.1b. Medicinal products for peptic ulcer and GERD, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	83.2	79.3	70.8	68.7	68.7	69.2	0.6
Valle d'Aosta	78.4	74.9	65.5	64.3	67.3	70.6	5.0
Lombardy	70.8	73.8	74.3	74.7	77.2	78.0	1.0
A.P. of Bolzano	43.2	44.1	44.5	45.2	46.9	47.0	0.1
A.P. of Trento	71.2	74.3	78.0	82.8	84.9	86.8	2.3
Veneto	80.8	76.3	68.9	64.8	64.7	65.8	1.7
Friuli VG	74.7	73.3	73.1	72.7	70.6	70.1	-0.7
Liguria	95.7	94.5	90.2	89.9	91.8	93.7	2.1
Emilia R.	77.4	76.6	68.1	65.4	66.4	66.6	0.4
Tuscany	71.0	70.0	68.0	67.3	64.4	61.1	-5.1
Umbria	87.9	89.1	85.7	86.6	88.6	83.5	-5.8
Marche	81.9	82.6	81.1	79.0	69.4	66.6	-4.1
Lazio	103.2	96.0	84.4	84.6	86.2	88.2	2.4
Abruzzo	83.2	85.0	75.8	76.4	78.6	81.7	4.0
Molise	90.6	88.8	65.5	69.8	75.5	80.3	6.4
Campania	99.7	105.1	104.1	106.6	110.9	115.6	4.2
Puglia	109.8	95.0	90.0	87.4	81.2	83.5	2.8
Basilicata	83.4	84.8	77.6	79.6	82.2	86.1	4.7
Calabria	117.8	103.4	89.9	90.4	91.3	92.5	1.3
Sicily	110.5	105.6	100.2	94.7	85.6	88.9	3.8
Sardinia	108.5	110.3	94.4	87.2	83.6	83.6	0.0
Italy	**88.6**	**86.4**	**81.0**	**79.9**	**79.4**	**80.5**	**1.5**

Table 3.4.1c. Medicinal products for peptic ulcer and GERD, prescription by therapeutic category and by substance in 2019

Subgroups and substances	per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Proton pump inhibitors	11.89	-6.1	72.6	2.5	0.45	-8.3
Other drugs for peptic ulcer and GERD	0.89	2.8	4.2	2.5	0.58	0.3
Antacids	0.40	-8.0	1.9	-8.0	0.58	0.0
H2 receptor antagonists	0.26	-25.7	1.8	-22.6	0.40	-3.9
Prostaglandins	0.01	-12.6	0.0	-12.0	1.04	-0.8
Drugs for peptic ulcer and GERD	**13.45**	**-6.1**	**80.5**	**1.5**	**0.46**	**-7.4**
pantoprazole	4.49	-2.0	24.4	6.6	0.50	-8.1
lansoprazole	2.52	-7.1	15.2	-3.1	0.45	-4.1
esomeprazole	2.28	-5.0	13.7	6.7	0.46	-10.9
omeprazole	2.24	-12.9	17.4	0.2	0.35	-13.0
sodium alginate/ + potassium bicarbonate	0.85	3.1	4.0	2.9	0.59	0.2
magaldrate	0.39	-8.2	1.8	-8.3	0.60	0.1
rabeprazole	0.36	-8.2	2.0	-7.3	0.50	-1.0
ranitidine	0.26	-26.6	1.8	-23.1	0.40	-4.5
sucralfate	0.04	-3.9	0.2	-3.4	0.47	-0.6
misoprostol	0.01	-12.6	0.0	-12.0	1.04	-0.8

Table 3.4.1d. Prescription of medicinal products for peptic ulcer and GERD with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	11.98	89.0	-6.9	73.9	91.8	1.5	0.44
Generic	5.94	49.6	-3.9	41.2	55.8	5.3	0.39
Ex originator	6.04	50.4	-9.6	32.7	44.2	-3.0	0.51
Patent covered	1.47	11.0	1.0	6.6	8.2	1.4	0.61
Drugs for peptic ulcer and GERD	**13.45**	**100.0**	**-6.1**	**80.5**	**100.0**	**1.5**	**0.46**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.4.1b. Medicinal products for peptic ulcer and GERD, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

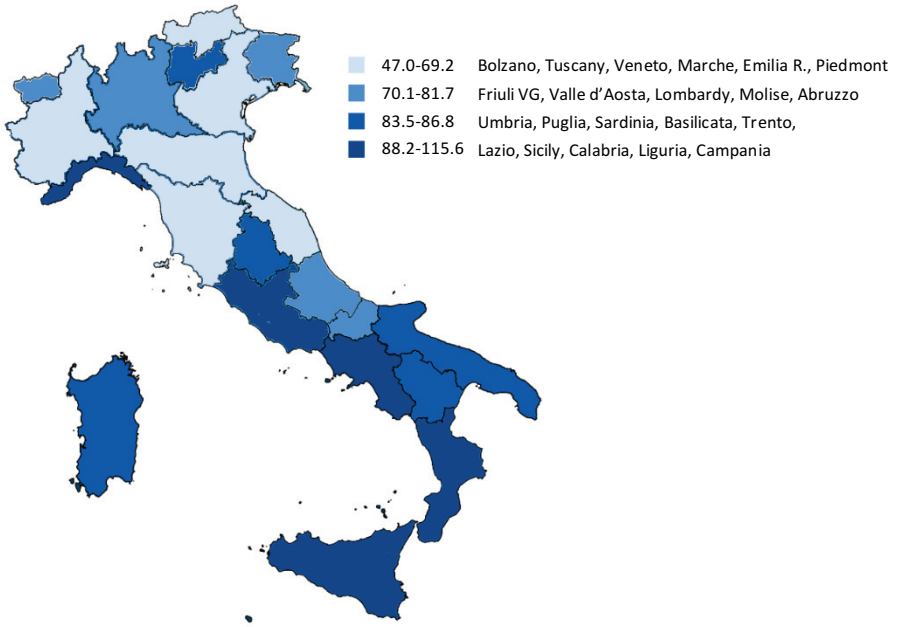


Figure 3.4.1c. Medicinal products for peptic ulcer and GERD, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

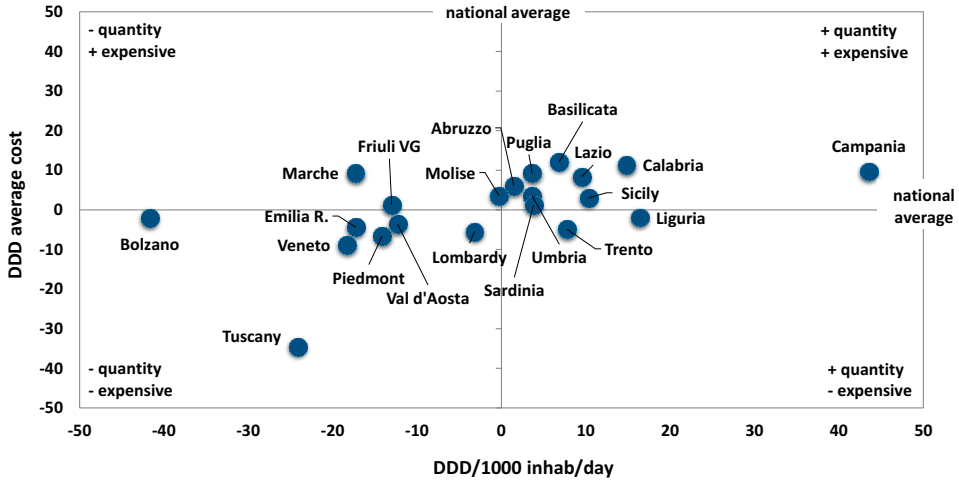


Figure 3.4.1d. Medicinal products for peptic ulcer and GERD, regional variability of consumption in 2019 (weighted DDD/1000 inhab./day) by subgroup

(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)

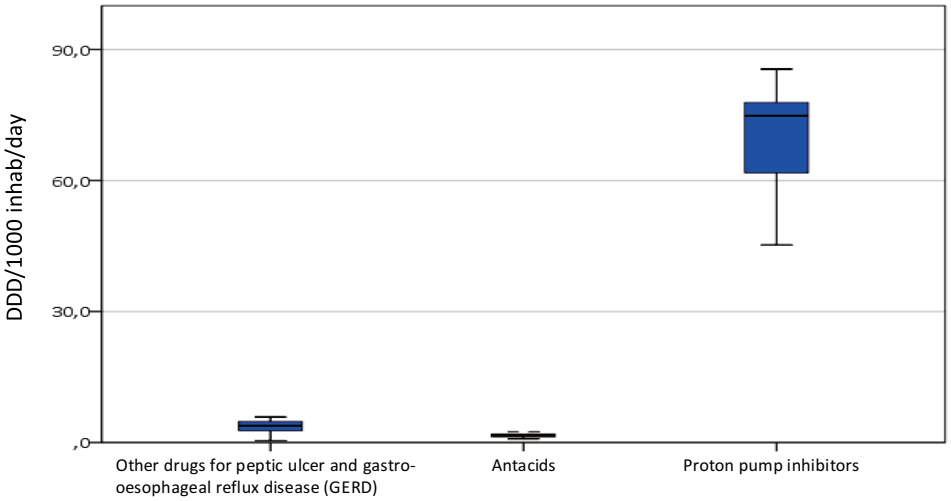


Figure 3.4.1e. Distribution of the prevalence of use and consumption of medicinal products for peptic ulcer and GERD for NHS outpatient expenditure in 2019

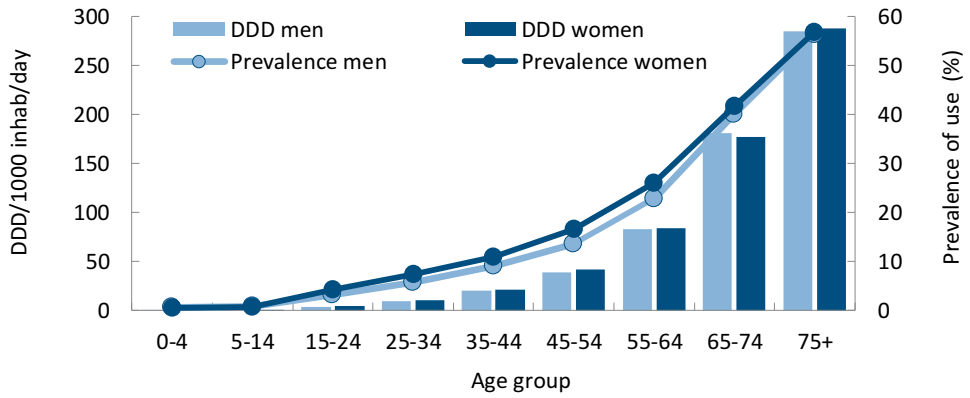


Table 3.4.1e. Duration of therapy with medicinal products for peptic ulcer and GERD by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	Users with 1 prescription
North	5.3	151.1	112.0	27.2
Centre	5.7	134.7	84.0	27.7
South and Islands	6.1	137.1	91.0	25.9
Drugs for peptic ulcer and GERD	**5.7**	**142.0**	**98.0**	**26.8**

3.4.2 Antidiabetics

- It is estimated that in Italy over 5% of the population has diabetic pathology, 10% of which have type 1 diabetes, which usually occurs in childhood or adolescence, while the remaining 90% of cases have type 2;
- in the 2014-2019 period the consumption of antidiabetics remained fairly stable going from 62.0 to 63.6 DDD, equal to an average annual change (CAGR) of 1%; spending was € 16.73 per capita, an increase of 7.1% over 2018, while the average DDD cost reached € 0.72 in 2019;
- metformin alone or in association represents about 38% of the total doses and is stable compared to the previous year and is the category with the greatest regional variability of use (CV 20%); while fast acting insulins, with € 3.84 down 3.9%, are the category with the highest spending. The associated insulins and GLP-1 analogues, on the other hand, show the highest increases (associated insulins +149.6% and GLP-1 +44.7%). Three insulins, glargine (€ 1.78), lispro (€ 1.73) and aspart (€ 1.62) are at the top in terms of spending; dulaglutide (+76.4%) and linagliptin (+16.7%) are the molecules with the greatest variation in 2018; metformin has a cost per DDD of € 0.19 while the dulaglutide reaches € 2.61;
- in the Autonomous Province of Bolzano are used less than half of the doses (41.2 DDD) used in Calabria (84.4 DDD). Abruzzo, Molise, Campania and Sardinia are the regions with consumption and average DDD cost which are higher than the national average;
- over half of the prescribed doses (55.1%) refer to molecules with an expired patent, even if the use of generics decreases by 3.5%; the average cost per day of therapy for patent-expired drugs is € 0.21 and rises to € 1.34 for those still covered by the patent;
- the median duration of therapy is consistent with the chronic use of these drugs, half of the users are treated for 10 months and 8.0% receive only one prescription; consumption in men is higher than in women. Confirming the epidemiological data, the prevalence in the population is 6%, up to 22.5% in men and 17.6% in women aged 75+.

Figure 3.4.2a. Antidiabetics, temporal consumption trend (2014-2019)

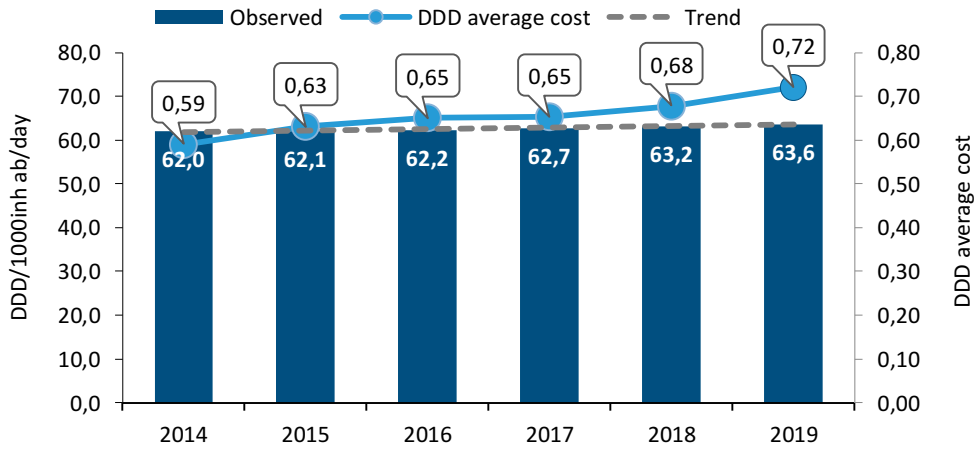


Table 3.4.2a. Antidiabetics, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Fast acting insulins	8.3	8.4	8.4	8.6	8.6	8.4	-1.7
Combined insulins (long/intermediate with fast)	6.1	6.4	6.5	6.7	6.7	6.6	-0.8
Glp-1 analogues (glucagon-like one)	0.7	0.8	1.0	1.3	1.7	2.5	43.6
Metformin alone and in association	25.1	24.5	24.1	24.2	24.1	24.0	-0.1
Gliptine (DPP-4 inhibitors) alone	1.4	1.7	2.1	2.3	2.7	3.0	12.1
Gliptine (DPP-4 inhibitors) in combination	2.0	2.4	2.7	2.8	3.0	3.1	3.5
Glyphozines associated with metformin	0.0	0.0	0.2	0.6	1.0	1.4	38.4
Glyphozines (SGLT2 inhibitors) alone	0.0	0.1	0.5	0.7	1.0	1.3	27.7
Associated insulins	0.0	0.0	0.0	0.0	0.1	0.3	153.1
Sulfonylureas alone	11.2	10.9	10.5	10.0	9.3	8.4	-9.5
Pioglitazone alone and in association	2.2	2.1	1.9	1.7	1.7	1.7	-0.9
Repaglinide	3.9	3.6	3.3	3.0	2.6	2.2	-16.1
Acarbose	0.7	0.7	0.7	0.7	0.6	0.6	-6.8
Intermediate acting insulins	0.4	0.3	0.2	0.0	0.0	0.0	-19.4
Antidiabetics	**62.0**	**62.1**	**62.2**	**62.7**	**63.2**	**63.6**	**0.7**
insulin glargine	4.0	4.0	4.2	4.4	4.6	4.7	1.9
insulin lispro	4.0	4.0	4.0	4.0	4.0	3.9	-2.3
insulin aspart	3.7	3.6	3.5	3.4	3.3	3.3	-0.6
metformin	20.3	20.6	21.0	21.6	22.1	22.5	2.0
dulaglutide	0.0	0.0	0.2	0.5	0.8	1.4	74.1
insulin degludec	0.0	0.7	1.0	1.2	1.3	1.3	3.9
liraglutide	0.6	0.6	0.6	0.7	0.8	0.9	18.5
linagliptin	0.2	0.5	0.7	0.9	1.1	1.3	17.2
insulin glulisine	1.3	1.4	1.4	1.4	1.4	1.3	-6.6
sitagliptin/metformin	1.1	1.1	1.3	1.3	1.4	1.5	3.3

Table 3.4.2b. Antidiabetics, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	59.6	59.5	59.3	59.7	59.2	59.8	1.0
Valle d'Aosta	60.3	60.3	57.0	58.9	59.7	59.2	-0.9
Lombardy	55.6	56.6	56.2	56.4	56.5	56.8	0.6
A.P. of Bolzano	43.1	42.8	40.6	40.8	40.6	41.2	1.6
A.P. of Trento	48.7	48.0	49.4	48.6	49.0	49.4	0.9
Veneto	52.3	52.6	52.2	52.4	53.3	55.1	3.4
Friuli VG	57.3	56.2	57.3	58.4	59.0	58.5	-0.9
Liguria	51.5	50.8	50.2	49.6	49.8	49.8	0.0
Emilia R.	58.1	58.7	59.1	60.8	61.2	61.5	0.5
Tuscany	58.2	57.7	56.6	56.8	57.4	56.2	-2.1
Umbria	57.5	57.3	57.5	57.9	58.4	58.9	0.9
Marche	50.4	53.0	54.7	55.3	56.0	56.9	1.7
Lazio	63.2	63.0	63.1	63.9	64.0	64.5	0.8
Abruzzo	63.9	63.8	63.5	64.5	65.5	65.0	-0.8
Molise	64.5	63.4	63.4	64.7	65.6	65.9	0.6
Campania	68.4	69.2	70.2	71.2	72.0	74.1	2.9
Puglia	73.5	73.1	74.1	74.7	75.4	74.6	-1.0
Basilicata	70.0	70.2	71.6	74.3	74.6	74.5	-0.1
Calabria	78.8	78.8	80.4	80.2	84.0	84.4	0.5
Sicily	79.0	78.2	78.0	77.8	78.0	79.3	1.6
Sardinia	67.1	66.2	64.9	66.7	67.5	66.4	-1.6
Italy	**62.0**	**62.1**	**62.2**	**62.7**	**63.2**	**63.6**	**0.7**

Table 3.4.2c. Antidiabetics, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Fast acting insulins	3.84	-3.9	8.4	-1.7	1.25	-2.2
Combined insulins (long/intermediate with fast)	2.94	-2.9	6.6	-0.8	1.21	-2.1
Glp-1 analogues (glucagon-like one)	2.35	44.7	2.5	43.6	2.58	0.8
Metformin alone and in association	1.64	-1.0	24.0	-0.1	0.19	-0.8
Gliptine (DPP-4 inhibitors) alone	1.39	10.6	3.0	12.1	1.27	-1.4
Gliptine (DPP-4 inhibitors) in combination	1.26	3.0	3.1	3.5	1.12	-0.5
Glyphozines associated with metformin	0.69	33.9	1.4	38.4	1.33	-3.2
Glyphozines (SGLT2 inhibitors) alone	0.64	21.8	1.3	27.7	1.33	-4.6
Associated insulins	0.61	149.6	0.3	153.1	4.95	-1.4
Sulfonylureas alone	0.53	-5.2	8.4	-9.5	0.17	4.7
Pioglitazone alone and in association	0.38	-19.6	1.7	-0.9	0.63	-18.9
Repaglinide	0.30	-14.9	2.2	-16.1	0.38	1.4
Acarbose	0.16	-7.9	0.6	-6.8	0.73	-1.2
Intermediate acting insulins	0.00	-21.3	0.0	-19.4	0.50	-2.4
Antidiabetics	**16.73**	**7.1**	**63.6**	**0.7**	**0.72**	**6.3**
insulin glargine	1.78	-0.1	4.7	1.9	1.04	-2.0
insulin lispro	1.73	-7.1	3.9	-2.3	1.20	-4.9
insulin aspart	1.62	-1.0	3.3	-0.6	1.35	-0.4
metformin	1.53	1.2	22.5	2.0	0.19	-0.7
dulaglutide	1.35	76.4	1.4	74.1	2.61	1.3
insulin degludec	0.88	0.9	1.3	3.9	1.80	-2.9
liraglutide	0.73	12.1	0.9	18.5	2.24	-5.4
linagliptin	0.62	16.7	1.3	17.2	1.32	-0.5
insulin glulisine	0.59	-6.6	1.3	-6.6	1.26	0.1
sitagliptin/metformin	0.59	3.2	1.5	3.3	1.11	0.0

Table 3.4.2d. Prescription of antidiabetics with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-187	DDD average cost
Patent expired	2.74	16.4	0.8	35.1	55.1	-1.3	0.21
Generic	0.94	34.2	-3.5	15.6	44.4	-3.9	0.16
Ex originator	1.80	65.8	3.1	19.5	55.6	0.8	0.25
Patent covered	14.00	83.6	8.4	28.6	44.9	3.4	1.34
Antidiabetics	**16.73**	**100.0**	**7.1**	**63.6**	**100.0**	**0.7**	**0.72**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.4.2b. Antidiabetics, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

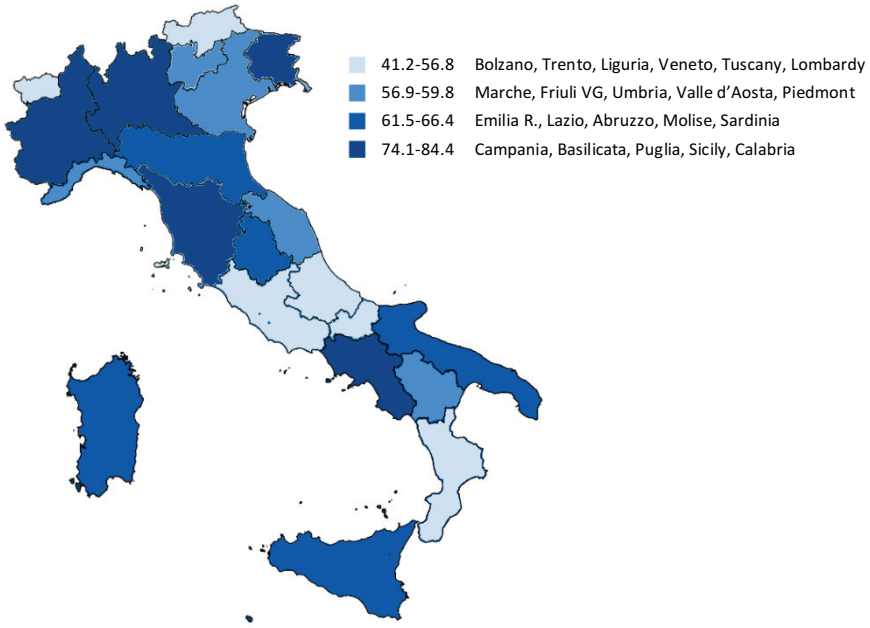


Figure 3.4.2c. Antidiabetics, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

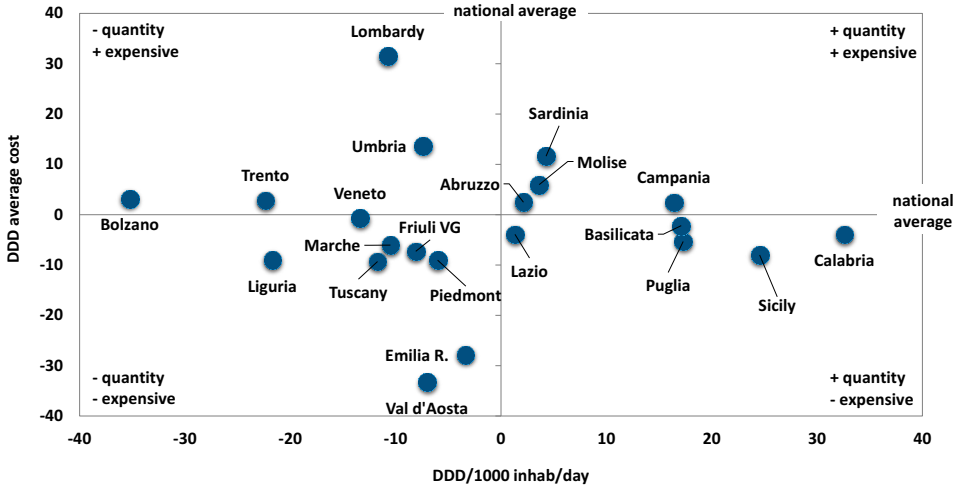


Figure 3.4.2d. Antidiabetics, regional variability of consumption in 2019 (weighted DDD/1000 inhab./day) by subgroup

(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).

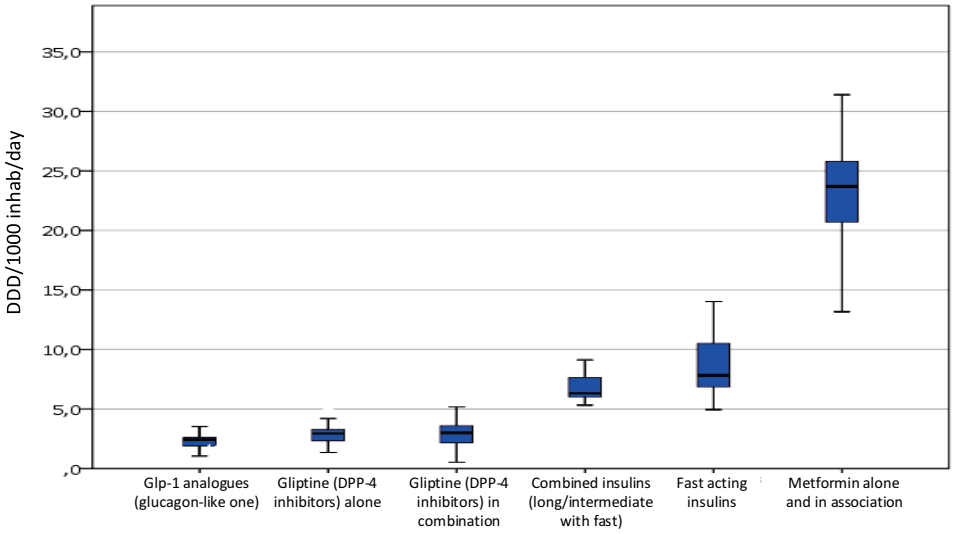


Figure 3.4.2e. Distribution of the prevalence of use and consumption of antidiabetics for NHS outpatient expenditure in 2019

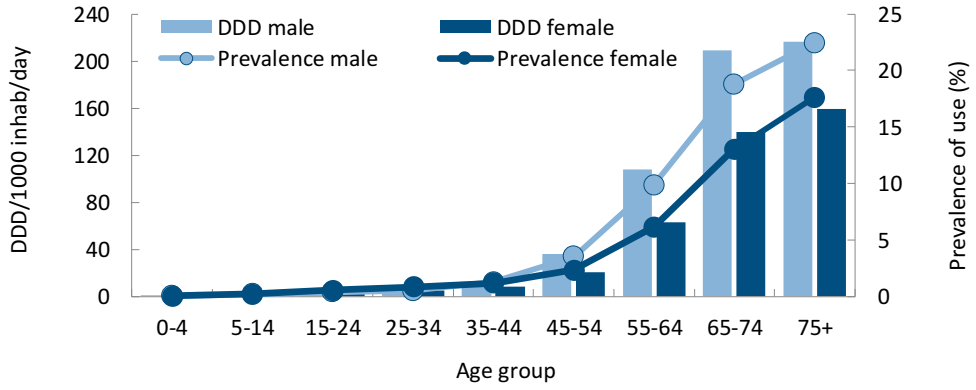


Table 3.4.2e. Duration of antidiabetic therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	User with 1 prescription
North	7.4	381.7	300.0	7.5
Centre	8.4	336.4	262.0	11.1
South and Islands	9.2	367.3	300.0	6.9
Antidiabetics	**8.3**	**366.2**	**300.0**	**8.0**

3.5 Blood and blood-forming organs

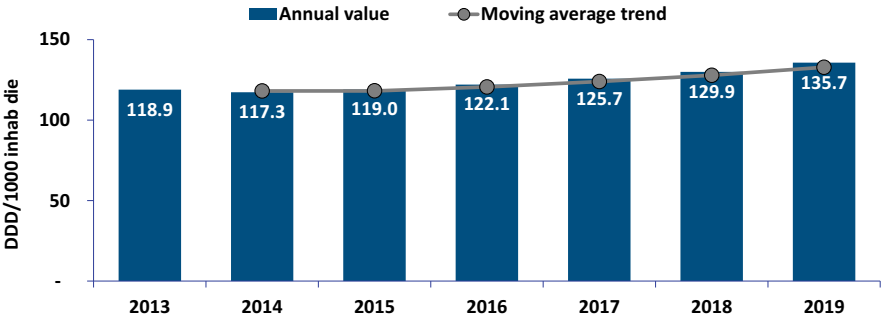
Medicinal products for blood and blood-forming organs are the fifth therapeutic category with the highest public expenditure for 2019, equal to € 2,178.5 million and 9.4% of total public expenditure. The total per capita expenditure for these drugs was € 36.09 per capita, mainly determined by the expenditure deriving from the purchase by public health structures (€ 28.2 per capita), which is a sharp increase compared to the previous year (+6.4%). On the contrary, the amount of NHS outpatient pharmaceutical expenditure is lower (€ 7.89 per capita) (Table 3.1).
Consumption for this category of medicinal products was 135.6 DDD, an increase of 4.4% compared to the previous year (Table 3.2), confirming the increasing trend in recent years. The medicine utilization profile analysis by age group and gender, (including NHS outpatient pharmaceuticals and *per conto* distribution), documents a progressive increase in the use of these medicinal products with increasing age, with a more marked increase in the male population, probably consequent to the different prevalence of cardio-cerebrovascular pathologies. At the same time, the per capita expenditure incurred by the NHS also shows a similar trend, reaching the maximum value of € 90.2 per capita in the age group over 75 years (€ 101.8 for men and € 82.5 for women).
As regards NHS outpatient pharmaceutical expenditure, the expenditure recorded a substantial stability compared to 2018 (-0.4%), with an increase in consumption (+1%) and a shift in the prescription towards less expensive specialties (mix effect: -1.1%) (Table 3.9). The therapeutic categories with the greatest impact on spending are the platelet aggregation inhibitors, excluding heparin (€ 3.07 per capita) and heparinics (€ 2.33 per capita). It should be noted that, compared to the previous year, factor Xa inhibitors continue to record the highest increase in spending (+28.2%) and consumption (+29.8%) compared to the previous year, albeit with a low expenditure value compared to that recorded for purchases by public health structures (€ 0.65 per capita) (Table 3.9). The only active ingredient in the category of medicinal products for blood and blood-forming organs that is among the top 30 with the greatest impact on the NHS outpatient pharmaceutical expenditure is enoxaparin sodium, which alone is responsible for 22.4% of the entire expenditure for this category (Tables 3.5 and 3.6). As for the first 30 molecules with the greatest impact on consumption, there are acetylsalicylic acid (ASA), used as an antiaggregant, and cyanocobalamin (Table 3.8).
As for purchases by public health structures, compared to 2018, there was an increase in both spending (+6.4%) and consumption (+10.6%). The therapeutic category with the highest spending impact is that of blood coagulation factors, with a per capita expenditure of € 8.25, followed by factor Xa inhibitors (€ 6.03 per capita). Among the most frequently used therapeutic categories we find platelet aggregation inhibitors, excluding heparin (9.5 DDD) and direct factor Xa inhibitors (8.9 DDD) (Table 3.10). Factor VIII is the active ingredient that ranks first in terms of per capita expenditure (€ 2.7), although there is a significant drop in both expenditure and consumption, by 39.7% and 40,7% respectively (Table 3.11). Among the top 30 most expensive active ingredients, factor VIII is no longer the active ingredient with the greatest expense impact, although it still remains the first of the therapeutic group, immediately followed by rivaroxaban and apixaban (Table 3.12). For

further information on the use of medicinal products of 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 use of resources according to the presence of patent-expired medicinal products and on a regional basis. These analyses focused on anticoagulant drugs, coagulation factors and antiaggregants (Table 3.5.1 and following).
Furthermore, in the section dedicated to monitoring registers, there is a focus dedicated to the new oral anticoagulants (NOA) used in the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (FANV) which provides a description of the baseline characteristics of patients undergoing treatment and their regional distribution (Section 6).

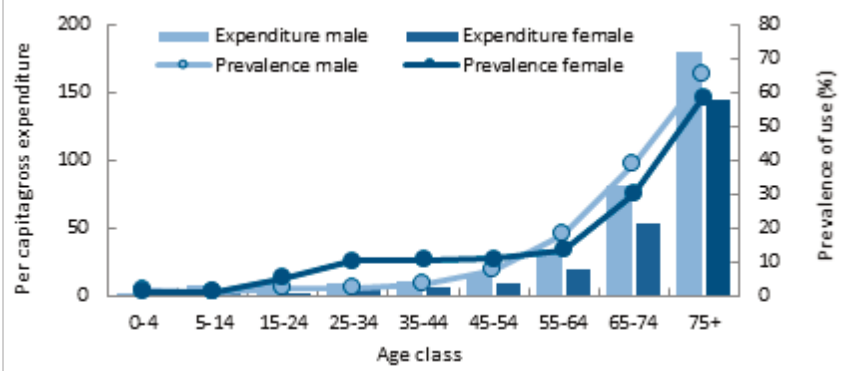
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
blood and hematopoietic organs

NHS expenditure, millions €* (% on the total)	**2,178.5**	**(9.4)**
Δ % 2019-2018		4.6
per capita gross expenditure, range among regions:	25.2	49.3
DDD/1000 inhab/day* (% on the totale)	**135.6**	**(11.7)**
Δ % 2019-2018		4.3
DDD/1000 inhab/day, range among regions:	90.6	209.0

** includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure and *per conto* distribution 2019 (Chart and Table)



Age (group)	Gross per capita expenditure			DDD/1000 inhab/day		
	Men	Women	Total	Men	Women	Total
0-4	2.8	0.3	1.6	1.6	1.4	1.5
5-14	4.4	0.4	2.4	1.3	1.2	1.2
15-24	6.8	1.4	4.3	3.6	8.9	6.1
25-34	6.4	3.3	4.9	4.9	24.1	14.4
35-44	6.9	4.7	5.8	11.3	27.5	19.4
45-54	9.4	5.5	7.4	37.8	32.6	35.2
55-64	21.3	10.7	15.8	121.5	68.9	94.4
65-74	48.5	31.1	39.3	307.2	201.7	251.5
75+	101.8	82.5	90.2	539.6	444.4	482.4

3.5.1 Anticoagulants

- From 2014 to 2019 the consumption of anticoagulants increased by 35%, from 18.8 to 25.4 DDD. At the same time, the average cost per day of therapy increased by 12% even if, compared to 2018, there was a decrease of 6% in the previous year;
- the new oral anticoagulants were the most used category (11.7 DDD) with an increase of 25% compared to the previous year, followed by low molecular weight heparins-LMWH (8.7 DDD and -2% compared to last year); these two categories are also those with the greatest differences among the different regions (CV 15% and 21% respectively);
- enoxaparin is the most expensive molecule (€ 2.8 per capita) with a 9.5% reduction compared to 2018, followed by four oral anticoagulants, in the order: apixaban (€ 2.69), rivaroxaban (€ 2.61), dabigatran (€ 1.43) and edoxaban (€ 1.38). The latter substance is the one with the highest increase (+36.8%) compared to the previous year and with the highest average cost per day of therapy (€ 2.43), while the average cost of NOA is € 1.90;
- almost all of the consumption relates to medicinal products which are still covered by a patent;
- the regional variability ranges from 19.9 DDD in Sicily to 32.1 DDD in Umbria; Friuli Venezia Giulia is the Region with the highest increase (+18.3%). Piedmont, Valle d'Aosta and the Autonomous Province of Bolzano are the only regional realities that have lower than the national average consumption and average cost per day of therapy;
- the prescription of anticoagulants tends to increase with age, with a higher use in men, and reaches a prevalence of use of about 25% in men aged 75+ years. Half of the users are treated for less than 3 months and about one in three patients has received only one prescription in the year.

Figure 3.5.1a. Anticoagulants, temporal consumption trend (2014-2019)

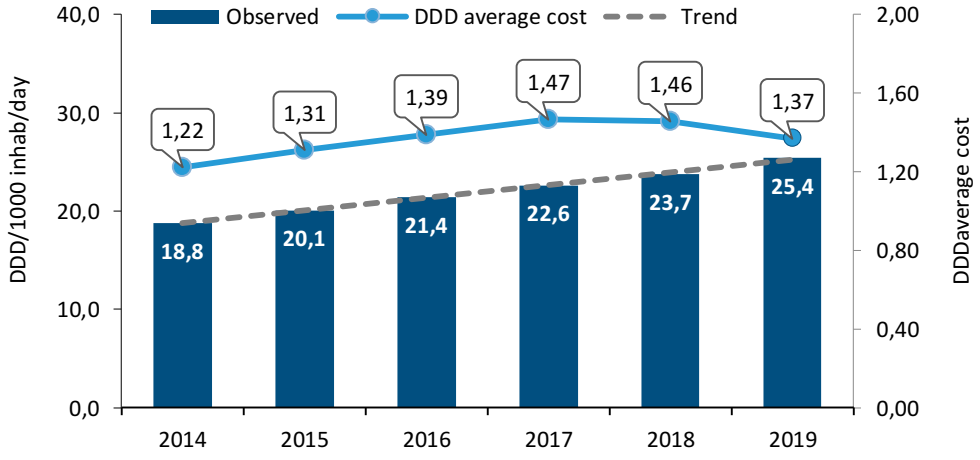


Table 3.5.1a. Anticoagulants, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
NOA	1.6	3.4	5.3	7.3	9.4	11.7	25.0
LMWH	9.7	9.7	9.5	9.2	8.9	8.7	-2.0
Antithrombotic	0.0	0.0	0.0	0.0	0.0	0.0	2.2
Fondaparinux	0.3	0.4	0.4	0.5	0.5	0.5	2.6
Heparin and heparinoids	0.6	0.4	0.5	0.4	0.4	0.4	-3.1
Vitamin K antagonists	6.5	6.1	5.6	5.1	4.6	4.1	-10.6
Anticoagulants	**18.8**	**20.1**	**21.4**	**22.6**	**23.7**	**25.4**	**7.0**
enoxaparin	7.5	7.6	7.7	7.3	7.2	7.6	6.0
apixaban	0.2	0.8	1.6	2.3	3.0	3.6	22.2
rivaroxaban	0.6	1.5	2.3	2.8	3.2	4.1	28.9
dabigatran	0.8	1.1	1.4	1.8	2.2	2.4	10.2
edoxaban	0.0	0.0	0.0	0.4	1.0	1.6	51.7
nadroparin calcium	1.4	1.4	1.2	1.2	1.1	0.8	-27.1
fondaparinux	0.3	0.4	0.4	0.5	0.5	0.5	2.6
parnaparin	0.5	0.5	0.5	0.6	0.5	0.3	-50.9
alteplase	0.0	0.0	0.0	0.0	0.0	0.0	5.2
heparin	0.6	0.4	0.4	0.4	0.4	0.4	-3.0

Table 3.5.1b. Anticoagulants, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	16.8	17.8	18.7	20.6	21.8	23.8	8.7
Valle d'Aosta	18.6	19.7	20.8	21.1	22.6	24.7	9.4
Lombardy	16.9	18.5	20.0	20.8	22.4	24.0	7.5
A.P. of Bolzano	20.5	21.9	22.2	28.0	23.8	25.0	5.1
A.P. of Trento	22.9	22.0	24.4	25.0	28.1	31.1	10.8
Veneto	23.6	24.2	25.1	25.9	27.4	29.7	8.4
Friuli VG	22.8	22.5	22.8	23.6	25.1	29.7	18.3
Liguria	22.7	23.9	25.0	26.2	28.0	29.1	4.0
Emilia R.	24.1	25.1	26.9	28.9	30.8	31.5	2.2
Tuscany	24.3	27.6	28.6	27.6	28.7	29.9	4.3
Umbria	23.6	25.7	27.5	29.2	31.5	32.1	2.0
Marche	16.0	19.8	25.4	27.9	25.7	29.7	15.8
Lazio	17.1	18.2	19.4	21.3	22.0	23.7	7.7
Abruzzo	17.5	18.6	19.7	21.2	22.8	23.9	4.8
Molise	16.1	17.1	17.5	19.0	20.3	21.2	4.4
Campania	14.4	15.9	17.0	18.1	19.1	21.2	11.1
Puglia	17.9	19.4	21.0	21.7	23.3	23.4	0.4
Basilicata	18.1	19.0	19.9	22.8	23.0	23.8	3.3
Calabria	17.9	19.4	20.1	21.5	21.1	22.6	7.0
Sicily	14.5	14.9	15.8	17.5	17.6	19.9	12.7
Sardinia	20.9	21.7	23.2	24.0	26.5	27.3	3.0
Italy	**18.8**	**20.1**	**21.4**	**22.6**	**23.7**	**25.4**	**7.0**

Table 3.5.1c. Anticoagulants, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
NOA	8.11	10.3	11.7	25.0	1.90	-11.8
LMWH	3.56	-15.9	8.7	-2.0	1.12	-14.2
Antithrombotic	0.39	6.4	0.0	2.2	1.007.30	4.1
Fondaparinux	0.27	-0.1	0.5	2.6	1.55	-2.7
Heparin and heparinoids	0.19	-7.1	0.4	-3.1	1.31	-4.1
Vitamin K antagonists	0.17	-10.8	4.1	-10.6	0.11	-0.1
Anticoagulants	**12.70**	**0.5**	**25.4**	**7.0**	**1.37**	**-6.1**
enoxaparin	2.80	-9.5	7.6	6.0	1.01	-14.6
apixaban	2.69	0.4	3.6	22.2	2.03	-17.8
rivaroxaban	2.61	20.2	4.1	28.9	1.73	-6.7
dabigatran	1.43	-4.4	2.4	10.2	1.65	-13.3
edoxaban	1.38	36.8	1.6	51.7	2.43	-9.8
nadroparin calcium	0.58	-28.3	0.8	-27.1	1.98	-1.6
fondaparinux	0.27	-0.1	0.5	2.6	1.55	-2.7
parnaparin	0.17	-45.1	0.3	-50.9	1.79	11.8
alteplase	0.16	5.3	0.0	5.2	822.90	0.0
heparin	0.15	-4.8	0.4	-3.0	1.08	-1.9

Table 3.5.1d. Prescription of anticoagulants with patent expired* in 2019

Categories	per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	0.02	0.2	-7.6	0.0	0.1	-7.0	1.62
Generic	0.01	36.9	-10.4	0.0	43.4	-14.8	1.37
Ex originator	0.01	63.1	-5.9	0.0	56.6	0.1	1.81
Patent covered	12.68	99.8	0.6	25.4	99.9	7.0	1.37
Anticoagulants	**12.70**	**100.0**	**0.5**	**25.4**	**100.0**	**7.0**	**1.37**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.5.1b. Anticoagulants, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

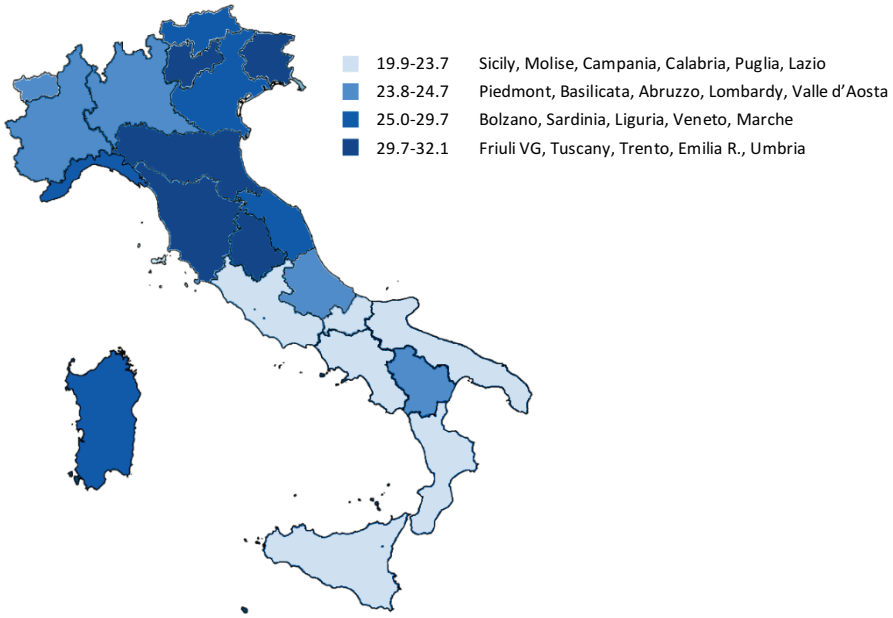


Figure 3.5.1c. Anticoagulants, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

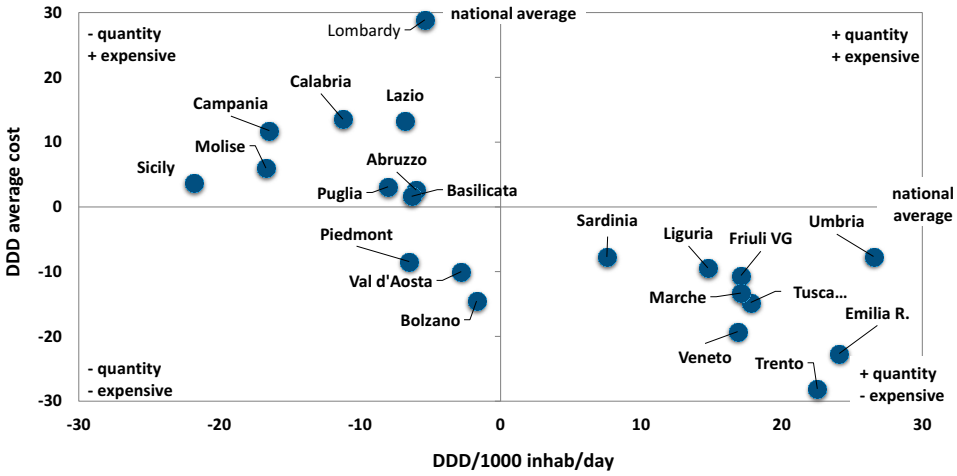


Figure 3.5.1d. Anticoagulants, regional variability of consumption in 2019 (weighted DDD/1000 inhab./day) by subgroup

(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)

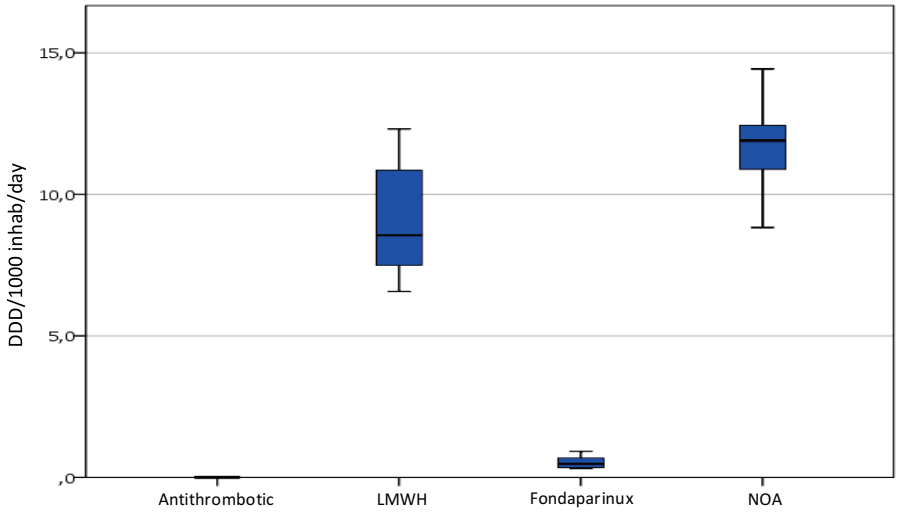


Figure 3.5.e. Distribution of the prevalence of use and consumption of anticoagulants for NHS outpatient expenditure in 2019

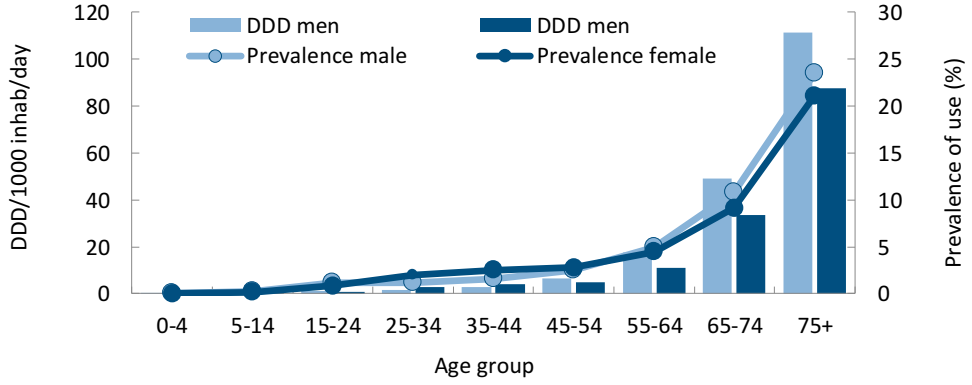


Table 3.5.1e. Duration of anticoagulant therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	Users with 1 prescription
North	3.9	143.6	96.0	29.0
Centre	4.5	125.9	62.0	33.0
South and islands	4.5	128.0	63.0	30.1
Anticoagulants	**4.2**	**134.4**	**80.0**	**30.3**

3.5.2 Coagulation factors

- In 2019 the expenditure for coagulation factors reached € 8.5 per capita, an increase of 11.4% compared to 2018 and 16% if compared to 2014. At the same time, the average cost per day of therapy remained stable reaching € 449.5;
- the recombinant drugs for the treatment of haemophilia A and B were the most expensive categories with values of € 5.53 and € 1.19 per capita and an increase of 9% and 15.9% respectively;
- Factor VIII, with an expenditure of € 2.79 per capita, was the most used molecule in 2019, while lonoctogoc alfa (>100%) and eftrenonacog alfa (+51.5%) are those with the highest increase compared to 2018. In 2019, emicizumab was authorized, used in routine prophylaxis in patients with haemophilia A with factor VIII inhibitors and with weekly administration, with a per capita expenditure of € 0.27;
- The expenditure in Calabria (€ 13.8) was more than three times higher than that in the Autonomous Province of Bolzano (€ 3.8), with variations compared to 2018 ranging from +31.2% in Veneto to -15.8 % in Molise. Abruzzo, Puglia and Calabria have a higher use and a higher DDD average cost than the national average.

Figure 3.5.2a. Coagulation factors, temporal trend of per capita expenditure (2014-2019)

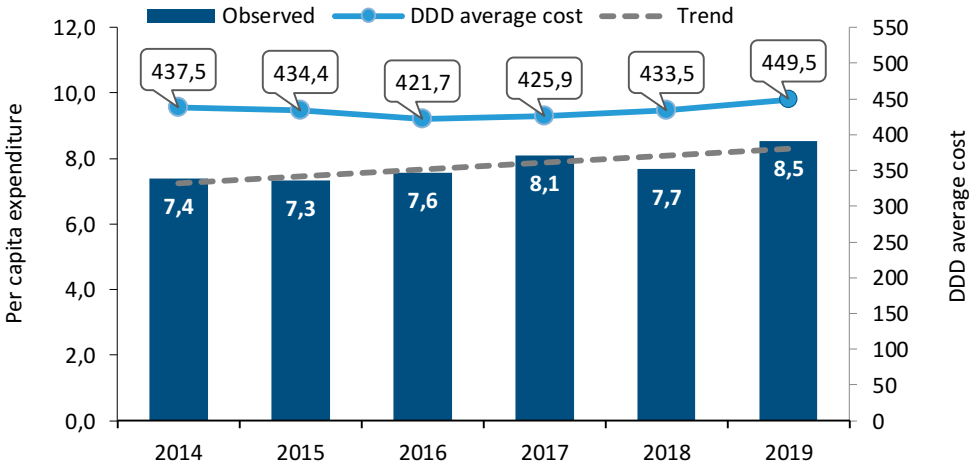


Table 3.5.2a. Coagulation factors, per capita expenditure by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Haemophilia A (recombinant)	4.7	4.7	5.0	5.1	5.1	5.5	9.0
Haemophilia B (recombinant)	0.6	0.6	0.7	0.9	1.0	1.2	15.9
Haemophilia A (plasma derivatives)	1.0	1.0	1.0	1.0	0.8	0.6	-26.6
Factor VII deficiency (recombinant)	1.0	1.0	0.9	1.0	0.6	0.5	-16.7
Coagulation factors	0.0	0.0	0.0	0.0	0.1	0.3	>100
Haemophilia A (monoclonal antibodies)	0.0	0.0	0.0	0.0	0.0	0.3	-
Factor VII deficiency (plasma derivatives)	0.0	0.0	0.0	0.1	0.1	0.1	4.9
Other deficiencies of coagulation factors (recombinant)	0.0	0.0	0.0	0.0	0.0	0.0	-1.0
Haemophilia B (plasma derivatives)	0.0	0.0	0.0	0.0	0.0	0.0	55.6
Other deficiencies of coagulation factors (plasma derivatives)	0.0	0.0	0.0	0.0	0.0	0.0	2.7
Factor VIII	0.0	0.0	0.0	0.0	0.0	0.0	-
von Willebrand disease (plasma derivatives)	0.0	0.0	0.0	0.1	0.0	0.0	-100.0
Coagulation factors	**7.4**	**7.3**	**7.6**	**8.1**	**7.7**	**8.5**	**11.4**
factor VIII	4.8	4.6	5.0	5.1	4.7	2.8	-41.3
octocog alfa	0.0	0.0	0.0	0.0	0.0	1.0	-
efmoroctocog alfa	0.0	0.0	0.0	0.0	0.0	0.9	-
factor VIII/Von Willebrand factor	0.5	0.6	0.5	0.5	0.6	0.8	32.0
activated eptacog alfa (recombinant DNA coagulation factor VII)	1.0	1.0	0.9	1.0	0.6	0.8	28.6
albutrepenonacog alfa	0.0	0.0	0.0	0.2	0.5	0.7	28.0
lonoctogoc alfa	0.0	0.0	0.0	0.0	0.2	0.4	>100
emicizumab	0.0	0.0	0.0	0.0	0.0	0.3	-
eftrenonacog alfa	0.0	0.0	0.0	0.0	0.2	0.3	51.5
nonacog alfa	0.6	0.6	0.7	0.6	0.3	0.3	-23.3

Table 3.5.2b. Coagulation factors, weighted regional trend of per capita expenditure: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	7.84	7.11	6.67	7.95	7.16	7.04	-1.6
Valle d'Aosta	3.25	2.44	2.88	5.51	4.60	4.64	0.9
Lombardy	5.53	5.63	5.67	5.82	6.27	7.00	11.6
A.P. of Bolzano	5.53	3.64	4.41	4.27	3.39	3.81	12.3
A.P. of Trento	4.48	4.52	4.79	4.21	4.57	4.88	6.7
Veneto	4.73	4.49	4.72	5.93	4.82	6.32	31.2
Friuli VG	9.01	11.49	12.78	12.95	6.70	8.66	29.2
Liguria	4.89	5.07	5.08	5.39	5.50	6.73	22.5
Emilia R.	6.02	5.54	6.48	6.95	6.26	7.51	20.0
Tuscany	7.12	6.64	6.69	6.69	5.79	6.84	18.1
Umbria	3.54	3.98	4.48	5.37	5.53	5.75	4.0
Marche	6.47	5.60	5.02	5.88	5.25	5.73	9.2
Lazio	9.41	9.72	10.20	10.51	10.29	11.65	13.2
Abruzzo	8.09	7.94	7.79	9.80	9.31	11.78	26.5
Molise	5.59	7.49	5.06	6.28	7.08	5.97	-15.8
Campania	11.36	11.55	11.03	11.80	11.15	12.34	10.7
Puglia	9.77	9.69	10.33	10.72	10.67	11.13	4.3
Basilicata	6.03	6.46	6.28	6.06	7.51	9.52	26.8
Calabria	9.11	9.47	11.27	12.34	13.35	13.80	3.4
Sicily	8.38	8.25	9.15	9.23	8.91	9.20	3.3
Sardinia	5.58	5.88	5.28	5.29	4.65	4.88	4.9
Italy	**7.38**	**7.35**	**7.58**	**8.09**	**7.67**	**8.54**	**11.4**

Table 3.5.2c. Coagulation factors, prescription by therapeutic category and by substance in 2019

Subgroups and substances	per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Haemophilia A (recombinant)	5.53	9.0	0.0	7.3	344.1	1.7
Haemophilia B (recombinant)	1.19	15.9	0.0	4.0	656.7	11.4
Haemophilia A (plasma derivatives)	0.58	-26.6	0.0	-9.7	789.0	-18.7
Factor VII deficiency (recombinant)	0.50	-16.7	0.0	-16.4	32,365.1	-0.4
Coagulation factors	0.33	>100	0.0	>100	32,912.8	72.4
Haemophilia A (monoclonal antibodies)	0.27	-	0.0	>100	1,046.0	-
Factor VII deficiency (plasma derivatives)	0.07	4.9	0.0	4.6	4,418.5	0.3
Other deficiencies of coagulation factors (recombinant)	0.04	-1.0	0.0	-1.0	15,524.2	0.0
Haemophilia B (plasma derivatives)	0.01	55.6	0.0	36.6	210.2	13.9
Other deficiencies of coagulation factors (plasma derivatives)	0.01	2.7	0.0	0.3	5,443.5	2.4
Factor VIII	0.00	-	0.0	-	210.3	-
von Willebrand disease (plasma derivatives)	0.00	-100.0	0.0	-100.0	-	-
Coagulation factors	**8.54**	**11.4**	**0.1**	**7.4**	**449.5**	**3.7**
factor VIII	2.79	-41.3	0.0	-43.5	351.7	3.9
octocog alfa	1.03	-	0.0	-	340.3	-
efmoroctocog alfa	0.94	-	0.0	-	351.5	-
factor VIII/von Willebrand factor	0.82	32.0	0.0	66.4	421.9	-20.7
activated eptacog alfa (recombinant DNA coagulation factor VII)	0.81	28.6	0.0	29.0	32,520.0	-0.3
albutrepenonacog alfa	0.66	28.0	0.0	28.0	1,088.9	0.0
lonoctogoc alfa	0.40	>100	0.0	>100	326.0	-2.3
emicizumab	0.27	-	0.0	>100	1,046.0	-
eftrenonacog alfa	0.25	51.5	0.0	50.8	671.5	0.5
nonacog alfa	0.25	-23.3	0.0	-23.0	339.7	-0.4

Figure 3.5.2b. Coagulation factors, distribution in quartiles of weighted per capita expenditure in 2019

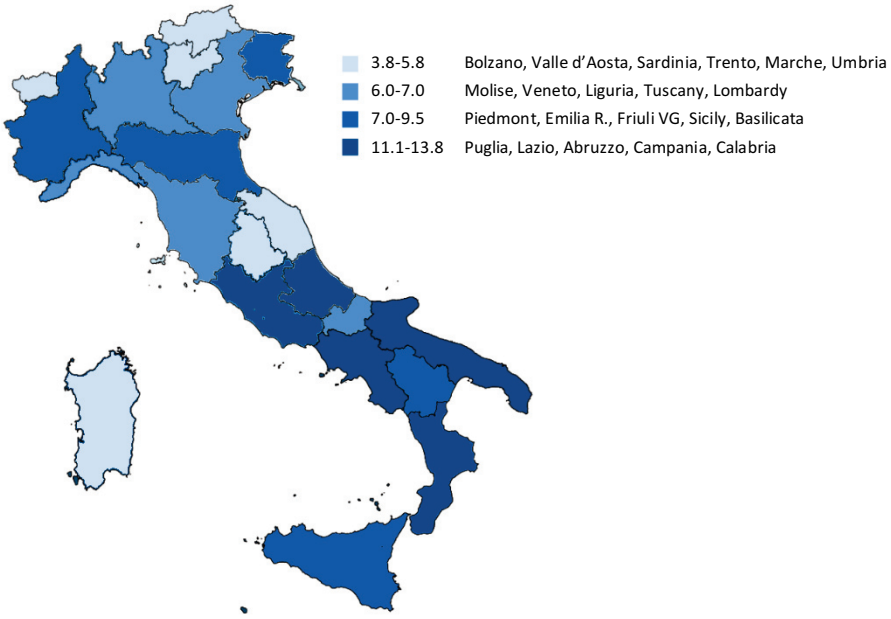
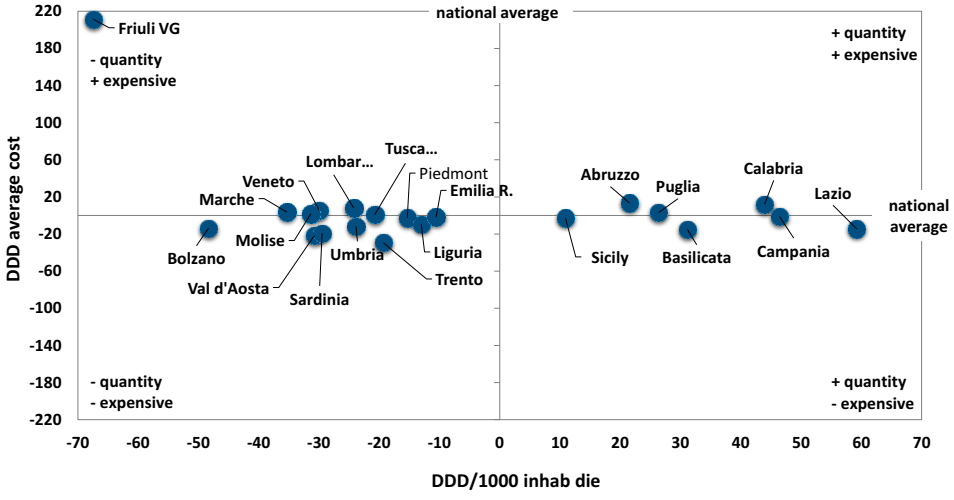


Figure 3.5.2c. Coagulation factors, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)



3.5.3 Antiaggregants

- Consumption of antiaggregants remained stable over the past six years, reaching 70.3 DDD/1000 inhabitants per day in 2019. In the same period, the average DDD cost remained around a value between € 0.20 and € 0.21;
- platelet antiaggregants had the greatest expense (€ 2.96) and the highest number of doses (56.3 DDD) and were also the category with the highest level of variability between the regions (CV 20%). Platelet receptor inhibitors ranked next (€ 1.52 and 13 DDD);
- clopidogrel with € 1.25 (+8.6% compared to 2018) was the molecule with the highest expenditure, while acetylsalicylic acid (used in low doses as an antiaggregant), with 45.4 DDD, was the most used one. The association between these two substances reached 2 DDD (+6.7% compared to 2018) with an average cost per day of therapy of € 0.57, that is higher than the sum of the two single molecules (€ 0.32 for clopidrogrel and € 0.07 for acetylsalicylic acid). Prasugrel and ticlopidine were the two molecules whose per capita expenditure compared to 2018 decreases the most (-47.7% and -14.7% respectively);
- patent-expired medicines represented 83% of the doses and approximately 50% of the category's expenditure, of which only one third related to equivalent products;
- regional variability went from 45.9 DDD in the Autonomous Province of Bolzano to 91.4 DDD in Molise (almost twice the DDD in the PA of Bolzano); Valle d'Aosta was the region with the highest consumption variation (+2.9%) compared to 2018, while in Friuli Venezia Giulia doses decreased by 3.1%. Many regions of Central and Southern Italy (Lazio, Abruzzo, Molise, Basilicata, Puglia and Calabria) had a consumption and an average cost per day of therapy above the national average;
- the prevalence of use in the population was slightly above 9% with a higher value in men (9.7% versus 8.7% in women) and reached 45% in men aged 75+ years. On average, each user was treated for about 9 months, half of the patients remained on therapy for over 10 months and one in ten patients received only one prescription.

Figure 3.5.3a. Antiaggregants, temporal consumption trend (2014-2019)

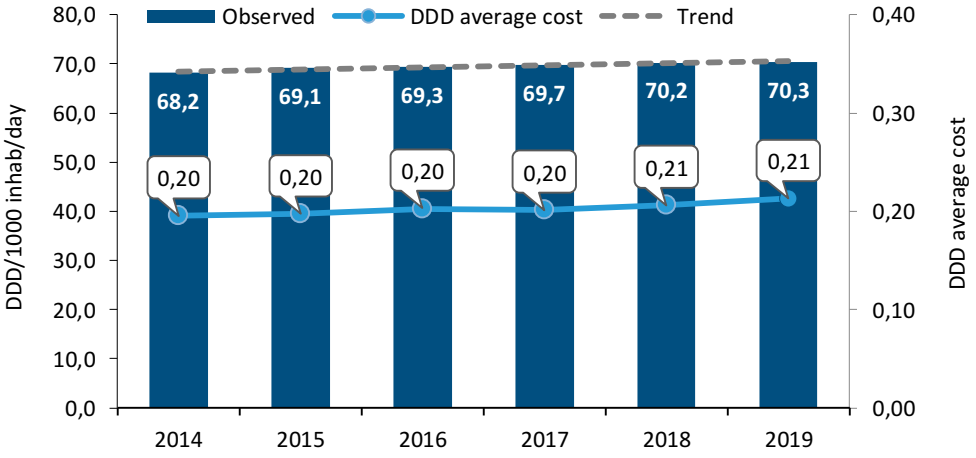


Table 3.5.3a. Antiaggregants, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Platelet antiaggregants excl. P2Y12 inhibitors	55.6	56.1	56.0	56.3	56.4	56.3	-0.2
P2Y12 platelet receptor inhibitors	12.0	12.4	12.6	12.5	12.9	13.0	0.3
Ticagrelor	0.5	0.6	0.7	0.8	1.0	1.1	13.1
Glycoprotein IIb/IIIa inhibitors	0.0	0.0	0.0	0.0	0.0	0.0	1.3
Antiaggregants	**68.2**	**69.1**	**69.3**	**69.7**	**70.2**	**70.3**	**0.1**
clopidogrel	7.1	8.1	8.8	9.3	10.2	10.7	4.5
acetylsalicylic acid	43.6	44.4	44.5	45.1	45.3	45.4	0.2
ticagrelor	0.5	0.6	0.7	0.8	1.0	1.1	13.1
treprostinil	0.0	0.0	0.0	0.0	0.0	0.0	2.9
clopidogrel/acetylsalicylic acid	1.3	1.5	1.6	1.8	1.9	2.0	6.7
iloprost	0.0	0.0	0.0	0.0	0.0	0.0	0.1
lysine acetylsalicylate	7.9	7.7	7.6	7.4	7.3	7.1	-2.2
ticlopidine	4.7	4.0	3.5	3.0	2.6	2.2	-14.8
selexipag	0.0	0.0	0.0	0.0	0.0	0.0	248.7
acetylsalicylic acid/magnesium hydroxide/algeldrate	2.7	2.4	2.2	2.0	1.8	1.6	-9.6

Table 3.5.3b. Antiaggregants, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	73.1	72.5	72.9	72.9	73.1	72.7	-0.6
Valle d'Aosta	75.7	75.5	57.4	60.2	59.5	61.3	2.9
Lombardy	48.6	49.6	49.5	49.3	49.0	48.9	-0.2
A.P. of Bolzano	50.3	49.0	47.7	47.1	47.1	45.9	-2.6
A.P. of Trento	75.7	76.9	76.3	77.7	77.2	76.5	-0.8
Veneto	43.9	47.1	49.5	49.3	50.0	49.2	-1.4
Friuli VG	77.1	76.3	74.9	74.4	74.9	72.6	-3.1
Liguria	61.4	60.1	58.0	58.5	58.1	57.9	-0.4
Emilia R.	87.0	86.1	83.1	85.4	85.0	84.2	-0.9
Tuscany	79.4	77.9	76.9	74.4	74.4	73.2	-1.7
Umbria	76.7	77.0	76.9	76.5	75.8	75.4	-0.5
Marche	78.9	81.5	83.9	84.6	84.8	84.9	0.1
Lazio	73.6	76.0	76.9	78.1	78.9	79.5	0.7
Abruzzo	85.5	86.6	87.8	88.4	89.8	89.9	0.2
Molise	87.8	86.8	87.2	89.1	90.5	91.4	1.0
Campania	61.2	63.5	64.8	66.3	69.5	70.9	2.0
Puglia	81.3	83.5	84.1	85.0	85.8	86.8	1.1
Basilicata	77.6	77.3	77.4	78.2	79.1	80.2	1.4
Calabria	81.4	81.6	83.4	82.8	85.3	86.6	1.5
Sicily	71.5	73.2	74.5	75.7	76.7	78.4	2.3
Sardinia	77.8	77.1	75.3	75.1	74.5	72.5	-2.8
Italy	**68.2**	**69.1**	**69.3**	**69.7**	**70.2**	**70.3**	**0.1**

Table 3.5.3c. Antiaggregants, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita gross expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Platelet antiaggregants excl. P2Y12 inhibitors	2.82	0.1	56.3	-0.2	0.14	0.3
P2Y12 platelet receptor inhibitors	1.52	2.5	13.0	0.3	0.32	2.2
Ticagrelor	0.95	9.7	1.1	13.1	2.40	-3.0
Glycoprotein IIb/IIIa inhibitors	0.04	-35.8	0.0	1.3	100.14	-36.6
Antiaggregants	**5.32**	**1.9**	**70.3**	**0.1**	**0.21**	**1.9**
clopidogrel	1.25	8.6	10.7	4.5	0.32	3.9
acetylsalicylic acid	1.16	0.1	45.4	0.2	0.07	-0.1
ticagrelor	0.95	9.7	1.1	13.1	2.40	-3.0
treprostinil	0.63	-0.6	0.0	2.9	601.75	-3.4
clopidogrel/acetylsalicylic acid	0.43	5.2	2.0	6.7	0.57	-1.4
iloprost	0.24	3.7	0.0	0.1	103.23	3.5
lysine acetylsalicylate	0.22	-2.8	7.1	-2.2	0.08	-0.7
ticlopidine	0.20	-14.7	2.2	-14.8	0.25	0.1
acetylsalicylic acid/magnesium hydroxide/algeldrate	0.07	-9.4	1.6	-9.6	0.11	0.2
prasugrel	0.05	-47.7	0.1	-28.1	0.11	-27.3

Table 3.5.3d. Prescription of antiaggregants with patent expired* in 2019

Categories	per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	2.63	49.5	3.8	58.3	82.9	0.5	0.12
Generic	0.70	26.7	4.6	19.0	32.7	7.4	0.10
Ex originator	1.93	73.3	3.6	39.2	67.3	-2.6	0.13
Patent covered	2.68	50.5	0.1	12.0	17.1	-1.8	0.61
Antiaggregants	**5.32**	**100.0**	**1.9**	**70.3**	**100.0**	**0.1**	**0.21**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.5.3b. Antiaggregants, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

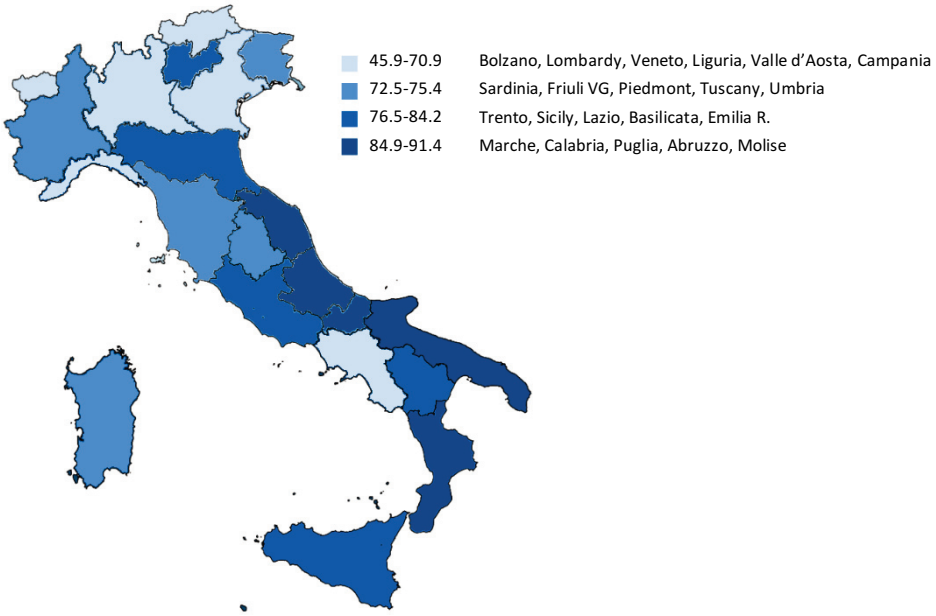


Figure 3.5.3c. Antiaggregants, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

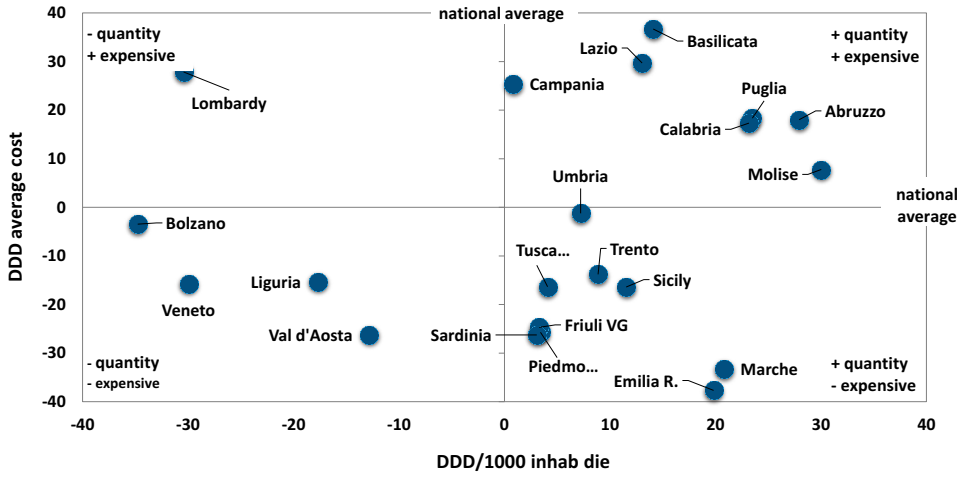


Figure 3.5.3d. Antiaggregants, regional variability of consumption in 2019 (weighted DDD/1000 inhab./day) by subgroup

(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)

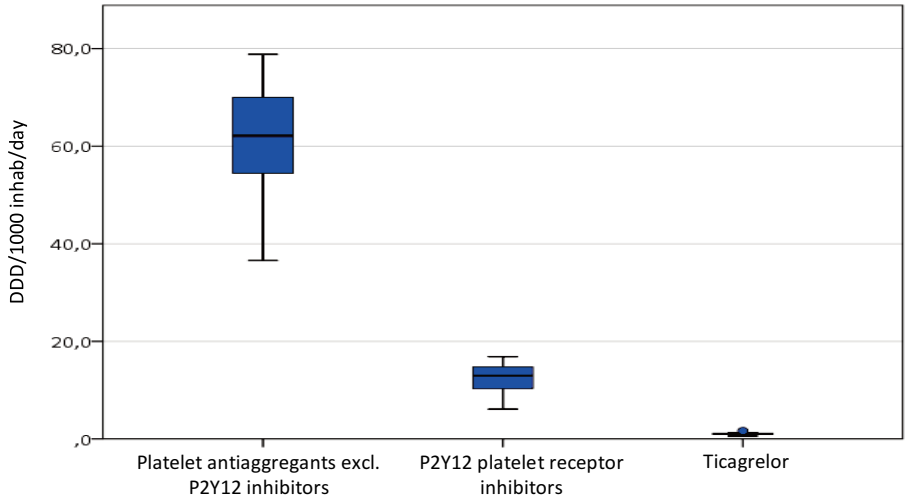


Figure 3.5.1e. Distribution of the prevalence of use and consumption of antiaggregants for NHS outpatient expenditure in 2019

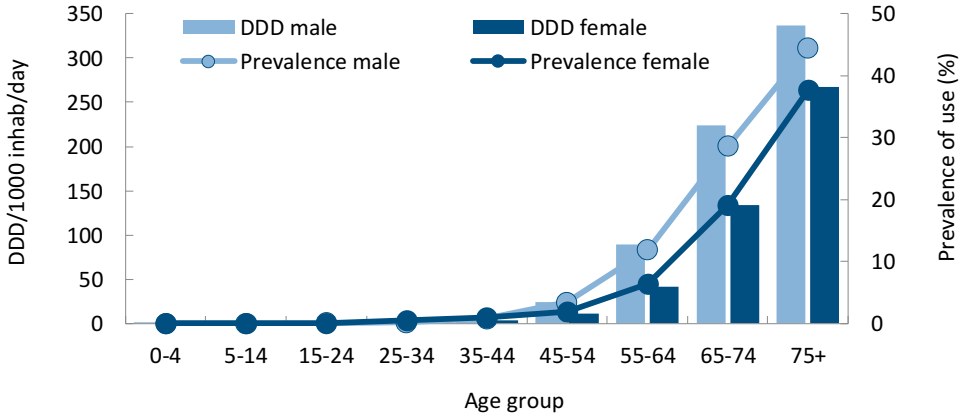


Table 3.5.1e. Duration of antiaggregant therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	User with 1 prescription
North	4.9	272.5	300.0	10.9
Centre	5.5	263.4	300.0	11.9
South and Islands	6.0	256.7	280.0	11.3
Antiaggregants	**5.5**	**264.3**	**300.0**	**11.3**

3.6 Central Nervous System

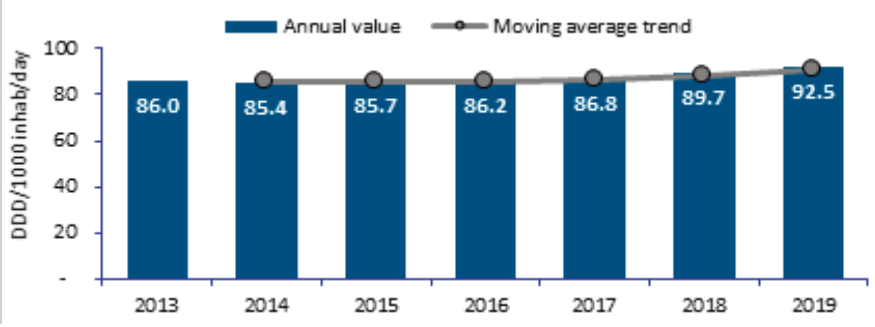
Central Nervous System drugs represent the sixth therapeutic category with the highest public expenditure in 2019, equal to approximately € 1,840.2 million and 7.9% of total public expenditure. The total per capita expenditure for these medicines was € 30.49 per capita, an increase (+3.5%) compared to 2018, mainly deriving from NHS outpatient pharmaceutical expenditure (€ 23.18 per capita), up on the previous year (+2.9%). On the contrary, the purchase by public health facilities was lower (€ 7.30 per capita), although there was an evident 5.3% increase within this supply method (Table 3.1).
The medicine utilization profile analysis by age group and gender (including NHS outpatient pharmaceuticals and *per conto* distribution) confirms the constant increase in the use of CNS pharmaceuticals with increasing age for both genders, with a higher prevalence of use in women from the age of 35 and up compared to men, in line with gender differences in the frequency of neuropsychiatric diseases. At the same time, the per capita expenditure incurred by the NHS also increases with the patient age, reaching the maximum levels of € 61.8 and € 78.3 per capita, respectively in men and women aged over 75 years.
As regards the NHS expenditure, the per capita expenditure for Central Nervous System drugs was equal to € 23.18, an increase of 2.9% compared to 2018. This trend was determined by a slight decrease in prices (-0.3%), an increase in consumption (+1.9%) and a slight shift of prescriptions towards more expensive specialties (mix effect: +1.1%; Table 3.9). Within this supply method, the other antiepileptics (e.g., topiramate, levetiracetam, pregabalin, etc.) are the first category in terms of expenditure (€ 4.36 per capita), increasing compared to the previous year (+ 5.9%). Selective serotonin reuptake inhibitors (SSRIs) continue to represent the category with the highest consumption (28.6 DDD) and the second for per capita expenditure (€ 3.27). Compared to the previous year, this category recorded a slight reduction in per capita expenditure (-0.6%) and a slight increase in consumption (+ 0.5%) (Table 3.9). Levetiracetam, a medicine indicated, among other things, for the treatment of epilepsy, is the first active ingredient in the category of drugs for the central nervous system for per capita expenditure (€ 1.55), with an increase compared to the previous year (+6.7%) (Table 3.5) and ranks among the top 30 active ingredients for NHS expenditure (Table 3.6). The active ingredient that recorded the greatest increase in consumption compared to the previous year was vortioxetine (+25.2%), a recently marketed antidepressant drug, followed by the antiepileptic drug lacosamide (+24.7%; Table 3.7).
As for purchases by public health structures, there was an increase in spending (+5.3%) and consumption (+5.7%) and a slight drop in prices (-0.6%). Within this supply method, the other antipsychotics represent the category with the greatest expense (€ 2.74), followed by the drugs used in opioid addiction with a per capita value of € 0.53. For both categories it is possible to notice an important increase in consumption, +9.6% and +12.8% respectively (Table 3.10). In 2019, paliperidone, indicated for the treatment of schizophrenia, is the medicine with the highest expenditure value per capita (€ 1.46), with a consumption of 0.7 DDD (Table 3.11). Methadone is the drug with the highest consumption (2.4 DDD), with an increase of 3.2% compared to 2018, while the antiepileptic lacosamide is the drug that has recorded the greatest increase both in terms of expenditure (+31,9%) and consumption (+ 36.6%) compared to the previous year (Table 3.11). No active substance belonging to the

category of CNS drugs appears among the first 30 drugs purchased by public health structures with the greatest expenditure (Table 3.12) and the greatest variation in expenditure in 2019 (Table 3.13).
For further information on the use of medicines of the same therapeutic area, analyses have been developed on the historical series of consumption by active principle and by Region and on the efficiency in the use of resources according to the presence of patent-expired pharmaceuticals and on a regional basis. Such analyses focused on antiparkinsonian, antipsychotic, antidepressant, antiepileptic, anti-dementia and pain therapy drugs.

