National Report on Medicines use in Italy Year 2018

ITALIAN MEDICINES AGENCY

National Report on Medicines use in Italy Year 2018

December, 2019

Dear Readers,
this is an extract/adaptation of 2018 OsMed Report.

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

The English version of the document was edited by Giuseppina Camposarcuno, Marco De Martino, Federica Mammarella and Federico Villa.

Linguistic revision by Linda Pierattini.

Technical revision by Paola Ruggeri, Agnese Cangini, Roberto Da Cas and Francesco Trotta.

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Italian Medicines Agency (AIFA)
Director General: *L. Li Bassi*

Working group who worked at this Report:

Coordination:
F. Trotta – Italian Medicines Agency (AIFA), Rome

Italian Medicines Agency (AIFA)

- Economic Strategy of Pharmaceutical Products Department:
A. Di Filippo, A. Di Vito, A. Pierantozzi

- HTA & Pharmaceutical Economy Division:
G. Altamura, A. Cangini, D. Deriu, A. La Greca, F. Mammarella, M. Petrelli, M.P. Trotta

- Health Budget Monitoring and Regional Relations Office:
S.M. Cammarata, F. Fortinguerra, M.A. Guerrizio, U. Finelli, R. Marini, F. Milozzi, E. Pieroni, R. Frulio, C. Rosiello, M. Sacconi, D. Settesoldi, F. Villa, F. Trotta

- Information Communication Technology (ICT) Department:
S. Celant, A. Fabrizi, M. Fontanella, S. Perna, G. Pistolesi, M. Trapanese

- Monitoring Registers Office:
V. Angelini, A. Cirilli, A. Colatrella, M. Cuomo, L. Gozzo, P. Olimpieri, D. Ricagni, G. Murri

FOR LAYOUT AND GRAPHIC DESIGN
- Press & Communication Office:
I. Comessatti
WITH THE CONTRIBUTE OF:
C. D'Ambrosio, B. Galante, F. Mazzeo, F. Pomponi, V. Tellini

Italian National Agency for Regional Healthcare Services (AGENAS)
F. Bevere, V. Arena, L. Orzella, A. Sferrazza, L. Velardi

National Institute of Health (ISS)
R. Da Cas, P. Ruggeri

Ministry of Health – Directorate general of the Health care statistical and information system
C. Biffoli, G. Viggiano

For the analysis on the use of drugs in pregnancy:
EMILIA ROMAGNA REGION: *S. Borsari, A. M. Marata, A. Puccini, V. Solfrini*
LAZIO REGION (DIPARTIMENTO DI EPIDEMIOLOGIA DEL S.S.R. REGIONE LAZIO-ASL ROMA): *A. Addis, V. Belleudi, F.R. Poggi, M. Davoli*
PUGLIA REGION: *V. Bavaro* (SEZIONE RISORSE STRUMENTALI E TECNOLOGICHE) *V. Montanaro* (DIPARTIMENTO PER LA PROMOZIONE DELLA SALUTE, DEL BENESSERE SOCIALE E DELLO SPORT PER TUTTI), *P. Stella* (SERVIZIO POLITICHE DEL FARMACO)
MINISTRY OF HEALTH – DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA: *R. Bortolus, C. D'Amario*

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Section 1

General characteristics of pharmaceutical use in Italy

Table 1.1.a Composition of pharmaceutical expenditure: 2018-2017 comparison (Table and Figure)

	Expenditure *(million)*	**%**	**Δ % 18-17**
Gross outpatient NHS expenditure^	10,141	35	-3.4
Class A medicines by direct and *per conto* distribution	4,620	16	-3.6
Private Class A	1,360	5	3.2
Class C with prescription	2,875	10	2.2
OTC medicines	2,270	7	7.6
Malls	266	1	-7.0
Local health authorities, Hospitals, Healthcare Residence and prisons*	7,594	26	3.6
Total	**29,126**	**100**	**-0.1**

^ Including expenditure for vaccines (€ 988,043) and oxygen (€ 52,8 million) and class C drugs reimbursed in accordance with Law No.203 of 19 July 2000 (€ 20 million)

* Including expenditure for vaccines (€ 528.1 million) and oxygen (€ 278.2 million). It does not include the expense for Class A drugs delivered in direct distribution and per conto

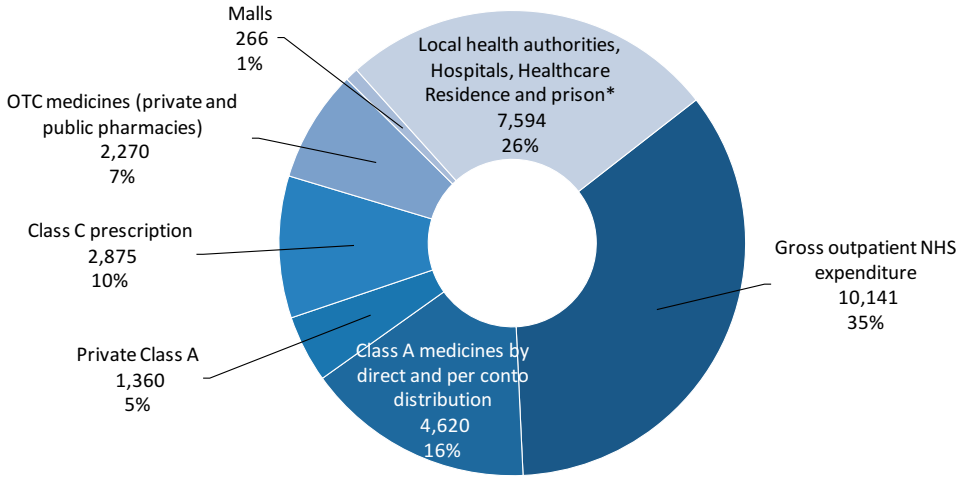
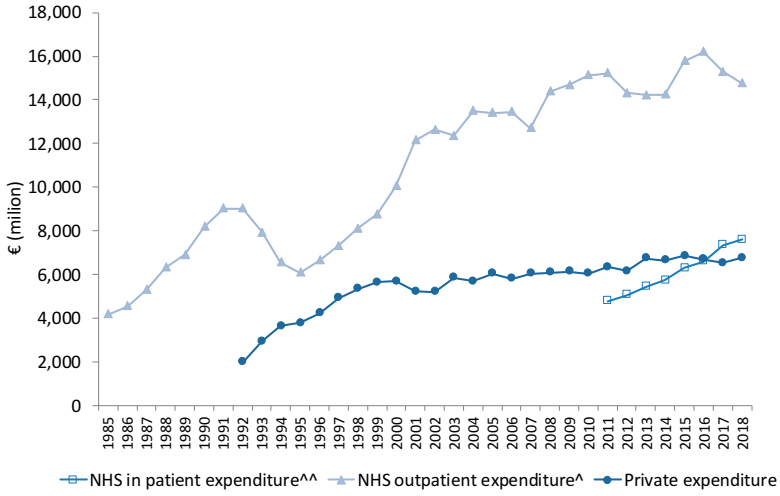


Figure 1.1.b Pharmaceutical expenditure in the period 1985 - 2018 (Figure and Table)



Years	Gross NHS outpatient expenditure *(million)*	Direct distribution Class A *(million)*	NHS outpatient expenditure^ *(million)*	Out of pocket expenditure *(million)*	Inpatient expenditure^^ *(million)*
1993	7,929		7,929	2,942	
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**

^ 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 quote paid by the citizen

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

Source: OsMed processing of data from the Ministry of Economy and Finance and from "Tracceability 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 2018 the overall outpatient pharmaceutical expenditure, that is composed by public and private expenses, amounts to € 20,781 millions, decreasing by -1.0% compared to 2017 (Table 1.1.2). The NHS outpatient pharmaceutical expenditure covers medicines supplied according to standard distribution (Tables 1.1.1 and 1.1.2) and Class A medicines supplied through direct and *per conto* distribution channels. This expenditure amounts to € 12,402 millions (€ 205.04 per capita), and represent 59.7% of the total outpatient pharmaceutical expenditure. The pharmaceutical expenditure decreased by -4.0% compared to 2017. This decrease is due both to a reduction of the expenditure for class A medicines supplied according to direct and *per conto* distribution (-3.6%) and to a reduction of the net standard distribution expenditure (-4.2%).
The citizen pharmaceutical expenditure (Out of pocket expenditure) (Table 1.1.2) amounted to € 8,379 million (+3.8% compared to 2017). It is composed by: per citizen co-payments (regional prescription/package ticket and the difference in price between an off-patent medicine and its lowest reference price), expenditure for class C medicines and for Class A medicines privately purchased by citizens.
This change was due to an increase in the consumption of self-medication medicines (SOP and OTC medicines) (+12.4%), in the citizen co-payment (+3.8%), and in the expenditure for Class C medicines with medical prescription (+2.2%), and on the other hand to a decrease in the expenditure for medicinal products purchased in stores (-7.0%).
The citizen cost-sharing (Tables 1.1.1 and 1.1.2) amounted to € 1,608 millions (approximately € 26.6 per capita); this amount represented 15.9% of the standard distribution gross expenditure.
The increase in citizen co-payment is mainly due to an increase of the co-payment for the reference price system for off-patent medicines (+7.2%), while a reduction was reported for the per prescription/package citizen co-payment (-3.4%), compared to 2017.
The amount of packages supplied according to standard distribution showed a slight decrement (-0.7%), in line with 2017 data. During 2018 (Table 1.13), an average of 978.8 daily doses of NHS reimbursed Class A medicines per 1,000 inhabitants (hereinafter called DDD/1000 inhab die) were consumed accounting to over 1 billion packages dispensed (18.3 packs per capita).
The -3.4% change of the NHS gross community pharmaceutical expenditure, compared to the previous year, was mainly due to prices reduction (-4.6%) in part related to the market entry of new generic substances. On the contrary, the consumption (+ 0.8% in terms of DDD) and the composition of dispensed medicines, high-price *vs* low-price medicines, (mix effect: + 0.3%) remained stable (Fig. 1.1.2).
The citizen expenditure for Class C medications with medical prescription and for Class A medicines amounted to € 111.9 per capita with a fair variability across Italian Regions.

Table 1.1.1. NHS oupatient expenditure: comparison 2014-2018

		2014 *million*	2015 *million*	2016 *million*	2017 *million*	2018 *million*	Δ % 15/14	Δ % 16/15	Δ % 17/16	Δ % 18/17
1+2+3+4	**Gross outpatient NHS expenditure**	**10,988**	**10,863**	**10,638**	**10,499**	**10,141**	**-1.1**	**-2.1**	**-1.3**	**-3.4**
1+2	Citizen copayment	1,500	1,521	1,540	1,549	1,608	1.4	1.2	0.6	3.8
1	Fixed co-payment (ticket)	546	524	518	499	482	-4.1	-1.2	-3.7	-3.4
2	Reference price share	954	997	1,022	1,050	1,126	4.5	2.5	2.8	7.2
3	Discount ^	889	865	845	830	751	-2.7	-2.4	-1.8	-9.4
4	**Net NHS expenditure**	**8,598**	**8,477**	**8,254**	**8,120**	**7,781**	**-1.4**	**-2.6**	**-1.6**	**-4.2**
5	Class A direct and *per conto* distribution°	3,250	4,921	5,556	4,792	4,620	51.4	12.9	-13.7	-3.6
4+5	**Outpatient expenditure**	**11,848**	**13,398**	**13,810**	**12,913**	**12,402**	**13.1**	**3.1**	**-6.5**	**-4.0**

^ 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 December 30, 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 expenditure and per conto 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 (2014-2018)

		2014 *million*	2015 *million*	2016 *million*	2017 *million*	2018 *million*	Δ% 15/14	Δ % 16/15	Δ % 17/16	Δ % 18/17
1	Net NHS expenditure	8,598	8,477	8,254	8,120	7,781	-1.4	-2.6	-1.6	-4.2
2	Class A medicines by Direct and *per conto* distribution	3,250	4,921	5,556	4,792	4,620	51.4	12.9	-13.7	-3.6
1+2	**Total public expenditure**	**11,848**	**13,398**	**13,810**	**12,913**	**12,402**	**13.1**	**3.1**	**-6.5**	**-4.0**
3	Citizen co-payment	1,500	1,521	1,540	1,549	1,608	1.4	1.2	0.6	3.8
4	Class A medicines paid by citizens	1,442	1,487	1,309	1,317	1,360	3.1	-11.9	0.6	3.2
5	Class C medicine With prescription	2,937	2,997	2,642	2,813	2,875	2.1	-11.8	6.5	2.2
6	OTC medicines	2,269	2,375	2,429	2,109	2,270	4.7	2.3	-13.2	7.6
7	Drugstores			301	286	266			-4.7	-7.0
3+4+5+6+7	**Total private expenditure**	**8,148**	**8,380**	**8,220**	**8,076**	**8,379**	**2.9**	**-1.9**	**-1.8**	**3.8**
	Total pharmaceutical expenditure	**19,996**	**21,778**	**22,030**	**20,988**	**20,781**	**8.9**	**1.2**	**-4.7**	**-1.0**
	Share (%) borne by the NHS	59.3	61.5	62.7	61.5	59.7				

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 2014-2018

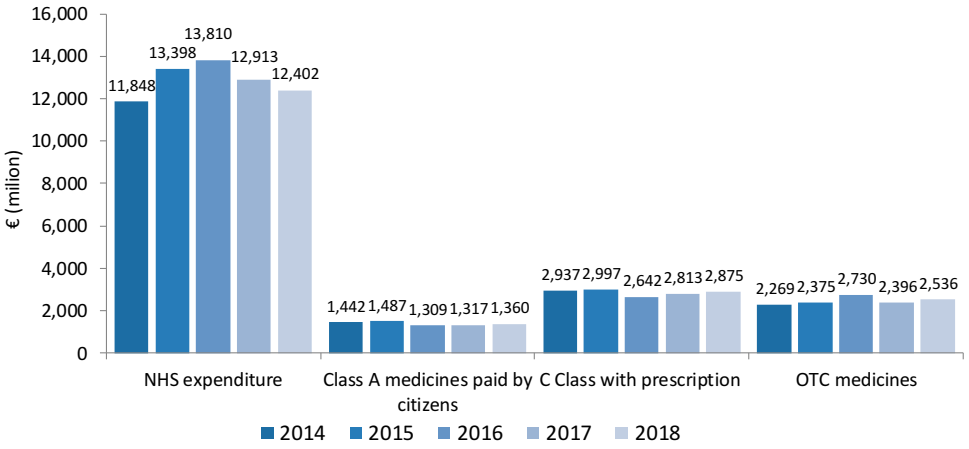


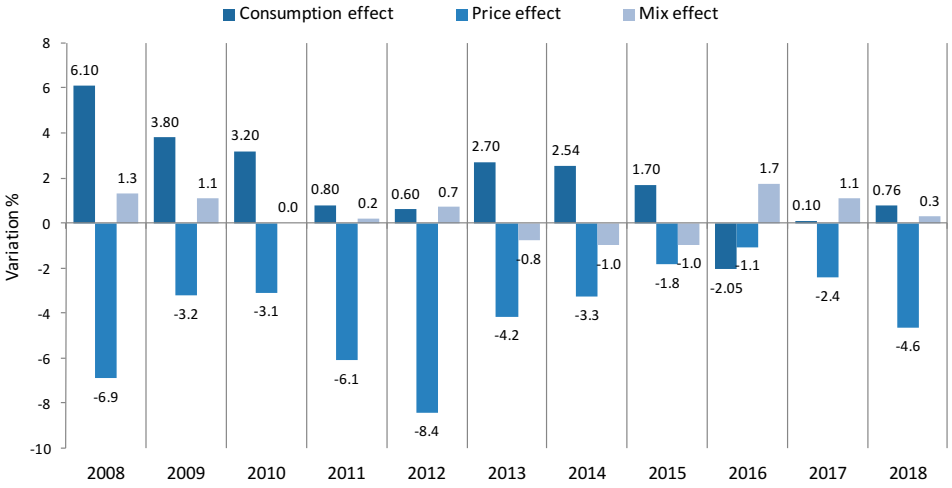
Table 1.1.3. Public and private outpatient pharmaceutical consumption: comparison 2014-2018

		2014	2015	2016	2017	2018	Δ %	Δ %	Δ %	Δ %
		*million^*	*million^*	*million^*	*million^*	*million^*	15/14	16/15	17/16	18/17
	Prescriptions #	609	596	587	581	609	-2.2	-1.5	-1.1	-0.8
	N. Packages									
1	NHS consumption	1,133	1,131	1,117	1,110	1,102	-0.2	-1.2	-0.7	-0.7
2	Class A medicines paid by citizen *	221	225	210	216	162	2.1	-6.7	2.8	-24.9
3	Class A medicines by direct and *per conto* distribution	ND	ND	86	105	105			21.5	0.2
1+2+3	Total class A medicines	1,354	1,356	1,414	1,430	1,369	0.2	4.2	1.2	-4.3
4	Class C medicines with prescription	250	248	209	222	229	-0.8	-15.6	6.1	3.0
5	OTC	277	280	259	231	241	0.8	-7.3	-10.8	4.1
6	Malls			32	30	29			-5.9	-5.8
4+5+6	Total Class C medicines	527	528	501	484	498	0.1	-5.1	-3.4	3.0
1+2+3 +4+5	Total packages	1,881	1,884	1,915	1,914	1,867	0.2	1.6	0.0	-2.5
	DDD/1000 inhab die#	983.5	980.0	971.4	969.7	978.8	-0.4	-0.9	-0.2	0.9

ND: data not available
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).
^ only the number of recipes and packages is expressed in millions of units.
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.

The following tables show expenditure and consumption values not including oxygen, unless otherwise indicated

Figure 1.1.2. Trend of Class A reimbursed medicines expenditure: consumption effect, price effect and mix effect, period 2008-2018



1.2 Medicines purchased by public health facilities

The expenditure for medicines purchased by public health facilities (hospitals, health local units (HLU), IRCCS etc) amounted to approximately € 11.9 billion (€ 197.45 per capita), remaining almost stable (+0.9%) compared to 2017 (Table 1.2.1). The pharmaceutical consumption, expressed as DDD, had an average value of 157.35 daily doses per 1000 inhabitants, this value is substantially stable compared to the one of the previous year (-0.8%).
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 (e.g. in the pediatric 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.

1.3 Pharmaceutical consumption by age and gender

The variability of pharmaceutical expenditure and consumption is primarily due to changes of 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 pharmaceutical prescriptions reimbursed by NHS and provided through public and private pharmacies (So-called Health Card); this flow covers the whole Italian population.
Overall, 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 229 euros and a consumption of 1,020 DDD/1000 inhabitants die in 2018 (this suggests that, on average, every Italian citizen received a medicine's dose every day of the year) (Table 1.3.1).
As expected there is a difference in the level of exposure to medicines in the population, with a prevalence of 62% in men and of 71% in women, but this difference is not observed in number of doses (1,016 DDD in men and 1,025 in women) and pharmaceutical expenditure (227 euros per capita in men and 231 in women) (Table 1.3.1).
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 1.3.1). This result is due both to the change in the prevalence of medicines use, which moves from some 50% in children and in adults up to 54 years, to over 95% in the elderly population over the age of 74, and to an increase in consumption ranging from about 500 doses in the age bracket between 40 and 50 years to over 3,000 in the 70-year-old population (Figure 1.3.1 and Table 1.3.1). Gender differences can be seen in the 15-64 age group, in which women show an average prevalence of medicines use higher than men (Figure 1.3.1). In particular, the highest levels of prescription concern medicines antibiotics for urinary tract infections, antianemics and medicines for the central nervous system (in particular antidepressants). The population over 64 years old absorbs more than 60% of the standard distribution expenditure and almost 70% of DDD (Table 1.3.1). In the pediatric population medicines use prevalence amounts on average to about 50%, which ranges from over 70% in children aged 0 to 4 years and 38.0% in the age range 10-14 years (for more details see section "2.1 Use of pharmaceuticals in pediatric population").

Table 1.3.1. Outpatient pharmaceutical expenditure and consumption by age, year 2018

Age (class)	Gross expenditure (per capita)			Total expenditure		DDD/1000 inhab die			DDD total	
	Men	Women	Total	%	% cum	Men	Women	Total	%	% cum
00-04	32	26	29	0.5	0.5	71	62	67	0.3	0.3
05-09	31	26	29	0.6	1.1	58	49	53	0.3	0.5
10-14	48	29	39	0.8	2.0	63	50	56	0.3	0.8
15-19	43	30	37	0.8	2.7	78	79	79	0.4	1.2
20-24	46	37	42	0.9	3.7	92	110	101	0.5	1.7
25-29	46	47	47	1.1	4.8	108	143	125	0.7	2.4
30-34	54	66	60	1.5	6.3	136	185	160	0.9	3.3
35-39	69	87	78	2.2	8.5	194	234	214	1.4	4.8
40-44	89	105	97	3.3	11.8	298	308	303	2.4	7.2
45-49	119	127	123	4.4	16.2	473	454	464	3.8	11.0
50-54	176	173	174	6.2	22.4	764	695	729	5.9	16.9
55-59	263	235	249	7.5	29.9	1,206	1,032	1,117	7.7	24.7
60-64	378	320	348	9.1	39.0	1,775	1,450	1,606	9.7	34.4
65-69	515	437	474	12.1	51.1	2,450	2,010	2,220	13.1	47.5
70-74	679	573	622	13.2	64.2	3,210	2,672	2,921	14.3	61.8
75-79	783	660	714	14.0	78.2	3,625	3,085	3,323	15.0	76.9
80-84	894	736	799	11.3	89.6	4,031	3,437	3,676	12.1	88.9
85+	909	680	752	10.4	100.0	3,968	3,227	3,460	11.1	100.0
Total	**228**	**230**	**229**			**985**	**994**	**989**		

Figure 1.3.1. Prevalence of use by age and gender in the outpatient setting, year 2018

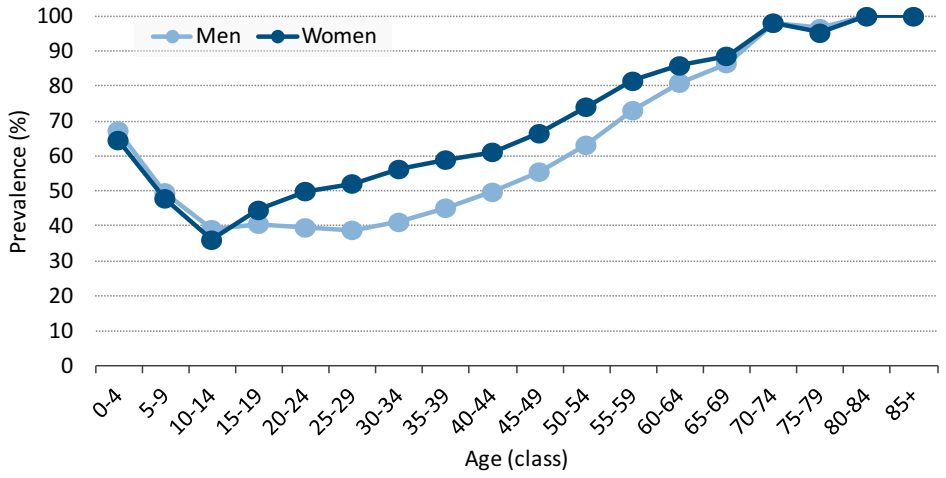
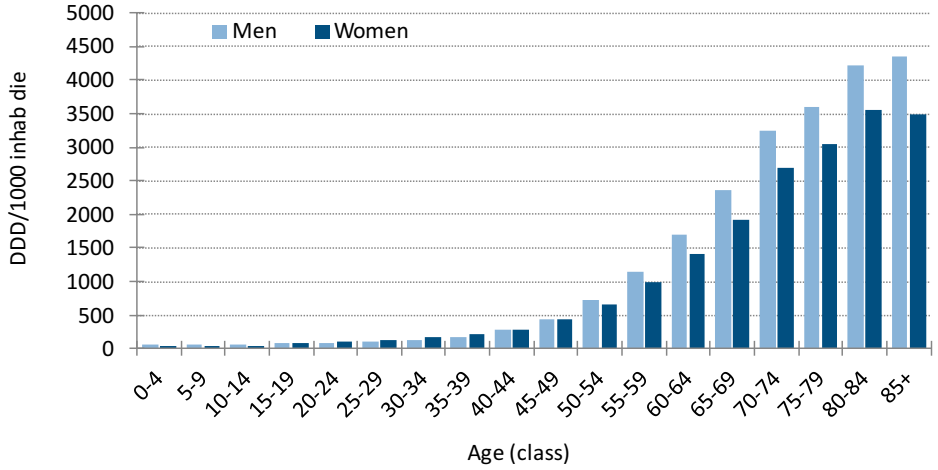


Figure 1.3.2. Outpatient consumption (DDD/1000 inhab die) by age and gender, year 2018



1.4 Pharmaceutical consumption on a monthly basis

Figure 1.4.1 shows consumption trend of Class A reimbursed medicines (consumption is expressed in DDD) according to the period 2004-2018. Over the last fourteen years, pharmaceutical consumption has registered a persistent upward trend and has increased from 736.8 DDD/1000 inhabitants per day in 2004 up to 978.8 DDD/1000 inhabitants per day in 2018. This results in a +28.1% increase. In addition to the increased trend, pharmaceutical consumption is associated to seasonal variations as proved by peaks in medicines' consumption detectable on a monthly basis (see Figure 1.4.1). As a result of this periodicity, consumption levels registered in the first half of 2018 are higher than the annual average of +2.7%, in contrast to the second half of the year, where the consumption is below -2.7%. In particular, the pharmaceutical consumptions registered in August are -12% lower than the average consumption of the same year. Generally, systemic antimicrobial medicines and respiratory medicines are the therapeutic categories on which seasonality of consumption has the highest impact.

Figure 1.4.2 shows consumption trend of Class C medicines with prescription from January 2004. This trend could have been affected by regulatory decisions whereby over time granting or not of the status of reimbursed medicine was determined. Starting from 2004, a downward trend in consumption of Class C medicines was observed; indeed, the tendency varied from 236.5 DDD/1000 inhabitants per day in 2004 up to 186.7 DDD/1000 inhabitants per day in 2018 (-22% lower than the 2014 value). The highest average consumption was recorded in September (199.5 DDD/1000 inhabitants per day) and January (198.4 DDD/1000 inhabitants per day), while the lowest levels of consumption are observed in August (152.6 DDD/1000 inhabitants per day).

Peaks in autumn are attributed to the consumption of vaccines, while peaks in the first months of the year are attributed to higher consumption of doses of respiratory system

medicines. Figure 1.4.3 shows consumption trend of medicines purchased by public health facilities in the period 2006-2018. In detail, an overall growing trend in consumption is recorded, increasing from 100.6 DDD/1000 inhabitants per day during 2006 up to 157.4 DDD/1000 inhabitants per day in 2018 (+56% higher than the 2014 value). During 2018 the lowest level in consumption is observed in August (-33.7%) and December (-23.9%), while January (+20.5%) and July (+26.1%) registered the highest levels in consumption.
For a correct interpretation of monthly consumption trends (consumption expressed as DDD/1000 inhabitants per day) of medicines purchased by public health facilities compared to annual consumption trends, it should be noted that these trends are influenced by purchasing procedures carried out by the 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 that were registered in the last six years.

Figure 1.4.1. Consumption trend of Class A medicines reimbursed by the NHS (DDD/1000 inhab die), years 2004-2018

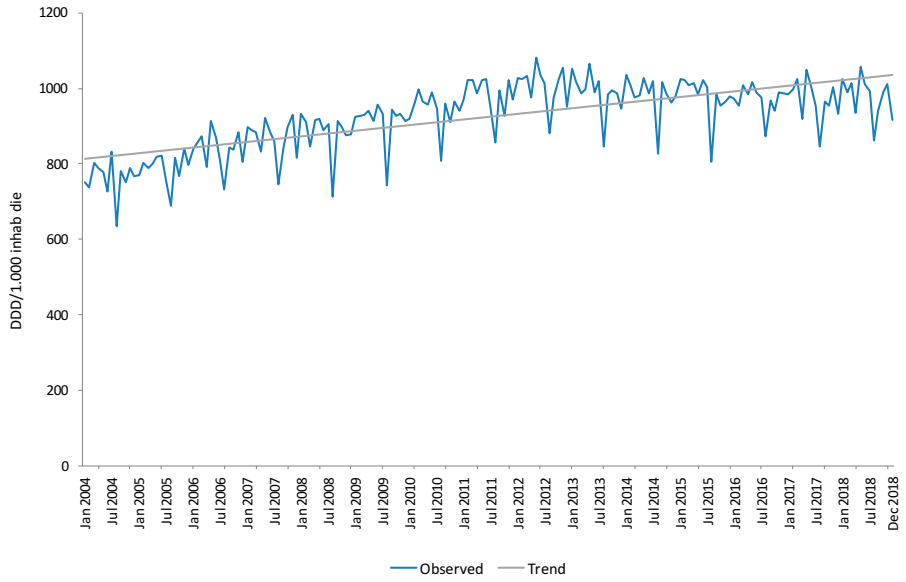


Figure 1.4.2. Consumption trend of Class C medicines requiring a medical prescription (DDD/1000 inhab die), years 2004-2018

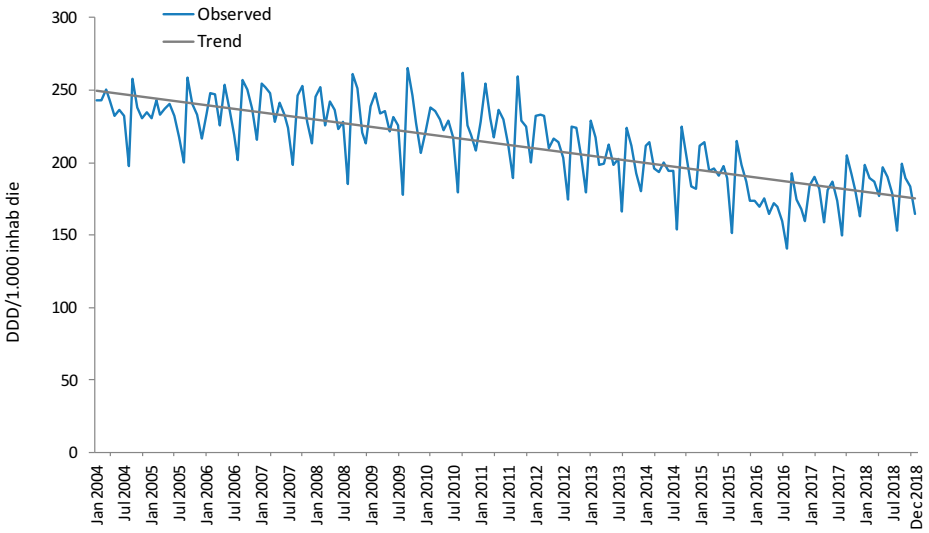
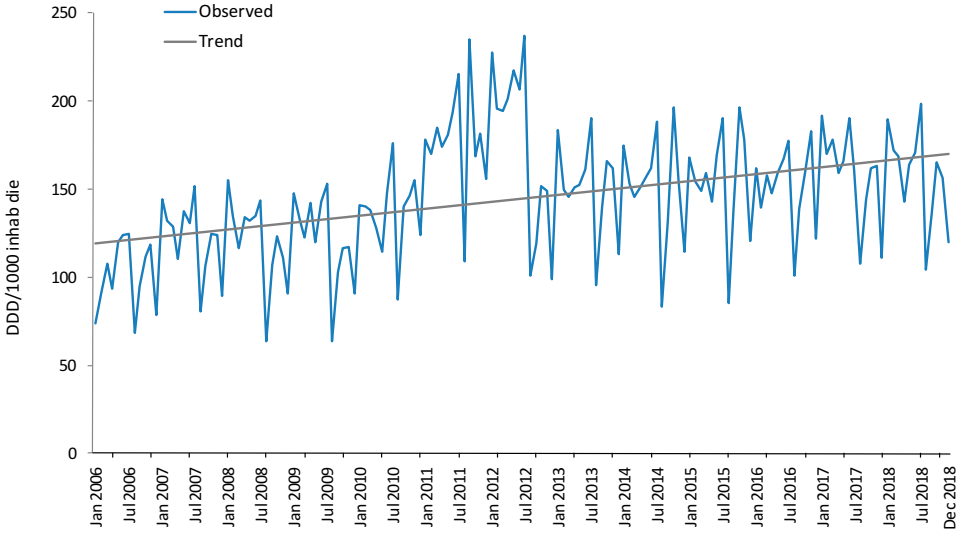


Figure 1.4.3. Consumption trend of medicines purchased by public health facilities (DDD/1000 inhab die), years 2006-2018



1.5 Trend of pharmaceutical prices

Data shown in Figure 1.5.1 represent the average price, weighted per package and per DDD, of Class A medicines reimbursed by the NHS in the period between January 2004 and December 2018. 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 measures of price reduction, which were 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 List (*Liste di trasparenza)* on the basis of a comparison carried out between the prices of generic medicines in Italy and the same pharmaceutical packages marketed in Germany, UK, France and Spain.

Figure 1.5.2 shows the average price trend, weighted per package and per DDD, of class C prescription medicines regarding the period between 2004 and 2018. Looking at the monthly time series data, the trend of the two indexes shows a steady growth rising from € 10.13 per package (and € 0.61 per DDD) during 2004 up to € 12.47 per package (and € 0.69 per DDD) during 2018, resulting in an increase of +23.1% of average price and of +13.1% of price per DDD, compared to 2004.

Figure 1.5.3 shows the average price trend, weighted per package and per DDD, of medicines purchased by public health-facilities in the period 2006-2018. Average prices increased from 2006 to 2010; they remained stable in the period between 2011 and 2012, to increase again in the period 2013-2016. While a slowdown in growth has been observed over the past two years, this finding is probably due to the marketing of biosimilars of high-use medicines. As above mentioned (Section 1.4), the average price of medicines purchased by public health facilities is mainly influenced by both purchasing procedures and by the average price of mixed medicines purchased from time to time.

Figure 1.5.1. Average price trend of Class A medicines reimbursed by the NHS, years 2004-2018

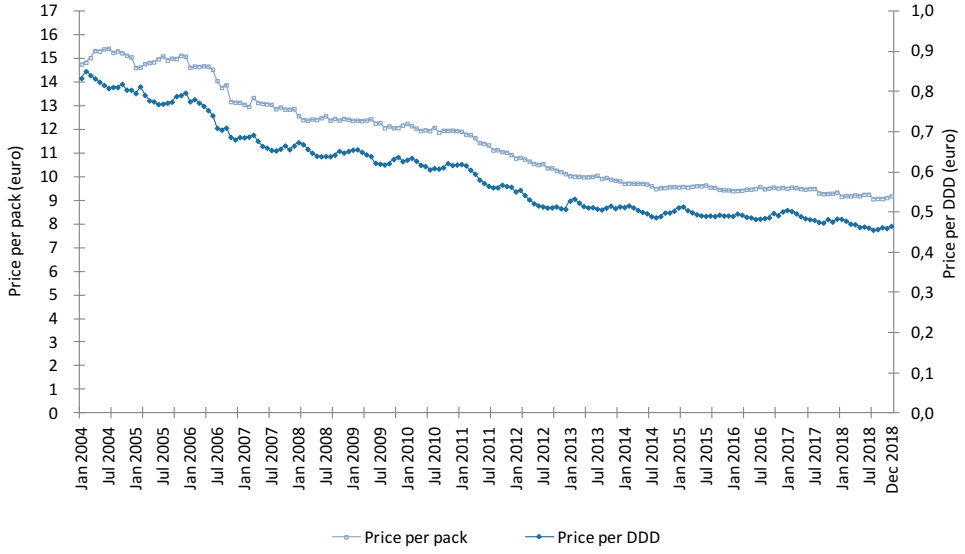


Figure 1.5.2. Average price trend of Class C medicines requiring a medical prescription, 2004-2018

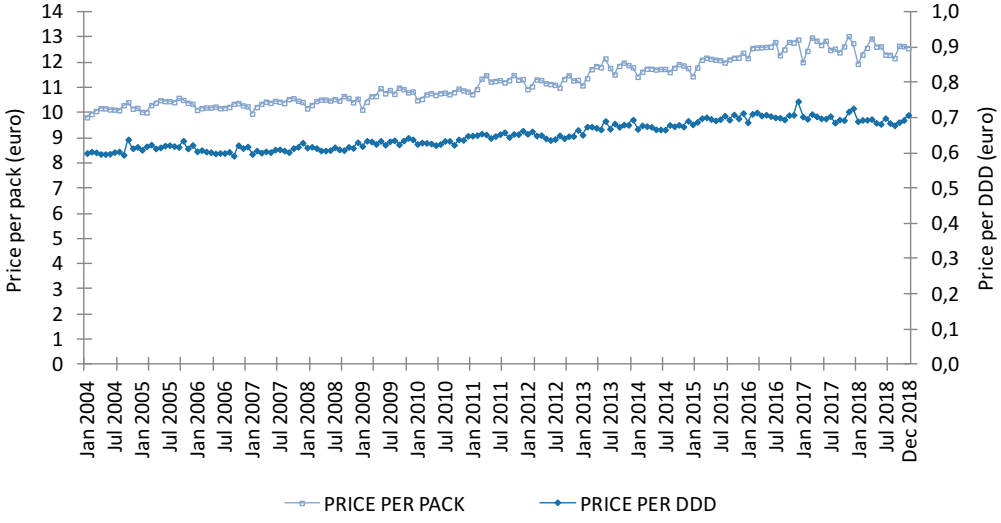
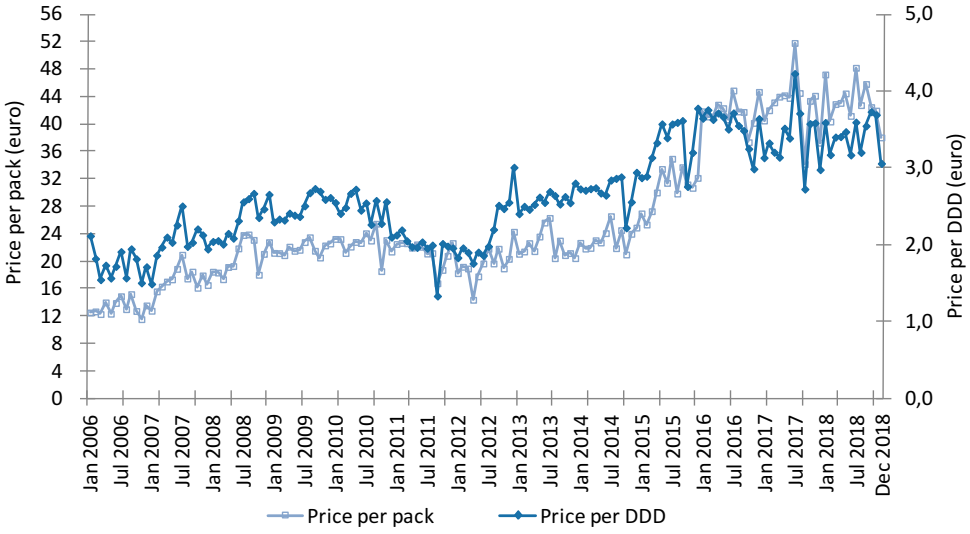


Figure 1.5.3. Average price trend of medicines purchased by public health facilities, years 2006-2018



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

In 2018 the expenditure for citizen co-payment on reference price of patent-expired medicines amounted to € 18.62 per capita (1.1 billion of euros) corresponding to the 70% of overall citizen co-payment (it includes also the payment of prescription/package ticket). Therapeutic classes with the highest level of expenditure in terms of citizen co-payment are lipid modifying agents, not associated (8.8% of the total), medicines for peptic ulcer and gastro-oesophageal reflux disease (GORD) (7.0%) and beta-blockers (6.7%). These three categories account for the 22.5% of the expenditure for citizen co-payment (Table 1.6.2). Bisoprolol, atorvastatin, colecalciferol, pantoprazole, ramipril and acetylsalicylic acid are the first 6 ingredients in terms of cost for citizen co-payment. They account approximately for the 18.2% of this expenditure (Table 1.6.3).

Table 1.6.2 Top 20 therapeutic categories with a higher share of expenditure on the reference price (year 2018)

ATC III	Description	Total expenditure	%*	% cum.
C10A	Non-associated lipid-modifying substances	99,251,807	8.8	8.8
A02B	Peptic Antiulcer	79,406,362	7.0	15.9
C07A	Beta-blockers	74,964,929	6.7	22.5
C09D	Angiotensin II antagonists, in association	60,040,749	5.3	27.8
C09B	Inhibitors of the angiotensin converting enzyme (ACE) in combination with	55,106,698	4.9	32.7
C09C	Angiotensin II antagonists	52,687,307	4.7	37.4
C09A	Non-associated angiotensin converting enzyme (ACE) inhibitors	52,295,474	4.6	42.0
N06A	Antidepressants	50,401,965	4.5	46.5
G04C	Drugs used in benign prostatic hypertrophy	39,588,086	3.5	50.0
B01A	Antithrombotic	39,328,531	3.5	53.5
A11C	Vitamins A and D, including their associations	39,214,984	3.5	57.0
M01A	Anti-inflammatory and anti-rheumatic, non-steroidal drugs	39,034,508	3.5	60.5
C08C	Selective calcium channel blockers with prevailing vascular effect	36,853,980	3.3	63.7
A10B	Oral hypoglycemic agents	31,672,050	2.8	66.5
N03A	Antiepileptics	29,357,549	2.6	69.2
J01C	Antibacterial beta-lactam, penicillins	24,622,535	2.2	71.3
J01D	Other beta-lactam antibacterial agents	23,740,983	2.1	73.4
S01E	Antiglaucoma and myocytic preparations	18,350,450	1.6	75.1
J01M	Quinolone antibacterial	17,327,536	1.5	76.6
M05B	Drugs that act on mineralization	15,156,683	1.3	78.0

*calculated on the total of the player sharing

Table 1.6.3. First 30 substances with a higher share of expenditure on the reference price (year 2018)

ATC V	Active substance	Total expenditure	%*	% cum.
C07AB07	bisoprolol	47,637,017	4.2	4.2
C10AA05	atorvastatin	38,592,721	3.4	7.7
A11CC05	cholecalciferol	36,487,340	3.2	10.9
A02BC02	pantoprazole	31,756,149	2.8	13.7
C09AA05	ramipril	27,620,273	2.5	16.2
B01AC06	acetyl salicylic acid	24,080,903	2.1	18.3
J01CR02	amoxicillin/clavulanic acid	21,078,507	1.9	20.2
C08CA01	amlodipine	20,593,764	1.8	22.0
C10AX06	omega 3	18,769,352	1.7	23.7
A10BA02	metformin	17,048,001	1.5	25.2
A02BC03	lansoprazole	16,875,549	1.5	26.7
G04CA02	tamsulosin	14,876,681	1.3	28.0
C09BB04	perindopril/amlodipine	14,260,633	1.3	29.3
G04CB02	dutasteride	13,465,993	1.2	30.5
C10AA07	rosuvastatin	13,462,062	1.2	31.6
A02BC05	exomeprazole	13,444,936	1.2	32.8
B01AC04	clopidogrel	13,395,310	1.2	34.0
C09DA08	olmesartan/hydrochlorothiazide	13,280,799	1.2	35.2
C10AA01	simvastatin	13,153,792	1.2	36.4
C09CA08	olmesartan	13,096,934	1.2	37.5
C07AB12	nebivolol	12,699,530	1.1	38.7
C09DA03	valsartan/hydrochlorothiazide	12,461,895	1.1	39.8
C09BA05	ramipril/hydrochlorothiazide	12,388,929	1.1	40.9
M01AB05	diclofenac	11,995,693	1.1	41.9
N06AB10	escitalopram	11,985,493	1.1	43.0
J01DD04	ceftriaxone	11,970,132	1.1	44.1
L04AD01	cyclosporine	11,443,437	1.0	45.1
C02CA04	doxazosin	11,120,596	1.0	46.1
H03AA01	levothyroxine	10,764,568	1.0	47.0
A02BC01	omeprazole	10,370,691	0.9	47.9

*calculated on the total of the player sharing

Section 2

Pharmaceutical use in fragile populations

2.1 Pharmaceutical use in pediatric age

This section presents an analysis of pharmaceutical use in pediatric age using data from all Italian regions, whose resident pediatric population (age <18 years) was 9.8 million individuals in 2018.
In 2018, over 4.8 million children and adolescents received at least one pharmaceutical prescription (49.1% of general pediatric population). Furthermore, in the same year, 19.8 million prescriptions were issued, for a total of 20.7 million packages and a total expenditure of 299 million euros (30.5 euros per capita and 62.10 per user). If compared to the previous year, a slight reduction was recorded in per capita expenditure (-0.8%) whereas an increase was reported in per user expenditure (1.4%); major decreases concern prescriptions and prescribed packages, respectively -2.8% and -3.3%. On average, in 2018, each child received 2.0 prescriptions and 2.1 packages of pharmaceuticals, with a slight difference between males and females: respectively 2.1 prescriptions versus 1.9 and 2.2 packages versus 2.0 (Table 2.1.1).

At a regional level, a marked variability was recorded in the use of pharmaceuticals in pediatric age, with a prevalence of use ranging from 40.7% in the Autonomous Province of Bolzano to 59.6% in Abruzzo (Figure 2.1.1).
As a confirmation of what has already been documented in the literature, the prescription prevalence records a peak in the first year of the child's life (77%), then it progressively decreases in the following years to almost halve in the 12-17 age group (39,4%) (Figure 2.1.2); overall the prevalence is higher in males than in females (49.9% vs 48.3%) (Table 2.1.1).
A similar trend by age concerns consumption, with a figure of per capita packages ranging from 3.4 in the first year of life to 1.7 in the 12-17 years bracket, with a more pronounced gender difference in the first year of age: 3.7 packages for males versus 3.0 packages for females (Table 2.2.2).
As expected, antimicrobials for systemic use show the highest consumption (46.4% of the total), followed by respiratory pharmaceuticals (24.3%) and hormones (excluding sex hormones) (8.4%), by pharmaceuticals for gastrointestinal tract and metabolism (7.5%) and by medicinal products for the central nervous system (7.1%) (Figure 2.1.3).

Analysis of consumption distribution by gender shows 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 2.1.4).
Antimicrobials for systemic use are the therapeutic category with the highest prescription prevalence (199.2 per 1000 children), amoxicillin/clavulanic acid combination being the most prescribed product in the category (356.3 prescriptions per 1000 children, with a 3.8% decrease compared to 2017), and also ranking first among the top 30 active ingredients with the highest consumption in 2018. On the contrary, amoxicillin, the first choice antibiotic in the treatment of the most common pediatric infections according to the guidelines, ranks second in the category (75.4 per 1000 children), showing a 3.2% increase in prescription compared to the previous year (Tables 2.1.3 and 2.1.4).

The rank list is followed by respiratory tract pharmaceuticals with a prevalence of 197.9 per 1000 children, beclomethasone being the most prescribed drug, with a prevalence of 70.3 per 1000 children, ranking sixth among the active ingredients with highest consumption in the pediatric age (94.2 packages per 1000 children), despite the pronounced reduction compared to the previous year (-34.0%). Hormones (excluding sex hormones), show a prevalence of 87.8 per 1000 inhabitants, betamethasone (74.9 per 1000 children) being the most prescribed pharmaceutical in the category. Pharmaceuticals for gastrointestinal system and metabolism have a prevalence of 53.0 per 1000 children and medicinal products for the central nervous system show a prevalence of 9.2 per 1000 children (Table 2.1.3 and 2.1.4).
Among the top 30 active ingredients with the highest consumption in the pediatric population in 2018, 11 active ingredients belong to the category of respiratory tract pharmaceuticals, 9 are antimicrobials for systemic use (8 antibacterials and one antiviral), 4 are hormones (excluding sex hormones) and 3 are active principles for central nervous system (antiepileptics). For all active ingredients, with the exception of levothyroxine (a medicinal product indicated for hypothyroidism), levetiracetam (an antiepileptic) and colecalciferol (vitamin D), consumption proves higher in males than in females (Table 2.1.4).

Table 2.1.1. General prescription data in the pediatric population in 2018

	Males	Females	Total
Users	2,517,513	2,297,788	4,815,301
prevalence (%)	49.9	48.3	49.1
Prescriptions	10,763,076	9,059,352	19,822,428
Per capita	2.1	1.9	2.0
Δ % 18-17	-2.9	-2.8	-2.8
Packages	11,232,578	9,432,755	20,665,333
Per capita	2.2	2.0	2.1
Δ % 18-17	-3.3	-3.3	-3.3
Expenditure	169,897,052	129,133,432	299,030,484
Per capita	33.7	27.1	30.5
Δ % 18-17	-0.7	-1.1	-0.8
Per user	67.49	56.20	62.10
Δ % 18-17	1.7	1.1	1.4

Figure 2.1.2. Prescription trend in the pediatric population by age and gender in 2018

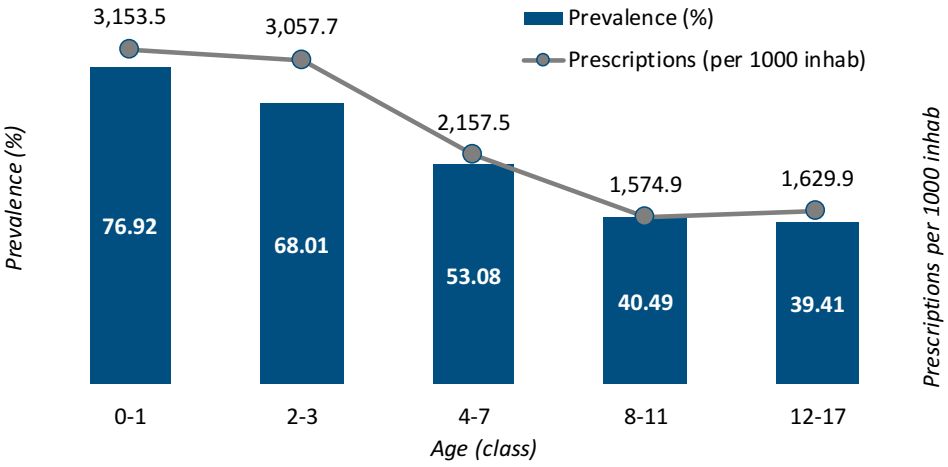


Table 2.2.2. Distribution of consumption (packages) by age and gender in the pediatric population in 2018

Age range	Per capita packages		
	Males	Females	Total
<1	3.7	3.0	3.4
1-5	3.1	2.8	2.9
6-11	1.8	1.6	1.7
12-17	1.8	1.7	1.7
Total	**2.2**	**2.0**	**2.1**

Figure 2.1.3. Percentage distribution of consumption (packages) in the pediatric age by I level ATC in 2018

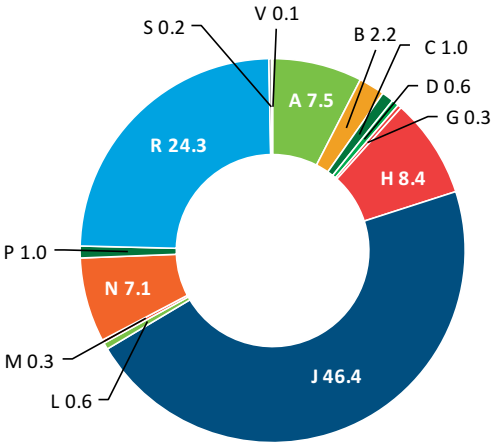
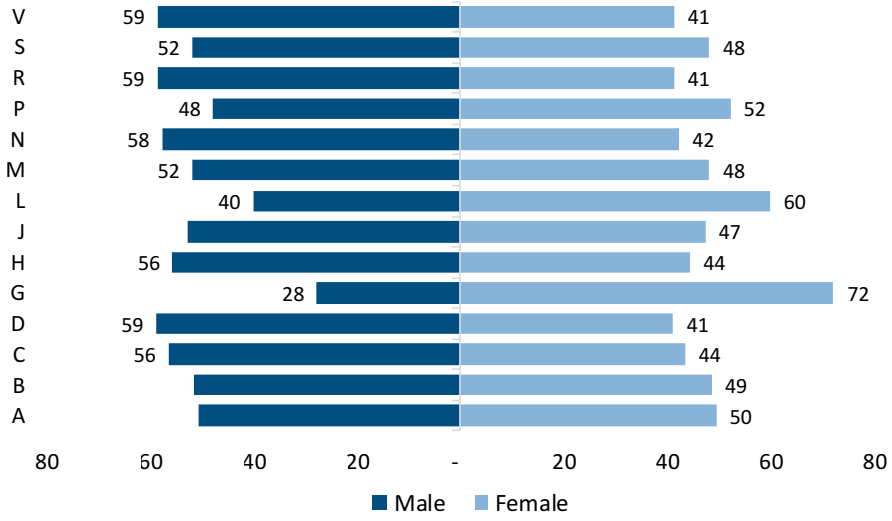


Figure 2.1.4. Percentage distribution of consumption (packages) in the pediatric age by I level ATC and gender in 2018



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 sysyem
D	Dermatologicals	M	Muscolo-skeletal system	S	Sensory organs
G	Genito-urinary system and sex hormones			V	Various

Table 2.1.3. Most prescribed susbstances in pediatric age by therapeutic category (75% of prescriptions) in 2018

Therapeutic category/substance	Prescriptions (x 1000 inhab.)	Δ % 18-17	Prevalence (x 1000 inhab.)	Ratio M/F
J – Antimicrobials for systemic use	**943.7**	**-2.8**	**387.2**	**1.02**
amoxicillin/clavulanic acid	356.3	-3.8	199.2	1.06
amoxicillin	142.3	3.2	75.4	1.02
cefixime	97.3	-3.7	65.3	0.97
azithromicyn	93.7	-1.7	63.4	1.05
clarithromycin	78.3	-4.2	55.6	1.09
R - Respiratory	**505.1**	**-7.6**	**197.9**	**1.18**
beclomethasone	93.5	-34.0	70.3	1.13
salbutamol	88.9	1.3	60.6	1.35
budesonide	63.0	11.7	45.1	1.16
cetirizine	58.8	-0.4	30.3	1.31
fluticasone	37.5	-1.3	22.3	1.45
montelukast	35.4	-5.7	11.0	1.54
salbutamol/ipratropium	35.3	-3.8	29.4	1.15
H - Hormones *(excl. sex hormones)*	**167.8**	**1.8**	**87.8**	**1.17**
betamethasone	109.1	1.5	74.9	1.18
somatropin	15.9	0.5	0.7	1.39
levothyroxine	15.5	2.7	2.6	0.56
prednisone	13.1	5.3	6.3	1.21
desmopressin	7.2	0.1	1.3	2.03
A - Gastrointestinal tract and metabolism	**149.9**	**1.7**	**53.0**	**0.94**
colecalciferol	69.7	5.8	32.7	0.94
lansoprazole	8.1	-4.3	1.9	0.91
insulin aspart	5.9	5.4	0.7	1.00
esomeprazole	5.7	-3.4	1.7	0.92
omeprazole	5.6	-10.7	1.6	0.89
insulin lispro	5.6	10.6	0.8	1.10
nystatin	4.6	-0.2	3.7	0.96
rifaximin	4.5	-12.8	3.0	1.25
ursodeoxycholic acid	4.1	5.1	0.4	0.91
N – Central Nervous System	**134.9**	**2.4**	**9.2**	**1.14**
valproic acid	52.4	-1.0	2.7	1.65
carbamazepine	13.3	3.3	0.8	1.15
levetiracetam	13.1	3.1	1.1	0.80
lamotrigine	6.3	7.4	0.4	0.62
topiramate	4.4	-4.3	0.4	0.74
aripiprazole	4.0	23.4	0.6	1.35
phenobarbital	3.8	-4.3	0.3	1.20
sertraline	3.7	12.6	0.6	0.73
risperidone	3.5	9.1	0.9	2.93

Table 2.1.4. First thirthy active ingredients by consumption in the pediatric age in 2018

ATC	Active ingredient	Packages (per 1000 inhab.)	Δ % 18-17	Consumption (%)*	
				Males	Females
J	amoxicillin/clavulanic acid	367.6	-4.2	53.6	46.4
J	amoxicillin	148.3	2.6	52.4	47.6
H	betamethasone	110.5	1.3	56.6	43.4
J	cefixime	99.3	-4.0	51.0	49.0
J	azithromycin	95.5	-2.0	53.2	46.8
R	beclomethasone	94.2	-34.0	55.3	44.7
R	salbutamol	89.6	1.1	60.2	39.8
J	clarithromycin	79.7	-4.5	53.8	46.2
A	colecalciferol	72.8	4.8	49.3	50.7
R	budesonide	63.4	11.5	55.9	44.1
R	cetirizine	60.2	-1.1	60.3	39.7
N	valproic acid	55.5	-2.3	64.1	35.9
J	cefpodoxime	48.6	2.4	52.9	47.1
R	fluticasone	38.1	-1.6	61.8	38.2
R	montelukast	36.6	-6.4	63.2	36.8
R	salbutamol/ipratropium	35.3	-3.8	55.4	44.6
J	ceftriaxone	31.4	-4.1	54.2	45.8
J	cefaclor	24.1	-10.1	49.9	50.1
R	flunisolide	23.0	30.6	54.2	45.8
H	somatropin	21.1	0.5	61.3	38.7
H	levothyroxine	16.3	1.5	37.9	62.1
P	mebendazole	15.3	9.5	48.1	51.9
N	carbamazepine	14.2	2.0	55.7	44.3
N	levetiracetam	14.2	2.4	45.8	54.2
R	levocetirizine	13.8	-5.3	62.2	37.8
H	prednisone	13.6	3.8	54.6	45.4
J	acyclovir	13.5	-13.6	51.5	48.5
R	salmeterol/fluticasone	11.9	-2.9	65.5	34.5
R	desloratadine	9.8	-6.3	61.6	38.4
A	lansoprazole	8.6	-5.5	53.4	46.6

*calculated with reference to overall consumption in the pediatric age

Prescription of respiratory pharmaceuticals in pediatrics

From the analysis of prescription of pharmaceuticals for the respiratory system it emerges that one child in five received at least one package in 2018. Overall, 5.2 million prescriptions were issued, equal to 26.1% of total consumption in children, with a reduction of 6.5% compared to 2017 (Table 2.1.5) and a peak prevalence in the first year of life (44%), which decreases with age (Figure 2.1.5).
Inhaled steroids are the most widely used therapeutic class (13.7% prevalence and 217.2 prescriptions per 1000 inhabitants) and beclomethasone is the most prescribed active ingredient (prevalence of use of 7.0%), followed by oral steroids (prevalence of 8.2%), with betamethasone among the most prescribed active ingredients (prevalence of 7.5%, although reduced compared to 2017) and SABA (short-acting adrenergic bronchodilators) with a prevalence of 6.1%, salbutamol being the most prescribed active ingredient (prevalence of 6.1%) (Table 2.1.6).
Analysis of prescription in different therapeutic classes by age group shows a higher prevalence of use in children up to 6 years of age for all medicines, with the exception of beta2-adrenergic agonists in combination - LABA (long acting beta adrenergic receptor agonists) and injectable steroids, which have a higher prevalence of use in children over 6 years of age. Furthermore, for all categories there is a high percentage of users with a single prescription in the year, due to their possible use when needed (Table 2.1.7).
Analysis of the percentage distribution of consumption of the different therapeutic categories by age group indicates a higher percentage of use for inhaled steroids in all age groups with a peak in children aged 2-3 years (except for the age group 12 - 17 years, where a greater use of oral steroids is recorded). Combination beta2-adrenergic agonist drugs - SABA (short-acting adrenergic bronchodilators) is mostly used in the first year of life and then decreases with age. However, use of SABAs is similar in all age groups, although it is reported to be used less in the first year of life (Figure 2.1.6).

Table 2.1.5 Prescription of respiratory pharmaceuticals in the pediatric population (2018)

	Total
Prescriptions	5,181,619
Per 1000 children	528.4
Δ % 18-17	-6.5
% share on overall consumption	26.1
Packages	5,246,761
Per prescription	1.0
Users	2,064,462
Prevalence (%)	21.1

Figure 2.1.5. Trend of prescription of respiratory pharmaceuticals by age in 2018

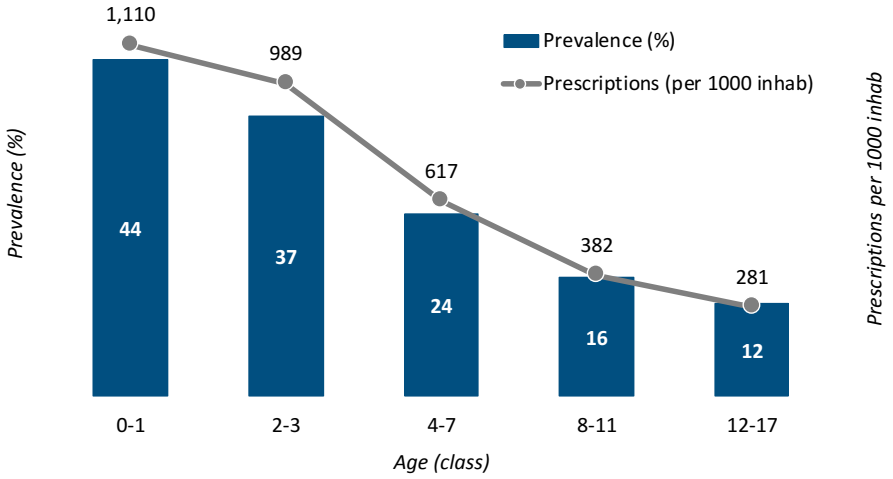


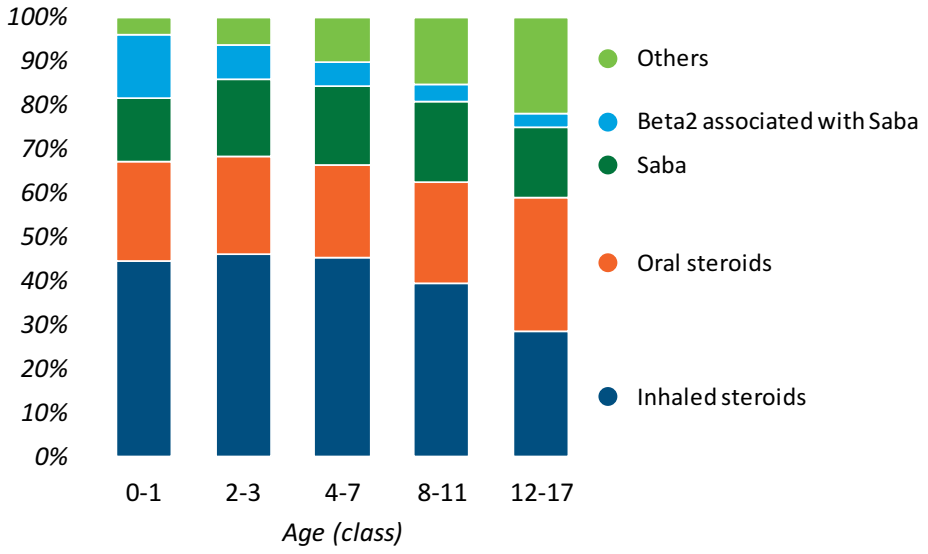
Table 2.1.6. Prescription of respiratory pharmaceuticals in the pediatric population by therapeutic class and substance (2018)

Categories and substances	Prevalence (%)	Prescriptions (per 1000 inhab.)	Δ % 18-17
inhaled steroids	13.7	217.2	-14.5
oral steroids	8.2	125.3	1.9
saba	6.1	88.9	1.3
beta2 in combination with- saba	3.1	36.9	-4.6
anti leukotrienics	1.1	35.4	-5.7
beta2 in combination with- laba	0.8	18.8	2.1
anticholinergic	0.2	2.6	0.0
injecting steroids	0.1	2.0	3.3
cromoglicate	<0.05	0.4	-41.6
Total	**21.1**	**528.4**	**-6.5**
betamethasone	7.5	109.1	1.5
beclomethasone	7.0	93.5	-34.0
salbutamol	6.1	88.9	1.3
budesonide	4.5	63.0	11.7
fluticasone	2.2	37.5	-1.3
montelukast	1.1	35.4	-5.7
salbutamol/ipratropium	2.9	35.3	-3.8
flunisolide	1.8	22.9	30.8
prednisone	0.6	13.1	5.3
salmeterol/fluticasone	0.5	11.6	-2.3

Table 2.1.7. Respiratory pharmaceuticals users in the pediatric age by number of prescriptions received during the year by therapeutic subgroup and age group (2018)

Categories	0-6 years					7-17 years				
	Prevalence %	Users for no. prescriptions (%)				Prevalence %	Users for no. prescriptions (%)			
		1	2	3	>3		1	2	3	>3
inhaled steroids	24.1	65.4	20.1	7.4	7.1	8.0	74.3	16.4	4.7	4.6
oral steroids	12.7	70.2	19.1	5.9	4.8	5.7	73.2	18.3	4.1	4.4
saba	10.3	75.1	16.5	4.9	3.5	3.7	70.5	18.4	5.2	5.9
beta2 in combination with-saba	6.7	83.9	12.3	2.6	1.1	1.0	88.3	9.1	1.6	1.0
antileukotrienics	1.6	35.6	22.9	11.3	30.2	0.8	30.2	24.5	9.8	35.5
beta2 in combination with -laba	0.3	54.5	20.7	9.3	15.4	1.1	47.7	22.3	9.3	20.7
anticholinergic	0.3	72.3	17.0	5.1	5.6	0.1	71.8	19.0	3.9	5.3
injecting steroids	0.1	84.8	11.4	1.8	2.0	0.2	73.9	19.9	2.7	3.5
cromoglycate	0.0	81.4	12.9	2.9	2.8	0.0	80.5	12.9	3.1	3.5

Figure 2.1.6. Percentage distribution of respiratory pharmaceuticals consumption in the pediatric age by therapeutic cathegory and age group (2018)



Antibiotics prescription in the pediatric population

About 4 out of 10 children received at least one antibiotic prescription in 2018 and, on average, each child was prescribed only one package during the year, for a total of 8.9 million prescriptions, equal to 45.1% of total consumption (Table 2.1.8), with a peak prevalence (about 6 children out of 10) in the 2-3 year age bracket (Figure 2.1.7).
The associations of penicillins (including beta-lactamase inhibitors) are the class of antibiotics with the highest prescription prevalence (19.9%), amoxicillin/clavulanic acid association showing the highest prescription (356.3 prescriptions per 1000 children). Following are macrolides and lincosamides (11.3%), with azithromycin as most prescribed molecule (93.7 prescriptions per 1000 children) and oral cephalosporins (prevalence of 10.2%), with cefixime among the most prescribed active ingredients (97.3 prescriptions per 1000 children). Instead, broad-spectrum penicillins (such as amoxicillin) are among the least used antibiotics, with a prescription level of 143.1 per 1000 children. Among the 10 most prescribed molecules in the category, a strong reduction was recorded for ceftibuten (-21.6%) while amoxicillin and cefpodoxime are the only substances showing an increase in use compared to 2017 (+3.2%) (Table 2.1.9).
The analysis of the percentage distribution of consumption in the different therapeutic categories by age group shows a greater use of penicillin associations in all age brackets. Macrolides and lincosamides record the highest consumption in the 12-17 age range, while oral cephalosporins are more used in children between 2 and 11 years of age. Finally, broad-spectrum penicillins are mostly used in the first year of life, and progressively decrease with age (Figure 2.1.8).
From the analysis of some indicators aimed at specific classes of antibiotics, the associations of penicillins (including beta-lactamase inhibitors) are the most widely used antibiotics (38.8%) particularly in Central Italy (44.7%), followed by cephalosporins (23.0%) and macrolides (18.9%), especially in Southern Italy. Broad-spectrum penicillins are the lowest prescription antibiotics (15.6%). Focusing on the Regions, a high variability was recorded in the use of the different classes of antibiotics; for example, Friuli Venezia-Giulia shows the highest prescription of broad-spectrum penicillins (47.6%), whereas associations of penicillins (47.9%) are most prescribed in the Autonomous Province of Trento, cephalosporins in Sicily (30.9%) and macrolides and lincosamides in Calabria (24.2%). Abruzzo is the Region with the lowest consumption of broad-spectrum penicillins (6.3%), while Friuli Venezia-Giulia records the lowest consumption of the other classes (respectively 26.1%, 7.6% and 13.6%). Finally, it should be emphasized that in Northern Italy, on average, more amoxicillin is used than in other geographical areas (amoxicillin/amoxicillin+clavulanic acid ratio equal to 0.6 in the North, 0.2 in the Center and 0.3 in the South). It is worth recalling that in the two most frequent clinical conditions in the pediatric population, pharyngotonsillitis and acute otitis media, the use of amoxicillin is recommended as a first choice option. The association amoxicillin+ clavulanic acid does not offer any advantage in pharyngotonsillitis whereas in otitis the addition of clavulanic acid is expected in severe/complicated and recurrent cases. In the uncomplicated and non-recurrent form, on the other hand, amoxicillin should be the drug of choice (Table 2.1.10).

Table 2.1.8. Prescription of antibiotics in the pediatric population (2018)

	Total
Prescriptions	8,943,269
Per 1000 children	912.0
Δ % 18-17	1.1
% share of overall consumption	45.1
Packages	9,269,047
Per prescription	1.0
Users	3,712,358
Prevalence (%)	37.9

Figure 2.1.7. Trend of antibiotics prescription by age group (2018)

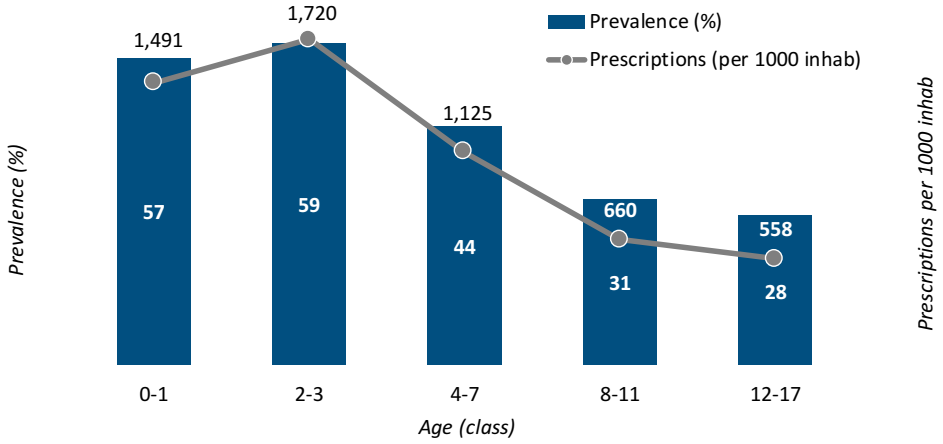


Table 2.1.9. Prescription of antibiotics in the pediatric population by therapeutic category and substance (2018)

Categories and substances	Prevalence (%)	Prescriptions (per 1000 inhab.)	Δ % 18-17
penicillin associations (including beta lactamase inhibitors)	19.9	356.8	-3.8
macrolides and lincosamides	11.3	177.7	-3.4
oral cephalosporins	10.2	175.6	-3.8
broad-spectrum penicillins and penicillins sensitive to beta lactamases	7.6	143.1	3.1
cephalosporine im/ev iii-iv gen	0.5	31.0	-2.1
tetracyclines	0.3	8.4	1.6
oher antibiotics	0.7	8.2	-4.4
quinolones	0.4	7.5	-3.4
cephalosporins im/ev ii gen	0.2	4.3	-7.7
sulfonamides and trimetropim	0.2	3.9	-3.6
aminoglycosides	<0.05	3.3	-16.1
cephalosporins im/ev i gen	<0.05	0.3	-15.6
Total	**37.9**	**912.0**	**1.1**
amoxicillin/clavulanic acid	19.9	356.3	-3.8
amoxicillin	7.5	142.3	3.2
cefixime	6.5	97.3	-3.7
azithromycin	6.3	93.7	-1.7
clarithromycin	5.6	78.3	-4.2
cefpodoximae	2.5	46.3	3.2
ceftriaxone	0.5	26.9	-1.7
cefaclor	1.3	23.3	-9.6
fosfomycin	0.7	8.2	-4.2
ceftibuten	0.5	7.5	-21.6

Figure 2.1.8. Percentage distribution of antibiotic consumption by therapeutic category and age group (2018)

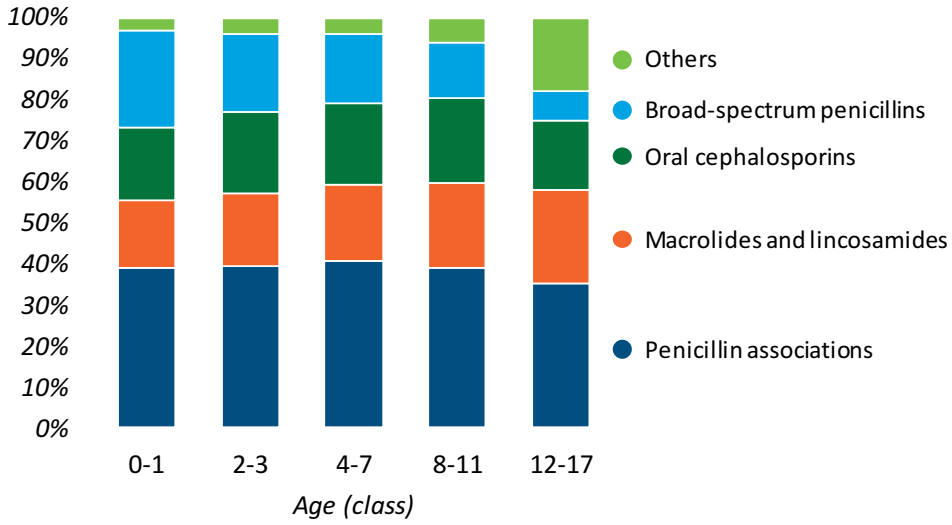


Table 2.1.10. Pediatric indicators related to specific classes of antibiotics and amoxicillin/amoxicillin-clavulanic in 2018 (agreed expenditure)

Region	Indicator				
	1	2	3	4	5
Piemonte	17.8	40.8	22.0	16.1	0.4
Valle d'Aosta	25.0	33.6	19.0	18.6	0.7
Lombardia	20.0	44.0	18.0	15.3	0.4
PA Bolzano	13.6	39.9	24.7	19.1	0.3
PA Trento	12.3	47.9	17.1	18.8	0.3
Veneto	22.3	34.8	17.5	21.4	0.6
Friuli VG	47.6	26.1	7.6	13.6	1.8
Liguria	11.2	42.8	27.9	14.5	0.3
Emilia R.	40.0	29.2	13.2	14.6	1.4
Toscana	9.0	51.5	22.0	14.7	0.2
Umbria	18.2	48.5	16.0	14.7	0.4
Marche	14.7	40.4	25.4	15.6	0.4
Lazio	10.0	41.9	24.5	19.6	0.2
Abruzzo	6.3	42.3	24.3	23.6	0.1
Molise	10.7	39.2	23.8	20.3	0.3
Campania	6.5	34.7	29.9	23.6	0.2
Puglia	14.6	35.9	25.1	20.4	0.4
Basilicata	17.4	32.6	24.2	21.4	0.5
Calabria	7.1	35.9	28.7	24.2	0.2
Sicilia	8.1	33.6	30.9	24.1	0.2
Sardegna	13.7	40.7	25.3	17.7	0.3
Italia	**15.6**	**38.8**	**23.0**	**18.9**	**0.4**
Nord	23.9	39.0	17.8	16.2	0.6
Centro	11.2	44.7	23.3	17.2	0.2
Sud e Isole	9.2	35.7	28.2	22.7	0.3

Indicator
1. % prescriptions of broad spectrum penicillins (J01CA-CE)
2. % prescriptions of penicillin associations – including beta lactamase inhibitors (J01CF-CR)
3. % prescriptions of cephalosporines (J01DB-DC-DD-DE)
4. % prescriptions of macrolides (J01FA)
5. *ratio* prescriptions amoxicillin/amoxicillin+clavulanic acid

Prescription of antiepileptic pharmaceuticals in pediatrics

The antiepileptic prescription has remained substantially stable compared to 2017 (+0.4%) and represents 4.9% of the total consumption of pharmaceuticals in the pediatric age. As expected, the prevalence in the pediatric population is low and is equal to 0.5% with a prescription rate of 100 per 1000 children (Table 2.1.11). The use of epileptic pharmaceuticals with an increasing trend by age is in line with the epidemiology of the condition and peaks in the 12-17 year age group, recording a prescription rate of 136 per 1000 children and a prevalence of 0.7% (Figure 2.1.9). Valproic acid is the most used substance (52.4 prescriptions per 1000 children and prevalence of 0.3%), showing a slight decrease (-1.0%) compared to 2017, followed by carbamazepine with 13.3 prescriptions for 1000 children (+3.3% compared to the previous year), and by levetiracetam which shows a 3.1% increase compared to the previous year, with 13.1 prescriptions per 1000 children (Table 2.1.12). The prescription of valproic acid is higher in the 2-11 years age group, while the proportion of carbamazepine and levetiracetam remains substantially similar in all age groups (Figure 2.1.10).

Table 2.1.11. Prescription of antiepileptic pharmaceuticals in the pediatric population (2018)

	Total
Prescriptions	980,652
Per 1000 children	100.0
Δ % 18-17	0.4
% share of overall consumption	4.9
Packages	1,072,090
Per prescription	1.1
Users	50,092
Prevalence (%)	0.5

Figure 2.1.9. Trend of antiepileptic drug prescriptions by age (2018)

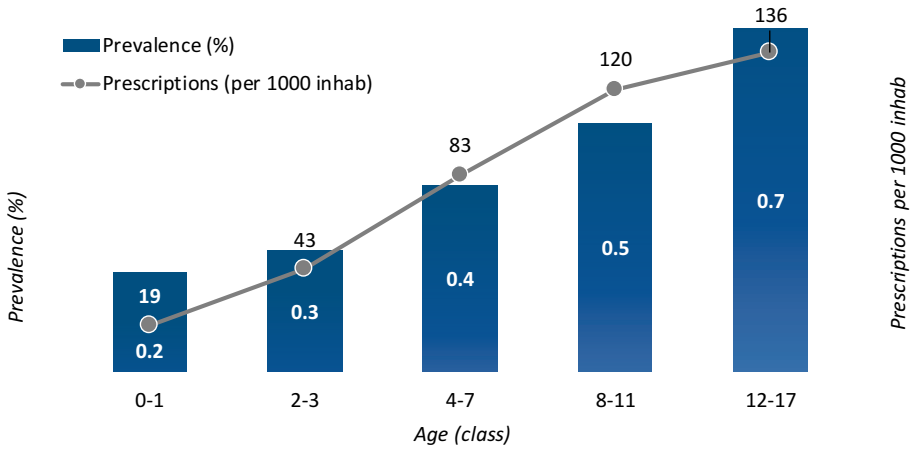
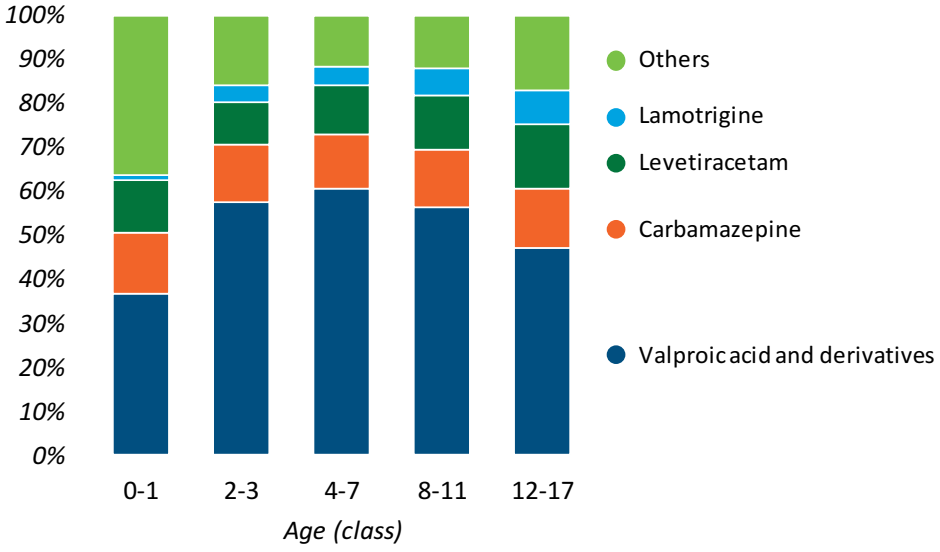


Table 2.1.12. Prescription of antiepileptic pharmaceuticals in the pediatric population by therapeutic category and substance (2018)

Categories and substances	Prevalence (%)	Prescriptions (per 1000 inhab.)	Δ % 18-17
valproic acid and derivatives	0.3	52.4	-1.0
carbamazepine	0.1	13.3	3.3
levetiracetam	0.1	13.1	3.1
lamotrigine	0.0	6.3	7.4
topiramate	0.0	4.4	-4.3
barbiturates and derivatives	0.0	3.8	-4.5
oxcarbazepine	0.0	2.0	-2.2
clonazepam	0.0	1.7	-4.8
Total	**0.5**	**100.0**	**0.4**
valproic acid	0.3	52.4	-1.0
carbamazepine	0.1	13.3	3.3
levetiracetam	0.1	13.1	3.1
lamotrigine	0.0	6.3	7.4
topiramate	0.0	4.4	-4.3
phenobarbital	0.0	3.8	-4.3
oxcarbazepine	0.0	2.0	-2.2
clonazepam	0.0	1.7	-4.8
zonisamide	0.0	1.0	-1.6
lacosamide	0.0	0.8	12.2

Figure 2.1.10. Percentage distribution of epileptic pharmaceuticals consumption by therapeutic category and age group (2018)



List of categories

Antibiotics	
other antibiotics	clofoctol, colistimethate, phosphomycin, metronidazol, nitrofurantoin
aminoglycosides	amikacin, gentamicin, netilmicin, tobramycin
antibiotics vs resistant germs	linezolid
penicillin associations (including beta lactamase inhibitors)	amoxicillin/clavulanic acid, ampicillin/sulbactam, flucloxacillin, oxacillin sodium, piperacillin/tazobactam
cephalosporins im/ev i gen	cefazolin
cephalosporins im/ev ii gen	cefazolin, cefoxitin
cephalosporins im/ev iii-iv gen	cefepime, cefodizime, cefotaxime, ceftazidime, ceftriaxone
oral cephalosporins	cefaclor, cefalexine, cefditoren, cefixime, cefpodoxime, cefprozil, ceftibuten
quinolones	pipemidic acid, ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, pefloxacin, prulifloxacin, rufloxacin
glycopeptides	teicoplanin
macrolides and lincosamides	azithromycin, clarithromycin, clindamycin, erythromycin, josamycin, lincomycin, miocamycin, roxithromycin, spiramycin, telithromycin
broad-spectrum penicillins and penicillins sensitive to beta-lactamases	amoxicillin, ampicillin, bacampicillin, benzathine benzilpenicillin, piperacillin
polymyxins	colistimetate
sulfonamides and trimetropim	trimetoprim/sulfamethoxazole
tetracyclines	doxycycline, limecycline (tetracycline-levo-methylenelysine), metacycline, minocycline
Antiepileptics	
valproic acid and derivatives	valproic acid, valpromide
gaba analogues	gabapentin, pregabalin
barbiturates and derivatives	phenobarbital, primidone
carbamazepine	carbamazepine
clonazepam	clonazepam
lacosamide	lacosamide
lamotrigin	lamotrigin
levetiracetam	levetiracetam
oxcarbazepine	oxcarbazepine
perampanel	perampanel
topiramate	topiramate
zonisamide	zonisamide

Respiratory	
other antiasthmatics	omalizumab, roflumilast
anticholinergics	aclidinium, glicopyrronium, ipratropium, oxitropium, tiotropium, umeclidinium
antileukotrienics	montelukast
beta2 in combination with saba	aclidinium/formoterol, beclomethason/formoterol, budesonide/formoterol, fenoterol/ipratropium bromide, fluticasone/formoterol, fluticasone/vilanterol, indacaterol/glicopyrronium, salmeterol/fluticasone
beta2 in combination with laba	beclomethasone/salbutamol, salbutamol/flunisolide, salbutamol/ipratropium
cromoglycate	nedocromil sodium
laba	formoterol, indacaterol, olodaterol, salmeterol
lama - laba	tiotropium/olodaterol, umeclidinium/vilanterol
saba	fenoterol, salbutamol, terbutaline
inhaled steroids	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone
injecting steroids	betamethasone, desamethasone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone
oral steroids	betamethasone, cortisone acetate, deflazacort, desamethasone, hyrocortisone, metihyprednisolone, prednisolone, prednisone
theophyllinics	ambroxol, doxofiyllin, theophylline

2.2 Pharmaceutical use in pregnancy

Methods

Using data from declarations of birth, an analysis was performed with women aged between 15 and 49, who gave birth between October 1, 2014 and September 30, 2017 and residing in the Regions Emilia-Romagna, Lazio and Puglia at the time of birth. In the case of multiparity, only the first birth in the study period was examined.
The date of start of pregnancy was estimated starting from the gestational[1] age and on the basis of this information the following data were identified:

- the pre-pregnancy quarter: 91 days before start of pregnancy
- I quarter: period between 0 and 91 days from start of pregnancy
- II quarter: period between 92 and 189 days from start of pregnancy (or date of delivery in case this happened in the second semester of pregnancy, that is between 20 and 27 weeks of gestation)
- III quarter: period between 190 days from start of pregnancy and date of delivery
- the post-pregnancy quarter: 91 days after date of delivery.

Only women were selected who were assisted in the period between 182 days prior to pregnancy and 91 days following date of delivery.
For each woman in the study, the socio-demographic and clinical information was collected inferable from declarations of birth and the pharmaceutical prescriptions provided in the identified 5 quarters were linked. For the identification of women who were new users of pharmaceuticals during pregnancy, a time window was used of 182 days before date of start of pregnancy.
Medicinal consumption before, during and after pregnancy was defined on the basis of the presence of at least one prescription of the medicines investigated.

Therapeutic categories considered

1. Antidiabetic pharmaceuticals (ATC: A10)
    - Insulins and analogues (ATC: A10A)
    - Oral hypoglycemic agents (ATC: A10B)
2. Antihypertensive pharmaceuticals (ATC: C02)
    - Diuretics (ATC: C03)
    - Beta-blockers (ATC: C07)
    - Calcium channel blockers (ATC: C08)
    - Pharmaceuticals for the renin-angiotensin system (ATC: C09)
3. Antibacterials for systemic use (ATC: J01)
4. Heparinics (ATC: B01AB)
5. Progestins (ATC: G03D)
6. Preparations for thyroid therapy (ATC: H03)
7. Antiepileptic pharmaceuticals (ATC: N03)
8. Antidepressant pharmaceuticals (ATC: N06A)

[1] Date beginning of pregnancy=date of delivery-(gestational age*7)

9. Vitamins (ATC: A11)
10. Minerals (ATC: A12)
11. Antianemic preparations (ATC: B03)
    - Iron-based preparations (ATC: B03A)
    - Vitamin B12 and folic acid (ATC: B03B)
    - Other antianemic preparations (ATC: B03X)

Results

The section provides an analysis of drug prescription in pregnant women considering data from the Regions Emilia Romagna, Lazio and Puglia, whose residing female population of fertile age (15-49 years) in 2015 was 3,2 million.

Using data from declarations of birth, the analysis included women aged 15 to 49 years who had a birth from 1 October 2014 to 30 September 2017, residing at the time of delivery in the three regions considered.

Table 2.2.1 shows some demographic, anamnestic and clinical characteristics of the study population: a total of 274,938 women, 37.7% of which residing in Lazio, 32.2% in Emilia Romagna and the remaining 30.1 % in Puglia. 15.9% of the total was of foreign citizenship, with a higher percentage for Emilia Romagna (29.1%).

The highest percentage (33.7%) of pregnant women was recorded in the 30-34 years age group. Of the more than 25,000 pregnant women belonging to the age group ≥ 40 years, 7.7% were aged ≥ 45 years. A total of 124,576 women (45.3% of the total) had already had a previous birth (33.4% by caesarean section). Furthermore, 22.1% of pregnant women had suffered at least one previous abortion (1.7% even in a number ≥3). The majority of deliveries (92.1%) were at full term, while 7% was pre-term. 1.9% of deliveries were twins.

For the time period considered, 221,066 pregnant women eligible for assistance received at least one pharmaceutical prescription during pregnancy (80.4% of the selected population). Furthermore, 36.5% and 50.7% of women with a birth in the period considered received at least one pharmaceutical prescription respectively in the quarter preceding pregnancy and in the quarter following birth (Table 2.2.2).

The distribution of women with at least one drug prescription before, during and after pregnancy shows a growing trend increasing with age in all quarters considered (Table 2.2.2 and Figure 2.2.1).

Pharmaceuticals belonging to the therapeutic category of blood and hematopoietic organs are those most commonly prescribed in pregnancy (55.9%), followed by antimicrobials for systemic use (41.5%), by medicinal products for the genitourinary system and sex hormones (25,5%), by systemic hormonal preparations- excluding sex hormones (14.9%),

by pharmaceuticals for the gastrointestinal tract and metabolism (13.5%) and by products for the respiratory system (10.5%) (Table 2.2.3 and Figure 2.2.2).

In the quarter preceding conception, antimicrobials for systemic use were the most prescribed drugs (18%), followed by those belonging to the therapeutic categories of blood and blood-forming organs (8.3%), gastrointestinal tract and metabolism (6.7%), systemic hormonal preparations (excluding sex hormones) (6.5%), genitourinary system and sex hormones (5.9%) and respiratory system (5.6%). The quarter following birth saw a distribution of prescriptions which mainly concerned the blood and hematopoietic organs category (33.5%), followed by antimicrobials for systemic use (16.1%), genito-urinary system drugs and sex hormones (10.1%), systemic hormone preparations (excluding sex hormones) (5.3%), gastrointestinal drugs and metabolism (3.8%) and respiratory system pharmaceuticals (3.5%) (Table 2.2.3, Figure 2.2.3).

Among the top 30 most prescribed active ingredients in pregnancy, 9 active ingredients were reported for the category of antimicrobial drugs for systemic use (J), 6 for blood and blood-forming organs (B), 4 for gastrointestinal tract and metabolism (A), 3 for genitourinary system and sex hormones (G) and 3 for systemic hormonal preparations (H) (Table 2.2.4).

Prescription of iron, vitamins and minerals

The overall distribution of women with at least one prescription of iron, vitamins and minerals before, during and after pregnancy shows a percentage increasing from 7.6% in the pre-pregnancy quarter to 36.4% in the first quarter and then progressively decreases in subsequent quarters (51.5% of women received at least one prescription during pregnancy) (Table 2.2.5).

Folic acid and ferrous sulfate represent the first and the third most prescribed active ingredients in pregnancy in the study population, with an overall percentage of respectively 41.9% and 21.6%; folic acid shows a reduction trend from 35% in the first quarter to 11.3% in the third quarter. In contrast, prescription of ferrous sulfate increases during pregnancy, going from 2.6% in the first quarter to 15.5% in the third quarter (Table 2.2.4).

It is likely that the distribution of prescriptions underestimates the actual consumption of folic acid and iron, as well as vitamin complexes and supplements, which can also be purchased without prescription. Nevertheless, Table 2.2.5 and Figure 2.2.4 highlight a clinical practice far from the international and national recommendations that support daily supplementation with folic acid before conception in women who plan or do not rule out the possibility to become pregnant, with an aim to reduce the risks of birth defects.

The distribution of prescriptions related to ferrous sulphate, even with the limits considered, appears in accordance with the Guideline of Physiological Pregnancy (2010) by

the National Guidelines System which, as regards iron supplementation, recommends not prescribing it routinely to all pregnant women.

Prescription of heparinics

Table 2.2.5 shows the overall distribution of prescriptions of such pharmaceuticals from the quarter preceding conception until the quarter following birth. In particular, in the pre-conception period the number of women receiving at least one prescription is equal to 1%, then it increases during all quarters of pregnancy, going from 2.9% in the first quarter to 6.2% in the third quarter. The overall percentage of users of heparinics in pregnancy is 7.5%, reaching a peak of 26.9% in the quarter following birth. The most prescribed active ingredient is enoxaparin, which ranks tenth among the most prescribed drugs in pregnancy (Table 2.2.4).

The clinical characteristics of the study population together with thromboprophylaxis after cesarean section probably represent the main determinants of this trend (SIGO Guideline, 2014). Furthermore, as age increases, an increase is also recorded in prescription of heparinics for all the quarters considered (Figure 2.2.5).

