# National Report on Medicines use in Italy

## Year 2013

Agenzia Italiana del Farmaco

AIFA

*Dear Readers,*

*this is an extract/adaptation of 2013 OsMed Report.*

*The original numeration was left unchanged, in order to allow easy data consultation.*

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## Executive Summary

Section 1. Pharmaceutical care regulation in Italy

Throughout 2013, AIFA's Evaluation & Assessment Unit and European Assessment Unit released 777 pharmaceutical marketing authorizations, mostly approved through mutual recognition or centralized procedures. In addition, the Agency received 522 ongoing marketing applications concerning new active ingredients. Amongst all applications submitted, those ascribable to the oncology area have revealed interesting results. Throughout the year, over 15.000 pharmaceutical packages have been consumed, whereof 60% are reimbursed by the National Health Service (NHS). All through 2013 significant pharmaceutical regulations were issued in Italy, with interventions ranging from authorisation and reimbursement of medicines, to provisions on pharmacovigilance and finally, administration of the pharmaceutical expenditure.

Section 3. Data source and methods

Sources and methods used for the elaboration of the hundreds of analyses enclosed in the Report are detailed in this Section.

Section 4. Medicines appropriateness: prescription and use profiles

A pharmaceutical prescription is considered appropriate if issued within the clinical indications for which the product's efficacy has been tested and according to its proper use (in terms of dose and treatment duration).
Any monitoring activity regarding pharmaceutical consumption cannot disregard considerations and analysis related to appropriateness of use. For this reason, suitable indicators have been identified, allowing to synthesize both physicians' prescription choices, and product utilization by patients. To this end, in addition to epidemiological data on the main chronic diseases in Italy, Section 4 contains all indicators related to prescriptions of general practitioners and diabetologists. Finally, the Report introduces the monitoring of pharmaceutical utilization profiles, according to the patients' geographical, demographic and clinical characteristics, as well as adherence to the treatment. The reader will be able to identify the economic impact on pharmaceutical expenditure represented by variations in the indicators for the different therapeutic areas (hypertension, hypercholesterolemia, diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, depression, peptic ulcers, esophagitis and anemic conditions)

Section 5. General characteristic of pharmaceutical use in Italy

Throughout 2013, the total amount of public and private pharmaceutical expenditure has been of 26,1 billion euros, of which 75,4% reimbursed by the NHS. The average pharmaceutical expenditure per Italian citizen was of 436 euros.
Moreover, the total amount of public and private pharmaceutical expenditure increased by 1,7% over the previous year and amounted to 19.708 million euros.
In more detail, the total NHS pharmaceutical expenditure, including direct distribution expenditure of Class A medicines, added up to 11.866 billion euros, corresponding to 60,2% of the outpatient pharmaceutical expenditure. A slight increase of +0,4% over the previous year was recorded, mainly due to an increase of pharmaceutical direct distribution expenditure (+5,9%), countervailed by a reduction of the net NHS pharmaceutical expenditure (-1,4%).
The private expenditure borne by citizens - including co-payment [being fixed prescription fees named "tickets" - corresponding to a fixed amount per prescription and/or per package - and the difference between the price of originator products whose patents expired and the reference price reimbursed by NHS] and privately purchased Class A and Class C medicines, registered an increase of 3,8% compared to 2012. Major elements of influence are represented by the increase in private purchase of Class A medicines (+11,2%), followed by OTC medicines (+8,1%) and co-payment share (+2,1%). Only expenditure for privately purchased Class C medicines registered a decrease in expenditure (1,1%).
Expenditure for so-called tickets and the difference between the price of products whose patents expired and the reference price amounts to 1.436 million euros, corresponding to 24,1 euros per capita.
During 2013, about 1.031,5 doses per thousand inhabitants were consumed daily, recording an increase of 2,5% over the previous year. The consumption boost in terms of number of packages was +2,2% (over 1 billion packs in 2013, corresponding to 18,7 packs per capita).

Regarding the total public and private outpatient consumption, 1,8 billion packages were dispensed, recording an increase of 1,7% over the previous year. This trend is mainly driven by the consumption increase of Class A medicines privately purchased by citizens (+7,6%), as well as OTC products (+2,9%) and reimbursed medicines consumption (+2,2 %), while a reduction in the consumption of Class C medicines (-5,6%) was registered.
Looking at the main components of the pharmaceutical expenditure throughout the years, a slight increase in consumption [quantity effect (DDD): +2,7%], a price reduction (price effect: -4,2%) and a mild shift towards lower price medicine prescriptions (negative mix effect: -0,8%) were registered. Expenditure concerning public health facilities purchases amounted to 8,4 billion euros (141,2 euros per capita), recording an increase of 6,2% compared to 2012.
Pharmaceutical expenditure and consumption are closely conditioned by the patient's age group. For patients aged 65 years and over, a per capita NHS expenditure up to 3 times higher than the national average and almost six times than the age groups below was revealed. The overall prevalence of use was 57%, recording the highest levels in children

and in the elderly population: half of the children and almost 90% of the population over 75 years of age received at least one prescription during the year.

Section 6. Consumption and expenditure by therapeutic class and epidemiological data

Cardiovascular medicines took up the first place in terms of total (public and private) pharmaceutical expenditure (4.194 billion euros) and in terms of pharmaceutical consumption (524,7 DDD/1000 inhab. die). Other therapeutic categories significantly impacting on expenditure were: gastrointestinal tract and metabolism medicines (3.601 billion euros), antineoplastic products (3.589 billion euros) and central nervous system medicines (3.275 million euros). In more details, statins (among cardiovascular system medicines), pump inhibitor products (among the tract and metabolism medicines) and selective serotonin reuptake inhibitors (among the central nervous system medicines) were the categories recording the greatest impact on the NHS pharmaceutical expenditure. Furthermore, during 2013 rosuvastatin, together with salmeterol and pantoprazole represented the three active ingredients subject to highest expenditure, while ramipril, acetylsalicylic acid and folic acid placed themselves at the highest positions in terms of NHS pharmaceutical consumption.

Section 8. Pharmaceutical adverse reactions monitoring

Pharmaceutical consumption monitoring is closely related to pharmacovigilance activities, which are focused on the monitoring of the pharmaceutical safety profile after marketing authorization. During 2013 the number of reports included in the National Network of Pharmacovigilance (RNF) was 40.957, corresponding to a reporting rate of 690 per million population, higher than the ones registered in other European Union countries with a strong tradition in pharmacovigilance and above the WHO gold standards which sets at 300 per million the number of reports necessary to define a pharmacovigilance system as effective. The number of reports is growing: in 2001 the alerts collected via web pertain 131 million inhabitants, revealing a +41% variation compared to data referring to 2012.
Most of the reports in 2013 concerned antineoplastics (18%), antimicrobials (16%), central nervous system products (15%), blood medicines (12%) and cardiovascular system products (9%), as well as muscle skeletal medicines (8%).
These results confirm that efforts made over the past years to increase the sensitivity of the health care workers and patients to the pharmacovigilance system are being made in the right direction. In this context cooperation between all stakeholders appears essential, ensuring steady monitoring of the pharmaceutical safety profile, with the overall objective of promoting the protection of public health.

# SECTION 1
# PHARMACEUTICAL CARE REGULATION IN ITALY

## 1.1 The Italian Medicines Agency

Since 2004, the national Authority responsible for the regulatory activity on pharmaceuticals in Italy is the Italian Medicine Agency (AIFA) (www.agenziafarmaco.it). The mission of AIFA mission consists of the following tasks:

1. improving human health care through pharmaceutical products
2. guaranteeing the economic equilibrium of the system by respecting annually planned pharmaceutical expenditure ceilings
3. ensuring consistent application of the pharmaceutical system nationwide
4. promoting pharmaceutical independent research and encouraging Research & Development investments in Italy
5. Strengthening relationswith Member States Agencies, the European Medicines Agency (EMA) and other international bodies.

AIFA's organization and competencies are defined by its own regulation (Official Journal (O. J.) n. 254 of October 31, 2009), which provides for the offices reorganisation and the introduction of a departmental structure, composed of fifteen executive offices grouped into five Technical-Scientific Areas and one Administrative Affairs Coordination Area. Each functional technical area is coordinated by one manager, also responsible for one of the executive offices set within the same area. Coordination functions are aimed at ensuring completeness, unity and integrity of action and legal responsibilities of the Areas.

**Area 1 - Pre Authorization procedure**:

• **Research and Clinical Trials Office** promotes the Guidelines on clinical trials, as well as the clinical research for non-commercial purpose and the dissemination of pharmaceutical independent information. Moreover, it supervises the accuracy of public and private clinical trials and also controls the pharmaceutical promotion activity conducted by pharmaceutical companies. Furthermore, it coordinates and supports, with its own resources, both research projects useful to the NHS and training programs for health professionals and Ethics Committees. Finally, it manages the National Observatory on Clinical Trials (OsSC).

• **Office for the inspection activities on Good Clinical Practice (GCP)** investigates on pharmaceutical clinical trials and their follow-up. It promotes the guidelines for good clinical practice, as well as the pharmacovigilance inspections.

**Area 2 – Registration procedure**:

• **Evaluation and Authorisation Office** ensures the registration process of medicinal products for human use in accordance with National and Community procedures (i.e. mutual recognition and decentralised procedures). It is responsible for procedures concerning the "sunset clause" (Article 38 of Law n. 219, 2006) and requirements relating to parallel imports and "free sales certificate" (FSC), as well as activities related to the

import/export of blood products. Finally, it provides information regarding requests received from other Regulatory Agencies.

• **European Assessment Office** guarantees preliminary investigation and provides support for centralised registration procedures in which Italy is involved as Rapporteur or Co-Rapporteur. In addition, it supports the activities of the EMA-CHMP (Committee for Human Medicinal Products).

**Area 3 - Post Marketing Surveillance procedure**:

• **Pharmacovigilance Office** performs the continuous monitoring functions of adverse reactions (ADRs) at national and international level. It promotes projects on active pharmacovigilance and evaluates the safety profile of marketing authorizations' renewals. Moreover, it defines the list of medicines undergoing intensive monitoring registries and manages the national ADRs Network in order to promptly identify potential risk signals and ensure a favourable benefit/risk ratio through the National Pharmacovigilance Network, together with the EudraVigilance European Network.

• **Product Quality Office** handles and takes care of the rapid alert quality reports as well as the post marketing controls, national and international warnings relating to quality flaws batch withdrawals and requisition , medicine shortages and suspension of marketing authorization.

• **Medical Scientific Information Office** provides pharmaceutical information/training addressed to healthcare professionals, together with the Guidelines for the authorisation of pharmaceutical products.

**Area 4 – Economic Strategies and Pharmaceutical Policy:**

• **Research Study Centre** implements and evaluates studies on pharmaceuticals research. It defines models and procedures in order to boost investment in R&D of generic pharmaceutical products in Italy. It predicts the impact of technological innovations on pharmaceutical and health expenditure, as well as the allocation of resources. Moreover, it proposes updates on the pricing & reimbursement system, also on the basis of the analysis of the generic products' reference prices at international level.

• **Pricing & Reimbursement Office** performs marketing analysis and is responsible for negotiations with pharmaceutical companies. It manages inquiries from the Pricing & Reimbursement Committee (CPR) for price negotiation . It analyses reimbursement and market prices of pharmaceutical products, including generics, at international level.

• **Medicines Utilisation and HTA Office** monitors pharmaceutical consumption and expenditure in outpatient and inpatient settings, through the support of the National Observatory on the Use of Medicines (OsMed). It also manages and updates the medicinal products database and produces statistical and epidemiological analysis with reference to different European Countries. It is responsible for the evaluation and the implementation

of Heath Technology Assessment (HTA) activities, through its participation in the EUnetHTA Joint Action project. Moreover, it conducts assessments on the consequences on welfare as well as the economic, social and ethical ones , resulting from the use of medicines on the market and from those new medicines introduced to support policies implemented by the Agency.

**Area 5 - Inspections and Certifications Office:**

• A**uthorisation production workshop Office** decides on authorizations, suspensions and production workshops withdrawals. Moreover, it performs controls over all the production cycle and grants authorization to import medicines and pharmacologically active raw materials. Furthermore, it issues the certificates of pharmaceutical product for exclusive export (CPP) and performs activities related to the production and import of experimental products within public hospitals.

• **Inspection Office** verifies the Good Manufacturing Practice (GMP) on the production of medicines, medical gases and raw materials intended for production of medicines. It also performs inspections among haematological facilities, together with the National Institute of Health (ISS)., .

Other offices operating at the AIFA include :

• **Presidency Bureau**, which assists the Board of Directors in carrying out its duties

• **Press and Communications Office**, responsible for the management of relations with other public and private information Organisations, as well as with national and international mass-media systems. It supervises Italian and foreign information and carries out press review activity and promotes programs and editorial initiatives of institutional information. Finally, it provides information to the public, including information on health and pharmaceutical education to citizens.

Finally, the following offices with staff functions provide technical and secretariat support to the activities of the General Directorate and of the above mentioned functional areas:

- Quality Assurance
- International Relations
- Technical Secretariat Office
- Performance and Management Control
- Executive Unit for Information Technology (IT).

AIFA's scientific authority and autonomy is supported by the activities of 2 Committees:

Technical Scientific Committee (CTS): it assesses the national and European marketing authorisation applications and delivers a consultative opinion on them. It provides binding opinions on the therapeutic value of medicines by defining the place in therapy and the role of the medicine in the specific therapeutic context; it expresses binding opinions on

the innovativeness and on the provision systems for a medicinal product. Moreover, it gives specific recommendations on the ways medicines are distributed and provides classification for reimbursement. It provides opinions on the clinical trials and on the results of pharmacovigilance activities;

Pricing & Reimbursement Committee (CPR): it carries out the negotiation activity with pharmaceutical companies for the setting of prices of medicinal products reimbursed by the National Health Service. It establishes the preliminary steps for the negotiation according to the dossier provided by the applicant and criteria set by the CTS concerning place in the therapy, innovativeness and provision of the medicinal product. In addition, this Committee endorses the outcome of the negotiation held with the manufacturer, including the price, reimbursement conditions and method for provision of the medicine. After two years of negotiation, the CPR reassesses the product, to ensure conditions of eligibility and price are efficient, according to the economic considerations.

## 1.3 Medicines' reimbursement and distribution

Decision-making processes concerning pricing and reimbursement of pharmaceuticals and provision methods vary across European countries. In Italy this process is in charge of AIFA. Those medicines included in the National Pharmaceutical Formulary and completely reimbursed by NHS are classified as Class A (Class H when medicines are dispensed in hospital setting or equivalents), (Art. 8, paragraph 10, letter A, Law n. 537 of December 24, 1993). Otherwise, medicines can be classified as Class C when not reimbursed by NHS, (with the exception of subjects with a lifetime war pension), (Act n. 203 July 19, 2000).
NHS reimbursed medicines include essential products, intended for chronic diseases care, reimbursed for each authorized therapeutic indication. In some cases, reimbursement is granted through so-called 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 C without obligation of prescription (C - SOP)). Among non-reimbursed pharmaceuticals, those classified as Class C-bis (Art. 8, paragraph 10, letter C - bis, Law n. 537 of December 24, 1993, modified by the Act n. 311 of 2004) are defined as over-the-counter(OTC). These products can be dispensed without prescription and can be promoted directly by pharmaceutical companies. When a pharmaceutical company submits to AIFA the pricing and reimbursement dossier, competent offices and advisory committees initiate a preliminary investigation to evaluate and establish the reimbursability of the product. At the end of the decision making process, once the Pricing & Reimbursement Committee (CPR) has concluded the negotiation procedure, the final decision concerning reimbursability classification, provision methods and price, is ratified by AIFA's Board of Directors and published in the Official Journal (*Gazzetta Ufficiale*).
In terms of provision methods (According to Article n. 87 of the Law Decree n. 219 of April24, 2006), medicines are classified as follows:

a) requiring a medical prescription (RR)
b) requiring a new medical prescription each time (RNR)
c) requiring a special medical prescription (RMS – Single Act (*Testo Unico*) about narcotics (Presidential Decree n. 309 of October 9, 1990 and following amendments)
d) under a restricted medical prescription, including:
    1) medicines dispensable only with a prescription released by Hospitals or Specialists (RRL and RNRL)
    2) medicines to be used exclusively in a Hospital or analogous healthcare facilities (OSP)
    3) medicines to be used/administered exclusively by the specialist (USPL)
e) medicines not requiring a medical prescription:
    1) over the counter medicines (OTC)
    2) medicines not requiring a medical prescription (SOP).

The repeatable prescription (RR) is the most common type of prescription. Its validity period is six months, 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 days validity and repeatable for no more than three times.
The repeated limited prescription (RNR) 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 (RR), since the patient cannot obtain the medicines without a new prescription being issued.
The validity is of thirty days and is restricted to the number of packages indicated (in case of compounding preparations containing narcotics the prescription has a three months validity). A peculiar case is represented by the isotretinoin, whose prescription and delivery can take place only within teratogenic risk prevention programs and with a RNR prescription with a seven day validity.
The RRL and RNRL prescriptions are used for medicines dispensable only by specific healthcare facilities' and/or specialists.
Some medicines cannot be sold to citizen, even if available in pharmacies, but can be provided only to specialists, who can also purchase them from pharmaceutical companies and wholesalers.
AIFA Resolution dated January 13, 2010, available on the Official Journal supplement n. 21, has updated the supply methods of OSPs. The previous system of supply, OSP1 and OSP2, was abrogated and the new system came into effect starting from February 16, 2010.
The OSP1 medicines became OSP (see above), without additional changes. The OSP2 system supply was modified in RR, RNR, RRL or RNRL. At a later stage, as a result of Article n. 11, paragraph 7 a of Law Decree n. 78 of May 31, 2010, transposed, with amendments, into Law n. 122 of July 30, 2010, many Class H medicines delivered by a RR, RNR, RRL or RNRL prescription were reclassified as Class A-PTH (AIFA Resolution dated November 2, 2010).
The Class A-PHT includes those medicines dispensed through direct distribution in order to ensure Hospital-Community continuity of care.

**Table 1.3.1.** Number, Class and prescription system of authorised and marketed medicines during 2013

| Class | Prescription System | N. AIC | % per Class | % on total |
|---|---|---|---|---|
| A | RR | 7.320 | 89,5 | 48,2 |
| | RNR | 335 | 4,1 | 2,2 |
| | RNRL | 206 | 2,5 | 1,4 |
| | RRL | 135 | 1,7 | 0,9 |
| | OSP | 82 | 1,0 | 0,5 |
| | RMS | 66 | 0,8 | 0,4 |
| | SOP | 29 | 0,4 | 0,2 |
| | USPL | 4 | 0,0 | 0,0 |
| **Total Class A** | | **8.177** | **100,0** | **53,9** |
| C | RR | 2.805 | 50,0 | 18,5 |
| | OTC | 884 | 15,8 | 5,8 |
| | SOP | 867 | 15,5 | 5,7 |
| | OSP | 771 | 13,8 | 5,1 |
| | RNR | 164 | 2,9 | 1,1 |
| | USPL | 70 | 1,2 | 0,5 |
| | RNRL | 23 | 0,4 | 0,2 |
| | RRL | 11 | 0,2 | 0,1 |
| | RMS | 11 | 0,2 | 0,1 |
| **Total Class C** | | **5.606** | **100,0** | **36,9** |
| H | OSP | 1.096 | 78,5 | 7,2 |
| | RR | 128 | 9,2 | 0,8 |
| | RLNR | 99 | 7,1 | 0,7 |
| | RRL | 35 | 2,5 | 0,2 |
| | RNR | 34 | 2,4 | 0,2 |
| | USPL | 5 | 0,4 | 0,0 |
| **Total Class H** | **TOTAL CLASS** | **1.397** | **100,0** | **9,2** |
| **Total** | | **15.180** | | **100,0** |

In Italy there are several ways to supply NHS reimbursed medicines according to the type of prescription and use (primary and secondary care).
Particularly, the prescription of reimbursed medicines for out-patients refers to GPs, Pediatricians and NHS specialists who can also prescribe medicines requiring a special authorization: *Piano Terapeutico – PT*, while the distribution occurs through two channels, being the standard and direct distribution.
The standard distribution consists of supply of medicines prescribed by GPs, Pediatricians and NHS specialists by public and private community pharmacies, while direct distribution provides for the supply to patients directly by Hospitals, in order to guarantee health

status of patients, cost containment and Hospital-Community therapeutic continuity (e.g. 1st cycle of treatment at patient's discharge, specialized out-patient visits), or, alternatively, supply by community pharmacies, following the drawing up of agreements between pharmacist and local health unit (so called *per conto* distribution), for subjects with chronic diseases requiring continuative pharmaceutical care (Article n. 8 of Law n. 405 of 2001).
Pharmaceutical hospital care concerns, refers specifically to the administration of medicines within NHS health facilities. However, hospital consumption of medicines also includes *direct* and *per conto* distribution Class C and H medications for the purpose of pharmaceutical hospital expenditure monitoring, in accordance with Law n. 135 of 2012 and its amendments.

## 1.4 Medicine distribution chain margins and discounts for NHS

According to Law n. 662 of 1996 and its amendments, distribution margins of pharmaceutical companies, wholesalers and pharmacies are fixed respectively at 66,65%, 3,0% and 30,35% of the retail price, net VAT. Moreover, Law n. 135 of August 7, 2012 establishes an additional discount amounting to 2,25% in favor of the NHS, to be applied to pharmacies. This discount pertains both off-patent and patented medicines, while it is not applied to:

- rural pharmacies with national assistance (pharmacies located in towns with less than 3.000 inhabitants) and sales volumes below 387.342,67 euros, net VAT, per year;
- rural and urban pharmacies, without national assistance, and sales volumes below 258.228,45 euros, net VAT, per year.

Moreover, pharmaceutical companies have to correspond to Regions an additional discount of 1,83% of the retail price, net VAT.
According to Law Decree n. 39 of April 28, 2009 distribution margins of generics are calculated as follows: 58,65% (pharmaceutical company), 6,65% (wholesaler) and 26,70% (pharmacist). In addition, a remaining 8% is shared between pharmacists and wholesalers, according to market agreements.
The pharmacies' discounts for NHS, starting from January 1, 2013, are reported in table 1.4.1.