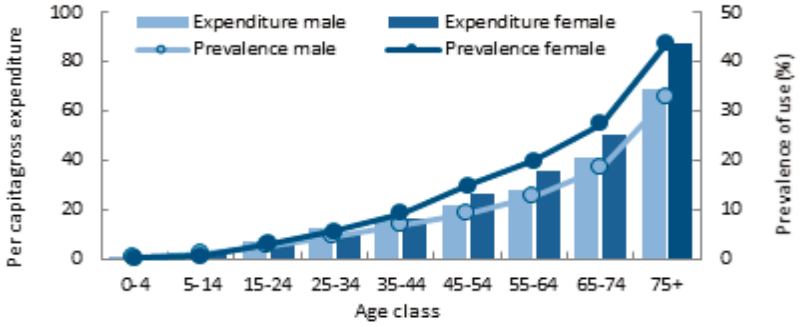
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Central nervous system

NHS expenditure, millions €* (% on the total)	**1,840.2**	**(7.9)**
Δ % 2019-2018		3.3
per capita gross expenditure, range among regions:	27.3	35.8
DDD/1000 inhab/day* (% on the total)	**92.1**	**(8.0)**
Δ % 2019-2018		3.0
DDD/1000 inhab/day, range among regions:	75.8	113.8

** includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure and *per conto* distribution 2019 (Chart and Table)



Age (group)	Gross per capita expenditure			DDD/1000 inhab/day		
	Men	Women	Total	Men	Women	Total
0-4	0.4	0.4	0.4	0.7	0.5	0.6
5-14	2.4	1.7	2.1	4.1	2.8	3.4
15-24	6.2	6.1	6.2	15.6	15.3	15.4
25-34	10.0	8.9	9.5	28.9	25.8	27.4
35-44	13.2	13.9	13.6	40.0	44.0	42.0
45-54	17.9	23.7	20.8	54.6	76.8	65.8
55-64	24.8	33.0	29.0	69.9	110.7	91.0
65-74	37.8	47.2	42.8	97.5	150.1	125.3
75+	61.8	78.3	71.7	164.1	231.4	204.5

3.6.1 Antiparkinsonians

- Parkinson's is a slow but progressive neurodegenerative disease that mainly involves some functions such as the control of movements and balance. The average age of onset is around 58-60 years, but about 5% of patients can have a juvenile onset between 21 and 40 years. It affects 1-2% of the population over 60, while the percentage rises to 3-5% in people over 85;
- consumption in 2019 was 5.3 DDD/1000 inhabitants/day (+2% compared to 2018). In the period 2014-2019 the average cost per day of therapy decreased from € 1.96 to € 1.75 (-11%); among the medicinal products that control the symptoms of the disease, dopa-derived agonists are the most used ones (2.4 DDD and +1.8% compared to 2018), followed by MAO inhibitors (1.6 DDD and +4.8%) and dopamine agonists (1.2 DDD; -3.6%). MAO inhibitors are also the category with the greatest regional variability (CV 36%);
- the associations of levodopa with benserazide and carbidopa are the most used molecules (1,1 and 0,9 DDD), while safinamide and malevodopa+carbidopa are those with the highest increase (+ 15,7% and +14,8 %). Opicapone (+500%), a COMT inhibitor marketed in 2018, is indicated as an additional therapy to the associations of levodopa/dopa decarboxylase inhibitors. The contraction in use regards in particular ropinirole (-7.3%), levodopa/carbidopa (-5.7%) and rotigotine (-1.9%), which remains, with € 0.73, the medicines with the highest expenditure;
- the regional variability ranges from a minimum of 3.7 DDD in the Autonomous Province of Bolzano to 6.5 in Abruzzo; Abruzzo, Umbria, Lazio, Puglia and Basilicata are the regions with consumption and average cost per day of therapy above the national average;
- the patent-expired drugs are more than half of the doses and about 40% of the expenditure, with a limited use of equivalent products (25% of the total), and an average cost per day of therapy which is about half that of the patent-covered drugs (1.20 vs 2.38);
- in line with the epidemiology of the condition, consumption increases with age and reaches a prevalence of over 4.3% in men aged ≥75 years; in particular, men aged 55 an over show a consumption more than 50% higher than that of women; on average, each user is treated for 9 months, half of the patients remain on therapy for less than five months and 14% receive only one prescription in the year.

Figure 3.6.1a. Antiparkinsonians, temporal consumption trend (2014-2019)

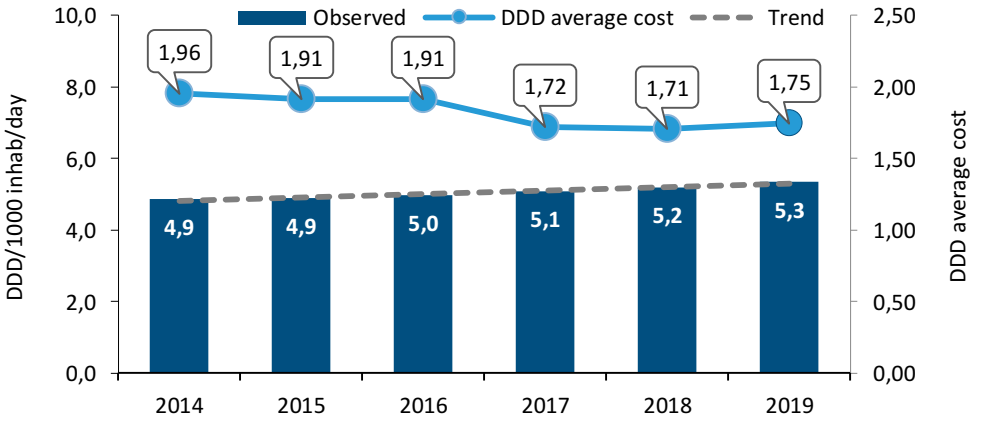


Table 3.6.1a. Antiparkinsonians, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Dopamine agonists	1.5	1.4	1.3	1.3	1.3	1.2	-3.6
Dopa-derived agonists	2.2	2.3	2.3	2.3	2.3	2.4	1.8
MAO inhibitors	1.1	1.2	1.3	1.4	1.6	1.6	4.8
COMT inhibitors	0.0	0.0	0.0	0.0	0.0	0.1	>100
Amantadine	0.0	0.0	0.0	0.0	0.0	0.0	>100
Antiparkinsonians	**4.9**	**4.9**	**5.0**	**5.1**	**5.2**	**5.3**	**2.8**
rotigotine	0.3	0.4	0.4	0.4	0.4	0.4	-1.9
levodopa/carbidopa	0.9	0.9	0.9	0.9	1.0	0.9	-5.7
pramipexole	0.6	0.5	0.5	0.5	0.5	0.5	-2.0
safinamide	0.0	0.0	0.1	0.1	0.2	0.2	15.7
levodopa/benserazide	0.9	0.9	0.9	0.9	1.0	1.1	10.1
rasagiline	0.4	0.4	0.4	0.4	0.4	0.4	4.9
melevodopa/carbidopa	0.2	0.2	0.3	0.3	0.2	0.2	14.8
opicapone	0.0	0.0	0.0	0.0	0.0	0.1	>100
ropinirole	0.5	0.5	0.4	0.4	0.4	0.3	-7.3
selegiline	0.7	0.8	0.9	0.9	1.0	1.0	2.7

Table 3.6.1b. Antiparkinsonians, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	5.4	5.4	5.4	5.6	5.7	5.8	3.1
Valle d'Aosta	4.4	4.4	4.4	4.6	5.0	5.2	3.9
Lombardy	4.2	4.2	4.3	4.4	4.5	4.6	1.7
A.P. of Bolzano	4.0	3.9	3.6	3.5	3.6	3.7	4.8
A.P. of Trento	4.4	4.4	4.4	4.5	4.5	4.5	-0.5
Veneto	4.8	4.9	4.9	5.0	5.1	5.3	3.4
Friuli VG	4.6	4.2	4.3	4.8	4.9	5.0	3.5
Liguria	5.9	6.0	6.0	6.2	6.3	6.3	0.0
Emilia R.	4.9	4.9	5.0	4.9	4.9	5.0	3.4
Tuscany	5.3	5.4	5.5	5.4	5.4	5.5	2.4
Umbria	5.5	5.6	5.7	5.7	5.9	6.1	2.9
Marche	5.8	5.9	5.9	6.0	6.1	6.1	0.1
Lazio	5.2	5.3	5.5	5.6	5.9	6.1	4.0
Abruzzo	5.3	5.6	5.7	5.9	6.3	6.5	2.9
Molise	4.9	4.8	5.0	5.0	5.1	5.3	3.7
Campania	4.4	4.5	4.6	4.8	5.0	5.2	4.0
Puglia	5.1	5.1	5.1	5.2	5.3	5.4	2.8
Basilicata	4.8	4.7	4.9	5.2	5.4	5.6	3.0
Calabria	4.6	4.7	4.7	4.8	4.8	4.9	2.6
Sicily	4.9	4.9	5.1	5.3	5.4	5.5	2.6
Sardinia	4.0	4.1	3.9	4.2	4.4	4.5	3.7
Italy	**4.9**	**4.9**	**5.0**	**5.1**	**5.2**	**5.3**	**2.8**

Table 3.6.1c. Antiparkinsonians, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Dopamine agonists	1.25	-2.7	1.2	-3.6	2.80	0.9
Dopa-derived agonists	1.24	4.8	2.4	1.8	1.42	2.9
MAO inhibitors	0.77	6.4	1.6	4.8	1.29	1.5
COMT inhibitors	0.16	>100	0.1	>1004	4.17	-3.2
Amantadine	0.00	69.8	0.0	>100	0.56	-22.9
Antiparkinsonians	**3.42**	**5.4**	**5.3**	**2.8**	**1.75**	**2.5**
rotigotine	0.73	-1.8	0.4	-1.9	5.27	0.1
levodopa/carbidopa	0.65	5.1	0.9	-5.7	1.95	11.4
pramipexole	0.39	-2.4	0.5	-2.0	2.13	-0.4
safinamide	0.37	11.5	0.2	15.7	4.42	-3.6
levodopa/benserazide	0.36	9.6	1.1	10.1	0.90	-0.4
rasagiline	0.28	2.0	0.4	4.9	2.05	-2.8
melevodopa/carbidopa	0.16	16.0	0.2	14.8	1.83	1.1
opicapone	0.14	>100	0.1	>100	4.20	-7.8
ropinirole	0.12	-7.4	0.3	-7.3	0.99	-0.1
selegiline	0.12	2.3	1.0	2.7	0.32	-0.3

Table 3.6.1d. Prescription of antiparkinsonians with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	1.24	36.4	-2.2	2.8	53.1	-0.2	1.20
Generic	0.29	23.2	3.4	0.7	23.4	9.2	1.19
Ex originator	0.95	76.8	-3.7	2.2	76.6	-2.8	1.20
Patent covered	2.17	63.6	10.2	2.5	46.9	6.4	2.38
Antiparkinsonians	**3.42**	**100.0**	**5.4**	**5.3**	**100.0**	**2.8**	**1.75**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.6.1b. Antiparkinsonians, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

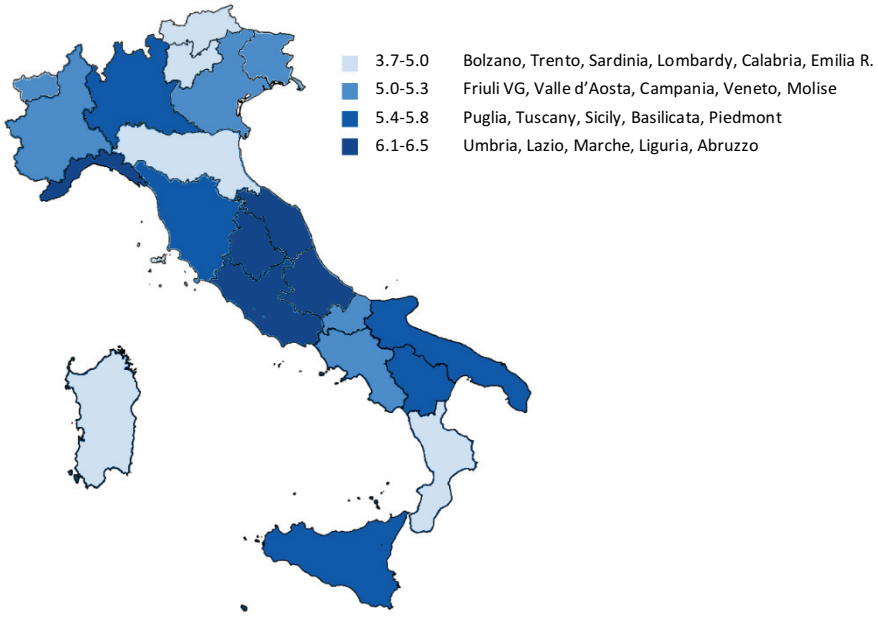


Figure 3.6.1c. Antiparkinsonians, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

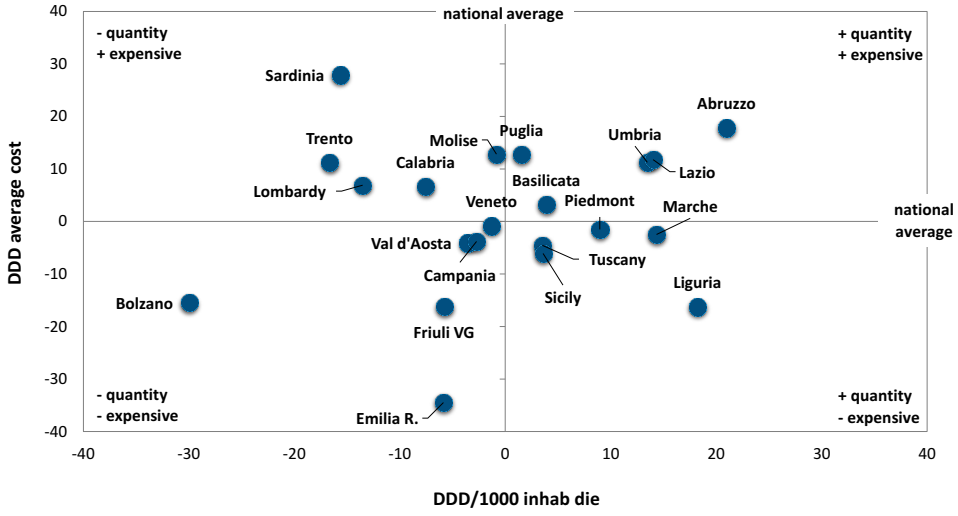


Figure 3.6.1d. Antiparkinsonians, regional variability of consumption in 2019 (weighted DDD/1000 inhab./day) by subgroup

(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)

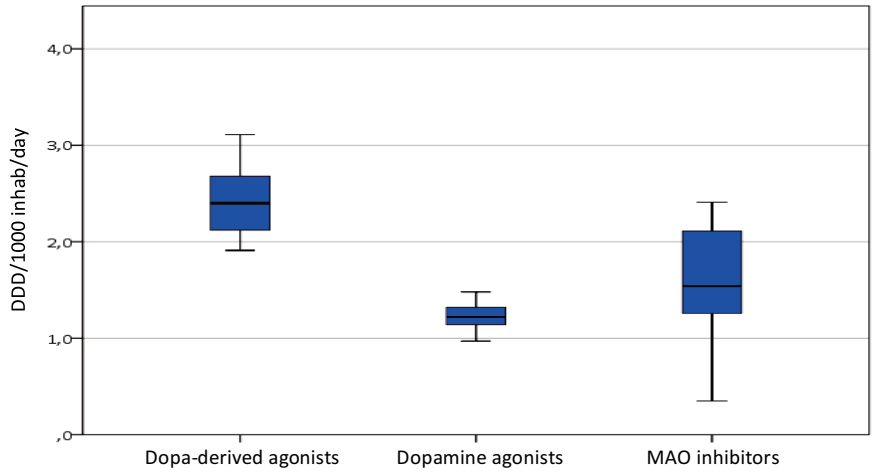


Figure 3.6.1e. Distribution of the prevalence of use and consumption of antiparkinsonians for NHS outpatient expenditure in 2019

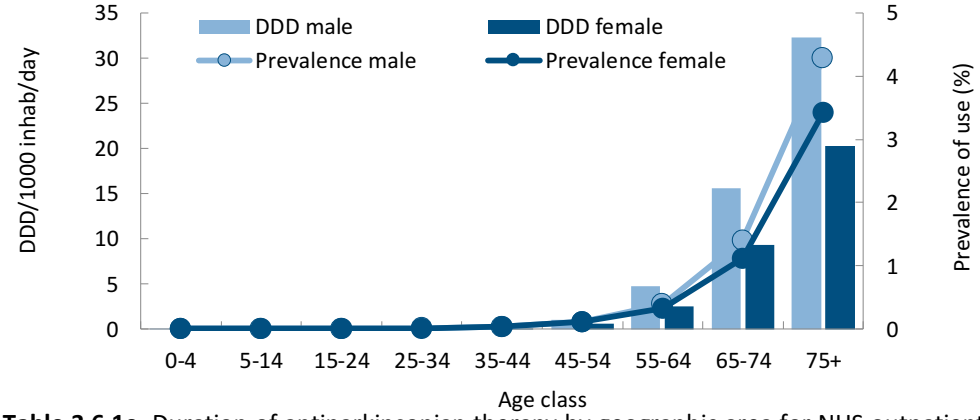


Table 3.6.1e. Duration of antiparkinsonian therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	User with 1 prescription
North	10.0	275.3	134.0	12.9
Centre	10.9	268.7	130.0	16.2
South and Islands	11.1	281.8	149.0	13.9
Antiparkinsonians	**10.6**	**275.9**	**136.0**	**14.0**

3.6.2 Antipsychotics

- In 2019 the use of antipsychotic medicinal products was 9.7 DDD/1000 inhabitants per day, a slight increase (+1.3%) compared to the previous year. Compared to 2014 the increase was +6,4%. On average, a day of therapy has a cost of € 1.34, a value not unlike that of previous years;
- about 80% of the doses are represented by atypical antipsychotics, an increase of 5% compared to the previous year, while at the same time the typical ones show an increase of 8.9%;
- also in 2019 paliperidone and aripiprazole are the two substances with the highest expenditure (€ 1.48 and € 1.03), both growing compared to 2018 (+10.2% and +8.0%); the only two typical antipsychotics included in the top ten are haloperidol and lithium with an increase of 0.8% and 3.8%. The only drug recently registered is lurasidone, an atypical antipsychotic indicated for the treatment of schizophrenia in adults from 18 years of age;
- Sardinia had an almost double consumption compared to the Autonomous Province of Trento (13.7 vs 7.8) and, in general, in almost all Southern regions (with the exception of Campania and Abruzzo), there is a greater use of these medicines compared to other geographical areas. Marche, Puglia and Calabria are also the regions that use the most doses, with a higher cost per day of therapy than the national average;
- the incidence of the use of patent-expired drugs is 71%, largely represented by the use of generics;
- in line with the epidemiology of the condition, the prevalence of use reaches about 6% in women aged ≥75 years; up to the age of 64, men use more doses than women, while in the following age groups the situation is reversed;
- half of the users have a treatment period of less than two months and about a quarter receive only one prescription in the year.

Figure 3.6.2a. Antipsychotics, temporal consumption trend (2014-2019)

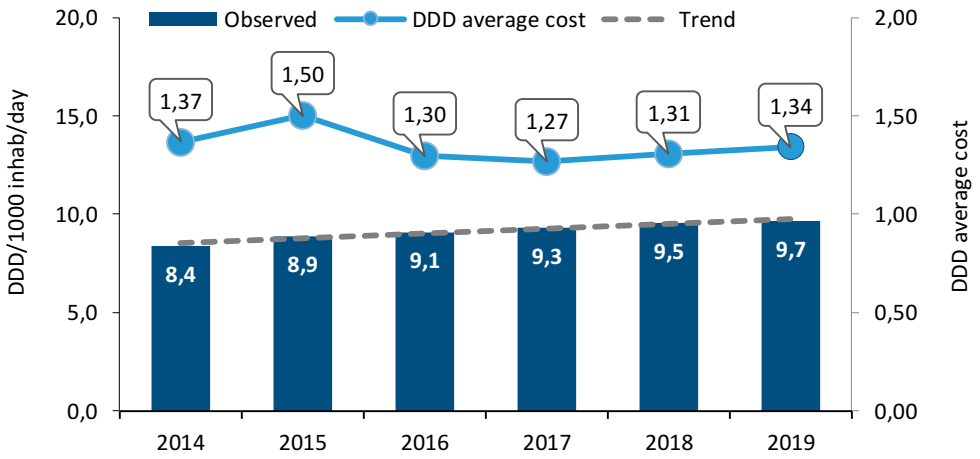


Table 3.6.2a. Antipsychotics, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Atypical and other antipsychotics	5.7	6.3	6.5	6.8	7.1	7.4	5.0
Typical antipsychotics	2.7	2.6	2.6	2.5	2.5	2.2	-9.6
Antipsychotics	**8.4**	**8.9**	**9.1**	**9.3**	**9.5**	**9.7**	**1.3**
paliperidone	0.4	0.5	0.5	0.6	0.7	0.8	10.2
aripiprazole	0.3	0.8	0.9	1.0	1.1	1.2	8.0
quetiapine	1.7	1.7	1.7	1.8	1.8	1.9	5.3
risperidone	0.9	0.9	0.9	0.9	0.8	0.9	4.4
olanzapine	1.9	2.0	2.0	2.0	2.0	2.0	-0.7
clozapine	0.4	0.4	0.4	0.4	0.4	0.4	4.2
haloperidol	1.2	1.1	1.2	1.1	1.1	1.1	0.8
lurasidone	0.0	0.0	0.0	0.0	0.0	0.1	>100
amisulpride	0.1	0.1	0.1	0.1	0.1	0.1	-2.6
lithium	0.3	0.4	0.4	0.4	0.3	0.4	3.8

Table 3.6.2b. Antipsychotics, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	8.7	8.9	9.4	9.4	9.6	9.6	0.2
Valle d'Aosta	6.4	6.4	5.7	6.6	7.1	8.4	18.6
Lombardy	6.5	7.0	7.2	7.5	7.8	7.9	0.7
A.P. of Bolzano	8.7	9.9	9.6	9.8	9.5	9.7	2.0
A.P. of Trento	6.9	8.4	8.2	8.1	9.2	7.8	-15.0
Veneto	9.0	9.3	9.3	9.4	9.5	9.8	2.5
Friuli VG	8.7	7.9	8.4	9.6	9.4	9.0	-4.1
Liguria	8.1	8.4	8.9	9.2	9.2	8.6	-6.4
Emilia R.	9.4	10.1	9.5	10.0	10.1	10.2	1.1
Tuscany	8.2	8.9	9.5	9.0	9.6	9.6	-0.5
Umbria	8.3	9.5	9.6	9.3	9.8	10.1	3.0
Marche	8.1	7.7	7.1	9.0	10.0	9.9	-1.7
Lazio	7.9	8.5	8.7	9.2	9.3	9.7	5.2
Abruzzo	9.1	9.3	9.6	9.4	10.2	9.6	-5.7
Molise	9.2	8.7	8.7	9.3	9.4	9.6	2.1
Campania	8.0	8.6	8.6	9.1	9.0	9.1	1.6
Puglia	9.2	9.7	10.2	10.4	10.8	11.0	1.3
Basilicata	8.9	9.8	10.4	11.0	10.2	11.2	9.7
Calabria	9.1	9.6	10.1	9.4	10.3	10.4	1.8
Sicily	9.5	10.1	10.6	10.4	10.3	10.9	6.1
Sardinia	11.3	13.0	13.1	13.0	13.8	13.7	-0.4
Italy	**8.4**	**8.9**	**9.1**	**9.3**	**9.5**	**9.7**	**1.3**

Table 3.6.2c. Antipsychotics, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
Atypical and other antipsychotics	4.43	4.4	7.4	5.0	1.63	-0.6
Typical antipsychotics	0.29	-1.5	2.2	-9.6	0.36	8.9
Antipsychotics	**4.72**	**4.0**	**9.7**	**1.3**	**1.34**	**2.7**
paliperidone	1.48	4.6	0.8	10.2	5.38	-5.1
aripiprazole	1.03	9.5	1.2	8.0	2.36	1.4
quetiapine	0.74	1.1	1.9	5.3	1.07	-4.0
risperidone	0.47	-4.2	0.9	4.4	1.48	-8.3
olanzapine	0.35	-0.3	2.0	-0.7	0.48	0.4
clozapine	0.15	3.2	0.4	4.2	0.90	-0.9
haloperidol	0.08	0.2	1.1	0.8	0.19	-0.6
lurasidone	0.08	>100	0.1	>100	2.47	-15.8
amisulpride	0.07	-3.0	0.1	-2.6	1.64	-0.4
lithium	0.06	0.8	0.4	3.8	0.48	-2.9

Table 3.6.2d. Prescription of antipsychotics with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	1.88	39.8	5.0	6.9	71.0	5.5	0.75
Generic	1.19	63.2	4.1	5.6	81.3	8.2	0.58
Ex originator	0.69	36.8	6.6	1.3	18.7	-5.0	1.48
Patent covered	2.84	60.2	3.3	2.8	29.0	-7.8	2.78
Antipsychotics	**4.72**	**100.0**	**4.0**	**9.7**	**100.0**	**1.3**	**1.34**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.6.2b. Antipsychotics, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

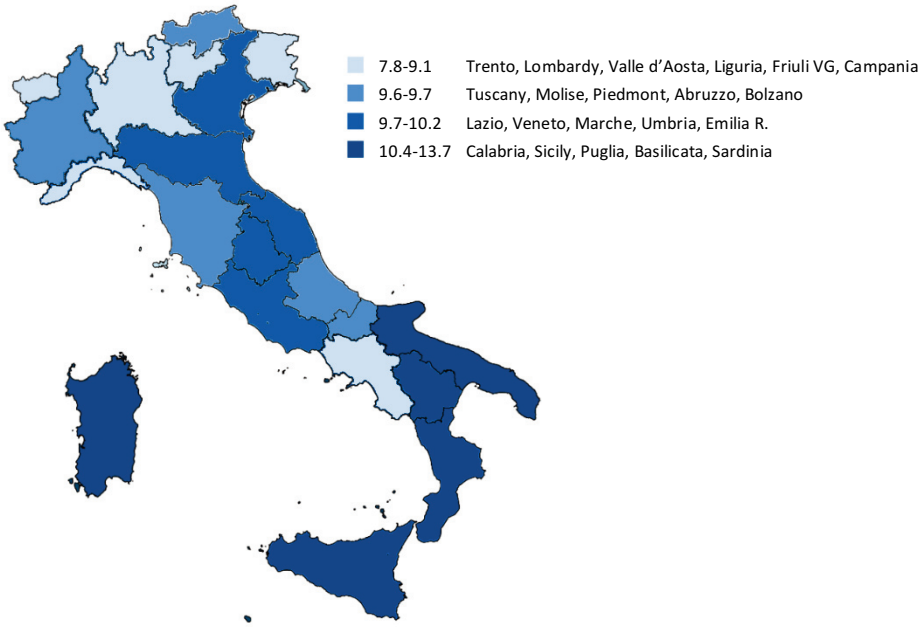


Figure 3.6.2c. Antipsychotics, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

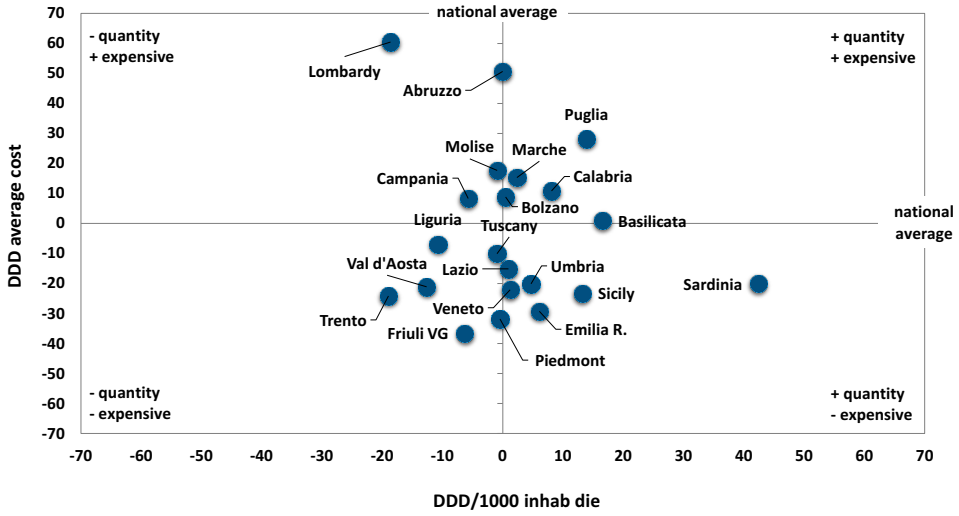


Figure 3.6.2d. Distribution of the prevalence of use and consumption of antipsychotics for NHS outpatient expenditure in 2019

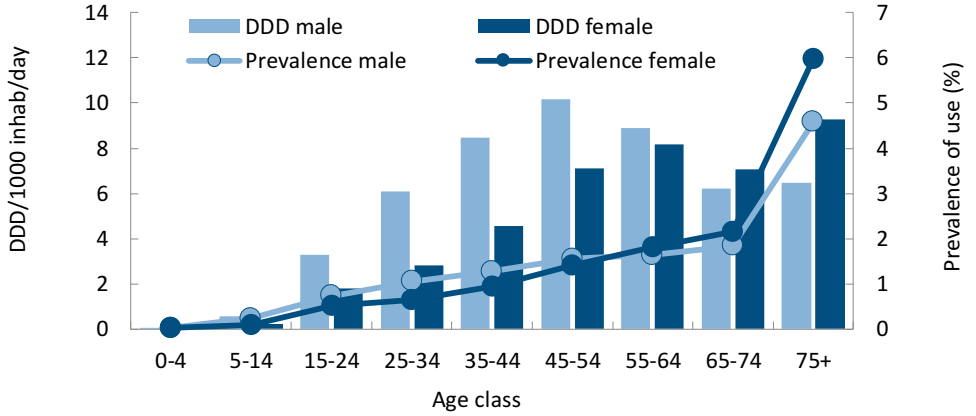


Table 3.6.2e. Duration of antipsychotic therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	Users with 1 prescription
North	6.0	118.8	50.0	21.9
Centre	6.4	112.1	45.0	25.1
South and Islands	7.8	154.6	69.0	17.6
Antipsychotics	**6.8**	**130.6**	**56.0**	**21.1**

3.6.3 Antidepressants

- Depressive disorders are part of mood disorders and include major depressive disorder (single episode or recurrent major depressive disorder), dysthymia and NOS (depressive disorder not otherwise specified). The prevalence in the population is around 5% and is higher in women with a peak in the 55-74 age group;
- antidepressants represent 3.7% of NHS consumption in Italy in 2019 equal to 42.4 DDD, an increase of 2.1% compared to 2018. In the last four years the average cost per day of therapy has remained stable at a value equal to € 0.42;
- SSRIs with 29.9 DDD are the most used category (71% of the total) increasing by 0.9% compared to the previous year with a marked regional variability (CV 21%); the serotonin modulating drugs, of which vortioxetine is the only approved medicine, are the category with the highest growth rate (+25.7%);
- also in 2019 paroxetine (SSRI) was confirmed as the most used active ingredient (7.9 DDD), even if it is sertraline that recorded the greatest increase (+3.7%) within that class; other molecules with significant increases are bupropion (+6.2%), a norepinephrine-dopamine reuptake inhibitor indicated for smoking cessation, and duloxetine (+5.3%);
- Tuscany with 63.1 DDD had a double consumption compared to Campania (32.9 DDD) with a very evident North-South gradient. Marche and Sardinia are the regions that use the most doses, with a higher cost per day of therapy than the national average;
- patent-expired drugs now represent about 90% of the doses and more than half of these are equivalent;
- consumption increases with age and, in women aged 75+ years, it reaches around 25% prevalence. The average duration of therapy is 223 days, but 50% of users are treated for less than 6 months and one patient in five receives only one prescription per year. Low adherence is a critical aspect of antidepressant therapy; moreover, sporadic use could indicate use for symptoms not relating to depression.

Figure 3.6.3a. Antidepressants, temporal consumption trend (2014-2019)

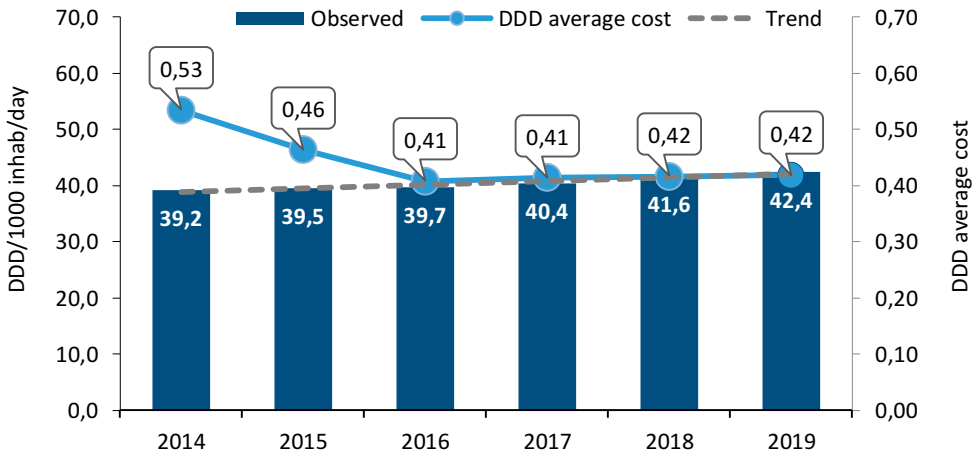


Table 3.6.3a. Antidepressants, consumption (DDD/1000 inhab./day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
SSRI antidepressants	29.2	29.3	29.2	29.1	29.7	29.9	0.9
SNRI antidepressants	6.1	6.2	6.2	6.3	6.5	6.7	3.3
Other antidepressants	2.4	2.6	2.7	2.9	3.0	3.1	2.9
SMS (serotonin modulators and stimulators)	0.0	0.0	0.2	0.8	1.1	1.4	25.7
Tricyclic antidepressants	1.2	1.1	1.1	1.1	1.1	1.1	-0.1
Bupropion	0.3	0.2	0.2	0.2	0.2	0.3	6.2
Nari (norepinephrine reuptake inhibitors)	0.0	0.0	0.0	0.0	0.0	0.0	-1.4
NaSSA (agomelatoninergic)	0.0	0.0	0.0	0.0	0.0	0.0	-35.2
Antidepressants	**39.2**	**39.5**	**39.7**	**40.4**	**41.6**	**42.4**	**2.1**
paroxetine	8.0	7.9	7.8	7.8	8.0	7.9	-0.5
escitalopram	7.3	7.3	7.3	7.2	7.3	7.4	1.0
venlafaxine	3.4	3.5	3.5	3.5	3.5	3.6	1.7
duloxetine	2.7	2.7	2.7	2.8	2.9	3.1	5.3
sertraline	7.2	7.6	7.7	7.9	8.2	8.5	3.7
vortioxetine	0.0	0.0	0.2	0.8	1.1	1.4	25.7
trazodone	0.8	1.0	1.1	1.1	1.2	1.2	3.3
citalopram	4.8	4.6	4.4	4.3	4.3	4.2	-1.8
mirtazapine	1.6	1.6	1.6	1.7	1.7	1.8	3.8
bupropion	0.3	0.2	0.2	0.2	0.2	0.3	6.2

Table 3.6.3b. Antidepressants, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	44.3	44.6	45.2	46.0	47.3	48.5	2.6
Valle d'Aosta	38.8	38.5	38.1	38.5	40.0	41.5	3.6
Lombardy	36.6	37.1	37.6	38.3	39.5	39.9	1.0
A.P. of Bolzano	52.1	53.0	53.5	53.6	54.5	56.0	2.7
A.P. of Trento	38.1	38.4	38.9	39.6	41.5	42.6	2.6
Veneto	37.3	37.9	37.8	38.7	40.3	41.2	2.4
Friuli VG	34.1	34.0	33.6	34.4	35.7	36.4	2.0
Liguria	53.3	53.4	52.8	54.2	55.2	56.2	1.9
Emilia R.	50.1	50.3	49.0	49.9	52.1	53.3	2.3
Tuscany	60.7	60.7	60.7	61.5	62.2	63.1	1.6
Umbria	50.4	51.0	51.9	52.5	53.9	54.5	1.2
Marche	41.3	41.7	42.2	42.6	43.6	44.9	2.8
Lazio	34.5	34.9	35.1	35.7	36.7	37.7	2.5
Abruzzo	36.8	37.2	37.8	38.7	40.1	41.3	2.9
Molise	33.1	32.1	31.8	32.9	34.4	35.5	3.1
Campania	29.3	29.9	30.5	31.0	32.1	32.9	2.4
Puglia	30.7	31.0	31.1	31.7	32.6	33.7	3.5
Basilicata	30.5	30.9	31.2	31.5	31.9	32.9	3.1
Calabria	36.6	37.0	37.4	37.8	38.8	39.5	1.7
Sicily	30.7	31.0	31.4	32.0	33.0	33.8	2.3
Sardinia	43.8	44.1	43.9	44.4	45.1	45.1	-0.1
Italy	**39.2**	**39.5**	**39.7**	**40.4**	**41.6**	**42.4**	**2.1**

Table 3.6.3c. Antidepressants, prescription by therapeutic category and by substance in 2019

Subgroups and substances	per capita expenditure	Δ % 19-18	DDD/1000 inhab./day	Δ % 19-18	DDD average cost	Δ % 19-18
SSRI antidepressants	3.28	-0.3	29.9	0.9	0.30	-1.2
SNRI antidepressants	1.53	2.7	6.7	3.3	0.63	-0.6
Other antidepressants	0.76	3.1	3.1	2.9	0.67	0.2
SMS (serotonin modulators and stimulators)	0.57	25.6	1.4	25.7	1.13	-0.1
Tricyclic antidepressants	0.17	-0.3	1.1	-0.1	0.44	-0.2
Bupropion	0.17	1.7	0.3	6.2	1.76	-4.2
Nari (norepinephrine reuptake inhibitors)	0.01	-0.7	0.0	-1.4	0.90	0.7
NaSSA (agomelatoninergic)	0.00	-38.1	0.0	-35.2	2.00	-4.5
Antidepressants	**6.49**	**2.7**	**42.4**	**2.1**	**0.42**	**0.6**
paroxetine	1.00	-2.6	7.9	-0.5	0.35	-2.1
escitalopram	0.94	0.2	7.4	1.0	0.35	-0.8
venlafaxine	0.78	1.3	3.6	1.7	0.59	-0.4
duloxetine	0.75	4.1	3.1	5.3	0.67	-1.1
sertraline	0.73	3.3	8.5	3.7	0.23	-0.4
vortioxetine	0.57	25.6	1.4	25.7	1.13	-0.1
trazodone	0.42	3.7	1.2	3.3	0.92	0.4
citalopram	0.41	-2.2	4.2	-1.8	0.27	-0.4
mirtazapine	0.33	3.8	1.8	3.8	0.51	0.0
bupropion	0.17	1.7	0.3	6.2	1.76	-4.2

Table 3.6.3d. Prescription of antidepressants with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab./day	%	Δ % 19-18	DDD average cost
Patent expired	4.99	77.0	1.4	37.7	88.9	1.8	0.36
Generic	2.05	41.1	4.6	19.2	50.8	3.5	0.29
Ex originator	2.94	58.9	-0.6	18.5	49.2	0.0	0.43
Patent covered	1.49	23.0	7.2	4.7	11.1	4.4	0.87
Antidepressants	**6.49**	**100.0**	**2.7**	**42.4**	**100.0**	**2.1**	**0.42**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.6.3b. Antidepressants, distribution in quartiles of consumption in 2019 (weighted DDD/1000 inhab./day)

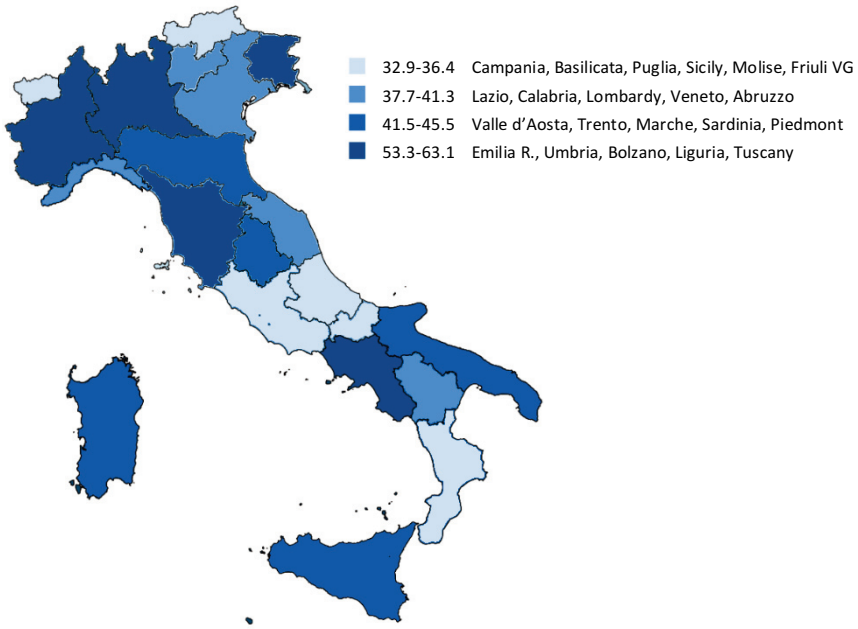


Figure 3.6.3c. Antidepressants, regional variability of pharmaceutical consumption 2019 by quantity and average cost per day of therapy (% deviations from the national average)

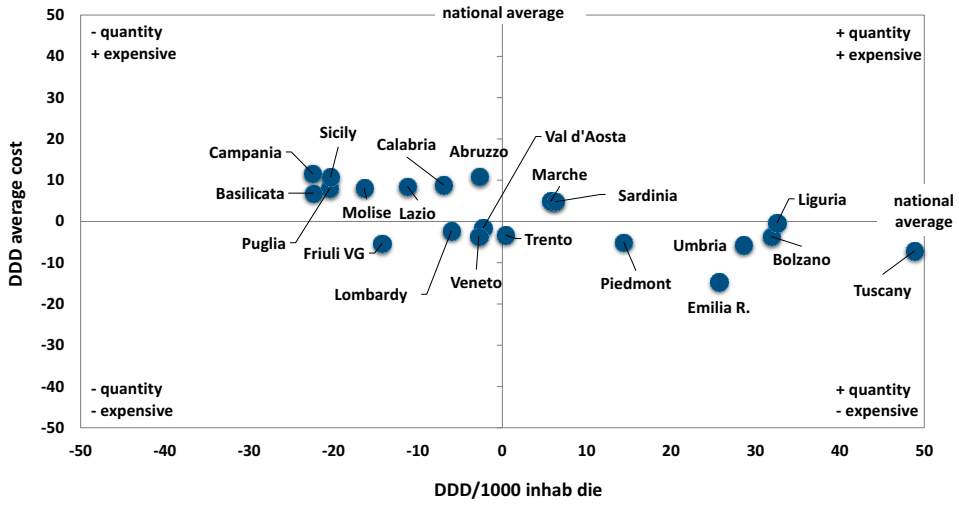


Figure 3.6.3d. Antidepressants, regional variability of consumption in 2019 (weighted DDD/1000 inhab./day) by subgroup

(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)

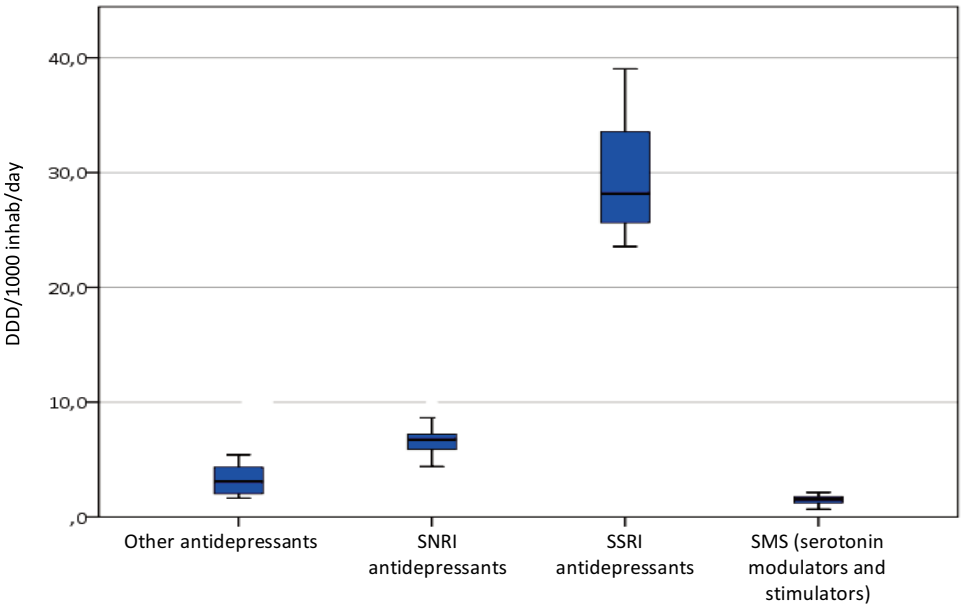


Figure 3.6.3e. Distribution of the prevalence of use and consumption of antidepressants for NHS outpatient expenditure in 2019

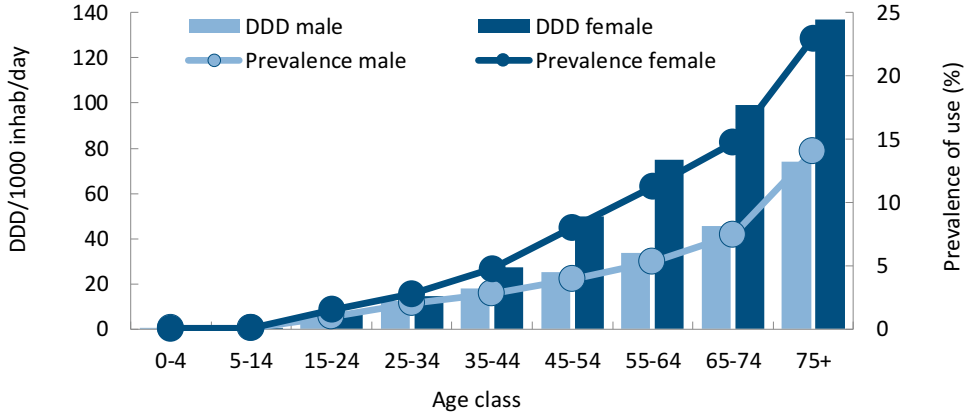


Table 3.6.3e. Duration of antidepressant therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	median DDD	User with 1 prescription
North	5.3	229.1	180.0	20.0
Centre	5.6	222.3	180.0	20.8
South and Islands	5.7	215.5	168.0	22.0
Antidepressants	**5.5**	**223.5**	**180.0**	**20.8**

3.6.4 Antiepileptic medicines

(prescription for pregabalin and gabapentin is not included)

- Epilepsy is one of the most frequent neurological pathologies, recognized as a social disease by the WHO. It can begin at all ages of life but its highest peaks in incidence occur in children and elderly people. Epilepsy affects about one person in 100 people: it is estimated that 500,000 - 600,000 people are affected in Italy;
- the consumption of antiepileptic drugs increased from 10 DDD to 10.6 in 2019 (+7%) in 2014 and, at the same time, the average cost per day of therapy reached € 1.28 with a growth of 15% compared to 2014;
- the category of other antiepileptic drugs reached 4.1 DDD (+6.4% compared to 2018) followed by fatty acid derivatives which is stable with 2.5 DDD but does show a marked regional difference (CV 20 %);
- levetiracetam and valproic acid are the two most used molecules (2.5 DDD), both increasing by 4.7% and 1.2% respectively; lacosamide is instead the ingredient that shows the highest increase (+26.2 %). Such ingredient is indicated as additional therapy in the treatment of partial seizures with or without secondary generalization in patients with epilepsy from 16 years of age;
- the use of antiepileptic drugs is quite heterogeneous among Italian regions; Calabria does outline a level of consumption 40% higher than the one in Lombardy (12.1 vs 8.6 DDD) with a growing North-South gradient; most of the Italian regions, together with Lazio, do use more doses and with a cost per day of therapy higher than the national average;
- patent expired drugs take into account 56% of the category's total number and, among these, one third is represented by equivalent drugs increasing up to 9% compared to 2018;
- consumption increases with age, and in male population of all age groups it is higher than women; the overall prevalence of use is around 2% and it does reach 4% in the population aged 75+;
- the average duration of therapy is 6 months, half of patients have been treated for just over three months (in the North patients have been treated for four months) and 1 user out of 5 does receive only a single prescription.

Figure 3.6.4a. Antiepileptics, temporal consumption trend (2014-2019)

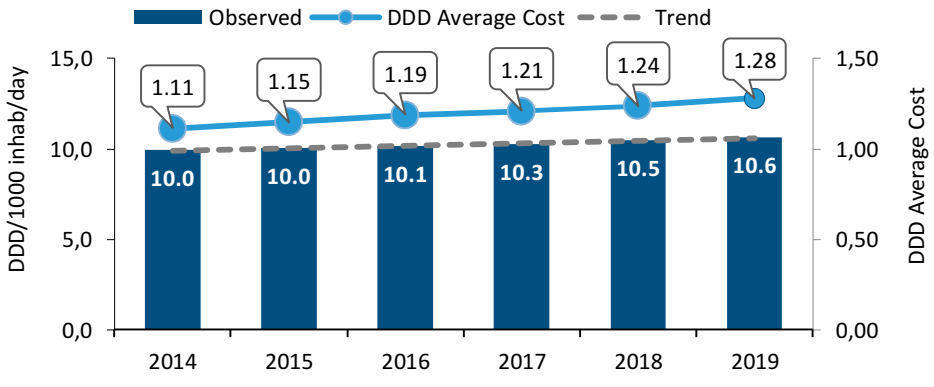


Table 3.6.4a. Antiepileptics, consumption (DDD/1000 inhab./per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Other antiepileptic drugs	2.9	3.2	3.4	3.6	3.9	4.1	6.4
Fatty acid derivatives - valproic acid and derivatives	2.4	2.4	2.4	2.5	2.5	2.5	0.9
Carboxamide derivatives	2.1	2.1	2.0	2.0	2.0	1.9	-1.6
Benzodiazepine derivatives	0.4	0.4	0.4	0.4	0.4	0.4	-0.2
Barbiturates and derivatives	1.9	1.7	1.6	1.6	1.5	1.4	-3.2
Fatty acid derivatives not associated/in combination with other ingredients	0.0	0.0	0.0	0.0	0.0	0.0	-4.1
Phenytoin not associated or combined with other ingredients	0.2	0.2	0.2	0.2	0.1	0.1	-6.4
Succinimide derivatives	0.0	0.0	0.0	0.0	0.0	0.0	27.5
Antiepileptics	**10.0**	**10.0**	**10.1**	**10.3**	**10.5**	**10.6**	**1.8**
levetiracetam	1.7	1.9	2.1	2.2	2.4	2.5	4.7
valproic acid	2.4	2.4	2.4	2.4	2.5	2.5	1.2
lacosamide	0.1	0.2	0.2	0.2	0.2	0.3	26.2
lamotrigine	0.6	0.6	0.7	0.7	0.7	0.8	4.5
topiramate	0.4	0.4	0.4	0.4	0.4	0.4	-0.9
carbamazepine	1.4	1.4	1.3	1.3	1.3	1.3	-2.0
oxcarbazepine	0.7	0.7	0.7	0.6	0.6	0.6	-1.3
perampanel	0.0	0.0	0.0	0.0	0.0	0.1	19.6
rufinamide	0.0	0.0	0.0	0.0	0.0	0.0	1.4
clonazepam	0.4	0.4	0.4	0.4	0.4	0.4	-0.2

Table 3.6.4b. Antiepileptics, weighted regional trend of DDD/1000 inhabitants: 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	9.7	9.7	9.9	10.2	10.3	10.5	2.1
Valle d'Aosta	9.3	9.3	8.7	8.9	8.8	8.9	0.9
Lombardy	8.1	8.2	8.3	8.4	8.5	8.6	1.2
A.P. of Bolzano	9.3	9.5	9.8	10.0	10.0	10.1	1.2
A.P. of Trento	10.6	10.6	10.5	10.8	10.7	10.8	0.4
Veneto	9.2	9.3	9.4	9.5	9.6	9.8	1.6
Friuli VG	9.4	9.3	9.5	9.6	9.8	10.0	2.2
Liguria	10.4	10.6	10.5	10.6	10.8	10.9	0.6
Emilia R.	9.8	9.9	9.9	10.0	10.2	10.3	0.7
Tuscany	11.1	11.6	11.6	11.6	11.7	11.9	1.1
Umbria	11.4	11.5	11.6	11.6	11.8	11.9	0.9
Marche	11.4	11.3	11.5	11.5	11.7	11.8	0.8
Lazio	10.4	10.5	10.7	10.9	11.0	11.3	2.8
Abruzzo	11.5	11.5	11.5	11.5	11.8	12.1	2.4
Molise	10.5	10.4	10.5	10.7	10.9	11.1	2.0
Campania	10.7	10.6	10.7	10.9	11.2	11.5	2.7
Puglia	10.3	10.4	10.5	10.6	10.8	11.1	2.9
Basilicata	11.1	11.4	11.5	11.6	11.7	11.9	2.3
Calabria	11.1	11.1	11.3	11.5	11.8	12.1	2.3
Sicily	10.1	10.2	10.5	10.7	10.9	11.2	2.4
Sardinia	11.2	11.2	11.1	11.3	11.4	11.4	-0.3
Italy	**10.0**	**10.0**	**10.1**	**10.3**	**10.5**	**10.6**	**1.8**

Table 3.6.4c. Antiepileptics, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab./per day	Δ % 19-18	Average Cost DDD	Δ % 19-18
Other antiepileptics	3.30	7.6	4.1	6.4	2.18	1.1
Fatty acid derivatives - valproic acid and derivatives	0.98	1.7	2.5	0.9	1.06	0.9
Carboxamide derivatives	0.53	-1.1	1.9	-1.6	0.74	0.4
Benzodiazepine derivatives	0.07	0.4	0.4	-0.2	0.45	0.5
Barbiturates and derivatives	0.05	-3.3	1.4	-3.2	0.10	-0.1
Fatty acid derivatives not associated and in combination with other ingredients	0.03	-4.4	0.0	-4.1	2.82	-0.3
Phenytoin not associated and in combination with other ingredients	0.01	-5.4	0.1	-6.4	0.18	1.1
Succinimide derivatives	0.01	22.4	0.0	27.5	0.65	-4.0
Antiepileptics	**4.97**	**5.1**	**10.6**	**1.8**	**1.28**	**3.2**
levetiracetam	1.71	2.3	2.5	4.7	1.89	-2.3
valproic acid	0.98	2.0	2.5	1.2	1.07	0.8
lacosamide	0.63	23.2	0.3	26.2	5.58	-2.3
lamotrigine	0.44	5.3	0.8	4.5	1.58	0.7
topiramate	0.29	-1.0	0.4	-0.9	2.19	-0.1
carbamazepine	0.25	-1.8	1.3	-2.0	0.53	0.3
oxcarbazepine	0.19	-2.4	0.6	-1.3	0.82	-1.2
perampanel	0.10	18.0	0.1	19.6	5.31	-1.3
rufinamide	0.07	0.6	0.0	1.4	9.79	-0.8
clonazepam	0.07	0.4	0.4	-0.2	0.45	0.5

Table 3.6.4d. Prescription of antiepileptics with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	Average Cost DDD
Patent expired	2.97	59.7	3.2	5.9	55.8	2.0	1.37
Generic	0.89	29.9	9.0	1.7	28.3	9.0	1.45
Ex originator	2.08	70.1	1.0	4.3	71.7	-0.6	1.34
Patent covered	2.00	40.3	7.9	4.7	44.2	1.5	1.17
Antiepileptics	**4.97**	**100.0**	**5.1**	**10.6**	**100.0**	**1.8**	**1.28**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.6.4b. Antiepileptics, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab./per day)

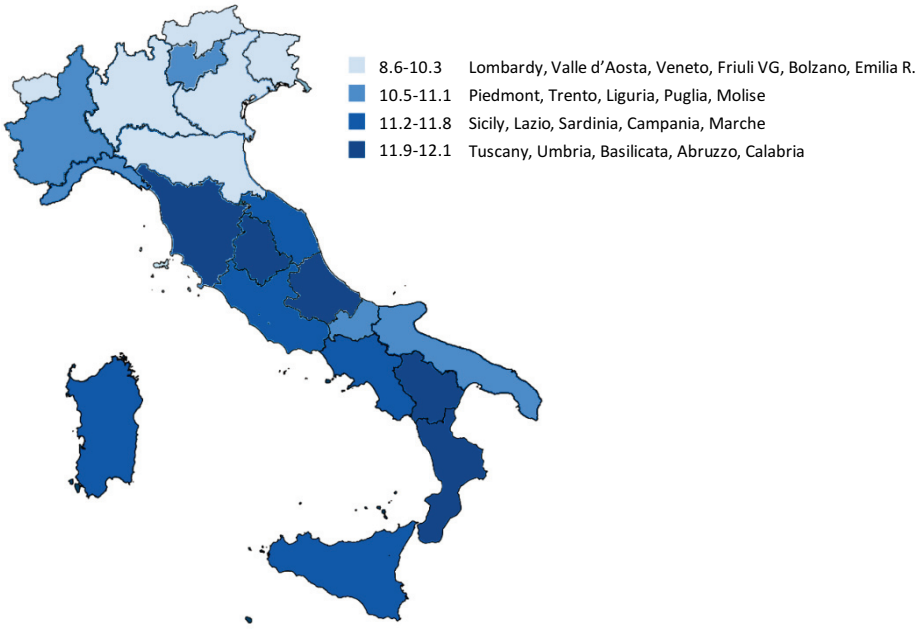


Figure 3.6.4c. Antiepileptics, regional variability of the 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviation from the national average)

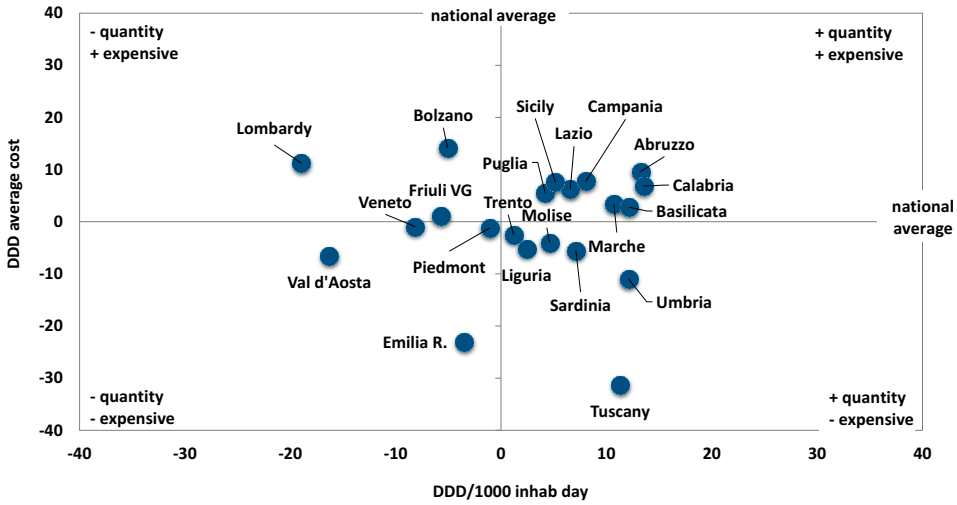


Figure 3.6.4d. Antiepileptics, regional variability of the 2019 consumption (weighted DDD/1000 inhab./per day) by sub-group

(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)

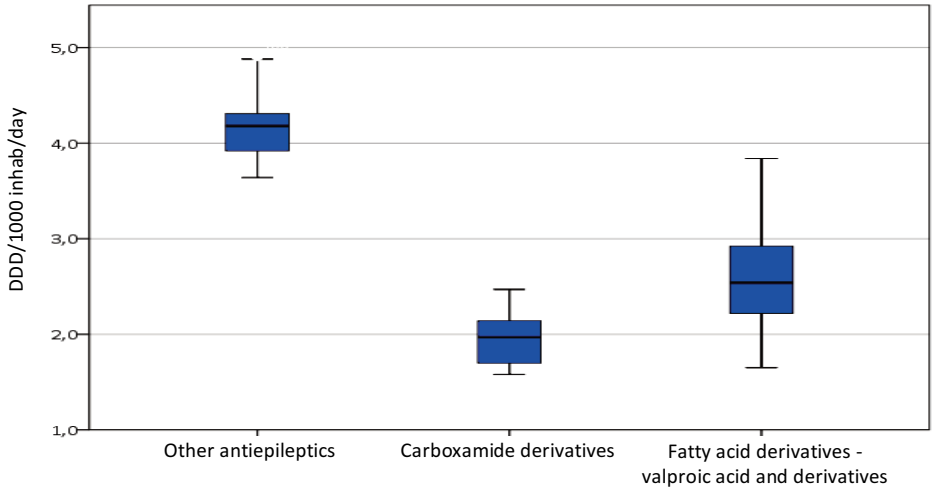


Figure 3.6.4e. Distribution of the prevalence of use and consumption of antiepileptics for NHS outpatient expenditure (year 2019)

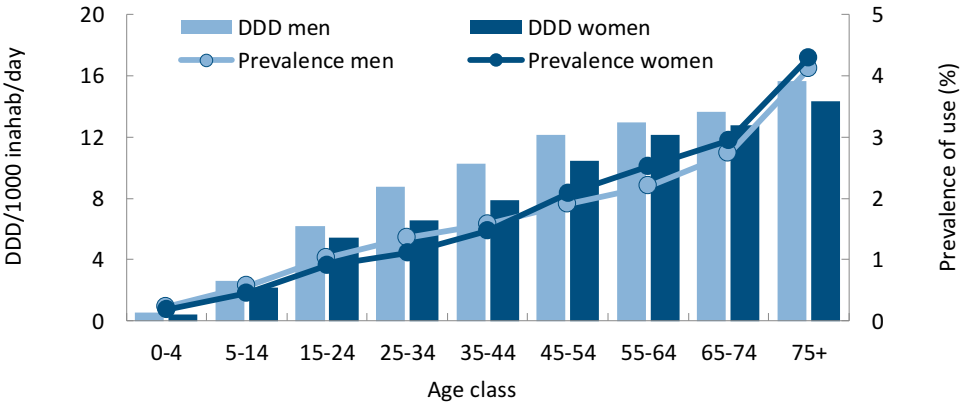


Table 3.6.4e. Duration of antiepileptic therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	8.0	197.9	123.0	15.0
Centre	7.7	154.5	80.0	21.3
South and Islands	8.6	180.4	108.0	16.3
Antiepileptic drugs	**8.2**	**180.3**	**108.0**	**17.1**

3.6.5 Anti-dementia medicines

- Dementia generally refers to a condition of chronic and progressive dysfunction of brain functions that leads to a decline in the cognitive faculties of the person affected. This condition affects 1 to 5% of the population over 65 years of age; the disease affects twice as many people every 4 years, thus reaching a percentage of about 30% in the age group over 80;
- in 2019 anti-dementia drugs increased by 4.9% compared to the previous year and by 10% compared to 2014. In the same period, the average cost per day of therapy halved (from € 1.19 to € 0.50) because of the expiry of all the molecules belonging to the category;
- acetylcholinesterase inhibitors represent 60% of the total (1.5 DDD) up to 3.6%, mainly determined by donepezil's consumption (+ 10.7%) while the other two molecules have decreased their trend with values of 5.3% for rivastigmine and of -8.2% for galantamine. The remaining 40% (1 DDD) refers to memantine, a NMDA receptor antagonist (N-methyl-d-aspartate), whose level of consumption has increased by 6.9% compared to 2018;
- the Autonomous Province (AP) of Bolzano is the region with the highest use of such drugs (4.7 DDD) and the Autonomous Province of Trento is the region with the lowest level of consumption (1.2 DDD). Marche and Sardinia highlight the most significant increases compared to 2018 (+55.8% and +41.5% respectively), while the Autonomous Province of Bolzano and Umbria are the regions that use the most doses and with a price above the national average;
- patent expired drugs (largely equivalents) take into account the 87% of doses and the 81% of the expenditure;
- as expected, their use is concentrated in people over 75 years of age, with a higher level of consumption in women (2.5% prevalence of use and 16.6 DDD);
- in one year, each user has been treated for about 242 days, half of the patients were on therapy for less than 7 months (6 months in the regions of the Centre of Italy) and 15.7% of the users obtained a single prescription (14.1% per North, 22.3% in the Centre and 12.4% in the South).

Figure 3.6.5a. Anti-dementia medicines, temporal consumption trend (2014-2019)

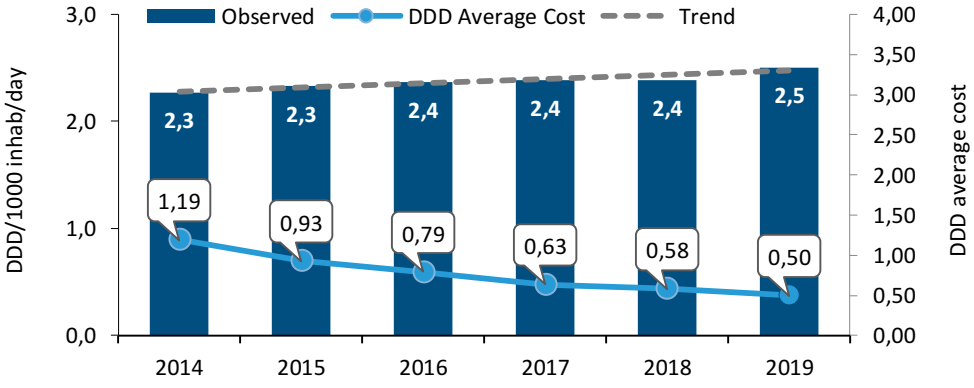


Table 3.6.5a. Anti-dementia medicines, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Anticholinesterase	1.5	1.5	1.5	1.5	1.4	1.5	3.6
Other anti-dementia drugs	0.8	0.8	0.9	0.9	0.9	1.0	6.9
Anti-dementia medicines	**2.3**	**2.3**	**2.4**	**2.4**	**2.4**	**2.5**	**4.9**
Rivastigmine	0.7	0.7	0.6	0.6	0.6	0.6	-5.3
Memantine	0.8	0.8	0.9	0.9	0.9	1.0	6.9
Donepezil	0.8	0.8	0.8	0.8	0.8	0.9	10.7
Galantamine	0.1	0.1	0.1	0.1	0.0	0.0	-8.2

Table 3.6.5b. Anti-dementia medicines, weighted regional trend of DDD / 1000 inhab.: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	2.2	2.2	2.1	2.1	2.0	2.2	6.2
Valle d'Aosta	2.0	1.4	1.8	1.8	2.0	2.1	2.4
Lombardy	2.0	2.2	2.2	2.2	2.3	2.2	-0.9
AP of Bolzano	3.5	4.2	4.6	4.1	4.7	4.7	0.6
AP of Trento	1.3	1.2	1.2	1.1	1.2	1.2	-1.1
Veneto	2.4	2.5	2.6	2.6	2.8	2.9	3.7
Friuli VG	2.0	1.5	1.6	2.2	2.1	2.1	1.0
Liguria	3.6	3.5	3.3	3.8	3.2	3.7	15.6
Emilia R.	1.9	1.8	1.9	1.9	1.9	2.0	3.2
Tuscany	3.1	3.5	3.7	3.2	3.5	3.4	-2.7
Umbria	3.3	3.4	3.7	3.7	4.0	4.2	4.8
Marche	2.5	2.2	1.5	1.6	2.4	3.7	55.8
Lazio	2.4	2.3	2.4	2.7	2.6	2.6	-0.2
Abruzzo	3.7	3.8	3.7	3.7	4.0	3.8	-6.3
Molise	1.7	1.8	2.0	2.3	2.3	2.5	5.9
Campania	2.1	2.3	2.4	2.5	2.1	2.5	21.2
Puglia	2.1	2.2	2.2	2.2	2.2	2.2	-0.4
Basilicata	1.7	1.8	1.8	2.3	2.1	2.3	11.5
Calabria	2.2	2.1	2.2	1.9	2.1	2.1	-0.2
Sicily	1.8	1.7	1.7	1.6	1.7	1.6	-1.5
Sardinia	2.3	2.1	2.2	2.1	1.5	2.2	41.5
Italy	**2.3**	**2.3**	**2.4**	**2.4**	**2.4**	**2.5**	**4.9**

Table 3.6.5c. Anti-dementia medicines, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	Average Cost DDD	Δ % 19-18
Anticholinesterase	0.32	-11.8	1.5	3.6	0.59	-14.8
Other anti-dementia drugs	0.14	-4.8	1.0	6.9	0.37	-10.9
Anti-dementia medicines	**0.46**	**-9.8**	**2.5**	**4.9**	**0.50**	**-14.0**
Rivastigmine	0.23	-14.6	0.6	-5.3	1.15	-9.9
Memantine	0.14	-4.8	1.0	6.9	0.37	-10.9
Donepezil	0.07	-2.3	0.9	10.7	0.23	-11.7
galantamine	0.01	-7.0	0.0	-8.2	0.99	1.3

Table 3.6.5d. Prescription of anti-dementia medicines with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	Average Cost DDD
Patent expired	0.37	80.6	-10.1	2.2	86.5	4.3	0.47
Generic	0.24	66.2	-3.4	1.6	74.2	5.7	0.42
Ex originator	0.12	33.8	-20.9	0.6	25.8	0.6	0.61
Patent covered	0.09	19.4	-8.4	0.3	13.5	8.6	0.72
Anti-dementia medicines	**0.46**	**100.0**	**-9.8**	**2.5**	**100.0**	**4.9**	**0.50**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.6.5b. Anti-dementia medicines, distribution in quartiles of 2019 consumption (weighted DDD / 1000 inhab. per day)

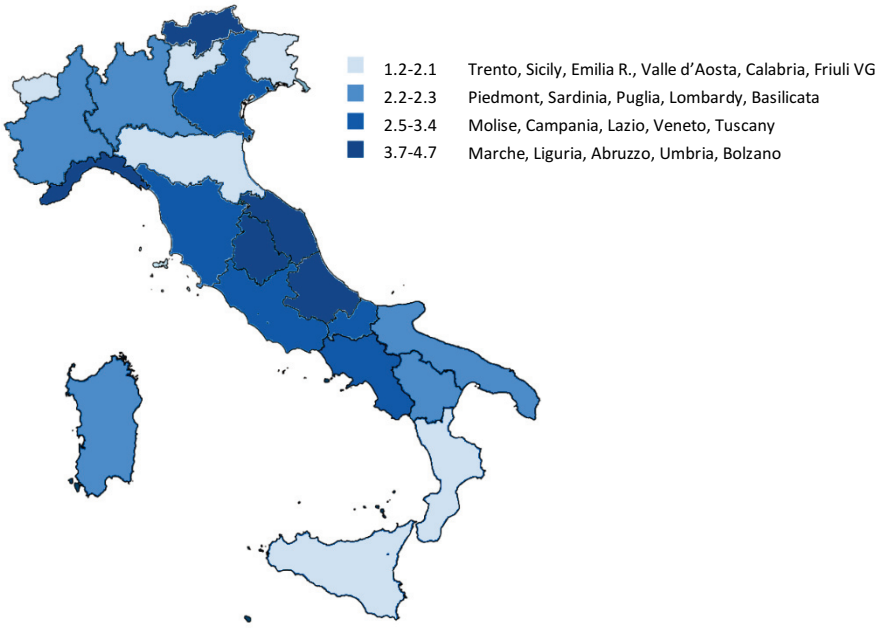


Figure 3.6.5c. Anti-dementia medicines, regional variability of 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviation from the national average)

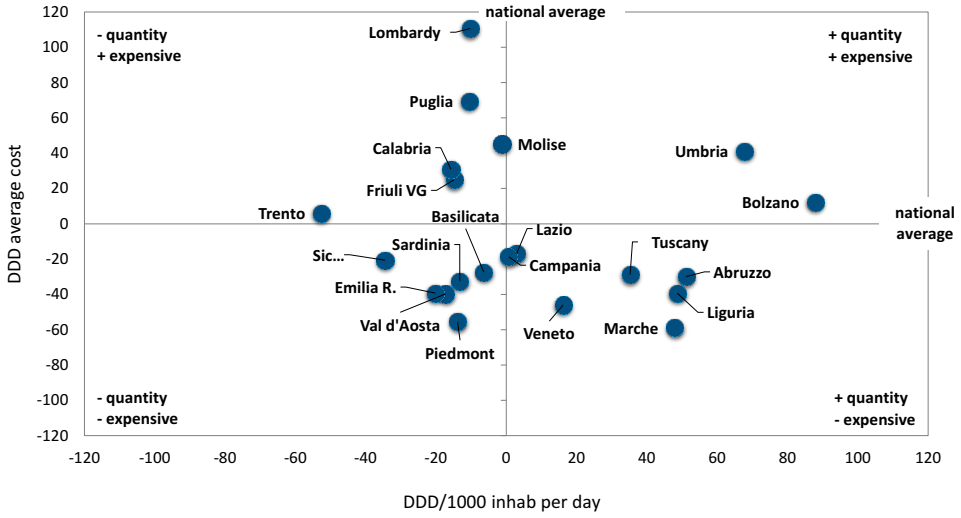


Figure 3.6.5d Distribution of 2019 use and consumption of anti-dementia medicines for NHS outpatient expenditure

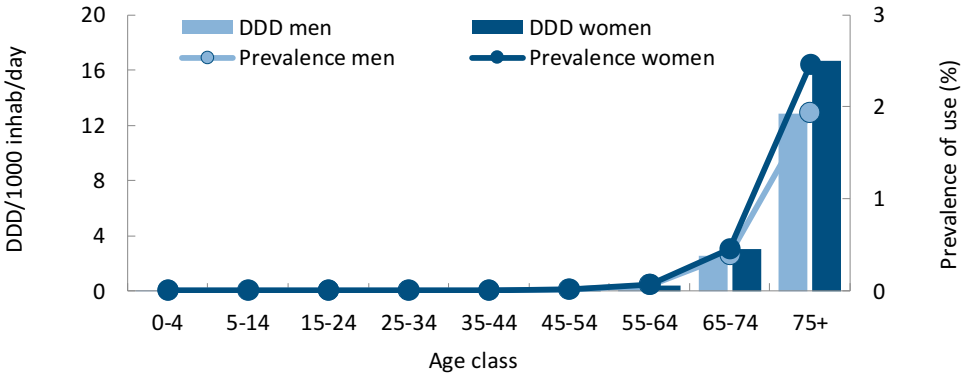


Table 3.6.5e. Duration of anti-dementia medicines therapy by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per users	DDD per user	Median DDD	Users with 1 prescription
North	5.3	253.5	224.0	14.1
Centre	5.9	220.2	180.0	22.3
South and Islands	6.7	245.3	224.0	12.4
Anti-dementia medicines	**5.9**	**242.0**	**223.0**	**15.7**

3.6.6 Pain therapy

(including prescription of pregabalin and gabapentin for all authorised indications)

- Pain is clinically a transversal and frequent symptom and is often an important signal for the initial diagnosis of the disease. It can be classified into the following: nociceptive pain (direct activation of nociceptors), neuropathic pain (involving the central nervous system and/or the peripheral nervous one), psychic pain (activated by psycho-relational stations) and mixed pain (with the presence of all the previous components);
- in the last six years the use of pain therapy medicines has increased by 12% (by 5.2% between 2019 and 2018 equal to 7.7 DDD); at the same time, the average cost per day of therapy has decreased by 10%;
- the major opioids represented about 40% of the doses with an increase of 9.2% compared to the previous year, mainly supported by fentanyl and tapentadol (+3.9% and +5.9% respectively); the increased access to buprenorphine should be outlined (+97.6% of doses and +51% of expenditure). Buprenorphine is not only used for the treatment of pain, chronic pain included, but also in opioid withdrawal programs. At the same time, the use of minor opioids has reduced by 2%. Among the drugs for the management of neuropathic pain (2.7 DDD and +6.6%), the increasing use of pregabalin (+ 7.7%) and gabapentin (+ 2.6%) should also be taken into consideration, even though to a lesser extent;
- Friuli Venezia Giulia was the region with the highest level of consumption (10.1 DDD), while Campania shows a limited use (half of it - 5.1 DDD): the use of these drugs is generally limited in the Southern Italian regions compared to other geographical areas. Lombardy, Friuli Venezia Giulia and Sardinia use more doses and with a cost higher than the national average; major opioids are the category where the greatest regional variability is observed (CV 28%);
- half of the doses and a quarter of the expenditure relate to patent-expired drugs, whose average cost per day of therapy is approximately three times lower than patent-covered drugs (1.24 vs 3.50). One out of three doses of patent-expired medicines relate to equivalent medicines.