Prescription of antibiotics

In pregnancy, the number of women with at least one prescription of antibiotics reaches 40.3%, showing (in the different quarters considered) relatively comparable percentages (from 16.8% in the pregravid quarter to 15.7% after delivery) with the exception of a peak in the second quarter (22.0%), also confirmed in Figure 2.2.6, which shows the distribution of antibiotic prescriptions by age group.

Azithromycin, amoxicillin in combination with clavulanic acid and fosfomycin are the most frequently prescribed active ingredients, in line with the choice of antibiotics compatible with pregnancy (Table 2.2.4).

Access to invasive prenatal diagnosis in the population considered, despite the absence of recommendations in favor of antibiotic prophylaxis (SIEOG 2015 Guidelines), together with the offer of screening for asymptomatic bacteriuria and subsequent treatment in positive cases in the first quarter of pregnancy, most likely represent the main causes of prescription increase detected in the second quarter for this class of drugs.

Prescription of progestin pharmaceuticals

Progesterone is used for the treatment of threatened abortion and preterm birth, as well as in medically assisted procreation.

Progesterone and hydroxyprogesterone caproate are respectively the second and eleventh most prescribed active active ingredient in pregnancy in the study population (Table 2.2.4), with an overall percentage of 22.3% and 5.8% and a progesterone trend

decreasing from 18.2% in the first quarter to 7.3% and 2.6% in the second and third quarters.

The overall distribution of women with at least one progestin prescription (Table 2.2.5) shows a prescription shifting from 3.1% in the preconception quarter, probably associated with medically assisted procreation, to 19.2% in the first quarter and progressively decreases in subsequent quarters and stops after delivery. Figure 2.2.7 also shows a prescription trend for progestins in line with the number of abortions in obstetric history.

The use of progesterone, in particular in prevention of non-recurrent spontaneous abortion, is the subject of discussion regarding a poorly appropriate clinical practice in terms of efficacy. On the other hand, recent systematic reviews concerning use of progesterone both in threatened abortion and in prevention of preterm birth, suggest a probable efficacy even in the early stages of pregnancy, so highlighting the utility of prescription monitoring in such area (Haas DM et al, 2018; Wahabi HA et al, 2018; Jarde A et al, 2019).

Prescription of pharmaceuticals for treatment of thyroid pathologies

Table 2.2.5 shows the overall distribution of women with at least one prescription of a preparation for thyroid therapy from the quarter before conception until the postpartum quarter. The prescription of preparations for thyroid therapy in the preconception period is 3.7% and reaches an overall percentage of 10.2% of pregnant women, decreasing to 4% in the quarter following delivery. The most prescribed active ingredient is levothyroxine sodium, a thyroid preparation indicated for treatment of hypothyroidism, which ranks sixth among the most prescribed drugs in pregnancy (Table 2.2.4).

The proportion of new users of preparations for thyroid therapy in pregnancy seems to indicate an increased incidence of diagnosis of thyroid disorders during this period (Figure 2.2.8), which highlights the importance of paying attention to thyroid evaluation, to diagnosis and possible treatment of related diseases, in the preconception period and at the beginning of pregnancy (Alexander EK, et al, 2017).

Prescription of antihypertensive pharmaceuticals

Table 2.2.6 shows the overall distribution of antihypertensives, from the quarter preceding conception to the quarter following birth. Prescription of antihypertensives in preconception age, expression of the treatments of the chronic forms, is recorded in 0.8% of women, which subsequently reaches an overall percentage of 2.2% in pregnancy, later to remain around 2% in the quarter following birth.

Chronic or pre-existing hypertension, gestational hypertension and preeclampsia represent the main clinical pictures subject to prescription and treatment and their distribution during pregnancy supports the prescriptive trend of the active ingredients taken into consideration for this class of drugs (Figure 2.2.9a and 2.2.9b).

Nifedipine (calcium channel blocker) and methyldopa (centrally acting antiadrenergic) are the most prescribed drugs in the category, ranking among the 30 most prescribed active ingredients, in line with the choice of antihypertensives compatible with pregnancy (Table 2.2.4).

The prescription profile of pharmaceuticals contraindicated in pregnancy, ace-inhibitors and sartans, shows limited values, which can probably be further improved with the planning of pregnancy, recommended in presence of chronic diseases. In fact, in the preconception period women with chronic hypertension should undergo a thorough examination of the disease, with the aim of choosing a treatment compatible with pregnancy.

Prescription of antidiabetic pharmaceuticals

Table 2.2.6 shows the overall distribution of women with at least one prescription of a medicinal product for treatment of diabetes, from the quarter preceding conception to the quarter following birth. Pre-gestational and gestational diabetes substantially represent the clinical pictures subject to prescription and treatment (Figures 2.2.10a and 2.2.10b). Prescription in preconception age, expression of the forms of diabetes mellitus existing prior to pregnancy, is around 0.7%, with an overall percentage of 2.4% in pregnancy, and showing a growing trend with 1.9% in the third quarter of pregnancy in favor of insulins and analogues, which decreases to 0.4% in the quarter following birth. Metformin prescription progressively decreases during pregnancy.

With reference to treatment of diabetes in pregnancy, the Italian standards for treatment of diabetes mellitus, drafted in 2018 by the Diabetes Specialists Association and by the Italian Diabetology Society, while addressing in detail use of oral hypoglycemic agents in pregnancy, confirm that oral anti-diabetics and non-insulin injection therapy are not currently recommended during pregnancy and a possible introduction of metformin shall be suspended pending reliable data on its long-term safety on the fetus and offspring.

These are relevant issues, also considering the increase of obesity and diabetes as well as of maternal age at conception which involve an increasing number of women with undiagnosed diabetes in childbearing age. In addition, diabetic women of childbearing age should plan pregnancy and be evaluated in the preconception period, in particular to obtain adequate glycemic control, in order to reduce the risk of adverse reproductive outcomes, as well as to steer choice of pathology treatments and its possible complications with a view to conception.

Areas of improvement

Evaluation and monitoring of prescriptions in the preconception period, during pregnancy and after childbirth are extremely interesting aspects, which the data presented in this section try to delve into.

At the same time, in line with the commitment to improve access, usability and usefulness of the data produced, and in anticipation of further research in this area, aspects of improvement and areas of specific interest in this field can be identified, namely:

- extension of the prescriptive detection, evaluation and monitoring in this area also to other Regions, with the aim of assessing interregional variability also in terms of appropriateness;
- evaluation and monitoring of prescriptions of pharmaceuticals with teratogenic and/or fetotoxic risk in preconception and in pregnancy;
- evaluation and monitoring of prescriptions of recently marketed active ingredients in women of childbearing age and in pregnancy;
- detailed assessment of prescriptions of specific classes of medicinal products such as antiepileptics and antidepressants or prescriptions for pathologies of interest in terms of prevalence, such as dysthyroidism.

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Table 2.2.1. Characteristics of the study population (women giving birth in the three-year period 1 October 2014 - 30 September 2017)

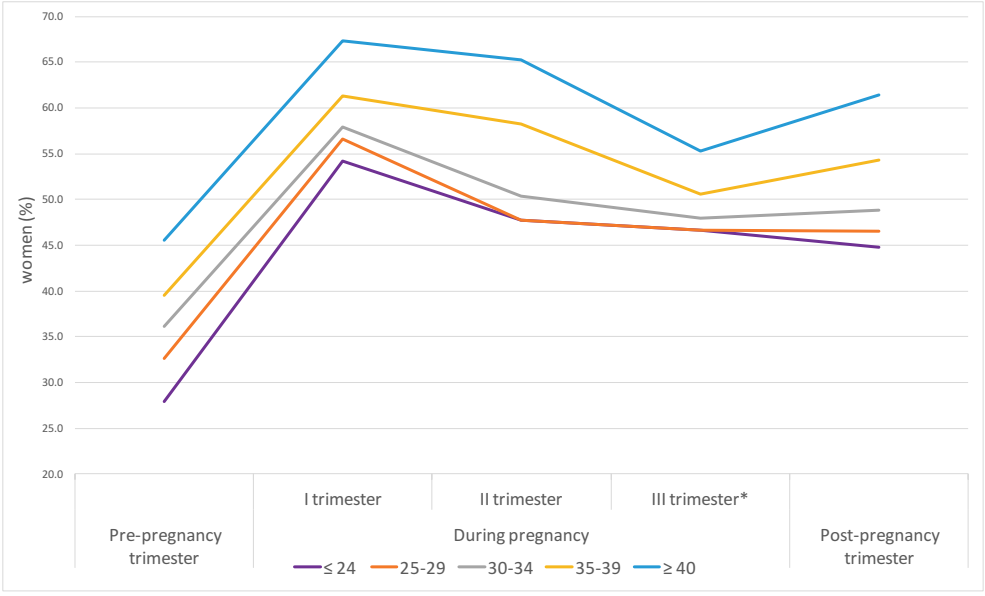
	Lazio 103,556		Emilia Romagna 88,440		Puglia 82,942		Total 274,938	
	N.	%	N.	%	N.	%	N.	%
Age								
≤ 24	7,169	6.9	7,576	8.6	9,404	11.3	24,149	8.8
25-29	19,266	18.6	19,459	22.0	18,647	22.5	57,372	20.9
30-34	34,783	33.6	29,761	33.6	28,178	34.0	92,722	33.7
35-39	30,684	29.6	23,588	26.7	20,585	24.8	74,857	27.2
≥ 40	11,654	11.3	8,056	9.1	6,128	7.4	25,838	9.4
of which ≥ 45	*1,038*	*8.9*	*564*	*7.0*	*396*	*6.0*	*1,998*	*7.7*
Citizenship								
Italian	89,780	86.7	62,828	70.9	78,572	94.7	231,180	84.1
Foreigner	13,776	13.3	25,612	29.1	4,370	5.3	43,758	15.9
Previous births								
no	61,655	59.5	45,732	51.7	42,975	51.8	150,362	54.7
yes	41,901	40.5	42,708	48.3	39,967	48.2	124,576	45.3
of which caesarean sections	*15,448*	*36.9*	*10,206*	*23.9*	*15,921*	*39.8*	*41,575*	*33.4*
Previous abortions								
0	79,575	76.8	66,261	74.9	68,308	82.4	214,144	77.9
1	17,434	16.8	15,764	17.8	10,479	12.6	43,677	15.9
2	4,732	4.6	4,640	5.2	3,005	3.6	12,337	4.5
3+	1,815	1.8	1,775	2.0	1,150	1.4	4,740	1.7
Gestational age								
preterm (<37 wks)	7,726	7.5	5,815	6.6	5,738	6.9	19,279	7.0
Full-term (37-41 wks)	94,643	91.4	81,482	93.2	76,960	93.1	253,085	92.1
Beyond term (>41 wks)	1,187	1.1	1,143	0.2	244	0.0	2,574	0.9
Number of newborns								
1	101,404	97.9	86,845	98.2	81,424	98.2	269,673	98.1
2+	2,152	2.1	1,595	1.8	1,518	1.8	5,265	1.9

Table 2.2.2. Distribution by age of women giving birth in the three-year period 1 October 2014 - 30 September 2017 and having received at least one pharmaceutical prescription before, during and after pregnancy

Age	Pre-pregnancy quarter		I quarter		II quarter		III quarter*		Post-pregnancy quarter		During pregnancy	
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
All medicines	100,393	36.5	162,534	59.1	146,123	53.1	134,176	49.0	139,310	50.7	221,066	80.4
≤24	6,741	27.9	13,082	54.2	11,539	47.8	11,233	46.7	10,805	44.7	18,852	78.1
25-29	18,713	32.6	32,462	56.6	27,415	47.8	26,696	46.6	26,730	46.6	44,711	77.9
30-34	33,542	36.2	53,701	57.9	46,680	50.3	44,315	47.9	45,268	48.8	73,077	78.8
35-39	29,615	39.6	45,877	61.3	43,620	58.3	37,708	50.5	40,642	54.3	61,969	82.8
≥40	11,782	45.6	17,412	67.4	16,869	65.3	14,224	55.3	15,865	61.4	22,457	86.9

*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.1. Distribution by age of women having received at least one pharmaceutical prescription before, during and after pregnancy



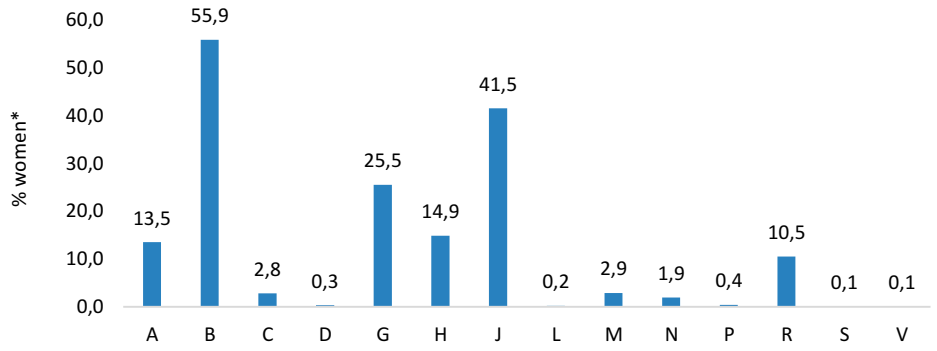
* denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Table 2.2.3. Distribution by ATC category of women having received at least one pharmaceutical prescription before, during and after pregnancy

ATC	Therapeutic category	Pre-pregnancy quarter		I quarter		II quarter		III quarter*		Post-pregnancy quarter	
		N.	%	N.	%	N.	%	N.	%	N.	%
A	Gastrointestinal tract and metabolism	18,381	6.7	17,044	6.2	15,591	5.7	19,067	7.0	10,319	3.8
B	Blood and blood forming organs	22,709	8.3	107,899	39.2	79,929	29.1	78,953	28.8	92,089	33.5
C	Cardiovascular system	2,825	1.0	2,567	0.9	2,598	0.9	5,335	1.9	6,852	2.5
D	Dermatologicals	764	0.3	431	0.2	312	0.1	263	0.1	470	0.2
G	Genito-urinary system and sex hormones	16,258	5.9	54,310	19.8	26,688	9.7	12,301	4.5	27,834	10.1
H	Systemic hormonal preparations, excl. sex hormones and insulins	17,963	6.5	22,805	8.3	24,758	9.0	24,042	8.8	14,651	5.3
J	Antimicrobials for systemic use	49,589	18.0	43,137	15.7	61,585	22.4	42,052	15.3	44,336	16.1
L	Antineoplastic and immunomodulating agents	1,147	0.4	485	0.2	183	0.1	132	0.0	416	0.2
M	Musculo-skeletal system	9,822	3.6	4,947	1.8	2,185	0.8	1,761	0.6	7,164	2.6
N	Central Nervous sysyem	7,027	2.6	4,317	1.6	2,188	0.8	1,938	0.7	3,773	1.4
P	Antiparasitic products	1,029	0.4	570	0.2	469	0.2	367	0.1	530	0.2
R	Respiratory system	15,511	5.6	11,633	4.2	12,462	4.5	10,198	3.7	9,662	3.5
S	Sensory organs	345	0.1	277	0.1	192	0.1	168	0.1	215	0.1
V	Various	99	0.0	80	0.0	48	0.0	92	0.0	71	0,0

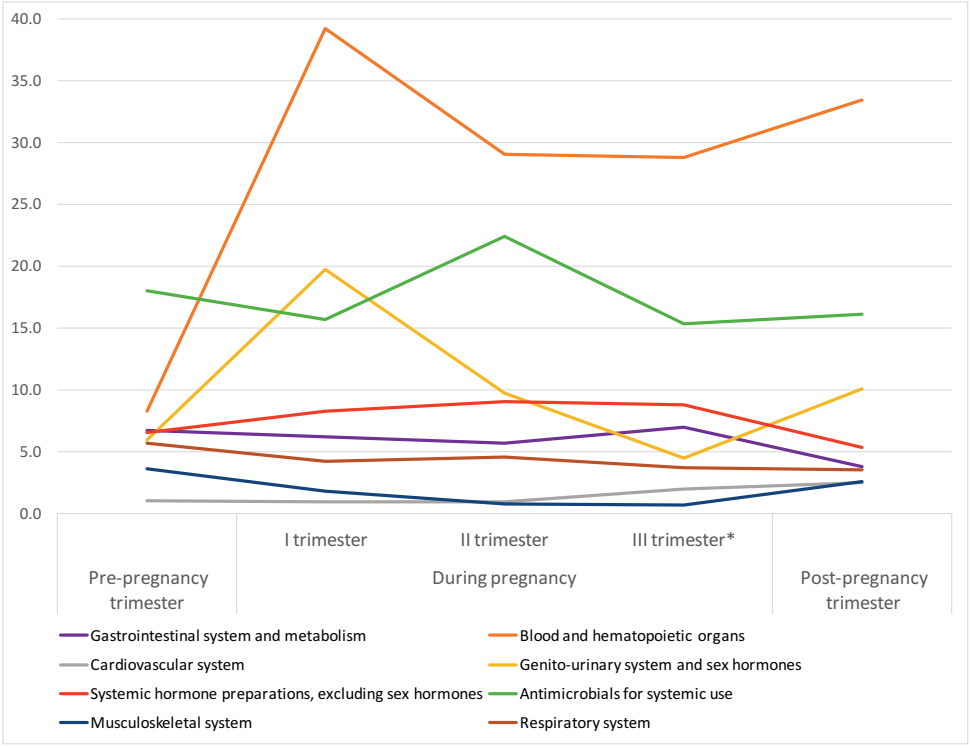
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.2. Distribution by ATC category (I level) of women having received at least one pharmaceutical prescription in pregnancy



* women taking medicines in all quarters of pregnancy

Figure 2.2.3. Distribution by ATC category (I level) of women having received at least one pharmaceutical prescription before, during and after pregnancy^



*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)
^ATC classes with % <2,5% in pregnancy are not reported

Table 2.2.4. First 30 most prescribed active ingredients in pregnancy and distribution by quarter

	ATC	Active ingredient	In pregnancy		I quarter		II quarter		III quarter*	
			N.	%	N.	%	N.	%	N.	%
1	B	folic acid	115,086	41.9	96,103	35.0	51,974	18.9	30,895	11.3
2	G	progesterone	61,274	22.3	49,944	18.2	20,081	7.3	7,246	2.6
3	B	ferrous sulfate	59,498	21.6	7,138	2.6	27,524	10.0	42,426	15.5
4	J	azithromycin	36,413	13.2	10,729	3.9	23,049	8.4	4,679	1.7
5	J	amoxicillin and clavulanic acid	33,689	12.3	11,270	4.1	13,418	4.9	12,910	4.7
6	H	levothyroxine sodium	27,614	10.0	15,807	5.8	20,585	7.5	18,200	6.6
7	J	fosfomycin	25,892	9.4	7,645	2.8	12,292	4.5	9,234	3.4
8	J	amoxicillin	20,279	7.4	5,706	2.1	9,610	3.5	6,797	2.5
9	R	beclomethasone	18,790	6.8	5,789	2.1	8,054	2.9	6,647	2.4
10	B	enoxaparin	16,151	5.9	5,715	2.1	7,181	2.6	13,497	4.9
11	G	hydroxyprogesterone caproate	15,809	5.8	7,157	2.6	9,029	3.3	5,419	2.0
12	B	acetylsalicylic acid	10,876	4.0	7,560	2.8	6,965	2.5	2,998	1.1
13	H	betamethasone	8,217	3.0	2,149	0.8	2,028	0.7	4,546	1.7
14	A	alginic acid	7,877	2.9	2,940	1.1	3,544	1.3	3,824	1.4
15	H	prednisone	6,874	2.5	5,290	1.9	2,423	0.9	1,625	0.6
16	J	cefixime	6,418	2.3	2,155	0.8	2,421	0.9	2,254	0.8
17	J	ampicillin	5,252	1.9	967	0.4	2,179	0.8	2,376	0.9
18	G	estradiol	5,046	1.8	5,032	1.8	292	0.1	27	0.0
19	A	magaldratoe	4,979	1.8	2,148	0.8	1,738	0.6	1,824	0.7
20	B	calcium nadroparin	4,559	1.7	2,120	0.8	2,222	0.8	3,417	1.2
21	J	clarithromycin	3,958	1.4	1,823	0.7	1,094	0.4	1,184	0.4
22	A	cholecalciferol	3,890	1.4	1,819	0.7	1,728	0.6	1,690	0.6
23	M	ketoprofene	3,477	1.3	1,959	0.7	1,073	0.4	879	0.3
24	R	salbutamolo	3,439	1.3	1,444	0.5	1,476	0.5	1,137	0.4
25	B	ferrous glycine sulfate	3,231	1.2	363	0.1	1,626	0.6	2,173	0.8
26	J	anti-d immunoglobulin (rh)	3,178	1.2	220	0.1	1,016	0.4	2,104	0.8
27	C	nifedipine	2,701	1.0	340	0.1	837	0.3	2,326	0.8
28	A	pantoprazole	2,601	0.9	1,756	0.6	693	0.3	701	0.3
29	C	methyldopa	2,496	0.9	539	0.2	937	0.3	2,137	0.8
30	J	fluconazole	2,433	0.9	1,437	0.5	653	0.2	427	0.2

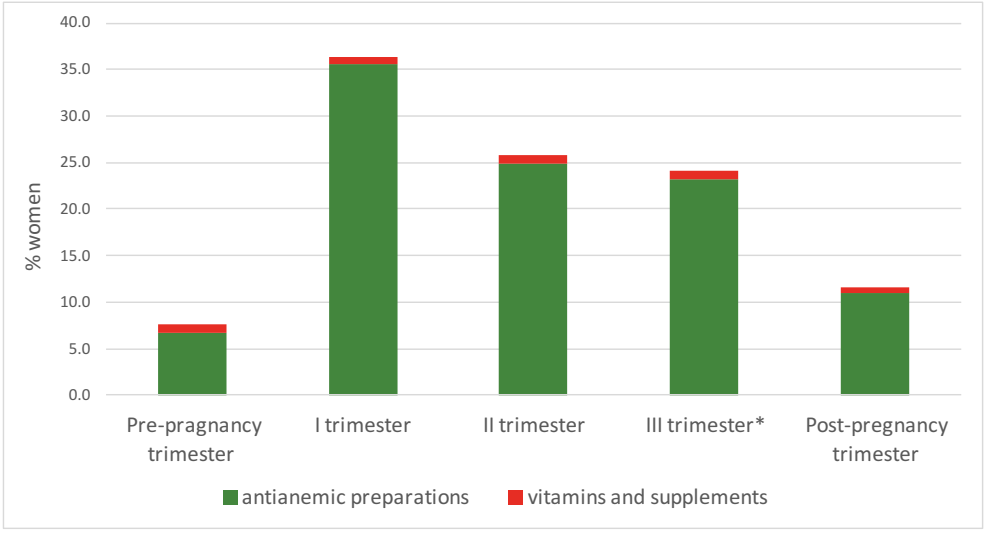
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Table 2.2.5. Distribution of women having received at least one prescription of iron, vitamins and minerals, heparins, antibiotics, progestins and thyroid hormones before, during and after pregnancy

	Pre-pregnancy quarter		I quarter		II quarter		III quarter*		Post-pregnancy quarter		During pregnancy	
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
Iron, vitamins and minerals	20,901	7.6	99,999	36.4	71,071	25.8	66,000	24.1	31,931	11.6	141,627	51.5
Heparins	2,628	1.0	7,943	2.9	9,402	3.4	17,004	6.2	73,937	26.9	20,491	7.5
Antibiotics	46,302	16.8	41,530	15.1	60,378	22.0	39,589	14.4	43,226	15.7	110,863	40.3
Progestins	8,398	3.1	52,856	19.2	26,457	9.6	11,809	4.3	358	0.1	68,325	24.9
Preparations for thyroid therapy	10,067	3.7	16,017	5.8	20,808	7.6	18,338	6.7	10,912	4.0	27,986	10.2

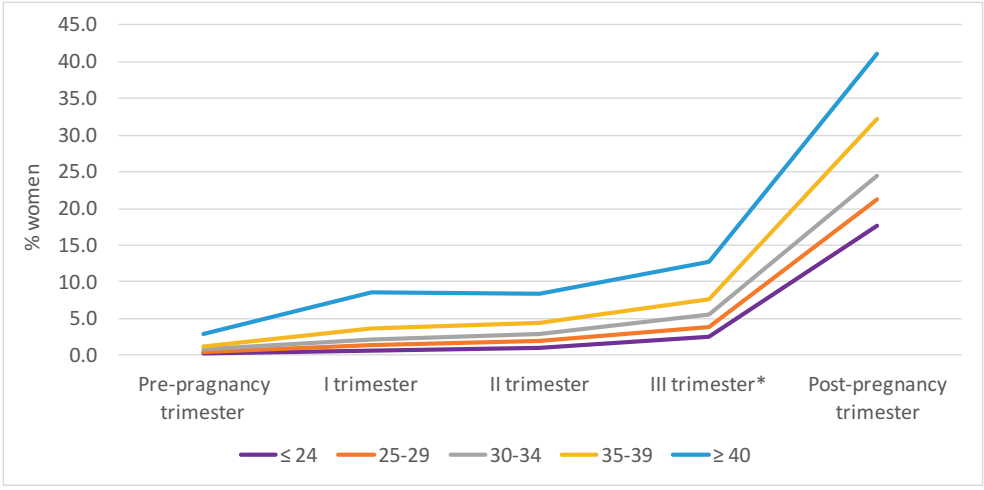
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.4. Distribution of women having received at least one prescription of iron, vitamins and minerals before, during and after pregnancy



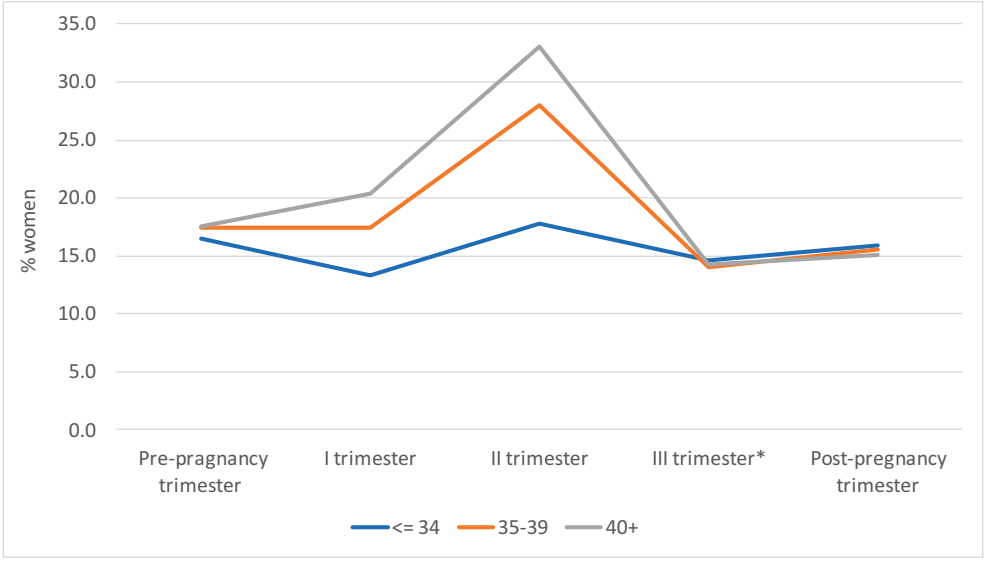
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.5. Distribution by age range of women having received at least one prescription of heparins before, during and after pregnancy



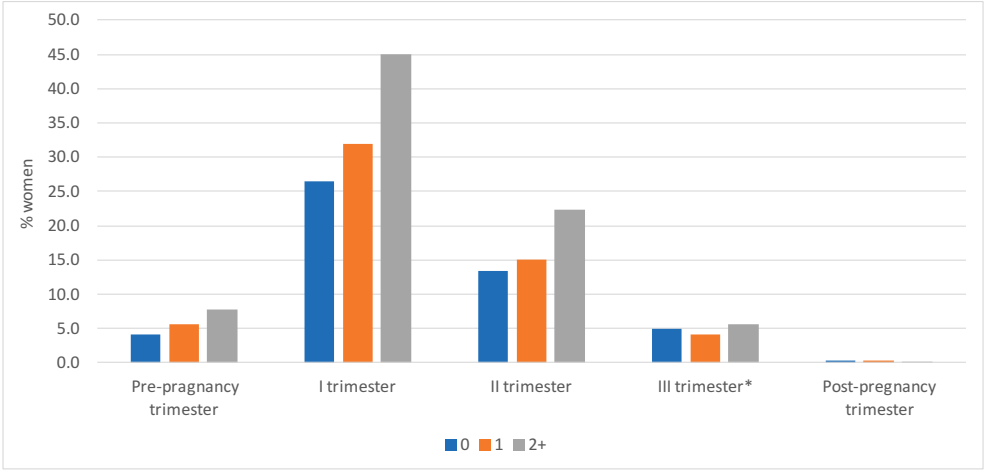
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.6. Distribution by age range of women having received at least one prescription of antibiotics before, during and after pregnancy



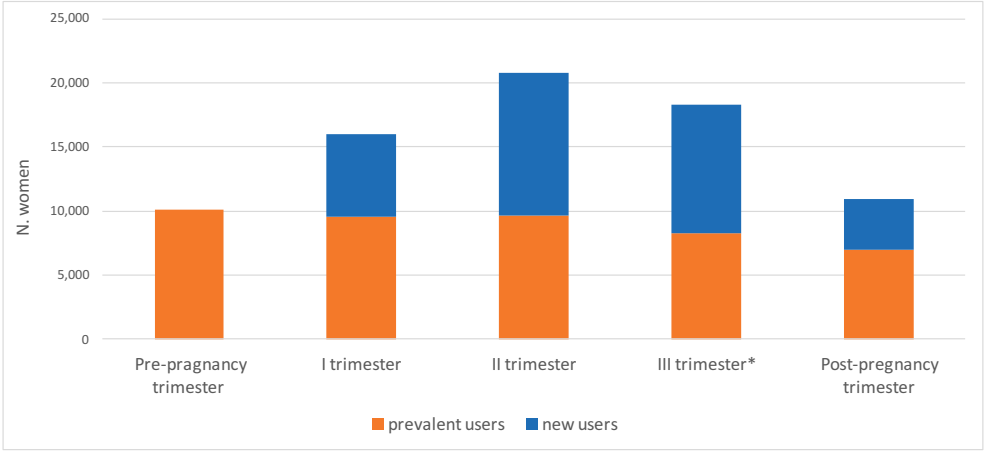
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.7. Distribution by number of previous abortions of women having received at least one prescription of prgestins before, during and after pregnancy



*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.8. Distribution of women having received at least one prescriptions of preparations for thyroid therapy before, during and after pregnancy



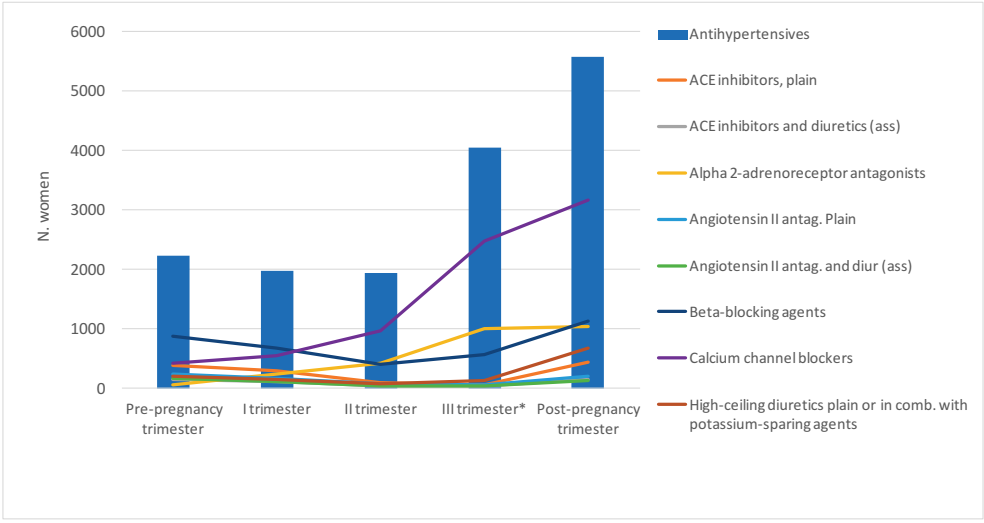
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Table 2.2.6. Distribution of women having received at least one prescription of antihypertensives, anti-diabetics, anti-epileptics, antidepressants before, during and after pregnancy

	Pre-pregnancy quarter		I quarter		II quarter		III quarter*		Post-pregnancy quarter		During pregnancy	
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
Antihypertensives	2,226	0.8	1,983	0.7	1,939	0.7	4,047	1.5	5,573	2.0	5,914	2.2
Anti-diabetics	1,882	0.7	2,015	0.7	2,686	1.0	5,112	1.9	981	0.4	66	2.4
Anti-epilectics	1,322	0.5	1,043	0.4	791	0.3	753	0.3	1,072	0.4	1,230	0.4
Antidepressants	3,156	1.1	1,973	0.7	942	0.3	794	0.3	1,647	0.6	2,421	0.9

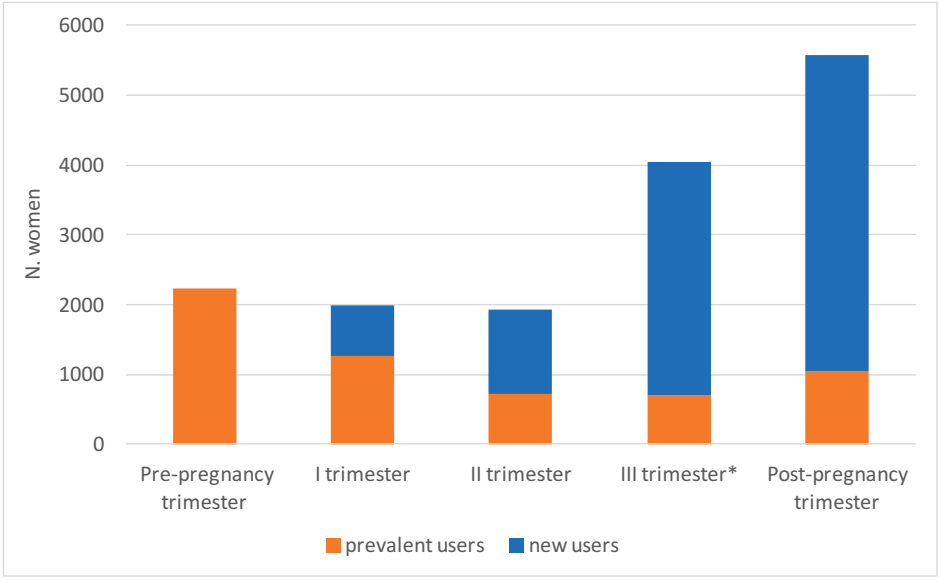
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.9a. Distribution of women having received at least one prescription of antihypertensives before, during and after pregnancy^



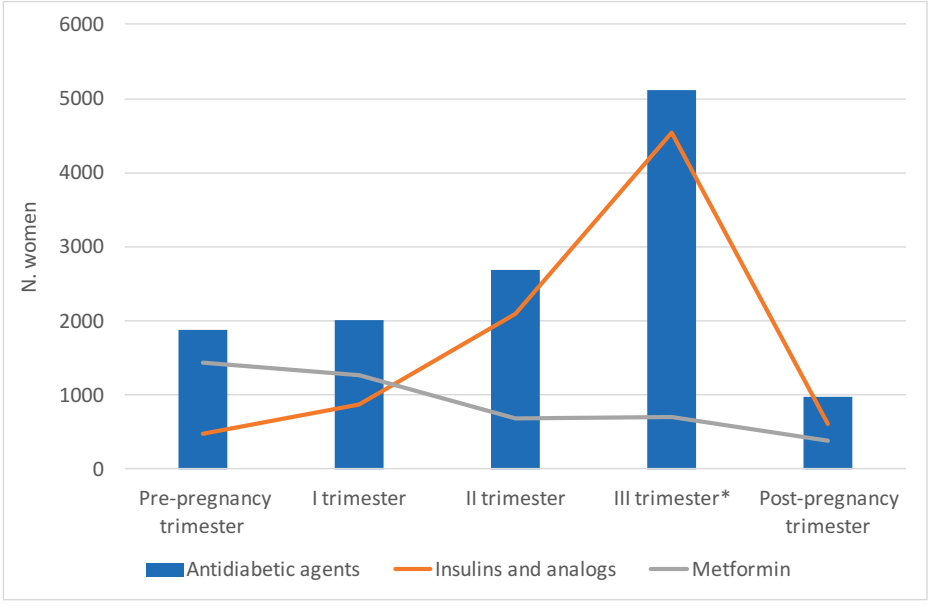
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)
^ the class of ACE inhibitors and diuretics (association) and that of angiotensin II antagonists and diuretics (association) have overlapping curves

Figure 2.2.9b. Distribution by prevalent users and new users of women having received at least one prescription of antihypertensives before, during and after pregnancy



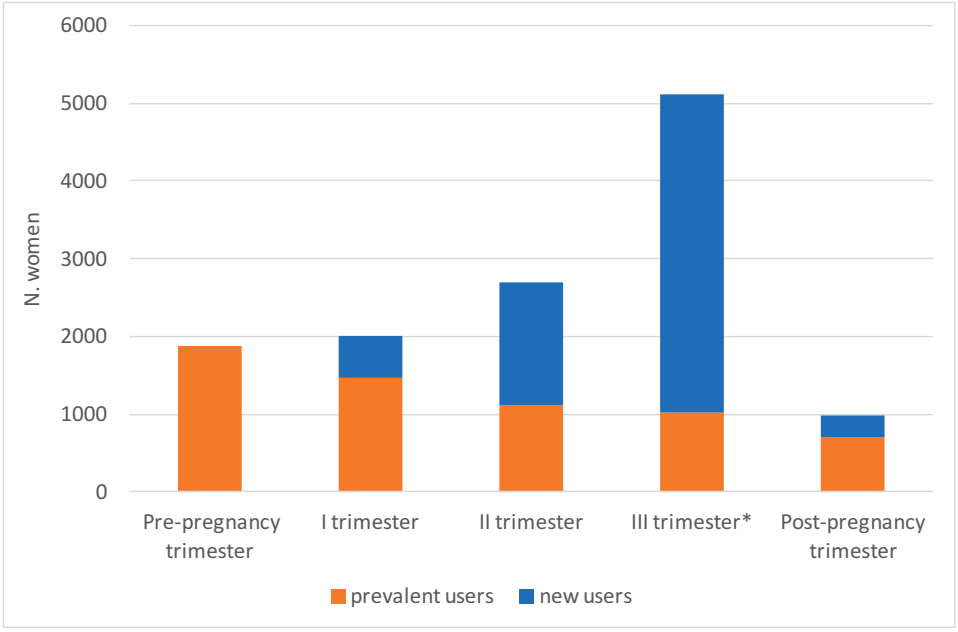
*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.10a. Distribution of women having received at least one prescription of anti-diabetics, before, during and after pregnancy



*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

Figure 2.2.10b. Distribution by prevalent users and new users of women having received at least one prescription of anti-diabetics before, during and after pregnancy



*denominator: pregnancies reaching the third quarter (excluding deliveries between 20-27 weeks of gestation)

2.3 Pharmaceutical use in the geriatric age

In Italy, in 2018, the geriatric population, aged 65 or over, amounted to approximately 14 million people, of which about 6 million men and 8 million women. An average expenditure of 656 euros per user was recorded in this population (714 euros in men and 611 in women; Table 2.3.1). The analysis of drug consumption in users who received at least one pharmacological prescription in 2018 showed that the number of DDD/1000 users was higher in men than in women (respectively 3,332 vs 2,862) and that 98% of the elderly in 2018 received at least one pharmacological prescription, without significant differences in prevalence of use between the two genders (Table 2.3.1).
The trend of doses and expenditure in the elderly population increases with age, up to the 80-84 age range, and then slightly decreases in the range of users aged 85 or over (Figure 2.3.1). The age groups which recorded the highest consumption are the 80-84 age group and the 85 or over age group (respectively 3,825 and 3,769 DDD/1000 users), with an expense per user respectively equal to 782 and 740 euros. Differences between genders can be observed in all age groups, men being reported to consume and spend more than women.
The polypharmacy in this segment of population has been studied using as a proxy the average number of substances prescribed per user. In the whole geriatric population, an average number of 6.7 different substances per user was recorded, with a lower average value of 5.4 recorded in the 65-69 age group and a higher average value of 7.7 substances per user registered in subjects aged 85 or over. In particular, both genders recorded a progressive increase in the number of different active ingredients taken with increasing decades. In the male gender, a shift was reported from the average value of 5.3 substances in the 65-69 age group to 7.8 different substances in subjects aged 85 or older. A similar trend was also found in the female gender with 5.6 different substances taken in the 65-69 age group and 7.7 different active ingredients taken by women aged 80 or over. In fact, in this population, no further increase was reported in the number of substances taken after the age of 84 years (Table 2.3.2). The distribution of users by number of different active ingredients showed that over 66% of elderly users received prescriptions for at least 5 different substances during the reference year and that little more than 22% of subjects aged 65 or over take at least 10 different active ingredients. These data are indicative of frequent recourse to polypharmacy in people aged over 65 (Figure 2.3.2). The most prescribed therapeutic categories in the geriatric population include medicinal products for the cardiovascular system, antimicrobials for systemic use and medicines for the gastrointestinal system and metabolism. As regards prevalence of use of drugs in the geriatric age, medicines for peptic ulcer and gastreoesophageal reflux disease rank first with a prevalence of use of 47.8% (46.6% in men and 48,7% in women), followed, in decreasing order, by antithrombotics with 43.8% (47.6% in men and 40.9% in women), by lipid modifying substances with 34.6% (36.9% in men and 32.9% in women) and non-steroidal anti-inflammatory and antirheumatic drugs with 32.8% (29.0% in men and 35.7% in women). The differences between the male and female gender regarding prevalence of use of pharmaceuticals reflect the overall frequency of the diseases for which these drugs are used in the two genders. The pharmacological classes showing greater differences between the two genders are the class of vitamins A and D, which are mainly used by

women (40.9% prevalence of use in women vs 12,0% prevalence of use in men), as they are normally prescribed in cases of osteoporosis. Also in the case of thyroid preparations, the prevalence of use in women was triple compared to men (respectively 12.8% vs 3.7%), as well as in the case of antidepressants, which showed a prevalence of use almost double in women compared to men (respectively 19.0% vs 10.0%), whereas prostate hypertrophy drugs are almost exclusively used by men (Table 2.3.3).

Table 2.3.1. Distribution by age and gender of pharmaceutical prescription in the population aged ≥65 years (2018)

Age group	Expenditure per user			DDD/1000 users/day			Prevalence of use (%)		
	M	W	Tot	M	W	Tot	M	W	Tot
65-69	549	455	499	2,354	1,925	2,130	87	89	88
70-74	668	564	613	3,238	2,685	2,943	98	98	98
75-79	775	663	713	3,607	3,042	3,293	97	95	96
80-84	856	728	782	4,214	3,555	3,825	100	100	100
≥85	850	684	740	4,349	3,493	3,769	100	100	100
Total	**714**	**611**	**656**	**3,332**	**2,862**	**3,066**	**97**	**98**	**98**

M-Men W-Women

Figure 2.3.1. Prescription trend in the population aged ≥65 years (DDD/1000 users/day and expenditure per user) (2018)

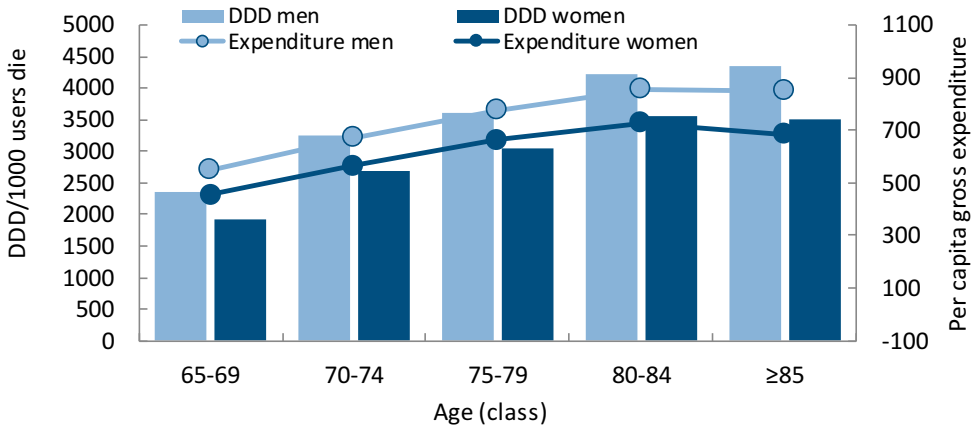


Table 2.3.2. Average number of substances by age and gender (2018)

Age group	Average number of substances		
	Men	Women	Total
65-69	5.3	5.6	5.4
70-74	6.1	6.4	6.3
75-79	6.8	7.1	7.0
80-84	7.5	7.7	7.6
≥85	7.8	7.7	7.7
Total	**6.5**	**6.8**	**6.7**

Figure 2.3.2. Distribution of users in the population aged ≥65 years by number of different substances (2018)

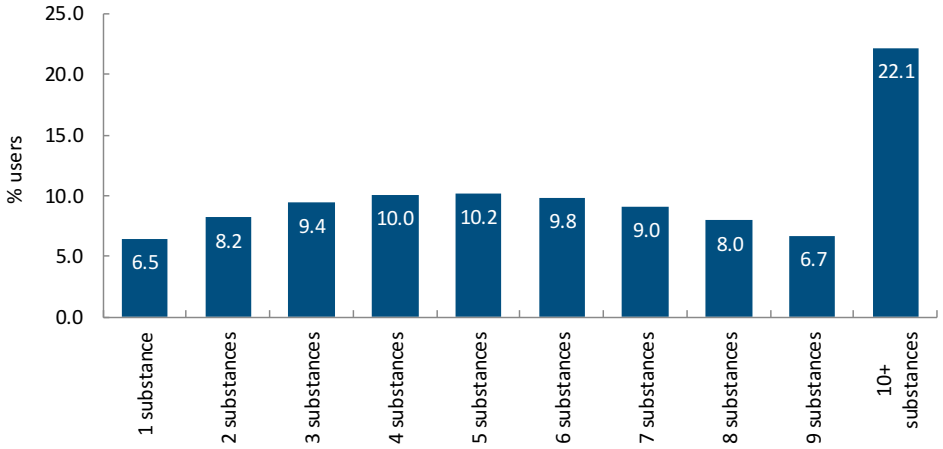


Table 2.3.3. Exposure to pharmaceuticals in the population aged ≥65 years by ATC III level (2018)

ATC III level	Category	Prevalence of use (%)		
		Men	Women	Total
A02B	Peptic antiulcer and gastroesophageal reflux disease	46.6	48.7	47.8
B01A	Antithrombotics	47.6	40.9	43.8
C10A	Lipid modifying substances, not associated	36.9	32.9	34.6
M01A	Non-steroidal anti-inflammatory and antirheumatic drugs	29.0	35.7	32.8
C07A	Beta blockers	30.1	31.0	30.6
A11C	Vitamins A and D, including their associations	12.0	40.9	28.3
J01C	Beta-lactam antibacterials, penicillins	25.0	23.9	24.4
J01M	Quinolone antibacterials	21.7	19.2	20.3
C09A	Ace inhibitors not associated	21.5	16.8	18.8
H02A	Systemic corticosteroids, not associated	17.4	19.2	18.4
C08C	Selective calcium channel blockers with prevalent vascular effect	19.0	17.1	17.9
C03C	Diuretics with greater diuretic action	16.4	18.2	17.4
C09D	Angiotensin II antagonists, associations	15.1	17.7	16.6
C09C	Angiotensin II antagonists, not associated	15.5	15.9	15.7
A10B	Hypoglycemic agents, excluding insulins	17.8	13.5	15.4
N06A	Antidepressants	10.4	19.0	15.3
J01D	Other beta-lactam antibacterials	14.7	14.7	14.7
C09B	Ace inhibitors, associations	14.2	13.9	14.0
G04C	Medicines used in benign prostatic hypertrophy	30.9	0.2	13.5
J01F	Macrolides, lincosamides and streptogramins	12.5	13.1	12.8
N02A	Opioids	9.4	14.7	12.4
R03B	Other drugs for obstructive airway disorders per aerosol	13.1	11.2	12.0
R03A	Adrenergics per aerosol	12.0	10.4	11.1
M04A	Antigout products	13.6	8.2	10.5
A07A	Intestinal anti-infectives	8.2	10.3	9.4
H03A	Thyroid preparations	3.7	12.8	8.9
J01X	Other antibacterials	3.5	10.2	7.3
S01E	Antiglaucoma and miotic preparations	7.2	7.1	7.2
N03A	Antiepileptics	6.3	7.5	7.0
B03B	Vitamin B12 and folic acid	6.3	6.9	6.6

Pharmaceutical interactions

In the population aged 65 or over, the presence of 7 different drug associations recognized as possible causes of pharmaceutical interaction risk was evaluated. In the analysis of drugs at risk of interaction, for each user, the days of exposure (based on DDD) were calculated in the period from 1 January to 31 December 2018 and the subjects identified had at least one concomitant (overlapping) use equal to 10% of the total exposure period.

The use of allopurinol in subjects treated with ACE inhibitors or ARBs recorded a prevalence of 7.7%, with a frequency approximately twice as high in men than in women (9.7% vs 5.9%) and increasing with age.

The use of amiodarone in subjects treated with carvedilol showed a prevalence of 4.2%, with a frequency about twice as high in men than in women (5.9% vs 2.6%), and with higher values in subjects belonging to the 75-84 years age group.

The use of quinolones in subjects treated with sulfonylureas showed a prevalence of 1.3%, with no significant differences between the two genders, and higher values in subjects aged 85 or over.

The use of corticosteroids in subjects treated with nonsteroidal anti-inflammatory drugs or ASA showed a prevalence of 8.2%, with more frequent response in women compared to men (8.5% vs 7.9%) and with higher values in the subjects aged 85 or over.

The use of corticosteroids in subjects treated with quinolones showed a prevalence of 12.5% without significant differences between the two genders, reaching the highest values in subjects aged 85 or over.

The use of potassium-sparing diuretics in subjects treated with ACE inhibitors or ARBs recorded a prevalence of 2.9%, more frequent in men than in women (3.2% vs 2.7%), reaching values about twice as high in subjects belonging to the age group ≥85 years compared to those registered in the 65-74 years age group.

The use of verapamil in subjects receiving digoxin showed a prevalence of 3.6%, occurring more frequently in women than in men (3.8% vs 3.4%), with higher values in subjects belonging to the 65-74 years age group.

As regards the geographical differences in the prevalence of the 7 drug associations, which were recognized as possible causes of drug interactions, such associations were reported more frequently in Central and Southern Italy.

Table 2.3.4. Indicators of interaction risk in the population aged ≥65 years (2018)

	Total (≥65 years)		North	Centre	South
	n.	%			
Use of allopurinol in users of ACE inhibitors or ARBs *	**4,514,478**	**7.7**	**6.9**	**8.7**	**8.2**
65-74 years		6.2	5.8	9.5	9.4
75-84 years		8.5	7.4	9.5	9.4
≥85		9.5	8.1	10.6	10.7
Men		9.7	9.0	11.2	9.7
Women		5.9	4.9	6.4	6.8
Use of amiodarone in carvedilol users*	**374,221**	**4.2**	**3.9**	**4.7**	**4.2**
65-74 years		3.9	3.6	5.4	4.6
75-84 years		4.7	4.4	5.4	4.6
≥85		3.7	3.4	3.8	4.0
Men		5.9	5.5	6.6	6.0
Women		2.6	2.3	2.7	2.8
Use of quinolones in sulfonylurea users*	**488,513**	**1.3**	**0.8**	**1.4**	**1.8**
65-74 years		1.2	0.7	1.4	1.9
75-84 years		1.3	0.8	1.4	1.9
≥85		1.6	1.1	1.9	2.3
Men		1.4	0.9	1.5	2.1
Women		1.2	0.8	1.3	1.6
Use of corticosteroids in users of nonsteroidal anti-inflammatory drugs or ASA *	**7,242,471**	**8.2**	**6.8**	**8.7**	**9.3**
65-74 years		8.2	6.7	8.7	9.2
75-84 years		8.2	6.9	8.7	9.2
≥85		8.6	6.9	9.5	9.7
Men		7.9	6.4	8.2	9.2
Women		8.5	7.1	9.0	9.4
Use of corticosteroids in quinolone users *	**3,167,903**	**12.5**	**10.4**	**13.3**	**13.7**
65-74 years		12.0	10.2	13.3	13.7
75-84 years		12.4	10.3	13.3	13.7
>85		13.6	10.9	14.9	15.2
Men		12.4	10.1	13.1	14.0
Women		12.5	10.7	13.6	13.5
Use of potassium-sparing diuretics among users of ACE inhibitors or ARBs*	**8,025,645**	**2.9**	**2.8**	**3.3**	**3.0**
65-74 years		2.1	1.9	3.4	3.4
75-84 years		3.2	3.0	3.4	3.4
>85		4.5	4.2	5.1	4.3
Men		3.2	3.1	3.5	3.2
Women		2.7	2.5	3.1	2.8
Use of verapamil in digoxin users *	**287,362**	**3.6**	**3.6**	**4.3**	**3.3**
65-74 years		4.2	3.9	4.7	3.5
75-84 years		3.8	3.7	4.7	3.5
≥85		3.3	3.4	3.7	2.8
Men		3.4	3.4	3.9	3.1
Women		3.8	3.7	4.5	3.4

* Concomitant use was calculated for prevalent users in the year 2018

Section 3

Indicators of adherence and persistence

Indicators of adherence and persistence

Methods

The administrative database of the prescriptions of NHS-A class medicinal products dispensed nationally has been used to monitor the use of medicinal products for chronic therapies. In particular, the analysis of repeated prescriptions has allowed us to estimate adherence and persistence to treatment.
An analysis on new users – at least 45 years old – was conducted, considering a one-year follow-up. In detail, the new users were defined as the individuals who received a prescription for medicinal products of the pharmacological class under consideration in the period between October 1, 2017 and December 31, 2017 and who did not receive prescriptions for medicinal products of the same class in the previous months starting from January 1, 2017. New users who at the time of the first prescription had not yet turned 45 and those who did not receive at least one prescription related to any drug in the last quarter of 2018 were excluded from the analysis.
Adherence was assessed through the Medical Possession Rate (MPR) indicator, defined as the ratio between the number of dispensed therapy days (calculated on the basis of DDD) and the number of days in the time interval between the beginning of the first and the theoretical conclusion of the last prescription, supplied during the follow-up period; in formula:

$$MPR = \frac{number\ of\ therapy\ days}{\begin{matrix} Interval\ between\ first\ and\ last\ prescription \\ (plus\ days\ of\ last\ prescription) \end{matrix}}\ x\ 100$$

Low adherence to treatment is defined as therapeutic coverage lower than 40% in the observation period while high adherence is defined as therapeutic coverage higher than or equal to 80% in the observation period.
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 gap periods between one prescription and another, if this gap does not exceed a number of days fixed *a priori*, in this case equal to 60 days. Therefore, a person who has started a pharmaceutical treatment on a t_0 date is defined as "persistent" to the treatment after *x* days from the beginning of the same if he/she took the drug without interruption until the day $(t_0 + x)$; consequently, 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 (Mazzaglia G et al, 2011; Borghi C, Cicero AFG, 2008; Santoni L et al, 2009). For this reason, no interruptions can be observed in the last 60 days from the end of the follow-up (365 days).
If a subject has received a prescription before the theoretical deadline of the previous prescription, that prescription is considered sequential, therefore its start date has been postponed to the day following the theoretical end of the previous prescription.

Persistence was calculated on subjects provided with at least two prescriptions and in conditions of therapeutic switch. Persistence was estimated through Kaplan-Meier analysis; the subjects were censored if at the end of the follow-up period they were still in therapy (persistent) or within the time gap between successive prescriptions defining 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 has 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 received a prescription for a period of time entirely contained in the therapeutic coverage of a previous prescription, such prescription was not considered.
The results obtained were stratified by gender and age classes (45-54, 55-64, 65-74, 75-84, > 84).

Medicinal products and therapeutic categories considered

1. Antidepressant medicinal products:
   - Antidepressants (ATC: N06A)
2. Statins:
   - Hydroxymethylglutaryl-CoA reductase inhibitors (ATC: C10AA)
3. Hypoglycemic medicinal products (ATC: A10)
4. Antiosteoporotic medicinal products
   - Raloxifene (ATC: G03XC01)
   - Bazedoxifene (ATC: G03XC02)
   - Bisphosphonates (ATC: M05BA)
   - Bisphosphonates, combination (ATC: M05BB)
   - Teriparatide (ATC: H05AA02)
5. 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)
6. Medicinal products for benign prostatic hypertrophy (ATC: G04C)
7. Medicinal products inhibiting formation of uric acid (ATC: M04AA)

References

1. Mazzaglia G, et al. Aderenza e persistenza: due elementi chiave per la determinazione dell'efficacia terapeutica in usual care. *Farmacoeconomia e percorsi terapeutici* 2011;12 (Suppl 2).
2. Borghi C, Cicero AFG. Aderenza e persistenza in terapia. *Giornale Italiano di Farmacoeconomia e Farmacoutilizzazione* 2008;1(2):5-13.
3. Santoni L, et al. Aderenza e persistenza alla terapia con statine: analisi di farmacoutilizzazione a partire dai database amministrativi di cinque ASL italiane. *Giornale Italiano di Farmacoeconomia e Farmacoutilizzazione* 2009;2(1):5-16.

3.1 Adherence and persistence to treatment with antidepressants medicines

The study population includes a total of 123,618 new users of antidepressants; the median age is 69 years (interquartile range IQR: 57-79), with a higher proportion of women than men (67.4% vs 32.6%).
The percentage of subjects with high and low adherence to antidepressant treatment was respectively 16.7% and 40.1%. In particular, the highest adherence was observed in subjects aged between 45 and 54 years (19.4%) and decreases with increasing age. In general, a slightly greater percentage of subjects with high adherence was recorded in men than in women (18.3% vs 15.9%) (Table 3.1.1).

Table 3.1.1. Adherence to treatment with antidepressants in the population aged ≥ 45 years

Age	Low adherence (%)*†	High adherence (%)*†
45-54 years	35.0	19.4
55-64 years	35.7	18.8
65-74 years	37.5	17.6
75-84 years	42.6	14.7
≥85 years	54.7	11.2
Women	40.7	15.9
Men	38.8	18.3
Total	**40.1**	**16.7**

*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.

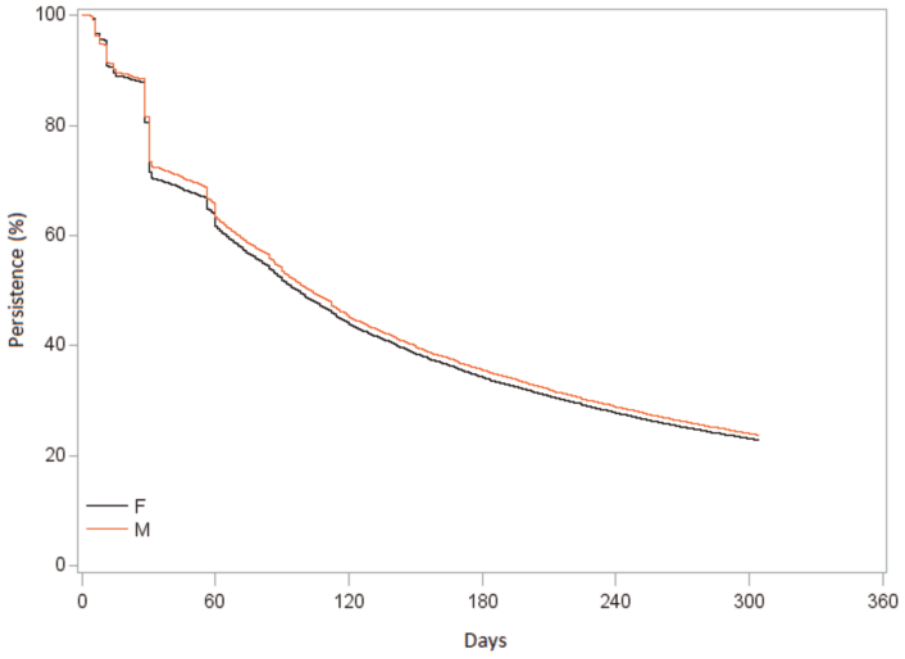
As regards persistence to treatment, that is the median time to discontinuation of the treatment with antidepressants, it can be observed that already 96 days after starting therapy the probability of interrupting the treatment is 50%, with a slight difference between men (100 days) and women (94 days) (Table 3.1.2).
Instead, more marked differences are observed between age groups; the median time to treatment interruption decreases with age, from a maximum of 112 days for subjects aged between 45 and 54 to a minimum of 73 days for subjects aged 85 and over (Table 3.1.2).
The median (IQR) of the number of prescriptions for the subjects analysed is 5 (3-7). Approximately 23% of new users is still in treatment one year after starting therapy (Figure 3.1.1).

Table 3.1.2. Median time (in days) to discontinuation of treatment with antidepressants in the population aged ≥ 45 years

Age	Total N=123.618	Women N=83.278	Men N=40.340
45-54 years	112	109	115
55-64 years	104	101	111
65-74 years	99	97	102
75-84 years	90	89	93
≥85 years	73	72	74
Total	**96**	**94**	**100**

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 further details see the statistical methods).
N: refers to new users, who received a first prescription in the period October 1, 2017 – December 31, 2017, not treated in the previous months starting from January 1, 2017.

Figure 3.1.1. Time (in days) to the discontinuation of treatment with antidepressants in the population aged ≥ 45 years stratified by gender; the curves are adjusted for age (the Cox model was used to estimate the persistence curves)



Note: An interruption in treatment occurs if the subject does not receive a prescription within 60 days (for further 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).

3.2 Adherence and persistence to treatment with statins

The study population includes a total of 191,276 new users of statins; the median age is 65 years (IQR 59-75), with a slightly higher proportion of women than men (52.7% vs 47.3%). Overall, the percentage of subjects with high and low adherence to statin treatment was 20.6% and 41.6%, respectively. Taking into consideration the different age groups, the highest adherence was observed in subjects aged ≥ 85 years (22.5%), while the less adherent subjects are those with an age between 65 and 84 years (42.3%). Compared to women, men had more frequent therapeutic coverage of more than 80% of the observation period (26.2% vs 15.6%) (Table 3.2.1).

Table 3.2.1. Adherence to statin treatment in the population ≥ 45 years old

Age	Low adherence (%)*†	High adherence (%)*†
45-54 years	40.4	21.7
55-64 years	41.0	20.8
65-74 years	42.1	19.7
75-84 years	42.3	20.7
≥ 85 years	41.1	22.5
Women	46.2	15.6
Men	36.4	26.2
Total	**41.6**	**20.6**

*Adherence to treatment was evaluated only for new users with at least 2 prescriptions. Low adherence to treatment was defined as therapeutic coverage (assessed on the basis of DDD) < 40% of the observation period 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.

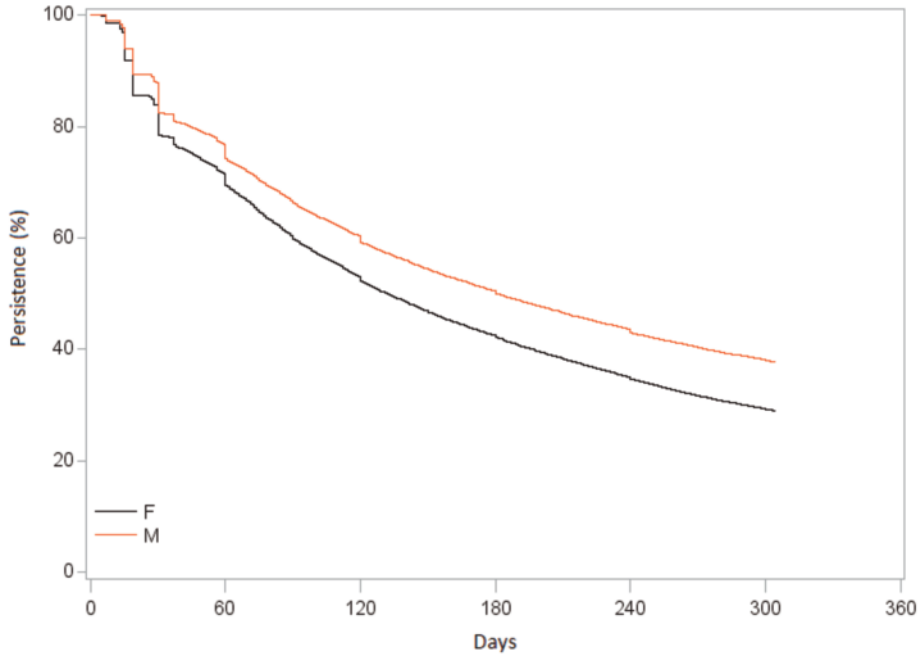
With reference to persistence of treatment, that is the median time to discontinuation of the treatment with statins, it can be observed that already 150 days after starting the therapy the probability of interrupting the treatment is 50%, with a marked difference between men (180 days) and women (130 days). The median (IQR) of the number of prescriptions provided in the subjects analysed is 6 (3-7). Furthermore, the median time to treatment interruption reaches a peak in the age group between 55 and 64 years, both for men (190 days) and for women (138 days) (Table 3.2.2). About 20% of users stop treatment after a month from the beginning and only 33% of new users are still being treated one year after starting treatment, with a higher percentage of men than women (38% vs 29%) (Figure 3.2.1).
It should be noted that numerous scientific evidences have shown that adequate adherence and persistence to statin therapy is associated with a risk reduction of cardiovascular events in subjects in primary and secondary prevention.

Table 3.2.2. Median time (in days) to discontinuation of statin treatment in the population aged ≥45 years

Age	Total N=191,276	Women N=100,776	Men N=90,500
45-54 years	152	127	177
55-64 years	159	138	190
65-74 years	154	134	183
75-84 years	136	120	166
≥85 years	131	120	162
Total	**150**	**130**	**180**

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).
N: refers to new users, who received a first prescription in the period October 1, 2017 – December 31, 2017, not treated in the previous months starting from January 1, 2017.

Figure 3.2.1. Time (in days) to the discontinuation of treatment with statins in the population aged ≥ 45 years stratified by gender; the curves are adjusted for age (the Cox model was used to estimate the persistence curves).



Note: An interruption in treatment 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).

3.3 Adherence and persistence to treatment with antiosteoporosis medicines

The study population includes a total of 18,111 new users of antiosteoporosis medicinal products; the median age is 62 years (IQR 56-70), with a significantly higher proportion of women than men (88.9% vs 11.1%).

The percentage of subjects with high and low adherence to antiosteoporosis treatment was respectively 29.8% and 14.1%. In particular, the percentage of subjects with low adherence increases with age, reaching a maximum of 15.7% in subjects ≥85 years. In general, compared to women, men recorded a more frequent therapeutic coverage higher than 80% of the observation period (38.8% vs 28.7%). Overall, high adherence increases with age, reaching 33.5% in the over 85 years age group (Table 3.3.1).

Table 3.3.1. Indicators of adherence to treatment with antiosteoporosis pharmaceuticals in the population aged ≥ 45 years

Age	Low adherence (%)*†	High adherence (%)*†
45-54 years	12.7	28.8
55-64 years	13.5	27.6
65-74 years	13.7	29.3
75-84 years	15.0	31.4
≥85 years	15.7	33.5
Women	14.3	28.7
Men	13.0	38.8
Total	**14.1**	**29.8**

*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 relating to the specified category.

With reference to persistence of treatment, that is the median time to discontinuation of treatment with antiosteoporosis pharmaceuticals, it is observed that 182 days after starting therapy the probability of interrupting the treatment is 50%, with a slight difference between women (184 days) and men (175 days). In particular, it can be noted that older subjects (aged ≥ 85 years) stop treatment earlier (149 days) than younger subjects. The median (IQR) of the number of prescriptions for the subjects analysed is 5 (3-7) (Table 3.3.2). Furthermore, only 34% of new users appear to be still in treatment one year after the start of therapy, with a negligible difference between women and men (34% vs 31%) (Figure 3.3.1).

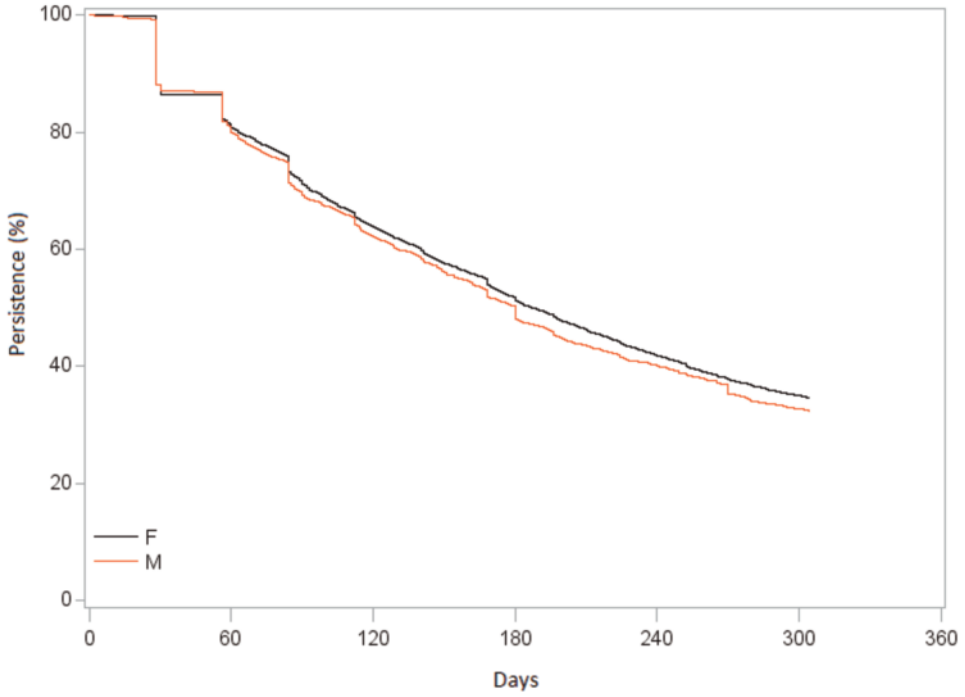
Table 3.3.2. Median time (in days) to discontinuation of treatment with antiosteoporosis pharmaceuticals in the population aged ≥45 years

Age	Total N=18,111	Women N=16,108	Men N=2,003
45-54 years	202	210	162
55-64 years	196	196	198
65-74 years	184	188	174
75-84 years	176	178	168
≥ 85 years	149	148	151
Total	**182**	**184**	**175**

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

N: refers to new users, subjects who received a first prescription in the period October 1, 2017 – December 31, 2017, not treated in the previous months starting from January 1, 2017.

Figure 3.3.1. Time (in days) to discontinuation of treatment with antiosteoporosis pharmaceuticals in the population aged ≥ 45 years stratified by gender; the curves are adjusted for age (the Cox model was used to estimate the persistence curves)



Note: An interruption in treatment 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 end of the follow-up (365 days).

3.4 Adherence and persistence to treatment with antihypertensive medicines

The study population includes a total of 270,497 new users of antihypertensive medicinal products; the median age is 63 years (IQR 55-73), with a proportion of women greater than men (52.9% vs 47.1%).
The percentage of subjects with high and low adherence to antihypertensive treatment was respectively 23.8% and 32.9%. Low adherence increases with age, while high adherence peaks in the 65-74 age group (25%) and then decreases in later age groups. In general, men record a higher percentage of subjects with therapeutic coverage of more than 80% of the observation period than women (26.4% vs 21.4%) (Table 3.4.1).

Table 3.4.1. Adherence to treatment with antihypertensive medicinal products in the population aged ≥45 years

Age	Low adherence (%)*†	High adherence (%)*†
45-54 years	30.6	23.8
55-64 years	30.8	24.3
65-74 years	32.5	25.0
75-84 years	36.8	22.6
≥ 85 years	43.7	18.6
Women	36.0	21.4
Men	29.3	26.4
Total	**32.9**	**23.8**

*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 relating to the specified category.

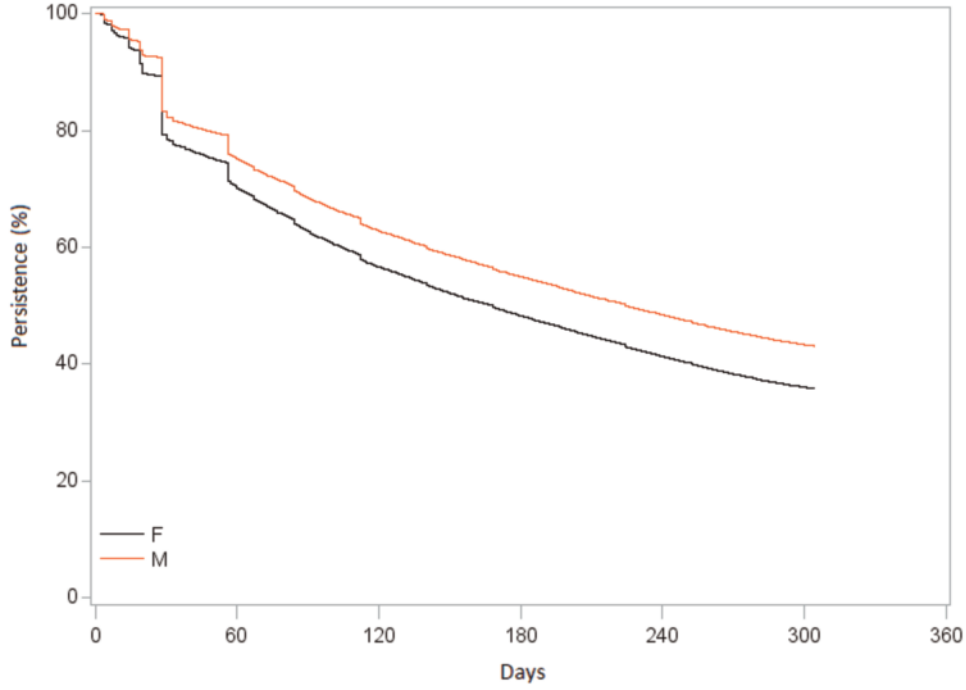
With reference to treatment persistence, that is the median time to discontinuation of the antihypertensive treatment, it is observed that already 189 days after starting therapy the probability of interrupting the treatment is 50%, with a remarkable difference between men (224 days) and women (162 days). In particular, it can be noted that in men the median time to treatment interruption decreases with increasing age, from a maximum of 249 days in younger subjects (aged 45-54) to a minimum of 114 days in older subjects (age ≥85 years), while women record a slight increase up to the age group of 65-74 years (176 days), and later decreases again (Table 3.4.2).
The median (IQR) of the number of prescriptions for the subjects analysed is 6 (4-9). Furthermore, around 40% of new users are still being treated one year after start of therapy, with a difference between men (43%) and women (35%) (Figure 3.4.1).

Table 3.4.2. Median time (in days) to discontinuation of treatment with antihypertensives in the population aged ≥ 45 years

Age	Total N=270,497	Women N=143,071	Men N=127,426
45-54 years	203	168	249
55-64 years	205	170	247
65-74 years	197	176	224
75-84 years	157	146	173
≥ 85 years	107	104	114
Total	**189**	**162**	**224**

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).
N: refers to new users, who received a first prescription in the period October 1, 2017 – December 31, 2017, not treated in the previous months starting from January 1, 2017.

Figure 3.4.1. Time (in days) to discontinuation of treatment with antihypertensives in the population aged ≥ 45 years stratified by gender; the curves are adjusted for age (the Cox model was used to estimate the persistence curves)



Note: An interruption in treatment 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 end of the follow-up (365 days).

3.5. Adherence and persistence to treatment with medicines for benign prostate hypertrophy

The study population includes a total of 93,607 new users of medicinal products for benign prostatic hypertrophy; the median age is 69 years (IQR 62-77). The percentage of subjects with high and low treatment adherence was respectively 22.4% and 24.6%. The highest adherence was observed in subjects aged between 55 and 64 years (23.2%), while the percentage of subjects with low adherence to treatment is greater in the 45-54 age group (Table 3.5.1).

Table 3.5.1. Adherence to treatment with medicinal products for benign prostate hypertrophy in the male population aged ≥45 years

Age	Low adherence (%)*†	High adherence (%)*†
45-54 years	28.8	21.9
55-64 years	24.4	23.2
65-74 years	23.4	22.7
75-84 years	24.9	21.7
≥ 85 years	26.6	21.2
Total	**24.6**	**22.4**

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

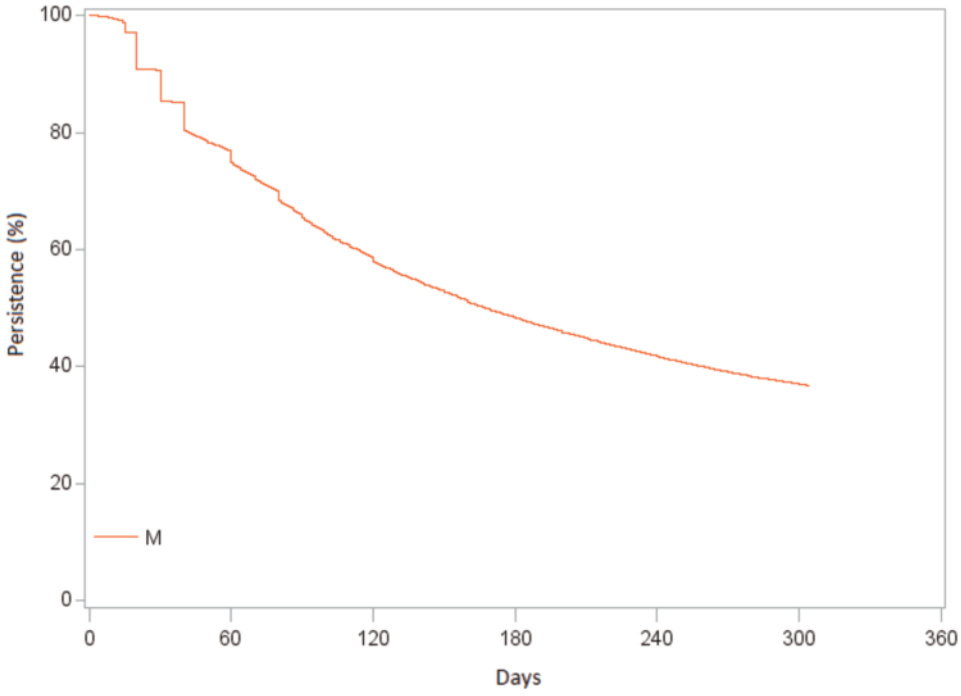
With reference to treatment persistence, that is the median time to discontinuation of treatment with medicinal products for benign prostatic hypertrophy, it can be observed that 165 days after starting therapy the probability of interrupting treatment is 50%; younger subjects (45-54 years) stop treatment earlier (120 days) than subjects in other age groups (Table 3.5.2). The median (IQR) of the number of prescriptions for the subjects analysed is 6 (3-8). Furthermore, only about 36.4% of new users are still being treated one year after starting therapy (Figure 3.5.1).

Table 3.5.2. Median time (in days) to discontinuation of treatment with medicinal products for benign prostatic hypertrophy in the male population aged ≥45 years

Age	Total N=93,607
45-54 years	120
55-64 years	160
65-74 years	180
75-84 years	171
≥ 85 years	166
Total	**165**

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).
N: refers to new users, who received a first prescription in the period October 1, 2017 – December 31, 2017, not treated in the previous months starting from January 1, 2017.

Figure 3.5.1. Time (in days) to discontinuation of treatment with medicinal products for benign prostatic hypertrophy in the male population ≥ 45 years; the curves are adjusted for age (the Cox model was used to estimate the persistence curves)



Note: An interruption in treatment 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 end of the follow-up (365 days).

3.6 Adherence and persistence to treatment with medicines inhibiting uric acid production

The study population includes a total of 86,873 new users of medicinal products that inhibit the production of uric acid; the median age is 75 years (IQR 66-82), with a proportion of men greater than women (56.1% vs 43.9%). The percentage of subjects with high and low adherence to treatment with medicinal products inhibiting the production of uric acid was respectively 6.3% and 57.5%, both with negligible differences between men and women (Table 3.6.1).

Table 3.6.1. Adherence to treatment with medicinal products inhibiting uric acid production in the population aged ≥ 45 years

Age	Low adherence (%)*†	High adherence (%)*†
45-54 years	55.7	6.6
55-64 years	57.2	6.5
65-74 years	58.1	6.2
75-84 years	57.8	6.3
≥ 85 years	56.6	6.3
Women	57.2	6.7
Men	57.7	6.1
Total	**57.5**	**6.3**

*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.

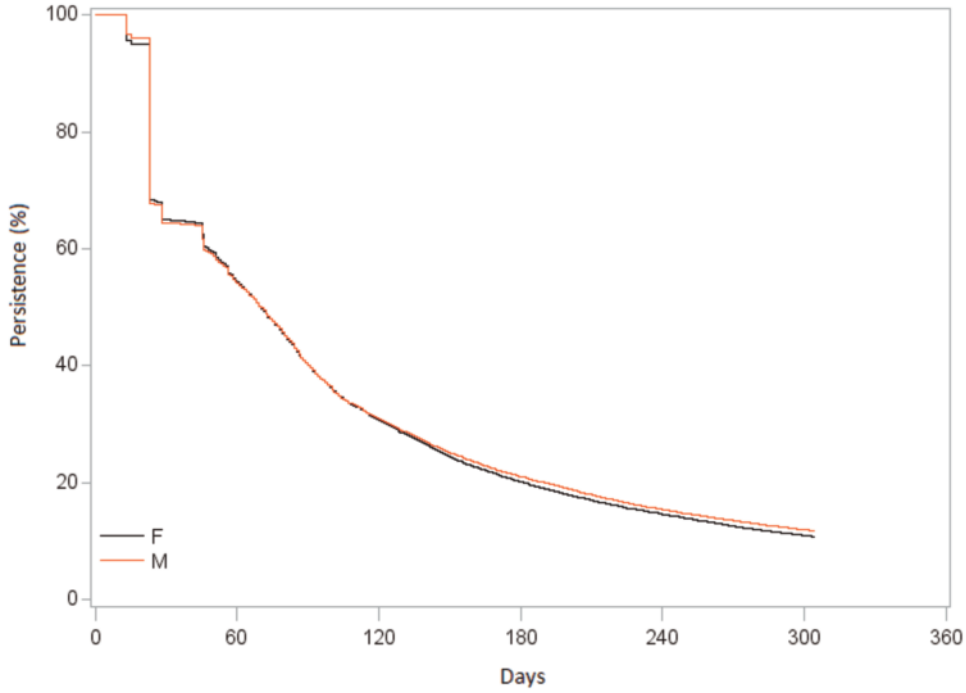
As regards treatment persistence, i.e. the median time to discontinuation of treatment with medicinal products inhibiting the production of uric acid, it can be observed that as early as 61 days after the start of therapy the probability of interrupting treatment is 50 %, with a slight difference between men (59 days) and women (62 days). Furthermore, as the age of the subjects increases, the median time to treatment interruption increases for women and decreases for men (Table 3.6.2). The median (IQR) of the number of prescriptions for the subjects analysed is 4 (2-6). Furthermore, approximately 10.4% of new users are still being treated one year after start of therapy, with a slight difference between men (10%) and women (10.7%) (Figure 3.6.1).
It is necessary to further investigate the low levels of adherence and persistence also considering the effect of specific dosage schemes providing for a beginning of therapy at a lower dosage followed by an increase over time.

Table 3.6.2. Median time (in days) to discontinuation of treatment with medicinal products inhibiting uric acid production in the population aged ≥ 45 years

Age	Total N=86,873	Women N=38,177	Men N=48,696
45-54 years	63	59	63
55-64 years	61	60	61
65-74 years	61	61	60
75-84 years	60	63	57
≥ 85 years	62	64	59
Total	**61**	**62**	**59**

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).
N: refers to new users, who received a first prescription in the period October 1, 2017 – December 31, 2017, not treated in the previous months starting from January 1, 2017.

Figure 3.6.1. Time (in days) to discontinuation of treatment with medicinal products inhibiting uric acid production in the population aged ≥ 45 years stratified by gender; the curves are adjusted for age (the Cox model was used to estimate the persistence curves)



Note: An interruption in treatment 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).

Conclusions

The therapeutic category with a higher percentage of subjects showing treatment coverage greater than or equal to 80% of the observed period is antiosteoporosis medicinal products (29.8%) followed by antihypertensives (23.8%) and, for the male population, by medicinal products for benign prostatic hypertrophy (22.4%). On the contrary, the therapeutic categories recording higher percentages of subjects with treatment coverage lower than 40% of the observed period are medicinal products inhibiting the formation of uric acid (57.5%), followed by statins (41.6%) and by antidepressants (40.1%).

As for persistence, the median time to treatment discontinuation is longer in subjects following therapy with antihypertensives (189 days) and antiosteoporosis medicinal products (182 days), while it decreases in subjects treated with medicinal products inhibiting uric acid production (61 days) and antidepressants (96 days).

Both adherence and persistence to therapeutic treatment were reported to decrease with age, in the case of treatment with statins, antihypertensives, antiosteoporosis medicinal products and antidepressants; moreover, as regards treatment with statins and antihypertensives, men generally show higher rates of therapeutic coverage of more than 80% and longer persistence times.

Given their retrospective nature, it is worth highlighting the main advantages and limitations of the analyses presented. One of the main strengths of the retrospective analyses performed through the administrative databases is the availability of a very large sample of patients, which allowed to obtain a rapid evaluation, at a national level, of the use of medicinal products for the main chronic diseases. Major limitations include the lack of additional data sources (for example, the patient's clinical characteristics and hospitalizations) and the impossibility of estimating the actual intake of the dispensed medicinal product. Furthermore, it should be highlighted that the potential distortive effect of private purchase by patients on the estimate of adherence and persistence was not examined in depth.

Section 4

Consumption and expenditure by therapeutic class

Therapeutic categories and active ingredients

This section presents the main data on individual therapeutic categories.