**Table 1.4.1** Discounts applied to pharmacies and in favor of the NHS

| **Price range** | **Rate for urban and rural pharmacies without national assistance** | | **Rate for rural pharmacies with national assistance** | |
|---|---|---|---|---|
| Price in euros | With sales volume >€ 258.228,45 | With sales volume <€ 258.228,45 | With sales volume >€ 387.342,67 | With sales volume <€ 387.342,67 |
| Range 0 - 25,82 | 3,75% | 1,50% | 3,75% | flat-rate 1,5% |
| Range 25,83 - 51,65 | 6,0% | 2,40% | 6,0% | flat-rate 1,5% |
| Range 51,66 - 103,28 | 9,0% | 3,60% | 9,0% | flat-rate 1,5% |
| Range 103,29 - 154,94 | 12,50% | 5,0% | 12,50% | flat-rate 1,5% |
| Over 154,94 | 19,0% | 7,60% | 19,0% | flat-rate 1,5% |
| Further discount | 2,25% | - | 2,25% | - |

## 1.5 Pharmaceutical price

Since January 1st, 2004, the prices of all medicines reimbursed by the NHS are set through negotiation procedure between AIFA and pharmaceutical companies, following methods and criteria previously adopted only for medicines approved under European procedures.
During negotiations the parameters taken into account are those defined by the CIPE Resolution n. 3 of 2001 (*CIPE- Comitato Interministeriale per la Programmazione*, Interministerial Committee for Economic Planning):

- economic impact on the NHS;
- prices in other EU Countries;
- cost of treatment per day compared to the cost of medicines with similar effectiveness;
- benefit/risk ratio compared to medicines with the same therapeutic indication;
- cost/effectiveness ratio when other treatment options are available;
- level of innovation.

According to the new AIFA Regulation of October 2009, pricing and reimbursement process occurs in four steps:

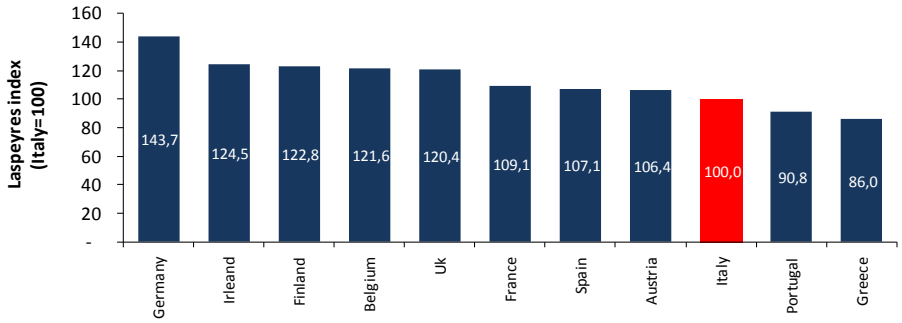
1. pharmaceutical company applies for the pricing and reimbursement procedure by submitting the dossier to AIFA
2. CTS provides its judgment concerning the reimbursement condition according to clinical-therapeutic evaluations
3. CPR evaluates the dossier and then meets the pharmaceutical company for the negotiation procedure
4. result of the negotiation are submitted to the Board of Directors for a final evaluation.

The CTS and CPR express their decisions within 180 days from the application and the *ex-factory* price is published in the Official Journal (*Gazzetta Ufficiale*).

Law Decree n. 69 of June 21, 2013 (converted with amendments in Law n. 98 of August 9, 2013) establishes as a priority, compared to other pending procedures, the assessment of orphan drugs and of medicines with exceptional therapeutic value and considered of social relevance, and sets a time limit for the assessment of these products of 100 days. This time limit is expected to be respected also by resorting to Committees' extraordinary sessions.
The price of Class A medicines, dispensed by community pharmacies, is published in the Official Journal and is equal to the retail price per single package, inclusive of citizen co-payment, as well as pharmacists and pharmaceutical companies mandatory discounts and VAT. Consequently, the price of the NHS reimbursed medicines corresponds to the retail price net of discounts, citizen co-payment and VAT.
The price of Class H and A medicines distributed by public health facilities corresponds to the price, VAT inclusive, resulting from procurement tenders or from HLUs (or Regions) negotiations with pharmaceutical company.
Pharmaceutical companies establish Class C pharmaceutical prices, which are then communicated to AIFA without any publication in the Official Journal. Increases in the price of Class C medicines are allowed only in the month of January of odd-numbered

years (Law Decree n. 87 of May 27, 2005, modified, with amendments, into Law n. 149 of July 26, 2005). The price level of pharmaceutical in Italy in year 2013 was estimated to be the lowest in Europe.
Figure 1.5.1 compares pharmaceutical prices across some EU Countries. This figure shows that almost all of European Countries, with the exceptions of Spain, Portugal and Greece, have higher average prices than Italy (Reference = 100), with a minimum of +7,1% in UK and a maximum of +19,6% in Ireland.
Note: the significant modification of prices (expressed as %) shown in Figure 1.5.1, when compared with those of 2012 OsMed Report, is due to the inclusion of medicines dispensed by hospital pharmacies.

**Figure 1.5.1.** Prices across European Countries in 2013 (Laspeyres index has been applied to ex-factory prices) *




*without hospital data

## 1.6 Citizens co-payment

According to Law n. 405 of 2001, Regions have the possibility to introduce or increase citizens co-payment, by introducing or increasing per medical prescription or per package co-payment (*ticket*), in order to balance possible Regional budget deficits. This financial measure has originally been implemented only in Regions undergoing debt rescheduling and, then, almost all across the Country.
However, citizens co-payment also derives from the payment of the difference between the price of the purchased medicine and that of the reference medicine (i.e. the lowest price) for off patent medicines. Since December 1, 2001 AIFA provides a monthly publication of the Transparency List (*Liste di trasparenza AIFA*), in order to identify a unique reference price for all substitutable packages. In more detail, if there are two medicines with the same active ingredient, administration route, pharmaceutical formulation and posological units, then the NHS reimburses only the one with the lowest price. Law n. 122 of July 30, 2010 provided for the reduction of pharmaceutical reference prices of products in the Transparency Lists, by conforming the prices of generics to EU

prices (Germany, UK, France and Spain). In accordance with Article 5, paragraph 4 of Law n. 222 of 2007, the option for a Region to reduce pharmaceutical expenditure became an obligation. In fact Regions must adopt measures for pharmaceutical expenditure containment. The minimum percentage of expenditure containment is fixed at 30% of the total NHS pharmaceutical expenditure deficit. These manoeuvres are considered as Regional fulfilments for the purpose of access to additional financing from the Government.
At National level, the total co-payment expenditure amounted to 1,4 billion euros, 12,8% of the NHS pharmaceutical expenditure. During 2013 the per capita co-payment expenditure was 24,1 euros, a booming 1,6% over the previous year, 39% of which derived from regional co-payment while the remaining 61% originated from the difference between the price of the off patent prescribed medicine and the reference price (determined by AIFA's Lists of transparency).

## 1.7 Off patent medicines

Off patent medicines' regulation has experienced a significant boost in Italy, mainly due to the legislative measures enacted starting from 2000. The Transparency List mentioned previously have indeed been introduced by Article 85, paragraph 28 of Law n. 338, 2000. These lists gather the off patent products together with the corresponding NHS price, which on a monthly basis are published on the AIFA website.
Several aspects concerning off patent medicines were clarified and strengthened with the adoption of Law n. 405 of 2001. The key points outlined by the aforementioned law can be summarized as follows:

- only patents on active ingredients are considered valid for the purpose of patent protection
- all products based on the same active ingredient, pharmaceutical formulation, number of standard units and route of administration (both branded and un-branded medicines) at the expiration of the patent protection date are considered reciprocally replaceable.
- the pharmaceutical package with the lowest price among those considered equivalent and reciprocally substitutable, shall be considered the reference price charged to the NHS. Any difference between the price of the prescribed medicine and the reference price is borne by the patients (with the exception of war invalid pension holders)
- Regions are given the opportunity to take appropriate measures on generic medicines based on their current availability within the regional distribution circuit.

It should be noted that in Italy in 1991, the Complementary Protection Certificate (*Certificato Complementare di Protezione*, CCP) was introduced, allowing the extension of the pharmaceutical patent protection of an extra 18 years, thus extending the possible total period for exclusivity rights of a molecule to a maximum of 38 years.

Furthermore, EC Regulation n. 1768 of 1992 outdated *de facto* the national legislation on the CCP introducing a Supplementary Protection Certificate (*Certificato Protettivo Supplementare*, SPC), providing an extra 5 year protection after patent has expired. However, given that the CCP came into force in Italy before the SPC, a large number of active ingredients available in the Italian market (about 80%) had already benefited of a considerably longer coverage compared to other European Countries. Consequently, savings for the NHS - resulting from the loss of patent protection - had been postponed as a result of the impossibility of marketing those generic medicines in Italy, whilst these had been marketed in other European Countries.
In order to mitigate the above mentioned negative effects, a progressive adaptation measure was introduced (according to the Law n. 112 of 2002), in an effort to align the CCP life spam to that of other European Countries. As a result, a reduction of six months in each calendar year from January 1 of 2004 was fixed.
In Accordance with Law Decree n. 39 of 2009 (converted with amendments in the Law n. 77, June 24, 2009) provisions regulating economic aspects of the pharmaceutical market in Italy were introduced. These can be described as follows:

1. generic medicines' reduction by 12% retail price;
2. 1,4% discount (on pharmaceutical gross expenditure) in favour of the NHS deducted from the pharmacists' remuneration, as a result of the discounts granted by pharmaceutical companies in 2008;
3. reduced distribution chain margins on generic medicines by 58,65% for pharmaceutical companies. The remaining 8% share (to 66,65%) is redistributed among wholesalers and pharmacies (shares of pharmacies and wholesalers have then been modified by Law n. 122 of 2010 -see section 1.4);
4. Off patent medicinal product marketing authorisation holders (MAH) can reduce a medicine's retail price after nine months from the licensing date of the first generic product, only if the difference between the new price and the price of the generic medicine exceeds:

- 0,50 euro for those medicines whose cost is ≤5 euros
- 1 euro for those medicines whose cost is between 5 and 10 euros
- 1,5 euros for those medicines whose cost is >10 euros (this provision was subsequently withdrawn by Law Decree n. 179 of October 18, 2012 (converted with amendments in Law n. 221 of December 17, 2012).

Subsequently, Law n. 122 of July 30, 2010 reduced – once again– the generic medicines retail price by 12,5%, from June 1 to December 31 of 2010, with the exception of originally patented medicines or those products which had benefited from licenses arising from such patents. Finally, following AIFA Resolution dated April 8, 2011, reference prices of medicines in the Transparency List were reduced, as a result of an analysis regarding prices in force in other countries of the European Union. A description of new reference price setting methodology is available on AIFA's website (http://www.agenziafarmaco.gov.it/it/content/elenco-dei-farmaci-lista-di-trasparenza-aifa-vigore-dal-15-aprile-2011).

**Table 1.7.1.** Active ingredients which have lost patent protections in 2013, or new active ingredient packages which had previously lost their patent protections and which were included in AIFA's lists of transparency, are listed below.

| Active ingredient | Price reduction effect | Price reduction |
|---|---|---|
| ***Active ingredients or new packages that lost patent protection before 2012/12/1*** | | |
| Zoledronic acid | 20/05/2013 | 66% |
| Ibandronic acid | 12/02/2013 | 40% |
| Acetilsalicilic acid | 16/09/2013 | 35% |
| Montelukast | 15/01/2013 | 60% |
| Acitretine | 15/04/2013 | 27% |
| ***Active ingredients that lost patent protection between 2012/12/1 and 2013/12/1*** | | |
| Irbesartan and hydrochlorothiazide | 16/10/2013 | 72% |
| Rizatriptan | 16/09/2013 | 60% |
| Ziprasidone | 15/05/2013 | 45% |
| Raloxifene | 16/09/2013 | 48% |
| Lamivudine/zidovudine | 24/04/2013 | 55% |
| Nevirapine | 24/06/2013 | 57% |

**Table 1.7.2.** List of Class A and H active ingredients which are going to lose their patent protection and are expected to be marketed as generic products in 2014

| Active ingredient | Marketing launch | Reimbursement class | Price reduction |
|---|---|---|---|
| ***Active ingredients or new packages that lost patent protection before 2013/12/1*** | | | |
| Aceclofenac | - | A | 45% |
| Lymecycline | - | A | 45% |
| Sildenafil | - | A | 30% |
| Oxycodone | - | A | 45% |
| Capecitabine | 16/12/2013 | H | 60% |
| Efavirenz | 02/12/2013 | H | 35% |
| Atosiban | 01/04/2014 | H | 30% |
| **Active ingredient** | **Patent expiration** | **Reimbursed class** | **Price reduction** |
| ***Active ingredients going to lose patent protection between 2013/12/1 and 2014/12/1*** | | | |
| Telmisartan | 16/12/2013 | A | 70% |
| Escitalopram | 01/06/2014 | A | 65% |
| Moxifloxacine | 20/06/2014 | A | 55% |

Provisions regulating medical prescriptions of off-patent medicines and medicines reimbursed by the NHS underwent a number of amendments. In fact, general prescribers (GPs) were encouraged to indicate on the medical prescription the active ingredient and dosage of a pharmaceutical product, rather than the brand name. This regulation arises from the combined application of Article 11, paragraph 12 of Law Decree n. 1, January 24, 2012, (so-called "*Decreto Liberalizzazioni*") and Article 15, paragraph 11-bis of Law Decree n. 95, July 6, 2012,followed by other amendments (Law n. 135, August 7, 2012 so - called "*Decreto sulla Spending Review*" , subsequently replaced by Article 13-bis, paragraph 1 of the Law Decree n. 179, October 18, 2012, and Law n. 221, December 17, 2012). For further information please refer to the guideline on the electronic prescription procedures (http://sistemats1.sanita.finanze.it/). In order to enable the legislation implementation, AIFA provides lists of Class A and H pharmaceutical prices, that are published on AIFA's website on a monthly basis. According to these lists, generic medicines are grouped into equivalent subgroups, in order to cluster medicines containing the same active ingredient, as well as, strength, pharmaceutical form, number of standard units and route of administration.
These interventions are aimed at fast-tracking generic medicines market access. In particular, Article 12, paragraph 6, of Law Decree n. 158 of September 13, 2012 (replaced by Law n. 189 of November 8, 2012) envisions the possibility to grant a generic product automatic insertion in reimbursement class, without undergoing price negotiation, in cases where the price proposed by the company is clearly convenient for the NHS. In 2013, a Decree of the Ministry of Health dated April 4 of 2013, established ranges of price reduction according to the expected sale volumes (Table 1.7.3).

**Table 1.7.3.** Pharmaceutical price reduction ranges based on average annual expenditure in the three previous years

| NHS pharmaceutical Exp. Ranges (Million €) | Class A medicine price reductions* | Class H medicine price reductions* |
|---|---|---|
| 0-19,99 | 45,0% | 30,0% |
| 20-39,99 | 47,5% | 31,7% |
| 40-59,99 | 50,0% | 33,3% |
| 60-79,99 | 55,0% | 36,7% |
| 80-99,99 | 60,0% | 40,0% |
| 100-139,99 | 65,0% | 43,3% |
| 140-179,99 | 70,0% | 46,7% |
| 180 and over | 75,0% | 50,0% |

With reference to off-patent medicines, an area of increasing importance is represented by biosimilar products. On May 2013, the Agency published a Position Paper summarizing the results of the activity undertaken in this regards in 2012. Three are the relevant points reflected upon:

1. definition and criteria to characterise the biological and biosimilar medicines
2. background of EU regulatory requirements about biosimilar medicines
3. biosimilar medicine role and the NHS economic sustainability.

The document can be downloaded by using the following link:
http://www.agenziafarmaco.gov.it/sites/default/files/AIFA_POSITION_PAPER_FARMACI_BIOSIMILARI.pdf).

This Biosimilars Position Paper clarified the Agency's position with regards to substitution of previously patented biological medicines with biosimilar medicine, through the provision of elements concerning economic sustainability and considerations on health care protection.

Following the publication of AIFA's position paper, the Agency received several clarification requests on biosimilar products' use. Thus AIFA considered worthwhile to conduct once again a public consultation, and fixed a deadline for a submission of comments (May 16, 2014).

## 1.8 Innovative medicines

The assessment of pharmaceutical innovation is a complex and dynamic process. The complexity in defining potential 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 is essentially due to the continuous evolution of scientific knowledge and to the consolidation of scientific evidences. Therefore, a medicine originally considered as innovative could later generate - in the real world practice - different benefits from those expected, or could simply become irrelevant as a result of the development of new therapeutic options. At a European level, Italy was among the first countries adopting a complex system of laws and rules for the assessment and patient access of innovative medicines. In particular, the pharmaceutical innovation definition and its evaluation, together with the procedures for awarding the innovative designation to a medicine, fall under the competence of AIFA's Committees. Pursuant to Law n. 222 of 2007 (Art. 5, paragraph 2, letter a), AIFA's CTS is responsible for the issuing of binding opinions on the innovativeness of a pharmaceutical product. The practical effects of the status of innovative medicine are essentially two:

- the opportunity of taking advantage of the suspension both of the first retail price's reduction (-5%), pursuant to AIFA Resolution of July 3, 2006 and of the second price reduction (- 5%), as provided for in AIFA Resolution of September 27, 2006
- concerning aspects related to pharmaceutical expenditure, innovative medicines are not subject to any budget constraints and benefit from a solely dedicated Innovation resource fund .In case the national pharmaceutical expenditure ceiling is exceeded (see next section 1.10), if expenditure for innovative medicines exceed the Innovation fund value set at the beginning of the year, then these medicines do not participate in the payback, which is conversely distributed among Marketing

Authorization Holders in proportion to their sales volumes for non- innovative and off patent medicines.

Provision of Law n. 222 of 2007, initially meant for the outpatient setting only, were subsequently extended to include the in-patient setting, in accordance with Article 15, paragraphs 4-11 of Law Decree n. 95 of 2012 (converted into Law n. 135 of August 7, 2012). The incremental resources allocated for pharmaceutical innovation, both in the outpatient sector and in the inpatient sector , are set at20% and 80% (as a maximum quota) respectively.

In order to define and assess pharmaceutical innovation of new pharmaceutical products entering the Italian market, the CTS set forth criteria (approved in the course of the meeting held on July 10 of 2007) to be met to determine the degree of innovation of a products. This evaluation initially considered therapeutic outcomes only . At a later stage, according to the Resolution n. 27 of December 18, 2009 of the Board of Directors, the CTS was conferred competence as regards the issuing of on the place in therapy and on the degree of innovation, both from a scientific and from a therapeutic point of view. In fact, the concept of innovation of a medicine was widened and its evaluation became more detailed. For this reason, the Agency decided to pursue a path, still ongoing, towards re-engineering, of the Commissions' preliminary activities and of the methods for participation of Members to decisions concerning innovation assessments. These methods were synthesised in the development of an algorithm , developed as an instrument to assess therapeutic innovation of medicinal products. A survey on the algorithm was preliminarily circulated to members of CTS, CPR and AIFA Board of Directors on April 8, 2013. A public consultation was then launched, resulting in approximately 84 requests for participation.

Currently, the algorithm is undergoing discussion by sector-specific experts, and Regions' representatives This tool aims at ensuring homogeneity of access nationwide to medicinal products appraised as innovative and thus considered as a priority for public health safeguard.

Against this background, the State-Regions Agreement dated November 18, 2010 (O.J. n. 6 of January 1, 2011) provides for the publication of a list of innovative medicines by AIFA and immediate inclusion of innovative medicines in the therapeutic regional hospital formularies. The agreement also includes rules regulating cases in which conflicting opinions are issued by CTS and Regions. This setup was confirmed and further extended by the so-called "*Balduzzi*" Law Decree (Article 10, paragraphs 2-5, Law Decree n. 158 of September 13, 2012, with amendments in the Law n. 189 of November 8, 2012).

Even though the connotation of the concept of innovation appears sufficiently general, recalling the State-Regions Agreement rather than Law n. 222 of 2007 and Law n. 135 of 2012, determine significant differences from a juridical point of view As mentioned previously, the status of innovative medicine entails a variety of economic benefits, as provided for by Law n. 222 of 2007 and Law n. 135 of 2012, which are limited in time (usually 36 months) and that can be subject to revaluation as new scientific evidence arises. However, innovative medicines are kept on the innovative medicines list issued by AIFA even after the expiration of economic benefits, unless otherwise decided by the CTS. The regulatory distinction between the two regulations allows to discern, on the one hand, the need for fast market entry of innovative medicines and timely patient access to

treatment, without considering economic constraints (i.e. the Innovation fund according to Law n. 222 of 2007 and Law n. 135 of 2012) and, on the other hand, the need for priority inclusion and maintenance of these medicines in regional therapeutic formularies, which depend on the availability or absence of more innovative medicines approved in the meantime. This approach was later modified by the CTS. In fact, it was decided to combine the status of innovative medicines included in the Innovation fund with the inclusion in the therapeutic regional formularies. An example of this list is available at: (http://www.agenziafarmaco.gov.it/sites/default/files/Lista_dei_farmaci_innovativi_31.10.2013.pdf).

**Table 1.8.1** List of innovative medicines updated by CTS on October 2013 and their classification in relation to the above referenced regulations

| ATC | Active ingredient | Grade of innovatineness | Reimbursement class | CTS opinion | Outpatient innovativeness fund L.222/2007 | Inpatient innovativeness fund L.135/2012 | Deadline |
|---|---|---|---|---|---|---|---|
| L04AA27 | Fingolimod | Potential | A | 30/05/2011 | X | X | 06/12/2014 |
| L02BX03 | Abirateron | Potential | H | 15/11/2012 | | X | 05/04/2016 |
| L01XC11 | Ipilimumab | Significant | H | 30/10/2012 | | X | 08/03/2016 |
| L03AX16 | Plerixafor | Potential | H | 03/05/2011 | | X | 08/12/2014 |
| M09AB02 | Collagenase | Potential | H | 06/03/2013 | | X | 13/03/2016 |

## 1.9 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 are excluded from the pay-back procedures according to the hospital pharmaceutical expenditure regulation, pursuant to Article 15, paragraph 8, letters i and i-bis of Law n. 135 of 2012,amended by Law n. 147 of December 27, 2013. All rare diseases amount to about seven thousand.
For this reason rare diseases represent a significant social problem, involving millions people: according to estimates, patients affected in Europe are over thirty million, of which2-3 million in Italy.