Table 3.6.6a. Pain therapy, consumption (DDD/1000 inhab./per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Major opioids associated or combined with other ingredients	2.2	2.3	2.5	2.6	2.7	2.9	9.2
Drugs for neuropathic pain	2.2	2.3	2.3	2.4	2.6	2.7	6.6
Minor opioids associated or combined with other ingredients	2.5	2.3	2.2	2.1	2.1	2.0	-2.0
Pain Therapy	**6.9**	**6.9**	**7.0**	**7.1**	**7.3**	**7.7**	**5.2**
fentanyl	0.7	0.7	0.7	0.7	0.8	0.8	3.9
tapentadol	0.3	0.3	0.4	0.5	0.5	0.5	5.9
pregabalin	1.7	1.8	1.8	1.9	2.1	2.2	7.7
naloxone/	0.3	0.3	0.4	0.4	0.4	0.4	-3.5
gabapentin	0.5	0.5	0.5	0.5	0.5	0.5	2.6
paracetamol/codeine	1.6	1.5	1.4	1.3	1.3	1.3	-3.1
tramadol	0.8	0.7	0.7	0.7	0.7	0.7	0.4
oxycodone hydrochloride	0.3	0.3	0.0	0.0	0.0	0.3	-
buprenorphine	0.1	0.1	0.1	0.1	0.2	0.4	97.6
oxycodone	0.1	0.1	0.1	0.1	0.1	0.1	5.8

Table 3.6.6b. Pain therapy, regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014 oxycodone	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	8.5	8.4	8.6	9.0	9.2	9.7	5.9
Valle d'Aosta	9.4	9.5	9.1	9.2	9.2	9.9	7.6
Lombardy	7.7	7.9	8.1	8.1	8.4	8.9	6.8
A.P. of Bolzano	7.2	7.3	7.5	7.6	7.7	7.9	2.8
A.P. of Trento	7.2	7.4	7.5	7.6	7.9	8.1	3.1
Veneto	6.9	6.8	7.0	7.1	7.3	7.9	7.5
Friuli VG	9.2	9.5	9.8	10.0	10.0	10.1	1.1
Liguria	8.4	8.4	8.3	8.6	8.8	9.2	4.5
Emilia R.	8.6	8.6	8.7	8.9	9.1	9.2	1.9
Tuscany	9.2	9.1	8.9	8.6	8.7	8.7	0.9
Umbria	6.5	6.7	6.9	7.0	7.5	7.9	5.5
Marche	6.4	6.4	6.4	6.5	6.5	6.7	2.5
Lazio	6.4	6.5	6.5	6.7	7.0	7.4	6.6
Abruzzo	5.4	5.5	5.6	5.7	5.8	6.0	3.5
Molise	4.8	5.0	5.2	5.1	5.3	5.4	1.9
Campania	4.4	4.4	4.5	4.5	4.8	5.1	6.4
Puglia	5.6	5.6	5.7	5.8	6.1	6.6	7.9
Basilicata	5.0	5.0	4.9	5.0	5.2	5.7	9.0
Calabria	4.7	4.8	4.9	4.9	5.0	5.2	2.8
Sicily	5.1	5.1	5.2	5.3	5.4	5.6	5.2
Sardinia	6.8	7.0	7.0	7.1	7.4	7.8	5.1
Italy	**6.9**	**6.9**	**7.0**	**7.1**	**7.3**	**7.7**	**5.2**

Table 3.6.6c. Pain therapy, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/ 1000 per day	Δ % 19-18	Average Cost DDD	Δ % 19-18
Major opioids associated or combined with other ingredients	4.45	2.5	2.9	9.2	4.16	-6.1
Medicines for neuropathic pain	1.48	6.0	2.7	6.6	1.48	-0.6
Minor opioids associated or combined with other ingredients	0.68	-3.2	2.0	-2.0	0.93	-1.3
Pain therapy	6.62	2.7	7.7	5.2	2.35	-2.4
fentanyl	1.38	2.7	0.8	3.9	4.73	-1.1
tapentadol	1.22	5.9	0.5	5.9	6.22	0.0
Pregabalin	1.14	7.0	2.2	7.7	1.41	-0.6
naloxone/ oxycodone	1.06	-6.4	0.4	-3.5	6.79	-3.0
gabapentin	0.34	3.0	0.5	2.6	1.78	0.5
paracetamol/codeine	0.34	-3.3	1.3	-3.1	0.73	-0.1
tramadol	0.28	-4.2	0.7	0.4	1.13	-4.6
oxycodone hydrochloride	0.27	-	0.3	-	2.13	-
buprenorphine	0.22	51.0	0.4	97.6	1.59	-23.6
oxycodone	0.16	0.9	0.1	5.8	3.05	-4.6

° The table includes the prescription of pregabalin and gabapentin for all authorized indications

Table 3.6.6d. Pain therapy, prescription for active ingredients with patent expired * in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	Average Cost DDD
Patent expired	1.77	26.8	4.5	3.9	50.7	3.7	1.24
Generic	0.62	35.2	10.1	1.2	30.3	7.7	1.44
Ex originator	1.15	64.8	1.7	2.7	69.7	2.1	1.15
Patent covered	4.85	73.2	2.0	3.8	49.3	6.7	3.50
Pain therapy	**6.62**	**100.0**	**2.7**	**7.7**	**100.0**	**5.2**	**2.35**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019.

Figure 3.6.6b. Pain therapy, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

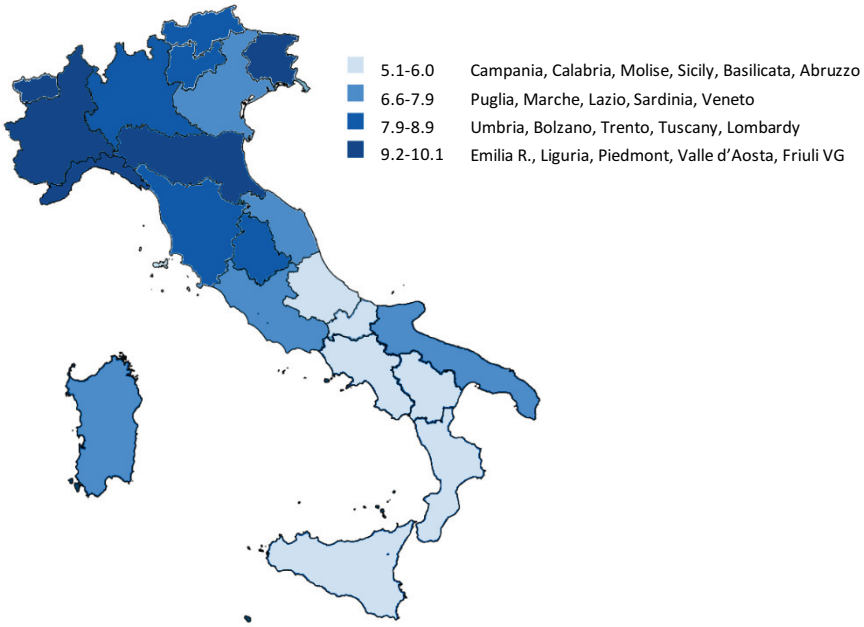


Figure 3.6.6c. Pain therapy, regional variability of the 2019 pharmaceutical consumption by quantity and average cost per day of therapy (% deviation from the national average)

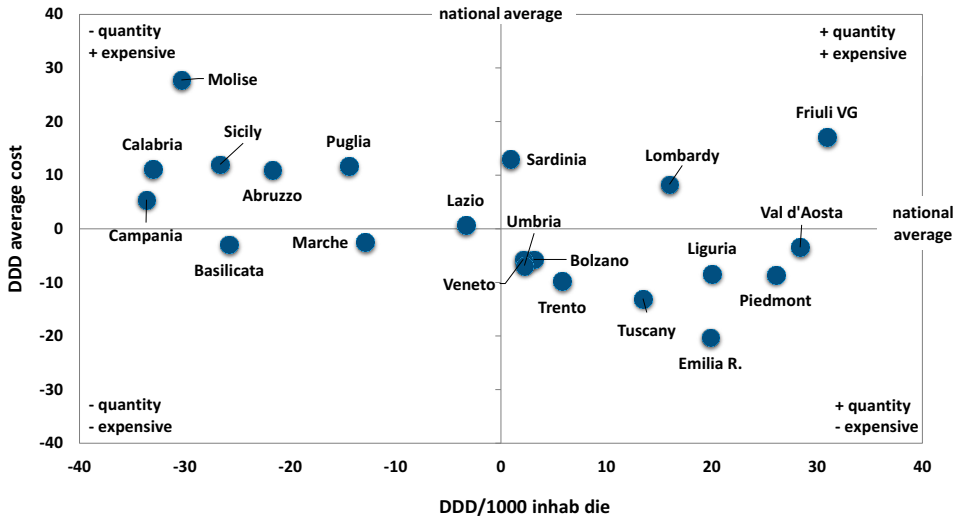
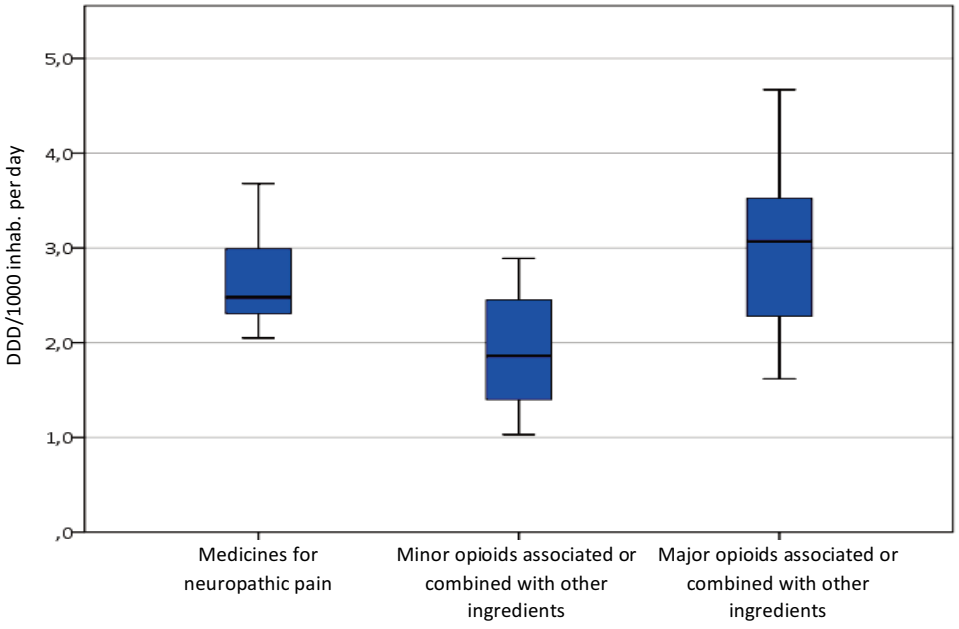


Figure 3.6.6d. Pain therapy, regional variability of the 2019 consumption (weighted DDD/1000 inhab. per day) by subgroup
(*The line inside the box represents the median of the regional distribution; the ends of the box represent the first and third quartiles; the horizontal lines represent the minimum and the maximum).*



3.7 Respiratory system

In 2019 respiratory system medicines were confirmed as the seventh therapeutic category with the highest public expenditure equivalent to € 1,242 million and to 5.4% of total public expenditure. The overall per capita expenditure amounted to € 20.58 for this type of medicinal products, mainly deriving from the pharmaceutical assistance reimbursed by the Italian National Health Service (€ 16.71 per capita). Such expenditure showed an increase compared to the previous year (+2.9%). On the contrary, the contribution coming from the expenditure of medicines purchased by public health facilities outlines a less significant cost (€ 3.87 per capita) (Table 3.1). The level of consumption amounted to 44.4 DDD/1000 inhabitants per day for this category of drugs; it showed an increase of 1.8% compared to 2018 (Table 3.2).
The analysis of medicine utilisation profile by age group and gender (including pharmaceuticals under NHS outpatient standard distribution and *per conto* distribution), shows that children under the age of 5 and people over the age of 75 are the main users (29.2% and 21.6% respectively). The analysis of consumption shows an increase in DDD, with increasing age and a maximum value in people over 75 years of age (106.8 DDD/1000 inhabitants per day). It is likely that this is related to the treatment of chronic obstructive pulmonary disease (COPD). With regard to gender differences, a higher prevalence is outlined in male population up to 15 years of age and after 65 years of age. At the same time, the per capita expenditure incurred by the NHS also varies with the age of patients, up to the maximum value of € 50.5 per capita in people aged over 75 years with a different contribution from the two genders (€ 67.6 in men and € 39.1 euros in women).
The per capita expenditure was equal to € 16.71, as regards reimbursed care assistance. It marked an increase of 2.9% compared to 2018. This trend is determined by an increase in consumption (+1.4%), by cost reduction (-0.4%) and a greater use of more expensive specialties (mix effect +1.7%) (Table 3.9). Within this delivery channel, bronchodilators, associated with corticosteroids, do represent the category with the highest expenditure and consumption, € 8.02 per capita and 12.5 DDD/1000 inhabitants per day respectively. The beclomethasone/formoterol association represents the medicine with the highest incidence of expenditure (14%), followed by vilanterol/fluticasone (12.8%) (Table 3.5). These active ingredients are LABA + ICS used for the treatment of asthma as well as for treating chronic obstructive pulmonary disease (COPD) which are included in the first 30 active ingredients by expenditure recording values of 141.2 and 128.7 million respectively (Table 3.6). Umeclidinium, a bronchodilator used for COPD, represents the active ingredient with a greater variation in the NHS reimbursed expenditure, equal to +72.9%, mainly determined by an increase of consumption (+74.9%) (Table 3.7).
As regards the expenditure of medicines purchased by public health facilities, an increase in spending amounting to 27.1%, compared to 2018, was reported. In addition, an increase in consumption (+3.9%) and in the average DDD cost of 22.1% was also reported (Table 3.11). The drug that has a major impact on the expenditure is the association of lumacaftor/ivacaftor. Such a drug is used for the treatment of cystic fibrosis, which represents 29.9% of the expenditure, followed by two monoclonal antibodies: omalizumab, used for treating allergic asthma and mepolizumab, used in adjunctive therapy for severe refractory eosinophilic asthma.

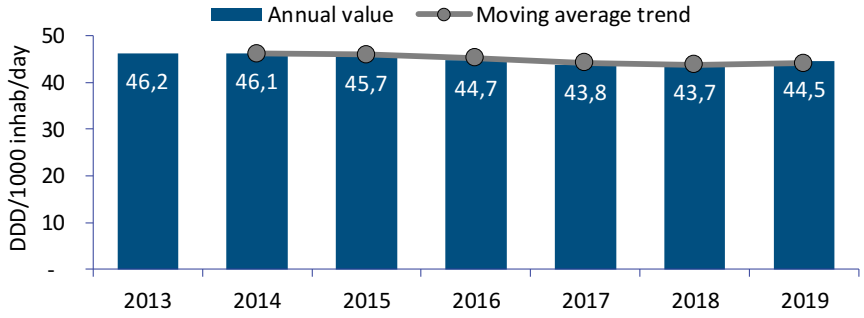
For further information about the use of medicines belonging to the same therapeutic area, several studies have been developed. These studies refer to the historical series of consumption by active principle and by Region as well as to the efficiency of recovering financial resources in relation to the existence of patent-expired medicines and on a regional basis. Furthermore, these studies were mainly focused on asthma and COPD drugs as well as on cystic fibrosis drugs (Table 3.7.1 and others to follow).

MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

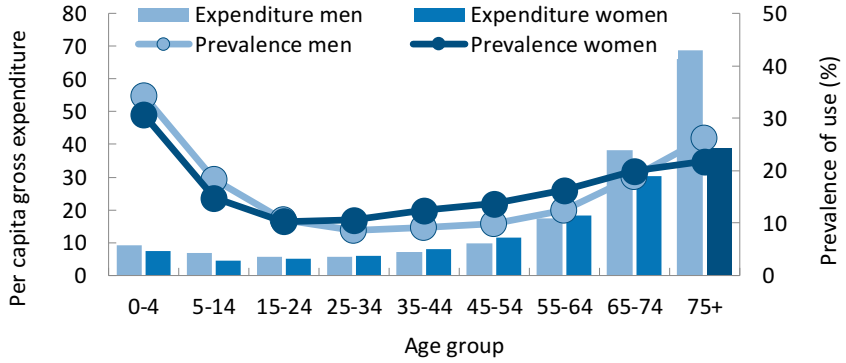
Respiratory system

NHS expenditure * millions € (% on the total)	**1,242.0**	**(5.4)**
Δ % 2019-2018		6.6
Per capita gross expenditure, range among regions	15.9	27.3
DDD/1000 inhab. per day* (% on the total)	**44.4**	**(3.9)**
Δ % 2019-2018		1.8
DDD/1000 inhab. per day – range among regions:	32.3	62.2

** Including NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure and *per conto* distribution in 2019 (Chart and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	8.6	7.1	7.9	26.5	21.4	24.0
5-14	6.6	4.6	5.6	23.8	16.2	20.1
15-24	5.8	5.0	5.4	22.8	19.3	21.1
25-34	5.7	5.8	5.8	19.1	19.6	19.3
35-44	7.0	8.0	7.5	20.5	24.5	22.5
45-54	9.7	11.4	10.6	25.8	33.4	29.6
55-64	17.4	18.4	17.9	40.2	46.8	43.6
65-74	38.1	30.5	34.1	78.6	70.0	74.1
75+	67.6	39.1	50.5	136.1	87.3	106.8

3.7.1 Medicines for asthma and for chronic obstructive pulmonary disease (COPD)

- Asthma and chronic obstructive pulmonary disease (COPD) both show airflow limitation. The goal of the treatment of patients suffering from asthma is to achieve and maintain control of the disease for prolonged periods. As far as COPD is concerned, the treatment mainly aims to reduce the symptoms, to prevent the progression of the disease, to improve the exercise tolerance and the state of health of people affected, to prevent and treat complications and exacerbations;
- in 2019 the consumption of medicines used for treating asthma and COPD was 34.2 DDD, an increase of 1.4% compared to 2018. The expenditure reached € 17.49 per capita (+ 5.6%); a day of therapy with such medicine costs € 1.40;
- the association between long-acting beta2-agonists and inhaled corticosteroids (LABA+ICS) was the most prescribed category in 2019: € 5.83 (per capita) and 9.1 DDD that remains stable compared to 2018, followed by antimuscarinics/long-acting anticholinergics (LAMA) with 6.6 DDD and ultra-LABA+ICS (3.4 DDD and + 13.6%). The significant increase of monoclonal antibodies need to be outlined (+44.1% of the doses,) in particular omalizumab and mepolizumab; the combination of LAMA+LABA+ICS should also be reported as, in 2019, it did show an extension of the indications for the prevention of exacerbations and for controlling symptoms in patients affected by COPD;
- the first three most prescribed substances are: beclomethasone+formoterol, fluticasone+vilanterol and salmeterol+fluticasone, whose variation compared to 2018 is equal to +4.9%, +13.6% and -11.6% respectively;
- Campania is the Region with the highest level of consumption (44.6 DDD), while Molise is the one with the lowest level of consumption (25.5 DDD). The largest increase compared to 2018 (+ 4.7%) is reported in Sicily; more doses are used in Puglia and Basilicata and at a price higher than the national average. Inhaled cortiscosteroids (ICS) are the category with the greatest regional differences (CV 26%);
- patent-expired drugs do represent 33% of the doses with a limited use of equivalent medicines (12.5%).

Figure 3.7.1a. Medicines for asthma and COPD, temporal consumption trend (2014-2019)

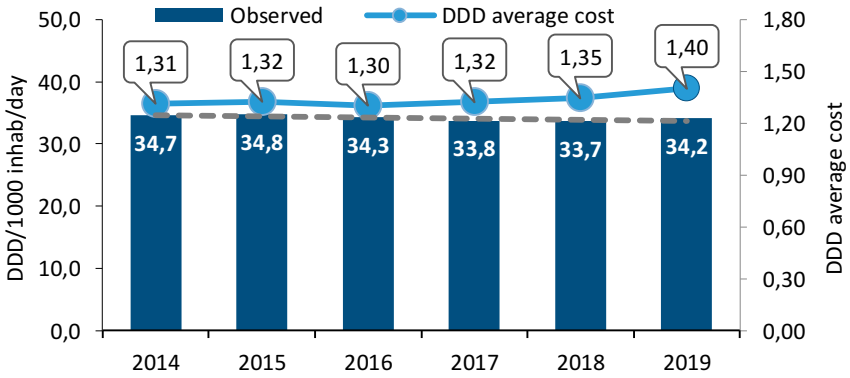


Table 3.7.1a. Medicines for asthma and COPD, consumption (DDD / 1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-87
LABA+ICS	10.5	10.0	9.4	9.0	9.1	9.1	-0.1
LAMA	5.6	5.8	5.7	5.5	5.7	5.8	1.7
Ultra-LABA+ICS	0.0	1.0	2.0	2.6	3.0	3.4	13.6
ICS	7.2	7.0	6.6	6.2	5.5	5.5	-1.0
Monoclonal antibodies	0.0	0.0	0.1	0.1	0.1	0.1	44.1
LABA+LAMA	0.0	0.1	0.5	0.9	1.1	1.2	7.7
Antileukotrienics (LTRA)	2.1	2.1	2.0	2.0	2.0	2.0	2.2
LAMA+LABA+ICS	0.0	0.0	0.0	0.0	0.0	0.3	2940.3
LABA	1.4	1.2	1.1	1.0	0.9	0.7	-16.6
SABA	3.5	3.3	3.2	3.0	3.0	2.9	-4.4
Ultra-LABA	1.1	1.1	0.9	0.7	0.6	0.5	-15.7
SABA+SAMA	0.9	0.9	0.8	0.8	0.8	0.8	-0.5
SABA+ICS	0.4	0.4	0.4	0.3	0.3	0.3	-6.9
SAMA	0.8	0.8	0.8	0.9	0.9	0.9	2.1
Theophylline bronchodilators	1.0	0.8	0.7	0.6	0.5	0.5	-9.5
PDE-4 inhibitor	0.0	0.0	0.0	0.0	0.0	0.0	-14.8
Cromones	0.1	0.1	0.1	0.1	0.0	0.0	-73.4
Medicines for asthma and COPD	**34.7**	**34.8**	**34.3**	**33.8**	**33.7**	**34.2**	**1.4**
beclomethasone/formoterol	2.7	2.8	3.0	3.2	3.5	3.7	4.9
fluticasone/vilanterol	0.0	1.0	2.0	2.6	3.0	3.4	13.6
salmeterol/fluticasone	5.9	5.3	4.4	3.8	3.3	2.9	-11.6
tiotropium	4.1	3.8	3.4	3.0	2.8	2.6	-9.3
budesonide/formoterol	1.5	1.4	1.4	1.4	1.7	2.0	13.1
omalizumab	0.0	0.0	0.1	0.1	0.1	0.1	15.8
beclomethasone	3.8	3.9	3.6	3.4	2.3	2.1	-7.3
aclidinium	0.6	0.9	1.1	1.2	1.2	1.2	-2.5
umeclidinium	0.0	0.0	0.1	0.3	0.7	1.1	74.2
mepolizumab	0.0	0.0	0.0	0.0	0.0	0.0	66.9

Table 3.7.1b. Medicines for asthma and COPD, weighted regional trend of DDD/1000 inhabitants: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	31.5	31.2	30.6	29.9	29.8	30.1	1.0
Valle d'Aosta	39.8	38.3	35.1	34.3	34.6	33.9	-1.9
Lombardy	31.1	31.4	31.5	31.1	31.9	31.7	-0.7
A.P. of Bolzano	26.6	27.1	27.0	26.3	26.7	25.9	-3.0
A.P. of Trento	31.7	31.6	31.3	30.8	31.3	31.1	-0.6
Veneto	29.3	29.2	29.2	29.0	28.9	29.2	0.9
Friuli VG	30.3	30.6	30.7	30.9	30.5	31.1	1.8
Liguria	33.3	33.8	33.3	33.3	33.7	34.3	1.7
Emilia R.	33.5	33.8	33.9	33.2	33.2	33.6	1.2
Tuscany	34.5	35.4	35.0	34.7	34.4	34.4	0.0
Umbria	31.9	31.7	31.7	31.4	32.0	32.3	0.6
Marche	31.3	30.7	31.0	30.4	29.9	30.5	2.1
Lazio	39.4	39.5	38.3	38.0	38.2	39.0	2.1
Abruzzo	29.7	29.6	29.8	29.5	29.9	30.8	3.2
Molise	28.1	27.3	26.1	25.4	24.7	25.5	3.0
Campania	43.8	44.1	43.7	42.6	43.8	44.6	1.9
Puglia	40.8	41.1	40.3	38.1	34.8	36.0	3.4
Basilicata	38.7	37.9	37.2	36.8	35.1	36.3	3.6
Calabria	34.5	34.4	34.1	33.4	32.8	33.9	3.3
Sicily	34.8	34.5	33.5	33.0	32.3	33.8	4.7
Sardinia	40.3	40.2	37.5	37.0	36.2	36.0	-0.5
Italy	**34.7**	**34.8**	**34.3**	**33.8**	**33.7**	**34.2**	**1.4**

Tale 3.7.1c. Medicines for asthma and COPD, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	DDD Average Cost	Δ % 19-18
LABA+ICS	5.83	-1.6	9.1	-0.1	1.76	-1.5
LAMA	3.19	2.2	5.8	1.7	1.51	0.5
Ultra-LABA+ICS	2.15	13.3	3.4	13.6	1.72	-0.3
ICS	1.90	-3.3	5.5	-1.0	0.96	-2.4
Monoclonal antibodies	1.53	46.8	0.1	44.1	28.66	1.9
LABA+LAMA	0.91	7.6	1.2	7.7	2.08	0.0
Antileukotrienics (LTRA)	0.47	0.8	2.0	2.2	0.64	-1.3
LAMA+LABA+ICS	0.35	>100	0.3	>100	2.76	-4.5
LABA	0.26	-16.5	0.7	-16.6	0.98	0.1
SABA	0.22	-4.4	2.9	-4.4	0.21	0.0
Ultra-LABA	0.20	-15.6	0.5	-15.7	1.06	0.1
SABA+SAMA	0.18	-0.8	0.8	-0.5	0.63	-0.3
SABA+ICS	0.13	-6.8	0.3	-6.9	1.20	0.1
SAMA	0.07	-1.0	0.9	2.1	0.23	-3.0
Theophylline bronchodilators	0.06	-6.3	0.5	-9.5	0.35	3.6
PDE-4 inhibitor	0.01	-14.7	0.0	-14.8	1.51	0.1
Cromones	0.00	-77.2	0.0	-73.4	0.63	-14.4
Medicines for asthma and COPD	**17.49**	**5.6**	**34.2**	**1.4**	**1.40**	**4.1**
beclomethasone/formoterol	2.38	4.8	3.7	4.9	1.77	-0.1
fluticasone/vilanterol	2.15	13.3	3.4	13.6	1.72	-0.3
salmeterol/fluticasone	1.84	-15.1	2.9	-11.6	1.72	-4.0
tiotropium	1.37	-8.9	2.6	-9.3	1.46	0.5
budesonide/formoterol	1.35	11.2	2.0	13.1	1.89	-1.7
omalizumab	0.82	15.4	0.1	15.8	25.74	-0.3
beclomethasone	0.72	-8.7	2.1	-7.3	0.92	-1.5
aclidinium	0.68	-2.4	1.2	-2.5	1.59	0.1
umeclidinium	0.64	72.4	1.1	74.2	1.55	-1.0
mepolizumab	0.55	67.0	0.0	66.9	34.88	0.0

Table 3.7.1d. Prescription of medicines for asthma and COPD with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	DDD Average Cost
Patent expired	3.00	17.2	-7.4	11.3	33.0	-3.1	0.73
Generic	0.27	8.9	6.8	1.4	12.5	7.0	0.52
Ex originator	2.73	91.1	-8.6	9.9	87.5	-4.4	0.76
Patent covered	14.49	82.8	8.8	22.9	67.0	3.8	1.73
Medicines for asthma and COPD	**17.49**	**100.0**	**5.6**	**34.2**	**100.0**	**1.4**	**1.40**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.7.1b. Drugs for asthma and COPD, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

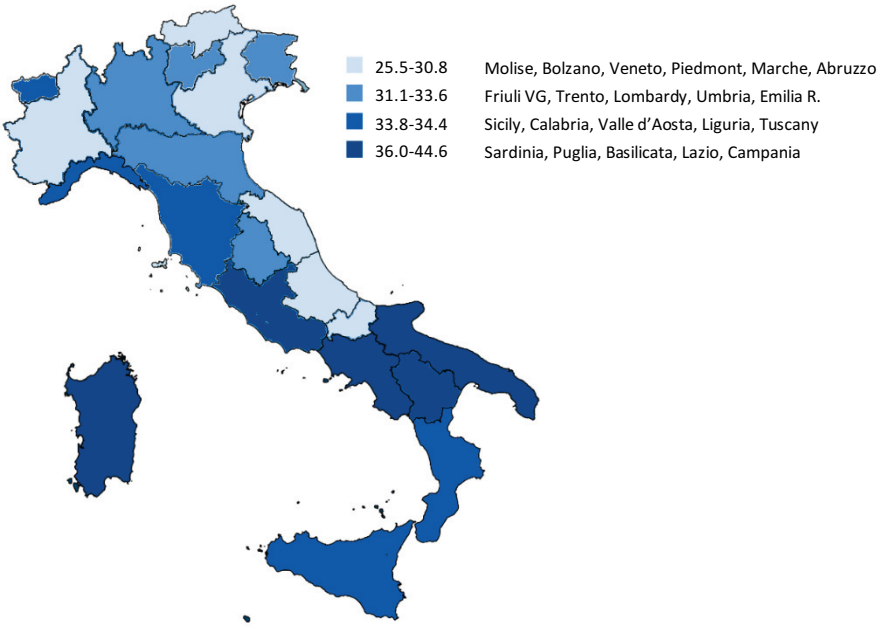


Figure 3.7.1c. Medicines for asthma and COPD, regional variability of pharmaceutical consumption in 2019 by quantity and average cost per day of therapy (% deviation from the national average)

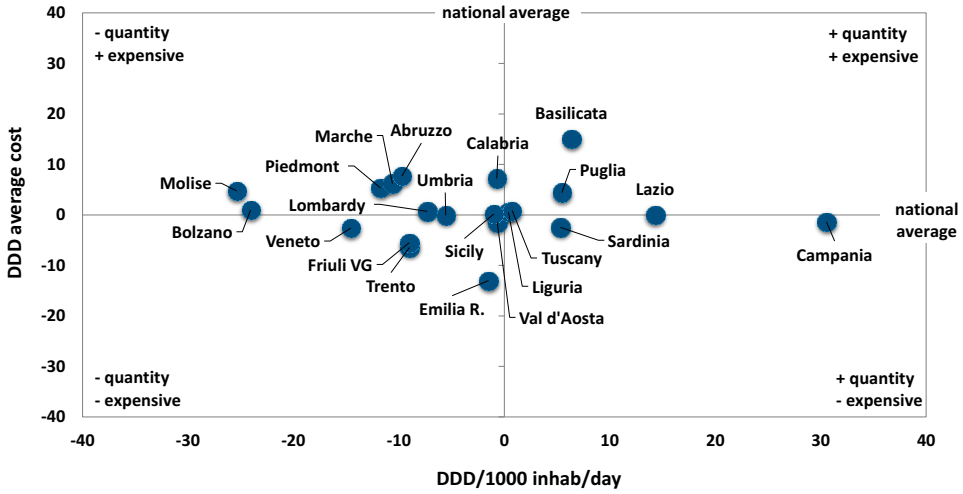
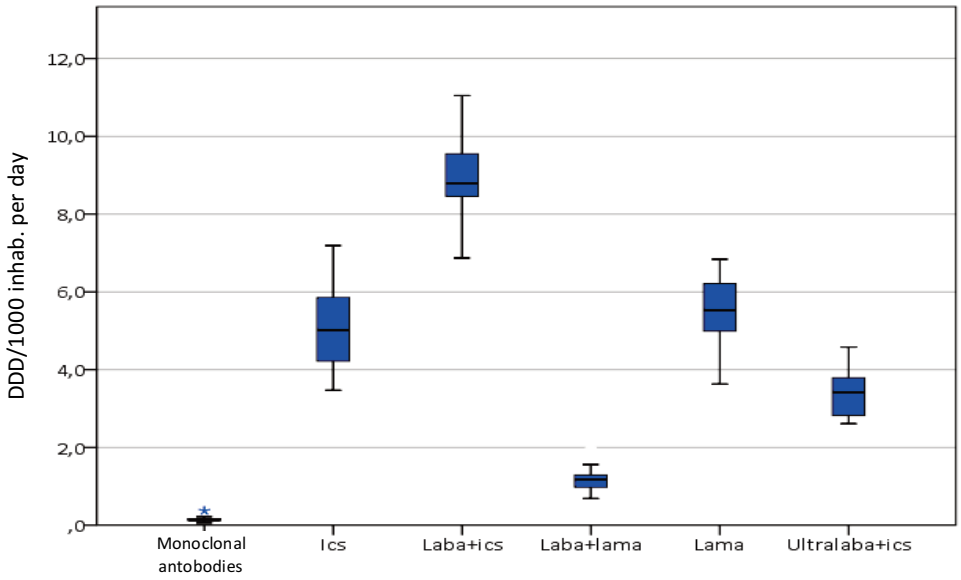


Figure 3.7.1d. Medicines for asthma and COPD, regional variation in 2019 consumption (weighted DDD/1000 inhab. per day) by subgroup

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



3.7.2 Medicines for cystic fibrosis

- Cystic fibrosis is a serious genetic disease with a progressive increase of the disease process. It is a multi-organ disease, which mainly affects the respiratory and digestive systems. It is estimated that out of 2,500-3,000 children born in Italy, one is affected by cystic fibrosis (200 new cases per year). The persistence of the infection and lung inflammation, which causes progressive deterioration of lung tissue, is the major cause of morbidity in patients, even though there are differences from person to person. The symptomatic treatment is focused on obtaining the control of the symptoms/signs of the disease and of the respiratory infections as well as on improving digestive and nutritional problems;
- per capita expenditure related to cystic fibrosis medicines has significantly increased over the past five years, from € 0.22 in 2015 to € 1.66 in 2019. It was equal to a percentage increase of 640% and an average annual change of +65%. In the same period, the cost for DDD dropped from € 707.2 in 2015 to € 464 in 2019, mainly due to the reduction of the price related to the lumacaftor/ivacaftor association;
- this association does represent over 70% of spending with an increase of 32.5% in 2019 compared to the previous year;
- a significant variability between the different regions is pointed out in 2019; Basilicata does show a per capita expenditure five times higher than Molise (4.2 vs 0.9);
- all the regions, with the exception of Valle d'Aosta (-56%) and the Autonomous Province of Trento (-3.8%), observe an increase of spending compared to the previous year, with values ranging from a minimum of + 2.7% as regards to Umbria to a maximum of +86.4% as for Molise.

Figure3.7.2a. Medicines for cystic fibrosis, temporal consumption trend (2014-2019)

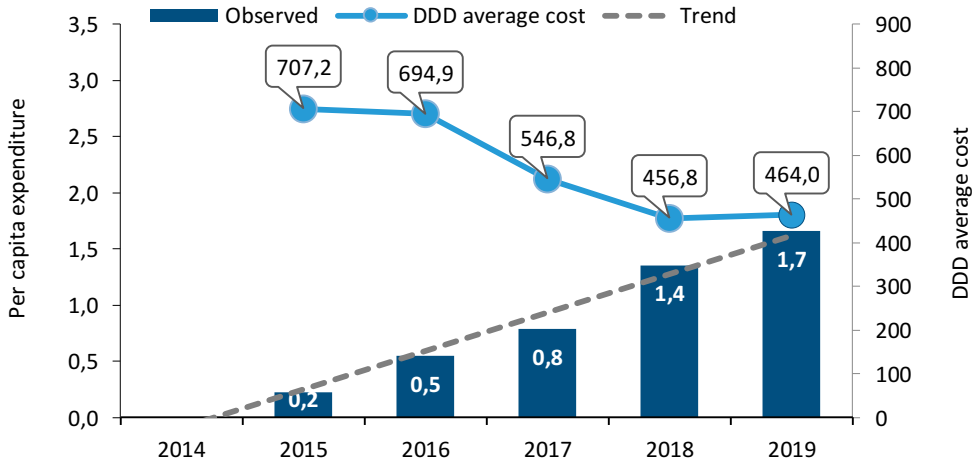


Table 3.7.2a. Medicines for cystic fibrosis, per capita expenditure by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2015	2016	2017	2018	2019	Δ % 19-18
Cystic fibrosis	**0.2**	**0.5**	**0.8**	**1.4**	**1.7**	**22.3**
lumacaftor/ivacaftor	0.0	0.0	0.3	0.9	1.2	32.5
ivacaftor	0.2	0.5	0.5	0.5	0.5	2.1

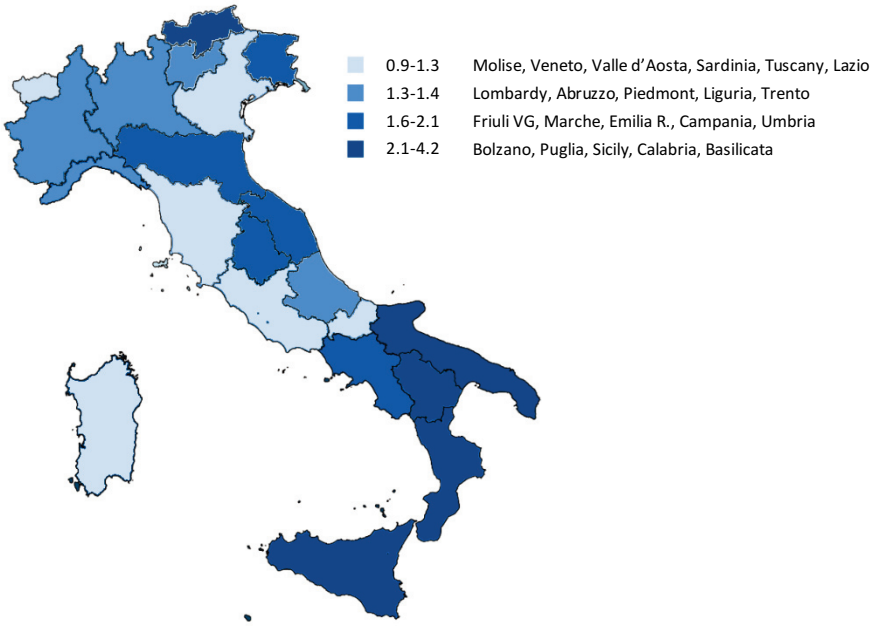
Table 3.7.2b. Medicines for cystic fibrosis, weighted regional trend of per capita expenditure: comparison 2015-2019

Region	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	0.10	0.29	0.61	1.20	1.40	16.0
Valle d'Aosta	0.00	1.52	1.91	2.43	1.07	-56.0
Lombardy	0.03	0.17	0.34	0.86	1.30	52.1
A.P. of Bolzano	0.28	0.46	0.50	1.67	2.11	26.9
A.P. of Trento	0.00	0.00	0.08	1.51	1.45	-3.8
Veneto	0.03	0.05	0.23	0.67	1.03	54.1
Friuli VG	0.09	0.18	0.46	1.18	1.57	33.4
Liguria	0.04	0.21	0.57	1.04	1.43	37.4
Emilia R.	0.06	0.26	0.72	1.34	1.66	23.4
Tuscany	0.24	0.49	0.43	1.03	1.23	19.3
Umbria	0.15	0.76	1.40	2.05	2.11	2.7
Marche	0.07	0.16	0.60	1.19	1.61	35.5
Lazio	0.47	0.98	1.09	1.20	1.29	7.0
Abruzzo	0.10	0.24	0.60	1.22	1.39	14.3
Molise	0.00	0.00	0.03	0.46	0.86	86.4
Campania	0.36	0.82	1.28	1.83	2.09	14.2
Puglia	0.51	0.99	1.58	2.08	2.31	11.0
Basilicata	0.58	2.74	3.23	3.73	4.22	13.3
Calabria	0.95	1.97	2.32	2.75	2.96	7.8
Sicily	0.37	1.03	0.87	2.04	2.58	26.7
Sardinia	0.07	0.12	0.15	0.86	1.20	40.3
Italy	**0.22**	**0.55**	**0.79**	**1.36**	**1.66**	**22.3**

Table 3.7.2c. Medicines for cystic fibrosis, prescription by therapeutic category and substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	Average Cost per DDD	Δ % 19-18
Cystic fibrosis	**1.66**	**22.3**	**0.0**	**20.4**	**464.04**	**1.6**
lumacaftor/ivacaftor	1.16	32.5	0.0	24.6	416.96	6.3
ivacaftor	0.49	2.1	0.0	3.5	641.16	-1.4

Figure 3.7.2b. Medicines for cystic fibrosis, distribution in quartiles of 2019 per capita expenditure



3.8 Musculo-skeletal system

Medicines for the musculo-skeletal system represent the eighth category for public expenditure in 2019, amounting to approximately € 537 million and 2.3% of public expenditure. The overall per capita expenditure for these medicines amounted to approximately € 8.90 per capita, mainly due to the outpatient NHS pharmaceutical expenditure (€ 5.43 per capita), reaching (-4,9%) compared to the previous year. The contribution coming from the expenditure of medicines purchased by public health facilities is less significant (€ 3.47), albeit strongly increasing compared to the previous year (+ 11.7%) (Table 3.1).
Consumption for this category of medicines amounted to 42.3 DDD/1000 inhabitants per day, slightly increasing by +0.3% compared to 2018, albeit the trend of recent years remained steady.
The analysis of medicine utilization profile by age group and gender (including outpatient NHS pharmaceutical expenditure and *per conto* distribution), does confirm that the use of such a medicine increases with age for both men and women. The level of consumption is higher in female population that in male population with the highest values in patients over 75 years of age for both men (109.8 DDD) and women (154.2 DDD). At the same time, the per capita expenditure incurred by the NHS also increases with the age of patients, up to the maximum value of € 21.4 in the last age group, albeit with an almost double value in women (€ 26.4) compared to men (€ 13.9). This difference is mainly due to the frequent use of bisphosphonates in women being treated for osteoporosis.
As regards the outpatient NHS pharmaceutical expenditure, the per capita expenditure decreased by 4.9% compared to 2018, amounting to € 5.43. This trend was determined by a price drop (-4.3%), as the number of prescriptions concerning cheaper medicinal products increased (mix effect: -0.5%), although the level of consumption did remain almost stable (-0.1%) (Table 3.9). Bisphosphonates have the greatest impact on spending through this supply channel (€ 1.34 per capita), with an increase by 6.8% as well as the preparations inhibiting the formation of uric acid, with a per capita expenditure of € 1.06; this does represent a decrease compared to the previous year (-17.7%) even though the level of consumption is higher for this category of medicines (10 DDD) compared to the previous year (+3.9%) (Table 3.9). Alendronic acid is the active ingredient that has the greatest impact on spending (€ 0.75 per capita) and on consumption (3.8 DDD), recording an increase of 4.2% and of 5.2% respectively compared to 2018. Febuxostat appears to be the second active ingredient in the category (€ 0.73) and does show an important reduction in terms of expenditure mainly linked to the reduction of the average cost per DDD amounting to 27.8% (Table 3.5). No active ingredient belonging to this category is included in the top 30 medicines for consumption and expenditure in relation to the outpatient NHS pharmaceutical expenditure for Class A (Tables 3.6 and 3.8). On the contrary, alendronic acid appears among the top 30 active ingredients with the greatest variation in NHS outpatient expenditure compared to the previous year (Table 3.7).

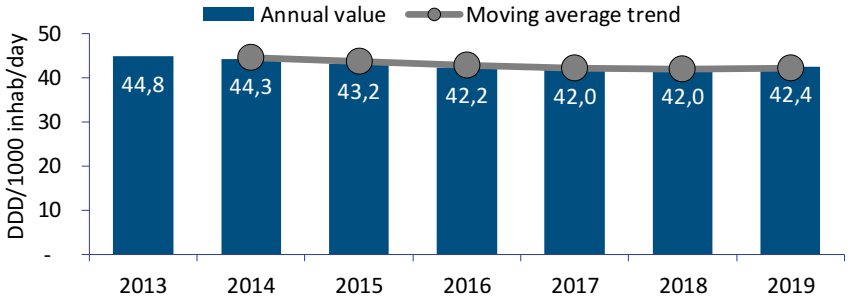
A significant increase in terms of spending (+11.5%) and of consumption (+6.5%) has been reported as regards the contribution coming from the expenditure of medicines purchased by public health facilities. The increase was also reported as to the average cost per DDD,

amounting to +4.6% compared to 2018 (Table 3.11). Medicines defined as other preparations for musculo-skeletal diseases represent the category with the highest incidence on expenditure reaching 56% and reporting a significant increase of the DDD average cost (Table 3.10). This sub-group does include Nusinersen, used for the treatment of spinal muscular atrophy (SMA) which recorded an increase of 11.2% compared to the previous year (Table 3.11). Nusinersen accounts for about 49% of the per capita expenditure related to medicines for the musculoskeletal system purchased by public health facilities (Table 3.13). The medicinal product is also among the top 30 active ingredients as for the expense of medicines purchased by public health structures (Table 3.12).
For further information on the use of medicinal products related to the same therapeutic area, analyses have been developed on the historical series of consumption by active substance and by Region as well as on the efficiency of recovering resources in relation to the presence of patent-expired medicines and on a regional basis. These analyses included medicines used for the treatment of osteoporosis and non-steroidal anti-inflammatory drugs (Tables 3.8.1 and others to follow).

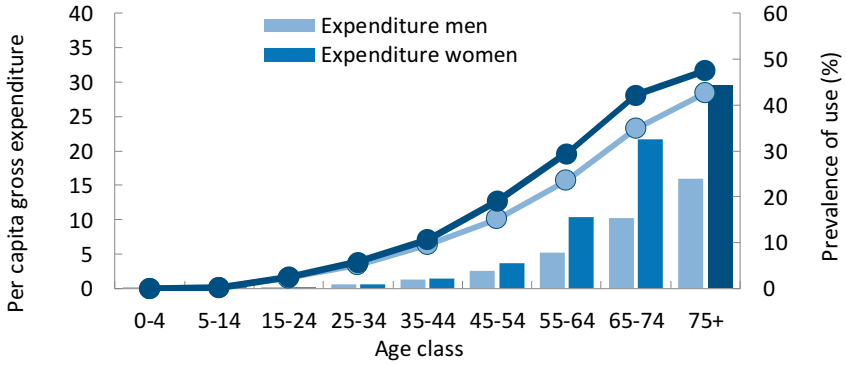
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Muscolo-skeletal system

NHS expenditure millions €* (% on the total)	**537.2**	**(2.3)**
Δ % 2019-2018		0.7
Per capita gross expenditure, range among regions:	5.9	11.5
DDD/1000 inhab. per day* (% on the total)	**42.3**	**(3.7)**
Δ % 2019-2018		0.7
Range regionale DDD/1000 ab *die*:	31,9	59,2

** Includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure 2019 (Chart and Table)

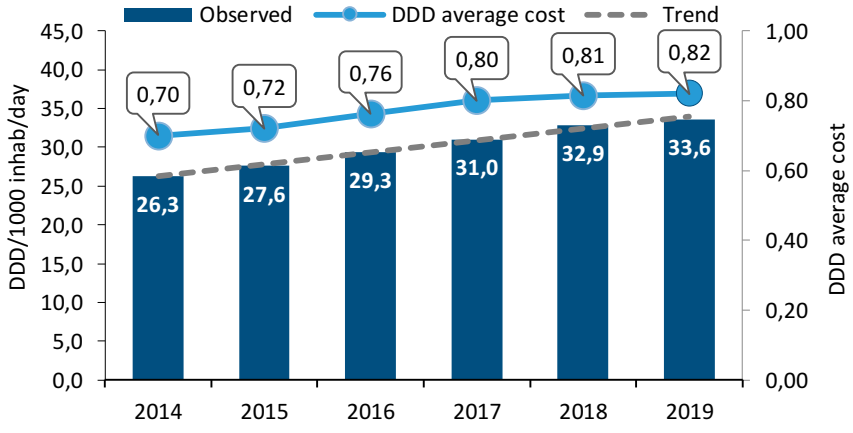


Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.0	0.0	0.0	0.1	0.1	0.1
5-14	0.0	0.0	0.0	0.2	0.2	0.2
15-24	0.2	0.2	0.2	1.7	1.7	1.7
25-34	0.5	0.6	0.6	4.0	4.2	4.1
35-44	1.2	1.3	1.3	9.0	9.4	9.2
45-54	2.4	3.5	3.0	18.4	23.4	20.9
55-64	4.8	9.7	7.4	37.9	57.7	48.1
65-74	9.3	20.0	14.9	74.3	114.6	95.6
75+	13.9	26.4	21.4	109.8	154.2	136.4

3.8.1 Medicines for osteoporosis

- Osteoporosis is a condition of the skeleton characterised by reduced bone resistance that leads the person suffering from it to an increased risk of fracture. Bone strength is based on the integration of bone density and quality. The decreases in bone mass occur in both sexes, even though women are mainly affected due to an acceleration of loss in the first 3-5 years after menopause. This may also depend on the change in hormonal balance, an insufficient amount of calcium in the diet, a reduced absorption of the mineral through the intestine, a deficiency in vitamin D due to low exposure to natural sunlight and, not least, from a less active lifestyle;
- In Italy the level of consumption related to medicines treating osteoporosis amounted to 26.3 DDD in 2015 and increased by 33.6% in 2019 (+27.7%), with the compound annual growth rate (CAGR) reaching + 5%. The CAGR is mainly determined by the increase of the number of prescriptions of vitamin D and analogue products which represent about 60% of the entire category (19.7 DDD). At the end of 2019, the Italian Medicines Agency published a document named "Note AIFA 96" which hanged the NHS prescribing procedures for medicines used for the prevention and treatment of vitamin D deficiency in adult population (> 18 years); it is likely that their effects will be showed in 2020;
- calcifediol and denosumab are the substances with the greatest variation in consumption compared to 2018 (+30.9% and +14.6%); with the exception of alendronic acid (+5.5%) and other bisphosphonates, including their combinations with other ingredients, which indicate a reduction of their use;
- Puglia, with 40,4 DDD, has a level 55% higher than that of Valle d'Aosta. Abruzzo, Lazio, Basilicata and Puglia are the regions that use more doses and at a higher cost than the national average. When looking at the data, it should be taken into consideration the fact that some regions have taken steps to limit vitamin D prescription;
- Patent-expired medicines account for 72% of doses, but only one third are equivalents.

Figure 3.8.1a. Medicines for osteoporosis*, temporal consumption trend (2014-2019)



** raloxifene excluded*

Table 3.8.1a. Medicines for osteoporosis, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Sub-groups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Vitamin D and analogues	13.0	14.2	15.9	17.5	19.3	19.7	2.3
Anabolic drugs	0.2	0.2	0.2	0.2	0.2	0.2	3.7
Bisphosphonates plain	6.9	6.7	6.6	6.7	6.7	6.9	2.2
Monoclonal antibodies	1.0	1.6	2.1	2.4	2.7	3.1	11.4
Bisphosphonates in combination	3.5	3.3	3.0	2.7	2.4	2.2	-8.4
Calcium	1.6	1.6	1.5	1.5	1.4	1.5	1.1
Serm – selective estrogen receptor modulators	0.1	0.1	0.1	0.1	0.0	0.0	-2.9
Dual-acting drugs	0.1	0.0	0.0	0.0	0.0	0.0	-83.4
Medicines for osteoporosis	**26.3**	**27.6**	**29.3**	**31.0**	**32.9**	**33.6**	**2.2**
cholecalciferol	5.6	7.2	9.1	10.9	12.6	13.4	5.7
teriparatide	0.2	0.2	0.2	0.2	0.2	0.2	3.7
denosumab	1.0	1.6	2.1	2.4	2.7	3.1	11.4
alendronic acid	2.9	3.1	3.2	3.5	3.7	3.9	6.3
alendronic acid / cholecalciferol	3.5	3.3	3.0	2.7	2.4	2.2	-8.4
calcium / cholecalciferol	5.7	5.3	5.1	4.9	4.7	4.3	-8.6
risedronate	2.8	2.6	2.4	2.3	2.2	2.2	-1.4
calcitriol	1.0	1.0	1.0	1.0	1.0	1.0	-0.7
calcifediol	0.1	0.1	0.1	0.1	0.1	0.1	30.6
ibandronic acid	1.2	1.1	1.0	0.9	0.8	0.8	-6.2

Table 3.8.1b. Medicines for osteoporosis, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	24.3	25.6	26.7	28.4	29.8	30.4	2.1
Valle d'Aosta	18.8	20.1	19.5	20.6	22.6	26.1	15.4
Lombardy	24.6	26.4	27.7	29.8	32.1	33.6	4.8
A.P. of Bolzano	30.0	33.1	35.4	37.2	38.2	35.7	-6.6
A.P. of Trento	23.4	24.1	25.9	28.4	30.5	32.4	6.3
Veneto	35.0	36.9	38.1	36.8	37.5	37.1	-1.1
Friuli VG	22.8	23.8	25.3	27.1	28.4	31.1	9.3
Liguria	22.5	23.9	25.4	26.7	28.2	29.6	4.8
Emilia R.	25.0	26.0	26.9	27.7	28.3	28.6	1.0
Tuscany	26.2	27.3	31.6	31.3	33.2	32.0	-3.7
Umbria	20.9	21.7	23.1	25.7	27.5	26.9	-2.2
Marche	24.2	25.9	28.1	31.0	32.6	33.4	2.4
Lazio	27.7	29.3	31.2	33.4	35.3	35.6	0.8
Abruzzo	29.0	30.9	32.8	35.9	39.0	38.5	-1.3
Molise	24.1	26.5	28.8	32.5	32.4	32.5	0.4
Campania	19.1	20.8	23.3	27.0	30.6	33.3	9.1
Puglia	31.7	33.6	35.9	38.1	40.0	40.4	0.9
Basilicata	28.4	30.4	31.5	34.4	36.0	37.3	3.7
Calabria	25.1	25.9	27.7	30.1	32.7	33.1	1.2
Sicily	28.0	25.9	26.1	27.8	30.0	31.5	5.2
Sardinia	33.2	35.5	38.5	40.0	40.5	39.5	-2.6
Italy	**26.3**	**27.6**	**29.3**	**31.0**	**32.9**	**33.6**	**2.2**

Table 3.8.1c. Medicines for osteoporosis, prescription by therapeutic category and by substance in 2019

Sub-groups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	Average Cost DDD	Δ % 19-18
Vitamin D and analogues	5.62	3.1	19.7	2.3	0.78	0.8
Anabolic medicines	1.44	1.4	0.2	3.7	16.69	-2.2
Bisphosphonates plain	1.43	2.0	6.9	2.2	0.57	-0.2
Monoclonal antibodies	0.98	14.6	3.1	11.4	0.88	2.9
Bisphosphonates in combination	0.47	-8.7	2.2	-8.4	0.58	-0.4
Calcium	0.12	0.1	1.5	1.1	0.23	-0.9
Serm – selective estrogen receptor modulators	0.01	-2.5	0.0	-2.9	0.74	0.3
Dual-acting medicines	0.00	-83.4	0.0	-83.4	1.45	0.0
Medicines for osteoporosis	**10.07**	**3.0**	**33.6**	**2.2**	**0.82**	**0.8**
cholecalciferol	4.67	3.3	13.4	5.7	0.96	-2.3
teriparatide	1.44	1.4	0.2	3.7	16.69	-2.2
denosumab	0.98	14.6	3.1	11.4	0.88	2.9
alendronic acid	0.76	5.5	3.9	6.3	0.53	-0.7
alendronic acid / cholecalciferol	0.47	-8.7	2.2	-8.4	0.58	-0.4
calcium/ cholecalciferol	0.40	-8.2	4.3	-8.6	0.26	0.4
risedronate	0.39	-2.6	2.2	-1.4	0.49	-1.2
calcitriol	0.22	-0.5	1.0	-0.7	0.60	0.2
calcifediol	0.17	30.9	0.1	30.6	3.62	0.2
ibandronic acid	0.16	-6.5	0.8	-6.2	0.56	-0.3

Table 3.8.1d. Prescription of medicines for osteoporosis with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	DDD Average Cost
Patent expired	6.74	67.0	0.9	24.2	72.0	1.1	0.76
Generic	1.35	20.0	21.1	7.1	29.4	15.0	0.52
Ex originator	5.40	80.0	-3.1	17.1	70.6	-3.7	0.86
Patent covered	3.33	33.0	7.7	9.4	28.0	5.1	0.97
Medicines for osteoporosis	**10.07**	**100.0**	**3.0**	**33.6**	**100.0**	**2.2**	**0.82**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.8.1b. Medicines for osteoporosis, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

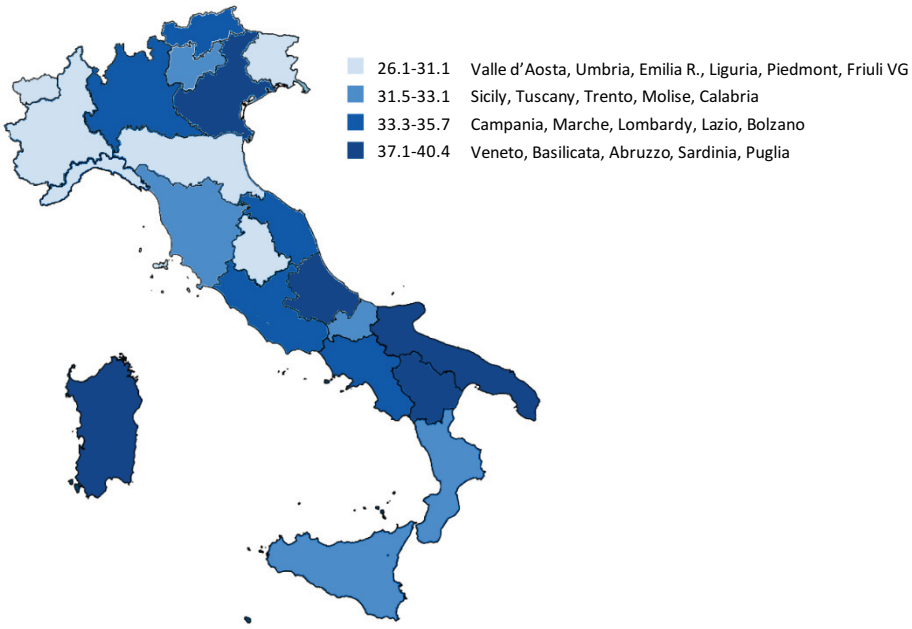


Figure 3.8.1c. Medicines for osteoporosis, regional variability of pharmaceutical consumption in 2019 by quantity and average cost per day of therapy (% deviation from the national average)

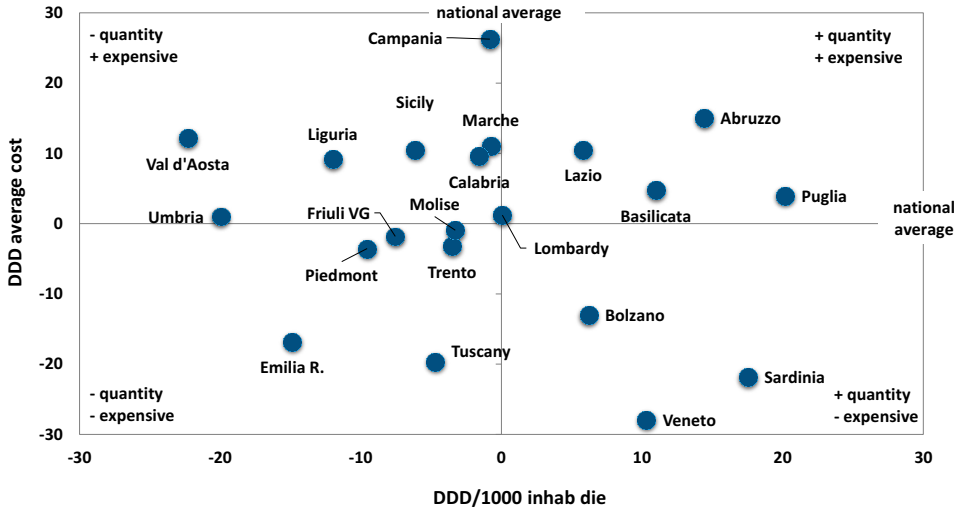
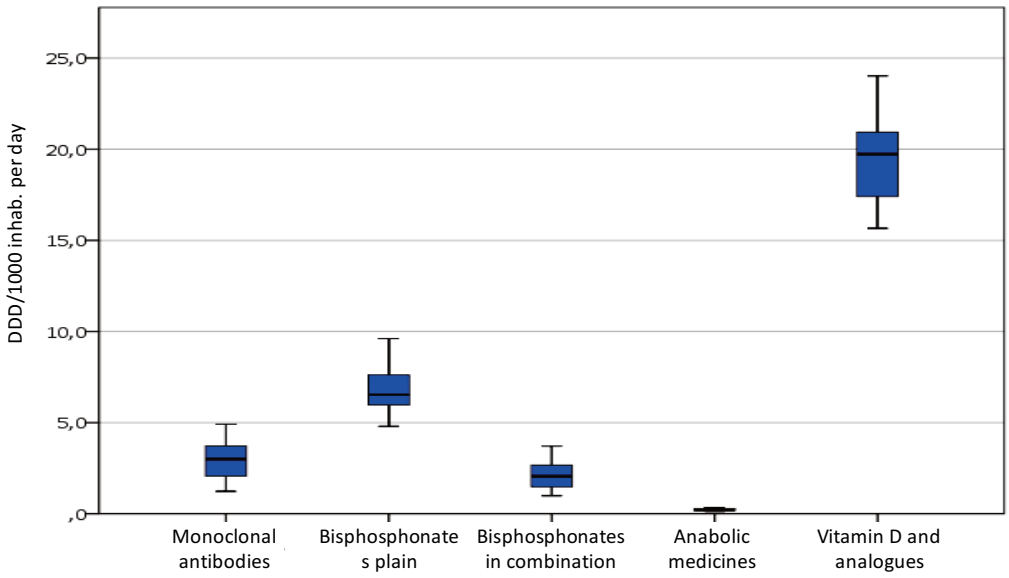


Figure 3.8.1d. Medicines for osteoporosis, regional variation in 2019 consumption (weighted DDD/1000 inhab. per day) by subgroup

(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).



3.8.2 Non-steroidal anti-inflammatory medicines (NSAIDs)

- The level of consumption of non-steroidal anti-inflammatory medicines decreases by 2% in 2019 (CAGR 14-19: -5%) compared to 2018; the average cost per day of therapy remains stable recording a value of € 0.37;
- traditional NSAIDs amounting to 13.4 DDD (-2.9% compared to 2018 and equal to 74% of the category) are the most prescribed medicines followed by coxibs with 3.8 DDD and oxicams with 0.9 DDD. Diclofenac, etoricoxib and ketoprofen are the substances most widely prescribed, while the first two substances increase by 1.1% and by 3.3%; however, the level of consumption of the third one decreases by 5.2%. Piroxicam does show the greatest increase (+12.3% of expenditure and +9.7% of doses) while celecoxib (-9.3% of doses) and numesulide (-6.6%) show a downward trend performance;
- about 90% of expenditure and doses relate to patent-expired medicines; 23% of these medicines relate to equivalent drugs;
- NSAIDs are most widely prescribed in the southern regions; Calabria recorded a value of 29.0 DDD in 2019. This value is almost three times higher than the one recorded in Emilia Romagna (10.9 DDD); a lower regional variability is outlined as regards to the average cost per day of therapy. In all regions, the prescription of NSAIDs recorded a reduction compared to 2018 with the exception of Liguria (+0.8%) and Molise (+1.0%). Traditional NSAIDs are the category with the highest level of regional variability (CV 37%);
- NSAIDs are one of the most used categories of medicinal products among the Italian population; 15% of Italian citizens received at least one prescription of these medicines in 2019 with a drug exposure and use higher in women than in men (prevalence of use: 17% vs 13%) - (DDD: 20.7 vs 13.3). In particular, the age group over 65 has a prevalence of use of about 25% higher. As expected, these medicines are used for short periods of time: each user is treated on average for about 41 days, 50% of users are treated for less than a month and more than half of them receive a single prescription per year, without marked differences between the different geographical areas.

Figure 3.8.2a. Non-steroidal anti-inflammatory medicines (NSAIDs), temporal consumption trend (2014-2019)

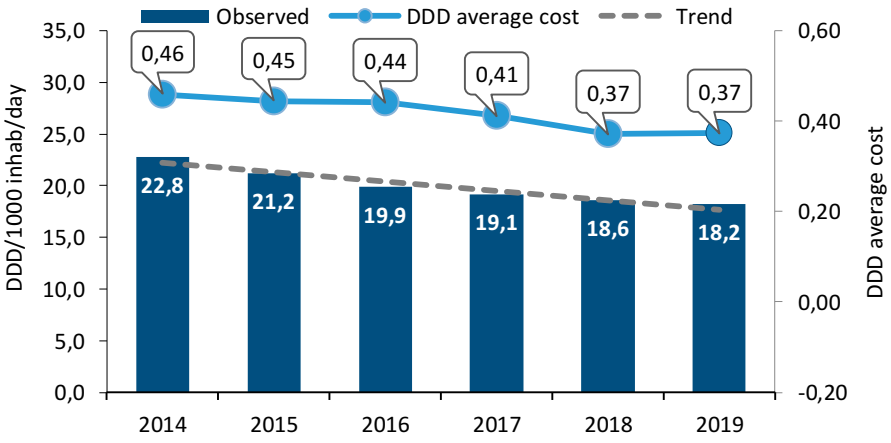


Table 3.8.2a. Non-steroidal anti-inflammatory medicines (NSAIDs), (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Traditional NSAIDs	16.7	15.5	14.7	14.3	13.8	13.4	-2.9
Coxib	4.7	4.4	4.1	3.8	3.8	3.8	0.9
Oxicam	1.3	1.2	1.1	1.0	0.9	0.9	-1.8
Other NSAIDs	0.0	0.0	0.0	0.0	0.0	0.0	12.4
NSAIDs	**22.8**	**21.2**	**19.9**	**19.1**	**18.6**	**18.2**	**-2.0**
diclofenac	4.2	4.0	4.0	4.1	4.0	4.1	1.1
etoricoxib	3.8	3.5	3.2	3.0	3.1	3.2	3.3
Ketoprofen	4.3	3.9	3.6	3.5	3.3	3.1	-5.2
ibuprofen	2.2	2.2	2.1	2.0	2.1	2.1	0.5
nimesulide	2.9	2.6	2.3	2.2	2.1	1.9	-6.6
celecoxib	1.0	0.9	0.9	0.8	0.7	0.7	-9.3
ketorolac	0.7	0.6	0.6	0.6	0.6	0.6	-5.3
aceclofenac	0.8	0.6	0.6	0.5	0.5	0.4	-7.3
piroxicam	0.7	0.6	0.5	0.5	0.5	0.5	9.7
dexibuprofen	0.3	0.4	0.4	0.4	0.4	0.3	-4.4

Table 3.8.2b. Non-steroidal anti-inflammatory medicines (NSAIDs), weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	18.3	16.8	15.9	15.4	15.0	14.8	-1.2
Valle d'Aosta	22.3	20.9	18.3	17.3	17.2	17.1	-0.4
Lombardy	13.4	12.9	12.3	11.9	11.6	11.3	-2.6
A.P. of Bolzano	15.9	15.3	14.4	13.3	12.6	12.0	-4.7
A.P. of Trento	16.6	16.0	15.9	15.8	16.1	15.8	-1.7
Veneto	15.9	14.5	13.6	12.7	12.1	11.8	-2.3
Friuli VG	20.9	20.0	19.5	18.8	18.4	18.4	-0.1
Liguria	16.0	14.5	13.8	13.5	13.0	13.1	0.8
Emilia R.	14.0	12.8	11.9	11.4	11.2	10.9	-3.3
Tuscany	18.3	16.7	16.0	15.5	14.7	13.8	-6.0
Umbria	17.0	15.4	14.7	14.1	14.3	14.1	-1.0
Marche	18.4	17.3	16.6	16.3	14.8	14.2	-4.4
Lazio	29.1	26.8	24.8	24.2	23.8	23.5	-1.3
Abruzzo	23.0	22.0	20.9	20.3	20.1	19.9	-0.9
Molise	28.3	26.7	23.4	22.5	22.3	22.5	1.0
Campania	32.7	30.8	28.4	27.9	28.4	28.0	-1.4
Puglia	39.2	36.5	34.9	32.6	29.0	28.1	-3.1
Basilicata	28.1	25.7	23.4	23.0	23.0	22.7	-1.2
Calabria	36.3	33.2	31.1	30.1	29.4	29.0	-1.3
Sicily	30.2	27.0	25.4	24.7	24.5	24.2	-1.3
Sardinia	35.5	34.2	30.0	27.5	25.7	25.2	-1.9
Italy	**22.8**	**21.2**	**19.9**	**19.1**	**18.6**	**18.2**	**-2.0**

Table 3.8.2c. Non-steroidal anti-inflammatory medicines (NSAIDs), prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	DDD Average Cost	Δ % 19-18
Traditional NSAIDs	1.70	-2.3	13.4	-2.9	0.35	0.6
Coxib	0.65	-0.1	3.8	0.9	0.47	-1.0
Oxicam	0.12	1.6	0.9	-1.8	0.37	3.4
Other NSAIDs	0.01	13.8	0.0	12.4	0.63	1.2
NSAIDs	**2.48**	**-1.5**	**18.2**	**-2.0**	**0.37**	**0.6**
diclofenac	0.59	1.5	4.1	1.1	0.40	0.5
etoricoxib	0.54	2.0	3.2	3.3	0.47	-1.2
Ketoprofen	0.32	-5.5	3.1	-5.2	0.28	-0.4
Ibuprofen	0.30	0.5	2.1	0.5	0.39	0.0
nimesulide	0.15	-6.3	1.9	-6.6	0.22	0.3
Celecoxib	0.11	-9.3	0.7	-9.3	0.47	-0.1
Ketorolac	0.10	-3.4	0.6	-5.3	0.51	2.0
aceclofenac	0.08	-7.7	0.4	-7.3	0.51	-0.4
Piroxicam	0.08	12.3	0.5	9.7	0.45	2.4
dexibuprofen	0.06	-4.4	0.3	-4.4	0.49	0.0

Table 3.8.2d. Prescription of non-steroidal anti-inflammatory medicines (NSAIDs), with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	DDD Average Cost
Patent expired	2.18	87.6	-1.4	16.2	89.3	-1.9	0.37
Generic	0.34	15.5	-0.2	3.7	22.7	-1.3	0.25
Ex originator	1.84	84.5	-1.6	12.6	77.3	-2.0	0.40
Patent covered	0.31	12.4	-2.4	2.0	10.7	-3.4	0.43
NSAIDs	**2.48**	**100.0**	**-1.5**	**18.2**	**100.0**	**-2.0**	**0.37**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.8.2b. Non-steroidal anti-inflammatory medicines (NSAIDs), distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

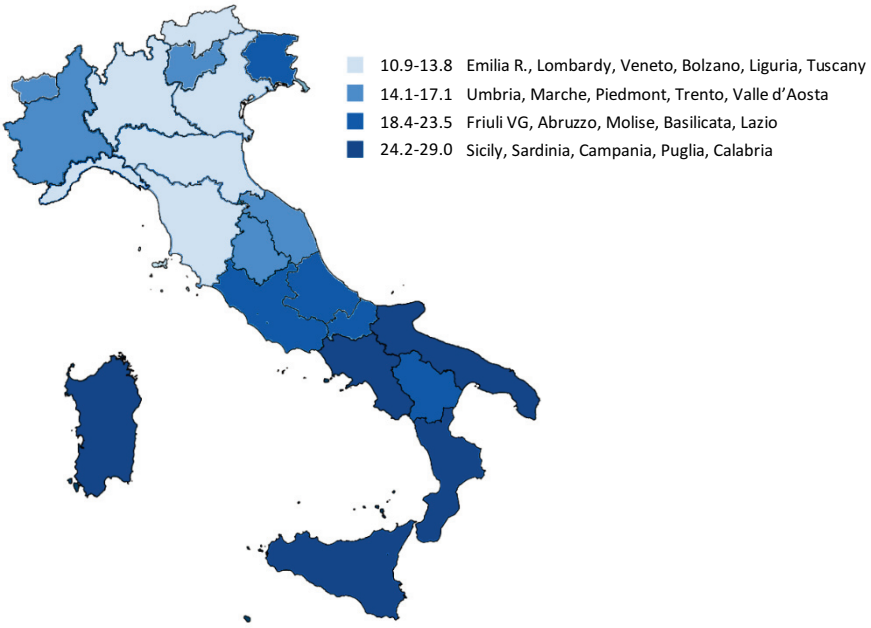


Figure 3.8.2c. Non-steroidal anti-inflammatory medicines (NSAIDs), regional variability of pharmaceutical consumption in 2019 by quantity and average cost per day of therapy (% deviation from the national average)

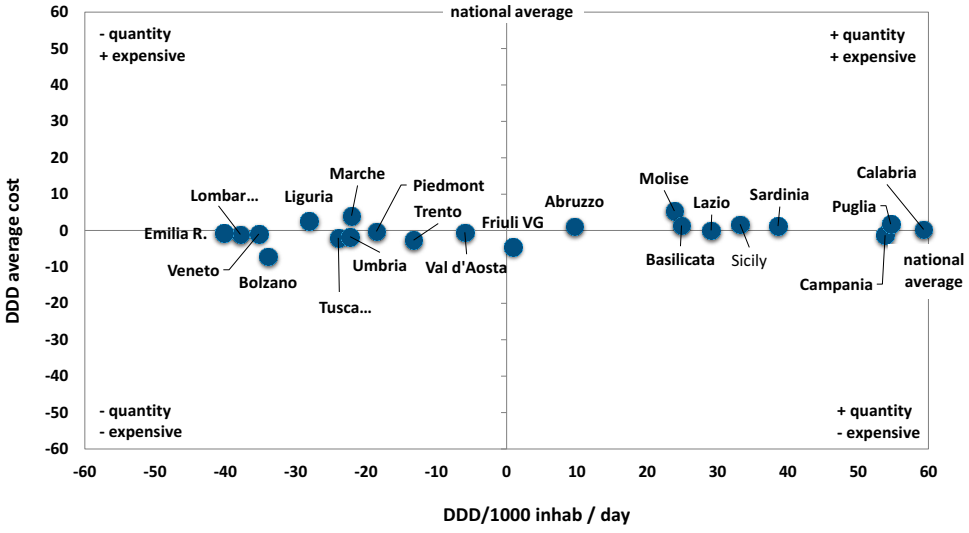


Figure 3.8.2d. Non-steroidal anti-inflammatory medicines (NSAIDs), regional variation in 2019 consumption (weighted DDD/1000 inhab. per day) by subgroup

(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).