Table 4.1. NHS expenditure per capita per I level ATC in descending order of expenditure: comparison 2018-2017

I level ATC	Per capita outpatient NHS expenditure Class A (a)	Δ% 18-17	Per capita inpatient NHS expenditure (b)	Δ% 18-17	NHS expenditure (a+b)	Δ% 18-17
L	4.10	4.3	89.46	9.7	93.56	9.5
C	48.98	-8.7	4.59	-7.0	53.57	-8.6
J	13.07	-0.6	35.16	-21.2	48.23	-16.6
A	33.01	0.6	13.87	10.0	46.88	3.2
B	7.91	-2.2	26.52	0.5	34.43	-0.1
N	22.53	0.4	6.94	1.1	29.46	0.6
R	16.23	-0.8	3.05	44.9	19.28	4.4
M	5.71	-6.0	3.11	103.7	8.82	16.0
H	3.98	4.9	4.62	0.3	8.6	2.4
G	5.64	-14.6	1.57	-15.4	7.22	-14.8
S	3.81	-0.1	2.81	-7.9	6.62	-3.6
V	0.15	4.6	5.33	3.7	5.48	3.7
D	1.13	19.1	0.39	10.0	1.52	16.6
P	0.22	3.1	0.03	-5.3	0.25	2.2
Total	**166.46**	**-3.2**	**197.45**	**0.9**	**363.91**	**-1.0**

A Alimentary tract and metabolism
B Blood and blood-forming organs
C Cardiovascular system
D Dermatologicals
G Genito-urinary system and sex hormones
H Systemic hormonal preparations, excl. sex hormones and insulins
J Anti-infectives for systemic use
L Antineoplastic and immunomodulating agents
M Musculo-skeletal system
N Nervous system
P Pesticides
R Respiratory system
S Sensory organs
V Various

Table 4.2. NHS consumption (DDD/1000 inhabitants die) for I ATC level in descending order of consumption: comparison 2018-2017

I level ATC	DDD/1000 inhab die outpatient NHS expenditure (a)	Δ% 18-17	DDD/1000 inhab die inpatient NHS expenditure (b)	Δ% 18-17	DDD/1000 inhab die NHS (a+b)	Δ% 18-17
C	470.5	0.8	16.9	-3.2	487.4	0.6
A	152.7	0.4	29.1	-6.0	181.8	-0.7
B	87.1	0.8	42.8	9.2	129.9	3.4
N	65.1	2.8	24.2	5.2	89.4	3.4
R	41.1	-0.2	2.5	1.7	43.6	-0.1
G	40.8	3.3	1.9	-2.2	42.7	3.1
M	37.4	-0.8	4.6	8.0	42.0	0.1
H	35.2	2.1	5.2	-4.3	40.4	1.2
J	17.2	-0.6	6.2	0.5	23.4	-0.3
S	20.5	2.3	2.8	8.0	23.2	2.9
L	6.0	3.9	9.5	4.1	15.6	4.0
D	4.3	5.2	8.4	-34.3	12.7	-24.7
V	0.1	6.6	3.1	2.3	3.2	2.4
P	0.9	2.7	0.0	-9.5	0.9	2.3
Total	**978.8**	**0.9**	**157.4**	**-0.8**	**1,136.1**	**0.7**

Table 4.3. Composition of pharmaceutical expenditure 2018 for I ATC level and reimbursement class (decreasing order for total expenditure)

I level ATC	Class A medicines reimbursed by the NHS^		Class A medicines privately purchased by citizens		Class C with medical prescription		Self-medication SOP and OTC medicines		Medicines purchased by Public Health Facilities		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°
L	248	4.3	50	0.9	16	0.3	-	-	5,411	94.5	5,724
A	1,996	49.7	267	6.6	211	5.2	703	17.5	839	20.9	4,015
C	2,963	83.2	146	4.1	37	1.0	140	3.9	278	7.8	3,563
N	1,362	42.7	137	4.3	993	31.1	278	8.7	420	13.2	3,190
J	791	25.5	115	3.7	73	2.3	-	-	2,126	68.5	3,105
B	478	20.4	183	7.8	79	3.4	4	0.2	1,604	68.3	2,348
R	982	51.6	117	6.1	154	8.1	464	24.4	184	9.7	1,901
M	345	25.3	138	10.1	200	14.7	493	36.1	188	13.8	1,365
G	341	30.1	32	2.8	596	52.6	70	6.1	95	8.4	1,134
S	230	32.9	12	1.7	198	28.3	90	12.8	170	24.3	700
D	68	10.4	22	3.3	247	37.8	293	44.8	24	3.6	654
H	241	38.7	65	10.4	37	6.0	-	-	280	44.9	622
V	9	2.0	74	16.8	32	7.3	0	0.1	322	73.7	437
P	13	56.1	4	15.2	3	11.8	2	10.1	2	6.6	24
Total	**10,068**	**35.0**	**1,360**	**4.7**	**2,875**	**10.0**	**2,536**	**8.8**	**11,942**	**41.5**	**28,782**

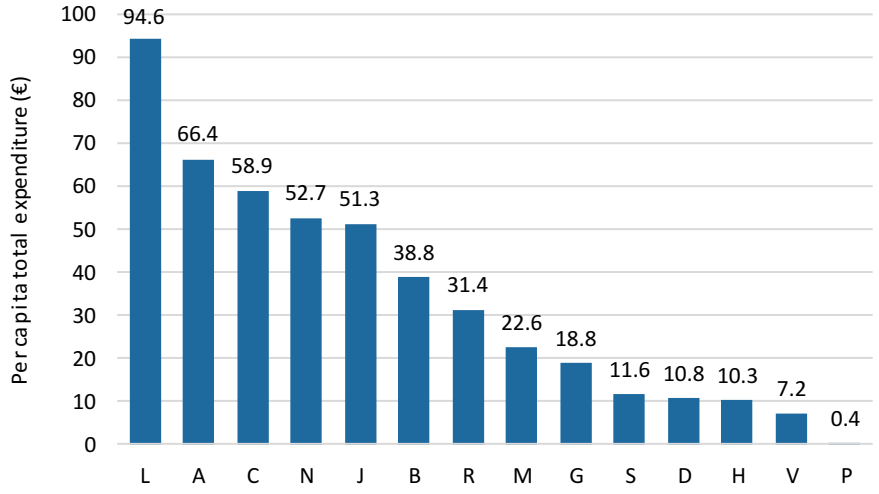
^ Expenditure for Class A net of Class C reimbursed for war pension holders of direct life annuity pursuant to Law n. 203 of 19 July 2000 (24 million euros); ° Gross in millions of euros; * Calculated on the category. Source: OsMed, Traceability of the drug

Table 4.4. Composition of consumption (in terms of DDD/1000 inhabitants die) 2018, for I ATC level and reimbursement class (decreasing order for total expenditure)

I level ATC	Class A medicines reimbursed by the NHS^		Class A medicines privately purchased by citizens		Class C with medical prescription		Self-medication SOP and OTC medicines		Medicines purchased by Public Health Facilities		Total
	DDD	%*	DDD	%*	DDD	%*	DDD	%*	DDD	%*	DDD
C	470.5	90.6	23.2	4.5	1.2	0.2	7.7	1.5	16.9	3.2	519.5
A	152.7	62.7	18.5	7.6	6.8	2.8	36.3	14.9	29.1	12.0	243.4
B	87.1	47.6	18.5	10.1	34.6	18.9	0.1	0.1	42.8	23.4	183.1
N	65.1	39.4	5.6	3.4	63.2	38.3	7.0	4.2	24.2	14.7	165.1
M	37.4	41.4	19.1	21.2	3.2	3.5	25.9	28.7	4.6	5.1	90.2
R	41.1	45.9	8.8	9.8	12.2	13.6	25.0	27.9	2.5	2.8	89.6
G	40.8	51.1	2.7	3.4	32.2	40.3	2.3	2.9	1.9	2.4	79.9
H	35.2	68.3	9.5	18.5	1.6	3.1	-	-	5.2	10.2	51.5
D	4.3	8.5	3.2	6.2	16.7	32.9	18.1	35.7	8.4	16.7	50.7
S	20.5	43.1	1.5	3.1	11.3	23.8	11.5	24.2	2.8	5.8	47.5
J	17.2	58.0	3.5	11.8	2.7	9.1	-	-	6.2	21.1	29.6
L	6.0	37.6	0.4	2.6	0.1	0.6	-	-	9.5	59.1	16.1
V	0.1	2.5	0.1	2.6	0.9	21.2	0.0	0.0	3.1	73.6	4.2
P	0.9	83.3	0.2	14.2	0.0	0.0	0.0	0.0	0.0	2.5	1.1
Total	**978.8**	**62.3**	**114.8**	**7.3**	**186.7**	**11.9**	**133.9**	**8.5**	**157.4**	**10.0**	**1,571.5**

* Calculated on the category
Source: OsMed and Traceability of the drug

Figure 4.1. Per capita total pharmaceutical expenditure by ATC I level (sorted for total per capita expenditure in 2018)



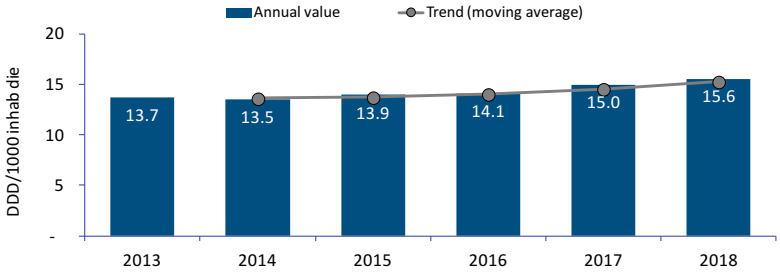
4.1 Antineoplastic and immunomodulating agents

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

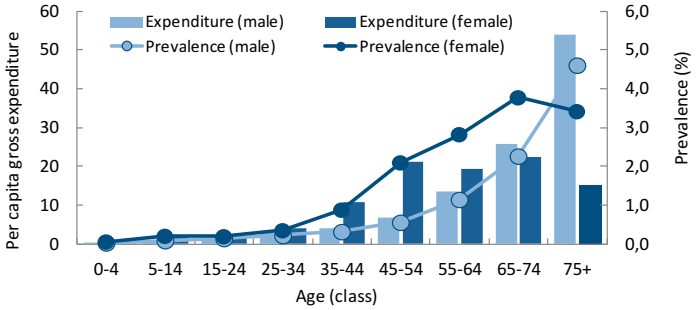
Antineoplastic and immunomodulating agents

NHS expenditure, million €* (% on the total)	**5,659.2**	**(25.7)**
Δ % 2018/2017		-14.6
Per capita gross expenditure, range among Regions:	64.5	113.6
DDD/1000 inhab die* (% on the total)	**15.6**	**(1.4)**
Δ % 2018/2017		1.4
DDD/1000 inhab die, range among Regions:	12.0	18.4

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	0.2	0.3	0.3	0.1	0.1	0.1
5-14	0.8	2.0	1.4	0.4	1.0	0.7
15-24	1.5	1.7	1.6	0.6	0.7	0.6
25-34	2.9	4.0	3.4	0.9	1.5	1.2
35-44	3.9	10.9	7.4	1.4	5.6	3.5
45-54	6.8	21.3	14.1	2.5	15.4	9.0
55-64	13.5	19.3	16.5	5.2	17.8	11.7
65-74	25.8	22.5	24.1	10.9	23.1	17.4
75+	53.9	15.0	30.5	28.5	19.0	22.8

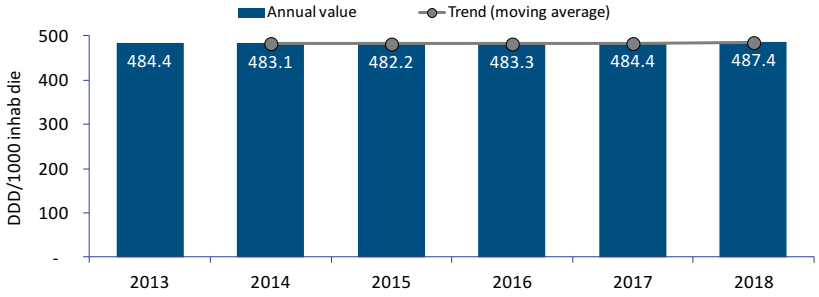
4.2 Cardiovascular system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

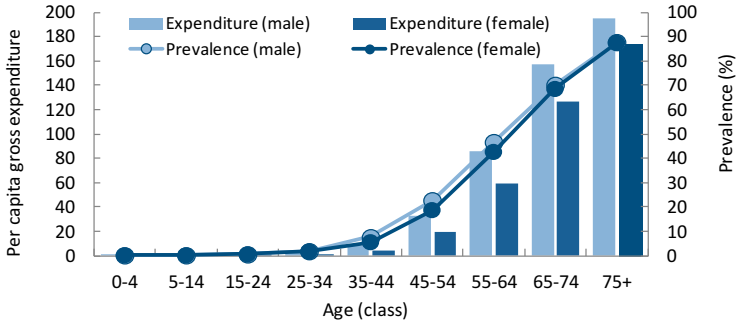
Cardiovascular system

NHS expenditure, million €* (% on the total)	**3,240.4**	**(14.7)**
Δ % 2018/2017		0.4
Per capita gross expenditure, range among Regions:	37.1	63.1
DDD/1000 inhab die* (% on the total)	**487.4**	**(42.9)**
Δ % 2018/2017		0.6
DDD/1000 inhab die, range among Regions:	370.2	589.3

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	0.2	0.3	0.2	0.5	0.4	0.5
5-14	0.2	0.1	0.1	0.9	0.7	0.8
15-24	0.4	0.3	0.4	3.8	2.3	3.1
25-34	1.6	0.9	1.3	14.6	7.7	11.2
35-44	8.5	4.1	6.3	77.9	38.9	58.4
45-54	32.8	19.0	25.8	299.8	179.4	238.8
55-64	85.8	59.3	72.1	776.1	535.2	651.7
65-74	157.6	126.2	141.0	1410.7	1113.7	1253.8
75+	194.8	173.8	182.1	1839.5	1635.7	1716.7

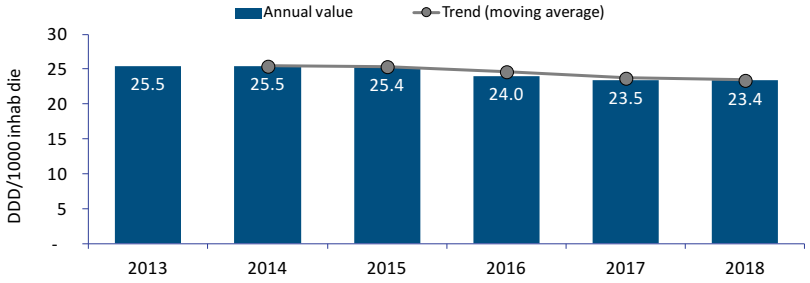
4.3 Anti-infectives for sistemic use

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

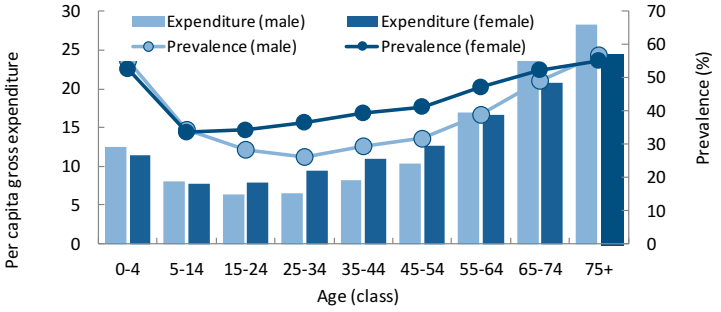
Anti-infectives for sistemic use

NHS expenditure, million €* (% on the total)	**2,917.0**	**(13.3)**
Δ % 2018/2017		-6.0
Per capita gross expenditure, range among Regions:	30.6	56.0
DDD/1000 inhab die* (% on the total)	**23.4**	**(2.1)**
Δ % 2018/2017		-0.3
DDD/1000 inhab die, range among Regions:	15.4	29.4

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age	Gross expenditure per capita			DDD/1000 inhab die		
(class)	Male	Female	Total	Male	Female	Total
0-4	12.5	11.4	12.0	17.9	16.2	17.1
5-14	8.1	7.8	7.9	12.2	11.6	11.9
15-24	6.3	7.9	7.1	10.5	12.0	11.2
25-34	6.5	9.4	7.9	9.6	13.5	11.6
35-44	8.2	11.0	9.6	11.5	15.6	13.6
45-54	10.4	12.7	11.6	13.1	17.1	15.1
55-64	16.9	16.7	16.8	18.0	21.1	19.6
65-74	24.7	20.8	22.6	25.6	24.9	25.3
75+	28.3	24.4	25.9	30.1	26.1	27.7

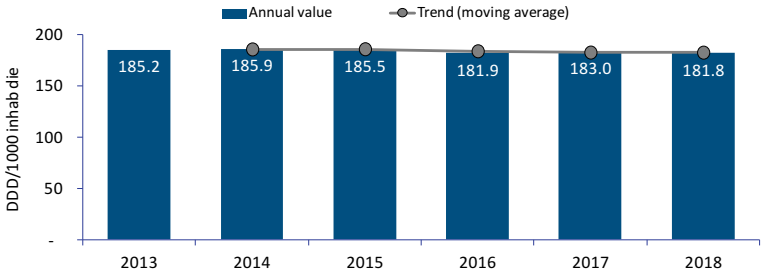
4.4 Alimentary Tract and metabolism

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

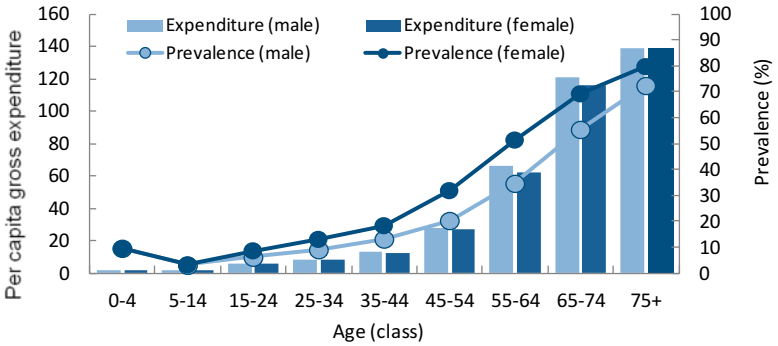
Alimentary tract and metabolism

NHS expenditure, million €* (% on the total)	**2,835.3**	**(12.9)**
Δ % 2018/2017		3.2
Per capita gross expenditure, range among Regions:	29.7	62.6
DDD/1000 inhab die* (% on the total)	**181.8**	**(16.0)**
Δ % 2018/2017		-0.7
DDD/1000 inhab die, range among Regions:	132.6	218.2

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	1.3	1.3	1.3	5.3	5.1	5.2
5-14	2.0	2.0	2.0	4.5	4.5	4.5
15-24	5.5	5.4	5.4	12.6	13.8	13.2
25-34	7.8	7.8	7.8	21.4	23.7	22.5
35-44	13.0	12.4	12.7	40.8	42.1	41.4
45-54	27.6	27.0	27.3	89.8	94.1	92.0
55-64	66.1	61.8	63.9	217.9	214.7	216.2
65-74	120.8	115.7	118.1	431.5	423.9	427.5
75+	138.7	139.3	139.0	559.3	565.3	562.9

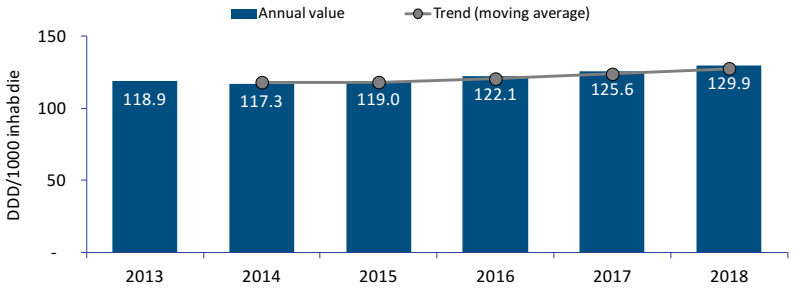
4.5 Blood and blood forming organs

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

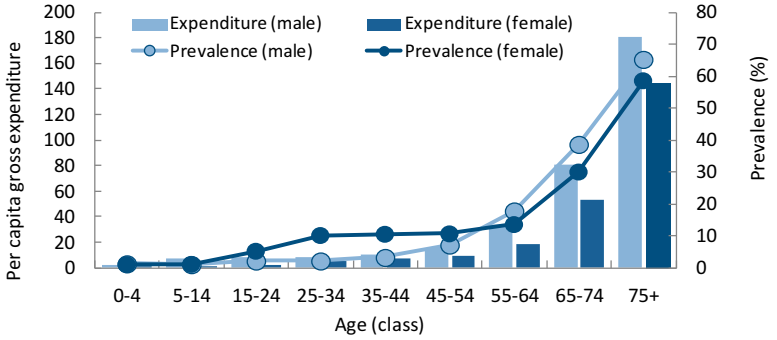
Blood and blood forming organs

NHS expenditure, million €* (% on the total)	**2,082.2**	**(9.5)**
Δ % 2018/2017		0.6
Per capita gross expenditure, range among Regions:	23.3	46.9
DDD/1000 inhab die* (% on the total)	**129.9**	**(11.4)**
Δ % 2018/2017		3.4
DDD/1000 inhab die, range among Regions:	89.1	182.0

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	2.3	0.3	1.3	1.4	1.1	1.3
5-14	7.5	0.5	4.1	1.3	1.3	1.3
15-24	8.6	2.1	5.5	3.5	9.2	6.2
25-34	8.7	4.8	6.8	4.7	24.9	14.7
35-44	10.0	6.7	8.4	11.2	26.9	19.1
45-54	15.5	8.9	12.2	37.7	31.7	34.7
55-64	34.1	18.7	26.2	121.4	68.3	93.9
65-74	81.0	53.3	66.4	302.5	199.0	247.8
75+	180.5	144.1	158.6	529.7	437.5	474.2

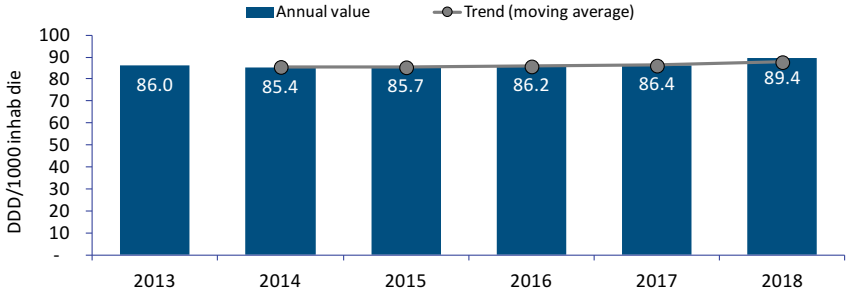
4.6 Nervous system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

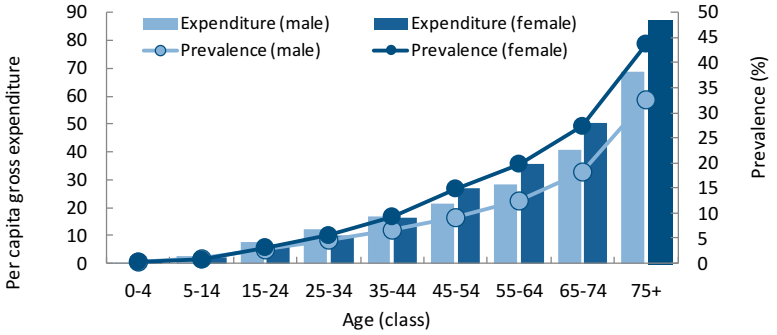
Nervous system

NHS expenditure, million €* (% on the total)	**1,782.1**	**(8.1)**
Δ % 2018/2017		4.9
Per capita gross expenditure, range among Regions:	26.6	35.5
DDD/1000 inhab die* (% on the total)	**89.4**	**(7.9)**
Δ % 2018/2017		3.4
DDD/1000 inhab die, range among Regions:	72.8	111.9

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	0.4	0.4	0.4	0.6	0.5	0.6
5-14	2.6	1.9	2.3	3.9	2.8	3.4
15-24	7.4	6.7	7.1	15.2	14.3	14.7
25-34	12.3	10.0	11.2	28.5	25.4	26.9
35-44	16.6	16.2	16.4	40.4	44.8	42.6
45-54	21.6	26.7	24.2	54.4	77.3	66.0
55-64	28.1	35.8	32.1	68.8	108.8	89.4
65-74	40.7	50.4	45.8	95.8	147.3	123.0
75+	68.7	87.1	79.8	162.7	228.0	202.1

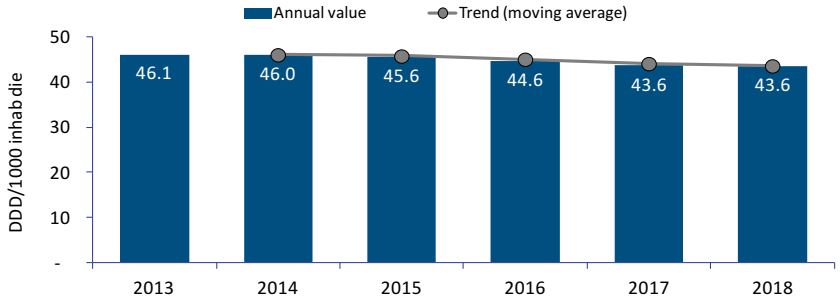
4.7 Respiratory system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

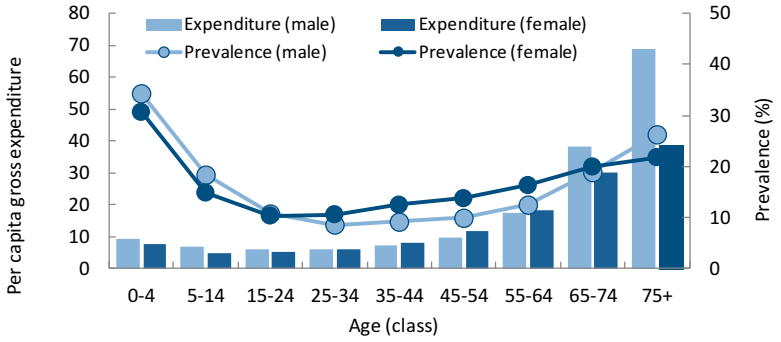
Respiratory system

NHS expenditure, million €* (% on the total)	**1,166.1**	**(5.3)**
Δ % 2018/2017		19.1
Per capita gross expenditure, range among Regions:	14.4	25.3
DDD/1000 inhab die* (% on the total)	**43.6**	**(3.8)**
Δ % 2018/2017		-0.1
DDD/1000 inhab die, range among Regions:	33.2	60.7

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	9.1	7.5	8.3	27.7	22.4	25.1
5-14	6.8	4.6	5.7	24.1	16.2	20.3
15-24	5.8	5.0	5.4	22.5	19.0	20.8
25-34	5.8	5.9	5.8	18.7	19.4	19.1
35-44	7.1	8.1	7.6	20.4	24.4	22.4
45-54	9.7	11.5	10.6	25.4	32.7	29.1
55-64	17.5	18.4	17.9	39.5	45.6	42.7
65-74	38.4	30.2	34.1	79.2	68.6	73.6
75+	68.8	38.7	50.7	139.3	86.6	107.5

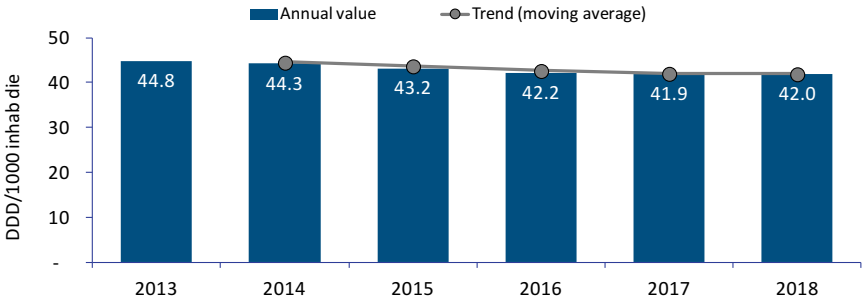
4.8 Musculo-skeletal system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

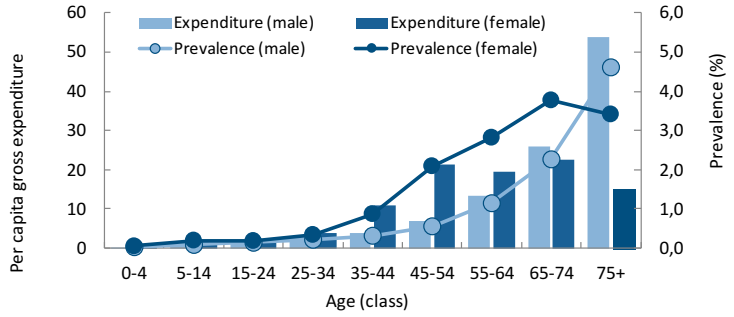
Musculo-skeletal system

NHS expenditure, million €* (% on the total)	**533.3**	**(2.4)**
Δ % 2018/2017		4.3
Per capita gross expenditure, range among Regions:	5.4	12.0
DDD/1000 inhab die* (% on the total)	**42.0**	**(3.7)**
Δ % 2018/2017		0.1
DDD/1000 inhab die, range among Regions:	31.6	59.9

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	0.2	0.3	0.3	0.1	0.1	0.1
5-14	0.8	2.0	1.4	0.4	1.0	0.7
15-24	1.5	1.7	1.6	0.6	0.7	0.6
25-34	2.9	4.0	3.4	0.9	1.5	1.2
35-44	3.9	10.9	7.4	1.4	5.6	3.5
45-54	6.8	21.3	14.1	2.5	15.4	9.0
55-64	13.5	19.3	16.5	5.2	17.8	11.7
65-74	25.8	22.5	24.1	10.9	23.1	17.4
75+	53.9	15.0	30.5	28.5	19.0	22.8

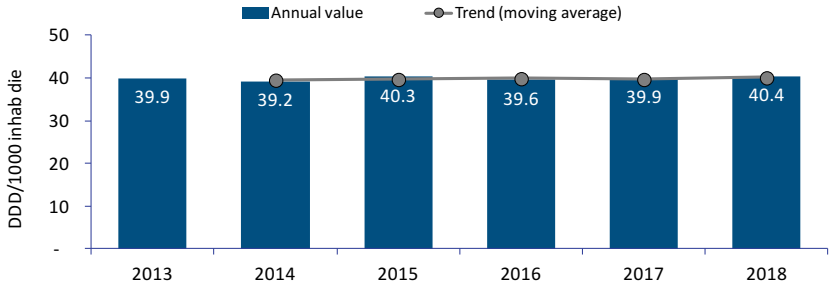
4.9 Systemic hormonal preparations, excluding sex hormones and insulins

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

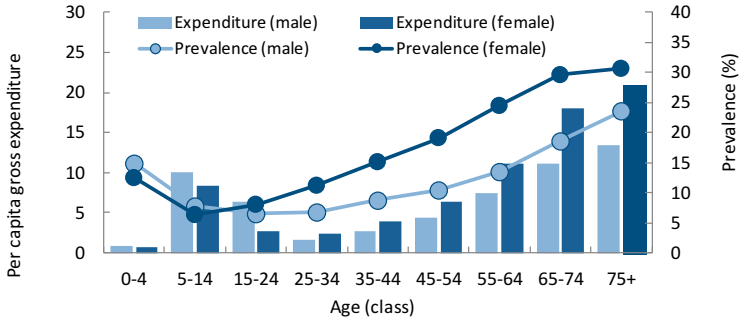
Systemic hormonal preparations, excluding sex hormones and insulins

NHS expenditure, million €* (% on the total)	**520.3**	**(2.4)**
Δ % 2018/2017		-2.2
Per capita gross expenditure, range among Regions:	7.3	11.0
DDD/1000 inhab die* (% on the total)	**40.4**	**(3.6)**
Δ % 2018/2017		1.2
DDD/1000 inhab die, range among Regions:	28.2	50.1

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	0.8	0.7	0.7	3.3	2.8	3.1
5-14	10.1	8.4	9.3	4.5	3.9	4.2
15-24	6.3	2.7	4.6	6.1	8.8	7.4
25-34	1.6	2.4	2.0	8.1	19.3	13.6
35-44	2.7	3.9	3.3	12.2	32.8	22.5
45-54	4.4	6.3	5.4	18.3	50.5	34.6
55-64	7.5	11.2	9.4	28.9	73.8	52.1
65-74	11.1	17.9	14.7	44.4	95.4	71.4
75+	13.4	20.9	17.9	57.6	93.3	79.1

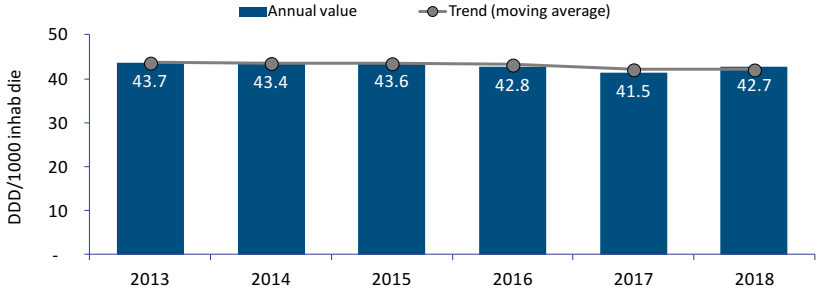
4.10 Genito-urinary system and sex hormones

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

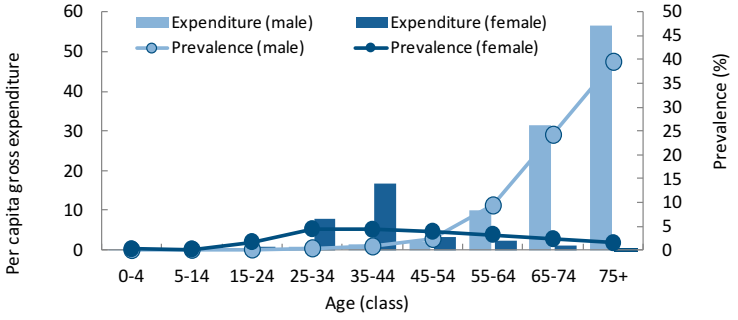
Genito-urinary system and sex hormones

NHS expenditure, million €* (% on the total)	**436.5**	**(2.0)**
Δ % 2018/2017		-0.6
Per capita gross expenditure, range among Regions:	5.6	8.7
DDD/1000 inhab die* (% on the total)	**42.7**	**(3.8)**
Δ % 2018/2017		3.1
DDD/1000 inhab die, range among Regions:	32.1	50.8

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	0.0	0.0	0.0	0.0	0.1	0.1
5-14	0.1	0.1	0.1	0.1	0.2	0.2
15-24	0.3	0.8	0.5	0.4	4.6	2.4
25-34	0.9	7.8	4.3	1.1	12.4	6.6
35-44	1.4	16.8	9.1	2.3	15.1	8.7
45-54	2.1	3.3	2.7	11.1	16.0	13.6
55-64	10.1	2.3	6.1	68.0	16.3	41.3
65-74	31.4	1.1	15.4	224.3	9.1	110.6
75+	56.6	0.6	22.9	409.0	4.3	165.1

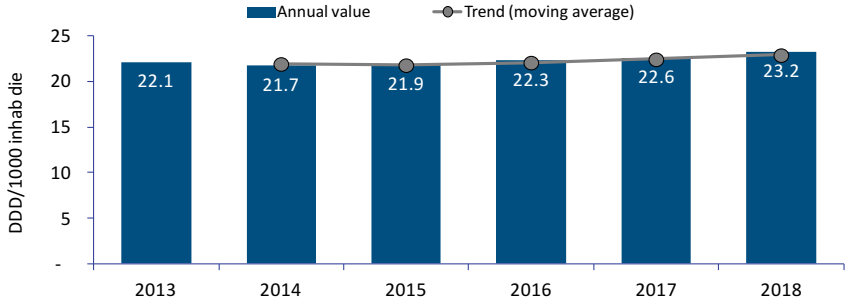
4.11 Sensory organs

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

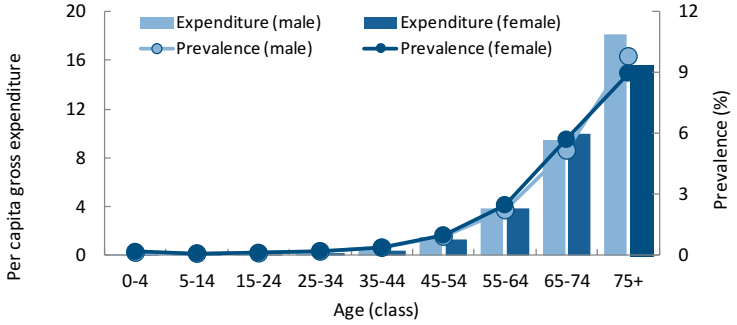
Sensory organs

NHS expenditure, million €* (% on the total)	**400.5**	**(1.8)**
Δ % 2018/2017		3.1
Per capita gross expenditure, range among Regions:	4.6	8.8
DDD/1000 inhab die* (% on the total)	**23.2**	**(2.0)**
Δ % 2018/2017		2.9
DDD/1000 inhab die, range among Regions:	18.2	32.2

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age (class)	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	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	1.2	0.9	1.1
35-44	0.5	0.4	0.5	2.8	2.2	2.5
45-54	1.5	1.3	1.4	7.9	7.1	7.5
55-64	3.9	3.9	3.9	20.5	20.8	20.7
65-74	9.5	9.9	9.7	50.0	52.9	51.5
75+	18.2	15.5	16.6	97.1	84.8	89.7

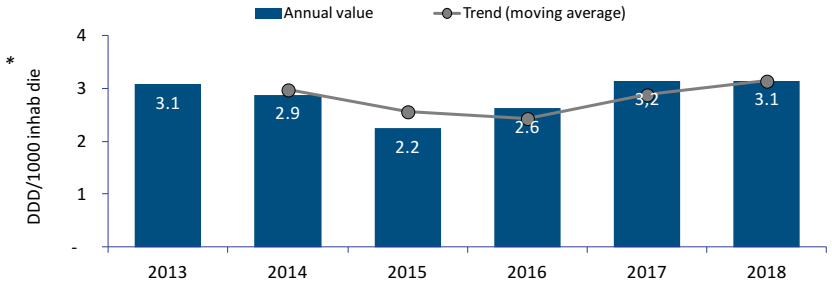
4.12 Various

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

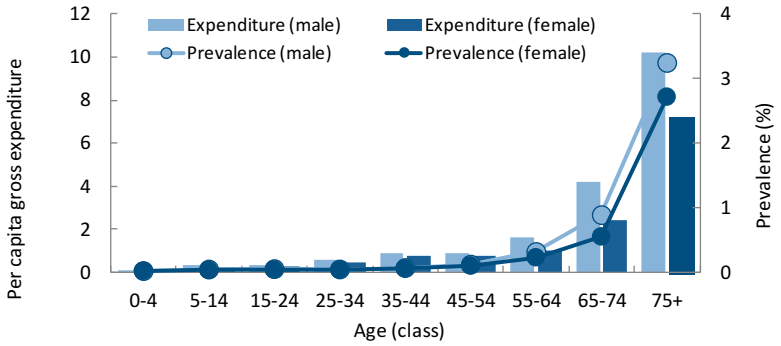
Various

NHS expenditure, million €* (% on the total)	**331.2**	**(1.5)**
Δ % 2018/2017		4.6
Per capita gross expenditure, range among Regions:	4.0	12.2
DDD/1000 inhab die* (% on the total)	**3.2**	**(0.3)**
Δ % 2018/2017		2.4
DDD/1000 inhab die, range among Regions:	1.5	6.2

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	Total
0-4	0.1	0.1	0.1	0.0	0.0	0.0
5-14	0.3	0.2	0.3	0.1	0.1	0.1
15-24	0.4	0.3	0.3	0.2	0.1	0.1
25-34	0.6	0.4	0.5	0.1	0.1	0.1
35-44	0.9	0.8	0.8	0.1	0.1	0.1
45-54	0.9	0.8	0.8	0.2	0.1	0.2
55-64	1.6	1.0	1.3	0.4	0.2	0.3
65-74	4.2	2.4	3.2	0.6	0.3	0.5
75+	10.2	7.2	8.4	0.9	0.4	0.6

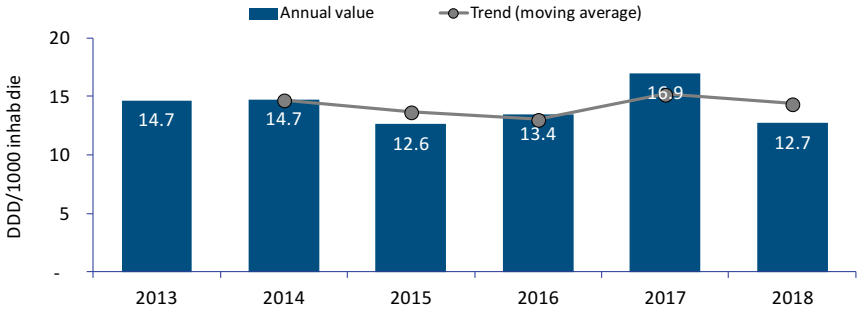
4.13 Dermatologicals

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

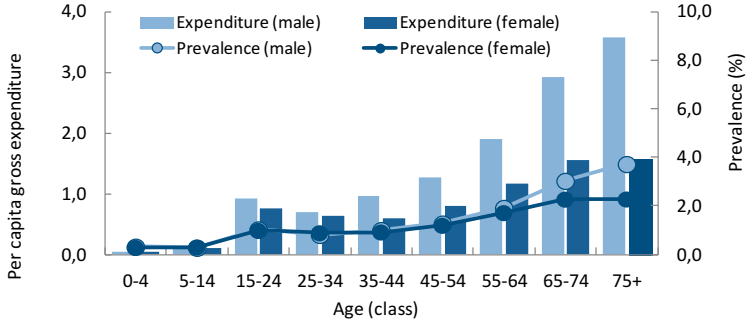
Dermatologicals

NHS expenditure, million €* (% on the total)	**91.9**	**(0.4)**
Δ % 2018/2017		-0.8
Per capita gross expenditure, range among Regions:	1.2	1.7
DDD/1000 inhab die* (% on the total)	**12.7**	**(1.1)**
Δ % 2018/2017		-24.7
DDD/1000 inhab die, range among Regions:	7.9	23.1

** Includes outpatient and inpatient NHS expenditure*



Distribution of expenditure by age and gender, prevalence of use and consumption for outpatient NHS expenditure 2018 (Chart and Table)



Age groups	Gross expenditure per capita			DDD/1000 inhab die		
	Male	Female	Total	Male	Female	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	0.9	0.8	0.8	2.5	2.2	2.3
25-34	0.7	0.6	0.7	2.5	2.2	2.4
35-44	1.0	0.6	0.8	3.7	2.4	3.0
45-54	1.3	0.8	1.0	4.9	3.1	4.0
55-64	1.9	1.2	1.5	7.2	4.7	5.9
65-74	2.9	1.5	2.2	10.7	6.4	8.4
75+	3.6	1.6	2.4	12.0	6.4	8.6

Table 4.5. Consumption, price and mix effects on outpatients Class A NHS pharmaceutical expenditure variation: comparison 2018-2017

(for each ATC category the therapeutic subgroups were included in decreasing order of expenditure, up to the per capita expenditure value of 0.10 euro)

ATC I level Subgroups	Per capita gross expenditure	DDD/ 1000 inhab die	Δ% 18-17				Δ% DDD average cost
			Exp	DDD	Price	Mix	
Italy	**166.46**	**978.8**	**-3.4**	**0.8**	**-4.6**	**0.3**	**-4.10**
C - Cardiovascular system	**48.98**	**470.5**	**-8.9**	**0.6**	**-10.0**	**0.7**	**-9.39**
HMG CoA reductase Inhibitors	7.89	75.1	-25.0	3.4	-25.8	-2.2	-27.42
Angiotensin II antagonists, non-associated	4.54	56.2	-4.6	0.7	-6.4	1.2	-5.26
Beta-blockers, selective	4.34	37.8	3.8	1.8	0.0	2.0	1.99
Angiotensin II antagonists and diuretics	4.31	35.9	-8.2	-2.2	-6.0	-0.2	-6.16
Dihydropyridine derivatives	4.27	49.7	-1.4	-0.8	0.0	-0.6	-0.61
Non-associated angiotensin converting enzyme (ACE) inhibitors	3.90	84.3	-1.2	-0.8	0.0	-0.4	-0.40
Other cholesterol-lowering and hypotriglyceride-demanding substances	3.24	7.8	-13.5	13.3	-18.9	-5.8	-23.65
Angiotensin Conversion Enzyme (ACE) Inhibitors and Diuretics	2.75	21.3	-3.3	-3.2	0.0	-0.1	-0.08
HMG inhibitors CoA reductase in association with other lipid-modifying substances	2.35	4.5	-23.9	9.6	-26.6	-5.4	-30.57
Inhibitors of the angiotensin converting enzyme (ACE) and calcium channel blockers	1.64	11.1	-5.2	5.6	-7.7	-2.7	-10.22
Angiotensin II antagonists associated with calcium antagonists	1.49	5.5	-2.8	15.6	-14.4	-1.8	-15.92
Adrenergic alpha receptor blockers	1.21	7.4	-0.6	-0.5	0.0	-0.1	-0.14
Antiarrhythmics, class IC	0.99	4.6	3.2	0.3	0.0	2.9	2.93
Sulphonamides, non-associated	0.94	27.1	-0.2	-0.3	0.1	0.0	0.09
Organic nitrates	0.86	8.2	-14.0	-13.6	-0.1	-0.3	-0.38
Blockers for alpha and beta adrenergic receptors	0.58	3.3	-5.4	-4.9	0.0	-0.6	-0.59
Selective beta-blockers and thiazides	0.55	5.5	-11.1	5.1	-14.4	-1.2	-15.33
Aldosterone antagonists	0.50	3.2	1.5	0.3	-0.3	1.5	1.20
Inhibitors of the angiotensin converting enzyme (ACE), other associations	0.45	2.7	35.4	64.6	-14.7	-3.6	-17.75
Fibers	0.38	2.7	2.3	2.7	0.0	-0.4	-0.44
Antiarrhythmics, class III	0.27	2.9	-1.6	-1.2	0.0	-0.4	-0.43
Imidazolin receptor agonists	0.22	1.6	-5.2	-5.1	0.0	0.0	-0.03
Benzotiazepine derivatives	0.20	1.2	-8.3	-8.2	0.0	-0.2	-0.18
Phenylalkylamine derivatives	0.15	1.3	-9.7	-8.9	0.0	-0.9	-0.93
Beta-blockers, non-selective	0.14	1.6	0.4	0.8	0.0	-0.5	-0.46
Other cardiac preparations	0.14	0.4	2.7	168.1	-45.6	-29.6	-61.69
Selective beta-blockers and other diuretics	0.14	2.0	-6.3	-6.2	0.0	-0.1	-0.09
Diuretics with minor diuretic action and potassium-sparing drugs	0.13	2.4	-6.3	-6.2	0.0	-0.1	-0.06
Diuretics with increased diuretic action and potassium-sparing drugs	0.12	0.6	-2.8	-2.9	0.0	0.0	0.03
Angiotensin II antagonists in association	0.11	0.0	177.0	177.0	0.0	0.0	0.00
A - Gastrointestinal system and metabolism	**33.01**	**152.7**	**0.4**	**0.2**	**0.0**	**0.2**	**0.18**

ATC I level Subgroups	Per capita gross expenditure	DDD/ 1000 inhab die	Δ% 18-17				Δ% DDD average cost
			Exp	DDD	Price	Mix	
Acid Pump Inhibitors	12.48	67.1	-5.3	-0.8	0.0	-4.6	-4.58
Vitamin D and analogues	4.99	14.1	16.2	15.1	-0.1	1.1	0.98
Insulin and the like, fast-acting	3.78	7.7	-2.0	-0.3	-1.7	-0.1	-1.72
Aminosalicylic acid and analogues	1.86	4.8	3.7	4.4	0.0	-0.7	-0.67
Antibiotics	1.51	2.0	0.0	0.0	0.0	-0.1	-0.07
Biguanides	1.50	21.6	3.4	2.1	-0.2	1.5	1.26
Other peptic antiulcer	0.86	4.1	1.8	1.5	0.0	0.3	0.28
Bile acid preparations	0.75	2.3	13.0	3.6	9.5	-0.4	9.03
Insulin and similar, long-acting	0.66	0.6	16.4	2.7	-0.2	13.5	13.33
Sulfonamides, urea derivatives	0.55	9.1	-2.6	-6.8	0.0	4.5	4.46
Calcium, associations with other drugs	0.44	4.6	-2.9	-3.7	0.0	0.9	0.86
Associations and complexes between aluminium, calcium and magnesium compounds	0.42	1.9	2.1	1.3	0.0	0.8	0.80
Biguanides and sulfonamides in association	0.40	2.3	-13.6	-19.6	0.5	6.9	7.46
Other oral hypoglycemic agents	0.36	2.5	-11.2	-11.9	0.0	0.8	0.82
H2 receptor antagonists	0.32	2.1	0.5	-0.1	0.0	0.6	0.61
GLP-1 receptor analogues	0.30	0.2	55.5	49.5	4.6	-0.6	4.00
Corticosteroids for topical use	0.29	0.4	0.3	-1.9	0.0	2.2	2.24
Serotonin antagonists (5HT3)	0.21	0.0	-0.4	1.9	0.1	-2.4	-2.27
Enzyme preparations	0.21	0.6	3.8	3.8	0.0	0.0	0.00
Insulin and similar, intermediate and fast-acting associated	0.18	0.4	-23.9	-20.7	-4.3	0.2	-4.07
Dipeptil Peptidase 4 Inhibitors (DPP-4)	0.18	0.2	-1.5	0.7	0.0	-2.1	-2.13
Alpha Glucosidase Inhibitors	0.17	0.6	-5.2	-3.5	0.0	-1.8	-1.76
Osmotic laxatives	0.12	1.1	-0.3	-0.5	0.0	0.1	0.11
Football	0.11	1.3	-0.3	-0.8	0.0	0.6	0.58
N - Nervous system	**22.53**	**65.1**	**0.2**	**2.6**	**-3.1**	**0.8**	**-2.28**
Other antiepileptics	4.09	5.6	-10.4	6.2	-14.8	-0.9	-15.62
Selective serotonin reuptake inhibitors	3.28	28.4	0.7	1.5	0.0	-0.8	-0.86
Other antidepressants	2.81	10.2	7.4	6.6	-0.2	1.0	0.74
Other opiates	1.42	1.1	5.0	1.3	0.0	3.7	3.65
Natural Opium Alkaloids	1.33	0.6	-0.3	0.4	0.0	-0.8	-0.76
Phenylpiperidine derivatives	1.31	0.6	3.5	3.7	0.0	-0.3	-0.25
Dopamine agonists	1.23	1.2	0.9	-1.4	0.0	2.4	2.37
5HT1 Selective Receptor Agonists	0.97	0.8	-0.5	1.8	0.0	-2.3	-2.26
Fatty acid derivatives	0.94	2.2	2.2	1.8	0.0	0.4	0.35
Diazepines, oxazepines and thiazepines	0.86	1.2	3.0	1.0	-0.4	2.4	1.93
Dopa and its derivatives	0.71	2.0	0.2	2.9	-0.1	-2.6	-2.68
Type B monoamine oxidase inhibitors	0.70	1.5	11.5	8.8	-0.3	2.8	2.52
Opiates in association with non-opioid analgesics	0.56	1.5	1.5	-0.8	0.0	1.2	2.29
Carboxamide derivatives	0.49	1.9	-1.8	-1.5	0.0	-0.3	-0.30
Starches	0.35	0.3	3.1	3.1	0.0	0.0	0.00
Other antipsychotics	0.25	0.4	13.4	15.7	0.0	-1.9	-1.92
Anticholinesterases	0.25	0.6	-1.8	-1.2	-0.2	-0.4	-0.55
Non-selective monoamine reuptake	0.17	1.0	-0.9	-0.7	0.0	-0.2	-0.21

ATC I level Subgroups	Per capita gross expenditure	DDD/ 1000 inhab die	Δ% 18-17				Δ% DDD average cost
			Exp	DDD	Price	Mix	
inhibitors							
Oripavine derivatives	0.14	0.2	30.2	76.0	0.0	-26.0	-26.00
R - Respiratory system	**16.23**	**41.1**	**-1.0**	**-0.4**	**-1.9**	**1.3**	**-0.63**
Adrenergics and other antiasthmatics	7.86	12.0	1.2	4.6	-2.9	-0.5	-3.33
Anticolinergic	3.10	6.0	0.8	2.8	-2.7	0.7	-1.98
Glycocorticoids	1.93	5.2	-14.2	-11.7	0.0	-2.8	-2.80
Adrenergics in combination with Anticolinergics	1.02	1.8	20.5	10.7	1.4	7.4	8.87
Selective agonists of beta2-adrenergic receptors	0.76	4.2	-10.2	-5.0	-0.4	-5.1	-5.43
Other antihistamines for systemic use	0.62	5.7	-2.9	-0.1	-1.7	-1.1	-2.85
Leukotriene receptor antagonists	0.47	2.0	-2.5	-0.6	0.0	-1.9	-1.88
Piperazine derivatives	0.36	3.7	-0.3	0.4	0.0	-0.7	-0.69
J - General systemic antimicrobials	**13.07**	**17.2**	**-0.8**	**-0.7**	**-0.1**	**0.0**	**-0.07**
Third generation cephalosporins	3.01	1.8	2.5	3.4	0.0	-0.9	-0.91
Penicillin associations, including beta-lactamase inhibitors	2.99	5.8	0.0	0.2	0.0	-0.3	-0.25
Fluoroquinolones	1.96	2.6	-6.8	-4.9	0.0	-2.0	-2.00
Macrolids	1.50	3.5	-1.9	-0.6	-0.9	-0.5	-1.40
Triazole derivatives	1.04	0.6	-0.6	-0.4	0.0	-0.2	-0.19
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.60	0.3	0.8	2.9	0.0	-2.1	-2.02
Other antibacterial agents	0.60	0.4	2.3	2.3	0.0	0.1	0.04
Specific immunoglobulins	0.57	0.0	4.2	3.1	0.0	1.1	1.07
Broad spectrum penicillins	0.25	1.2	-5.1	-4.8	0.0	-0.3	-0.30
Second generation cephalosporins	0.11	0.2	-5.7	-5.9	0.0	0.2	0.21
B - Blood and hematopoietic organs	**7.91**	**87.1**	**-2.4**	**0.6**	**-0.1**	**-2.9**	**-2.98**
Platelet aggregation inhibitors, excl. heparin	2.99	60.8	-0.2	-0.4	0.0	0.2	0.23
Heparins	2.57	2.7	-14.8	-14.1	0.0	-0.8	-0.82
Direct Xa Factor Inhibitors	0.50	0.3	89.1	90.0	1.0	-1.5	-0.46
Folic acid and derivatives	0.47	5.7	7.0	9.9	0.5	-3.1	-2.58
Bivalent iron, oral preparations	0.36	2.8	2.4	2.2	0.0	0.3	0.25
Blood substitutes and plasma protein fractions	0.22	0.0	2.7	3.1	0.0	-0.4	-0.41
Vitamin K antagonists	0.18	4.4	-10.3	-10.3	0.0	0.0	-0.00
Solutions that influence the electrolyte balance	0.16	0.3	-2.0	-1.8	-0.3	0.1	-0.17
Other antianemic preparations	0.11	0.0	26.7	27.9	-1.2	0.3	-0.91
M - Musculoskeletal system	**5.71**	**37.4**	**-6.2**	**-1.0**	**-5.5**	**0.2**	**-5.29**
Biphosphonates	1.32	6.7	-0.4	0.5	0.0	-0.9	-0.92
Preparations inhibiting the formation of uric acid	1.28	9.6	10.1	5.0	0.0	4.9	4.85
Acetic acid derivatives and related substances	0.78	4.8	-2.8	-3.0	0.0	0.1	0.12
Propionic acid derivatives	0.75	6.2	-4.0	-3.7	-0.1	-0.2	-0.34
Coxibs	0.65	3.8	-30.5	-0.2	-28.4	-2.7	-30.36
Biphosphonates and calcium, sequential preparations	0.51	2.4	-20.2	-9.5	-10.8	-1.3	-11.90
Other non-steroidal anti-inflammatory and	0.17	2.0	-7.4	-7.1	0.0	-0.3	-0.34

ATC I level Subgroups	Per capita gross expenditure	DDD/ 1000 inhab die	Δ% 18-17				Δ% DDD average cost
			Exp	DDD	Price	Mix	
anti-rheumatic drugs							
Oxicam-derivatives	0.12	0.9	-9.2	-8.9	0.0	-0.4	-0.36
G - Genitourinary system and sexual hormones	**5.64**	**40.8**	**-14.8**	**3.1**	**-15.5**	**-2.2**	**-17.34**
Alpha adrenergic receptor antagonists	3.03	25.1	4.3	3.9	-0.1	0.4	0.34
Testosterone-5-alpha reductase inhibitors	1.58	10.4	-39.6	4.5	-39.0	-5.3	-42.21
Prolactin Inhibitors	0.16	0.1	1.7	-0.7	0.0	2.4	2.41
Gonadotropins	0.13	0.0	6.6	-14.3	0.0	24.4	24.42
Pregnene derivatives	0.12	1.0	-1.4	-4.6	0.0	3.4	3.39
Other estrogens	0.11	0.7	1.0	1.5	0.0	-0.5	-0.47
Estro-progestinic associations	0.11	0.6	0.4	-1.0	0.0	1.4	1.39
L - Antineoplastic and immunomodulatory drugs	**4.10**	**6.1**	**4.2**	**3.7**	**-0.7**	**1.1**	**0.44**
Enzyme inhibitors	1.89	2.6	8.8	8.4	0.0	0.4	0.34
Other substances with immunosuppressive action	0.71	1.5	5.8	3.5	0.0	2.2	2.23
Calcineurin inhibitors	0.69	0.2	-1.8	-2.0	0.0	0.3	0.26
Other antineoplastics	0.16	0.3	3.6	4.3	0.0	-0.7	-0.74
Antiandrogens	0.16	0.3	-1.4	0.1	0.0	-1.5	-1.47
Folic acid analogues	0.11	0.1	-6.8	-6.8	0.0	0.0	-0.02
H - Systemic hormonal preparations, excluding sex hormones	**3.98**	**35.2**	**4.7**	**1.9**	**-0.7**	**3.5**	**2.72**
Glycocorticoids	1.40	13.2	1.4	2.2	0.0	-0.8	-0.79
Parathyroid hormones	1.19	0.2	2.7	5.2	-2.4	0.0	-2.37
Thyroid Hormones	0.99	20.3	7.1	1.9	0.0	5.1	5.10
Vasopressin and analogues	0.14	0.1	0.5	0.1	0.0	0.4	0.36
Somatotropin and analogues	0.10	0.0	53.6	50.0	-0.1	2.4	2.38
S - Sense organs	**3.81**	**20.5**	**-0.3**	**2.1**	**-3.0**	**0.7**	**-2.32**
Beta-blockers	2.19	11.5	0.2	2.0	-3.6	1.9	-1.76
Prostaglandins analogues	1.27	5.6	-1.4	1.7	-2.9	-0.2	-3.09
Carbon Dioxide Inhibitors	0.22	1.4	-1.5	-0.4	0.0	-1.1	-1.11
D - Dermatological	**1.13**	**4.3**	**18.9**	**5.0**	**0.1**	**12.4**	**13.16**
Other antipsoriatic agents for topical use	0.68	2.1	31.2	25.0	0.0	4.9	4.92
P - Antiparasitic drugs, insecticides and repellents	**0.22**	**0.9**	**2.9**	**2.5**	**0.0**	**0.4**	**0.41**
Aminoquinoline	0.14	0.8	3.1	2.9	0.0	0.2	0.21
V - Miscellaneous	**0.15**	**0.1**	**4.4**	**6.5**	**-0.3**	**-1.7**	**-1.94**
Drugs for the treatment of hyperkalemia and hyperphosphat	0.12	0.1	7.0	6.8	0.1	0.1	0.19

Table 4.6. Expenditure and consumption of medicines purchased by public health facilities in 2018 by ATC I level

(for each ATC category at 1st level the therapeutic subgroups were included in decreasing order of expenditure, up to the per capita expenditure value of 0.1 euro)

ATC I level Subgroups	Per capita NHS expenditure	%	Δ% 18-17	DDD/ 1000 inhab die	%	Δ% 18-17
L - Antineoplastic and immunomodulatory drugs	**89.46**		**9.7**	**9.5**		**4.1**
Monoclonal antibodies	24.11	27.0	18.4	1.1	11.7	6.8
Protein kinase inhibitors	15.27	17.1	18.7	0.4	4.4	18.2
Tumor necrosis factor inhibitors alpha (TNF-alpha)	10.51	11.8	-3.9	1.2	12.5	6.0
Substances with a selective immunosuppressive action	9.34	10.4	7.1	1.0	10.1	16.1
Other substances with immunosuppressive action	6.99	7.8	9.6	0.4	4.2	12.4
Interleukin inhibitors	4.43	5.0	28.6	0.4	4.2	33.3
Other antineoplastics	3.51	3.9	9.3	0.2	2.1	0.7
Interferons	2.28	2.6	-13.6	0.5	5.1	-10.9
Analogues of the gonadotropin releasing hormone	1.78	2.0	3.6	1.0	10.4	5.0
Other hormonal antagonists and related agents	1.73	1.9	-0.8	0.1	1.3	12.5
Pyrimidine analogues	1.49	1.7	22.1	0.4	4.3	-4.1
Other cytokines and immunomodulators	1.22	1.4	-11.7	0.1	1.1	-8.9
Antiandrogens	1.20	1.4	36.8	0.7	7.1	-9.0
Folic acid analogues	0.90	1.0	-17.1	0.1	0.9	-8.3
Calcineurin inhibitors	0.85	1.0	2.2	0.4	3.7	-0.3
Taxanes	0.78	0.9	6.1	0.2	1.8	-5.6
Colony stimulation factors	0.77	0.9	-14.9	0.1	0.9	-3.2
Antiestrogens	0.63	0.7	10.5	0.3	2.9	6.6
Anthracyclines and related substances	0.44	0.5	-8.0	0.1	1.1	-4.9
Other plant alkaloids and natural products	0.31	0.4	0.9	0.0	0.0	0.9
Vinca alkaloids and analogues	0.22	0.3	-2.9	0.0	0.4	-3.7
J - General systemic antimicrobials	**35.16**		**-21.2**	**6.3**		**0.5**
Antivirals for the treatment of HIV infections, ass.	7.69	21.9	6.3	1.3	21.1	7.8
Antivirals for the treatment of HCV infections	6.85	19.5	-56.1	0.2	3.0	-25.6
Meningococcal vaccines	2.35	6.7	-13.3	0.1	2.1	-12.8
Other antivirals	2.00	5.7	8.1	0.4	5.9	18.0
Normal human immunoglobulins	1.71	4.9	10.8	0.0	0.3	-1.9
Pneumococcal vaccines	1.66	4.7	0.1	0.1	1.6	2.9
Bacterial and viral vaccines in association	1.23	3.5	-2.3	0.1	1.6	9.3
Reverse Transcriptase Inhibitors, Nucleosides	1.00	2.9	-55.6	0.8	12.5	3.4
Papillomavirus vaccine	0.93	2.7	>100	0.0	0.7	64.8
Flu vaccines	0.92	2.6	18.5	0.4	6.9	-2.8
Other antimycotics for systemic use	0.80	2.3	-35.1	0.0	0.2	2.1
Protease inhibitors	0.70	2.0	-42.0	0.1	2.2	-42.9
Measles vaccines	0.66	1.9	11.2	0.1	1.0	2.8
Specific immunoglobulins	0.58	1.6	12.5	0.0	0.2	-6.2
Triazole derivatives	0.58	1.6	1.4	0.1	2.0	14.2
Other antibacterial agents	0.54	1.5	-20.3	0.1	0.9	15.8
Penicillins, including beta-lactamase inhibitors	0.51	1.5	25.0	0.5	8.6	-1.6
Antibiotics	0.51	1.4	6.7	0.1	1.0	-7.4
Antibacterial glycopeptide	0.42	1.2	-26.4	0.1	0.9	-1.7
Tetracyclines	0.37	1.1	-15.7	0.0	0.5	2.6

ATC I level Subgroups	Per capita NHS expenditure	%	Δ% 18-17	DDD/ 1000 inhab die	%	Δ% 18-17
Third generation cephalosporins	0.36	1.0	>100	0.3	5.0	15.4
Reverse Transcriptase Inhibitors, Non-Nucleosides	0.32	0.9	-23.2	0.2	2.7	-13.8
Varicellosis vaccines	0.29	0.8	64.0	0.0	0.3	54.8
Rotavirus diarrhea vaccines	0.28	0.8	>100	0.0	0.4	>100
Carbapenemas	0.24	0.7	-3.9	0.1	0.7	39.8
Polymyxins	0.21	0.6	-17.6	0.0	0.3	-12.3
Other cephalosporins and penemas	0.18	0.5	86.3	0.0	0.0	85.2
B - Blood and hematopoietic organs	**26.52**		**0.5**	**42.8**		**9.2**
Factors of blood clotting	7.66	28.9	-5.1	0.1	0.1	-6.8
Direct Xa Factor Inhibitors	5.36	20.2	22.0	6.9	16.1	27.9
Other antianemic preparations	3.30	12.4	-9.3	3.3	7.7	3.8
Platelet aggregation inhibitors, excl. heparin	2.30	8.7	8.1	9.5	22.1	8.4
Heparins	1.87	7.1	-10.5	6.6	15.5	1.0
Direct thrombin inhibitors	1.48	5.6	-6.5	2.1	5.0	20.9
Other systemic haemostats	0.87	3.3	14.3	0.0	0.1	21.6
Solutions that influence the electrolyte balance	0.74	2.8	-2.1	6.2	14.5	15.5
Parenteral Nutritional Solutions	0.55	2.1	-8.4	0.6	1.5	-7.2
Drugs used in hereditary angioedema	0.39	1.5	11.6	0.0	0.0	11.7
Other antithrombotic agents	0.34	1.3	31.6	0.5	1.1	-1.4
Blood substitutes and plasma protein fractions	0.29	1.1	-10.0	0.1	0.1	-7.6
Enzymes	0.27	1.0	7.3	0.0	0.0	-4.1
Trivalent iron, parenteral preparations	0.23	0.9	66.6	0.1	0.2	64.8
Local hemostats	0.21	0.8	-30.6	0.0	0.0	-38.9
Hypertonic solutions	0.20	0.8	-12.0	0.1	0.2	-6.4
A - Gastrointestinal system and metabolism	**13.87**		**10.0**	**29.1**		**-6.0**
Enzymes	4.65	33.5	6.2	0.0	0.0	6.5
Insulin and similar, long-acting	2.42	17.5	5.7	5.8	20.0	3.4
Biguanides and sulfonamides in association	1.86	13.4	10.1	4.7	16.1	11.8
GLP-1 receptor analogues	1.33	9.6	17.0	1.6	5.4	26.9
Dipeptil Peptidase 4 Inhibitors (DPP-4)	1.08	7.8	13.6	2.5	8.4	17.8
Various products of the gastrointestinal system and metabolism	0.55	4.0	77.7	0.0	0.0	18.9
Co-transporter SGLT-2 inhibitors	0.44	3.2	48.8	0.9	3.2	51.6
Insulin and the like, fast-acting	0.21	1.5	-7.8	0.9	3.0	-0.9
Acid Pump Inhibitors	0.18	1.3	-9.6	3.7	12.8	-5.1
N - Nervous system	**6.94**		**1.1**	**24.2**		**5.2**
Other antipsychotics	2.59	37.4	11.5	2.3	9.3	5.0
Drugs used in opiate addiction	0.53	7.6	-2.2	3.2	13.3	-2.4
Dopa and its derivatives	0.47	6.8	-9.0	0.3	1.2	-10.6
Diazepines, oxazepines and thiazepines	0.47	6.8	-18.7	3.4	14.2	1.5
Other antiepileptics	0.37	5.4	-15.3	0.9	3.8	5.9
Other medicines of the nervous system	0.31	4.4	20.7	0.1	0.3	2.9
Starches	0.22	3.2	-11.8	1.7	6.8	-9.8
Anticholinesterases	0.19	2.8	-7.4	1.1	4.3	-1.2
Halogenated hydrocarbons	0.19	2.7	-14.3	0.0	0.0	-14.8

ATC I level Subgroups	Per capita NHS expenditure	%	Δ% 18-17	DDD/ 1000 inhab die	%	Δ% 18-17
V - Miscellaneous	**5.33**		**3.7**	**3.1**		**2.3**
Iron chelating substances	1.46	27.5	15.2	0.1	1.8	-5.2
Water-soluble, nephrotropic, low osmolarity radiological contrast media	1.13	21.3	4.6	0.1	2.0	1.6
Antidotes	0.69	12.9	15.2	0.1	2.7	-28.4
Paramagnetic contrast media	0.33	6.2	-1.3	0.0	0.7	3.7
Other diagnostic radiopharmaceuticals for cancer detection	0.30	5.6	4.5	0.0	0.1	-27.3
Drugs for the treatment of hyperkalemia and hyperphosphatemia	0.27	5.0	-15.9	0.2	7.0	-4.7
Detoxifying substances for antineoplastic treatments	0.20	3.7	9.4	0.2	7.0	-4.9
H - Systemic hormonal preparations, excluding sex hormones	**4.62**		**0.3**	**5.2**		**-4.3**
Somatostatin and analogues	1.48	32.1	2.3	0.2	3.7	1.6
Somatotropin and analogues	1.40	30.2	-1.4	0.3	5.1	0.9
Other antiparathyroid substances	0.69	14.9	5.5	0.3	5.8	3.9
Other anterior pituitary gland hormones and analogues	0.40	8.7	0.2	0.0	0.3	1.4
Glycocorticoids	0.35	7.6	-4.4	3.9	74.9	-6.1
Parathyroid hormones	0.23	5.0	-7.9	0.1	1.0	-5.5
C - Cardiovascular system	**4.59**		**-7.0**	**16.9**		**-3.2**
Other cardiac preparations	1.48	32.2	-14.5	2.3	13.7	-3.9
Other antihypertensives	1.47	32.0	-32.4	0.1	0.4	-1.0
Other cholesterol-lowering and hypotriglyceride-demanding substances	0.55	11.9	>100	0.3	1.7	43.4
Angiotensin II antagonists in association	0.34	7.5	>100	0.2	1.4	>100
M - Musculoskeletal system	**3.11**		**103.7**	**4.6**		**8.0**
Other medications for diseases of the musculoskeletal system	1.74	55.9	>100	0.1	1.1	23.8
Other drugs that act on mineralization	0.84	27.2	18.0	2.7	59.1	14.2
Other peripheral muscle relaxants	0.24	7.9	8.5	0.0	0.1	12.2
R - Respiratory system	**3.05**		**44.9**	**2.5**		**1.8**
Other preparations for the respiratory system	1.39	45.5	70.7	0.0	0.3	>100
Other antiasthmatics for systemic use	1.05	34.3	56.2	0.1	4.6	39.0
Mucolytics	0.21	6.8	13.1	0.2	9.4	-2.4
S - Sense organs	**2.81**		**-7.9**	**2.8**		**8.0**
Anti-vascularisation substances	2.19	77.8	12.3	0.4	13.1	13.2
Corticosteroids, non-associated	0.35	12.6	1.9	0.2	7.4	-4.9
G - Genitourinary system and sexual hormones	**1.57**		**-15.4**	**1.9**		**-2.2**
Gonadotropins	0.97	61.4	-7.5	0.1	7.0	-3.0
Drugs used in erectile dysfunction	0.28	18.0	-26.8	0.2	11.6	15.8
D - Dermatological	**0.39**		**10.0**	**8.4**		**-34.3**

Table 4.7. Outpatient NHS consumption and expenditure for the year 2018: most frequently prescribed active ingredients for ATC level 1 categories (up to 75% of expenditure within the therapeutic category)

Therapeutic category	Per capita gross expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17	Average cost DDD
C - Cardiovascular	**48.98**		**-8.7**	**470.5**		**0.8**	**0.29**
atorvastatin	4.11	8.4	6.1	44.1	9.4	7.2	0.26
bisoprolol	2.30	4.7	7.0	10.5	2.2	6.7	0.60
ezetimibe/simvastatin	2.29	4.7	-25.8	4.3	0.9	4.8	1.47
ramipril	2.03	4.1	0.6	61.8	13.1	0.7	0.09
omega 3	1.86	3.8	0.5	4.2	0.9	5.6	1.23
simvastatin	1.65	3.4	-3.6	13.8	2.9	-3.4	0.33
amlodipine	1.55	3.2	0.4	26.5	5.6	0.6	0.16
olmesartan/amlodipine	1.49	3.0	-2.8	5.5	1.2	15.4	0.74
nebivolol	1.40	2.9	2.3	15.0	3.2	2.7	0.26
ezetimibe	1.37	2.8	-26.9	3.6	0.8	24.3	1.03
rosuvastatin	1.28	2.6	-68.4	12.2	2.6	2.2	0.29
olmesartan	1.21	2.5	-10.9	10.2	2.2	18.3	0.33
doxazosin	1.21	2.5	-0.4	7.4	1.6	-0.3	0.45
olmesartan/hydrochlorothiazide	1.00	2.0	-15.7	8.1	1.7	12.4	0.34
valsartan/hydrochlorothiazide	0.96	2.0	-10.6	9.0	1.9	-11.4	0.29
barnidipine	0.86	1.8	-0.6	4.7	1.0	-0.8	0.50
valsartan	0.85	1.7	-6.2	13.3	2.8	-8.7	0.18
perindopril/amlodipine	0.81	1.7	-3.7	5.0	1.1	0.9	0.44
losartan	0.79	1.6	-1.3	7.4	1.6	-0.5	0.29
lercanidipine	0.76	1.6	0.3	9.3	2.0	0.5	0.22
flecainide acetate	0.75	1.5	8.5	2.5	0.5	10.0	0.84
furosemide	0.73	1.5	0.0	24.5	5.2	-0.1	0.08
nitroglycerin	0.71	1.4	-14.0	5.9	1.3	-13.8	0.33
irbesartan/hydrochlorothiazide	0.68	1.4	-3.3	5.8	1.2	-2.5	0.32
irbesartan	0.67	1.4	0.0	8.2	1.8	-0.1	0.22
zofenopril/hydrochlorothiazide	0.65	1.3	3.7	4.1	0.9	4.0	0.43
ramipril/hydrochlorothiazide	0.62	1.3	-3.5	7.0	1.5	-2.7	0.24
zofenopril	0.62	1.3	6.6	4.1	0.9	6.2	0.41
carvedilol	0.58	1.2	-5.2	3.2	0.7	-4.7	0.49
telmisartan/hydrochlorothiazide	0.56	1.1	-1.7	4.4	0.9	-1.0	0.35
losartan/hydrochlorothiazide	0.55	1.1	-4.8	4.9	1.0	-4.4	0.31
A - Gastrointestinal and metabolism	**33.01**		**0.6**	**152.7**		**0.4**	**0.59**
cholecalciferol	4.51	13.7	16.9	12.3	8.0	16.2	1.01
pantoprazole	4.50	13.6	-1.9	21.5	14.1	5.3	0.57
lansoprazole	2.71	8.2	-8.9	14.5	9.5	-5.8	0.51
omeprazole	2.50	7.6	-7.2	16.5	10.8	-3.0	0.42
exomeprazole	2.37	7.2	-3.7	12.7	8.3	1.0	0.51
mesalazine	1.79	5.4	4.1	4.5	2.9	4.9	1.09
insulin lyspro	1.69	5.1	-1.5	3.5	2.3	2.7	1.34
metformin	1.50	4.6	3.6	21.6	14.1	2.3	0.19
insulin aspart	1.46	4.4	-1.6	2.9	1.9	-1.4	1.39
rifaximin	1.39	4.2	0.2	1.8	1.2	0.2	2.08
sodium alginate/potassium bicarbonate	0.82	2.5	2.3	3.9	2.5	2.0	0.58

Therapeutic category	Per capita gross expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17	Average cost DDD
N - Nervous system	**22.53**		**0.4**	**65.1**		**2.8**	**0.95**
levetiracetam	1.50	6.7	6.0	2.0	3.0	7.0	2.08
fentanyl	1.31	5.8	3.7	0.6	1.0	3.9	5.65
tapentadol	1.14	5.0	7.4	0.5	0.8	7.4	6.30
naloxone/oxycodone	1.07	4.7	0.8	0.4	0.6	1.4	7.20
pregabalin	1.05	4.7	-37.4	1.9	2.9	7.6	1.53
paroxetine	1.03	4.6	-0.3	7.7	11.9	0.7	0.36
escitalopram	0.93	4.1	0.6	7.2	11.1	1.6	0.35
valproic acid	0.91	4.0	2.5	2.2	3.3	2.1	1.15
venlafaxine	0.77	3.4	1.5	3.4	5.2	1.8	0.63
duloxetine	0.72	3.2	4.4	2.9	4.4	5.7	0.69
rotigotine	0.71	3.2	3.2	0.4	0.6	3.1	5.39
sertraline	0.71	3.1	4.6	7.7	11.8	4.5	0.25
quetiapine	0.51	2.2	8.0	0.4	0.6	6.2	3.33
vortioxetine	0.45	2.0	39.7	1.1	1.7	39.6	1.14
lacosamide	0.43	1.9	14.4	0.2	0.3	18.7	5.52
citalopram	0.41	1.8	-1.2	4.0	6.2	-0.7	0.28
lamotrigine	0.41	1.8	4.0	0.6	1.0	4.3	1.77
pramipexol	0.38	1.7	0.5	0.5	0.7	0.5	2.26
trazodone	0.37	1.6	4.7	1.0	1.6	4.2	0.98
lidocaine	0.35	1.6	3.3	0.3	0.4	3.3	3.61
gabapentin	0.32	1.4	1.9	0.4	0.6	1.9	2.14
safinamide	0.32	1.4	30.6	0.2	0.3	34.4	4.72
mirtazapine	0.32	1.4	3.5	1.5	2.4	5.4	0.56
levodopa/benserazide	0.31	1.4	5.6	0.9	1.4	5.7	0.93
paracetamol/codeine	0.29	1.3	-1.9	1.1	1.7	-1.7	0.71
topiramate	0.29	1.3	-0.1	0.3	0.5	0.5	2.42
R - Respiratory	**16.23**		**-0.8**	**41.1**		**-0.2**	**1.08**
beclomethasone/formoterol	2.24	13.8	9.2	3.4	8.3	9.3	1.79
salmeterol/fluticasone	2.13	13.2	-19.8	3.2	7.7	-11.7	1.84
fluticasone/vilanterol	1.88	11.6	18.0	3.0	7.2	17.4	1.74
tiotropium	1.44	8.8	-9.7	2.6	6.4	-4.7	1.50
budesonide/formoterol	1.21	7.4	17.6	1.6	3.8	22.9	2.09
beclomethasone	0.75	4.6	-36.6	2.0	5.0	-33.8	1.01
aclidinium	0.69	4.2	2.0	1.2	2.9	1.9	1.61
glycopyrrolate	0.55	3.4	-4.3	1.0	2.4	-4.3	1.51
montelukast	0.47	2.9	-1.7	2.0	4.8	-0.1	0.65
fluticasone	0.42	2.6	3.5	0.9	2.2	3.0	1.26
humeclidinium	0.37	2.3	>100	0.6	1.6	>100	1.57
budesonide	0.36	2.2	6.0	0.7	1.8	6.5	1.35
J - Antimicrobials	**13.07**		**-0.6**	**17.2**		**-0.6**	**2.09**
amoxicillin/clavulanic acid	2.87	22.0	0.2	5.8	33.6	0.4	1.36
ceftriaxone	1.28	9.8	0.7	0.3	1.7	0.6	11.74
cefixima	0.89	6.8	3.7	1.0	6.0	3.7	2.34
ciprofloxacin	0.87	6.7	-10.4	0.9	5.3	-7.3	2.61
fluconazole	0.82	6.3	1.1	0.4	2.4	1.6	5.57
levofloxacin	0.78	5.9	-2.6	1.4	8.4	-2.5	1.47
clarithromycin	0.73	5.5	-4.0	2.1	12.4	-1.3	0.93
azithromycin	0.67	5.1	2.1	1.2	7.3	2.2	1.47

Therapeutic category	Per capita gross expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17	Average cost DDD
phosphomycin	0.60	4.6	2.4	0.4	2.1	2.5	4.58
human immunoglobulin antihepatitis B	0.54	4.1	4.7	0.0	0.0	4.3	317.47
B - Blood and hematopoietic organs	**7.91**		**-2.2**	**87.1**		**0.8**	**0.25**
enoxaparin	1.78	22.5	-13.2	1.9	2.2	-12.3	2.52
acetyl salicylic acid	1.15	14.5	0.2	43.6	50.1	0.9	0.07
clopidogrel	1.02	12.9	4.6	4.9	5.6	4.1	0.57
nadroparin calcium	0.55	7.0	-17.0	0.5	0.6	-16.9	2.92
folic acid	0.47	5.9	7.3	5.7	6.6	10.1	0.22
edoxaban	0.31	3.9	>100	0.2	0.2	>100	4.67
ferrous sulphate	0.25	3.2	2.1	2.2	2.5	2.1	0.31
clopidogrel/acetylsalicylic acid	0.24	3.0	0.6	0.7	0.9	0.6	0.86
ticlopidin	0.23	2.9	-14.0	2.5	2.9	-14.1	0.25
M - Musculoskeletal	**5.71**		**-6.0**	**37.4**		**-0.8**	**0.42**
febuxostat	0.97	16.9	12.7	2.0	5.4	12.6	1.32
alendronic acid	0.72	12.6	5.0	3.6	9.7	5.2	0.54
diclofenac	0.57	9.9	-1.3	3.9	10.4	-1.7	0.40
etoricoxib	0.53	9.2	-33.6	3.0	8.2	3.3	0.47
alendronic acid/cholecalciferol	0.51	9.0	-20.1	2.4	6.4	-9.3	0.58
relocated	0.40	7.0	-4.4	2.2	6.0	-2.6	0.49
ketoprofen	0.33	5.7	-5.6	3.2	8.5	-4.8	0.28
allopurinol	0.32	5.6	3.7	7.6	20.3	3.5	0.11
G - Urinary genitalia and sex hormones	**5.64**		**-14.6**	**40.8**		**3.3**	**0.38**
tamsulosin	1.05	18.6	2.7	10.0	24.4	3.2	0.29
dutasteride	1.02	18.0	-50.0	7.8	19.1	7.1	0.36
silodosin	1.00	17.7	9.8	5.3	13.0	9.8	0.51
alfuzosin	0.79	13.9	3.3	8.3	20.3	3.6	0.26
finasteride	0.56	9.9	-2.4	2.6	6.3	-2.1	0.60
L - Antineoplastics and immunomodulators	**4.10**		**4.3**	**6.0**		**3.9**	**1.86**
letrozole	1.14	27.9	11.5	1.4	22.7	12.1	2.28
cyclosporine	0.61	14.9	-6.0	0.2	3.3	-4.9	8.30
methotrexate	0.60	14.6	7.7	1.2	19.8	5.5	1.37
anastrozole	0.41	10.0	-1.0	0.8	13.4	0.5	1.39
exemestane	0.33	8.1	14.5	0.4	6.7	15.1	2.25
H - Systemic Hormones	**3.98**		**4.9**	**35.2**		**2.1**	**0.31**
teriparatide	1.19	30.0	2.9	0.2	0.5	5.4	18.45
levothyroxine	0.96	24.2	7.4	20.3	57.7	2.1	0.13
prednisone	0.64	16.0	1.5	6.1	17.3	3.4	0.29
betametasone	0.32	8.1	3.5	2.1	6.0	3.9	0.42
methylprednisolone	0.22	5.6	0.4	3.5	9.9	0.7	0.17
S - Sense organs	**3.81**		**-0.1**	**20.5**		**2.3**	**0.51**
bimatoprost	0.46	12.1	0.9	1.9	9.1	1.9	0.67
thymol/bimatoprost	0.44	11.6	4.8	1.4	6.9	4.8	0.86
brinzolamide/stimulus	0.41	10.8	2.1	1.7	8.1	7.4	0.68
tafluprost	0.40	10.5	7.2	1.3	6.2	7.2	0.86
thymol	0.33	8.5	4.4	3.0	14.8	1.0	0.30
dorzolamide/stimulus	0.28	7.3	1.9	1.9	9.5	2.8	0.39

Therapeutic category	Per capita gross expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17	Average cost DDD
thymole/travoprost	0.22	5.8	-25.3	0.8	3.8	-9.1	0.78
latanoprost	0.21	5.4	-10.2	1.5	7.3	-4.7	0.38
travoprost	0.20	5.3	-10.5	1.0	4.9	6.4	0.55
D - Dermatological	**1.13**		**19.1**	**4.3**		**5.2**	**0.72**
calcipotriol/betametasone	0.60	53.1	44.3	1.8	42.9	36.2	0.89
diclofenac	0.08	7.2	44.1	0.1	1.9	17.1	2.66
isotretinoin	0.07	6.5	4.4	0.1	3.3	4.3	1.43
clobetasol	0.06	5.4	-11.1	0.8	19.7	-24.0	0.20
terbinafine	0.06	5.2	-4.1	0.1	2.7	-4.4	1.42
P - Pesticides	**0.22**		**3.1**	**0.9**		**2.7**	**0.67**
hydroxychloroquine	0.14	63.9	3.5	0.7	81.4	3.5	0.52
mefloquine	0.03	13.8	-2.7	0.0	0.7	-2.7	13.27
mebendazole	0.02	9.5	-0.2	0.1	10.0	-3.9	0.63
metronidazole	0.01	5.0	8.1	0.0	3.2	8.1	1.03
tinidazole	0.01	2.8	3.8	0.0	0.7	3.8	2.71
V - Miscellaneous	**0.15**		**4.6**	**0.1**		**6.6**	**3.80**
sevelamer	0.05	33.2	10.2	0.0	23.3	26.6	5.40
sodium polystyrene sulphonate	0.03	20.5	0.0	0.0	27.0	0.0	2.88
sucroferric oxidroxide	0.02	11.9	23.6	0.0	5.1	22.9	8.88
calcium polystyrene sulphonate	0.01	9.0	8.4	0.0	13.1	8.4	2.62
calcium acetate/magnesium carbonate	0.01	5.1	-4.7	0.0	19.0	-4.7	1.02

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

Table 4.8 First thirty active ingredients in terms of outpatient NHS expenditure: comparison 2018-2017

ATC	Active ingredient	Exp *(million)*	%*	Per capita expenditure	Rank 2018	Rank 2017
A	cholecalciferol	272.9	2.7	4.51	1	4
A	pantoprazole	272.3	2.7	4.50	2	1
C	atorvastatin	248.3	2.5	4.11	3	3
J	amoxicillin/clavulanic acid	173.7	1.7	2.87	4	7
A	lansoprazole	164.1	1.6	2.71	5	6
A	omeprazole	151.5	1.5	2.50	6	8
A	exomeprazole	143.5	1.4	2.37	7	10
C	bisoprolol	139.2	1.4	2.30	8	11
C	ezetimibe/simvastatin	138.3	1.4	2.29	9	5
R	beclomethasone/formoterol	135.2	1.3	2.24	10	12
R	salmeterol/fluticasone	129.1	1.3	2.13	11	9
C	ramipril	122.8	1.2	2.03	12	15
R	fluticasone/vilanterol	113.8	1.1	1.88	13	22
C	omega 3	112.7	1.1	1.86	14	17
A	mesalazine	108.4	1.1	1.79	15	18
B	enoxaparin	107.4	1.1	1.78	16	13
A	insulin lyspro	102.1	1.0	1.69	17	19
C	simvastatin	99.9	1.0	1.65	18	20
C	amlodipine	93.9	0.9	1.55	19	24
A	metformin	90.8	0.9	1.50	20	27
N	levetiracetam	90.8	0.9	1.50	21	28
C	olmesartan/amlodipine	89.9	0.9	1.49	22	25
A	insulin aspart	88.0	0.9	1.46	23	26
R	tiotropium	86.9	0.9	1.44	24	23
C	nebivolol	84.7	0.8	1.40	25	30
A	rifaximin	84.2	0.8	1.39	26	29
C	ezetimibe	83.0	0.8	1.37	27	16
N	fentanyl	79.2	0.8	1.31	28	33
J	ceftriaxone	77.6	0.8	1.28	29	32
C	rosuvastatin	77.3	0.8	1.28	30	2
	Total	**3.761.5**	**37.4**			
	Total expenditure class A-SSN	**10068.3**				

*calculated on the total of outpatient expenditure

Table 4.9. First thirty active ingredients* with greater variation of outpatient expenditure compared to the previous year: comparison 2018-2017

ATC	Active ingredient	Per capita expenditure	Δ% 18-17	DDD/1000 inhab die	Δ% 18-17
D	calcipotriol/betametasone	0.60	44.3	1.8	36.2
R	fluticasone/vilanterol	1.88	18.0	3.0	17.4
R	budesonide/formoterol	1.21	17.6	1.6	22.9
A	cholecalciferol	4.51	16.9	12.3	16.2
A	ursodeoxycholic acid	0.72	13.6	2.2	3.8
M	febuxostat	0.97	12.7	2.0	12.6
L	letrozole	1.14	11.5	1.4	12.1
G	silodosin	1.00	9.8	5.3	9.8
R	beclomethasone/formoterol	2.24	9.2	3.4	9.3
C	flecainide acetate	0.75	8.5	2.5	10.0
N	quetiapine	0.51	8.0	0.4	6.2
L	methotrexate	0.60	7.7	1.2	5.5
H	levothyroxine	0.96	7.4	20.3	2.1
N	tapentadol	1.14	7.4	0.5	7.4
C	bisoprolol	2.30	7.0	10.5	6.7
C	zofenopril	0.62	6.6	4.1	6.2
C	atorvastatin	4.11	6.1	44.1	7.2
N	levetiracetam	1.50	6.0	2.0	7.0
M	alendronic acid	0.72	5.0	3.6	5.2
J	human immunoglobulin antihepatitis B	0.54	4.7	0.0	4.3
N	sertraline	0.71	4.6	7.7	4.5
B	clopidogrel	1.02	4.6	4.9	4.1
N	duloxetine	0.72	4.4	2.9	5.7
A	mesalazine	1.79	4.1	4.5	4.9
N	fentanyl	1.31	3.7	0.6	3.9
C	zofenopril/hydrochlorothiazide	0.65	3.7	4.1	4.0
J	cefixima	0.89	3.7	1.0	3.7
A	metformin	1.50	3.6	21.6	2.3
G	alfuzosin	0.79	3.3	8.3	3.6
N	rotigotine	0.71	3.2	0.4	3.1

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

Table 4.10. First thirty active ingredients in terms of outpatient NHS consumption: comparison 2018-2017

ATC	Active ingredient	DDD/1000 inhab die	%*	Rank 2018	Rank 2017
C	ramipril	61.8	6.3	1	1
C	atorvastatin	44.1	4.5	2	3
B	acetyl salicylic acid	43.6	4.5	3	2
C	amlodipine	26.5	2.7	4	4
C	furosemide	24.5	2.5	5	5
A	metformin	21.6	2.2	6	6
A	pantoprazole	21.5	2.2	7	7
H	levothyroxine	20.3	2.1	8	8
A	omeprazole	16.5	1.7	9	9
C	nebivolol	15.0	1.5	10	11
A	lansoprazole	14.5	1.5	11	10
C	simvastatin	13.8	1.4	12	13
C	valsartan	13.3	1.4	13	12
A	exomeprazole	12.7	1.3	14	14
A	cholecalciferol	12.3	1.3	15	16
C	rosuvastatin	12.2	1.2	16	15
C	bisoprolol	10.5	1.1	17	18
C	olmesartan	10.2	1.0	18	24
G	tamsulosin	10.0	1.0	19	20
C	enalapril	9.3	0.9	20	19
C	lercanidipine	9.3	0.9	21	21
C	valsartan/hydrochlorothiazide	9.0	0.9	22	17
C	telmisartan	8.7	0.9	23	23
C	atenololol	8.4	0.9	24	22
B	cyanocobalamin	8.3	0.9	25	30
G	alfuzosin	8.3	0.8	26	27
C	candesartan	8.2	0.8	27	26
C	irbesartan	8.2	0.8	28	25
C	olmesartan/hydrochlorothiazide	8.1	0.8	29	35
G	dutasteride	7.8	0.8	30	34
	Total	**498.4**	**50.9**		
	Total DDD class A-SSN	**978.8**			

* calculated on the total of outpatient expenditure

Table 4.11. Consumption and expenditure of medicines purchased by public health facilities for the year 2018: most frequently prescribed active ingredients for ATC level I categories (up to 75% of expenditure within the therapeutic category)

ATC I level	Per capita expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17
L - Antineoplastics and immunomodulators	**89.46**		**9.7**	**9.5**		**4.1**
adalimumab	4.77	5.3	1.5	0.4	4.4	9.3
nivolumab	4.41	4.9	47.0	0.1	0.7	51.8
trastuzumab	4.05	4.5	-12.3	0.2	2.2	0.4
lenalidomide	3.55	4.0	6.2	0.1	0.9	15.2
drinkzumab	3.22	3.6	-12.4	0.1	1.3	-7.8
pembrolizumab	3.21	3.6	>100	0.1	1.0	>100
ethanercept	2.68	3.0	-11.2	0.3	3.0	2.2
fingolimod	2.28	2.5	9.9	0.1	1.2	9.4
rituximab	2.17	2.4	-29.3	0.5	5.3	-8.3
pertuzumab	2.08	2.3	24.3	0.0	0.4	24.3
dimethylfumarate	1.94	2.2	16.9	0.2	1.7	16.9
ibrutinib	1.84	2.1	37.4	0.0	0.4	45.1
interferon beta 1a	1.66	1.9	-14.2	0.4	4.3	-10.2
abiraterone	1.60	1.8	-1.9	0.1	0.5	8.8
natalizumab	1.49	1.7	10.2	0.1	0.8	10.2
ustekinumab	1.44	1.6	8.2	0.2	1.8	14.9
secukinumab	1.35	1.5	62.2	0.1	1.2	62.0
infliximab	1.25	1.4	-16.7	0.3	3.3	5.1
palbocyclicliib	1.24	1.4	>100	0.0	0.4	>100
golimumab	1.23	1.4	0.3	0.1	1.2	1.8
dasatinib	1.22	1.4	1.8	0.0	0.3	1.7
daratumumab	1.17	1.3	>100	0.0	0.2	>100
nilotinib	1.16	1.3	4.2	0.0	0.3	4.5
enzalutamide	1.14	1.3	39.6	0.0	0.4	38.8
eculizumab	1.11	1.2	-36.0	0.0	0.1	6.5
ruxolitinib	1.09	1.2	15.6	0.0	0.3	49.6
abatacept	1.04	1.2	9.9	0.1	0.6	9.1
leuprorelin	1.00	1.1	1.9	0.2	2.0	-1.0
bortezomib	0.96	1.1	-23.1	0.1	1.1	-4.9
glatiramer	0.94	1.1	-15.7	0.1	1.0	-9.5
imatinib	0.92	1.0	-47.0	0.1	1.0	-8.3
azocydine	0.90	1.0	10.0	0.0	0.1	10.0
sunitinib	0.88	1.0	-3.9	0.0	0.1	-3.9
pemetrexed	0.87	1.0	-17.3	0.0	0.3	-16.5
trastuzumab emtansine	0.83	0.9	-7.9	0.0	0.1	0.0
tocilizumab	0.81	0.9	-2.9	0.1	0.8	10.6
pyrfenidone	0.76	0.9	19.4	0.0	0.3	19.4
triptorelin	0.76	0.9	6.6	0.8	8.2	7.0
tacrolimus	0.76	0.8	4.0	0.3	3.2	1.4
nintedanib	0.75	0.8	99.0	0.0	0.2	68.7
dabrafenib	0.75	0.8	20.2	0.0	0.1	26.4
J - Antimicrobials	**35.16**		**-21.2**	**6.2**		**0.5**
glecaprevir/pibrentasvir	3.58	10.2	>100	0.1	1.2	>100
sofosbuvir/velpatasvir	2.27	6.5	-12.2	0.1	1.3	22.3
group B meningococcal vaccine	1.83	5.2	-6.6	0.1	1.3	-3.9
pneumococcal vaccine conjugated saccharide	1.59	4.5	-2.9	0.1	1.4	-3.1

ATC I level	Per capita expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17
adsorbed saccharide						
dolutegravir/abacavir/lamivudine	1.51	4.3	45.9	0.2	3.0	39.2
elvitegravir/cobicistat/emtricitabina/tenofovir alafenamide	1.41	4.0	>100	0.1	2.3	>100
emtricitabine/rilpivirine/tenofovir alafenamide	1.32	3.7	>100	0.2	2.9	>100
dolutegravir	1.17	3.3	46.8	0.2	3.1	40.4
emtricitabine/tenofovir alafenamide	1.09	3.1	>100	0.2	3.9	>100
hexavalent vaccine	0.96	2.7	-8.7	0.1	1.0	-0.3
normal human immunoglobulin for extravascular administration	0.91	2.6	18.4	0.0	0.1	-2.0
elbasvir/grazoprevir	0.83	2.4	-42.9	0.0	0.4	-19.0
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	0.82	2.3	>100	0.0	0.5	>100
darunavir/cobicistat	0.82	2.3	41.4	0.2	2.9	41.4
human immunoglobulin intravenous use	0.80	2.3	4.5	0.0	0.1	-1.7
raltegravir	0.68	1.9	-14.6	0.2	2.6	5.8
entecavir	0.57	1.6	-60.6	0.4	6.0	13.8
measles vaccine of rubella mumps and chickenpox	0.55	1.6	21.0	0.0	0.5	28.2
meningococcal vaccine ACWY	0.49	1.4	-28.8	0.0	0.6	-23.9
amphotericin b	0.48	1.4	7.4	0.0	0.2	4.0
emtricitabine/rilpivirine/tenofovir disoproxil	0.45	1.3	-64.9	0.1	1.0	-64.9
darunavir	0.41	1.2	-37.0	0.1	1.0	-37.1
caspofungin	0.40	1.1	-42.4	0.0	0.1	18.5
piperacillin/tazobactam	0.38	1.1	37.0	0.1	1.6	-11.1
tigecycline	0.37	1.1	-15.8	0.0	0.2	3.6
posaconazole	0.37	1.1	8.6	0.0	0.2	-0.6
inactivated split virione influenza vaccine	0.37	1.1	55.6	0.2	2.6	52.6
B - Blood and hematopoietic organs	**26.52**		**0.5**	**42.8**		**9.2**
factor VIII	4.87	18.3	-3.7	0.0	0.1	-3.4
apixaban	2.53	9.6	12.9	2.9	6.7	27.5
rivaroxaban	2.12	8.0	12.2	3.2	7.4	14.0
dabigatran	1.47	5.6	-6.0	2.1	5.0	20.9
epoetin alpha	1.45	5.5	-4.4	1.7	3.9	-1.0
enoxaparin	1.32	5.0	-12.5	5.2	12.2	2.7
darbepoetin alpha	1.15	4.4	-13.6	0.5	1.2	-12.1
ticagrelor	0.83	3.1	14.8	0.9	2.2	14.8
edoxaban	0.70	2.6	>100	0.8	2.0	>100
activated heptacog alpha (recombinant DNA coagulation factor VII)	0.63	2.4	-37.3	0.0	0.0	-37.7
treprostinyl	0.63	2.4	3.5	0.0	0.0	3.2
sodium chloride	0.61	2.3	0.6	5.4	12.7	17.6
elthrombopag olamine	0.59	2.2	27.4	0.0	0.1	39.0
albutrepenonacog alpha	0.51	1.9	>100	0.0	0.0	>100
epoetin zeta	0.43	1.6	26.9	0.9	2.1	49.3
activated human prothrombinic antihemophilic complex	0.36	1.3	-18.7	0.0	0.0	-18.3
A - Gastrointestinal and metabolism	**13.87**		**10.0**	**29.1**		**-6.0**
insulin glargo	1.55	11.2	0.7	4.3	14.6	3.4
recombinant human acid alglucosidase	1.10	7.9	4.9	0.0	0.0	5.0
agalsidase alpha	0.87	6.3	4.4	0.0	0.0	4.3