### European legislation

The first regulation concerning orphan medicinal products, the so - called Orphan Drug Act, was introduced in the USA in 1983,. In the European Union, the issue of orphan drugs was addressed by Regulation(EC) n. 141 of 2000 of the European Parliament and of the

Council of the European Union and later Regulation (EC) n. 847 of 2000 of the European Parliament and of the Council. These regulations set up criteria and procedure for orphan drug designation, and provides 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 drug is achieved through a centralised procedure. In some cases, for the purpose of accelerating marketing of the product, a medicine may be granted an authorisation, even though the trials have not yet been completed. This authorisation under conditional approval is eventually renewed on an annual basis. For a product to be granted conditional marketing authorisation, the following conditions should be respected:

- Positive benefit/risk ratio
- It is likely that the applicant will be able to provide more comprehensive clinical data
- Fulfilment of an unmet medical needs
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required

Once the evaluation is completed, if the Committee for Medicinal Products for Human Use (CHMP) issues a favourable opinion as to whether to grant the authorisation, the European Commission formally issues the authorisation. Furthermore, Article 14, paragraph 8 of EC Regulation n. 726 of 2004, states that in exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident 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 reasonably be expected to provide comprehensive evidence).
Continuation of the authorisation shall be linked to the annual reassessment of these conditions.

**Italian legislation**

Throughout 2013, in order to facilitate orphan drugs access some regulations were issued. In particular, the so-called Legge di Stabilità has introduced a mechanism of economic protection for orphan medicinal product marketing authorization holders. In fact, in case the national pharmaceutical expenditure ceiling is exceeded, orphan medicinal products MAHs are excluded from the payback, which is conversely distributed among marketing authorization holders in proportion to their respective pharmaceutical income sales volumes. Pursuant to Article 15, paragraph 8, letter i, and i-bis of Law Decree n. 95 of 2012, converted with amendments into Law n. 135 of 2012, then modified by Article 1, paragraph 228, of Law n. 147 of December 27, 2013,AIFA's Board of Directors (February 27, 2014) approved the list of orphan medicinal products for the treatment of rare diseases and the chosen criteria as prescribed by law. On the basis of this list, AIFA identifies orphan medicinal products which will benefit from the 2013 hospital pharmaceutical expenditure legislation provisions. 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) n. 141 of 2000 of the European Parliament and of the Council of December 16, 1999 (concerning the 10 years of market exclusivity) and Article 8 of Regulation of December 31, 2013
2. medicines referred to in paragraph 1, are included in the list only if they hold a marketing authorisation in Italy. The following are thus excluded:

a. orphan medicinal products not reimbursed by the NHS as referred to in letter c) and c - bis) of Article 8, paragraph 10, of Law n. 537 of December 24, 1993
b. orphan drugs reimbursed by the NHS, as referred to in letter 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 authorization 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 then lost the orphan designation, as a result of the Marketing Authorization Holder's request or following COMP (EMA) revaluation.

3. any medicinal product which, pursuant to Article 15, paragraph 8, letter I - bis of Law Decree n. 95 of 2012, converted into Law n. 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, letters 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. These are:

a. product authorised also for the treatment of non - rare diseases or conditions
b. products authorized for the treatment of diseases or conditions, whose MAH has not submitted as at December 31, 2013 the requests to benefit from provisions of Article 15, paragraph 8, letter i) of Law Decree n. 95 of 2012, converted into Law n. 135 of 2012 and later amended by Article 1, paragraph 228, of Law n. 147 of December 27, 2013.

The list resulting from the application of the above-mentioned criteria has been drawn upon for the analysis on orphan drug expenditure and consumption (Table 1.9.6). In order to increase orphan drugs availability nationwide, the so-called Balduzzi Law (Law n. 189 of 2012, Article 12, paragraph 3) provides for the possibility for marketing authorization holders to apply 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 n. 69 of June 21, 2013, and Law n. 98 of August 9, 2013 (article 44), AIFA gives orphan drugs pricing and reimbursement dossiers (together with those concerning medicines of

exceptional therapeutic relevance) 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 main access route; in cases where an orphan drug has no marketing authorization, a patient access is ensured through one of the following:

- Law n. 648 of 1996, allowing the use of a medicine on a national basis
- Law n. 326 of 2003, Article 48 (5% AIFA Fund) , Ministerial Decree of May 8, 2003 (compassionate use) in addition to Law n. 94 of 1998 (former *Legge Di Bella*), that, unlike Law n. 648, regulate pharmaceutical prescription for individual patient on a nominal basis.

**Law n. 648 of 1996**

This regulation 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). For the purpose of inclusion of a medicines in Law n. 648 list, one of the following conditions must be met:

- innovative medicines holding marketing authorization in other European countries, but not in Italy;
- medicinal products not yet authorized, but undergoing clinical trials, and for which results phase two clinical studies results are available;
- medicines intended for different therapeutic indication compared to those for which it is already authorised in Italy, and which have undergone phase two clinical trials.

The inclusion of a pharmaceutical product in the 648 list is performed by AIFA on documented request of patients associations, scientific societies, health facilities, and universities' or following recommendation of the CTS.

**Law n. 326 of 2003 (Article 48) the so – called 5% AIFA Fund**

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 of the treatment of serious conditions (i). The remaining 50% of the Fund is used to conduct research on the use of pharmaceutical products (ii; i.e. comparative trials on medicines intended to prove their additional therapeutic value, studies on the appropriateness of use and on information). This Fund is fuelled for 5% by pharmaceutical companies' annual expenditure for promotional activities intended for physicians (seminars, workshops, etc.) (Article 48, paragraph 19, letter a, Law Decree n. 269 of September 30, 2003, converted into Law. n.326 of November 24, 2003).
In 2013, the Fund amounted approximately to 17 million euros.

With reference to the purchase of the above-mentioned pharmaceutical products (i), requests to access the Fund are submitted to AIFA, through the 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, possible supporting scientific literature papers and a brief clinical report including a description of the therapeutic plan for each patient. The application must be supported by specific information, such as: dose per cycle, number of cycles and the price of the medicine. The application is assessed by the CTS which 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 the patient's treatment, AIFA releases the invoice reimbursement. In 2013, the total expenditure for patients accessing the AIFA Fund amounted to 183.382 euros.

The remaining 50% of the Fund is dedicated to the independent research on the use of medicines (ii). AIFA was the first medicines agency in Europe to include, among its tasks, the promotion of independent research on medicines intended for public and non -profit institutions. This need arises from the acknowledgment of the importance of independent research in areas lacking of a sufficient commercial interest. During 2005-2007, AIFA has dedicated particular attention to calls relating to rare diseases and orphan drugs, in order to carry out studies on the efficacy and safety profiles of these medicines and to improve assistance to these particular subsets of patients.
In particular, the specific topics were:

- evaluation of the benefit/risk profile of orphan drugs for rare diseases, approved or designated by the EMA
- evaluation of the benefit/risk profile in off-label use in rare diseases.

During these three years, AIFA allocated over 13 million euros for rare diseases. Moreover, in 2008 AIFA contributed to activity set forth by the Ministry of Health, with a 3.000.000 euros contribution for the initiation of 12 rare diseases studies

**Ministerial Decree of May 8, 2003 "**Therapeutic use of a medicine undergoing clinical trials" (compassionate use)

Despite considerable medical advances in the diagnosis and treatment of many diseases, there are still several therapeutic areas (so - called "niche") associated to unmet clinical needs which represent both a challenge and a major goal for health care providers. Against this background, the Italian Ministerial Decree of May 8, 2003 establishes procedures for "Therapeutic use of medicines undergoing clinical trials" (so - called "compassionate use of medicinal products"). The compassionate use provisions provide a pathway for patients to gain access to medicinal products for the treatment of serious, life threatening conditions, or rare diseases, for which no satisfactory authorised alternative therapy exists. Ethics Committees are responsible for granting authorization for access to experimental medicines, it being understood that the pharmaceutical company's declaration of willingness to supply the medicine free of charge. The application of this decree is intended to ensure access to experimental and innovative

therapies, as well as access to orphan drugs for a rare disease, in accordance with the therapeutic and non-testing purposes stated in the Ministerial Decree of May 8, 2003.

**Law n. 94 of 98, Art. 3, paragraph 2 (so - called Legge Di Bella)**

This legislation allows to prescribe a medicine for use outside the terms of its marketing authorisation, at the request of and under the responsibility of the prescribing physician, and with informed consent of the patient, in cases in which the patient cannot be usefully treated with treatments approved for that same therapeutic indication. Documents on the use of the medicine, in addition to positive results referred to phase two clinical trials successfully concluded, are required for such a prescription to be issued.

**Table 1.9.5**. Synoptic table regarding main requirements on orphan drug access according to Italian regulations

| Requirement | Law n. 648 of 96 | Law n. 326 of 2003 | M.D. of May 8, 2003 | Law n. 94 of 98 |
|---|---|---|---|---|
| Lack of alternative therapies | YES | Not detailed | YES | YES |
| Patient informed consent | YES | Not detailed | YES | YES |
| Supporting scientific documents | Phase II study positive results (concerning experimental medicines) | Patient's clinical report | Phase III study positive results, or in case of a patient life threatening conditions completed phase II results | Phase II study positive results |
| Physician responsibility | YES | Not detailed | YES | YES |
| Monitoring data transmission | AIFA and regional departments | - | Documents required by the M D of May 8, 2003, and approved by the local Ethics Committee | - |
| Payer's cost therapy | NHS | AIFA | Free supply by pharmaceutical companies | Patient, or NHS in case of hospitalisation |

**Orphan drug expenditure and consumption in Italy**

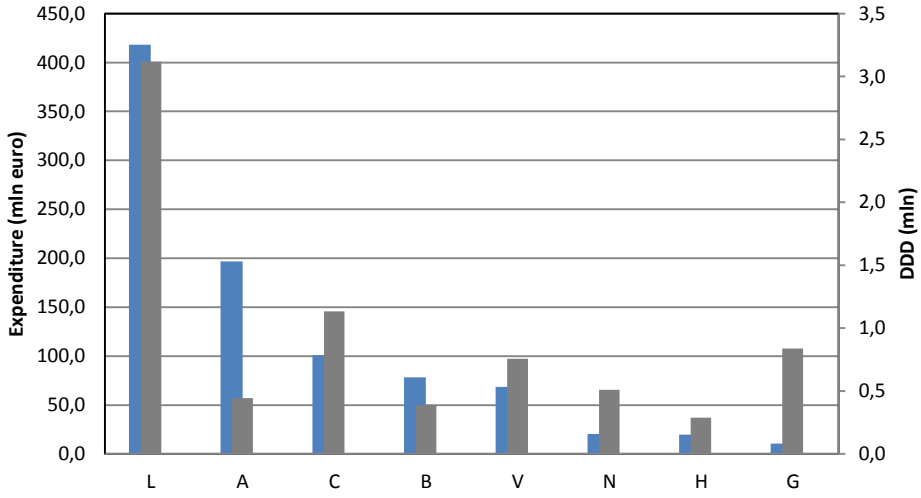
Expenditure and consumption data for year 2013 reported here below have been elaborated on the basis of the new classification approved by the AIFA's Board of Directors (Resolution n. 10 of February 27, 2014). For this reason these results are not comparable with those referring to previous years. During 2013, orphan drugs expenditure, inclusive of purchases made by public health facilities, amounted to 914 million euros, corresponding to 4,7% of the total pharmaceutical expenditure. with regards to consumption measured in DDDs for the same period, it ) amounted to 7,5 million DDDs. In particular, 46% of the expenditure regarded antineoplastic agents and immuno-modulators, followed by gastrointestinal tract and metabolism medicines (22%), and, finally, cardiovascular system medicines (11%).
42% of the consumption of these drugs was absorbed by antineoplastic agents and immuno-modulators, followed by cardiovascular system medicines (15%) and medicines of the genito-urinary system (11%) (Table 1.9.6 and Figure 1.9.1).

**Table 1.9.6.** Trend of orphan drugs expenditure and consumption, years 2008-2013*

| YEAR | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|
| Orphan drug expenditure | 381.575.880 | 506.678.965 | 656.650.964 | 799.862.219 | 671.151.042 | 913.602.076 |
| % share of orphan drug Exp. on total pharmaceutical expenditure | 6,8 | 8,43 | 10,04 | 11,4 | 8,04 | 4,65 |
| Orphan drug DDD-consumption | 3.950.037 | 5.271.295 | 6.595.432 | 7.494.000 | 5.905.112 | 7.474.114 |
| % share of orphan drug consumption on pharmaceutical consumption | 0,16 | 0,21 | 0,23 | 0,2 | 0,16 | 0,03 |

*2013 expenditure and consumption data are analysed according to the new orphan drugs classification (approved by AIFA's Board of Directors, Resolution n. 10 February 7, 2013). For this reason these results are not comparable with those from previous years. In fact, starting from 2013, expenditure and consumption data are related to both purchases made by public health facilities and to outpatient NHS expenditure/consumption.

**Figure 1.9.1.** Orphan drugs expenditure and consumption by ATC I level, year 2013




L= Antineoplastic and immunomodulating agents; A= Alimentary tract and metabolism; C= Cardiovascular system; B= Blood and blood forming organs; V= Various; N= Nervous system; H= Systemic hormonal preparations, excl. sex hormones and insulins; G= Genito urinary system and sex hormones

Active ingredients with major impact on expenditure are the following: lenalidomide (14,0%), bosentan (9,8%), deferasirox (7,5%), eculizumab (6,6%) and nilotinib (6,0%), that together accounted for 43,7% of total orphan drug expenditure. With regards to consumption, over half (52,5%) of delivered DDDs are represented by the following active ingredients: bosentan (13,5%), lenalidomide (11,3%), sildenafil (11, 2%), deferasirox (10,1%) and anagrelide (6,4%).

## 1.10 The management of pharmaceutical expenditure

The management of pharmaceutical expenditure consists of the set of financial actions aimed at adjusting NHS expenditure for the delivering of pharmaceuticals to the financial resources available (i.e. planned expenditure). This task is considered highly relevant for AIFA's mission, being the pharmaceutical expenditure management the process through which equilibrium of the economic system is ensured. Any action intended to limit appropriateness of use settings or any action intended to restrain regional expenditure (e.g. prices granted through local tenders lower than the current ones) contributes to expenditure regulation. In this context, the activity of the CPR-CTS represents a significant tool to control pharmaceutical expenditure, particularly in the context of price negotiations with pharmaceutical companies and when deciding on reimbursed indications. Regions and/or healthcare institutions also contribute to public expenditure management when setting the price of a medicinal product or when encouraging the

appropriate use of a medicine. According to Laws n.222 of 2007 and most recent Law n. 135 of 2012, pharmaceutical expenditure control is obtained through a set of measures, notably outpatient and inpatient pharmaceutical expenditure ceilings, pharmaceutical expenditure monitoring, fixed maximum budget ceilings for companies, pay back mechanisms when budget is exceeded. In 2013, the outpatient pharmaceutical expenditure was set at 11,35% of the National Health Fund (Article 15, paragraph 3, of Law Decree n. 95 of July 6, 2012, followed by Law n. 135 of August 7, 2012). This implies that the total NHS pharmaceutical expenditure, including ticket costs paid by the citizens and excluding citizen reference price system co-payment, requited according to Article 11, paragraph 9 of Law Decree n. 78 of May 31, 2010, (followed by Law n. 122, July 30, 2010)] and expenditure for Class A medicines supplied through direct distribution (including *per conto* distribution and first cycle therapy distribution), should have remained within 12.078 million euros. This threshold is determined excluding sums paid by pharmaceutical companies for the pay back mechanism. In 2013, NHS pharmaceutical expenditure monitoring highlighted a 12.141 million euros expenditure, with an overall deficit of +62,9 million euros compared to the planned ceiling (+0,5% compared to 12.078 million euros), fixed at 11,35% of the National Health Fund (FSN). The NHS pharmaceutical expenditure decreased (-0,8%,) compared to the previous year 12.237 million euros )

**Table 1.10.1** Trend of main parameters intended to manage NHS pharmaceutical expenditure during 2010-2014

| **Outpatient setting** | **2010** | **2011** | **2012** | **2013** | **2014*** ** |
|---|---|---|---|---|---|
| Ceiling | 13,30% | 13,30% | 13,10% | 11,35% | 11,35% |
| Pharmaceutical company budget * | 13.741,5 | 13.950,7 | 13.358,8 | 12,184,7 | 12.118,5 |
| % difference of outpatient pharmaceutical expenditure vs previous years** | 2,48% | 1,33% | 5,19% | -0,88% | 2,41% |
| Absolute difference vs budget ** | 330,4 | 182,6 | 685,0 | -106,6 | 286,9 |
| Fund of innovativeness | 33,7 | 98,2 | 75,1 | 18,9 | 94,9 |
| Innovative medicine ceiling | 10,9 | 0,4 | 23,8 | 63,9 | NA |
| Programmed expenditure | 13.941,0 | 14.005,8 | 13.069,9 | 12.127,6 | NA |
| % share on National Health Fund (FSN) | 13,28% | 13,18% | 12,20% | 11,40% | NA |
| Not allocated resources | -24,0 | -127,4 | -968,7 | 0,0 | NA |
| Breakthrough ceiling | 0,0 | 0,0 | 0,0 | 49,8 | NA |

Note: value expressed as million euros, unless otherwise indicated; since 2013 the ceiling threshold was modified; NA=not available data
* inclusive of additional funds
** net of additional funds
***data susceptible to modifications due to temporary budget

Pursuant to the newly introduced hospital pharmaceutical expenditure legislation (entered into force on January 1, 2013), the hospital pharmaceutical expenditure ceiling was increased from 2,4% to 3,5% of the National Health Fund (*Fondo Sanitario Nazionale*,

FSN) (Article 15, paragraph 4, of the Law Decree n. 95 of July 6, 2012, converted with amendments into Law n. 135 of August 7, 2012). The new Law provides that in case of a failure in respecting the 3,5% expenditure ceiling, the marketing authorization holder is responsible for 50% of the national exceedances of the expenditure ceiling while the remaining 50% is paid-back by Regions registering a local deficit.
Moreover, for the purpose of hospital pharmaceutical expenditure monitoring, data transmitted by pharmaceutical companies is collected through a new health information system (so - called "medicine traceability flow", *flusso della tracciabilità del farmaco*)in accordance with the Decree of the Minister of Health of July 15, 2004.In this context, the amount of the hospital pharmaceutical expenditure is calculated excluding Class A (reimbursed) pharmaceuticals expenditure of the supplied through direct distribution method, as well as pharmaceutical companies pay-back (according to Article 15, paragraph 6 of Law n. 135 of 2012). Furthermore, for the purpose of balancing exceedances of the expenditure ceiling at the national level, the hospital pharmaceutical expenditure attributable to pharmaceutical companies is calculated by deducting the expenses attributed to vaccines, non-reimbursed medicines (Class C and C-bis), compounding preparations, herbals and regional plasma productions (Article 15, paragraph 5 of Law n. 135 of 2012).
Finally, following regulatory changes introduced throughout 2013, the hospital pharmaceutical expenditure fund for the year 2013 must stay within 3.725 billion euros (Table 1.10.2).

**Table 1.10.2.** Main parameters of hospital pharmaceutical expenditure management in the period 2010-2014

| **Inpatient setting** | **2010** | **2011** | **2012** | **2013** | **2014*** ** |
|---|---|---|---|---|---|
| Ceiling | 2,40% | 2,40% | 2,40% | 3,50% | 3,50% |
| Pharmaceutical company budget * | | | | 4.460,8 | 4.156,7 |
| % difference of outpatient pharmaceutical expenditure vs previous years** | | | | -17,6% | -8,15% |
| Absolute difference vs budget** | | | | -736,2 | -331,2 |
| Innovativeness Fund | | | | 153,2 | 83,8 |
| Innovative medicines ceiling | | | | 60,8 | NA |
| Programmed expenditure | 5.288,2 | 4.979,6 | 5.170,6 | 4.497,6 | NA |
| % share on National Health Fund (FSN) | 5,04% | 4,69% | 4,82% | 4,23% | NA |
| Not allocated resources | 0,0 | 0,0 | 0,0 | 0,0 | NA |
| Ceiling exceedance | 2.768,1 | 2.429,2 | 2.598,7 | 773,2 | NA |

Note: value expressed as million euros, unless otherwise indicated; since 2013 the ceiling threshold was modified; NA=not available
* inclusive of additional funds
**net of additional funds
***data susceptible to modification, from temporary Budget

In 2013, hospital pharmaceutical expenditure monitoring highlighted a 4.489,5 billion euros expenditure, with an overall deficit of +765,1 million euros, compared to the planned pharmaceutical expenditure (+20,5% equal to 3.725 million euros) set at 3,5% of the FSN. Hospital pharmaceutical expenditure increased compared to the previous year (4.408,7 billion euros equal to +1.8%).