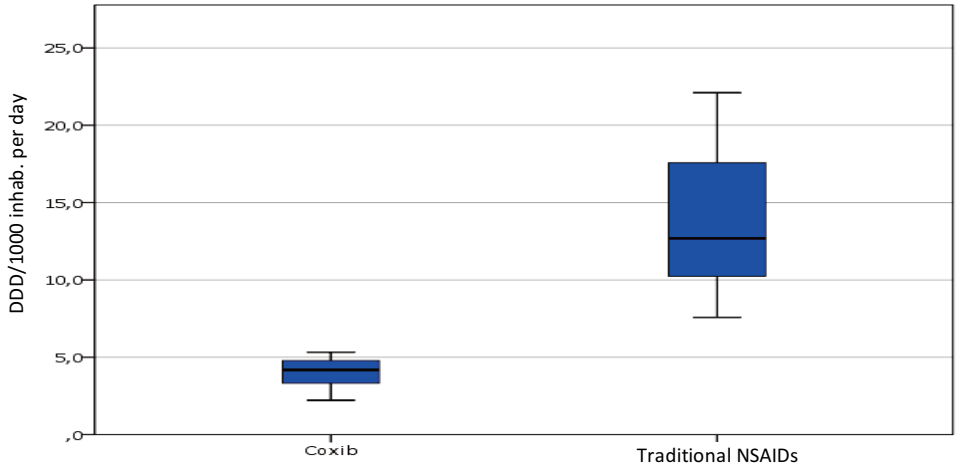


Figure 3.8.2e. Distribution of the prevalence of use and consumption of non-steroidal anti-inflammatory medicines (NSAIDs) under NHS outpatient standard distribution (year 2019)

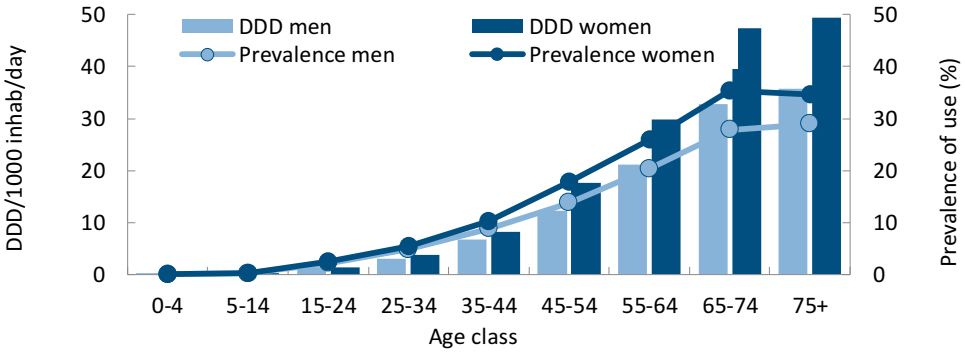


Table 3.8.2e. Duration of NSAIDs therapy by geographic area under NHS outpatient standard care (year 2019)

	Prescriptions per user	DDD per user	DDD Median	Users with 1 prescription
North	1.9	40.4	22.0	60.7
Centre	2.1	39.3	22.0	55.3
South and Islands	2.4	42.6	30.0	49.2
NSAIDs	**2.2**	**41.2**	**28.0**	**54.2**

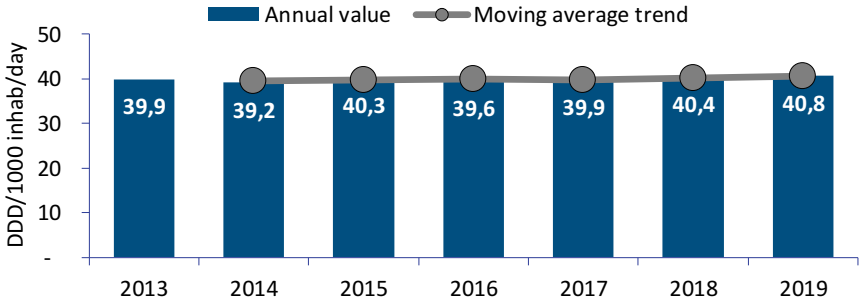
3.9 Systemic Hormonal Preparations, excluding Sex Hormones

In 2019 the category of systemic hormonal preparations, excluding sex hormones, ranked ninth for public expenditure. It amounted to € 534 million and was equal to 2.3% of total public expenditure. Total per capita expenditure amounted to € 8.85; it was mainly represented by expenditure by public health facilities (€ 4.75 per capita). On the contrary, the contribution from outpatient NHS pharmaceutical expenditure is less significant (€ 4.11 per capita) (Table 3.1).
The level of consumption for this category of medicines amounted to 40.7 DDD/1000 inhabitants per day, slightly increasing (+0.9%) compared to 2018 (Table 3.2), thus confirming the upward trend performance of recent years.
The analysis of medicine utilization profile by age group and gender (including NHS outpatient pharmaceutical expenditure and *per conto* distribution), does confirm that the use of these medicines increases with age for both men and women, even though the level of consumption increases in patients over 55 years of age for both men and women.
However, the prevalence of use is consistently higher in women than in men, with the exception of patients aged 5-24 years; this is probably due to the early use of corticosteroids as well as to the treatment of subclinical hypothyroidism from the paediatric age. At the same time, the per capita expenditure incurred by the NHS also increases with the age of patients, reaching the maximum level of € 14.9 per capita in patients over 75 years old (€ 18.2 for women and € 9.9 for men).
As regards outpatient NHS expenditure, the per capita expenditure amounted to € 4.11, recording an increase of 3.2% compared to the previous year. While the level of consumption and prices tend to remain basically steady, the use of more expensive specialties is greater (mix effect: +2.9%) (Table 3.9). Glucocorticoids have the greatest impact on outpatient NHS expenditure (€ 1.39 per capita), followed by parathyroid hormones and analogues (€ 1.23). Teriparatide is the active ingredient with the highest per capita expenditure (€ 1.23), followed by levothyroxine (€ 1.04); they both represent 29.9% and 25.2% of the category (Table 3.5). Levothyroxine also ranks thirteenth among the thirty active ingredients with the greatest variation in outpatient NHS expenditure compared to 2018 (+7.4%) (Table 3.7).
As for the contribution coming from the expenditure of medicines purchased by public health facilities, an increase of expenditure (+2.7%) and consumption (+1.2%) was recorded (Table 3.11). Somatostatin and analogues are the medicines that have the greatest impact on expenditure, accounting for 32.4% of the expenditure of the entire class (Table 3.10).

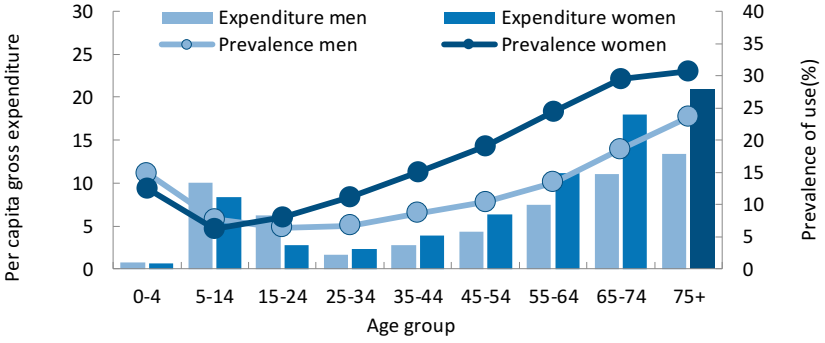
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Systemic Hormonal Preparations, excluding Sex Hormones

NHS expenditure millions € (% on the total)	**534.2**	**(2.3)**
Δ % 2019-2018		2.7
Per capita gross expenditure, range among regions:	7.2	11.1
DDD/1000 inhab. per day* (% on the total)	**40.7**	**(3.5)**
Δ % 2019-2018		0.9
DDD/1000 inhab. per day: range among regions:	27.3	51.5

** Including NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure 2019 (Chart and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.7	0.6	0.6	3.3	2.7	3.0
5-14	7.1	5.9	6.5	4.5	3.9	4.2
15-24	4.6	2.2	3.4	6.1	8.6	7.3
25-34	1.3	2.1	1.7	7.9	18.9	13.3
35-44	2.0	3.3	2.6	11.8	32.2	22.0
45-54	3.1	5.3	4.2	18.0	49.7	34.1
55-64	5.1	9.3	7.3	28.8	73.4	51.8
65-74	7.8	15.2	11.7	44.2	95.8	71.4
75+	9.9	18.2	14.9	57.5	94.2	79.5

3.9.1 Thyroid Medicines

- Thyroid diseases arise when the thyroid gland produces too much hormone or not enough. The thyroid gland is an endocrine gland, located at the front of the neck, which produces the hormones named thyroxine (referred to as T4) and triiodothyronine (referred to as T3). Thyroid hormone (TH) regulates various functions of metabolism, including the development of the central nervous system and body growth. The production of an adequate quantity of thyroid hormones is therefore essential for normal body growth and for the development of various body systems. Women are much more affected by thyroid disorders than men in adulthood: women have a 20% chance of developing thyroid problems in their lifetime;
- the use of thyroid preparations has remained stable during the last 6 years; 22.6 DDD/1000 inhabitants per day were consumed in 2019, showing an increase of 2.3% compared to 2018; furthermore, the average cost for DDD did increase and reached €0.14;
- thyroid hormones, specifically, levothyroxine, are the most prescribed medicines. Levothyroxine is used to treat hypothyroidism; the level of consumption of such a medicine amounted to 21.2 DDD in 2019 (+2.5% compared to 2018), while the use of antithyroid preparations decreased by 1.2%;
- the level of consumption of such a medicine is three times higher in Lazio compared to Liguria (31 vs 11 DDD); Lazio, together with the AP of Trento, Umbria and Puglia, are the regions that use more doses and with a higher cost per day of therapy compared to the national average;
- the incidence of the consumption of patent-expired medicines reported about 87% of the doses and 60% of the expenditure in 2019, with little use of equivalent medicinal products;
- on the basis of the epidemiology of the medical condition, the level of consumption of such medicines in higher in women than in men; the prevalence of use increases with age (with a slight reduction in women over 75 years) and it does reach a value of 14% in women over 55 years of age. On average, each user is treated for about 5.5 months, half of patients stay in therapy for less than 5 months and 13.7% receive only one prescription per year, with no significant differences between geographic areas.

Figure 3.9.1a. Thyroid medicines, temporal consumption trend (2014-2019)

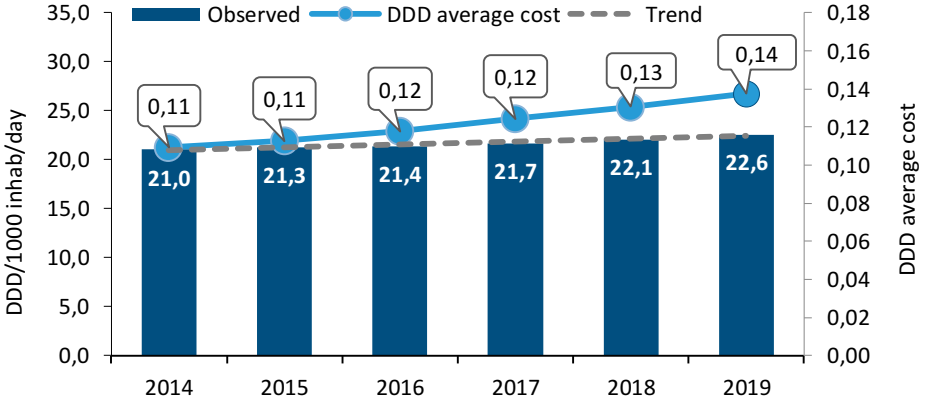


Table 3.9.1a. Thyroid medicines, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Sub-groups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Thyroid hormones	19.6	19.8	20.0	20.3	20.7	21.2	2.5
Antithyroid preparations	1.5	1.4	1.4	1.4	1.4	1.4	-1.2
Thyroid medicines	**21.0**	**21.3**	**21.4**	**21.7**	**22.1**	**22.6**	**2.3**
Levothyroxine	19.5	19.8	19.9	20.2	20.6	21.2	2.5
Thiamazole	1.5	1.4	1.4	1.4	1.4	1.4	-1.2
Liothyronine	0.0	0.0	0.0	0.0	0.0	0.0	23.0

Table 3.9.1b. Thyroid medicines, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	19.6	20.1	20.5	20.9	21.5	22.2	3.4
Valle d'Aosta	24.7	25.3	17.9	18.0	18.9	19.5	2.7
Lombardy	13.8	14.2	14.3	14.7	15.2	15.5	2.4
A.P. of Bolzano	21.2	21.2	21.3	21.4	21.6	22.0	1.5
A.P. of Trento	25.3	26.1	26.5	27.3	28.2	29.1	3.4
Veneto	17.7	18.0	18.4	18.8	19.3	19.9	3.1
Friuli VG	22.4	23.1	23.7	23.9	24.6	25.3	2.6
Liguria	11.7	11.6	11.0	10.9	10.9	11.0	0.6
Emilia R.	27.8	28.2	28.0	28.1	28.5	29.2	2.4
Tuscany	22.3	22.1	22.0	22.2	22.3	22.6	1.3
Umbria	25.0	25.7	26.5	27.0	28.0	28.9	3.4
Marche	23.5	24.0	24.5	24.6	25.1	25.7	2.4
Lazio	30.0	29.9	30.0	30.2	30.5	31.0	1.7
Abruzzo	21.3	22.0	22.4	23.0	23.8	24.6	3.5
Molise	30.0	29.3	28.5	29.0	29.7	30.2	2.0
Campania	17.4	17.4	17.3	17.5	17.8	18.2	2.3
Puglia	24.5	25.1	25.4	26.0	26.5	27.4	3.6
Basilicata	26.0	26.0	25.9	26.5	26.9	27.9	3.7
Calabria	22.8	22.4	22.4	22.5	22.8	23.2	1.7
Sicily	19.8	20.0	20.1	20.5	20.9	21.4	2.2
Sardinia	29.2	29.6	28.9	28.7	28.5	28.1	-1.5
Italy	**21.0**	**21.3**	**21.4**	**21.7**	**22.1**	**22.6**	**2.3**

Table 3.9.1c. Thyroid medicines, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	DDD Average Cost	Δ % 19-18
Thyroid hormones	1.08	7.8	21.2	2.5	0.14	5.1
Antithyroid preparations	0.06	4.1	1.4	-1.2	0.11	5.3
Thyroid Medicines	**1.13**	**7.6**	**22.6**	**2.3**	**0.14**	**5.2**
Levothyroxine	1.04	7.3	21.2	2.5	0.13	4.7
Thiamazole	0.06	4.1	1.4	-1.2	0.11	5.3
Liothyronine	0.03	23.5	0.0	23.0	2.07	0.4

Table 3.9.1d. Prescription of medicines for thyroid with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	DDD Average Cost
Patent expired	0.66	58.7	1.8	19.5	86.3	1.3	0.09
Generic	0.01	2.0	10.6	0.6	3.1	15.3	0.06
Ex originator	0.65	98.0	1.6	18.9	96.9	0.9	0.09
Patent covered	0.47	41.3	17.1	3.1	13.7	9.0	0.41
Thyroid Medicines	**1.13**	**100.0**	**7.6**	**22.6**	**100.0**	**2.3**	**0.14**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.9.1b. Thyroid medicines, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

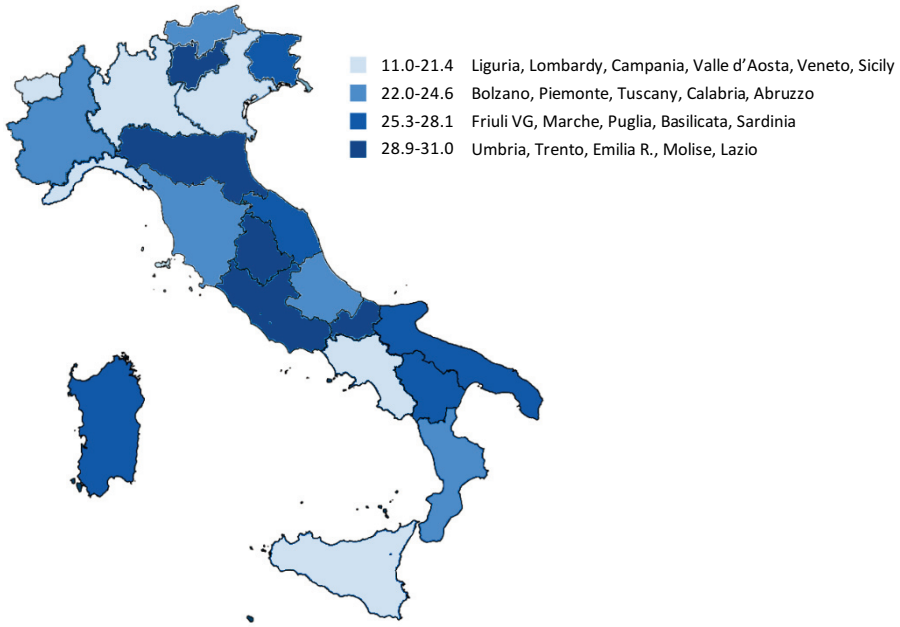


Figure 3.9.1c. Thyroid medicines, regional variability of pharmaceutical consumption in 2019 by quantity and average cost per day of therapy (% deviation from the national average)

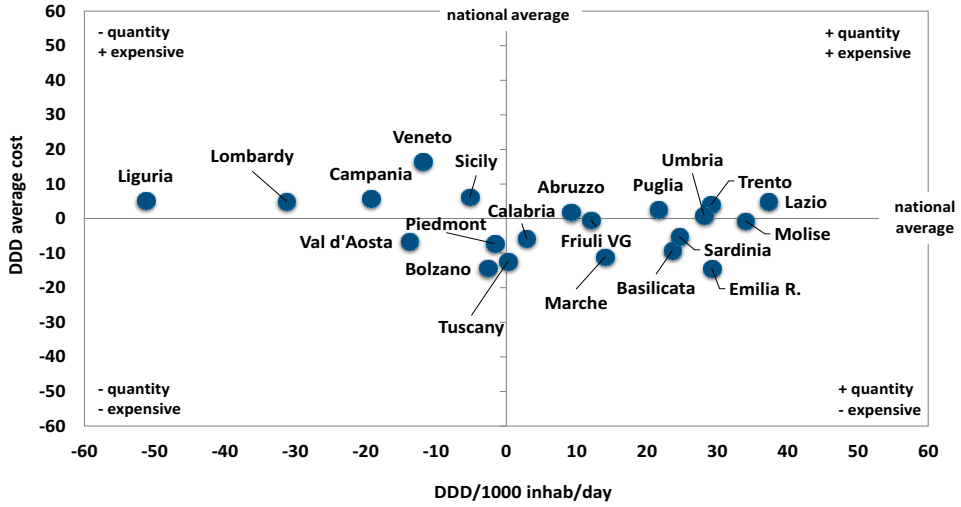


Figure 3.9.1d. Distribution of the prevalence of use and consumption of thyroid medicines for NHS outpatient expenditure (year 2019)

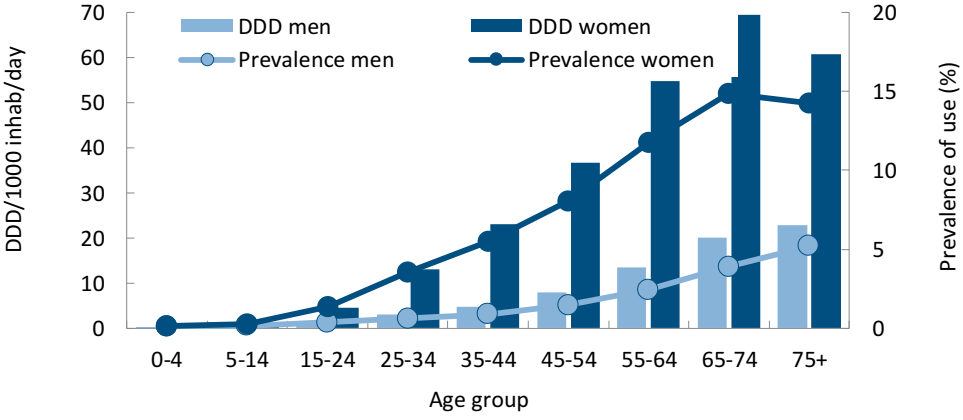


Table 3.9.1e. Duration of therapy with thyroid medicines by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	DDD Median	Users with 1 prescription
North	3.6	164.1	150.0	13.9
Centre	4.0	166.1	150.0	13.0
South and Islands	4.1	165.5	150.0	14.1
Thyroid medicines	**3.9**	**165.1**	**150.0**	**13.7**

3.10 Genitourinary System and Sex Hormones

In 2019, medicines used to treat genitourinary diseases and sex hormones represented the tenth category with the highest public expenditure, amounting to € 440.7 million and 1.9% of total public expenditure. The overall per capita expenditure for these medicines was equal to approximately € 7.30 per capita, mainly due to outpatient NHS pharmaceutical expenditure (€ 5.77 euros per capita). However, it increased by up to 2.3% compared to the previous year. On the contrary, the contribution coming from the expenditure of these medicines purchased by public health facilities was less significant (€ 1.53) (Table 3.1).
Consumption for this category of medicines amounted to 44.2 DDD/1000 inhabitants per day, outlining an increase of 3.4% compared to 2018, thus confirming the fluctuating pattern of recent years. The analysis of medicine utilization profile by age group and gender (including outpatient NHS pharmaceutical expenditure and *per conto* distribution) confirms that women aged 15-44 are the main users. The level of consumption is higher in women aged 25-44 years due to the use of hormonal preparations. However, there is a clear shift in the use of these medicines as regards to men aged 55 years and over, mainly in relation to the treatment of prostatic hypertrophy. The prevalence of use of these medicines in men over 75 years of age reaches 40% of the population in this age group. At the same time, the per capita expenditure incurred by the NHS also increases with the age of patients, reaching a maximum value of € 56.5 per capita in men over 75 years of age. On the other hand, the highest rate of expenditure is reported in women aged 35-44 with a value of € 11.6 per capita.
As regards outpatient NHS expenditure, the per capita expenditure of medicines related to the genitourinary system was equal to € 5.77 in 2019, reporting an increase of 2.3% compared to 2018. This pattern was determined by an increase in consumption (+2.3%) and by substantial price stability as well as by the use of less expensive specialties (mix effect 0.3%) (Table 3.9). In this context, the therapeutic category that shows the highest values of expenditure and consumption is represented by alpha-adrenergic receptor antagonists, with € 3.15 of per capita expenditure and 26 DDD/1000 inhabitants per day, followed by inhibitors of testosterone-5-alpha reductase with € 1.58 and 10.7 DDD (Table 3.9). Tamsulosin, silodosin and dutasteride are the molecules with the greatest incidence of expenditure (Table 3.5). Silodosin is the first active ingredient belonging to this category of medicines included among the top 30 with the greatest variation in outpatient NHS expenditure compared to the previous year (+7.3%) (Table 3.7).
A decrease in per capita expenditure (-2.7%) and a significant increase in consumption (+23.3%) were recorded as regards medicines purchased by public health facilities. The therapeutic categories with the greatest increase in expenditure are represented by gonadotropins, used for the treatment of infertility (€ 0.96 per capita); they showed a decrease of expenditure compared to the previous year (-0.4%) together with medicines used for the treatment of erectile dysfunction which both represent 62.8% and 13.3% of the total expenditure of the category (Table 3.10). Follitropin alfa is the active ingredient with the highest incidence of expenditure (24.2%), showing a decrease of expenditure (10.6%), of consumption (-4.1%) and of price (-6.8%) (Table 3.11).
No active ingredient belonging to this category of medicines appears in the top 30 with the greatest incidence on expenditure for medicines purchased by public health facilities, nor

in the top 30 with the greatest variation in expenditure compared to the previous year (Tables 3.12 and 3.13).

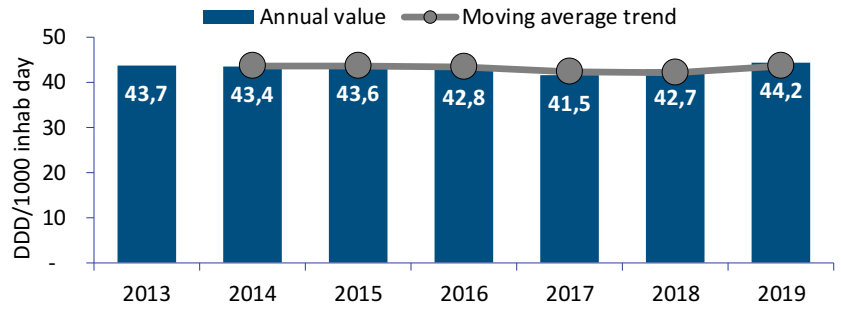
For further information on the use of medicinal products related to the same therapeutic area, analyses have been developed on the historical series of consumption by active substance and by Region as well as on the efficiency of recovering resources in relation to the presence of patent-expired medicines and on a regional basis. These analyses were focused on medicines used for the treatment of genitourinary disorders (Tables 3.12 and 3.13).

MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE

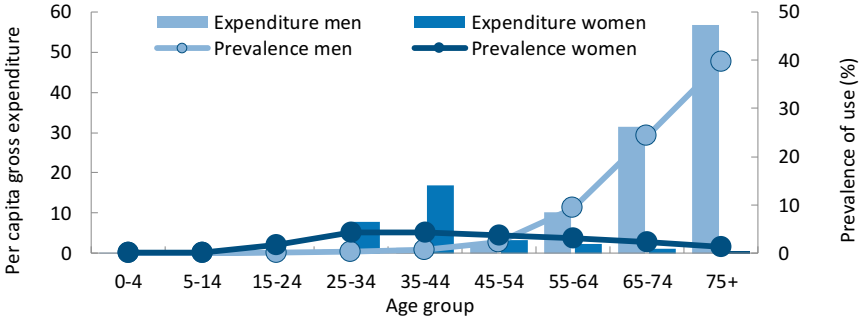
Genitourinary System and Sex Hormones

NHS expenditure millions € (% on the total)	**440.7**	**(1.9)**
Δ % 2019-2018		1.0
Per capita gross expenditure, range among regions	5.6	8.6
DDD/1000 inhab. per day* (% on the total)	**44.2**	**(3.8)**
Δ % 2019-2018		3.4
DDD/1000 inhab. per day: range among regions:	31.7	52.6

** Includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure 2019 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.0	0.0	0.0	0.0	0.1	0.1
5-14	0.0	0.0	0.0	0.1	0.2	0.2
15-24	0.2	0.7	0.4	0.4	4.2	2.2
25-34	0.6	5.3	2.9	1.0	11.6	6.2
35-44	1.0	11.6	6.3	2.4	14.7	8.5
45-54	1.9	2.9	2.4	11.3	15.1	13.2
55-64	9.3	2.2	5.7	68.2	15.7	41.1
65-74	30.3	1.0	14.8	226.7	8.8	111.6
75+	56.5	0.5	22.9	415.0	4.2	168.4

3.10.1 Medicines for Genitourinary Disorders

- The consumption of medicines for genitourinary disorders increased from 31.8 to 37.6 DDD between 2014 and 2019; it was equal to an increase of 18.2%; the average cost per day of therapy remained stable at € 0.35 even though it fell by 26.3% due to the patent expiry of dutasteride (which occurred in the second half of 2017);
- medicines for benign prostatic hypertrophy (BPH) represent almost all of the consumption of the category (37.3 DDD; +3.5% compared to 2018), while the use of medicines for incontinence and urination disorders is less significant (0.2 DDD; + 10.2%); tamsulosin, alfuzosin, dutasteride and silodosin are the most prescribed molecules (10.5; 8.8; 8.2 and 5.7 DDD respectively); the level of consumption related to such molecules showed an increase compared to the previous year ranging from 3.0% of tamsulosin to 7,3% of silodosin. The use of tolterodine reported an increase of 35.3% even though its use was reduced. This medicine is included in the document named "Note 87", published by the Italian Medicines Agency. The document outlines the restrictions related to the reimbursement of such a medicine to patients suffering from urgency urinary incontinence, in cases where the voiding disorder is related to central nervous system diseases (e.g. stroke, Parkinson's disease, trauma, tumours, spina bifida, multiple sclerosis);
- Marche is the Region that shows a double consumption compared to the Autonomous Province of Bolzano (46.8 vs 23.2 DDD); however, the use of such a medicine is less significant in the North compared to the South of Italy;
- expired patent medicines represent approximately 85% of doses and 77% of expenditure; one third is represented by equivalent medicinal products;
- as expected, consumption increases with age in male population, reaching 40% of the prevalence in the age group over 75 years and over 400 DDD for 1000 inhabitants;
- the median duration of the treatment of 320 days is in line with the therapeutic schemes for this disease and only 13.6% of users received a single prescription in 2019.

Figure 3.10.1a. Medicines for genitourinary disorders, temporal consumption trend (2014-2019)

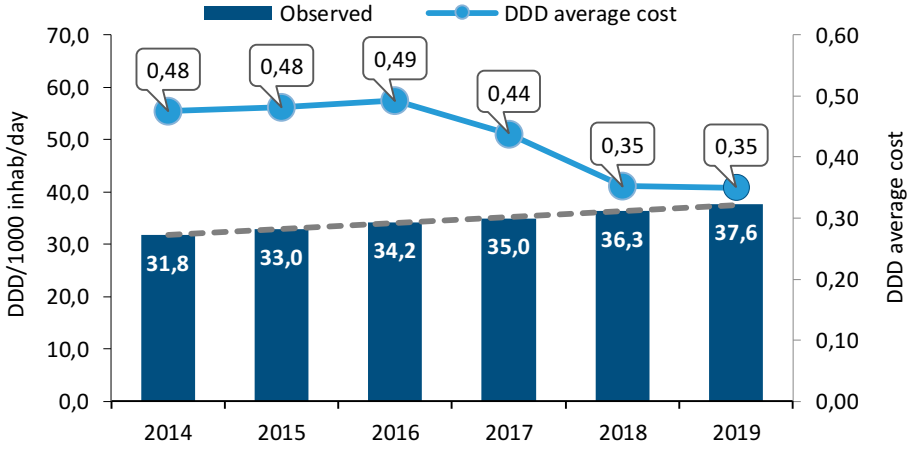


Table 3.10.1a. Medicines for genitourinary disorders, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ % 19-18
Medicines used for benign prostatic hypertrophy	31.6	32.8	34.0	34.7	36.1	37.3	3.5
Medicines for incontinence and urination disorders	0.2	0.2	0.2	0.2	0.2	0.2	10.2
Other medicines used for benign prostatic hypertrophy	0.0	0.0	0.0	0.0	0.0	0.0	5.4
Medicines for genitourinary disorders	**31.8**	**33.0**	**34.2**	**35.0**	**36.3**	**37.6**	**3.6**
tamsulosin	9.4	9.5	9.8	9.9	10.2	10.5	3.0
silodosin	3.4	4.0	4.5	4.9	5.3	5.7	7.3
dutasteride	6.5	7.0	7.3	7.4	7.9	8.2	4.5
alfuzosin	7.7	7.8	8.0	8.2	8.4	8.8	4.0
finasteride	2.7	2.7	2.7	2.7	2.6	2.6	-1.4
terazosin	1.7	1.6	1.5	1.4	1.4	1.3	-4.5
oxybutynin	0.2	0.2	0.2	0.2	0.2	0.2	7.0
doxazosin	0.3	0.3	0.2	0.2	0.2	0.2	-7.3
tolterodine	0.0	0.0	0.0	0.0	0.0	0.0	35.3
solifenacin	0.0	0.0	0.0	0.0	0.0	0.0	8.7

Table 3.10.1b. Medicines for genitourinary disorders, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	31.6	32.4	33.5	34.1	35.0	36.1	3.2
Valle d'Aosta	28.5	29.3	29.5	29.6	30.7	31.2	1.8
Lombardy	28.5	29.7	30.8	31.6	32.9	33.6	2.3
A.P. of Bolzano	21.5	21.9	22.1	22.6	22.8	23.2	1.9
A.P. of Trento	28.8	29.8	30.5	31.5	33.0	34.1	3.3
Veneto	27.9	28.8	30.0	30.6	31.8	33.1	4.0
Friuli VG	28.3	29.2	30.1	30.5	31.5	32.7	4.0
Liguria	33.6	34.6	35.7	36.3	37.4	38.7	3.6
Emilia R.	33.2	35.0	36.2	36.8	37.6	39.0	3.9
Tuscany	31.6	32.4	33.4	34.2	35.3	36.6	3.7
Umbria	36.7	37.9	39.3	40.1	41.8	43.2	3.3
Marche	39.5	40.9	42.7	43.3	45.1	46.8	3.7
Lazio	34.4	35.4	36.3	36.9	38.0	39.2	3.2
Abruzzo	32.2	33.3	34.7	35.6	37.4	38.8	3.7
Molise	30.2	30.6	31.7	32.8	34.3	35.7	3.9
Campania	31.4	33.1	34.9	36.2	38.3	40.1	4.7
Puglia	33.5	34.9	36.6	37.9	39.5	41.5	5.2
Basilicata	34.5	36.6	38.5	39.8	41.9	43.7	4.3
Calabria	34.1	34.9	36.4	37.1	38.4	39.4	2.6
Sicily	34.3	35.4	36.5	37.3	38.8	40.4	4.0
Sardinia	31.4	32.9	34.0	35.0	36.6	37.6	2.8
Italy	**31.8**	**33.0**	**34.2**	**35.0**	**36.3**	**37.6**	**3.6**

Table 3.10.1c. Medicines for genitourinary disorders, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	DDD Average Cost	Δ % 19-18
Medicines used for benign prostatic hypertrophy	4.74	2.8	37.3	3.5	0.35	-0.8
Medicines for incontinence and urination disorders	0.06	8.5	0.2	10.2	0.65	-1.6
Other medicines used for benign prostatic hypertrophy	0.00	9.9	0.0	5.4	1.17	4.3
Medicines for genitourinary disorders	**4.80**	**2.8**	**37.6**	**3.6**	**0.35**	**-0.7**
tamsulosin	1.08	2.6	10.5	3.0	0.28	-0.4
silodosin	1.07	7.3	5.7	7.3	0.51	0.0
dutasteride	1.04	2.0	8.2	4.5	0.35	-2.4
alfuzosin	0.82	3.8	8.8	4.0	0.25	-0.2
finasteride	0.55	-2.1	2.6	-1.4	0.58	-0.8
terazosin	0.16	-5.5	1.3	-4.5	0.34	-1.0
oxybutynin	0.04	5.6	0.2	7.0	0.61	-1.3
doxazosin	0.03	-7.2	0.2	-7.3	0.42	0.0
tolterodine	0.01	28.7	0.0	35.3	0.68	-4.9
solifenacin	0.00	8.9	0.0	8.7	1.18	0.2

Table 3.10.1d. Prescription of medicines for genitourinary disorders with patent expired* in 2019

Categories	Per capita Expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	DDD Average Cost
Patent expired	3.68	76.7	1.4	31.6	84.1	2.6	0.32
Generic	1.24	33.6	6.1	12.4	39.3	7.0	0.27
Ex originator	2.45	66.4	-0.8	19.2	60.7	0.0	0.35
Patent covered	1.12	23.3	7.8	6.0	15.9	9.0	0.51
Medicines for genitourinary disorders	**4.80**	**100.0**	**2.8**	**37.6**	**100.0**	**3.6**	**0.35**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.10.1b. Medicines for genitourinary disorders, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

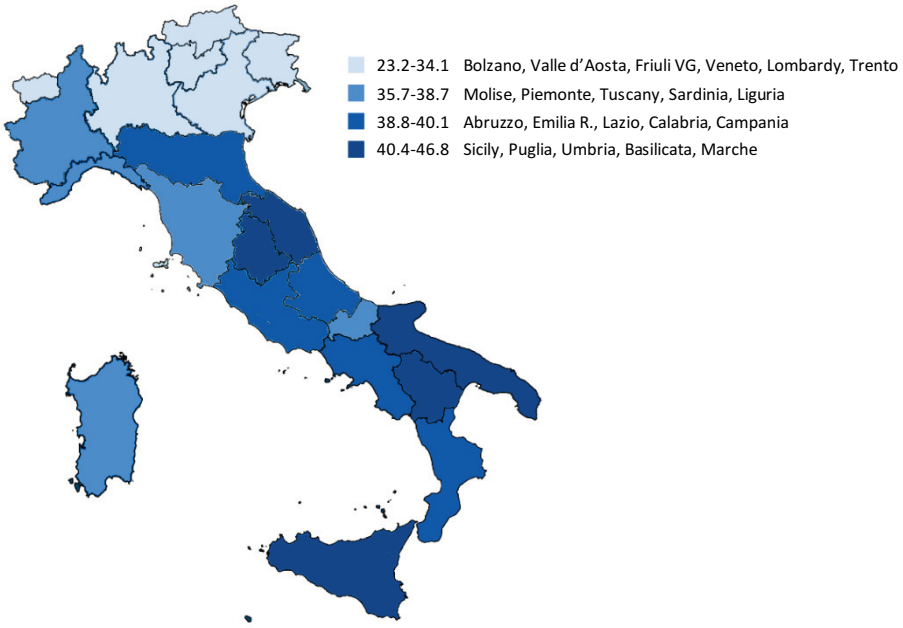


Figure 3.10.1c. Medicines for genitourinary disorders, regional variability of pharmaceutical consumption in 2019 by quantity and average cost per day of therapy (% deviation from the national average)

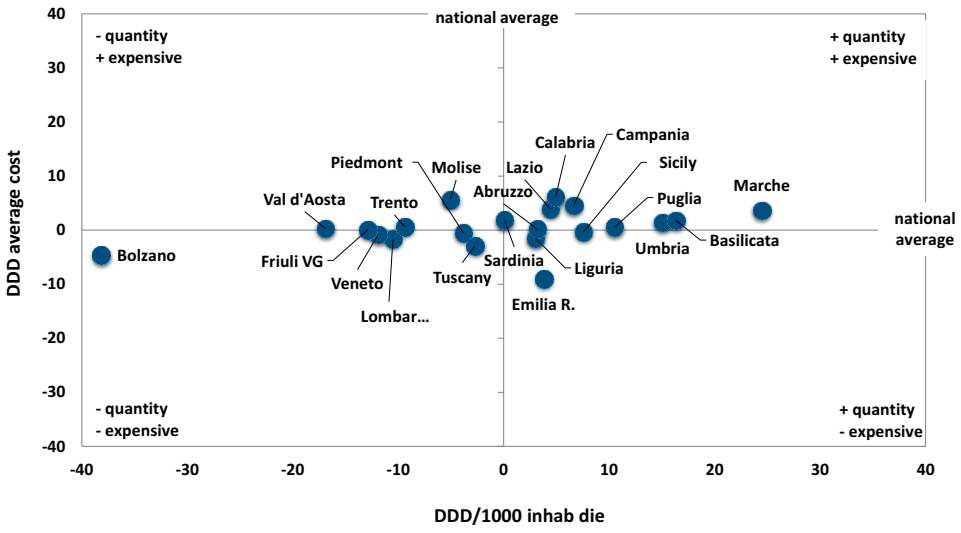


Figure 3.10.1d. Distribution of the prevalence of use and consumption of medicines for genitourinary disorders for NHS outpatient expenditure (year 2019)

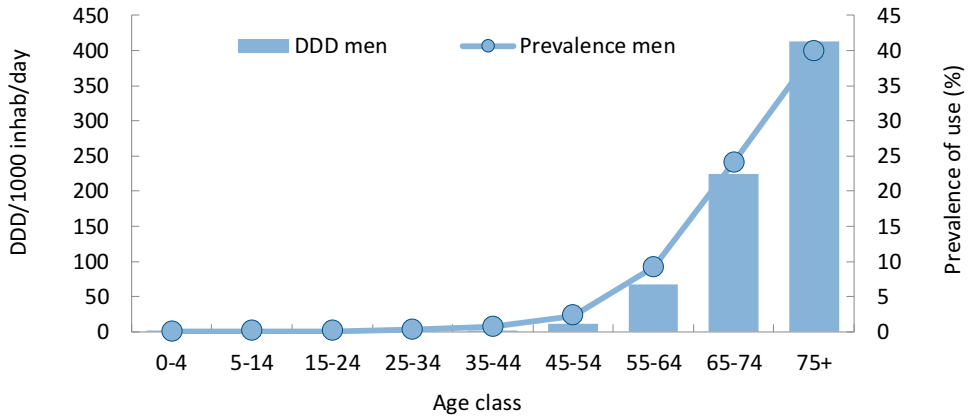


Table 3.10.1e. Duration of therapy with medicines for genitourinary disorders by geographic area for NHS outpatient expenditure (year 2019)

	Prescriptions per user	DDD per user	DDD Median	Users with 1 prescription
North	7.4	332.6	320.0	12.9
Centre	7.4	326.2	320.0	15.0
South and Islands	7.5	326.5	320.0	13.7
Medicines for genitourinary disorders	**7.4**	**329.0**	**320.0**	**13.6**

3.11 Sense Organs

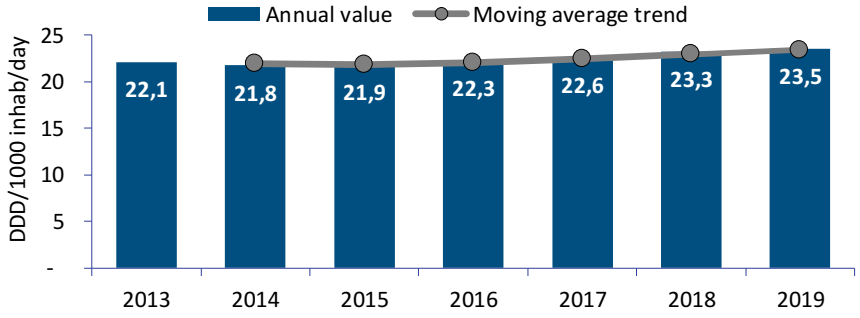
In 2019, medicines related to the treatment of sense organs diseases are ranked as eleventh in relation to public expenditure, amounting to approximately € 422 million (1.8% of total expenditure). The overall per capita expenditure for these medicines amounted to approximately € 7, mainly due to outpatient NHS pharmaceutical expenditure (€ 3.89 per capita). It reported an increase of up 2.3% compared to the previous year. On the contrary, the contribution coming from the expenditure of these medicines purchased by public health facilities was less significant (€ 3.10 per capita) (Table 3.1).
The level of consumption for this category of medicines amounted to 23.5 DDD/1000 inhabitants per day, showing an increase (+1.1%) compared to 2018 (Table 3.2).
The analysis of the medicine utilization profile by age group and gender (including outpatient NHS pharmaceutical expenditure and *per conto* distribution) confirms the less significant use of these medicines in patients up to the age of 55. The level of consumption is slightly higher in women than in men, with a reversal pattern after the age of 75 (97.1 DDD for men compared to 84.6 DDD for women). At the same time, per capita expenditure also increases with the age of patients, reaching the maximum value of € 16.7 in the age group over 75, with a higher prevalence of expenditure for men (€ 18.3) compared to women (€ 15.6).
As far as the outpatient NHS expenditure is concerned, the 2.3% increase, compared to 2018, is due to an increase in consumption (+1%), a decrease in prices (-0.3%) and a shift in prescriptions towards more expensive medicinal products (mix effect: +1.3%) (Table 3.9).
Beta-blocking substances do represent the category with the highest expenditure (€ 2.24) and consumption (11.7 DDD) within this distribution channel, followed by prostaglandin analogues, with values of € 1.30 and 5,7 DDD respectively. (Table 3.9). The use of bimatoprost plain and in association with timolol accounts for 23.2% of the expenditure of the entire category (Table 3.5).
An increase in per capita expenditure and the average DDD cost of 10.3% was recorded in relation to medicines purchased by public health facilities. The therapeutic category with the greatest incidence on outpatient NHS pharmaceutical expenditure is represented by antineovascular agents, which account for 75.9% of the expenditure, such as, for instance, medicines used for the treatment of age-related neovascular macular degeneration (AMD) as well as medicines used for the treatment of visual impairment caused by diabetic macular edema (DME). Its level of consumption recorded an increase of 14.9% compared to 2018 (Table 3.10). Aflibercept is the active ingredient with the highest expenditure and consumption and accounts for 38% of the incidence on the expenditure of the category within this subgroup of medicines, followed by ranibizumab which affects the expenditure of such category of 37.1% (Table 3.10).
For further information on the use of medicinal products related to the same therapeutic area, analyses have been developed on the historical series of consumption by active substance and by Region as well as on the efficiency of recovering resources in relation to the presence of patent-expired medicines and on a regional basis. These analyses were focused on medicines used for the treatment of eye disorders (Tables 3.11.1 and others to follow).

Furthermore, in the section related to the monitoring programs, special attention is given to the active ingredients used for the treatment of AMD with regard to the description of the baseline characteristics of patients undergoing treatment and their regional distribution (Section 6).

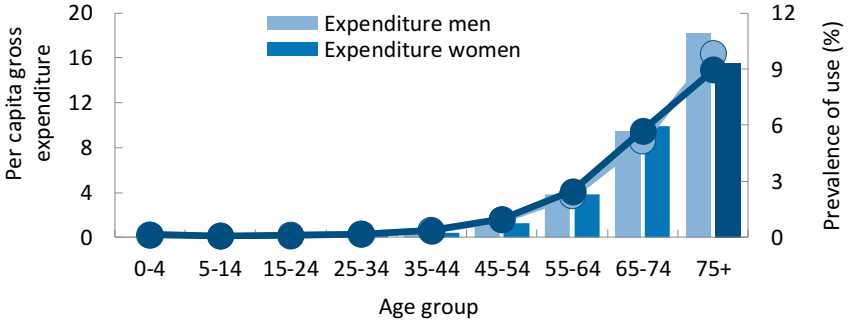
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Sense Organs

NHS expenditure millions € (% on the total)	**422.4**	**(1.8)**
Δ % 2019-2018		5.5
Per capita gross expenditure, range among regions	5.1	8.8
DDD/1000 inhab. per day* (% on the total)	**23.5**	**(2.0)**
Δ % 2019-2018		1.1
DDD/1000 inhab. per day: range among regions	18.6	32.7

** Includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure 2019 (Chart and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.0	0.0	0.0	0.2	0.2	0.2
5-14	0.0	0.0	0.0	0.2	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	0.5	2.8	2.1	2.4
45-54	1.5	1.3	1.4	7.7	6.9	7.3
55-64	3.8	3.8	3.8	20.3	20.4	20.3
65-74	9.6	9.9	9.7	50.1	52.5	51.4
75+	18.3	15.6	16.7	97.1	84.6	89.6

3.11.1 Medicines for Eye Disorders

- The level of consumption has remained almost stable over the last 6 years, ranging from 19.9 DDD in 2014 to 21.3 DDD in 2019 with a variation of 7%. In the same period, the average cost per day of therapy increased by 18%, reaching € 0.87 in 2019;
- 56% of consumption (11.8 DDD) is represented by antiglaucoma preparations - beta-blockers plain or in combination, followed by antiglaucoma preparations - prostaglandin analogues with 5.8 DDD. Antineovascular agents, with € 2.36 per capita, represent the category with the highest expenditure; they are up to 7.7% compared to 2018. Significant increases in relation to expenditure are also reported for cortisones (+13.1%), especially for cortisone intravitreal implants (+31.7%);
- aflibercept (€ 1.18) and ranibizumab (€ 1.15) are the two substances with the highest expenditure: these medicines are used for the treatment of age-related neovascular macular degeneration (AMD). However, the use of these medicines showed a different trend compared to 2018: the first ingredient reported an increase of 23.9%, while the second one decreased of 4.9%. The use of dexamethasone (cortisone medicine) showed an upward trend even though it did not report high expenditure (€ 0.37) and consumption (0.2 DDD) values;
- a certain variability in regional consumption is outlined, with values ranging from 16.9 DDD in the Autonomous Province of Bolzano to 30.6 DDD in Marche (a gap of over 80%). Friuli Venezia Giulia, Liguria and Umbria are the regions where multiple doses are used; the cost per day of therapy is higher than the national average. Antiglaucoma preparations - prostaglandin analogues are the category with the most marked regional differences (CV 20%);
- patent expired medicines accounted for 41% of doses and 17% of expenditure in 2019, with limited use of equivalent medicines.

Figure 3.11.1a. Medicines for eye disorders, temporal consumption trend (2014-2019)

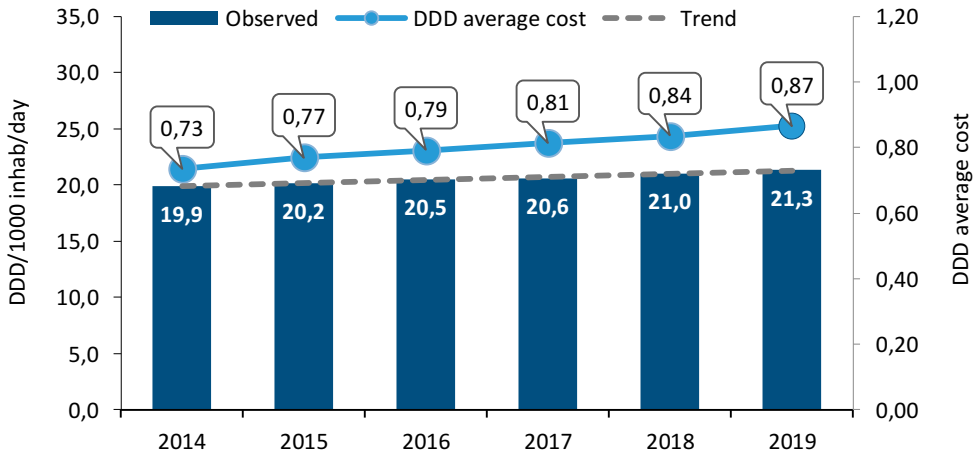


Table 3.11.1a. Medicines for eye disorders, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2019

Subgroups and substances	2014	2015	2016	2017	2018	2019	Δ% 19-18
Antineovascularizing agents	0.2	0.2	0.3	0.3	0.4	0.4	14.0
Antiglaucoma preparations - beta blockers plain or in association	11.2	11.4	11.4	11.5	11.7	11.8	1.3
Antiglaucoma preparations - analogues of prostaglandins	5.6	5.6	5.7	5.7	5.8	5.8	0.8
Cortisones	0.1	0.2	0.2	0.2	0.2	0.2	18.1
Antiglaucoma preparations - carbonic anhydrase inhibitors	1.5	1.5	1.5	1.5	1.5	1.5	-1.0
Antiglaucoma sympathomimetic preparations	1.3	1.3	1.3	1.4	1.5	1.5	2.6
Other ophthalmologists	0.0	0.0	0.0	0.0	0.0	0.0	86.5
Cortisones (intravitreal implants)	0.0	0.0	0.0	0.0	0.0	0.0	32.0
Antiglaucoma preparations - parasympathomimetics	0.1	0.1	0.1	0.1	0.0	0.0	-11.7
Antiglaucoma preparations - others	0.0	0.0	0.0	0.0	0.0	0.0	-32.5
Medicines for eye disorders	**19.9**	**20.2**	**20.5**	**20.6**	**21.0**	**21.3**	**1.4**
aflibercept	0.0	0.1	0.2	0.2	0.2	0.3	21.1
ranibizumab	0.2	0.1	0.1	0.1	0.1	0.1	0.2
bimatoprost	1.8	1.9	1.9	1.9	1.9	2.0	1.0
timolol/bimatoprost	1.2	1.3	1.3	1.4	1.4	1.4	1.3
tafluprost	0.8	0.9	1.2	1.2	1.3	1.4	10.3
brinzolamide/timolol	1.2	1.3	1.5	1.6	1.7	1.8	4.1
dexamethasone	0.1	0.2	0.2	0.2	0.2	0.2	18.1
timolol	3.2	3.1	3.3	3.0	3.1	3.1	0.9
dorzolamide/timolol	2.0	2.0	1.8	1.9	2.0	2.1	5.8
travoprost	1.1	1.0	1.0	1.0	1.0	1.1	3.0

Table 3.11.1b. Medicines for eye disorders, weighted regional trend of DDD/1000 inhabitants per day: comparison 2014-2019

Region	2014	2015	2016	2017	2018	2019	Δ % 19-18
Piedmont	21.9	22.1	22.4	22.4	23.0	23.6	2.5
Valle d'Aosta	20.6	20.8	20.4	19.9	19.3	19.6	1.7
Lombardy	16.2	16.6	16.8	16.9	17.3	17.3	0.1
A.P. of Bolzano	14.3	15.0	15.5	16.0	16.5	16.9	2.1
A.P. of Trento	15.1	15.4	16.1	16.5	17.3	17.4	0.2
Veneto	17.7	17.8	18.2	18.5	19.2	19.4	0.8
Friuli VG	22.9	23.1	23.1	23.7	24.2	24.5	1.1
Liguria	21.2	21.3	21.7	21.5	21.7	21.7	0.3
Emilia R.	25.2	25.5	26.0	27.0	27.7	28.1	1.4
Tuscany	25.8	25.8	26.4	26.4	26.7	27.0	1.0
Umbria	23.0	23.2	23.9	24.0	24.7	25.2	1.8
Marche	28.5	28.9	29.5	29.5	30.0	30.6	2.1
Lazio	22.0	22.3	22.4	22.1	22.3	22.6	1.2
Abruzzo	25.4	25.7	25.9	25.9	26.5	27.0	1.7
Molise	15.9	15.7	16.3	16.1	16.3	17.0	4.2
Campania	16.8	17.1	17.5	17.4	17.9	18.3	2.2
Puglia	18.4	18.6	18.8	18.8	19.1	19.6	2.7
Basilicata	19.1	19.5	20.1	20.0	20.7	21.0	1.6
Calabria	18.9	19.3	19.3	19.2	19.5	19.9	2.0
Sicily	16.1	16.3	16.6	16.8	17.3	17.8	2.6
Sardinia	19.7	19.8	19.7	19.7	19.8	19.8	-0.1
Italy	**19.9**	**20.2**	**20.5**	**20.6**	**21.0**	**21.3**	**1.4**

Table 3.11.1c. Medicines for eye disorders, prescription by therapeutic category and by substance in 2019

Subgroups and substances	Per capita expenditure	Δ % 19-18	DDD/1000 inhab. per day	Δ % 19-18	DDD Average Cost	Δ % 19-18
Antineovascularizing agents	2.36	7.7	0.4	14.0	15.63	-5.5
Antiglaucoma preparations - beta blockers plain or in association	2.25	2.3	11.8	1.3	0.52	1.0
Antiglaucoma preparations - analogues of prostaglandins	1.31	2.4	5.8	0.8	0.62	1.6
Cortisones	0.38	13.1	0.2	18.1	4.29	-4.2
Antiglaucoma preparations - carbonic anhydrase inhibitors	0.22	-0.2	1.5	-1.0	0.42	0.8
Antiglaucoma sympathomimetic preparations	0.10	4.4	1.5	2.6	0.18	1.8
Other ophthalmologists	0.09	49.0	0.0	86.5	227.11	-20.1
Cortisones (intravitreal implants)	0.03	31.7	0.0	32.0	6,676.58	-0.3
Antiglaucoma preparations - parasympathomimetics	0.01	20.3	0.0	-11.7	0.61	36.3
Antiglaucoma preparations - others	0.00	-32.5	0.0	-32.5	0.35	0.0
Medicines for eye disorders	**6.75**	**5.2**	**21.3**	**1.4**	**0.87**	**3.7**
aflibercept	1.18	23.9	0.3	21.1	11.05	2.3
ranibizumab	1.15	-4.9	0.1	0.2	26.12	-5.1
bimatoprost	0.47	0.2	2.0	1.0	0.66	-0.8
timolol/bimatoprost	0.45	0.9	1.4	1.3	0.85	-0.4
tafluprost	0.44	10.3	1.4	10.3	0.86	0.0
brinzolamide/timolol	0.43	4.2	1.8	4.1	0.67	0.1
dexamethasone	0.37	13.5	0.2	18.1	4.20	-3.9
timolol	0.34	4.5	3.1	0.9	0.30	3.6
dorzolamide/timolol	0.29	4.4	2.1	5.8	0.38	-1.3
travoprost	0.21	4.4	1.1	3.0	0.54	1.4

Table 3.11.1d Prescription of medicines for eye disorders with patent expired* in 2019

Categories	Per capita expenditure	%	Δ % 19-18	DDD/1000 inhab. per day	%	Δ % 19-18	DDD Average Cost
Patent expired	1.15	17.0	3.5	8.7	40.8	0.6	0.36
Generic	0.15	12.9	0.8	1.7	19.9	-3.1	0.23
Ex originator	1.00	87.1	3.9	7.0	80.1	1.5	0.39
Patent covered	5.60	83.0	5.6	12.6	59.2	2.0	1.22
Medicines for eye disorders	**6.75**	**100.0**	**5.2**	**21.3**	**100.0**	**1.4**	**0.87**

* Source: monthly transparency lists published by the Italian Medicines Agency in 2019

Figure 3.11.1b. Medicines for eye disorders, distribution in quartiles of 2019 consumption (weighted DDD/1000 inhab. per day)

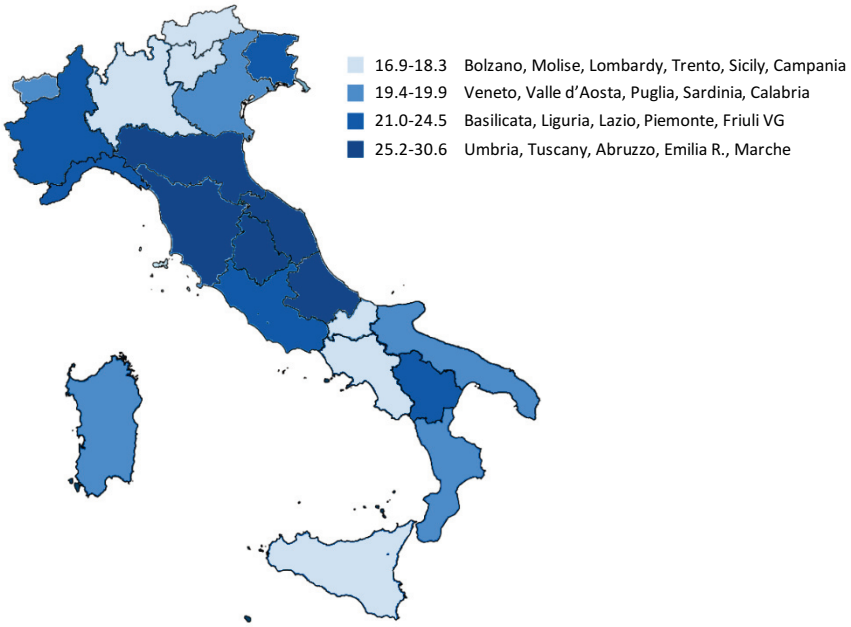


Figure 3.11.1c. Medicines for eye disorders, regional variability of pharmaceutical consumption in 2019 by quantity and average cost per day of therapy (% deviation from the national average)

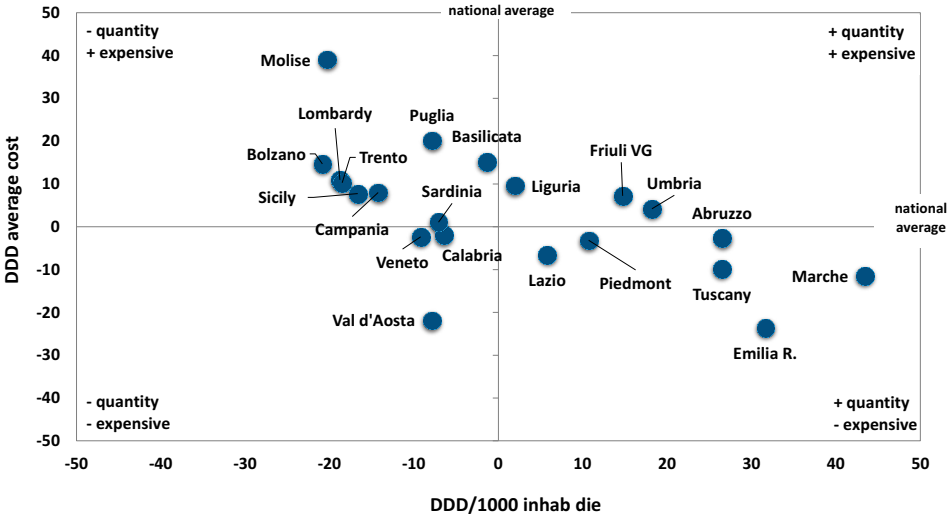
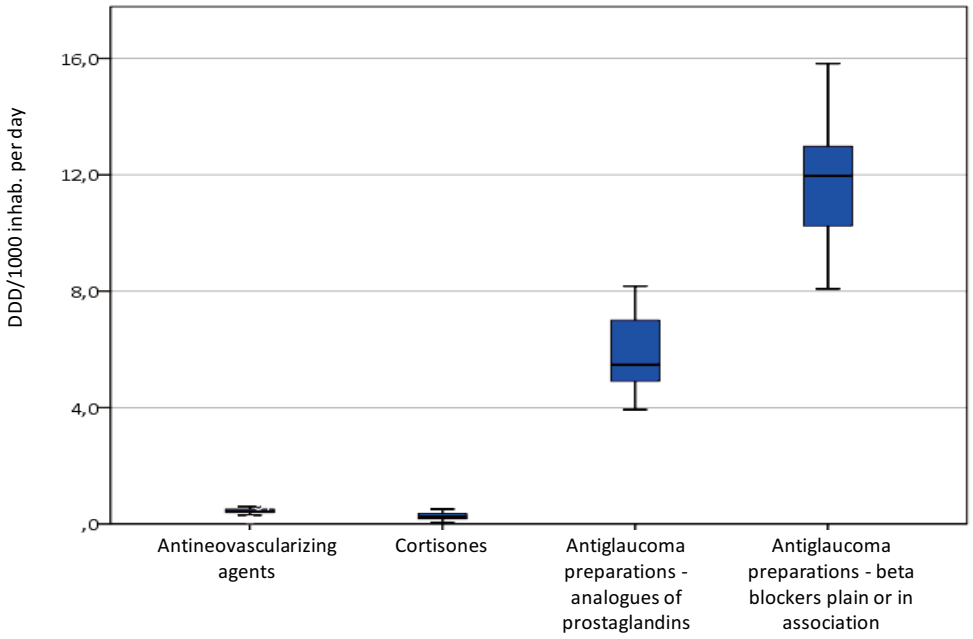


Figure 3.11.2d. Medicines for eye disorders, regional variation in 2019 consumption (weighted DDD/1000 inhab. per day) by subgroup

(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).



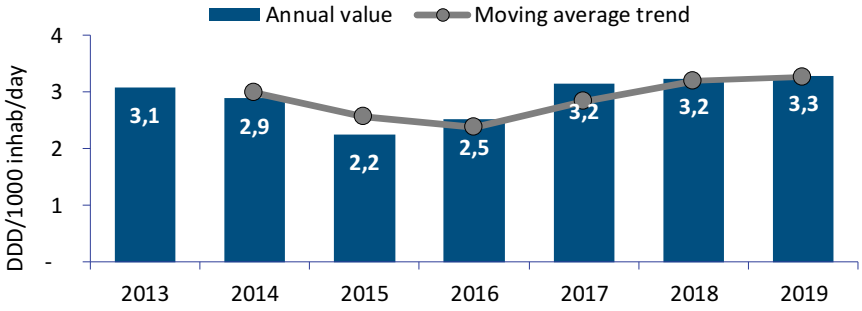
3.12 Various Groups of Medicines

In 2019 the therapeutic category of various medicines ranked twelfth for public expenditure; it amounted to € 352.6 million and to 1.5% of total public expenditure. The total per capita expenditure for these medicines was equal to € 5.84, mainly due to the expenditure related to the purchase of these medicines by public health structures (€ 5.70 per capita). On the contrary, the financial contribution from outpatient NHS assistance is less significant (€ 0.15 per capita) (Table 3.1).
Consumption for this category of medicines amounted to 3.3 DDD/1000 inhabitants per day, reporting an increase of approximately 1.5% compared to 2018 (Table 3.2) and confirming the upward trend of recent years.
The analysis of the medicine utilization profile by age group and gender (including outpatient NHS pharmaceutical expenditure and *per conto* distribution) highlights a marginal use of these medicines up to the age group between 55 and 64 years for both genders. However, the use of these medicines outlines an upward trend with the increasing of age, especially in male population, reaching a prevalence of use of 3.8% after 75 years of age. At the same time, the per capita expenditure incurred by the NHS also increases with the age of patients, reaching the maximum level of 9.3 euros per capita in men and 6.7 in women over 75 years of age.
As far as the outpatient NHS expenditure is concerned, per capita expenditure was equal to € 0.15, showing a downward trend performance by 1.4%. However, the same trend performance was also reported for consumption (-1.1%) and prices (-1.4%); the number of prescriptions of more expensive medicinal products showed an increase (mix effect: +1.1%) (Table 3.9). Medicines for the treatment of hyperkalaemia and hyperphosphatemia (€ 0.13 per capita) are listed in the ATC category -IV level- belonging to the various medicines that have the greatest impact on the outpatient NHS pharmaceutical expenditure. Sevelamer is the active ingredient most widely used and with the highest cost with, an incidence of 35.1% of the total (Tables 3.5).
As for medicines purchased by public health facilities, an increase of expenditure (+6.0%), consumption (+1.6%) was reported, as well as for the average DDD cost (+4.3%). Iron chelating substances (€ 1.55 per capita) represent the sub-category with the greatest impact on expenditure, accounting for 27.3% of the expenditure of the entire class (Table 3.14). Among iron chelators, the use of deferasirox has an impact on the expenditure of public health facilities of 25.0%, followed by sugammadex, antagonist of neuromuscular blockade from rocuronium and vecuronium, which has an impact of 12.3% (Table 3.11).
None of the active ingredients included in the category is listed among the thirty medicines with the greatest impact on the cost of medicines purchased by public health facilities. However, deferasirox ranks twenty-seventh out of the first thirty active ingredients with the greatest variation in expenditure (+18.5%) compared to the previous year (Tables 4.12 and 4.13).

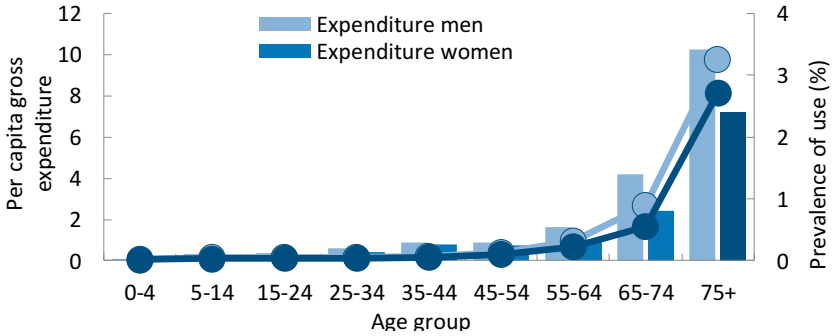
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Various Medicines

NHS expenditure millions € (% on the total)	**352.6**	**(1.5)**
Δ % 2019-2018		5.8
Per capita gross expenditure, range among regions	4.4	13.3
DDD/1000 inhab. per day* (% on the total)	**3.3**	**(0.3)**
Δ % 2019-2018		1.7
	1.5	6.5

Includes NHS outpatient expenditure and purchases by public health facilities



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure 2019 (Chart and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.1	0.1	0.1	0.0	0.0	0.0
5-14	0.2	0.2	0.2	0.1	0.1	0.1
15-24	0.3	0.3	0.3	0.1	0.1	0.1
25-34	0.6	0.4	0.5	0.1	0.1	0.1
35-44	0.8	0.7	0.8	0.1	0.1	0.1
45-54	0.8	0.8	0.8	0.2	0.1	0.2
55-64	1.3	0.9	1.1	0.4	0.2	0.3
65-74	3.7	2.0	2.8	0.7	0.3	0.5
75+	9.3	6.7	7.8	0.9	0.4	0.6

3.13 Dermatological Medicines

In 2019 dermatological medicines were the thirteenth therapeutic category with the highest public expenditure, amounting to € 128.5 million and 0.6% of total public expenditure. The total per capita expenditure for these medicines was € 2.13, mainly due to the outpatient NHS pharmaceutical assistance (€ 1.29 per capita). It reported a sharp increase compared to the previous year (+ 14.5%). On the contrary, the contribution from the purchase of these medicines by public health facilities was less significant (€ 0.84), although a net increase is outlined (Table 3.1).

The level of consumption for this category of medicines was steady compared to 2018 and amounted to 12.7 DDD/1000 inhabitants per day. (Table 3.2).

The analysis of drug utilization profile by age group and gender (including outpatient NHS pharmaceutical expenditure and *per conto* distribution) shows an increase of the use of these medicines among female and male patients from 15 years of age, especially in men, in particular with a prevalence of almost 4% in men over 75 years of age. A less evident trend is observed in the female population with the increasing of age; as in the male population, the prevalence of use reaches the highest level in women over 75 years of age (over 2%). The per capita expenditure incurred by the NHS increases with the age of patients, reaching the maximum value of € 2.5 per capita in people over 75 years old (€ 3.7 in men and € 1.7 in women).

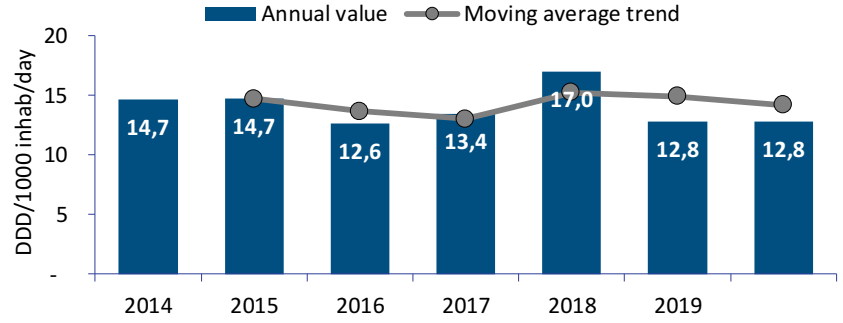
As far as the outpatient NHS expenditure is concerned, the per capita expenditure was equal to € 1.29, an increase of 14.1% compared to 2018. This trend was determined by an increase in consumption (+5.9%), a slight reduction in consumption and greater use of more expensive specialties (mix effect: +8.2%). The other antipsoriatic medicines for topical use (€ 0.87 per capita) do represent the category that has the greatest impact on the outpatient NHS pharmaceutical expenditure (Table 3.10). Calcipotriol/betamethasone association is the medicine with the greatest expenditure and consumption and accounts for 61.8% of gross expenditure for the category and 52% of consumption (Table 3.5).

As for medicines purchased by public health facilities, a strong upward trend is registered in expenditure (> 100%) and a downfall trend in consumption (-3.3%) (Table 3.10). Povidone iodine represent 14.3% of the expenditure, chlorhexidine associated with benzalkonium (13.1%) and silver sulfadiazine (12.8%) (Table 3.11).

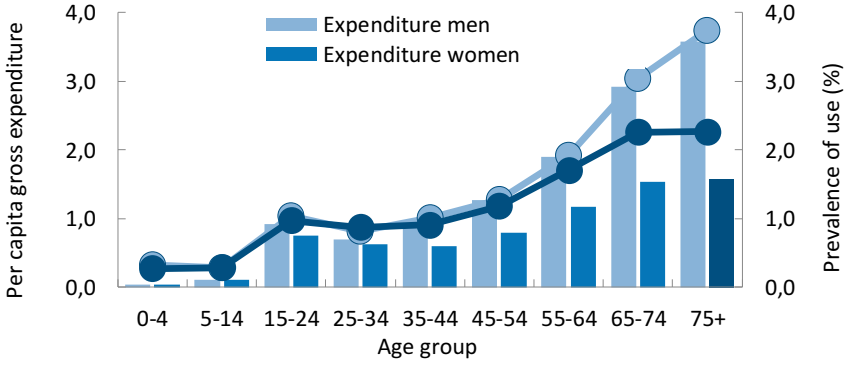
MAIN MEASURES OF EXPENDITURE, CONSUMPTION AND EXPOSURE
Dermatological Medicines

NHS expenditure millions € (% on the total)	**128.5**	**(0.6)**
Δ % 2019-2018		39.7
Per capita gross expenditure, range among regions	1.7	2.8
DDD/1000 inhab. per day* (% on the total)	**12.7**	**(1.1)**
Δ % 2019-2018		-0.1
DDD/1000 inhab. per day among regions:	8.1	22.4

** Includes NHS outpatient expenditure and purchases by public health facilities*



Distribution by age and gender of expenditure, prevalence of use and consumption for NHS outpatient expenditure 2019 (Figure and Table)



Age group	Gross per capita expenditure			DDD/1000 inhab. per day		
	Men	Women	Total	Men	Women	Total
0-4	0.0	0.0	0.0	0.4	0.3	0.4
5-14	0.1	0.1	0.1	0.5	0.5	0.5
15-24	1.0	0.8	0.9	2.6	2.3	2.5
25-34	0.8	0.7	0.8	2.7	2.2	2.4
35-44	1.1	0.7	0.9	3.9	2.5	3.2
45-54	1.5	0.9	1.2	5.2	3.2	4.2
55-64	2.2	1.3	1.8	7.7	4.9	6.2
65-74	3.2	1.7	2.4	11.3	6.6	8.8
75+	3.7	1.7	2.5	12.6	6.6	9.0

Section 4

Prescription appropriateness

Indicators of adherence and persistence

Methods

The administrative database of prescriptions of NHS-Class A medicinal products dispensed nationally was employed to monitor the use of medicinal products for chronic therapies ("art.50 flow" as per article 50, paragraph 5, of Law Decree no. 269 dated 30 September 2009 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 medicinal products belonging to the class under consideration in the period between 1 October 2017 and 31 December 2017. Such individuals had not received prescriptions for medicinal products of the same class in the previous months starting from 1 January 2017. The year 2019 was used for the follow-up of subjects enrolled in 2018.
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, as supplied during the follow-up period. The corresponding formula is the following:

$$MPR = \frac{number\ of\ therapy\ days}{time\ interval\ between\ first\ and\ last\ prescription\ (plus\ days\ to\ last\ prescription)}\ x\ 100$$

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". It is a dynamic measure describing 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 fixed *a priori* (in this case, 60 days). Therefore, a person who started a pharmaceutical treatment on a t_0 date is defined as "persistent" to the treatment after *x* days from the beginning of the treatment, if such person has taken the medicine without interruptions until day $(t_0 + x)$. An interruption occurs if, between the theoretical end (calculated on the basis of the DDD) of a prescription and the beginning of the next or the end of the follow-up, a temporal gap higher than 60 days is observed (2-4).
If a subject received a prescription before the theoretical deadline of the previous prescription, that prescription is considered sequential. Therefore, its start date is postponed to the day following the theoretical end of the previous prescription. Persistence was calculated on subjects provided with at least two prescriptions and under therapeutic

switch. Persistence was estimated through Kaplan-Meier analysis, and persistence probability was calculated at 3 months (91 days), 6 months (182 days) and 12 months (365 days). 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, which defines the maintenance of the therapeutic regime.
Before the calculation of adherence and persistence, it was necessary to carry out a series of data cleaning procedures. In particular, if a subject had received more prescriptions, relating to different medicinal products, on the same date, only the prescription with a longer duration was considered. Furthermore, if a subject had received a prescription for a period of time included in the therapeutic coverage of a previous prescription, such prescription was not considered.
The results obtained were stratified by gender and age groups (45-54, 55-64, 65-74, 75-84, > 84) and by geographical area (North: Piedmont, Valle d'Aosta, Liguria, Lombardy, Trentino-Alto Adige, Veneto, Friuli-Venezia Giulia, Emilia-Romagna; Centre: Tuscany, Umbria, Marche, Lazio; South and islands: Abruzzo, Molise, Campania, Puglia, Basilicata, Calabria, Sicily, Sardinia).
For each therapeutic class considered, the analyses carried out included only those regions in which the proportion of medicines dispensed through NHS outpatient standard distribution over the total (including direct and *per conto* distribution [Health Ministry Decree of 31 July 2007 regulating the new healthcare information system – NSIS, and Law 405/2001 as amended]) was equal to or higher than 90%. In case such criteria was not met, the analyses carried out included those regions in which the proportion of medicines distributed by authorised pharmacies, both public and private, on behalf of local health facilities over the total (including direct and *per conto* distribution [Health Ministry Decree of 31 July 2007 regulating the new healthcare information system – NSIS, and Law 405/2001 as amended]) was equal to or higher than 85%.

Medicinal products and therapeutic classes considered

1. **Antidepressant medicinal products:**
   - Antidepressants (ATC: N06A*)

2. **Lipid lowering medicinal products:**
   - Hydroxymethylglutaryl-CoA reductase inhibitors (ATC: C10AA*)
   - Fibrates (C10AB*)
   - Ezetimibe (ATC: C10AX09)
   - Combinations: simvastatin/ezetimibe (ATC: C10BA02), ezetimibe/rosuvastatin (ATC: C10BA06)

3. **Antiosteoporosis medicinal products:**
   - Raloxifene (ATC: G03XC01)
   - Bazedoxifene (ATC: G03XC02)
   - Bisphosphonates (ATC: M05BA*)
   - Bisphosphonates, combination (ATC: M05BB*)
   - Teriparatide (ATC: H05AA02)
   - Strontium ranelate (ATC: M05BX03)

4. **Antihypertensive medicinal products:**
   - Antihypertensives (ATC: C02*)
   - Diuretics (ATC: C03*)
   - Beta-blockers (ATC: C07*)
   - Calcium channel blockers (ATC: C08*)
   - Medicinal products for the renin-angiotensin system (ATC: C09*)

5. **Medicinal products for benign prostatic hypertrophy** (ATC: G04C*)

6. **Medicinal products inhibiting formation of uric acid** (ATC: M04AA*)

7. **Anticoagulant medicinal products:**
   - Direct thrombin inhibitors (ATC: B01AE*)
   - Direct Xa factor inhibitors (ATC: B01AF*)
   - Vitamin K antagonists (ATC: B01AA*)

8. **Antidiabetics:**
   - Hypoglycaemic agents, excluding insulins (ATC: A10B*)

9. **Other medicines for obstructive airway disorders** (ATC: R03*)

References

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4.1 Adherence and persistence to treatment with antidepressant medicinal products

The study population included a total of 126,191 new users of antidepressant medicinal products. The median age was 70 years (interquartile range IQR: 57-79), with a higher proportion of women than men (66.9% vs 33.1%).
The percentage of subjects with high and low adherence to antidepressant treatment was 37.6% and 27.2%, respectively. In particular, the highest percentages of high adherence were observed in subjects aged between 45 and 54 years (42.2%) and between 55-64 years (42.1%). Adherence decreased with increasing age and this trend also occurred by stratifying by geographical area. In general, men had a slightly higher percentage of high adherence than women (39.7% vs 36.5%) and this difference was slightly more pronounced in the North (42.0% vs 37.8%). The percentage of subjects with high adherence to treatment was higher in Northern regions (39.2%) and in Central regions (37.5%) compared to those in the South and the Islands (35.2%). This difference was observed for each age group and gender (Table 4.1.1).

Table 4.1.1. Adherence to antidepressant treatment in the population aged ≥ 45 years

	Total N=126,191	North N=59,051	Centre N=28,534	South N=38,606
Low adherence to antidepressant treatment (%)*†				
45-54 years	22.3	21.1	21.8	24.4
55-64 years	22.1	20.3	22.1	24.6
65-74 years	24.3	22.5	24.6	26.6
75-84 years	29.5	28.3	29.2	31.9
≥ 85 years	43.2	42.7	43.5	43.8
Women	27.6	26.5	27.7	29.1
Men	26.4	24.8	26.6	28.5
Total	**27.2**	**26.0**	**27.3**	**28.9**
High adherence to antidepressant treatment (%)*†				
45-54 years	42.2	44.0	42.0	39.3
55-64 years	42.1	44.1	42.2	39.5
65-74 years	39.4	41.5	39.5	36.4
75-84 years	34.8	36.3	35.3	31.7
≥ 85 years	25.8	26.6	25.5	24.7
Women	36.5	37.8	36.6	34.5
Men	39.7	42.0	39.3	36.6
Total	**37.6**	**39.2**	**37.5**	**35.2**

* Adherence to treatment was evaluated only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) < 40% of the observation period, while high adherence was defined as therapeutic coverage ≥ 80% of the observation period (for further details see the statistical methods).
† Percentages of subjects with low/high adherence relating to the specified category.
Median time (IQR) of follow-up (in days): 306 (188-342).