ATC I level	Per capita expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17
imiglucerase	0.84	6.1	-3.6	0.0	0.0	-3.6
liraglutide	0.64	4.6	7.8	0.8	2.6	10.8
sitagliptin/metformin	0.56	4.0	1.3	1.4	4.8	8.1
insulin degludec	0.55	4.0	12.5	1.1	3.6	11.2
hydrosulphase	0.53	3.8	6.3	0.0	0.0	6.2
agalsidase beta	0.51	3.7	13.2	0.0	0.0	13.3
dulaglutide	0.49	3.6	48.6	0.7	2.2	68.7
sitagliptin	0.48	3.5	11.4	1.0	3.6	15.5
linagliptin	0.40	2.9	23.3	0.9	3.2	28.6
pioglitazone/metformin	0.30	2.2	-5.7	0.8	2.9	-5.5
vildagliptin/metformin	0.26	1.9	-6.0	0.7	2.3	0.8
velaglucerase alpha	0.26	1.9	4.9	0.0	0.0	4.9
empagliflozin	0.24	1.7	55.1	0.5	1.8	61.4
elosulfase alpha	0.24	1.7	14.0	0.0	0.0	3.7
dapagliflozin/metformin	0.20	1.4	77.5	0.4	1.4	77.3
Insulin Detemir	0.18	1.3	-29.6	0.4	1.4	-27.0
dapagliflozin	0.18	1.3	51.5	0.4	1.3	51.1
exenatid	0.18	1.3	-3.9	0.2	0.5	-3.8
N - Nervous system	**6.94**		**1.1**	**24.2**		**5.2**
paliperidone	1.41	20.3	16.4	0.7	2.8	17.1
aripiprazole	0.78	11.2	18.2	0.9	3.7	7.5
levodopa/carbidopa	0.42	6.0	-4.0	0.1	0.4	-2.2
risperidone	0.41	5.9	-9.8	0.7	2.7	-7.7
methadone	0.30	4.3	-4.1	2.3	9.6	-3.8
quetiapine	0.23	3.3	-28.6	1.4	5.8	-0.3
tafamidis meglumine	0.20	2.8	31.8	0.0	0.0	30.6
buprenorfine/naloxone	0.19	2.8	1.2	0.2	0.8	3.2
levetiracetam	0.17	2.5	-9.9	0.4	1.6	3.6
rivastigmine	0.16	2.4	-6.1	0.5	1.9	-1.2
sevoflurane	0.15	2.2	8.5	0.0	0.0	15.4
dexmedetomidine	0.13	1.9	33.1	0.0	0.1	34.3
olanzapine	0.13	1.9	2.6	1.6	6.5	3.5
sodium oxybate	0.11	1.6	2.0	0.1	0.5	1.8
propofol	0.11	1.6	11.5	0.4	1.5	20.5
delta-9-tetrahydrocannabinol/cannabidiol	0.10	1.5	0.7	0.0	0.1	1.7
lidocaine	0.09	1.3	1.2	1.2	4.9	-5.4
paracetamol	0.09	1.3	-14.9	2.0	8.3	>100
lacosamide	0.08	1.1	30.3	0.0	0.1	25.1
V - Miscellaneous	**5.33**		**3.7**	**3.1**		**2.3**
deferasirox	1.33	25.0	18.5	0.0	1.1	-1.6
sugammadex	0.60	11.2	17.2	0.0	0.6	17.2
iomeprole	0.43	8.1	10.2	0.0	0.6	5.5
fluorine-18f-deoxyglucose	0.26	4.9	-1.1	0.0	0.1	-29.0
iodixanol	0.24	4.4	2.1	0.0	0.3	2.6
iodine 123	0.16	3.0	4.9	0.0	0.0	2.7
iopromide	0.15	2.8	-9.9	0.0	0.3	-12.9
gadobutrol	0.14	2.6	7.8	0.0	0.2	8.3
iobitridol	0.13	2.5	1.9	0.0	0.3	2.7
sevelamer	0.13	2.4	-25.1	0.1	4.5	-5.0
sodium molybdate (99 mo)	0.12	2.2	-2.2	0.0	0.0	3.6
lanthanum carbonate hydrate	0.11	2.1	-9.0	0.0	1.5	-9.0

ATC I level	Per capita expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17
deferiprone	0.11	2.0	-5.8	0.0	0.6	-5.6
rasburicase	0.10	1.9	16.0	0.0	0.0	13.8
H - Systemic Hormones	**4.62**		**0.3**	**5.2**		**-4.3**
somatropin	1.39	30.2	-0.2	0.3	5.0	0.9
octreotide	0.76	16.5	-3.7	0.1	2.1	-3.1
lanreotide	0.55	12.0	6.6	0.1	1.5	7.7
cinacalcet	0.53	11.4	-0.3	0.1	2.2	0.2
pegvisomant	0.40	8.7	0.2	0.0	0.3	1.4
C - Cardiovascular	**4.59**		**-7.0**	**16.9**		**-3.2**
ranolazine	1.13	24.6	18.5	1.1	6.4	18.6
macitentan	0.78	17.1	13.2	0.0	0.1	7.9
sacubitril/valsartan	0.34	7.5	>100	0.2	1.4	>100
ivabradine	0.29	6.4	-58.9	1.2	6.9	-18.8
bosentan	0.27	6.0	-75.8	0.0	0.2	-13.2
ambrisentan	0.27	5.8	5.0	0.0	0.1	4.6
evolocumab	0.24	5.1	>100	0.0	0.2	>100
alirocumab	0.18	3.9	>100	0.0	0.3	>100
M - Musculoskeletal	**3.11**		**103.7**	**4.6**		**8.0**
nusinersen	1.52	49.0	>100	0.0	0.2	>100
denosumab	0.84	27.2	18.0	2.7	59.1	14.2
clostridium botulinum toxin type A	0.24	7.9	8.5	0.0	0.1	12.2
ataluren	0.19	6.2	38.1	0.0	0.0	46.6
zoledronic acid	0.06	1.9	19.3	0.0	0.1	-23.3
R - Respiratory	**3.05**		**44.9**	**2.5**		**1.7**
snail/ivacaftor	0.87	28.6	>100	0.0	0.2	>100
omalizumab	0.71	23.3	18.5	0.1	3.0	18.9
ivacaftor	0.48	15.9	1.3	0.0	0.1	6.0
mepolizumab	0.33	10.8	>100	0.0	1.0	>100
deoxyribonuclease	0.19	6.1	11.4	0.0	1.0	11.5
S - Sense organs	**2.81**		**-7.9**	**2.8**		**8.0**
ranibizumab	1.21	43.0	10.6	0.1	4.4	10.8
aflibercept	0.95	33.8	14.7	0.2	8.7	14.6
dexamethasone	0.32	11.5	-4.6	0.2	7.3	-4.9
cenegermin	0.06	2.1	0.0	0.0	0.0	0.0
cefuroxime	0.03	1.2	30.5	0.0	0.5	29.0
G - Urinary genitalia and sex hormones	**1.57**		**-15.4**	**1.9**		**-2.2**
follitropin alpha from recombinant DNA	0.41	26.3	-16.3	0.1	2.8	-8.0
menotropin	0.22	13.9	1.4	0.0	2.3	2.4
tadalafil	0.15	9.6	-18.0	0.2	8.2	17.7
follitropin beta	0.14	8.8	-17.0	0.0	0.7	-17.1
sildenafil	0.11	6.9	-40.1	0.0	2.4	2.5
dinoprostone	0.09	5.9	1.1	0.0	2.5	0.4
follitropin alpha/lutropin alpha	0.09	5.7	49.2	0.0	0.2	49.1
D - Dermatological	**0.39**		**10.0**	**8.4**		**-34.3**
iodopovidone	0.06	14.3	1.1	0.8	8.9	-86.1
chlorhexidine / benzalkonium	0.05	13.1	-1.4	1.6	19.0	11.6
silver sulfadiazine	0.05	12.8	15.5	0.7	8.0	3.2
sodium hypochlorite	0.04	9.0	2.2	2.6	30.3	0.6
hyaluronan	0.03	7.7	4.3	0.2	2.8	3.6
aqueous extract of triticum vulgare	0.02	5.6	36.2	0.1	1.2	36.8
imiquimod	0.02	5.0	11.8	0.1	0.6	14.3

ATC I level	Per capita expenditure	%*	Δ % 18-17	DDD/1000 inhab die	%*	Δ % 18-17
dupilumab	0.02	4.2	0.0	0.0	0.0	0.0
silver sulfadiazine/hyaluronic acid	0.01	2.8	-9.2	0.2	2.6	-0.6
chlorhexidine	0.01	2.0	-2.6	0.3	3.2	-32.9
P - Pesticides	**0.03**		**-5.3**	**<0.05**		**-9.5**
atovaquone	0.01	54.1	15.7	0.0	9.2	15.7
atovaquone/proguanile	0.00	15.0	18.2	0.0	4.8	9.7
permethrin	0.00	11.4	-56.9	0.0	2.7	-65.2
hydroxychloroquine	0.00	5.4	-5.6	0.0	40.7	-4.4
pentamidine isationate	0.00	4.9	7.6	0.0	1.2	7.7

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

Table 4.12. First thirty active active ingredients purchased by public health facilities in terms of expenditure: comparison 2018-2017

ATC	Active ingredient	Exp (million)	%*	Per capita expenditure	Rank 2018	Rank 2017
B	factor VIII	294.3	2.5	4.87	1	1
L	adalimumab	288.8	2.4	4.77	2	3
L	nivolumab	266.6	2.2	4.41	3	10
L	trastuzumab	245.1	2.1	4.05	4	4
J	glecaprevir/pibrentasvir	216.4	1.8	3.58	5	126
L	lenalidomide	214.8	1.8	3.55	6	7
L	drinkzumab	194.9	1.6	3.22	7	6
L	pembrolizumab	194.3	1.6	3.21	8	50
L	ethanercept	162.1	1.4	2.68	9	9
B	apixaban	153.3	1.3	2.53	10	12
L	fingolimod	137.8	1.2	2.28	11	13
J	sofosbuvir/velpatasvir	137.3	1.2	2.27	12	11
L	rituximab	131.3	1.1	2.17	13	8
B	rivaroxaban	128.4	1.1	2.12	14	16
L	pertuzumab	125.8	1.1	2.08	15	19
L	dimethylfumarate	117.6	1.0	1.94	16	20
L	ibrutinib	111.6	0.9	1.84	17	32
J	group B meningococcal vaccine	110.8	0.9	1.83	18	14
L	interferon beta 1a	100.3	0.8	1.66	19	15
L	abiraterone	96.6	0.8	1.60	20	22
J	pneumococcal vaccine	96.4	0.8	1.59	21	21
A	insulin glargo	93.9	0.8	1.55	22	24
M	nusinersen	92.1	0.8	1.52	23	242
J	dolutegravir/abacavir/lamivudine	91.3	0.8	1.51	24	49
L	natalizumab	89.9	0.8	1.49	25	31
B	dabigatran	89.2	0.7	1.47	26	23
B	epoetin alpha	87.8	0.7	1.45	27	25
L	ustekinumab	87.1	0.7	1.44	28	34
J	elvitegravir/cobicistat/emtricitabina/tenofovir alafenamide	85.3	0.7	1.41	29	98
N	paliperidone	85.0	0.7	1.41	30	38
	Total	**4.326.1**	**36.2**			
	Total expenditure on health care facilities	**11.942.2**				

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

Table 4.13. First thirty active ingredients* purchased by public health facilities with greater variation of expenditure compared to the previous year: comparison 2018-2017

ATC	Active ingredient	Per capita expenditure	Δ% 18/17	DDD/1000 inhab die	Δ% 18/17
L	palbociclib	1.24	>100	0.0	>100
M	nusinersen	1.52	>100	0.0	>100
J	glecaprevir/pibrentasvir	3.58	>100	0.1	>100
J	emtricitabine/rilpivirine/tenofovir alafenamide	1.32	>100	0.2	>100
J	human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	0.82	>100	0.0	>100
L	daratumumab	1.17	>100	0.0	>100
L	osimertinib	0.67	>100	0.0	>100
L	pembrolizumab	3.21	>100	0.1	>100
J	emtricitabine/tenofovir alafenamide	1.09	>100	0.2	>100
R	lumacaftor/ivacaftor	0.87	>100	0.0	>100
B	edoxaban	0.70	>100	0.8	>100
J	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	1.41	>100	0.1	>100
L	nintedanib	0.75	99.0	0.0	68.7
L	secukinumab	1.35	62.2	0.1	62.0
L	vedolizumab	0.73	59.7	0.1	51.3
L	nivolumab	4.41	47.0	0.1	51.8
J	dolutegravir	1.17	46.8	0.2	40.4
J	dolutegravir/abacavir/lamivudine	1.51	45.9	0.2	39.2
L	carfilzomib	0.68	43.1	0.0	42.7
J	darunavir/cobicistat	0.82	41.4	0.2	41.4
L	enzalutamide	1.14	39.6	0.0	38.8
L	ibrutinib	1.84	37.4	0.0	45.1
B	eltrombopag	0.59	27.4	0.0	39.0
L	pertuzumab	2.08	24.3	0.0	24.3
L	dabrafenib	0.75	20.2	0.0	26.4
L	pirfenidone	0.76	19.4	0.0	19.4
V	deferasirox	1.33	18.5	0.0	-1.6
R	omalizumab	0.71	18.5	0.1	18.9
C	ranolazine	1.13	18.5	1.1	18.6
J	human normal immunoglobulin for extravascular administration	0.91	18.4	0.0	-2.0

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

Section 5

Detailed analysis of pharmaceutical expenditure and consumption

National Report
on Medicines
use in Italy
Year 2018

5.2 Therapeutic categories

The following pages present an in-depth analysis on the following categories:

- Cancer drugs
- Drugs for hypertension and heart failure
- Immunosuppressants and immunomodulators
- Anti-aggregants and anticoagulants
- Antiasthmatics
- Antidiabetics
- Lipid-lowering
- Antacids and antiulcer
- Antibiotics
- Anti-HIV
- Medicines for multiple sclerosis
- Drugs for osteoporosis
- Vaccines
- Coagulation factors
- Anti-HCV
- Pain therapy
- Drugs for eye disorders
- Antidepressants
- Drugs for genitourinary disorders
- Antipsychotics
- Antiparkinsonian products
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Cystic fibrosis drugs
- Thyroid drugs
- Anti-dementia drugs

For each category the time trend of consumption (DDD /1000 inhabitants per day) was analysed in the 2013-2018 period; the same analysis is presented for the main therapeutic subgroups, for the 10 substances with the highest expenditure in 2018 and for all the Regions. The data of the various categories refer both to the provision of an agreed assistance scheme and to the purchase of medicines by public health facilities. As regards the agreed assistance, gross expenditure was considered, including cost-sharings and discounts. Data relating to expenditure borne by citizens were included only for the analysis of consumption and of vaccine expenditure.
The 2018 prescription levels and their variation compared to the previous year are presented for the whole group, by therapeutic subgroups, by substances and by Region. Where consumption was not representative of the trend in the category prescription (values below 0.05 DDD / 1000 inhabitants per day), the expenditure trend was provided.
The in-depth study concludes with an analysis of regional variability of consumption (DDD/ 1000 inhabitants per day) and of per capita expenditure. For some therapeutic categories, the analyses of consumption variability in the main subgroups as well a
consumption and prevalence in the population and some indicators of intensity of use are also presented.

Table 5.2.1 Largest prescription pharmaceutical groups in 2018

Group Subgroup	Total expenditure (in mil)	% on NHS expenditure	Per capita expenditure	Δ% 18-17	DDD/ 1000 inhab day	Δ% 18-17
Cancer Drugs	**3,365.0**	**15.3**	**55.63**	**14.2**	**9.8**	**2.9**
Monoclonal antibodies	1,458.0	6.6	24.11	18.4	1.1	6.8
Tyrosin kinase inhibitors	923.6	4.2	15.27	18.7	0.4	18.2
Cytostatic antineoplastics - cytostatic – others	172.3	0.8	2.85	-1.7	0.4	1.4
Cytostatic antineoplastics – antimetabolites	156.7	0.7	2.59	2.2	0.6	-5.2
Endocrine therapy - aromatase inhibitors	117.1	0.5	1.94	8.9	3.1	7.0
Endocrine therapy - hormones and GnRH analogs	112.9	0.5	1.87	3.9	1.0	4.8
Endocrine therapy - other hormonal antagonists	104.5	0.5	1.73	-0.8	0.1	12.1
Endocrine therapy - antiandrogens	82.3	0.4	1.36	31.0	1.0	-6.2
Antineoplastic -Other	50.8	0.2	0.84	72.2	<0.05	64.5
Cytotoxic antineoplastics - products derived from natural-taxanes	47.1	0.2	0.78	6.1	0.2	-5.6
Endocrine therapy - anti-estrogens	43.6	0.2	0.72	8.3	1.1	-1.1
Cytotoxic antineoplastics - products of natural derivation - other	33.5	0.2	0.55	-0.7	0.1	-2.3
Cytotoxic antineoplastics - cytotoxic-anthracycline antibiotics and related substances	26.5	0.1	0.44	-7.9	0.1	-4.9
Cytostatic antineoplastics - alkylating agents	25.1	0.1	0.42	-27.9	0.2	6.4
Cytotoxic antineoplastics - cytotoxic antibiotics - other	5.5	0.0	0.09	-1.1	0.1	1.5
Cytostatic antineoplastics - platinum compounds	5.5	0.0	0.09	-25.7	0.2	-5.6
Hypertension and heart failure pharmaceuticals	**2,013.8**	**9.1**	**33.29**	**-1.4**	**372.5**	**0.1**
Beta blocking agents	310.9	1.4	5.14	3.2	43.6	1.3
Calcium channel blockers (dihydropyridines)	259.3	1.2	4.29	-1.3	50.8	-0.6
Ace inhibitors	236.1	1.1	3.90	-1.0	86.7	-0.8
Angiotensin II receptor blockers (ARBs)	201.2	0.9	3.33	-1.9	46.7	-2.4
Angiotensin II receptor blockers and diuretics (combinations)	200.6	0.9	3.32	-5.5	27.9	-5.6
ACE inhibitors and diuretics (combinations)	166.1	0.8	2.75	-3.1	21.4	-3.1
ACE inhibitors and calcium channel blockers (combinations)	99.3	0.5	1.64	-5.1	11.1	5.7
Olmesartan+amlodipin	89.9	0.4	1.49	-2.8	5.5	15.3
Alpha-adrenoreceptor antagonists	74.1	0.3	1.22	-0.4	7.6	-0.4
Olmesartan	73.4	0.3	1.21	-10.9	10.2	18.3
High-ceiling diuretics, plain or in combination with potassium-sparing agents	62.4	0.3	1.03	-1.4	30.3	-0.6
Olmesartan+Hydrochlorothiazide	60.3	0.3	1.00	-15.7	8.1	12.4
Beta blocking agents and diuretics (combinations)	41.3	0.2	0.68	-10.0	7.4	2.0
Potassium-sparing diuretics	32.6	0.1	0.54	2.1	3.5	0.6
Angiotensin II receptor blockers and neprilysin inhibitor	27.6	0.1	0.46	>100	0.3	>100
ACE inhibitors, other combinations	24.5	0.1	0.40	24.7	2.3	46.4
Calcium channel blockers (not dihydropyridines)	21.7	0.1	0.36	-8.5	2.5	-8.6
Thiazides and similars (including combinations)	14.9	0.1	0.25	-2.1	4.6	-2.9
Alpha-2 adrenergic agonists	13.1	0.1	0.22	-4.9	1.6	-5.2
Aliskiren plain or in combination	4.4	0.0	0.07	-14.9	0.2	-15.4

Group Subgroup	Total expenditure (in mil)	% on NHS expen diture	Per capita expen diture	Δ% 18-17	DDD/ 1000 inhab day	Δ% 18-17
Immunosuppressants and immunomodulators	**1,642.7**	**7.5**	**27.16**	**2.8**	**3.1**	**8.8**
Tumor necrosis factor alpha (TNFα) inhibitors	635.6	2.9	10.51	-3.9	1.2	6.0
Other Immunosuppressants and immunomodulators	321.0	1.5	5.31	6.9	0.1	13.6
Interleukin inhibitors	268.0	1.2	4.43	28.6	0.4	33.2
Selective immunosuppressants	267.6	1.2	4.42	-0.2	0.7	12.8
Calcineurin inhibitors	92.8	0.4	1.53	0.5	0.6	-0.9
Growth factors (G-CSF)	51.2	0.2	0.85	-12.5	0.1	-2.6
Interferons	6.5	0.0	0.11	-21.8	<0.05	-22.8
Antiplatelet agents and anticoagulants	**1,062.0**	**4.8**	**17.56**	**3.5**	**94.0**	**1.8**
New Oral Anticoagulant (NOA)	445.2	2.0	7.36	17.8	9.4	27.6
Low molecular weight heparins	256.3	1.2	4.24	-13.1	8.9	-3.8
Platelet aggregation inhibitors excluding clopidogrel, prasugrel and ticagrelor	133.6	0.6	2.21	2.3	58.9	-0.7
Clopidogrel plain or in combination	69.8	0.3	1.15	4.5	10.2	9.7
Antiplatelet agents with vasodilating effect	55.6	0.3	0.92	2.8	<0.05	-0.9
Ticagrelor	52.1	0.2	0.86	15.2	1.0	14.7
Fondaparinux	16.4	0.1	0.27	-3.2	0.5	-2.0
Vitamin K antagonists	11.4	0.1	0.19	-10.1	4.6	-10.1
Heparin	9.9	0.0	0.16	-4.0	0.4	-5.5
Prasugrel	5.5	0.0	0.09	-20.0	0.2	-24.5
Glycoprotein IIb/IIIa inhibitors	3.7	0.0	0.06	-42.3	<0.05	-12.4
Antithrombin III	2.5	0.0	0.04	-25.0	<0.05	-10.9
Antiasthmatics	**980.7**	**4.5**	**16.21**	**-0.2**	**33.5**	**-0.3**
Beta2 agonists in combination	544.0	2.5	8.99	3.1	14.2	5.4
Bronchodilators - anticholinergics	193.4	0.9	3.20	0.4	6.6	2.7
Anti-inflammatory - cortisone inhal.	119.2	0.5	1.97	-13.8	5.5	-11.0
Bronchodilators - beta-2-adrenoreceptor agonists	47.5	0.2	0.78	-9.7	4.5	-4.5
Other antiasthmatic	43.6	0.2	0.72	17.7	0.1	11.2
Antagonists of leukotrienic receptors	28.3	0.1	0.47	-2.3	2.0	-0.4
Bronchodilators - theophylline	4.0	0.0	0.07	-9.6	0.5	-14.4
Anti-inflammatories - chromones	0.7	0.0	0.01	-41.5	<0.05	-43.5
Antidiabetics	**945.4**	**4.3**	**15.63**	**4.7**	**63.2**	**0.8**
Insulins and analogues	424.9	1.9	7.03	-2.3	15.3	-0.4
Gliptins (DPP-4 inhibitors) plain or in combination	150.1	0.7	2.48	4.4	5.7	10.1
Glucagon-like peptide 1 (GLP-1) analogues	98.3	0.4	1.62	22.6	1.7	28.9
Metformin	91.5	0.4	1.51	3.7	22.1	2.0
Gliflozine plain or in combination	62.8	0.3	1.04	42.6	2.1	50.5
Other oral hypoglycemic agents	52.7	0.2	0.87	-6.7	11.9	-9.3
Pioglitazone plain and in combination	28.7	0.1	0.48	-6.0	1.7	-3.6
Repaglinide	21.7	0.1	0.36	-11.1	2.6	-11.8
Insulins in combination with GLP-1	14.8	0.1	0.25	>100	0.1	>100
Lipid lowering agents	**870.5**	**4.0**	**14.39**	**-20.1**	**92.5**	**4.2**
Statins	477.8	2.2	7.90	-25.0	77.4	3.3
Ezetimibe plain or in combination	225.1	1.0	3.72	-26.2	8.1	13.2
Omega 3	112.8	0.5	1.86	0.3	4.3	5.2
PCSK9 inhibitor	25.0	0.1	0.41	>100	0.1	>100

Group Subgroup	Total expenditure (in mil)	% on NHS expenditure	Per capita expenditure	Δ% 18-17	DDD/ 1000 inhab day	Δ% 18-17
Fibrates	22.9	0.1	0.38	2.5	2.7	3.0
MTP inhibitors	6.9	0.0	0.11	16.3	<0.05	31.9
Statins and fibrates	<0.05	0.0	0.00	-76.0	<0.05	-75.0
Antacids and anti-ulcer	**866.2**	**3.9**	**14.32**	**-5.0**	**79.4**	**-0.6**
Proton pump inhibitors	765.7	3.5	12.66	-5.2	70.9	-0.8
Other drugs for peptic ulcer	52.3	0.2	0.87	1.9	4.1	1.7
Antacids	26.0	0.1	0.43	2.4	2.0	2.7
H2 receptor antagonists	21.5	0.1	0.36	-18.0	2.3	-0.1
Prostaglandins	0.6	0.0	0.01	-10.2	<0.05	-9.6
Antibiotics	**864.3**	**3.9**	**14.29**	**-0.6**	**18.0**	**-0.4**
Penicillin associations (including beta lactamase inhibitors)	213.0	1.0	3.52	3.1	6.3	0.2
Quinolones	127.4	0.6	2.11	-4.8	3.0	-5.0
Cephalosporins im / ev III-IV gen	109.6	0.5	1.81	3.2	0.6	6.9
Antibiotics vs resistant germs	71.1	0.3	1.18	1.3	0.1	18.9
Other antibiotics	54.5	0.2	0.90	-0.6	0.4	4.5
Glycopeptides	30.9	0.1	0.51	-24.1	0.1	-1.9
Broad-spectrum penicillins and penicillins sensitive to beta lactamases	18.7	0.1	0.31	2.5	1.2	-4.8
Carbapenems	14.8	0.1	0.24	-3.9	<0.05	39.8
Aminoglycosides	12.5	0.1	0.21	2.1	0.1	-3.1
Cephalosporins im / ev I gen	6.5	0.0	0.11	-7.3	0.1	1.4
Tetracyclines	4.6	0.0	0.08	3.7	0.3	4.6
Sulfonamides and trimetropim	4.2	0.0	0.07	4.1	0.4	3.6
Cephalosporins im / ev II gen	4.0	0.0	0.07	-1.7	0.1	-4.5
Monobactams	2.4	0.0	0.04	-11.4	<0.05	-11.4
Anti-HIV anti-virals	**672.1**	**3.1**	**11.11**	**-3.1**	**2.4**	**0.3**
Anti-HIV anti-virals in coformulated regimens	306.5	1.4	5.07	19.5	0.6	18.3
Nucleosides and nucleotides inhibitors of reverse transcriptase	114.8	0.5	1.90	-33.4	0.9	-7.1
Integrase inhibitors	111.8	0.5	1.85	10.8	0.4	19.5
Protease inhibitors plain or in combination	110.6	0.5	1.83	-13.5	0.4	-12.5
Non-nucleoside inhibitors of reverse transcriptase	19.2	0.1	0.32	-23.2	0.2	-13.8
Other anti-HIV antivirals	9.2	0.0	0.15	-16.6	0.0	-15.5
Multiple sclerosis pharmaceuticals	**642.2**	**2.9**	**10.62**	**2.9**	**2.6**	**1.8**
Immunosuppressants	161.7	0.7	2.67	13.7	1.8	4.8
Fingolimod	137.8	0.6	2.28	9.9	0.1	9.4
Interferons	132.3	0.6	2.19	-12.9	0.5	-10.3
Monoclonal antibody	110.9	0.5	1.83	9.6	0.1	13.3
Glatiramer	57.1	0.3	0.94	-15.7	0.1	-9.5
Teriflunomide	42.4	0.2	0.70	18.0	0.1	18.6
Osteoporosis pharmaceuticals	**590.7**	**2.7**	**9.77**	**7.7**	**32.8**	**6.1**
Vitamin D and analogues	329.4	1.5	5.45	14.5	19.3	10.0
Teriparatide	86.1	0.4	1.42	1.0	0.2	2.7
Oral and injectable bisphosphonates	84.6	0.4	1.40	-0.2	6.7	0.7
Denosumab	51.7	0.2	0.85	18.3	2.7	14.4
Alendronic acid + colecalciferol	31.1	0.1	0.51	-20.1	2.4	-9.3
Calcium	7.1	0.0	0.12	-0.3	1.4	-1.5

Group Subgroup	Total expenditure (in mil)	% on NHS expen diture	Per capita expen diture	Δ% 18-17	DDD/ 1000 inhab day	Δ% 18-17
SERM (selective estrogen-receptor modulators)	0.8	0.0	0.01	-6.7	<0.05	-7.4
Strontium ranelate	<0.05	0.0	0.00	-91.7	<0.05	-91.8
Vaccines	**529.0**	**2.4**	**8.75**	**8.7**	**1.0**	**2.2**
Meningococcal vaccines	142.2	0.6	2.35	-13.3	0.1	-12.7
Pneumococcal vaccines	101.5	0.5	1.68	0.8	0.1	3.2
Bacterial and viral vaccines in combination	74.7	0.3	1.23	-2.3	0.1	9.3
Vaccines against papillomavirus	56.3	0.3	0.93	>100	<0.05	64.8
Influenza vaccines	55.8	0.3	0.92	18.5	0.4	-2.8
Measles vaccines	39.6	0.2	0.66	11.2	0.1	2.8
Varicella zoster vaccines	17.3	0.1	0.29	64.0	<0.05	54.8
Vaccines agains rotavirus diarrhea	17.1	0.1	0.28	>100	<0.05	>100
Hepatitis vaccines	9.3	0.0	0.15	25.7	<0.05	31.8
Other vaccines	7.8	0.0	0.13	25.5	<0.05	-4.4
Pertussis vaccines	7.5	0.0	0.12	-4.7	<0.05	-5.3
Coagulation factors	**463.9**	**2.1**	**7.67**	**-5.3**	**<0.05**	**-7.1**
Hemophilia A (recombinant)	308.0	1.4	5.09	0.1	<0.05	0.2
Hemophilia B (recombinant)	62.1	0.3	1.03	20.8	<0.05	-11.3
Hemophilia A (plasma derivatives)	47.7	0.2	0.79	-17.9	<0.05	-18.9
Factor VII deficiency (recombinant)	38.3	0.2	0.63	-37.3	<0.05	-37.7
Factor VII deficiency (plasma derivatives)	4.0	0.0	0.07	17.8	<0.05	23.8
Other deficiencies of coagulation factors (recombinant)	2.6	0.0	0.04	13.7	<0.05	11.5
Hemophilia B (plasma derivatives)	0.5	0.0	0.01	-50.4	<0.05	-56.2
Other deficiencies of coagulation factors (plasma-derivatives)	0.5	0.0	0.01	1.4	<0.05	14.9
Von Willebrand's disease (plasma-derivatives)	0.1	0.0	0.00	-96.8	<0.05	-96.9
Anti-HCV antivirals	**415.3**	**1.9**	**6.87**	**-56.1**	**0.2**	**-25.6**
Anti-HCV anti-viral in combination	415.2	1.9	6.86	-33.4	0.2	3.2
Nucleosides and nucleotides excluding reverse transcriptase inhibitors	0.1	0.0	0.00	-83.4	<0.05	-87.0
Pain therapy	**389.7**	**1.8**	**6.44**	**-8.0**	**7.3**	**2.8**
Major opioids	178.3	0.8	2.95	5.3	1.9	4.7
Minor opioids / opioids in combination	126.8	0.6	2.10	0.1	2.8	-0.9
Neuropathic pain	84.6	0.4	1.40	-33.6	2.6	5.9
Pharmaceuticals for eye disorders	**383.7**	**1.7**	**6.34**	**3.9**	**21.0**	**2.1**
Other antiglaucoma preparations	152.9	0.7	2.53	0.5	14.7	2.1
Antineovascular agents	132.3	0.6	2.19	12.3	0.4	13.2
Glaucoma prostaglandin analogues plain or in combination with beta blocking agents	77.5	0.4	1.28	-1.3	5.8	1.7
Corticosteroids	19.6	0.1	0.32	-4.7	0.2	-5.2
Corticosteroids (intravitreal implants)	1.3	0.0	0.02	>100	<0.05	>100
Ocriplasmin	0.1	0.0	0.00	-27.4	<0.05	-31.1
Antidepressants	**382.1**	**1.7**	**6.32**	**3.7**	**41.6**	**2.9**
Antidepressants-SSRI	199.2	0.9	3.29	0.8	29.7	1.8
Antidepressants-SNRI	90.0	0.4	1.49	2.7	6.5	3.4
Antidepressants-others	44.3	0.2	0.73	3.7	3.0	4.3
Antidepressants -SMS (serotonin modulators and stimulators)	27.6	0.1	0.46	40.2	1.1	40.5
Antidepressants -tricyclic	10.4	0.0	0.17	-0.9	1.1	-0.8
Bupropion	10.1	0.0	0.17	2.3	0.2	6.0

Group Subgroup	Total expenditure (in mil)	% on NHS expenditure	Per capita expenditure	Δ% 18-17	DDD/ 1000 inhab day	Δ% 18-17
Antidepressants -NaRI (norepinephrine reuptake inhibitors)	0.5	0.0	0.01	-17.2	<0.05	-16.7
Agomelatine	<0.05	0.0	0.00	-27.7	<0.05	-28.9
Pharmaceuticals for genitourinary disorders	**277.5**	**1.3**	**4.59**	**-16.7**	**35.9**	**3.8**
Alfa blocking agents	181.8	0.8	3.01	4.5	25.4	3.9
5-alpha reductase inhibitors	95.7	0.4	1.58	-39.9	10.5	3.7
Beta 3 selective agonist	0.1	0.0	0.00	-11.9	<0.05	-12.7
Alfa blocking agents in combination	<0.05	0.0	0.00	-10.0	<0.05	-9.6
Antipsychotics	**275.9**	**1.3**	**4.56**	**5.8**	**9.6**	**2.6**
Atypical and other antipsychotics	252.7	1.1	4.18	6.4	7.0	3.8
Typical antipsychotics	23.2	0.1	0.38	0.0	2.6	-0.6
Antiparkinson pharmaceuticals	**196.1**	**0.9**	**3.24**	**1.5**	**5.2**	**2.3**
Dopamine-agonists	77.7	0.4	1.28	0.7	1.3	-2.4
Dopa-derivatives agonists	71.4	0.3	1.18	-3.6	2.3	1.1
MAO-B inhibitors	43.7	0.2	0.72	10.3	1.6	8.3
COMT inhibitors	3.3	0.0	0.05	49.2	<0.05	46.9
Amantadinae	<0.05	0.0	0.00	-75.7	<0.05	-85.8
NSAID	**152.6**	**0.7**	**2.52**	**-12.6**	**18.6**	**-3.1**
NSAID (traditional)	96.9	0.4	1.60	-4.0	12.2	-3.7
Coxib	39.4	0.2	0.65	-30.3	3.8	0.0
Nimesulide	9.9	0.0	0.16	-6.3	2.1	-6.5
Ketorolac	6.4	0.0	0.11	-2.7	0.6	2.8
Pharmaceuticals for cystic fibrosis	**82.0**	**0.4**	**1.36**	**72.0**	**<0.05**	**105.2**
Thyroid phamaceuticals	**63.6**	**0.3**	**1.05**	**6.9**	**22.1**	**1.9**
Thyroid hormones	60.4	0.3	1.00	7.1	20.7	2.0
Antithyroid preparations	3.3	0.0	0.05	4.2	1.4	-0.5
Antidementia pharmaceuticals	**30.7**	**0.1**	**0.51**	**-7.9**	**2.4**	**0.3**
Anticholinesterase pharmaceuticals	22.1	0.1	0.37	-5.8	1.4	-1.9
Other antidementia pharmaceuticals	8.6	0.0	0.14	-12.8	0.9	3.9

Cancer medicines

- The supply of cancer medicines has significantly increased in the last 6 years; in fact, expenditure has shifted from 31.8 euros in 2013 to 55.6 in 2018 with a 75% variation; this category represents 5% of the expenditure borne by the NHS;
- monoclonal antibodies and tyrosine kinase inhibitors are the two most expensive categories, respectively 24.1 and 15.3 euros per capita; both show an increase of more than 18% compared to 2017;
- major expenditure increases are reported in particular for nivolumab and pembrolizumab (+47% and +217.9%). Nivolumab is used in the treatment of some cancers including melanoma, small cell lung cancer, Hodgkin's lymphoma and head and neck cancers while pembrolizumab is indicated for advanced melanoma and non-small cell lung cancer in advanced stage;
- all Regions recorded an increase compared to 2017 even if with different levels, going from +3.8% in Toscana to +23.9% in Lazio; the Region with the highest per capita expenditure is Campania with 66.14 euros;
- as expected, 94% of expenditure is related to medicines still covered by a patent;
- Abruzzo, Umbria, Friuli Venezia Giulia and Puglia are the Regions reporting a consumption and a cost per day of therapy higher than the national average, while Val d'Aosta, Sicilia, Autonomous Province of Trento and Piemonte record a smaller quantity of drugs with a lower cost than the national average.

Figure 5.2.2. Cancer medicines, temporal trend of per capita expenditure (2013-2018)

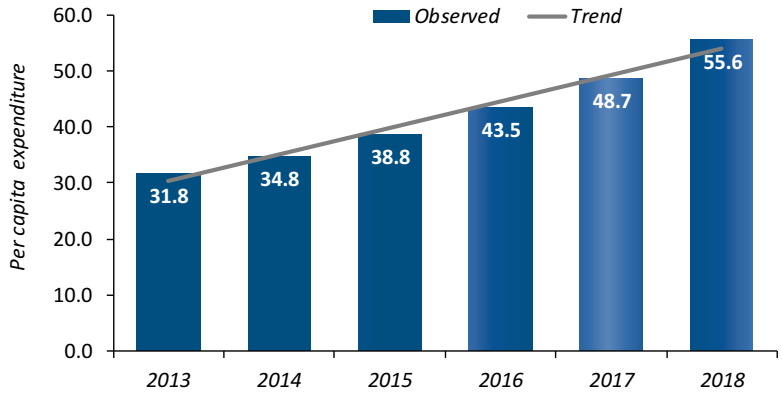


Table 5.2.2a. Cancer medicines, per capita expenditure by therapeutic category and by substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Monoclonal antibodies	11.1	12.4	15.0	16.7	20.4	24.1	18.4
Protein kinase inhibitors	8.5	9.8	10.1	12.2	12.9	15.3	18.7
Cytostatic antineoplastic - cytostatic - others	1.9	2.1	2.2	2.6	2.9	2.8	-1.7
Cytostatic antineoplastics - antimetabolites	3.1	2.8	2.7	2.6	2.5	2.6	2.2
Endocrine therapy - aromatase inhibitors	1.5	1.5	1.6	1.7	1.8	1.9	8.9
Endocrine therapy - hormones and GnRH analogues	2.0	2.0	1.9	1.9	1.8	1.9	3.9
Endocrine therapy - other hormonal antagonists	0.5	1.0	1.7	1.8	1.7	1.7	-0.8
Endocrine therapy - antiandrogens	0.3	0.3	0.5	0.7	1.0	1.4	31.0
Antineoplastic - others	-	-	-	<0.05	0.5	0.8	72.2
Cytotoxic antineoplastics – natural products-taxanes	0.5	0.5	0.6	0.7	0.7	0.8	6.1
Endocrine therapy - anti-estrogens	0.5	0.5	0.5	0.6	0.7	0.7	8.3
Cytotoxic antineoplastics – natural products - others	0.5	0.5	0.5	0.6	0.6	0.6	-0.7
Cytotoxic antineoplastics - cytotoxic-anthracycline antibiotics and related substances	0.5	0.5	0.5	0.5	0.5	0.4	-7.9
Cytostatic antineoplastics - alkylating agents	0.6	0.7	0.8	0.7	0.6	0.4	-27.9
Cytotoxic antineoplastics - cytotoxic antibiotics - others	0.1	0.1	0.1	0.1	0.1	0.1	-1.1
Cytostatic antineoplastics - platinum compounds	0.1	0.1	0.1	0.1	0.1	0.1	-25.7
Cancer medicines	**31.8**	**34.8**	**38.8**	**43.5**	**48.7**	**55.6**	**14.2**
nivolumab	-	-	<0.05	1.0	3.0	4.4	47.0
trastuzumab	4.0	4.0	4.3	4.5	4.6	4.1	-12.3
bevacizumab	2.4	2.8	3.3	3.6	3.7	3.2	-12.4
pembrolizumab	-	-	-	0.2	1.0	3.2	>100
rituximab	3.2	3.1	3.2	3.1	3.1	2.2	-29.3
pertuzumab	<0.05	0.3	0.9	1.3	1.7	2.1	24.3
Ibrutinib	-	-	-	0.6	1.3	1.8	37.4
abiraterone	0.4	0.9	1.6	1.7	1.6	1.6	-1.9
palbociclib	-	-	-	-	<0.05	1.2	>100
dasatinib	0.8	1.0	1.1	1.1	1.2	1.2	1.8

Table 5.2.2b. Cancer medicines, weighted regional trend of per capita expenditure: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	31.68	33.79	35.47	39.85	43.20	51.23	18.6
Valle d'Aosta	25.79	26.10	34.09	38.78	39.23	42.12	7.4
Lombardia	26.64	29.06	33.32	37.68	41.40	45.91	10.9
PA Bolzano	32.47	37.25	39.22	41.51	52.19	58.05	11.2
PA Trento	25.18	26.89	27.89	34.88	40.11	44.21	10.2
Veneto	30.41	33.43	36.14	40.73	45.22	51.97	14.9
Friuli VG	40.04	41.63	43.42	47.65	59.83	63.61	6.3
Liguria	33.50	35.62	41.03	46.40	51.35	61.61	20.0
Emilia R.	32.45	35.29	40.10	45.16	49.82	59.65	19.7
Toscana	36.85	41.67	44.71	51.92	55.86	58.01	3.8
Umbria	34.78	37.54	43.26	50.69	54.99	63.97	16.3
Marche	35.94	40.26	45.06	51.04	55.56	62.70	12.9
Lazio	32.00	33.56	36.91	39.29	46.22	57.29	23.9
Abruzzo	37.38	42.62	46.24	51.17	54.68	63.72	16.5
Molise	26.91	30.69	33.37	39.52	48.10	53.88	12.0
Campania	35.44	40.52	46.09	51.51	57.82	66.14	14.4
Puglia	35.05	39.70	44.04	48.93	56.29	65.53	16.4
Basilicata	35.60	40.20	45.78	53.74	60.87	64.58	6.1
Calabria	29.49	31.72	38.38	43.00	48.85	56.41	15.5
Sicilia	26.12	28.44	32.13	36.28	42.45	45.62	7.5
Sardegna	34.86	37.87	42.18	46.31	50.30	56.71	12.7
Italy	**31.77**	**34.83**	**38.76**	**43.48**	**48.73**	**55.63**	**14.2**

Table 5.2.2c. Cancer medicines, prescription by therapeutic category and by substance in 2018

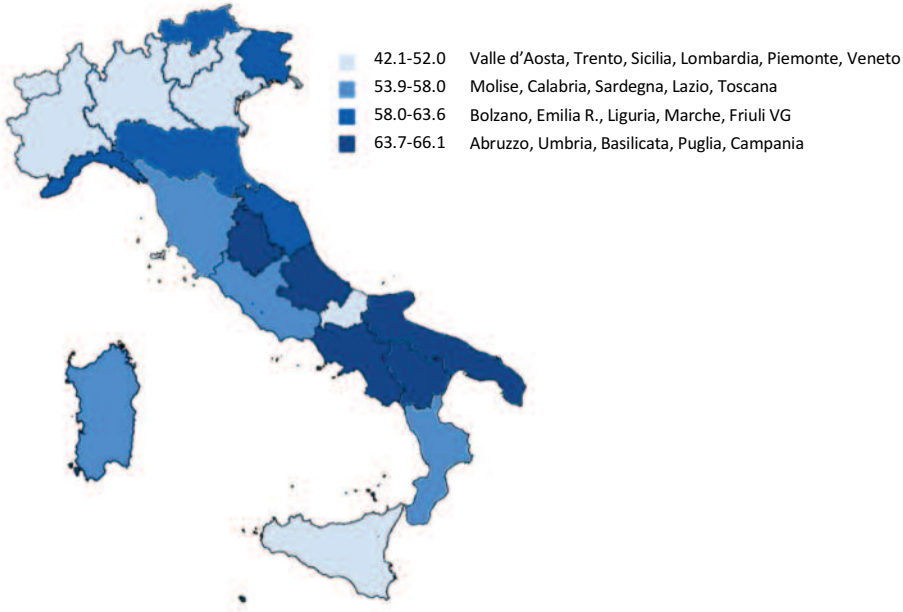
Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab per day	Δ % 18-17
Monoclonal antibodies	24.11	18.4	1.1	6.8
Protein kinase inhibitors	15.27	18.7	0.4	18.2
Cytostatic antineoplastics - cytostatic - others	2.85	-1.7	0.4	1.4
Cytostatic antineoplastics - antimetabolites	2.59	2.2	0.6	-5.2
Endocrine therapy - aromatase inhibitors	1.94	8.9	3.1	7.0
Endocrine therapy - hormones and GnRh analogues	1.87	3.9	1.0	4.8
Endocrine therapy - other hormonal antagonists	1.73	-0.8	0.1	12.1
Endocrine therapy – anti-androgens	1.36	31.0	1.0	-6.2
Antineoplastic -others	0.84	72.2	0.0	64.5
Cytotoxic antineoplastics - natural products - taxanes	0.78	6.1	0.2	-5.6
Endocrine therapy - anti-estrogens	0.72	8.3	1.1	-1.1
Cytotoxic antineoplastics – natural products - others	0.55	-0.7	0.1	-2.3
Cytotoxic antineoplastics - cytotoxic antibiotics - anthracycline and related substances	0.44	-7.9	0.1	-4.9
Cytostatic antineoplastics - alkylating agents	0.42	-27.9	0.2	6.4
Cytotoxic antineoplastics - cytotoxic antibiotics - others	0.09	-1.1	0.1	1.5
Cytostatic antineoplastics - platinum compounds	0.09	-25.7	0.2	-5.6
Cancer medicines	**55.63**	**14.2**	**9.8**	**2.9**
nivolumab	4.41	47.0	0.1	51.8
trastuzumab	4.05	-12.3	0.2	0.4
bevacizumab	3.22	-12.4	0.1	-7.8
pembrolizumab	3.21	>100	0.1	>100
rituximab	2.17	-29.3	0.5	-8.3
pertuzumab	2.08	24.3	<0.05	24.3
ibrutinib	1.84	37.4	<0.05	45.1
abiraterone	1.60	-1.9	0.1	8.8
palbociclib	1.24	>100	<0.05	>100
dasatinib	1.22	1.8	<0.05	1.7

Table 5.2.2d. Prescription of cancer medicines, with patent expired* in 2018

Categories	Per-capita expenditure	%	Δ % 18-17	DDD/1000 inhab per day	%	Δ % 18-17	DDD average cost
Expired patent	3.36	6.0	-3.8	5.2	52.7	2.2	1.78
Equivalent	1.14	33.9	4.5	3.0	58.1	3.7	1.04
Ex originator	2.22	66.1	-7.6	2.2	41.9	0.3	2.82
Patent covered	52.28	94.0	16.2	4.6	47.3	3.9	30.93
Cancer medicines	**55.63**	**100.0**	**14.8**	**9.8**	**100.0**	**3.0**	**15.58**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.2b. Cancer medicines, distribution in quartiles of 2018 per capita expenditure



Pharmaceuticals for hypertension and heart failure

- Consumption of pharmaceuticals for hypertension and heart failure has remained stable in recent years with a value of 372.5 DDD in 2018;
- considerable variability was recorded across the Regions: in fact, in 2018 a minimum value of 284 DDD was reported for the Autonomous Province of Bolzano and a maximum of 476.4 for Umbria. Campania, Sicilia, Calabria and Puglia are the Regions with an average cost per day of therapy and consumption higher than the national average; a high regional variability was recorded particularly in consumption of Ace inhibitors;
- a stable consumption was recorded in 2018 even between different categories, albeit with a certain variability between the different geographical areas; while at substance level a 10% increase was reported in olmesartan alone or in combination;
- over 90% of doses refer to expired patent medicines;
- prescription of medicines for hypertension and heart failure increase with age; in particular, in the over-75 age group, about one in 10 people received at least one prescription for such medicines in 2018. For all age groups consumption is higher in men than in women.

Figure 5.2.3a. Medicines for hypertension and heart failure, temporal consumption trend (2013-2018)

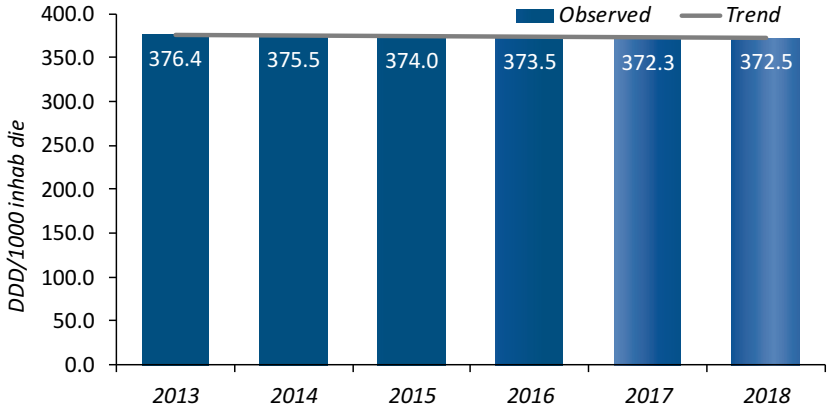


Table 5.2.3a. Medicines for hypertension and heart failure, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Beta blocking agents	41.6	41.8	42.2	42.5	43.1	43.6	1.3
Calcium channel blockers (dihydropyridines)	55.1	54.0	52.8	52.2	51.2	50.8	-0.6
Ace inhibitors	91.3	90.6	89.3	88.6	87.4	86.7	-0.8
Angiotensin II receptor blockers (ARBs)	49.4	49.1	48.5	48.3	47.8	46.7	-2.4
Angiotensin II receptor blockers (ARBs) and diuretics (combination)	34.0	32.9	31.7	30.8	29.6	27.9	-5.6
Ace inhibitors and diuretics (combination)	25.9	25.0	23.9	23.0	22.1	21.4	-3.1
Ace inhibitors and calcium channel blockers (combination)	5.0	6.6	8.0	9.6	10.5	11.1	5.7
Olmesartan+amlodipin	2.3	2.8	3.6	4.2	4.8	5.5	15.3
Peripheral alpha blockers	7.8	7.8	7.7	7.7	7.6	7.6	-0.4
Olmesartan	7.0	7.3	7.7	8.0	8.6	10.2	18.3
High-ceiling diuretics plain or in combination with potassium-sparing agents	29.3	29.7	30.7	30.7	30.5	30.3	-0.6
Olmesartan+idroclorotiazide	6.2	6.6	6.9	7.1	7.2	8.1	12.4
Beta blockers and diuretics (combination)	5.8	6.4	6.7	7.1	7.3	7.4	2.0
Potassium-sparing diuretics	3.4	3.5	3.5	3.0	3.5	3.5	0.6
Angiotensin II receptor blockers (ARBs) and neprisylin inhibitor	0.0	0.0	0.0	0.0	0.1	0.3	>100
Ace inhibitors, other combinations	0.0	0.0	0.0	0.5	1.6	2.3	46.4
Calcium channel blockers (non dihydropyridines)	3.9	3.6	3.3	3.0	2.8	2.5	-8.6
Thiazide and similars (including combinations)	5.8	5.5	5.2	4.9	4.7	4.6	-2.9
Alpha-2 adrenergic receptor agonists	2.1	2.0	1.9	1.8	1.7	1.6	-5.2
Aliskiren plain or in combination	0.6	0.5	0.4	0.3	0.3	0.2	-15.4
Medicines for hypertension and heart failure	**376.4**	**375.5**	**374.0**	**373.5**	**372.3**	**372.5**	**0.1**
bisoprolol	7.6	8.2	8.9	9.5	10.2	10.9	6.6
ramipril	60.9	62.1	62.7	63.6	63.6	63.9	0.4
amlodipin	28.5	28.2	27.8	27.7	27.4	27.5	0.6
olmesartan/amlodipin	2.3	2.8	3.6	4.2	4.8	5.5	15.3
nebivolol	13.2	13.5	13.9	14.3	14.7	15.1	2.7
olmesartan	7.0	7.3	7.7	8.0	8.6	10.2	18.3
doxazosin	7.8	7.8	7.7	7.7	7.6	7.6	-0.4
olmesartan/idroclorotiazide	6.2	6.6	6.9	7.1	7.2	8.1	12.4
valsartan/idroclorotiazide	11.6	11.3	10.9	10.6	10.2	9.0	-11.5
barnidipine	4.3	4.5	4.6	4.8	4.8	4.7	-0.9

Table 5.2.3b. Medicines for hypertension and heart failure, weighted regional trend of DDD/1000 inhab. per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	366.9	365.4	362.0	363.7	361.3	359.0	-0.7
Valle d'Aosta	343.3	343.7	336.9	321.8	314.9	310.3	-1.5
Lombardia	354.8	356.9	355.6	354.4	351.1	350.3	-0.2
PA Bolzano	298.5	301.4	297.6	293.2	288.5	284.0	-1.5
PA Trento	333.7	334.1	332.1	330.5	330.1	329.5	-0.2
Veneto	382.4	385.9	381.8	375.7	370.7	368.5	-0.6
Friuli VG	385.2	384.0	377.5	375.1	376.0	375.8	0.0
Liguria	356.3	348.6	343.6	336.2	331.6	327.1	-1.3
Emilia R.	414.4	414.4	414.5	413.5	408.7	408.5	-0.1
Toscana	373.8	373.5	370.2	367.5	366.8	366.9	0.0
Umbria	473.7	463.8	467.5	470.9	471.4	476.4	1.1
Marche	372.7	372.2	371.5	373.5	370.0	372.8	0.7
Lazio	391.9	374.1	373.3	372.1	374.8	376.1	0.4
Abruzzo	355.1	357.3	356.0	357.6	358.4	360.9	0.7
Molise	350.2	365.5	353.3	350.4	353.3	356.8	1.0
Campania	372.8	378.2	380.9	389.0	392.8	397.4	1.2
Puglia	387.4	387.9	383.6	382.0	380.1	378.3	-0.5
Basilicata	351.3	355.0	353.7	356.7	359.0	363.2	1.2
Calabria	382.7	385.1	382.3	382.9	381.8	383.9	0.5
Sicilia	383.1	382.3	385.0	387.3	390.1	392.3	0.6
Sardegna	354.7	353.6	350.7	344.2	341.8	341.3	-0.1
Italy	**376.4**	**375.5**	**374.0**	**373.5**	**372.3**	**372.5**	**0.1**

Table 5.2.3c. Medicines for hypertension and heart failure, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Beta blocking agents	5.14	3.2	43.6	1.3
Calcium channel blockers (dihydropyridines)	4.29	-1.3	50.8	-0.6
Ace inhibitors	3.90	-1.0	86.7	-0.8
Angiotensin II receptor blockers (ARBs)	3.33	-1.9	46.7	-2.4
Angiotensin II receptor blockers (ARBs) and diuretics (combination)	3.32	-5.5	27.9	-5.6
Ace inhibitors and diuretics (combination)	2.75	-3.1	21.4	-3.1
Ace inhibitors and calcium channel blockers (combination)	1.64	-5.1	11.1	5.7
Olmesartan+amlodipin	1.49	-2.8	5.5	15.3
Peripheral alpha blockers	1.22	-0.4	7.6	-0.4
Olmesartan	1.21	-10.9	10.2	18.3
High-ceiling diuretics plain or in combination with potassium-sparing agents	1.03	-1.4	30.3	-0.6
Olmesartan+idroclorotiazide	1.00	-15.7	8.1	12.4
Beta blockers and diuretics (combination)	0.68	-10.0	7.4	2.0
Potassium-sparing diuretics	0.54	2.1	3.5	0.6
Angiotensin II receptor blockers (ARBs) and neprisylin inhibitor	0.46	>100	0.3	>100
Ace inhibitors, other combinations	0.40	24.7	2.3	46.4
Calcium channel blockers (non dihydropyridines)	0.36	-8.5	2.5	-8.6
Thiazide and similars (including combinations)	0.25	-2.1	4.6	-2.9
Alpha-2 adrenergic receptor agonists	0.22	-4.9	1.6	-5.2
Aliskiren plain or in combination	0.07	-14.9	0.2	-15.4
Medicines for hypertension and heart failure	**33.29**	**-1.4**	**372.5**	**0.1**
bisoprolol	2.32	7.1	10.9	6.6
ramipril	2.03	0.5	63.9	0.4
amlodipin	1.55	0.4	27.5	0.6
olmesartan/amlodipin	1.49	-2.8	5.5	15.3
nebivolol	1.40	2.2	15.1	2.7
olmesartan	1.21	-10.9	10.2	18.3
doxazosin	1.21	-0.4	7.6	-0.4
olmesartan/idroclorotiazide	1.00	-15.7	8.1	12.4
valsartan/idroclorotiazide	0.96	-10.7	9.0	-11.5
barnidipine	0.86	-0.7	4.7	-0.9

Table 5.2.3d. Prescription of medicines for hypertension and heart failure with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	Average cost DDD
Patent expired	28.15	84.5	3.1	344.9	92.6	1.9	0.22
Equivalent	7.18	25.5	5.2	120.8	35.0	3.0	0.16
Ex originator	20.97	74.5	2.4	224.0	65.0	1.3	0.26
Patent covered	5.15	15.5	-20.3	27.7	7.4	-18.2	0.51
Medicines for hypertension and heart failure	**33.29**	**100.0**	**-1.4**	**372.5**	**100.0**	**0.1**	**0.24**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.3b. Medicines for hypertension and heart failure, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

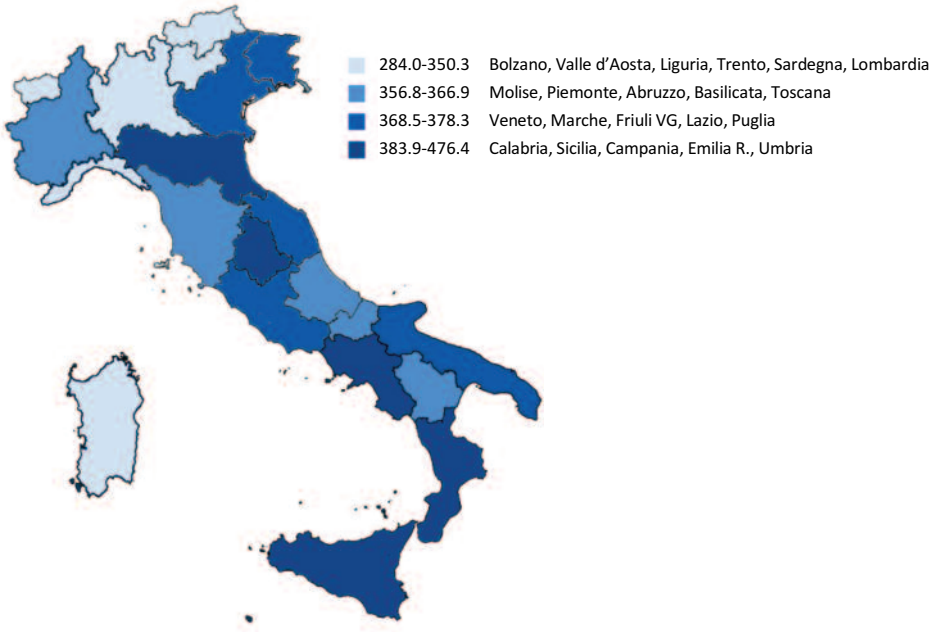


Table 5.2.3e. Duration of therapy with medicines for hypertension and heart failure by geographic area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	8.8	522.1	392.0	6.3
Centre	10.4	522.0	392.0	6.9
South and islands	10.6	494.9	378.0	6.2
Antihypertensives	**9.8**	**512.3**	**392.0**	**6.4**

Immunosuppressants and immunomodulators

- In 2018 expenditure for immunosuppressants and immunomodulators reached 27.2 euros per capita, equal to 7.5% of total expenditure, with an increase by 33.2% compared to 2013 and by 2.8% compared to 2017;
- anti-TNFα is the category with the highest expenditure (10.5 euros per capita), which decreased by 3.9% compared to 2017, while the increase for interleukin inhibitors is more consistent (+28.6 %);
- it is worth highlighting the increase of secukinumab (+62.2%), which was marketed in 2016; the expenditure of adalimumab (4.68 euros per capita) is stable, which however remains the most prescribed substance in the category followed by lenalidomide and etanercept (3.6 and 2.7 euros per capita);
- among the Italian regions the variability of expenditure ranges from a minimum of 12.9 euros in Valle d'Aosta to 35.5 in Puglia; these differences also remain with regard to the average cost per day of therapy (Valle d'Aosta -31% from national average and Molise +28.3%);
- over 70% of the doses and 90% of expenditure is supported by medicines still covered by a patent.

Figure 5.2.4a. Immunosuppressants and immunomodulators, temporal trend of per capita expenditure (2013-2018)

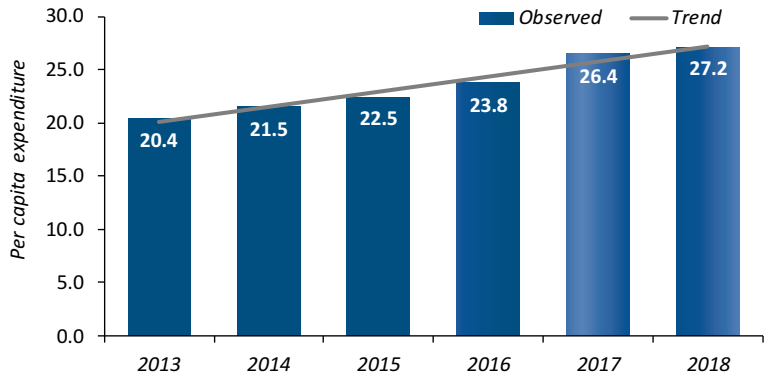


Table 5.2.4a. Immunosuppressants and immunomodulators, per capita expenditure by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Tumor necrosis factor alpha (TNF-alpha) inhibitors	9.7	10.2	10.9	10.7	10.9	10.5	-3.9
Other immunosuppressant and immunomodulating agents	2.5	3.0	3.6	4.5	5.0	5.3	6.9
Interleukin inhibitors	1.1	1.4	1.7	2.2	3.4	4.4	28.6
Selective Immunosuppressants	2.5	2.8	3.0	3.6	4.4	4.4	-0.2
Calcineurin inhibitors	1.7	1.7	1.7	1.5	1.5	1.5	0.5
Growth factors (G-CSF)	1.6	1.4	1.2	1.0	1.0	0.8	-12.5
Interferons	1.3	1.0	0.4	0.2	0.1	0.1	-21.8
Immunosuppressants and immunomodulators	**20.4**	**21.5**	**22.5**	**23.8**	**26.4**	**27.2**	**2.8**
adalimumab	3.8	4.1	4.4	4.4	4.7	4.8	1.5
lenalidomide	2.1	2.4	2.7	3.0	3.3	3.6	6.2
etanercept	3.7	3.5	3.6	3.2	3.0	2.7	-11.2
ustekinumab	0.5	0.7	0.9	1.1	1.3	1.4	8.2
secukinumab	0.0	0.0	0.0	0.1	0.8	1.3	62.2
infliximab	1.5	1.6	1.7	1.6	1.5	1.3	-16.7
golimumab	0.5	0.7	1.0	1.2	1.2	1.2	0.3
eculizumab	1.0	1.2	1.3	1.5	1.7	1.1	-36.0
abatacept	0.4	0.5	0.7	0.8	1.0	1.0	9.9
tacrolimus	0.6	0.6	0.7	0.7	0.8	0.8	7.3

Table 5.2.4b. Immunosuppressants and immunomodulators, weighted regional trend of per capita expenditure: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	16.98	18.74	18.97	19.75	22.14	23.05	4.1
Valle d'Aosta	12.92	12.16	13.77	16.03	13.10	12.86	-1.8
Lombardia	18.54	18.66	19.40	20.16	22.58	22.84	1.2
PA Bolzano	21.51	24.36	25.71	27.58	29.96	29.82	-0.5
PA Trento	13.68	15.14	15.61	17.41	18.67	19.26	3.1
Veneto	19.42	20.15	20.61	21.80	23.58	23.54	-0.2
Friuli VG	22.20	21.73	22.40	24.24	28.55	30.40	6.5
Liguria	15.86	16.47	16.83	19.19	20.95	22.39	6.8
Emilia R.	17.87	18.45	20.23	22.43	24.55	25.86	5.3
Toscana	22.91	25.02	26.53	29.43	30.40	26.20	-13.8
Umbria	20.97	21.92	23.12	24.87	27.22	30.65	12.6
Marche	21.48	23.86	25.46	28.02	30.55	33.09	8.3
Lazio	20.33	20.49	20.90	20.58	25.54	27.25	6.7
Abruzzo	21.91	23.32	24.48	24.79	27.76	31.58	13.7
Molise	24.52	25.24	26.50	28.72	31.54	32.90	4.3
Campania	22.65	24.10	26.04	26.66	29.80	31.89	7.0
Puglia	27.46	29.16	29.77	31.42	33.05	35.47	7.3
Basilicata	23.10	24.06	25.98	27.38	31.18	31.61	1.4
Calabria	22.76	26.82	27.49	28.75	31.66	34.37	8.6
Sicilia	18.48	20.22	21.49	23.84	27.97	27.39	-2.1
Sardegna	25.54	26.63	27.72	27.95	29.67	28.48	-4.0
Italy	**20.39**	**21.51**	**22.48**	**23.75**	**26.41**	**27.16**	**2.8**

Table 5.2.4c. Immunosuppressants and immunomodulators, prescription by therapeutic category and substance in 2018

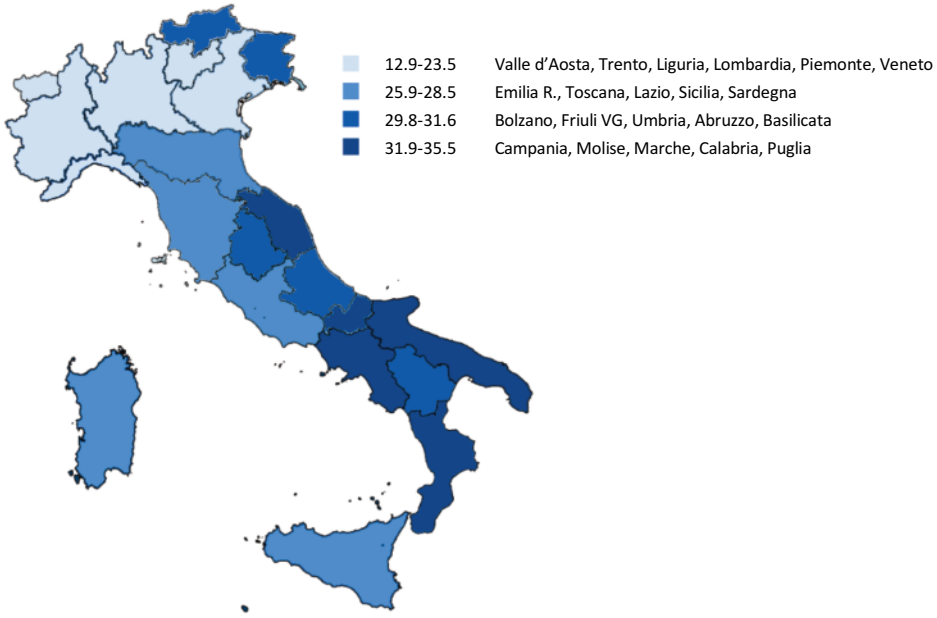
Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab per day	Δ % 18-17
Tumor necrosis factor alpha (TNF-alfa) inhibitors	10.51	-3.9	1.2	6.0
Other immunosuppressants and immunomodulators	5.31	6.9	0.1	13.6
Interleukin inhibitors	4.43	28.6	0.4	33.2
Selective Immunosuppressants	4.42	-0.2	0.7	12.8
Calcineurin inhibitors	1.53	0.5	0.6	-0.9
Growth factors (G-CSF)	0.85	-12.5	0.1	-2.6
Interferons	0.11	-21.8	0.0	-22.8
Immunosuppressants and immunomodulators	**27.16**	**2.8**	**3.1**	**8.8**
adalimumab	4.77	1.5	0.4	9.3
lenalidomide	3.55	6.2	0.1	15.2
etanercept	2.68	-11.2	0.3	2.2
ustekinumab	1.44	8.2	0.2	14.9
secukinumab	1.35	62.2	0.1	62.0
infliximab	1.25	-16.7	0.3	5.1
golimumab	1.23	0.3	0.1	1.8
eculizumab	1.11	-36.0	<0.05	6.5
abatacept	1.04	9.9	0.1	9.1
tacrolimus	0.83	7.3	0.3	3.3

Table 5.2.4d. Prescription of immunosuppressants and immunomodulators with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab per day	%	Δ % 18-17	Average cost DDD
Patent expired	1.44	5.3	15.8	0.9	27.1	7.8	4.63
Equivalent	0.06	4.5	88.3	0.2	22.8	20.0	0.91
Ex-originator	1.38	95.5	13.7	0.7	77.2	4.6	5.73
Patent covered	25.72	94.7	2.3	2.3	72.9	9.2	30.79
Immunosuppressants and immunomodulators	**27.16**	**100.0**	**2.8**	**3.1**	**100.0**	**8.8**	**23.70**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.4b. Immunosouppressants and immunomodulators, distribution in quartiles of 2018 per capita expenditure



Lipid-lowering agents

- In 2018 consumption of lipid-lowering was up to 92.5 DDD/1000 inhabitants (equal to 8% of consumption borne by the NHS), increasing by 4.2% compared to 2017 and by 20% compared to 2013;
- about 84% of prescriptions is represented by statins (77.4 DDD), increasing by 3.3% compared to 2017; significant increases are also reported for ezetimibe plain or in combination (+13.2%) and for PCSK9 inhibitors (+264.8%); statins are the category with the greatest variability between regions;
- atorvastatin is the most used molecule, with 46 DDD and 4.11 euros per capita, followed by simvastatin (14.1 DDD and 1.65 euros) and rosuvastatin (12.3 DDD and 1.28 euros); the 68.5% decrease in rosuvastatin expenditure and the 25.9% reduction of the combination simvastatin + ezetimibe was due to patent expiry in 2018;
- the regional variability of consumption varies from 62.9 DDD in Valle d'Aosta to 107.1 DDD in Sardegna; the latter (together with Campania, Lazio, Puglia and Calabria) shows the highest use and cost per day of therapy for lipid-lowering medicines compared to the national average;
- consumption increases with age up to a prevalence of around 40% in the >75 year age group; all age groups reported a greater use in men than in women;
- about half of the users of lipid-lowering medicines have a duration of therapy of more than 7 months even if one user out of 10 receives a single prescription in a year;
- expired patent medicines represent 95.2% of the doses and 78.2% of the expenditure with an average cost per day of therapy of 0.35 euros compared to 1.95 euros of the medicines still covered by patent.

Figure 5.2.5a. Lipid-lowering agents, temporal trend of consumption (2013-2018)

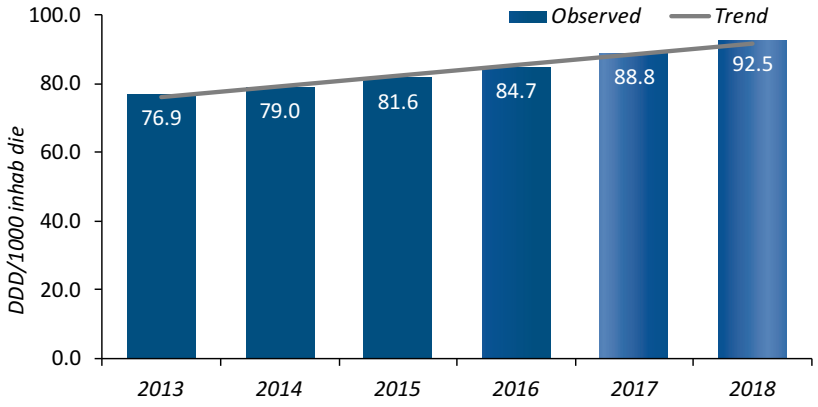


Table 5.2.5a. Lipid lowering agents, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Statins	65.6	67.9	69.8	72.0	74.9	77.4	3.3
Ezetimibe plain or in combination	4.4	4.9	5.5	6.3	7.2	8.1	13.2
Omega 3	4.5	3.6	3.7	3.8	4.1	4.3	5.2
PCSK9 inhibitor	-	-	-	<0.05	<0.05	0.1	>100
Fibrates	2.4	2.5	2.6	2.6	2.6	2.7	3.0
MTP inhibitor	-	-	<0.05	<0.05	<0.05	<0.05	31.9
Statins and fibrates	-	-	-	<0.05	<0.05	<0.05	-75.0
Lipid lowering agents	**76.9**	**79.0**	**81.6**	**84.7**	**88.8**	**92.5**	**4.2**
atorvastatin	29.0	33.0	36.2	39.5	43.1	46.0	6.8
ezetimibe/simvastatin	3.4	3.5	3.7	3.9	4.2	4.4	4.9
omega 3	4.5	3.6	3.7	3.8	4.1	4.3	5.2
simvastatin	16.1	15.7	15.3	15.0	14.6	14.1	-3.8
ezetimibe	1.0	1.4	1.9	2.4	3.0	3.7	24.8
rosuvastatin	15.2	14.0	13.1	12.5	12.1	12.3	1.6
lovastatin	0.9	0.9	1.0	1.1	1.2	1.2	3.7
pravastatin	3.1	3.1	3.0	3.0	3.0	2.9	-1.8
fenofibrate	2.1	2.3	2.3	2.3	2.4	2.5	3.7
evolocumab	-	-	-	<0.05	<0.05	<0.05	>100

Table 5.2.5b. Lipid lowering agents, weighted regional trend of DDD/1000 inhab. per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	65.4	66.2	67.8	69.7	72.7	76.1	4.7
Valle d'Aosta	56.0	57.6	58.7	57.4	60.5	62.9	3.9
Lombardia	71.1	72.7	76.2	79.5	83.7	87.5	4.6
PA Bolzano	55.8	59.1	63.4	67.1	70.7	74.8	5.8
PA Trento	64.1	65.1	67.2	70.2	74.6	79.0	5.8
Veneto	76.1	78.5	80.7	84.1	88.0	91.7	4.1
Friuli VG	80.1	81.5	83.5	86.3	90.7	94.4	4.1
Liguria	67.0	67.8	70.0	71.6	74.5	77.9	4.5
Emilia R.	81.8	82.4	86.3	91.2	96.1	99.1	3.2
Toscana	69.8	71.9	74.4	77.7	81.6	84.3	3.3
Umbria	71.8	72.4	75.2	78.7	83.2	88.4	6.2
Marche	85.6	89.1	92.2	96.3	100.4	103.8	3.4
Lazio	84.4	89.4	87.8	89.1	92.9	96.5	3.9
Abruzzo	69.1	71.2	74.9	78.3	82.6	87.1	5.5
Molise	64.1	67.7	68.1	68.7	73.0	76.0	4.1
Campania	80.2	84.5	89.3	93.5	98.9	104.9	6.0
Puglia	82.7	85.9	89.4	93.0	96.6	99.3	2.8
Basilicata	71.0	74.9	78.2	81.7	87.3	92.3	5.7
Calabria	82.6	84.8	86.3	87.8	91.4	95.0	4.0
Sicilia	85.2	83.2	86.2	90.0	94.5	98.8	4.6
Sardegna	94.3	96.9	100.6	101.5	104.6	107.1	2.4
Italy	**76.9**	**79.0**	**81.6**	**84.7**	**88.8**	**92.5**	**4.2**

Table 5.2.5c. Lipid lowering agents, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Statins	7.90	-25.0	77.4	3.3
Ezetimibe plain or in combination	3.72	-26.2	8.1	13.2
Omega 3	1.86	0.3	4.3	5.2
PCSK9 inhibitor	0.41	>100	0.1	>100
Fibrates	0.38	2.5	2.7	3.0
MTP inhibitor	0.11	16.3	<0.05	31.9
Statins and fibrates	0.00	-76.0	<0.05	-75.0
Lipid lowering agents	**14.39**	**-20.1**	**92.5**	**4.2**
atorvastatin	4.11	6.0	46.0	6.8
ezetimibe/simvastatin	2.33	-25.9	4.4	4.9
omega 3	1.86	0.3	4.3	5.2
simvastatin	1.65	-3.7	14.1	-3.8
ezetimibe	1.39	-26.7	3.7	24.8
rosuvastatin	1.28	-68.5	12.3	1.6
lovastatin	0.43	3.8	1.2	3.7
pravastatin	0.37	-2.6	2.9	-1.8
fenofibrate	0.35	3.3	2.5	3.7
evolocumab	0.24	>100	<0.05	>100

Table 5.2.5d. Prescription of lipid lowering agents with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab per day	%	Δ % 18-17	Average cost DDD
Patent expired	11.26	78.2	36.3	88.1	95.2	29.3	0.35
Equivalent	3.37	30.0	40.7	33.4	37.9	23.4	0.28
Ex originator	7.88	70.0	34.5	54.7	62.1	33.2	0.39
Patent covered	3.13	21.8	-67.9	4.4	4.8	-78.6	1.95
Lipid lowering agents	**14.39**	**100.0**	**-20.1**	**92.5**	**100.0**	**4.2**	**0.43**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.5b. Lipid lowering agents, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

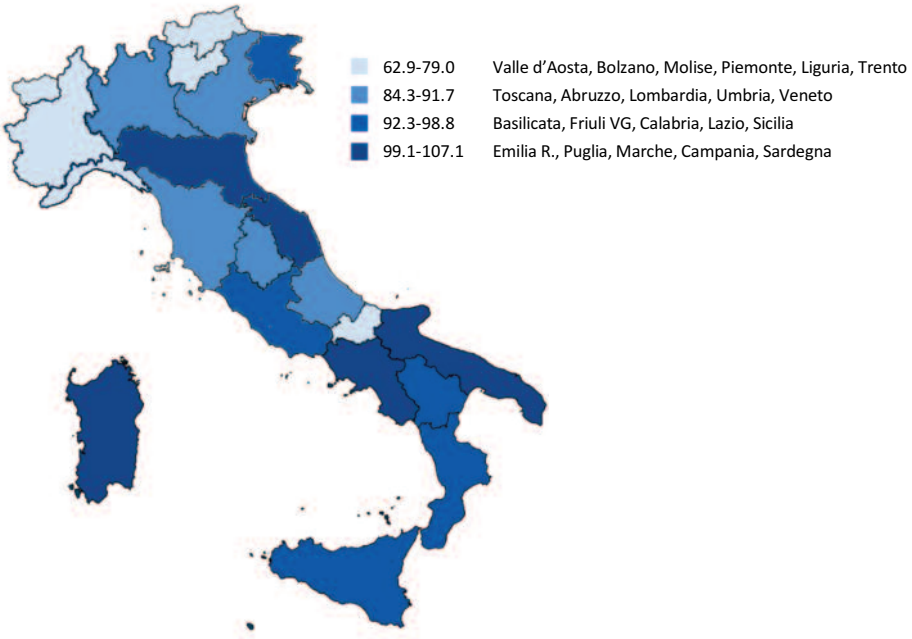


Table 5.2.5e. Duration of therapy with lipid lowering agents by geographic area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	5.4	288.6	224.0	9.1
Centre	6.4	280.4	224.0	9.9
South and islands	6.8	272.8	224.0	10.0
Lipid-lowering agents	**6.1**	**281.0**	**224.0**	**9.6**

Platelet aggregation inhibitors and anticoagulants

- Consumption of platelet aggregation inhibitors and anticoagulants in the last 6 years is stable, recording 94 DDD in 2018; new oral anticoagulants are the category with the greatest increase compared to the previous year (+27.6%), followed by ticagrelor (+14.7%) and by clopidogrel plain or in combination (+9.7%); platelet aggregation inhibitors are the most used category with 58.9 DDD, also showing a high difference in use at the regional level;
- the trend of use of NOAs is confirmed also at the level of single substances; in fact apixaban, rivaroxaban, dabigatran and edoxaban are the molecules with the greatest variation compared to 2017;
- expired patent medicines represent 61.8% of the doses and 14.6% of the category expenditure, of which only a third refers to equivalent products;
- regional variability shifts from 70.8 DDD of the Autonomous Province of Bolzano to 115.9 DDD of Emilia Romagna, which is the region with the lowest average cost per day of therapy, while Lombardia shows the highest cost.

Figure 5.2.6a. Platelet aggregation inhibitors and anticoagulants, temporal consumption trend (2013-2018)

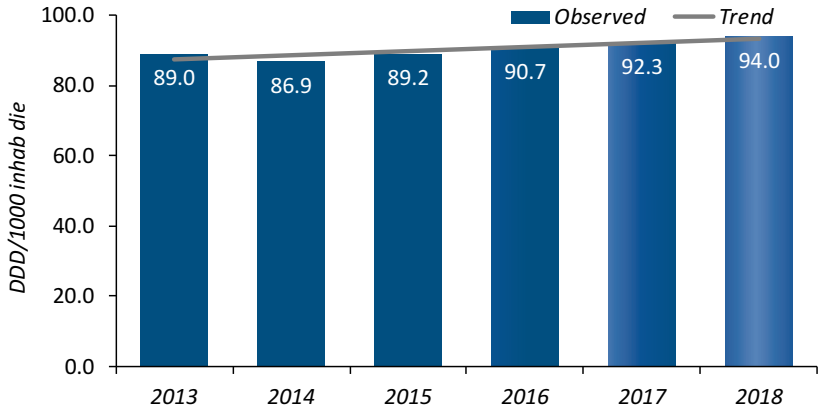


Table 5.2.6a. Platelet aggregation inhibitors and anticoagulants, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
New oral anticoagulants	0.2	1.6	3.4	5.3	7.3	9.4	27.6
Low molecular weight heparins	9.7	9.7	9.7	9.5	9.2	8.9	-3.8
Platelet aggregation inhibitors excl. clopidogrel, prasugrel and ticagrelor	64.9	60.3	60.2	59.5	59.3	58.9	-0.7
Clopidogrel plain or in association	5.9	7.1	8.1	8.8	9.3	10.2	9.7
Platelet aggregation inhibitors with vasodilator effect	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-0.9
Ticagrelor	0.3	0.5	0.6	0.7	0.8	1.0	14.7
Fondaparinux	0.3	0.3	0.4	0.4	0.5	0.5	-2.0
Vitamin K antagonists	6.9	6.5	6.1	5.6	5.1	4.6	-10.1
Heparin	0.5	0.6	0.4	0.5	0.4	0.4	-5.5
Prasugrel	0.3	0.3	0.3	0.3	0.2	0.2	-24.5
Glycoprotein IIb/IIIa inhibitors	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-12.4
Thrombin III inhibitors	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-10.9
Platelet aggregation inhibitors and anticoagulants	**89.0**	**86.9**	**89.2**	**90.7**	**92.3**	**94.0**	**1.8**
enoxaparin	7.1	7.5	7.6	7.7	7.3	7.2	-1.8
apixaban	0.0	0.2	0.8	1.6	2.3	3.0	28.0
rivaroxaban	0.1	0.6	1.5	2.3	2.8	3.2	14.6
dabigatran	0.2	0.8	1.1	1.4	1.8	2.2	21.0
acetylsalicylic acid	47.0	43.6	44.4	44.5	45.1	45.3	0.4
clopidogrel	5.9	7.1	8.1	8.8	9.3	10.2	9.7
edoxaban	-	-	-	<0.05	0.4	1.0	>100
ticagrelor	0.3	0.5	0.6	0.7	0.8	1.0	14.7
calcium nadroparin	1.6	1.4	1.4	1.2	1.2	1.1	-8.2
treprostinil	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	3.2

Table 5.2.6b. Platelet aggregation inhibitors and anticoagulants, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	88.2	90.0	90.3	91.6	93.5	95.0	1.5
Valle d'Aosta	91.7	94.3	95.1	78.2	81.3	82.1	1.0
Lombardia	78.5	65.6	68.1	69.6	70.0	71.3	1.9
PA Bolzano	75.8	70.8	70.9	69.9	75.2	70.8	-5.8
PA Trento	95.2	98.6	98.9	100.7	102.6	105.3	2.5
Veneto	86.8	67.5	71.4	74.6	75.2	77.4	2.9
Friuli VG	100.5	99.9	98.7	97.7	98.0	100.0	2.1
Liguria	89.6	84.1	84.0	83.0	84.7	86.1	1.7
Emilia R.	111.5	111.1	111.2	110.0	114.3	115.9	1.4
Toscana	105.3	103.7	105.6	105.5	102.0	103.1	1.0
Umbria	102.2	100.3	102.7	104.4	105.6	107.3	1.6
Marche	93.4	95.0	101.3	109.3	112.5	110.5	-1.7
Lazio	85.8	90.7	94.1	96.3	99.4	100.9	1.5
Abruzzo	100.4	102.9	105.3	107.5	109.6	112.6	2.8
Molise	96.5	103.9	103.8	104.6	108.1	110.8	2.5
Campania	69.3	75.6	79.4	81.8	84.4	88.6	5.0
Puglia	92.9	99.2	102.9	105.1	106.7	109.1	2.3
Basilicata	95.5	95.7	96.2	97.3	101.0	102.1	1.1
Calabria	96.8	99.3	101.0	103.5	104.3	106.4	2.0
Sicilia	84.9	86.1	88.1	90.3	93.2	94.3	1.2
Sardegna	94.1	98.6	98.8	98.5	99.1	101.1	2.0
Italy	**89.0**	**86.9**	**89.2**	**90.7**	**92.3**	**94.0**	**1.8**

Table 5.2.6c. Platelet aggregation inhibitors and anticoagulants, prescription by therapeutic category and substance in 2018

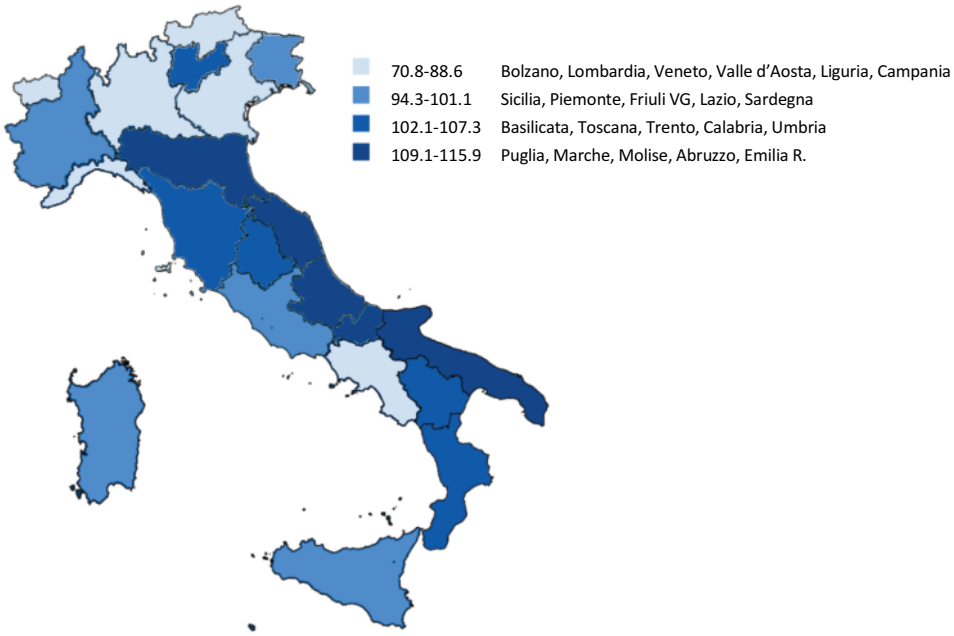
Subgroups and substances	Gross per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
New oral anticoagulants	7.36	17.8	9.4	27.6
Low molecular weight heparins	4.24	-13.1	8.9	-3.8
Platelet aggregation inhibitors excl. clopidogrel, prasugrel and ticagrelor	2.21	2.3	58.9	-0.7
Clopidogrel plain or in association	1.15	4.5	10.2	9.7
Platelet aggregation inhibitors with vasodilating effect	0.92	2.8	<0.05	-0.9
Ticagrelor	0.86	15.2	1.0	14.7
Fondaparinux	0.27	-3.2	0.5	-2.0
Vitamin K antagonists	0.19	-10.1	4.6	-10.1
Heparin	0.16	-4.0	0.4	-5.5
Prasugrel	0.09	-20.0	0.2	-24.5
Glycoprotein IIb/IIIa inhibitors	0.06	-42.3	<0.05	-12.4
Thrombin III inhibitors	0.04	-25.0	<0.05	-10.9
Platelet aggregation inhibitors and anticoagulants	**17.56**	**3.5**	**94.0**	**1.8**
enoxaparin	3.09	-12.9	7.2	-1.8
apixaban	2.68	13.8	3.0	28.0
rivaroxaban	2.17	13.4	3.2	14.6
dabigatran	1.50	-5.5	2.2	21.0
acetylsalicylic acid	1.16	-0.1	45.3	0.4
clopidogrel	1.15	4.5	10.2	9.7
edoxaban	1.01	>100	1.0	>100
ticagrelor	0.86	15.2	1.0	14.7
calcium nadroparin	0.80	-12.0	1.1	-8.2
treprostinil	0.63	3.5	<0.05	3.2

Table 5.2.6d. Prescription of platelet aggregation inhibitors and anticoagulants with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	Average cost DDD
Patent expired	2.56	14.6	0.5	58.0	61.8	1.2	0.12
Equivalent	0.68	26.6	0.7	17.7	30.5	8.9	0.11
Ex originator	1.88	73.4	0.5	40.3	69.5	-1.8	0.13
Patent covered	15.00	85.4	4.0	35.9	38.2	2.9	1.14
Platelet aggregation inhibitors and anticoagulants	**17.56**	**100.0**	**3.5**	**94.0**	**100.0**	**1.8**	**0.51**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.6b. Platelet aggregation inhibitors and anticoagulants, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)



Antiasthmatics

- In 2018 the DDD of anti-asthmatic medicines were 33.5, recording a reduction by 3.6% compared to 2013; expenditure reached euro 16.21 per capita;
- beta2 agonists in combination were the most prescribed category in 2018: 8.99 euro per capita and 14.2 DDD (+5.4% compared to 2017) followed by anticholinergic bronchodilators (6.6 DDD) and by anti-inflammatory inhaled corticosteroids which, with 5.5 DDD, show a reduction by 11% compared to the previous year;
- the first three substances with the highest prescription are beta2 agonists: beclometasone+formoterol, salmeterol+fluticasone and fluticasone+vilanterol whose variation compared to 2017 is respectively +9.2%, -12% and +18%;
- Campania is the Region with the highest consumption (43.6 DDD) while Puglia is the region recording a major reduction compared to 2017 (-8.6%);
- expired patent medicines represent 34.7% of the doses of anti-asthmatics even if the use of equivalent medicines decreases; the average cost per day of treatment for patented medicines is more than double compared to those with expired patents (1.62 vs 0.76).