# SECTION 3
# DATA SOURCE AND METHODS

## 3.7 NHS reimbursed medicines use per individual patient[8]

Local Health Units (LHUs - Azienda Sanitaria Locale - ASL) are public entities responsible for delivering pharmaceutical care at local level.
LHUs equip themselves with information flows, so-called "administrative databases", which also represent an important source of health and functional information, allowing, for instance, the identification and description of medicines use profiles in daily clinical practice.[9,10,11]
Within administrative databases, information is recorded according to patient ID code and date of the services rendered, in order to meet different needs of the administration This system allows to collect all information available for each subject and to draw an analytical and chronological profile of services supplied. These flows are representative of the whole population, properly stored (e.g. encrypted, historicized) and easily analyzable. Current administrative flow only include NHS covered services. Main flows concern demographic registriesr, deaths records, community pharmaceutical flow, *direct* and *per conto* distribution flow, hospital discharge records (*SDO – Scheda di Dimissione Ospedaliera*), outpatient specialist care, "ex Article 26" rehabilitation services and integrated home-care services.
In details:

- demographic registries provide information, such as birth date and gender of subjects who receive NHS health assistance supplied by LHU

- the community pharmaceutical flow collects all reimbursement requests submitted by pharmacies for medicinal products partially and completely reimbursed by the NHS. The most relevant information provided concerns patients and prescribers identification codes, Marketing Authorizations Code codes (so-called AIC, Codice di Autorizzazione all'Immissione in Commercio)), ATC codes, number of delivered packages with the total amount of standard units, strengths, prices and date of prescription

- the *direct* and the *per conto* pharmaceutical distribution flow provides information mainly equivalent to that coming from community pharmaceutical distribution flow (see above) but, unlike the latter, it allows to identify medicines dispensed by NHS hospitals for outpatients use.

[8] This section is edited by Clicon S.r.l..
[9] Birnbaum HG, Cremieux PY, Greenberg PE, et al. Using healthcare claims data for outcome research and pharmacoeconomic analyses. Pharmacoeconomics 1999; 16: 1-8.
[10] Motheral BR, Fairman KA. The use of claims databases for outcome research: rational challenges and strategies. Clin Ther 1997; 19: 346-66.
[11] Degli Esposti L, Valpiani G, Baio G. Valutare l'efficacia degli interventi in Sanità. Guida alla raccolta ed alla gestione dei dati clinici ed amministrativi. Il Pensiero Scientifico Editore. Rome, 2002.

- the hospital discharge flow provides administrative and clinical information concerning hospitalization. This information originate from SDOs (Discharge Hospital Records) and consist of: patient ID code; admission and discharge date; admission and discharge unit; date and unit of internal transfers, if applicable; principal and secondary discharge diagnoses coded according to the ICD-9 classification (International Classification of Diseases 9th version); procedures performed during the hospitalization; clinical status at discharge (recovered, died, transferred); hospitalization type (Day-Hospital admission, or ordinary hospitalization); assigned DRG (diagnosis related groups); amount of the reimbursement per hospital stay

- the outpatient specialist care flow includes information on visits, services, exams instrumental laboratory exams and instrumental diagnostics supplied in outpatient settings. The most important information concerns patient identification number, booking and service supply date, activity description and code, amount of reimbursement

- the “ex Article 26” rehabilitation services flow includes all rehabilitation activities supplied both by private health care facilities part of the state-run healthcare and by NHS health facilities. This flow records information on residential and semi-residential intensive rehabilitation following acute episodes; homecare and outpatient rehabilitation; residential and semi-residential extensive rehabilitation and care services for people with disabilities. The most important information provided concerns patient and facilities ID numbers, payment system, route of admission, initiation and conclusion of the treatment, code and description of rehabilitation activities, number of days and number of rehabilitative treatments provided, price

- the integrated home care flow encloses information on all sanitary and socio-sanitary activities and procedures supplied at home by NHS personnel. This information concerns main phases of the care process: multidimensional assessment and follow-up, definition of an individualized care program, taking in charge of the patient, methods of supply, conclusion of care activities. The most important information provided concerns patients identification number, request date, reason of request, assessment date, code and type of prevailing disease, taking in charge date, Code and type of care, beginning and conclusion date of the service supply

- death records flow includes subject identification code, date and cause of death.

A further information flow originates from laboratories, but it is available only for some LHUs. It provides patients biographical data and information regarding laboratory exams such as request and execution date, code and description, results and units of measurement. Improvements of this flow could be obtained through integration of clinical data concerning the supply of sanitary services.

**Use Indicators and methodology of analysis**

Within this Report, CliCon calculated some indicators developed in the Health-DB project in partnership with AIFA and a selection of LHUs. Health-DB is a business intelligence tool with a data warehouse and dashboard function.

- The data warehouse is based on the acquisition of data from the current administrative flows (community pharmaceutical flow, *direct* distribution flow, hospital discharge records, outpatient specialist care flow, mental health services department flow, demographic data of people receiving care and death certificates) or from other electronic archives (analysis laboratories, pathological anatomy, etc.), usually available at LHUs and Regional level.

- The dashboard is based on a set of performance indicators designed to evaluate the compliance of medical prescriptions to therapeutic care standards (based on scientific evidence, guidelines, Ministerial notes, treatment plans). These indicators can be calculated in relation to specific aspects (e.g. age, gender, treatment status (new or old users), risk level) or contexts (e.g. Regions, LHUs, GPs).

Health-DB has been developed by CliCon - Health, Economics & Outcomes Research - to support different health care professionals (e.g. Regions, LHUs, GPs, specialists) in the monitoring of the compliance of prescribing with therapeutic care standards and in assessing the effects of measures implemented to improve the adherence to these standards.

CliCon is a company specialized in the planning/design and implementation of Pharmacoutilization and outcome analysis based on clinical and administrative databases, in collaboration with LHUs, GPs and specialist Centre. Since 1996, CliCon has conducted analysis in various therapeutic areas in partnership with several LHUs and Regions, taken into account community and hospital pharmaceutical consumptions as well as medical devices use.

Indicators presented in this Report are calculated on administrative flows provided by a selection of 32 LHUs covering almost all Italian Regions. This database includes about 18 million subjects (about 30% of the Italian population), homogeneously distributed throughout the Country: ( North (28.7%), Center (33.7%) and South (29.8%) (Figure 3.7.1).

The average age of the LHU sample is 43.5 years *versus* 43.3 years of the Italian population. The percentage of males is estimated to 48.5%, in accordance with the national data available.
For each LHU the following currents administrative flows have been acquired:

- Demographic data (including deaths)
- Standard pharmaceutical distribution
- *Direct* pharmaceutical distribution

- *Per conto* pharmaceutical distribution
- Hospital discharge records.

**Figure 3.7.1.** Geographic representation of the LHU sample that contributed to 2013 OsMed Report

For some LHUs, the flow of laboratories was experimentally acquired and used to design/define and calculate diabetes mellitus medicines indicators.
Data retrieved from single administrative flows are listed below: gender, birth and death date, ATC code, prescription date, number of prescribed packages, price per pack (both community and direct distribution price), admission and discharge date, type of admission (e.g. ordinary, day-hospital), discharge data (e.g. discharged, moved), primary diagnosis (ICD9), secondary diagnosis (ICD9), main procedure (ICD9), secondary procedures (ICD9), DRG, reimbursement per hospital stay (Hospital discharge records), laboratory data and value of laboratory testing (laboratory flow). Information from these flows was combined through a data linkage procedure on the patient identification code (e.g. using the tax identification code). This procedure was performed, in site, by LHU staff.
The database contains the information necessary to calculate indicators for the following chronic diseases:
- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- COPD
- Osteoporosis

- Depression
- Ulcers and esophagitis
- Anemia.

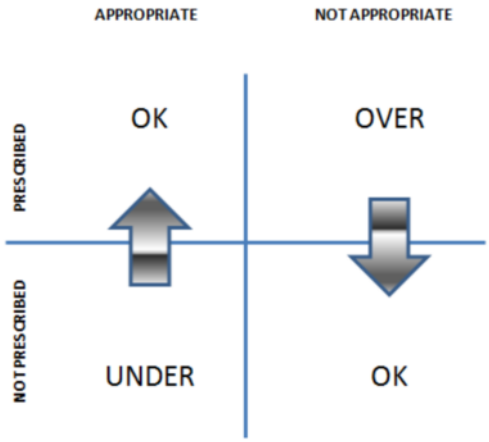
Pharmacoutilization data was analyzed for all therapeutic areas and for all distribution methods. Increased awareness of the overall expenditure volumes by therapeutic category and patient use (compared to standard), is essential for management control activity. In this context, the current administrative flows represent the most appropriate source of information, as they contain the overall amount of medical prescriptions (an thus, of pharmaceutical expenditure), as well as the total amount of assistance services covered by the NHS. Furthermore, the prescription traceability allows to assess therapeutic appropriateness. Within the Health-DB project, among the indicators measuring compliance of prescribing with standards some assess appropriateness in terms of treatment duration (e.g. therapeutic continuity for chronic treatment), while others evaluate the appropriateness with respect to patients (e.g. a patient tailored pharmacological prescription).
Health-DB project adherence Indicators adopt a novel perspective for the evaluation and assessment of prescribing appropriateness. In fact, they consider the appropriateness rather than the consumption.
The Health-DB project indicators have two main objectives: therapeutic appropriateness and financial sustainability.
In particular with regards to:

1. *therapeutic appropriateness (individual and collective*): each indicator has been selected based on the assumption that its increase is closely associated with an improvement in the patient's health status and in a more efficient allocation of resources. For example, prescription compliance with treatment recommendations increases the chances of achieving a favorable therapeutic outcome and, at the same time, reduces the probability of resorting to other services (such as diagnostic tests, treatment for side effects, hospital admissions) and therefore ultimately decreases the overall cost for patient care. In other words, the selection of indicators was made both on a clinical and on an economic basis.

2. *financial sustainability*: these indicators have been selected as they are "iso-resources" within the programmed pharmaceutical expenditure budget All indicators are cost-effective in the medium term, as the improvement of the outcomes results in a decrease of exacerbations, hospitalizations and thus of overall costs for patients care.
The Italian NHS having a fixed budget, is not able to bear in the short run, uncontrolled growth of pharmaceutical expenditure. Indicators have therefore been designed to identify areas of under spending (e.g. therapeutic discontinuity in chronic treatments) and overspending areas (e.g. use of unnecessary high-cost medicines for patients with reduced disease severity) (Figure 3.6.3). The purpose is to be "iso-resource" within the budget for pharmaceutical expenditure.
If a resources reallocation process (from overspending to under spending areas) appears insufficient, the implementation of policies to limit reimbursement or increase budget for pharmaceutical expenditure would be considered appropriate.

Health-DB project indicators undergo continuous development and improvement as result of new information coming from other flows.

Figure 3.6.3




**Data ownership and treatment**

According to the privacy legislation (Legislative Decree n. 196 of 2003 and following amendments), patient ID code are anonymized by HLUs, in site, so that CliCon cannot retrieve the patient ID code. CliCon, by signing a specific agreement with each HLU, becomes responsible for the data analysis. All results are produced only in an aggregated form. Finally, CliCon returns data to the respective LHU (the data owner) after the conclusion of the analysis.

**METHODOLOGICAL NOTE**
When comparing the different editions of the Report, readers should be reminded that the OsMed data warehouse is systematically updated. For this reason, differences with data published in previous Report editions could be observed (e.g. in expenditure, consumption and exposure data). The update may derived from the release of new DDD definitions by the WHO or from the availability of new information (e.g. updated population data) or control activity resulting from new data flows.
OsMed releases a yearly-based Report containing both current data and updates regarding previous four years, in order to give a "self-consistent" reading of the Report.

## SECTION 4

# THERAPEUTIC APPROPRIATENESS: PRESCRIPTION AND USE PROFILES

## 4.4 Medicines use and treatment adherence profiles[9]

**Indicators for antihypertensive medicines**

- Percentage of patients with comorbid conditions in treatment with renin-angiotensin-aldosterone system inhibitors (Indicator H-DB 1.1)

- Percentage of patients in treatment with off-patent Angiotensin II antagonists (Within December 2013) (Indicator H-DB 1.2)

- Percentage of adherent patients in treatment with antihypertensive medicines (Indicator H-DB 1.3)

- Percentage of occasional patients in treatment with antihypertensive medicines (Indicator H-DB 1.4)

- Percentage of patients who began a fixed-dose combination therapy with antihypertensive drugs and calcium channel blockers without having previously taken the same active ingredients neither as monotherapy nor as free-dose combination therapy (Indicator H-DB 1.5)
- Percentage of patients in treatment with a calcium channel blocker in free combination therapy with another antihypertensive agent which have not shifted to a fixed-dose combination therapy with calcium channel blockers (Indicator H-DB 1.6)

*Calculation methodology*

The antihypertensive medicines considered for the analysis are: diuretics (ATC CODE C03); beta-blockers (ATC CODE C07); calcium channel blockers (ATC CODE C08); renin-angiotensin-aldosterone system inhibitors (ATC CODE C09) distinguished in ACE-inhibitors (ATC CODE C09A and C09B) and angiotensin II antagonists (ATC CODE C09C and C09D); other medicines acting on the renin-angiotensin system (ATC CODE C09X).
The subjects in analysis have been categorized as patients having experienced a previous cardio-cerebral vascular event or diabetes and in patients who had not experienced a previous cardio-cerebral vascular event or diabetes, in relation to the presence or to the absence of at least one of the following diagnosis and/or procedures:

- Diabetes: at least two prescriptions of antidiabetic medicines (ATC CODE A10) or one hospitalization with diagnosis of diabetes (ICD-9 CODE 250)

[9]This section is edited by Clicon S.r.l..

- Coronary heart disease: at least one hospitalization with diagnosis of acute myocardial infarction (ICD-9 CODE 410), acute cardiac ischemia (ICD-9 CODE 411), pectoris angina (ICD-9 CODE 413), chronic heart ischemia (ICD-9 CODE 414)
- Cerebrovascular disease: at least one hospitalization with diagnosis of subarachnoid hemorrhage (ICD-9 CODE 430), intracerebral hemorrhage (ICD-9 CODE 431-432), ischemic stroke (ICD-9 CODE 434; 436), transient ischemic attack (TIA) (ICD-9 CODE 435), other cerebrovascular diseases (ICD-9 CODE 433; 437-438)

- Peripheral vascular disease: at least one hospitalization with diagnosis of atherosclerosis (ICD-9 CODE 440), other vascular peripheral diseases (ICD-9 CODE 443)

- Percutaneous transluminal coronary angioplasty (PTCA): at least one hospitalization with diagnosis of status-post PTCA (ICD-9 CODE V4582) or at least one hospitalization with a procedure of PTCA (ICD-9 CODE 0066), other removal of coronary artery obstruction (ICD-9 CODE 3609)

- Chronic kidney disease: at least one hospitalization with diagnosis of chronic kidney disease (ICD-9 CODE 585 ).

The subjects in analysis have been categorized as patients with or without comorbidity in relation to the presence of at least one of the following diagnosis:

- Diabetes: at least two prescriptions of antidiabetic medicines (ATC CODE A10) or one hospitalization with diagnosis of diabetes (ICD-9 CODE 250)

- Hypertension: at least one hospitalization with diagnosis of hypertension (ICD-9 CODE 401-405)

- Coronary heart disease: at least one hospitalization with diagnosis of acute myocardial infarction (ICD-9 CODE 410), acute cardiac ischemia (ICD-9 CODE 411), pectoris angina (ICD-9 CODE 413), chronic heart ischemia (ICD-9 CODE 414)

- Heart failure: at least one hospitalization with diagnosis of heart failure (ICD-9 CODE 428)

- Cerebrovascular disease: at least one hospitalization with diagnosis of subarachnoid hemorrhage (ICD-9 CODE 430), intracerebral hemorrhage (ICD-9 CODE 431-432), ischemic stroke (ICD-9 CODE 434; 436), transient ischemic attack (TIA) (ICD-9 CODE 435), other cerebrovascular diseases (ICD-9 CODE 433; 437-438)

- Arterial disease: at least one hospitalization with diagnosis of atherosclerosis (ICD-9 CODE 440), aortic aneurysm (ICD-9 CODE 441); other aneurysms (ICD-9 CODE: 442)

- Chronic kidney disease: at least one hospitalization with diagnosis of chronic kidney disease (ICD-9 CODE 585).

The subjects in treatment with antihypertensive medicines have been categorized in two groups: new users and patients already in treatment (old users) in relation to, respectively, the absence or presence, of at least one prescription of an antihypertensive medicine within the 12 months following the first prescription of the reporting year (index date).
Furthermore, subjects in treatment with antihypertensive agents have been defined as occasional or adherent users in relation to a pharmaceutical coverage <20% or ≥80%, respectively, within the 12 months following the first prescription.
The therapeutic coverage has been calculated considering all DDDs (defined daily doses) prescribed within the 12 months following the index date. The presence in the same prescription of different type of antihypertensive agents and/or the consumption of at least two antihypertensive medicines for the same indication, either together or separately, have been considered as a free-dose combination therapy. The therapeutic coverage has been compared with the observation period and multiplied by 100.
The exposition time for each medicine, defined as the period between the first and last prescription for a specific time range, has been identified.

*Cohort of subjects in analysis*

The number of subjects aged 18 years and older in treatment with antihypertensive medicines amounts to 3.752.804 in 2013 (N) (Table 4.4.1). The prevalence of subjects in treatment with antihypertensive agents amounts to 28,3% of the overall study sample (27,1% in Northern, 29,4% in Center and 29,2% in Southern of Italy). The prevalence of subjects in treatment with antihypertensive medicines increases with age (3,2% in the age group ≤45 years, 29,6% in the age group 46-65 years, 64,5% in the age group 66-75 years and 82,1% in the age group >75 years) and over the years (+3,4% in 2013 compared to 2012 and +2,3% in 2012 compared to 2011).

**Table 4.4.1.** Distribution of patients in treatment with antihypertensive medicines

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % SS | Var.% | N | % SS | Var.% | N | % SS | Var.% |
| TOTAL | 3.752.804 | 28,3 | 3,4 | 3.630.508 | 27,5 | 2,3 | 3.548.245 | 27,0 | / |
| Geographic distribution | | | | | | | | | |
| North | 1.672.558 | 27,1 | 3,6 | 1.614.164 | 26,2 | 1,2 | 1.594.488 | 26,1 | / |
| Centre | 816.986 | 29,4 | 3,4 | 789.834 | 28,6 | 2,4 | 771.072 | 28,0 | / |
| South | 1.263.260 | 29,2 | 3,0 | 1.226.510 | 28,5 | 3,7 | 1.182.685 | 27,6 | / |
| Gender | | | | | | | | | |
| Male | 1.702.042 | 26,4 | 4,0 | 1.636.709 | 25,5 | 3,0 | 1.589.055 | 24,9 | / |
| Female | 2.050.762 | 30,0 | 2,9 | 1.993.799 | 29,3 | 1,8 | 1.959.190 | 28,9 | / |
| Age group | | | | | | | | | |
| ≤45 | 188.840 | 3,2 | -2,5 | 193.764 | 3,3 | -3,5 | 200.871 | 3,5 | / |
| 46-65 | 1.282.211 | 29,6 | 0,1 | 1.281.019 | 29,7 | -0,1 | 1.282.487 | 29,9 | / |
| 66-75 | 1.039.235 | 64,5 | 3,1 | 1.007.679 | 62,9 | 3,5 | 973.847 | 61,1 | / |
| >75 | 1.242.518 | 82,1 | 8,2 | 1.148.046 | 76,2 | 5,2 | 1.091.040 | 72,8 | / |
| Mean age | 68.5 ± 13.3 | | | 68.0 ± 13.2 | | | 67.7 ± 13.2 | | |

N: subjects in treatment aged ≥18 years
SS: study sample

*Results and considerations*

**Percentage of comorbid patients in treatment with renin-angiotensin-aldosterone system inhibitors (Indicator H-DB 1.1)**

The number of comorbid subjects aged 18 years or older in treatment with antihypertensive medicines amounts to 728.867 in 2013.
The percentage of comorbid patients treated with medicines acting on renin-angiotensin system amounts to 83,3% in 2013, a percentage slightly lower compared to the previous year (-1,2% in 2013 compared to 2012). This percentage appears slightly higher in Southern Italy (85,7%) than in Northern and Central regions of the country (82,3% and 81,0% respectively) and in males compared to females (84,1% vs 82,5%).
The percentage of comorbid patients in treatment with renin-angiotensin system inhibitors amounts to 76,3% in the age group ≤45 years, 84,9% in the age group 46-65 years, 85,8% in the age group 66-75 years and 80,7% in the age group >75 years. This percentage is lower in new users than in old ones.

**Table 4.4.2**. Number of comorbid patients in treatment with renin-angiotensin-aldosterone system inhibitors [numerator]/Total number of comorbid patients in treatment with antihypertensive medicines [denominator]

| | 2013 N = 728.867 | | 2012 N = 694.879 | | 2011 N = 632.992 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 83,3 | -1,2 | 84,3 | -0,2 | 84,4 | / |
| Geographic distribution | | | | | | |
| North | 82,3 | -1,2 | 83,3 | -0,1 | 83,4 | / |
| Centre | 81,0 | -1,8 | 82,4 | 0,3 | 82,2 | / |
| South | 85,7 | -0,7 | 86,3 | -0,3 | 86,6 | / |
| Gender | | | | | | |
| Male | 84,1 | -1,1 | 85,1 | -0,2 | 85,2 | / |
| Female | 82,5 | -1,2 | 83,5 | -0,2 | 83,6 | / |
| Age group | | | | | | |
| ≤45 | 76,3 | -1,6 | 77,6 | 0,2 | 77,4 | / |
| 46-65 | 84,9 | -0,5 | 85,3 | 0,2 | 85,2 | / |
| 66-75 | 85,8 | -0,6 | 86,3 | -0,1 | 86,4 | / |
| >75 | 80,7 | -1,8 | 82,2 | -0,5 | 82,5 | / |
| Treatment status | | | | | | |
| New users | 61,6 | -3,5 | 63,8 | -8,5 | 69,8 | / |
| Old users | 84,6 | -1,2 | 85,7 | -0,2 | 85,9 | / |

N: number of comorbid subjects aged 18 years or older in treatment with antihypertensive medicines

**Percentage of patients in treatment with off-patent Angiotensin II antagonists (within December 2013) (Indicator H-DB 1.2)**

The number of subjects aged 18 years or older taking angiotensin II antagonists in monotherapy amounts to 1.450.491 in 2013.
The percentage of patients receiving off-patent angiotensin II antagonists amounts to 73,9% in December 2013; this value decreases if compared to previous years (-1,3% in 2013 compared to 2012 and -2,5% in 2012 compared to 2011). This data is slightly higher in Central Italy (76,2%) compared to Northern (74,5%) and to Southern (71,9%) areas of the country. There are no significantly differences between males and females (73,3% and 74,4%, respectively). The percentage of patients treated with off-patent angiotensin II antagonists within December 2013 amounts to 66,1% in ≤45 age group, to 70,2% in 46-65 age group, to 74,6% in 66-75 age group and to 78,2% in age group >75 years and is lower among new users compared to old ones (69,4% vs 74,3%).