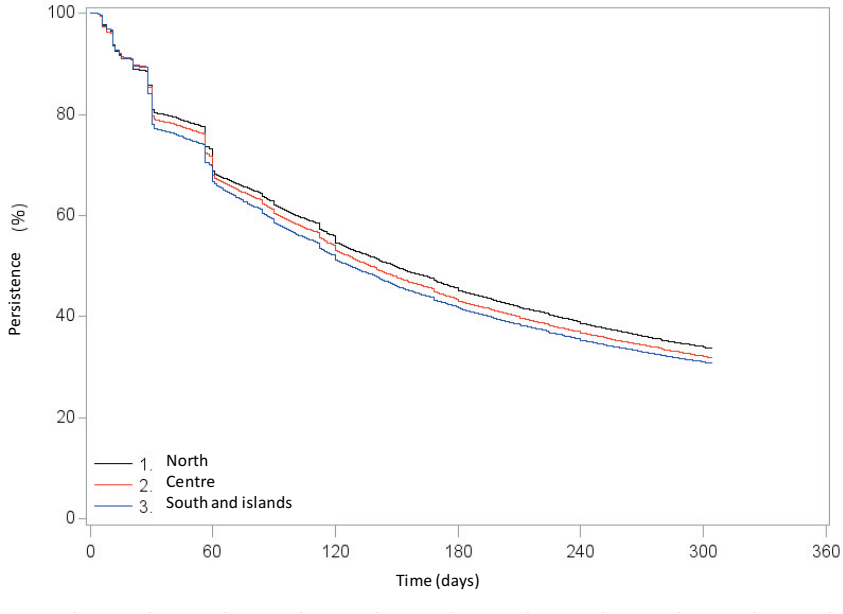
The percentage of subjects persisting in treatment decreased with increasing time from the start of treatment, passing from 59.9% at 3 months, to 43.1% at 6 months and to 32.2% at 12 months. This means that already at 3 months, about 40% of subjects had a treatment interruption of at least 60 days. At 12 months, persistent subjects varied from 34.5% to 26.9% starting from the 45-54 age group up to subjects aged at least 85 years. Although this gap occurred for each geographical area considered, the percentage variation was less marked for the South and the Islands (Δ%=-17% for the South and Islands vs Δ%=-24% for the North and the Centre respectively).
Men showed slightly higher persistence rates than women (32.8% vs 31.9) (Table 4.1.2).
Considering the median time to discontinuation of antidepressant treatment, a 50% probability of discontinuing treatment was achieved at approximately 150 days for the North, 135 days for the Centre and 125 days for the South and the Islands (Figure 4.1.1).

Table 4.1.2. Persistence on antidepressant treatment in the population aged ≥ 45 years

Persistence (%)	Total N=126,191			North N=59,051			Centre N=28,534			South N=38,606		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	63.1	46.1	34.5	64.8	48.5	36.7	62.7	44.9	33.4	60.7	43.0	32.1
55-64 years	62.8	45.4	33.7	64.8	48.0	35.7	62.9	44.8	33.2	60.0	42.4	31.3
65-74 years	61.1	43.8	32.7	62.3	45.0	33.7	61.8	44.2	33.1	59.1	41.9	31.2
75-84 years	57.9	41.4	31.3	59.4	42.3	32.1	57.9	41.0	30.8	55.5	40.3	30.4
≥ 85 years	52.3	36.6	26.9	53.3	37.7	27.8	50.6	35.1	25.5	52.0	35.9	26.5
Women	59.3	42.7	31.9	60.5	43.9	32.8	58.9	42.0	31.3	57.9	41.3	30.8
Men	61.1	43.9	32.8	63.1	46.1	34.8	61.1	43.3	32.1	58.0	41.0	30.3
Total	**59.9**	**43.1**	**32.2**	**61.3**	**44.6**	**33.5**	**59.6**	**42.4**	**31.6**	**58.0**	**41.2**	**30.6**

Treatment persistence was evaluated only for new users with at least 2 prescriptions. A treatment interruption occurs if the subject does not receive a prescription within 60 days (for more details see the statistical methods).

Figure 4.1.1. Time (in days) to discontinuation of antidepressant treatment in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves)



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

4.2 Adherence and persistence to treatment with lipid-lowering medicinal products

The study population included a total of 209,595 new users of lipid-lowering medicinal products. The median age was 67 years (IQR 59-75), with a slightly higher proportion of women than men (52.8% vs 47.2%).
Overall, the percentage of subjects with high and low adherence to lipid-lowering treatment was 41.5% and 15.8%, respectively. If different age groups are considered, the highest percentage of subjects with high adherence was observed in subjects aged between 55 and 64 years living in the North (45.3%), while the least adherent subjects were those aged over 84 years and living in the South (19.8%). Men had more frequently than women a therapeutic coverage of more than 80% of the observation period (47.3% vs 36.3%) and this difference remained almost constant in all geographical areas. The percentage of subjects with high adherence to treatment was higher in the North (43.9%) and the Centre (42.4%) compared to the South and the Islands (38.5%). Higher percentages of subjects with low adherence were also found for subjects aged ≥ 85 years compared to younger subjects in all geographical areas (Table 4.2.1).

Table 4.2.1. Adherence to lipid-lowering treatment in the population aged ≥45 years

	Total N=209,595	North N=85,084	Centre N=42,365	South N=82,146
Low adherence to lipid-lowering treatment (%)*†				
45-54 years	15.0	12.6	14.5	17.2
55-64 years	14.8	12.4	14.6	17.2
65-74 years	15.9	14.2	15.6	17.9
75-84 years	16.9	15.4	16.6	19.0
≥ 85 years	18.0	16.4	18.0	19.8
Women	17.8	15.8	17.8	19.8
Men	13.5	11.9	13.0	15.5
Total	**15.8**	**13.9**	**15.6**	**17.9**
High adherence to lipid-lowering treatment (%)*†				
45-54 years	41.2	43.8	43.0	38.2
55-64 years	42.2	45.3	43.2	38.9
65-74 years	41.0	43.2	41.9	38.4
75-84 years	41.3	43.5	41.6	38.3
≥ 85 years	41.9	43.9	43.5	38.5
Women	36.3	38.6	37.1	33.6
Men	47.3	49.5	48.5	44.3
Total	**41.5**	**43.9**	**42.4**	**38.5**

* 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 see the statistical methods).
† Percentages of subjects with low/high adherence relating to the specified category.
Median time (IQR) of follow-up (in days): 320 (251-345).

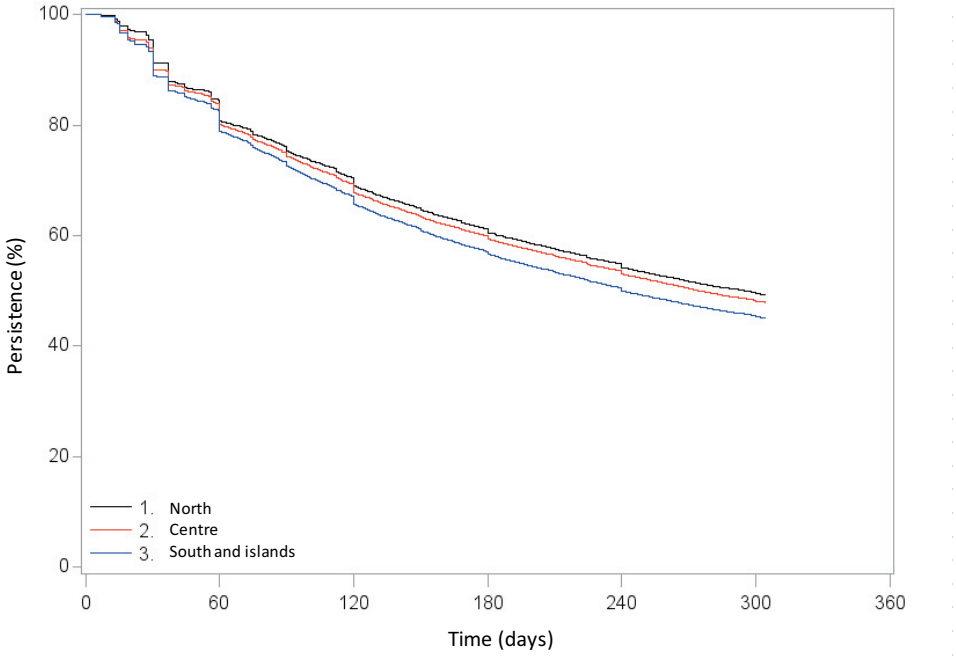
Considering the persistence to treatment, the probability of persistence was 73.5% at 3 months, 58.2% at 6 months and 47.1% at 12 months. Higher probabilities of persistence after one year of treatment were observed for subjects aged between 55 and 64 years for the Northern and Central areas and between 65 and 74 years for the South and the Islands. One year after the start of therapy, men were on average more persistent than women (51.3% vs 43.1%), regardless of the geographical area considered (Table 4.2.2). Considering the median time to discontinuation of treatment with lipid-lowering medicinal products, it can be observed that 265 days from the start of therapy, the probability of discontinuing treatment was 50%, with a slight difference between geographical areas: 290 days in the North, 270 days in the Centre and 240 days in the South (Figure 4.2.1).
It should be remembered that numerous scientific evidences have shown that adequate adherence and persistence to lipid-lowering therapy are associated with a reduction in the risk of cardiovascular events in subjects in primary and secondary prevention (1-3).

Table 4.2.2. Persistence on lipid-lowering treatment in the population aged ≥ 45 years

Persistence (%)	Total N=209,595			North N=85,084			Centre N=42,365			South N=82,146		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	74.2	57.8	46.1	75.7	59.8	48.6	74.9	59.1	47.7	72.7	55.5	43.3
55-64 years	74.8	59.6	48.3	76.5	62.0	51.0	75.3	60.6	49.6	73.0	56.8	45.2
65-74 years	73.7	58.8	47.8	74.9	60.6	49.5	74.1	59.0	47.9	72.2	56.8	46.0
75-84 years	71.8	56.8	45.9	73.1	58.3	47.6	71.9	56.8	45.6	70.1	54.8	43.9
≥85 years	69.4	53.7	43.0	70.7	55.5	44.8	69.7	54.7	43.9	67.7	50.8	40.4
Women	71.3	55.0	43.1	72.3	56.5	44.5	71.6	55.5	43.6	70.1	53.5	41.5
Men	75.9	61.7	51.5	77.4	63.9	53.9	76.4	62.5	52.1	74.0	58.9	48.5
Total	**73.5**	**58.2**	**47.1**	**74.8**	**60.1**	**49.1**	**73.8**	**58.7**	**47.6**	**71.9**	**56.0**	**44.7**

Treatment persistence was evaluated only for new users with at least 2 prescriptions. A treatment interruption occurs if the subject does not receive a prescription within 60 days (for more details see the statistical methods).

Figure 4.2.1. Time (in days) to discontinuation of lipid-lowering treatment in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves)



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

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4.3 Adherence and persistence to medicinal products for the treatment of osteoporosis

The study population included a total of 36,037 new users of anti-osteoporotic medicinal products. The median age was 70 years (IQR 62-78), with a greater proportion of women than men (91.9% vs 8.1%).
The percentage of subjects with high and low adherence to treatment with anti-osteoporotic medicinal products was 67.2% and 7.1%, respectively. In particular, the highest percentage of subjects with high adherence was observed in subjects aged between 65 and 74 years living in the North (72.8%), while for low adherence the maximum of 11% was reached by subjects aged ≥ 85 years living in the South and in the Islands. In general, men more frequently than women had a therapeutic coverage of less than 40% of the observation period (10.7% vs 6.7%) with a more pronounced difference in the Southern regions (14.2% vs 7.5%). The percentage of subjects with high adherence to treatment was higher in the Northern (71%) and Central (68.1%) regions compared to those in the South including the Islands (64.7%), regardless of age group and gender (Table 4.3.1).

Table 4.3.1. Indicators of adherence to anti-osteoporotic treatment in the population aged ≥45 years

	Total N=36,037	North‡ N=9,105	Centre N=9,147	South N=17,785
Low adherence to treatment with anti-osteoporotic medicinal products (%)*†				
45-54 years	7.2	4.7	6.8	8.6
55-64 years	6.2	4.9	6.4	6.6
65-74 years	6.8	5.3	6.2	7.7
75-84 years	7.4	5.8	7.2	8.5
≥ 85 years	9.8	8.7	8.8	11.0
Women	6.7	5.5	6.5	7.5
Men	10.7	6.6	9.4	14.2
Total	**7.1**	**5.6**	**6.8**	**7.9**
High adherence to treatment with anti-osteoporotic medicinal products (%)*†				
45-54 years	64.8	72.6	66.4	60.2
55-64 years	67.8	71.4	68.5	65.9
65-74 years	68.0	72.8	68.0	65.8
75-84 years	67.5	70.2	69.0	64.9
≥ 85 years	62.5	64.6	65.4	59.4
Women	67.3	70.8	68.3	65.0
Men	66.1	73.1	66.2	61.2
Total	**67.2**	**71.0**	**68.1**	**64.7**

* 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 see the statistical methods).
† Percentages of subjects with low/high adherence relating to the specified category.
‡ Excluding: Piedmont, Veneto and Emilia Romagna.
Median time (IQR) of follow-up (in days): 314 (192-343).

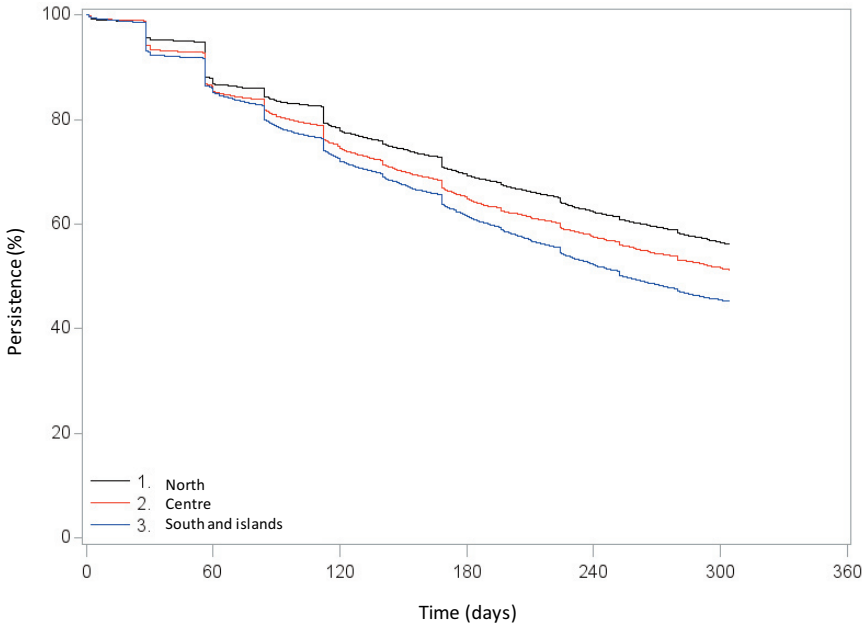
Considering persistence to treatment, 79.8%, 63.6% and 49.3% of new users were still being treated at 3, 6 and 12 months respectively from the start of therapy. In particular, stratifying by geographical area, the probability of persistence at one year was equal to 55.6% for the Northern regions, 50.9% for the Central regions and 45.1% for the Southern regions. This means that the median time to discontinuation of treatment was greater than 365 days for the Northern and Central regions, while it was equal to 253 days for the Southern regions and the Islands (Table 4.3.2 and Figure 4.3.1). It is also noted that older subjects (age ≥ 85 years) discontinued treatment earlier than younger subjects, regardless of the geographical area, while at one year of treatment subjects who proved to be more persistent were those among 45 and 64 years of age, living in the Northern regions (58.8%). On the other hand, subjects living in the South recorded the lowest persistence to treatment, especially those aged at least 85 (37.8%). Women were on average more persistent than men (49.8% vs 43.5% at one year of treatment): this difference stands out in particular in the regions of the Centre (51.7% vs 42.9% at one year of treatment) and the South (45.7% vs 37.3% at one year of treatment) (Table 4.3.2).
It is known from the literature that an intake of less than 50% or equal to 50% of the medicinal product prescribed for osteoporosis does not modify the fracture risk, i.e. the therapeutic intervention is ineffective, and therefore inadequate adherence to therapy is associated with an increased risk of fractures (1-3).

Table 4.3.2. Persistence on anti-osteoporotic treatment in the population aged ≥ 45 years

Persistence (%)	Total N=36,037			North‡ N=9,105			Centre N=9,147			South N=17,785		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	78.9	63.9	51.1	84.6	69.7	58.8	79.6	65.3	54.1	75.8	60.3	45.9
55-64 years	81.0	66.4	51.8	83.5	70.7	58.0	83.0	68.9	55.6	79.1	63.2	47.2
65-74 years	80.5	64.6	49.9	84.2	70.1	57.6	79.7	63.8	50.5	79.1	62.4	46.0
75-84 years	79.3	62.0	47.9	81.9	66.9	54.0	79.6	62.4	48.8	77.5	58.8	43.7
≥ 85 years	76.1	55.6	41.4	78.7	59.5	44.5	76.2	55.5	44.4	74.4	53.3	37.8
Women	80.4	64.2	49.8	83.2	68.7	55.9	80.7	64.9	51.7	78.8	61.7	45.7
Men	73.6	56.2	43.5	81.0	65.5	53.0	73.5	54.9	42.9	68.6	50.6	37.3
Total	**79.8**	**63.6**	**49.3**	**82.9**	**68.4**	**55.6**	**80.1**	**64.0**	**50.9**	**78.1**	**60.9**	**45.1**

Treatment persistence was evaluated only for new users with at least 2 prescriptions. A treatment interruption occurs if the subject does not receive a prescription within 60 days (for more details see the statistical methods).

Figure 4.3.1. Time (in days) to discontinuation of anti-osteoporotic treatment in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves)



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

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4.4 Adherence and persistence to treatment with antihypertensive medicinal products

The study population included a total of 266,457 new users of antihypertensive medicinal products. The median age was 63 years (IQR 55-73), with a higher proportion of women than men (52.7% vs 47.3%).
The percentage of subjects with high and low adherence to antihypertensive treatment was 53.1% and 17.7%, respectively. Low adherence increased with age and the highest percentage of subjects with low adherence was recorded in subjects living in Southern Italy with at least 85 years of age (28.2%). High adherence reached its maximum value in the age group between 55 and 64 years (55.4%) and then decreased in subsequent age groups, in all the geographical areas considered. In general, men had a higher percentage of subjects with a therapeutic coverage greater than 80% of the observation period compared to women (58.0% vs 48.7%) and regardless of the geographical area considered (Table 4.4.1).

Table 4.4.1. Adherence to antihypertensive treatment in the population aged ≥ 45 years

	Total N=266,457	North N=119,719	Centre N=54,262	South N=92,476
Low adherence to antihypertensive treatment (%)*†				
45-54 years	16.4	15.1	16.6	17.6
55-64 years	16.1	15.0	16.0	17.4
65-74 years	17.7	16.7	17.5	19.2
75-84 years	20.2	18.8	20.8	22.2
≥ 85 years	25.0	22.8	25.7	28.2
Women	20.5	19.1	20.8	22.1
Men	14.7	13.9	14.7	15.8
Total	**17.7**	**16.6**	**18.0**	**19.1**
High adherence to antihypertensive treatment (%)*†				
45-54 years	54.8	56.7	55.8	52.3
55-64 years	55.4	56.5	56.7	53.5
65-74 years	53.9	54.6	55.9	51.8
75-84 years	49.5	50.6	50.0	47.3
≥ 85 years	41.0	42.1	41.2	39.0
Women	48.7	49.9	49.5	46.7
Men	58.0	58.7	59.5	56.2
Total	**53.1**	**54.1**	**54.1**	**51.2**

* Adherence to treatment was evaluated only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) < 40% of the observation period, while high adherence was defined as therapeutic coverage ≥ 80% of the observation period (for further details see the statistical methods).
† Percentages of subjects with low/high adherence relating to the specified category.
Median time (IQR) of follow-up (in days): 328 (279-348).

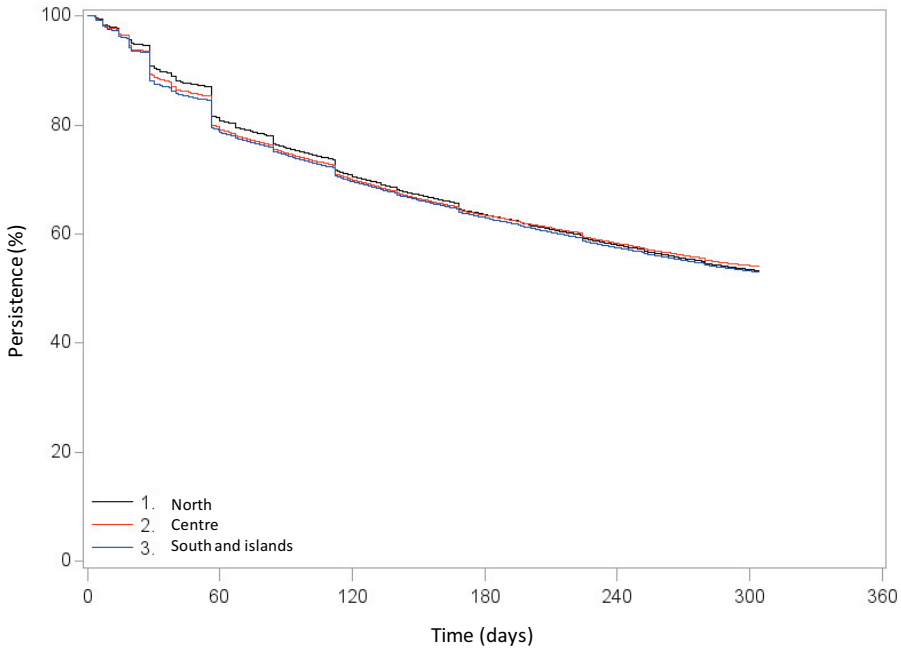
Considering the persistence to treatment with antihypertensives, 74.5%, 62.7% and 53% of new users were still on treatment at 3, 6 and 12 months respectively from the start of therapy. This means that, after about one year of treatment, 47% experienced an interruption of treatment for at least 60 days. Persistence to treatment decreased with age: at 12 months, persistent subjects varied from 55% to 41.1% starting from the age group of 45-54 years up to subjects with at least 85 years of age, with similar differences observed for each geographical area considered. Men showed higher percentages of persistence than women, with differences that starting from three months from the start of therapy (77.8% vs 71.6%) tended to increase over time (57.5% vs 48.9% after one year) (Table 4.4.2).
There were no differences in persistence by geographical area, where the median time to discontinuation of treatment with antihypertensives was greater than 365 days (Figure 4.4.1).

Table 4.4.2. Persistence on antihypertensive treatment in the population aged ≥ 45 years

Persistence (%)	Total N=266,457			North N=119,719			Centre N=54,262			South N=92,476		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	76.2	64.7	55.0	77.1	65.2	55.2	75.3	64.2	55.4	75.6	64.3	54.6
55-64 years	76.5	64.9	55.4	76.9	64.9	55.4	76.2	65.3	56.4	76.0	64.7	55.0
65-74 years	75.2	63.5	53.5	75.7	63.4	53.1	75.9	64.3	54.7	74.2	63.0	53.5
75-84 years	71.2	58.8	49.0	72.3	59.2	49.0	70.5	58.8	49.4	69.9	58.1	48.6
≥ 85 years	64.5	50.8	41.1	65.6	51.4	41.0	63.7	50.0	40.9	63.4	50.4	41.4
Women	71.6	59.1	48.9	72.3	59.3	48.7	71.0	59.0	49.3	71.0	58.9	48.9
Men	77.8	66.7	57.5	78.2	66.6	57.1	77.8	67.0	58.4	77.4	66.7	57.6
Total	**74.5**	**62.7**	**53.0**	**75.1**	**62.7**	**52.7**	**74.1**	**62.7**	**53.5**	**74.1**	**62.6**	**53.0**

Treatment persistence was evaluated only for new users with at least 2 prescriptions. A treatment interruption occurs if the subject does not receive a prescription within 60 days (for more details see the statistical methods).

Figure 4.4.2. Time (in days) to discontinuation of antihypertensive treatment in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves)



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

4.5 Adherence and persistence to treatment with medicinal products for benign prostatic hypertrophy

The study population included a total of 94,878 new users of medicinal products for benign prostatic hypertrophy. The median age was 69 years (IQR 62-76). The percentage of subjects with high and low adherence to treatment was 62.7% and 10.3%, respectively.
The percentage of subjects with high adherence increased with age, reaching a maximum for the 65-74 age group (64.2%), and then decreasing in the more advanced age groups, in all geographical areas. In fact, no differences were observed at the level of geographical area (Table 4.5.1).

Table 4.5.1. Adherence to treatment with medicinal products for benign prostatic hypertrophy in the male population aged ≥ 45 years

	Total N=94,878	North N=39,177	Centre N=19,953	South N=35,748
Low adherence to treatment with drugs for benign prostatic hypertrophy (%)*†				
45-54 years	14.3	12.9	13.5	15.8
55-64 years	10.2	9.3	10.2	11.2
65-74 years	9.4	8.4	9.8	10.2
75-84 years	10.0	9.1	10.1	11.2
≥ 85 years	11.6	10.3	12.6	12.7
Total	**10.3**	**9.2**	**10.4**	**11.3**
High adherence to treatment with drugs for benign prostatic hypertrophy (%)*†				
45-54 years	56.9	56.9	58.3	56.0
55-64 years	62.9	62.6	64.0	62.6
65-74 years	64.2	65.2	64.1	63.1
75-84 years	62.8	63.8	62.9	61.4
≥ 85 years	60.1	62.0	58.7	58.5
Total	**62.7**	**63.5**	**63.0**	**61.7**

* 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 see the statistical methods).
† Percentages of subjects with low/high adherence relating to the specified category.
Median time (IQR) of follow-up (in days): 322 (215-346).

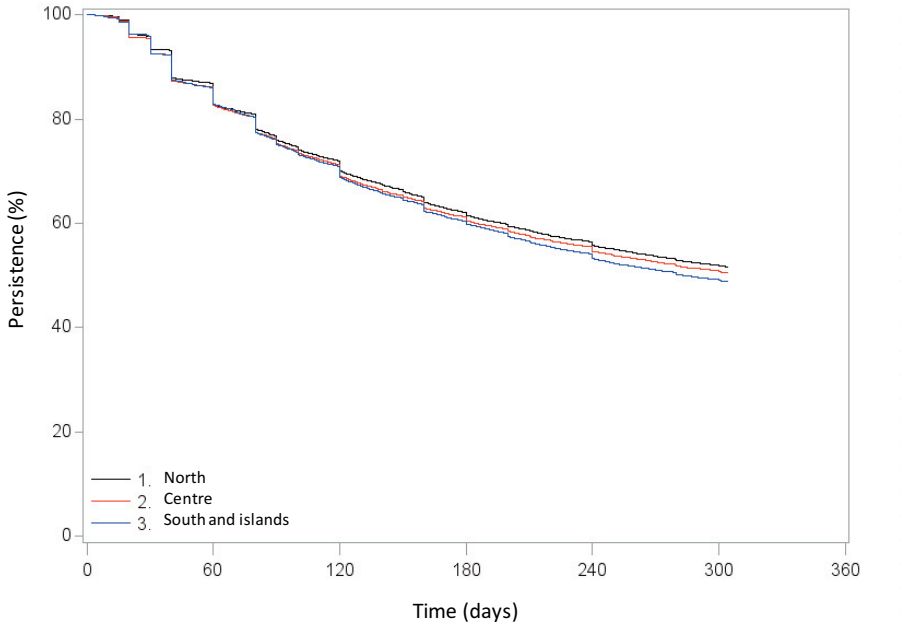
Analysing persistence to treatment, 50% of new users experienced an interruption after about a year of treatment. Younger subjects (45-54 years) stopped treatment earlier than subjects in other age groups. It is observed, in fact, that 182 days from the start of therapy the probability of interrupting the treatment was approximately 50%, while from 65 years the median time to interruption was more than 365 days (Table 4.5.2). There were no major discrepancies in persistence to treatment between the different geographical areas (Figure 4.5.2).

Table 4.5.2. Persistence to treatment with medicinal products for benign prostatic hypertrophy in the male population aged ≥ 45 years

Persistence (%)	Total N=94,878			North N=39,177			Centre N=19,953			South N=35,748		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	68.2	50.6	39.8	67.7	50.8	40.8	69.1	53.0	42.1	68.1	49.2	37.9
55-64 years	75.0	59.8	49.2	74.7	60.1	50.0	75.0	59.5	49.3	75.3	59.6	48.5
65-74 years	76.4	61.6	51.5	76.9	62.3	52.8	76.1	61.7	52.2	76.0	60.7	49.8
75-84 years	75.5	61.6	51.8	76.3	62.7	53.2	75.2	60.9	51.3	74.6	60.7	50.2
≥ 85 years	73.0	58.7	50.0	74.9	61.0	52.7	72.3	57.2	48.8	70.8	56.5	47.3
Total	**75.0**	**60.1**	**50.1**	**75.5**	**61.1**	**51.5**	**74.8**	**59.9**	**50.2**	**74.5**	**59.2**	**48.3**

Treatment persistence was evaluated only for new users with at least 2 prescriptions. A treatment interruption occurs if the subject does not receive a prescription within 60 days (for more details see the statistical methods).

Figure 4.5.1. Time (in days) to discontinuation of treatment with medicinal products for benign prostatic hypertrophy in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age (the Cox model was used to estimate the persistence curves)



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

4.6 Adherence and persistence to treatment with medicines inhibiting uric acid production

The study population included a total of 91,389 new users of medicinal products that inhibit the production of uric acid. The median age was 74 years (IQR 66-82), with a proportion of men greater than women (56.3% vs 43.7%).
The percentage of subjects with high and low adherence to treatment with medicinal products inhibiting the production of uric acid was 15.1% and 36.1%, respectively. As far as the percentage of subjects with high adherence is concerned, the difference between men and women was negligible (15.5% vs 14.6%). In terms of low adherence, more frequently women had a therapeutic coverage of less than 40% of the observation period (38.2% vs 34.4%), irrespective of the geographical area. The percentage of subjects with low adherence increased with increasing age (from 33.3% in the 45-54 age group to 37% in the ≥ 85 age group). Overall, no significant differences were found among the geographical areas (Table 4.6.1).

Table 4.6.1. Adherence to treatment with medicinal products inhibiting uric acid production in the population aged ≥ 45 years

	Total N=91,389	North N=34,053	Centre N=19,876	South N=37,460
Low adherence to treatment with medicinal products inhibiting uric acid production (%)*†				
45-54 years	33.3	32.9	32.4	34.1
55-64 years	34.5	33.6	35.3	34.9
65-74 years	36.6	34.7	37.1	38.0
75-84 years	36.5	35.2	37.4	37.2
≥ 85 years	37.0	37.1	35.9	37.5
Women	38.2	37.2	38.4	39.0
Men	34.4	33.5	35.0	35.1
Total	**36.1**	**35.0**	**36.4**	**37.0**
High adherence to treatment with medicinal products inhibiting uric acid production (%)*†				
45-54 years	16.1	16.1	16.7	15.9
55-64 years	16.1	15.6	16.0	16.6
65-74 years	14.8	15.3	14.6	14.4
75-84 years	14.9	15.4	14.0	14.9
≥ 85 years	14.8	14.9	14.9	14.7
Women	14.6	15.1	14.1	14.4
Men	15.5	15.6	15.3	15.5
Total	**15.1**	**15.4**	**14.8**	**15.0**

*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 see the statistical methods).
† Percentages of subjects with low/high adherence relative to the specified category.
Median time (IQR) of follow-up: 290 (186-335).

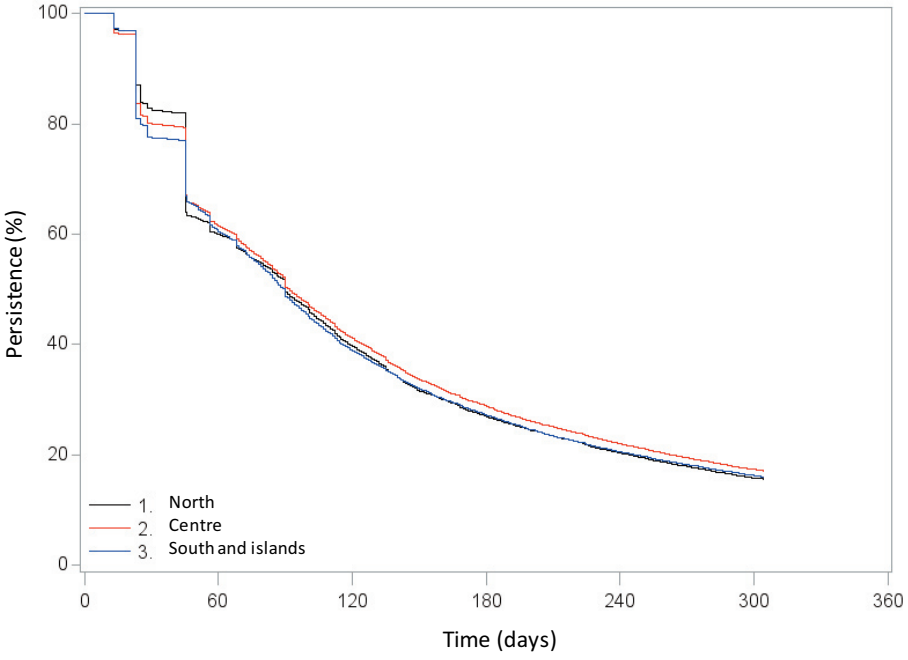
As regards treatment persistence with medicinal products inhibiting the production of uric acid, as early as 3 months after the start of therapy, the probability of interrupting treatment was equal to 52.7%, up to 84.5% after one year of treatment. There was a slight difference among men (16.4% vs 14.4% at 12 months), which remained unchanged in the three geographical areas considered (Table 4.6.2). The median time to treatment interruption was equal to 87 days for all new users: 90 days in Central regions, 88 in Northern regions and 85 in Southern regions (Figure 4.6.1).
The low levels of adherence and persistence should be further investigated, also considering the effect of specific dosage schemes which provide for a lower dosage at the beginning of therapy, followed by an increase over time.

Table 4.6.2. Persistence to treatment with medicinal products inhibiting uric acid production in the population aged ≥ 45 years

Persistence (%)	Total N=91,389			North N=34,053			Centre N=19,876			South N=37,460		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	47.1	25.5	14.7	45.6	25.5	15.3	49.3	27.6	16.1	47.3	24.2	13.3
55-64 years	47.5	25.8	15.4	47.5	25.6	14.9	49.6	28.0	17.3	46.2	24.7	14.8
65-74 years	46.7	25.8	15.5	46.7	25.1	14.7	47.5	27.1	16.5	46.4	25.9	15.6
75-84 years	47.2	26.2	15.3	47.2	25.7	14.9	48.7	27.3	15.9	46.5	26.0	15.4
≥ 85 years	48.2	27.2	16.3	46.9	25.7	15.3	49.4	28.8	17.6	48.6	27.8	16.5
Women	46.5	25.1	14.4	46.4	24.7	13.9	48.1	26.6	15.6	45.7	24.6	14.1
Men	47.9	27.0	16.4	47.3	26.0	15.6	49.1	28.3	17.3	47.7	27.2	16.6
Total	**47.3**	**26.1**	**15.5**	**47.0**	**25.5**	**14.9**	**48.7**	**27.6**	**16.6**	**46.8**	**25.9**	**15.4**

Treatment persistence was evaluated only for new users with at least 2 prescriptions. A treatment interruption occurs if the subject does not receive a prescription within 60 days (for more details see the statistical methods).

Figure 4.6.1. Time (in days) to discontinuation of treatment with medicinal products inhibiting uric acid production in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves).



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

4.7 Adherence and persistence to treatment with anticoagulants

The study population included a total of 64,329 new users of anticoagulant medicinal products. The median age was 77 years (IQR 69-83), with a proportion of men slightly greater than women (51% vs 49%).
The percentage of subjects with high and low adherence to anticoagulant treatment was 49.6% and 9.4%, respectively. Low adherence increased with age. Specifically, the higher percentage increase occurred in the 75-84 age group and among subjects aged ≥ 85 (9.2% vs 15.8%). The higher percentage change was found in subjects living in Central regions (Δ%=+75%). Similarly, the percentage of subjects with a coverage of more than 80% of the observation period decreased with increasing age and showed significant reductions after 74 years of age (Δ%=-27% between the 65-74 age group and the 75-84 age group, and Δ%=-46% between the 75-84 age group and ≥84 years). In general, a slightly greater percentage of subjects with high adherence was recorded among men than among women (53.1% vs 46.0%). Such difference was less significant in Southern regions (Table 4.7.1).

Table 4.7.1. Adherence to anticoagulant treatment in the population aged ≥45 years

	Total N=64,329	North‡ N=28,585	Centre N=13,451	South N=22,293
Low adherence to anticoagulant treatment (%)*†				
45-54 years	6.7	4.1	10.7	7.6
55-64 years	6.2	5.1	8.8	6.1
65-74 years	6.6	6.1	7.9	6.5
75-84 years	9.2	9.2	10.3	8.5
≥ 85 years	15.8	15.5	18.1	14.5
Women	10.6	10.3	13.3	9.3
Men	8.3	7.9	9.4	8.2
Total	**9.4**	**9.1**	**11.3**	**8.8**
High adherence to anticoagulant treatment (%)*†				
45-54 years	62.8	66.5	56.1	62.1
55-64 years	64.9	65.3	61.0	66.5
65-74 years	64.0	63.5	60.0	66.9
75-84 years	47.0	47.1	45.3	47.8
≥ 85 years	25.5	26.2	22.9	26.3
Women	46.0	45.3	42.3	48.9
Men	53.1	53.4	49.6	54.8
Total	**49.6**	**49.6**	**46.0**	**51.8**

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 see the statistical methods).
† Percentages of subjects with low/high adherence relative to the specified category.
‡ Excluding Emilia Romagna.
Median time (IQR) of follow-up (in days): 334 (296-350).

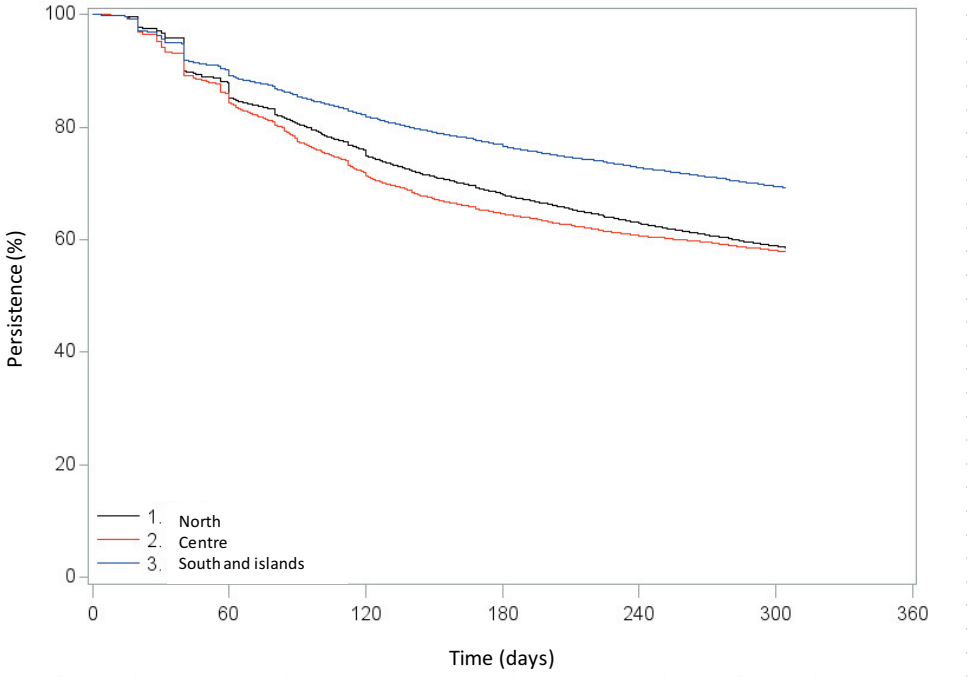
Taking into account persistence to treatment with anticoagulants, 81.2%, 69.9% and 62% of new users was still being treated at 3, 6 and 12 months after start of therapy, respectively. This means that after one year of treatment, 38% showed a treatment interruption of at least 60 days. Higher persistence probabilities after one year of treatment were observed among subjects in the 65-74 age group in all geographical areas. Minimum differences were recorded in the two genders, with men being slightly more persistent then women (62.8% vs 61.1%). If median time to discontinuation of treatment with anticoagulants is taken into account, the probability of treatment interruption was equal to 50% at 289 days in subjects residing in the South and in the Islands, and at 261 days in subjects residing in the Centre and in the North (Figure 4.7.1). It is necessary to further explore the causes of differences among geographical areas.

Table 4.7.2. Persistence to anticoagulant treatment in the population aged ≥45 years

Persistence (%)	Total N=64,329			North‡ N=28,585			Centre N=13,451			South N=22,293		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	82.0	66.9	55.9	84.4	67.7	56.0	72.7	56.4	47.2	84.3	71.8	60.6
55-64 years	83.6	70.7	61.8	84.0	69.0	58.5	78.6	65.0	57.4	85.9	75.5	67.6
65-74 years	84.2	74.1	67.2	83.6	72.2	64.6	79.7	68.0	61.8	87.2	79.6	73.2
75-84 years	81.9	71.1	63.5	80.4	68.2	59.4	78.4	66.3	60.3	86.2	78.0	71.2
≥ 85 years	74.8	62.2	53.7	72.2	59.2	49.0	71.5	57.1	50.3	80.5	70.0	62.5
Women	80.1	68.9	61.1	78.3	66.0	57.1	74.9	62.4	56.1	85.2	76.1	68.9
Men	82.4	70.8	62.8	81.7	68.8	59.5	79.0	65.8	59.1	85.4	76.6	69.5
Total	**81.2**	**69.9**	**62.0**	**80.1**	**67.5**	**58.4**	**77.0**	**64.1**	**57.6**	**85.3**	**76.4**	**69.2**

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

Figure 4.7.1. Time (in days) to discontinuation of treatment with anticoagulants in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves).



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

4.8 Adherence and persistence to treatment with antidiabetics

The study population included a total of 65,855 new users of antidiabetic medicinal products. The median age was 67 years (interquartile range IQR: 59-76), with a proportion of women smaller than men (53.8% vs 46.2%).
The percentage of subjects with high and low adherence to antidiabetic treatment was 28.6% and 28.3%, respectively. In particular, the highest rates of high adherence were observed in subjects aged between 45 and 54 years (35.7% in total: 41.4% in the North, 30% in the Centre and 34.6% in the South). They then decreased with increasing age. The higher percentage of subjects with low adherence was found in individuals living in Central regions belongingto the 85+ age group (41%). In general, a slightly greater percentage of subjects with high adherence was recorded in men than in women (31.2% vs 25.6%), especially in Southern regions (23.8% vs 30.3%). The percentage of subjects with high treatment adherence was more pronounced in Northern (33.0%) and Southern regions (27.3%) compared to Central regions (24%). This trend was observed in every age group and in the two genders (Table 4.8.1).

Table 4.8.1. Adherence to antidiabetic treatment in the population aged ≥45 years

	Total N=65,855	North‡ N=23,618	Centre N=14,642	South N=27,595
Low adherence to antidiabetic treatment (%)*†				
45-54 years	22.7	17.6	26.6	24.2
55-64 years	24.2	19.1	27.3	26.5
65-74 years	28.5	22.3	32.7	31.7
75-84 years	34.5	29.5	36.6	38.7
≥ 85 years	36.7	31.8	41.0	38.9
Women	31.5	25.9	34.7	34.3
Men	25.5	21.1	29.0	27.7
Total	**28.3**	**23.2**	**31.7**	**30.8**
High adherence to antidiabetic treatment (%)*†				
45-54 years	35.7	41.4	30.0	34.6
55-64 years	31.7	38.3	27.0	29.1
65-74 years	27.2	31.3	22.2	26.1
75-84 years	23.5	26.9	20.0	22.0
≥ 85 years	22.7	26.2	19.0	21.5
Women	25.6	30.5	21.5	23.8
Men	31.2	35.0	26.4	30.3
Total	**28.6**	**33.0**	**24.0**	**27.3**

*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 see the statistical methods).
† Percentages of subjects with low/high adherence relative to the specified category.
‡ Excluding Emilia Romagna.
Median time (IQR) of follow-up: 326 (273-348).

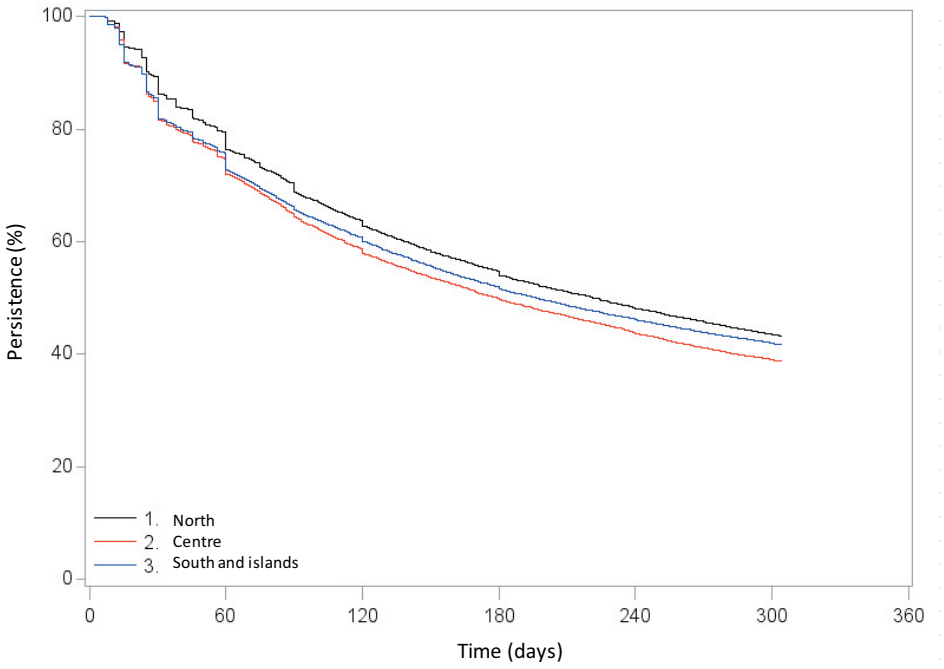
The percentage of subjects persistent to treatment decreased with increasing time from start of treatment, going from 65.9% at 3 months to 51.5% at 6 months and 41.4% at 12 months. Approximately 60% of subjects discontinued treatment before 12 months. The probability of being persistent decreased with increasing age: at 12 months persistent subjects ranged from 45.8% to 31.4% starting from the 45-54 age group up to subjects aged ≥85 years.
Men had higher persistence rates compared to women (44.1% vs 38.2%) (Table 4.8.2).
If median time to discontinuation of treatment with antidiabetics is taken into account, the probability of treatment interruption was equal to 50% at 215 days among subjects residing in the North, 196 days among subjects residing in the South and the islands and at 175 days among subjects residing in the Centre (Figure 4.8.1).

Table 4.8.2. Persistent to antidiabetic treatment in the population aged ≥45 years

Persistence (%)	Total N=65,855			North‡ N=23,618			Centre N=14,642			South N=27,595		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	69.6	55.5	45.8	71.5	57.4	48.2	66.3	52.7	42.3	70.1	55.6	46.0
55-64 years	68.7	55.2	45.3	71.5	58.6	48.5	66.2	51.9	41.4	67.8	54.3	44.8
65-74 years	66.7	52.4	42.1	69.1	53.9	43.2	64.2	49.7	39.1	65.8	52.3	42.7
75-84 years	61.1	45.8	35.3	63.3	47.2	35.9	60.3	45.1	34.0	59.2	44.6	35.3
≥ 85 years	57.3	41.9	31.4	60.3	44.3	33.5	55.2	39.3	28.9	55.6	41.2	30.8
Women	63.5	48.7	38.2	65.8	50.8	39.8	61.2	45.9	35.2	63.0	48.5	38.6
Men	67.9	53.9	44.1	69.8	55.2	45.1	65.8	52.0	41.4	67.2	53.7	44.5
Total	**65.9**	**51.5**	**41.4**	**68.0**	**53.3**	**42.8**	**63.6**	**49.0**	**38.4**	**65.2**	**51.3**	**41.7**

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

Figure 4.8.1. Time (in days) to discontinuation of treatment with antidiabetics in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves).



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

4.9 Adherence and persistence to treatment with medicines for obstructive airway disorders

The study population included a total of 194,295 new users of medicines for obstructive airway disorders. The median age was 68 years (interquartile range IQR: 58-78), with a proportion of women greater than men (57.5% vs 42.5%).
The percentage of subjects with high and low treatment adherence was 19.9% and 49.9%, respectively. High adherence rates increased slightly by age group, and then somewhat decreased in the older age group, with the exception of Central regions, where high adherence increased in older subjects. In general, a slightly greater percentage of subjects with high adherence was recorded among men than women (21.7% vs 18.6%), especially in Northern regions (24.1% vs 19.8%). The percentage of subjects with high treatment adherence was more pronounced in Northern (21.7%) and Central regions (20.8%) compared to the South and islands (18.3%) (Table 4.9.1).

Table 4.9.1. Adherence to treatment with medicines for obstructive airway disorders in the population aged ≥45 years

	Total N=194,295	North‡ N=57,429	Centre N=47,333	South N=89,533
Low adherence to treatment with medicines for obstructive airway disorders (%)*†				
45-54 years	55.0	51.6	54.8	57.3
55-64 years	51.8	49.6	52.2	52.9
65-74 years	48.8	46.3	47.9	50.7
75-84 years	46.1	44.5	44.6	48.2
≥ 85 years	48.9	48.6	46.5	50.5
Women	51.9	50.0	50.5	53.9
Men	47.2	44.6	47.0	48.9
Total	**49.9**	**47.7**	**49.1**	**51.8**
High adherence to treatment with medicines for obstructive airway disorders (%)*†				
45-54 years	15.8	17.3	16.3	14.6
55-64 years	18.6	20.4	18.9	17.4
65-74 years	20.9	22.7	22.0	19.3
75-84 years	22.3	24.3	22.9	20.6
≥ 85 years	21.4	22.7	23.8	19.1
Women	18.6	19.8	19.9	16.9
Men	21.7	24.1	22.0	20.1
Total	**19.9**	**21.7**	**20.8**	**18.3**

*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 see the statistical methods).
† Percentages of subjects with low/high adherence relative to the specified category.
‡ Excluding Emilia Romagna.
Median time (IQR) of follow-up: 204 (96-324).

Taking into account the persistence to treatment with medicines for obstructive airway disorders, the probability was equal to 27.3% at 3 months, 13% at 6 months and 8.2% at 12 months. This means that at 3 months, 73% of subjects showed a treatment discontinuation of at least 60 days. At 12 months persistent subjects ranged from 5.2% to 9.5% starting from the 45-54 age group up to subjects aged ≥85 years, with a maximum value recorded in the 75-84 age group (10.2%). Men had higher persistence rates compared to women (10.4% vs 6.5%) (Table 4.9.2).

If median time to discontinuation of treatment is taken into account, the probability of treatment interruption was equal to 50% at 50 days among subjects residing in the North, 45 days among subjects residing in the Centre and at 41 days among subjects residing in the South and the islands (Figure 4.9.1).

Results confirm that obstructive airway disorders recorded the lowest adherence and persistence data of all conditions considered (1-2).

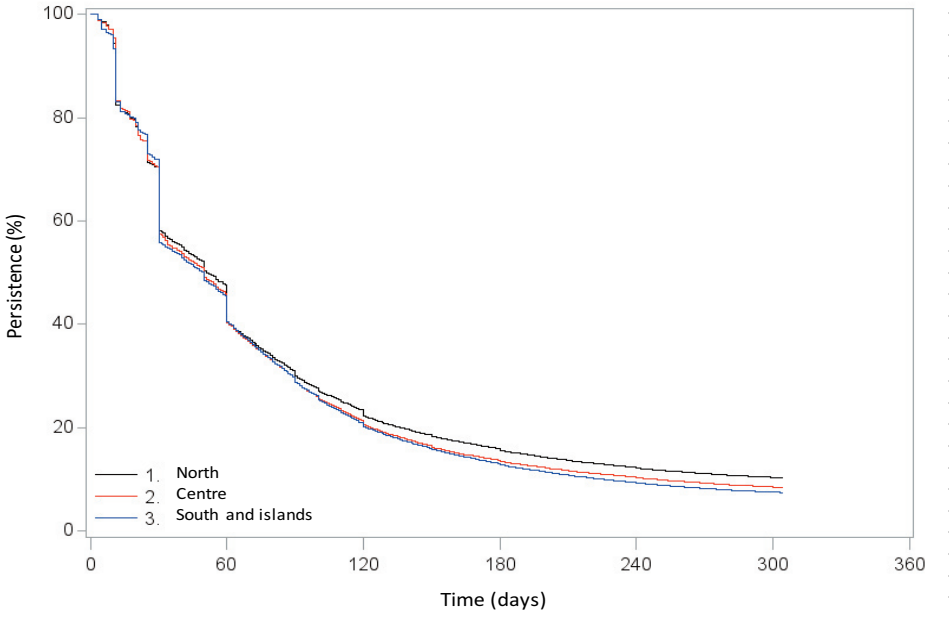
Adequate level of adherence to therapy produces different effects on the patient's quality of life, such as a greater control over symptoms and a decrease in flareups and in the need for healthcare assistance (2-3).

Table 4.9.2. Persistence to treatment with medicines for obstructive airway disorders in the population aged ≥45 years

Persistence (%)	Total N=194,295			North‡ N=57,429			Centre N=47,333			South N=89,533		
	months			months			months			months		
	3	6	12	3	6	12	3	6	12	3	6	12
45-54 years	22.7	9.3	5.2	23.8	11.0	6.6	22.5	9.2	5.5	22.0	8.4	4.2
55-64 years	25.5	11.3	6.9	27.0	13.2	8.7	24.2	10.6	6.2	25.3	10.5	6.1
65-74 years	28.2	13.8	8.9	29.2	16.0	11.0	28.6	13.7	8.9	27.4	12.6	7.7
75-84 years	30.6	15.6	10.2	31.3	17.2	11.9	30.2	15.0	9.8	30.4	14.8	9.1
≥ 85 years	29.0	14.5	9.5	28.0	14.6	9.8	29.2	14.9	10.0	29.6	14.2	9.0
Women	25.2	11.0	6.5	25.7	12.5	7.9	25.4	11.1	6.7	24.7	9.9	5.5
Men	30.2	15.7	10.4	31.6	17.6	12.5	29.5	15.0	10.0	29.6	14.7	9.4
Total	**27.3**	**13.0**	**8.2**	**28.2**	**14.7**	**9.9**	**27.1**	**12.7**	**8.1**	**26.9**	**12.0**	**7.2**

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

Figure 4.9.1. Time (in days) to discontinuation of treatment with medicines for obstructive airway disorders in the population aged ≥ 45 years, stratified by geographical area. The curves are adjusted for age and gender (the Cox model was used to estimate the persistence curves).



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

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2. Sanduzzi A, Balbo P, Candoli P, et al. COPD: adherence to therapy. Multidiscip Respir Med 2014: 9, 60.
3. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.

Section 5

Pharmaceutical use in fragile populations

National Report
on Medicines
use in Italy
Year 2019

5.1 Pharmaceutical use in the paediatric age

This section presents an analysis of the pharmaceutical use in the paediatric age taking into consideration data from all Italian regions, whose resident paediatric population (age <18 years) was 9.7 million individuals in 2019.
In 2019 over 4.6 million children and adolescents received at least one pharmaceutical prescription (47.6% of the general paediatric population). Furthermore, in the same year, 19 million prescriptions were issued, for a total of 19.8 million packages and a total expenditure of €273 million (€28.2 per capita and €59.2 per user). If compared with the previous year, an increase was recorded both in the per capita expenditure (+4.6%) and in the per user expenditure (+4.4%); smaller increases concerned prescriptions and prescribed packages, +0.9% and +0.7% respectively. On average, in 2019, each child received 2.0 prescriptions and 2.0 packages of pharmaceuticals, with a slight difference between males and females: 2.1 versus 1.8 prescriptions and 2.2 versus 1.9 packages, respectively (Table 5.1.1).
At regional level, a marked variability was recorded in the use of pharmaceuticals in the paediatric age, with a prevalence of use ranging from 36% in the A.P. of Bolzano to 58% in Abruzzo (Figure 5.1.1).
The prevalence of prescriptions recorded a peak between the second and third year of the child's life (66%), then it progressively decreased with age to 38.9% in the 12-17 age group (Figure 5.1.2). Overall, the prevalence was higher in males than in females (48.5% vs 46.8%) (Table 5.1.1).
A similar trend by age concerned consumption, with a figure of per capita packages ranging from 3.0 in the 2-3 age group to 1.7 in the 12-17 age group, with a gender difference: 3.2 packages for males versus 2.8 packages for females (Table 5.2.2).
As expected, antimicrobials for systemic use showed the highest level of consumption (46.7% of the total), followed by respiratory pharmaceuticals (24.2%) and hormones (excluding sex hormones) (8.5%), pharmaceuticals for the gastrointestinal tract and metabolism (7.4%) and medicinal products for the central nervous system (7.1%) (Figure 5.1.3).
The analysis of distribution of consumption by gender showed a greater use in males than females for all therapeutic categories, with the exception of genito-urinary tract pharmaceuticals and sex hormones, antineoplastic and immunomodulatory agents and antiparasitic products, insecticides and repellents (Figure 5.1.4).
Antimicrobials for systemic use were the therapeutic category with the highest prescription prevalence in the paediatric age (377.3 per 1000 children), with the amoxicillin/clavulanic acid combination being the most prescribed product in the category (345.6 prescriptions per 1000 children), and remained stable compared to 2018 (-0.2%). As in the previous year, the amoxicillin/clavulanic acid combination ranked first among the top 30 active ingredients with the highest consumption in 2019. On the contrary, in terms of prevalence, amoxicillin, the first-choice antibiotic in the treatment of the most common paediatric infections according to the guidelines, ranked second in the category (80.3 per 1000 children), showing a 10.6% increase in prescription compared to the previous year (Tables 5.1.3 and 5.1.4).
The ranking includes respiratory tract pharmaceuticals (prevalence of 193.4 per 1000 children), with beclomethasone being the most prescribed drug (prevalence of 66.1 per

1000 children), ranking sixth among the active ingredients with the highest level of consumption in the paediatric age (87.5 packages per 1000 children), showing a reduction compared to the previous year (-6.2%). Hormones (excluding sex hormones) showed a prevalence of 86.4 per 1000 children, with betamethasone being the most prescribed pharmaceutical in the category (106.3 per 1000 children) and ranking third among the top 30 active ingredients consumed in the paediatric age in 2019.
Pharmaceuticals for gastrointestinal system and metabolism had a prevalence of 50.9 per 1000 children, with cholecalciferol being the most prescribed active ingredient in the category (69.5 prescriptions per 1000 children), whereas medicinal products for the central nervous system showed a prevalence of 8.7 per 1000 children, with valproic acid being the most prescribed active ingredient (49.4 prescriptions per 1000 children; Tables 5.1.3 and 5.1.4).
Among the top 30 active ingredients with the highest level of consumption in the paediatric population in 2019, 10 active ingredients belonged to the category of respiratory tract pharmaceuticals, 9 were antimicrobials for systemic use (8 antibacterials and one antiviral), 4 were hormones (excluding sex hormones) and 3 were active ingredients for the central nervous system (antiepileptics), 2 belonged to the category of gastrointestinal tract pharmaceuticals, 1 belonged to the category of antiparasitic products, insecticides and repellents, and 1 belonged to the category of blood and blood-forming organs. Among all active ingredients with the highest level of consumption, levothyroxine (a medicinal product indicated for hypothyroidism), colecalciferol and levetiracetam showed a higher level of consumption in females than in males (Table 5.1.4).

Table 5.1.1. General prescription data in the paediatric population in 2019

	Males	Females	Total
Users	2,415,095	2,196,563	4,611,658
prevalence (%)	48.5	46.8	47.6
Prescriptions	10,347,504	8,665,626	19,013,130
Per capita	2.1	1.8	2.0
Δ % 19-18	0.9	0.9	0.9
Packages	10,769,360	8,998,970	19,768,330
Per capita	2.2	1.9	2.0
Δ % 19-18	0.8	0.7	0.7
Expenditure	162,439,153	110,481,883	272,921,036
Per capita	32.6	23.5	28.2
Δ % 19-18	6.3	2.2	4.6
Per user	67.3	50.3	59.2
Δ % 19-18	6.1	1.9	4.4

Figure 5.1.1. Regional trend in prescriptions in the paediatric population in 2019

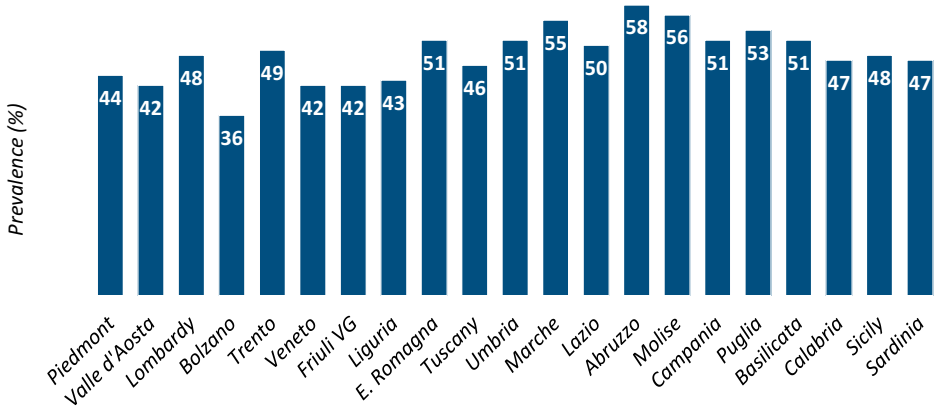


Figure 5.1.2. Prescription trend in the paediatric population by age in 2019

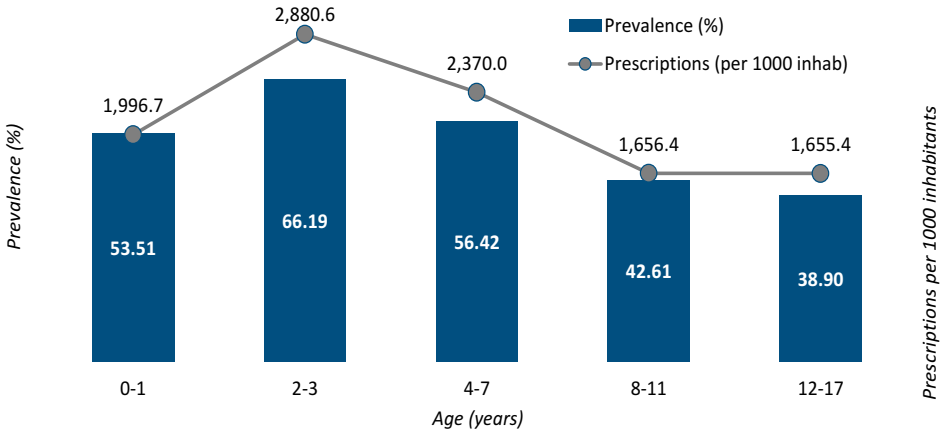


Table 5.2.2. Distribution of consumption (packages) by age and gender in the paediatric population in 2019

Age group	Per capita packages		
	Males	Females	Total
<1	1.3	1.1	**1.2**
1-5	3.2	2.8	**3.0**
6-11	1.9	1.7	**1.8**
12-17	1.8	1.6	**1.7**
Total	**2.2**	**1.9**	**2.1**

Figure 5.1.3. Percentage distribution of consumption (packages) in the paediatric age by I level ATC in 2019

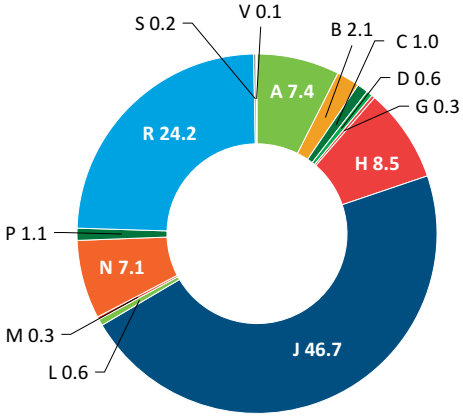
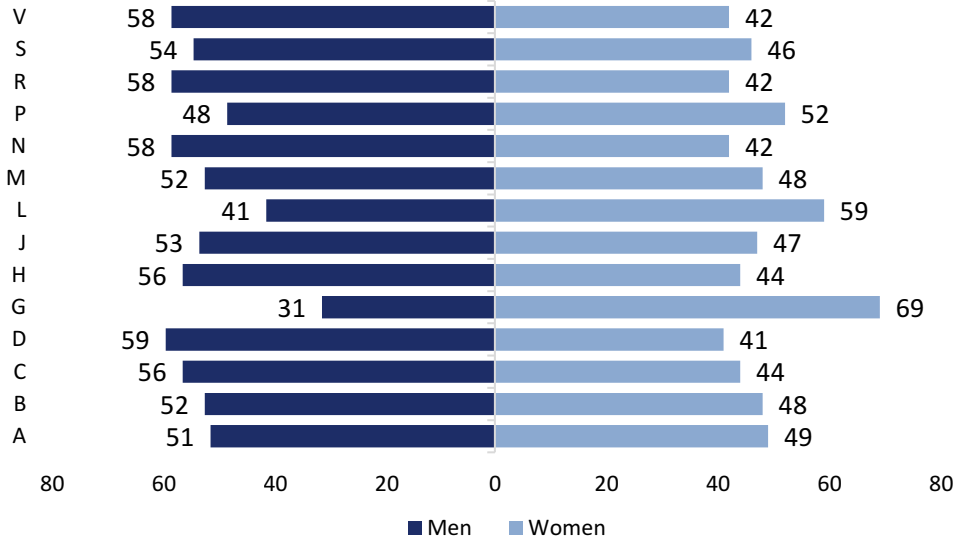


Figure 5.1.4. Percentage distribution of consumption (packages) in the paediatric age by I level ATC and gender in 2019



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

Table 5.1.3. Most prescribed substances in the paediatric age by therapeutic category (75% of prescriptions) in 2019

Therapeutic category/substance	Prescriptions (per 1000 inhab.)	Δ % 19-18	Prevalence (per 1000 inhab.)	Ratio M/F
J – Antimicrobials for systemic use	**922.5**	**0.9**	**377.3**	**1.09**
amoxicillin/clavulanic acid	345.6	-0.2	193.2	1.13
amoxicillin	154.8	10.6	80.3	1.08
cefixime	92.0	-2.3	62.3	1.04
azithromicyn	91.2	0.9	62.4	1.12
clarithromycin	76.2	0.3	54.5	1.16
R - Respiratory	**488.4**	**-0.4**	**193.4**	**1.25**
beclomethasone	87.0	-4.9	66.1	1.20
salbutamol	86.3	-0.8	59.8	1.41
budesonide	66.4	6.9	48.3	1.22
cetirizine	56.6	-0.6	28.8	1.38
fluticasone	36.3	-1.3	21.2	1.55
salbutamol/ipratropium	35.2	1.5	29.7	1.21
montelukast	33.9	-1.7	10.5	1.63
H - Hormones *(excl. sex hormones)*	**164.6**	**1.5**	**86.4**	**1.23**
betamethasone	106.3	0.2	74.0	1.24
somatropin	16.7	7.1	0.8	1.47
levothyroxine	14.6	1.3	2.3	0.61
prednisone	12.6	3.6	6.2	1.30
desmopressin	7.1	0.4	1.3	2.21
dexamethasone	3.5	11.3	2.3	1.16
A - Gastrointestinal tract and metabolism	**143.2**	**0.6**	**50.9**	**1.00**
cholecalciferol	69.5	2.7	33.1	1.00
lansoprazole	7.9	2.7	1.9	1.01
insulin lispro	6.2	13.2	0.8	1.15
insulin aspart	6.0	6.3	0.6	1.07
esomeprazole	5.5	2.2	1.7	1.03
omeprazole	4.7	-10.1	1.5	0.94
nystatin	4.4	-1.8	3.4	1.00
ursodeoxycholic acid	4.1	4.7	0.4	1.00
N – Central Nervous System	**131.0**	**3.7**	**8.7**	**1.29**
valproic acid	49.4	-1.3	2.4	1.86
carbamazepine	13.0	3.1	0.8	1.26
levetiracetam	12.4	0.9	1.1	0.85
lamotrigin	6.3	7.7	0.4	0.67
aripiprazole	4.4	23.5	0.6	1.59
methylphenidate	4.0	24.9	0.6	6.78
topiramate	4.0	-2.8	0.4	0.87
ethosuximide	3.8	16.1	0.3	0.78
sertraline	3.7	15.5	0.6	0.80
B Blood and blood-forming organs	**38.1**	**1.6**	**14.2**	**0.92**
sodium chloride	6.7	0.3	1.4	1.20
enoxaparin	5.3	11.8	2.0	1.65
iron	4.4	5.1	2.3	1.27
ferrous sulfate	4.3	6.9	2.5	0.31
folic acid	4.3	-2.5	2.2	0.55
tranexamic acid	3.2	-3.8	1.8	1.07
sodium ferric gluconate	1.6	-4.9	0.8	1.32

P - Antiparasitic products, insecticides and repellents	**21.5**	**8.0**	**13.4**	**0.94**
mebendazole	16.1	10.0	10.3	0.94
pyrantel pamoate	3.4	0.4	2.4	0.92
C - Cardiovascular system	**18.9**	**2.5**	**2.6**	**1.26**
ramipril	2.0	-1.1	0.3	1.47
enalapril	2.0	-1.1	0.3	1.24
furosemide	1.5	8.0	0.3	1.13
flecainide acetate	1.4	6.3	0.1	1.07
losartan	1.2	-0.2	0.1	1.70
carvedilol	1.2	0.9	0.1	1.36
bisoprolol	1.1	13.5	0.2	1.21
amlodipine	1.0	6.8	0.2	1.29
spironolactone	0.8	-1.8	0.1	0.78
propranolol	0.7	-1.2	0.1	0.72
L - Antineoplastic and immunomodulating agents	**10.5**	**6.3**	**1.2**	**0.56**
methotrexate	2.7	1.5	0.4	0.48
triptorelin	2.1	9.0	0.3	0.13
tacrolimus	1.6	17.3	0.1	1.19
azathioprine	1.0	-1.8	0.1	0.95
ciclosporin	1.0	-5.8	0.1	1.24
D - Dermatologicals	**10.3**	**1.7**	**4.0**	**1.26**
isotretinoin	4.7	4.6	1.1	2.04
calcipotriol/betamethasone	1.4	13.0	0.6	0.87
methylprednisolone	0.9	4.7	0.7	1.15
mometasone	0.7	24.2	0.6	1.10
clobetasol	0.7	6.9	0.3	0.87
G - Genito-urinary system and sex hormones	**5.5**	**-1.0**	**1.5**	**0.3**
oxybutynin	1.8	-1.1	0.3	1.7
cyproterone/ethinylestradiol	0.9	-7.9	0.2	0.00
estradiol	0.4	5.3	0.1	0.04
dydrogesterone	0.4	1.7	0.2	0.00
cabergoline	0.3	11.7	0.1	0.14
progesterone	0.2	-4.0	0.1	0.05
estriol	0.2	-10.3	0.2	0.01
M - Musculo-skeletal system	**5.3**	**-2.6**	**3.2**	**1.00**
ketoprofen	1.3	-8.9	1.0	1.03
ibuprofen	0.8	4.4	0.6	0.91
baclofen	0.7	-2.2	0.1	1.51
diclofenac	0.4	-12.5	0.4	1.01
allopurinol	0.4	8.5	0.1	1.52
nimesulide	0.2	-9.8	0.2	0.97
naproxen	0.2	5.1	0.1	0.52
ketorolac	0.2	-5.0	0.1	0.84
S - Sensory organs	**4.1**	**-5.0**	**0.8**	**1.00**
acetazolamide	1.0	1.4	0.1	1.02
timolol	0.6	3.7	0.2	0.67
dorzolamide/timolol	0.5	-0.3	0.1	1.34
V - Various	**1.4**	**18.9**	**0.4**	**1.44**
oxygen	0.4	11.1	0.1	1.18
pollen of phleum pratense/dactylis glomerata/anthoxanthum odoratum/lolium perenne/poa pratensis	0.3	-5.5	0.1	1.90

Table 5.1.4. Top thirty active ingredients by consumption in the paediatric age in 2019

ATC	Active ingredient	Packages (per 1000 inhab.)	Δ % 19-18	Consumption (%)*	
				Males	Females
J	amoxicillin/clavulanic acid	356.1	-1.6	53.7	46.3
J	amoxicillin	161.0	8.9	52.4	47.6
H	betamethasone	107.6	-1.2	56.4	43.6
J	cefixime	93.8	-3.7	51.0	49.0
J	azithromicyn	92.9	-0.4	53.3	46.7
R	beclomethasone	87.5	-6.2	55.2	44.8
R	salbutamol	86.9	-2.2	59.7	40.3
J	clarithromycin	77.4	-1.2	53.9	46.1
A	cholecalciferol	73.2	2.3	49.5	50.5
R	budesonide	66.8	5.4	55.8	44.2
R	cetirizine	57.9	-2.0	60.4	39.6
N	valproic acid	52.2	-3.0	65.3	34.7
J	cefpodoxime	49.2	1.8	52.9	47.1
R	fluticasone	36.8	-2.7	61.7	38.3
R	salbutamol/ipratropium	35.3	0.1	55.2	44.8
R	montelukast	34.9	-3.3	63.1	37.0
J	ceftriaxone	28.7	-3.7	54.5	45.5
R	flunisolide	23.1	1.4	54.2	45.9
H	somatropin	21.4	2.0	61.0	39.0
J	cefaclor	21.2	-11.8	50.4	49.6
P	mebendazole	16.6	8.4	48.3	51.7
H	levothyroxine	15.3	-0.3	38.9	61.1
N	carbamazepine	13.8	1.3	56.0	44.0
N	levetiracetam	13.3	-0.7	45.3	54.8
H	prednisone	13.0	1.9	54.9	45.2
R	levocetirizine	12.3	-6.3	63.0	37.0
R	salmeterol/fluticasone	11.6	-0.4	65.7	34.3
J	acyclovir	11.6	-13.4	51.8	48.3
A	lansoprazole	8.3	0.7	53.9	46.1
B	sodium chloride	8.3	0.8	55.7	44.3

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

Prescription of respiratory pharmaceuticals in the paediatric age

The analysis of the prescription of pharmaceuticals for the respiratory system showed that one child in five received at least one package in 2019. Overall, 5 million prescriptions were issued, equal to 26.3% of total consumption in the paediatric age. This value was stable compared with 2018 (Table 5.1.5), and showed a peak prevalence in the 2-3 age group (37%) which decreased with age (Figure 5.1.5).
Inhaled steroids were the most widely used therapeutic class (prevalence of 13.6% and 212.9 prescriptions per 1000 children). Beclomethasone was the most prescribed active ingredient (prevalence of use of 6.6%, despite a decrease compared to 2018), followed by oral steroids (prevalence of 8.1%), with betamethasone being one of the most prescribed active ingredients (prevalence of 7.4%) and SABAs (short-acting adrenergic bronchodilators) with a prevalence of 6.0%, with salbutamol being the most prescribed active ingredient (prevalence of 6.0%) (Table 5.1.6).
An analysis of prescriptions in different therapeutic classes by age group showed a higher prevalence of use in children up to 6 years of age for all medicines, with the exception of long acting beta2-adrenergic agonists - LABAs (long-acting inhaled bronchodilators) in combination with inhaled steroids (ICSs) and injectable steroids, which had a higher prevalence of use in children over 6 years of age. Furthermore, there is a high percentage of users with a single prescription in the year for all categories, due to their possible use when needed (Table 5.1.7).
An analysis of the percentage distribution of consumption of the different therapeutic categories by age group indicated a higher percentage of use for inhaled steroids in all age groups, except for the 12-17 age group, where a greater use of oral steroids was recorded. Short acting beta2-adrenergic agonists - SABAs (short-acting inhaled bronchodilators) in combination with short-acting muscarinic antagonists - SAMAs were mostly used in the first year of life of the child and then their use decreased with age. However, the use of SABAs alone was similar in all age groups, although to a lesser extent in the first year of life (Figure 5.1.6).