Figure 5.2.7a. Antiasthmatics, temporal consumption trend (2013-2018)

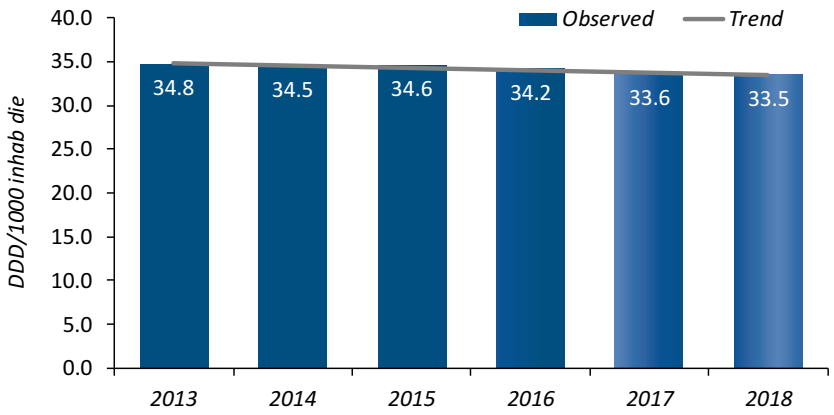


Table 5.2.7a. Antiasthmatics, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Beta-2-adrenoreceptor agonists in combination	11.4	11.6	12.2	13.0	13.5	14.2	5.4
Bronchodilators - anticholinergics	6.0	6.4	6.7	6.5	6.4	6.6	2.7
Anti-inflammatory - corticosteroids inhal.	7.6	7.2	7.0	6.6	6.2	5.5	-11.0
Bronchodilators - beta2 agonists	6.3	6.0	5.7	5.2	4.7	4.5	-4.5
Other antiasthmatics	<0.05	0.1	0.1	0.1	0.1	0.1	11.2
Leukotriene receptor antagonists	2.2	2.1	2.1	2.0	2.0	2.0	-0.4
Bronchodilators - theophylline	1.2	1.0	0.8	0.7	0.6	0.5	-14.4
Anti-inflammatory - chromones	0.1	0.1	0.1	0.1	0.1	<0.05	-43.5
Antiasthmatics	**34.8**	**34.5**	**34.6**	**34.2**	**33.6**	**33.5**	**-0.3**
beclometasone/formoterole	2.5	2.7	2.8	3.0	3.2	3.5	9.2
salmeterol/fluticasone	6.0	5.9	5.3	4.4	3.8	3.3	-12.0
fluticasone/vilanterol	-	-	1.0	2.0	2.6	3.0	18.0
tiotropium	4.7	4.1	3.8	3.4	3.0	2.8	-4.8
budesonide/formoterole	1.4	1.4	1.3	1.3	1.3	1.6	22.6
beclometasone	4.0	3.8	3.9	3.6	3.4	2.3	-31.1
omalizumab	<0.05	<0.05	<0.05	0.1	0.1	0.1	18.8
aclidinium	0.2	0.6	0.9	1.1	1.2	1.2	2.0
glycopyrronium	0.2	0.8	1.1	1.1	1.1	1.0	-4.5
montelukast	2.1	2.1	2.1	2.0	2.0	2.0	-0.2

Table 5.2.7b. Antiasthmatics, weighted regional trend of DDD/1000 inhab. per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	31.8	31.4	31.1	30.5	29.8	29.7	-0.3
Valle d'Aosta	41.3	39.7	38.2	35.0	34.2	34.5	0.7
Lombardia	30.8	31.0	31.3	31.3	31.0	31.7	2.5
PA Bolzano	26.7	26.4	26.9	26.8	26.1	26.5	1.7
PA Trento	31.3	31.6	31.5	31.2	30.7	31.2	1.6
Veneto	29.4	29.2	29.1	29.1	28.9	28.8	-0.5
Friuli VG	30.4	30.1	30.5	30.5	30.8	30.4	-1.3
Liguria	33.6	33.1	33.7	33.2	33.2	33.5	1.0
Emilia R.	34.1	33.3	33.7	33.7	33.0	33.1	0.1
Toscana	34.7	34.4	35.2	34.9	34.6	34.3	-1.0
Umbria	33.2	31.9	31.6	31.6	31.3	31.9	2.0
Marche	30.8	31.2	30.6	30.9	30.4	29.8	-1.9
Lazio	40.7	39.2	39.3	38.2	37.8	38.1	0.6
Abruzzo	29.7	29.6	29.5	29.7	29.4	29.7	1.2
Molise	27.2	28.0	27.2	26.0	25.3	24.6	-2.6
Campania	42.7	43.6	43.9	43.5	42.5	43.6	2.6
Puglia	39.9	40.7	40.9	40.2	37.9	34.7	-8.6
Basilicata	37.9	38.6	37.8	37.1	36.7	34.9	-4.8
Calabria	34.1	34.3	34.3	33.9	33.3	32.7	-1.8
Sicilia	36.5	34.7	34.3	33.4	32.9	32.2	-2.2
Sardegna	40.4	40.2	40.1	37.3	36.9	36.0	-2.4
Italy	**34.8**	**34.5**	**34.6**	**34.2**	**33.6**	**33.5**	**-0.3**

Table 5.2.7c. Antiasthmatics, prescription by therapeutic category and substance in 2018

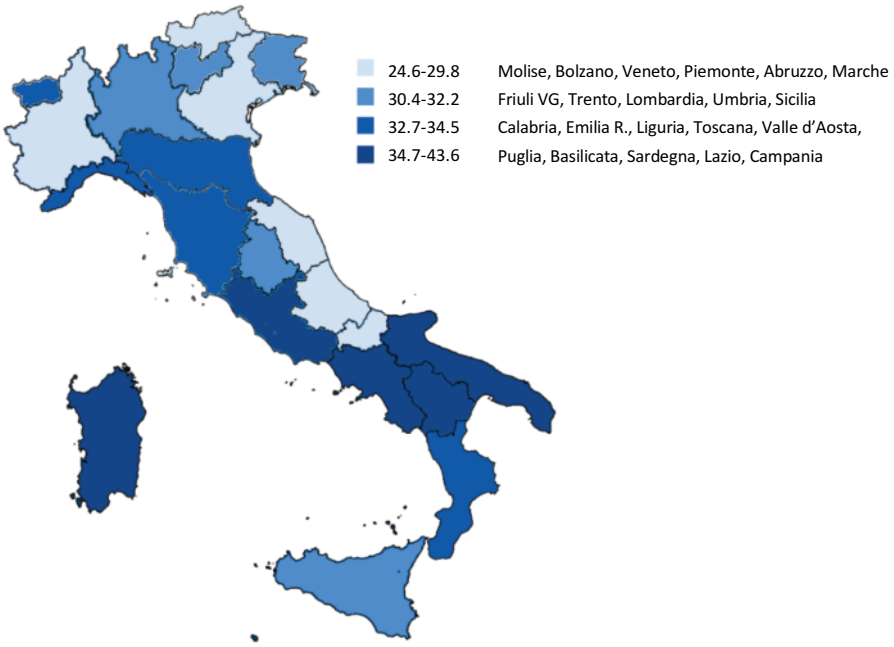
Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 ab die	Δ % 18-17
Beta-2-adrenoreceptor agonists in combination	8.99	3.1	14.2	5.4
Bronchodilators - anticholinergics	3.20	0.4	6.6	2.7
Anti-inflammatory - corticosteroids inhal.	1.97	-13.8	5.5	-11.0
Bronchodilators - beta2 agonists	0.78	-9.7	4.5	-4.5
Other antiasthmatics	0.72	17.7	0.1	11.2
Leukotriene receptor antagonists	0.47	-2.3	2.0	-0.4
Bronchodilators - theophylline	0.07	-9.6	0.5	-14.4
Anti-inflammatory - chromones	0.01	-41.5	<0.05	-43.5
Antiasthmatics	**16.21**	**-0.2**	**33.5**	**-0.3**
beclometasone/formoterol	2.27	9.1	3.5	9.2
salmeterol/fluticasone	2.17	-19.9	3.3	-12.0
fluticasone/vilanterol	1.90	18.2	3.0	18.0
tiotropium	1.50	-10.5	2.8	-4.8
budesonide/formoterol	1.21	17.3	1.6	22.6
beclometasone	0.79	-35.6	2.3	-31.1
omalizumab	0.71	18.3	0.1	18.8
aclidinium	0.69	1.9	1.2	2.0
glycopyrronium	0.56	-4.5	1.0	-4.5
montelukast	0.47	-1.8	2.0	-0.2

Table 5.2.7d. Prescription of antiasthmatics with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	3.24	20.0	102.6	11.6	34.7	47.8	0.76
Equivalent	0.25	7.7	35.8	1.3	11.3	24.7	0.52
Ex originator	2.99	92.3	111.3	10.3	88.7	51.4	0.80
Patent covered	12.98	80.0	-11.4	21.9	65.3	-15.0	1.62
Antiasthmatics	**16.21**	**100.0**	**-0.2**	**33.5**	**100.0**	**-0.3**	**1.33**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.7b. Antiasthmatics, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)



Anti-HCV antivirals

- The analysis of this category should highlight that, in recent years, some important molecules such as sofosbuvir and ledispavir+sofosbuvir have been reclassified to band C (not charged to the NHS);
- in 2018 per capita expenditure amounted to 6.9 euros, decreasing by 56.1% compared to 2017; almost all expenditure is concentrated on the combination of antivirals;
- glecaprevir+pibrentasvir and sofosbuvir+velpatasvir are the most used substances with an expenditure of respectively 3.6 and 2.3 euros, showing an opposite trend compared to 2017, in that the expenditure of the former increased by 717.4% while the latter decreased by 12.2%;
- the regional level also records a general contraction in expenditure, albeit with some variability, ranging from -17.5% in Valle d'Aosta to -80.6% in Calabria; per capita expenditure ranges from a minimum of 3 euros in Calabria to a maximum of 9.4 euros in Campania.

Figure 5.2.8a. Anti-HCV antivirals, temporal trend of per capita expenditure (2013-2018)

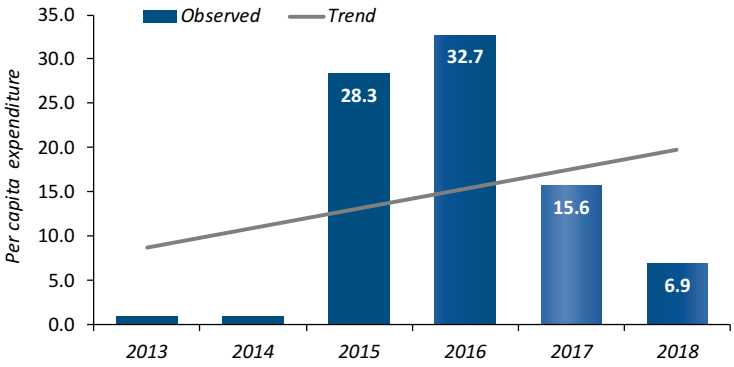


Table 5.2.8a. Anti-HCV antivirals, per capita expenditure by category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Anti-HCV antivirals in combination	-	-	9.5	18.1	10.3	6.9	-33.4
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0.1	0.1	0.1	<0.05	<0.05	<0.05	-83.4
Anti-HCV antivirals	**0.9**	**1.0**	**28.3**	**32.7**	**15.6**	**6.9**	**-56.1**
glecaprevir/pibrentasvir	-	-	-	-	0.4	3.6	>100
sofosbuvir/velpatasvir	-	-	-	-	2.6	2.3	-12.2
elbasvir/grazoprevir	-	-	-	-	1.4	0.8	-42.9
sofosbuvir/velpatasvir/voxilaprevir	-	-	-	-	-	0.2	-
ombitasvir/paritaprevir/ritonavir	-	-	2.2	2.4	0.9	<0.05	-96.5

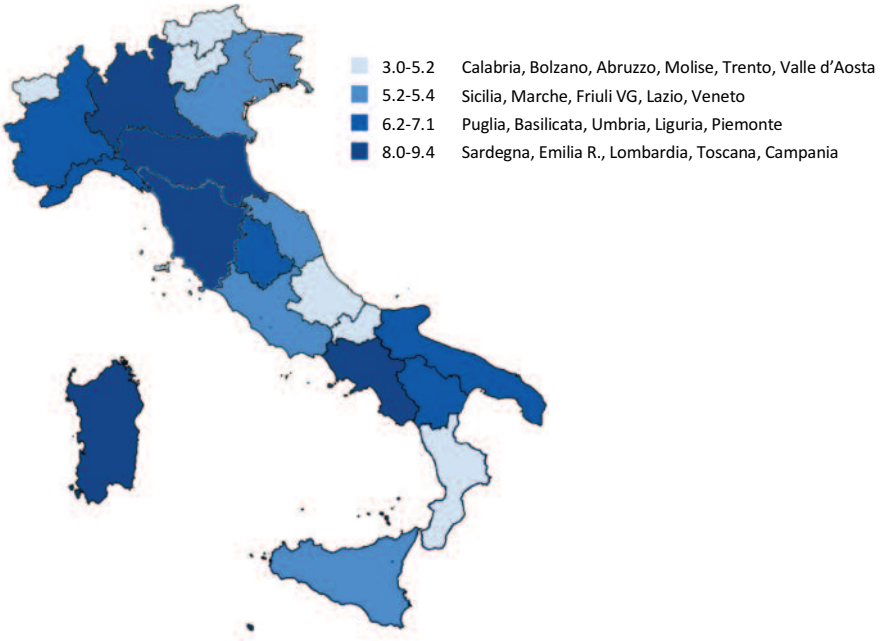
Table 5.2.8b. Anti-HCV antivirals, weighted regional trend of per capita expenditure: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	0.91	0.73	16.82	28.38	16.60	7.11	-57.2
Valle d'Aosta	2.09	0.84	21.20	17.35	6.25	5.15	-17.5
Lombardia	0.88	0.74	31.75	34.99	18.37	8.46	-53.9
PA Bolzano	0.37	0.27	16.91	20.81	7.01	3.50	-50.0
PA Trento	0.22	0.21	13.99	18.92	7.37	5.11	-30.7
Veneto	0.74	0.87	20.38	25.01	12.41	5.42	-56.4
Friuli VG	0.89	0.58	20.17	11.34	9.95	5.28	-46.9
Liguria	1.51	0.69	25.37	25.98	14.79	6.51	-56.0
Emilia R.	0.60	1.45	28.57	30.98	14.92	8.40	-43.7
Toscana	0.57	0.90	37.43	35.87	12.71	8.89	-30.0
Umbria	1.04	0.61	13.88	25.65	10.63	6.36	-40.2
Marche	0.37	0.79	20.35	19.23	9.98	5.28	-47.1
Lazio	0.73	0.63	24.96	30.15	11.36	5.29	-53.4
Abruzzo	0.70	0.78	21.47	18.51	9.94	3.88	-61.0
Molise	0.38	0.43	20.44	25.79	10.64	4.37	-59.0
Campania	1.96	1.88	40.77	53.24	26.71	9.36	-65.0
Puglia	1.46	1.27	37.26	37.28	16.87	6.17	-63.4
Basilicata	0.78	0.99	30.00	32.70	15.40	6.32	-58.9
Calabria	0.59	1.01	30.88	32.91	15.68	3.04	-80.6
Sicilia	0.66	1.41	26.57	34.42	14.46	5.19	-64.1
Sardegna	0.58	0.80	33.91	40.50	18.96	8.00	-57.8
Italy	**0.91**	**0.99**	**28.32**	**32.71**	**15.61**	**6.86**	**-56.1**

Table 5.2.8c. Anti-HCV antivirals, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Anti-HCV antivirals in combination	6.86	-33.4	0.2	3.2
Nucleosides and nucleotides excl.reverse transcriptase inhibitors	<0.005	-83.4	<0.05	-87.0
Anti-HCV antivirals	**6.86**	**-56.1**	**0.2**	**-25.6**
glecaprevir/pibrentasvir	3.58	>100	0.1	>100
sofosbuvir/velpatasvir	2.27	-12.2	0.1	22.3
elbasvir/grazoprevir	0.83	-42.9	<0.05	-19.0
sofosbuvir/velpatasvir/voxilaprevir	0.18	-	<0.05	-
ombitasvir/paritaprevir/ritonavir	0.03	-96.5	<0.05	-96.5

Figure 5.2.8b. Anti-HCV antivirals, distribution in quartiles of 2018 per capita expenditure



Antacid and antiulcer pharmaceuticals

- The declining trend in the use of antacids and anti-ulcer pharmaceuticals continues (DDD: -8.3% compared to 2013); in 2018 per capita expenditure was euro 14.32 and the DDD were 79.4, representing about 7% of the doses charged to the NHS;
- proton pump inhibitors is the most prescribed category (70.9 DDD equal to 90% of the entire category), showing a slight decrease compared to 2017 (-0.8%), and 5 substances belonging to this category are among the most prescribed ones (pantoprazole, lansoprazole, omeprazole, esomeprazole and rabeprazole);
- the levels of use of Campania (110.9 DDD) are more than double compared to the Autonomous Province of Bolzano (46.1 DDD); Marche (-12.1%), Sicilia (-9.6%) and Puglia (-7.2%) are the regions with the largest reduction in doses compared to 2017;
- expired patent medicines represent more than 90% of antacid and antiulcer doses;
- the analysis of the 2018 prescription in the population shows an increasing use with age without differences between men and women; the prevalence reaches about 60% in the age group >75 years; overall, the average duration of treatment is 3 months and 26% of users receive a single prescription in a year.

Figure 5.2.9a. Antacid and antiulcer pharmaceuticals, temporal consumption trend (2013-2018)

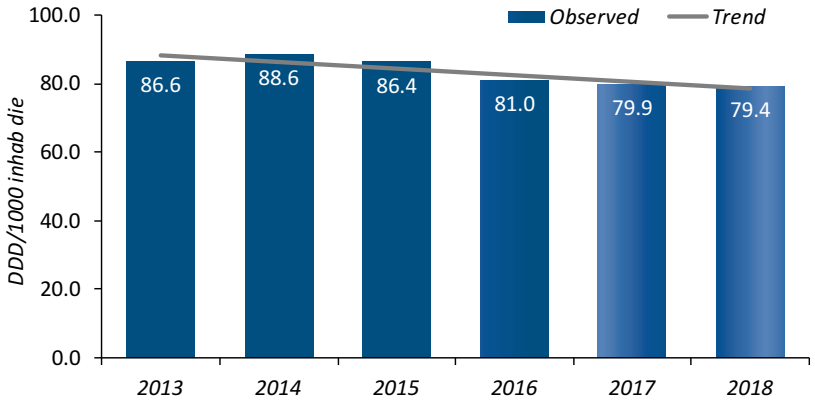


Table 5.2.9a. Antacid and antiulcer pharmaceuticals, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Proton pump inhibitors	78.2	80.1	77.9	72.6	71.5	70.9	-0.8
Other medicines for peptic ulcer	3.9	4.0	4.0	4.1	4.0	4.1	1.7
Antacids	1.8	1.9	2.0	2.0	2.0	2.0	2.7
H2-receptor antagonists	2.6	2.5	2.4	2.4	2.3	2.3	-0.1
Prostaglandins	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-9.6
Antacid and antiulcer pharmaceuticals	**86.6**	**88.6**	**86.4**	**81.0**	**79.9**	**79.4**	**-0.6**
pantoprazole	19.8	21.7	22.1	21.5	21.8	22.8	4.7
lansoprazole	22.9	21.8	20.0	17.8	16.7	15.7	-6.0
omeprazole	20.4	20.5	19.8	18.5	17.9	17.4	-2.8
esomeprazole	12.6	13.4	13.2	12.4	12.7	12.8	0.7
sodium alginate/potassium bicarbonate	3.5	3.7	3.8	3.8	3.8	3.9	2.0
magaldrate	1.7	1.8	1.8	1.9	1.9	1.9	1.6
rabeprazole	2.4	2.7	2.7	2.5	2.3	2.1	-9.7
ranitidine	2.6	2.5	2.4	2.4	2.3	2.3	-0.1
sucralfate	0.4	0.3	0.3	0.3	0.2	0.2	-3.6
misoprostol	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-9.6

Table 5.2.9b. Antacid and antiulcer pharmaceuticals, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	80.7	83.2	79.3	70.8	68.7	68.7	0.0
Valle d'Aosta	75.4	78.4	74.9	65.5	64.3	67.3	4.6
Lombardia	66.9	70.8	73.8	74.3	74.7	77.2	3.3
PA Bolzano	40.6	43.2	44.1	44.5	45.2	46.9	3.8
PA Trento	70.8	71.2	74.3	78.0	82.8	84.9	2.5
Veneto	80.3	80.8	76.3	68.9	64.8	64.7	-0.2
Friuli VG	73.3	74.7	73.3	73.1	72.7	70.6	-2.9
Liguria	94.7	95.7	94.5	90.2	89.9	91.8	2.1
Emilia R.	75.6	77.4	76.6	68.1	65.4	66.4	1.4
Toscana	68.2	71.0	70.0	68.0	67.3	64.4	-4.4
Umbria	85.6	87.9	89.1	85.7	86.6	88.6	2.4
Marche	77.2	81.9	82.6	81.1	79.0	69.4	-12.1
Lazio	104.7	103.2	96.0	84.4	84.6	86.2	1.8
Abruzzo	78.6	83.2	85.0	75.8	76.4	78.6	2.9
Molise	84.4	90.6	88.8	65.5	69.8	75.5	8.0
Campania	90.7	99.7	105.1	104.1	106.6	110.9	4.0
Puglia	103.1	109.8	95.0	90.0	87.4	81.2	-7.2
Basilicata	77.0	83.4	84.8	77.6	79.6	82.2	3.3
Calabria	113.3	117.8	103.4	89.9	90.4	91.3	0.9
Sicilia	123.5	110.5	105.6	100.2	94.7	85.6	-9.6
Sardegna	103.6	108.5	110.3	94.4	87.2	83.6	-4.2
Italy	**86.6**	**88.6**	**86.4**	**81.0**	**79.9**	**79.4**	**-0.6**

Table 5.2.9c. Antacid and antiulcer pharmaceuticals, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Proton pump inhibitors	12.66	-5.2	70.9	-0.8
Other medicines for peptic ulcer	0.87	1.9	4.1	1.7
Antacids	0.43	2.4	2.0	2.7
H2-receptor antagonists	0.36	-18.0	2.3	-0.1
Prostaglandins	0.01	-10.2	0.0	-9.6
Antacid and antiulcer pharmaceuticals	**14.32**	**-5.0**	**79.4**	**-0.6**
pantoprazole	4.58	-2.1	22.8	4.7
lansoprazole	2.72	-9.0	15.7	-6.0
omeprazole	2.57	-7.2	17.4	-2.8
esomeprazole	2.40	-3.9	12.8	0.7
sodium alginate/potassium bicarbonate	0.83	2.2	3.9	2.0
magaldrate	0.42	2.3	1.9	1.6
rabeprazole	0.39	-8.6	2.1	-9.7
ranitidine	0.35	-18.1	2.3	-0.1
sucralfate	0.04	-3.7	0.2	-3.6
misoprostol	0.01	-10.2	<0.05	-9.6

Table 5.2.9d. Prescription of antacid and antiulcer pharmaceuticals with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 ab die	%	Δ % 18-17	DDD average cost
Patent expired	12.86	89.8	-4.8	72.8	91.8	-0.6	0.48
Equivalent	6.18	48.0	2.0	39.1	53.7	9.1	0.43
Ex originator	6.68	52.0	-10.4	33.7	46.3	-9.9	0.54
Patent covered	1.46	10.2	-5.5	6.5	8.2	0.3	0.61
Antacid and antiulcer pharmaceuticals	**14.32**	**100.0**	**-5.0**	**79.4**	**100.0**	**-0.6**	**0.49**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.9b. Antacid and antiulcer pharmaceuticals, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

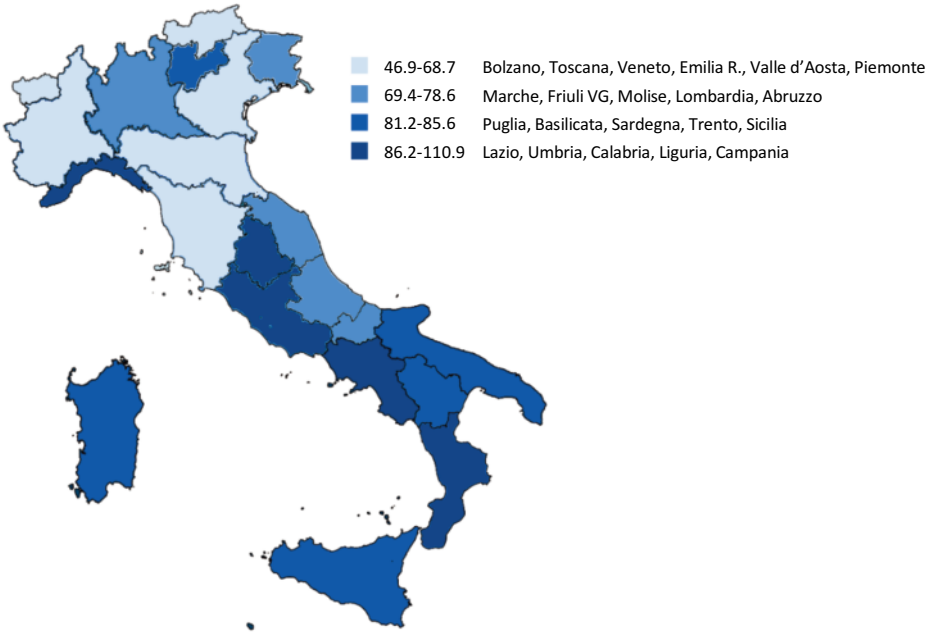


Table 5.2.9e. Duration of therapy with antacid and antiulcer pharmaceuticals by geographic area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	5.9	148.1	102.7	26.2
Centre	6.2	134.4	84.0	26.8
South and islands	6.5	135.1	84.0	25.4
Antacid and antiulcer pharmaceuticals	**6.2**	**140.0**	**93.3**	**26.0**

Antidiabetics

- In the last 6 years consumption of antidiabetics has remained stable; in 2018 the doses were 63.2 with an expenditure of 15.63 euros per capita, so increasing by 4.7%; metformin alone accounts for about 35% of total doses, with a 2% increase compared to the previous year, followed by insulins and analogues with 15.3 DDD and other oral hypoglycemic agents with 11.9 DDD; incretino-mimetic medicines, in particular GLP-1 analogues, show a marked increase in use (GLP-1: + 28.9% and DPP-4; + 10.1%);
- insulins, in particular insulin lispro (1.87 euro), glargine (1.78 euro) and aspart (1.54 euro), are the highest-spending category, although decreasing by 2.3% compared to the previous year; the greatest variability of use at regional level is also reported for this class;
- in 2018 the lowest consumption of antidiabetics was found in the Autonomous Province of Bolzano (40.6 DDD), while Calabria is the region with the highest value, equal to 84 DDD;
- more than half of the prescribed doses (56.2%) refers to patent-expired molecules, even if the use of equivalent medicines decreases; the average cost per day of therapy for patent-expired medicines is € 0.21 and rises to € 1.28 for those still covered by patent;
- the duration of therapy is consistent with the chronic use of these medicines; in fact, half of the population has been in treatment for more than 10 months and only 7.5% of the patients received a single prescription in 2018; all age groups reported a consumption in men of about 50% higher than in women and this difference also remains in terms of prevalence; for example, in the age group above 75 years, the prevalence is 22% in men and 17.4% in women.

Figure 5.2.10a. Antidiabetics pharmaceuticals, temporal consumption trend (2013-2018)

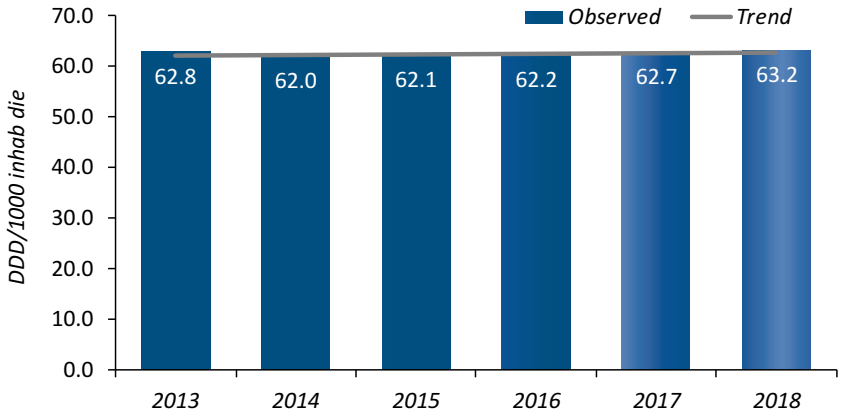


Table 5.2.10a. Antidiabetic pharmaceuticals, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Insulins and analogues	14.7	14.8	15.1	15.2	15.4	15.3	-0.4
Gliptins (DPP-4 inhibitors) plain or in combination	3.5	3.4	4.1	4.8	5.1	5.7	10.1
GLP-1 (glucagon-like peptide 1) analogues	0.8	0.7	0.8	1.0	1.3	1.7	28.9
Metformin	19.8	20.3	20.6	21.0	21.6	22.1	2.0
Gliflozine plain or in combination	-	-	0.1	0.7	1.4	2.1	50.5
Other oral hypoglycemic pharmaceuticals	17.9	16.6	15.5	14.3	13.1	11.9	-9.3
Pioglitazone plain or in combination	2.1	2.2	2.1	1.9	1.7	1.7	-3.6
Repaglinide	4.0	3.9	3.6	3.3	3.0	2.6	-11.8
Insulins in combination with GLP-1	-	-	-	-	<0.05	0.1	>100
Antidiabetics	**62.8**	**62.0**	**62.1**	**62.2**	**62.7**	**63.2**	**0.8**
insulin lispro	4.0	4.0	4.0	4.0	4.0	4.0	1.1
insulin glargine	3.9	4.0	4.0	4.2	4.4	4.6	3.1
insulin aspart	3.1	3.2	3.2	3.2	3.1	3.1	-1.3
metformin	19.8	20.3	20.6	21.0	21.6	22.1	2.0
insulin degludec	-	<0.05	0.7	1.0	1.2	1.3	8.8
dulaglutide	-	-	-	0.2	0.5	0.8	64.6
liraglutide	0.7	0.6	0.6	0.6	0.7	0.8	11.0
insulin glulisine	1.3	1.3	1.4	1.4	1.4	1.4	-1.5
sitagliptin/metformin	1.3	1.1	1.1	1.3	1.3	1.4	7.3
linagliptin	0.0	0.2	0.5	0.7	0.9	1.1	26.8

Table 5.2.10b. Antidiabetic pharmaceuticals, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	60.2	59.6	59.5	59.3	59.7	59.2	-0.8
Valle d'Aosta	59.6	60.3	60.3	57.0	58.9	59.7	1.3
Lombardia	56.5	55.6	56.6	56.2	56.4	56.5	0.0
PA Bolzano	41.9	43.1	42.8	40.6	40.8	40.6	-0.5
PA Trento	49.5	48.7	48.0	49.4	48.6	49.0	0.8
Veneto	53.7	52.3	52.6	52.2	52.4	53.3	1.8
Friuli VG	57.4	57.3	56.2	57.3	58.4	59.0	1.1
Liguria	52.6	51.5	50.8	50.2	49.6	49.8	0.4
Emilia R.	58.8	58.1	58.7	59.1	60.8	61.2	0.7
Toscana	59.8	58.2	57.7	56.6	56.8	57.4	1.0
Umbria	60.5	57.5	57.3	57.5	57.9	58.4	0.8
Marche	50.1	50.4	53.0	54.7	55.3	56.0	1.3
Lazio	66.2	63.2	63.0	63.1	63.9	64.0	0.1
Abruzzo	65.0	63.9	63.8	63.5	64.5	65.5	1.6
Molise	62.4	64.5	63.4	63.4	64.7	65.6	1.3
Campania	67.3	68.4	69.2	70.2	71.2	72.0	1.2
Puglia	73.6	73.5	73.1	74.1	74.7	75.4	0.9
Basilicata	69.8	70.0	70.2	71.6	74.3	74.6	0.3
Calabria	78.5	78.8	78.8	80.4	80.2	84.0	4.7
Sicilia	80.3	79.0	78.2	78.0	77.8	78.0	0.3
Sardegna	67.6	67.1	66.2	64.9	66.7	67.5	1.2
Italy	**62.8**	**62.0**	**62.1**	**62.2**	**62.7**	**63.2**	**0.8**

Table 5.2.10c. Antidiabetic pharmaceuticals, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Insulins and analogues	7.03	-2.3	15.3	-0.4
Gliptins (DPP-4 inhibitors) plain or in combination	2.48	4.4	5.7	10.1
GLP-1 (glucagon-like peptide 1) analogues	1.62	22.6	1.7	28.9
Metformin	1.51	3.7	22.1	2.0
Gliflozine plain or in combination	1.04	42.6	2.1	50.5
Other oral hypoglycemic pharmaceuticals	0.87	-6.7	11.9	-9.3
Pioglitazone plain or in combination	0.48	-6.0	1.7	-3.6
Repaglinide	0.36	-11.1	2.6	-11.8
Insulins in combination with GLP-1	0.25	>100	0.1	>100
Antidiabetics	**15.63**	**4.7**	**63.2**	**0.8**
insulin lispro	1.87	-3.8	4.0	1.1
Insulin glargine	1.78	0.6	4.6	3.1
insulin aspart	1.54	-1.4	3.1	-1.3
metformin	1.51	3.7	22.1	2.0
insulin degludec	0.87	7.2	1.3	8.8
dulaglutide	0.77	52.7	0.8	64.6
liraglutide	0.65	8.2	0.8	11.0
insulin glulisine	0.63	-1.3	1.4	-1.5
sitagliptin/metformin	0.57	0.1	1.4	7.3
linagliptin	0.54	21.8	1.1	26.8

Table 5.2.10d. Prescription of antidiabetic pharmaceuticals with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	2.72	17.4	-0.6	35.5	56.2	-1.5	0.21
Equivalent	0.97	35.7	-0.4	16.2	45.5	-0.6	0.16
Ex originator	1.75	64.3	-0.7	19.3	54.5	-2.2	0.25
Patent covered	12.91	82.6	6.0	27.6	43.8	3.8	1.28
Antidiabetic pharmaceuticals	**15.63**	**100.0**	**4.7**	**63.2**	**100.0**	**0.8**	**0.68**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.10b. Antidiabetic pharmaceuticals, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

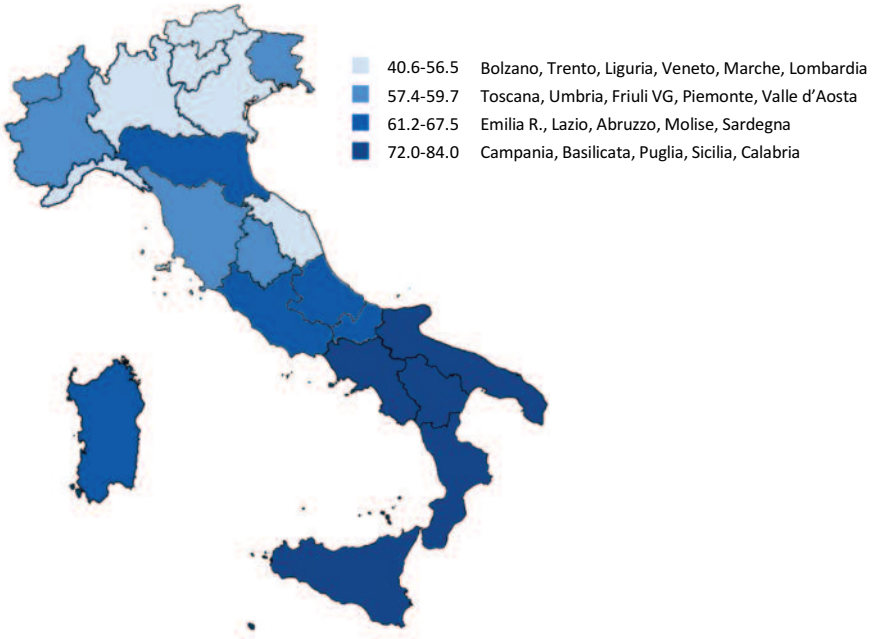


Table 5.2.10e. Duration of therapy with antidiabetic pharmaceuticals by geographic area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	7.4	384.7	300.0	7.3
Centre	8.7	353.2	275.0	8.9
South and islands	9.3	372.6	300.0	6.9
Antidiabetics	**8.5**	**373.3**	**300.0**	**7.5**

Antibiotics

- Since 2013 a slight but steady decrease (CAGR: -2%) was recorded in the consumption of antibiotics, shifting from 20.3 DDD to 18 DDD in 2018;
- the combinations of penicillins, almost entirely represented by amoxicillin + clavulanic acid, is the most prescribed category; in 2018 they recorded an expenditure of 3.52 euros and 6.3 DDD per 1000 inhabitants, followed by quinolones with 2.11 euro per capita and 3 DDD (-5% compared to 2017). It is worth recalling that this category was the subject of an intervention by the EMA in November 2018, namely through marketing suspension of medicines containing cinoxacin, nalidixic acid, flumechin and pipemidic acid and restriction of fluoroquinolones use;
- ceftriaxone is the second substance with the largest expenditure (1.37 euros), showing a 6.5% increase in prescription;
- major differences of use were reported in the Italian regions, in that the prescribed doses vary from 11.2 of the Autonomous Province of Bolzano to 24.7 of Campania; Campania, Umbria, Calabria, Puglia, Lazio, Marche and Basilicata are the regions which record doses and average cost for days of therapy above the national average;
- around 4 out of 10 people received at least one antibiotic prescription in 2018, with higher levels of use in children up to 4 years of age and in people over 75, where the prevalence is over 50%; one user out of two receives a single prescription and, as expected, these medicines are used for a short period (14 days).

Figure 5.2.11a. Antibiotics, temporal consumption trend (2013-2018)

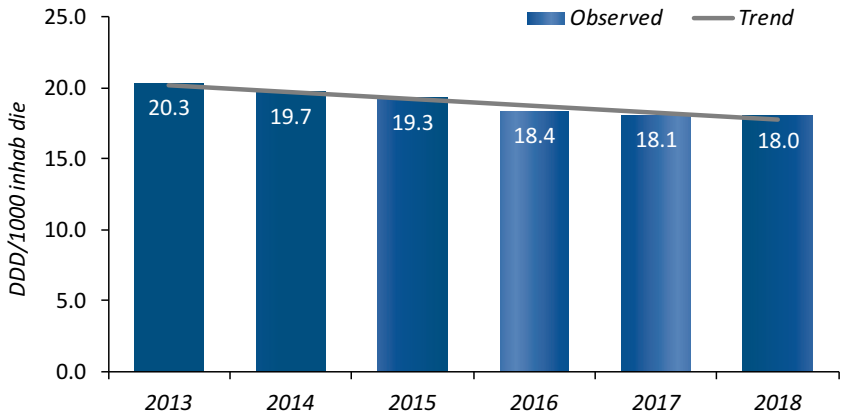


Table 5.2.11a. Antibiotics, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Combinations of penicillins, incl. betalactamase inhibitors	6.6	6.5	6.4	6.3	6.3	6.3	0.2
Quinolones	3.7	3.5	3.5	3.2	3.1	3.0	-5.0
Cephalosporins im/ev III-IV gen	0.7	0.6	0.6	0.6	0.6	0.6	6.9
Macrolides and licosamides	4.4	4.3	4.1	3.9	3.7	3.7	-0.5
Oral cephalosporins	1.7	1.6	1.6	1.6	1.6	1.6	3.5
Antibiotics vs resistant germs	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	18.9
Other antibiotics	0.4	0.4	0.4	0.4	0.4	0.4	4.5
Glycopeptides	0.1	0.1	0.1	0.1	0.1	0.1	-1.9
Broad –spectrum penicillins and penicilllins sensitive to betalactamases	1.8	1.6	1.5	1.4	1.3	1.2	-4.8
Carbapenems	0.1	0.1	<0.05	<0.05	<0.05	<0.05	39.8
Aminoglycosides	0.1	0.1	0.1	0.1	0.1	0.1	-3.1
Cephalosporins im/ev I gen	0.1	0.1	0.1	0.1	0.1	0.1	1.4
Tetracyclines	0.3	0.3	0.3	0.3	0.3	0.3	4.6
Sulfonamides and trimetropim	0.3	0.3	0.3	0.3	0.3	0.4	3.6
Cephalosporins im/ev II gen	0.2	0.2	0.1	0.1	0.1	0.1	-4.5
Monobactams	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-11.4
Antibiotics	**20.3**	**19.7**	**19.3**	**18.4**	**18.1**	**18.0**	**-0.4**
amoxicillin/clavulanic acid	6.4	6.4	6.3	6.1	6.2	6.2	0.5
ceftriaxone	0.5	0.5	0.5	0.5	0.5	0.5	6.5
ciprofloxacin	1.2	1.2	1.2	1.2	1.1	1.0	-7.5
levofloxacin	1.9	1.9	1.9	1.8	1.7	1.7	-3.1
cefixime	1.0	1.0	1.0	1.0	1.0	1.1	3.8
clarithromycin	2.8	2.7	2.6	2.4	2.3	2.2	-1.6
azithromycin	1.4	1.4	1.4	1.3	1.3	1.3	2.3
fosfomycin	0.4	0.4	0.4	0.4	0.4	0.4	2.9
piperacillin/tazobactam	0.1	0.1	0.1	0.1	0.1	0.1	-10.4
teicoplanin	0.1	<0.05	<0.05	<0.05	<0.05	<0.05	-6.6

Table 5.2.11b. Antibiotics, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	17.0	16.4	16.1	15.1	14.8	15.1	1.9
Valle d'Aosta	17.4	16.9	16.8	14.7	14.8	15.3	2.9
Lombardia	16.6	16.1	16.0	15.2	15.0	15.1	0.2
PA Bolzano	12.7	12.2	12.0	11.1	10.9	11.2	2.5
PA Trento	16.4	16.4	16.2	15.1	15.6	15.5	-0.6
Veneto	16.1	15.8	15.0	14.2	14.3	14.3	-0.2
Friuli VG	15.9	14.9	14.8	13.8	14.5	14.2	-1.8
Liguria	15.4	14.4	14.2	13.1	13.5	13.7	1.3
Emilia R.	18.3	17.7	17.0	16.2	15.9	16.1	1.4
Toscana	19.4	18.9	18.9	17.9	17.4	17.0	-2.4
Umbria	22.9	22.2	21.5	20.7	20.5	20.5	-0.4
Marche	21.7	21.3	20.5	20.1	19.6	19.8	1.0
Lazio	22.9	21.3	20.8	19.7	19.5	19.4	-0.6
Abruzzo	22.8	22.8	22.3	21.9	21.5	22.3	3.6
Molise	21.8	22.2	21.3	19.8	19.0	19.4	2.2
Campania	27.4	27.1	26.6	25.9	24.7	24.7	-0.1
Puglia	26.0	26.1	25.3	24.5	22.8	21.8	-4.2
Basilicata	23.1	23.1	21.9	20.8	20.9	20.6	-1.4
Calabria	24.3	24.3	23.6	22.6	22.6	21.9	-3.0
Sicilia	23.8	22.6	21.7	21.0	21.0	21.0	-0.3
Sardegna	18.4	18.1	17.8	16.3	16.6	16.5	-0.9
Italy	**20.3**	**19.7**	**19.3**	**18.4**	**18.1**	**18.0**	**-0.4**

Table 5.2.11c. Antibiotics, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Combinations of penicillins, incl. betalactamase inhibitors	3.52	3.1	6.3	0.2
Quinolones	2.11	-4.8	3.0	-5.0
Cephalosporins im/ev III-IV gen	1.81	3.2	0.6	6.9
Macrolides and licosamides	1.59	-2.5	3.7	-0.5
Oral cephalosporins	1.55	3.7	1.6	3.5
Antibiotics vs resistant germs	1.18	1.3	0.1	18.9
Other antibiotics	0.90	-0.6	0.4	4.5
Glycopeptides	0.51	-24.1	0.1	-1.9
Broad –spectrum penicillins and penicilllins sensitive to betalactamases	0.31	2.5	1.2	-4.8
Carbapenems	0.24	-3.9	<0.05	39.8
Aminoglycosides	0.21	2.1	0.1	-3.1
Cephalosporins im/ev I gen	0.11	-7.3	0.1	1.4
Tetracyclines	0.08	3.7	0.3	4.6
Sulfonamides and trimetropim	0.07	4.1	0.4	3.6
Cephalosporins im/ev II gen	0.07	-1.7	0.1	-4.5
Monobactams	0.04	-11.4	<0.05	-11.4
Antibiotics	**14.29**	**-0.6**	**18.0**	**-0.4**
amoxicillin/clavulanic acid	2.99	0.5	6.2	0.5
ceftriaxone	1.37	1.5	0.5	6.5
ciprofloxacin	0.90	-10.0	1.0	-7.5
levofloxacin	0.89	1.3	1.7	-3.1
cefixime	0.89	3.7	1.1	3.8
clarithromycin	0.75	-5.5	2.2	-1.6
azithromycin	0.70	2.3	1.3	2.3
fosfomycin	0.67	4.5	0.4	2.9
piperacillin/tazobactam	0.49	26.2	0.1	-10.4
teicoplanin	0.43	-29.5	<0.05	-6.6

Table 5.2.11d. Prescription of antibiotics with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	10.04	70.2	0.0	16.0	88.8	-0.1	1.72
Equivalent	2.23	22.2	0.3	4.1	25.7	-0.2	1.48
Ex originator	7.81	77.8	0.0	11.9	74.3	-0.1	1.80
Patent covered	4.25	29.8	-1.0	2.0	11.2	-1.9	5.79
Antibiotics	**14.29**	**100.0**	**-0.6**	**18.0**	**100.0**	**-0.4**	**2.18**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.11b. Antibiotics, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

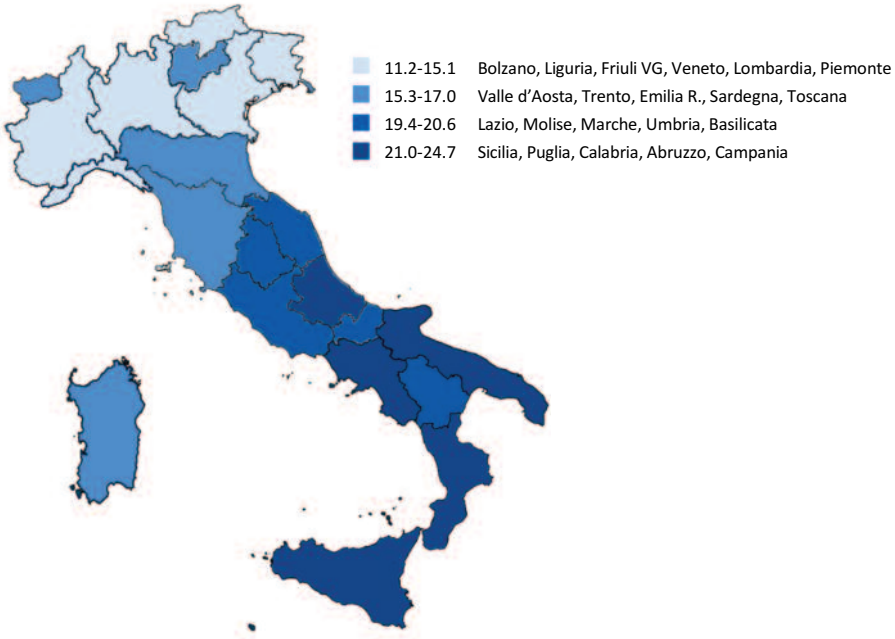


Table 5.2.11e. Duration of therapy with antibiotics by geographic area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	Median DDD	Users with 1 prescription
North	1.9	14.1	10.0	57.5
Centre	2.2	15.1	10.0	50.7
South and islands	2.4	15.5	10.0	46.6
Antibiotics	**2.1**	**14.9**	**10.0**	**51.7**

Anti-HIV antivirals

- The 2018 expenditure for anti-HIV antivirals was higher than 600 million euros, recording a slight decrease compared to 2017;
- antivirals in co-formulated regimes represent 46% of expenditure of this category and in 2018 show an increase of 19.5% compared to 2017, while the expenditure of nucleoside and nucleotide inhibitors of reverse transcriptase decreased by more than 33%;
- the substances with highest per capita expenditures are emtricitabine/ rilpivirine/tenofovir disoproxil (1.77 euros) and dolutegravir/abacavir/lamivudine (1.51 euros), which increased respectively by 22.4% and 38.1%;
- a wide regional variability was recorded in spending, ranging from 2.93 euros in Molise to 18.23 euros in Lombardia.

Figure 5.2.12a. Anti-HIV antivirals, temporal trend of per capita expenditure (2013-2018)

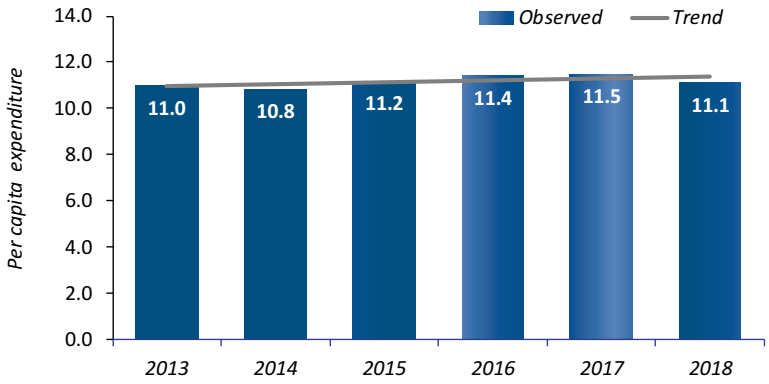


Table 5.2.12a. Anti-HIV antivirals, per capita expenditure by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Anti-HIV antivirals in co-formulated schemes	1.8	2.1	2.5	3.2	4.2	5.1	19.5
Nucleoside and nucleotide reverse transcriptase inhibitors	4.4	4.1	4.0	3.5	2.8	1.9	-33.4
Integrase inhibitors	0.8	0.9	1.3	1.6	1.7	1.8	10.8
Protease inhibitors plain or in combination	3.0	2.9	2.7	2.4	2.1	1.8	-13.5
Non-nucleoside reverse transcriptase inhibitors	0.7	0.6	0.5	0.5	0.4	0.3	-23.2
Other anti-HIV antivirals	0.3	0.3	0.3	0.2	0.2	0.2	-16.6
Anti-HIV antivirals	**11.0**	**10.8**	**11.2**	**11.4**	**11.5**	**11.1**	**-3.1**
dolutegravir/abacavir/lamivudine	-	-	-	0.3	1.1	1.5	38.3
elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide	-	-	-	-	0.5	1.4	>100
emtricitabine/rilpivirine/tenofovir alafenamide	-	-	-	-	0.2	1.3	>100
dolutegravir	-	-	0.3	0.7	0.9	1.2	33.9
emtricitabine/tenofovir alafenamide	-	-	-	-	0.4	1.1	>100
darunavir/cobicistat	-	-	-	0.1	0.6	0.8	41.4
raltegravir	0.8	0.9	0.9	0.9	0.8	0.7	-14.6
emtricitabine/rilpivirine/tenofovir disoproxil	0.1	0.5	1.0	1.3	1.3	0.4	-64.9
darunavir	1.0	1.1	1.2	1.1	0.6	0.4	-37.0
tenofovir disoproxil	0.7	0.7	0.8	0.8	0.7	0.3	-49.8

Table 5.2.12b. Anti-HIV antivirals, weighted regional trend of per capita expenditure: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	10.15	10.07	10.45	11.05	11.12	10.56	-5.0
Valle d'Aosta	4.58	4.75	5.26	5.79	6.64	5.39	-18.9
Lombardia	18.96	18.44	18.74	18.97	18.70	18.23	-2.5
PA Bolzano	7.10	7.19	8.60	6.39	7.14	7.66	7.3
PA Trento	8.18	7.50	8.50	8.05	8.76	8.32	-5.0
Veneto	9.64	9.53	9.26	9.13	9.48	8.42	-11.2
Friuli VG	7.38	6.65	6.28	7.47	7.91	7.21	-8.8
Liguria	10.81	11.10	11.46	11.50	11.63	11.74	0.9
Emilia R.	16.54	15.28	15.49	15.28	15.20	14.16	-6.8
Toscana	11.66	11.57	13.15	13.57	13.71	12.73	-7.2
Umbria	9.49	9.65	9.70	10.41	10.66	11.29	5.9
Marche	9.69	10.03	10.25	10.59	10.63	10.37	-2.5
Lazio	14.22	14.02	14.32	14.63	14.97	14.75	-1.5
Abruzzo	5.83	6.15	6.82	6.70	7.16	7.66	7.1
Molise	1.74	2.17	2.23	2.44	2.73	2.93	7.3
Campania	5.37	5.53	5.92	6.15	6.13	6.21	1.2
Puglia	6.67	6.78	7.06	7.16	7.00	7.58	8.3
Basilicata	3.05	3.19	3.39	3.65	3.78	3.96	4.6
Calabria	2.89	3.14	3.05	3.35	3.68	3.48	-5.5
Sicilia	5.36	5.78	6.07	6.68	6.87	6.71	-2.4
Sardegna	11.67	11.41	12.14	11.86	11.40	10.77	-5.6
Italy	**10.97**	**10.82**	**11.17**	**11.39**	**11.47**	**11.11**	**-3.1**

Table 5.2.12c. Anti-HIV antivirals, prescription by therapeutic category and substance in 2018

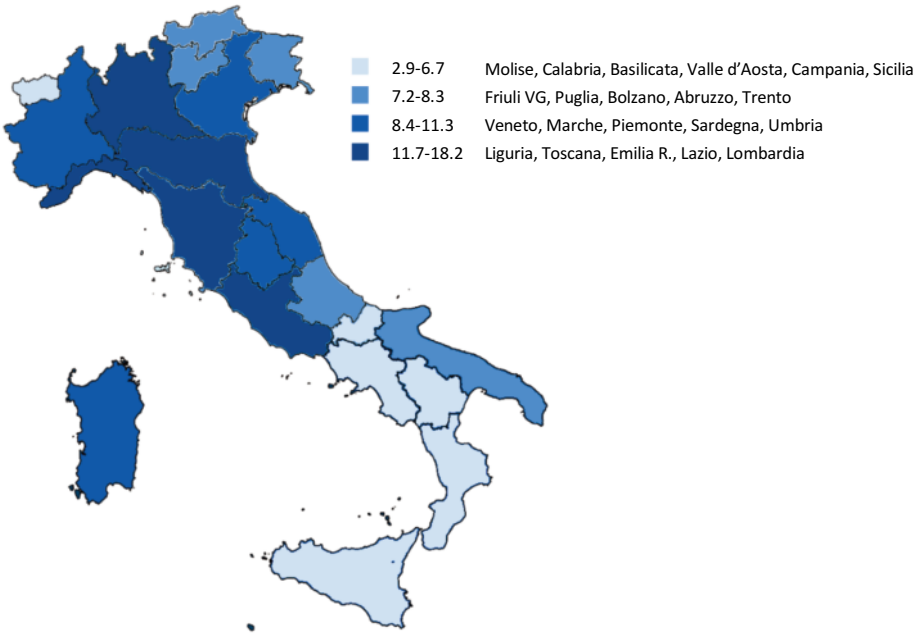
Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Anti-HIV antivirals in co-formulated schemes	5.07	19.5	0.6	18.3
Nucleoside and nucleotide reverse transcriptase inhibitors	1.90	-33.4	0.9	-7.1
Integrase inhibitors	1.85	10.8	0.4	19.5
Protease inhibitors plain or in combination	1.83	-13.5	0.4	-12.5
Non-nucleoside reverse transcriptase inhibitors	0.32	-23.2	0.2	-13.8
Other anti-HIV antivirals	0.15	-16.6	0.0	-15.5
Anti-HIV antivirals	**11.11**	**-3.1**	**2.4**	**0.3**
dolutegravir/abacavir/lamivudine	1.51	38.3	0.2	39.2
elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide	1.41	>100	0.1	>100
emtricitabine/rilpivirine/tenofovir alafenamide	1.32	>100	0.2	>100
dolutegravir	1.17	33.9	0.2	34.0
emtricitabine/tenofovir alafenamide	1.09	>100	0.2	>100
darunavir/cobicistat	0.82	41.4	0.2	41.4
raltegravir	0.68	-14.6	0.2	5.8
emtricitabine/rilpivirine/tenofovir disoproxil	0.45	-64.9	0.1	-64.9
darunavir	0.41	-37.0	0.1	-37.1
tenofovir disoproxil	0.34	-49.8	0.2	-1.2

Table 5.2.12d. Prescription of anti-HIV antivirals with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	0.04	0.3	-8.0	0.1	2.8	-1.6	1.55
Equivalent	0.03	69.3	1.2	0.0	64.9	13.6	1.66
Ex-originator	0.01	30.7	-23.6	0.0	35.1	-21.1	1.36
Patent covered	11.07	99.7	-1.5	2.3	97.2	0.6	12.97
Anti-HIV antivirals	**11.11**	**100.0**	**-3.1**	**2.4**	**100.0**	**0.3**	**12.65**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.12b. Anti-HIV antivirals, distribution in quartiles of 2018 per capita expenditure



Medicines for multiple sclerosis

- In the last six years the prescription of medicines for multiple sclerosis has increased from 2 in 2013 to 2.6 DDD in 2018 (a variation of + 28%); this trend was determined by immunosuppressants and especially by methotrexate, which alone represents more than half of consumption of the entire category (shifting from 0.7 DDD in 2013 to 1.3 DDD in 2018);
- fingolimod is the substance with the highest expenditure (2.28 euros per capita; + 9.9% compared to 2017), followed by dimethyl fumarate (1.94 euros; + 16.9%);
- it is noteworthy that Sardegna is the Region recording with the greatest use, thus confirming epidemiological data on prevalence of multiple sclerosis in the Italian regions: in 2018 4.8 DDD were prescribed for every 1000 inhabitants;
- patent-expired medicines represent more than half of the doses and 6.7% of the expenditure.

Figure 5.2.13a. Medicines for multiple sclerosis, temporal consumption trend (2013-2018)

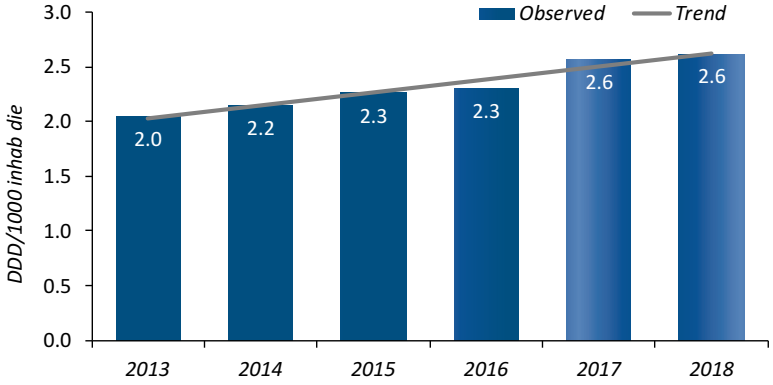


Table 5.2.13a. Medicines for multiple sclerosis, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Immunosuppressants	1.1	1.2	1.3	1.5	1.7	1.8	4.8
Fingolimod	0.0	0.1	0.1	0.1	0.1	0.1	9.4
Interferons	0.8	0.8	0.7	0.5	0.5	0.5	-10.3
Monoclonal antibody	0.1	0.1	0.1	0.1	0.1	0.1	13.3
Glatiramer	0.1	0.1	0.1	0.1	0.1	0.1	-9.5
Teriflunomide	-	<0.05	<0.05	<0.05	0.1	0.1	18.6
Pharmaceuticals for multiple sclerosis	**2.0**	**2.2**	**2.3**	**2.3**	**2.6**	**2.6**	**1.8**
fingolimod	<0.05	0.1	0.1	0.1	0.1	0.1	9.4
dimethyl fumarate	-	-	<0.05	<0.05	0.1	0.2	16.9
interferon beta 1a	0.7	0.7	0.6	0.4	0.5	0.4	-10.2
natalizumab	0.1	0.1	0.1	0.1	0.1	0.1	10.2
glatiramer	0.1	0.1	0.1	0.1	0.1	0.1	-9.5
teriflunomide	-	<0.05	<0.05	<0.05	0.1	0.1	18.6
metotrexate	0.7	0.8	0.9	1.2	1.2	1.3	5.5
peginterferon beta-1	-	-	<0.05	<0.05	<0.05	<0.05	-0.9
alemtuzumab	-	-	<0.05	<0.05	<0.05	<0.05	-4.6
interferon beta 1b	0.1	0.1	0.1	<0.05	<0.05	<0.05	-22.9

Table 5.2.13b. Medicines for multiple sclerosis, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	2.0	2.1	2.2	2.2	2.5	2.6	4.0
Valle d'Aosta	1.7	1.8	2.1	1.9	2.1	2.1	0.3
Lombardia	1.9	2.0	2.1	2.2	2.4	2.5	3.7
PA Bolzano	2.6	2.9	3.0	3.0	3.3	3.4	2.5
PA Trento	2.3	2.5	2.6	2.8	3.1	3.1	1.8
Veneto	2.0	2.1	2.2	2.3	2.6	2.6	2.1
Friuli VG	3.1	3.1	3.2	3.2	3.6	3.5	-2.6
Liguria	1.8	1.9	2.0	2.1	2.3	2.4	4.9
Emilia R.	1.7	1.8	2.0	2.0	2.2	2.3	2.8
Toscana	1.7	1.8	2.1	2.0	2.3	2.2	-4.5
Umbria	2.3	2.4	2.5	2.5	2.7	2.7	-0.8
Marche	2.0	2.2	2.3	2.3	2.4	2.5	2.9
Lazio	1.9	2.0	2.0	2.1	2.4	2.4	-0.5
Abruzzo	2.2	2.3	2.4	2.5	2.8	2.8	1.2
Molise	1.9	2.0	1.9	2.0	2.3	2.3	-1.2
Campania	1.8	2.0	2.0	2.1	2.4	2.4	0.4
Puglia	2.4	2.5	2.6	2.7	3.0	3.0	1.0
Basilicata	2.1	2.1	2.3	2.4	2.8	2.8	-1.9
Calabria	1.9	2.1	2.2	2.3	2.6	2.7	3.3
Sicilia	2.1	2.2	2.2	2.3	2.6	2.7	4.7
Sardegna	4.2	4.3	4.4	4.2	4.6	4.8	3.9
Italy	**2.0**	**2.2**	**2.3**	**2.3**	**2.6**	**2.6**	**1.8**

Table 5.2.13c. Medicines for multiple sclerosis, prescription by therapeutic category and substance in 2018

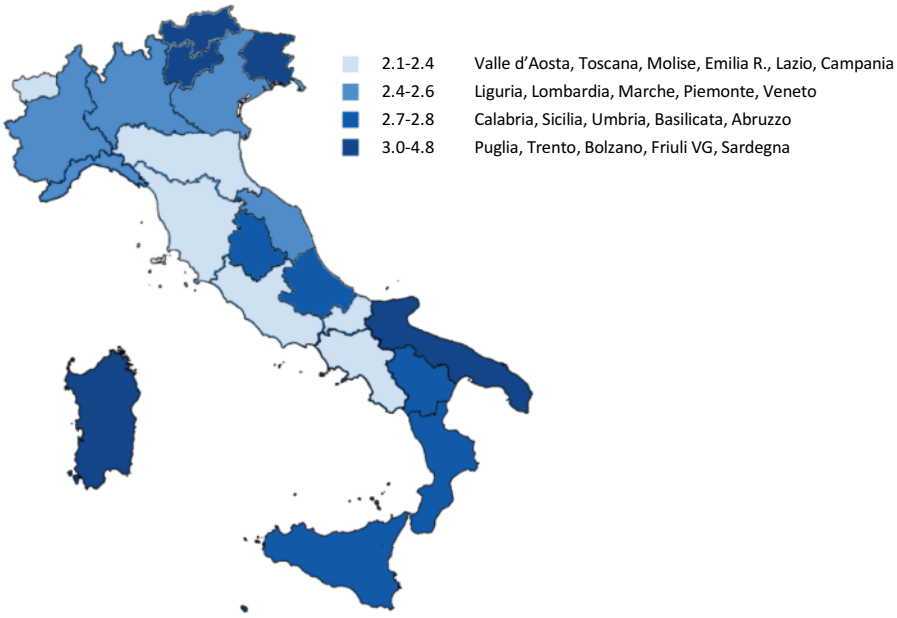
Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Immunosuppressants	2.67	13.7	1.8	4.8
Fingolimod	2.28	9.9	0.1	9.4
Interferons	2.19	-12.9	0.5	-10.3
Monoclonal antibody	1.83	9.6	0.1	13.3
Glatiramer	0.94	-15.7	0.1	-9.5
Teriflunomide	0.70	18.0	0.1	18.6
Pharmaceuticals for multiple sclerosis	**10.62**	**2.9**	**2.6**	**1.8**
fingolimod	2.28	9.9	0.1	9.4
dimethyl fumarate	1.94	16.9	0.2	16.9
interferon beta 1a	1.66	-14.2	0.4	-10.2
natalizumab	1.49	10.2	0.1	10.2
glatiramer	0.94	-15.7	0.1	-9.5
teriflunomide	0.70	18.0	0.1	18.6
metotrexate	0.62	7.6	1.3	5.5
peginterferon beta-1	0.41	-0.9	<0.05	-0.9
alemtuzumab	0.31	-4.6	<0.05	-4.6
interferon beta 1b	0.11	-28.1	<0.05	-22.9

Table 5.2.13d. Prescription of medicines for multiple sclerosis with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	0.71	6.7	-1.9	1.3	50.0	5.0	1.49
Equivalent	0.12	16.6	4.0	0.4	27.5	0.9	0.90
Ex originator	0.59	83.4	-3.0	1.0	72.5	6.6	1.71
Patent covered	9.91	93.3	3.2	1.3	50.0	-1.1	20.72
Pharmaceuticals for multiple sclerosis	**10.62**	**100.0**	**2.9**	**2.6**	**100.0**	**1.8**	**11.10**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

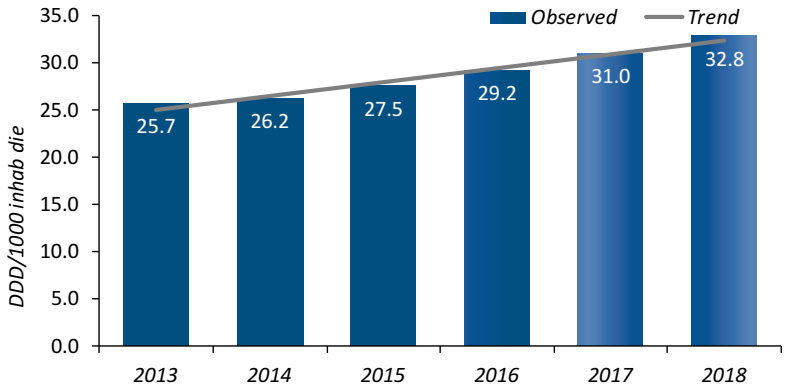
Figure 5.2.13b. Medicines for multiple sclerosis, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)



Medicines for osteoporosis

- DDDs increased from 25.7 in 2013 to 32.8 in 2018 (+ 27.7%) with a + 5% average annual variation (CAGR), mainly due to higher prescription of vitamin D and analogues which represent about 60% of the entire category (shifting from 12.3 DDD in 2013 to 19.3 DDD in 2018);
- denosumab is the substance with the greatest variation in consumption compared to the previous year (+14.4% in 2018); with the exception of alendronic acid, all other bisphosphonates, including combinations, show a reduction in consumption;
- Italian regions record a marked variability in consumption, with a consumption value ranging from 22.6 DDD of the Valle d'Aosta to 40.5 DDD of Sardegna (with a difference of 80%); interpretation of data should take into account that some regions have implemented measures to limit the prescription of vitamin D; Abruzzo, Lazio and Puglia are the regions using more doses, with a cost per day of therapy higher than the national average;
- the incidence of patent-expired drug consumption reached 73% in 2018, with a limited use of equivalent medicines.

Figure 5.2.14a. Medicines for osteoporosis*, temporal consumption trend (2013-2018)



** excluding raloxifene*

Table 5.2.14a. Medicines for osteoporosis, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Vitamin D and analogues	12.3	13.0	14.2	15.9	17.5	19.3	10.0
Teriparatide	0.2	0.2	0.2	0.2	0.2	0.2	2.7
Oral and injectable bisphosphonates	6.8	6.9	6.7	6.6	6.7	6.7	0.7
Denosumab	0.3	1.0	1.6	2.1	2.4	2.7	14.4
Alendronic acid + cholecalciferol	3.3	3.5	3.3	3.0	2.7	2.4	-9.3
Calcium	1.6	1.5	1.5	1.5	1.4	1.4	-1.5
SERM (selective modulators of the estrogen-receptor)	0.1	0.1	0.1	0.1	0.1	<0.05	-7.4
Strontium ranelate	1.2	0.1	<0.05	<0.05	<0.05	<0.05	-91.8
Pharmaceuticals for osteoporosis	**25.7**	**26.2**	**27.5**	**29.2**	**31.0**	**32.8**	**6.1**
cholecalciferol	4.5	5.6	7.2	9.1	10.9	12.6	16.3
teriparatide	0.2	0.2	0.2	0.2	0.2	0.2	2.7
denosumab	0.3	1.0	1.6	2.1	2.4	2.7	14.4
alendronic acid	2.7	2.9	3.1	3.2	3.5	3.7	5.3
alendronic acid/cholecalciferol	3.3	3.5	3.3	3.0	2.7	2.4	-9.3
calcium/cholecalciferol	6.1	5.7	5.3	5.1	4.9	4.7	-3.5
risedronate	2.8	2.8	2.6	2.4	2.3	2.2	-2.7
calcitriol	1.0	1.0	1.0	1.0	1.0	1.0	-0.7
ibandronic acid	1.3	1.2	1.1	1.0	0.9	0.8	-8.5
alfacalcidol	0.6	0.5	0.6	0.6	0.7	0.8	21.1

Table 5.2.14b. Medicines for osteoporosis, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	23.1	24.0	25.3	26.4	28.2	29.7	5.3
Valle d'Aosta	18.3	18.8	20.2	19.5	20.4	22.6	10.8
Lombardia	23.5	24.6	26.4	27.7	29.8	32.0	7.7
PA Bolzano	28.3	29.9	33.0	35.4	37.2	38.2	2.6
PA Trento	23.2	23.4	24.1	25.9	28.4	30.5	7.5
Veneto	33.9	35.0	36.9	38.1	36.7	37.4	1.9
Friuli VG	22.4	22.8	23.8	25.3	27.1	28.4	5.0
Liguria	22.5	22.4	23.8	25.4	26.7	28.2	5.5
Emilia R.	25.3	25.0	26.1	26.9	27.7	28.3	2.3
Toscana	25.3	25.9	27.4	31.6	31.4	33.2	6.0
Umbria	20.8	20.8	21.6	23.1	25.7	27.5	7.0
Marche	23.2	24.1	25.7	28.0	31.0	32.5	5.0
Lazio	28.4	27.6	29.2	31.0	33.4	35.3	5.6
Abruzzo	27.8	28.9	30.8	32.7	35.8	38.9	8.7
Molise	21.7	24.1	26.5	28.7	32.5	32.4	-0.4
Campania	17.6	19.1	20.8	23.3	27.0	30.6	13.2
Puglia	29.7	31.5	33.5	35.7	38.1	40.0	5.0
Basilicata	26.6	27.9	30.1	31.0	33.6	35.9	6.8
Calabria	24.2	25.0	25.9	27.7	30.0	32.6	8.7
Sicilia	30.2	27.9	25.8	26.0	27.8	29.9	7.8
Sardegna	31.7	32.8	35.4	38.4	39.9	40.5	1.3
Italy	**25.7**	**26.2**	**27.5**	**29.2**	**31.0**	**32.8**	**6.1**

Table 5.2.14c. Medicines for osteoporosis, prescription by therapeutic category and substance in 2018

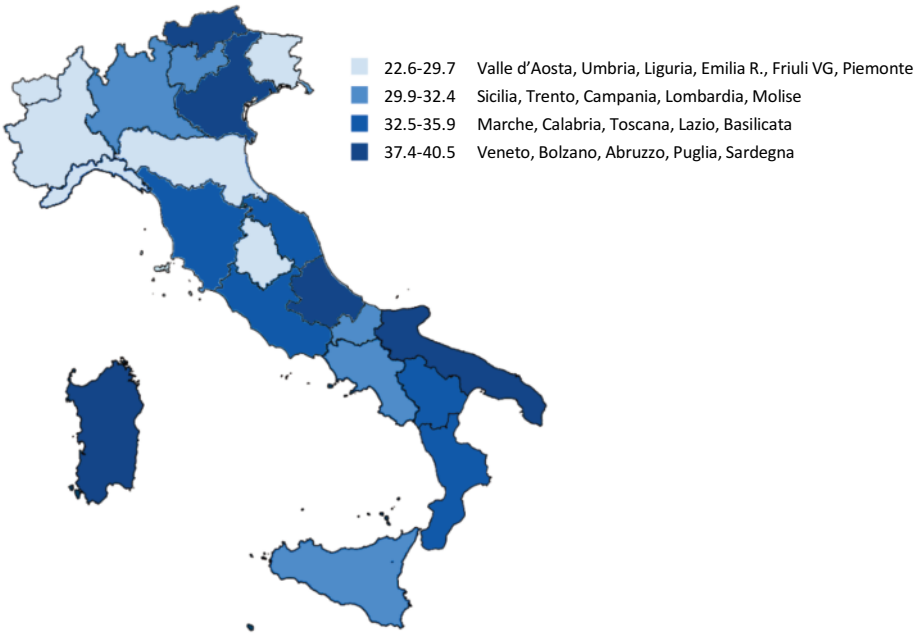
Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Vitamin D and analogues	5.45	14.5	19.3	10.0
Teriparatide	1.42	1.0	0.2	2.7
Oral and injectable bisphosphonates	1.40	-0.2	6.7	0.7
Denosumab	0.85	18.3	2.7	14.4
Alendronic acid + cholecalciferol	0.51	-20.1	2.4	-9.3
Calcium	0.12	-0.3	1.4	-1.5
SERM (selective modulators of the estrogen-receptor)	0.01	-6.7	<0.05	-7.4
Strontium ranelate	0.00	-91.7	<0.05	-91.8
Pharmaceuticals for osteoporosis	**9.77**	**7.7**	**32.8**	**6.1**
cholecalciferol	4.52	16.8	12.6	16.3
teriparatide	1.42	1.0	0.2	2.7
denosumab	0.85	18.3	2.7	14.4
alendronic acid	0.72	5.1	3.7	5.3
alendronic acid/cholecalciferol	0.51	-20.1	2.4	-9.3
calcium/cholecalciferol	0.44	-2.7	4.7	-3.5
risedronate	0.40	-4.4	2.2	-2.7
calcitriol	0.22	0.4	1.0	-0.7
ibandronic acid	0.17	-9.7	0.8	-8.5
alfacalcidol	0.13	21.5	0.8	21.1

Table 5.2.14d. Prescription of medicines for osteoporosis, with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	6.68	68.4	8.6	23.9	72.9	5.2	0.76
Equivalent	1.11	16.6	25.8	6.2	25.9	6.2	0.49
Ex originator	5.57	83.4	5.7	17.7	74.1	4.9	0.86
Patent covered	3.09	31.6	6.1	8.9	27.1	8.4	0.95
Pharmaceuticals for osteoporosis	**9.77**	**100.0**	**7.7**	**32.8**	**100.0**	**6.1**	**0.81**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.14b. Medicines for osteoporosis, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)



Coagulation factors

- Expenditure has remained stable over the past six years, reaching a per capita value of 7.7 euros in 2018; 66% of expenditure is represented by recombinant medicines for haemophilia A;
- albutrepenonacog alfa, lonoctogoc alfa and eftrenonacog alfa, new active ingredients marketed in 2017, are the substances with the greatest variation in per capita consumption and expenditure compared to the previous year (>100%);
- a marked regional variability was recorded in per capita expenditure, with a value ranging from a maximum of 13.35 euros in Calabria to a minimum of 3.39 euros in the Autonomous Province of Bolzano; Friuli Venezia-Giulia was the region showing the greatest reduction in expenditure compared to the previous year (-48.3%), while Basilicata recorded the largest expenditure increase (+24.2%); Abruzzo was the region using more doses with a higher cost per day than the national average.

Figure 5.2.15a. Coagulation factors, temporal trend of per capita expenditure (2013-2018)

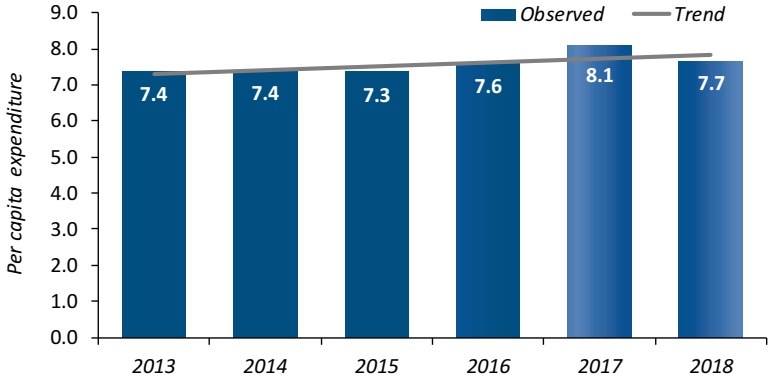


Table 5.2.15a. Coagulation factors, per capita expenditure by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Hemophilia A (recombinant)	4,7	4,7	4,7	5,0	5,1	5,1	0,1
Hemophilia B (recombinant)	0,5	0,6	0,6	0,7	0,9	1,0	20,8
Hemophilia A (plasmaderivatives)	0,9	1,0	1,0	1,0	1,0	0,8	-17,9
Factor VII deficiency (recombinant)	1,2	1,0	1,0	0,9	1,0	0,6	-37,3
Factor VII deficiency (plasmaderivatives)	<0,05	<0,05	<0,05	<0,05	0,1	0,1	17,8
Other deficiencies of coagulation factors (recombinant)	-	<0,05	<0,05	<0,05	<0,05	<0,05	13,7
Hemophilia B (plasmaderivatives)	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05	-50,4
Other deficiencies of coagulation factors (plasmaderivatives)	-	-	<0,05	<0,05	<0,05	<0,05	1,4
Von Willebrand's disease (plasmaderivatives)	<0,05	<0,05	<0,05	<0,05	0,1	<0,05	-96,8

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Coagulation factors	**7,4**	**7,4**	**7,3**	**7,6**	**8,1**	**7,7**	**-5,3**
factor VIII	4,8	4,7	4,7	5,0	5,1	4,9	-4,1
eptacog alpha activated (recombinant DNA coagulation factor VII)	1,2	1,0	1,0	0,9	1,0	0,6	-37,3
albutrepenonacog alpha	-	-	-	-	0,2	0,5	>100
human anti-hemophilic prothrombin complex activated	0,5	0,4	0,4	0,5	0,5	0,4	-21,0
nonacog alpha (coagulation factor IX, recombinant)	0,5	0,6	0,6	0,7	0,6	0,3	-41,9
factor VIII/Von Willebrand factor	0,2	0,2	0,2	0,2	0,2	0,2	-5,8
human coagulation factor VIII / Von Willebrand factor	0,2	0,3	0,3	0,3	0,3	0,2	-24,5
lonoctogoc alpha	-	-	-	-	<0,05	0,2	>100
eftrenonacog alpha	-	-	-	-	<0,05	0,2	>100
lyophilized human blood factor VII of coagulation	<0,05	<0,05	<0,05	<0,05	0,1	0,1	17,8

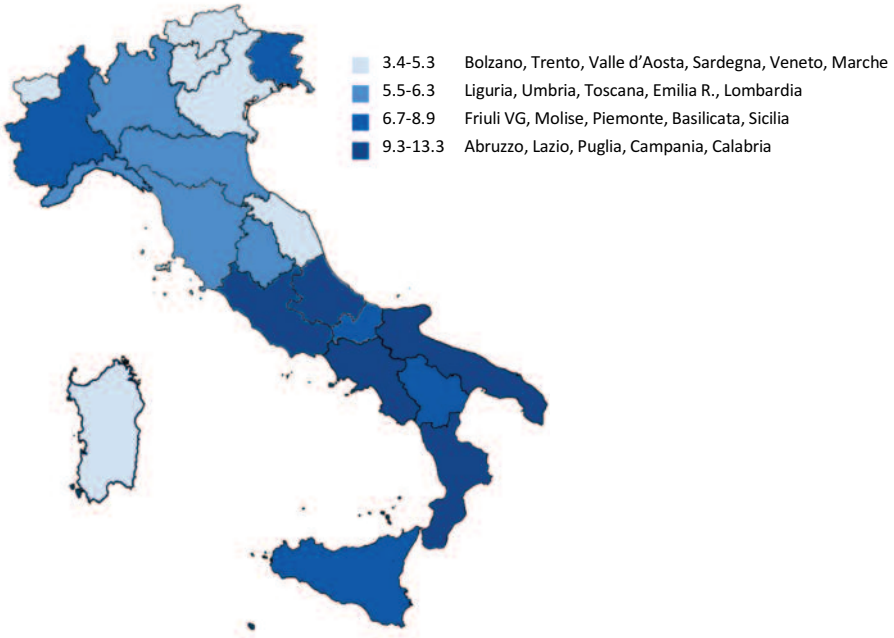
Table 5.2.15b. Coagulation factors, weighted regional trend of per capita expenditure: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	7.22	7.84	7.11	6.67	7.95	7.16	-10.0
Valle d'Aosta	3.24	3.25	2.44	2.88	5.51	4.60	-16.5
Lombardia	5.96	5.53	5.64	5.67	5.82	6.27	7.7
PA Bolzano	4.25	5.53	3.64	4.41	4.27	3.39	-20.4
PA Trento	4.09	4.48	4.52	4.79	4.21	4.57	8.7
Veneto	4.30	4.73	4.49	4.72	5.93	4.82	-18.7
Friuli VG	9.13	9.01	11.49	12.78	12.95	6.70	-48.3
Liguria	5.63	4.89	5.07	5.08	5.39	5.50	1.9
Emilia R.	6.67	6.02	5.54	6.48	6.95	6.26	-9.9
Toscana	7.93	7.12	6.64	6.69	6.69	5.79	-13.5
Umbria	3.86	3.54	3.98	4.48	5.37	5.53	3.1
Marche	5.41	6.47	5.60	5.02	5.88	5.25	-10.7
Lazio	9.00	9.41	9.72	10.20	10.51	10.29	-2.0
Abruzzo	8.23	8.09	7.94	7.79	9.80	9.31	-4.9
Molise	5.98	5.59	7.49	5.06	6.28	7.08	12.9
Campania	11.85	11.36	11.55	11.03	11.80	11.15	-5.5
Puglia	9.15	9.77	9.69	10.33	10.72	10.67	-0.4
Basilicata	4.63	6.03	6.46	6.28	6.06	7.53	24.2
Calabria	9.05	9.11	9.47	11.27	12.34	13.35	8.2
Sicilia	7.83	8.38	8.25	9.15	9.23	8.91	-3.5
Sardegna	5.84	5.58	5.88	5.28	5.29	4.65	-12.1
Italy	**7.37**	**7.38**	**7.35**	**7.58**	**8.09**	**7.67**	**-5.3**

Table 5.2.15c. Coagulation factors, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Hemophilia A (recombinant)	5.09	0.1	<0.05	0.2
Hemophilia B (recombinant)	1.03	20.8	<0.05	-11.3
Hemophilia A (plasmaderivatives)	0.79	-17.9	<0.05	-18.9
Factor VII deficiency (recombinant)	0.63	-37.3	<0.05	-37.7
Factor VII deficiency (plasmaderivatives)	0.07	17.8	<0.05	23.8
Other deficiencies of coagulation factors (recombinant)	0.04	13.7	<0.05	11.5
Hemophilia B (plasmaderivatives)	0.01	-50.4	<0.05	-56.2
Other deficiencies of coagulation factors (plasmaderivatives)	0.01	1.4	<0.05	14.9
Von Willebrand's disease (plasmaderivatives)	0.00	-96.8	<0.05	-96.9
Coagulation factors	**7.67**	**-5.3**	**<0.05**	**-7.1**
factor VIII	4.88	-4.1	<0.05	-3.6
eptacog alpha activated (recombinant DNA coagulation factor VII)	0.63	-37.3	<0.05	-37.7
albutrepenonacog alpha	0.51	>100	<0.05	>100
human anti-hemophilic prothrombin complex activated	0.36	-21.0	<0.05	-20.5
nonacog alpha (coagulation factor IX, recombinant)	0.33	-41.9	<0.05	-42.3
factor VIII/Von Willebrand factor	0.23	-5.8	<0.05	-2.5
human coagulation factor VIII / Von Willebrand factor	0.20	-24.5	<0.05	-21.1
lonoctogoc alpha	0.20	>100	<0.05	>100
eftrenonacog alpha	0.17	>100	<0.05	>100
lyophilized human blood factor VII of coagulation	0.07	17.8	<0.05	23.8

Figure 5.2.15b. Coagulation factors, distribution in quartiles of 2018 per capita expenditure



Vaccines

- Expenditure for vaccines has progressively increased over the past six years, starting from a value of 5.3 euros per capita in 2013 and reaching a value of 8.7 euros in 2018 (+ 66%) with an average annual variation (CAGR) of + 11%;
- the highest variation in consumption and expenditure per capita compared to the previous year was observed for the papillomavirus vaccine and the rotavirus vaccine (>100%);
- in 2018 a marked variability was reported in per capita expenditure in the Italian regions, with a value ranging from a minimum of 5.75 euros in the Valle d'Aosta to a maximum of 13.10 euros in the Autonomous Province of Trento, which also recorded the greatest percentage change in per capita expenditure compared to the previous year (+ 33.2%);
- the Autonomous Provinces of Bolzano and Trento, together with Puglia and Sicilia, are reported to use more doses, with a higher cost per day than the national average.

Figure 5.2.16a. Vaccines, temporal trend of per capita expenditure (2013-2018)

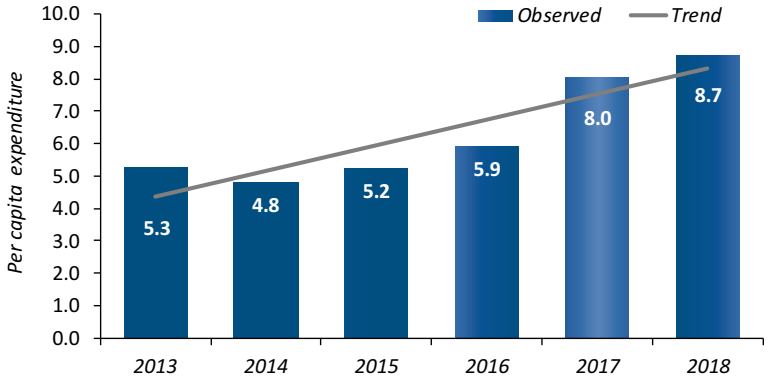


Table 5.2.16a. Vaccines, per capita expenditure by therapeutic category and substance: comparison 2013-2018

Subgroups abd substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Meningococcal vaccines	0.2	0.2	0.6	1.3	2.7	2.4	-13.3
Pneumococcal vaccines	1.4	1.4	1.5	1.5	1.7	1.7	0.8
Bacterial and viral vaccines (in combination)	1.5	1.4	1.3	1.2	1.3	1.2	-2.3
Papillomavirus vaccines	0.6	0.4	0.3	0.3	0.4	0.9	>100
Influenza vaccines	0.8	0.6	0.7	0.7	0.8	0.9	18.5
Measles vaccines	0.4	0.3	0.4	0.4	0.6	0.7	11.2
Varicella zoster vaccines	0.1	0.1	0.1	0.1	0.2	0.3	64.0
Rotavirus diarrhea vaccines	0.0	0.1	0.1	0.1	0.1	0.3	>100
Hepatitis vaccines	0.1	0.1	0.1	0.1	0.1	0.2	25.7
Other vaccines	0.1	0.1	0.1	0.1	0.1	0.1	25.5
Pertussis vaccines	0.1	0.1	0.1	0.1	0.1	0.1	-4.7
Vaccines	**5.3**	**4.8**	**5.2**	**5.9**	**8.0**	**8.7**	**8.7**
meningococcal B group vaccine	0.0	0.1	0.3	1.0	2.0	1.8	-6.6
pneumococcal saccharide conjugated vaccine, adsorbed	1.4	1.4	1.5	1.5	1.6	1.6	-2.2
hexavalent vaccine	1.3	1.2	1.2	1.0	1.1	1.0	-8.7
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	0.0	0.0	0.0	0.0	0.1	0.8	>100
measles/mumps/rubella/varicella vaccine	0.2	0.2	0.2	0.2	0.5	0.5	21.0
meningococcal ACWY vaccine	0.1	0.1	0.2	0.2	0.7	0.5	-28.8
inactivated split virion influenza vaccine	0.1	0.1	0.1	0.1	0.2	0.4	55.8
influenza virus, fragmented	0.1	0.1	0.0	0.2	0.2	0.3	61.4
live attenuated anti rotavirus vaccine	0.0	0.1	0.1	0.1	0.1	0.3	>100
diphtheria/pertussis/poliomyelitis/tetanus vaccine	0.2	0.2	0.1	0.2	0.2	0.3	32.5

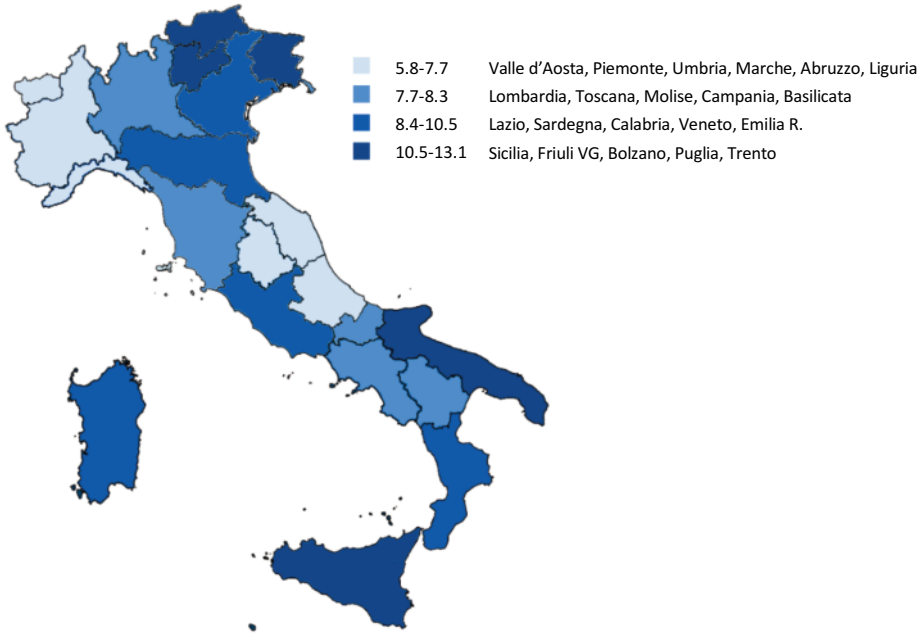
Table 5.2.16b. Vaccines, weighted regional trend of per capita expenditure: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	4.16	3.75	3.45	3.45	5.37	6.04	12.3
Valle d'Aosta	4.74	4.18	3.30	3.98	5.18	5.75	11.2
Lombardia	4.45	4.08	3.96	4.10	5.82	7.71	32.4
PA Bolzano	5.19	5.30	5.68	5.79	9.39	11.56	23.1
PA Trento	5.67	5.22	4.73	6.31	9.84	13.10	33.2
Veneto	5.45	5.23	5.60	7.31	9.55	9.17	-4.0
Friuli VG	7.42	5.46	5.39	7.51	10.71	11.25	5.0
Liguria	4.43	4.10	4.87	5.97	7.14	7.65	7.1
Emilia R.	4.94	4.58	4.60	5.38	9.94	10.50	5.6
Toscana	3.58	3.23	8.88	8.57	7.34	8.02	9.2
Umbria	5.02	4.56	4.36	5.01	6.38	7.25	13.7
Marche	4.47	4.07	4.06	4.48	7.64	7.31	-4.3
Lazio	5.04	4.44	4.86	6.18	8.91	8.43	-5.4
Abruzzo	4.52	4.27	4.13	4.40	6.91	7.37	6.7
Molise	5.46	5.08	5.27	4.65	6.43	8.22	27.7
Campania	5.39	4.73	4.87	5.12	7.63	8.29	8.7
Puglia	8.02	7.68	7.71	8.21	11.40	11.96	4.9
Basilicata	7.81	5.78	6.80	6.21	6.74	8.30	23.2
Calabria	5.38	4.72	5.27	7.21	9.46	9.00	-4.9
Sicilia	7.42	6.86	6.69	7.77	9.46	10.52	11.2
Sardegna	5.27	4.27	4.41	5.20	6.65	8.43	26.8
Italy	**5.28**	**4.79**	**5.23**	**5.89**	**8.05**	**8.75**	**8.7**

Table 5.2.16c. Vaccines, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Meningococcal vaccines	2,35	-13,3	0,1	-12,7
Pneumococcal vaccines	1,68	0,8	0,1	3,2
Bacterial and viral vaccines (in combination)	1,23	-2,3	0,1	9,3
Papillomavirus vaccines	0,93	>100	<0,05	64,8
Influenza vaccines	0,92	18,5	0,4	-2,8
Measles vaccines	0,66	11,2	0,1	2,8
Varicella zoster vaccines	0,29	64,0	<0,05	54,8
Rotavirus diarrhea vaccines	0,28	>100	<0,05	>100
Hepatitis vaccines	0,15	25,7	<0,05	31,8
Other vaccines	0,13	25,5	<0,05	-4,4
Pertussis vaccines	0,12	-4,7	<0,05	-5,3
Vaccines	**8,75**	**8,7**	**1,0**	**2,2**
meningococcal B group vaccine	1,83	-6,6	0,1	-3,9
pneumococcal saccharide conjugated vaccine, adsorbed	1,61	-2,2	0,1	-2,7
hexavalent vaccine	0,96	-8,7	0,1	-0,3
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	0,82	>100	0,0	>100
measles/mumps/rubella/varicella vaccine	0,55	21,0	0,0	28,2
meningococcal ACWY vaccine	0,49	-28,8	0,0	-23,9
inactivated split virion influenza vaccine	0,37	55,8	0,2	52,7
influenza virus, fragmented	0,30	61,4	0,1	62,8
live attenuated anti rotavirus vaccine	0,28	>100	0,0	>100
diphtheria/pertussis/polyomyelitis/tetanus vaccine	0,27	32,5	0,0	33,6

Figure 5.2.16b. Vaccines, weighted distribution in quartiles of per capita expenditure (2018)



Pain therapy

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

- Between 2013 and 2018 a slight but steady increase was recorded in the prescription of pain therapy pharmaceuticals (from 6.7 DDD in 2013 to 7.3 in 2018: +9.2%), while per capita expenditure (6.44 euros) decreased by 8% compared to 2017;
- strong opioids show an increase of 4.7% compared to 2017, especially fentanyl and tapentadol (respectively +2.8% and +7.5%); as regards pharmaceuticals for neuropathic pain, it is noteworthy the increase in use of pregabalin (DDD +6.9%) and to a lower extent of gabapentin (+1.9%);
- Friuli VG is the region with the highest level of consumption (10 DDD), while the southern regions show a limited use, with a minimum of 4.8 DDD in Campania and, in general, an average of 5 DDD;
- half of the doses and a quarter of the expenditure relate to patent-expired medicines, whose average cost per day of therapy is three times lower than patent-covered medicines (1.23 vs 3.66).