**Table 4.4.3**. Number of subjects who assume off-patent angiotensin II antagonists in monotherapy within December 2013 [numerator]/Total number of patients receiving angiotensin II antagonists in monotherapy [denominator]

| | 2013 N =1.450.491 | | 2012 N = 1.398.750 | | 2011 N = 1.359.758 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 73,9 | -1,3 | 74,9 | -2,5 | 76,9 | / |
| Geographic distribution | | | | | | |
| North | 74,5 | -1,3 | 75,5 | -2,6 | 77,5 | / |
| Centre | 76,2 | -1,1 | 77,0 | -1,8 | 78,4 | / |
| South | 71,9 | -1,5 | 73,0 | -2,9 | 75,2 | / |
| Gender | | | | | | |
| Male | 73,3 | -1,4 | 74,4 | -2,9 | 76,6 | / |
| Female | 74,4 | -1,2 | 75,4 | -2,2 | 77,1 | / |
| Age group | | | | | | |
| ≤45 | 66,1 | -0,9 | 66,7 | -3,3 | 68,9 | / |
| 46-65 | 70,2 | -1,9 | 71,5 | -3,2 | 73,9 | / |
| 66-75 | 74,6 | -1,5 | 75,8 | -2,5 | 77,8 | / |
| >75 | 78,2 | -1,2 | 79,1 | -2,1 | 80,8 | / |
| Treatment status | | | | | | |
| New users | 69,4 | 1,9 | 68,1 | -6,6 | 72,9 | / |
| Old users | 74,3 | -1,6 | 75,5 | -2,8 | 77,7 | / |

N: number of subjects aged 18 years or older that assume angiotensin II antagonists in monotherapy

**Percentage of adherent patients in treatment with antihypertensive medicines (Indicator H-DB 1.3)**

The number of subjects aged 18 years or older in treatment with antihypertensive medicines amounts to 3.529.021 in 2012.
The percentage of adherent subjects in treatment with antihypertensive medicines amounts to 55,1%, in 2012; this value is slightly higher than in the previous year (+3,9% in 2012 compared to 2011). There aren't significant differences across the Country: 55,4% in the North, 56,1% in the Center and 54,2% in the South of Italy. The adherence is higher in males (56,9% vs 53,6% of females), in older subjects (the higher level, 60,2%, is in the age group 66-75 years), in old users (59,6% compared to 23,7% of new users) and in comorbid users (the adherence of subjects with a previous CV event or diabetes amounts to 65,8% vs 52,8% of subjects without a previous CV event or diabetes). Excluding occasional users from the analysis, the percentage of adherent patients in treatment with antihypertensive medicines amounts to 58,9% in 2012.

**Table 4.4.4**. Number of adherent patients in treatment with antihypertensive medicines [numerator]/Total number of patients in treatment with antihypertensive agents [denominator]

| | 2012 N = 3.529.021 | | 2011 N =3.448.821 | | 2010 N = 3.333.423 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 55,1 | 3,9 | 53,0 | -1,4 | 53,8 | / |
| Geographic distribution | | | | | | |
| North | 55,4 | 0,5 | 55,1 | 0,1 | 55,0 | / |
| Centre | 56,1 | 0,8 | 55,6 | 1,1 | 55,0 | / |
| South | 54,2 | 11,0 | 48,9 | -5,5 | 51,7 | / |
| Gender | | | | | | |
| Male | 56,9 | 3,6 | 54,9 | -1,8 | 56,0 | / |
| Female | 53,6 | 4,1 | 51,5 | -1,1 | 52,1 | / |
| Age group | | | | | | |
| ≤45 | 32,4 | 5,4 | 30,8 | -1,4 | 31,2 | / |
| 46-65 | 50,9 | 3,6 | 49,1 | -2,2 | 50,2 | / |
| 66-75 | 60,2 | 3,4 | 58,2 | -1,4 | 59,0 | / |
| >75 | 59,3 | 3,6 | 57,2 | -1,2 | 57,9 | / |
| Treatment status | | | | | | |
| New users | 23,7 | -5,7 | 25,1 | -8,1 | 27,3 | / |
| Old users | 59,6 | 3,9 | 57,3 | -2,2 | 58,6 | / |
| Comorbidity status | | | | | | |
| Without previous CV event or diabetes | 52,8 | 3,4 | 51,1 | -1,0 | 51,6 | / |
| With previous CV event or diabetes | 65,8 | 4,1 | 63,2 | -2,6 | 64,8 | / |
| TOTAL without occasional users | 58,9 | 3,7 | 56,8 | -1,4 | 57,7 | |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.

Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of subjects aged 18 years or older in treatment with antihypertensive

**Percentage of occasional patients in treatment with antihypertensive medicines (Indicator H-DB 1.4)**

The number of subjects aged 18 years or older in treatment with anti-hypertensive medicine is 3.529.021 in 2012. The percentage of occasional subjects in treatment with anti-hypertensive medicines amounts to 6,5%; this value is slightly decreased if compared to the previous year (-2,4% in 2012 compared to 2011). The percentage of occasional users is higher in Southern Italy (7,5%) compared to Northern (5,9%) and to Central (6,1%) regions of the Country and is slightly higher in females (6,9% vs 6,0% of males). This percentage is higher among younger (22,4% in the age group ≤45 years, 7,5% in the age group 46-65 years, 4,3% in the age group 66-75 years and 4,5% in the age group ≥75 years ), among new users (33,9% vs 2,6% of old users) and in the subjects without a previous CV event or diabetes (7,2% vs 3,4% of subjects with a previous CV event or diabetes).

**Table 4.4.5**. Number of occasional patients in treatment with antihypertensive medicines [numerator] / Total number of patients in treatment with antihypertensive medications [denominator]

| | 2012 N = 3.529.021 | | 2011 N =3.448.821 | | 2010 N = 3.333.423 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 6,5 | -2,4 | 6,7 | -0,4 | 6,7 | / |
| Geographic distribution | | | | | | |
| North | 5,9 | -0,8 | 5,9 | 6,8 | 5,6 | / |
| Centre | 6,1 | -2,1 | 6,2 | -1,1 | 6,3 | / |
| South | 7,5 | -4,4 | 7,9 | -4,8 | 8,3 | / |
| Gender | | | | | | |
| Male | 6,0 | -2,0 | 6,1 | 0,2 | 6,1 | / |
| Female | 6,9 | -2,7 | 7,1 | -0,8 | 7,2 | / |
| Age group | | | | | | |
| ≤45 | 22,4 | -3,5 | 23,2 | -2,4 | 23,7 | / |
| 46-65 | 7,5 | -1,3 | 7,6 | 1,1 | 7,6 | / |
| 66-75 | 4,3 | 0,9 | 4,3 | 2,9 | 4,2 | / |
| >75 | 4,5 | -0,2 | 4,5 | 1,6 | 4,4 | / |
| Treatment status | | | | | | |
| New users | 33,9 | 3,3 | 32,8 | 7,4 | 30,6 | / |
| Old users | 2,6 | 2,8 | 2,5 | 10,0 | 2,3 | / |
| Comorbidity status | | | | | | |
| Without previous CV event or diabetes | 7,2 | -1,5 | 7,3 | -1,1 | 7,3 | / |
| With previous CV event or diabetes | 3,4 | -1,4 | 3,5 | 3,6 | 3,3 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).
N: number of subjects aged 18 years or older in treatment with anti-hypertensive medicine

**Percentage of patients who began a fixed-dose combination therapy with a calcium channel blocker without having ever taken the same active ingredients neither as monotherapy or free-dose combination therapy (Indicator H-DB 1.5)**

The number of subjects in analysis aged 18 years or older in treatment with antihypertensive medications in fixed-dose combination with calcium channel blocker amounts to 69.423 in 2013.
The percentage of patients treated with antihypertensive medications in fixed-dose combination with calcium channel blockers without having ever taken the same active ingredients separately or in free-dose combinations amounts to 86,1% in 2013. This value is increased if compared to previous years (+6,1% in 2013 compared to 2012, +2,6% in 2012 compared to 2011). The percentage is slightly higher in Southern Italy (88,4%) than in Northern (84,5%) and Central (84,6%) Italy, as well as in females (86,9% vs 85,3% of males). This percentage decreases with the age of patients (90,8% in the age group ≤45 years, 87,5% in the age group 46-65 years, 84,7% in the age group 66-75 years and 84,2% in over 75 years). The 82,6% of old users have ever taken the same active ingredients either in free combination or fixed-dose combination or in monotherapy.

**Table 4.4.6**. Number of patients who began a fixed-dose combination therapy with calcium channel blocker without having ever taken the same active ingredients in monotherapy or in free combination therapy [numerator]/Total number of patients who began a fixed-dose combination therapy with calcium channel blockers [denominator]*

| | 2013 N = 69.423 | | 2012 N = 99.121 | | 2011 N = 67.424 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 86,1 | 6,1 | 81,2 | 2,6 | 79,1 | / |
| Geographic distribution | | | | | | |
| North | 84,5 | 6,4 | 79,4 | 2,2 | 77,7 | / |
| Centre | 84,6 | 5,0 | 80,6 | 3,8 | 77,7 | / |
| South | 88,4 | 6,8 | 82,8 | 2,4 | 80,9 | / |
| Gender | | | | | | |
| Male | 85,3 | 5,8 | 80,6 | 3,5 | 77,9 | / |
| Female | 86,9 | 6,4 | 81,7 | 1,9 | 80,2 | / |
| Age group | | | | | | |
| ≤45 | 90,8 | 6,2 | 85,5 | 2,7 | 83,2 | / |
| 46-65 | 87,5 | 6,5 | 82,2 | 2,7 | 80,0 | / |
| 66-75 | 84,7 | 6,2 | 79,8 | 2,8 | 77,6 | / |
| >75 | 84,2 | 5,0 | 80,2 | 2,2 | 78,4 | / |
| Treatment status | | | | | | |
| New users | 100,0 | 0,0 | 100,0 | 0,0 | 100,0 | / |
| Old users | 82,6 | 6,1 | 77,8 | 2,0 | 76,3 | / |

N: number of subjects in analysis aged 18 years or older in treatment with antihypertensive medications in fixed-dose combination with calcium channel blocker
*List of fixed-dose combination medicines taken in account: amlodipine/perindopril: ATC CODE C09BB04, lercanidipine/enalapril: ATC CODE C09BB02, felodipine/ramipril: C09BB05, manidipine/delapril: ATC CODE C09BB12, amlodipine-olmesartan: ATC CODE C09DB02

**Percentage of patients in treatment with a calcium channel blocker in free combination with another antihypertensive agent who don't shift to a fixed-dose combination therapy with calcium channel blockers (Indicator H-DB 1.6)**

The number of subjects in analysis aged 18 years or older in treatment with calcium channel blockers in free combination with another antihypertensive agent amounts to 79.021 in 2012. The percentage of patients in free combination, who do not shift to a fixed-dose combination therapy amounts to 97,7%; this value is slightly increased if compared to the previous year (+1,9% in 2012 compared to 2011). There are no significant differences across Italy (North 97,9%; Center 97,5%; South 97,7%), or in males compared to females (97,4% vs 98,0%) or in new users compared to old users (97,4% vs 97,7%). This percentage slightly rises with the age of patients (96,6% in the age group ≤45 years, 97,5% in the age group 46-65 years, 97,6% in the age group 66-75 years and 98,1% in the age group over 75 years).

**Table 4.4.7**. Number of patients in treatment with calcium channel blocker in free combination with another antihypertensive agent who do not shift to a fixed-dose combination therapy [numerator]*/Total number of patients receiving a fixed-dose combination therapy with calcium channel blockers [denominator]

| | 2012 | | 2011 | | 2010 | |
|---|---|---|---|---|---|---|
| | N = 79.021 | | N = 78.603 | | N = 71.709 | |
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 97,7 | 1,9 | 95,9 | -2,1 | 98,0 | / |
| Geographical distribution | | | | | | |
| North | 97,9 | 1,6 | 96,3 | -2,0 | 98,3 | / |
| Centre | 97,5 | 1,9 | 95,7 | -2,0 | 97,6 | / |
| South | 97,7 | 2,2 | 95,5 | -2,3 | 97,8 | / |
| Gender | | | | | | |
| Male | 97,4 | 1,9 | 95,6 | -2,2 | 97,7 | / |
| Female | 98,0 | 1,8 | 96,3 | -2,0 | 98,2 | / |
| Age group | | | | | | |
| ≤45 | 96,6 | 1,9 | 94,7 | -2,9 | 97,5 | / |
| 46-65 | 97,5 | 2,1 | 95,4 | -2,2 | 97,6 | / |
| 66-75 | 97,6 | 2,0 | 95,6 | -2,3 | 97,9 | / |
| >75 | 98,1 | 1,6 | 96,6 | -1,8 | 98,4 | / |
| Treatment status | | | | | | |
| New users | 97,4 | 0,7 | 96,7 | -1,6 | 98,3 | / |
| Old users | 97,7 | 1,8 | 96,0 | -2,0 | 97,9 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of subjects aged 18 years old and older in treatment with a calcium channel blocker in free combination with another antihypertensive agent
*Active ingredients associations with calcium channel blockers taken into account: amlodipine (ATC CODE C08CA01) and perindopril (ATC CODES C09AA04, C09BA04); lercanidipine (ATC CODE C08CA03) and enalapril (ATC CODES C09AA02, C09BA02); felodipine (ATC CODE C08CA02) and ramipril (ATC CODES C09AA05, C09BA05); manidipine (ATC CODE C08CA11) and delapril (ATC CODES C09AA12, C09BA12); amlodipine and olmesartan (ATC CODES C09CA08, C09DA08)

***Economic impact of Indicators***

The improvement of indicators described in this section is associated with an improvement of health status and with a reduction of patient care overall cost (as these indicators have been designed according to therapeutic standards of efficacy). They can impact on pharmaceutical expenditure in different ways, depending on the features of the single indicator (Table 4.4.8).

**Table 4.4.8**. Pharmaceutical expenditure flexibility for antihypertensive medicines with regard to the improvement of the related indicator

| Indicator | % Overall expenditure variation for 1% variation of Indicator | Overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-1.1 | +0,13 | € 2.992.352 |
| H.DB-1.2 | -0,19 | € -4.434.974 |
| H.DB-1.3 | +0,96 | € 21.905.801 |
| H.DB-1.4 | -0,17 | € -3.960.288 |
| H.DB-1.5 | -0,04 | € -982.745 |
| H.DB-1.6 | +0,01 | € 206.938 |

A preferential use of off-patent angiotensin II antagonists and the beginning of a fixed-dose combinations therapy with calcium channels blockers, for those patients receiving the same active ingredients in free combinations, would result in savings in pharmaceutical expenditure for antihypertensive medicines. These savings, together with those produced as a result of the reduction of occasional users (obtained through a better selection of patients to treat), could allow, for example, a reinvestment in policies to improve adherence.

## Indicators for lipid lowering medicines

- Percentage of patients with a previous CV event or diabetes in treatment with statins (Indicator H-DB 2.1)
- Percentage of patients without a previous CV event or diabetes in treatment with statins (Indicator H-DB 2.2)
- Percentage of patients without a previous CV event or diabetes in treatment with low-intensity statins (Indicator H-DB 2.3)
- Percentage of patients with a previous CV event or diabetes in treatment with high-intensity statins (Indicator H-DB 2.4)
- Percentage of adherent patients in treatment with statins (Indicator H-DB 2.5)
- Percentage of occasional patients in treatment with statins (Indicator H-DB 2.6)

*Methodology of calculation*

For the purpose of the analysis, HMG-CoA reductase inhibitors (statins: ATC CODE C10AA) and statins in combination with others lipid modifying agents (ATC CODE C10BA)have been considered, Statins have been categorized in two groups:

- high-intensity statins: atorvastatin (ATC CODE C10AA05), rosuvastatin (ATC CODE C10AA07), simvastatin/ezetimibe (ATC CODE C10BA02 )
- low - intensity statins: simvastatin (ATC CODE C10AA01 ), lovastatin (ATC CODE C10AA02 ), pravastatin (ATC CODE C10AA03), fluvastatin (ATC CODE C10AA04).

The subjects in analysis have been categorized as patients with or without comorbidity in relation to the presence of at least one of the following diagnosis:

- Diabetes: at least two prescriptions of anti-diabetic medicines (ATC CODE A10) or an hospitalization with diagnosis of diabetes (ICD-9 CODE 250)
- Coronary heart disease: at least one hospitalization with diagnosis of acute myocardial infarction (ICD-9 CODE 410), acute cardiac ischemia (ICD-9 CODE 411), pectoris angina (ICD-9 CODE 413), chronic heart ischemia (ICD-9 CODE 414)
- Cerebrovascular disease: at least one hospitalization with diagnosis of subarachnoid hemorrhage (ICD-9 CODE 430), intracerebral hemorrhage (ICD-9 CODE 431-432), ischemic stroke (ICD-9 CODE 434; 436), transient ischemic attack (TIA) (ICD-9 CODE 435), other cerebrovascular diseases (ICD-9 CODE 433; 437-438)
- Vascular peripheral disease: at least one hospitalization with diagnosis of atherosclerosis (ICD-9 CODE 440), other vascular peripheral diseases (ICD-9 CODE 443)

- Transluminal coronary angioplasty (PTCA): at least one hospitalization with diagnosis of status-post PTCA (ICD-9 CODE V4582) or at least an hospitalization with a procedure of PTCA (ICD-9 CODE 0066), other removal of coronary artery obstruction (ICD-9 CODE 3609)

- Chronic kidney disease: at least one hospitalization with diagnosis of chronic kidney disease (ICD-9 CODE 585).

The subjects in treatment with statins have been categorized in two groups: new users and already treated patients (old users) in relation to the absence or presence, respectively, of at least one prescription of a statin within the 12 months following the first prescription of the reporting year (index date).
Furthermore, subjects in treatment with statins have been defined as occasional or adherent users in relation to a pharmaceutical coverage <20% or ≥80%, respectively, within the 12 months following the first prescription.
The presence in the same prescription of different classes of lipid lowering agents and/or the consumption of at least two different classes of lipid lowering agents, either together or separately, have been considered as a free combination therapy. The therapeutic coverage has been compared with the observation period and multiplied by 100.

*Cohort of subjects in analysis*

The number of subjects in analysis aged 18 years or older in treatment with statins amounts to 1.490.295 in 2013 (Table 4.4.9). The prevalence of the treatment with statins amounts to 11,2% of the study sample (10,4% in the North, 12,0% in the Center and 11,9% in the South of Italy). The prevalence of statins treatment increases with the patients' age (0,7% in age group ≤45 years, 11,1% in age group 46-65 years, 31,0% in age group 66-75 years and 30,8% in the group ≥75 years) and over the years (+3,9% in 2013 compared to 2012 and +6,2% in 2012 compared to 2011).

**Table 4.4.9**. Distribution of patients in treatment with statins

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % SS | Var.% | N | % SS | Var.% | N | % SS | Var.% |
| TOTAL | 1.490.295 | 11,2 | 3,9 | 1.434.586 | 10,9 | 6,2 | 1.351.190 | 10,3 | / |
| Geographic distribution | | | | | | | | | |
| North | 642.762 | 10,4 | 4,2 | 617.005 | 10,0 | 5,4 | 585.653 | 9,6 | / |
| Centre | 334.236 | 12,0 | 4,3 | 320.543 | 11,6 | 5,6 | 303.594 | 11,0 | / |
| South | 513.297 | 11,9 | 3,3 | 497.038 | 11,6 | 7,6 | 461.943 | 10,8 | / |
| Gender | | | | | | | | | |
| Male | 725.109 | 11,3 | 4,1 | 696.580 | 10,9 | 5,9 | 657.720 | 10,3 | / |
| Female | 765.186 | 11,2 | 3,7 | 738.006 | 10,8 | 6,4 | 693.470 | 10,2 | / |
| Age group | | | | | | | | | |
| ≤45 | 42.474 | 0,7 | -4,2 | 44.349 | 0,8 | -1,8 | 45.163 | 0,8 | / |
| 46-65 | 481.890 | 11,1 | -0,2 | 482.882 | 11,2 | 2,0 | 473.632 | 11,0 | / |
| 66-75 | 499.042 | 31,0 | 4,4 | 478.163 | 29,8 | 7,7 | 443.825 | 27,8 | / |
| >75 | 466.889 | 30,8 | 8,8 | 429.192 | 28,5 | 10,5 | 388.570 | 25,9 | / |
| Mean age | 69.2 ± 11.4 | | | 68.7 ± 11.4 | | | 68.3 ± 11.4 | | |

N: number of subjects in analysis aged 18 years or older in treatment with statins
SS: study sample

*Results and considerations*

**Percentage of patients with a previous CV event or diabetes in treatment with statins (Indicator H-DB 2.1)**

The number of subjects in analysis aged 18 years or older with a previous CV event or diabetes in the year of reporting amounts to 853.504 in 2012.
The percentage of patients with a previous CV event or diabetes treated with statins amounts to 54,1%, slightly increased compared to previous years (+1,2% in 2012 compared to 2011 and +2,3% in compared to 2010). The percentage of subjects in treatment with statins is similar across Italy: North (54,2%), Center (54,0%) and South (54,0%) of the country with a prevalence in males (56,0% vs 51,9% in females). Age seems to affect significantly the use of statins: the higher percentage of patients in treatment with statins is in the age group 66 -75 years (62,3%).