Table 5.1.5 Prescription of respiratory pharmaceuticals in the paediatric population (2019)

	Total
Prescriptions	**4,992,120**
Per 1000 children	515.8
Δ % 19-18	0.1
% share of overall consumption	26.3
Packages	**5,048,337**
Per prescription	1.0
Users	**2,009,167**
Prevalence (%)	20.8

Figure 5.1.5. Trend in prescription of respiratory pharmaceuticals by age in 2019

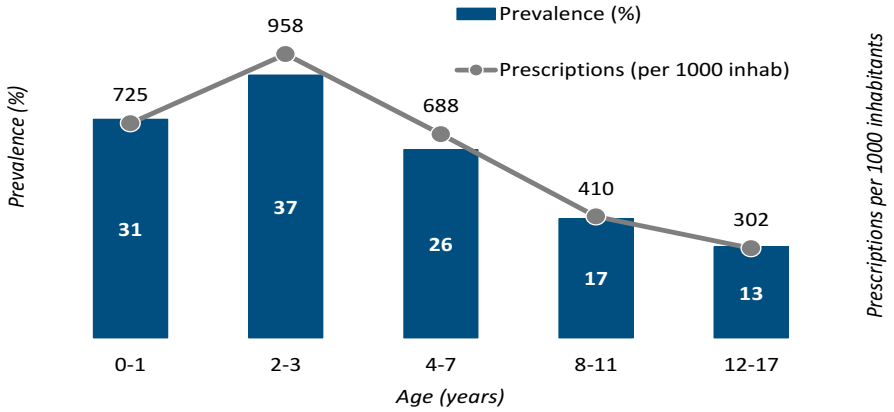


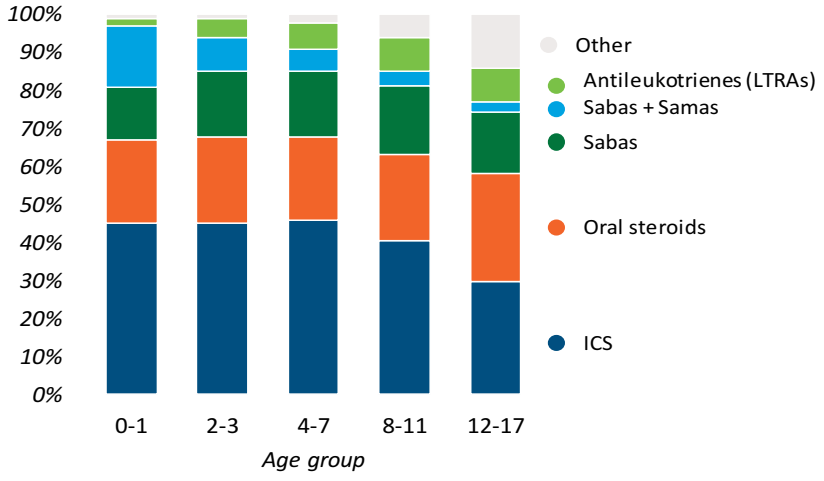
Table 5.1.6. Prescription of respiratory pharmaceuticals in the paediatric population by therapeutic category and substance (2019)

Categories and substances	Prevalence (%)	Prescriptions (per 1000 inhab.)	Δ % 19-18
ICSs	13.6	212.9	0.0
Oral steroids	8.1	122.3	0.7
SABAs	6.0	86.3	-0.8
SABAs+SAMAs	3.0	35.2	1.5
Antileukotrienes (LTRAs)	1.0	33.9	-1.7
LABAs+ICSs	0.7	16.1	6.0
SAMAs	0.2	2.5	3.6
Injectable steroids	0.1	1.7	-2.4
SABAs+ICSs	0.1	1.4	-12.7
UltraLABAs+ICSs	0.1	2.5	8.8
Theophylline-based bronchodilators	0.0	0.2	-15.7
LABAs	0.0	0.2	0.5
LAMAs	0.0	0.1	15.0
Chromones	0.0	0.0	-88.3
Monoclonal antibodies	0.0	0.4	31.7
LABAs+LAMAs	0.0	0.0	1.3
Ultra-LABAs	0.0	0.0	-16.4
LAMAs+LABAs+ICSs	0.0	0.0	>100%
PDE-4 inhibitor	0.0	0.0	1.3
Total	**20.8**	**515.8**	**0.1**
betamethasone	7.4	106.3	0.2
beclomethasone	6.6	87.0	-4.9
salbutamol	6.0	86.3	-0.8
budesonide	4.8	66.4	6.9
salbutamol/ipratropium	3.0	35.2	1.5
fluticasone	2.1	36.3	-1.3
flunisolide	1.8	23.0	2.8
montelukast	1.0	33.9	-1.7
prednisone	0.6	12.6	3.6
salmeterol/fluticasone	0.5	11.4	1.2

Table 5.1.7. Respiratory pharmaceuticals users by number of prescriptions received during the year by therapeutic category and age group (2019)

Categories	0-6 years					7-17 years				
	Prevalence %	Users per no. of prescriptions (%)				Prevalence %	Users per no. of prescriptions (%)			
		1	2	3	>3		1	2	3	>3
ICSs	22.4	66.0	20.0	7.3	6.7	8.8	74.0	16.5	4.8	4.7
Oral steroids	12.0	71.2	18.7	5.7	4.5	6.0	73.4	18.2	4.1	4.3
SABAs	9.6	76.2	16.1	4.6	3.2	4.0	72.0	17.5	5.1	5.4
SABAs+SAMAs	6.5	84.6	12.0	2.4	0.9	1.1	90.2	8.0	1.2	0.6
Antileukotrienes (LTRAs)	1.4	35.9	23.0	10.9	30.2	0.9	29.8	23.7	9.8	36.8
LABAs+ICSs	0.2	57.4	20.1	9.0	13.4	0.9	48.3	22.4	9.7	19.6
SAMAs	0.3	73.4	16.5	5.0	5.2	0.1	73.2	18.0	4.2	4.6
Injectable steroids	0.1	83.6	12.9	1.7	1.8	0.2	74.1	20.1	2.7	3.0
SABAs+ICSs	0.1	86.8	9.8	2.3	1.1	0.1	84.4	11.2	2.3	2.0
Ultra-LABAs+ICSs	0.0	78.7	13.8	4.3	3.2	0.1	39.3	20.4	10.1	30.2
Theophylline-based bronchodilators	0.0	81.4	13.4	2.7	2.4	0.0	82.7	13.0	1.9	2.4
LABAs	0.0	60.3	21.0	10.7	7.9	0.0	63.2	18.5	6.9	11.4
LAMAs	0.0	80.8	15.2	2.0	2.0	0.0	72.0	15.8	4.8	7.4
Chromones	0.0	77.5	7.5	5.0	10.0	0.0	63.1	21.2	5.5	10.2
Monoclonal antibodies	0.0	33.3	50.0	-	16.7	0.0	5.3	8.3	2.9	83.5
LABAs+LAMAs	0.0	75.6	22.2	-	2.2	0.0	73.9	21.6	1.1	3.4
Ultra-LABAs	0.0	100	-	-	-	0.0	78.6	14.3	-	7.1
LAMAs+LABAs+ICSs	0.0	82.4	17.6	-	-	0.0	91.7	8.3	-	-
PDE-4 inhibitor	-	-	-	-	-	0.0	100.0	-	-	-

Figure 5.1.6. Percentage distribution of respiratory pharmaceuticals consumption in the paediatric age by therapeutic category and age group (2019)



Prescription of antibiotics in the paediatric population

About 4 out of 10 children received at least one antibiotic prescription in 2019 and, on average, each child was prescribed only one package during the year, for a total of 8.7 million prescriptions, equal to 45.9% of total consumption (Table 5.1.8). A peak prevalence, about 6 children out of 10, in the 2-3 age group was recorded (Figure 5.1.7).
Combinations of penicillins (including beta-lactamase inhibitors) were the class of antibiotics with the highest prescription prevalence (19.3%), with the amoxicillin/clavulanic acid combination showing the highest prescription rate (345.6 prescriptions per 1000 children). This was followed by macrolides and lincosamides (prevalence of 11.1%), with azithromycin being the most prescribed molecule (91.2 prescriptions per 1000 children), and third-generation cephalosporins (prevalence of 9.2%), with cefixime among the most prescribed active ingredients (92.0 prescriptions per 1000 children). Broad-spectrum penicillins, such as amoxicillin, were among the least used antibiotics, with a prescription level of 155.0 prescriptions per 1000 children, despite an increase by 10.6% compared with the previous year. Among the 10 most prescribed molecules in the category, a strong reduction was recorded for cefaclor (-10.5%), while ceftibuten and amoxicillin were the only active ingredients showing an increase in use compared to 2018 (+10.6% and +11.6%, respectively) (Table 5.1.9).
The analysis of the percentage distribution of consumption in the different therapeutic categories by age group showed a greater use of penicillin combinations in all age groups. Macrolides and lincosamides, together with third-generation cephalosporins, recorded the highest level of consumption in the 12-17 age group, whereas broad-spectrum penicillins were mostly used in the first year of life of the child, and their use progressively decreased with age (Figure 5.1.8).
They analysis of some indicators relating to specific classes of antibiotics prescribed in the paediatric population in 2019 (Table 5.1.10) showed that combinations of penicillins (including beta-lactamase inhibitors) were the most widely used antibiotics (38.4%), particularly in Central Italy (44.0%), followed by cephalosporins (22.4%) and macrolides (18.8%), especially in Southern Italy. Broad-spectrum penicillins were the antibiotics with the lowest prescription level (17.2%), especially in Southern and insular Italy.
At regional level, a high variability was recorded in the use of the different classes of antibiotics. For example, broad-spectrum penicillins were the most prescribed in Liguria (50.2%), combinations of penicillins were the most prescribed in Tuscany (50.1%) and cephalosporins (30.4%) and macrolides and lincosamides (24.7%) were the most prescribed in Sicily. Abruzzo was the region with the lowest level of consumption of broad-spectrum penicillins (6.4%), while Liguria recorded the lowest level of consumption of the other classes (26.1%, 6.6% and 12.6% respectively).
Finally, it should be emphasized that in Northern Italy more amoxicillin was used on average compared with other geographical areas (amoxicillin/amoxicillin+clavulanic acid ratio equal to 0.7 in the North, 0.3 in the Centre and 0.3 in the South), with Liguria and Emilia Romagna reaching the highest levels. It is worth recalling that in the two most frequent clinical conditions in the paediatric population, i.e. pharyngotonsillitis and acute otitis media, the use of amoxicillin was recommended as the first-choice option. The combination of amoxicillin and clavulanic acid does not offer any advantage in pharyngotonsillitis, whereas

the addition of clavulanic acid is expected in otitis in severe/complicated and recurrent cases. In the uncomplicated and non-recurrent form, amoxicillin should be the drug of choice.

Table 5.1.8. Prescription of antibiotics in the paediatric population (2019)

	Total
Prescriptions	**8,733,482**
Per 1000 children	902.3
Δ % 19-18	1.2
% share of overall consumption	45.9
Packages	**9,033,912**
Per prescription	1.0
Users	**3,604,813**
Prevalence (%)	37.2

Figure 5.1.7. Trend in antibiotics prescription by age group (2019)

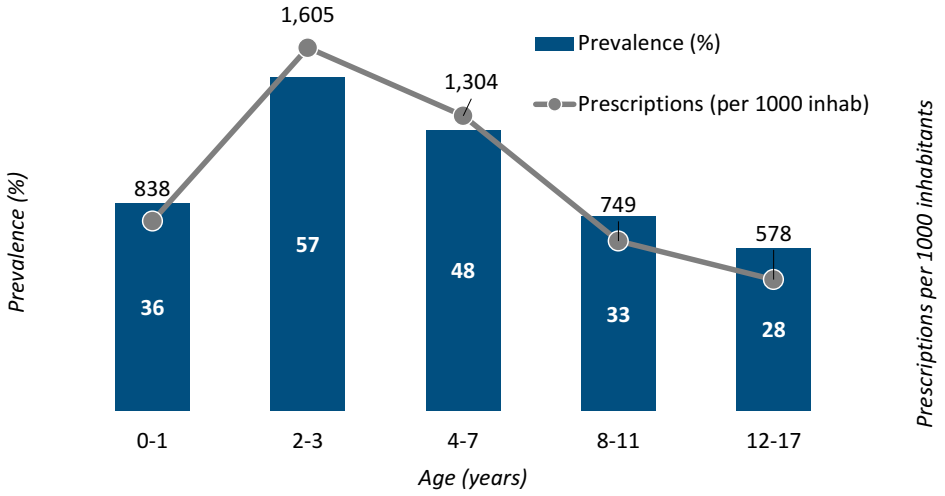


Table 5.1.9. Prescription of antibiotics in the paediatric population by therapeutic category and substance (2019)

Categories and substances	Prevalence (%)	Prescriptions (per 1000 inhab.)	Δ % 19-18
Combinations of penicillins (including beta lactamase inhibitors)	19.3	346.0	-0.2
Macrolides and lincosamides	11.1	172.4	0.4
Third-generation cephalosporins	9.2	176.0	-0.2
Broad-spectrum penicillins	8.0	155.0	10.5
Second-generation cephalosporins	1.4	25.2	-7.0
Other antibacterials	0.6	7.3	-3.6
Tetracyclines	0.3	7.5	2.9
Fluroquinolones	0.3	4.8	-25.1
Sulphonamides (alone or in combination)	0.2	3.8	0.0
Aminoglycosides	0.0	2.9	-6.6
First-generation cephalosporins	0.0	0.7	14.5
Beta-lactamase sensitive penicillins	0.0	0.4	-2.6
Beta-lactamase resistant penicillins	0.0	0.1	20.1
Fourth-generation cephalosporins	0.0	0.1	26.5
Glycopeptides	0.0	0.1	45.8
Amphenicols	0.0	0.0	83.3
Other quinolones	0.0	0.0	-80.5
Imidazole derivatives	0.0	0.0	178.6
Nitrofuran derivatives	0.0	0.0	-32.5
Polymyxin	0.0	0.0	-43.0
Total	**37.2**	**902.3**	**1.2**
Amoxicillin/clavulanic acid	19.3	345.6	-0.2
Amoxicillin	8.0	154.8	10.6
Azithromicyn	6.2	91.2	0.9
Cefixime	6.2	92.0	-2.3
Clarithromycin	5.5	76.2	0.2
Cefpodoxime	2.5	47.1	3.4
Cefaclor	1.2	20.5	-10.5
Fosfomycin	0.6	7.3	-3.5
Ceftibuten	0.6	8.1	11.6
Ceftriaxone	0.5	24.9	-1.5

Figure 5.1.8. Percentage distribution of antibiotic consumption by therapeutic category and age group (2019)

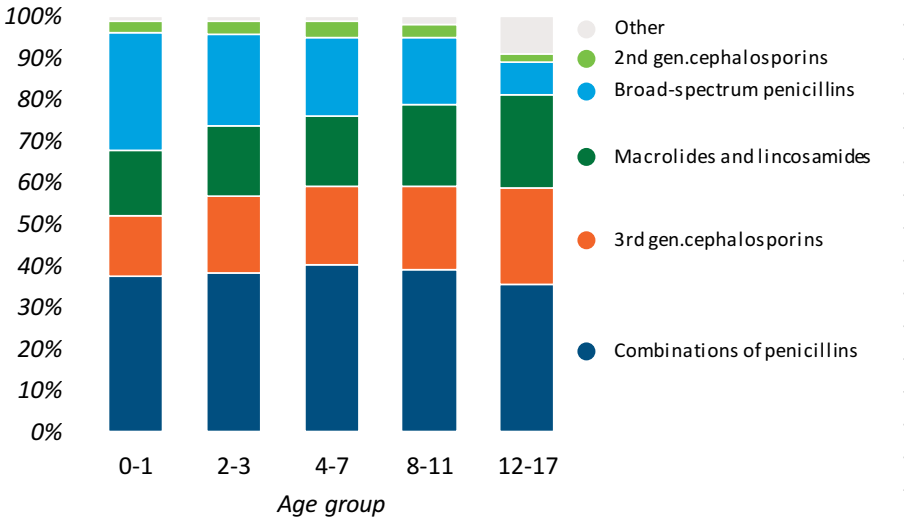


Table 5.1.10. Paediatric indicators related to specific classes of antibiotics and amoxicillin/amoxicillin-clavulanic ratio in 2019 (agreed expenditure)

Region	Indicator				
	1	2	3	4	5
Piemonte	19.7	39.9	21.8	15.7	0.5
Valle d'Aosta	23.6	35.7	17.1	19.7	0.7
Lombardia	22.7	42.7	17.2	14.9	0.5
Bolzano area	15.6	41.2	23.8	16.9	0.4
Trento area	12.9	48.2	17.7	17.8	0.3
Veneto	24.1	33.4	17.8	21.2	0.7
Friuli Venezia Giulia	13.3	41.1	27.7	14.9	0.3
Liguria	50.2	26.1	6.6	12.6	1.9
Emilia Romagna	42.2	28.4	12.7	14.2	1.5
Toscana	11.8	50.1	21.6	14.0	0.2
Umbria	17.9	49.4	15.6	14.7	0.4
Marche	14.7	40.4	25.7	15.6	0.4
Lazio	11.0	41.3	24.3	19.6	0.3
Abruzzo	6.4	43.0	23.6	24.2	0.1
Molise	11.4	39.5	22.4	20.4	0.3
Campania	7.1	35.2	29.9	22.8	0.2
Puglia	15.8	34.9	24.3	21.7	0.5
Basilicata	17.3	31.6	24.6	22.4	0.5
Calabria	6.7	36.1	28.4	24.9	0.2
Sicilia	7.9	33.9	30.4	24.7	0.2
Sardegna	14.2	41.9	24.6	17.1	0.3
Italy	**17.2**	**38.4**	**22.4**	**18.8**	**0.4**
North	26.7	37.6	17.1	15.7	0.7
Centre	12.4	44.0	23.2	17.1	0.3
South and Islands	9.9	36.2	27.4	22.7	0.3

Indicator
1. % prescriptions of broad-spectrum penicillins (J01CA-CE)
2. % prescriptions of combinations of penicillins – including beta lactamase inhibitors (J01CF-CR)
3. % prescriptions of cephalosporines (J01DB-DC-DD-DE)
4. % prescriptions of macrolides (J01FA)
5. amoxicillin/amoxicillin+clavulanic acid prescription ratio

Prescription of antiepileptic pharmaceuticals in the paediatric population

Prescription of antiepileptics registered a slight increase compared with 2018 (+1.0%), representing 5.2% of the total consumption of pharmaceuticals in the paediatric age. As expected, the prevalence in the paediatric population was low (0.5%), with a prescription rate of 101.4 per 1000 children (Table 5.1.11). The use of epileptic pharmaceuticals increased with age and was in line with the epidemiology of the condition, reaching a peak in the 12-17 age group (prescription rate of 148 per 1000 children and prevalence of 0.7%) (Figure 5.1.9). Valproic acid was the most used substance (49.4 prescriptions per 1000 children and prevalence of 0.2%), showing a slight decrease (-1.3%) compared to 2018, followed by carbamazepine with 13.0 prescriptions per 1000 children (+3.1% compared to the previous year) and by levetiracetam, which showed a 1.0% increase compared to the previous year, with 12.4 prescriptions per 1000 children (Table 5.1.12). The prescription of the valproic acid and derivatives was higher in all age groups, reaching a maximum value in the 4-7 age group. The use of other antiepileptic (e.g. levetiracetam) and carboxamide derivatives (e.g. carbamazepine) showed a slight increase with age, whereas the prescription of barbiturates and derivatives (e.g. phenobarbital), which is the most prescribed category in the first year of life of a child, recorded a progressive decrease with age (Figure 5.1.10).

Table 5.1.11. Prescription of antiepileptic pharmaceuticals in the paediatric population (2019)

	Total
Prescriptions	**980,990**
Per 1000 children	101.4
Δ % 19-18	1.0
% share of overall consumption	5.2
Packages	**1,067,428**
Per prescription	1.1
Users	**47,453**
Prevalence (%)	0.5

Figure 5.1.9. Trend in antiepileptic drug prescriptions by age (2019)

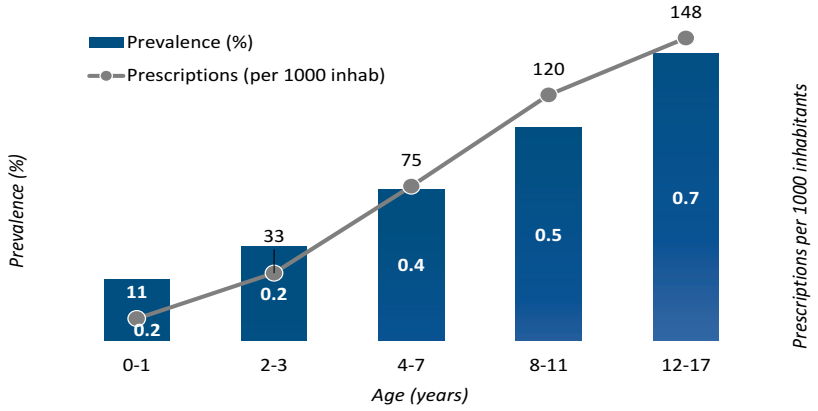
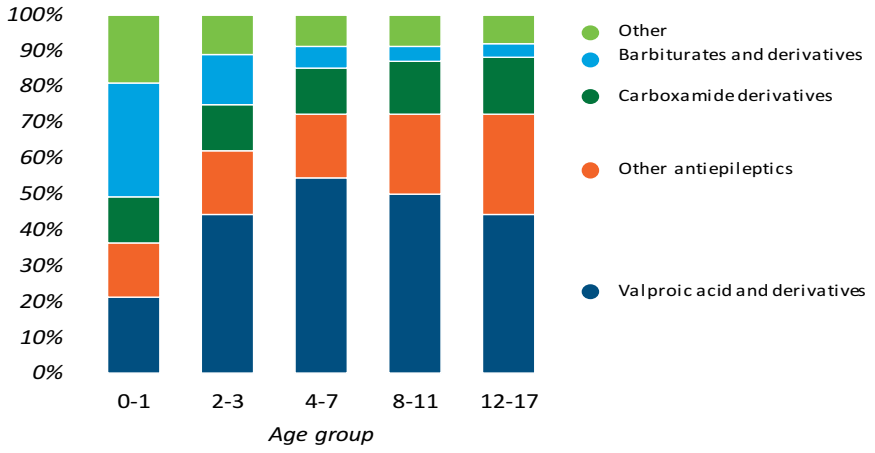


Table 5.1.12. Prescription of antiepileptic pharmaceuticals in the paediatric population by therapeutic category and substance (2019)

Categories and substances	Prevalence (%)	Prescriptions (per 1000 inhab.)	Δ % 19-18
Fatty acid derivatives - valproic acid and derivatives	0.2	49.4	-1.4
Other antiepileptics	0.2	25.0	2.7
Carboxamide derivatives	0.1	15.4	2.5
Succinimide derivatives	0.0	3.8	16.1
Barbiturates and derivatives	0.0	3.5	-4.3
Benzodiazepine derivatives	0.0	1.6	-0.2
GABA analogues	0.0	1.0	33.8
Fatty acid derivatives (alone or in combination)	0.0	1.4	3.3
Phenyotin (alone or in combination)	0.0	0.3	9.5
Total	**0.5**	**101.4**	**1.0**
valproic acid	0.2	49.4	-1.3
carbamazepine	0.1	13.0	3.1
levetiracetam	0.1	12.4	1.0
Lamotriginlamotrigin	0.0	6.3	7.7
topiramate	0.0	4.0	-2.8
ethosuximide	0.0	3.8	16.1
phenobarbital	0.0	3.5	-4.1
clonazepam	0.0	1.6	-0.2
oxcarbazepine	0.0	1.8	-2.1
vigabatrin	0.0	1.4	3.4

Figure 5.1.10. Percentage distribution of epileptic pharmaceuticals consumption by therapeutic category and age group (2019)



List of categories

Antibiotics	
Other cephalosporins and penems	ceftaroline, ceftobiprole, ceftolozane/tazobactam
Other antibacterials	clofoctol, daptomycin, fosfomycin, linezolid, tedizolid phosphate
Other quinolones	pipemidic acid, cinoxacin
Amphenicols	chloramphenicol, thiamphenicol
Aminoglycosides	amikacin, gentamicin, netilmicin, streptomycin, tobramycin
Combinations of penicillins (including beta lactamase inhibitors)	amoxicillin/clavulanic acid, ampicillin/sulbactam, piperacillin/tazobactam
Carbapenems	ertapenem, imipenem/cilastatin, meropenem
First-generation cephalosporins	cephalexin, cephazolin
Second-generation cephalosporins	cefaclor, cefmetazole, cefonicid, cefoxitin, cefprozil, cefuroxime
Third-generation cephalosporins	avibactam/ceftazidime, cefditoren, cefixime, cefodizime, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftriaxone
Fourth-generation cephalosporins	cefepime
Imidazole derivatives	metronidazole
Nitrofuran derivatives	nitrofurantoin
Fluroquinolones	ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin
Glycopeptides	dalbavancin, teicoplanin, vancomycin
Macrolides and lincosamides	azithromycin, clarithromycin, clindamycin, erythromycin, josamycin, lincomycin, miocamycin, roxithromycin, spiramycin, telithromycin
Monobactams	aztreonam
Broad-spectrum penicillins	amoxicillin, ampicillin, bacampicillin, piperacillin
Beta-lactamase resistant penicillins	flucloxacillin, oxacillin sodium
Beta-lactamase sensitive penicillins	benzilpenicillin, benzilpenicillina benzathine, G penicillin
Polymyxin	colistimetate
Sulphonamides (alone or in combination)	sulfadiazine, trimetoprim/sulfametoxazole
Tetracyclines	doxycycline, limecycline (tetracycline-levo-methylenelysine), metacycline, minocycline, tetracycline, tigecycline
Anti-epileptics	
Other antiepileptics	brivaracetam, felbamate, lacosamide, lamotrigine, levetiracetam, perampanel, retigabine, stiripentol, sulthiame, topiramate, zonisamide
GABA analogues	gabapentin, pregabalin
Barbiturates and derivatives	barbexaclone, phenobarbital, primidone

Benzodiazepine derivatives	clonazepam
Carboxamide derivatives	carbamazepine, eslicarbazepine, oxcarbazepine, rufinamide
Fatty acid derivatives - valproic acid and derivatives	valproic acid, valproic acid sodium salt/valproic acid, valpromide
Fatty acid derivatives (alone or in combination)	buxamine, buxamine/diazepam, buxamine/phenobarbital/phenytoin, tiagabine, vigabatrin
Succinimide derivatives	ethosuximide
phenyotin (alone or in combination)	Phenytoin sodium, phenytoin/methylphenobarbital, phenytoin/methylphenobarbital/phenobarbital
Respiratory	
Monoclonal antibodies	benralizumab, mepolizumab, omalizumab
Antileukotrienes (LTRAs)	montelukast, zafirlukast
Theophylline-based bronchodilators	ambroxol acefylline, aminophylline, bamifylline, diprophylline, doxophylline, teophylline
Chromones	cromoglicic acid, nedocromil sodium
ICSs	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone
PDE-4 inhibitor	roflumilast
LABAs	clenbuterol, formoterol, olodaterol, salmeterol
LABAs+ICSs	beclomethasone/formoterol, budesonide/formoterol, fluticasone/formoterol, salmeterol/fluticasone
LABAs+LAMAs	aclidinium/formoterol, indacaterol/glycopyrronium, olodaterol/tiotropium, umeclidinium/vilanterol
LAMAs	aclidinium, glycopyrronium, tiotropium, umeclidinium
LAMAs+LABAs+ICSs	glycopyrronium/beclometasone/formoterol, vilanterol/fluticasone/umeclidinium
SABAs	fenoterol, salbutamol, terbutaline
SABAs+ICSs	beclomethasone/salbutamol, fenoterol/ipratropium, salbutamol/flunisolide
SABAs+SAMAs	fenoterol/ipratropium, salbutamol/ipratropium
SAMAs	ipratropium, oxitropium
Injectable steroids	betamethasone, desamethasone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone
Oral steroids	betamethasone, cortisone acetate, deflazacort, desamethasone, hyrocortisone, methylprednisolone, prednisolone, prednisone
Ultra-LABAs	indacaterol
Ultra-LABAs+ICSs	fluticasone/vilanterol

5.2 Pharmaceutical use in the geriatric age

In 2019 the geriatric population aged 65 or over in Italy amounted to approximately 13.8 million people, equal to 23% of the total population. Women were approximately 7.8 million, representing 57% of individuals in this age group.
As expected, pharmaceutical consumption increased with age up to the 80-84 age group, and then decreased slightly in the ≥85 age group (Figure 5.2.1). The highest level of pharmaceutical consumption was recorded in the 80-84 and ≥85 age groups (3,824 and 3,791 DDD/1000 users per day, respectively), with a per user expenditure equal to € 800 and € 765, respectively (Table 5.2.1). In all age groups, a difference between the two genders was registered, with men consuming and spending more than women. Specifically, the greatest difference emerged in the ≥85 age group, where dose consumption among men was 24% higher than in women.
Overall, the average expenditure per user was equal to € 671 (€ 734 for men and € 623 for women) and almost all the geriatric population (98%) received at least one pharmacological prescription during the year. The analysis of pharmaceutical consumption in users who received at least one pharmacological prescription in 2019 showed that the number of DDD/1000 users per day was higher in men than in women (3,341 vs 2,858).
Polypharmacy in this segment of the population was studied using as a proxy the average number of substances prescribed per user.
In 2019 each user took 7.7 different substances on average, with the lowest rate (6.2 substances per user) recorded in the 65-69 age group, and the highest rate (8.8 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. In men, a shift was reported from 6.1 substances taken in the 65-69 age group to 9.1 in subjects aged 85 years or older. A similar trend was also found in women, with 6.3 different substances taken in the 65-69 age group and 8.7 different active ingredients taken by women aged 80 years or over (Table 5.2.2).
Additionally, the breakdown of users by number of different active ingredients (Figure 5.2.2) showed that around 69.4% of elderly users received prescriptions for at least 5 different substances (i.e. polypharmacy) during the reference year and that approximately one subject in three (29.8%) aged 65 years or over took at least 10 different active ingredients. These data indicated that polypharmacy is very frequent in people aged over 65 years, and that there is a higher risk of pharmacological interactions.
The most prescribed therapeutic categories in the geriatric population included medicinal products for the cardiovascular system, antimicrobials for systemic use and medicines for the gastrointestinal system and metabolism. As regards prevalence of use of pharmaceuticals in the geriatric age, medicines for peptic ulcer and gastroesophageal reflux disease ranked first in the 65-74 and 75-84 age groups, with a prevalence of use of 39.5% and 52.4% respectively. They ranked second in the ≥85 age group, with a prevalence of use of 62.3%, with no significant differences between men and women. Antithrombotics were the most used category in the ≥85 age group (prevalence of use of 67.8% - 74.7% in men and 64.5% in women), whereas lipid modifying substances ranked second in the 65-74 age group (prevalence of use of 33% - 34.7% in men and 31.4% in women), and third in the 75-84 age group (prevalence of use of 40.1%). A similar level of prevalence of use (31.9%) was

found in the ≥85 age group. Note 13 specifies that reimbursement by the NHS for primary prevention patients is envisaged only up to 80 years of age. Beyond that age there is no sufficient evidence supporting the advisability of the treatment.
Differences between men and women regarding the prevalence of use of pharmaceuticals reflected the overall frequency of the diseases for which such pharmaceuticals were used in both genders. The pharmacological classes showing the greatest differences between genders were vitamins A and D, which were mainly used by women. For example, in the 65-74 age group the prevalence of use was equal to 10% in men and 43.1% in women, since such vitamins are normally prescribed in the case of osteoporosis. Also in the case of thyroid preparations, the prevalence of use in women was triple compared to men, especially in the 65-84 age group. Antidepressants showed a prevalence of use almost double in women compared to men in all age groups, whereas prostate hypertrophy drugs were almost exclusively used by men (Tables 5.2.3, 5.2.4 and 5.2.5).
To assess the care load in this age group, the prescription pattern was analysed taking into account those users who took 5 or more substances in one year. Only those categories with at least two prescriptions were considered for the purposes of the analysis.
Over the year, 4.3% of users in the 65-74 age group only received antibacterials for systemic use (3.1% men and 5.4% women), whereas 3.9% (5.8% men and 2.2% women) received medicinal products for hypertension and/or heart failure (C07 and C09), lipid-lowering therapy (C10), antithrombotics (B01) and gastro-protective agents (A02). In this age group the most used pharmaceutical categories, both alone or in combination, related to the cardiovascular system, gastrointestinal system, musculo-skeletal system, blood and blood-forming organs and antibacterials (Table 5.2.6). Drug combinations ranked first in the 75-84 age group (prevalence of use of 3.7%), whereas during the year, 2.2% of patients received only pharmaceuticals for the renin-angiotensin system, another 2.2% received only antibacterials for systemic use and 1.5% received only drugs against heartburn (Table 5.2.7). Finally, in the ≥85 age group, antibacterials for systemic use were used by 3.4% of the population (without major differences between men and women), followed by different combinations of antihypertensives, antithrombotics, lipid-lowering agents and gastro-protective agents (Table 5.2.8).

Table 5.2.1. Distribution by age and gender of pharmaceutical prescription in the population aged ≥65 years (2019)

Age group	Per user expenditure			DDD/1000 users/day			Prevalence of use (%)		
	M	W	Tot	M	W	Tot	M	W	Tot
65-69	560	458	506	2,373	1,930	2,141	88	90	89
70-74	684	570	623	3,197	2,645	2,903	97	97	97
75-79	797	674	729	3,598	3,016	3,275	96	95	95
80-84	877	743	800	4,217	3,546	3,824	100	100	100
≥85	878	707	765	4,367	3,510	3,791	100	100	100
Total	**734**	**623**	**671**	**3,341**	**2,858**	**3,068**	**98**	**98**	**98**

M: men; W: women

Figure 5.2.1. Prescription trend in the population aged ≥65 years (DDD/1000 users/day and gross expenditure per user) (2019)

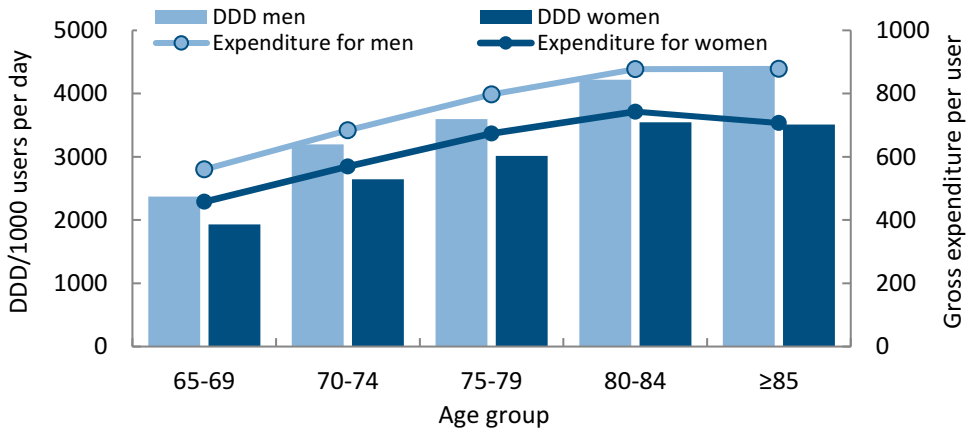


Table 5.2.2. Average number of substances by age and gender (2019)

Age group	Average number of substances		
	Men	Women	Total
65-69	6.1	6.3	6.2
70-74	7.1	7.3	7.2
75-79	8.0	8.1	8.0
80-84	8.7	8.7	8.7
≥85	9.1	8.7	8.8
Total	**7.6**	**7.7**	**7.7**

Figure 5.2.2. Breakdown of users in the population aged ≥65 years by number of different substances (2019)

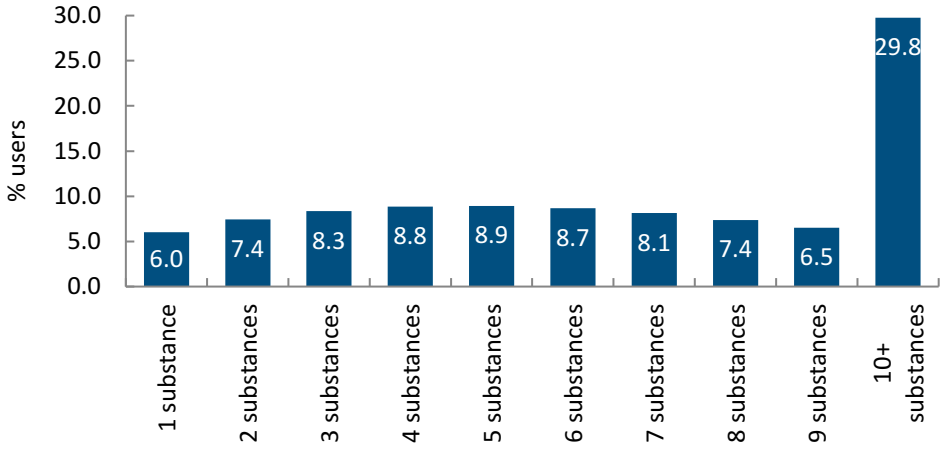


Table 5.2.3. Exposure to pharmaceuticals in the population aged 65-74 years by level III ATC (2019)

Level III ATC	Category	Prevalence of use (%)		
		Men	Women	Total
A02B	Peptic antiulcer and gastroesophageal reflux disease	38.9	40.1	39.5
C10A	Lipid modifying substances, not associated	34.7	31.4	33.0
M01A	Non-steroidal anti-inflammatory and antirheumatic drugs	27.9	35.3	31.8
B01A	Antithrombotics	36.2	26.3	30.9
A11C	Vitamins A and D, including their combinations	10.0	43.1	27.5
C07A	Beta blockers	26.2	25.4	25.8
J01C	Beta-lactam antibacterials, penicillins	24.7	24.8	24.8
H02A	Systemic corticosteroids, not in combination	15.4	18.3	16.9
C09A	Ace inhibitors, not in combination	18.4	13.3	15.7
C09D	Angiotensin II receptor blockers, combinations	14.1	14.9	14.5
A10B	Hypoglycaemic agents, excluding insulins	17.1	12.0	14.4
C09C	Angiotensin II receptor blockers, not in combination	14.5	13.6	14.0
J01M	Quinolone antibacterials	14.5	13.4	13.9
C08C	Selective calcium channel blockers with prevalent vascular effect	15.6	12.3	13.9
J01F	Macrolides, lincosamides and streptogramins	12.4	14.2	13.3
J01D	Other beta-lactam antibacterials	12.8	12.9	12.9
C09B	Ace inhibitors, combinations	13.2	11.9	12.5
G04C	Medicines used in benign prostatic hypertrophy	24.0	0.2	11.4
N06A	Antidepressants	7.4	14.7	11.3
R03B	Other drugs for obstructive airway disorders for aerosol	10.1	9.9	10.0
R03A	Adrenergics for aerosol	9.3	9.4	9.4
H03A	Thyroid preparations	3.5	14.1	9.1
N02A	Opioids	7.2	10.7	9.1
C03C	Diuretics with greater diuretic action	8.9	9.1	9.0
A07A	Intestinal anti-infectives	7.1	8.7	8.0
M04A	Antigout products	10.1	4.7	7.2
J01X	Other antibacterials	3.0	9.4	6.3
R06A	Antihistamines for systemic use	5.1	6.7	6.0
N03A	Anti-epileptics	5.3	6.3	5.8
S01E	Antiglaucoma and miotic preparations	5.1	5.4	5.2

Table 5.2.4. Exposure to pharmaceuticals in the population aged 75-84 years by level III ATC (2019)

Level III ATC	Category	Prevalence of use (%)		
		Men	Women	Total
A02B	Peptic antiulcer and gastroesophageal reflux disease	52.0	52.7	52.4
B01A	Antithrombotics	56.7	47.4	51.4
C10A	Lipid modifying substances, not in combination	42.2	38.4	40.1
C07A	Beta blockers	34.8	35.6	35.2
M01A	Non-steroidal anti-inflammatory and antirheumatic drugs	29.2	36.7	33.5
A11C	Vitamins A and D, including their combinations	15.5	45.7	32.6
J01C	Beta-lactam antibacterials, penicillins	25.0	22.9	23.8
C08C	Selective calcium channel blockers with prevalent vascular effect	22.1	20.1	21.0
C03C	Diuretics with greater diuretic action	20.2	20.4	20.3
C09A	Ace inhibitors, not in combination	23.3	18.0	20.3
H02A	Systemic corticosteroids, not in combination	18.3	19.3	18.9
C09D	Angiotensin II receptor blockers, combinations	16.5	20.1	18.5
C09C	Angiotensin II receptor blockers, not in combination	17.2	18.1	17.7
A10B	Hypoglycaemic agents, excluding insulins	20.1	15.6	17.5
N06A	Antidepressants	12.2	21.0	17.2
J01M	Quinolone antibacterials	18.1	15.1	16.4
G04C	Medicines used in benign prostatic hypertrophy	37.4	0.3	16.3
J01D	Other beta-lactam antibacterials	17.0	15.0	15.9
C09B	Ace inhibitors, combinations	15.4	15.6	15.5
N02A	Opioids	11.2	17.4	14.7
M04A	Antigout products	16.7	9.9	12.8
J01F	Macrolides, lincosamides and streptogramins	12.9	12.6	12.7
R03B	Other drugs for obstructive airway disorders for aerosol	14.3	11.0	12.4
R03A	Adrenergics for aerosol	13.6	10.8	12.0
A07A	Intestinal anti-infectives	8.9	11.2	10.2
H03A	Thyroid preparations	4.3	13.5	9.5
S01E	Antiglaucoma and miotic preparations	9.0	8.4	8.7
N03A	Anti-epileptics	7.7	8.9	8.4
J01X	Other antibacterials	4.4	11.2	8.3
B03B	Vitamin B12 and folic acid	7.9	8.0	8.0

Table 5.2.5. Exposure to pharmaceuticals in the population aged ≥85 years by level III ATC (2019)

Level III ATC	Category	Prevalence of use (%)		
		Men	Women	Total
B01A	Antithrombotics	74.7	64.5	67.8
A02B	Peptic antiulcer and gastroesophageal reflux disease	64.8	61.1	62.3
C07A	Beta blockers	40.1	40.5	40.4
C03C	Diuretics with greater diuretic action	41.0	38.9	39.6
A11C	Vitamins A and D, including their combinations	19.9	38.5	32.4
C10A	Lipid modifying substances, not in combination	37.0	29.4	31.9
M01A	Non-steroidal anti-inflammatory and antirheumatic drugs	28.3	30.5	29.8
J01C	Beta-lactam antibacterials, penicillins	28.3	24.4	25.7
N06A	Antidepressants	19.3	26.8	24.3
C08C	Selective calcium channel blockers with prevalent vascular effect	25.1	23.4	23.9
C09A	Ace inhibitors, not in combination	27.4	22.1	23.8
J01D	Other beta-lactam antibacterials	26.1	22.5	23.7
H02A	Systemic corticosteroids, not in combination	23.3	21.1	21.8
J01M	Quinolone antibacterials	23.6	17.6	19.5
C09C	Angiotensin II receptor blockers, not in combination	18.1	19.3	18.9
N02A	Opioids	15.4	20.4	18.8
M04A	Antigout products	22.7	15.2	17.6
C09D	Angiotensin II receptor blockers, combinations	14.8	17.9	16.9
G04C	Medicines used in benign prostatic hypertrophy	46.7	0.3	15.5
A10B	Hypoglycaemic agents, excluding insulins	17.8	14.2	15.4
R03B	Other drugs for obstructive airway disorders for aerosol	19.6	13.4	15.4
C09B	Ace inhibitors, combinations	14.9	14.8	14.8
R03A	Adrenergics for aerosol	18.4	12.4	14.4
J01F	Macrolides, lincosamides and streptogramins	14.5	12.7	13.3
B03B	Vitamin B12 and folic acid	13.8	12.8	13.1
A07A	Intestinal anti-infectives	11.0	12.5	12.0
J01X	Other antibacterials	7.7	13.6	11.7
B03A	Iron-based preparations	10.5	10.1	10.2
S01E	Antiglaucoma and miotic preparations	11.7	9.2	10.0
N05A	Antipsychotics	8.7	10.4	9.8

Table 5.2.6. Most frequent level II ATC prescription models* in the 65-74 age group population (2019)

ATC	Model	Prevalence of use (%)		
		Men	Women	Total
J01	Antibacterials for systemic use	3.1	5.4	4.3
A02, B01, C07, C09, C10	Pharmaceuticals against heartburn+antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	5.8	2.2	3.9
C09, J01	Pharmaceuticals for the renin-angiotensin system+antibacterials for systemic use	2.9	3.9	3.4
C09	Pharmaceuticals for the renin-angiotensin system	2.2	3.7	3.0
A02, J01	Pharmaceuticals against heartburn+antibacterials for systemic use	2.0	3.6	2.8
A02	Pharmaceuticals against heartburn	1.5	3.3	2.4
A02, C09	Pharmaceuticals against heartburn+pharmaceuticals for the renin-angiotensin system	1.7	3.0	2.4
J01, M01	Antibacterials for systemic use+anti-inflammatory and antirheumatic drugs	1.6	2.6	2.1
A02, B01, C09, C10	Pharmaceuticals against heartburn+antithrombotics+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	2.7	1.6	2.1
C09, C10	Pharmaceuticals for the renin-angiotensin system+lipid modifying substances	1.4	2.7	2.1
B01, C07, C09, C10	Antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	2.7	1.3	2.0
A02, C09, J01	Pharmaceuticals against heartburn+pharmaceuticals for the renin-angiotensin system+antibacterials for systemic use	1.6	2.3	2.0
C09, M01	Pharmaceuticals for the renin-angiotensin system+anti-inflammatory and antirheumatic drugs	1.4	2.3	1.9
J01, R03	Antibacterials for systemic use+drugs for obstructive airway disorders	1.6	2.1	1.8
C07, C09	Beta blockers+pharmaceuticals for the renin-angiotensin system	1.0	2.6	1.8
M01	Anti-inflammatory and antirheumatic drugs	1.2	2.4	1.8
A02, J01, M01	Pharmaceuticals against heartburn+antibacterials for systemic use+anti-inflammatory and antirheumatic drugs	1.3	2.2	1.7
A10, C09, C10	Pharmaceuticals for diabetes+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	2.0	1.5	1.7
C09, J01, M01	Pharmaceuticals for the renin-angiotensin system+antibacterials for systemic use+anti-inflammatory and antirheumatic drugs	1.3	1.9	1.6
A02, M01	Pharmaceuticals against heartburn+anti-inflammatory and antirheumatic drugs	1.1	2.1	1.6

** Calculated among subjects who took 5 or more substances in 2019. Only those categories with at least two prescriptions were considered.*

Table 5.2.7. Most frequent level II ATC prescription models* in the 75-84 age group population (2019)

ATC	Model	Prevalence of use (%)		
		Men	Women	Total
A02, B01, C07, C09, C10	Pharmaceuticals against heartburn+antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	4.4	3.1	3.7
A02, B01, C09, C10	Pharmaceuticals against heartburn+antithrombotics+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	2.6	2.3	2.4
C09	Pharmaceuticals for the renin-angiotensin system	1.5	2.9	2.3
J01	Antibacterials for systemic use	1.9	2.3	2.2
C09, J01	Pharmaceuticals for the renin-angiotensin system+antibacterials for systemic use	1.6	2.4	2.0
A02, C09	Pharmaceuticals against heartburn+pharmaceuticals for the renin-angiotensin system	1.3	2.6	2.0
B01, C07, C09, C10	Antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	2.1	1.7	1.9
A02, B01, C09	Pharmaceuticals against heartburn+antithrombotics+pharmaceuticals for the renin-angiotensin system	1.4	1.8	1.6
A02, B01, C07, C09	Pharmaceuticals against heartburn+antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system	1.1	1.8	1.5
B01, C09, C10	Antithrombotics+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	1.4	1.5	1.5
C09, C10	Pharmaceuticals for the renin-angiotensin system+lipid modifying substances	0.8	2.0	1.5
A02	Pharmaceuticals against heartburn	1.1	1.8	1.5
C09, M01	Pharmaceuticals for the renin-angiotensin system+anti-inflammatory and antirheumatic drugs	0.9	1.9	1.5
C07, C09	Beta blockers+pharmaceuticals for the renin-angiotensin system	0.6	2.0	1.4
A02, J01	Pharmaceuticals against heartburn+antibacterials for systemic use	1.1	1.5	1.3
A02, C09, J01	Pharmaceuticals against heartburn+pharmaceuticals for the renin-angiotensin system+antibacterials for systemic use	0.9	1.6	1.3
A02, C09, C10	Pharmaceuticals against heartburn+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	0.8	1.7	1.3
A02, C09, M01	Pharmaceuticals against heartburn+pharmaceuticals for the renin-angiotensin system+anti-inflammatory and antirheumatic drugs	0.7	1.7	1.3
A02, B01, C07, C08, C09, C10	Pharmaceuticals against heartburn+antithrombotics+beta blockers+calcium channel blockers+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	1.4	1.1	1.3
B01, C07, C09	Antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system	1.0	1.5	1.3

***** *Calculated among subjects who took 5 or more substances in 2019. Only those categories with at least two prescriptions were considered.*

Table 5.2.8. Most frequent level II ATC prescription models* in the ≥85 age group population (2019)

ATC	Model	Prevalence of use (%)		
		Men	Women	Total
J01	Antibacterials for systemic use	3.3	3.4	3.4
A02, B01, C09	Pharmaceuticals against heartburn+antithrombotics+pharmaceuticals for the renin-angiotensin system	1.8	2.5	2.3
A02, B01, C07, C09, C10	Pharmaceuticals against heartburn+antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	2.2	2.1	2.1
C09	Pharmaceuticals for the renin-angiotensin system	1.3	2.3	2.0
A02, B01, C07, C09	Pharmaceuticals against heartburn+antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system	1.1	2.3	1.9
A02, B01, C09, C10	Pharmaceuticals against heartburn+antithrombotics+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	1.9	1.8	1.8
C09, J01	Pharmaceuticals for the renin-angiotensin system+antibacterials for systemic use	1.3	1.9	1.7
A02, C09	Pharmaceuticals against heartburn+pharmaceuticals for the renin-angiotensin system	1.0	2.0	1.7
A02, B01, C03, C07, C09	Pharmaceuticals against heartburn+antithrombotics+diuretics+beta blockers+pharmaceuticals for the renin-angiotensin system	1.1	1.8	1.6
A02	Pharmaceuticals against heartburn	1.3	1.6	1.5
B01, C09	Antithrombotics+pharmaceuticals for the renin-angiotensin system	1.3	1.6	1.5
A02, B01, C03, C07, C09, C10	Pharmaceuticals against heartburn+antithrombotics+diuretics+beta blockers+pharmaceuticals for the renin-angiotensin system+lipid modifying substances	1.4	1.3	1.3
B01, C07, C09	Antithrombotics+beta blockers+pharmaceuticals for the renin-angiotensin system	0.9	1.5	1.3
A02, J01	Pharmaceuticals against heartburn+antibacterials for systemic use	1.2	1.4	1.3
A02, B01, C09, J01	Pharmaceuticals against heartburn+antithrombotics+pharmaceuticals for the renin-angiotensin system+antibacterials for systemic use	1.0	1.4	1.3
B01, C03, C07, C09	Antithrombotics+diuretics+beta blockers+pharmaceuticals for the renin-angiotensin system	0.9	1.4	1.2
B01, J01	Antithrombotics+antibacterials for systemic use	1.1	1.3	1.2
B01	Antithrombotics	1.1	1.2	1.2
A02, B01, C03, C07	Pharmaceuticals against heartburn+antithrombotics+diuretics+beta blockers	0.8	1.3	1.1
A02, B01, J01	Pharmaceuticals against heartburn+antithrombotics+antibacterials for systemic use	0.9	1.2	1.1

** Calculated among subjects who took 5 or more substances in 2019. Only those categories with at least two prescriptions were considered.*

Pharmaceutical interactions

In the population aged 65 years or over, the presence of 8 different drug combinations recognized as at high risk of pharmaceutical interaction was evaluated. To this end, for each user, the days of exposure (based on DDD) were calculated in the period from 1 January to 31 December 2019 and the subjects identified showed a concomitant (overlapping) use equal to at least 10% of the total exposure period (Table 5.2.9).
The concomitant use of allopurinol and ACE inhibitors or ARBs may entail an increased risk of hypersensitivity, especially in case of pre-existing renal damage. In the ≥65 age group population, this drug combination was observed in 8.1% of subjects treated with ACE inhibitors or ARBs, with a frequency approximately 1.6 times higher in men than in women (10.2% vs 6.4%) and increasing with age (from 6.6% in the 65-74 age group to 10.2% in the ≥85 age group) and by geographical area (North 7.1%, Centre 9.2% and South 8.8%).
In patients with heart failure, amiodarone may reduce the clearance of S-carvedilol by inhibiting CYP2C9. In 2019 4% of patients taking carvedilol was treated also with amiodarone, with no significant difference by geographical area. The age trend showed a peak of 4.6% in the 75-84 age group and then a decrease to 3.7% in the subsequent age group. The frequency recorded in men was more than double that recorded in women (5.7% vs 2.5%) and this value did not vary according to the geographical area.
The co-administration of quinolones and oral anti-diabetics in elderly patients may cause hypoglycaemia and, more rarely, hyperglycaemia. This drug combination in the Italian population is limited. Only 1% of subjects aged 65 years or over treated with sulfonylureas also received quinolones. There were no significant differences by gender and age, with higher values recorded for subjects aged 85 years or over (1.3%). The difference is more pronounced at territorial level, with Southern regions registering a prevalence that was twice that of the Northern regions (1.5% vs 0.6%).
The combination of corticosteroids and NSAIDs or anticoagulants/antiplatelet drugs may involve a higher risk of serious complications in the upper gastrointestinal tract, and therefore may require the use of proton-pump inhibitors, as envisaged by AIFA Note 1. 32.5% of patients treated with corticosteroids also received a prescription for NSAIDs or anticoagulants/antiplatelet drugs. The highest prevalence value was recorded in the South (35.7%) and was equal to 28.2% in the North. There are no differences between men and women, although a higher frequency is recorded in subjects aged 85 years or over (36%).
The concomitant use of corticosteroids and quinolones may increase the risk of Achilles tendon rupture, a warning that is also included in the AIFA information notice issued in April 2019, which reported the safety data assessed by EMA and the restrictions on the use of such pharmaceuticals. Among corticosteroid users, 12.3% received a prescription for quinolones, with no significant differences by gender and geographical area. The highest value was recorded in the ≥85 age group.
Subjects treated with ACE inhibitors and potassium-sparing diuretics may face an increased risk of hyperkalaemia, which may cause heart rhythm disturbances. The use of potassium-sparing diuretics in subjects treated with ACE inhibitors or ARBs recorded a prevalence of 2.9%, with a higher frequency in men than in women (3.2% vs 2.7%), reaching values about twice as high in subjects belonging to the ≥85 age group as in the 65-74 age group (4.3% vs 2%).

Table 5.2.9. Indicators of interaction risk in the population aged ≥65 years (2019)

	Total (≥65 years)		North (%)	Centre (%)	South (%)
	no.	%			
Use of allopurinol among users of ACE inhibitors or ARBs *	**8,573,425**	**8.1**	**7.1**	**9.2**	**8.8**
65-74 years		6.6	6.0	10.0	10.0
75-84 years		9.0	7.7	10.0	10.0
≥85 years		10.0	8.3	11.2	11.5
Men		10.2	9.4	11.9	10.3
Women		6.4	5.2	7.0	7.5
Use of amiodarone among carvedilol users*	**351,753**	**4.0**	**3.6**	**4.6**	**4.1**
65-74 years		3.7	3.4	5.3	4.6
75-84 years		4.6	4.1	5.3	4.6
≥85 years		3.7	3.2	3.8	4.0
Men		5.7	5.2	6.4	5.8
Women		2.5	2.1	2.7	2.7
Use of quinolones among sulfonylurea users*	**462,462**	**1.0**	**0.6**	**1.0**	**1.5**
65-74 years		0.9	0.5	1.0	1.5
75-84 years		1.0	0.6	1.0	1.5
≥85 years		1.3	0.9	1.3	2.0
Men		1.1	0.7	1.1	1.7
Women		0.9	0.5	1.0	1.3
Use of NSAIDs or anticoagulants/antiplatelet drugs among corticosteroid users*	**3,757,353**	**32.5**	**28.2**	**32.7**	**35.7**
65-74 years		29.3	24.3	34.7	37.7
75-84 years		34.3	30.1	34.7	37.7
≥85 years		36.0	32.4	36.7	38.3
Men		33.4	29.4	33.7	36.1
Women		31.9	27.3	31.9	35.5
Use of corticosteroids among quinolone users*	**2,462,688**	**12.3**	**10.3**	**13.0**	**13.5**
65-74 years		11.8	10.2	13.0	13.5
75-84 years		12.3	10.3	13.0	13.5
>85 years		13.5	10.8	14.4	15.0
Men		12.3	10.1	12.8	13.8
Women		12.3	10.6	13.2	13.2
Use of potassium-sparing diuretics among users of ACE inhibitors or ARBs*	**8,108,837**	**2.9**	**2.7**	**3.2**	**2.9**
65-74 years		2.0	1.9	3.3	3.3
75-84 years		3.1	2.9	3.3	3.3
≥85 years		4.3	4.1	4.9	4.3
Men		3.2	3.1	3.4	3.1
Women		2.7	2.4	3.0	2.8

* Concomitant use was calculated for prevalent users in the year 2019.

The long QT syndrome is mainly due to patient-dependent factors, such as old age and certain electrolytic imbalances, or it is drug-induced. Such condition increases the risk of developing ventricular arrhythmia and sudden death. 6.4% of the population aged ≥65 years was treated with at least 2 pharmaceuticals that may cause QT prolongation, with marked differences at territorial level, varying from 4.3% in the North to 9.2% in the South and on the islands. Significant differences were also found among the different age groups, with a prevalence of use equal to 8.5% in the ≥85 age group, reaching 12.1% in the same age group in Southern regions (Table 5.2.10).
The use of ACE inhibitors and/or ARBs in combination with NSAIDs, coxib or spironolactone may seriously impair the renal function and/or cause hyperkalaemia. Given the increased risk of renal failure, the combined use of these pharmaceuticals should be avoided. Over one fifth of the population aged ≥65 years was prescribed these pharmaceuticals at least once during 2019, with Southern regions registering a prevalence that was more than double compared with Northern regions (32.6% vs 14.5%). In all age groups, a higher frequency was recorded in women than in men. In the 75-84 age group, prevalence reached approximately 25%, amounting to 36.5% in the South.

Table 5.2.10. Prevalence of use (%) of therapeutic combinations at high risk of interaction in the population aged ≥65 years (2019)

	Total (≥65 years)		North (%)	Centre (%)	South (%)
	no.	%			
Concomitant use* of 2 or more pharmaceuticals causing QT prolongation^	**884,417**	**6.4**	**4.3**	**7.1**	**9.2**
65-74 years		5.4	3.5	5.7	7.8
75-84 years		6.9	4.7	7.8	9.9
≥85 years		8.5	5.6	10.0	12.1
Men		6.3	4.1	7.0	9.0
Women		6.5	4.4	7.3	9.3
Concomitant use* of 2 or more pharmaceuticals increasing the risk of renal failure°	**3,029,865**	**22.0**	**14.5**	**22.9**	**32.6**
65-74 years		19.6	12.4	19.7	29.7
75-84 years		24.9	17.1	26.2	36.5
≥85 years		22.7	15.0	24.8	33.8
Men		20.0	12.9	21.0	29.8
Women		23.5	15.7	24.3	34.8

* Concomitant use was calculated for prevalent users in the year 2019.

^ Macrolides (J01FA), quinolones (J01MA), antiarrhythmic agents (C01B), sotalol (C07AA07), citalopram or escitalopram (N06AB04 or N06AB10), fluconazole (J02AC01), domperidone (A03FA03), chlorpromazine (N05AA), haloperidol (N05AD01).

° NSAIDs or coxib (M01A or M01B), spironolactone (C03DA01), ACE inhibitors (C09A or C09B), ARBs (C09C or C09D).

Section 6

Medicines monitoring registries and managed entry agreements

6.1 Medicines monitoring registries

AIFA Monitoring Registries are an information tool that, through a web-based platform, manages the prescription and dispensation of medicinal products reimbursed by the Italian NHS, in line with indications authorised by the European Medicines Agency (EMA) and within the limits set by AIFA's advisory committees, the Technical-Scientific Committee (CTS) and the Price and Reimbursement Committee (CPR). Therefore, AIFA registries ensure supervision on the appropriate use of medicinal products, in accordance with both regulatory constraints arising from the authorisation and the conditions for eligibility for reimbursement laid down by AIFA's advisory committees.
AIFA registries also allow to access relevant and often very expensive treatments in a uniform way across the national territory, regardless of the patient's location or place of residence.
Additionally, they also have an impact on the national pharmaceutical expenditure. This is because they allow the application of specific reimbursement conditions to a medicinal product for a given therapeutic indication, as agreed between AIFA and the relevant pharmaceutical company in a Managed Entry Agreement (MEA). In other words, AIFA Monitoring Registries are a tool for enforcing economic agreements, some which are based on the efficacy of the medicinal product in clinical practice.
In this context, in line with regulations introduced since 2015, AIFA registries are also used to allocate among regions the economic resources earmarked by the State for financing innovative medicines.
Last but not least, AIFA registries are useful in assessing the clinical and therapeutic impact of medicines in the specific Italian healthcare setting. Therefore, registries support the collection of technical and scientific information that is necessary for informing the decision making process of physicians and healthcare professionals.

Types of monitoring

AIFA Monitoring Registries allow a number of different types of monitoring. First of all, traditional registries ensure a detailed monitoring of how pharmaceuticals are used in clinical practice, from eligibility criteria to treatment outcome, including the application of a MEA. Other registries monitor medicines reimbursed by the NHS according to Law 648/96, that is to say, before a medicine is actually authorised (so-called Law 648/96 registries). Web-based therapeutic plans (TP) focus on aspects associated with medicine prescription, eligibility criteria and, in some cases, with the assessment and re-assessment of treatment outcomes. At the end of 2019 simplified multidrug monitoring registries were introduced, which are a tool for prescribing and monitoring the use of multiple medicinal products within the same therapeutic indication. This monitoring registry works in a similar way as web-based TPs, and application of specific reimbursement criteria is guaranteed by pre-defined eligibility to patient treatment.

AIFA registries: legal basis

Since 2012, AIFA monitoring registries have been an integral part of the National Health Service Information System[1]. Subsequently, further legislation was introduced[2] in order to assign different purposes to registries: evaluating medicines' efficacy to support the renegotiation of pharmaceuticals subject to monitoring; monitoring expenditure for innovative medicines; allocating resources to regions for the purchase of innovative medicines[3] , as well as to support the monitoring of avoidable costs in the healthcare sector.

AIFA registries and the regions

AIFA Monitoring Registries are an infrastructure intended to support the regions. Through them, the regions coordinate their health structures and, consequently, certify both physicians for the prescription of medicines subject to monitoring, and pharmacists for their dispensation.
When managing the infrastructure, regions decide on the authorisation of prescribing centres. Subsequently, managers of local health authorities to which such centres belong, authorise physicians and pharmacists to use the platform. Qualified physicians and pharmacists are responsible for the correct and timely entry of data collected in the AIFA Monitoring Registries.

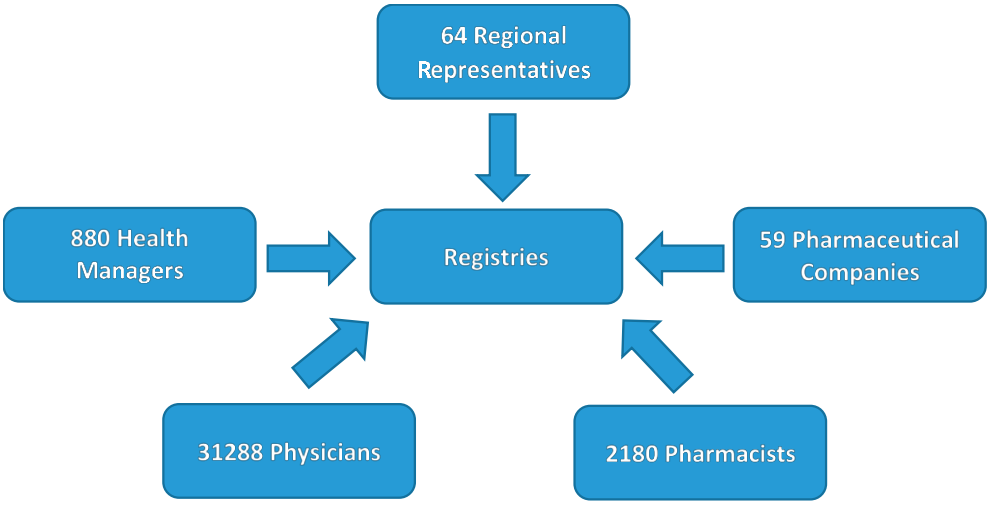
The collaborative network of AIFA registries

AIFA Monitoring Registries are a collaborative network that allows the exchange of information between AIFA, regions, healthcare structures, physicians, pharmacists and pharmaceutical companies. The network comprises approximately 1,532 active health facilities (with at least one treatment started in 2019), located in every Region, 64 regional representatives, 880 health managers, 31,288 physicians registered with the platform and 2,044 pharmacists (Figure 6.1). The network also includes 56 pharmaceutical companies holding at least one monitoring registry managed through the AIFA platform. Through their dedicated profile, pharmaceutical companies can interact with each pharmacy of the accredited health facilities for registries of medicinal products for which they hold an MA and that are reimbursed in compliance with a registry-based Managed Entry Agreement (MEA).
Within such network, the AIFA Monitoring Registry Office is responsible for creating a monitoring file and ensuring its approval and testing within the AIFA web platform, as well

[1] Article 15, paragraph 10, Law-Decree 95/2012, converted with amendments into Law 135 of 7 August 2012.
[2] Law 125/2015, Law 232/2016, Law 205/2017, Law 302/2018.
[3] Ministerial decree dated 9 October 2015 published in the Italian Official Journal no. 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 no. 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".

as for managing the interaction with stakeholders with regard to activities connected with the registries and related report production.

Figure 6.1.1 Personnel involved in the registry network in 2019



Access to and structure of AIFA registries

AIFA Monitoring Registries can be accessed through https://servizionline.aifa.gov.it/. The user is required to select "Registries for pharmaceuticals subject to monitoring" and enter credentials or register, in case of first access. In general, through the platform, accredited physicians are able to navigate to the pre-compiled therapeutic indication for which the medicinal product subject to monitoring is to be prescribed. Physicians can then select the medicinal product they intend to prescribe or, in case more medicinal products subject to monitoring are available for the same therapeutic indication, they can select the appropriate product from a list.
Given their modularity, Monitoring Registries can collect clinical, therapeutic and administrative data. Physicians and pharmacists are required to enter the following information:

1. Patient details (common to all registries and/or therapeutic plans)
2. Eligibility and clinical data
3. Prescription data (medicinal product requested)
4. Distribution of medicinal products
5. Follow-up (re-evaluation)
6. End of treatment data
7. Pregnancy (for medicinal products with a Risk Management Plan).

As previously indicated, in addition to traditional registries, web-based TPs are available and can be used only by specialised physicians. In that case, the following information needs to be entered:

1. Patient details (common to all registries and/or therapeutic plans)
2. Eligibility and clinical data
3. Prescription data (medicinal product requested)
4. Follow-up (re-evaluation)
5. End of treatment data

As at 31 December 2019, 194 Monitoring Registries (including the respective updated versions) were available online. During 2019, 61 registries and web-based TPs were activated online.

The real-time updated list of active and closed registries of medicinal products subject to monitoring is available at the following link: http://www.aifa.gov.it/content/lista-aggiornata-dei-registri-e-dei-piani-terapeutici-web-based.

Data relating to Monitoring Registries

Table 6.1.1. Summary data of Monitoring Registries available on the web platform: cumulative trend 2017-2019

	No.			Δ (%) 19-18
	2017	2018	2019	
Registries	151	179	194	8.4
Web-based TPs	16	16	18	12.5
Treatments	1,657,272	2,164,492	2,705,225	25.0
Patients	1,439,656	1,857,894	2,285,899	23.0

In 2019 the highest number of patients was included in the registry of pharmaceuticals belonging to ATC B category "Blood and blood-forming organs" (mainly new oral anticoagulants), and of antineoplastic and immunomodulating agents (Table 6.1.2 and following). Considering the percentage change of new patients per ATC category compared to 2018, it should be noted that ATC C category for "Cardiovascular system" registered approximately a 300% increase.

Table 6.1.2. Number of patients* per ATC category (level I) in the period 2017-2019

ATC code	No. of patients			Incidence (%)			Δ%	
	2017	2018	2019	2017	2018	2019	18-17	19-18
A	59	64	64	0.0	0.0	0.0	8.5	0.0
B	769,774	1,019,625	1,278,255	51.7	52.7	53.2	32.5	25.4
C	4,445	10,919	45,574	0.3	0.6	1.9	145.6	317.4
D	1,919	2,292	5,421	0.1	0.1	0.2	19.4	136.5
H	183	217	237	0.0	0.0	0.0	18.6	9.2
J	109,510	164,386	200,444	7.4	8.5	8.3	50.1	21.9
L	291,279	346,900	408,983	19.6	17.9	17.0	19.1	17.9
M	144,013	184,136	227,310	9.7	9.5	9.5	27.9	23.4
N	7,804	8,943	11,437	0.5	0.5	0.5	14.6	27.9
R	2,814	3,178	3,358	0.2	0.2	0.1	12.9	5.7
S	157,845	191,999	222,051	10.6	9.9	9.2	21.6	15.7
V	272	326	521	0.0	0.0	0.0	19.9	59.8
Total	**1,489,917**	**1,932,985**	**2,403,655**	**100**	**100**	**100**	**29.7**	**24.3**

* The table reports the number of *naïve* patients per ATC category. For each patient, only the first treatment with a medicinal product belonging to an ATC category (level I) is calculated.

Table 6.1.3. Number of registries and TPs active per ATC category (level I) in the period 2017-2019

ATC code	No. of registries			No. of TPs			Total		
	2017	2018	2019	2017	2018	2019	2017	2018	2019
A	2	2	3	0	0	0	2	2	3
B	2	3	3	9	11	11	11	14	14
C	4	4	6	0	0	1	4	4	7
D	1	2	2	0	0	0	1	2	2
H	1	1	1	0	0	0	1	1	1
J	22	24	13	2	0	0	24	24	13
L	101	123	151	0	0	0	101	123	151
M	2	2	3	3	3	3	5	5	6
N	3	4	4	1	1	2	4	5	6
R	3	3	4	1	1	1	4	4	5
S	9	11	2	0	0	0	9	11	2
V	1	0	2	0	0	0	1	0	2
Total	**151**	**179**	**194**	**16**	**16**	**18**	**167**	**195**	**212**

Table 6.1.4. Number of enrolled patients* per ICD-11 category (period 2017-2019)
ICD: International Classification of Diseases

ICD 11	No. of patients			Incidence (%)			Δ%	
	2017	2018	2019	2017	2018	2019	18-17	19-18
Infectious and parasitic diseases	108,436	163,064	198,304	7.4	8.6	8.4	50.4	21.6
Neoplasms	264,958	312,160	361,355	18.0	16.4	15.3	17.8	15.8
Diseases of the blood and blood-forming organs	3,639	4,602	5,842	0.2	0.2	0.2	26.5	26.9
Diseases of the immune system	934	1,213	1,638	0.1	0.1	0.1	29.9	35.0
Endocrine, nutritional or metabolic diseases and immune disorders	4,611	9,075	14,946	0.3	0.5	0.6	96.8	64.7
Diseases of the nervous system	8,967	10,695	11,838	0.6	0.6	0.5	19.3	10.7
Diseases of the visual system	174,153	212,353	246,561	11.9	11.1	10.5	21.9	16.1
Diseases of the circulatory system	766,904	1,017,328	1,294,744	52.2	53.4	54.9	32.7	27.3
Diseases of the respiratory system	7,526	9,754	12,276	0.5	0.5	0.5	29.6	25.9
Diseases of the digestive system	2,922	3,117	3,119	0.2	0.2	0.1	6.7	0.1
Diseases of the skin	1,919	2,299	5,476	0.1	0.1	0.2	19.8	138.2
Diseases of the musculoskeletal system or connective tissue	124,489	160,600	200,119	8.5	8.4	8.5	29.0	24.6
Diseases of the genitourinary system	37	194	348	0.0	0.0	0.0	424.3	79.4
Mental and behavioural disorders	-	-	1,645	0.0	0.0	0.1	-	-
Total	**1,469,495**	**1,906,454**	**2,358,211**	**100**	**100**	**100**	**29.7**	**23.7**

* The table reports the number of *naïve* patients per ICD-11 code. For each patient, only the first treatment with a medicinal product belonging to a specific ICD-11 is calculated.

Demographic characteristics of treated patients included in AIFA Monitoring Registries and web-based TPs

Regulatory decisions are based on information obtained by taking into account the characteristics of the population enrolled and studied in clinical trials. In the actual clinical practice, the benefit-risk profile of the approved medicinal product may vary in the treated population.
In this respect, in 2015 the European Medicines Agency (EMA) began to draw up a document, adopted by the CHMP in January 2018, which intended to define how to assess the degree of fragility of the elderly population with a view to adequately include it in clinical trials. Although the elderly are among the major users of medicines, they are not always enrolled in these studies, since they are affected by concomitant (often chronic) conditions. In terms of efficacy and safety, the effects of pharmaceuticals on the population aged ≥ 65 may vary considerably compared to the younger adult population. Therefore, the collection and analysis of clinical practice data (real world data) is essential also for any reassessment. The post-marketing monitoring via AIFA registries is an important information base.
The percentage breakdown of treatments based on gender and age is reported below. As data show, the high number of patients aged 60 or above is undeniable. Specifically, tables 6.1.5 and 6.1.6 show the breakdown of treatments by age and gender, separated by Registries and Therapeutic Plans. As for registries, the highest number of treatments was recorded in the 70-79 age group, for both women and men. For therapeutic plans, the highest number of treatments was observed in the 70-79 age group for men and in the ≥80 age group for women. In the breakdown by age group and ATC code, more than one million patients are in code B and in the 60+ age groups, including about 300,000 patients initially treated with code L medicines. As regards code J, about half of the patients was below 60 years of age at the start of treatment (Table 6.1.7).

Table 6.1.5. Number of patients by age group and gender included in the registries (2019)

Age group	Men		Women	
	No. of patients	Incidence (%)	No. of patients	Incidence (%)
<40	18,999	4.1	15,825	3.8
40-49	41,534	9.0	32,608	7.9
50-59	86,276	18.8	67,797	16.4
60-69	113,703	24.7	96,720	23.4
70-79	137,982	30.0	127,467	30.8
≥80	61,299	13.3	73,087	17.7
Total	**459,793**	**100**	**413,504**	**100**

Table 6.1.6. Number of patients by age group and gender included in the therapeutic plans (2019)

Age group	Men		Women	
	No. of patients	Incidence (%)	No. of patients	Incidence (%)
<40	9,088	1.3	7,206	0.9
40-49	18,839	2.7	16,605	2.0
50-59	53,043	7.7	46,926	5.6
60-69	133,584	19.4	127,669	15.3
70-79	247,117	35.9	282,392	33.9
≥80	227,515	33.0	353,390	42.4
Total	**689,186**	**100**	**834,188**	**100**

Table 6.1.7. Number of patients* per ATC category (level I) up to 2019

Level I ATC	<40			40-49			50-59			60-69			70-79			≥80		
	M	W	Tot	M	W	Tot	M	W	Tot	M	W	Tot	M	W	Tot	M	W	Tot
A	8	54	62	0	1	1	-	1	1	0	0	0	0	0	0	0	0	0
B	5,927	7,472	13,399	9,928	17,087	27,015	22,405	47,561	69,966	78,297	12.2696	20.0993	213,492	230,967	444459	306642	215781	522423
C	228	748	976	619	2,340	2,959	1,835	6,051	7,886	3,363	9,369	12,732	3,927	10,101	14028	2380	4613	6993
D	907	1,309	2,216	424	562	986	575	534	1,109	319	366	685	119	197	316	43	66	109
H	52	20	72	59	9	68	32	12	44	24	8	32	14	2	16	5	0	5
J	4,636	9,094	13,730	8,856	23,276	32,132	18,077	39,097	57,174	19,115	18,849	37,964	27,419	18,667	46086	8051	5307	13358
L	7,116	5,295	12,411	17,689	11,221	28,910	35,838	30,313	66,151	51,418	62,529	11.3947	56,137	77,150	133287	26039	28238	54277
M	1,738	627	2,365	6,818	1,100	7,918	24,438	3,518	27,956	49,166	7,926	57,092	69,872	10,463	80335	45478	6166	51644
N	942	2,045	2,987	1,748	1,291	3,039	1,937	1,318	3,255	947	760	1,707	226	189	415	19	15	34
R	310	367	677	43	53	96	99	148	247	217	665	882	172	940	1112	46	298	344
S	1,217	1,152	2,369	2,766	3,446	6,212	9,016	11,038	20,054	21,827	24,821	46,648	42,504	37,475	79979	39905	26884	66789
V	5	3	8	17	13	30	27	48	75	37	117	154	28	151	179	8	67	75
Tot	**23,086**	**28,186**	**51,272**	**48,967**	**60,399**	**109,366**	**114,279**	**139,639**	**253,918**	**224,730**	**248,106**	**472,836**	**413,910**	**386,302**	**800,212**	**428,616**	**287,435**	**716,051**

* The table reports the number of *naïve* patients per ATC category. For each patient, only the first treatment with a medicinal product belonging to an ATC category (level I) is calculated.

Chronic C hepatitis

In December 2014, AIFA introduced monitoring registries for the 2nd generation of Direct Antiviral Antigens (DAAs) indicated for the treatment of chronic hepatitis C (CHC). As of 31 December 2019 a registry was developed and data collection started for monitoring the appropriateness and implementation of MEAs for the following DAAs:

Active ingredient (brand name)	Registry activation date	Genotype
Sofosbuvir (Sovaldi)	6 December 2014	All genotypes
Simeprevir (Olysio)	24 February 2015	1 and 4
Daclatasvir (Daklinza)	5 May 2015	1,2,3 and 4
Ledipasvir/sofosbuvir (Harvoni)	14 May 2015	1,3,4
Ombitasvir/paritaprevir/ritonavir (Viekirax) and dasabuvir (Exviera)	24 May 2015	1 and 4
Elbasvir/grazoprevir (Zepatier)	4 February 2017	1 and 4
Sofosbuvir/velpatasvir (Epclusa)	27 April 2017	All genotypes
Glecaprevir/pibrentasvir (Maviret)	28 September 2017	All genotypes
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)	19 April 2018	All genotypes

With the aim of facilitating access to new therapies for all chronic hepatitis C patients while ensuring the sustainability of the NHS, at the beginning it was necessary to identify an access strategy based on the treatment clinical urgency. As a result, priority reimbursement criteria were developed on the basis of the results of the work of the Hepatitis C Technical Table, set up at the Agency. In 2017, as part of the HCV infection eradication plan in Italy, AIFA redefined the treatment criteria for chronic hepatitis C (AIFA decision no. 500/2017 published in OJ no. 75 of 30 March 2017). The 11 criteria, stemming from the dialogue with scientific societies and shared with AIFA's Technical-Scientific Committee, allowed to treat patients for whom therapy was indicated and appropriate. In the same year, AIFA gave the possibility to include in the Registries patients who needed to be re-treated with a combination of at least 2nd generation of Direct Antiviral Antigens (DAAs), after treatment regimens without interferon had failed. Lastly, on 17 October 2019, an additional treatment criterion (so-called "criterion 12") was added for patients unable to undergo hepatic biopsy and/or fibroscan, and for whom the availability of certain clinical laboratory scores such as APR (AST to Platelet Ratio Index) or Fib-4 (Fibrosis 4 Score) was considered sufficient for the preliminary assessment of the hepatic impairment (cirrhosis/non cirrhosis). At the same time, the definition of criterion 10 was modified.
The 12 treatment criteria are described below.