Figure 5.2.17a. Pain therapy, temporal consumption trend (2013-2018)

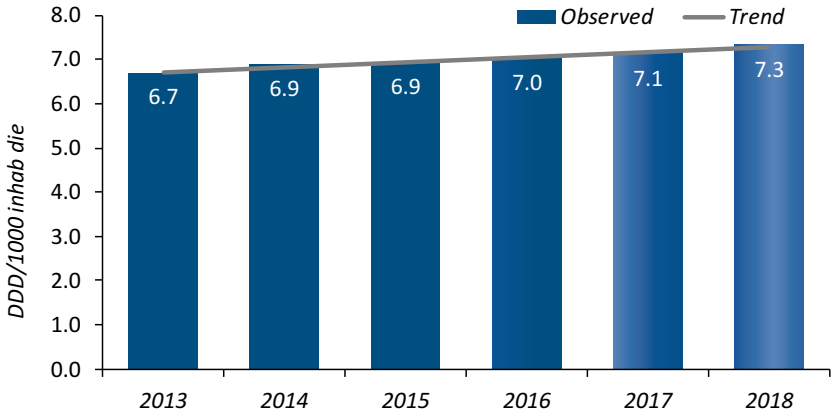


Table 5.2.17a. Pain therapy, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Strong opioids	1.6	1.6	1.7	1.8	1.8	1.9	4.7
Weak opioids/opioids in combination	3.1	3.1	3.0	2.9	2.9	2.8	-0.9
Neuropathic pain	2.0	2.2	2.3	2.3	2.4	2.6	5.9
Pain therapy	**6.7**	**6.9**	**6.9**	**7.0**	**7.1**	**7.3**	**2.8**
fentanyl	0.7	0.7	0.7	0.7	0.7	0.8	2.8
tapentadol	0.2	0.3	0.3	0.4	0.5	0.5	7.5
naloxone/oxycodone	0.2	0.3	0.3	0.4	0.4	0.4	1.8
pregabalin	1.6	1.7	1.8	1.8	1.9	2.1	6.9
paracetamol/codeine	1.7	1.6	1.5	1.4	1.3	1.3	-2.2
gabapentin	0.5	0.5	0.5	0.5	0.5	0.5	1.9
tramadol	0.8	0.8	0.7	0.7	0.7	0.7	-1.8
oxycodone/paracetamol	0.3	0.3	0.3	0.3	0.3	0.3	3.4
oxycodone	0.2	0.1	0.1	0.1	0.1	0.1	1.5
buprenorphine	0.1	0.1	0.1	0.1	0.1	0.2	66.2

Table 5.2.17b. Pain therapy, regional trend of DDD/1000 ihabitans per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	8.3	8.5	8.4	8.6	9.0	9.2	2.2
Valle d'Aosta	9.2	9.4	9.5	9.1	9.2	9.2	0.4
Lombardia	7.4	7.7	7.9	8.1	8.1	8.4	2.9
PA Bolzano	7.2	7.2	7.3	7.5	7.6	7.7	0.9
PA Trento	7.0	7.2	7.4	7.5	7.6	7.9	3.9
Veneto	6.7	6.9	6.8	7.0	7.1	7.3	3.0
Friuli VG	9.0	9.2	9.5	9.8	10.0	10.0	-0.2
Liguria	8.2	8.4	8.4	8.3	8.6	8.8	2.7
Emilia R.	8.5	8.6	8.6	8.7	8.9	9.1	2.2
Toscana	8.7	9.2	9.1	8.9	8.6	8.7	0.6
Umbria	6.5	6.5	6.7	6.9	7.0	7.5	5.8
Marche	6.3	6.4	6.4	6.4	6.5	6.5	1.1
Lazio	6.2	6.4	6.5	6.5	6.7	7.0	4.7
Abruzzo	5.4	5.4	5.5	5.6	5.7	5.8	2.9
Molise	4.7	4.8	5.0	5.2	5.1	5.3	4.1
Campania	4.2	4.4	4.4	4.5	4.5	4.8	5.5
Puglia	5.5	5.6	5.6	5.7	5.8	6.1	4.8
Basilicata	4.9	5.0	5.0	4.9	5.0	5.2	5.5
Calabria	4.6	4.7	4.8	4.9	4.9	5.0	1.3
Sicilia	5.1	5.1	5.1	5.2	5.3	5.4	1.8
Sardegna	6.5	6.8	7.0	7.0	7.1	7.4	3.8
Italy	**6.7**	**6.9**	**6.9**	**7.0**	**7.1**	**7.3**	**2.8**

Table 5.2.17c. Pain therapy, prescription by therapeutic category and substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Strong opioids	2.95	5.3	1.9	4.7
Weak opioids/opioids in combination	2.10	0.1	2.8	-0.9
Neuropathic pain°	1.40	-33.6	2.6	5.9
Pain therapy	**6.44**	**-8.0**	**7.3**	**2.8**
fentanyl	1.34	3.8	0.8	2.8
tapentadol	1.15	7.4	0.5	7.5
naloxone/oxycodone	1.13	1.1	0.4	1.8
pregabalin	1.07	-40.0	2.1	6.9
paracetamol/codeine	0.35	-2.7	1.3	-2.2
gabapentin	0.33	1.6	0.5	1.9
tramadol	0.29	-2.6	0.7	-1.8
oxycodone/paracetamol	0.26	3.4	0.3	3.4
oxycodone	0.15	-1.7	0.1	1.5
buprenorphine	0.14	27.4	0.2	66.2

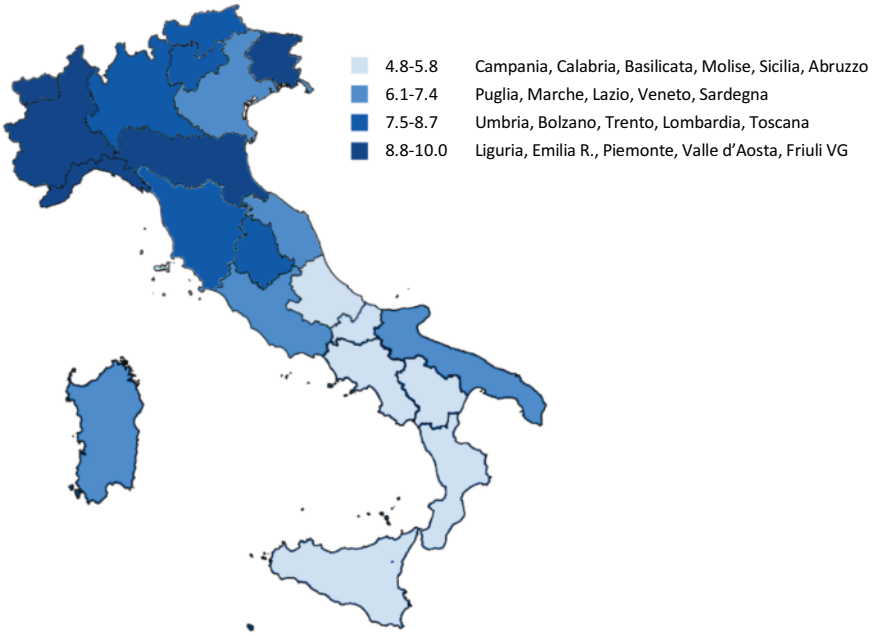
° including prescription of pregabalin and gabapentin for all authorised indications

Table 5.2.17d. Pain therapy, prescription of pharmaceuticals with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	1.69	26.3	-29.6	3.8	51.4	3.5	1.23
Equivalent	0.57	33.4	32.6	1.1	29.2	41.0	1.41
Ex originator	1.13	66.6	-43.0	2.7	70.8	-6.7	1.16
Patent covered	4.75	73.7	3.5	3.6	48.6	2.2	3.66
Pain therapy	**6.44**	**100.0**	**-8.0**	**7.3**	**100.0**	**2.8**	**2.41**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.17b. Pain therapy, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)



Pharmaceuticals for eye disorders

- Consumption remained almost stable over time, going from 20 DDD in 2013 to 21 DDD in 2018; 70% of consumption is represented by pharmaceuticals for the treatment of glaucoma;
- corticosteroid intravitreal implants register the greatest variation in consumption and expenditure compared to the previous year (>100%);
- a certain variability was recorded in regional consumption, with a value ranging from 16.3 DDD in Molise to 30.0 DDD in the Marche region (about 85% difference);
- Liguria is the region using more doses, with a cost per day of therapy higher than the national average;
- the consumption incidence of patent-expired medicines reached 41.2% in 2018, albeit with a limited use of equivalent medicines.

Figure 5.2.18a. Pharmaceuticals for eye disorders, temporal consumption trend (2013-2018)

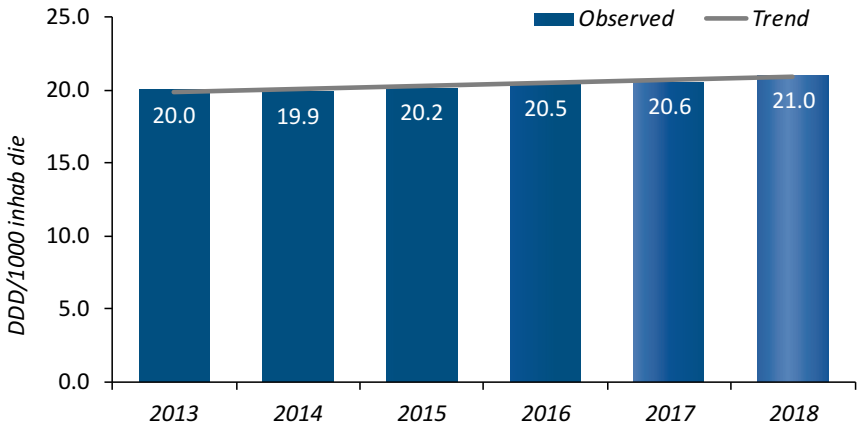


Table 5.2.18a. Pharmaceuticals for eye disorders, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Other antiglaucoma preparations	14.2	14.0	14.2	14.3	14.4	14.7	2.1
Antineovascularisation agents	0.2	0.2	0.2	0.3	0.3	0.4	13.2
Antiglaucoma prostaglandin analogues plain or in combination with beta blocking agents	5.6	5.6	5.6	5.7	5.7	5.8	1.7
Corticosteroids	0.1	0.1	0.2	0.2	0.2	0.2	-5.2
Corticosteroids (intravitreal implants)	-	-	-	-	<0.05	<0.05	>100
Ocriplasmin	-	<0.05	<0.05	<0.05	<0.05	<0.05	-31.1
Pharmaceuticals for eye disorders	**20.0**	**19.9**	**20.2**	**20.5**	**20.6**	**21.0**	**2.1**
ranibizumab	0.1	0.2	0.1	0.1	0.1	0.1	10.8
aflibercept	<0.05	<0.05	0.1	0.2	0.2	0.2	14.6
bimatoprost	1.7	1.8	1.9	1.9	1.9	1.9	1.9
timolol/bimatoprost	1.1	1.2	1.3	1.3	1.4	1.4	4.5
brinzolamide/timolol	1.1	1.2	1.3	1.5	1.6	1.7	7.6
tafluprost	0.7	0.8	0.9	1.2	1.2	1.3	7.1
timolol	3.3	3.2	3.1	3.3	3.0	3.1	0.8
dexamethasone	0.1	0.1	0.2	0.2	0.2	0.2	-5.2
dorzolamide/timolol	2.0	2.0	2.0	1.8	1.9	2.0	1.9
timolol/travoprost	0.9	0.9	0.9	0.9	0.9	0.8	-8.8

Table 5.2.18b. Pharmaceuticals for eye disorders, weighted regional trend of DDD/1000 inhabitants: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	21.9	21.9	22.1	22.4	22.4	23.0	2.6
Valle d'Aosta	20.0	20.6	20.8	20.4	19.9	19.3	-3.1
Lombardia	15.9	16.2	16.6	16.8	16.9	17.3	2.0
PA Bolzano	13.7	14.3	15.0	15.5	16.0	16.5	3.4
PA Trento	14.8	15.1	15.4	16.1	16.5	17.3	4.9
Veneto	17.4	17.7	17.8	18.2	18.5	19.2	3.8
Friuli VG	22.5	22.9	23.1	23.1	23.7	24.2	2.1
Liguria	21.6	21.2	21.3	21.7	21.5	21.7	0.6
Emilia R.	26.9	25.2	25.5	26.0	27.0	27.7	2.7
Toscana	25.9	25.8	25.8	26.4	26.4	26.7	1.1
Umbria	23.5	23.0	23.2	23.9	24.0	24.7	3.0
Marche	28.3	28.5	28.9	29.5	29.5	30.0	1.6
Lazio	22.7	22.0	22.3	22.4	22.1	22.3	0.8
Abruzzo	25.2	25.3	25.7	25.9	25.9	26.5	2.2
Molise	15.3	15.9	15.7	16.3	16.1	16.3	1.2
Campania	16.6	16.8	17.1	17.5	17.4	17.9	2.7
Puglia	18.3	18.4	18.6	18.8	18.8	19.1	1.7
Basilicata	18.8	19.0	19.5	20.1	20.0	20.7	3.3
Calabria	18.7	18.9	19.3	19.3	19.2	19.5	1.9
Sicilia	16.1	16.1	16.3	16.6	16.8	17.3	2.8
Sardegna	19.7	19.7	19.8	19.7	19.7	19.8	0.7
Italy	**20.0**	**19.9**	**20.2**	**20.5**	**20.6**	**21.0**	**2.1**

Table 5.2.18c. Pharmaceuticals for eye disorders, prescription by therapeutic category and substance in 2018

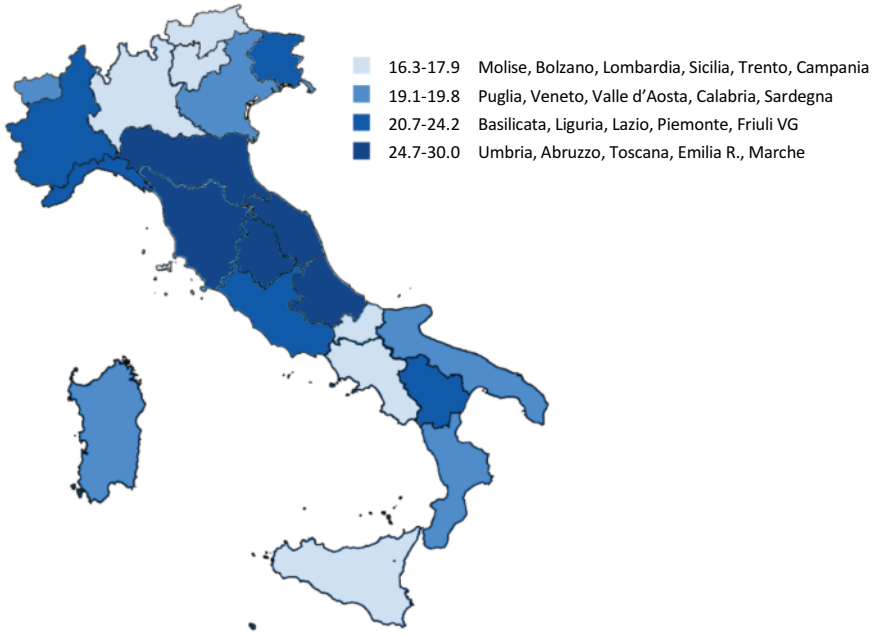
Subgroups and substances	Spesa pro capite	Δ % 18-17	DDD/1000 ab die	Δ % 18-17
Other antiglaucoma preparations	2.53	0.5	14.7	2.1
Antineovascularisation agents	2.19	12.3	0.4	13.2
Antiglaucoma prostaglandin analogues plain or in combiantion with beta blocking agents	1.28	-1.3	5.8	1.7
Corticosteroids	0.32	-4.7	0.2	-5.2
Corticosteoids (intravitreal implants)	0.02	>100	<0.05	>100
Ocriplasmin	<0.005	-27.4	<0.05	-31.1
Pharmaceuticals for eye disorders	**6.34**	**3.9**	**21.0**	**2.1**
ranibizumab	1.21	10.6	0.1	10.8
aflibercept	0.95	14.7	0.2	14.6
bimatoprost	0.47	0.8	1.9	1.9
timololo/bimatoprost	0.44	4.7	1.4	4.5
brinzolamide/timolol	0.41	2.2	1.7	7.6
tafluprost	0.40	7.0	1.3	7.1
timolol	0.33	4.3	3.1	0.8
dexamethasone	0.32	-4.7	0.2	-5.2
dorzolamide/timolol	0.28	2.1	2.0	1.9
timolol/travoprost	0.22	-25.2	0.8	-8.8

Table 5.2.18d. Prescription of pharmaceuticals for eye disorders with patent-expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	1.11	17.4	9.7	8.7	41.2	4.1	0.35
Equivalent	0.15	13.3	14.7	1.8	20.7	5.9	0.23
Ex originator	0.96	86.7	9.0	6.9	79.3	3.6	0.38
Patent covered	5.24	82.6	2.8	12.4	58.8	0.8	1.16
Pharmaceuticals for eye disorders	**6.34**	**100.0**	**3.9**	**21.0**	**100.0**	**2.1**	**0.83**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.18b. Pharmaceuticals for eye disorders, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)



Antidepressants

- Consumption of antidepressants has slightly increased over the past few years, rising from 39 DDD in 2013 to 41.6 DDD in 2018 (+ 6.5%); consumption is mostly represented by SSRI antidepressants (29.7% of antidepressant consumption in 2018);
- prevalence of use increases with age and for all age groups it is always higher in women than in men;
- paroxetine (SSRI) is the active ingredient showing the highest consumption in 2018 (8 DDD), although within the SSRI class sertraline recorded the greatest increase in consumption compared to the previous year (+4.3 %); vortioxetine (antidepressant belonging to the class of serotonin modulators and stimulators, marketed in 2016), despite recording the lowest consumption after bupropion, is the drug with the greatest increase compared to the previous year (+ 40.5%);
- a marked variability was reported in regional consumption, with Sardegna (62.2 DDD) consuming about twice as much as Basilicata (31.9 DDD); the greatest variability is observed for the SSRI class;
- a decreasing gradient is observed in the duration of therapy from North to South, with the Northern regions showing a more sporadic use compared to the Southern regions;
- Marche and Sardegna are the regions using more doses, with a cost per day of therapy higher than the national average;
- the incidence of patent-expired drug consumption reached 89.2% in 2018, half of which due to use of equivalent medicines.

Figure 5.2.19a. Antidepressants, regional consumption trend (2013-2018)

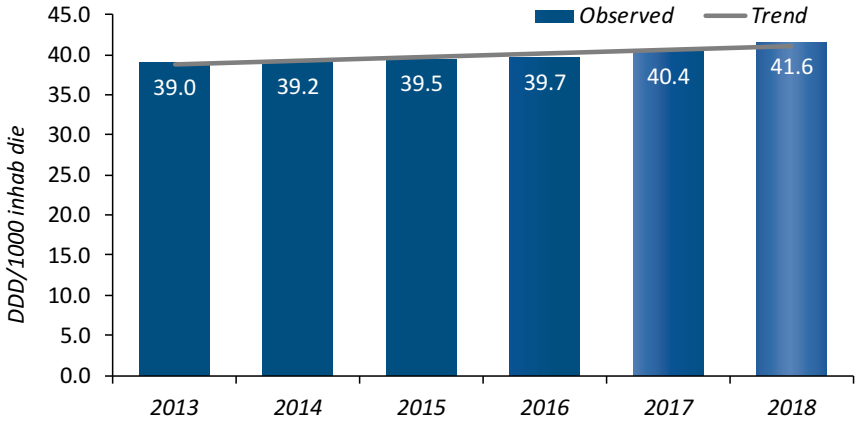


Table 5.2.19a. Antidepressants, consumption (DDD/1000 inhab. per day) by therapeutic category and substance: comparison 2013-2018

Subgroups and sustances	2013	2014	2015	2016	2017	2018	Δ % 18-17
SSRI-antidepressants	29.2	29.2	29.3	29.2	29.1	29.7	1.8
SNRI-antidepressants	6.0	6.1	6.2	6.2	6.3	6.5	3.4
Other antidepressants	2.3	2.4	2.6	2.7	2.9	3.0	4.3
SMS-antidepressants (serotonin modulators and stimulators)	-	-	-	0.2	0.8	1.1	40.5
Tricyclic antidepressants	1.1	1.2	1.1	1.1	1.1	1.1	-0.8
Bupropion	0.3	0.3	0.2	0.2	0.2	0.2	6.0
NaRI-antidepressants (noradrenaline reuptake inhibitors)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-16.7
Agomelatine	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-28.9
Antidepressants	**39.0**	**39.2**	**39.5**	**39.7**	**40.4**	**41.6**	**2.9**
paroxetine	8.0	8.0	7.9	7.8	7.8	8.0	1.6
escitalopram	7.4	7.3	7.3	7.3	7.2	7.3	1.4
venlafaxine	3.4	3.4	3.5	3.5	3.5	3.5	1.6
duloxetine	2.6	2.7	2.7	2.7	2.8	2.9	5.6
sertraline	7.0	7.2	7.6	7.7	7.9	8.2	4.3
vortioxetine	-	-	-	0.2	0.8	1.1	40.5
citalopram	5.0	4.8	4.6	4.4	4.3	4.3	-0.9
trazodone	0.7	0.8	1.0	1.1	1.1	1.2	5.1
mirtazapine	1.5	1.6	1.6	1.6	1.7	1.7	4.5
bupropion	0.3	0.3	0.2	0.2	0.2	0.2	6.0

Table 5.2.19b. Antidepressants, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	44.0	44.3	44.6	45.2	46.0	47.3	2.8
Valle d'Aosta	37.9	38.8	38.5	38.1	38.5	40.0	3.9
Lombardia	36.1	36.6	37.1	37.6	38.3	39.5	3.1
PA Bolzano	51.7	52.1	53.0	53.5	53.6	54.5	1.6
PA Trento	37.5	38.1	38.4	38.9	39.6	41.5	4.7
Veneto	37.1	37.3	37.9	37.8	38.7	40.3	4.0
Friuli VG	34.3	34.1	34.0	33.6	34.4	35.7	3.8
Liguria	53.4	53.3	53.4	52.8	54.2	55.2	1.9
Emilia R.	50.2	50.1	50.3	49.0	49.9	52.1	4.4
Toscana	60.0	60.7	60.7	60.7	61.5	62.2	1.1
Umbria	51.2	50.4	51.0	51.9	52.5	53.9	2.6
Marche	40.8	41.3	41.7	42.2	42.6	43.6	2.4
Lazio	35.6	34.5	34.9	35.1	35.7	36.7	2.8
Abruzzo	36.2	36.8	37.2	37.8	38.7	40.1	3.5
Molise	31.0	33.1	32.1	31.8	32.9	34.4	4.7
Campania	28.6	29.3	29.9	30.5	31.0	32.1	3.6
Puglia	30.4	30.7	31.0	31.1	31.7	32.6	2.9
Basilicata	30.1	30.5	30.9	31.2	31.5	31.9	1.5
Calabria	36.0	36.6	37.0	37.4	37.8	38.8	2.6
Sicilia	30.9	30.7	31.0	31.4	32.0	33.0	3.3
Sardegna	43.6	43.8	44.1	43.9	44.4	45.1	1.6
Italy	**39.0**	**39.2**	**39.5**	**39.7**	**40.4**	**41.6**	**2.9**

Table 5.2.19c. Antidepressants, prescription by therapeutic category and substance in 2018

Subgroups and substances	Spesa pro capite	Δ % 18-17	DDD/1000 ab die	Δ % 18-17
SSRI-antidepressants	3.29	0.8	29.7	1.8
SNRI-antidepressants	1.49	2.7	6.5	3.4
Other antidepressants	0.73	3.7	3.0	4.3
SMS-antidepressants (serotonin modulators and stimulators)	0.46	40.2	1.1	40.5
Tricyclic antidepressants	0.17	-0.9	1.1	-0.8
Bupropion	0.17	2.3	0.2	6.0
NaRI-antidepressants (noradrenaline reuptake inhibitors)	0.01	-17.2	<0.05	-16.7
Agomelatine	<0.005	-27.7	<0.05	-28.9
Antidepressants	**6.32**	**3.7**	**41.6**	**2.9**
paroxetine	1.03	-0.2	8.0	1.6
escitalopram	0.94	0.5	7.3	1.4
venlafaxine	0.77	1.5	3.5	1.6
duloxetine	0.72	4.2	2.9	5.6
sertraline	0.71	4.5	8.2	4.3
vortioxetine	0.46	40.2	1.1	40.5
citalopram	0.42	-1.3	4.3	-0.9
trazodone	0.40	5.1	1.2	5.1
mirtazapine	0.32	2.9	1.7	4.5
bupropion	0.17	2.3	0.2	6.0

Table 5.2.19d. Prescription of antidepressants with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	4.92	77.9	3.3	37.1	89.2	2.6	0.36
Equivalent	1.96	39.8	6.3	18.5	50.0	5.0	0.29
Ex originator	2.96	60.2	1.3	18.5	50.0	0.3	0.44
Patent covered	1.39	22.1	5.4	4.5	10.8	6.2	0.85
Antidepressants	**6.32**	**100.0**	**3.7**	**41.6**	**100.0**	**2.9**	**0.42**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.19b. Antidepressants, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

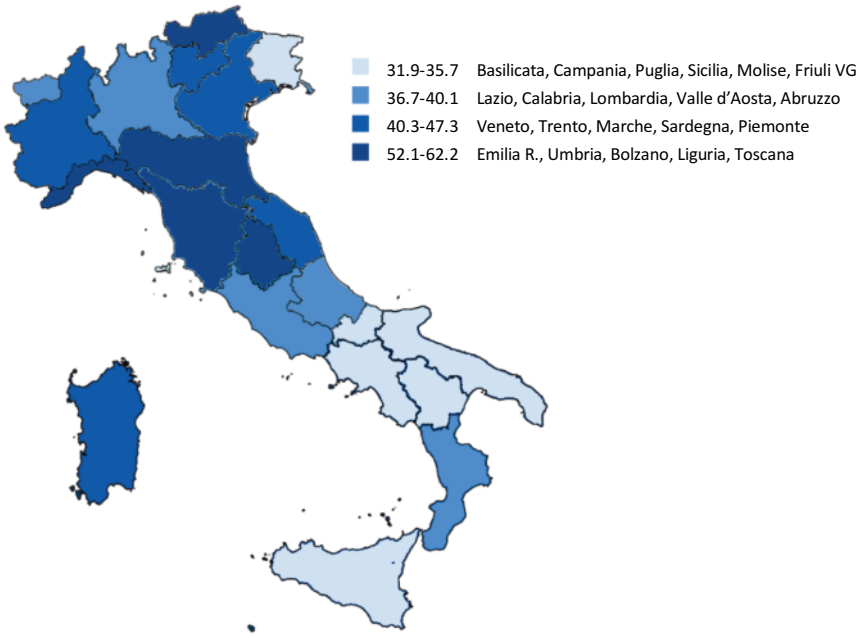


Table 5.2.19e. Duration of antidepressant therapy per geographical area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	DDD median	Users with 1 prescription
North	5,2	226,7	180,0	20,3
Centre	5,6	221,8	178,5	21,0
South and islands	5,8	215,4	168,0	22,3
Antidepressants	**5,5**	**222,2**	**178,5**	**21,0**

Pharmaceuticals for genitourinary disorders

- In 2018 the consumption of pharmaceuticals for genitourinary disorders reached 35.9 DDD with an increase of 3.8% compared to the previous year and approximately 19% compared to 2013; on the contrary, the expenditure, due to the patent expiry of Dutasterid in the second half of 2017, decreased by 16.7%;
- alpha-blockers are the most used category and represent 70% of the total, followed by 5-alpha reductase inhibitors with 10.5 DDD; Tamsulosin, Alfuzosin and Dutasterid are the most prescribed molecules (respectively 10.2, 8.4 and 7.9 DDD);
- the region Marche show a consumption twice as much than the Autonomous Province of Bolzano (44.6 vs 22.2 DDD) and, overall, the consumption is lower in the North;
- patent-expired pharmaceuticals account for about 85% of doses and 78% of expenditure;
- as expected, the consumption in the male population increases with age up to 40% of the prevalence in the class over 75 years and about 400 DDD per thousand inhabitants;
- the median duration of therapy (320 days) is in line with the therapeutic schemes of this pathology and only 13.5% of users received a single prescription during 2018.

Figure 5.2.20a. Pharmaceuticals for genitourinary disorders, consumption trend (2013-2018)

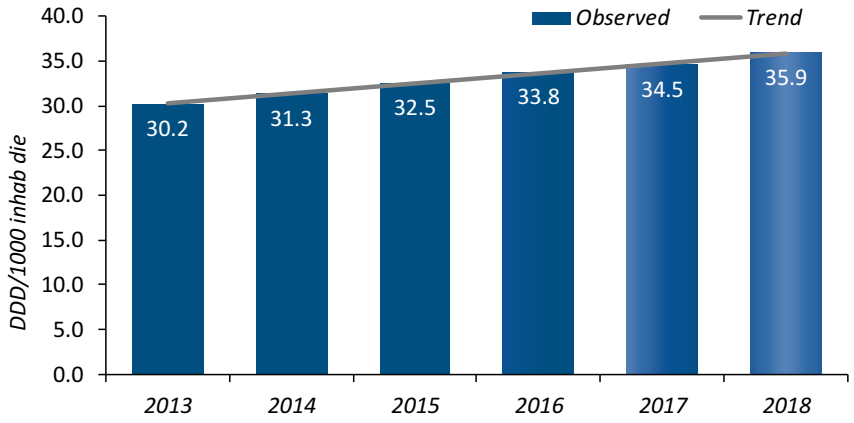


Table 5.2.20a. Pharmaceuticals for genitourinary disorders, consumption (DDD/1000 inhab die) by therapeutic category and by substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Alfpha blockers	21.4	22.2	22.9	23.8	24.4	25.4	3.9
5-alpha reductase inhibitors	8.8	9.2	9.6	10.0	10.1	10.5	3.7
Beta 3 selective agonist	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-12.7
Alpha blocker in ass.	-	<0.05	<0.05	<0.05	<0.05	<0.05	-9.6
Pharmaceuticals for genitourinary disorders	**30.2**	**31.3**	**32.5**	**33.8**	**34.5**	**35.9**	**3.8**
tamsulosin	9.4	9.4	9.5	9.8	9.9	10.2	2.7
dutasterid	6.0	6.5	7.0	7.3	7.4	7.9	6.2
silodosin	2.6	3.4	4.0	4.5	4.9	5.3	9.8
alfuzosin	7.6	7.7	7.8	8.0	8.2	8.4	3.3
finasterid	2.8	2.7	2.7	2.7	2.7	2.6	-3.3
terazosin	1.9	1.7	1.6	1.5	1.4	1.4	-4.8

Table 5.2.20b. Pharmaceuticals for genitourinary disorders, regional trend of DDD/1000 inhabitants per day weighted: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	30.1	31.0	31.8	33.0	33.6	34.5	2.7
Valle d'Aosta	26.7	28.3	29.1	29.3	29.4	30.5	3.6
Lombardia	26.9	28.2	29.4	30.5	31.3	32.6	4.0
PA Bolzano	20.6	20.9	21.3	21.5	22.0	22.2	0.9
PA Trento	26.7	28.5	29.5	30.2	31.3	32.7	4.6
Veneto	26.1	27.5	28.4	29.6	30.2	31.4	4.1
Friuli VG	26.9	27.9	28.8	29.8	30.2	31.1	3.1
Liguria	32.2	33.3	34.3	35.4	36.1	37.1	2.9
Emilia R.	32.1	32.8	34.6	35.8	36.3	37.1	2.1
Toscana	29.7	30.8	31.7	32.8	33.6	34.6	3.2
Umbria	35.5	35.5	36.8	38.3	39.1	40.9	4.6
Marche	37.4	39.0	40.4	42.2	42.8	44.6	4.4
Lazio	33.9	33.8	34.8	35.8	36.3	37.5	3.1
Abruzzo	30.5	31.9	33.0	34.4	35.4	37.1	4.9
Molise	27.0	30.0	30.4	31.4	32.6	34.1	4.7
Campania	29.2	31.1	32.8	34.6	35.9	37.9	5.7
Puglia	31.3	33.2	34.6	36.3	37.6	39.2	4.3
Basilicata	32.4	34.3	36.4	38.2	39.6	41.7	5.4
Calabria	32.3	33.7	34.6	36.1	36.8	38.1	3.6
Sicilia	32.7	33.9	35.0	36.1	36.9	38.5	4.3
Sardegna	29.5	30.9	32.4	33.5	34.5	36.1	4.5
Italy	**30.2**	**31.3**	**32.5**	**33.8**	**34.5**	**35.9**	**3.8**

Table 5.2.20c. Pharmaceuticals for genitourinary disorders, prescription by therapeutic category and by substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab die	Δ % 18-17
Alpha blockers	3.01	4.5	25.4	3.9
5-alpha reductase inhibitors	1.58	-39.9	10.5	3.7
Beta 3 selective agonist	<0.005	-11.9	<0.05	-12.7
Alpha blockers in combination	<0.005	-10.0	<0.05	-9.6
Pharmaceuticals for genitourinary disorders	**4.59**	**-16.7**	**35.9**	**3.8**
tamsulosin	1.05	2.7	10.2	2.7
dutasterid	1.02	-50.3	7.9	6.2
silodosin	1.00	9.7	5.3	9.8
alfuzosin	0.79	3.2	8.4	3.3
finasterid	0.56	-2.6	2.6	-3.3
terazosin	0.17	-5.6	1.4	-4.8

Table 5.2.20d. Prescription of pharmaceuticals for genitourinary disorders with patent expired* in 2018

Categories	per capita expenditure	%	Δ % 18-17	DDD/1000 inhab die	%	Δ % 18-17	DDD average cost
Patent expired	3.56	77.5	18.4	30.4	84.7	21.0	0.32
Equivalent	1.14	32.0	18.8	11.5	37.8	19.4	0.27
Ex originator	2.42	68.0	18.3	18.9	62.2	22.1	0.35
Patent covered	1.03	22.5	-58.8	5.5	15.3	-41.9	0.52
Pharmaceuticals for genitourinary disorders	**4.59**	**100.0**	**-16.7**	**35.9**	**100.0**	**3.8**	**0.35**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.20b. Pharmaceuticals for genitourinary disorders, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

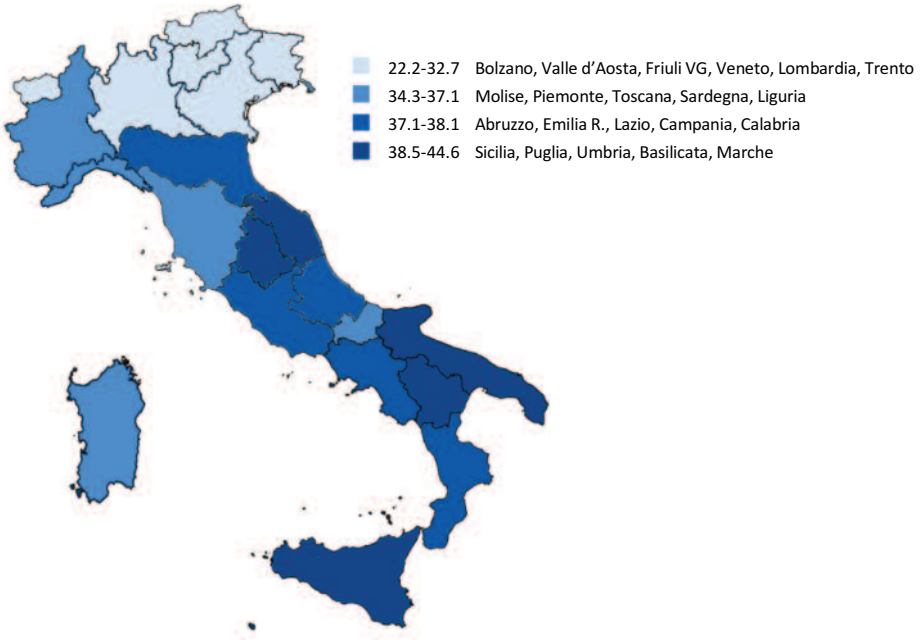


Table 5.2.20e. Duration of therapy with pharmaceuticals for genitourinary disorders in approved care regime by geographic area (year 2018)

	Prescriptions per user	DDD per user	DDD median	Users with 1 prescription
North	7.4	334.9	320.0	12.7
Centre	7.5	329.8	320.0	14.9
South and islands	7.7	331.8	320.0	13.6
Pharmaceuticals for genitourinary disorders	**7.5**	**332.7**	**320.0**	**13.5**

Antipsychotics

- The consumption of antipsychotics has increased over the past few years, from 8.2 DDD in 2013 to 9.6 in 2018 (+16.8%); most of the consumption is represented by atypical antipsychotics and others: 7% of consumption for 2018, with an increase of 3.8% compared to the previous year;
- paliperidone and aripiprazole show the greatest increase in consumption in 2018, respectively +16.3% and +10.5% compared to the previous year; risperidone is the active ingredient with the most significant reduction in consumption (-5%);
- there is some variability in consumption in the Italian regions, with Sardegna (13.9 DDD) consuming almost twice as much than the Valle d'Aosta (7.1 DDD);
- Puglia, Marche, Calabria and Basilicata are the regions using more doses, with a cost per day of therapy higher than the national average;
- the incidence of patent-expired drug consumption reached 67.7% in 2018, most of which are equivalent medicines;
- in line with epidemiological data, the maximum prevalence of use is reached in the age group above 75 years, with a value of 6.2% in women and 4.6% in men;
- about half of users have a treatment period of less than 45 days and about a quarter receive a single prescription in the year.

Figure 5.2.21a. Antipsychotics, temporal consumption trend (2013-2018)

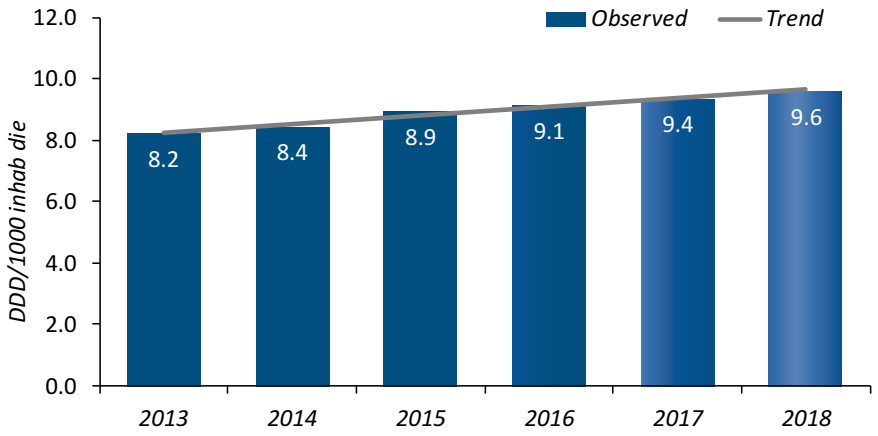


Table 5.2.21a. Antipsychotics, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Atypical antipsychotics and others	5.3	5.6	6.2	6.4	6.7	7.0	3.8
Typical antipsychotics	2.9	2.9	2.7	2.7	2.6	2.6	-0.6
Antipsychotics	**8.2**	**8.4**	**8.9**	**9.1**	**9.4**	**9.6**	**2.6**
paliperidone	0.3	0.4	0.5	0.5	0.6	0.7	16.3
aripiprazole	0.6	0.3	0.8	0.9	1.0	1.1	10.5
quetiapine	1.5	1.7	1.7	1.7	1.8	1.8	1.1
risperidone	0.8	0.9	0.9	0.9	0.9	0.8	-5.0
olanzapine	1.6	1.9	2.0	2.0	2.0	2.0	2.4
clozapine	0.4	0.4	0.4	0.4	0.4	0.4	2.3
haloperidol	1.2	1.2	1.1	1.2	1.1	1.1	-1.9
amisulpride	0.1	0.1	0.1	0.1	0.1	0.1	-0.3
lithium	0.3	0.3	0.4	0.4	0.4	0.3	-3.0
asenapine	0.1	0.1	0.1	0.1	0.1	<0.05	-16.8

Table 5.2.21b. Antipsychotics, regional trend of DDD/1000 inhabitants per day weighted: comparison 2013-2018

Regions	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	8.4	8.8	8.9	9.5	9.5	9.7	2.3
Valle d'Aosta	6.0	6.4	6.4	5.7	6.6	7.1	7.9
Lombardia	6.5	6.5	7.0	7.2	7.5	7.8	4.1
PA Bolzano	9.4	8.7	9.9	9.6	9.8	9.5	-2.5
PA Trento	6.2	7.0	8.4	8.3	8.2	9.2	13.0
Veneto	9.0	9.1	9.4	9.4	9.5	9.6	1.1
Friuli VG	8.8	8.8	7.9	8.5	9.6	9.5	-1.5
Liguria	8.1	8.1	8.4	8.9	9.2	9.2	0.1
Emilia R.	9.3	9.5	10.2	9.6	10.1	10.3	1.6
Toscana	7.7	8.2	8.9	9.5	9.0	9.6	6.7
Umbria	7.7	8.4	9.5	9.6	9.3	9.9	6.3
Marche	7.5	8.2	7.8	7.2	9.2	10.1	10.4
Lazio	8.6	7.9	8.5	8.7	9.2	9.3	0.6
Abruzzo	8.9	9.2	9.4	9.7	9.5	10.3	8.2
Molise	8.8	9.3	8.8	8.7	9.4	9.4	0.2
Campania	7.6	8.1	8.6	8.6	9.1	9.0	-1.2
Puglia	7.5	9.3	9.8	10.2	10.5	10.9	4.3
Basilicata	9.5	9.0	9.8	10.4	11.1	10.3	-6.9
Calabria	9.4	9.1	9.7	10.2	9.5	10.3	8.9
Sicilia	9.6	9.6	10.2	10.7	10.5	10.4	-1.4
Sardegna	10.6	11.4	13.1	13.2	13.0	13.9	6.5
Italy	**8.2**	**8.4**	**8.9**	**9.1**	**9.4**	**9.6**	**2.6**

Table 5.2.21c. Antipsychotics, prescription by therapeutic category and by substance in 2018

Subgroups e substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab die	Δ % 18-17
Atypical antipsychotics and others	4.18	6.4	7.0	3.8
Typical antipsychotics	0.38	0.0	2.6	-0.6
Antipsychotics	**4.56**	**5.8**	**9.6**	**2.6**
paliperidone	1.42	15.7	0.7	16.3
aripiprazole	0.94	18.4	1.1	10.5
quetiapine	0.73	-8.7	1.8	1.1
risperidone	0.49	-7.5	0.8	-5.0
olanzapine	0.35	0.0	2.0	2.4
clozapine	0.15	1.8	0.4	2.3
haloperidol	0.08	0.3	1.1	-1.9
amisulpride	0.07	-0.3	0.1	-0.3
lithium	0.06	-4.0	0.3	-3.0
asenapine	0.06	-18.1	<0.05	-16.8

Table 5.2.21d. Prescription of Antipsychotics with patent expired* in 2018

Categories	Per capita expenditure	%	Δ % 18-17	DDD/1000 inhab die	%	Δ % 18-17	DDD average cost
Patent expired	1.79	39.2	-2.3	6.5	67.7	1.3	0.76
Equivalent	1.14	63.8	2.9	5.1	79.3	6.0	0.61
Ex originator	0.65	36.2	-10.3	1.3	20.7	-13.3	1.32
Patent covered	2.77	60.8	12.9	3.1	32.3	5.2	2.45
Antipsychotics	**4.56**	**100.0**	**5.8**	**9.6**	**100.0**	**2.6**	**1.30**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.21b. Antipsychotics, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

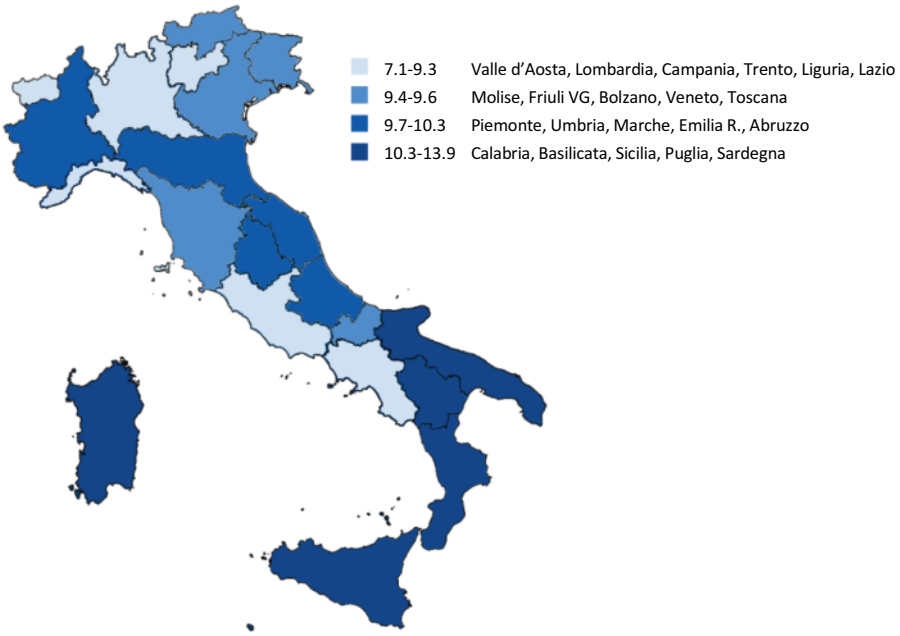


Table 5.2.21e. Duration of antipsychotic therapy per geographical area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	DDD median	User with 1 prescription
North	5.7	112.7	45.0	24.7
Centre	6.5	114.5	45.0	25.5
South and islands	7.1	140.1	51.5	25.8
Antipsychotics	**6.4**	**124.2**	**46.9**	**25.3**

Antiparkinsonians

- Over the last six years, the consumption of antiparkinsonian medicines has increased on average (CAGR) by about 2% every year, reaching 5.2 DDD in 2018;
- DOPA-derived agonists (2.3 DDD) and MAO-B inhibitors (1.6 DDD) are the most prescribed categories, both increasing compared to 2017 (respectively +1.1% and +8.3%);
- the associations of levodopa with carbidopa and bensezaride are the most commonly used substances, while safinamide is the molecule with the largest increase (+33%). This substance, marketed in 2016, is indicated as an adjunctive therapy to levodopa plain or in combination with other therapies;
- the regional variability ranges from a minimum of 3.6 DDD in the Autonomous Province of Bolzano to 6.3 in Liguria;
- more than half of the doses and 40% of the expenditure refer to patent-expired pharmaceuticals with an average cost per day of therapy which is about half of patented pharmaceuticals (1.22 vs 2.29). Equivalent pharmaceuticals only account for 21.4% of patent-expired medicinal products;
- in line with the epidemiology of conditions, consumption increases with age and reaches a prevalence of use of over 4% in men in the >75-year age group; significant differences in use are recorded between men and women in all age groups; on average each user in one year is treated for 9 months and 14% of users receive a single prescription in a year.

Figure 5.2.22a. Antiparkinsonian pharmaceuticals, consumption trend (2013-2018)

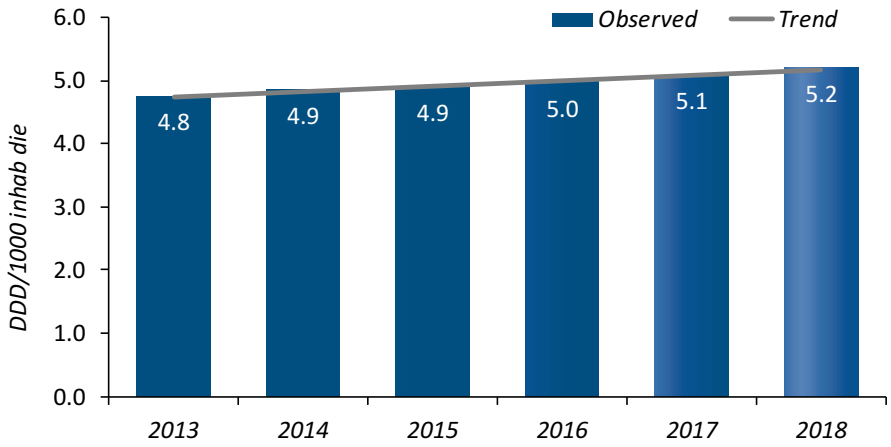


Table 5.2.22a. Antiparkinsonian pharmaceuticals, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Dopamine-agonists	1.5	1.5	1.4	1.3	1.3	1.3	-2.4
Dopa-derived agonists	2.2	2.2	2.3	2.3	2.3	2.3	1.1
MAO-B inhibitors	1.0	1.1	1.2	1.3	1.4	1.6	8.3
COMT inhibitors	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	46.9
Amantadine	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-85.8
Antiparkinsonian pharmaceuticals	**4.8**	**4.9**	**4.9**	**5.0**	**5.1**	**5.2**	**2.3**
rotigotine	0.3	0.3	0.4	0.4	0.4	0.4	2.8
levodopa/carbidopa	0.8	0.9	0.9	0.9	0.9	1.0	5.1
pramipexole	0.6	0.6	0.5	0.5	0.5	0.5	-2.1
safinamide	-	-	-	0.1	0.1	0.2	33.0
levodopa/benserazide	0.9	0.9	0.9	0.9	0.9	1.0	4.8
rasagiline	0.4	0.4	0.4	0.4	0.4	0.4	1.3
melevodopa/carbidopa	0.2	0.2	0.2	0.3	0.3	0.2	-16.0
ropinirole	0.6	0.5	0.5	0.4	0.4	0.4	-7.8
selegiline	0.6	0.7	0.8	0.9	0.9	1.0	7.0
levodopa/carbidopa/entacapone	0.3	0.3	0.2	0.2	0.2	0.2	-12.5

Table 5.2.22b. Antiparkinsonian pharmaceuticals, regional trend of weighted DDD/1000 inhabitants per day: comparison 2013-2018

Regions	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	5.3	5.4	5.4	5.4	5.6	5.7	1.3
Valle d'Aosta	4.2	4.4	4.4	4.4	4.6	5.0	7.0
Lombardia	4.1	4.2	4.2	4.3	4.4	4.5	2.6
PA Bolzano	3.9	4.0	3.9	3.6	3.5	3.6	1.3
PA Trento	4.4	4.4	4.4	4.4	4.5	4.5	0.4
Veneto	4.6	4.8	4.9	4.9	5.0	5.1	2.2
Friuli VG	4.5	4.6	4.2	4.3	4.8	4.9	1.7
Liguria	5.8	5.9	6.0	6.0	6.2	6.3	1.8
Emilia R.	4.8	4.9	4.9	5.0	4.9	4.9	-0.2
Toscana	5.2	5.3	5.4	5.5	5.4	5.4	-0.1
Umbria	5.6	5.5	5.6	5.7	5.7	5.9	2.7
Marche	5.6	5.8	5.9	5.9	6.0	6.1	1.4
Lazio	5.2	5.2	5.3	5.5	5.6	5.9	4.0
Abruzzo	5.1	5.3	5.6	5.7	5.9	6.3	6.3
Molise	4.6	4.9	4.8	5.0	5.0	5.1	2.2
Campania	4.2	4.4	4.5	4.6	4.8	5.0	4.9
Puglia	5.0	5.1	5.1	5.1	5.2	5.3	2.3
Basilicata	4.5	4.8	4.7	4.9	5.2	5.4	3.8
Calabria	4.4	4.6	4.7	4.7	4.8	4.8	1.2
Sicilia	4.9	4.9	4.9	5.1	5.3	5.4	2.3
Sardegna	3.9	4.0	4.1	3.9	4.2	4.4	3.8
Italy	**4.8**	**4.9**	**4.9**	**5.0**	**5.1**	**5.2**	**2.3**

Table 5.2.22c. Antiparkinsonian pharmaceuticals, prescription by therapeutic category and by substance in 2018

Subgroups and substances	per capita expenditure	Δ % 18-17	DDD/1000 inhab die	Δ % 18-17
Dopamine-agonists	1.28	0.7	1.3	-2.4
Dopa-derived agonists	1.18	-3.6	2.3	1.1
MAO-B inhibitors	0.72	10.3	1.6	8.3
COMT inhibitors	0.05	49.2	<0.05	46.9
Amantadine	<0.005	-75.7	<0.05	-85.8
Antiparkinsonian pharmaceuticals	**3.24**	**1.5**	**5.2**	**2.3**
rotigotine	0.74	2.9	0.4	2.8
levodopa/carbidopa	0.62	-1.0	1.0	5.1
pramipexole	0.40	-0.4	0.5	-2.1
safinamide	0.33	29.6	0.2	33.0
levodopa/benserazide	0.32	5.2	1.0	4.8
rasagiline	0.27	-5.5	0.4	1.3
melevodopa/carbidopa	0.14	-17.0	0.2	-16.0
ropinirole	0.13	-6.7	0.4	-7.8
selegiline	0.12	7.2	1.0	7.0
levodopa/carbidopa/entacapone	0.10	-20.6	0.2	-12.5

Table 5.2.22d. Prescription of antiparkinsonian pharmaceuticals with patent-expired* in 2018

Categories	per capita expenditure	%	Δ % 18-17	DDD/1000 inhab die	%	Δ % 18-17	DDD average cost
Patent expired	1.27	39.1	-3.5	2.8	54.7	-1.9	1.22
Equivalent	0.28	21.9	3.7	0.6	21.4	1.3	1.25
Ex originator	0.99	78.1	-5.3	2.2	78.6	-2.7	1.21
Patent covered	1.97	60.9	5.2	2.4	45.3	8.0	2.29
Antiparkinsonian	**3.24**	**100.0**	**1.5**	**5.2**	**100.0**	**2.3**	**1.71**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.22b. Antiparkinsonian pharmaceuticals, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

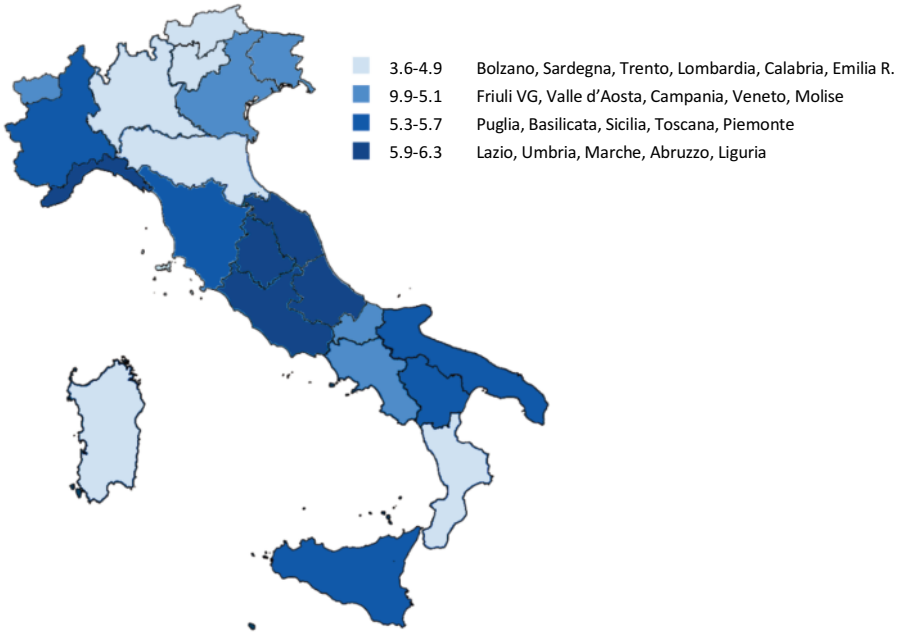


Table 5.2.22e. Duration of antiparkinsonian therapy per geographical area in approved care regime (year 2018)

	Prescriptions per user	DDD per user	DDD median	User with 1 prescription
North	9.8	272.4	136.0	12.9
Centre	10.9	267.6	133.3	15.7
South and islands	11.2	282.9	150.0	14.0
Antiparkinsonian pharmaceuticals	**10.6**	**274.8**	**138.6**	**13.9**

Non-steroidal anti-inflammatory medicines (NSAIDs)

- The downward trend (CAGR: -5%) in the consumption of NSAIDs continues also in 2018; they fell by 21.5% compared to 2013;
- traditional NSAIDs with 12.2 DDD, equal to 66% of the total, are the most prescribed category followed by coxibs with 3.8 DDD and nimesulide with 2.1 DDD; the 33.6% reduction in etoricoxib expenditure is due to the patent expiry in the second half of 2017;
- approximately 90% of expenditure of the doses refers to patent-expired medicinal products and, among these, the use of equivalent pharmaceuticals is still limited;
- southern regions record a higher use of NSAIDs and, in particular, Calabria shows a value of 29.4 DDD in 2018, while Emilia Romagna is the region with the lowest level (11.2 DDD); a lower inter-regional variability is reported with reference to the average cost per day of therapy;
- women use more NSAIDs than men, particularly in the age group >65 years, in which men have a prevalence of use of about 40% higher than that of women. These medicines are used for short periods: on average each user is treated for 40 days and about half receives only one prescription a year.

Figure 5.2.23a. Non-steroidal anti-inflammatory medicines (NSAIDs), temporal consumption trend (2013-2018)

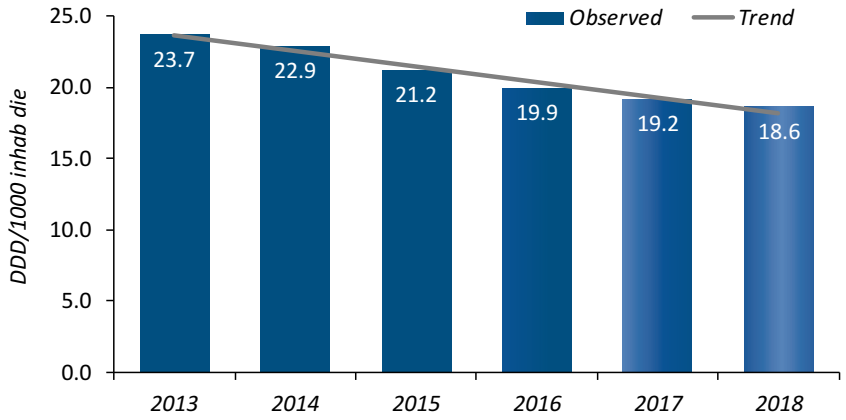


Table 5.2.23a. Non-steroidal anti-inflammatory medicines (NSAIDs), consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Traditional NSAIDs	15.0	14.6	13.7	13.0	12.7	12.2	-3.7
Coxib	4.9	4.7	4.4	4.1	3.8	3.8	0.0
Nimesulide	3.1	2.9	2.6	2.3	2.2	2.1	-6.5
Ketorolac	0.7	0.7	0.6	0.6	0.6	0.6	2.8
NSAIDs	**23.7**	**22.9**	**21.2**	**19.9**	**19.2**	**18.6**	**-3.1**
diclofenac	4.3	4.2	4.0	4.0	4.1	4.0	-1.8
etoricoxib	3.7	3.8	3.5	3.2	3.0	3.1	3.3
ketoprofen	4.4	4.3	4.0	3.7	3.5	3.3	-4.9
ibuprofen	2.2	2.2	2.2	2.1	2.0	2.1	1.4
nimesulide	3.1	2.9	2.6	2.3	2.2	2.1	-6.5
celecoxib	1.2	1.0	0.9	0.9	0.8	0.7	-11.7
ketorolac	0.7	0.7	0.6	0.6	0.6	0.6	2.8
aceclofenac	0.8	0.8	0.6	0.6	0.5	0.5	-7.7
piroxicam	0.7	0.7	0.6	0.5	0.5	0.5	-8.8
dexibuprofen	0.3	0.3	0.4	0.4	0.4	0.4	-4.1

Table 5.2.23b. Non-steroidal anti-inflammatory medicines (NSAIDs), regional trend of DDD/1000 inhabitants per day weighted: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	19.3	18.3	16.8	15.9	15.4	15.0	-2.7
Valle d'Aosta	22.8	22.3	20.9	18.3	17.3	17.2	-0.8
Lombardia	13.6	13.4	12.9	12.4	11.9	11.7	-2.1
PA Bolzano	18.0	17.4	16.1	15.6	14.3	13.4	-5.8
PA Trento	16.6	16.6	16.0	15.9	15.8	16.1	1.6
Veneto	17.2	16.1	14.7	13.8	12.9	12.2	-5.2
Friuli VG	21.7	21.1	20.1	19.6	18.9	18.5	-2.0
Liguria	17.4	16.1	14.6	13.8	13.6	13.0	-3.9
Emilia R.	14.8	14.0	12.8	11.9	11.4	11.2	-1.7
Toscana	19.2	18.3	16.8	16.1	15.5	14.7	-5.0
Umbria	18.7	17.2	15.5	14.8	14.3	14.4	1.2
Marche	18.8	18.4	17.3	16.6	16.4	14.8	-9.3
Lazio	31.2	29.1	26.8	24.8	24.3	23.8	-1.9
Abruzzo	23.5	23.0	22.0	20.9	20.3	20.1	-0.6
Molise	28.6	28.3	26.7	23.4	22.5	22.3	-0.7
Campania	32.7	32.7	30.8	28.4	27.9	28.4	1.7
Puglia	40.0	39.2	36.5	34.9	32.6	29.0	-11.1
Basilicata	29.2	28.1	25.7	23.4	23.0	23.0	-0.1
Calabria	36.8	36.3	33.2	31.1	30.1	29.4	-2.4
Sicilia	32.0	30.2	27.0	25.4	24.7	24.5	-0.6
Sardegna	36.1	35.5	34.2	30.0	27.5	25.7	-6.4
Italy	**23.7**	**22.9**	**21.2**	**19.9**	**19.2**	**18.6**	**-3.1**

Table 5.2.23c. Non-steroidal anti-inflammatory medicines (NSAIDs), prescription by therapeutic category and by substance in 2018

Subgroups and substances	per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Traditional NSAIDs	1.60	-4.0	12.2	-3.7
Coxib	0.65	-30.3	3.8	0.0
Nimesulide	0.16	-6.3	2.1	-6.5
Ketorolac	0.11	-2.7	0.6	2.8
NSAIDs	**2.52**	**-12.6**	**18.6**	**-3.1**
diclofenac	0.58	-1.2	4.0	-1.8
etoricoxib	0.53	-33.6	3.1	3.3
ketoprofen	0.34	-5.7	3.3	-4.9
ibuprofen	0.29	-0.2	2.1	1.4
nimesulide	0.16	-6.3	2.1	-6.5
celecoxib	0.12	-12.1	0.7	-11.7
ketorolac	0.11	-2.7	0.6	2.8
aceclofenac	0.09	-8.2	0.5	-7.7
piroxicam	0.07	-9.3	0.5	-8.8
dexibuprofen	0.07	-4.1	0.4	-4.1

Table 5.2.23d. Prescription of non-steroidal anti-inflammatory medicines (NSAIDs) with patent expired* in 2018

Categories	per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD average cost
Patent expired	2.21	87.5	8.6	16.5	88.9	7.2	0.37
Equivalent	0.34	15.3	16.9	3.7	22.6	9.7	0.25
Ex originator	1.87	84.7	7.2	12.8	77.4	6.5	0.40
Patent covered	0.32	12.5	-62.9	2.1	11.1	-45.0	0.42
NSAIDs	**2.52**	**100.0**	**-12.6**	**18.6**	**100.0**	**-3.1**	**0.37**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.23b. Non-steroidal anti-inflammatory medicines (NSAIDs), distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

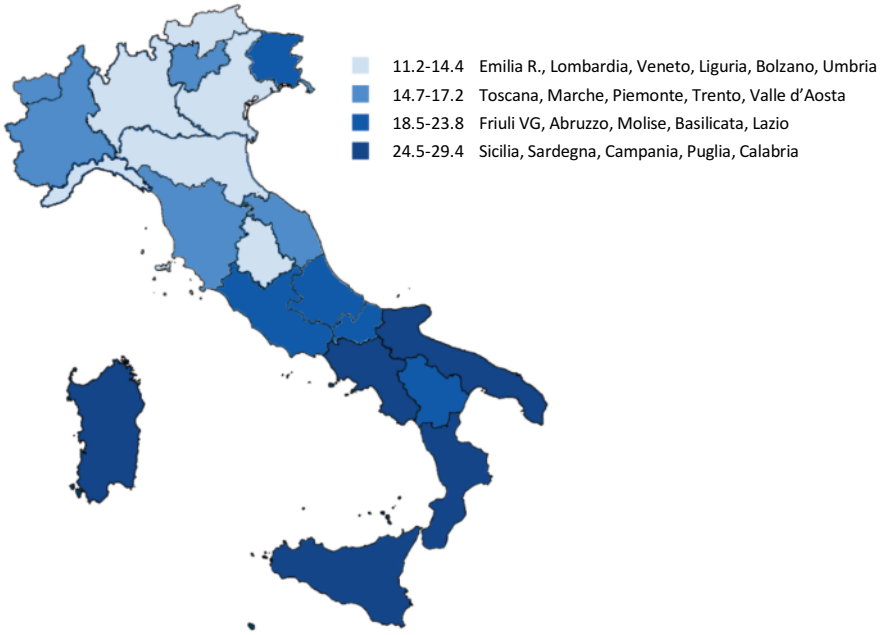


Table 5.2.23e. Duration of NSAIDs therapy per geographical area in approved care regime (year 2018)

	Prescription per user	DDD per user	DDD median	User with 1 prescription
North	2.0	40.8	22.5	60.0
Centre	2.2	40.0	23.0	54.4
South and islands	2.5	43.3	30.0	48.2
NSAIDs	**2.2**	**41.8**	**29.3**	**53.3**

Thyroid disease medications

- The DDD remained almost stable over the years, rising from 21.8 in 2013 to 22.1 in 2018; almost all of the consumption in the category is represented by levothyroxine, a medication indicated in cases of hypothyroidism;
- the prevalence of use increases with age and with a value that is always higher in women than in men; a slight decrease in consumption is only recorded in women over 75 years of age;
- there is a marked regional variability in 2018 consumption, ranging from a minimum value of 10.9 DDD in Liguria to 30.5 DDD in Lazio, although there are no differences in the duration of therapy between the geographical macro-areas of North, Centre and South;
- Lazio, the Autonomous Province of Trento and Umbria are the regions using more doses, with a cost per day of therapy higher than the national average;
- the incidence of consumption of patent-expired pharmaceuticals reached 87.1% in 2018, but with a low use of equivalent pharmaceuticals;
- the prevalence of use increases with age and reaches 14.4% in women in the 65-74 age group; on average each user is treated for about 6 months and 13.8% receives a single prescription in a year.

Figure 5.2.24a. Thyroid medications, temporal consumption trend (2013-2018)

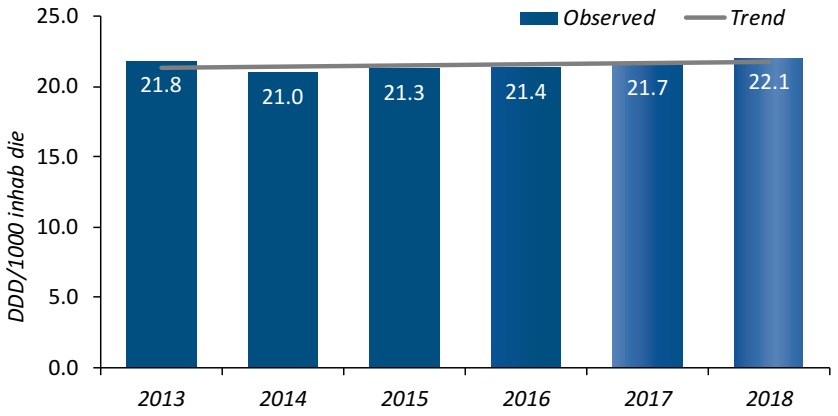


Table 5.2.24a. Thyroid medications, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Thyroid hormones	20.4	19.6	19.8	20.0	20.3	20.7	2.0
Anti-thyroid agents	1.5	1.5	1.4	1.4	1.4	1.4	-0.5
Thyroid medications	**21.8**	**21.0**	**21.3**	**21.4**	**21.7**	**22.1**	**1.9**
levothyroxine	20.3	19.5	19.8	19.9	20.2	20.6	2.0
thiamazole	1.5	1.5	1.4	1.4	1.4	1.4	-0.5
liothyronine	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-1.8

Table 5.2.24b. Thyroid medications, weighted regional trend of DDD/1000 inhabitants per day: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	19.2	19.6	20.1	20.5	20.9	21.5	2.6
Valle d'Aosta	24.0	24.7	25.3	17.9	18.0	18.9	5.4
Lombardia	16.3	13.8	14.2	14.3	14.7	15.2	3.2
PA Bolzano	24.9	21.2	21.2	21.3	21.4	21.6	1.3
PA Trento	24.2	25.3	26.1	26.5	27.3	28.2	3.0
Veneto	20.8	17.7	18.0	18.4	18.8	19.3	2.7
Friuli VG	22.1	22.4	23.1	23.7	23.9	24.6	3.2
Liguria	17.8	11.7	11.6	11.0	10.9	10.9	0.4
Emilia R.	27.5	27.8	28.2	28.0	28.1	28.5	1.2
Toscana	23.3	22.3	22.1	22.0	22.2	22.3	0.8
Umbria	25.5	25.0	25.7	26.5	27.0	28.0	3.5
Marche	23.0	23.5	24.0	24.5	24.7	25.1	1.9
Lazio	30.3	30.0	29.9	30.0	30.2	30.5	0.8
Abruzzo	20.9	21.3	22.0	22.4	23.0	23.8	3.7
Molise	28.3	30.0	29.3	28.5	29.0	29.7	2.1
Campania	17.0	17.4	17.4	17.3	17.5	17.8	1.6
Puglia	23.6	24.5	25.1	25.4	26.0	26.5	2.0
Basilicata	27.8	26.0	26.0	25.9	26.5	26.9	1.6
Calabria	23.3	22.8	22.4	22.4	22.5	22.8	1.6
Sicilia	20.1	19.8	20.0	20.1	20.5	20.9	2.1
Sardegna	29.1	29.2	29.6	28.9	28.7	28.5	-0.7
Italy	**21.8**	**21.0**	**21.3**	**21.4**	**21.7**	**22.1**	**1.9**

Table 5.2.24c. Thyroid medications, prescription by therapeutic category and by substance in 2018

Subgroups and substances	per capita expenditure	Δ % 18-17	DDD/1000 inhab die	Δ % 18-17
Thyroid hormones	1.00	7.1	20.7	2.0
Anti-thyroid agents	0.05	4.2	1.4	-0.5
Thyroid medications	**1.05**	**6.9**	**22.1**	**1.9**
levothyroxine	0.97	7.4	20.6	2.0
thiamazole	0.05	4.2	1.4	-0.5
liothyronine	0.03	-3.5	<0.05	-1.8

Table 5.2.24d. Prescription of thyroid medications with patent expired* in 2018

Categories	per capita expenditure	%	Δ % 18-17	DDD/1000 inhab die	%	Δ % 18-17	DDD average cost
Patent expired	0.65	62.1	1.1	19.2	87.1	0.7	0.09
Equivalent	0.01	1.9	8.9	0.5	2.7	8.2	0.06
Ex originator	0.64	98.1	1.0	18.7	97.3	0.5	0.09
Patent covered	0.40	37.9	18.1	2.8	12.9	10.9	0.38
Thyroid medications	**1.05**	**100.0**	**6.9**	**22.1**	**100.0**	**1.9**	**0.13**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.24b. Thyroid medications, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

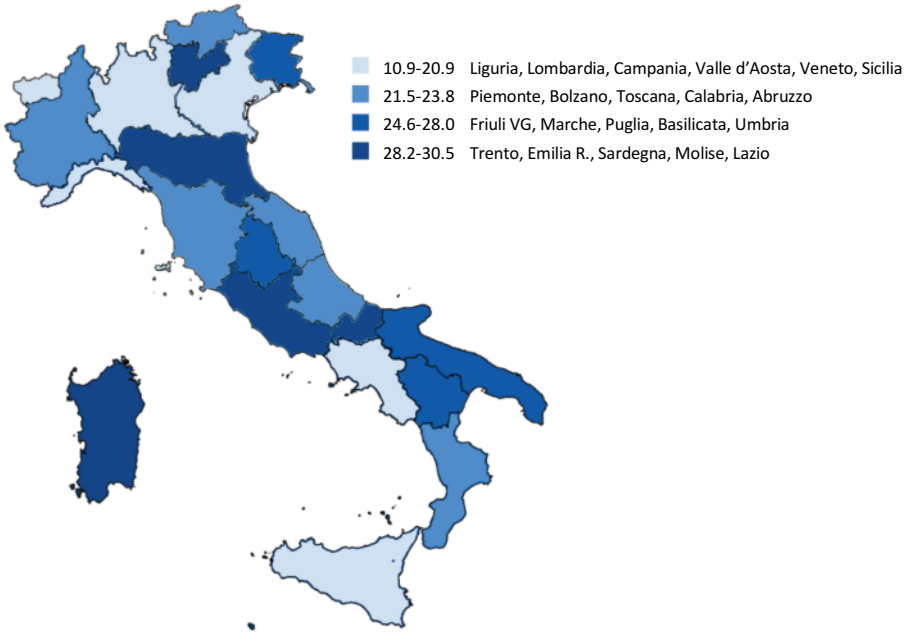


Table 5.2.24e. Duration of thyroid disease therapy by geographical area in approved care regime (year 2018)

	Prescription per user	DDD per user	DDD median	Users with 1 prescription
North	3.6	165.3	150.0	13.9
Centre	4.0	167.9	150.0	13.2
South and islands	4.1	167.7	150.0	14.1
Thyroid medications	**3.9**	**166.8**	**150.0**	**13.8**

Pharmaceuticals for cystic fibrosis

- Per capita expenditure for cystic fibrosis medicines has increased significantly over the past four years, shifting from € 0.22 in 2015 to € 1.36 in 2018 (+84%);
- the highest variation in expenditure (>100%) compared to the previous year was observed for the association lumacaftor/ivacaftor, a medicinal product marketed in 2017;
- in 2018 a marked regional variability was recorded in per capita expenditure, with a value ranging from a minimum of 0.5 euros in Molise to a maximum of 3.7 euros in Basilicata;
- all regions show a marked increase in expenditure compared to the previous year and for almost half of them the increase exceeds 100%; Lazio is the Region with the lowest increase in expenditure (+10.2%).

Table 5.2.25a. Pharmaceuticals for cystic fibrosis, per capita expenditure by therapeutic category and by substance: comparison 2015-2018

Subgroups and substances	2015	2016	2017	2018	Δ % 18-17
Cystic fibrosis	**0.22**	**0.55**	**0.79**	**1.36**	**72.0**
lumacaftor/ivacaftor	<0.005	0.04	0.31	0.87	>100
ivacaftor	0.22	0.51	0.48	0.48	1.3

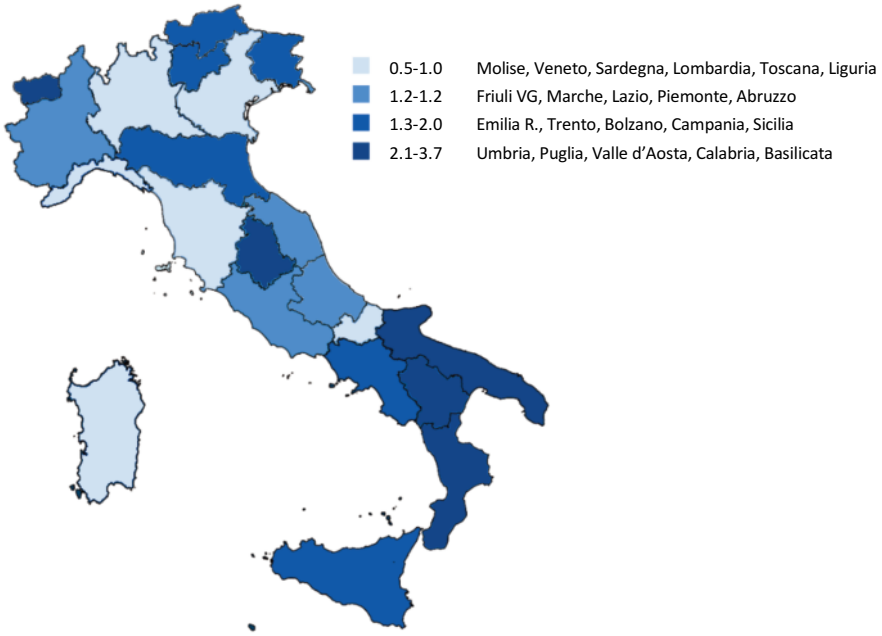
Table 5.2.25b. Pharmaceuticals for cystic fibrosis, weighted regional trend of per capita expenditure: comparison 2015-2018

Region	2015	2016	2017	2018	Δ % 18-17
Piemonte	0.10	0.29	0.61	1.20	97.8
Valle d'Aosta	0.00	1.52	1.91	2.43	27.1
Lombardia	0.03	0.17	0.34	0.86	>100
PA Bolzano	0.28	0.46	0.50	1.67	>100
PA Trento	-	-	0.08	1.51	>100
Veneto	0.03	0.05	0.23	0.67	>100
Friuli VG	0.09	0.18	0.46	1.18	>100
Liguria	0.04	0.21	0.57	1.04	82.5
Emilia R.	0.06	0.26	0.72	1.34	85.7
Toscana	0.24	0.49	0.43	1.03	>100
Umbria	0.15	0.76	1.40	2.05	46.7
Marche	0.07	0.16	0.60	1.19	96.5
Lazio	0.47	0.98	1.09	1.20	10.2
Abruzzo	0.10	0.24	0.60	1.22	>100
Molise	-	-	0.03	0.46	>100
Campania	0.36	0.82	1.28	1.83	42.6
Puglia	0.51	0.99	1.58	2.08	31.8
Basilicata	0.58	2.74	3.23	3.73	15.5
Calabria	0.95	1.97	2.32	2.75	18.2
Sicilia	0.37	1.03	0.87	2.04	>100
Sardegna	0.07	0.12	0.15	0.86	>100
Italy	**0.22**	**0.55**	**0.79**	**1.36**	**72.0**

Table 5.2.25c. Pharmaceuticals for cystic fibrosis, prescription by therapeutic category and by substance in 2018

Subgroups and substances	per capita expenditure	Δ % 18-17	DDD/1000 inhab die	Δ % 18-17
Cystic fibrosis	**1.36**	**72.0**	**<0.05**	**>100**
lumacaftor/ivacaftor	0.87	>100	<0.05	>100
ivacaftor	0.48	1.3	<0.05	6.0

Figure 5.2.25b. Pharmaceuticals for cystic fibrosis, weighted distribution in quartiles of per capita expenditure in 2018



Antidementia pharmaceuticals

- In the period 2013-2018 the consumption of antidementia pharmaceuticals remained stable, reaching 201 DDD in 2018, with the exception of memantine; the other molecules show a decrease in use compared to 2017;
- a wide regional variability is reported in the regional use of these medicines, ranging from 1.2 DDD of the Autonomous Province of Trento to 4.7 of the Autonomous Province of Bolzano, while Marche is the Region with the highest increase compared to 2017
  (+50.1%);
- patent-expired pharmaceuticals (largely equivalent) account for 87% of doses and 81% of expenditure;
- as expected, use is concentrated in the >75 years age group, with a higher level of exposure in women (over 2% of prevalence of use and 17 DDD);
- each user is treated on average for 250 days and 13.7% receives a single prescription.

Figure 5.2.26a. Antidementia pharmaceuticals, temporal consumption trend (2013-2018)

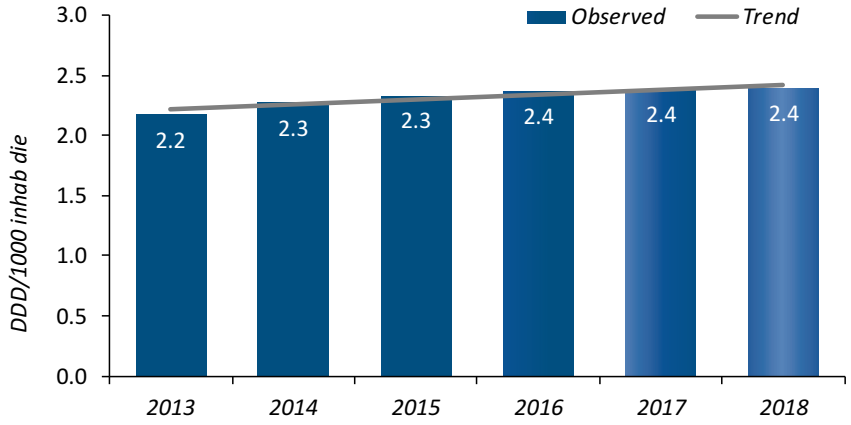


Table 5.2.26a. Antidementia pharmaceuticals, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2013-2018

Subgroups and substances	2013	2014	2015	2016	2017	2018	Δ % 18-17
Anticholinesterases	1.5	1.5	1.5	1.5	1.5	1.4	-1.9
Other antidementia pharmaceuticals	0.7	0.8	0.8	0.9	0.9	0.9	3.9
Antidementia pharmaceuticals	**2.2**	**2.3**	**2.3**	**2.4**	**2.4**	**2.4**	**0.3**
rivastigmine	0.6	0.7	0.7	0.6	0.6	0.6	-2.2
memantine	0.7	0.8	0.8	0.9	0.9	0.9	3.9
donepezil	0.7	0.8	0.8	0.8	0.8	0.8	-0.9
galantamine	0.1	0.1	0.1	0.1	0.1	<0.05	-13.6

Table 5.2.26b. Antidementia pharmaceuticals, regional trend of DDD/1000 inhabitants per day weighted: comparison 2013-2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	2.0	2.2	2.2	2.1	2.1	2.0	-2.0
Valle d'Aosta	2.1	2.0	1.4	1.8	1.8	2.0	14.7
Lombardia	2.0	2.0	2.2	2.2	2.2	2.3	1.0
PA Bolzano	3.0	3.5	4.2	4.6	4.1	4.7	14.4
PA Trento	1.3	1.3	1.2	1.2	1.1	1.2	11.8
Veneto	2.1	2.4	2.5	2.6	2.6	2.8	6.4
Friuli VG	2.0	2.0	1.5	1.6	2.2	2.1	-1.8
Liguria	3.4	3.6	3.5	3.3	3.8	3.2	-14.9
Emilia R.	2.0	1.9	1.8	1.9	1.9	1.9	1.5
Toscana	2.9	3.1	3.5	3.7	3.2	3.5	8.6
Umbria	3.2	3.3	3.4	3.7	3.7	4.0	7.7
Marche	2.5	2.5	2.2	1.5	1.6	2.4	50.1
Lazio	2.3	2.4	2.3	2.4	2.7	2.6	-4.6
Abruzzo	3.5	3.7	3.8	3.7	3.7	4.0	9.2
Molise	1.7	1.7	1.8	2.0	2.3	2.3	0.2
Campania	1.8	2.1	2.3	2.4	2.5	2.1	-16.0
Puglia	2.0	2.1	2.2	2.2	2.2	2.2	1.8
Basilicata	1.5	1.7	1.8	1.8	2.3	2.1	-9.5
Calabria	2.1	2.2	2.1	2.2	1.9	2.1	12.3
Sicilia	1.7	1.8	1.7	1.7	1.6	1.7	5.3
Sardegna	2.2	2.3	2.1	2.2	2.1	1.5	-27.9
Italy	**2.2**	**2.3**	**2.3**	**2.4**	**2.4**	**2.4**	**0.3**

Table 5.2.26c. Antidementia pharmaceuticals, prescription by therapeutic category and by substance in 2018

Subgroups and substances	per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Anticholinesterases	0.37	-5.8	1.4	-1.9
Other antidementia pharmaceuticals	0.14	-12.8	0.9	3.9
Antidementia pharmaceuticals	**0.51**	**-7.9**	**2.4**	**0.3**
rivastigmine	0.27	-6.3	0.6	-2.2
memantine	0.14	-12.8	0.9	3.9
donepezil	0.08	-2.4	0.8	-0.9
galantamine	0.02	-12.6	<0.05	-13.6

Table 5.2.26d. Prescription of antidementia pharmaceuticals with patent expired* in 2018

Categories	per capita expenditure	%	Δ % 18-17	DDD/1000 inhab. per day	%	Δ % 18-17	DDD Average cost
Patent expired	0.41	80.9	-8.1	2.1	86.9	-2.1	0.54
Equivalent	0.25	61.6	4.0	1.5	73.2	4.3	0.46
Ex originator	0.16	38.4	-22.5	0.6	26.8	-16.2	0.78
Patent covered	0.10	19.1	-3.4	0.3	13.1	20.2	0.85
Antidementia pharmaceuticals	**0.51**	**100.0**	**-7.9**	**2.4**	**100.0**	**0.3**	**0.58**

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.2.26b. Antidementia pharmaceuticals, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

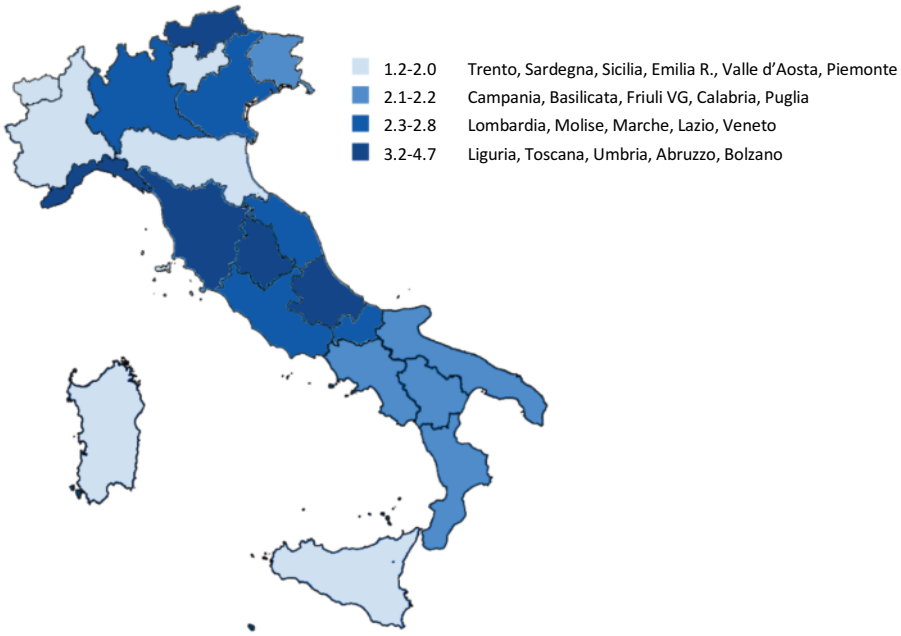


Table 5.2.26e. Duration of therapy with antidementia pharmaceuticals by geographical area in approved care regime (year 2018)

	Prescription per user	DDD per user	DDD median	Users with 1 prescription
North	5.3	252.7	224.0	13.7
Centre	6.5	245.0	212.6	15.1
South and islands	6.7	248.1	224.0	12.7
Antidementia pharmaceuticals	**6.1**	**249.3**	**224.0**	**13.7**

5.3 Patent-expired pharmaceuticals and biosimilars

In 2018, patent-expired pharmaceuticals accounted for 65.9% of expenditure and 82.7% of consumption reimbursed by the NHS. Equivalent pharmaceuticals, i.e. medicinal products based on patent-expired active principles, with the exception of those provided with patent coverage, represented 19.0% of expenditure and 29.4% of consumption (Figure 5.3.1 and Figure 5.3.2).

The expenditure for patent-expired pharmaceuticals mainly focuses on the categories of cardiovascular and antimicrobial pharmaceuticals, accounting respectively for 84.5% and 84.0% of the expenditure reimbursed by the NHS (Table 5.3.1). The growing trend of both expenditure and consumption of patent-expired pharmaceuticals is confirmed. The consumption and the expenditure of equivalent pharmaceuticals also show an increasing trend (Figure 5.3.3 and Figure 5.3.4).

Four active ingredients of the category of pump inhibitors (pantoprazole, lansoprazole, omeprazole and esomeprazole) can be found among the first 20 patent-expired active principles, with an expenditure of respectively 272.3, 164.1, 151.5 and 142.2 million euros (Table 5.3.2). No less than 10 active ingredients can be found belonging to the category of pharmaceuticals for the cardiovascular system, including rosuvastatin (77.3 million euros), whose patent coverage expired in 2017.

Emilia Romagna is the Region with the highest incidence of patent-expired pharmaceuticals in the regional pharmaceutical expenditure reimbursed by the NHS (70.7%), followed by Umbria (69.6%) and the Autonomous Province of Trento (69.2%) – on the contrary, Lombardia (60.7%), Valle d'Aosta (64.4%) and Sardegna (64.5%) show the lowest level of expenditure (Table 5.3.3).

The Regions with the highest incidence of consumption of patent-expired pharmaceuticals in 2018 were Umbria (84.3%), Emilia Romagna (84.2%) and the Autonomous Province of Trento (84.0 %), while Toscana (81.1%), Abruzzo (81.6%) and Valle d'Aosta and Basilicata (81.8%; Table 5.3.4) are those with the lowest incidence.

The Regions Calabria, Basilicata and Campania showed the highest percentages of expenditure in 2018 for patent-covered pharmaceuticals (repectively 82.2%, 81.3% and 81.1%), while the Autonomous Province of Trento, Lombardia and Friuli Venezia Giulia showed the highest incidence of expenditure for equivalent pharmaceuticals (respectively 42.6%, 40.6% and 36.4%; Figure 5.3.5).