**Table 4.4.10**. Number of patients with a previous CV event or diabetes in treatment with statins [numerator]/Total number of patients with a previous CV event or diabetes [denominator]

| | 2012 N = 853.504 | | 2011 N =829.726 | | 2010 N = 807.353 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 54,1 | 1,2 | 53,4 | 2,3 | 52,2 | / |
| Geographic distribution | | | | | | |
| North | 54,2 | 2,0 | 53,1 | 2,7 | 51,7 | / |
| Centre | 54,0 | 1,2 | 53,3 | 1,0 | 52,8 | / |
| South | 54,0 | 0,4 | 53,8 | 2,7 | 52,4 | / |
| Gender | | | | | | |
| Male | 56,0 | 1,3 | 55,3 | 1,8 | 54,3 | / |
| Female | 51,9 | 1,1 | 51,4 | 2,9 | 49,9 | / |
| Age group | | | | | | |
| ≤45 | 23,7 | -0,7 | 23,9 | -2,8 | 24,6 | / |
| 46-65 | 55,5 | 0,5 | 55,3 | 0,4 | 55,0 | / |
| 66-75 | 62,3 | 1,2 | 61,6 | 2,4 | 60,1 | / |
| >75 | 49,5 | 1,9 | 48,5 | 5,1 | 46,2 | / |
| Follow-up until 31-December 2013 | 54,1 | | 57,6 | | 59,9 | |

Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

**Percentage of patients in treatment with statins without a previous CV event or diabetes (Indicator H-DB 2.2)**

The number of subjects in analysis aged 18 years or older in treatment with statins amounts to 1.490.295 in 2013.
The percentage of patients treated with statins without a previous CV event or diabetes amounts to 76,3% in 2013; this value is slightly decreased if compared to previous years (-0,4% in 2013 compared to 2012 and -2,3% in 2012 compared to 2011). This percentage becomes 72,8% if the evaluation for previous CV event or diabetes starts from January 1, 2009. The percentage of patients treated with statins is slightly higher in North (78,0%) and Center (78,7%) than in South of Italy (72,5%) and in females (78,3% vs 74,2% of males).
Age seems to significantly affect statins use: the higher percentage of patients in treatment and without a previous CV event or diabetes is in the age group ≤45 years (86,9%). The number of new user is higher than the one of old users (83,5% vs 74,6%).

**Table 4.4.11.** Number of patients in treatment with statins and without a previous CV event or diabetes [numerator]/Total number of patients in treatment with statins [denominator]

| | 2013 N =1.490.295 | | 2012 N = 1.434.586 | | 2011 N = 1.351.190 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 76,3 | -0,4 | 76,6 | -2,3 | 78,4 | / |
| Geographic distribution | | | | | | |
| North | 78,0 | 0,0 | 78,1 | -2,4 | 80,0 | / |
| Centre | 78,7 | -0,6 | 79,1 | -3,6 | 82,1 | / |
| South | 72,5 | -0,9 | 73,2 | -1,1 | 74,0 | / |
| Gender | | | | | | |
| Male | 74,2 | -0,6 | 74,6 | -2,6 | 76,6 | / |
| Female | 78,3 | -0,3 | 78,5 | -2,0 | 80,1 | / |
| Age group | | | | | | |
| ≤45 | 86,9 | -0,1 | 87,0 | -0,8 | 87,7 | / |
| 46-65 | 77,8 | 0,1 | 77,7 | -1,6 | 79,0 | / |
| 66-75 | 74,1 | -0,6 | 74,6 | -2,6 | 76,5 | / |
| >75 | 76,0 | -0,7 | 76,5 | -2,7 | 78,6 | / |
| Treatment status | | | | | | |
| New users | 83,5 | -0,3 | 83,8 | -3,0 | 86,4 | / |
| Old users | 74,6 | -0,1 | 74,7 | -0,8 | 75,3 | / |
| Assessment from 01-January-2009° | 72,8 | | 74,0 | | 76,8 | |

N: number of subjects in analysis aged 18 years or older in treatment with statins

**Percentage of patient without a previous CV event or diabetes in treatment with low-intensity statins (Indicator H-DB 2.3)**

The number of patients in analysis aged 18 years or older in treatment with statins without a previous CV event or diabetes amounts to 1.136.536 in 2013.
The percentage of patient without a previous CV event or diabetes treated with low-intensity statins during 2013 amounts to 41,2%; this value is slightly decreased if compared to previous years (-5,9% in 2013 compared to 2012 and -0,5% in 2012 compared to 2011). The percentage of patients in treatment with low-intensity is slightly higher in Central Italy (46,0%) if compared to Northern (39,9%) and Southern (39,6%) regions of the Country, in females (45,0% vs 37,1% of males) and in the elderly (35,7% in the age group ≤45 years, 37,5%, in the age group 46-65 years, 41,6% in the age group 66-75 years and 45,3% in the age group≥75 years). There are no significant differences between the number of new and old users (41,8% vs 41,1%).

**Table 4.4.12.** Number of patient without a previous CV event or diabetes treated with low-intensity statins* [numerator]/Total number of patients receiving statins without a previous CV or diabetes [denominator]

| | 2013 N = 1.136.536 | | 2012 N = 1.098.874 | | 2011 N = 1.059.063 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 41,2 | -5,9 | 43,8 | -0,5 | 44,1 | / |
| Geographical distribution | | | | | | |
| North | 39,9 | -6,8 | 42,8 | 0,7 | 42,5 | / |
| Centre | 46,0 | -5,7 | 48,8 | -1,5 | 49,6 | / |
| South | 39,6 | -5,0 | 41,7 | -1,0 | 42,1 | / |
| Gender | | | | | | |
| Male | 37,1 | -7,2 | 40,0 | -2,2 | 40,9 | / |
| Female | 45,0 | -5,0 | 47,3 | 0,7 | 47,0 | / |
| Age group | | | | | | |
| ≤45 | 35,7 | -7,7 | 38,6 | -1,0 | 39,0 | / |
| 46-65 | 37,5 | -7,2 | 40,5 | -0,3 | 40,6 | / |
| 66-75 | 41,6 | -6,0 | 44,3 | -0,5 | 44,5 | / |
| >75 | 45,3 | -5,2 | 47,8 | -1,3 | 48,5 | / |
| Treatment status | | | | | | |
| New users | 41,8 | -13,2 | 48,1 | 5,2 | 45,7 | / |
| Old users | 41,1 | -3,5 | 42,6 | -1,7 | 43,3 | / |

N: Number of subjects aged 18 years or older without previous CV event or diabetes in treatment with statins
*List of low-intensity statins taken into account: simvastatin (C10AA01), lovastatin (C10AA02), pravastatin (C10AA03), fluvastatin (C10AA04)

**Percentage of patients with a previous CV event or diabetes in treatment with high-intensity statins (Indicator H-DB 2.4)**

The number of subjects in analysis, with a previous CV event or diabetes, aged 18 years or older, and in treatment with statins amounts to 353.759 in 2013.
The percentage of patients, with a previous CV event or diabetes, in treatment with high-intensity statins amounts to 62,6% in the same year; this value is slightly increased compared to previous years (+3,6% in 2013 compared to 2012 and +2,2% in 2012 compared to 2011). The percentage of subjects in treatment with high-intensity-statins is slightly lower in Central Italy than in Northern and Southern Italy (56,6%). This percentage is slightly higher in males (65,0% vs 59,8% in females) and in younger age group (65,8% in the age group ≤45 years and in the age group 46-65 years, 62,8% in the age group 66-75 years and 59,1% in the age group ≥75 years ). There are no significant differences between new users and old users.

**Table 4.4.13.** Number of patient with a previous CV event or diabetes treated with high-intensity statins* [numerator]/Total number of patients receiving statins with a previous CV or diabetes [denominator]

| | 2013 N = 353.759 | | 2012 N = 335.712 | | 2011 N = 292.127 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 62,6 | 3,6 | 60,4 | 2,2 | 59,1 | / |
| Geographic distribution | | | | | | |
| North | 63,2 | 3,6 | 61,0 | 1,4 | 60,2 | / |
| Centre | 57,6 | 4,5 | 55,1 | 2,2 | 53,9 | / |
| South | 64,4 | 3,4 | 62,3 | 3,4 | 60,3 | / |
| Gender | | | | | | |
| Male | 65,0 | 3,6 | 62,8 | 2,4 | 61,3 | / |
| Female | 59,8 | 3,7 | 57,7 | 2,0 | 56,5 | / |
| Age group | | | | | | |
| ≤45 | 65,8 | 2,1 | 64,5 | 0,2 | 64,3 | / |
| 46-65 | 65,8 | 3,2 | 63,7 | 1,6 | 62,7 | / |
| 66-75 | 62,8 | 4,0 | 60,4 | 2,5 | 58,9 | / |
| >75 | 59,1 | 4,5 | 56,5 | 3,6 | 54,6 | / |
| Treatment status | | | | | | |
| New users | 62,9 | 10,1 | 57,2 | 0,2 | 57,1 | / |
| Old users | 62,5 | 2,6 | 60,9 | 2,4 | 59,5 | / |

N: Number of patient aged 18 years and over with a previous CV event or diabetes in treatment with statins.
*List of high-intensity statins taken into account: atorvastatin (C10AA05), rosuvastatin (C10AA07), simvastatin and ezetimibe (C10BA02)

**Percentage of patients adhering to a treatment with statins (Indicator H-DB 2.5)**

The number of subjects in analysis aged 18 years and older in treatment with statins amounts to 1.388.687 in 2012.
The percentage of adherent subjects in treatment with statins amount to 43,0%; this value is increased compared to previous years (+6,2% in 2012 compared to 2011 and +0,4% in 2011 compared to 2010). The percentage of adherent subjects is slightly higher in Northern Italy (46,6%) compared to Central (42,8%) and Southern (38,6%) Italy and in males (46,3% vs 39,8% of females). The higher adherence has been observed in the age group 66-75 years (46,2%) compared to 26,0% of the age group ≤45 years, 41,0% of the age group 46-65 years and 43,4% of the age group ≥75 years, and in old users (47,8% vs 24,6% of new users). The adherence to the treatment with statins varies in relation to subject's clinical status (47,8% in subjects with a previous CV event or diabetes and 41,5% in subjects without a previous CV event or diabetes).
Excluding occasional users, the percentage of adherent patients amounts to 47,4%.

**Table 4.4.14.** Number of adherent patients in treatment with statins [numerator]/Total number of patients in treatment with statins [denominator]

| | 2012 N = 1.388.687 | | 2011 N = 1.306.401 | | 2010 N = 1.215.992 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 43,0 | 6,2 | 40,4 | 0,4 | 40,3 | / |
| Geographic distribution | | | | | | |
| North | 46,6 | 3,5 | 45,0 | 2,2 | 44,0 | / |
| Centre | 42,8 | 2,5 | 41,7 | 1,8 | 41,0 | / |
| South | 38,6 | 13,7 | 33,9 | -4,8 | 35,7 | / |
| Gender | | | | | | |
| Male | 46,3 | 5,5 | 43,9 | 0,4 | 43,7 | / |
| Female | 39,8 | 7,0 | 37,1 | 0,5 | 37,0 | / |
| Age group | | | | | | |
| ≤45 | 26,0 | 6,3 | 24,5 | 0,0 | 24,5 | / |
| 46-65 | 41,0 | 5,6 | 38,8 | -1,0 | 39,2 | / |
| 66-75 | 46,2 | 6,4 | 43,4 | 0,6 | 43,1 | / |
| >75 | 43,4 | 6,0 | 41,0 | 1,3 | 40,5 | / |
| Treatment status | | | | | | |
| New users | 24,6 | -0,6 | 24,7 | -1,0 | 25,0 | / |
| Old users | 47,8 | 6,2 | 45,0 | -0,4 | 45,2 | / |
| Comorbidity status | | | | | | |
| Without previous CV event or diabetes | 41,5 | 5,6 | 39,3 | 0,8 | 39,0 | / |
| With previous CV event or diabetes | 47,8 | 6,9 | 44,7 | -0,7 | 45,0 | / |
| TOTAL without occasional users | 47,4 | 5,6 | 44,9 | 0,2 | 44,8 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).
N: number of subjects in analysis aged 18 years or older in treatment with statins

**Percentage of occasional patients in treatment with statins (Indicator H-DB 2.6)**

The number of subjects in analysis aged 18 years and older in treatment with statins amounts to 1.388.687 in 2012. The percentage of occasional users amounts to 9,3%; this value is decreased if compared to previous years (-5,6% in 2012 compared to 2011 and -1,7% in 2011 compared to 2010). The percentage of occasional users is higher in the Center (8,8%) and in the South (12,7%) compared to North (6,8%) of Italy and is slightly higher in females (9,9% compared to 8,6% of the males). Poor adherence is higher in younger (23,3% in the age group ≤45 years, 10,4% in the age group 46-65 years, 7,5% in the age group 66-75 years and 8,6% in the age group ≥75 years ), in new users (29,2% compared to 4,1% of old users) and in subjects without a previous CV event or diabetes (10,1% compared to 6,5% of subjects with a previous CV event or diabetes).

**Table 4.4.15.** Number of occasional patients in treatment with statins [numerator] / Total number of patients in treatment with statins [denominator].

| | 2012 N = 1.388.687 | | 2011 N = 1.306.401 | | 2010 N = 1.215.992 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 9,3 | -5,6 | 9,8 | -1,7 | 10,0 | / |
| Geographic distribution | | | | | | |
| North | 6,8 | -7,8 | 7,3 | 2,4 | 7,1 | / |
| Centre | 8,8 | -4,1 | 9,2 | 7,0 | 8,6 | / |
| South | 12,7 | -5,3 | 13,4 | -4,2 | 14,0 | / |
| Gender | | | | | | |
| Male | 8,6 | -5,2 | 9,1 | -2,1 | 9,3 | / |
| Female | 9,9 | -5,9 | 10,6 | -1,3 | 10,7 | / |
| Age group | | | | | | |
| ≤45 | 23,3 | -3,2 | 24,1 | -6,9 | 25,9 | / |
| 46-65 | 10,4 | -5,0 | 10,9 | -1,2 | 11,1 | / |
| 66-75 | 7,5 | -4,5 | 7,8 | 0,4 | 7,8 | / |
| >75 | 8,6 | -5,7 | 9,1 | -0,1 | 9,1 | / |
| Treatment status | | | | | | |
| New users | 29,2 | 1,0 | 29,0 | 2,4 | 28,3 | / |
| Old users | 4,1 | -6,3 | 4,3 | 4,0 | 4,2 | / |
| Comorbidity status | | | | | | |
| Without previous CV event or diabetes | 10,1 | -4,0 | 10,6 | -2,4 | 10,8 | / |
| With previous CV event or diabetes | 6,5 | -9,7 | 7,3 | 1,7 | 7,1 | / |

This indicator has not been calculated in all LHUs , as extra-site data management appeared infeasible.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).
N: number of subjects in analysis aged 18 years or older in treatment with statins

***Economic impact of indicators***

The improvement of indicators described in this section is associated with an improvement in the health status and with a reduction of patient care overall cost (as these Indicators have been designed according to therapeutic standards of efficacy). They can impact on pharmaceutical expenditure in different ways, depending on the features of the single indicator (Table 4.4.16).

**Table 4.4.16**. Pharmaceutical expenditure flexibility for statins with regard to the improvement of related indicators

| Indicator | % Overall expenditure variation per 1% variation of Indicator | Overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-2.1 | +0,53% | € 4.181.728 |
| H.DB-2.2 | -0,97% | € -7.694.025 |
| H.DB-2.3 | -0,65% | € -5.152.201 |
| H.DB-2.4 | +0,22% | € 1.737.824 |
| H.DB-2.5 | +0,63% | € 4.989.847 |
| H.DB-2.6 | -0,16% | € -1.255.390 |

A preferential use of low-intensity statins in patients without a previous CV event or diabetes could result in savings in pharmaceutical expenditure for statins, while a preferential use of high-intensity statins in patients with a previous CV event or diabetes could increase pharmaceutical expenditure for statins. Nonetheless, these measures are likely to lead to an overall economic saving. Even though low-intensity statins are low-priced, the number of patients needing low-intensity statins is indeed higher than the number of patients needing high-intensity statins. These saving, together with those produced as a result of the reduction of occasional users (obtained through a better selection of patients to treat), the improvement of adherence could allow, for example, a reinvestment in policies to improve adherence and appropriateness (e.g. high-intensity statins for subjects with a previous CV event or diabetes).

## Indicators for hypoglycemic agents

- Percentage of adherent patients in treatment with hypoglycemic agents (Indicator H-DB 3.1)

- Percentage patients in treatment with DPP-IV inhibitors who do not meet DPP-IV inhibitors reimbursement criteria (Indicator H-DB 3.2)

- Percentage of patients who are not in treatment with DPP-IV inhibitors and meet DPP-IV inhibitors reimbursement criteria (Indicator H-DB 3.3)

*Methodology of calculation*

The following hypoglycemic agents have been taken into account for the analysis: ATC CODE A10B medicines (e.g. metformin with ATC CODE: A10BA02), sulfonamides, urea derivatives (ATC CODE: A10BB), combinations of oral blood glucose lowering agents (ATC CODE: A10BD), alpha glucosidase inhibitors (ATC CODE: A10BF), thiazolidinediones (ATC CODE: A10BG), dipeptidyl peptidase 4 inhibitors (DPP-IV inhibitors ATC CODE: A10BH), other blood glucose lowering agents, excluding insulins (ATC CODE: A10BX).
The subjects in analysis have been categorized as patients with a previous cardio-cerebral vascular event or diabetes and patients without a cardio-cerebral vascular event or diabetes, according to presence or absence of at least one of the following diagnosis and/or procedures:

- Hypertension: at least one hospitalization with diagnosis of hypertension (ICD-9 CODE 401-405)
- Coronary heart disease: at least one hospitalization with diagnosis of acute myocardial infarction (ICD-9 CODE 410), acute cardiac ischemia (ICD-9 CODE 411), pectoris angina (ICD-9 CODE 413), chronic heart ischemia (ICD-9 CODE 414)
- Heart failure: at least one hospitalization with diagnosis of heart failure (ICD-9 CODE 428)
- Cerebrovascular disease: at least one hospitalization with diagnosis of subarachnoid hemorrhage (ICD-9 CODE 430), intracerebral hemorrhage (ICD-9 CODE 431-432), ischemic stroke (ICD-9 CODE 434; 436), Transient ischemic attack (TIA) (ICD-9 CODE 435), other cerebrovascular diseases (ICD-9 CODE 433; 437-438)
- Vascular peripheral disease: at least one hospitalization with diagnosis of atherosclerosis (ICD-9 CODE 440), other vascular peripheral diseases (ICD-9 CODE 443)
- Percutaneous transluminal coronary angioplasty (PTCA): at least one hospitalization with diagnosis of status-post PTCA (ICD-9 CODE V4582) or at least a hospitalization with a procedure of PTCA (ICD-9 CODE 0066), other removal of coronary artery obstruction (ICD-9 CODE 3609)

- Chronic kidney disease: at least one hospitalization with diagnosis of Chronic kidney disease (ICD-9 CODE 585).

The subjects in treatment with hypoglycemic agents have been categorized in two groups: new users and patients already in treatment (old users) in relation to absence or presence, respectively, of at least one prescription of any hypoglycemic agents within the 12 months following the first prescription of the reporting year (index date). Furthermore, subjects in treatment with hypoglycemic agents have been defined as occasional or adherent users in relation to a pharmaceutical coverage <20% or ≥80%, respectively, within the 12 months following the first prescription.
The therapeutic coverage has been calculated considering all DDDs (defined daily doses) prescribed within the 12 months following the first prescription of the reporting year. The presence, in the same prescription, of different classes of hypoglycemic agents has been considered as a combination therapy. The therapeutic coverage has been compared with the observation period and then multiplied by 100.

The following parameters have been taken into account to evaluate the presence or absence of DPP-IV inhibitors reimbursement criteria:

- value of the last glycosylated hemoglobin (HbA1c) in the two months preceding the beginning of therapy
- presence of at least one of following frailty criteria: age >75 years; severe chronic kidney disease with a glomerular filtrate [GFR] <30 ml/min (Criteria satisfied by the presence of, at least, one hospitalization with diagnosis of chronic kidney disease (ICD-9 CODE 585) or a GFR <30 ml/min (parameter calculated by the short MDRD equation); complications or and/or concomitant diseases that reduce the life expectancy (criteria identified by the presence of at least one hospitalization with diagnosis of hypertension, coronary heart disease, heart failure, cerebrovascular disease, vascular peripheral disease)
- beginning or continuation of a DPP-IV inhibitors therapy, defined as the absence or presence of at least one DPP-IV inhibitors prescription in the year before the first prescription of the reporting year.

As mentioned above, patients have been categorized as:

- fitting AIFA DPP-IV inhibitors reimbursement criteria if meeting one of the following criteria:
  - ✓ ≥7.5% HbA1c ≤8,5% at the beginning of the treatment
  - ✓ HbA1 <9% at the treatment beginning in frail subjects
  - ✓ HbA1 ≤8,5% for treatment prosecution
  - ✓ HbA1c <9% for treatment prosecution in frail subjects
- not fitting AIFA DPP-IV inhibitors reimbursement criteria if meeting one of the following criteria :
  - ✓ HbA1c <7.5% or ≥8,5% HbA1c <9% or at the beginning of the treatment

- ✓ HbA1 ≥9% at the treatment beginning of frail subjects
- ✓ ≥8,5% HbA1c <9% for treatment prosecution
- ✓ HbA1c ≥ 9% for treatment prosecution in frail subjects

*Cohort of subjects in analysis*

The number of subjects aged 18 years or older in treatment with hypoglycemic agents amounts to 737.252 in 2013 (Table 4.4.17). The prevalence of the treatment with hypoglycemic agents amounts to 5,6% of the study sample (4,7% in Northern Italy, 5,5% in Central and 6,8% in Southern Italy). The prevalence of treatment with anti-diabetic agents increases with age (0,5% in the age group ≤45 years, 5,5% in the age group 46-65 years, 14,7% in the age group 66-75 years and 15,6% in the age group ≥75 years) and over the years (+3,8% in 2013 compared to 2012 and +2,4% in 2012 compared to 2011).