Criterion 1: Patients with Child A or B Class cirrhosis and/or HCC with complete response to surgical or loco-regional resective therapies not eligible for liver transplantation where liver disease is crucial for prognosis.
Criterion 2: Recurrent HCV-RNA positive hepatitis in the transplanted liver in a clinically stable patient, with optimal levels of immunosuppression.

Criterion 3: Chronic hepatitis with severe extra-hepatic HCV-related manifestations (cryoglobulinemia syndrome with organ damage, B-cell lymphoproliferative syndromes, renal failure).
Criterion 4: Chronic hepatitis with METAVIR F3 fibrosis (or Ishak equivalent).
Criterion 5: Patient on a transplant waiting list for liver with MELD <25 cirrhosis and/or with an HCC within the Milan criteria, with waiting times of at least 2 months.
Criterion 6: Chronic hepatitis after solid organ (non-liver) or bone marrow transplantation into a clinically stable patient with optimal immunosuppression levels.
Criterion 7: Chronic hepatitis with METAVIR F2 fibrosis (or Ishak equivalent) and/or comorbidity at risk of progression of liver injury [HBV co-infection, HIV co-infection, chronic non-viral liver disease, pharmacologically-treated diabetes mellitus, obesity (body mass index ≥30 kg/m^2), haemoglobinopathies and congenital coagulopathies].
Criterion 8: Chronic hepatitis with METAVIR F0-F1 fibrosis (or Ishak equivalent) and/or comorbidity at risk of liver injury progression [HBV co-infection, HIV co-infection, chronic non-viral liver disease, pharmacologically-treated diabetes mellitus, obesity (body mass index ≥30 kg/m^2), haemoglobinopathies and congenital coagulopathies].
Criterion 9: Infected healthcare professionals.
Criterion 10: Chronic hepatitis or liver cirrhosis in patients with chronic renal failure receiving dialysis.
Criterion 11: Chronic hepatitis in a patient on transplant waiting list for solid organ (non-liver) or bone marrow transplantation.
Criterion 12: Chronic hepatitis or liver cirrhosis in patients who cannot access liver biopsy and/or fibroscan for socio-assistance reasons.

At 31 December 2019, 202,113 treatments were started in total (Figure 6.1.2). With 70,417 treatments, criterion 1, patients with cirrhosis, was the largest, followed by criterion 8 (56,273 treatments), criterion 4 (36,937 treatments) and criterion 7 (29,139 treatments). Worthy of note are also the 2,429 treatments in patients who had already undergone liver transplantation and had recurrent HCV-positive hepatitis, criterion 2 (Figure 6.1.3). 2018 recorded the largest number of started treatments (55,954) compared to the previous years (2014: 31; 2015: 31,042; 2016: 33,698; 2017: 44,967) and compared with 2019 (36,421). The most used criteria in 2019 were, in descending order, 8, 7 and 1 (16,821; 7,535; 7,115 treatments, respectively). Figures 6.1.4 and 6.1.5 show the monthly trend of treatments started at national level by single criterion (criteria 1, 4, 7 and 8 and the other criteria, respectively). Table 6.1.8 reports the treatments started during 2019 by single treatment region and by criterion. This table shows that Lombardy and Campania are the regions with the highest number of annual treatments, followed by Emilia Romagna, Piedmont, Lazio and Tuscany.

Figure 6.1.2. Number of started treatments as at 2019 (cumulative)

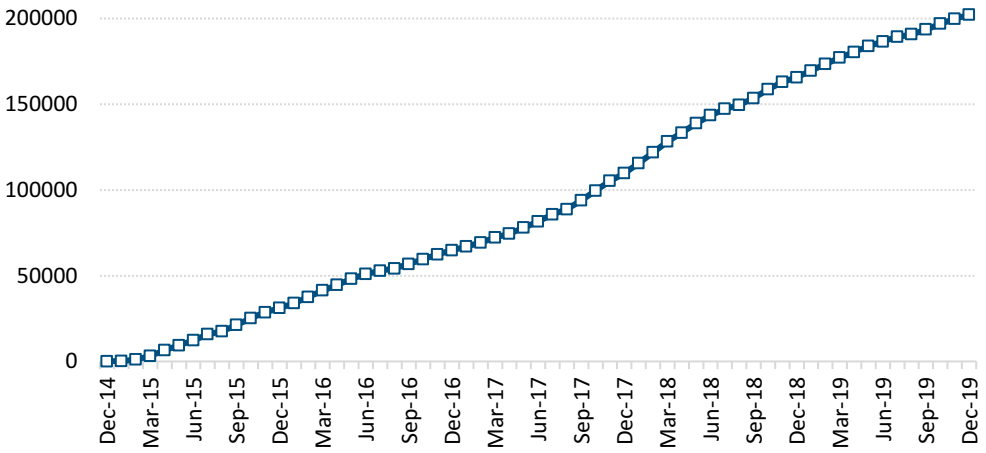
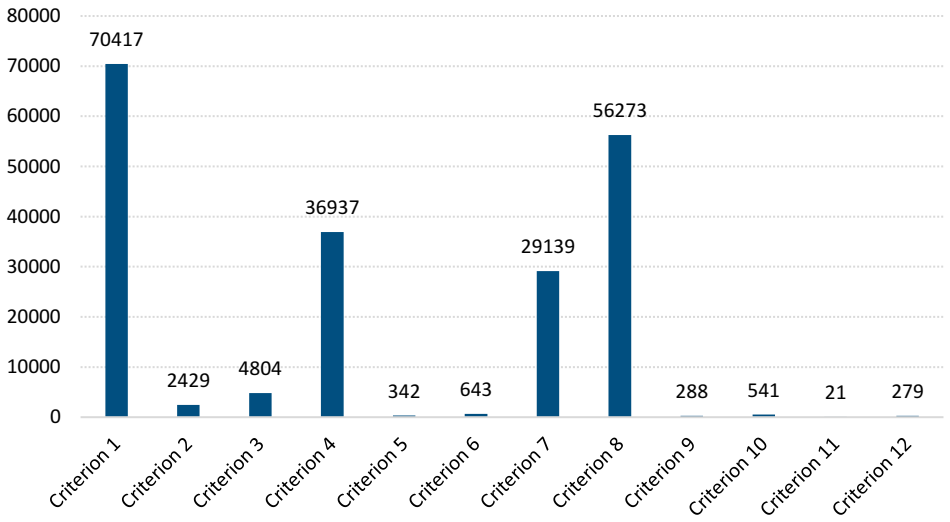


Figure 6.1.3. Number of started treatments up to 2019 per criterion



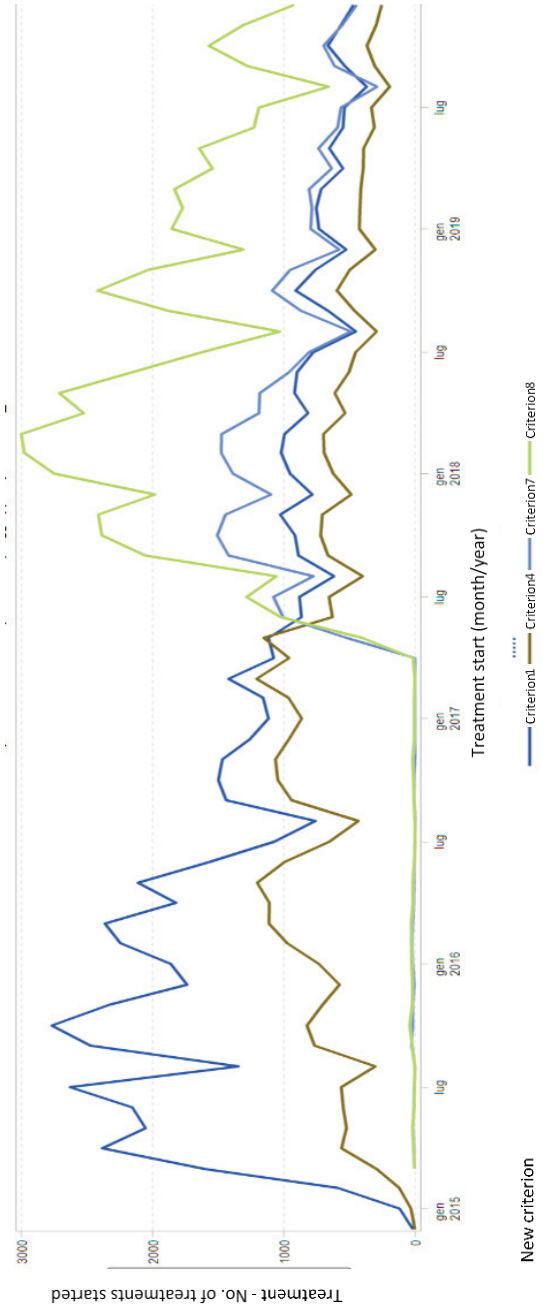


Figure 6.1.4. Monthly trend of started treatments up to 2019 per criterion (criteria 1, 4, 7, 8)

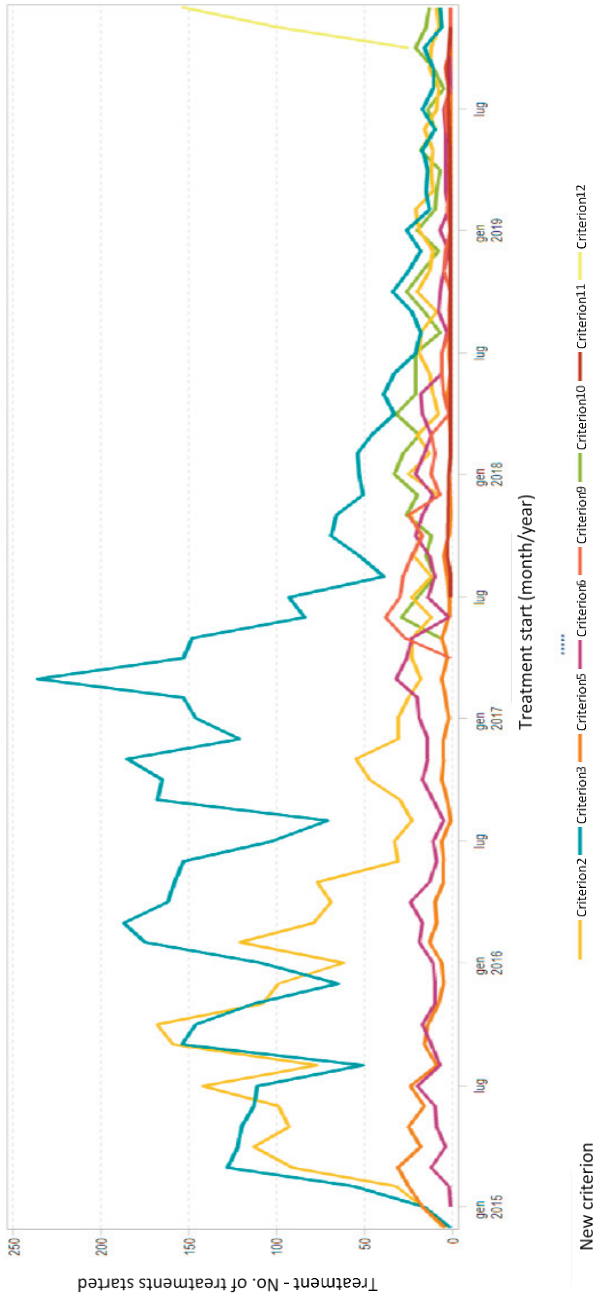


Figure 6.1.5. Monthly trend of started treatments up to 2019 per criterion (criteria 2, 3, 5, 6, 9, 10, 11)

Table 6.1.8. Breakdown of treatments started in 2019 per criterion and Region of treatment

Region	Criteria													Per 1000 inhab.
	1	2	3	4	5	6	7	8	9	10	11	12	All	
Lombardy	1,236	30	48	718	2	10	1,511	4,195	5	36	0	26	7,817	0.78
Campania	1,044	15	6	493	0	3	936	1,469	4	19	1	98	4,088	0.70
Emilia Romagna	606	14	30	334	1	9	701	1,899	6	13	0	28	3,641	0.82
Piedmont	595	18	4	335	0	0	703	1,314	1	9	0	3	2,982	0.68
Lazio	476	14	14	314	2	0	506	1,342	1	7	0	20	2,696	0.46
Tuscany	466	19	12	230	0	1	461	1,195	2	9	0	10	2,405	0.64
Veneto	463	9	8	227	0	1	465	1,212	1	7	0	8	2,401	0.49
Sicily	564	6	9	339	2	5	553	823	0	15	3	11	2,330	0.47
Puglia	494	3	6	367	0	2	456	689	3	18	0	33	2,071	0.51
Sardinia	304	3	7	178	0	1	274	361	0	1	0	12	1,141	0.70
Liguria	148	4	2	94	0	0	139	576	0	3	1	6	973	0.63
Friuli Venezia Giulia	161	8	1	94	0	0	149	363	1	3	1	10	791	0.65
Marche	126	4	4	61	0	0	157	386	0	1	0	2	741	0.49
Calabria	127	0	3	112	0	3	147	148	0	1	0	6	547	0.28
Umbria	82	2	1	70	0	0	91	263	0	0	1	0	510	0.58
Abruzzo	57	0	7	76	0	0	110	220	0	8	0	6	484	0.37
Basilicata	62	0	0	34	0	0	67	109	1	1	0	0	274	0.49
A.P. of Trento	44	0	0	21	0	0	30	170	0	0	0	0	265	0.49
A.P. of Bolzano	32	0	0	17	0	0	57	47	0	1	0	0	154	0.29
Molise	17	0	1	13	0	0	15	24	0	1	0	0	71	0.23
Valle d'Aosta	11	0	0	5	0	0	7	16	0	0	0	0	39	0.31
Italy	**7,115**	**149**	**163**	**4,132**	**7**	**35**	**7,535**	**16,821**	**25**	**153**	**7**	**279**	**36,421**	**0.60**

Novel oral anticoagulants (NOACs)

Novel oral anticoagulants have been reimbursed in Italy since 2013 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), as well as for the treatment and the prevention of relapsed deep vein thrombosis (DVT) and pulmonary embolism in adults.
In this section, the updated reported data concern the indication for stroke and systemic embolism prevention in adult patients with NVAF, with one or more risk factors, such as congestive heart failure, hypertension, age≥75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA).
The first medication available has been dabigatran (since 16 June 2013), followed by rivaroxaban (13 September 2013), apixaban (7 January 2014) and edoxaban (admitted to reimbursement since 9 September 2016). Following renegotiation and review of access conditions, whose costs are fully borne by the NHS, since March 2019 the four NAOCs have been prescribed to patients with NVAF only in defined circumstances: on the basis of values of CHA_2DS_2-Vasc or if cardioversion with rivaroxaban and apixaban is needed.
At 31 December 2019, 1,200,191 patients (both men and women) with NVAF had initiated therapy with NAOCs, 32.1% of patients were treated with rivaroxaban, 31% with apixaban, 24.1% with dabigatran and 12.8% with edoxaban (Table 6.1.9). The average age of the population treated is 78.5 years, with a high percentage of patients aged ≥85 years, mainly treated with apixaban and edoxaban (more than 25%).
Most patients present a baseline CHA_2DS_2-VASc score varying between 3 and 5 (68.7%), and a HAS-BLED score ≤4 (97.8%). Hypertension is the most represented comorbidity (86.3%), followed by heart failure/left ventricular dysfunction (28.3%).
When considering the basic characteristics of the groups of patients treated with the four NAOCs, it is possible to state that, comprehensively, differences (expressed as a percentage) are very limited. Nevertheless, patients treated with apixaban present higher incidences of basal comorbidities: impaired renal function (7.8%), heart failure (30.3%) and previous bleedings (13.3%).
Moreover, 11.9% of treatments with edoxaban and 10.3% with apixaban were started after treatment with another NAOC. The percentage of patients who switched to another NAOC was lower in the case of rivaroxaban (5.9%) and dabigatran (3.4%).
Figure 6.1.6 shows the monthly trend of new patients who started treatment. A growing trend is recorded for apixaban (with more than 7,000 new treatments per month - December 2019) and edoxaban (more than 5,000 new treatments per month - December 2019).
As for regional distribution (Table 6.1.10), more than 35% of patients who started treatment live in the Italian regions with the highest number of citizens (Lombardy, Lazio, Campania). During the period considered, variability in the regional use of treatments was very limited for edoxaban and apixaban, and there was greater variability for dabigatran and rivaroxaban, as shown in Figure 6.1.7.

Table 6.1.9. Patients treated at 31/12/2019 with average age of patients (details per medicine)

	Apixaban		Dabigatran		Edoxaban		Rivaroxaban		Total	
	N	%	N	%	N	%	N	%	N	%
Patients	371978	31.0	289759	24.1	153354	12.8	385100	32.1	1200191	100
Age, average (range)	79.8 (18 - 109)		77.2 (18 - 103)		79.7 (19 - 106)		77.8 (18 - 108)		78.5 (18-109)	
<65	28974	7.8	35889	12.4	12960	8.5	47941	12.4	125764	10.5
65-74	83643	22.5	82535	28.5	34722	22.6	100477	26.1	301377	25.1
75-84	163024	43.8	125718	43.4	64654	42.2	163736	42.5	517132	43.1
≥85	96337	25.9	45617	15.7	41018	26.7	72946	18.9	255918	21.3
Gender										
Women	194648	52.3	132772	45.8	81335	53	186823	48.5	595578	49.6
Men	177330	47.7	156987	54.2	72019	47	198277	51.5	604613	50.4
CHA_2DS_2VASc scores										
0	1308	0.4	1884	0.7	543	0.4	4425	1.1	8160	0.7
1	9649	2.6	12063	4.2	4167	2.7	17231	4.5	43110	3.6
2	35530	9.6	37397	12.9	16676	10.9	47032	12.2	136635	11.4
3	78038	21	68186	23.5	35317	23	86880	22.6	268421	22.4
4	105441	28.3	77864	26.9	44940	29.3	105565	27.4	333810	27.8
5	74727	20.1	50480	17.4	28926	18.9	68234	17.7	222367	18.5
6	42584	11.4	26916	9.3	14638	9.5	35614	9.2	119752	10.0
7	18013	4.8	11172	3.9	6094	4	14718	3.8	49997	4.2
8	5720	1.5	3281	1.1	1772	1.2	4593	1.2	15366	1.3
9	968	0.3	516	0.2	281	0.2	808	0.2	2573	0.2
10	-	0.0	1884	0.7	-	0.0	-	0.0	-	0.0
HAS BLED scores										
0	4876	1.3	6271	2.2	2306	1.5	10461	2.7	23914	2.0
1	50098	13.5	44730	15.4	24997	16.3	60967	15.8	180792	15.1
2	156668	42.1	114914	39.7	72124	47	165079	42.9	508785	42.4
3	101903	27.4	79851	27.6	35841	23.4	96751	25.1	314346	26.2
4	48769	13.1	37401	12.9	15421	10.1	43719	11.4	145310	12.1
5	8502	2.3	5875	2	2375	1.5	7131	1.9	23883	2.0
6	1040	0.3	633	0.2	251	0.2	823	0.2	2747	0.2
7	107	0	67	0	29	0	128	0	331	0.0
8	13	0	11	0	7	0	35	0	66	0.0
9	2	0	6	0	3	0	6	0	17	0.0
Comorbidity										
Heart failure/left ventricular dysfunction	112693	30.3	74500	25.7	43080	28.1	109216	28.4	339489	28.3
Hypertension	320614	86.2	251316	86.7	131986	86.1	331773	86.2	1035689	86.3
Diabetes mellitus	74775	20.1	58024	20.0	28768	18.8	74246	19.3	235813	19.6
Previous stroke	69003	18.6	52493	18.1	22078	14.4	58537	15.2	202111	16.8
Vascular diseases	104130	28.0	80496	27.8	40022	26.1	104364	27.1	329012	27.4

continued

continued Table 6.1.9

	Apixaban		Dabigatran		Edoxaban		Rivaroxaban		Total	
	N	%	N	%	N	%	N	%	N	%
Impaired renal function	28862	7.8	8342	2.9	10419	6.8	19890	5.2	67513	5.6
Impaired hepatic function	3541	1.0	3079	1.1	1213	0.8	3041	0.8	10874	0.9
Previous bleeding	49369	13.3	30360	10.5	15183	9.9	33522	8.7	128434	10.7
Previous treatment with AVK	86527	23.3	93911	32.4	28025	18.3	102229	26.5	310692	25.9
Narrow INR	63998	17.2	65994	22.8	20627	13.5	75576	19.6	226195	18.8
Previous treatment with NAO	38454	10.3	9834	3.4	18242	11.9	22635	5.9	89165	7.4

Table 6.1.10. Distribution of patients treated with NAOCs per Italian region

Region	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Total (%)
Abruzzo	9,515	4,551	3,090	12,016	29,172 (2.4)
Basilicata	4,089	2,635	1,853	6,071	14,648 (1.2)
Calabria	9,327	9,061	4,436	11,291	34,115 (2.8)
Campania	36,717	25,166	14,409	40,207	116,499 (9.7)
Emilia R.	262	436	166	413	1,277 (0.1)
Friuli VG	8,203	7,142	3,233	9,291	27,869 (2.3)
Lazio	43,897	32,397	13,407	44,060	133,761 (11.1)
Liguria	15,175	11,465	6,159	14,436	47,235 (3.9)
Lombardy	62,172	53,105	28,845	48,559	192,681 (16.1)
Marche	10,795	6,918	4,973	14,397	37,083 (3.1)
Molise	1,820	965	458	3,616	6,859 (0.6)
Piedmont	31,389	27,387	11,153	29,418	99,347 (8.3)
A.P. of Bolzano	2,725	1,837	1,207	2,624	8,393 (0.7)
A.P. of Trento	2,416	1,463	945	1,788	6,612 (0.6)
Puglia	28,534	26,747	12,056	30,916	98,253 (8.2)
Sardinia	11,328	12,980	4,012	14,475	42,795 (3.6)
Sicily	26,363	19,410	11,154	30,717	87,644 (7.3)
Tuscany	26,594	22,676	13,823	27,101	90,194 (7.5)
Umbria	10,061	5,429	2,650	8,716	26,856 (2.2)
Valle d'Aosta	981	594	313	1,035	2,923 (0.2)
Veneto	29,615	17,395	15,012	33,953	95,975 (8.0)
Total	**371,978**	**289,759**	**153,354**	**385,100**	**1,200,191 (100.0)**

Note: Data of treatments initiated in Emilia Romagna are not complete

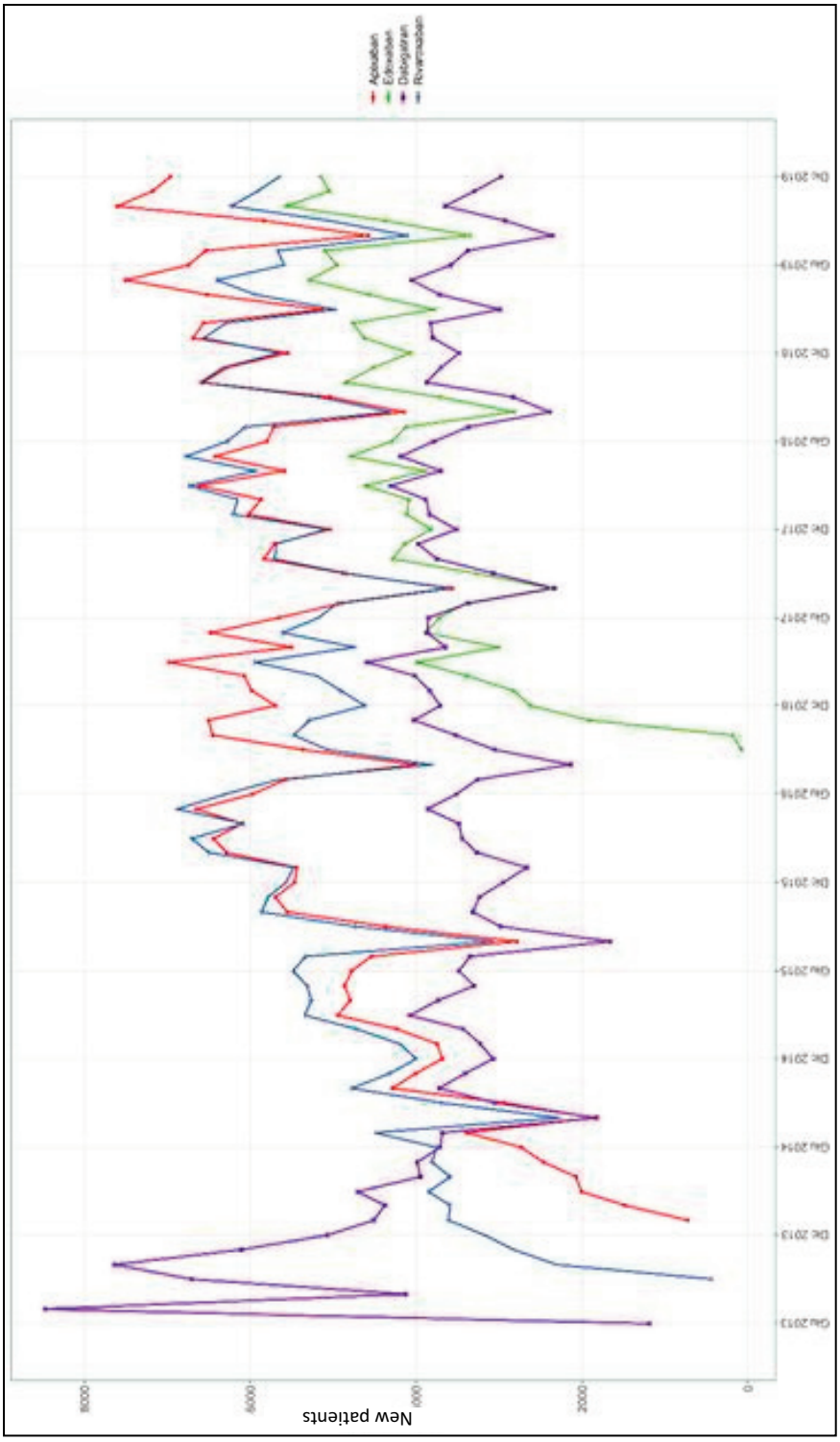


Figure 6.1.6. Treatments with four NAOCs, from the date of the marketing authorisation in Italy until December 2019 (monthly trend)

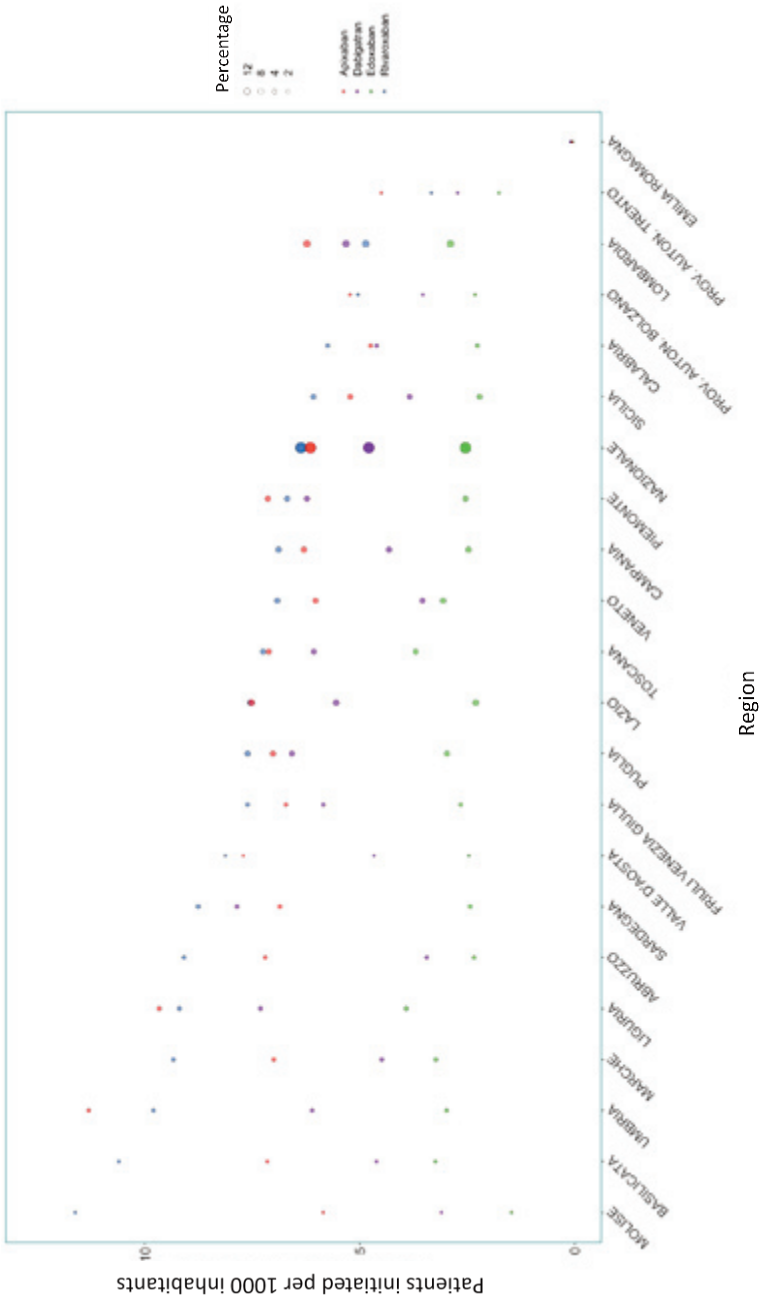


Figure 6.1.7. Regional distribution of patients on treatment (per 1000 inhabitants)

PCSK9 Inhibition for the treatment of hypercholesterolemia

In 2017 two new treatments with novel mechanisms of action (monoclonal antibodies targeted against protein PCSK9 recycling the LDL receptor) were admitted to reimbursement for the treatment of hypercholesterolemia: evolocumab, marketed since 8 February 2017, and alirocumab, available since 7 March 2017.
The indications reimbursed by the NHS for both medications are as follows:

- primary prevention of patients ≤80 years of age with heterozygous familial hypercholesterolemia (heFH) and LDL levels ≥130 mg/dL, treated for 6 months with the maximum tolerated doses of the strongest statins + ezetimibe or with statin intolerance;
- secondary prevention of patients ≤80 years of age with heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolaemia or mixed dyslipidemia and LDL-C levels ≥100 mg/dL treated for 6 months with the maximum tolerated doses of the strongest statins + ezetimibe or with statin intolerance.

Moreover, on the basis of more extended authorised indications, evolocumab is reimbursed also in homozygous familial hypercholesterolemia in patients aged 12-80 years. Besides this, since 13 December 2019 evolocumab has obtained reimbursement for patients with ezetimibe intolerance or after detection of LDL cholesterol in patients with recent IMA (during the last 12 months) or recurrent CVD events. At 31 December 2019, 12,497 patients were initiated to treatment with PCSK-9 inhibitors; 6,950 of them with evolocumab and 5,547 with alirocumab (Table 6.1.11).
The monthly trend of treatments initiated since the beginning of monitoring is reported in Figure 6.1.8., which shows a significant and gradual increase in new treated patients initiated on both therapies, with a constant ratio between them.
About 65% of patients treated were men, whereas the average age was 62 years (range 18-83 years). In accordance with the different prevalence of forms of hypercholesterolemia, most treatments were prescribed to patients with a diagnosis of non-familial hypercholesterolemia (50%), followed by those with mixed dyslipidemia (25.1%) and with heterozygous familial hypercholesterolemia (24.3%) and, finally, with homozygous familial hypercholesterolemia (0.6%). In the last case, the indication was authorised only for evolocumab.
Around 117 patients (0.9% of the total) were treated with at least one of the two medications, after being treated with another PCSK9 inhibitor reimbursed by the NHS, which was then withdrawn for different reasons.
85.9% of patients started treatment for secondary prevention, whereas 14.1% for primary prevention. As far as relevant comorbidities are concerned, 70.1% of the sample presents cardiovascular disease, 63.4% hypertension and 20.8% diabetes mellitus. Only 8.8% of patients do not present any relevant comorbidity at the baseline. Moreover, 13.4% of patients had smoking habit and 36.9% had past smoking habit.
More than 54.5% of patients started treatment with PCSK9 inhibitors because they were intolerant to statins. The remaining subjects in the group initiated treatment because the target of LDL cholesterol was not properly attained, even though they were treated with the maximum doses of the strongest statins (atorvastatin or rosuvastatin), plus ezetimibe.
A higher number of patients intolerant to ezetimibe is treated with evolocumab (n=28 *vs* 3 with alirocumab), probably due to the recent admission to reimbursement.

If patients treated with evolocumab and alirocumab are taken into consideration, baseline characteristics are very similar. The main difference is found in the prevalence of hypertension which is higher in patients treated with evolocumab. As far as hypercholesterolemia is concerned, a higher percentage of patients with heterozygous familial hypercholesterolemia is treated with alirocumab and, vice versa, a higher percentage of patients with non-familial hypercholesterolemia is treated with evolocumab; similar percentages of patients with mixed dyslipidemia for both therapies.
The regional distribution shows that almost half of the patients (44.2%) treated with PCSK9 inhibitors is distributed among three regions (Campania, Lombardy and Lazio) (Table 6.1.12).

Table 6.1.11. Baseline characteristics of patients initiated on treatment with PCSK9 inhibitors

	Alirocumab	Evolocumab	Total
	N (%)	N (%)	N (%)
Total patients	5,547 (44.4)	6,950 (55.6)	12,497 (100)
Women	1,933 (34.8)	2,439 (35.1)	4,372 (35.0)
Men	3,614 (65.2)	4,511 (64.9)	8,125 (65.0)
Average age (range)	62 (18- 81)	62 (18 - 83)	62 (18,0 - 83)
Past treatment with PCSK9 inhibitors	52 (0.9)	65 (0.9)	117 (0.9)
Types of hypercholesterolemia			
HoFH*	0 (0.0)	81 (1.2)	81 (0.6)
HeFH	1,430 (25.8)	1,606 (23.1)	3,036 (24.3)
noFH	2,698 (48.6)	3,548 (51.1)	6,246 (50.0)
MD	1,419 (25.6)	1,715 (24.7)	3,134 (25.1)
Use in CVD prevention			
Primary prevention	811 (14.6)	949 (13.7)	1,760 (14.1)
Secondary prevention	4,736 (85.4)	6,001 (86.3)	10,737 (85.9)
Relevant comorbidities §			
Cardiovascular disease (heart disease…)	3,821 (68.9)	4,945 (71.2)	8,766 (70.1)
Cerebrovascular disease (previous stroke)	474 (8.5)	524 (7.5)	998 (8.0)
Peripheral arterial disease	944 (17.0)	1,189 (17.1)	2,133 (17.1)
Diabetes mellitus	1,200 (21.6)	1,405 (20.2)	2,605 (20.8)
Hypertension	3,391 (61.1)	4,537 (65.3)	7,928 (63.4)
No comorbidities	540 (9.7)	555 (8.0)	1,095 (8.8)
Prevalence of smoking			
Present	735 (13.3)	936 (13.5)	1,671 (13.4)
Past	1,979 (35.7)	2,627 (37.8)	4,606 (36.9)
No prevalence	2,833 (51.1)	3,387 (48.7)	6,220 (49.8)
Use of statins			
Intolerance to statins	2,978 (53.7)	3,829 (55.1)	6,807 (54.5)
In association with statin, treatment with^			
Atorvastin	1,256 (22.6)	1,569 (22.6)	2,825 (22.6)
Rosuvastatin	1,313 (23.7)	1,540 (22.2)	2,853 (22.8)
Use of ezetimibe			
Intolerance to ezetimibe	5 (0.1)	28 (0.4)	33 (0.3)

HoFH= homozygous familial hypercholesterolemia; HeFH= heterozygous familial hypercholesterolemia
noFH= non familial hypercholesterolemia; MD= mixed dyslipidemia.
* only evolocumab is indicated for the treatment of HoFH
§ multiple items may be selected
^ information is not available on the statin used for 12 treatments in association with statin

Table 6.1.12. Regional distribution of prescribing centres and patients starting treatment

regions	Centres No.		Patients starting treatment with		Total No. (%)
	Alirocumab	Evolocumab	Alirocumab	Evolocumab	
Abruzzo	6	6	112	162	274 (2.2%)
Basilicata	3	8	82	183	265 (2.1%)
Calabria	6	11	173	368	541 (4.3%)
Campania	33	47	949	1626	2575 (20.6%)
Emilia R.	14	13	235	308	543 (4.3%)
Friuli VG	10	11	84	140	224 (1.8%)
Lazio	24	24	703	536	1239 (9.9%)
Liguria	14	15	331	218	549 (4.4%)
Lombardy	74	76	704	1004	1708 (13.7%)
Marche	11	13	83	165	248 (2.0%)
Molise	5	4	43	9	52 (0.4%)
Piedmont	23	22	641	385	1026 (8.2%)
A.P. of Bolzano	5	3	23	20	43 (0.3%)
A.P. of Trento	2	2	17	22	39 (0.3%)
Puglia	7	7	273	545	818 (6.5%)
Sardinia	6	8	137	186	323 (2.6%)
Sicily	17	17	214	158	372 (3.0%)
Tuscany	15	17	327	443	770 (6.2%)
Umbria	10	8	120	106	226 (1.8%)
Valle d'Aosta	1	1	9	21	30 (0.2%)
Veneto	12	12	287	345	632 (5.1%)
Total	**298**	**325**	**5547**	**6950**	**12497**

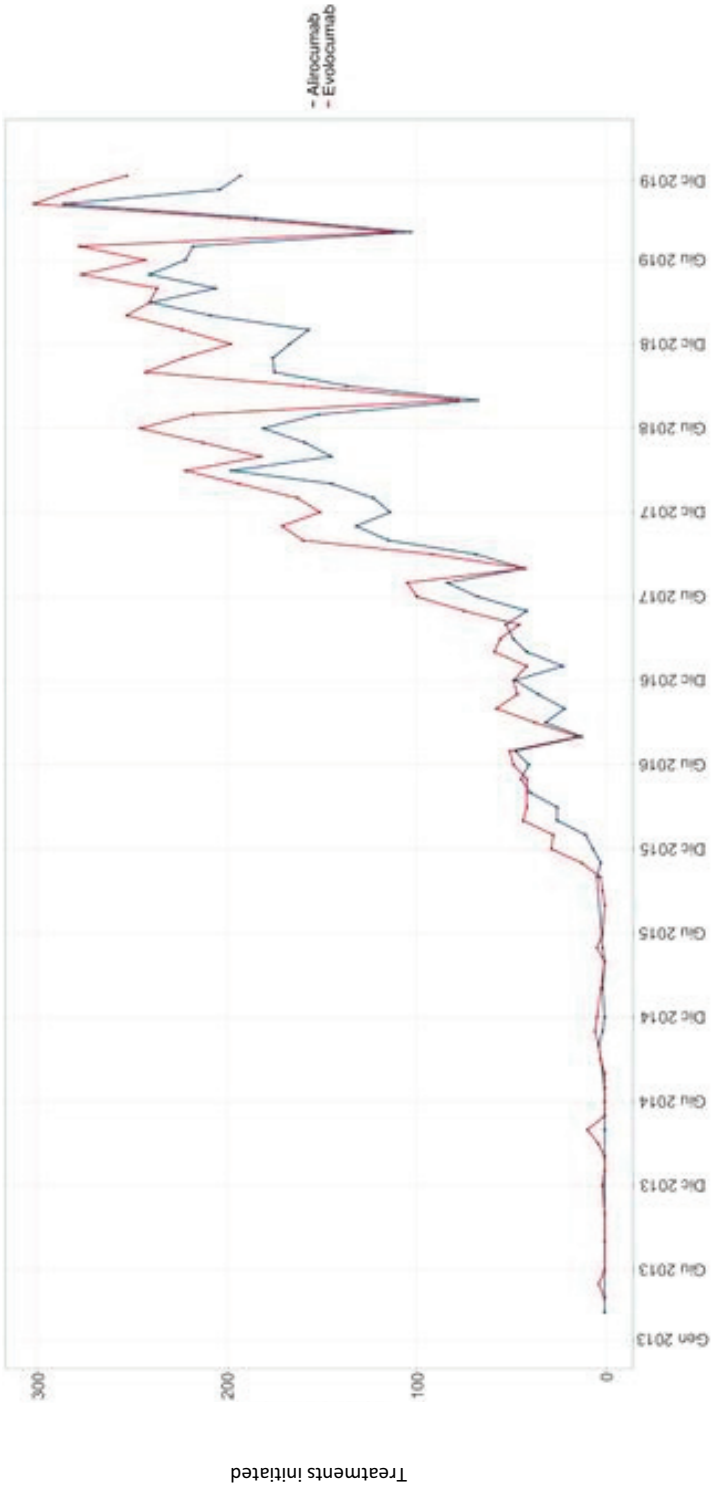


Figure 6.1.8. Treatments with PCSK9 inhibitors at December 2019 (monthly trend)

Intravitreal anti-VEGF medicines

Medicines used to treat wet age-related macular degeneration (AMD) are intravitreal anti-VEGF therapies. Data are referred to medications authorized 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 authorized for the treatment of wet AMD.
Since 1 January 2019 request for withdrawal of Macugen® (pegaptanib) from the marketing authorisation holder have been effective [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 Registries operating for pegaptanib since 25 February 2013, for ranibizumab since 28 June 2014, for bevacizumab since 28 June 2014 and for aflibercept since 15 April 2014.
Registries, except for pegaptanib, were closed on 8 October 2019 and a temporary paper-form was first introduced. Since 6 February 2020 it has been substituted by a new simplified form of monitoring of all anti-VEGF agents.
The new tool aims at collecting all past treatments recorded in the old electronic registries or paper-forms in order to integrate the management of monitoring in a single platform.
Data reported in the present Report are referred to the monitoring period up to 8 October 2019. During the reference period, 220,218 patients initiated treatment with AMD. 79.2% of treatments were monocular, whereas the remaining 10.4% relates to patients whose eyes were both treated. The total number of naïve patients (receiving first treatment with intravitreal VEGT inhibitors) is 159,709.
Almost half of treatments (no. eyes) were initiated with ranibizumab (98,290; 44.6%); followed by aflibercept (72,969; 33.1%), bevacizumab (47,890; 21.7%), and pegaptanib (1,069; 0.5%) (Table 6.1.13).
Baseline characteristics of naïve patients (on first treatment with anti-VEGT therapy) show a higher prevalence of use in women (57.1%) compared to men (42.9%).
The average age of patients treated is 78 years (range 50-105 years), the maximum age is 105 years and the highest number of patients treated are in the 75-84 age group.
81.1% of treatments were initiated following evaluation by optical tomography (OCT), compared to 18.9% started after fluoro angiography (FAG) and indocyanine green (ICG).
Optical coherence tomography (OCT) examinations (178,590) confirmed retinal thickness was 352 µm (range 300-427) and in 87% of cases (155,373) there was subretinal fluid.
Eyes whose retinal thickness was lower than 352 µm and equal to 335 µm (range 290-400) are treated with pegaptanib, whereas those whose value is higher and equal to 354 µm (range 300-430) are treated with ranibizumab. Evaluations carried out after FAG/ICG (41,624) report subretinal haemorrhage or intraretinal haemorrhage in 56.2% (23,413) of total cases and vascular leakage in 97.7% of cases (40,683).
Baseline visual acuity* was evaluated through a decimal scale with three different levels of severity. 62.2% of treatments were initiated in case of severely reduced visual acuity, 23.3% for moderately reduced visual acuity and 14.5% for mildly reduced visual acuity.
Among 136,922 therapies initiated to treat severely reduced visual acuity, 45.4% were initiated with ranibizumab, 31.8% with aflibercept and 22.2% with bevacizumab. Among 51,399 treatments for moderately reduced visual acuity, 42.4% were initiated with

ranitizumab, 35.4% with aflibercept and 21.8% with bevacizumab. Treatments with pagaptanib are in both cases above lower than 1%.
15.8% of treatments were initiated to treat eyes previously treated with novel anti-vascular therapies. Particularly, 28.4% of eyes treated with aflibercept, 19.5% of those treated with bevacizumab and 4.6% of eyes treated with ranitizumab were previously treated with another anti VEGT therapy.
The average number of injections per eyes during the first year of treatment is equal to 3.6, with a value higher of 3.8 in the case of aflibercept, and lower of 2.6 for pegaptanib. The number of injections was similar between bevacizumab and ranibizumab with an average of 3.5 in the first year of treatment.
Figure 6.1.9 reports the trend of treatments initiated since the beginning of monitoring. It shows as, since 2016, aflibercept has been the anti VEGF therapy used to treat the highest number of eyes per month (1,200), whereas ranibizumab and bevacizumab maintain a steady trend (about 1,000 and 650 eyes per month respectively) until August 2019.
Since August 2019 an increase in treatments with bevacizumab has been observed at national level. It is due to Decision of the Lombardy Region (Decision N° XI/1986 issued by the Council of the Lombardy Region on 23 July 2019) having a significant impact on the number of treatments initiated in Italy.
Regional distribution of prescribing centres and of patients initiated on treatment shows that more than half of treatments for AMD are distributed in five Italian regions: Lombardy, Veneto, Lazio, Tuscany and Emilia-Romagna. Nevertheless, prescribing habits are different from region to region. In Lombardy, Lazio and Tuscany, ranibizumab and aflibercept, followed by bevacizumab, are the most used anti VEGF therapies, whereas in the Veneto and Emilia Romagna they use the same therapies in the following order: 1. bevacizumab, 2. ranibizumab, 3. Aflibercept (Table 6.1.14 and Figure 6.1.10).

* ETDRS score does not present values that can be used, since it was reported inconsistently by physicians. Patients reporting an ETDRS score do not present a corresponding value of visual acuity on the tenths scale. Therefore, percentage related to visual acuity is referred to the total number of treatments for which this information is available.

Table 6.1.13. Baseline characteristics of patients* starting anti-VEGF treatment

	Aflibercept		Bevacizumab (L. 648/96)		Pegaptanib		Ranibizumab		Total	
	N	%	N	%	N	%	N	%	N	%
No. of Patients	42,325	26.5	32,882	20.6	720	0.5	83,782	5.5	159,709	100.0
Age, average (range)	78 (50-104)		79 (50-103)		80 (51-100)		78 (50-105)		78 (50-105)	
50 - 64	4197	9.9	2207	6.7	36	5.0	8735	10.4	15175	9.5
65 - 74	11491	27.1	7639	23.2	149	20.7	22291	26.6	41570	26.0
75 - 84	19255	45.5	15817	48.1	359	49.9	37687	45.0	73118	45.8
≥ 85	7382	17.4	7219	22.0	176	24.4	15069	18.0	29846	18.7
Gender										
Women	23795	56.2	19313	58.7	356	49.4	47761	57.0	91.225	57.1
Men	18530	43.8	13569	41.3	364	50.6	36021	43.0	68484	42.9
No. of treatments (eyes)	72969	33.1	47890	21.7	1069	0.5	98290	44.6	220218	100.0
Examination										
OCT	60216	82.5	39264	82.0	1036	96.9	78074	79.4	178590	81.1
FAG/FAG + ICG	12753	17.5	8626	18.0	33	3.1	20212	20.6	41624	18.9
Retinal thickness, mm (1 and 3 quartile)	353 (300-427)		350 (300-421)		335 (290-400)		354 (300-430)		352 (300-427)	
Subretinal fluid										
Present	52353	86.9	34402	87.6	871	84.1	67747	86.8	155373	87.0
Questionable	3325	5.5	2308	5.9	78	7.5	4372	5.6	10083	5.6
Absent	4497	7.5	2534	6.5	87	8.4	5900	7.6	13018	7.3
Sub or intraretinal haemorrhage										
Present	7056	55.3	5058	58.6	25	75.8	11274	55.8	23413	56.2
Questionable	1223	9.6	1140	13.2	1	3.0	1671	8.3	4035	9.7
Absent	4460	35.0	2426	28.1	7	21.2	7257	35.9	14150	34.0
Leakage										
Present	12467	97.8	8502	98.6	32	97.0	19682	97.4	40683	97.7
Absent	272	2.1	122	1.4	1	3.0	520	2.6	915	2.2
Visual acuity (Decimal scale)										
Unexploited	5542	7.6	2637	5.5	-	0.0	7744	7.9	15923	7.2
Severe vision loss (1-3)	43575	59.7	30455	63.6	790	73.9	62102	63.2	136922	62.2
Moderate vision loss (4-6)	18188	24.9	11199	23.4	226	21.1	21786	22.2	51399	23.3
Mild vision loss (7-10)	5664	7.8	3599	7.5	53	5.0	6658	6.8	15974	7.3
Past treatment with anti-VEGF IV	20703	28.4	9328	19.5	300	28.1	4539	4.6	34870	15.8
Monocular treatment	55947	76.7	37900	79.1	1055	98.7	79414	80.8	174316	79.2
Binocular treatment	8511	11.7	4995	10.4	7	0.7	9438	9.6	22951	10.4
Average number (median) of treatments, first 12 months		**3.8 (4)**		**3.5 (3)**		**2.6 (2)**		**3.5 (3)**		**3.6 (3)**

*Demographic characteristics are referred to naïve patients starting the first treatment with intravitreal anti VEGF

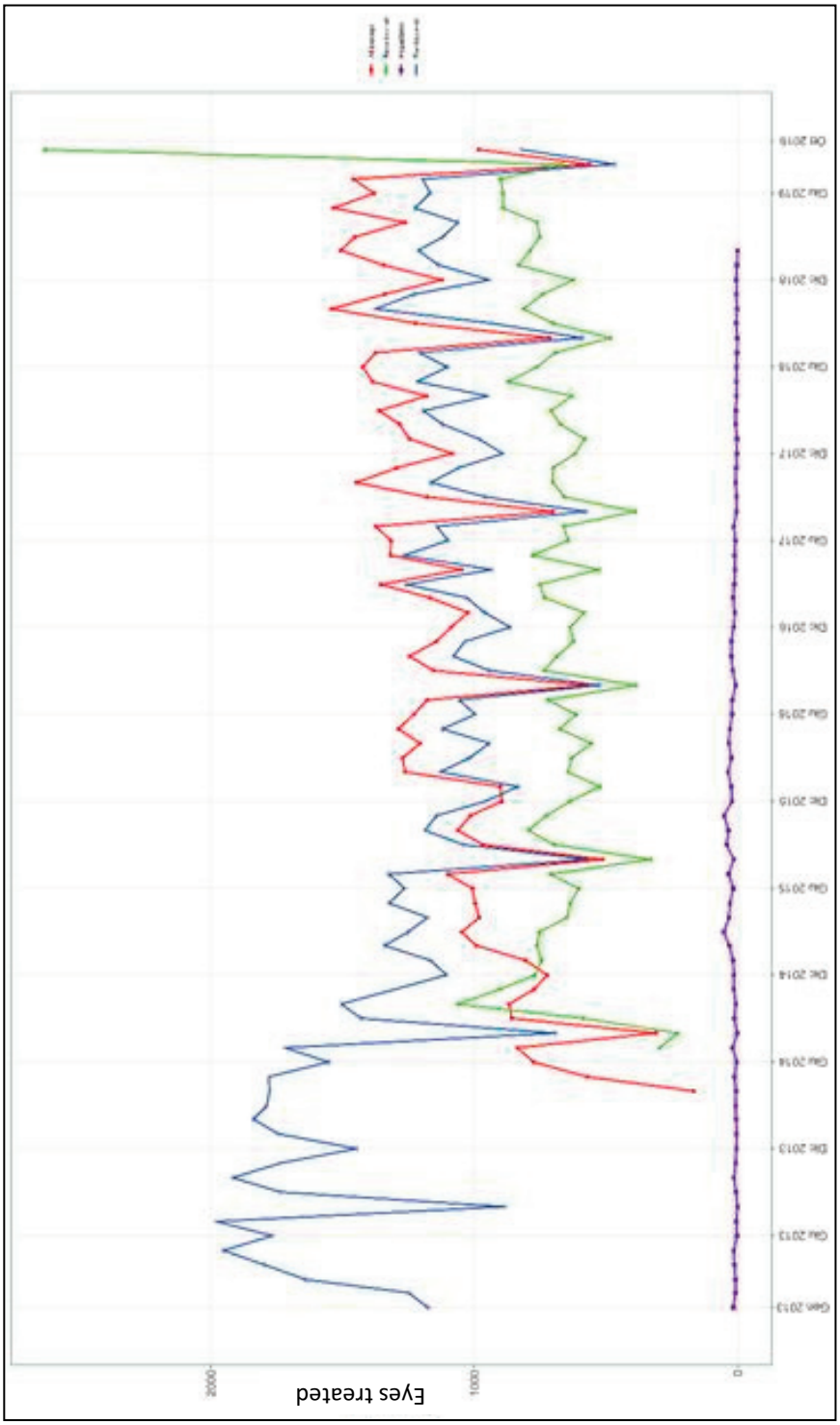


Figure 6.1.9. Trend of treatments initiated with 4 intravitreal anti VEGF from January 2013 to October 2019 (monthly trend)

Table 6.1.14. Regional distribution of prescribing centres and of patients starting treatment

Region	Prescribing Centres No.			
	Aflibercept	Bevacizumab	Pegaptanib	Ranibizumab
Abruzzo	9	4	4	11
Basilicata	4	1	2	5
Calabria	10	-	5	14
Campania	26	3	5	26
Emilia R.	18	20	7	19
Friuli VG	6	6	-	6
Lazio	30	13	10	33
Liguria	9	8	4	8
Lombardy	67	29	23	74
Marche	14	12	8	15
Molise	4	1	-	5
Piedmont	25	19	6	25
AP of Bolzano	3	3	1	3
AP of Trento	2	2	-	2
Puglia	27	2	25	36
Sardinia	8	-	5	8
Sicily	23	7	6	23
Tuscany	17	12	11	20
Umbria	7	5	-	7
V. d'Aosta	1	1	1	1
Veneto	27	27	15	28
			Eyes No.	
Abruzzo	1714	186	16	2612
Basilicata	409	11	8	950
Calabria	939	-	22	1618
Campania	3434	699	8	6282
Emilia R.	3722	8187	32	3917
Friuli VG	1951	4024	-	2069
Lazio	8088	2836	49	8798
Liguria	2715	3087	10	3852
Lombardy	17757	4554	260	24998
Marche	1844	3876	91	3046
Molise	291	28	-	800
Piedmont	5624	5242	28	4666
AP of Bolzano	827	1184	2	725
AP of Trento	460	524	-	575
Puglia	5158	99	295	8515
Sardinia	1554	-	39	2930
Sicily	4716	155	17	5644
Tuscany	5820	2997	104	7626
Umbria	1104	386	-	2490
V. d'Aosta	152	645	5	80
Veneto	4690	9170	83	6097

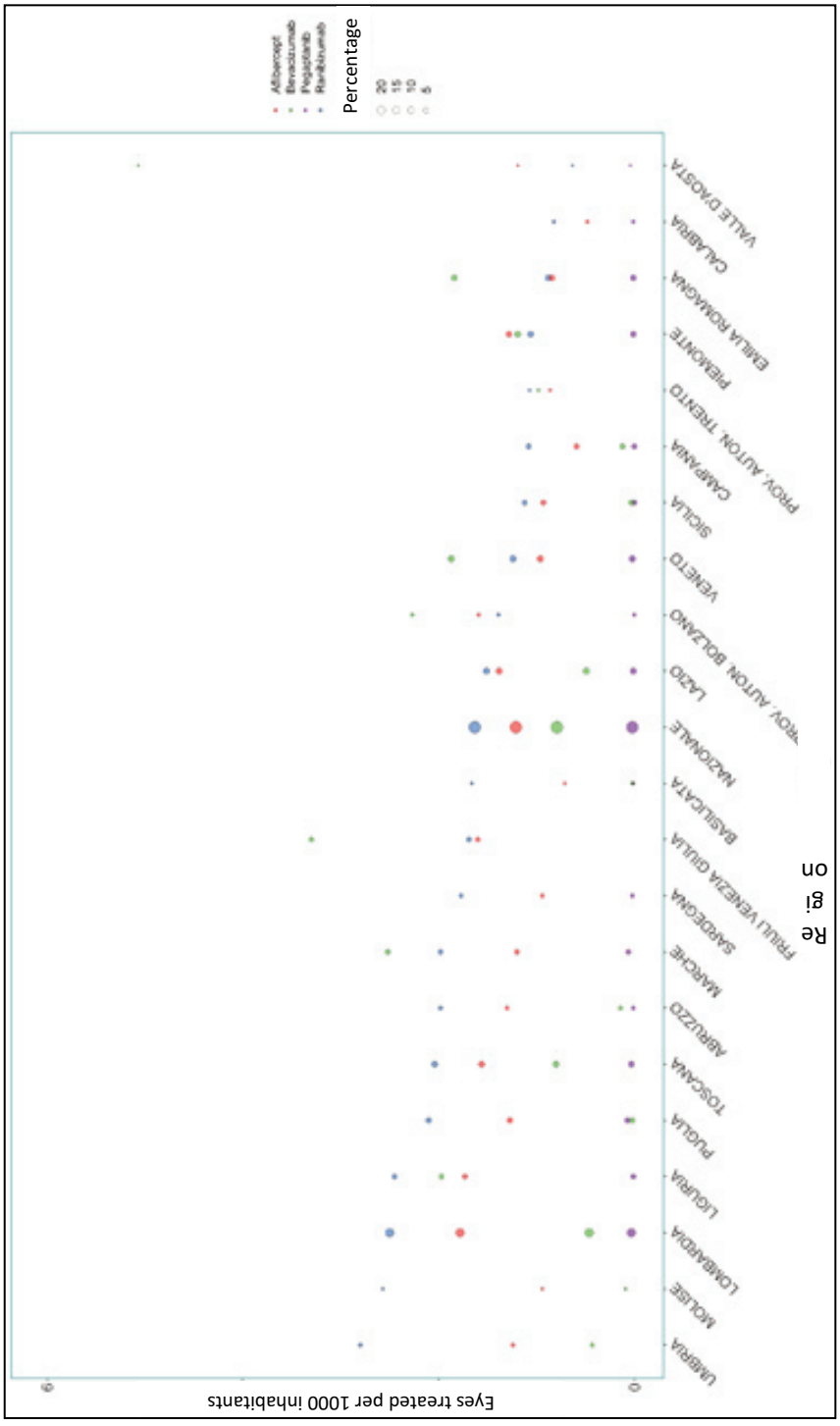


Figure 6.1.10. Regional distribution of eyes treated (per 1000 inhabitants)

6.2 Financial impact of Managed Entry Agreements (MEAs)

Italy has been one of the first European countries to adopt Managed Entry Agreements (MEAs), in order to foster access to new medicines with high cost and high level of uncertainty on clinical benefit at launch. AIFA can negotiate different types of MEAs with pharmaceutical companies: at patient level and at population level MEAs. The first type is monitored through AIFA Monitoring Registries, while the second one is monitored through information flows which collect data on NHS reimbursed expenditure and consumption such as the OsMed flow.

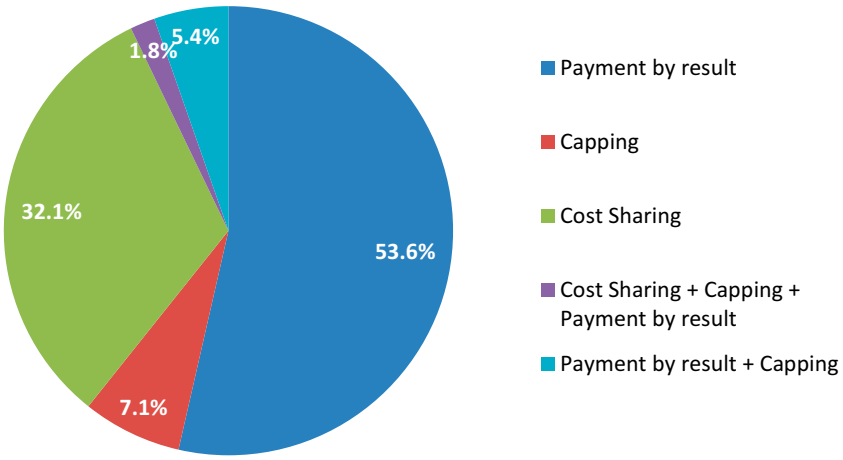
Managed Entry Agreements monitored through AIFA Monitoring Registries (Patient level):

MEAs that are monitored through AIFA Monitoring Registries are classified according to an international taxonomy[4], in two main categories: a) Performance-based risk sharing schemes and b) Financial-based schemes. The first category includes Payment by Result (PbR) and Risk Sharing (RS) models, while the second one includes Cost Sharing (CS) and Capping models.

- The **CS** model provides for a discount on the price of first courses of therapy or of the total duration, for all patients eligible for treatment. This tool is usually implemented in case of uncertainty both on financial impact and on clinical efficacy of a medical product.
- The **Capping** model provides that the pharmaceutical company pays therapy costs when the quantities established by the agreement are exceeded.
- The **RS** model, in comparison to the CS model, provides for a discount to be applied to non-responder patients.
- The **PbR** model extends the RS and provides for the full refund from the pharmaceutical company for all non-responder patients (100% payback of therapeutic failures). Usually the PbR model is implemented when the benefit/risk ratio has a higher level of uncertainty and the definition of non-responder patient is based on results of pivotal clinical trials.

[4] Garrison Jr LP et al. Value in Health. 2013

Figure 6.2.1. Percentage distribution of types of MEAs (as of 31/12/2019)



The distribution of each MEA for 2019 is reported in Figure 6.2.1. The most applied model is the payment by result agreement, accounting for 100% of the outcome-based agreements (53.6% of the total number of existing agreements, corresponding to 30 different agreements). In fact, no risk sharing model was implemented in 2019. This finding reflects the AIFA directive of refunding the treatment costs only for responder patients. The cost sharing and capping agreements rank below. The concurrent application of MEAs relating to distinct categories (outcome-based and financial-based agreements) for the management of both clinical and financial uncertainty is also implemented.
Table 6.2.1 shows reimbursement issued from implementation of MEAs per each Italian Region.
69% of total reimbursement (€119,368,022) derives from the implementation of financial based schemes (Figure 6.2.2): 44.8% is due to Cost Sharing agreements and 24.2% is due to Capping agreements. Payment by Result and Risk-Sharing agreements account for 20.8% of total reimbursement, with Risk sharing representing a very low percentage (0.06%).
The 2019 reimbursement percentages for the ATC level (Figure 6.2.3) are instead spread over two categories: 79.5% of the reimbursement is due to antineoplastic and immunomodulating agents (L) and 18.9% is due to general antimicrobials for systemic use (J). They are followed by sensory organs medicines (S): 1.3% of reimbursement; medicines for the nervous system (N): 0.2%; systemic hormonal preparations, excluding sex hormones (H): 0.04%; and treatments for the musculoskeletal system (M): 0.0004%.
In the overall evaluation of efficacy of MEAs it is important to take into consideration the impact (not easily quantifiable) on the appropriateness of use of medicines ensured by Registries, which allow to dispense medications to patients for whom treatment efficacy was highly demonstrated during the authorization process.

Moreover, it should be underlined that, regarding the evaluation of efficacy of outcome-based agreements, it is not sufficient to consider the reimbursement issued since it may be due to failing treatments. In fact, optimization of eligibility criteria allows to reduce the rate of treatment failure recorded by Registries and the amount of reimbursement.

Table 6.2.1 Reimbursement issued from MEAs, year 2019

Region	Reimbursement 2019 (€)
Abruzzo	3 551 689
Basilicata	1 200 691
Calabria	2 733 155
Campania	15 570 670
Emilia Romagna	11 425 176
Friuli Venezia Giulia	2 341 654
Lazio	8 383 726
Liguria	3 261 973
Lombardy	20 938 350
Marche	3 766 917
Molise	251 825
Piedmont	6 346 751
A.P. of Bolzano	1 902 342
A.P. of Trento	680 717
Puglia	7 346 545
Sardinia	2 156 710
Sicily	9 676 137
Tuscany	8 643 847
Umbria	1 169 618
Valle d'Aosta	214 841
Veneto	7 774 687
Total	**119 368 022**

Figure 6.2.2. Reimbursement 2019, percentage per MEA

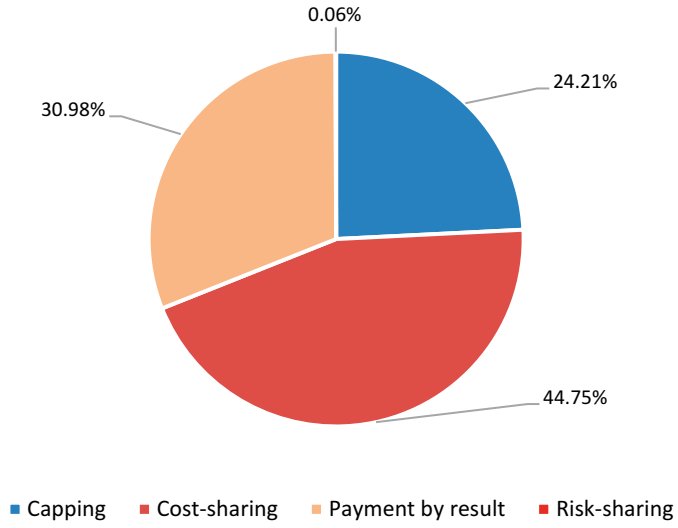
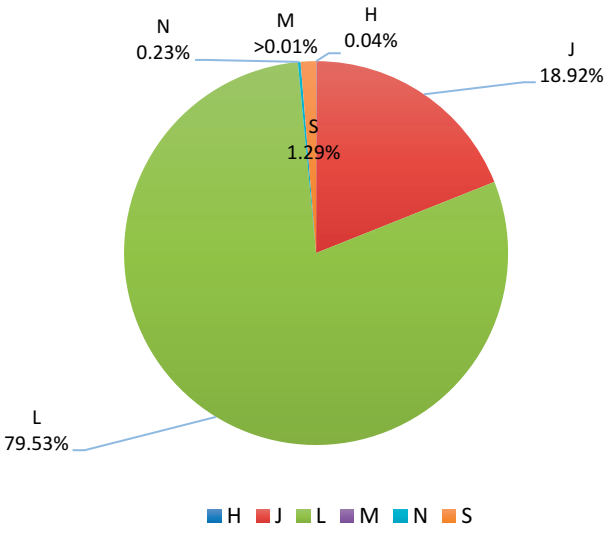


Figure 6.2.3. Reimbursement 2019, percentage per ATC I level



Section 7

Innovative medicines and orphan medicines

7.1 Innovative medicines

Definition of Innovativeness

The definition and assessment of pharmaceutical innovation is a complex and dynamic process. Such complexity is the result of the difficulties in identifying criteria applicable to different categories of medicinal products and therapeutic areas, as well as of the continuous evolution of the care context, given the growing availability of new therapeutic alternatives. At international level, Italy is among the first countries to adopt operating rules and a well-structured legislative framework for the assessment and access to innovative medicines.
The definition of innovativeness, its assessment and the granting of the innovative status are procedures falling within the remit of the Italian Medicines Agency (AIFA) and of its Technical Scientific Committee, which expresses binding opinions[1]. But what does the recognition of innovative status imply? What are the practical implications of such status?

- In order to ensure homogeneity of access to innovative products across the national territory, pursuant to the agreement dated 18 November 2010 between the Government and the Regional Authorities, medicines which are granted innovative status are immediately inserted in Regional Formularies (*Prontuario Terapeutico Regionale*); the updated list of innovative medicinal products is published on AIFA's institutional website.
- From an economic point of view, innovative medicines benefit from the suspension of statutory 5% reductions[2].
- With regard to governance of pharmaceutical expenditure, innovative medicines are not subject to budget constraints, benefitting from a dedicated incremental resources fund[1,3]. Indeed, when the national pharmaceutical expenditure ceiling is exceeded, if expenditure for innovative medicines exceeds the value of the fund set at the beginning of the year, orphan medicinal products are excluded from the payback mechanism, which is conversely distributed among all other MAHs in proportion to their pharmaceutical sales volumes for on patent non-innovative products. The 2015 Stability Law (L. no. 190 of 23 December 2014) has however introduced a safeguard mechanism to limit economic benefits resulting from the recognition of innovative status of a product: if the innovative medicinal product, supplied within outpatient standard distribution, exceeds a €300 million sale volume, the MAH shall contribute 20% of the breakthrough value (art. 1, paragraph 595).
- Moreover, the 2017 Financial Law (art. 1, para. 397-408, Law 232/2016) provides for specific financing of innovative products, actualized through the creation of two *ad hoc* funds: one dedicated exclusively to the purchase of innovative oncology medicines, the other for all other innovative medicinal products, and amounting to €500 million each for the period 2017-2019. The aforementioned Law also provided for AIFA, with prior opinion by the CTS, to establish new criteria to classify innovative medicines.

[1] D.L. 159/2007, converted with modifications by L. 222/2007
[2] AIFA Determination 3 July 2006 e AIFA Determination 27 September 2006
[3] D.L. 95/2012, converted with modifications by L. 135/2012 as amended.

AIFA Determination no. 519/2017 of 31 March 2017, updated by the Determination no. 1535/2017 of 12 September 2017, established new criteria to define innovative medicinal products, as well as the assessment procedure and parameters for the duration of the requirement for the purpose of a possible reduction of the reimbursed price.
The opinion on innovativeness is based on a multidimensional model taking into account three basic elements: medical need, added therapeutic value and overall quality of clinical evidence presented by the company requesting the innovative status. AIFA established that the evaluation shall be performed through a single model for all medicines, allowing, if necessary, the use of additional specific indicators.
The assessment of the medical need considers the possible availability of other therapeutic options for the same pathology and how much the introduction on the market of the medicine is necessary to respond to therapeutic needs of a specific patient population. The medical need is graded in five levels: maximum, important, moderate, low or absent.
The added therapeutic value expresses the extent of the clinical benefit brought by the medicine compared to the available alternatives, if any, on clinically relevant and validated endpoints for the pathology taken into consideration. Also this criterion is graded in five levels: maximum, important, moderate, low or absent.
Finally, the overall quality of clinical evidence expresses the degree of robustness of the evidence presented to support the request for innovativeness. The assessment is performed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation)[4] system.
The GRADE approach was created in the year 2000 and represents the reference tool for assessing the reliability of scientific evidence, for formulating evidence-based clinical recommendations, as well as for systematic reviews within the Cochrane Library. To date, it is estimated that over 100 organizations in 19 countries around the world are using this method, including the World Health Organization. Such approach considers not only appropriateness of the study design, but also alternative criteria of methodological appropriateness and the relevance of the results in terms of direct applicability, evaluating quality of evidence for patient-relevant outcomes. The GRADE approach classifies the quality of evidence in one of four levels: high, moderate, low and very low.

Based on the new criteria, the possible outcomes of the evaluation are:

- recognition of the innovative status for a specific therapeutic indication, which entitles to the economic benefits previously mentioned, such as access to the Innovative Fund (or Innovative oncology medicines Fund), suspension of the statutory 5% reductions and immediate inclusion in Regional Formularies;
- recognition of **conditional innovativeness** which allows immediate access to all Regional formularies;
- no innovativeness is recognized.

The 2017 Financial Law establishes that recognition of innovation and related benefits have a maximum duration of thirty-six months. Moreover, the innovation status can be

[4] http://www.gradeworkinggroup.org/

reconsidered in the case of new evidences becoming available. If the status is not confirmed, the associated benefits shall lapse and a new pricing and reimbursement negotiation is initiated. In the case of medicines with conditionally innovative designation, the status is reviewed after 18 months, upon request by the MAH or ex officio by AIFA.
For first in class medicines (medicines with a different mechanism of action compared to those available on the market), benefits associated with the innovative status have a maximum duration of thirty-six months, while follower medicines can benefit for the time remaining from the initial first-in-class assessment.
In order to guarantee the maximum level of transparency, a report explaining the rationale for the innovativeness assessment of each molecule is made publicly available on AIFA's website https://www.aifa.gov.it/farmaci-innovativi) as of January 2018.

Expenditure and consumption of innovative medicines

The following tables show an analysis of expenditure and consumption for innovative medical products in the period 2016-2019. For each medicinal product, expenditure and consumption were considered only for the period of effectiveness of the innovative status (innovativeness and conditional innovativeness). The data refer to the total value of expenditure and consumption of the medicinal product and not only to the indication to which the innovative status was recognized in case of several indications reimbursed. Table 7.1.1 lists the medicines considered in the analysis and the respective dates of effectiveness and expiry of the innovation requirement.
In 2019, expenditure for innovative medicines amounted to €2.6 billion, showing an increase compared to year 2018 (+62.6%). The sofosbuvir/velpatasvir association is the specialty with major impact on expenditure for innovative medicines (28.4%), together with pembrolizumab (10.6%) and nivolumab (10.3%) (Table 7.1.3).
For a correct interpretation of expenditure data and of differences compared to the previous year, it should be noted that these values are net of credit notes issued for lenalidomide for year 2019 and of those issued for sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, lenalidomide e nusinersen for year 2018.
In terms of consumption, in 2019 the daily doses dispensed were 30.5 million, compared to 21.7 million in 2018 and 13.4 million in 2017, resulting in an increase of +40.5% compared to 2018 (Table 7.1.2 and Table 7.1.3).
It should be noted that among all medicines included in the innovative list in 2019, tocilizumab records the highest consumption. This medicine was granted conditional innovativeness for the indication giant cell arteritis (ACG) in adults, with a consumption value amounting to a 0.98 million DDD in 2019, equal to 3.2% of total consumption for innovative medicines. Moreover, it should be noted that the sacubitril-valsartan combination, which was granted conditional innovativeness in 2018 for the indication in the treatment of symptomatic chronic heart failure in adults with reduced ejection fraction, in 2019 recorded the highest consumption among innovative medicines, with almost 9 million DDD, corresponding to 29.4% of total consumption for innovative medicines. Other active ingredients with major impact on expenditure variation compared to 2018 were:

alemtuzumab, avelumab, dupilumab, canakinumab, ribociclib, midostaurina and regorafenib.
The regions with the highest expenditure for innovative medicines in 2019 are Lombardy (€443.4 million), Campania (€281.1 million) and Lazio (€244.8 million), accounting for 16.7%, 10.6% and 9.2% of the total expenditure, respectively.
Expenditure by Region for innovative products accessing the Funds in accordance with the 2017 Budget Law is reported in Table 7.1.6. Expenditure amounted to €1 billion and 108.7 million for innovative non oncology medicines and to €584.9 million for innovative oncology medicines. If these figures are considered net of the paybacks related to conditional reimbursement agreements, expenditure for innovative non oncology and oncology medicines amounts respectively to €403 million and €519.9 million.

Table 7.1.1. List of innovative medicines in the period 2016-2019

ATC	Medicine	Active ingredient	Class	Effective date (Official Gazette G.U.)	Expiry date Requirement
L01XC12	Adcetris	brentuximab vedotin	H	01/11/2019	30/04/2021
L01XE36	Alecensa	alectinib	H	01/08/2018	31/07/2021
L01XC31	Bavencio	avelumab	H	25/09/2018	24/09/2021
L01XC26	Besponsa	inotuzumab ozogamicin	H	08/06/2018	07/06/2021
M05BX05	Crysvita	burosumab	H	06/09/2019	05/03/2021
L01XC24	Darzalex	daratumumab	H	19/04/2018	18/04/2021
D11AH05	Dupixent	dupilumab	H	08/09/2018	07/09/2021
J05AP55	Epclusa	sofosbuvir/velpatasvir	A	27/04/2017	26/04/2020
B02BX06	Hemlibra	emicizumab	A	07/12/2018	06/12/2021
L04AB04	Humira	adalimumab	H	23/05/2018	22/11/2019
L01XE33	Ibrance	palbociclib	H	23/12/2017	22/06/2019
L04AC08	Ilaris	canakinumab	H	26/09/2018	25/03/2020
L01XE27	Imbruvica	ibrutinib	H	05/01/2016	06/03/2020*
L01XC28	Imfinzi	durvalumab	H	06/09/2019	06/09/2022
L01XC18	Keytruda	pembrolizumab	H	25/06/2017	10/12/2022*
L01XE42	Kisquali	ribociclib	H	25/09/2018	24/03/2020
L01XX71	Kymriah	tisagenlecleucel	H	13/08/2019	12/08/2020
L01XC27	Lartruvo	olaratumab	H	05/08/2017	04/02/2019
V10XX04	Lutathera	lutezio-177Lu-oxodotreotide	H	30/03/2019	29/03/2022
J05AP57	Maviret	glecaprevir/pibrentasvir	A	28/09/2017	26/04/2020
L01XE25	Mekinist	trametinib	H	17/12/2019	16/12/2022
L01XC17	Opdivo	nivolumab	H	18/03/2016	17/12/2022*
S01XA24	Oxervate	cenegermin	H	24/01/2018	23/01/2021
J05AX18	Prevymis	letermovir	H/A	18/09/2018	17/09/2021
L01XC16	Qarziba	dinutuximab beta	H	01/08/2018	31/07/2021
L04AX04	Revlimid	lenalidomide	H	25/05/2018	24/11/2019

continued

Table 7.1.1 (continued)

ATC	Medicine	Active ingredient	Class	Effective date (Official Gazette G.U.)	Expiry date Requirement
L04AC07	Roactemra	tocilizumab	H	05/06/2019	17/12/2020
L01XE39	Rydapt	midostaurin	H	17/08/2018	16/08/2021
L01XE21	Stivarga	regorafenib	A	26/09/2018	25/03/2020
M09AX07	Spinraza	nusinersen	H	28/09/2017	27/09/2020
L03	Strimvelis	autologous CD34+ cells	H	16/08/2016	15/08/2019
L01XE23	Tafinlar	dabrafenib	H	17/12/2019	16/12/2022
L01XE35	Tagrisso	osimertinib	H	30/11/2019	29/05/2021
L01XC32	Tecentriq	atezolizumab	H	15/07/2018	24/03/2019
L01XX52	Venclyxto	venetoclax	H	12/08/2017	12/06/2021
J05AP56	Vosevi	sofosbuvir/velpatasvir/voxilaprevir	A	19/04/2018	26/04/2020
L01XE50	Verzenios	abemaciclib	H	13/12/2019	12/06/2021
L01XY01	Vyxeos	citarabina/daunorubicina	H	19/06/2019	18/06/2022
L01XX70	Yescarta	axicabtagene ciloleucel	H	12/11/2019	11/11/2020
L01XX54	Zejula	niraparib	H	21/09/2018	20/03/2020
J05AP54	Zepatier	elbasvir/grazoprevir	A	04/02/2017	03/02/2020

* The requirement expiry date is referred to the most recent indication.