The 2018 data confirmed the increase, compared to 2017, in the use of all biosimilar medicinal products already available on the market for several years, such as, for example, follitropin, epoetins (+24.4%), somatropin (+22.3 %) and growth factors (+12.7%), which contributed to a reduction in spending by -5.9%, -8.6% and -12.7%, respectively for follitropin, epoetins and growth factors (Table 5.3.5).

Furthermore, the positive trend should be highlighted regarding the use of the most recently commercialized biosimilars, i.e. infliximab, etanercept, insulin glargine and rituximab. Moreover, biosimilar medicines of adalimumab, low molecular weight heparin, trastuzumab and insulin lispro were marketed in 2018 for the first time.

Finally, a wide regional variability in the use of biosimilars can be noted also in 2018 (Figure 5.3.8-5.3.14).

Figure 5.3.1 NHS A-class pharmaceutical outpatient expenditure by patent coverage in 2018

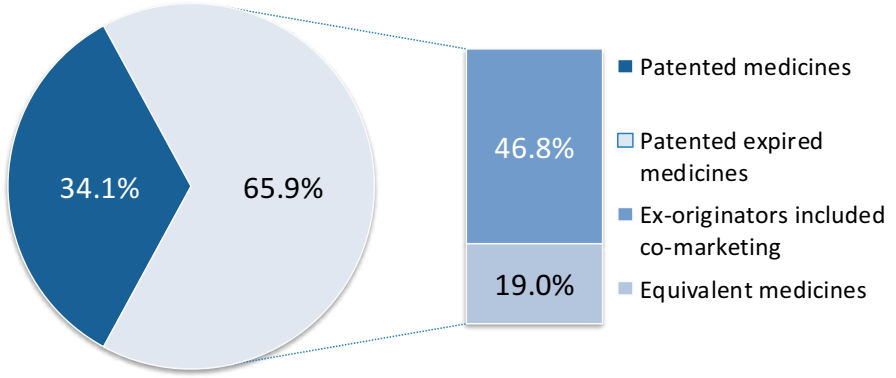
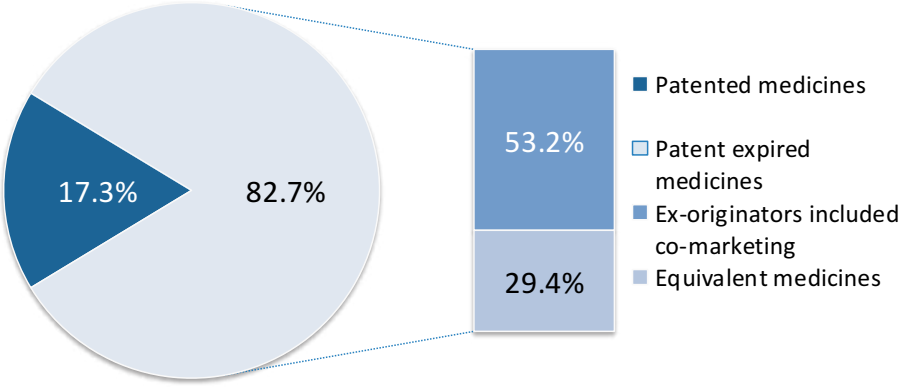


Figure 5.3.2 NHS A-class pharmaceutical outpatient consumption by patent coverage in 2018



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 the Law Decree no. 87 of 27 May 2005, converted with amendments into Law no. 149 of July 26, 2005.

Table 5.3.1 Incidence of NHS A-class pharmaceutical outpatient expenditure and consumption of patent-expired medicinal products by therapeutic area in 2018

ATC I level	NHS pharmaceutical expenditure in approved care regime		NHS pharmaceutical consumption (DDD) in approved care regime	
	% Patent expired by therapeutic category	% Generic drug by therapeutic category	% Patent expired by therapeutic category	% Generic drug by therapeutic category
A	69.0	25.0	82.2	38.8
B	39.2	10.7	65.0	15.4
C	84.5	22.5	92.9	33.4
D	21.9	5.9	22.8	3.7
G	71.9	21.4	77.8	28.4
H	38.5	2.5	76.8	3.9
J	84.0	20.6	92.9	24.7
L	83.6	27.2	86.7	39.0
M	70.5	14.9	83.3	26.3
N	56.9	21.6	76.5	35.1
P	6.0	1.0	6.1	2.9
R	25.1	2.8	47.6	9.9
S	29.0	3.8	41.5	8.6
V	38.1	30.8	24.3	22.1

Table 5.3.2 NHS-A class pharmaceutical outpatient expenditure and consumption, first twenty patent-expired* active ingredients with highest expenditure: 2018-2017 comparison

ATC	Active ingredient	Expenditure *(million)*	Δ % 18-17	% generic drug**	DDD/1000 inhab per day	DDD average cost
A	pantoprazole	272.3	-2.1	50.1	21.5	0.57
A	colecalciferol	268.7	17.0	11.7	9.4	1.30
C	atorvastatin	248.3	5.9	35.4	44.1	0.26
J	amoxicillin/clavulanic acid	172.8	0.0	18.8	5.8	1.36
A	lansoprazole	164.1	-9.1	66.1	14.5	0.51
A	omeprazole	151.5	-7.3	35.6	16.5	0.42
A	esomeprazole	142.2	-3.6	38.8	12.7	0.51
C	bisoprolol	139.2	6.8	29.8	10.5	0.60
C	ramipril	122.7	0.2	37.3	61.8	0.09
C	omega 3	112.7	0.3	25.5	4.2	1.23
C	simvastatin	99.9	-3.7	50.2	13.8	0.33
C	amlodipine	93.9	0.2	31.5	26.5	0.16
A	metformin	90.8	3.8	36.8	21.6	0.19
N	levetiracetam	86.3	6.9	37.3	1.9	2.04
C	nebivolol	84.7	2.0	22.7	15.0	0.26
J	ceftriaxone	77.6	0.5	21.3	0.3	11.74
C	rosuvastatin	77.3	-68.5	15.2	12.2	0.29
C	olmesartan	73.3	23.2	15.3	10.2	0.33
C	doxazosin	73.1	-0.6	30.8	7.4	0.45
A	mesalazine	73.0	0.5	11.6	3.3	1.01

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

Figure 5.3.3 Incidence trend of patent-expired and generic drug expenditure on the total NHS A-class outpatient expenditure: comparison 2011-2018

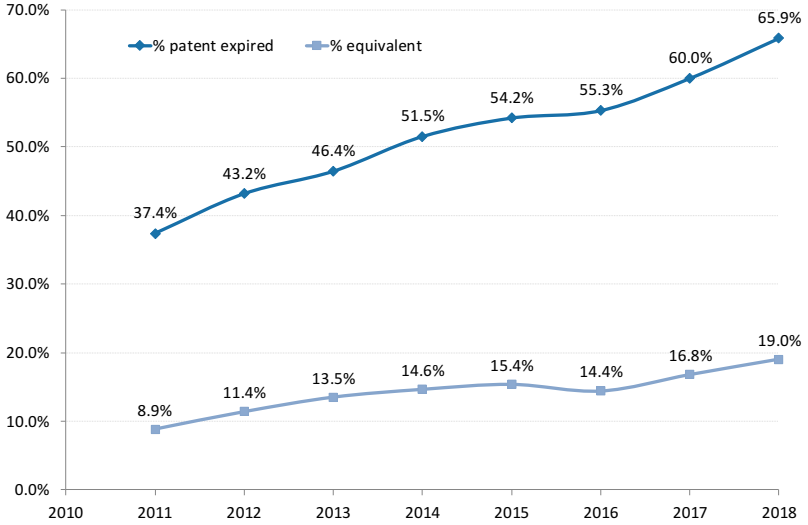


Table 5.3.3 Regional outpatient expenditure for NHS A-class patent-expired* pharmaceuticals: comparison 2018-2017

Regions	Weighted per capita expenditure (euro)		% of total expenditure	
	2017	2018	2017	2018
Piemonte	90.8	95.2	60.0	65.8
Valle d'Aosta	81.3	87.8	58.4	64.4
Lombardia	98.5	105.8	56.2	60.7
PA Bolzano	72.7	78.2	59.0	65.1
PA Trento	89.6	96.8	62.2	69.2
Veneto	87.1	91.7	60.5	67.0
Friuli VG	94.3	99.1	59.5	66.2
Liguria	92.4	98.4	60.6	66.6
Emilia R.	84.7	90.0	64.7	70.7
Toscana	87.9	91.8	60.7	65.6
Umbria	108.2	116.1	64.3	69.6
Marche	108.4	112.8	61.3	67.5
Lazio	116.5	124.5	59.9	66.4
Abruzzo	115.9	124.4	57.4	64.8
Molise	105.6	113.8	62.4	69.1
Campania	126.1	136.3	61.6	67.7
Puglia	122.3	127.5	60.1	66.9
Basilicata	108.9	118.7	59.9	66.2
Calabria	119.2	128.2	59.7	67.2
Sicilia	112.4	117.1	62.2	66.9
Sardegna	105.1	111.2	57.9	64.5
Italy	**103.3**	**109.6**	**60.0**	**65.9**
North	91.8	97.6	59.2	64.7
Centre	105.6	111.8	60.6	66.5
South and islands	118.1	125.4	60.6	66.8

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.3.4 Incidence trend of consumption (doses) of patent-expired medicines and generic medicines on the total outpatient consumption of NHS A-class medicines: comparison 2011-2018

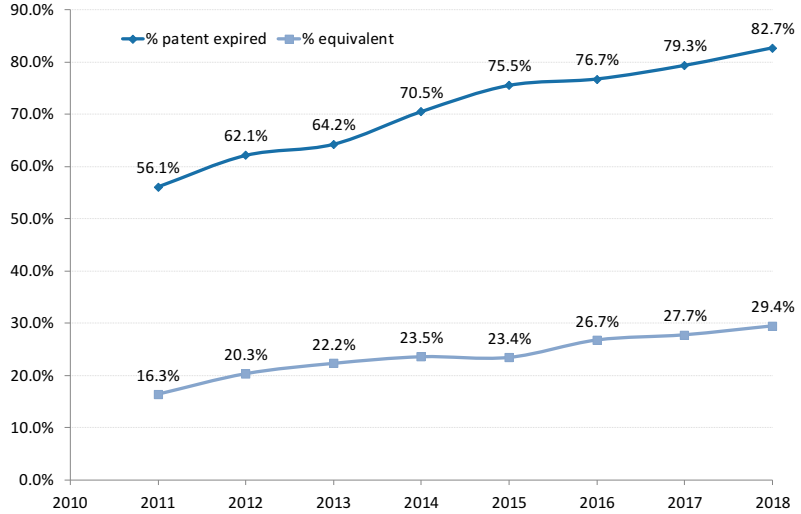
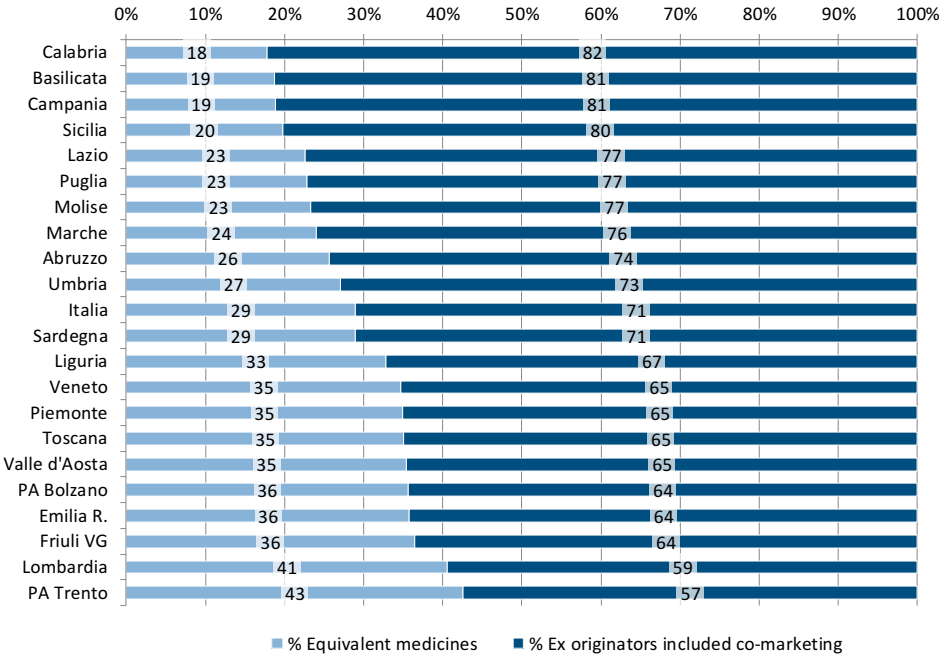


Table 5.3.4 Outpatient consumption of regional NHS A-class patent-expired* medicines: comparison 2018-2017

Regions	wieghted DDD/1000 inhabitants per day		% of total DDD	
	2017	2018	2017	2018
Piemonte	719.3	752.6	79.2	82.4
Valle d'Aosta	634.1	669.5	78.1	81.8
Lombardia	713.2	759.1	78.4	82.1
PA Bolzano	570.6	601.3	79.4	83.4
PA Trento	717.2	760.6	80.5	84.0
Veneto	694.9	725.5	79.3	82.7
Friuli VG	761.9	796.2	80.1	83.8
Liguria	669.4	705.1	78.4	82.2
Emilia R.	743.3	780.3	81.6	84.2
Toscana	749.1	776.9	78.7	81.1
Umbria	878.3	925.8	81.8	84.3
Marche	795.9	831.3	79.0	82.6
Lazio	828.6	877.6	79.4	83.1
Abruzzo	791.5	841.4	77.6	81.6
Molise	757.3	805.6	79.5	83.0
Campania	840.0	897.6	79.3	82.9
Puglia	851.5	886.9	78.6	82.5
Basilicata	775.4	831.6	78.0	81.8
Calabria	827.3	876.0	78.3	82.2
Sicilia	829.9	859.4	80.7	83.2
Sardegna	786.8	823.4	78.1	82.0
Italy	**768.8**	**809.0**	**79.3**	**82.7**
North	712.6	750.8	79.4	82.7
Centre	802.6	842.9	79.3	82.5
South and islands	827.7	870.8	79.2	82.6

* source: monthly transparency lists published by the Italian Medicines Agency in 2018

Figure 5.3.5 Composition by Region of patent-expired NHS A-class pharmaceuticals outpatient expenditure



Biosimilars

Table 5.3.5 Biosimilar medicinal products, inpatient and outpatient NHS supply in 2018

Group Subgroup	per capita expenditure	Inc %	Δ% 18-17	DDD/1000 inhab per day	Inc %	Δ% 18-17
Epoetin	**3.41**		**-8.6**	**3.3**		**3.8**
Originator[1]	0.71	20.9	-20.1	0.5	16.0	-19.5
Biosimilar[2]	1.23	36.0	13.9	2.1	61.6	24.4
Other epoetins[3]	1.47	43.0	-16.5	0.8	22.4	-17.0
Growth factors	**0.85**		**-12.7**	**0.1**		**-2.8**
Originator[4]	0.04	4.9	-28.9	0.0	1.5	-31.4
Biosimilar[5]	0.14	17.0	-6.6	0.0	44.8	12.7
Other growth factors[6]	0.66	78.0	-12.7	0.1	53.6	-11.8
Somatropin	**1.50**		**1.0**	**0.3**		**2.3**
Originator[7]	0.26	17.2	-8.9	0.0	15.0	-4.0
Biosimilar[8]	0.24	16.2	23.7	0.1	21.6	22.3
Other somatropin[9]	1.00	66.6	-0.7	0.2	63.4	-1.6
Long acting insulin	**2.84**		**-0.8**	**6.3**		**1.0**
Originator insulin glargine[10]	1.16	40.9	-16.0	2.9	46.5	-15.0
Biosimilar insulin glargine[11]	0.25	8.6	2.8	0.7	11.1	7.1
Other insulin glargine[12]	0.37	13.1	>100	1.0	15.2	>100
Other long acting insulin[13]	1.06	37.3	-2.7	1.7	27.2	-3.7
Follitropin alfa	**1.06**		**-5.9**	**0.1**		**-2.3**
Originator[14]	0.38	36.2	-20.8	0.1	33.7	-14.5
Biosimilar[15]	0.09	8.1	59.7	0.0	8.6	55.2
Other follitropin[16]	0.59	55.6	0.4	0.1	57.7	0.5
TNF-alpha inhibitors	**10.51**		**-4.1**	**1.2**		**5.8**
Originator etanercept[17]	1.91	18.2	-29.9	0.2	15.0	-27.0
Biosimilar etanercept[18]	0.77	7.4	>100	0.1	8.9	>100
Originator infliximab[19]	0.55	5.2	-36.6	0.1	7.0	-37.1
Biosimilar infliximab[20]	0.70	6.7	9.7	0.2	19.3	38.4
Originator adalimumab[21]	4.74	45.1	0.5	0.4	34.8	6.9
Biosimilar adalimumab[22]	0.04	0.4	.	0.0	0.7	.
Other TNF-alpha inhibitors[23]	1.80	17.1	5.1	0.2	14.4	6.5
Rituximab	**2.17**		**-29.4**	**0.5**		**-8.5**
Originator SC[24]	0.61	28.1	-16.2	0.2	41.8	-5.3
Originator EV[25]	0.83	38.2	-63.4	0.1	24.9	-59.8
Biosimilar EV[26]	0.73	33.6	>100	0.2	33.3	>100
Low Molecular Weight Heparin	**4.51**		**-12.8**	**9.4**		**-3.9**
Originator[27]	2.83	62.8	-20.4	5.9	63.1	-19.3
Biosimilar[28]	0.26	5.8	.	1.3	13.5	.
Other Low Molecular Weight Heparin.[29]	1.42	31.4	-12.1	2.2	23.4	-9.4
Trastuzumab	**4.05**		**-12.5**	**0.2**		**0.3**
Originator SC[30]	1.94	47.8	-12.8	0.1	61.4	-0.7
Originator EV[31]	2.03	50.0	-15.9	0.1	35.0	-7.6
Biosimilar EV[32]	0.09	2.2	.	0.0	3.6	.
Fast acting insulin	**4.00**		**-2.3**	**8.6**		**-0.3**
Originator insulin lispro[33]	1.75	43.9	-4.4	3.8	43.8	-0.6
Biosimilar insulin lispro[34]	0.03	0.7	.	0.1	1.2	.
Other fast acting insulin[35]	2.21	55.4	-1.9	4.7	54.9	-2.3

[1] Eprex®; [2] Binocrit®; Retacrit®; [3] Aranesp®, Eporatio®, Mircera®, Neorecormon®; [4] Granulokine®; [5]Accofil®, Ratiograstim®, Nivestim®, Tevagrastim®, Zarzio®; [6] Neulasta®, Myelostim®, Lonquex®, Granocyte®; [7] Genotropin®; [8] Omnitrope®; [9] Humatrope®, Norditropin®, Nutropinaq®, Saizen®, Zomacton®; [10] Lantus®; [11] Abasaglar®; [12] Toujeo®; [13] Tresiba®, Levemir®; [14] Gonal-F®; [15] Ovaleap®, Bemfola®; [16] Meriofert®, Puregon®, Elonva®, Pergoveris®, Fostimon®, Rekovelle®, Meropur®; [17] Enbrel®; [18]Benepali®, Erelzi®; [19] Remicade®; [20] Inflectra®, Remsina®; [21] Humira®, [22] Amgevita®, Imraldi®; [23] Cimzia®, Simponi®; [24] Mabthera SC®; [25] Mabthera EV®; [26] Truxima®; [27] Clexane®; [28] Inhixa®, Enoxaparina Rovi®; [29] Fragmin®, Fraxiparina®, Seledie®, Seleparina®, Fluxum®, Clivarina®, Ivor®, Arixtra®; [30] Herceptin SC®; [31] Herceptin EV®; [32] Ontruzant®, Herzuma®, Kanjinti®; [33] Humalog®, [34] Insulina Lispro Sanofi®; [35] Humulin®, Insuman®, Novarapid®, Actrapid®, Apidra®, Fiasp®

The biosimilars of adalimumab, enoxaparin, trastuzumab and insulin lispro have been marketed in Italy since 2018.

Figure 5.3.6. Incidence (%) of biosimilars on expenditure of biosimilar medicinal products and originator drug: 2014-2018

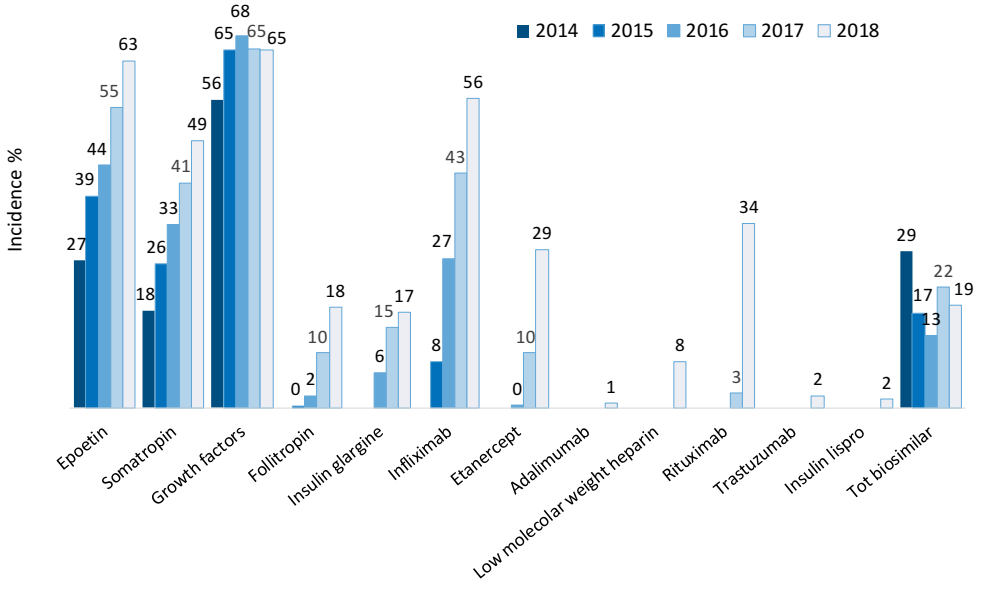


Figure 5.3.7. Incidence (%) of biosimilars on consumption of biosimilar medicinal products and originator drug: 2014-2018

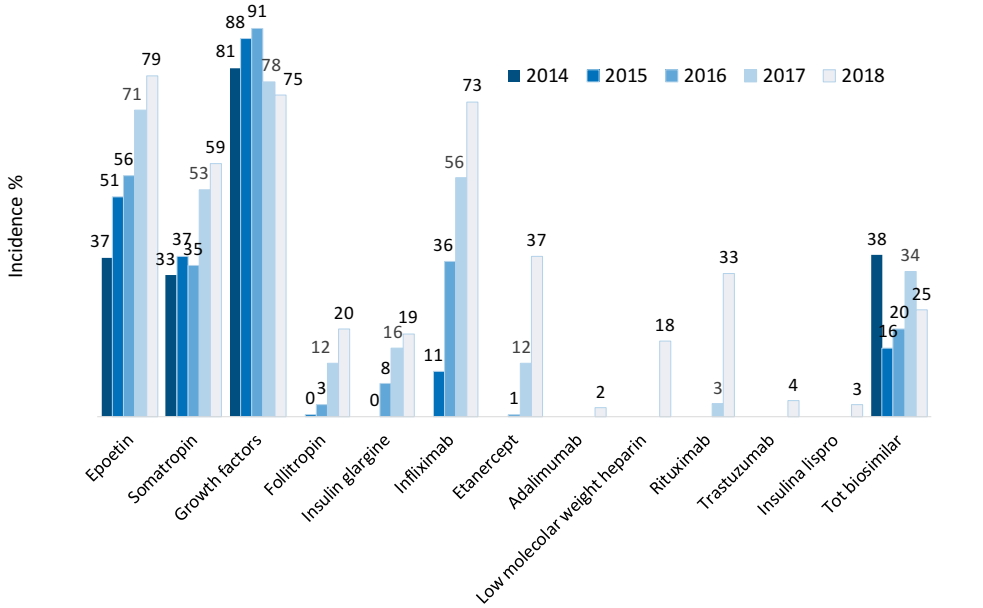


Table 5.3.6 Biosimilar medicinal products, inpatient and outpatient NHS supply in 2018: comparison between biosimilar and drug originator

Group Subgroup	per capita expenditure	Inc %	Δ% 18-17	DDD/1000 inhab per day	Inc %	Δ% 18-17
Epoetin	**1.94**		**-1.4**	**2.6**		**12.1**
Originator[1]	0.71	36.8	-20.0	0.5	20.6	-19.4
Biosimilar[2]	1.23	63.2	14.1	2.1	79.4	24.7
Growth factors	**0.19**		**-12.6**	**0.0**		**10.5**
Originator[3]	0.04	22.4	-28.7	0.0	3.3	-31.3
Biosimilar[4]	0.12	65.2	-12.7	0.0	74.9	6.0
Somatropin	**0.50**		**4.7**	**0.1**		**10.1**
Originator[5]	0.26	51.4	-8.7	0.0	41.0	-3.8
Biosimilar[6]	0.24	48.6	23.9	0.1	59.0	22.6
Follitropin alpha	**0.47**		**-12.6**	**0.1**		**-5.8**
Originator[7]	0.38	81.7	-20.7	0.1	79.7	-14.4
Biosimilar[8]	0.09	18.3	60.0	0.0	20.3	55.5
Insulin glargine	**1.41**		**-13.1**	**3.6**		**-11.3**
Originator[9]	1.16	82.6	-15.9	2.9	80.7	-14.8
Biosimilar[10]	0.25	17.4	3.0	0.7	19.3	7.3
Etanercept	**2.68**		**-11.2**	**0.3**		**2.2**
Originator[11]	1.91	71.2	-29.8	0.2	62.7	-26.9
Biosimilar[12]	0.77	28.8	156.1	0.1	37.3	206.6
Infliximab	**1.25**		**-16.7**	**0.3**		**5.1**
Originator[13]	0.55	43.7	-36.5	0.1	26.6	-37.0
Biosimilar[14]	0.70	56.3	9.9	0.2	73.4	38.7
Adalimumab	**4.77**		**1.5**	**0.4**		**9.3**
Originator[15]	4.74	99.2	0.7	0.4	98.0	7.0
Biosimilar[16]	0.04	0.8	.	0.0	2.0	.
Rituximab	**2.17**		**-29.3**	**0.5**		**-8.3**
Originator SC[17]	0.61	28.1	-16.0	0.2	41.8	-5.1
Originator EV[18]	0.83	38.2	-63.3	0.1	24.9	-59.7
Biosimilar EV[19]	0.73	33.6	>100	0.2	33.3	>100
Low Molecular Weight Heparin	**3.09**		**-12.9**	**7.2**		**-1.8**
Originator[20]	2.83	91.6	-20.3	5.9	82.4	-19.2
Biosimilar[21]	0.26	8.4	.	1.3	17.6	.
Trastuzumab	**4.05**		**-12.3**	**0.2**		**0.4**
Originator SC[22]	1.94	47.8	-12.6	0.1	61.4	-0.5
Originator EV[23]	2.03	50.0	-15.8	0.1	35.0	-7.4
Biosimilar EV[45]	0.09	2.2	.	0.0	3.6	.
Insulin lispro	**1.78**		**-2.6**	**3.9**		**2.4**
Originator[25]	1.75	98.4	-4.2	3.8	97.3	-0.4
Biosimilar[26]	0.03	1.6	.	0.1	2.7	.

[1] Eprex®; [2] Binocrit®; Retacrit®; [3] Granulokine®; [4]Accofil®, Ratiograstim®, Nivestim®, Tevagrastim®, Zarzio®; [5] Genotropin®; [6] Omnitrope®; [7]Gonal-F ®; [8] Ovaleap®, Bemfola®; [9] Lantus®; [10] Abaglasar®;[11] Enbrel®; [12]Benepali®, Erelzi®; [13] Remicade®; [14] Inflectra®, Remsina®; [15] Humira®, [16] Amgevita®, Imraldi®; [17] Mabthera SC®; [18] Mabthera EV®; [19] Truxima®; [20] Clexane®; [21] Inhixa®, Enoxaparina Rovi®; [22] Herceptin SC®; [23] Herceptin EV®; [24] Ontruzant®, Herzuma®, Kanjinti®; [25] Humalog®,[26] Insulina Lispro Sanofi®.

Biosimilars of adalimumab, enoxaparin, trastuzumab and insulin lispro have been marketed in Italy since 2018.

5.4 Consumption of medicinal products directly purchased by citizens

In 2018 the expenditure for C-class medicines amounted to over 5.4 billion euro: 53.1% (2.9 billion) is due to C-class medicinal products with prescription and 46.9% (2.5 billion) to self-medication medicines (SOP and OTC).
The 2.2% increase in expenditure of C-class medicinal products with prescription compared to the previous year was mainly determined by an increase in quantities (+1.8%), by a reduction in prices (-1.8%) and by an almost stable mix effect (Figure 5.4.1).
At the 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 per capita income. For example, per capita expenditure in Liguria is more than double compared to Marche (63.0 euros vs. 26.4) and expenditure in the North is almost 19% higher than the South; the largest increases in consumption were recorded in Lazio (+8.7%), Toscana (+6.4%) and Lombardia (+5.3%), while Abruzzo, Marche and Emilia Romagna showed the largest reductions (respectively -5.6%, -5.4% and -3.6%; Table and figure 5.4.4).
Paracetamol, with 159 million euros, is the active ingredient with the highest expenditure, accounting for 5.6% of the total. This medicinal product, which is predominantly used in pediatrics due to its analgesic and antipyretic action, showed a 11.6% increase compared to 2017. Lorazepam, alprazolam and tadalafil are the other active ingredients which recorded an expenditure exceeding 100 million euros, increasing respectively by 3.9%, 3.9% and 3.7% compared to 2017 (Table 5.4.2).
Benzodiazepines are the most purchased category, representing 18.5% of the expenditure and 26% of DDD of C-class with prescription (Table 5.4.1). The consumption in the last four years has remained substantially stable, with 49.2 DDD in 2018. Benzodiazepines with an anxiolytic effect and those with a hypnotic effect represent more than 90% of consumption of the category and respectively rank first and fifth in terms of expenditure within the C-class categories (the former increasing by 3.2% compared to 2017 and the latter by 1.9%). Lormetazepam (13.2 DDD), lorazepam (10.3 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 2017 (+10.2%) (Tables 5.4.1 and 5.4.9a). Furthermore, among the top twenty most expensive class C medicines with prescription (Table 5.4.2) numerous active ingredients can be found of this class: lorazepam, alprazolam, zolpidem, lormetazepam, 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 79.1 DDD in Liguria to 27.2 DDD in Basilicata. Furthermore, the Southern Regions with the exception of Sardegna show a benzodiazepine consumption lower than the national average while Lazio, Toscana and Valle d'Aosta are the Regions with the highest increase compared to the previous year (Table 5.4.9.b).
With an expenditure of 256 million euros, oral contraceptives rank second, with a stable consumption over the past four years. Estro-progestin fixed combinations represent almost 80% of the category doses. Major increases in consumption can be highlighted for progestins (+62.0%) and for emergency contraceptives (+13.5%). The first four active

ingredients with the highest expense are the fixed estro-progestin combinations: drospirenone/ethinyl estradiol (2.27 euros per capita; -3.2% compared to 2017); gestodene/ethinyl estradiol (€ 1.09; -7.3% compared to 2017); dienogest/ethinyl estradiol (€0.95; +22.2% compared to 2017); dienogest/estradiol (€0.91; +18.9% compared to 2017). There is a high variability at regional level, with Southern regions showing an average consumption lower than the national average, with the exception of Sardegna (Table 5.4.10a and following).

With a 219 million euros consumption, medicinal products for the treatment of erectile dysfunction are the third largest category, increasing from 2.9 DDD in 2014 to 3.6 DDD in 2018 (Table 5.4.11a). Tadalafil, marketed subsequently to sildenafil, was the most expensive substance in 2018 (3.98 euros per capita), followed by sildenafil, with 2.87 euros (Table 5.4.11c). Tadalafil, whose patent coverage expired in 2017, recorded an increase in doses by over 30% compared to 2017, despite an expenditure reduction by about 9%. Basilicata, with 2 DDD, is the Region with the lowest consumption while Liguria shows the highest (5.0 DDD). Lazio, Lombardia and Piemonte record the highest increases in consumption, ranging between 20.0% and 11.3% (Table 5.4.6b).

Among self-medication medicines, diclofenac (increasing by 11.2% compared to 2017) is the first active ingredient for expenditure among self-medication medicinal products, followed by another non-steroidal anti-inflammatory drug (ibuprofen with € 169.7 million) (Table 5.4.3).

Umbria and Marche (27.6 euros and 28.7 euros per capita) are the regions with the lowest expenditure, while Valle d'Aosta and Liguria record the highest values (respectively 56.1 euros and 54.7 euros; Table 5.4 .4).

Among the A-class medicinal products purchased privately by the citizen, ketoprofen and amoxicillin in association with clavulanic acid are those with the highest expenditure (respectively, 44.1 and 41.2 million euros). Moreover, among the first twenty highest-cost pharmaceuticals, there are four pump inhibitors: pantoprazole, omoprazole, lansoprazole and esomeprazole (Table 5.4.5). An analysis of the consumption breakdown of A-Class medicines by price range shows that most of the private purchase concentrates on medicines with a price between 3 and 6 euros and between 6 and 10 euros. A wide regional variability in the distribution of consumption can be observed, especially for the price range higher than 30 euros, with a maximum percentage in Friuli VG and a minimum in Basilicata.

In 2018, the cost of self-medication pharmaceuticals supplied by shops amounted to 266.4 million euro, with a reduction by 7% compared to 2017. The highest expenditure was recorded in Sardegna (7.3 euros per capita) and in Emilia Romagna (6.9 euros per capita), while the Autonomous Province of Bolzano and Campania show the lowest values (0.3 and 2.5 euros per capita). The medicines most often supplied by shops are diclofenac, ibuprofen and paracetamol (Tables 5.4.7 and 5.4.8).

Table 5.4.1. First twenty highest-expenditure therapeutic categories of C-class medicines, with prescription, in 2018

ATC	Subgroup	DDD/1000 inhab per day	Expenditure *(million)*	%*	Δ% 18-17
N	Anxiolytics benzodiazepine derivatives	25.7	357.7	12.4	3.2
G	Medicines used in erectile dysfunction	1.5	219.1	7.6	-14.1
G	Estro-progestin fixed combinations	18.9	189.0	6.6	-2.5
N	Anilides	5.4	167.8	5.8	11.9
N	Hypnotic benzodiazepine derivatives	18.9	122.2	4.2	1.9
D	Active corticosteroids, combination with antibiotics	4.2	78.4	2.7	5.5
S	Antimicrobial corticosteroids in combination	2.9	65.0	2.3	3.6
R	Corticosteroids	4.6	60.6	2.1	6.2
R	Mucolytics	5.6	58.0	2.0	2.5
M	Other centrally-acting muscle relaxants	1.1	57.5	2.0	0.1
N	Benzodiazepine analogues	4.6	55.6	1.9	8.4
A	Laxatives with osmotic action	1.6	55.1	1.9	11.5
N	Other psychostimulants and nootropics	1.1	50.0	1.7	0.6
N	Antivertigo preparations	2.7	46.8	1.6	2.0
M	Bisphosphonates	0.0	45.4	1.6	5.1
B	Heparins	2.0	44.1	1.5	4.6
M	Other peripheral muscle relaxants	0.0	38.1	1.3	3.3
G	Estro-progestin sequential preparations	3.2	34.5	1.2	12.6
D	Other antibiotics for topical use	3.2	34.3	1.2	2.8
N	Benzamides	1.0	34.3	1.2	3.2

* calculated on total expenditure

Table 5.4.2. First twenty highest-expenditure C-class active ingredients with prescription in 2018

ATC	Active ingredient	DDD/1000 inhab per day	Expenditure *(million)*	%*	Δ% 18-17
N	paracetamol	5.1	159.6	5.6	11.6
N	lorazepam	10.2	111.1	3.9	1.1
N	alprazolam	9.1	110.7	3.9	6.0
G	tadalafil	0.7	106.9	3.7	-11.9
G	sildenafil	0.6	76.3	2.7	-11.8
G	drospirenone/ethinyl estradiol	5.6	67.4	2.3	-7.7
D	gentamicin/betamethasone	3.7	67.1	2.3	4.9
N	lormetazepam	13.1	53.1	1.8	0.6
N	zolpidem	4.4	53.0	1.8	9.0
N	bromazepam	1.4	47.6	1.7	2.2
R	acetylcysteine	4.6	47.2	1.6	3.6
N	delorazepam	2.4	43.3	1.5	5.3
M	thiocolchicoside	0.5	38.7	1.3	-1.5
N	triazolam	3.4	38.5	1.3	3.0
M	botulinum toxin of type a clostridium botulinum	0.0	38.1	1.3	7.9
N	levoacetilcarnitin	0.7	35.3	1.2	0.2
N	betahistine	2.1	34.0	1.2	1.1
G	gestodene/ethynil estradiol	5.7	33.3	1.2	-8.5
G	ethynil estradiol/etonogestrel	2.2	33.0	1.1	3.1
S	dexamethasone/tobramycin	1.5	33.0	1.1	7.4

* calculated on total expenditure

Table 5.4.3. First twenty highest-expenditure self-medication (SOP and OTC) active ingredients in 2018

ATC	Active ingredient	DDD/1000 inhab per day	Expenditure *(million)*	%*	Δ % 18-17	% SOP	% OTC
M	diclofenac	13.7	191.1	7.5	11.2	4.9	95.1
M	ibuprofen	7.0	169.7	6.7	20.7	17.7	82.3
G	probiotic	3.0	148.5	5.9	21.2	8.2	91.8
N	paracetamol	2.9	122.1	4.8	16.1	91.5	8.5
M	flurbiprofen	3.9	103.8	4.1	21.4	-	100.0
C	diosmin	2.2	60.3	2.4	12.6	100.0	0.0
M	ketoprofen	1.6	58.0	2.3	19.1	-	100.0
S	naphazoline	12.9	57.7	2.3	25.7	-	100.0
A	glycerol	6.1	52.9	2.1	32.9	1.6	98.4
N	acetylsalicylic acid/ascorbic acid	1.2	46.9	1.8	7.2	-	100.0
R	ambroxol	0.7	46.0	1.8	-7.1	68.3	31.7
R	carbocysteine	2.3	38.2	1.5	8.6	12.1	87.9
A	loperamide	0.4	37.5	1.5	27.3	19.7	80.3
G	clotrimazole	1.0	31.4	1.2	10.3	6.5	93.5
N	paracetamol/ascorbic acid/phenilephrine	0.6	31.0	1.2	17.2	-	100.0
A	aluminium hydroxide/magnesium hydroxide	0.4	30.1	1.2	193.5	-	100.0
S	oxymetazolin	2.5	25.7	1.0	54.6	-	100.0
M	benzydamine	0.7	24.3	1.0	8.8	0.3	99.7
R	bromexina	0.8	22.3	0.9	29.0	-	100.0
M	naproxen	1.1	22.2	0.9	22.6	8.3	91.7

* calculated on total expenditure

Table 5.4.4. 2018 outpatient pharmaceutical prescription of C Class medicines with prescription and self-medication medicines (Table) and % deviation of gross expenditure from national average (Figure)

Regions	C Class with prescription				Self-medication (SOP e OTC)			
	Per capita expenditure	Δ % 18-17	DDD/1000 inhab die	Δ % 18-17	Per capita expenditure	Δ % 18-17	DDD/1000 inhab per day	Δ % 18-17
Piemonte	54.20	1.1	223.9	3.2	46.50	18.6	154.8	17.5
Valle d'Aosta	53.70	-1.1	245.3	-2.1	56.10	15.7	173.4	17.6
Lombardia	52.50	2.5	206.8	5.3	46.80	17.3	144.9	16.5
PA Bolzano	39.40	0.5	152.9	0.3	47.60	4.4	142.5	2.4
PA Trento	44.00	-0.2	179.3	1.6	49.00	11.9	150.4	9.7
Veneto	48.80	-0.8	195.2	0.0	46.30	14.3	142.9	13.1
Friuli VG	43.40	-0.9	178.5	-0.8	42.40	14.3	136.1	15.6
Liguria	63.00	1.3	265.5	2.7	54.70	19.7	181.4	18.6
Emilia R.	48.80	-6.2	191.7	-3.6	45.50	16.1	146.7	16.0
Toscana	51.40	3.8	228.0	6.4	45.50	17.9	148.9	18.6
Umbria	30.70	-1.6	105.9	-0.1	27.60	24.9	85.4	23.4
Marche	26.40	-3.3	97.3	-5.4	28.70	33.5	93.6	31.1
Lazio	49.20	5.8	177.8	8.7	43.00	23.9	139.1	24.8
Abruzzo	41.50	-7.0	144.2	-5.6	37.40	21.0	120.4	20.0
Molise	36.10	-3.2	155.6	-3.1	30.50	16.0	98.6	16.3
Campania	48.80	-1.4	181.1	-1.9	39.20	13.0	130.3	14.3
Puglia	41.40	2.7	156.3	1.6	34.70	22.2	107.0	21.5
Basilicata	37.80	-0.3	148.6	-1.6	31.50	26.0	97.4	24.9
Calabria	41.30	-0.2	182.4	0.3	34.30	20.8	110.1	20.5
Sicilia	38.60	-2.0	135.4	-0.3	31.70	18.7	102.7	19.7
Sardegna	49.90	-0.2	219.0	-0.2	40.40	29.9	122.2	29.9
Italy	**47.50**	**0.4**	**186.8**	**2.0**	**41.90**	**18.4**	**133.9**	**18.1**
North	51.40	0.2	206.1	0.1	46.80	-	148.5	0.1
Centre	45.50	0.2	178.0	0.2	40.80	0.2	132.3	0.2
South and islands	43.30	0.5	164.6	0.2	35.70	0.3	114.3	0.3

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

Table 5.4.5. First twenty A Class active ingredients privately purchased by citizens in decreasing order of expenditure, year 2018

ATC I	Active ingredient	DDD/1000 inhab per day	Expenditure *(million)*	%*	% private purchase**
M	ketoprofen	7.5	44.1	3.2	68.2
J	amoxicillin/clavulanic acid	1.3	41.2	3.0	18.6
A	pantoprazole	3.2	36.8	2.7	11.7
A	omeprazole	2.8	25.9	1.9	14.3
A	lansoprazole	2.4	25.8	1.9	13.6
A	esomeprazole	2.2	24.5	1.8	14.5
B	rivaroxaban	0.3	23.9	1.8	15.4
B	apixaban	0.2	22.9	1.7	12.4
M	ibuprofen	2.3	21.5	1.6	54.2
N	acetylsalicylic acid	11.8	19.7	1.5	93.5
M	diclofenac	2.0	18.7	1.4	34.5
A	insulin glargine	0.4	18.5	1.4	14.7
B	dabigatran	0.2	17.2	1.3	16.0
C	rosuvastatin	2.7	16.0	1.2	17.1
H	betametasone	1.7	15.6	1.2	42.6
R	cetirizine	2.2	14.5	1.1	48.1
C	omega 3	0.6	14.4	1.1	11.3
H	levothyroxine	5.9	13.4	1.0	18.7
M	nimesulide	2.5	13.3	1.0	57.4

* calculated on total expenditure of A Class 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 5.4.6. Consumption breakdown of A class medicines privately purchased by citizens, by price range in 2018

Regions	<2 euro	2-3 euro	3-6 euro	6-10 euro	10-30 euro	>30 euro
	%	%	%	%	%	%
Piemonte	6.7	10.9	29.8	27.8	14.3	10.4
Valle d'Aosta	8.3	17.8	28.3	20.1	14.6	10.9
Lombardia	12.6	23.7	33.3	18.6	10.4	1.5
PA Bolzano	8.5	18.3	35.2	24.9	11.5	1.6
PA Trento	12.4	11.0	35.5	25.0	14.0	2.1
Veneto	11.8	22.7	32.7	20.1	10.3	2.3
Friuli VG	5.9	9.1	34.0	26.5	11.5	13.0
Liguria	11.1	20.3	31.4	19.7	12.3	5.2
Emilia R.	9.2	10.6	41.1	23.0	13.1	2.9
Toscana	12.0	18.1	36.9	19.9	11.1	2.1
Umbria	17.0	4.1	48.0	18.4	7.7	4.8
Marche	11.5	3.5	44.3	17.7	11.0	12.0
Lazio	12.3	18.1	36.3	18.9	12.2	2.2
Abruzzo	16.6	12.4	41.6	19.5	8.9	1.0
Molise	8.1	13.1	37.8	22.4	12.7	6.0
Campania	12.7	28.6	33.4	16.7	6.4	2.2
Puglia	13.1	14.4	40.3	17.2	9.0	6.1
Basilicata	9.9	23.6	39.3	17.6	8.9	0.7
Calabria	10.0	26.4	43.5	13.6	5.3	1.2
Sicilia	9.9	18.8	32.7	11.1	26.6	0.9
Sardegna	13.1	14.2	36.2	22.4	13.0	1.1
Italy	**11.2**	**19.5**	**34.4**	**19.8**	**11.6**	**3.5**

Table 5.4.7. Expenditure and consumption of self-medication medicines supplied by shops, by Region and % deviation from national average (figure), year 2018

Regions	Per capita expenditure	Expenditure *(millions)*	DDD/1000 inhab per day
Piemonte	4.9	23	15.9
Valle d'Aosta	5.4	1	16.1
Lombardia	4.8	48	15.2
PA Bolzano	0.3	0.1	0.9
PA Trento	3.6	2	10.6
Veneto	4.6	23	14.2
Friuli VG	3.6	5	11.3
Liguria	5.6	10	19.3
Emilia R.	6.9	32	23.1
Toscana	3.8	15	12.5
Umbria	4.1	4	13.7
Marche	5.0	8	16.8
Lazio	3.6	21	12.1
Abruzzo	5.7	8	18.6
Molise	3.5	1	11.6
Campania	2.5	13	8.7
Puglia	4.4	18	14.7
Basilicata	5.6	3	17.5
Calabria	4.4	8	14.5
Sicilia	2.7	13	9.9
Sardegna	7.3	12	22.6
Italy	**4.4**	**266**	**14.4**

Table 5.4.8. First twenty self-medication active ingredients supplied by shops in decreasing order of expenditure in 2018

Active ingredient	Per capita expenditure	Inc %*	Cum. %	DDD/1000 inhab per day
diclofenac	0.56	12.6	12.6	1.53
ibuprofen	0.12	2.6	15.3	0.32
paracetamol	0.16	3.6	18.9	0.43
flurbiprofen	0.18	4.0	22.9	0.48
spores of polyantibiotic-resistant bacillus clausii	0.08	1.9	24.8	0.23
ketoprofen	0.07	1.6	26.3	0.19
paracetamol	0.07	1.5	27.8	0.18
naphazoline	0.45	10.3	38.1	1.24
acetylsalicylic acid	0.05	1.2	39.3	0.15
glycerol	0.13	3.0	42.3	0.36
diosmin	0.07	1.6	44.0	0.20
magnesium hydroxide / algeldrate / dimethicone	0.02	0.3	44.3	0.04
l-cystein	0.04	0.8	45.1	0.10
oxymetazoline hydrochloride	0.15	3.4	48.6	0.41
glycerol	0.25	5.6	54.2	0.68
paracetamol/pseudoephedrine	0.02	0.5	54.7	0.06
loperamide	0.01	0.3	55.0	0.04
benzydamine/cetylpyridine	0.03	0.7	55.7	0.08
senna leaf	0.13	2.9	58.6	0.35
bisacodyl	0.09	2.1	60.8	0.26
Italy	**4.40**	**100**		**14.4**

*calculated on total expenditure

Table 5.4.9a. Benzodiazepines, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2018

Subgroups and substances	2014	2015	2016	2017	2018	Δ % 18-17
Anxiolytics	25.2	21.2	23.3	25.0	25.7	2.8
Hypnotics	18.5	15.6	17.0	18.6	19.0	2.2
Sedatives	3.7	3.1	3.6	4.3	4.6	9.7
Benzodiazepines	**47.4**	**40.0**	**43.9**	**47.9**	**49.2**	**3.2**
lorazepam	10.8	9.2	9.7	10.2	10.3	0.1
alprazolam	8.1	7.0	8.0	8.7	9.2	6.0
lormetazepam	13.1	11.1	11.9	13.0	13.2	1.4
zolpidem	3.5	3.0	3.5	4.1	4.4	10.2
bromazepam	1.5	1.2	1.3	1.4	1.4	2.1
delorazepam	2.2	1.9	2.0	2.3	2.4	5.3
triazolam	3.1	2.7	3.0	3.3	3.4	4.1
diazepam	1.3	1.0	1.1	1.2	1.2	2.6
brotizolam	1.4	1.1	1.2	1.4	1.4	4.7
flurazepam	0.6	0.5	0.6	0.6	0.7	4.3

Table 5.4.9b. Benzodiazepines, regional trend of DDD/1000 inhabitants per day weighted: comparison 2014-2018

Regions	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	67.6	54.5	66.8	66.6	70.2	5.4
Valle d'Aosta	68.7	53.9	66.6	67.3	72.3	7.6
Lombardia	48.8	42.7	45.5	55.6	57.8	4.9
PA Bolzano	37.9	34.9	35.7	35.5	35.8	1.0
PA Trento	62.2	59.4	59.5	59.1	60.2	1.8
Veneto	61.9	57.1	56.0	69.9	68.8	-2.0
Friuli VG	60.9	47.6	56.5	60.9	60.7	-0.3
Liguria	82.3	63.7	75.8	74.9	79.1	5.5
Emilia R.	51.4	48.2	53.1	55.4	52.8	-4.8
Toscana	45.7	40.6	42.3	44.8	48.3	8.2
Umbria	52.2	28.2	31.0	31.3	31.3	0.0
Marche	54.4	26.8	29.7	29.9	28.1	-6.3
Lazio	42.9	33.4	36.2	41.0	45.1	11.2
Abruzzo	39.0	36.1	37.8	37.5	36.6	-2.2
Molise	29.0	24.9	29.7	29.7	30.7	3.3
Campania	35.3	31.8	33.8	35.0	35.8	2.5
Puglia	28.2	25.0	27.0	27.0	28.7	6.1
Basilicata	22.6	20.7	26.3	26.5	27.2	2.6
Calabria	34.6	25.4	31.2	32.1	33.3	4.0
Sicilia	28.8	24.4	28.0	30.1	30.8	2.4
Sardegna	57.8	50.6	61.5	60.7	62.7	3.3
Italy	**47.4**	**40.0**	**43.9**	**47.9**	**49.2**	**3.2**

Table 5.4.9c. Benzodiazepines, prescription by therapeutic category and by substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab per day	Δ % 18-17
Anxiolytics	5.92	3.1	25.7	2.8
Hypnotics	2.04	2.2	19.0	2.2
Sedatives	0.92	8.6	4.6	9.7
Benzodiazepines	**8.88**	**3.4**	**49.2**	**3.2**
lorazepam	1.84	0.7	10.3	0.1
alprazolam	1.83	6.1	9.2	6.0
lormetazepam	0.88	0.7	13.2	1.4
zolpidem	0.88	9.1	4.4	10.2
bromazepam	0.79	2.2	1.4	2.1
delorazepam	0.72	4.9	2.4	5.3
triazolam	0.64	3.3	3.4	4.1
diazepam	0.33	2.8	1.2	2.6
brotizolam	0.29	3.7	1.4	4.7
flurazepam	0.14	3.8	0.7	4.3

Figure 5.4.9b. Benzodiazepines, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

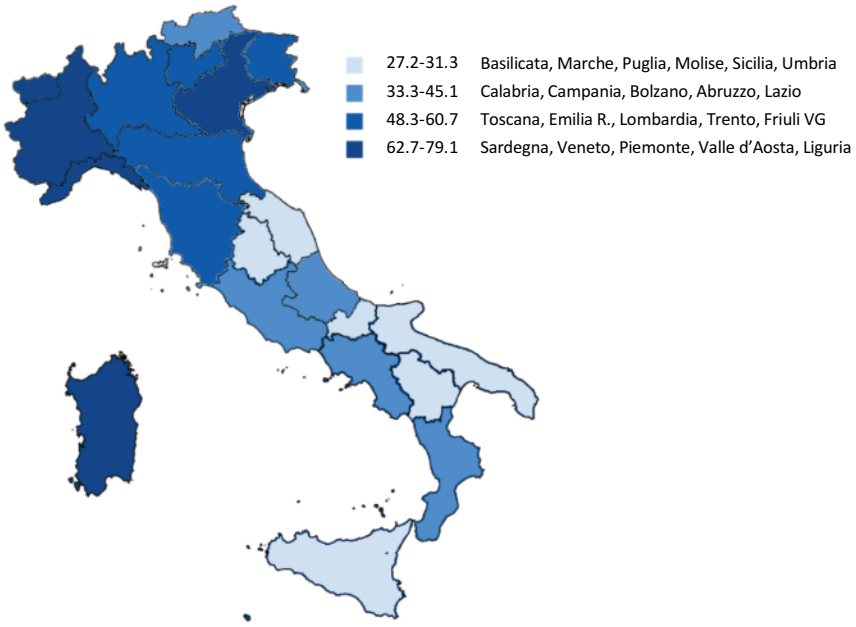


Table 5.4.10a. Oral contraceptives, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2018

Subgroups and substances	2014	2015	2016	2017	2018	Δ % 18-17
Estro-progestin fixed associations	42.4	33.2	36.0	37.9	37.8	-0.1
Estrogen-progestin sequential preparations	6.4	5.1	5.4	5.7	6.2	8.3
Progestin	1.8	1.7	2.1	2.6	3.9	62.0
Emergency contraceptives	<0.05	<0.05	<0.05	<0.05	<0.05	13.5
Oral contraceptives	**50.7**	**40.0**	**43.5**	**46.2**	**47.9**	**3.9**
drospirenone/ethinyl estradiol	16.3	12.1	12.0	11.8	11.5	-2.6
gestodene/ethinyl estradiol	16.1	11.9	12.5	12.1	11.2	-6.9
dienogest/ ethinyl estradiol	1.7	2.2	3.3	4.3	5.2	29.4
dienogest/estradiol	2.7	2.4	2.8	3.4	4.0	21.5
levonorgestrel/ethinyl estradiol	4.2	3.7	4.5	5.1	5.2	2.2
estradiol/nomegestrol	1.6	1.5	1.9	2.4	2.4	1.9
desogestrel	1.7	1.6	1.9	2.4	2.8	19.5
ethinyl estradiol/norelgestromin	1.5	1.1	1.2	1.4	1.3	-2.9
ulipristal	<0.05	<0.05	<0.05	<0.05	<0.05	18.0
desogestrel/ethinyl estradiol	2.6	1.8	1.7	1.7	1.6	-5.7

Table 5.4.10b. Oral contraceptives, regional trend of DDD/1000 inhabitants per day weighted: comparison 2014-2018

Regions	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	70.3	51.9	63.5	64.1	67.4	5.2
Valle d'Aosta	84.8	62.5	77.0	77.4	80.2	3.7
Lombardia	60.2	48.4	51.8	63.0	68.9	11.3
PA Bolzano	84.6	77.2	73.2	69.4	70.0	0.8
PA Trento	63.2	59.3	57.7	58.7	62.0	5.8
Veneto	52.6	45.6	42.8	54.2	56.2	4.6
Friuli VG	55.3	40.6	46.7	51.7	53.3	3.4
Liguria	68.4	49.3	61.5	61.4	63.3	3.1
Emilia R.	57.1	50.6	54.4	58.0	54.6	-6.1
Toscana	55.0	45.8	46.7	49.7	54.1	9.5
Umbria	48.2	24.2	25.1	24.2	24.1	-0.3
Marche	44.5	20.2	19.3	17.5	16.0	-8.0
Lazio	43.9	30.6	31.0	36.1	40.6	14.4
Abruzzo	41.7	37.2	36.5	34.8	33.0	-5.0
Molise	30.8	22.7	26.0	24.6	23.5	-4.2
Campania	29.5	24.2	32.0	22.9	21.1	-5.7
Puglia	35.1	29.3	29.0	28.0	29.1	3.8
Basilicata	22.4	19.5	24.2	23.4	23.2	-0.8
Calabria	31.3	20.2	24.0	24.1	23.8	-1.1
Sicilia	31.5	24.0	26.2	26.7	25.8	-3.4
Sardegna	118.9	98.0	114.4	111.5	110.6	-0.8
Italy	**50.7**	**40.0**	**43.5**	**46.2**	**47.9**	**3.9**

Table 5.4.10c. Oral contraceptives, prescription by therapeutic category and by substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Estro-progestin fixed associations	6.24	0.2	37.8	-0.1
Estrogen-progestin sequential preparations	1.12	13.6	6.2	8.3
Progestin	0.49	23.4	3.9	62.0
Emergency contraceptives	0.39	12.7	<0.05	13.5
Oral contraceptives	**8.24**	**3.6**	**47.9**	**3.9**
drospirenone/ ethinyl estradiol	2.27	-3.2	11.5	-2.6
gestodene/ethinyl estradiol	1.09	-7.3	11.2	-6.9
dienogest/ ethinyl estradiol	0.95	22.2	5.2	29.4
dienogest/estradiol	0.91	18.9	4.0	21.5
levonorgestrel/ ethinyl estradiol	0.83	1.3	5.2	2.2
estradiol/nomegestrol	0.52	1.5	2.4	1.9
desogestrel	0.43	12.4	2.8	19.5
ethinyl estradiol/norelgestromina	0.28	-2.1	1.3	-2.9
ulipristal	0.22	15.1	0.0	18.0
desogestrel/ ethinyl estradiol	0.22	-7.6	1.6	-5.7

Figure 5.4.10b. Oral contraceptives, distribution in quartiles of 2018 consumption (weighted DDD/1000 inhab. per day)

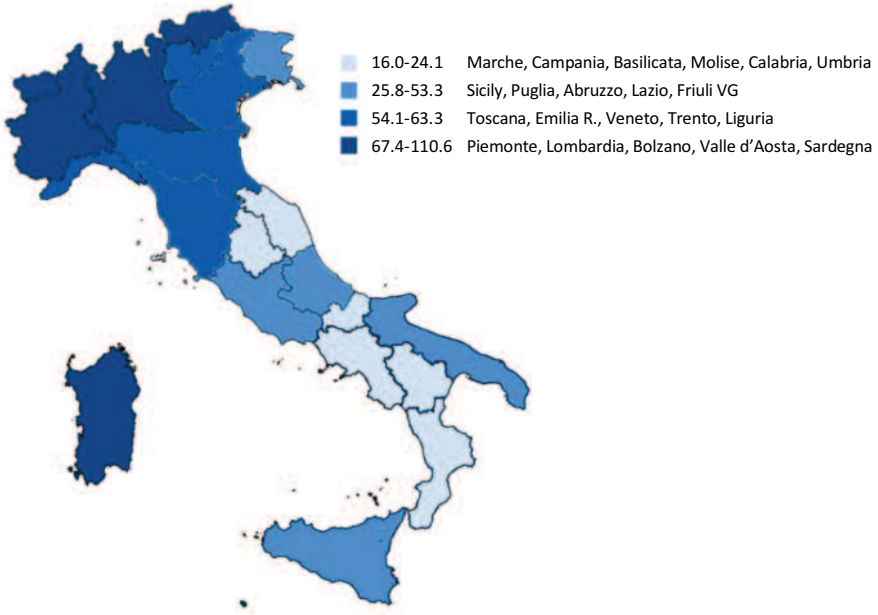


Table 5.4.11a. Pharmaceuticals used in erectile dysfunction, consumption (DDD/1000 inhab. per day) by therapeutic category and by substance: comparison 2014-2018

Subgroups and substances	2014	2015	2016	2017	2018	Δ % 18-17
Medicines used in erectile dysfunction	**2.9**	**2.4**	**2.9**	**3.3**	**3.6**	**9.3**
tadalafil	1.3	1.0	1.2	1.4	1.8	31.7
sildenafil	1.0	1.0	1.2	1.4	1.4	0.4
vardenafil	0.5	0.3	0.4	0.3	0.2	-20.0
avanafil	0.1	0.1	0.2	0.2	0.2	-22.1
alprostadil	<0.05	<0.05	<0.05	<0.05	<0.05	-2.9

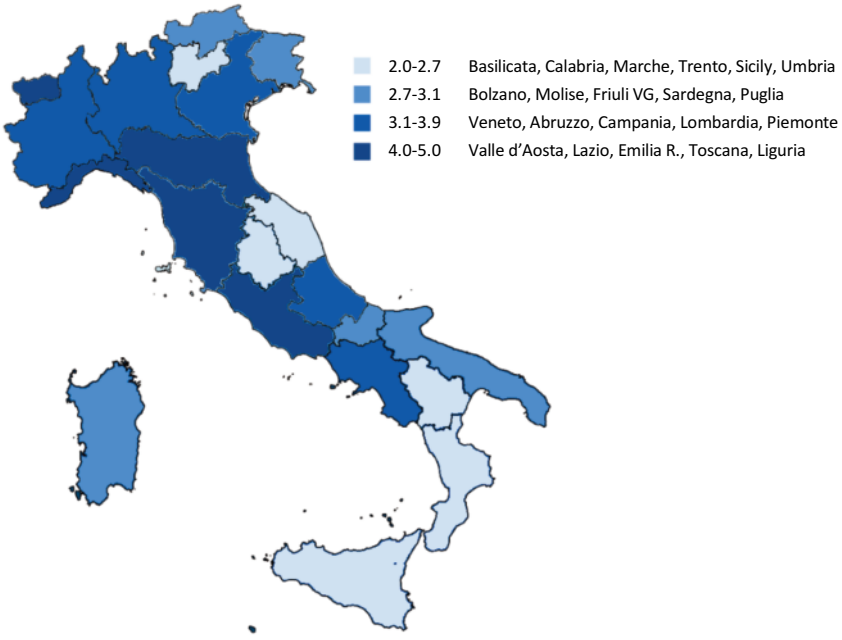
Table 5.4.11b. Pharmaceuticals used in erectile dysfunction, regional trend of DDD/1000 inhabitants per day weighted: comparison 2014-2018

Regions	2014	2015	2016	2017	2018	Δ % 18-17
Piemonte	3.3	2.6	3.4	3.5	3.9	11.3
Valle d'Aosta	2.7	2.1	3.2	3.8	4.0	6.6
Lombardia	2.6	2.2	2.7	3.5	3.9	15.9
PA Bolzano	2.5	2.4	2.5	2.5	2.7	9.8
PA Trento	2.1	2.1	2.2	2.2	2.4	9.2
Veneto	2.3	2.1	2.2	3.0	3.1	7.4
Friuli VG	2.4	1.9	2.4	2.7	2.8	4.2
Liguria	4.4	3.4	4.2	4.6	5.0	9.4
Emilia R.	3.6	3.3	3.9	4.3	4.2	-1.6
Toscana	4.1	3.5	4.0	4.5	4.9	10.0
Umbria	3.7	2.0	2.6	2.7	2.7	0.6
Marche	3.4	2.0	2.3	2.5	2.3	-9.2
Lazio	3.5	2.6	3.0	3.5	4.1	20.0
Abruzzo	3.1	3.0	3.4	3.8	3.8	0.9
Molise	2.2	2.1	2.4	2.7	2.8	4.1
Campania	3.2	2.9	3.5	3.6	3.9	7.8
Puglia	2.4	2.2	2.5	2.8	3.1	10.6
Basilicata	1.3	1.4	1.7	1.9	2.0	7.2
Calabria	2.0	1.4	2.0	2.2	2.2	1.6
Sicilia	1.9	1.6	2.1	2.5	2.7	8.1
Sardegna	2.3	2.0	2.7	2.7	3.0	8.0
Italy	**2.9**	**2.4**	**2.9**	**3.3**	**3.6**	**9.3**

Table 5.4.11c. Pharmaceuticals used in erectile dysfunction, prescription by therapeutic category and by substance in 2018

Subgroups and substances	Per capita expenditure	Δ % 18-17	DDD/1000 inhab per day	Δ % 18-17
Pharmaceuticals used in erectile dysfunction	**8.24**	**-8.9**	**3.6**	**9.3**
tadalafil	3.98	-8.6	1.8	31.7
sildenafil	2.87	-2.9	1.4	0.4
vardenafil	0.85	-23.9	0.2	-20.0
avanafil	0.31	-20.9	0.2	-22.1
alprostadil	0.22	4.6	<0.05	-2.9

Figure 5.4.11b. Pharmaceuticals used in erectile dysfunction, distribution in quartiles of 2018 territorial consumption (weighted DDD/1000 inhab. per day)



5.5 Direct and per conto distribution

In 2018, expenditure on pharmaceuticals dispensed through alternative supply methods, i.e. direct and *per conto* distribution, amounted to € 8,245 million, 78.2% of which – at a national level – for *stricto sensu* direct distribution expenditure and the remaining 21.8% for in name and *per conto* distribution. However, a wide regional variability was recorded due to the organizational differences of the regional health systems. Direct distribution represents over 90% of the expenditure for medicines distributed through alternative channels in Abruzzo, where in name and *per conto* distribution was performed for the first time in 2018, while it showed the lowest incidence in Calabria (63.7%), Lazio and the Autonomous Province of Trento (66.9%) (Table 5.5.1). Class A medicines represent the main share of expenditure (56.0%), followed by class H medicines (43.1%), while class C medicines constitute a residual share (0.8%) (Table 5.5.2). The Regions showing the highest expenditure in absolute terms are Lombardia (1,006,9 million euro), Lazio (832 million) and Campania (827.3 million), while Valle d'Aosta (12.6 million), the Autonomous Province of Trento (44.3 million) and Molise (48.3 million) are those with the lowest values (Table 5.5.1 and Table 5.5.2).
The first two highest-expenditure medicines (among those supplied by direct and *per conto* distribution) are a combination for the treatment of hepatitis C virus (sofosbuvir/velpatasvir) and factor VIII. The first 30 active ingredients for expenditure also include another molecule for the treatment of hepatitis C (glecaprevir/pibrentasvir), 4 medicinal products for the treatment of HIV infection and 13 antineoplastics and immunomodulators (Table 5.5.3).
The cost for hospital and outpatient pharmaceuticals was 3,180.5 million euros, 75.7% of which was for class H medicines, 17.0% for class C medicines and residually for class A medicines (7.2%) (Table 5.6.1). The regions recording the highest expenditure in absolute terms were Lombardia (480.5 million euros), Lazio (295.7 million), Emilia Romagna (280.3 million). Valle d'Aosta (5.3 million), Molise (13.7 million) and Basilicata (30 million), on the other hand, showed the lowest values (Table 5.6.1).
Trastuzumab (€ 182.9 million) is confirmed in first place in terms of expenditure, followed by nivolumab (€ 122.7 million), which ranked fourth in the previous year after bevacizumab and rituximab (currently third and fifth position). Pembrolizumab, with 122.7 million euros, rises from the twenty-fourth position held in 2017 to the fourth in 2018. Altogether 18 antineoplastics and immunomodulators are included in this ranking (Table 5.6.2).

Table 5.5.1. Composition of 2018 regional expenditure for medicinal products supplied in direct distribution (DD) and *per conto* distribution (DPC)

Regions	DD *(millions of euro)*	DPC *(millions of euro)*	Total *(millions of euro)*	Inc % DD	Inc % DPC
Piemonte	497.3	119.1	616.4	80.7	19.3
Valle d'Aosta	9.7	2.9	12.6	77.0	23.0
Lombardia	799.3	207.6	1.006.9	79.4	20.6
PA Bolzano	45.5	9.8	55.3	82.3	17.7
PA Trento	29.7	14.7	44.3	66.9	33.1
Veneto	445.8	105.0	550.8	80.9	19.1
Friuli VG	123.0	41.0	164.0	75.0	25.0
Liguria	199.1	41.8	240.9	82.6	17.4
Emilia R.	594.2	59.4	653.7	90.9	9.1
Toscana	415.9	113.6	529.5	78.5	21.5
Umbria	114.3	43.1	157.4	72.6	27.4
Marche	171.2	58.4	229.6	74.6	25.4
Lazio	562.5	269.5	832.0	67.6	32.4
Abruzzo	178.9	15.8	194.6	91.9	8.1
Molise	32.7	15.6	48.3	67.7	32.3
Campania	620.2	207.1	827.3	75.0	25.0
Puglia	495.0	153.7	648.7	76.3	23.7
Basilicata	71.7	19.2	91.0	78.8	21.2
Calabria	191.7	109.3	301.0	63.7	36.3
Sicilia	579.9	128.9	708.9	81.8	18.2
Sardegna	271.9	60.0	331.8	81.9	18.1
Italy	**6.449.5**	**1.795.5**	**8.245.0**	**78.2**	**21.8**

Note: consolidated data as of April 25, 2019 relating to medicinal products with marketing authorization

Table 5.5.2. Composition by reimbursement class of 2018 regional expenditure for medicinal products supplied in direct distribution (DD) and *per conto* distribution (DPC)

Regions	Class A *(mil euro)*	Class C *(mil euro)*	Class H *(mil euro)*	Total *(mil euro)*	Inc % A	Inc % C	Inc % H
Piemonte	377.9	5.4	233.2	616.4	61.3	0.9	37.8
Valle d'Aosta	7.7	0.2	4.7	12.6	61.3	1.4	37.4
Lombardia	527.5	6.8	472.7	1.006.9	52.4	0.7	46.9
PA Bolzano	27.3	1.2	26.8	55.3	49.4	2.2	48.4
PA Trento	28.1	1.0	15.3	44.3	63.4	2.1	34.5
Veneto	294.3	12.5	244.0	550.8	53.4	2.3	44.3
Friuli VG	82.6	2.8	78.5	164.0	50.4	1.7	47.9
Liguria	143.1	1.5	96.3	240.9	59.4	0.6	40.0
Emilia R.	347.4	9.8	296.4	653.7	53.2	1.5	45.3
Toscana	292.4	4.0	233.1	529.5	55.2	0.8	44.0
Umbria	74.2	0.8	82.4	157.4	47.1	0.5	52.4
Marche	120.7	0.8	108.1	229.6	52.6	0.3	47.1
Lazio	482.5	4.7	344.7	832.0	58.0	0.6	41.4
Abruzzo°	102.8	0.8	91.1	194.6	52.8	0.4	46.8
Molise	29.9	0.2	18.2	48.3	61.9	0.4	37.7
Campania	459.3	3.6	364.5	827.3	55.5	0.4	44.1
Puglia	378.2	4.1	266.4	648.7	58.3	0.6	41.1
Basilicata	55.9	0.9	34.1	91.0	61.5	1.0	37.5
Calabria	184.1	1.8	115.1	301.0	61.2	0.6	38.2
Sicilia	415.7	3.6	289.5	708.9	58.6	0.5	40.8
Sardegna	188.8	2.5	140.6	331.8	56.9	0.7	42.4
Italy	**4.620.4**	**68.9**	**3.555.7**	**8.245.0**	**56.0**	**0.8**	**43.1**

° does not provide for in name and *per conto* distribution

Note: consolidated data as of April 25, 2019 relating to medicinal products with marketing authorization

Table 5.5.3. First 30 active ingredients in decreasing order of 2018 regional expenditure for medicinal products supplied in direct and *per conto* distribution

Active ingredient	ATC I	Expenditure *(millions of euro)*	Inc %*	Cum %
sofosbuvir/velpatasvir	J	499.7	6.1	6.1
factor VIII	B	302.6	3.7	9.7
adalimumab	L	292.9	3.6	13.3
lenalidomide	L	225.6	2.7	16.0
glecaprevir/pibrentasvir	J	220.1	2.7	18.7
etanercept	L	166.1	2.0	20.7
rivaroxaban	B	151.2	1.8	22.5
apixaban	B	150.3	1.8	24.4
oxygen	V	138.1	1.7	26.0
fingolimod	L	133.1	1.6	27.7
dimethyl fumarate	L	113.6	1.4	29.0
ibrutinib	L	107.9	1.3	30.3
interferon beta 1a	L	101.6	1.2	31.6
dabigatran	B	99.8	1.2	32.8
abiraterone	L	94.2	1.1	33.9
insulin glargine	A	92.5	1.1	35.0
dolutegravir/abacavir/lamivudine	J	86.8	1.1	36.1
somatropin	H	83.6	1.0	37.1
ustekinumab	L	80.4	1.0	38.1
elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	J	79.5	1.0	39.1
deferasirox	V	78.5	1.0	40.0
secukinumab	L	78.2	0.9	41.0
emtricitabine, tenofovir alafenamide, rilpivirine	J	73.2	0.9	41.8
golimumab	L	72.1	0.9	42.7
dasatinib	L	70.8	0.9	43.6
nilotinib	L	69.4	0.8	44.4
epoetin alpha	B	67.2	0.8	45.2
enzalutamide	L	66.7	0.8	46.0
dolutegravir	J	66.7	0.8	46.8
ranolazine	C	66.1	0.8	47.7
Total		**8.245.0**	**100.0**	**100.0**

*Calculated on total expenditure
Note: consolidated data as of April 25, 2019 relating to medicinal products with marketing authorization

5.6 Hospital and ambulatory pharmaceutical care

Table 5.6.1. Composition by reimbursement class of regional expenditure for medicinal products supplied in hospital and ambulatory pharmaceutical care (2018)

Regions	Class A *(mln euro)*	Class C *(mln euro)*	Class H *(mln euro)*	Total *(mln euro)*	Inc % A	Inc % C	Inc % H
Piemonte	16.6	23.2	186.1	225.9	7.4	10.3	82.4
Valle d'Aosta	0.3	1.4	3.6	5.3	5.9	25.8	68.3
Lombardia	34.4	82.9	363.2	480.5	7.1	17.3	75.6
PA Bolzano	1.8	6.4	23.0	31.3	5.8	20.6	73.6
PA Trento	4.2	6.6	24.4	35.1	11.9	18.7	69.5
Veneto	19.2	53.1	205.5	277.8	6.9	19.1	74.0
Friuli VG	4.4	15.4	64.5	84.4	5.2	18.3	76.5
Liguria	7.2	17.5	80.5	105.2	6.8	16.6	76.5
Emilia R.	19.6	54.6	206.0	280.3	7.0	19.5	73.5
Toscana	29.3	35.5	198.0	262.8	11.2	13.5	75.3
Umbria	4.3	10.5	30.3	45.1	9.6	23.3	67.1
Marche	9.1	18.7	73.4	101.2	9.0	18.5	72.5
Lazio	15.2	42.9	237.6	295.7	5.1	14.5	80.4
Abruzzo	6.7	13.7	55.6	76.1	8.8	18.1	73.1
Molise	1.5	2.2	10.1	13.7	10.9	15.8	73.3
Campania	14.6	41.6	207.7	263.9	5.5	15.8	78.7
Puglia	12.5	38.9	161.1	212.4	5.9	18.3	75.8
Basilicata	2.2	4.1	23.7	30.0	7.4	13.8	78.8
Calabria	8.5	17.8	66.5	92.8	9.2	19.2	71.7
Sicilia	12.8	37.7	149.7	200.2	6.4	18.8	74.8
Sardegna	5.9	17.1	37.7	60.6	9.7	28.2	62.1
Italy	**230.3**	**542.0**	**2.408.2**	**3.180.5**	**7.2**	**17.0**	**75.7**

Note: consolidated data as of April 25, 2019 relating to medicinal products with marketing authorization

Table 5.6.2. First 30 active ingredients in decreasing order of expenditure for medicinal products supplied in hospital and ambulatory pharmaceutical care (2018)

Active ingredient	ATC I	Expenditure *(million of euro)*	Inc %*	Cum %
trastuzumab	L	182.9	5.7	5.7
nivolumab	L	181.7	5.7	11.5
bevacizumab	L	140.8	4.4	15.9
pembrolizumab	L	122.7	3.9	19.7
rituximab	L	102.6	3.2	23.0
pertuzumab	L	86.3	2.7	25.7
nusinersen	M	78.0	2.5	28.1
meningococcal vaccine group b	J	72.1	2.3	30.4
eculizumab	L	62.3	2.0	32.4
aflibercept	S	56.7	1.8	34.1
human immunoglobulin intravenous use	J	54.3	1.7	35.9
natalizumab	L	48.4	1.5	37.4
ranibizumab	S	47.2	1.5	38.9
bortezomib	L	46.0	1.4	40.3
oxygen	V	45.1	1.4	41.7
infliximab	L	41.3	1.3	43.0
pneumococcal saccharide conjugated vaccine, adsorbed	J	40.8	1.3	44.3
pemetrexed	L	39.2	1.2	45.5
azacitidine	L	37.6	1.2	46.7
vaccine diphtheria/recombinant hepatitis b/haemophilus influenzae b conjugated and adjuvanted/acellular pertussis/inactivated poliomyelitis/tetanus	J	36.1	1.1	47.9
trastuzumab emtansine	L	35.9	1.1	49.0
daratumumab	L	34.9	1.1	50.1
sodium chloride	V	32.6	1.0	51.1
recombinant human acid alglucosidase	A	32.2	1.0	52.1
carfilzomib	L	27.3	0.9	53.0
cetuximab	L	26.5	0.8	53.8
sugammadex	V	24.1	0.8	54.6
human papillomavirus vaccine (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	J	22.9	0.7	55.3
panitumumab	L	21.9	0.7	56.0
vedolizumab	L	21.4	0.7	56.7
Total		**3,180.5**	**100.0**	**100.0**

Note: consolidated data as of April 25, 2019 relating to medicinal products with marketing authorization
* Calculated on total expenditure

5.7 Reimbursement of extra DRG medicinal products

Table 5.7.1. Regional distribution of expenditure and consumption for extra DRG medicinal products: comparison 2018-2017

Regions	per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
Lombardia	27.35	11.3	3.6	-1.4
Veneto	2.94	15.5	0.5	20.1
Liguria	10.99	-8.5	3.2	-19.7
Lazio	21.98	-20.8	3.1	-57.4
Molise	3.25	24.7	0.2	21.9
Campania	0.41	5.0	0.2	1.5

Table 5.7.2. Distribution by I level ATC of expenditure and consumption for extra DRG medicinal products: comparison 2018-2017

I level ATC	Per capita expenditure	Δ % 18-17	DDD/1000 inhab. per day	Δ % 18-17
A	0.44	-5.6	0.1	-4.0
B	0.26	-9.1	0.2	-14.7
C	0.21	-7.3	0.1	1.6
D	0.00	-36.4	0.0	-24.7
G	0.03	-12.3	0.0	0.4
H	0.07	-2.7	0.0	-22.7
J	2.73	-4.6	0.4	-4.3
L	10.55	-1.4	0.8	-42.5
M	0.20	19.5	0.3	-38.3
N	0.06	-23.3	0.1	-4.0
P	0.00	-3.5	0.0	4.9
R	0.17	34.3	0.0	-2.7
S	0.69	21.2	0.1	-14.6
V	0.14	1.2	0.0	-38.6

Section 6

Aifa medicines monitoring registries and managed entry agreements

6.1 AIFA Monitoring Registries

Monitoring registries are an advanced tool for the governance of prescribing appropriateness; they have been developed by the Italian Medicines Agency since 2005 and represent an additional regulatory tool, such as the Therapeutic Plans (TP) and the AIFA Notes.
Medicines are usually monitored through Monitoring Registries immediately after their marketing authorization, or after the authorization of an extension of the therapeutic indication.
In special cases registers are also used to monitor medicines reimbursed by NHS according to Law 648/96. The initial regulatory experience was gathered through the Cancer Medicines Registry and was then extended to other therapeutic areas. In such cases AIFA deems this tool necessary to check prescribing appropriateness and NHS pharmaceutical expenditure.
AIFA Registries have become a well-established reality also in function of several laws passed over time, starting from Law no. 135 of 7 August 2012, which recognized Registries as an integral part of the National Health Service Information System (Art.15, paragraph 10). Subsequently, further regulations were introduced (Law 125/2015, Law 232/2016, Law 205/2017, Law 302/2018) in order to assign different purposes to Registries: evaluating medicines' efficacy, acting as support for renegotiations, monitoring expenditure for innovative medicines and monitoring avoidable costs in the health care sector.
As reported in Figure 4.1.1, several stakeholders are involved in the registry process. In particular, within AIFA, the definition and the implementation of a registry firstly requires the definition of specific indicators of full treatment response and the identification of patients' subgroups who can obtain the maximum therapeutic benefit.
The registry platform management network includes about 3,500 health facilities, 59 regional managers, 728 Health Directors, 29,691 physicians and 2,044 pharmacists.
It is a very important network that allows Regions to regulate the organization of pharmaceutical assistance at a local level.

Currently, 56 Pharmaceutical Companies hold at least one monitoring registry, managed through the AIFA platform. This platform allows pharmaceutical companies to interact with individual pharmacies, in compliance with Managed Entry Agreements (MEAs). In fact, the Registries platform allows the application of MEAs (for more details see section 4.2).

Moreover, AIFA Monitoring Registries satisfy the need for a rapid access to those medicines considered potentially very important for health, but also limiting the NHS expenditure through the implementation of reimbursement strategies, in order to guarantee the sustainability of NHS pharmaceutical expenditure, in particular for those medicines with very high marginal costs.

The role of registries is particularly relevant for recently authorized medicines that despite a positive benefit/risk ratio still have some uncertainty or in the case that the benefit/risk

ratio might change according to the modality of use. Instead, in the case of an extension approval of any of the already authorised and commercialised therapeutic indication, the registries allow the use of the medicine in strictly accordance with the new indication.
In fact, most medicines included in the AIFA Registries received a centralized authorization (often accelerated and/or conditioned) mainly concerning biological and/or high cost medicines for the NHS.
In particular, the definition and the implementation of a registry require, first of all, the definition of specific indicators of full treatment response and the identification of patients subpopulations that can obtain the maximum therapeutic benefit. The selection of indicators and their parametrisation according to the treatment outcome are a process carried out within the AIFA commissions, scientific-technical committee (Commisione tecnico scientifica - CTS) and price and reimbursement committee (Comitato Prezzi e Rimborso - CPR), together with the assessment of the economic implications arising from the medicinal product authorization. After that, the Commissions shall appoint the Monitoring Registers Office to implement and validate a dedicated medicine monitoring form.

Structure of AIFA Monitoring Registries

The Monitoring Registries are designed to collect both clinical and administrative data and to make an automatic check of consistency and quality of data inputted.

Each AIFA Monitoring registry is based on data collected specifically for one single indication of a medicinal product. Physicians and pharmacists are due to insert information in the following order:

1. Patient demographic data (collected by a form common to all Registries and/or therapeutic plan)
2. Eligibility and clinical data
3. Prescription data (such as medicine name, dosage etc.)
4. Eligibility and clinical data at Re-evaluation visit
5. Eligibility and clinical data at Follow-up visit
6. End of treatment data
7. Pregnancy data (for medicine requiring a Risk Management Plan)

Italy is also provided with another online tool, the web-based *Therapeutic Plan* (TP), which similarly to Monitoring Registries, can be used only by specialized and authorized physicians. The number of web-based Therapeutic Plans (TP) implemented in the period 2013-2018 amounts to 16.

As of December 31, 2018, there were on-line 179 Monitoring Registries and 16 PT web-based (including the updated versions of the same Registry).
The complete updated list of AIFA Monitoring Registries is available through the following link: http://www.aifa.gov.it/content/lista-aggiornata-dei-registri-e-dei-piani-terapeutici-web-based

AIFA Monitoring Registries Data

An analysis of AIFA monitoring registries is presented in the following tables.

Table 6.1.1. Summary data of the monitoring registries in the web platform: cumulative trend 2016-2018

	N.			Δ (%)
	2016	2017	2018	18-17
Registries	132	151	179	18.5
PT web based	16	16	16	0
Treatments	1,197,142	1,651,422	2,151,936	30.3
Patients	1,054,330	1,438,228	1,853,844	28.9

Table 6.1.2. Number of treatments in 2016-2018 for the ATC I level

ATC I Level	Patients N.			Incidence %			Δ%	
	2016	2017	2018	2016	2017	2018	17-16	18-17
A	47	58	62	0.0	0.0	0.0	23.4	6.9
B	570,532	819,036	1,097,323	48.1	50.0	51.4	43.6	34.0
C	1,469	4,074	9,436	0.1	0.2	0.4	177.3	131.6
D	1,760	1,919	2,299	0.1	0.1	0.1	9.0	19.8
H	158	183	217	0.0	0.0	0.0	15.8	18.6
J	66,622	111,819	168,077	5.6	6.8	7.9	67.8	50.3
L	274,747	346,665	413,394	23.1	21.2	19.4	26.2	19.2
M	111,186	150,005	192,406	9.4	9.2	9.0	34.9	28.3
N	6,636	7,746	8,845	0.6	0.5	0.4	16.7	14.2
R	2,326	2,511	2,666	0.2	0.2	0.1	8.0	6.2
S	151,683	193,830	238,371	12.8	11.8	11.2	27.8	23.0
V	103	125	133	0.0	0.0	0.0	21.4	6.4
Total	**1,187,269**	**1,637,971**	**2,133,229**	**100**	**100**	**100**	**38.0**	**30.2**

* The total number is not comparable with the number reported in table 6.1.1, considering that a patient may have received several treatments belonging to different categories

Table 6.1.3. Number of patients in the ATC categories (I Level) for the period 2016-2018

ICD 11	Patients N.			Incidence %			Δ%	
	2016	2017	2018	2016	2017	2018	17-16	18-17
Infectious and parasitic diseases	65,574	110,551	166,514	5.5	6.7	7.8	68.59	50.62
Tumors	263,192	329,181	389,612	22.2	20.1	18.3	25.07	18.36
Blood diseases and hematopoietic organs	3,021	3,949	4,946	0.3	0.2	0.2	30.72	25.25
Diseases of the immune system	647	912	1,173	0.1	0.10	0.1	40.96	28.62
Endocrine gland diseases of nutrition and metabolism and immune disorders	2,392	4,663	9,022	0.2	0.3	0.4	94.94	93.48
Diseases of the nervous system	7,704	9,145	10,907	0.6	0.6	0.5	18.70	19.27
Sight Diseases	171,953	221,532	273,751	14.5	13.5	12.8	28.83	23.57
Diseases of the circulatory system	567,540	815,549	1,093,929	47.8	49.8	51.3	43.70	34.13
Respiratory diseases	5,647	7,261	9,267	0.5	0.4	0.4	28.58	27.63
Diseases of the digestive system	2,317	3,085	3,287	0.2	0.2	0.2	33.15	6.55
Skin Diseases	1,760	1,919	2,299	0.1	0.1	0.1	9.03	19.80
Diseases of the musculoskeletal system and connective tissue	95,522	130,226	168,524	8.0	8.0	7.9	36.33	29.41
Total	**1,187,269**	**1,637,973**	**2,133,231**	**100.0**	**100.0**	**100.0**	**37.96**	**30.24**

Demographic characteristics of patients included in AIFA Monitoring Registries and in web based Therapeutic Plans (TPs)

The percentage distribution of treatments included in Monitoring Registries and in web - based TPs, stratified by gender and age, is reported in the following tables. These data clearly show the high prevalence of patients aged over 60 years.
The distribution of treatments by age and gender is reported and distincted for Monitoring Registries and Therapeutic Plans in tables 6.1.4 and 6.1.5. Data of Registries show that the largest number of treatments was recorded in the 70-79 years age group, in both genders, while TPs data show that the highest number of treatments can be found in the 70-79 years age group for males and in over-80s age group for females.

Table 6.1.4. Number of patients by age group and gender in the Registers (Year 2018)

Age (class)	Men		Women	
	N° Patients	Inc %	N° Patients	Inc %
<40	13,941	3.8	12,237	3.7
40-49	33,592	9.0	26,914	8.2
50-59	71,202	19.2	55,293	16.8
60-69	94,732	25.5	79,244	24.0
70-79	111,551	30.0	101,528	30.8
≥80	46,369	12.5	54,647	16.6
Total	**371,387**	**100.0**	**329,863**	**100.0**

Table 6.1.5. Number of patients by age group and gender in Therapeutic Plans (Year 2018)

Age (class)	Men		Women	
	N° Patients	Inc %	N° Patients	N° Patients
<40	5,732	1.1	4,920	0.8
40-49	13,809	2.7	10,609	1.7
50-59	38,307	7.5	32,948	5.2
60-69	100,249	19.5	98,000	15.3
70-79	186,615	36.3	221,742	34.7
≥80	168,683	32.9	270,980	42.4
Total	**513,395**	**100.0**	**639,199**	**100.0**

Chronic C hepatitis

AIFA launched the monitoring registries for the 2nd generation of Direct Antiviral Antigens (DAAs) indicated for treatment of chronic hepatitis C (CHC) in December 2014. These registries aim to monitor appropriatness of prescription and implementation of MEAs. In total there are 9 DAAs Monitoring Registries as of 31 December 2018. The active ingredients with brand name, registry activation date and genotypic target are listed below. Figure 4.1.2 shows the time serie of treatments started (cumulative datum).