**Table 4.4.17 Ditribution of patients in treatment with anti-diabetic agents**

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % SS | Var.% | N | % SS | Var.% | N | % SS | Var.% |
| TOTAL | 737.252 | 5,6 | 3,8 | 710.228 | 5,4 | 2,4 | 693.813 | 5,3 | / |
| Geographic distribution | | | | | | | | | |
| North | 289.965 | 4,7 | 4,4 | 277.682 | 4,5 | 1,1 | 274.726 | 4,5 | / |
| Centre | 153.344 | 5,5 | 3,7 | 147.856 | 5,3 | 2,2 | 144.631 | 5,3 | / |
| South | 293.943 | 6,8 | 3,3 | 284.690 | 6,6 | 3,7 | 274.456 | 6,4 | / |
| Gender | | | | | | | | | |
| Male | 380.439 | 5,9 | 4,3 | 364.694 | 5,7 | 3,0 | 353.988 | 5,6 | / |
| Female | 356.813 | 5,2 | 3,3 | 345.534 | 5,1 | 1,7 | 339.825 | 5,0 | / |
| Age group | | | | | | | | | |
| ≤45 | 27.530 | 0,5 | -2,1 | 28.121 | 0,5 | -7,7 | 30.466 | 0,5 | / |
| 46-65 | 237.459 | 5,5 | -0,8 | 239.275 | 5,5 | -1,9 | 244.029 | 5,7 | / |
| 66-75 | 236.230 | 14,7 | 4,1 | 226.896 | 14,2 | 4,6 | 216.815 | 13,6 | / |
| >75 | 236.033 | 15,6 | 9,3 | 215.936 | 14,3 | 6,6 | 202.503 | 13,5 | / |
| Mean age | 69.5 ± 11.4 | | | 68.5 ± 12.1 | | | 68.0 ± 12.2 | | |

N: number of subjects aged 18 years or older in treatment with hypoglycemic agent, excluding insulins from the analysis
SS: study sample

*Results and considerations*

**Percentage of adherent patients in treatment with hypoglycemic agents (Indicator H-DB 3.1)**

The number of subjects in analysis aged 18 years or older in treatment with hypoglycemic agents amounts to 691.590 in 2012.
The percentage of adherent patients amounts to 62,1%; this value is slightly increased compared to previous year (+2,0% in 2012 compared to 2011; -1,2% in 2011 compared to 2010). The percentage of adherent patients is slightly lower in the South of Italy (60,4%) compared to North and to Center (63,2%) of the country. There are no significant differences between males and females (62,9% vs 61,2%). The adherence is higher in old users (67,9% vs 29,2% of new users). There are no differences among patients with a previous CV event compared to patients without a previous CV event (62,3% vs 62,0%).The adherence improves with age (41,5% in the age group ≤45 years, 62,7% in the age group 46-65 years, 66,6% in the age group 66-75 years and of 59,2% in the age group >75 years). Excluding occasional users, the percentage of adherent patients amounts to 66,7% in 2012.

**Table 4.4.18**. Number of adherent patients in treatment with anti-diabetic agents [numerator]/Total number of patients in treatment with antidiabetic agents [denominator]

| | 2012 N = 691.590 | | 2011 N = 675.538 | | 2010 N = 643.153 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 62,1 | 2,0 | 60,9 | -1,2 | 61,6 | / |
| Geographic distribution | | | | | | |
| North | 63,2 | 0,6 | 62,8 | 0,2 | 62,7 | / |
| Centre | 63,2 | 1,6 | 62,2 | -1,1 | 62,9 | / |
| South | 60,4 | 3,7 | 58,3 | -3,1 | 60,2 | / |
| Gender | | | | | | |
| Male | 62,9 | 1,8 | 61,8 | -1,0 | 62,4 | / |
| Female | 61,2 | 2,1 | 59,9 | -1,4 | 60,8 | / |
| Age group | | | | | | |
| ≤45 | 41,5 | 3,9 | 40,0 | -4,2 | 41,7 | / |
| 46-65 | 62,7 | 1,2 | 61,9 | -2,3 | 63,4 | / |
| 66-75 | 66,6 | 2,0 | 65,3 | -0,6 | 65,7 | / |
| >75 | 59,2 | 2,3 | 57,9 | -0,2 | 58,0 | / |
| Treatment status | | | | | | |
| New users | 29,2 | -3,1 | 30,2 | -9,0 | 33,1 | / |
| Old users | 67,9 | 1,0 | 67,2 | -1,9 | 68,5 | / |
| Comorbidity status | | | | | | |
| Without previous CV event or diabetes | 62,0 | 2,0 | 60,8 | -1,3 | 61,6 | / |
| With previous CV event or diabetes | 62,3 | 0,3 | 62,1 | -1,0 | 62,7 | / |
| TOTAL without occasional users | 66,7 | 1,6 | 65,7 | -1,0 | 66,4 | |

This indicator has not been calculated in all LHUs ,as extra-site data management appeared infeasible. Being the data available only until

Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of subjects in analysis aged 18 years or older in treatment with hypoglycemic agents

**Percentage of patients in treatment with DPP-IV inhibitors who do not meet DPP-IV inhibitors reimbursement criteria (Indicator H-DB 3.2)**

The number of subjects in analysis aged 18 years or older in treatment with DPP-IV inhibitors amounts to 924 in 2013.
The percentage of patients in treatment with DPP-IV inhibitors who don't meet DPP-IV inhibitors reimbursement criteria amounts to 31,2%; this value is decreased compared to previous year (-20,4% in 2013 compared to 2012). The percentage is higher in females (35,4% vs 27,5% of males) and in younger subjects (48,5% in the age group ≤45 years, 31,9% in the age group 46-65 years, of 32,1% in the age group 66-75 years and of 26,1% in the age group >75 years). The 13,0% of patients in treatment with DPP-IV inhibitors who don't meet DPP-IV inhibitors reimbursement criteria comes from a previous DPP-IV inhibitor therapy, while the 58,5% of subjects are new DPP-IV users.

**Table 4.4.19**. Number of patients in treatment with DPP-IV inhibitors who don't meet DPP-IV inhibitors reimbursement criteria [numerator^]/Total number of patients in treatment with DPP-IV inhibitors [denominator]

| | 2013 N = 924 | | 2012 N = 853 | | 2011 N = 657 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 31,2 | -20,4 | 39,2 | -23,4 | 51,1 | / |
| Gender | | | | | | |
| Male | 27,5 | -32,3 | 40,6 | -22,3 | 52,3 | / |
| Female | 35,4 | -5,5 | 37,5 | -25,0 | 50,0 | / |
| Age group | | | | | | |
| ≤45 | 48,5 | 41,0 | 34,4 | -36,7 | 54,3 | / |
| 46-65 | 31,9 | -23,8 | 41,8 | -21,2 | 53,1 | / |
| 66-75 | 32,1 | -16,6 | 38,5 | -26,1 | 52,1 | / |
| >75 | 26,1 | -26,8 | 35,7 | -17,9 | 43,5 | / |
| DPP-IV inhibitors treatment status | | | | | | |
| Treatment beginning | 58,5 | 1,7 | 57,5 | -0,5 | 57,8 | / |
| Treatment continuation | 13,0 | -21,3 | 16,5 | -5,4 | 17,4 | / |

This indicator has been calculated only for LHUs with a laboratory flow.
The value of the last glycosylated hemoglobin (HbA1c) performed within two months before the beginning of therapy has been taken into account.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of subjects in analysis aged 18 years or older in treatment with hypoglycemic agents
^With regard to patients in treatment with DPP-IV inhibitors who do not meet DPP-IV inhibitors reimbursement criteria:

- during 2011 among patients who don't present elements of frailty the 50,0% has a HbA1c value <7,5% and the 50,0% has HbA1c value ≥8,5% and <9,0% or ≥9,0% in frail subjects
- during 2012 among patients who don't present elements of frailty the 41,0% has a HbA1c value <7,5% and the 59,0% has HbA1c value ≥8,5% and <9,0% or ≥9,0% in frail subjects
- during 2013 among patients who don't present elements of frailty the 36,8% has a HbA1c value <7,5% and the 63,2% has HbA1c value ≥8,5% and <9,0% or ≥9,0% in frail subjects.

**Percentage of patients who are not in treatment with DPP-IV inhibitors and meet DPP-IV inhibitors reimbursement criteria (Indicator H-DB 3.3)**

The number of diabetic patients aged 18 years and older who meet DPP-IV inhibitors reimbursement criteria is of 1.729 in 2013.

The percentage of patients who meet DPP-IV inhibitors reimbursement criteria but who are not in treatment with DPP-IV inhibitors amounts to 63,2% in 2013; this value has decreased compared to previous year (-10,9% in 2013 compared to 2012). This percentage is higher in females (68,5% vs 57,8% of males) and in older patients (71,2% in the age group ≤45 years, 55,0% in the age group 46-65 years, of 59,9% in the age group 66-75 years and of 72,6% higher to 75 years).

With regards to previous treatments, the percentages observed for patients not in treatment with DPP-IV inhibitors, although they fit DPP-IV inhibitors reimbursement criteria, are the following 87,4% of subjects coming from a monotherapy with metformin; 85,8% from metformin and sulfonamides in association; 77,2% from metformin and thiazolidinedione in association; 69,6% from metformin, sulfonamide and thiazolidinedione in association; 86,1% from a monotherapy with sulfonamide; 17,4% from other agents in association, also with DPP-IV inhibitors; and 96,5% of subjects who don't come from any antidiabetic therapy. Excluding from the analysis patients who continue a previous DPP-IV inhibitors therapy, the percentage of patients who meet DPP-IV inhibitors reimbursement criteria and who don't take a DPP-IV inhibitor amounts to of 87,1% in 2013.

**Table 4.4.20**. Number of patients who are not in treatment with DPP-IV inhibitors and meet DPP-IV inhibitors reimbursement criteria [numerator^]/Total number of patients who fit DPP-IV inhibitors reimbursement criteria [denominator]

| | 2013 N = 1.729 | | 2012 N = 1.758 | | 2011 N = 1.494 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 63,2 | -10,9 | 70,9 | -9,7 | 78,5 | / |
| Gender | | | | | | |
| Male | 57,8 | -17,7 | 70,2 | -11,1 | 79,0 | / |
| Female | 68,5 | -4,4 | 71,6 | -8,2 | 78,0 | / |
| Age group | | | | | | |
| ≤45 | 71,2 | -5,1 | 75,0 | 5,0 | 71,4 | / |
| 46-65 | 55,0 | -8,4 | 60,1 | -13,1 | 69,2 | / |
| 66-75 | 59,9 | -13,6 | 69,4 | -11,7 | 78,5 | / |
| >75 | 72,6 | -10,4 | 81,0 | -7,2 | 87,3 | / |
| Therapy | | | | | | |
| Monotherapy with metformin | 87,4 | 1,2 | 86,4 | 1,5 | 85,0 | / |
| Metformin and sulfonamides | 85,8 | 5,5 | 81,3 | -2,1 | 83,0 | / |
| Metformin and thiazolidinedione | 77.2 | 6,7 | 72,4 | 5,4 | 68,6 | / |
| Metformin, sulfonamide and thiazolidinedione | 69,6 | 5,0 | 66,3 | 4,4 | 63,5 | / |
| Monotherapy with sulfonamide | 86,1 | -4,3 | 90,0 | -4,2 | 93,9 | / |
| Other combination therapy | 17,4 | -43,9 | 31,1 | -14,9 | 36,5 | / |
| No anti-diabetic therapy | 96,5 | 0,2 | 96,4 | -1,4 | 97,8 | / |
| Without patients who continue a previous DPP-IV inhibitors therapy | 87,1 | 1,8 | 85,6 | 2,8 | 83,2 | / |

This indicator has been calculated only for LHUs with a laboratory flow.
The value of the last glycosylated hemoglobin (HbA1c) performed within two months before the beginning of therapy has been taken into account.

N: number of patients aged 18 year or older in treatment with hypoglycemic agents who meet DPP-IV reimbursement criteria
^With regard to not in treatment with DPP-IV inhibitors subjects, but who meet DPP-IV inhibitors reimbursement criteria:

- During 2011 29,6% comes from a monotherapy with metformin, 24,2% comes from metformin and sulfonamides in association; 6,9% comes from metformin and thiazolidinedione in association; 6,2% comes from metformin, sulfonamide and thiazolidinedione in association; 5,3% comes from a monotherapy with sulfonamide; 5,5% comes from other agents in association, also with DPP-IV inhibitors, and 22,3% doesn't come from any antidiabetic therapy.
- During 2012 30,0% comes from a monotherapy with metformin, 22,4% comes from metformin and sulfonamides in association; 4,3% comes from metformin and thiazolidinedione in association; 4,3% comes from metformin, sulfonamide and thiazolidinedione in association; 4,3% comes from a monotherapy with sulfonamide; 11,7% comes from other agents in association, also with DPP-IV inhibitors, and 23,0% doesn't come from any antidiabetic therapy.
- During 2013 31,8% comes from a monotherapy with metformin, 22,0% comes from metformin and sulfonamides in association; 4,0% comes from metformin and thiazolidinedione in association; 4,4% comes from metformin, sulfonamide and thiazolidinedione in association; 2,8% comes from a monotherapy with sulfonamide; 9,6% comes from other agents in association, also with DPP-IV inhibitors, and 25,3% doesn't come from any antidiabetic therapy.

***Economic impact of indicators***

The improvement of indicators described in this section is associated with an improvement of patients' health status and with a reduction of patient care overall cost (since these indicators have been designed according to therapeutic standards of efficacy). They can impact on pharmaceutical expenditure in different ways depending on the features of the single indicator (Table 4.4.21).

**Table 4.4.21.** Pharmaceutical expenditure flexibility for antidiabetic agents with regard to the improvement of related indicators

| Indicator | % Overall expenditure variation per 1% variation of Indicator | Overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-3.1 | +1,01 | € 3.931.717 |
| H.DB-3.2 | -0.39% | € -1,527,669 |
| H.DB-3.3 | +0.88% | € 3,418,156 |

The reduction of prescriptions of DPP-IV inhibitor to patients who don't meet reimbursement criteria for DPP-IV inhibitors could result in savings in pharmaceutical expenditure for antidiabetic medicines and could allow a reinvestment in measures to ensure appropriateness (e.g. DPP-IV inhibitor for those patients who meet criteria) and in policies to improve adherence.

**Indicators for obstructive pulmonary diseases medicines**

- Percentage of patients with one hospitalization for COPD in treatment with ICS (Indicator H-DB 4.1)

- Percentage of patients with one hospitalization for COPD in treatment with LABA and/or LAMA (Indicator H-DB 4.2)

- Percentage of patients in treatment with ICS without exacerbations (Indicator H-DB 4.3)

- Percentage of adherent patients in treatment with medicines for obstructive airway diseases (Indicator H-DB 4.4)

- Percentage of occasional patients in treatment with medicines for obstructive pulmonary diseases (Indicator H-DB 4.5).

*Methodology of calculation*

Medicines taken into account for the analysis are agents with ATC CODE R03 such as inhalator corticosteroids (ICS: glucocorticoids - ATC CODE R03BA, adrenergics in association with corticosteroids and other medicines for obstructive airway diseases - ATC CODE R03AK); long-acting beta-adrenoceptor agonists (LABA: salmeterol - ATC CODE R03AC12, formoterol - ATC CODE R03AC13, clenbuterol - ATC CODE R03AC14, indacaterol - ATC CODE R03AC18, salmeterol in association - ATC CODE R03AK06, formoterol in association - ATC CODE R03AK07, bambuterol - ATC CODE R03CC12); long-acting antimuscarinic agents (LAMA: ATC CODE R03BB).

The subjects in analysis have been defined as patients with exacerbations in relation to the presence or absence of at least one of following conditions:

- Oxygen therapy: at least one hospitalization with diagnosis for respirator dependence (ICD-9 CODE: V461), treatment with breathing exercises (ICD-9 CODE: V570), respiratory failure in other conditions (ICD-9 CODE: 518.81; 518.83; 518.84) or at least one hospitalization with breathing exercises (ICD-9 CODE: 9318), continuous positive airway pressure (CPAP) breathing (ICD-9 CODE: 9390), intermittent positive pressure breathing (ICD-9 CODE: 9391) or at least one prescription of oxygen (ATC CODE V03AN01)
- Antibiotics and/or corticosteroids therapy: at least two prescriptions of antibiotics (ATC CODE: J01) and/or oral corticosteroids (ATC CODE: H02)
- COPD: at least one hospitalization with diagnosis for bronchitis, not specified as acute or chronic (ICD-9 CODE: 490), chronic bronchitis (ICD-9 CODE: 491), emphysema (ICD-9 CODE: 492), bronchiectasis (ICD-9 code: 494), extrinsic allergic

alveolitis (ICD-9 code: 495), chronic airway obstruction, not elsewhere classified (ICD-9 code: 496)
- surgical reduction of the lung volume: (ICD-9 CODE: 3222)
- lung transplantation: at least one hospitalization with an intervention for lung transplantation, not otherwise specified (ICD-9 CODE: 3350), unilateral lung transplantation (ICD-9 CODE: 3351), bilateral lung transplantation (ICD-9 CODE: 3352).

The subjects in analysis have been categorized as new users or already in treatment (old users) in relation to the absence or presence, respectively, of at least one prescription of obstructive airway diseases medications within the 12 months following the first prescription of the reporting year. Furthermore, subjects in treatment with medicines for obstructive pulmonary diseases have been defined as occasional or adherent users in relation to a pharmaceutical coverage <20% or ≥80%, respectively, within the 12 months following the first prescription.
The therapeutic coverage has been calculated considering all DDDs (defined daily doses) for obstructive airway diseases medications prescribed within the 12 months following the first prescription. The presence in the same prescription of different classes of agents for obstructive airway diseases has been considered as an association therapy. The therapeutic coverage has been compared with the observation period and multiplied by 100.
Subjects with diagnosis of asthma, identified by consumption of leukotriene receptor antagonists (ATC CODE R03DC) or presence of a discharge diagnosis of asthma (ICD-9 code 493), but not combined with COPD, have been excluded from the analysis.

*Cohort of subjects in analysis*

The number of subjects in analysis aged 40 years or older in treatment with medicines for obstructive pulmonary diseases amounts to 1.165.167 in 2013 (Table 4.4.22). The prevalence of treatment with medicines for obstructive pulmonary diseases amounts to 12,9% of study sample (10,6% in Northern Italy, 13,6% in Central Italy and 15,8% in Southern Italy). The prevalence of treatment with medicines for obstructive pulmonary diseases increases with age (8,7% in the age group ≤45 years, 10,3% in the age group 46-65 years, 16,9% in the age group 66-75 years and 20,4% in the age group ≥75 years).

**Table 4.4.22**. Distribution of patients in treatment with medicines for obstructive pulmonary diseases

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % SS | Var.% | N | % SS | Var.% | N | % SS | Var.% |
| TOTAL | 1.165.167 | 12,9 | 4,7 | 1.113.107 | 12,4 | -0,4 | 1.117.539 | 12,5 | / |
| Geographic distribution | | | | | | | | | |
| North | 446.372 | 10,6 | 3,6 | 430.991 | 10,3 | -1,0 | 435.269 | 10,5 | / |
| Centre | 256.260 | 13,6 | 7,8 | 237.680 | 12,7 | -2,9 | 244.787 | 13,1 | / |
| South | 462.535 | 15,8 | 4,1 | 444.436 | 15,2 | 1,6 | 437.483 | 15,1 | / |
| Gender | | | | | | | | | |
| Male | 519.516 | 11,9 | 4,6 | 496.508 | 11,4 | 0,4 | 494.725 | 11,4 | / |
| Female | 645.651 | 13,9 | 4,7 | 616.599 | 13,4 | -1,0 | 622.814 | 13,6 | / |
| Age group | | | | | | | | | |
| ≤45 | 135.021 | 8,7 | 4,1 | 129.753 | 8,4 | -9,9 | 143.948 | 9,4 | / |
| 46-65 | 448.172 | 10,3 | 4,4 | 429.386 | 10,0 | -5,1 | 452.277 | 10,5 | / |
| 66-75 | 272.601 | 16,9 | 4,3 | 261.278 | 16,3 | 4,9 | 249.056 | 15,6 | / |
| >75 | 309.373 | 20,4 | 5,7 | 292.690 | 19,4 | 7,5 | 272.258 | 18,2 | / |
| Mean age | 64.8 ± 14.3 | | | 64.7 ± 14.2 | | | 63.8 ± 14.2 | | |

N: number of subjects in analysis aged 40 years or older in treatment with medicines for obstructive pulmonary diseases, with the exclusion of subjects with a previous hospitalization for asthma
SS: study sample

*Results and considerations*

**Percentage of patients with one hospitalization for COPD in treatment with ICS (Indicator H-DB 4.1)**

The number of patients aged 40 years and older with one hospitalization for COPD amounts to 35.318 in 2012.
The percentage of patients in treatment with ICS in the period following hospital discharge amounts to 55,5%; this value has slightly decreased if compared to the previous year (-0,6% in 2012 compared to 2011). If the presence of a therapy with ICS is evaluated until December 31, 2013, the percentages registered are the following: 59,2% in 2012, 65,4% in 2011 and 68,0% in year 2010. The percentage of subject in treatment is slightly lower in Southern Italy (50,7%) compared to Northern Italy (58,7%) and to Central (56,8%) Italy, and in females (53,8% vs 56,6% of males). This percentage changes with age (31,9% in the age group ≤45 years, 48,3% in age group 46-65 years, 59,7% in age group 66-75 years and 56,0% in age group ≥75 years ) and is higher in old users than in new users (74,4% your 27,5%).