Table 7.1.2 Expenditure and consumption trends for innovative medicines (years 2015-2019) purchased by public health facilities

	2015	2016	2017	2018^	2019°	Δ% 19-18
Innovative expenditure*	2,226	2,636	1,635	1,629	2,649	62.6
Inc. % NHS expenditure	10.1	11.7	7.4	7.4	11.4	
DDD*	9.2	12.0	13.4	21.7	30.5	40.5
Inc. % DDD NHS	0.03	0.05	0.05	0.09	0.12	

*Million

^ In 2018 expenditure data is net of the credit notes issued for sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, lenalidomide e nusinersen.

° In 2019 expenditure data is net of the credit notes issued for lenalidomide.

Note: The expense does not take into account the paybacks paid by pharmaceutical companies for the application of conditional reimbursement agreements.

Table 7.1.3. Expenditure and consumption for innovative medicines (innovativeness and conditional innovativeness) purchased by public health facilities (years 2016-2019)

Active Ingredient	2016			2017			2018^			2019°		
	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *
alectinib							6.2	35.6	0.4	40.8	234.8	1.5
avelumab							0.3	1.7	0.0	3.7	21.6	0.1
inotuzumab ozogamicin							1.5	2.1	0.1	6.6	9.1	0.3
blinatumomab				4.0	1.9	0.2	8.5	4.1	0.5	11.8	5.8	0.4
burosumab										0.4	2.0	0.0
daratumumab							58.3	312.1	3.6	156.3	838.4	5.9
dupilumab							1.0	30.4	0.1	26.7	817.6	1.0
sacubitril/valsartan				5.2	1193.4	0.3	20.8	5046.6	1.3	36.6	8958.7	1.4
sofosbuvir/velpatasvir				156.7	1423.8	9.6	137.3	1737.7	8.4	751.9	1148.1	28.4
emicizumab										16.5	15.7	0.6
adalimumab							152.4	5111.1	9.4	99.8	5814.4	3.8
palbociclib							75.0	912.5	4.6	79.7	943.4	3.0
canakinumab							6.4	37.7	0.4	40.3	247.6	1.5
ibrutinib	38.2	245.8	1.4	81.4	522.6	5.0	111.6	757.2	6.9	132.0	1014.8	5.0
durvalumab										3.2	31.5	0.1
pembrolizumab	11.1	46.3	0.4	61.2	478.3	3.7	194.3	2010.7	11.9	281.4	3204.1	10.6
ribociclib							0.9	12.1	0.1	22.2	303.3	0.8
tisagenlecleucel										1.2	0.0	0.0
olaratumab				0.9	3.4	0.1	10.1	37.0	0.6	1.4	5.0	0.1
lutezio-177Lu-oxodotreotide										3.5	0.2	0.1
glecaprevir/pibrentasvir				26.5	189.5	1.6	216.4	1596.8	13.3	124.7	1043.7	4.7
trametinib									0.0	0.0	0.0	0.0
nivolumab	62.0	286.5	2.4	181.7	1009.5	11.1	266.6	1529.9	16.4	272.8	1768.7	10.3
cenegermin							3.6	13.1	0.2	4.0	15.2	0.2
letermovir										10.8	26.7	0.4
dinutuximab beta										3.2	0.9	0.1
lenalidomide	184.6	1208.1	7.0	149.2	1144.0	9.1	127.0	1065.7	7.8	241.7	1966.1	9.1
tocilizumab										25.2	984.4	1.0
midostaurin							1.2	2.3	0.1	12.6	23.5	0.5
nusinersen				8.0	12.5	0.5	74.6	174.1	4.6	102.2	242.4	3.9
regorafenib							2.1	26.1	0.1	10.4	122.9	0.4

Table 7.1.3 (continued)

Active Ingredient	2016			2017			2018^			2019°		
	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *
autologous CD34+ cells												
dabrafenib										0.0	0.0	0.0
osimertinib										4.4	35.5	0.2
atezolizumab)							4.1	39.8	0.3	7.2	49.4	0.3
venetoclax				0.9	5.2	0.1	10.0	54.1	0.6	20.5	111.9	0.8
sofosbuvir/velpatasvir/voxilaprevir							10.8	79.7	0.7	47.4	73.1	1.8
citarabina/daunorubicina										2.4	0.6	0.1
axicabtagene ciloleucel												
niraparib							1.4	7.0	0.1	19.3	96.3	0.7
elbasvir/grazoprevir				87.7	751.8	5.4	50.0	607.7	3.1	24.4	312.1	0.9
nab paclitaxel#	22.7	600.8	0.9	23.1	650.4	1.4	4.3	114.2	0.3			
daclatasvir#	189.5	1018.9	7.2	56.9	477.9	3.5	0.0	0.1	0.0			
dasabuvir#	10.8	588.7	0.4	4.5	488.0	0.3	0.2	18.1	0.0			
pomalidomide#	34.1	111.5	1.3	38.3	122.6	2.3	24.4	81.5	1.5			
ivacaftor#	31.0	43.3	1.2	28.9	42.4	1.8	11.1	16.5	0.7			
simeprevir#	5.9	49.1	0.2	0.5	4.8	0.0	0.0	0.0	0.0			
ombitasvir/paritaprevir/ritonavir#	146.0	685.8	5.5	57.4	542.6	3.5	2.2	20.4	0.1			
crizotinib#	19.2	113.9	0.7	24.3	141.2	1.5	22.6	144.8	1.4			
radio ra 223 dicloruro#	6.1	2.1	0.2	7.9	2.7	0.5	1.1	0.4	0.1			
idelalisib#	10.7	100.2	0.4	12.6	115.1	0.8	10.3	93.3	0.6			
brentuximab vedotin§	23.0	58.8	0.9	11.3	34.3	0.7						
ledipasvir/sofosbuvir§	940.1	1763.9	35.7	252.1	473.0	15.4						
trastuzumab emtansine§	57.4	246.0	2.2	42.6	182.2	2.6						
pertuzimab§	78.3	550.0	3.0	49.2	343.3	3.0						
bedaquilina§	0.6	5.7	0.0	0.1	1.3	0.0						
sofosbuvir§	689.6	1423.2	26.2	221.1	456.3	13.5						
dolutegravir§	40.4	2616.9	1.5	40.9	2617.0	2.5						
collagenasi Clostridium histolyticum**	0.2	0.2	0.0									
ipilimumab**	7.4	12.5	0.3									
abiraterone**	26.9	267.2	1.0									
Total	**2,635.6**	**12,045.4**	**100**	**1,635.3**	**13,431.0**	**100**	**1,628.6**	**21,734.0**	**100**	**2,649.4**	**30,489.6**	**100**

* calculated on the total expenditure of innovative medicines; ** innovation requirement expired in 2016; § innovation requirement expired in 2017; # innovation requirement expired in 2018; ^ In 2018 expenditure data is net of the credit notes issued for sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, lenalidomide e nusinersen.

° In 2019 expenditure data is net of the credit notes issued for lenalidomide.

Note: Expenditure does not take into account paybacks paid by pharmaceutical companies for the application of conditional reimbursement agreements.

Table 7.1.4. Expenditure and consumption for innovative medicines (innovativeness and conditional innovativeness) purchased by public health facilities (years 2016-2019) by Region

Region	2016			2017			2018^			2019°		
	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *	Expenditure *(million)*	DDD *(thousand)*	Inc. % *
Piedmont	176.7	887.0	6.7	117.9	963.4	7.2	115.0	1385.0	7.1	201.8	1827.2	7.6
Valle d'Aosta	3.5	13.6	0.1	1.8	9.4	0.1	2.1	26.5	0.1	3.1	34.0	0.1
Lombardy	445.9	2462.9	16.9	285.8	2486.8	17.5	251.3	2553.6	15.4	443.4	3519.8	16.7
A.P. of Bolzano	16.7	97.5	0.6	10.2	84.9	0.6	13.1	177.3	0.8	20.7	233.5	0.8
A.P. of Trento	13.2	57.4	0.5	7.7	67.3	0.5	9.5	129.7	0.6	16.7	161.2	0.6
Veneto	170.0	773.9	6.5	112.7	984.9	6.9	119.5	1420.3	7.3	191.5	2092.1	7.2
Friuli VG	28.9	166.6	1.1	30.4	257.1	1.9	37.2	468.4	2.3	63.8	699.6	2.4
Liguria	66.1	306.3	2.5	48.2	354.1	2.9	49.4	572.1	3.0	73.1	768.8	2.8
Emilia R.	195.4	973.8	7.4	130.6	1133.9	8.0	141.0	1687.4	8.7	213.5	2245.7	8.1
Tuscany	200.2	881.5	7.6	110.8	1010.3	6.8	116.8	1520.5	7.2	181.8	1841.9	6.9
Umbria	35.7	180.8	1.4	23.4	225.7	1.4	28.7	415.0	1.8	46.3	627.9	1.7
Marche	47.7	247.8	1.8	34.9	289.9	2.1	43.8	610.0	2.7	70.4	959.1	2.7
Lazio	230.8	970.4	8.8	141.3	1255.3	8.6	169.3	2428.3	10.4	244.8	3347.2	9.2
Abruzzo	37.6	190.9	1.4	27.8	233.3	1.7	31.0	466.8	1.9	45.9	771.2	1.7
Molise	11.0	44.6	0.4	6.8	52.1	0.4	6.9	100.6	0.4	12.2	153.8	0.5
Campania	354.6	1333.8	13.5	201.8	1464.7	12.3	169.6	2812.6	10.4	281.1	4310.7	10.6
Puglia	197.7	843.8	7.5	117.7	886.7	7.2	116.0	1708.7	7.1	187.1	2461.2	7.1
Basilicata	26.4	97.5	1.0	15.0	121.1	0.9	14.0	248.1	0.9	23.9	366.1	0.9
Calabria	82.7	298.4	3.1	47.7	310.2	2.9	39.4	645.0	2.4	71.2	1138.0	2.7
Sicily	209.3	810.3	7.9	114.6	868.6	7.0	110.0	1774.5	6.8	188.4	2308.1	7.1
Sardinia	85.3	406.4	3.2	48.4	371.4	3.0	44.9	583.6	2.8	68.6	622.5	2.6
Italy	**2,635.4**	**12,045.2**	**100**	**1,635.5**	**13,431.1**	**100**	**1,628.5**	**21,734.0**	**100**	**2,649.3**	**30,489.6**	**100**
Northern	1116.4	5739.1	42.4	745.3	6341.8	45.6	738.0	8420.4	45.3	1227.7	11582.0	46.3
Central	514.4	2280.5	19.5	310.4	2781.2	19.0	358.7	4973.8	22.0	543.3	6776.1	20.5
Southern	1004.7	4025.7	38.1	579.8	4308.1	35.5	532.0	8339.9	32.7	878.4	12131.6	33.2

* calculated on the total expenditure of innovative medicines; ^ In 2018 expenditure data is net of the credit notes issued for sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, lenalidomide e nusinersen. ° In 2019 expenditure data is net of the credit notes issued for lenalidomide.

Note: Expenditure does not take into account paybacks paid by pharmaceutical companies for the application of conditional reimbursement agreements.

Table 7.1.5. List of medicines accessing the Innovative Funds as of 31 December 2019 (2017 Budget Law)

Innovative non-oncology	Innovative oncology
dupilumab	alectinib
sofosbuvir/velpatasvir	daratumumab
emicizumab	durvalumab
glecaprevir/pibrentasvir	pembrolizumab
cenegermin	tisagenlecleucel
letermovir	lutezio-177Lu-oxodotreotide
nusinersen	glecaprevir/pibrentasvir
autologous CD34+ cells*	nivolumab
sofosbuvir/velpatasvir/voxilaprevir	dinutuximab beta
elbasvir/grazoprevir	midostaurin
	dabrafenib
	osimertinib
	atezolizumab
	citarabine/daunorubicine
	axicabtagene ciloleucel *

* Data not in the traceability flow. As far as Strimvelis is concerned, the medicine is dispensed by an Accredited Private Healthcare Facility.

Table 7.1.6. List of innovative medicines accessing the Innovative Funds (2017 Budget Law) in 2019.

Region	Innovative non-oncology		Innovative oncology	
	Expenditure^ (€)	Expenditure net of *payback*	Expenditure (€)	Expenditure net of *payback*
Piedmont	100,546,680	33,931,917	42,284,387	37,551,218
Valle d'Aosta	1,393,870	365,267	829,509	750,172
Lombardy	216,579,017	83,525,826	96,223,748	87,096,787
A.P. of Bolzano	5,731,087	2,397,989	6,243,870	5,649,672
A.P. of Trento	8,016,507	2,772,143	3,075,706	2,674,274
Veneto	77,698,781	32,076,210	39,694,837	35,368,859
Friuli VG	25,820,119	9,300,467	13,764,566	12,206,395
Liguria	24,237,069	7,390,462	20,405,231	17,838,906
Emilia R.	86,253,224	35,578,756	54,424,396	48,266,265
Tuscany	76,492,815	22,918,771	40,524,548	35,013,340
Umbria	15,209,074	5,710,788	10,914,042	9,802,357
Marche	25,820,822	11,115,555	16,770,413	14,873,333
Lazio	88,888,920	36,238,835	70,925,182	63,617,349
Abruzzo	10,895,141	5,132,784	11,067,811	9,684,783
Molise	4,213,871	1,347,726	1,734,059	1,447,905
Campania	123,345,673	40,090,719	50,859,509	44,013,491
Puglia	70,504,902	24,196,397	39,131,234	35,111,741
Basilicata	7,791,474	2,353,010	5,459,969	5,011,614
Calabria	24,227,131	8,934,600	11,697,492	10,293,467
Sicily	84,503,063	26,905,566	34,693,649	31,115,708
Sardinia	30,537,153	10,734,207	14,142,345	12,511,978
Italy	**1,108,706,392**	**403,017,993**	**584,866,502**	**519,899,614**

* Data on Yescarta not in the traceability flow.

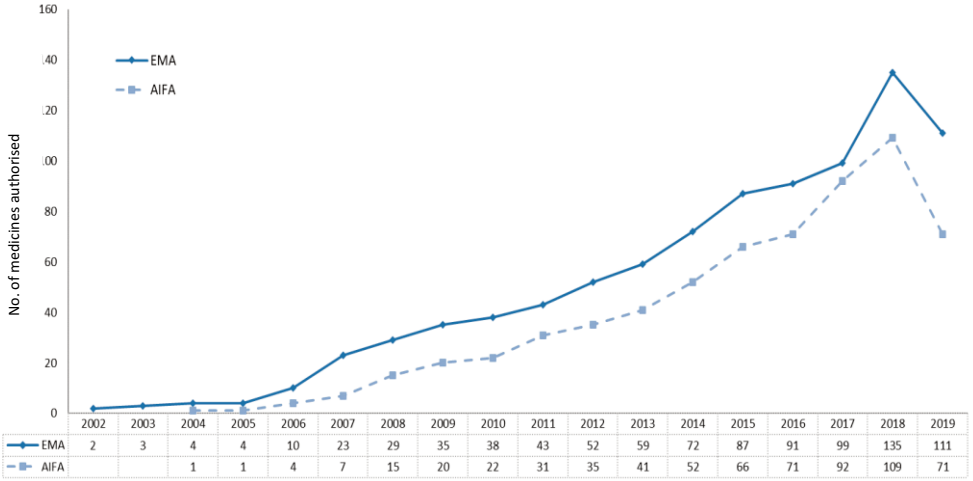
Note: Friuli-Venezia Giulia, Valle d'Aosta and Sardinia, as well as the autonomous provinces of Bolzano and Trento do not participate in the Innovative Funds. Sicily participates partially (50%).

7.2 Orphan medicines

Orphan medicines expenditure and consumption in Italy

In 2019 the European Medicines Agency (EMA) authorized 7 orphan medicines. The main therapeutic areas involved were those of haematology (gilteritinib, polatuzumab vedotin-piiq and autologous CD34+ cells encoding βA-T87Q-globin gene), metabolic system (pegvaliase-pqpz and volanesorsen), endocrinology (osilodrostat) and neurology (cannabidiol).
Furthermore, out of 111 medicines authorised by EMA (7 of which no longer included the orphan medicines list due to patent expiry during 2019; 106 still active), 71 are included in AIFA's list of orphan medicines and have been marketed in Italy as of 31 December 2019 (6 included although expired during the year; 65 still active). Out of the remaining 40 medicines: for 11, a P&R application has never been submitted by the pharmaceutical company; for 9 a P&R application was submitted but the negotiation process has not been concluded yet. Of these, 5 are however made available as they have been classified as Class CNN products and 7 have been classified as Class C products, therefore available but not reimbursed by NHS. As far as the remaining 13 medicines are concerned, these are available to patients through alternative channels[5] encouraged by AIFA.

Figure 7.2.1 Comparison between EMA authorized orphan medicines and those approved by AIFA (data 2002-2019)



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
EMA	2	3	4	4	10	23	29	35	38	43	52	59	72	87	91	99	135	111
AIFA			1	1	4	7	15	20	22	31	35	41	52	66	71	92	109	71

[5] For example, Law no. 648/96 and Law no. 326/2003.

Starting from 2019, the list of orphan medicinal products has undergone changes compared to those published in previous years. In accordance with the 2019 Budget Law (Law no. 145 of 2018), only orphan medicines authorized by the EMA and inserted in the Community Register of orphan medicinal products for human use will benefit from the exclusion from the payback procedures.
Interestingly, more than half of the medicines included in AIFA's orphan list is subject to a monitoring Registry; to a little more than 25%, a Managed Entry Agreement was applied during the pricing and reimbursement phase; approximately 15% of the medicines was also granted full innovativeness.
Expenditure and consumption data for the period 2010-2018 concerning orphan drugs (Table 7.2.1) were elaborated on the basis of the classification approved by AIFA's Board of Directors (Resolution no. 10 of 27 February 2014). For 2019, expenditure and consumption data were elaborated on the basis of the criteria introduced by the 2019 Budget Law, which changed the list of orphan medicines. As a result, starting from 2019, an interruption in the time-series can be observed and data resulting from current analysis are not comparable with those referring to previous years.
In 2019 orphan medicine expenditure, including purchases by public health facilities and supply in approved care regime, amounted to approximately €1.5 billion, corresponding to 6.6% of the total NHS pharmaceutical expenditure. Consumption of orphan medicines amounted to 9.7 million DDD, corresponding to 0.04% of overall pharmaceutical consumption. As regards therapeutic classes, 72.5% of orphan medicine expenditure was covered by antineoplastic agents and immuno-modulators, followed by musculo-skeletal system medicines (7.5%) and gastrointestinal tract and metabolism medicines (5.6%).
Alongside, in terms of consumption, 73.6% of orphan medicines consumption was covered by antineoplastic agents and immuno-modulators, followed by cardiovascular system medicines (about 8%) and systemic hormone preparations, excluding sex hormones (7.1%) (Figure 7.2.2).

Table 7.2.1 Expenditure and consumption trends for orphan medicines, years 2010-2019*

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Expenditure for orphan medicines (million)	657	800	671	917	1,060	1,212	1,393	1,599	1,781	1,547
Incidence (%) of orphan medicines on pharmaceutical expenditure	3.5	4.2	3.5	4.67	5.31	5.49	6.13	7.2	8.1	6.6
Consumption (DDD) orphan medicines (million)	6.6	7.5	5.9	7.5	8.5	10.3	11.4	12.7	12.2	9.7
Incidence (%) of orphan medicines on consumption	0.03	0.03	0.02	0.03	0.03	0.04	0.04	0.05	0.05	0.04

* Expenditure and consumption data have been processed for the years 2013-2018 on the basis of the classification approved by AIFA's Board of Directors (Resolution no. 10 of 27 February 2014) and for year 2019 on the basis of Law 145/2018 (2019 Budget Law). These results are therefore not comparable with those for previous years.

In 2019, expenditure for orphan medicines also meeting the innovation requirement amounted to €428.4 million (Table 7.2.2). The number of innovative orphan medicines increased from 8 in 2018 to 10 in 2019. Consumption and expenditure have therefore increased.

Table 7.2.2. Orphan medicines accessing the fund for oncology and non-oncology innovative medicines: expenditure and consumption, year 2019

Medicine	2019	
	Expenditure	DDD
daratumumab	156,322,451	838,428
ibrutinib	132,023,792	1,014,790
nusinersen	102,249,840	242,400
midostaurin	12,589,777	23,543
letermovir	10,794,001	26,653
cenegermin	4,040,510	15,232
lutezio-177Lu-oxodotreotide	3,491,520	244
dinutuximab beta	3,216,868	926
citarabine/daunorubicine	2,436,630	608
tisagenlecleucel	1,191,200	16
Total	**428,356,590**	**2,162,839**

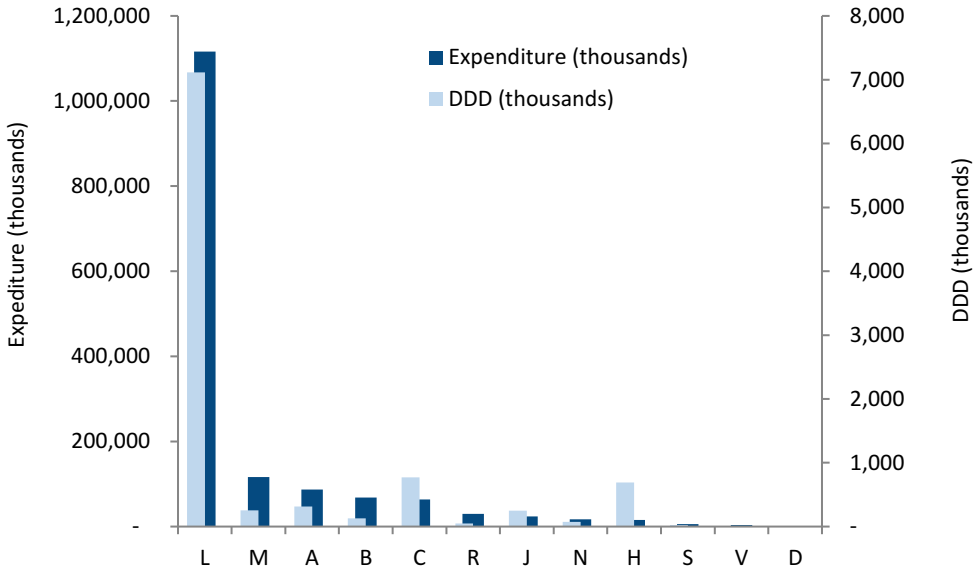
In 2019 a greater consumption of orphan medicines in terms of DDD/1000 inhabitants per day can be observed in northern regions and, consequently, also a major expenditure. As regards per capita expenditure, the highest value was recorded in Umbria (€31.6) and Puglia (€30.5), while Valle d'Aosta (€14.5) and the autonomous province of Trento (€20.1) show the lowest values (Table 7.2.3).

Table 7.2.3 Expenditure and consumption of orphan medicines (AIFA list) by Region, year 2019

Region	Expenditure	DDD	Inc.%*	Per capita expenditure	DDD/1000 inhab.per day
Piedmont	115,913,954	757,234	7.5	25.3	0.45
Valle d'Aosta	1,872,112	13,150	0.1	14.5	0.28
Lombardy	236,261,267	1,366,839	15.3	23.6	0.37
A.P. of Bolzano	14,445,972	83,477	0.9	29.0	0.46
A.P. of Trento	10,707,391	63,521	0.7	20.1	0.33
Veneto	127,273,354	767,067	8.2	25.8	0.43
FriuliVG	35,427,534	220,093	2.3	27.4	0.47
Liguria	46,150,552	284,008	3.0	26.8	0.45
Emilia R.	131,268,219	760,639	8.5	28.8	0.46
Tuscany	104,233,516	636,909	6.7	26.7	0.45
Umbria	29,236,735	190,338	1.9	31.6	0.56
Marche	47,065,143	315,568	3.0	29.8	0.55
Lazio	143,962,477	927,522	9.3	24.9	0.44
Abruzzo	32,935,200	243,368	2.1	24.7	0.50
Molise	7,983,385	50,008	0.5	25.3	0.43
Campania	137,198,055	927,857	8.9	25.7	0.48
Puglia	120,433,691	755,803	7.8	30.5	0.52
Basilicata	14,897,976	100,252	1.0	26.4	0.49
Calabria	49,048,417	307,339	3.2	26.0	0.45
Sicily	105,680,903	657,462	6.8	22.0	0.37
Sardinia	35,068,249	235,246	2.3	20.8	0.38
Italy	**1,547,064,100**	**9,663,700**	**100.0**	**25.6**	**0.44**
Northern	719,320,354	4,316,028	46.5	25.4	0.42
Central	324,497,871	2,070,338	21.0	26.6	0.46
Southern and insular	503,245,876	3,277,335	32.5	25.3	0.45

* Calculated on the total expenditure of orphan medicines nationwide

Figure 7.2.2 Expenditure and consumption of orphan drugs in Italy for ATC level, year 2019



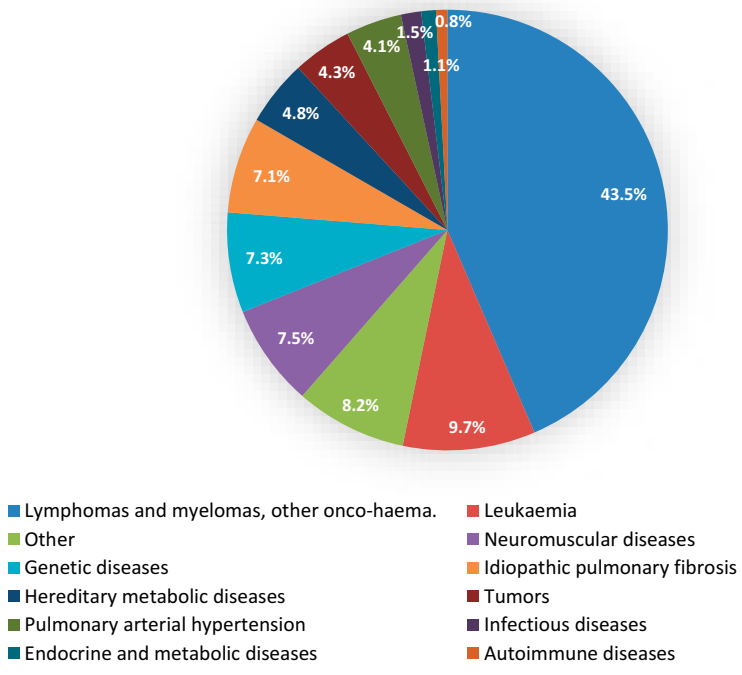
L	Antineoplastic and immunomodulating agents	N	Nervous system	G	Genito urinary system and sex hormones
A	Alimentary tract and metabolism	H	Systemic hormonal preparations, excl.sex hormones	J	Anti-infectives for sistemic use
C	Cardiovascular system	V	Various	D	Dermatologicals
B	Blood and blood forming organs	R	Respiratory system	S	Sensory organs
		M	Musculo-skeletal system		

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 other onco-haematologic diseases, followed by leukaemias (43.5% and 9.7% respectively). The analysis also shows the highest consumption for lymphomas, myelomas and other onco-haematologic diseases, though a high consumption for medicines for pulmonary arterial hypertension is also observed (Table and Figure 7.2.4).

Table 7.2.4. Expenditure and consumption of orphan medicines in Italy by therapeutic area, year 2019 (Table and Figure)

Therapeutic Area	Expenditure	DDD	Per capita expenditure	DDD/1000 inhab.per day	Inc.% *
Lymphomas and myelomas, other onco-haema	673,589,337	4,512,148	11.2	0.2	43.5
Leukaemia	150,374,391	798,479	2.5	0.0	9.7
Other	126,555,704	179,469	2.1	0.0	8.2
Neuromuscular diseases	116,018,682	250,905	1.9	0.0	7.5
Genetic diseases	113,639,566	209,720	1.9	0.0	7.4
Idiopathic pulmonary fibrosis	109,193,937	1,274,714	1.8	0.1	7.1
Hereditary metabolic diseases	74,632,085	200,471	1.2	0.0	4.8
Tumors	67,174,417	361,224	1.1	0.0	4.3
Pulmonary arterial hypertension	63,401,791	771,607	1.1	0.0	4.1
Infectious diseases	22,972,342	142,173	0.4	0.0	1.5
Endocrine and metabolic diseases	16,672,385	794,191	0.3	0.0	1.1
Autoimmune diseases	12,839,463	168,599	0.2	0.0	0.8
Total	**1,547,064,100**	**9,663,700**	**25.6**	**0.44**	**100.0**

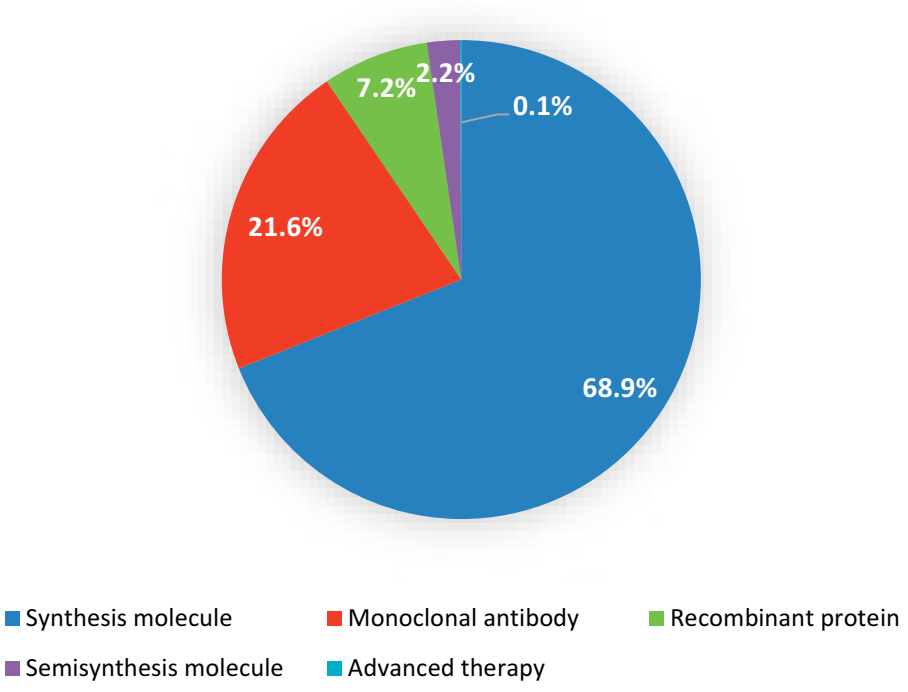
* Calculated on the total expenditure of orphan medicines nationwide



Analysis by product type shows that most orphan medicines are synthesis molecules (69.0%), followed by monoclonal antibodies (21.6%), while advanced therapies account for 0.1% only (Table and Figure 7.2.5).

Table 7.2.5 Expenditure and consumption of orphan medicines in Italy by type, year 2019 (Table and Figure)

Type of product	Expenditure	DDD	Per capita expenditure	DDD/1000 inhab.per day	Inc.% *
Synthesis molecule	1,066,686,956	8,049,638	17.7	0.4	69.0
Monoclonal antibody	333,649,470	1,220,056	5.5	0.1	21.6
Recombinant protein	110,977,450	278,851	1.8	0.0	7.2
Semisynthesis molecule	34,370,403	115,139	0.6	0.0	2.2
Advanced therapy	1,379,821	18	0.0	0.0	0.09
Total	**1,547,064,100**	**9,663,700**	**25.6**	**0.44**	**100.00**



Appendix 1

Regulation of pharmaceutical assistance in Italy

National Report
on Medicines
use in Italy
Year 2019

1. Main measures enacted in 2019

Budget Law 2019

The 2019 Budget Law[1] introduced some important innovations regarding pharmaceutical expenditure, also in the light of the document concerning the governance of pharmaceutical care:

- Application of a payback system per market share, therefore going beyond the budget company procedure. The payback is calculated for each pharmaceutical company, with separate computation of direct purchases of medicinal gases compared with other direct purchases, proportionally to their market share;
- Amendment as of 2019 of AIFA's list of orphan drugs, which will include only class A and H products authorised by EMA and marketed in Italy and which have not yet exhausted market exclusivity.

New criteria for pricing and reimbursement

In August 2019 the Ministry of Health issued a Decree establishing new criteria for pricing and reimbursement (pending publication in the Italian Official Journal). The main changes concern:

- Focus on the added therapeutic value, which means that the company will have to submit the documentation showing added therapeutic value.
  If the added therapeutic value is proven, the company will be required to submit further data deemed of interest in terms of economic benefit for the NHS. This is in line with the principles set forth in the document on pharmaceutical governance.
- Scope of the Decree: the Decree also applies to the inclusion of medicinal products in the list pursuant to Law 648/1996 and to the purchase of specific categories of medicinal products of Class C and Cnn by NHS bodies, for public health needs.
- Start of negotiation: the Decree establishes that the negotiation procedure may be started both by the company, as already provided for in CIPE (Interministerial Committee for Economic Planning) Resolution of 2001, and by AIFA, in the case of medicines whose reimbursement has a significant impact in terms of NHS expenditure or prescriptive inappropriateness, or in case of medicines that have never been subject to previous negotiations. The procedure may be started by AIFA also if previous negotiations were unsuccessful and the medicinal product was therefore assigned to Class C.
- Submission of economic assessments: in case benchmarks are available, the company is required to submit, together with the documentation, an economic assessment supporting the price proposal, also based on R&D costs incurred and production costs.

[1] Law no. 145 dated 30 December 2018

WHA Resolution 72/2019 on transparency of markets for medicines

After complex negotiations, on 28 May 2019 the World Health Assembly (WHA) approved a resolution on improving the transparency of markets for medicines, vaccines and other health products. The initiative, promoted in February by the Italian Government, was supported by twenty-two countries (Algeria, Andorra, Botswana, Brazil, Egypt, Eswatini, Greece, India, Indonesia, Kenya, Luxembourg, Malaysia, Malta, Portugal, Russian Federation, Serbia, Slovenia, South Africa, Spain, Sri Lanka, Uganda and Uruguay). The Resolution urged States to improve public sharing of information on actual prices paid by governments and other purchasers for health products and greater transparency on pharmaceutical patents, the results of clinical trials and other price elements at each stage of the chain, from laboratory to patient's medicine cabinet.

EMA communication on omega-3 fatty acids (29 March 2019)

On 29 March 2019 the European Medicines Agency (EMA) confirmed that omega-3 fatty acid medicinal products are not effective in preventing heart and blood vessels problems in patients who have had a heart attack. The conclusion, based on a reassessment of the data collected over the years, is that these medicinal products will no longer be authorised for such use.
The assessment was carried out by the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted an opinion in December 2018.
Following a request from some marketing authorisation holders, the CHMP re-examined its original opinion and adopted its final opinion, which was forwarded to the European Commission. On 6 June 2019, the European Commission issued a final legally binding decision applicable in all EU Member States.
At the time of authorisation of such medicines, the available data showed some benefits in reducing serious heart and blood vessels problems, although these benefits were considered modest.

Additional data, which became subsequently available, did not confirm the efficacy of these medicines for such use. Although no new safety problems have arisen, the CHMP concluded that the benefit-risk balance of these medicines in preventing recurrence of heart disease or stroke is now negative. These medicines can still be used to reduce the levels of certain types of fat in the blood, called triglycerides.

Table 1.1. Context indicators of pharmaceutical care in Italy

	2016	2017	2018	2019
Total hospital discharges (1)	9,061,064	8,872,090		
Total days provided (1)	61,236,601	59955328		
Ratio between days in Day Hospital and Ordinary hospitalisation (acute cases)	0.12	0.11		
Average length of stay for acute cases in ordinary regime	6.90	6.90		
Average stay for Rehabilitation in ordinary regime	25.80	25.50		
Medium term in long-term care	27.60	24.10		
Medium weight (2) (3)	1.19	1.19		
Average number of diagnoses for hospital discharge (2)	2.50	2.80		
Average number of procedures for hospital discharge (2)	2.90	2.90		
no. MA Holders (4)			817	849
no. medicine distributors (5)			2,323	2,352
no. pharmacies (5)			19,854	20,524
no. retail shops (5)			6,443	6,784
no. GPs (6)	44,279			
no. GPs per 10,000 inhab. (6)	7.3			
no. PFCs (6)	7,662			
no. PFCs per 10,000 inhab. (6)	9.3			
no. ASL (Local Health Authorities) (7)		101		
no. Health authorities (8)		102		
no. hospital beds in ordinary regime per 1000 inhab.	3.18	3.12		
no. hospital beds in Day Hospital regime per 1000 inhab.	0.36	0.35		

(1) Total hospital admissions, including Neonatal care
(2) Admissions for acute cases in ordinary regime
(3) DRG relative weight pursuant to Ministerial decree 1997 (until 2005), Medicare 2002 (2006-2008), pursuant to Ministerial decree 18 Dec. 2008.
(4) Data source: Medicinal Products Database of the Italian Medicines Agency (AIFA)
(5) Data source: Dataset on the production and distribution chain of medicinal products in the "Open data" section
(6) Data source: Dataset "Basic health care" of the ISTAT website
(7) Data source: Dataset "Local Health Authorities" published in the Open data section of the Ministry of Health
(8) Data source: Dataset "NHS Structures" published in the Open data section of the Ministry of Health

2. Medicines reimbursement and supply regime

Decision-making processes concerning reimbursement of pharmaceuticals and methods of supply vary across both European and non-European countries. In Italy, these procedures are attributed to AIFA and its advisory bodies. Medicinal products included in the National Pharmaceutical Formulary and completely reimbursed by the NHS are classified as Class A (Class H when they are dispensed in hospital settings or equivalent facilities), (Art. 8, paragraph 10, point A, Law no. 537 of 24 December 1993, as amended). Conversely, medicinal products are classified as Class C when they are not reimbursed by the NHS, with the exception of individuals with a lifetime war pension, whereby the general practitioner attests their proven therapeutic utility for the patient (Law no. 203 of 19 July 2000).
NHS reimbursed medicines include essential products intended for the treatment of chronic diseases and reimbursed for each authorised therapeutic indication. In some cases, reimbursement is granted through AIFA Notes, which restrict reimbursement only to some indications in order to ensure appropriate use.
Therefore, Class A products, whose therapeutic indications are not included in AIFA Notes, are entirely paid by patients. Class C medicines are not considered to be essential and can be dispensed to citizens with or without a medical prescription (Class C prescription and Class C non-prescription, respectively).
Non-reimbursed pharmaceuticals include both those classified as Class C-(a) (Art. 8, paragraph 10, point C – (a), Law no. 537 of 24 December 1993, as amended), also known as over-the-counter (OTC) medicines, which may be advertised, and Class C without prescription (but not OTC), for which advertising is not permitted. Through Ministerial Decree dated 18 April 2012 (implementing provisions of Art. 32, paragraph 1, Law Decree no. 201 of 6 December 2011, as amended and converted into Law no. 214 dated 22 December 2011), AIFA updated the supply regime of Class C medicines with prescription, establishing which medicines needed compulsory prescription and which could be sold in shops and para-pharmacies, as provided for in Art. 32, paragraph 1, Law Decree no. 201/2011. Ministerial decree of 18 April 2012 was later updated, integrating the list of non-prescription medicines with medicines reclassified as non-prescription based on the opinion of AIFA's CTS (Scientific and Technical Committee) (Ministerial Decree of 15 November 2012). This provision was further amended by Decree of 21 February 2014, in turn amended by Decree of 8 May 2014 (published in the Italian Official Journal no. 119 dated 24 May 2014).
Moreover, Art. 12, paragraph 5 of Law Decree no. 158 of 13 September 2012, converted with amendments into Law no. 189 of 8 November 2012 (so-called "Balduzzi Decree"), as amended, established that medicinal products which are granted a marketing authorization through centralised, mutual recognition, decentralised or national procedure as well as through parallel import, are automatically classified in the new group of "C- non negotiation" (C-NN), pending submission, by the concerned pharmaceutical company, of an application for a different classification and for price negotiation, following submission of a specific dossier according to CIPE indications (CIPE deliberation no. 3 of 1 February 2001). Before marketing, the MAH is required to communicate to AIFA the ex factory and retail price of the medicinal product classified in class C-NN, together with the marketing date.

When a pharmaceutical company submits the pricing and reimbursement dossier to AIFA, the competent offices and advisory committees perform a preliminary assessment to evaluate the product's efficacy and safety and establish its reimbursement class. At the end of the decision-making and negotiation processes - performed by AIFA's Scientific and Technical Committee and Pricing and Reimbursement Committee - the final provision is ratified by AIFA's Board of Directors. This decision authorises the reimbursement of the medicinal product concerned, its supply regime and the price. The decision is then published in the Italian Official Journal (OJ).

With reference to supply methods (pursuant to Article 87 of Legislative Decree no. 219 of 24 April 2006, as amended), medicinal products can be classified as follows:

a) medicinal products subject to medical prescription (RR);
b) medicinal products subject to medical prescription to be renewed each time (RNR);
c) medicinal products subject to a special medical prescription (RMS) (Consolidated Law on narcotics, Presidential Decree no. 309 of 9 October 1990, as amended);
d) medicinal products subject to restricted medical prescription, including:
   - medicines dispensable only with a prescription issued by hospitals or specialist doctors (RRL; RNRL);
   - medicines to be exclusively used in hospitals or similar healthcare facilities (OSP);
   - medicines to be used/administered exclusively by specific healthcare professionals pursuant to the provisions of the Regions or Autonomous Provinces (USPL);
e) medicines not subject to medical prescription, including:
   - over the counter medicinal products (OTC);
   - other non-prescription medicinal products.

The repeatable prescription is the most common type of prescription. It has a six-month validity, during which the patient can use the prescription for a maximum of ten times. A peculiar case is represented by psychotropic medicines (tranquillizers, sedatives, hypnotics): their prescription has a thirty-day validity and can be used for no more than three times.
The non-repeatable prescription is necessary for all medications with a potential risk of acute or chronic toxicity, addiction and tolerance, or abuse. This kind of prescription is more restrictive than the previous one, in that the general practitioner is required to issue a new prescription each time the patient needs the medicine.
This prescription is valid for thirty days and is restricted to the number of packages indicated (in case of galenic formulations not containing narcotics, the prescription has a three-month validity). Worthy of note is the case of isotretinoin, whose prescription and supply are allowed only within teratogenic risk prevention programs, with prescription having a seven-day validity and being non repeatable.
The limited-repeat prescription and the non repeatable prescription are used for specific medicinal products and can be issued only by specific healthcare facilities and/or specialist doctors.

The following types of medicines are included:

- medicines for exclusive hospital use (Art. 92, Legislative decree no. 219/2006);
- medicines supplied only if prescribed by a specific specialist doctor or hospital (Art. 93, Legislative decree no. 219/2006);
- medicines for exclusive use by specialist doctors in outpatient clinics (Art. 94, Legislative decree no. 219/2006).

Pharmacists cannot sell medicines to be used or administered exclusively by specific healthcare professionals directly to patients. However, they are allowed to have such medicines available in their pharmacies. Specialist doctors can be provided with such medications also by manufacturers and wholesalers.
AIFA resolution no. 1522 of 13 January 2010 (published on the Supplement no. 21 to Italian OJ no. 25 of 1 February 2010) updated the supply regime of medicines for hospital use. In particular, the previous classifications OSP1 and OSP2 were depleted and the new system entered into force on 16 February 2010. Medicinal products previously classified under OSP1 supply regime were reclassified as OSP, without additional changes. The OSP2 supply regime was modified into RR, RNR, RRL or RNRL supply regime. At a later stage, following AIFA's implementation of the provisions laid down by Article 11, paragraph 7, letter a) of Decree-Law no. 78 of 31 May 2010, converted with amendments into Law no. 122 of 30 July 2010, as amended, many Class H medicines with RR, RNR, RRL or RNRL prescription were reclassified as Class A-PTH (AIFA Resolution of 2 November 2010).
National regulations governing the reimbursement of medicinal products and their supply regime provide for the possibility to identify different methods for supplying medicines to be reimbursed by the NHS, according to their dispensation and use both at local level and in hospital facilities. In particular, medicines consumption at local level follows prescription by general practitioners and paediatricians, as well as prescription or treatment plans by specialist doctors working in public health facilities. While in the first case the medical prescription implies dispensation of the prescribed medicine to patients through affiliated pharmacies, both public and private (affiliation supply regime), in the second case the dispensation of the medicine that is taken by the patient at his own domicile, is carried out either directly by health facilities (direct distribution) or, alternatively, as a result of specific agreements signed at local level, through the pharmacies (*per conto* distribution). Article 8 of Law Decree no. 347 of 18 September 2001 converted with amendments into Law no. 405 of 16 November 2001, as amended, has in fact introduced direct and *per conto* distribution as alternative methods of distributing medicines, compared to the affiliation regime. According to these methods, the purchase of high-consumption medicines by public health facilities and their dispensation takes place in two different ways:

- by Public Health Facilities to patients for the first cycle of therapy, on discharge from hospitalization or following specialist outpatient visits, or to patients who require periodic checks. This dispensing system does not exclusively assume a cost containment value, but has above all the purpose of clinically protecting patients and guaranteeing the therapeutic continuity between hospital and the local level, along with the appropriateness of use of medicinal products;

- on behalf of local health authorities, by pharmacies open to the public on the basis of specific agreements stipulated by the Regions and Autonomous Provinces with Associations of pharmacies affiliated with the NHS, in order to allow patients suffering from chronic diseases and requiring continuous pharmaceutical assistance to obtain supplies from local pharmacies (so-called *per conto* distribution).

Table 2.1. Number of medicines authorised and marketed in 2019 by reimbursement class

Class of	Marketing Authorization (MA)		Medicinal product		Active ingredients	
	No.	% of total	No.	% of total	No.	% of total
Class A	9,852	53.0	4,528	49.9	814	31.4
Class C	6,956	37.4	3,639	40.1	1,293	49.9
Class H	1,785	9.6	914	10.1	482	18.6
Total	**18,593**	**100.0**	**9,081**	**100.0**	**2,589**	**100.0**

3. Medicines distribution chain margins and discounts for the NHS

According to Law no. 662/1996, as amended, distribution margins of pharmaceutical companies, wholesalers and pharmacies on medicinal products to be reimbursed by the NHS are set at 66.65%, 3.0% and 30.35% of the retail price, net of VAT, respectively. At the same time, the NHS withholds, as a discount, a percentage equal to 1.82% of the retail price net of VAT from the share of pharmacists (this share does not apply to rural pharmacies with national assistance – resident population lower than 3000 inhabitants – with annual sales volume not exceeding € 387,324.67 and to other affiliated pharmacies with annual turnover, net of VAT, not exceeding € 258,228.45). Pharmaceutical companies pay 1.83% of the retail price net of VAT to the regions. The described variation in the margins of wholesalers and pharmacists – set out in art. 11, paragraph 6, of Law Decree no. 78/2010, converted with amendments into Law no. 122/2010, as amended – also involved patent-expired medicinal products. In case of generics, excluding medicinal products originally covered by a patent or that benefited from licences due to such patent, the share attributable to pharmaceutical companies remains equal to 58.65% as established by Law Decree no. 39 dated 28 April 2009, converted with amendments into Law no. 77 of 24 June 2009. The remaining 8% share (66.65%) is allocated among pharmacies and wholesalers, according to market rules.
Law Decree no. 95/2012, converted with amendments into Law no. 135/2012, as amended, introduced some important provisions concerning the management of pharmaceutical expenditure, including an increase in the discount paid by pharmacies from 1.82% to 2.25%, currently in force, and the temporary increase in the tax burden on pharmaceutical companies from 1.83% to 4.1% until 31 December 2012.
Table 3.1 shows the discounts charged to pharmacies to the benefit of the NHS, updated by Law Decree No. 148 of 16 October 2017, converted with amendments into Law no. 172 of 4 December 2017 (art. 18-(a), paragraph 2) and these amendments apply as of 1 January 2018.

Table 3.1. Discounts charged to pharmacies on medicines provided by the NHS

Price range (€)	Rates for urban and rural pharmacies without national assistance			Rates for rural pharmacies with national assistance		
	NHS turnover (%)					
	over €300,000	< €300,000 and > €150,000	less than €150,000*	more than 450,000	< €450,000 and > €150,000	less than €150,000*
Range 0-25.82	3.75	1.50	Full exemption	3.75	fixed rate 1.5%	Full exemption
Range 25.83-51.65	6.0	2.40		6.0	fixed rate 1.5%	
Range 51.66-103.28	9.0	3.60		9.0	fixed rate 1.5%	
Range 103.29-154.94	12.50	5.0		12.50	fixed rate 1.5%	
Over 154.94	19.0	7.60		19.0	fixed rate 1.5%	
Further deduction	2.25	-		2.25	-	

* introduced by Law no. 145 of 30 December 2018

4. Cost sharing

Law no. 405/2001, as amended, provided for the possibility for the regions to adopt resolutions concerning the introduction/tightening of cost sharing for citizens, through the introduction or modulation of tickets per prescription (or per package), in order to compensate for any deficits in regional pharmaceutical expenditure compared to the planned expenditure ceiling. This provision has been applied primarily in the regions subject to Deficit Recovery Plans and, to date, in almost all the others.
However, the participation of citizens in the pharmaceutical expenditure does not derive exclusively from regional tickets, but also from the cost sharing on patent-expired medicinal products. As of 1 December 2001, medicinal products without patent coverage reimbursed by the NHS, including generics have been grouped into AIFA transparency lists – currently drafted on a monthly basis – in order to identify a unique reference price for all interchangeable packages. The differential between the prescribed medicine price and the economically lower medicine price of the same composition is charged to the patient. Specifically, if two medicinal products are available with the same active ingredient and route of administration, pharmaceutical form and dosage units, but with different prices, the NHS reimburses the price of the medicinal product with the lowest reference value.
Since Art. 7 of Law no. 405/2001, as amended, defines the reimbursement level by the NHS up to the lowest price of the corresponding product available in the normal regional distribution cycle, lawmakers have granted the possibility of setting reference prices through regional measures. This provision played an important role in particular in the early 2000s, when a homogeneous availability on the national territory of generics, which are generally those with the lowest retail price, could not be guaranteed. In practice, to date, in most Italian regions, reference prices correspond to the prices published in the AIFA transparency lists. A detailed analysis of cost sharing for the reference price of generics has been provided in section 2.1. Although cost sharing for citizens (given by the difference between the retail price of the prescribed medicinal product and the reference price in the

AIFA transparency lists) is substantially homogeneous on the national territory, with the exception of some regions, the procedures for applying the regional ticket to citizens are very diversified (Table 4.1). This condition is expressly allowed by Art. 4 of Law no. 405/2001, as amended, which gives the regions the faculty to apply measures to cover any deficits through the introduction of various initiatives, including the introduction of forms of co-responsibility of the main subjects contributing to the determination of expenditure (the so-called "tickets"). Such faculty has become a legal obligation for regional governments pursuant to Art. 5, paragraph 4 of Law Decree no. 159 of 1 October 2007, converted with amendments into Law no. 222 of 29 November 2007, which expressly provided for the adoption of measures to contain expenditure, including direct distribution, for an amount equal to at least 30% of the Region's local pharmaceutical expenditure deficit with respect to the expenditure ceiling. These measures represent a regional obligation for accessing the supplementary financing paid by the State.
regions that in 2019 did not envisage a ticket as a measure to contain pharmaceutical expenditure reimbursed by the NHS are three (Friuli VG, Marche and Sardinia).
At national level, the cost sharing borne by Italian citizens amounts to €1.58 billion (71% of which is attributable to the share of the reference price and the remaining 29% to the fixed ticket), accounting for 15.7% of gross pharmaceutical expenditure reimbursed by the NHS and with a change rate of -1.5% compared to 2018. As for the per capita cost sharing, a marked variability was recorded at regional level: against a national value of €26.2 per capita (€33.3 in the South and islands and €22.1 in the North), Campania had a value of almost €40 per capita, while in Friuli Venezia Giulia every citizen spent on average little more than €15 (Table 2.3.3).
The following table (Table 4.1) shows the main ticket-related measures in the Italian regions in the year 2019, with the aim of providing a thorough summary (Source: Federfarma[2]), without prejudice to the exemptions provided for by current legislation (exemptions for income, for chronic diseases, for rare diseases, disabilities and situations of particular social interest - Table 4.2 - which summarises the information published on the website of the Ministry of Health).

[2] https://www.federfarma.it/Ticket-Regionali.aspx

Table 4.1. Procedures for applying regional tickets in 2019

Regions	Exemption		Ticket (€)			Transparency lists *	Notes	Legal reference
	Income (€)	Condition	Package	Max prescription	Prescription share			
Valle d'Aosta°	0-9,999	yes	no	no	no	yes	Patients suffering chronic and disabling diseases are excluded from ticket payment	DGR no. 1899 of 28/12/2017
	10,000-25,000	no	1	2	no			
	> 25,000	no	2	4	no			
Piedmont	N/A					yes	Patients identified by exemption codes E92, G01, G02, V01, V01.2 are not required to pay the difference between the price for the public and the reference price of medicines included in transparency lists	DGR no. 57- 5740 of 3/4/2002 DGR no. 36-7965 of 28/12/2007 DGR no.16-3096 of 12/11/2011 DGR no. 39-8425 of 15/02/2019
		yes	no	no	no			
		no	no	no	no			
Lombardy	> 20,000.00	no	2	4	no	yes + ticket		DGR no. 4230 of 25/10/2012
		yes	1	3	no	yes	Chronic conditions and rare diseases; certain types of disabilities limited to single-dose antibiotics, IFN for hepatitis, medicines administered through intravenous infusion (Law 405/2001)	
	Up to 20,000.00	no	no	no	no	yes		
A.P. of Bolzano	N/A	yes	no	no	1	yes + ticket	Chronic conditions, rare diseases, incapacitated for work, civilian invalids, deaf-mutes, victims of terrorism	DGR no. 1862 of 27/05/2002
		no	1	2	no		Children fiscally dependent on parents	
		no	2	4	no			
A.P. of Trento	N/A	no	no	no	1	yes		DGP no. 769 of 12/05/2015

Regions	Exemption		Ticket (€)			Transparency lists *	Notes	Legal reference
	Income (€)	Condition	Package	Max prescription	Prescription share			
	Up to 12,000	yes	no	no	no	yes	Pain therapy, major invalids, chronic conditions, rare diseases, pain therapy	DGR 744 of 11/03/2005
Liguria	N/A	no	2	4	no	yes + ticket	Incl. for single-dose antibiotics and medicines administered through intravenous infusion	DGR no. 163 of 20/02/2002
		yes	no	no	no	yes	Victims of terrorism and war invalid are excluded from the cost sharing.	DGR no. 1116 of 9/09/2011
Tuscany	0 - 36,151.98	no	no	no	no	yes	Patients with chronic and disabling diseases and patients suffering from rare diseases with an income ≤€70,000 are excluded from ticket payment for medicines linked to their conditions. During the year, ticket sum on the reimbursed expenditure cannot exceed € 400 for each individual user.	DGR no. 753 of 10/08/2012
	36,151.99-70,000		2	4	no	yes + ticket		
	70,001-100,000		3	6	no			
	> 100.000		4	8	no			
Emilia Romagna	0 - 100,000	no	no	no	no	yes	Residents and non residents who can choose their GP in Emilia Romagna.	DGR no. 2075 of 3/12/2018
	> 100,000		3	6	no	yes + ticket		
Umbria§	0 - 36,151.98	no	no	no	no	yes	Patients suffering chronic and disabling diseases are excluded from ticket payment.	DGR no. 911 of 5/08/2011
	36,151.99-70,000		1	2	no	yes + ticket		
	70,001-100,000		2	4	no			
	> 100,001		3	6	no			
Lazio	N/A	yes	2	no	no	yes	Medicines with a retail price >€5 not included in AIFA's transparency lists	DCA no. 45 of 17/11/ 2008
		no	4	no	no			
		yes	1	no	no		Medicines with a retail price ≤€5 not included in AIFA's transparency lists	
		no	2.5	no	no			
Abruzzo	N/A	no	2	6	no	yes + ticket	Medicines with a retail price > €5	

Regions	Exemption		Ticket (€)			Transparency lists *	Notes	Legal reference
	Income (€)	Condition	Package	Max prescription	Prescription share			
		yes	1	3	no			
		no	0.5	1.5	no		Medicines with a retail price ≤ €5	DCA no. 26 of 4/07/2012
		yes	0.25	0.75	no			
		no	no	no	no	yes	Chronic and disabling diseases Non patent-covered medicines with retail price in line with reference price	
Molise	N/A	no	2	6	0.5	yes + ticket	Patent-covered medicines with a retail price >€5	DGR no. 1188 of 29/07/2002 DD.CC.AA 87 and 97 /2011 Circular no. 4702 of 3/4/2012
			0.5	no			Patent-expired medicines with a retail price > €5	
			no	no		yes	Pain therapy	
Campania	N/A	no	1.5	no	2	yes + ticket	The ticket per package does not apply to medicines not covered by a patent with a price in line with the regional reference price. The prescription fee does not apply to oxygen prescriptions and PHT medications	DCA no. 67 of 4/11/2010
			no	no	2	yes	Non patent-covered medicines with retail price in line with reference price	
		yes	no	no	1	yes	Disability and chronic and disabling diseases with income up to €22,000	
Puglia	N/A	no	2	5.5	1	yes + ticket	Single-dose antibiotics, IFN for hepatitis, drugs administered through intravenous infusion (Law 405/2001)	DGR no. 1718 of 19/11/2004
		yes	0.5	no	1			
		no	no	no	1		Medicines included in transparency lists	DGR no. 1198 of 6/08/2005
		no	no	no	1		Disability, pain therapy, victims of terrorism, chronic and disabling diseases, rare diseases	
		no	no	no	no		Minimum pensions	DGR no. 2789 of 14/12/2010

Regions	Exemption		Ticket (€)			Transparency lists *	Notes	Legal reference
	Income (€)	Condition	Package	Max prescription	Prescription share			
								DGR no. 1389 of 21/06/2011 DGR no. 1391 of 21/06/2011
Basilicata	Up to 8,2163.31	no	no	no	1	yes		DGR no. 699 of 11/06/2013
	> 8,2163.31				2	yes		
Calabria	N/A	no	2	5	1	yes		DGR no. 247 of 5/05/2009
		yes	no	no	no	yes	Chronic diseases Rare diseases	
		yes	no	no	1		Disability	
Sicily	N/A	no	4	no	no	yes	Medicines with a retail price ≤ €25	Reg. Law no. 6 of 10/01/2012
		yes	1.5					
		no	2				Generics with a retail price ≤ €25	
		yes	1					
		no	4.5			yes	Medicines with a retail price > €25	
		yes	2					
		no	2.5				Generics with a retail price ≤ €25	
		yes	1.5					

* difference between the retail price of the medicine and the reference price

§ OXYGEN - The ticket is applied to oxygen prescriptions by equating the cylinder to the packaging. If the prescriber does not indicate the number of cylinders but rather the volume, the ticket is applied to the number of cylinders needed to reach that volume

° DPC - To be paid by patients with an exemption for income (E01 - E02 - E03 - E04) pursuant to the current State legislation and by patients with ordinary ISEE (Equivalent Financial Situation Index) certification between €10,000.00 and €25,000.00, a fixed fee of €1 per package up to a maximum of €2 per prescription for NHS pharmaceutical assistance and per conto distribution, and a fixed fee of €1 per prescription for supplementary assistance

Exemptions

(Source Ministry of Health, 2019[3])

Exemptions due to income

E01: Citizens aged less than six years and over sixty-five years, belonging to a family unit with a total annual income not exceeding €36,151.98.

E02: Unemployed people and their dependent family members belonging to a family unit with a total annual income lower than € 8,263.31, increased up to €11,362.05 in the presence of a spouse and by additional €516.46 for any dependent child.

E03: Holders of social pensions and their dependent family members.

E04: Holders of minimum pensions aged over sixty and their dependent family members, belonging to a family unit with a total annual income lower than €8,263.31, increased up to €11,362.05 in the presence of a spouse and by additional € 516.46 for any dependent child.

Chronic diseases

The list of chronic diseases exempt from cost-sharing of the services provided has been redefined and updated by Annex 8 of the Decree of the President of the Council of Ministers on the new basic levels of healthcare of 12 January 2017.

Rare diseases

The list of rare diseases exempt from cost-sharing was extended by Annex 7 of the Decree of the President of the Council of Ministers of 12 January 2017 defining the new basic levels of healthcare. The new exemptions by rare disease and/or groups came into force on 15 September 2017, to allow the regions to identify the reference Centres experienced in treating new diseases.

Disability

Only invalids of war, holders of direct life pensions and victims of terrorism have the right to receive Class C medicinal products free of charge, upon a medical prescription certifying their proven therapeutic usefulness.

Other exemptions for situations of particular social interest

Protection of maternity, limited to the services defined by Decree of the President of the Council of Ministers dated 12 January 2017 (annex 10).
Preventing the spread of HIV infection, limited to ascertaining the status of the infection, in favour of subjects belonging to categories at risk, with risk behaviours or incidentally exposed to the risk of infection.
Promotion of donations of blood, organs and tissues, limited to the benefits related to the donation activity.
Protection of subjects damaged by irreversible complications due to compulsory vaccinations, transfusions and administration of blood products pursuant to Law no. 210 of 25 February 1992, limited to the services indicated therein.
Victims of terrorism and organised crime.

[3] http://www.salute.gov.it/portale/esenzioni/homeEsenzioni.jsp

5. Price of medicinal products

As of 1 January 2004, prices of all medicinal products reimbursed by the NHS are set through negotiation procedures between AIFA and the pharmaceutical companies, following methods and criteria previously adopted only for medicinal products approved under the European procedure.
During negotiations, the parameters taken into account are those defined by the CIPE Resolution no. 3 of 1 February 2001:

- assessment of the economic impact on the NHS;
- prices charged in other EU Member States;
- cost of treatment per day compared to the cost of medicinal products with similar effectiveness;
- benefit/risk ratio compared to medicinal products with the same therapeutic indication;
- cost/effectiveness ratio when no other treatment options are available;
- level of innovation.

The pricing and reimbursement process occurs in four stages, which can be summarized as follows:

1. a pharmaceutical company applies for pricing and reimbursement by submitting the dossier to AIFA;
2. AIFA's CTS issues a binding opinion on the therapeutic value of the medicinal product - by defining its place in therapy -, on its supply regime and on its possible degree of innovation;
3. AIFA's CPR evaluates the dossier and, when necessary, convenes the applicant pharmaceutical company for negotiation;
4. if a medicinal product is considered eligible for reimbursement, the result of the negotiation is submitted to the Board of Directors for a final evaluation. The CTS decisions and the CPR opinions are provided within 180 days from submission of a duly filled out request of the interested party and the ex-factory price is published in the Italian Official Journal.

By way of derogation to such provisions, Law Decree no. 69 of 21 June 2013, converted with amendments into Law no. 98 of 09 August 2013amended Law Decree no. 158 of 13 September 2012, converted with amendments into Law no. 189 of 8 November 2012, introducing paragraph 5-bis, which provided that orphan, hospital or exceptionally therapeutic and social medicinal products should be evaluated as a priority, with respect to the pending proceedings at the date of the application, also by setting extraordinary committee sessions, within 100 days (see also section 7, Orphan medicinal products). Furthermore, for these medicines, the current legislation provides for a further facilitation, that is the faculty for the company to submit the request for classification and price before a marketing authorization is granted.

With regard to Class A medicines dispensed through local pharmacies, under the conventional supply regime, the price published in the Official Journal coincides with the retail price of the single package, including the quota paid by the citizen, the mandatory discounts to be paid by pharmacists and pharmaceutical companies and the value added tax. Consequently, the price charged to the NHS coincides with the retail price net of both discounts and cost-sharing paid by citizens. In addition, the ex-factory price (excluding VAT) is published in the Italian Official Journal.
For Class A and H medicines purchased from public health facilities, the price borne by the NHS coincides with the ex-factory price as resulting from purchase tenders or the price defined after direct negotiation between the local health authority (or the Region) and the pharmaceutical company, including VAT.
In the case of Class C medicines, the price is defined independently by the pharmaceutical company; it is not published in the Italian Official Journal, but it is communicated to AIFA. For Class C medicines with prescription, with the exception of C-bis pharmaceuticals, the price may increase only in January of each odd year (Decree Law no. 87 of 27 May 2005, converted with amendments into Law no. 149 of 26 July 2005), whereas price reductions are always permitted.

Moreover, Art. 9-(b), paragraph 11, of Law Decree No. 78 dated 19 June 2015, converted with amendments into Law 125/2015, contributed to defining the price of medicines, by integrating Art. 48 of Law Decree no. 269 of 30 September 2003, converted with amendments into Law no. 326 of 24 November 2003, as amended. It introduced paragraph 33-bis, which states that, upon patent expiry of the active ingredient of a biotechnological medicinal product and without starting a concurrent price negotiation procedure relating to a biosimilar or therapeutically similar medicinal product, the Agency initiates a new price negotiation procedure with the marketing authorisation holder of the same biotechnological medicinal product, in order to reduce the reimbursement by the NHS. Furthermore, it introduced paragraph 33-(b), providing that the Agency starts a new bargaining procedure with the marketing authorisation holder for medicines subject to an AIFA monitoring registry, in order to reduce the price in the event that reported benefits, after two years from the granting of the marketing authorisation, are lower than those identified in the negotiation agreement.

6. AIFA Notes for the appropriate use of medicinal products

AIFA Notes define the therapeutic indications for which medicinal products can be reimbursed by the NHS and are a regulatory tool for guaranteeing the appropriate use of medicinal products, directing doctors' prescriptions on the basis of the best evidence of efficacy in literature. Notes may be introduced in case the medicinal product is authorised for different clinical indications, some of which are for relevant diseases, or if it is used to prevent a significant risk in one or more population groups, and if it is used inappropriately, where there is no proven efficacy or its safety may be reduced.
Additionally, the periodic revision of the Notes makes this tool more responsive to new scientific evidence and, above all, more flexible to the needs of daily medical practice on

the national territory. The changes are aimed at a simpler and more direct management of the patient by the physician, at a better correspondence between indications of proven efficacy and those that can be totally charged to the NHS and at preventing improper use or significant risks only for one or more population groups.
During 2019, AIFA approved the following amendments: depletion of Note 94 on the supply regime of medicines containing N3 PUFAs reimbursed by the NHS; amendment of Note 87 on medicines for urgent urinary incontinence; amendment of Note 13 relating to the updating of the text; drafting and implementation of Note 96 on the reimbursement of medicines for prevention and treatment of vitamin D deficiency in adults.
The main changes are described below (for a more detailed description of the Notes, please see the text published in the Italian Official Journal and also available on the Agency's website):

Note 94 - medicines containing N3 PUFAs containing eicosapentaenoic acid (EPA)' and docosahexaenoic acid (DHA)'s ethyl esters for a maximum of 85%, equal to 850 mg/g. The Note was depleted with resolution no. 999/2019 published in the Italian OJ no. 144 of 21 June 2019, following an EMA communication on the effectiveness of omega-3 fatty acids of 29 March 2019, by which the European Commission issued a legally binding decision on 6 June 2019. The note had been introduced with resolution no. 1081 of 22 November 2013 (Italian OJ General series no. 285 dated 5 December 2013) establishing the prescription of N-3 PUFAs with reimbursement by the NHS in a hospital setting for acute coronary syndrome with or without QT elevation and acute coronary syndrome with or without QT elevation over the previous 90 days.

Reimbursement was guaranteed for 12 months for patients with >40 % ejection fraction at hospital discharge and 18 months for patients with <40 % ejection fraction at hospital discharge. Therefore, the indication of these medicines for secondary prevention in patients with previous myocardial infarction is abolished, for which the related medicines are not reimbursed by the NHS. However, such medicines can still be prescribed at the conditions provided for in Note 13.

Note 13 - lipid-lowering medicines: amendment of Note 13 with resolution no. 1433 of 27 September 2019 (Italian OJ no. 238 of 10 October 2019), which replaces the text of the above-mentioned note, referred to in AIFA resolution no. 617/2014 (Italian OJ – General Series no. 156 of 8 April 2014), concerns the inclusion of atorvastatin, amlodipine and perindopril fixed combination in the continuation of treatment with statins in the context of combination therapies with lipid-lowering agents, limited to adult patients suffering from primary hypercholesterolaemia or mixed hyperlipidaemia, essential hypertension and/or stable chronic disorder, already adequately controlled with the above-mentioned active ingredients, administered concurrently and on an impromptu basis. The reimbursement of the fixed-dose combination is permitted only for the same dosages and the treatment of dyslipidaemias already included in the Note.

Note 87 - medicines for urgent urinary incontinence: the new text of the Note, amended by resolution no. 1433/2019 (Italian OJ General series no. 238 of 10 October 2019), comprises an addendum which replaces the text of the note pursuant to AIFA resolution dated 4 January 2007. The amendment mainly concerns the introduction of solifenacin and tolterodine for this specific therapeutic indication, which add to oxybutynin. For these three active substances, reimbursement by the NHS is limited only to negotiated packs in Class A/RR for patients with urgent urinary incontinence, if the disorder is related to central nervous system disorders such as stroke, Parkinson's disease, trauma, tumours, spina bifida, multiple sclerosis.

Note 96 - medicines for the prevention and treatment of vitamin D deficiency in adults. The Note was introduced with resolution no. 1533/2019 (Italian OJ no. 252 of 26 October 2019) and was integrated by resolution no. 1630/2019 (Italian OJ no. 258 of 4 November 2019).
The Note provides for the reimbursement by the NHS of medicinal products containing colecalciferol, colecalciferol/calcium salts and calcifediol, according to two different clinical scenarios that take/do not take into account the serum levels of 25(OH) vitamin D. Specifically, it is not necessary to carry out blood dosage for institutionalised persons, pregnant and breastfeeding women, people with osteoporosis (irrespective of the cause) or with established osteopathy, not eligible for remineralisation therapy. Instead, serum levels of 25(OH) D should be measured in a limited number of patients, as suggested by a flow chart, which facilitates not only the assessment of the appropriateness of the clinical examination, but also guides the prescription of the correct vitamin dosage, this being an integral part of the measure (Annex 1). Users for whom prescription is considered appropriate are those with serum levels below 20 ng/ml, with symptoms attributable to hypovitaminosis, persons diagnosed with hyperparathyroidism secondary to hypovitaminosis D, persons with osteoporosis of any cause, or persons with established osteopathies who are candidates for remineralisation therapy.
The addendum, provided for in resolution no. 1630 of 2019 (Italian OJ no. 258 of 4 November 2019), clarified that the capsule formulation of active substances colecalciferol, colecalciferol/calcium salts and calcifediol, can be reimbursed by the NHS as provided for in Note 96 for the adult population aged 18 years or older.

The Note and its addendum leave the prescriptive modalities for the paediatric population unchanged.

Appendix 2

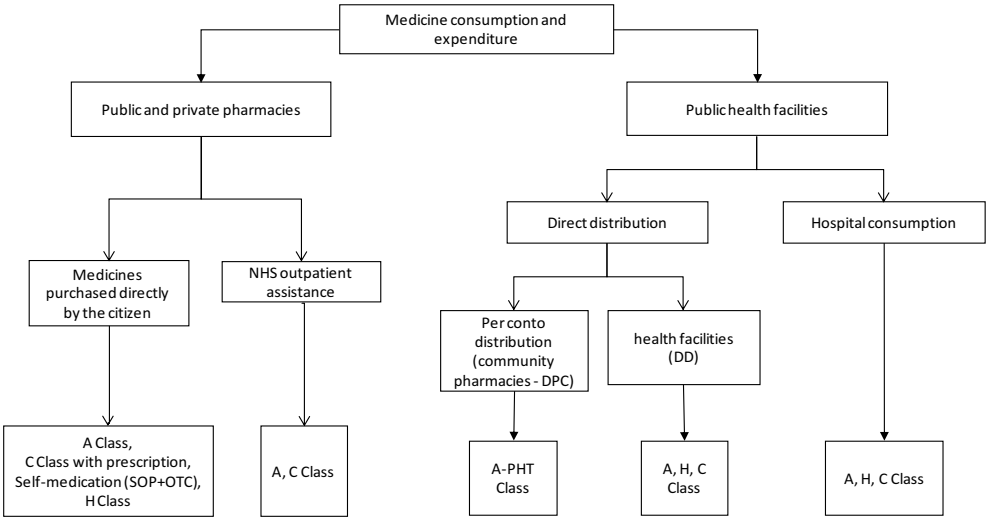
Data source and methods

National Report
on Medicines
use in Italy
Year 2019

1. Pharmaceutical consumption and expenditure data

The 2019 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.

Figure 1.1. Summary of Report data



The description of medicine consumption made available by the Report is based on the analysis and integration of data collected through different information flows:

- OsMed (National Observatory on the Use of 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

[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 organization 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").

completeness by geographical area and by month; the national data coverage in 2019 was generally 97.5% of expenditure. The share of expenditure and missing consumption was obtained through an expansion procedure, which uses the data issuing from the Itemized Summary Lists, periodically updated by AIFA, as the reference value of the pharmaceutical expenditure. 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 analyzed 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 drugs 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 drugs 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 analyzing the consumptions related to a wide time span, any misalignment between sell-in and sell-out is minimized, consequent to

the re-composition 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 hospitalization 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 authorized 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 drugs 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, analyzes 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[2], 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 pharmaceuticals 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 pharmaceuticals 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").

[2] Budget Law 2017

- Hospital consumption. The information flow for monitoring hospital consumption was established by the Decree of Ministry of Health of 4 February 2009, which governs the New Health Information System (NSIS) of the Ministry of Health for consumption of medicines in hospitals. This flow, fed by the Regions or by the Autonomous Provinces of Trento and Bolzano, records consumption and relative economic value of the medicines used in the health facilities directly managed by the NHS, with the exception of the medicines dispensed through direct distribution. Medicinal products fall within the scope of this flow which are intended for internal administration and delivered from hospital pharmacies to hospital wards, as well as medicines intended for internal administration delivered by district pharmacies to laboratories, clinics and other types of territorial structures. The survey, as well as the flow of direct distribution, is extended to the prescriptions of all medicines provided with MA, regardless of the class of supply paid by the NHS and of the supply regime, to foreign drugs, to "magistral formulae" and " officinal formulae".
- 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 drug delivery method. This means that, in the case of prescription of drugs 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 use of 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*[3] 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 parametrize the number of packages delivered to patients, according to the formula shown in section 4. In some specific analyses, a grouping of different ATC and/or active ingredients was applied, in order to analyse consumption patterns according to the therapeutic field. The list of pharmaceuticals for direct distribution is represented by the Direct Distribution Guide (PHT - Guide 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 2019.

[3] http://www.whocc.no/

3. National population and standardization 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 optimize 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[4]. 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 (60,359,546 inhabitants in 2019).
The implementation of this process of population standardization 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 2018 and 2019.

[4] Data source: http://demo.istat.it/

Table 3.2. Resident population measured by ISTAT and weighted population for 2018 and 2019

Region	Resident population as of al 1.1.2018	Weighted population 2018	Resident population as of 1.1.2019	Weighted population 2019
Piedmont	4,375,865	4,607,636	4,356,406	4,582,727
Valle d'Aosta	126,202	129,445	125,666	128,939
Lombardy	10,036,258	10,015,557	10,060,574	10,024,134
AP Bolzano	527,750	495,399	531,178	497,490
AP Trento	539,898	531,348	541,098	532,711
Veneto	4,905,037	4,941,080	4,905,854	4,939,047
Friuli VG	1,215,538	1,297,253	1,215,220	1,294,259
Liguria	1,556,981	1,735,087	1,550,640	1,720,657
Emilia R.	4,452,629	4,564,671	4,459,477	4,558,718
Tuscany	3,736,968	3,926,459	3,729,641	3,909,954
Umbria	884,640	925,670	882,015	923,787
Marche	1,531,753	1,584,588	1,525,271	1,577,546
Lazio	5,896,693	5,795,831	5,879,082	5,787,806
Abruzzo	1,315,196	1,340,023	1,311,580	1,335,576
Molise	308,493	317,614	305,617	315,223
Campania	5,826,860	5,345,218	5,801,692	5,334,689
Puglia	4,048,242	3,957,455	4,029,053	3,948,443
Basilicata	567,118	567,939	562,869	564,566
Calabria	1,956,687	1,894,077	1,947,131	1,888,306
Sicily	5,026,989	4,826,747	4,999,891	4,809,687
Sardinia	1,648,176	1,684,876	1,639,591	1,685,282
Italy	**60,483,973**	**60,483,973**	**60,359,546**	**60,359,546**

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:

$$IV = \frac{S^{19}}{S^{18}} = \frac{\sum_i q_i^{19}}{\sum_i q_i^{18}} \times \frac{\sum_i p_i^{19} q_i^{19}}{\sum_i p_i^{18} q_i^{18}} \times \frac{\frac{\sum_i p_i^{19} q_i^{19}}{\sum_i q_i^{19}}}{\frac{\sum_i p_i^{19} q_i^{18}}{\sum_i q_i^{18}}}$$

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 2018 and 2019
S^{19} = pharmaceutical expenditure in 2019
S^{18} = pharmaceutical expenditure in 2018
qi^{19} = quantity of the "i" package (expressed in DDD) sold in 2019
qi^{18} = quantity of the "i" package (expressed in DDD) sold in 2018
pi^{19} = average price in 2019 of the single DDD with the "i" package
pi^{18} = average price in 2018 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 drugs with lower prices are mostly consumed (mix effect).

In the analysis of the one-year mix effect, the use of DDD 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 drugs 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 drugs 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 drugs, of Class C drugs with prescription, of drugs purchased by public health facilities, collected and processed by OsMed. Prices relating to a single specialty are obtained as the ratio between the expenditure values (in euros) and the quantities sold (both in terms of DDD and packaging). Starting from the prices relating to single specialties, the Weighted Average Prices (PMP) were calculated for each month, for which the weights consist of either the number of DDD or the number of packages, according to the following formula:

$$PMP_i = \frac{\sum_{j=1}^{n} p_j^i q_j^i}{\sum_{j=1}^{n} q_j^i}$$

where:

n = is the number of specialties marketed in the month "i"

p_j^i = is the price of a DDD (or of a package) of the specialty "j" in the month "i"

q_j^i = is the number of DDDs (or of the packages) of the specialities "j" sold in the month "i"

The monthly temporal dynamics of prices is analyzed 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.

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:

$$CV = \frac{DS}{mean} \text{ x100}$$

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 (SD): 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 drug 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:

$$\frac{\text{Total number of DDD consumed in the period}}{\text{N.of subjects x N. of days in the period}} \times 1000$$

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, x_i 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 drug. 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)

Median: in relation to an orderly distribution of values in a population (DDD, per capita expenditure) the median represents the value which divides the population into two equal parts.

Prevalence of use: the prevalence (P) of a given condition in a population is the proportion of the population presenting the condition. The prevalence of drug 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.)

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: $(X_i - Mean)/(Mean) * 100$

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.

METHODOLOGICAL NOTE

Comparing the different editions of the Report, it is worth considering that in drafting the National Reports, operations updating the information recorded in the OsMed data warehouse are systematically carried out, they may lead to slight differences in the values (of 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 16 April 2019 and, therefore, do not take into account any further revisions by companies and regions.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