Active ingredient (Brand name)	Activation date of Registry	Genotype
sofosbuvir (Sovaldi)	6 dec 2014	All genotypes
simeprevir (Olysio)	24 feb 2015	1 e 4
daclatasvir (Daklinza)	5 may 2015	1, 2, 3 e 4
ledipasvir/sofosbuvir (Harvoni)	14 may 2015	1, 3, 4
ombitasvir/paritaprevir/ritonavir (Viekirax) e dasabuvir (Exviera)	24 may 2015	1 e 4
elbasvir/grazoprevir (Zepatier)	4 feb 2017	1 e 4
sofosbuvir/velpatasvir (Epclusa)	27 apr 2017	All genotypes
glecaprevir/pibrentasvir (Maviret)	28 sep 2017	All genotypes
sofosbuvir/velpatasvir/voxilaprevir (Vosevi)	19 apr 2018	All genotypes

Figure 6.1.2. Number of treatments started (cumulative)

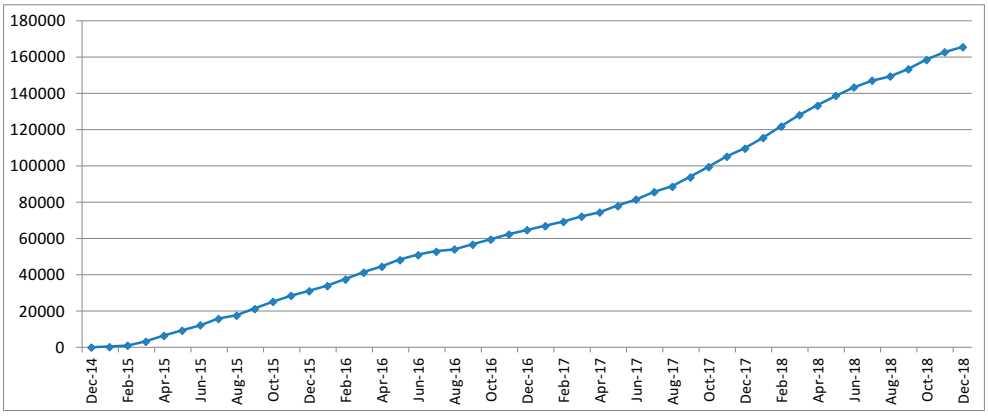


Figure 6.1.3. Number of treatments undertaken up to 2018 by criterion

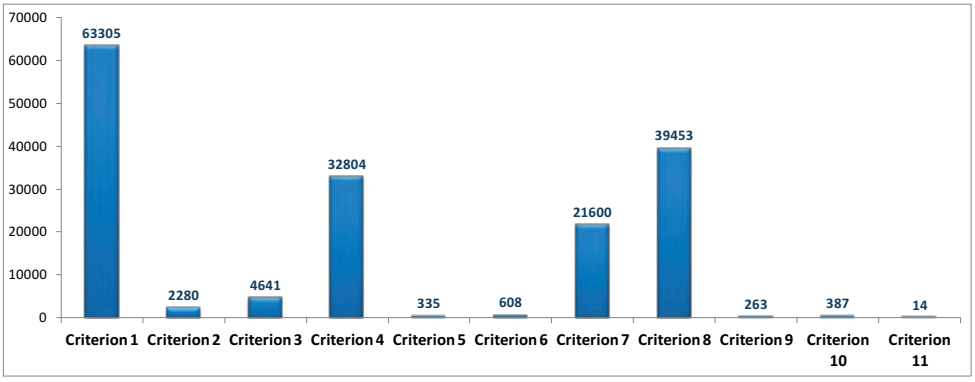


Figure 6.1.4. Monthly trend of treatments started up to 2018 by criteria (criteria 1, 4, 7 and 8)

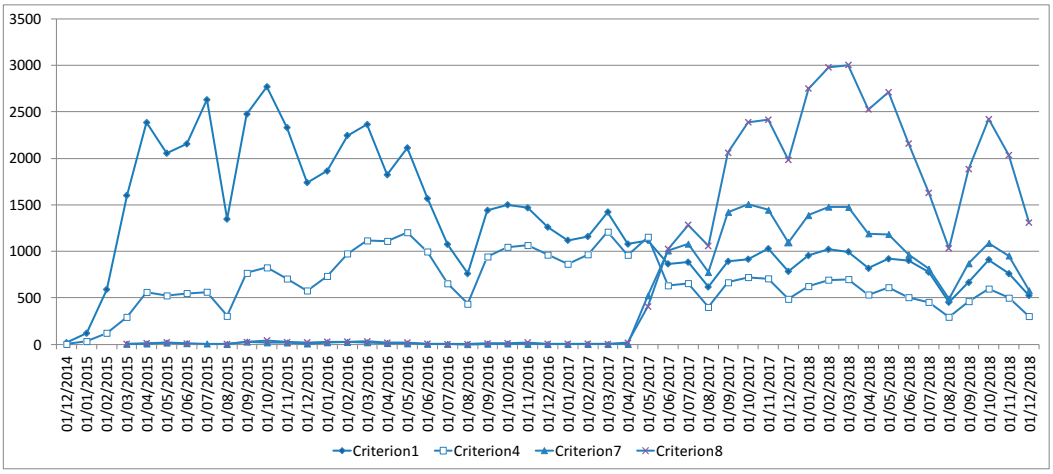
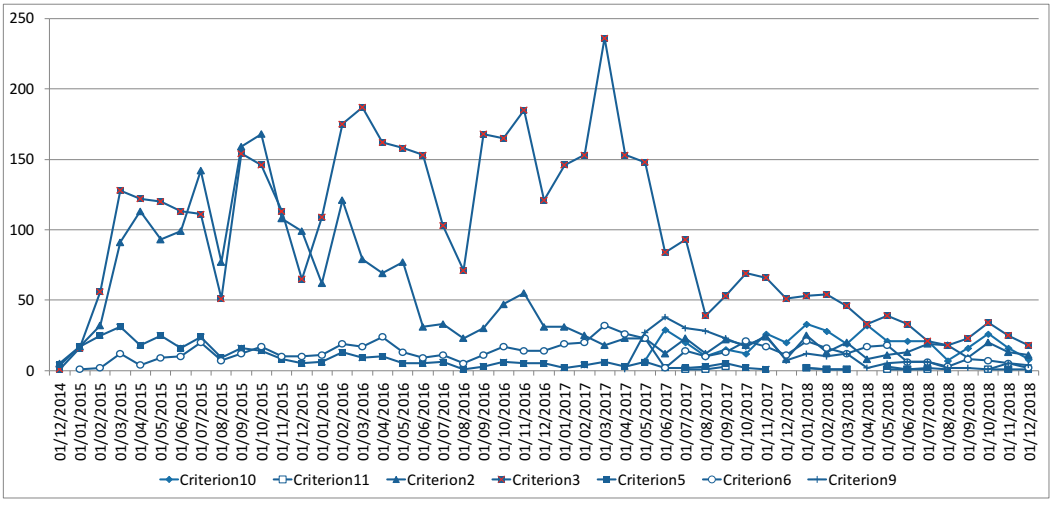


Figure 6.1.5. Monthly trend of treatments started up to 2018 by criteria (criteria 2, 3, 5, 6, 9, 10 and 11)



Novel oral anticoagulants (NOACs)

In Italy, the novel oral anticoagulants (NOACs), dabigatran, rivaroxaban, apixaban and edoxaban, have been reimbursed since 2013 for the prevention of cerebral stroke and systemic embolism in patients with non-valvular atrial fibrillation (FANV), and for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence of DVT and PE in adults. Dabigatran was the first NOAC available (16/06/2013), followed by rivaroxaban (13/09/2013) and apixaban (07/01/2014) while edoxaban was the last reimbursed (09/09/2016).

Tables of this paragraph report data related to the following therapeutic indications "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack".

In particular, in Italy, in order to be enrolled in the NOACs registries a patient was required to be older than 18 years old and to meet one of the following main criteria:

- CHA2DS2VASc and the HAS-BLED scores ≥1 and >3, respectively (or both >3 for rivaroxaban);
- previous treatment with VKA with a time of therapeutic range (TTR) ≤70% (60% for rivaroxaban);
- anticoagulant treatment with VKA not feasible for objective difficulties to carry out INR monitoring;
- patients undergoing cardioversion (just for rivaroxaban as of December 2016).

Table 6.1.7. Baseline characteristics of patients treated with NOACs at the date of 31 December 2018

	Apixaban		Dabigatran		Edoxaban		Rivaroxaban		Total	
	N	%	N	%	N	%	N	%	N	%
Patients	294,721	30.7	249,976	26.1	97,175	10.1	317,359	33.1	959,231	100
Age, aa median (range)	79.6 (18-109)		77.1 (18-102)		79.4 (19-105)		77.9 (18-106)		78 (18-109)	
<65	23,434	8.0	31,038	12.4	8,725	9.0	37,823	11.9	101,020	10.5
65-74	67,315	22.8	71,850	28.7	22,572	23.2	82,501	26.0	244,238	25.5
75-84	130,117	44.1	108,876	43.6	41,250	42.4	136,718	43.1	416,961	43.5
≥85	73,855	25.1	38,212	15.3	24,628	25.3	60,317	19.0	197,012	20.5
Gender										
Women	154,919	52.6	115,954	46.4	51,428	52.9	156,072	49.2	478,373	49.9
Men	139,802	47.4	134,022	53.6	45,747	47.1	161,287	50.8	480,858	50.1
CHA_2DS_2CASc Score										
0	1,119	0.4	1,720	0.7	454	0.5	3,245	1.0	6,538	0.7
1	8,790	3.0	11,370	4.5	3,513	3.6	14,513	4.6	38,186	4.0
2	28,555	9.7	31,957	12.8	10,865	11.2	37,504	11.8	108,881	11.4
3	60,369	20.5	57,928	23.2	21,467	22.1	69,499	21.9	209,263	21.8
4	82,587	28.0	66,938	26.8	28,014	28.8	86,949	27.4	264,488	27.6
5	58,900	20.0	43,411	17.4	18,200	18.7	57,384	18.1	177,895	18.5
6	34,197	11.6	23,426	9.4	9,364	9.6	30,559	9.6	97,546	10.2
7	14,684	5.0	9,856	3.9	3,968	4.1	12,908	4.1	41,416	4.3
8	4,700	1.6	2,902	1.2	1,143	1.2	4,072	1.3	12,817	1.3
9	820	0.3	468	0.2	187	0.2	726	0.2	2,201	0.2
10	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
HAS BLED Score										
0	3,931	1.3	5,362	2.1	1,645	1.7	7,797	2.5	18,735	2.0
1	38,372	13.0	37,450	15.0	15,737	16.2	47,525	15.0	139,084	14.5
2	120,327	40.8	96,572	38.6	44,065	45.3	131,971	41.6	392,935	41.0
3	82,426	28.0	70,306	28.1	22,996	23.7	83,358	26.3	259,086	27.0
4	41,424	14.1	34,213	13.7	10,853	11.2	39,276	12.4	125,766	13.1
5	7,262	2.5	5,407	2.2	1,672	1.7	6,522	2.1	20,863	2.2
6	881	0.3	589	0.2	178	0.2	756	0.2	2,404	0.3
7	89	0.0	60	0.0	24	0.0	115	0.0	288	0.0
8	8	0.0	11	0.0	4	0.0	33	0.0	56	0.0
9	1	0.0	6	0.0	1	0.0	6	0.0	14	0.0
Comorbidity										
Heart failure / left ventricular dysfunction	88,982	30.2	64,121	25.7	27,504	28.3	92,169	29.0	272,776	28.4
Hypertension	253,551	86.0	216,611	86.7	83,160	85.6	273,373	86.1	826,695	86.2
Diabetes mellitus	58,854	20.0	49,641	19.9	18,115	18.6	61,485	19.4	188,095	19.6
Previous Stroke	56,385	19.1	46,054	18.4	14,296	14.7	50,576	15.9	167,311	17.4
Vascular diseases	81,210	27.6	67,673	27.1	24,589	25.3	85,743	27.0	259,215	27.0
Impaired renal function	22,405	7.6	7,229	2.9	6,603	6.8	16,797	5.3	53,034	5.5
Impaired liver function	2,894	1.0	2,674	1.1	820	0.8	2,655	0.8	9,043	0.9
History of bleeding	40,122	13.6	26,775	10.7	10,089	10.4	29,445	9.3	106,431	11.1

	Apixaban		Dabigatran		Edoxaban		Rivaroxaban		Total	
	N	%	N	%	N	%	N	%	N	%
Previous treatment with AVK	75,951	25.8	88,436	35.4	20,066	20.6	92,915	29.3	277,368	28.9
Labile INR	55,225	18.7	61,976	24.8	14,006	14.4	68,290	21.5	199,497	20.8
Previous treatment with NAO	28,050	9.5	6,896	2.8	10,978	11.3	17,888	5.6	63,812	6.7

PCSK-9 inhibitors for the treatment of hypercholesterolaemia

Evolocumab and alirocumab have been reimbursed for the treatment of hypercholesterolemia since 2017. These are monoclonal antibodies that inactivate proprotein convertase subtilsin-kexin type 9 (PCSK-9) involved in the recycling of LDL receptors to the cell surface.

In Italy, in the context of primary hypercholesterolaemia (heterozygote familial and non-familial) or mixed dyslipidaemia, PCSK9 inhibitors are reimbursed according to the following prescribing criteria:

In adult patients aged 12-80 years who do not reach pre-defined LDL-C levels despite at least 6 months of prior combination therapy with maximum tolerated dose of high-potency statin agent and ezetimibe or ezetimibe monotherapy in case of statin-intolerant patients both in primary and secondary CVD prevention:
- Primary CVD prevention in patients with familial heterozygote hypercholesterolaemia (HeFH) and LDL-C ≥130mg/dL;
- Secondary CVD prevention in patients with HeFH or non-familial hypercholesterolaemia or mixed dyslipidaemia with LDL-C ≥100mg/dL.

Then evolocumab, consistently with the more extensive authorized indication, is also reimbursed in homozygous familial hypercholesterolemia for patients aged 12-80 years.

Tables of this paragraph report data related to reimbursed therapeutic indications.

Table 6.1.9. Baseline characteristics of patients treated with PCSK-9 inhibitors

Medicine	Alirocumab	Evolocumab	TOTAL
	N (%)	N (%)	N (%)
Total patients	3,056 (43.3)	4,000 (56.7)	7,056
Women	1,037 (33.9)	1,377 (34.4)	2,414 (34.2)
Men	2.019 (66.1)	2,623 (65.6)	4,642 (65.8)
Median age (range)	62 (19-81)	62 (18-83)	62 (18-83)
Previous treatment with anti-pcsk9	27 (0.9)	23 (0.6)	50 (0.7)
Type of hypercholesterolemia			
HoFH*	0	53 (1.3)	53 (0.8)
HeFH	921 (30.1)	1,040 (26.0)	1,961 (27.8)
noFH	1,384 (45.3)	1,937 (48.4)	3,321 (47.1)
MD	751 (24.6)	970 (24.3)	1,721 (24.4)
Use in CVD prevention			
Primary prevention	475 (15.5)	572 (14.3)	1,047 (14.8)
Secondary prevention	2,581 (84.5)	3,428 (85.7)	6,009 (85.2)
Relevant comorbidity §			
Cardiovascular disease	2,133 (69.8)	2,876 (71.9)	5,009 (71.0)
Cerebrovascular disease	267 (8.7)	306 (7.7)	573 (8.1)
Peripheral arterial disease	480 (15.7)	662 (16.6)	1,142 (16.2)
Diabetes mellitus	631 (20.6)	791 (19.8)	1,422 (20.2)
Hypertension	1,842 (60.3)	2,604 (65.1)	4,446 (63.0)
None	316 (10.3)	332 (8.3)	648 (9.2)
Smoking habit			
Present	412 (13.5)	555 (13.9)	967 (13.7)
Previous	1,059 (34.7)	1,531 (38.3)	2,590 (36.7)
Absent	1,585 (51.9)	1,914 (47.9)	3,499 (49.6)
Use of statins			
Intolerance to statins	1,608 (52.6)	2,144 (53.6)	3,752 (53.2)
Basal statin treatment^:			
Atorvastin	701 (22.9)	963 (24.1)	1,664 (23.6)
Rosuvastatin	747 (24.4)	881 (22.0)	1,628 (23.1)

HoFH= Homozygous familial hypercholesterolemia; HeFH= familial hypercholesterolemia heterozygous
noFH= Non-familial hypercholesterolemia; MD= mixed dyslipidemia.
* only evolocumab has indication in the HoFH; § you can select multiple items
^ for 12 treatments there is no information on the statins used in combination

Anti-angiogenic agents for intravitreal use

The treatment of exudative age-related macular degeneration (AMD) involves the use of intravitreal (IVT) anti-angiogenic agents (VEGF inhibitors). Tables of this paragraph regard the ranimizumab, aflibercept, pegaptanib, that all authorized for such indication and bevacizumab that, although not authorized for the above indication, is employed for the treatment of the age-related exudative macular degeneration since it is included for this indication in the list pursuant to Law 648/96.
In particular, the following information refers to active Monitoring Registries starting from 25 February 2013 for pegaptanib, from 07 March 2013 for ranibizumab, from 28 June 2014 for bevacizumab and from 15 April 2014 for aflibercept.

Table 6.1.11. Basic patient characteristics at start of treatment with anti VEGF

	Aflibercept		Bevacizumab (L. 648/96)		Pegaptanib		Ranibizumab		Total	
	N	%	N	%	N	%	N	%	N	%
Patients	34,814	25.3	25,879	18.8	717	0.5	75,977	55.3	137,387	100.0
Age, aa median (range)	78 (50-104)		80 (50-103)		80 (51-100)		78 (50-105)		78 (50-105)	
50 - 64	3,393	9.7	1,688	6.5	36	5.0	7,758	10.2	12,875	9.4
65 - 74	9,414	27.1	6,017	23.3	146	20.4	20,204	26.6	35,781	26.0
75 - 84	15,847	45.5	12,448	48.1	359	50.1	34,216	45.0	62,870	45.8
≥ 85	6,160	17.7	5,726	22.1	176	24.5	13,799	18.2	25,861	18.8
Gender										
Women	19,620	56.4	15,279	59.0	354	49.4	43,379	57.1	78,632	57.2
Men	15,194	43.6	10,600	41.0	363	50.6	32,598	42.9	58,755	42.8
No. of treatments (eyes)	59,893	32.6	35,137	19.1	1,063	0.6	87,593	47.7	183,686	100.0
Examination Executed										
OCT	48,896	81.6	29,438	83.8	1,030	96.9	68,997	78.8	148,361	80.8
FAG/FAG + ICG	10,997	18.4	5,699	16.2	33	3.1	18,592	21.2	35,321	19.2
Retinal thickness, mm (1 and 3 quartiles)	354 (300-428)		350 (300-424)		335 (290-400)		355 (300-432)		352 (300-430)	
Subretinal fluid										0.0
Present	42,754	87.4	25,550	86.8	865	84.0	59,730	86.6	128,899	86.9
Disputable	2,595	5.3	1,961	6.7	78	7.6	3,966	5.7	8,600	5.8
Absent	3,506	7.2	1,907	6.5	87	8.4	5,246	7.6	10,746	7.2
Presence of under or intraretinal bleeding										-
Present	5,922	53.9	3,109	54.6	25	75.8	10,207	54.9	19,263	54.5
Disputable	1,053	9.6	627	11.0	1	3.0	1,550	8.3	3,231	9.1
Absent	4,008	36.4	1,961	34.4	7	21.2	6,825	36.7	12,801	36.2
Leakage										3.0
Present	10,753	97.8	5,604	98.3	32	97.0	18,122	97.5	34,511	97.7
Absent	230	2.1	93	1.6	1	3.0	460	2.5	784	2.2
Visual Acuity (Decimal Scale)										
Not valorized	4,740	7.9	2,143	6.1	-	0.0	7,046	8.0	13,929	7.6
Severe visual reduction (1-3)	35,408	59.1	22,322	63.5	785	73.8	55,160	63.0	113,675	61.9

	Aflibercept		Bevacizumab (L. 648/96)		Pegaptanib		Ranibizumab		Total	
	N	%	N	%	N	%	N	%	N	%
Moderate visual reduction (4-6)	15,075	25.2	8,032	22.9	225	21.2	19,372	22.1	42,704	23.2
Slight visual reduction (7-10)	4,670	7.8	2,640	7.5	53	5.0	6,015	6.9	13,378	7.3
Previous treatment with anti-VEGF IV	17,443	29.1	5,168	14.7	297	27.9	3,297	3.8	26,205	14.3
Monocular treatment	47,277	78.9	28,193	80.2	1,049	98.7	71,841	82.0	148,360	80.8
Biocular treatment	6,308	10.5	3,472	9.9	7	0.7	7,876	9.0	17,663	9.6
Average number (median) of treatments in the first 12 months	**3.8 (4)**		**3.4 (3)**		**2.6 (2)**		**3.4 (3)**		**3.5 (3)**	

*Demographic characteristics refer to naïve patients at the beginning of the first treatment with anti VEGF IVT drugs

6.2 Financial impact of Managed Entry Agreements (MEAs)

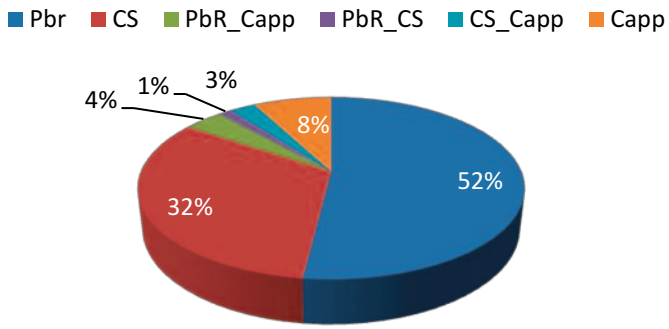
Italy has been one of the first European Country to adopt Managed Entry Agreements (MEAs), in order to foster access to new medicines with high cost and high level of uncertainty on clinical benefit at launch. AIFA can negotiate with pharmaceutical companies different types of MEAs: at patient level 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 motitored through AIFA Monitoring Registries (Patient level):

MEAs that are monitored through AIFA Monitoring Registries are classified according to an international taxonomy, 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 for 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.

Figure 6.2.1. Percentage distribution of the types of MEAs (as of 31/12/2018)

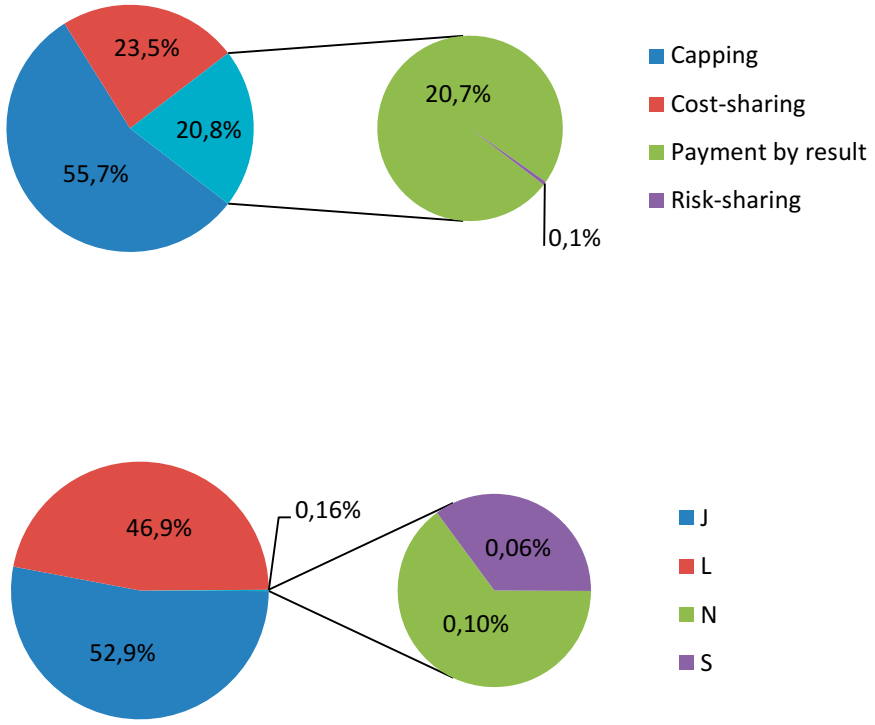


The distribution of each MEA for 2018 is reported in Figure 6.2.1. The most applied model is the payment by result agreement, accounting for 100% of the outcome-based agreements. In fact, no risk sharing model was implemented in 2018. This finding reflects the AIFA directive of refunding the treatment costs only for responder patients. The cost sharing and capping agreements rank below. The contextual 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.

At a national level, the total reimbursement issuing from implementation of MEAs amounted to 172,746,483 euros in 2018. The 79.2% of this value derives from implementation of financial based schemes: 55.7% is due to Capping agreements and 23.5% is due to Cost-sharing agreements. The payment by result and risk-sharing agreements account for 20.8% of the total reimbursement.

The 2018 reimbursement percentages for the ATC level are instead spread over 3 categories: 52.9% of the reimbursement is due to general antimicrobials for systemic use (J), 46.9% to antineoplastic medicines and immunomodulators (L) and 0.2% to medicines of the nervous system (N).

Figure 6.2.2. Payback 2018, percentages by agreement and for the I ATC level



Managed Entry Agreements monitored through information flows collecting data on NHS reimbursed expenditure and consumption (population level).

These are financial agreements which can be mainly classified into: a) spendig caps by product and b) price/volume agreements.

a) Spending caps by product are used to promote the appropriate use of medicines. When an expenditure cap is settled, the Price and Reimbursement Committee finalizes the agreement with the pharmaceutical company, both in relation to the price of the medicine and in relation to the maximum sustainable NHS expenditure in the first 12/24 months of marketing. This parameter is based on the estimated number of patients expected in Italy for the reimbursed therapeutic indication, according to

epidemiological data. Consequently, at the end of the period defined by the contract, if the monitoring of pharmaceutical expenditure shows that the amount is higher than the agreed ceiling, AIFA communicates to the pharmaceutical company the value of the pay-back shelf for the benefit of Italian regions.

b) Price/volume agreements provide for progressive discounts on the price of a medicine based on the volumes achieved during the contract period. These discounts can be obtained through a reduction in the medicine price or, if provided for in the agreement, through a payback to the Regions.

Moreover, AIFA, in some cases, can negotiate confidential discounts with pharmaceutical companies which, however, do not entail a payback for the Regions, but involve a direct price reduction in favour of NHS healthcare facilities. It should be noted that the aforementioned confidentiality is only limited to the discount and not to the presence or absence of this type of negotiating agreement.

The Table 6.2.2 reports medicines which were subject to verification procedures for the application of spending caps and price-volume agreements and obtained reimbursement during 2018. Overall 15 medical products were involved, for a total of € 196.4 million. The reimbursements obtained due to the implementation of product spending caps agreements amounted to € 57,1 million, and the reimbursements obtained as consequence of the implementation of price/volume agreements amounted to € 139,3. In particular a total amount of 106.6 million euros was paid by pharmaceutical companies for Class A medical products and 89.8 million euros for Class H medicines.

Table 6.2.2 List of medicinal products subject to verification procedures for the application of spending caps and price-volume agreements and obtained reimbursement

Medicinal product	Official Italian Gazzette	Type of agreement
Tafinlar	Serie Generale n.37 del 14-02-2018	Spending cap
Lyrica	Serie Generale n.58 del 10-03-2018	Spending cap
Plenadren	Serie Generale n.69 del 23-03-2018	Spending cap
Opdivo	Serie Generale n.92 del 20-04-2018	Price/volume
Striverdi Respimat	Serie Generale n.127 del 04-06-2018	Price/volume
Perjeta	Serie Generale n.140 del 19-06-2018	Price/volume
Xadago	Serie Generale n.139 del 18-06-2018	Spending cap
Epclusa (P/V Conguaglio)	Serie Generale n. 139 del 18-06-2018	Price/volume
Nplate	Serie Generale n.154 del 05-07-2018	Spending cap
Opdivo	Serie Generale n.176 del 31-07-2018	Price/volume
Kalydeco	Serie Generale n.199 del 28-08-2018	Spending cap
Grazax	Serie Generale n.223 del 25-09-2018	Spending cap
Lojuxta	Serie Generale n.237 del 11-10-2018	Spending cap
Maviret (P/V Conguaglio)	Serie Generale n.254 del 31-10-2018	Price/volume
Oralair	Serie Generale n.284 del 06-12-2018	Spending cap

Section 7

Innovative medicines

7.1 Innovative medicines

The assessment and definition of pharmaceutical innovation is a complex and dynamic process. The complexity in defining criteria of pharmaceutical innovation is the result of the heterogeneity of available treatment options, as well as of the mutable perception of priorities and expectations towards a new medicine in relation to the health and social context. The dynamism of pharmaceutical innovation evaluation mainly depends on the continuous evolution of scientific knowledge and the consolidation of scientific evidence.
The Italian Medicines Agency (AIFA), which has the dual function of a regulatory and reimbursement authority, has recently established new criteria to define innovative medicinal products (AIFA Determination n. 519/2017, 31 March 2017, updated by the determination n. 1535/2017, 12 September 2017). Indeed, the decision making process to grant the innovative status is based on the evaluation of the unmet medical need, the added therapeutic value compared to existing therapeutic options and the overall quality of clinical evidence, which is assessed based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation, http://www.gradeworkinggroup.org/) system. Following this evaluation, if a medicinal product is granted the status of "full innovativeness" for a specific therapeutic indication, its manufacturer can access dedicated funds amounting yearly to 500 million Euros each, depending on the type of medicine (one fund for oncology, the other for all other innovative medicinal products). Alternatively, the product can be granted the status of "conditional innovativeness" which allows immediate access to all Regional formularies, with no additional re-assessments at local level. The third possible outcome is that 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 reconsidered in the case of new evidences becoming available. If it is not confirmed the associated benefits shall lapse, with the consequence of starting a new negotiation of price and reimbursement.
In order to guarantee the maximum level of transparency, a full report explaining the rationale for the Agency Committee's decision is made publicly available on AIFA's website (https://www.aifa.gov.it/web/guest/farmaci-innovativi), as of January 2018.

7.2 Expenditure and consumption of innovative medical products

The following tables show an analysis of expenditure and consumption for innovative medical products in the period 2015-2018. For each medical product, expenditure and consumption were considered only for the period of effectiveness of the status of innovation (innovativeness and conditioned innovation). The data refer to the total value of expenditure and consumption of the medicinal product and not only to the indication to which the innovation was recognized in case of several indications reimbursed. Table 7.2.1 lists the medicines considered in the analysis and the respective dates of effectiveness and expiry of the innovation requirement.

Table 7.2.1. List of innovative medicines in the period 2015-2018

ATC IV	Medicine	Active ingredient	Class	Effective date (G.U.)	Expiry date Requirement
L01CD01	Abraxane	nab paclitaxel	H	21/02/2015	20/02/2018
L01XE36	Alecensa	alectinib	H	01/08/2018	31/01/2020
L01XC31	Bavencio	avelumab	H	25/09/2018	24/09/2021
L01XC26	Besponsa	inotuzumab ozogamicin	H	08/06/2018	07/06/2021
L01XC19	Blincyto	blinatumomab	H	24/02/2017	23/02/2020
J05AP07	Daklinza	daclatasvir	A	05/05/2015	04/05/2018
L01XC24	Darzalex	daratumumab	H	19/04/2018	18/04/2019
D11AH05	Dupixent	dupilumab	H	08/09/2018	07/09/2021
C09DX04	Entresto	sacubitril/valsartan	A	12/03/2017	11/03/2020
J05AP55	Epclusa	sofosbuvir/velpatasvir	A	27/04/2017	26/04/2020
J05AP09	Exviera	dasabuvir	A	24/05/2015	23/05/2018
B02BX06	Hemlibra	emicizumab	A	07/12/2018	06/12/2021
L04AB04	Humira	adalimumab	H	23/05/2018	22/05/2021
L01XE33	Ibrance	palbociclib	H	23/12/2017	22/12/2020
L04AC08	Ilaris	canakinumab	H	26/09/2018	25/09/2021
L01XE27	Imbruvica	ibrutinib	H	05/01/2016	06/09/2021*
L04AX06	Imnovid	pomalidomide	H	20/08/2015	19/08/2018
R07AX02	Kalydeco	ivacaftor	A	05/05/2015	04/05/2018
L01XC18	Keytruda	pembrolizumab	H	11/05/2016	11/05/2019
L01XE42	Kisqali	ribociclib	H	25/09/2018	24/09/2021
L01XC27	Lartruvo	olaratumab	H	05/08/2017	04/08/2020
J05AP57	Maviret	glecaprevir/pibrentasvir	A	28/09/2017	26/04/2020
J05AP05	Olysio	simeprevir	A	27/06/2015	23/02/2018
L01XC17	Opdivo	nivolumab	H	25/03/2016	26/09/2021*
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	24/05/2021
L01XE39	Rydapt	midostaurina	H	17/08/2018	16/08/2021
M09AX07	Spinraza	nusinersen	H	28/09/2017	27/09/2018
L01XE21	Stivarga	regorafenib	A	26/09/2018	25/09/2021
L03	Strimvelis	cellule autologhe CD34+	H	16/08/2016	15/08/2019

ATC IV	Medicine	Active ingredient	Class	Effective date (G.U.)	Expiry date Requirement
L01XC32	Tecentriq	atezolizumab	H	15/07/2018	24/03/2019
L01XX52	Venclyxto	venetoclax	H	12/08/2017	11/08/2020
J05AP53	Viekirax	ombitasvir/paritaprevir/ritonavir	A	24/05/2015	23/05/2018
J05AP56	Vosevi	sofosbuvir/velpatasvir/voxilaprevir	A	19/04/2018	26/04/2020
L01XE16	Xalkori	crizotinib	H	11/04/2015	10/04/2018
V10XX03	Xofigo	radio ra 223 dicloruro	H	11/06/2015	10/06/2018
L01XX54	Zejula	niraparib	H	21/09/2018	20/09/2021
J05AP54	Zepatier	elbasvir/grazoprevir	A	04/02/2017	03/02/2020
L01XX47	Zydelig	idelalisib	H	11/09/2015	10/09/2018

Table 7.2.2. Expenditure and consumption trends for innovative medicines (years 2015-2018) purchased by public health facilities

	2015	2016	2017	2018	Δ% 18-17
Innovative expenditure*	2,226	2,636	1,635	1,629	-0.4
Inc. % NHS expenditure	10.1	11.7	7.4	7.4	
DDD*	9.2	12.0	13.4	21.7	61.8
Inc. % DDD NHS	0.03	0.05	0.05	0.09	

* million. Note: The expense does not take into account the paybacks paid by pharmaceutical companies for the application of conditional reimbursement agreements

Table 7.2.3. Expenditure and consumption for innovative medicines (innovation and conditioned innovation) purchased by public health facilities for medicinal specialties (years 2016-2018)

Medicine	2016			2017			2018		
	Expen-diture *million*	DDD *thousand*	Inc. % **	Expen-diture *million*	DDD *thousand*	Inc. % **	Expen-diture *million*	DDD *thousand*	Inc. % **
Abraxane	22.7	600.8	0.9	23.1	650.4	1.4	4.3	114.2	0.3
Blincyto	-	-	-	4.0	1.9	0.2	8.5	4.1	0.5
Daklinza	189.5	1,018.9	7.2	56.9	477.9	3.5	0.0	0.1	0.0
Entresto	-	-	-	5.2	1,193.4	0.3	20.8	5,046.6	1.3
Epclusa	-	-	-	156.7	1,423.8	9.6	137.3	1,737.7	8.4
Exviera	10.8	588.7	0.4	4.5	488.0	0.3	0.2	18.1	0.0
Imbruvica	38.2	245.8	1.5	81.4	522.6	5.0	111.6	757.2	6.8
Imnovid	34.1	111.5	1.3	38.3	122.6	2.3	24.4	81.5	1.5
Kalydeco	31.0	43.3	1.2	28.9	42.4	1.8	11.1	16.5	0.7
Keytruda	11.1	46.3	0.4	61.2	478.3	3.7	194.3	2,010.7	11.9
Lartruvo	-	-	-	0.9	3.4	0.1	10.1	37.0	0.6
Maviret	-	-	-	26.5	189.5	1.6	216.4	1,596.8	13.3
Olysio	5.9	49.1	0.2	0.5	4.8	0.0	0.0	0.0	0.0
Opdivo	62.0	286.5	2.4	181.7	1,009.5	11.1	266.6	1,529.9	16.4
Revlimid^	184.6	1,208.1	7.0	149.2	1,144.0	9.1	127.0	1,065.7	7.8
Spinraza	-	-	-	8.0	12.5	0.5	74.6	174.1	4.6
Venclyxto	-	-	-	0.9	5.2	0.1	10.0	54.1	0.6
Viekirax	146.0	685.8	5.5	57.4	542.6	3.5	2.2	20.4	0.1
Xalkori	19.2	113.9	0.7	24.3	141.2	1.5	22.6	144.8	1.4
Xofigo	6.1	2.1	0.2	7.9	2.7	0.5	1.1	0.4	0.1
Zepatier	-	-	-	87.7	751.8	5.4	50.0	607.7	3.1

Medicine	2016			2017			2018		
	Expen-diture *million*	DDD *thousand*	Inc. % **	Expen-diture *million*	DDD *thousand*	Inc. % **	Expen-diture *million*	DDD *thousand*	Inc. % **
Zydelig	10.7	100.2	0.4	12.6	115.1	0.8	10.3	93.3	0.6
Xiapex*	0.2	0.2	0.0	-	-	-	-	-	-
Yervoy*	7.4	12.5	0.3	-	-	-	-	-	-
Zytiga*	26.9	267.2	1.0	-	-	-	-	-	-
Harvoni^	940.1	1,763.9	35.7	252.1	473.0	15.4	-	-	-
Sovaldi^	689.6	1,423.2	26.2	221.1	456.3	13.5	-	-	-
Adcetris^	23.0	58.8	0.9	11.3	34.3	0.7	-	-	-
Perjeta^	78.3	550.0	3.0	49.2	343.3	3.0	-	-	-
Kadcyla^	57.4	246.0	2.2	42.6	182.2	2.6	-	-	-
Sirturo^	0.6	5.7	0.0	0.1	1.3	0.0	-	-	-
Tivicay^	40.4	2,616.9	1.5	40.9	2,617.0	2.5	-	-	-
Alecensa	-	-	-	-	-	-	6.2	35.6	0.4
Bavencio	-	-	-	-	-	-	0.3	1.7	0.0
Besponsa	-	-	-	-	-	-	1.5	2.1	0.1
Darzalex	-	-	-	-	-	-	58.3	312.1	3.6
Dupixent	-	-	-	-	-	-	1.0	30.4	0.1
Humira	-	-	-	-	-	-	152.4	5,111.1	9.4
Ibrance	-	-	-	-	-	-	75.0	912.5	4.6
Ilaris	-	-	-	-	-	-	6.4	37.7	0.4
Kisqali	-	-	-	-	-	-	0.9	12.1	0.1
Oxervate	-	-	-	-	-	-	3.6	13.1	0.2
Rydapt	-	-	-	-	-	-	1.2	2.3	0.1
Stivarga	-	-	-	-	-	-	2.1	26.1	0.1
Tecentriq	-	-	-	-	-	-	4.1	39.8	0.2
Vosevi	-	-	-	-	-	-	10.8	79.7	0.7
Zejula	-	-	-	-	-	-	1.4	7.0	0.1
Total	**2,635.6**	**12,045.4**	**100.0**	**1,635.3**	**13,431.0**	**100.0**	**1,628.6**	**21,734.0**	**100.0**

** calculated on the total expense of innovative drugs; * innovation requirement expired in 2016; ^ innovation requirement expired in 2017. Note: Expenditure does not take into account paybacks paid by pharmaceutical companies for the application of conditional reimbursement agreements.

Table 7.2.5. List of medicines accessing to the Innovative Funds as of 31 December 2018 (2017 Budget Law)

Innovative non-oncologic	Innovative oncologic
Olysio	Abraxane
Kalydeco	Zydelig
Daklinza	Imbruvica
Exviera	Opdivo
Viekirax	Keytruda
Epclusa	Imnovid
Zepatier	Darzalex
Strimvelis*	Tecentriq
Spinraza	Alecensa
Maviret	Rydapt
Oxervate	Qarziba*
Vosevi	
Dupixent	
Prevymis	
Hemlibra	

*Data that are not in the traceability flow. As far as Strimvelis is concerned, the drug is dispensed by an Accredited Private Healthcare Facility.

Section 8

Orphan drugs

National Report
on Medicines
use in Italy
Year 2018

Orphan drugs

"Orphan" drugs are medicines used for the diagnosis, prevention and treatment of rare diseases. In Europe, a disease is considered rare when it affects no more than five people per 10.000 inhabitants. Generally, "orphan" drugs require research and development investments that may not be profitable for the manufacturer. For this reason, orphan medicinal products have been excluded from the pay-back procedures foreseen under the hospital pharmaceutical expenditure regulation (Article 15, paragraph 8, points i and i-bis of Law no. 135 of 2012, amended by Law no. 147/2013-2014 Stability Act).
Starting in 2019, in accordance with Article 1, paragraphs 575-584 of Law no. 145 of 2018 (2019 Stability Act), that modifies what established by the 2014 Stability Act, medicines benefitting from the exclusion from the pay-back procedures will be the only orphan drugs authorized by the EMA, excluding the so-called Orphan Likes medicines, the medical products included in the Orphanet register and all the medicines that were authorized as orphans by the EMA but that have exhausted the period of market exclusivity.
To date, more than seven thousand rare diseases have been discovered, thus representing a significant social issue, which involves millions of people: according to estimates, patients affected in Europe are over thirty million, about 3 million of which in Italy.

European legislation

The first regulation concerning orphan medicinal products, the *Orphan Drug Act* was introduced in USA in 1983. In the European Union, the issue of orphan drugs was addressed by Regulation (EC) no. 141 of 2000 of the European Parliament and of the Council of the European Union and later Regulation (EC) no. 847 of 2000 of the European Parliament and of the Council. The aforementioned regulations define criteria and procedures for orphan drug designation, and provide for awards and incentives. The orphan status is granted by the Committee of Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA). The marketing authorization (MA) of an orphan medicinal product is achieved through a centralised procedure. In some cases, for the purpose of accelerating marketing of an orphan product, a medicine may be granted an authorisation, even though the clinical trials have not been completed yet. Such authorisation under conditional approval is eventually renewed on an annual basis. In order to grant a conditional marketing authorization for a product, the following conditions are to be respected:

- Positive benefit/risk ratio;
- The applicant shall be later required to provide more comprehensive clinical data;
- Fulfilment of an unmet medical need;
- Benefits for public health due to the immediate availability outweigh risks associated to the lack of additional data.

Once the evaluation is completed, if the EMA's Committee for Medicinal Products for Human Use (CHMP) issues a favourable opinion as to whether the authorization is granted, the European Commission formally issues the authorisation. Furthermore,

pursuant to Article 14, paragraph 8 of EC Regulation n. 726 of 2004, in exceptional circumstances (approval under exceptional circumstances) and following consultation with the applicant, the authorisation may be granted due to a requirement for the applicant to introduce specific procedures, in particular concerning safety of the medicinal product, notification to the competent authorities of any adverse reaction relating to its use, and action to be taken (when the indications for which the product is intended are encountered so rarely that the applicant cannot be reasonably expected to provide comprehensive evidence).
Continuation of the authorisation shall be linked to the annual reassessment of these conditions.

Italian legislation

In order to facilitate orphan drugs access, several regulations were issued. In particular, the 2014 Stability Act introduced a mechanism of economic protection for marketing authorization holders (MAHs) of orphan medicinal products. Indeed, when the national pharmaceutical expenditure ceiling is exceeded, MAHs of orphan medicinal products are excluded from the payback mechanism, which is conversely distributed among all other MAHs in proportion to their pharmaceutical sales volumes. Pursuant to Article 15, paragraph 8, points i, and i-bis of Decree-Law no. 95 of 2012, converted with amendments into Law no. 135 of 2012, then modified by Article 1, paragraph 228, of Law no. 147 of 2013, AIFA's Board of Directors (on February 27, 2014) approved the list of orphan medicinal products for the treatment of rare diseases and the related chosen criteria, as prescribed by law. On the basis of this list, AIFA identifies orphan medicinal products which will benefit from the provisions of 2013 hospital pharmaceutical expenditure legislation. The list was approved by AIFA's Board of Directors and was drafted on the basis of the following criteria:

1. medicines qualified as orphan products in accordance with Regulation (EC) no. 141 of 2000 of the European Parliament and of the Council of December 16, 1999 (including orphan drugs, whose 10 years market exclusivity expired) and Article 8 of Regulation December 31, 2013;
2. medicines, referring to paragraph 1, are included in the list only if they hold a marketing authorisation in Italy. The following are therefore excluded:
   a. orphan medicinal products not reimbursed by the NHS as referred to points c) and c-bis of Article 8, paragraph 10, of Law n. 537 of December 24, 1993;
   b. orphan drug packages reimbursed by the NHS, as referred to point c) and c-bis of Article 8, paragraph 10, of Law n. 537 of December 24, 1993;
   c. any orphan medicinal product previously authorized and whose authorisation was then suspended or withdrawn as of December 31, 2013;
   d. any medicinal product initially inserted in the Community Register of orphan medicinal products for human use and which have then lost the orphan designation, as a result of the MAH's request or following COMP (EMA) re-evaluation;

3. any medicinal product which, pursuant to Article 15, paragraph 8, point I – bis of Decree-Law no. 95 of 2012, converted into Law no. 135 of 2012, then modified by Article 1, paragraph 228, of Law n. 147 of December 27, 2013, is included in the European Medicines Agency Note EMEA/7381/01/en. dated March 30, 2001 – if not excluded according to the criteria described in paragraph 2, points a) to d);
4. any medicinal product holding a marketing authorization for the treatment of a rare disease or condition included in the Orphanet register (*http://www.orpha.net/*), although not included in the Community Register of orphan medicinal products pursuant to (EC) Regulation n. 141 of 2000 of the European Parliament and of the EU Council of December 16, 1999. Moreover the following criteria are excluded:
   a. any product authorised for the treatment of non-rare diseases or non-rare conditions;
   b. products authorized for the treatment of rare diseases or conditions, for which as of December 31, 2013 MAHs had not submitted the requests to benefit from provisions of Article 15, paragraph 8, point i) of Decree-Law no. 95 of 2012, converted into Law no. 135 of 2012 and later amended by Article 1, paragraph 228, of Law no. 147 of December 27, 2013.

Law no. 145 of 2018 (2019 Stability Act; Article 1, paragraphs 575-584), modifying the 2014 Stability Act, establishes that orphan list adopted by AIFA includes only Class A and Class H orphan drugs commercialized and authorized by the EMA, excluding orphan drugs that have exhausted their period of market exclusivity.

In order to increase orphan drugs availability nationwide, the *Balduzzi Law* (Law no. 189/ 2012, Article 12, paragraph 3) provides for the possibility for MAHs to apply to AIFA for pricing & reimbursement procedure as soon as the CHMP positive opinion is released and, therefore, before the marketing authorization is formally granted by the European Commission. Moreover, following Decree Law no. 69 of June 21, 2013, and Law no. 98 of August 9, 2013 (Article 44), AIFA provides for orphan drugs pricing and reimbursement dossiers (together with those concerning medicines of exceptional therapeutic relevance) with a priority over other pending applications. In such cases, the assessment period is reduced from 180 days to 100 days (so-called "fast track authorisation").

Access to rare disease treatments

In Italy, access to treatment for patients suffering from a rare disease is guaranteed through various legislative instruments. The centralised procedure represents the standard access route; whenever an orphan drug has no marketing authorisation, patient access is ensured through the following:

- Law n. 648/ 1996, allowing the use of a medicine on a national basis;
- Law n. 326/2003, Article 48 (also known as 5% AIFA Fund) and Ministerial Decree of September 7, 2017 (also known as “compassionate use”) in addition to Law n. 94/1998 (formerly *Legge Di Bella*) that, unlike Law no. 648, regulate pharmaceutical prescription for individual patient on a nominal basis.

Law no. 648/1996

This law allows the supply of certain medicines reimbursed by the NHS, in order to respond to pathological conditions for which no alternative therapeutic option is available (see Table 1.9.1). In order to include a medicine into the lists laid down by Law no. 648, one of the following conditions shall be met:

- innovative medicines holding a marketing authorisation granted in any European country, but not in Italy;
- medicinal products not yet authorised, but undergoing clinical trials, and for which results are available concerning phase two clinical studies;
- medicines to be used for a different therapeutic indication compared to the one already authorised in Italy, and which have undergone a phase two clinical trial.

The inclusion of a pharmaceutical product into Law no. 648 list is performed by AIFA on the basis of a documented request from patients' associations, scientific societies, health facilities, universities or following recommendations of AIFA's Scientific-Technical Committee (CTS). The list of orphan drugs included in Law no. 648/1996 can be downloaded from AIFA website at the following link: http://www.agenziafarmaco.gov.it/it/content/legge-64896.

Following the entry into force of Law no.79 of 2014, it was established that the supply of medicines used for a therapeutic indication different from the authorised one, through the list provided by Law no. 648/96 (100% reimbursement by the NHS), is allowed even if therapeutic alternatives are available, according to affordability and appropriateness parameters. Bosentan constitutes an example of orphan drug that has benefited from this provision.

Law n. 326/ 2003 (Article 48): 5% AIFA Fund

The 50% of the AIFA Fund is dedicated to the purchase of orphan drugs intended for the treatment of rare diseases and medicinal products not yet authorized, but representing a chance for the treatment of serious conditions (i). The remaining 50% of the Fund is used to carry out scientific researches (independent research) on the use of pharmaceutical products (i.e. comparative trials on medicines aimed at demonstrating their additional therapeutic value, or studies aimed at demonstrating the appropriateness of use of medicines, or focusing on scientific information). This Fund is fed by the 5% of pharmaceutical companies' annual expenditure issuing from promotional activities intended for physicians (seminars, workshops, etc.) (Article 48, paragraph 19, point a, Decree-Law no. 269 of September 30, 2003, converted into Law. no. 326 of November 24, 2003).

In 2018, this Fund amounted approximately to €18.3 million.

As regards the purchase of the above-mentioned pharmaceutical products (i), requests to access the Fund are submitted to AIFA, through Italian regions, by local reference centres or designated structures treating patients affected by a rare disease.

The following documents are required in order to access the Fund: a formal request, supporting scientific literature (if any) and a brief clinical report including a description of

the therapeutic plan for each patient. The application shall be supported by specific information, such as: dose per treatment cycles, number of cycles and price of the medicine. The application is assessed by AIFA's Scientific-Technical Committee that issues an opinion after having verified the existence of the conditions provided by law. On the basis of the supporting documents submitted as proof of costs incurred for patient's treatment, AIFA reimburses the invoices submitted.

Ministerial Decree of September 7, 2017 "Therapeutic use of a medicine undergoing clinical trials" (compassionate use)

Despite considerable medical progress achieved in the diagnosis and treatment of many diseases, there are still several therapeutic areas (so-called "niches") associated to unmet medical needs which represent both a challenge and a major goal for health care providers. The Italian Ministerial Decree of September 7, 2017 establishes procedures for "Therapeutic use of medicines undergoing clinical trials" (so-called "compassionate use of medicinal products"). The provisions of compassionate use represent a pathway for patients to access medicinal products for the treatment of serious, life-threatening conditions, or rare diseases, for which no satisfactory authorised alternative therapy exists. Ethic Committees are responsible for granting authorisation for access to experimental medicines, it being understood that the pharmaceutical company shall provide a declaration of willingness to supply the medicine free of charge. This Decree represents the transposition of the "Guideline on Compassionate use of Medical Products, pursuant to Article 83 of Regulation (EC) no. 726/2004", as laid down in Art. 158, paragraph 10, Decree-Law no. 219/2006.

Law no. 94/1998, Art. 3, paragraph 2 (formerly *Legge Di Bella*)

This legislation allows medical prescription of an off-label medicine. The prescription of an off-label medicine is granted under the responsibility of the prescribing physician, and followed by an informed consent of the patient, if the patient cannot be beneficially treated with available treatments approved for the same therapeutic indication. For such a prescription to be issued, documents on the use of a medicine are required from successfully concluded phase two clinical trials (Finance Law 2008).

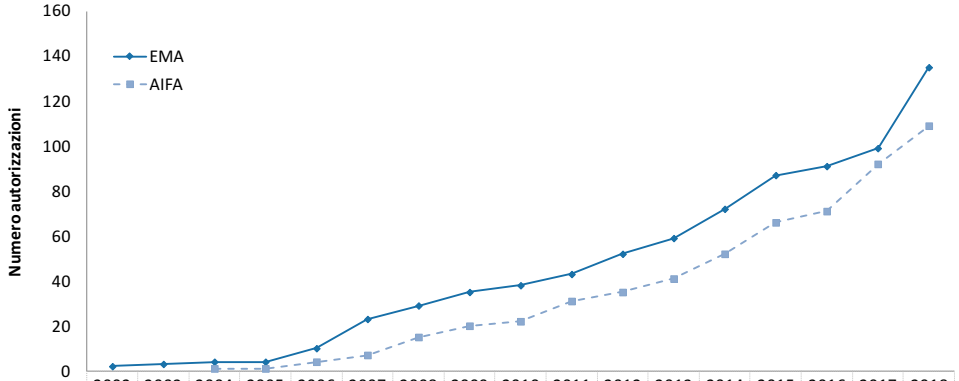
Table 8.1.1. Overview of the main requirements for access to the orphan drug based on the different regulations in force

Requirement	Law n.648/96	Law n. 326/2003	D.M. 7 september 2017	Law n.94/98
Lack of a viable therapeutic alternative	YES	Not Explained	YES	YES
Informed consent of the patient	YES	Not Explained	YES	YES
Supporting scientific documentation	Results of phase II studies (for investigational drugs)	Patient's clinical report	Phase III studies, or phase II clinical studies already concluded in particular cases of disease conditions that put the patient in danger of life. In the case of rare diseases or rare cancers, completed at least phase I clinical trials which documented the activity and safety of the medicinal product (not applicable to advanced therapies).	At least results of successful Phase II studies
Assumption of responsibility by the doctor	YES	Not Explained	YES	YES
Transmission of monitoring data	AIFA and Regional Council (only for the "classic" or "historical" list)	-	Notification of documentation relating to applications for medicinal products made in accordance with Ministerial Decree 7/9/2017 and approved by the local Ethics Committee	-
Contribution to the cost of therapy	NHS	AIFA	Free supply by the Pharmaceutical Company	Citizen, except in case of hospitalization

8.2 Orphan drugs expenditure and consumption in Italy

In 2018 the European Medicines Agency authorized 21 medicines for the treatment of rare diseases. The main therapeutic areas involved were those of endocrinology (Lamzede and Mepsevii), followed by the central nervous system (Namuscla) and two CAR-T gene therapies (Yescarta and Kymriah), which are still in the negotiation phase in Italy at the time of writing this report.
Furthermore, in the last 17 years, out of 135 orphan drugs authorised by EMA, 109 (including 9 products classified as C-nn) were marketed in Italy as of 31 December 2018. Of the remaining 26 medicines: in the case of 6 a P&R application has never been submitted by the pharmaceutical company, in the case of 11 a P&R application has been submitted, but the negotiation process has not been concluded yet, in the case of 2 the medicines have been classified as Class C products and so they are available but not reimbursed by NHS. As far as the remaining 7 medicines are concerned, they are available to patients through alternative channels (e.g. Law no. 648/96, Law no. 326/2003, etc.) encouraged by AIFA.

Figure 8.2.1. Comparison between EMA authorized orphan drugs and ones marketed in Italy (cumulative data 2002-2018)



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
EMA	2	3	4	4	10	23	29	35	38	43	52	59	72	87	91	99	135
AIFA			1	1	4	7	15	20	22	31	35	41	52	66	71	92	109

Moreover, according to criteria approved by AIFA's Board of Directors, the list of orphan drugs reimbursed by the Italian NHS has increased from 100 (C-nn class medicine excluded) to 104 authorised orphan drugs, due to the inclusion of orphan-like products, as well as to the addition of orphan drugs, whose market exclusivity awarded by EMA has expired, so being removed from the Community register, as well as drugs for the treatment of rare diseases present in the orphanet register.

During the period 2010-2018 expenditure and consumption data concerning orphan drugs were elaborated on the basis of the new lists approved by AIFA's Board of Directors (Resolution no. 10 of February 27, 2014). Due to the use of these new lists, data resulting from current analysis are not comparable with those referring to previous years. In 2017, orphan drugs expenditure (inpatient + outpatient settings) amounted to €1,6 billion, corresponding to 7.2% of the total NHS pharmaceutical expenditure. The share in the expenditure of orphan drugs not reimbursed by the NHS on the total expenditure of orphan drugs (reimbursed + not reimbursed by the NHS) is 0.85% (it was 0.11% in 2014).
In 2017, consumption of orphan drugs, evaluated in both settings, amounted to 12.7 million DDD, corresponding to 0.05% of overall pharmaceutical consumption. As regards therapeutic classes, 57.9% of orphan drug consumption was covered by antineoplastic agents and immuno-modulators, followed by gastrointestinal tract and metabolism medicines (18.3%) and medicines acting on blood and blood forming organs (7%).
Alongside, in terms of consumption, about 61% of orphan drug consumption was covered by antineoplastic agents and immuno-modulators, followed by cardiovascular system medicines (about 10.5%) and systemic hormone preparations, excluding sex hormones (7.8%) (Figure 8.2.2).

Table 8.2.1. Expenditure and consumption trends for orphan drugs, 2010-2018*

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018
Expenditure for orphan drugs (million)	657	800	671	917	1.060	1.212	1.393	1.599	1.781
Incidence % orphan drugs on pharmaceutical expenditure	3.50	4.20	3.50	4.67	5.31	5.49	6.13	7.20	8.10
Consumption (DDD) orphan drugs (million)	6.6	7.5	5.9	7.5	8.5	10.3	11.4	12.7	12.2
Incidence % orphan drugs on consumption	0.03	0.03	0.02	0.03	0.03	0.04	0.04	0.05	0.05

*Expenditure and consumption data have been processed for the years 2013-2018 on the basis of the classification approved by the Board of Directors of AIFA (resolution no. 10 of 27 February 2014); these results are not comparable with those for previous years.

Table 8.2.2. Orphan drugs accessing the fund of innovative cancer drugs and innovative non-cancer drugs: expenditure and consumption for 2018

Medicine	2018	
	Expenditure	DDD
Imbruvica	111,559,586	757,150
Spinraza	92,105,860	242,880
Darzalex	70,961,798	378,215
Imnovid	38,005,965	126,217
Kalydeco	27,620,136	43,708
Oxervate	3,643,746	13,104
Rydapt	1,228,027	2,296
Prevymis*	8,186	1
Total	**345,125,118**	**1,563,570**

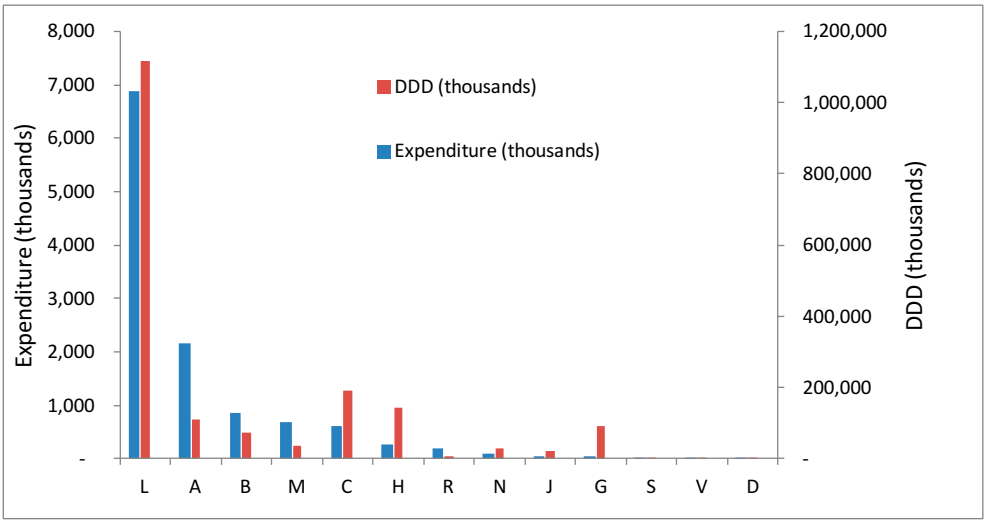
Note: As regards Strimvelis, even though two patients are treated according to AIFA Registries, the drug does not appear in the flow data of public health facilities, as dispensed by an Accredited Private Health Facility.

*On the market since December 2018.

In 2018 orphan drugs recognized also as innovative medicines resulted in € 345.1 millions expenditure (Table 8.2.2).

Further analysis of the distribution of orphan drug expenditure by therapeutic area shows that the highest incidence is found for medicines for the treatment of leukemias as well as of lymphomas and myelomas (21.2% and 22.4%, respectively) though a high consumption for medicines for pulmonary arterial hypertension is also observed (Table and Figure 8.2.4).

Figure 8.2.2. Expenditure and consumption of orphan drugs in Italy for ATC level, year 2018

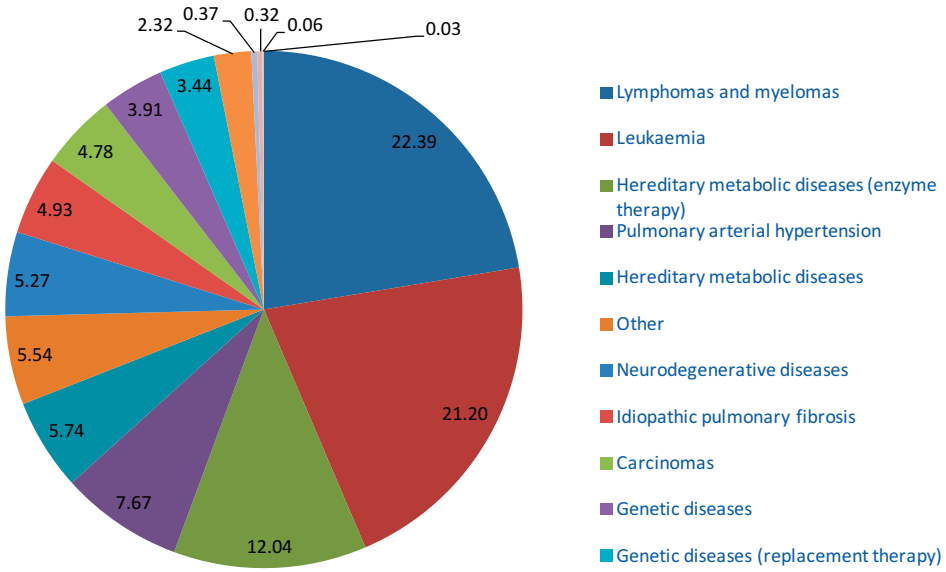


L = Antineoplastic and immunomodulating agents
A = Alimentary tract and metabolism
C = Cardiovascular system
B = Blood and blood forming organs
H = Systemic hormonal preparations, excl.sex hormones and insulins
V = Various
R = Respiratory system
M = Musculo-skeletal system
N = Nervous system
G = Genito urinary system and sex hormones
J = Anti-infectives for sistemic use
D = Dermatologicals
S = Sensory organs

Table 8.2.4. Expenditure and consumption of orphan drugs in Italy by therapeutic area, year 2018 (Table and Figure)

Therapeutic area	Expenditure	DDD	Per capita expenditure	DDD/1000 inhab die	Inc. % exp on tot orphan drugs*
Lymphomas and myelomas	398,772,403	2,874,621	6.6	0.1	22.4
Leukaemia	377,491,167	2,421,088	6.2	0.1	21.2
Hereditary metabolic diseases (enzyme therapy)	214,391,333	200,173	3.5	0.0	12.0
Pulmonary arterial hypertension	136,592,324	1,962,768	2.3	0.1	7.7
Hereditary metabolic diseases	102,217,096	324,322	1.7	0.0	5.7
Other	98,657,752	581,730	1.6	0.0	5.5
Neurodegenerative diseases	93,922,221	261,330	1.6	0.0	5.3
Idiopathic pulmonary fibrosis	87,727,185	970,228	1.5	0.0	4.9
Carcinomas	85,105,766	528,389	1.4	0.0	4.8
Genetic diseases	69,595,130	812,166	1.2	0.0	3.9
Genetic diseases (replacement therapy)	61,257,742	107,512	1.0	0.0	3.4
Hormonal disorders	41,389,108	1,025,884	0.7	0.0	2.3
Infectious diseases	7,070,089	65,585	0.1	0.0	0.4
Transplants	5,718,309	40,882	0.1	0.0	0.3
Hereditary metabolic diseases (replacement therapy)	1,004,576	849	0.0	0.0	0.1
Total	**1,780,912,201**	**12,177,527**	**29.4**	**0.6**	**100.0**

* Calculated on the total expenditure of orphan drugs nationwide



In 2018 the active ingredients with major impact on expenditure were: lenalidomide (12.0%), ibrutinib (6.3%), dasatinib (6.3%) and nusinersen (5.2%). It is interesting to

observe that the first 15 active ingredients account for the 62% of the expenditure. As regards consumption, 30.9% of DDD dispensed was due to the following active ingredients: lenalidomide (14.6%), ibrutinib (6.2%), pirfenidone (5.6%), nilotinib (4,3%) and hidrocortisone (4.0%).

Appendix 1

Regulation of pharmaceutical assistance in Italy

National Report
on Medicines
use in Italy
Year 2018

1. Main measures enacted in 2018

Document on new pharmaceutical governance

In December 2018 the Document on the new pharmaceutical governance was presented. The document intends to submit to the Ministry of Health the guidelines for a new governance of medicinal products, also taking into account the proposals of the Conference of Italian Regions and Autonomous Provinces, submitted to the Minister of Health in June 2018.

The Document provides three types of indications: i) guidelines which can be implemented in short time by AIFA under current legislation; ii) guidelines requiring detailed implementation documents; iii) guidelines requiring new regulatory or administrative tools or organizational adjustments in the Agency for their implementation.

The areas of intervention mentioned in the Document include sharing with the Regions the data collected in the AIFA Registers and the regional data of the Observatory on the Use of Medicines. In this regard, it is proposed that AIFA makes available to the Regions the data used by the OsMed so that each Region may carry out comparisons and analyses, also independently; moreover, it is proposed that monitoring be carried out on regional tenders and related prices, the results of which shall be made available to the Regions.

As regards the governance of pharmaceutical expenditure, the legislation relating to compliance with expenditure ceilings and *payback* needs to be simplified in order to ensure the implementation of these instruments for all stakeholders, by avoiding use of dispute resolution mechanisms.

It should be emphasised that, in general terms, the *ad hoc* funds can be useful in exceptional conditions, but under ordinary conditions, the marketing of new medicinal products and the reimbursement by the NHS shall take place in accordance with the general management criteria of the pharmaceutical sector and the financial compatibility shall be part of the ordinary administration of the pharmaceutical sector itself.

Furthermore, the document includes interventions aimed at enhancing the use of generics and biosimilars, also through specific information initiatives for citizens.

Position paper on biosimilars

As marketing of biosimilars of different biological medicinal products is fast approaching, in the first quarter of 2018 AIFA issued the Second Position Paper on Biosimilars to clarify the scientific, regulatory and statutory aspects concerning these drugs. This document also represents an instrument of awareness-raising and cultural incentive, also enabling health professionals to provide patients with correct information on the characteristics of these drugs and to contribute to the NHS sustainability. The document is available on the website of the Italian Medicines Agency at the following link http://www.aifa.gov.it/content/presentato-secondo-position-paper-aifa-sui-farmaci-biosimilari

Table 1.1. Context indicators of pharmaceutical care in Italy

	2016	2017	2018
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
no. Drug distributors (5)			2,323
no. Pharmacies (5)			19,854
no. retail shops (5)			6,443
no. GP (6)	44,279		
no. GP per 10.000 inhab (6)	7.3		
no. PFC (6)	7,662		
no. PFC per 10.000 inhab (6)	9.3		
no. ASL (Local Health Authorities) (7)		101	
no. Health authorities (8)		102	

(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 18/12/2008.
(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 provision methods vary across both European and non-European countries. In Italy, this competence is ascribed 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 medicines are dispensed in hospital settings or equivalent facilities), (Art. 8, paragraph 10, point A, Law no. 537 of 24 December 1993, as amended). Otherwise, medicinal products are classified as Class C when not reimbursed by the NHS, with the exception of subjects with a lifetime war pension, whereby the general practitioner attests the proven therapeutic utility for the patient (Law no. 203 of 19 July 2000).

NHS reimbursed medicines include essential products, intended for care of chronic diseases, reimbursed for each authorized therapeutic indication. In some cases, reimbursement is granted through AIFA Notes, which restrict reimbursement only to some indications. Therefore, Class A products, whose therapeutic indications are not included in AIFA Notes, are entirely paid by patients.

On the contrary, Class C medicines are not considered to be essential and can be dispensed to citizens with or without a medical prescription (respectively Class C with prescriptions and Class C non-prescription). 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), which may be advertised, and Class C non-prescription (but not OTC), for which advertising is not permitted.

Through Ministerial Decree of 18 April 2012 (implementation of regulations of Art. 32, paragraph 1, Legislative Decree no. 201 of 6 December 2011, as amended), AIFA updated the supply regime of C–medications. The decree established medications requiring medical prescription and those for which the supply regime could be changed into non-prescription, so allowing sale in other settings besides conventional Pharmacies, such as malls and Para-Pharmacies. The 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 the Decree of 21 February 2014, in turn amended by the Decree of 8 May 2014 (published in the Official Journal of 24 May 2014, No. 119).

Moreover, Art. 12, paragraph 5 of Legislative Decree no. 158 of 13 September 2012, converted with amendments into Law no. 189 of 8 November 2012 (so-called "Decreto Balduzzi"), as amendend, established that medicinal products which are granted Marketing Authorization through centralized, mutual recognition, decentralized 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, after submitting a specific dossier according to CIPE (Interministerial Committee for Economic Planning) indications (CIPE deliberation no. 3 of 1 February 2001). Before marketing, the MAH is required to communicate to AIFA the ex factory and

the retail price of the medicinal product classified in class C-NN, together with the marketing date.
When a pharmaceutical company submits to AIFA the pricing and reimbursement dossier, competent offices and advisory committees perform a preliminary assessment to evaluate and establish the reimbursement class of the pharmaceutical product. At the end of the decision-making and negotiation processes - performed by AIFA's Scientific and Technical Committee (CTS) and Pricing and Reimbursement Committee (CPR) - the final provision is ratified by AIFA's Board of Directors which authorises reimbursement of the medicinal product, its supply regime and price reimbursed by the NHS, and then published in the Official Gazette of the Italian Republic.

With reference to supply methods (pursuant to Article no. 87 of Decree-Law no. 219 of 24 April 2006, as amended), medicinal products can be classified as follows:
a) medical products subject to medical prescription (RR);
b) medical products subject to medical prescription to be renewed each time (RNR);
c) medical products subject to a special medical prescription (RMS) (Consolidated Law on narcotics Presidential Decree no. 309 of 9 October 1990, as amended);
d) medical 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 analogous 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 period, during which the patient can use the prescription for a maximum of ten times. A peculiar case is represented by the prescription of psychotropic medicines (tranquilizers, sedatives, hypnotics), having a thirty-day validity and repeatable for no more than three times.
The limited 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 this kind of medicines. The validity is of 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). A peculiar case is represented by isotretinoin, whose prescription and delivery are allowed only within teratogenic risk prevention programs and with a seven-day validity non-repeatable prescription.
The limited repeatable prescription and the limited non-repeatable prescriptions are used for medicinal products dispensable only by specific healthcare facilities and/or specialist doctors. These types of medicines include:

- medicines for exclusive hospital use (Art. 92, Legislative decree no. 219/2006);
- medicines provided 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 directly to patients medicines to be used or administered exclusively by specific healthcare professionals pursuant to the provisions of the Regions or Autonomous Provinces, but they are allowed to have such medicines available in pharmacies. Specialist doctors can be provided with such medications also by manufacturers and wholesalers.
AIFA Resolution of 13 January 2010, available on the supplement no. 21 of the Official Gazette of 1 February 2010, updated the supply regime of medicines for hospital use. In particular, the previous classifications OSP1 and OSP2 were abrogated and the new system entered into force as of 16 February 2010.
Medicinal products previously classified under OSP1 supply regime were reclassified as OSP (see above), without additional changes. The OSP2 supply regime was modified into RR, RNR, RRL or RNRL supply regime. At a later stage, following the implementation by AIFA of the provisions laid down by Article no. 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 delivered by a RR, RNR, RRL or RNRL prescription were reclassified as Class A-PTH (AIFA Resolution of 2 November 2010).
The national regulations governing the reimbursement of medicinal products and their supply regime provide for the possibility to identify different methods of supplying medicines to be reimbursed by the NHS, according to their dispensation and use both at a community level and in hospital facilities. In particular, the consumption of medicines at a local level takes place following the prescription by general practitioners and freely chosen paediatricians, as well as upon 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 - taken by the patient at his own home - is carried out either directly by health facilities (direct distribution) or, alternatively, as a result of specific agreements signed at the local level, through the pharmacies (in name and *per conto* distribution). Article 8 of Legislative Decree no. 347 September 18, 2001 converted with modifications by 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 one. 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 the Local health authorities, by pharmacies open to the public on the basis of specific agreements stipulated by the Regions and Autonomous Provinces with the Associations of the pharmacies affiliated with the National Health Service (SSN), in order to allow patients suffering from chronic pathologies and requiring continuous pharmaceutical assistance to obtain supplies from local pharmacies (so-called *per conto* distribution).

Table 2.1. Number of medicines authorized and marketed in 2018 by reimbursement class

Class	Marketing Authorization (MA)		Medicinal product		Active ingredients	
	No.	% of total	No.	% of total	No.	% of total
Class A	9,952	54.5	4,630	51.7	829	32.7
Class C	6,469	35.4	3,397	37.9	1,231	48.5
Class H	1,845	10.1	928	10.4	479	18.9
Total	**18,266**	**100.0**	**8,955**	**100.0**	**2,539**	**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 fixed respectively at 66,65%, 3,0% and 30,35% of the retail price, net of VAT.
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 to the Regions 1.83% of the retail price net of VAT. The described variation in the margins of wholesalers and pharmacists – set out in art. 11, paragraph 6, of Legislative Decree no. 78/2010, converted with modifications into Law n. 122/2010, as amended – also involved patent-expired medicinal products. In the case of equivalent medicinal products, excluding medicinal products originally covered by a patent or which have benefited from licenses deriving from this patent, the share attributable to pharmaceutical companies remains 58.65%, as laid down by Legislative Decree no. 39 of 28 April 2009 converted with modifications into Law no. 77 June 24, 2009, and the remaining share of 8% (at 66.65%) is redistributed among pharmacists and wholesalers according to market rules.
Decree Law no. 95/2012, converted with modifications into Law no. 135/2012, as amended, introduced some important provisions concerning the management of pharmaceutical expenditure, including the 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 paid by pharmacies to the NHS, updated by Legislative Decree no. 148 of 16 October 2017, converted with amendments into Law no. 172 of 4

December 2017 (namely with art. 18-bis, 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 (euro)	Rates for urban and rural pharmacies without national assistance			Rates for rural pharmacies with national assistance		
	NHS turnover > 300,000 euros	**NHS turnover < 300,000 euros and > 150,000 euros**	**NHS turnover < 150,000 euros***	**NHS turnover > 450,000 euros**	**NHS turnover < 450,000 euros and > 150,000 euros**	**NHS turnover > 150,000***
0-25.82	3.75%	1.50%	Full exemption	3.75%	fixed rate 1.5%	Full exemption
25.83-51.65	6.0%	2.40%		6.0%	fixed rate 1.5%	
51.66-103.28	9.0%	3.60%		9.0%	fixed rate 1.5%	
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 the citizen, 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 the citizen in the pharmaceutical expenditure does not derive exclusively from regional tickets, but also from the cost sharing shares on patent-expired medicinal products. In fact, as of 1 December 2001, medicinal products without patent coverage to be reimbursed by the NHS, including generics (so-called "equivalent medicines"), have been grouped into the 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 drug price and the economically lower drug 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 a lower price.
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 the reference prices through regional measures. This provision played an important role in particular in the early 2000s, when the uniform availability on the national territory of equivalent medicines, which are generally those with the lowest retail price, could not be guaranteed. In practice, to date, in most Italian regions the reference prices correspond to the prices published in the AIFA transparency lists. A detailed analysis of the cost sharing for the reference price of equivalent medicinal products has been provided in section 1.
Although the cost sharing for the citizen (given by the difference between the retail price of the dispensed medicinal product and the reference price in the AIFA transparency lists) is substantially homogeneous on the national territory, with the exception of some regions, on the other hand, 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 that contribute 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 Legislative Decree no. 159 of 1 October 2007, converted with modifications 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 compliance aimed at accessing the supplementary financing paid by the State. The Regions that in 2018 do not envisage a ticket as a measure

to contain the pharmaceutical expenditure reimbursed by the NHS are three (Friuli VG, Marche and Sardinia).
The Regions that in 2018 do not envisage a ticket as a measure to contain the 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 1.6 billion euros (of which 70% is attributable to the share of the reference price and the remaining 30% to the fixed ticket), equal to 15.9% of gross pharmaceutical expenditure reimbursed by the NHS and with a change rate of + 3.8% compared to 2017. As for the per capita cost sharing, a marked variability was recorded at a regional level: against a national value of 26.6 euros per capita (33.3 euros in the South and islands and 22.9 euros in the North), Campania has a value of almost 40 euros per capita while in Friuli Venezia Giulia every citizen spends on average little more than 15 euros (Table 5.1.3).
The following table (Table 4.1) shows the main ticket-related measures in the Italian Regions in the year 2018, with the aim of providing a thorough summary (Source: Federfarma, https://www.federfarma.it/Ticket-Regionali.aspx), 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 summarizes the information published on the website of the Ministry of Health).

Table 4.1. Procedures for applying regional tickets in 2018

Region	Exemption			Ticket (€)		Transparency lists *	Notes	Legal reference
	Income (€)	Pathology	Package	Max prescription	Prescription share			
Aosta Valley°	0-10,000	yes	no	no	no	yes		DGR no. 1899 28/12/2017
	10,001-25,000	no	1	2	no			
	> 25,000	no	2	4	no			
Piedmont	> 36,151.98	no	2	4	no	yes		DGR no. 57- 5740 3/4/2002
		no	1	4	no		Single-dose antibiotics, IFN for hepatitis, medicines administered through intravenous infusion	DGR no. 36-7965 28/12/2007
		yes	1	3	no		Chronic diseases	
	0 – 36,151.98	yes	no	no	no			DGR no. 16-3096 12/11/2011
Lombardy	> 20,000.00	no	2	4	no	yes + ticket		DGR 4230 25/10/2012
		yes	1	3	no	yes	Rare diseases	
	Up to 20,000.00	no	no	no	no	yes		
PA Bolzano	N/A	yes	no	no	1	yes + ticket	Chronic diseases Rare diseases	DGR 1862 27/05/2002
		no	1	2	no		Children fiscally dependent on parents	
		no	2	4	no			
PA Trento	N/A	no	no	no	1	yes		
Veneto	>12,000	no	2	4	no	yes + ticket		DGR 744 11/03/2005
	Up to 12,000	yes	no	no	no	yes	Pain therapy Helpless persons	
Liguria	N/A	no	2	4	no	yes + ticket	Single-dose drugs and IFN for hepatitis (Law no. 405/2001)	DGR 163 20/02/2002
		yes	no	no	no	yes	Victims of terrorism and invalids of war	DGR 1116 9/09/2011

Region	Exemption		Ticket (€)			Transparency lists *	Notes	Legal reference
	Income (€)	Pathology	Package	Max prescription	Prescription share			
Tuscany	0 – 36,151.98	no	no	no	no	yes	Patients with chronic or disabling diseases are excluded from cost sharing In the calendar year the sum of the tickets on the pharmaceutical expenditure reimbursed by the NHS, paid by a single user, cannot exceed the amount of 400 euros	DGR 753 10/08/2012
	36,151.99-70,000		2	4	no	yes + ticket		
	70,001-100,000		3	6	no			
	> 100,001		4	8	no			
Emilia Romagna[§]	0 – 36,151.98	no	no	no	no	yes	In case of chronic and invalidating diseases, no form of cost sharing is provided	DGR 1190 30/07/2012
	36,151.99-70,000		1	2	no	yes + ticket		
	70,001-100,000		2	4	no			
	> 100,001		3	6	no			
Umbria[§]	0 – 36,151.98	no	no	no	no	yes	In case of chronic and invalidating diseases, no form of cost sharing is provided	DGR 911 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	Medicinal products with retail price > 5€	DCA 45 17/11/ 2008
		no	4	no	no			
		yes	1	no	no		Medicinal products with retail price ≤ 5€	
		no	2,5	no	no			
Abruzzo	N/A	no	2	6	no	yes + ticket	Medicinal products with retail price > 5€	DCA 26 4/6/2012
		yes	1	3	no			
		no	0.5	1.5	no		Medicinal products with retail price ≤ 5€	
		yes	0.25	0.75	no			
		no	no	no	no	yes	Chronic and disabling diseases Patent-covered medicinal products that adapt to the reference price	
Molise	N/A	no	2	6	0.5	yes + ticket	Patent-covered medicinal products with retail	DGR 1188

Region	Exemption		Ticket (€)			Transparency lists *	Notes	Legal reference
	Income (€)	Pathology	Package	Max prescription	Prescription share			
							price >5€	29/07/2002 DD.CC.AA 87 and 97/2011 Circolare 4702 3/4/2012
			0.5	no			Patent-expired medicinal products with 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 drugs 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 67 4/11/10
			no	no	1	yes	Patent-covered medicinal products that adapt to the 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 thorugh intravenous infusion	DGR 1718 19/11/2004
		yes	0,5	no	1			
		no	no	no	1		Disability, pain therapy, victims of terrorism	DGR 1198 6/08/ 2005
		no	no	no	1			
		no	no	no	no		Minimum pensions	DGR 2789 14/12/2010 DGR 21/06/2011
Basilicata	until 8,2163.31	no	no	no	1	yes		DGR 699 11/06/13
	> 8,2163,31				2	yes		
Calabria	N/A	no	2	5	1	yes	Chronic diseases Rare diseases	DGR 247 5/05/2009
		yes	no	no	no			
		yes	no	no	1		Disability	

Region	Exemption		Ticket (€)			Transparency lists *	Notes	Legal reference
	Income (€)	Pathology	Package	Max prescription	Prescription share			
Sicily	N/A	no	4	no	no	yes	Medicinal products with retail price ≤ 25€	L.R. 6 10/01/2012
		yes	1.5					
		no	2				Equivalents with retail price ≤ 25€	
		yes	1					
		no	4.5			yes	Medicinal products with retail price > 25€	
		yes	2					
		no	2.5				Equivalents with retail price > 25€	
		yes	1.5					

* difference between the retail price of the medicinal product 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 the patients with an exemption for income (E01 - E02 - E03 - E04) pursuant to the current State legislation and by the patients with ordinary ISEE (Equivalent Financial Situation Index) certification between 10,000.00 euros and 25,000.00 euros, a fixed fee of 1 euro per package up to a maximum of 2 euros per prescription for NHS pharmaceutical assistance and *per conto* distribution, and a fixed fee of 1 euro per prescription for supplementary assistance

Exemptions

(Source Ministry of Health, 2019; http://www.salute.gov.it/portale/esenzioni/homeEsenzioni.jsp)

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 euros.

E02: Unemployed 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 euros 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 euros, increased up to 11,362.05 euros 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 the Decree of the President of the Council of Ministers of 12 January 2017 (annex 10).
Preventing the spread of HIV infection, limited to ascertaining the status of infection, in favour of subjects belonging to categories at risk, with risk behaviors 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 organized crime.

5. Price of medicinal products

As of January 1st, 2004, prices of all medicinal products reimbursed by the NHS are fixed 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 (Interministerial Committee for Economic Planning) 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 the pricing and reimbursement procedure by submitting the dossier to AIFA;
2. AIFA's CTS provides 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 Official Gazette of the Italian Republic.

Notwithstanding these provisions, the Legislative Decree no. 69 of 21 June 2013, converted with modifications into Law no. 98 of 9 August 2013, amended the Legislative 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 sessions of the Commissions, within 100 days (see also section 8, Orphan medicinal products). Furthermore, for these drugs, the current legislation provides for a further facilitation, that is the faculty for the company to submit the request for classification and price before the release of their marketing authorization.

With regard to class A medicines dispensed through local pharmacies, under the conventional supply regime, the price published in the Official Gazette coincides with the retail price of the individual package, including the shareholdings 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 all the cost-sharing paid by citizens. In addition, the ex-factory price (excluding VAT) is published in the Official Gazette.
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 the 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 Official Gazette, but it is communicated to AIFA. For class C drugs with prescription, with the exception of drugs C-bis, the price may increase only in January of each odd year (Decree Law 27 May 2005, n. 87, converted with modifications, into Law no. 149 of 26 July 2005), while price reductions are always permitted.

Article. 9-ter, paragraph 11 of Legislative Decree no. 78 of 19 June 2015, converted with modifications into Law 125/2015, intervened in the definition of the price of drugs, by integrating Art. 48 of Legislative Decree no. 269 of 30 September, converted with modifications into Law no. 326 of 24 November 2003, as amended; it has in fact 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 initiate a new price negotiation procedure with the marketing authorization holder of the same biotechnological medicinal product, in order to reduce the reimbursement price by the NHS. Furthermore, it has inserted paragraph 33 ter, providing that the Agency start a new bargaining procedure with the marketing authorization holder, for the drugs subject to AIFA monitoring registry, in order to reduce the price in the event that reported benefits, after two years from granting of the marketing authorization, are lower than those identified in the negotiation agreement.

6. AIFA Notes for the appropriate use of medicinal products

AIFA Notes, which define the eligibility for reimbursement of some medicinal products, are the regulatory instrument aimed at guaranteeing an appropriate use of the medicinal products, directing doctors' prescriptions on the basis of the best evidence of efficacy in

the literature. 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 risk only for one or more population groups.
During 2018, AIFA decided the following changes: Note 65 concerning the modification of dispensation of medicinal products for treatment of multiple sclerosis; Note 74 concerning the insertion of follitropin delta among the medicinal products included in the Note; Note 95 on the inclusion of 5-Fluorouracil/Salicylic acid among the reimbursed medicinal products for treatment of actinic keratosis; Note 66 on reimbursement of the fixed-dose combination ibuprofen/codeine-based.
The main changes are described below (for a more detailed description of the Notes, please see the text published in the Official Gazette and also available on the Agency's website):

Note 65 – medicinal products for treatment of multiple sclerosis: amendments to the text of the Note made by resolution no. 354/2018 published in the Offical Gazette no. 56 of 8 March 2018, do not modify the indications for which it is possible to issue a prescription to be charged to the NHS; they are instead related to the redefinition of the dispensation regime for the medicinal products covered by the Note. As a result of the same administrative provision, in fact, to all medicinal products included in the Note shall be applied the conditions and methods of use laid down in Annex 2, as amended, of determination 29 October 2004 - PHT Handbook of direct distribution - published in the ordinary supplement of the Official Gazette no. 259 of 4 November 2004. The Note does not apply to second-line DMT (disease modifying therapy) drugs, whose prescription appropriateness is monitored by AIFA through specific Monitoring Registries or Therapeutic Plans reporting the eligibility criteria according to the therapeutic indications reimbursed by AIFA.

Note 74 – medicinal products for female and male infertility: the update exclusively concerned the insertion of follitropin delta among the active ingredients subject to Note 74 (Resolution No. 1334/2018 published in Official Gazette no. 199 of 20 August 2018).

Note 95 – medicinal products for treatment of actinic keratosis: the new version of the Note, amended with Resolution 1435/2018 (Official Gazette no. 223 of 25 September 2018), includes 5-Fluorouracil/Salicylic acid exclusively for grade I/II lesions located on the

face and/or bald scalp and provides for the updating of the text based on the most recent evidence in the literature.

Note 66 - non-steroidal anti-inflammatory drugs (NSAIDs): the update relates to the inclusion in the Note of the fixed-dose combination Ibuprofen/codeine-based, which can be reimbursed only for short-term treatment of acute pain of moderate severity in subjects with symptoms which are not adequately managed with other painkillers taken alone (Resolution AIFA of 10 October 2018, published in the Official Gazette no. 246 of 22 October 2018).

Appendix 2

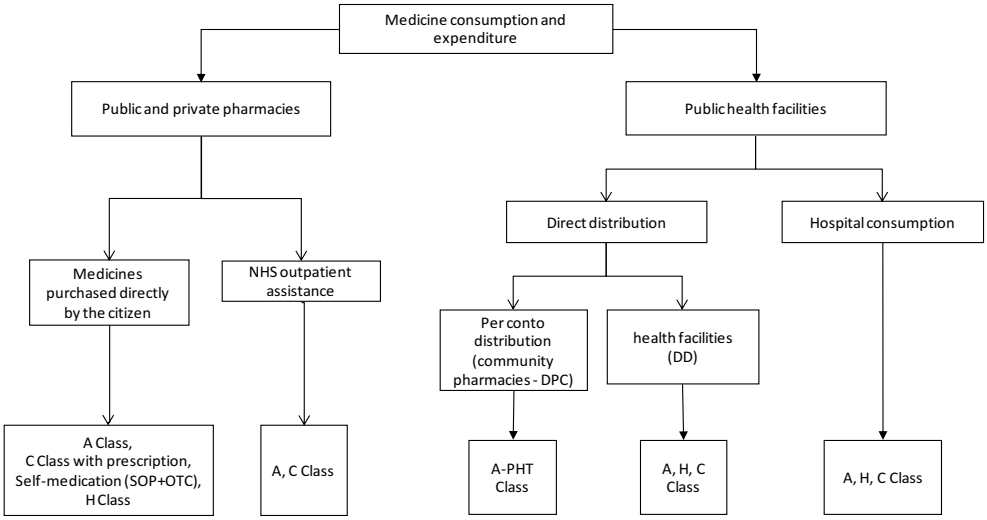
Data source and methods

National Report
on Medicines
use in Italy
Year 2018

1. Pharmaceutical consumption and expenditure data

This Report provides a summary of data on consumption and expenditure of medicines supplied by the National Health Service (NHS) in conventional, 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:

1. 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 n. 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

[1] Art. 68, paragraph 9 of Law 23-12-1998, n. 448 as amended, implemented by art. 18 of the Ministerial Decree 20-9-2004, n. 245 ("Regulation on the organization and functioning of the Italian Medicines Agency, pursuant to article 48, paragraph 13, of Legislative Decree 30-9-2003, No. 269, converted into Law 24-11-2003, No. 3").

(Association of Public Pharmacies), which receive data from their provincial offices and subsequently aggregate them at the regional level. The OsMed flow has a variable degree of completeness by geographical area and by month; the national data coverage in 2018 was generally 96% 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 is guaranteed of the retail price of the single medicinal package.

2. 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 (both in terms of 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.

3. 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 Decree of the Minister of Health 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.

4. 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 July 31, 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 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 (Budget Law 2017), article 1 paragraph 399, the ceiling of territorial pharmaceutical expenditure, renamed "agreed pharmaceutical expenditure ceiling", is calculated net of direct and *per conto* distribution.
5. 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").

6. Hospital consumption. The information flow for monitoring hospital consumption was established by the Decree of Ministry of Health February 4, 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".
7. 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, n.269, converted, with modificatons, by Law 24 November 2003, n. 326, as amended (Health Card, TS). 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* (http://www.whocc.no/) of the World Health Organisation (WHO), based on the ATC/DDD system (respectively: Anatomical-Therapeutic-Chemical category and *Defined-Daily Dose*). The ATC identifies a system for classifying the active ingredients of pharmaceuticals, grouping them in different categories on the basis of the apparatus/organ on which they exert their therapeutic action and according to their chemical and pharmacological properties. Each active ingredient is generally associated with a unique 5-level code; frequently the second, third and fourth levels are used to identify the pharmacological classes.
The defined-daily dose (DDD) represents the maintenance dose per day of therapy, in adult subjects, related to the main therapeutic indication of the substance (therefore it is a standard unit and not the recommended dose for the single patient). The DDD is generally assigned to an active ingredient already classified with a specific ATC code. The number of DDD prescribed refers to 1000 inhabitants for each day of the time period in question (week, month, year, etc.). The DDD allows to aggregate the prescriptions regardless of the prescribed substance, the administration route, the number of dosage units and the dosage of the single package. The WHO annually provides for a revision of the ATC and DDD classification; consequently, it is likely that consumption and spending by category change over time, depending at least in part on these updating processes.
Ultimately, DDD was used in the analysis of drug consumption to parametrize the number of packages delivered to patients, according to the formula shown in section 4. In some specific analyzes, a grouping of different ATC and/or active ingredients was applied, in order to analyze 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-territory assistance) in force since November 2004.
For equivalent medicines, the "transparency lists" published monthly by AIFA for the year 2018 were used.

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 (data source: http://demo.istat.it/); the number in each class was then multiplied by the corresponding weight; then, the sum of the values thus obtained at regional level was re-proportioned to the Italian population of the reference year (60,483,973 inhabitants in 2018).
The implementation of this process of population standardization implies that a Region with an older population than the national average will have a weighted population greater 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 2017 and 2018.

Table 3.2. Resident population measured by ISTAT and weighted population for 2017 and 2018

Region	Resident population as of 1.1.2017	Weighted population 2017	Resident population as of 1.1.2018	Weighted population 2018
Piemonte	4,392,526	4,628,131	4,375,865	4,607,636
Valle d'Aosta	126,883	129,972	126,202	129,445
Lombardia	10,019,166	10,001,573	10,036,258	10,015,557
PA Bolzano	524,256	492,592	527,750	495,399
PA Trento	538,604	529,986	539,898	531,348
Veneto	4,907,529	4,939,756	4,905,037	4,941,080
Friuli VG	1,217,872	1,300,822	1,215,538	1,297,253
Liguria	1,565,307	1,750,237	1,556,981	1,735,087
Emilia R.	4,448,841	4,573,207	4,452,629	4,564,671
Toscana	3,742,437	3,939,500	3,736,968	3,926,459
Umbria	888,908	931,326	884,640	925,670
Marche	1,538,055	1,592,874	1,531,753	1,584,588
Lazio	5,898,124	5,795,347	5,896,693	5,795,831
Abruzzo	1,322,247	1,346,187	1,315,196	1,340,023
Molise	310,449	319,877	308,493	317,614
Campania	5,839,084	5,350,258	5,826,860	5,345,218
Puglia	4,063,888	3,964,110	4,048,242	3,957,455
Basilicata	570,365	570,681	567,118	567,939
Calabria	1,965,128	1,901,631	1,956,687	1,894,077
Sicilia	5,056,641	4,849,243	5,026,989	4,826,747
Sardegna	1,653,135	1,682,136	1,648,176	1,684,876
Italy	**60,589,445**	**60,589,445**	**60,483,973**	**60,483,973**

4. Indicators and measures of use of medicinal products

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:

$$IV = \frac{S^{18}}{S^{17}} = \frac{\sum_i q_i^{18}}{\sum_i q_i^{17}} \times \frac{\sum_i p_i^{18} q_i^{17}}{\sum_i p_i^{17} q_i^{17}} \times \frac{\frac{\sum_i p_i^{18} q_i^{18}}{\sum_i q_i^{18}}}{\frac{\sum_i p_i^{18} q_i^{17}}{\sum_i q_i^{17}}}$$

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 2017 and 2018
S^{17} = pharmaceutical expenditure in 2018
S^{16} = pharmaceutical expenditure in 2017
qi^{17} = quantity of the "i" package (expressed in DDD) sold in 2018
qi^{16} = quantity of the "i" package (expressed in DDD) sold in 2017
pi^{17} = average price in 2018 of the single DDD with the "i" package
pi^{16} = average price in 2017 of the single DDD with the "i" package

This indicator consists of three factors:

- the first factor relates to variation in the quantities of pharmeceuticals 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 specialties "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.

Definition of indicators

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.

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*:* 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 25 April 2019 and, therefore, do not take into account any further revisions by companies and regions.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