**Table 4.4.23.** Number of patients with one hospitalization for COPD in treatment with ICS [numerator]/Total number of patients with a hospitalization for COPD [denominator]

| | 2012 N = 35.318 | | 2011 N = 34.808 | | 2010 N = 36.397 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 55,5 | -0,6 | 55,8 | 2,6 | 54,4 | / |
| Geographic distribution | | | | | | |
| North | 58,7 | -0,2 | 58,8 | 1,6 | 57,9 | / |
| Centre | 56,8 | 1,4 | 56,0 | 6,5 | 52,6 | / |
| South | 50,7 | -2,7 | 52,1 | 0,6 | 51,8 | / |
| Gender | | | | | | |
| Male | 56,6 | -0,3 | 56,8 | 2,6 | 55,3 | / |
| Female | 53,8 | -1,0 | 54,3 | 2,4 | 53,0 | / |
| Age group | | | | | | |
| ≤45 | 31,9 | -20,8 | 40,3 | 11,2 | 36,2 | / |
| 46-65 | 48,3 | -1,4 | 49,0 | 0,4 | 48,8 | / |
| 66-75 | 59,7 | -0,5 | 60,0 | 2,6 | 58,5 | / |
| >75 | 56,0 | -0,4 | 56,3 | 3,2 | 54,5 | / |
| Treatment status | | | | | | |
| New users | 27,5 | -0,8 | 27,7 | -2,0 | 28,3 | / |
| Old users | 74,4 | -2,0 | 75,9 | -1,4 | 76,9 | / |
| Follow-up until 31 Dec 2013 | 59,2 | | 65,4 | | 68,0 | / |

Since data were was available until up until December 31, 2013, the last reporting year is 2012 (, in order to have a complete one full observation year also for subjects included at in December 2012).The presence of one hospitalization for COPD has been evaluated with respect to the reporting year. The discharge date (in case of more than one hospitalization the last discharge date is taken into account) is the index date. The presence of a therapy with ICS has been evaluated with regard to 365 days following the index date.
N: number of patients aged 40 years and older with exacerbations, with the exclusion of patients with a previous hospitalization for asthma and/or treatment with leukotriene receptor antagonists

**Percentage of patients with one hospitalization for COPD in treatment with LABA and/or LAMA (Indicator H-DB 4.2)**

The number of patients aged 40 years and older with a discharge diagnosis of COPD amounts to 35.318 in 2012.
The percentage of patients in treatment with LABA and/or LAMA in the period following hospital discharge amounts to 53,5%; this value is slightly higher than previous years (+0,5% in 2012 compared to 2011; +4,4% in 2011 compared to 2010). If the presence of a therapy with LABA and/or LAMA is evaluated until December 31, 2013, the percentages are the following: 55,9% in 2012, 59,6% in 2011 and 60,5% in 2010,. This percentage is slightly lower in Southern (45,0%) than in Northern (59,5%) and Central Italy (55,2%), and in females (49,7% compared to 56,0% of males), it changes with age (25,3% in the age group ≤45 years, 45,5% in the age group 46-65 years, 58,5% in the age group 66-75 years and 54,0% in the age group ≥75 years) and is higher in old users (73,7% vs 23,5% of new ones).

**Table 4.4.24.** Number of patients with one hospitalization for COPD in treatment with LABA and/or LAMA [numerator]/Total number of patients with one hospitalization for COPD [denominator]

| | 2012 N = 35.318 | | 2011 N = 34.808 | | 2010 N = 36.397 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 53,5 | 0,5 | 53,2 | 4,4 | 51,0 | / |
| Geographic distribution | | | | | | |
| North | 59,5 | 1,8 | 58,5 | 3,2 | 56,6 | / |
| Centre | 55,2 | 1,8 | 54,3 | 8,2 | 50,2 | / |
| South | 45,0 | -2,3 | 46,1 | 2,7 | 44,9 | / |
| Gender | | | | | | |
| Male | 56,0 | 1,3 | 55,3 | 4,1 | 53,1 | / |
| Female | 49,7 | -0,6 | 50,0 | 4,9 | 47,6 | / |
| Age group | | | | | | |
| ≤45 | 25,3 | -19,4 | 31,4 | 7,7 | 29,1 | / |
| 46-65 | 45,5 | 0,9 | 45,1 | 3,5 | 43,6 | / |
| 66-75 | 58,5 | 1,5 | 57,7 | 3,4 | 55,8 | / |
| >75 | 54,0 | -0,3 | 54,2 | 5,4 | 51,4 | / |
| Treatment status | | | | | | |
| New users | 23,5 | -1,3 | 23,8 | -1,0 | 24,1 | / |
| Old users | 73,7 | -0,7 | 74,2 | 0,1 | 74,1 | / |
| Follow-up until 31 December 2013 | 55,9 | | 59,6 | | 60,5 | / |

Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).
The presence of one hospitalization for COPD has been evaluated with reference to the reporting year. The discharge date (in case of more than one hospitalization, the last discharge date is taken into account) is the index date. The presence of a therapy with LABA and/or LAMA has been evaluated with regards to the 365 days following the index date.

N: Number of patients aged 40 years and older with exacerbations, with the exclusion of patients with a previous hospitalization for asthma and/or treatment with leukotriene receptor antagonists

**Percentage of patients in treatment with ICS without exacerbations (Indicator H-DB 4.3)**

The number of patients aged 40 years or older in treatment with ICS, amounts to 971.009 in 2012.
The percentage of subjects in treatment with ICS without exacerbations amounts to 52,2%; this value is slightly lower than in the previous year (-4,7% in 2012 compared to 2011). This percentage amounts to 20,2% in 2012, 31,8% in 2011 and 42,2% in 2010 if the absence of exacerbations is evaluated starting from January 1, 2009. This percentage is higher in Northern Italy (63,1%) than in Central (49,0%) and Southern Italy (43,2%), in younger subjects (64,0% in the age group ≤45 years, 57,7% in the age group 46-65 years, 47,2% in the age group 66-75 years and 42,7% in the age group >75 years), in new users (60,2% compared to 39,2% of old users) and in males (53,1% vs 51,4% of females).

**Table 4.4.25.** Number of patients in treatment with ICS without exacerbations [numerator]/Total number of patients in treatment with ICS [denominator]

| | 2012 N = 971.009 | | 2011 N = 976.679 | | 2010 N = 938.203 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 52,2 | -4,7 | 54,8 | 3,5 | 52,9 | / |
| Geographic distribution | | | | | | |
| North | 63,1 | -4,7 | 66,3 | 1,9 | 65,0 | / |
| Centre | 49,0 | -9,8 | 54,3 | 6,5 | 51,0 | / |
| South | 43,2 | -0,8 | 43,5 | 1,2 | 43,0 | / |
| Gender | | | | | | |
| Male | 53,1 | -5,0 | 55,9 | 7,7 | 51,9 | / |
| Female | 51,4 | -4,5 | 53,8 | -0,5 | 54,1 | / |
| Age group | | | | | | |
| ≤45 | 64,0 | 0,1 | 63,9 | 4,0 | 61,4 | / |
| 46-65 | 57,7 | -1,5 | 58,5 | 4,0 | 56,3 | / |
| 66-75 | 47,2 | -7,3 | 50,9 | 3,4 | 49,2 | / |
| >75 | 42,7 | -8,5 | 46,7 | 3,2 | 45,2 | / |
| Treatment status | | | | | | |
| New users | 60,2 | -4,7 | 63,1 | 3,4 | 61,0 | / |
| Old users | 39,2 | 0,7 | 38,9 | -0,5 | 39,1 | / |
| From 01-January-2009 | 20,2 | | 31,8 | | 42,2 | / |

The presence of a therapy with ICS has been evaluated with regards to the reporting year. The date of the first prescription is the index rate. The presence of exacerbations has been evaluated with regards to the year before the index date.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: Number of patients aged 40 years and older in treatment with ICS, with the exclusion of patients with a previous hospitalization for asthma and/or treatment with leukotriene receptor antagonists

**Percentage of adherent patients in treatment with obstructive pulmonary disease medications (Indicator H-DB 4.4)**

The number of patients aged 40 years or older in treatment with medicines for obstructive pulmonary diseases taken into account amounts to 1.078.597 in 2012.
The percentage of adherent patients is of 14,3%; this value is slightly increased than the previous year (+2,4% in 2012 compared to 2011). The adherence is higher in Northern Italy (16,6%) compared to Central (15,2%) and Southern (11,8%) Italy, in males (18,6% vs 10,9% of females), in old users (32,4% compared to 2,9% in new users) and in patients with exacerbations (18,5% compared to 10,5% of patients without exacerbations). Moreover, the adherence to the treatment improves with age (4,3% in the age group ≤45 years, 8,2% in the age group 46-65 years, 17,7% in the age group 66-75 years, 24,8% in the age group ≥75 years), excluding occasional users from the analysis, the percentage of adherent patients amounts to 35,6% in 2012..

**Table 4.4.26.** Number of adherent patients in treatment with obstructive pulmonary disease medications [numerator]/Total number of patients in treatment with medicines for obstructive pulmonary diseases [denominator]

| | 2012 N = 1.078.597 | | 2011 N = 1.082.655 | | 2010 N = 1.030.687 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 14,3 | 2,4 | 14,0 | -1,8 | 14,3 | / |
| Geographic distribution | | | | | | |
| North | 16,6 | 0,4 | 16,5 | -2,3 | 16,9 | / |
| Centre | 15,2 | 2,5 | 14,8 | -0,7 | 14,9 | / |
| South | 11,8 | 5,8 | 11,2 | -4,5 | 11,7 | / |
| Gender | | | | | | |
| Male | 18,6 | 2,0 | 18,3 | -2,0 | 18,6 | / |
| Female | 10,9 | 2,5 | 10,6 | -1,4 | 10,8 | / |
| Age group | | | | | | |
| ≤45 | 4,3 | 2,1 | 4,2 | -4,4 | 4,4 | / |
| 46-65 | 8,2 | 0,1 | 8,2 | -2,4 | 8,4 | / |
| 66-75 | 17,7 | -0,9 | 17,8 | -3,0 | 18,4 | / |
| >75 | 24,8 | -2,1 | 25,4 | -2,7 | 26,1 | / |
| Treatment status | | | | | | |
| New users | 2,9 | 5,5 | 2,8 | -17,0 | 3,3 | / |
| Old users | 32,4 | 2,0 | 31,8 | -2,0 | 32,4 | / |
| Exacerbation status | | | | | | |
| Without exacerbations | 10,5 | -4,5 | 11,0 | 1,5 | 10,8 | / |
| With exacerbations | 18,5 | 4,8 | 17,7 | -2,4 | 18,1 | / |
| Total without occasional users | 35,6 | 0,8 | 35,3 | 0,2 | 35,2 | / |

This indicator has not been calculated in LHUs for which extra-site data management was impossible.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of patients age 40 years and older in treatment with medicines for obstructive pulmonary diseases, with the exclusion of patients with a previous hospitalization for asthma and/or treatment with leukotriene receptor antagonists

**Percentage of occasional patients in treatment with medicines for obstructive pulmonary diseases (Indicator H-DB 4.5)**

The number of patients aged 40 years or older in treatment with medicines for obstructive pulmonary diseases amounts to 1.078.597 in 2012.
The percentage of occasional users amounts to 59,6%; this value is slightly decreased than the previous year (-1.0% in 2012 compared to 2011). There are no significant differences across Italy (North 58,7%; Central 60,9%; South 60,0%). The percentage of occasional users is slightly higher in females (63,4% vs 55,0% of males), in new users (78,4% compared to 29,9% of old users ) and in subjects without exacerbations (66,0% compared to 52,7% in patients with exacerbations). Poor adherence is higher among younger subjects (74,9% in age group ≤45 years, 68,1% in age group 46-65 years, 54,3% in age group 66-75 years and 45,2% in age group ≥75 years).

**Table 4.4.27.** Number of occasional patients in treatment with medicines for obstructive pulmonary diseases [numerator]/Total number of patients in treatment with medicines for obstructive pulmonary diseases [denominator]

| | 2012 N = 1.078.597 | | 2011 N = 1.082.655 | | 2010 N = 1.030.687 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 59,6 | -1,0 | 60,3 | 1,3 | 59,5 | / |
| Geographic distribution | | | | | | |
| North | 58,7 | -0,2 | 58,8 | 0,6 | 58,5 | / |
| Centre | 60,9 | -1,4 | 61,8 | -1,0 | 62,4 | / |
| South | 60,0 | -1,6 | 61,0 | 2,9 | 59,2 | / |
| Gender | | | | | | |
| Male | 55,0 | -1,0 | 55,6 | 1,4 | 54,8 | / |
| Female | 63,4 | -0,9 | 64,0 | 1,2 | 63,3 | / |
| Age group | | | | | | |
| ≤45 | 74,9 | 0,0 | 74,9 | 2,2 | 73,3 | / |
| 46-65 | 68,1 | -0,2 | 68,2 | 1,8 | 67,0 | / |
| 66-75 | 54,3 | -0,1 | 54,3 | 1,1 | 53,8 | / |
| >75 | 45,2 | 1,3 | 44,6 | 1,1 | 44,1 | / |
| Treatment status | | | | | | |
| New users | 78,4 | -0,8 | 79,1 | 2,2 | 77,4 | / |
| Old users | 29,9 | -1,9 | 30,5 | 2,8 | 29,7 | / |
| Exacerbation status | | | | | | |
| Without exacerbations | 66,0 | 0,9 | 65,5 | 0,1 | 65,4 | / |
| With exacerbations | 52,7 | -2,3 | 53,9 | 2,0 | 52,9 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: Number of patients age 40 years and older in treatment with medicines for obstructive pulmonary diseases, with the exclusion of patients with a previous hospitalization for asthma and/or treatment with leukotriene receptor antagonists

***Economic impact of indicators***

The improvement of indicators described in this section is associated with an improvement of health status and with a reduction of patient care overall cost (since these indicators have been designed according to therapeutic standards of efficacy). They can impact on pharmaceutical expenditure in different ways, depending on the features of the single indicator (Table 4.4.28).

**Table 4.4.28.** Pharmaceutical expenditure flexibility for obstructive pulmonary diseases with regard to the improvement of related indicators

| Indicator | % Overall expenditure variation per 1% variation of Indicator | Overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-4.1 | 0,14% | € 1.378.262 |
| H.DB-4.2 | 0,16% | € 1.536.116 |
| H.DB-4.3 | -0,13% | € -1.254.379 |
| H.DB-4.4 | 3,86% | € 38.130.002 |
| H.DB-4.5 | -0,16% | € -1.566.157 |

The reduction of ICS use for patients without exacerbations could result in savings in the pharmaceutical expenditure for airway obstruction syndromes. This saving, together with the one resulting from the improvement of treatment adherence could allow, for example, reinvestment in policies to improve adherence and appropriateness (e.g. a higher use of ICS for patients with exacerbations).

**Indicators for osteoporosis medications**

- Percentage of patients in treatment with osteoporosis medications who have a vertebral or hip fracture or assume corticosteroids (Indicator H-DB 5.1)

- Percentage of patients in treatment with osteoporosis medications without a previous vertebral or hip fracture and without a previous treatment with corticosteroids (Indicator H-DB 5.2)

- Percentage of patients in treatment with osteoporosis medications who combine calcium or vitamin D intake (Indicator H-DB 5.3)

- Percentage of adherent patients in treatment with osteoporosis medications (Indicator H-DB 5.4)

- Percentage of occasional patients in treatment with osteoporosis medications (Indicator H-DB 5.5).

The following medicines have been taken into account for the analysis: Bisphosphonates (ATC CODE: M05BA with the exception of neridronic acid 100 mg and oledronic acid 4 mg solution for infusion; ATC CODE: M05BB), strontium ranelate (ATC CODE: M05BX03), Parathyroid hormones and analogues (ATC CODE: H05AA), calcitonin preparations (ATC CODE: H05BA), raloxifene (ATC CODE: G03XC01).

Moreover, the combination of above mentioned medicines with calcium (ATC code A12AA), calcium in fixed-combinations with vitamin D and/or other drugs (ATC CODE: A12AX) and vitamin D (ATC CODE: A11CC) has been considered.

Patients have been categorized as patients with a hip or vertebral fracture or in therapy with corticosteroids or without hip or vertebral fracture or not-taking corticosteroids in relation to the presence or absence of at least one of the following conditions:

- Patients with a hip or vertebral fracture: at least one hospitalization with diagnosis of vertebral column fracture without mention of spinal cord injury or vertebral column fracture with spinal cord injury (ICD-9 CODES: 805 and 806 respectively), femoral neck fracture or other and unspecified femoral fracture (ICD-9 CODES: 820; 821) in females aged over 55 years or in males aged over 65 years.
- Patients aged over 50 years in treatment with corticosteroids: Patients aged over 50 years in treatment with corticosteroids (ATC CODE: H02) from at least 3 months.

Subjects in treatment with medicines for osteoporosis have been categorized in two groups: new users and patients already in treatment (old users) in relation to the absence or presence, respectively, of at least one prescription of a medication for osteoporosis within the 12 months following the first prescription of the reporting year (index date).
Furthermore, subjects in treatment with antihypertensive agents have been defined as occasional or adherent users in relation to a pharmaceutical coverage <20% or ≥80%, respectively, within the 12 months following the first prescription (index date).
The therapeutic coverage has been calculated considering all DDDs (defined daily doses) prescribed within the 12 months following the first prescription. The presence of different classes of osteoporosis agents, in the same prescription, and/or the consumption of medicines for osteoporosis in association with calcium or vitamin D, either together or separately, have been considered a free-dose combination therapy. The therapeutic coverage has been compared with the observation period and multiplied by 100.
For each medicine, the exposition time (the period between the first and last prescription for a specific time range) has been calculated.

*Cohort of patients in analysis*

The number of patients aged 18 years or older in treatment with medicines for osteoporosis amounts to 294.319 in 2013 (Table 4.4.29). The prevalence of the treatment with osteoporosis medicines amounts to 2,2% of the study sample (1,8% in Northern, 2,2% in Central and 2,8% in Southern of Italy). This value increases with age (1,6% in the age group 46-65 years, 6,0% in the age group 66-75 years and 8,4% in the age group ≥75 years) and is slightly decreased if compared to the previous year (-2,9% in 2013 compared to 2012).

**Table 4.4.29.** Distribution of patients in treatment with medicines for osteoporosis

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % SS | Var.% | N | % SS | Var.% | N | % SS | Var.% |
| TOTAL | 294.319 | 2,2 | -2,9 | 302.960 | 2,3 | -2,8 | 311.718 | 2,4 | / |
| Geographic distribution | | | | | | | | | |
| North | 113.275 | 1,8 | -1,6 | 115.078 | 2 | -4,6 | 120.607 | 2 | / |
| Centre | 62.196 | 2,2 | -1,1 | 62.886 | 2 | -3,4 | 65.073 | 2 | / |
| South | 118.848 | 2,8 | -4,9 | 124.996 | 3 | -0,8 | 126.038 | 3 | / |
| Gender | | | | | | | | | |
| Male | 20.465 | 0,3 | -1,4 | 20.758 | 0,3 | -4,7 | 21.776 | 0,3 | / |
| Female | 273.854 | 4,0 | -3,0 | 282.202 | 4,1 | -2,7 | 289.942 | 4,3 | / |
| Age group | | | | | | | | | |
| ≤45 | 2.505 | 0,0 | -8,3 | 2.733 | 0,0 | -13,9 | 3.175 | 0,1 | / |
| 46-65 | 67.333 | 1,6 | -6,9 | 72.358 | 1,7 | -7,4 | 78.176 | 1,8 | / |
| 66-75 | 96.860 | 6,0 | -3,5 | 100.361 | 6,3 | -1,3 | 101.686 | 6,4 | / |
| >75 | 127.621 | 8,4 | 0,1 | 127.508 | 8,5 | -0,9 | 128.681 | 8,6 | / |
| Mean age | 72.9 ± 10.3 | | | 72.5 ± 10.3 | | | 72.2 ± 10.4 | | |

N: subjects aged 18 years and older in treatment with medicines for osteoporosis
SS: study sample

*Results and considerations*

**Percentage of patients in treatment with osteoporosis medications, who have a vertebral or hip fracture, or assume corticosteroids (Indicator H-DB 5.1)**

The number of patients aged 18 years in treatment with osteoporosis medications, who have a vertebral or hip fracture, or assume corticosteroids amounts to 47.598 in 2012.
The percentage of subjects who received osteoporosis medicines within one year from a vertebral or hip fracture, or a treatment with corticosteroids amounts to 24,0%; this value is lower than in the previous year (-12,1% in 2012 compared to 2011). If the presence of a therapy with medicines for osteoporosis is evaluated until 31 December 2013, the observed percentages are the following:24,6% in 2012, 30,3% in 2011 and 34,1% in 2010,. There are no significant differences across Italy: 24,5% in Northern Italy, 23,0% in Central Italy, 23,7% in Southern Italy. The prevalence of osteoporotic therapy changes with gender (11,0% in males and 30,5% in females) and with age (The highest percentage amounts to 28.2% in the age group 66-75 years).

**Table 4.4.30.** Number of patients in treatment with osteoporosis medications, who have a vertebral or hip fracture, or assume corticosteroids [numerator]/Total number of patients who have a hip or vertebral fracture or assume corticosteroids [denominator]

| | 2012 N:47.598 | | 2011 N:44.608 | | 2010 N:39.213 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 24,0 | -12,1 | 27,3 | -6,5 | 29,2 | / |
| Geographic distribution | | | | | | |
| North | 24,5 | -10,1 | 27,3 | -4,9 | 28,7 | / |
| Centre | 23,0 | -12,9 | 26,4 | -6,6 | 28,2 | / |
| South | 23,7 | -15,7 | 28,1 | -9,9 | 31,2 | / |
| Gender | | | | | | |
| Male | 11,0 | -12,1 | 12,6 | -8,2 | 13,7 | / |
| Female | 30,5 | -11,6 | 34,5 | -5,5 | 36,5 | / |
| Age group | | | | | | |
| ≤45 | 11,0 | -12,1 | 12,6 | -8,2 | 13,7 | / |
| 46-65 | 21,5 | -11,5 | 24,3 | -6,6 | 26,0 | / |
| 66-75 | 28,2 | -9,0 | 31,0 | -7,0 | 33,3 | / |
| >75 | 22,9 | -14,2 | 26,7 | -6,1 | 28,4 | / |
| Follow up until 31December 2013 | 24,6 | | 30,3 | | 34,1 | / |

Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).
The presence of a vertebral or hip fracture or a therapy with corticosteroids has been evaluated with respect to the reporting year. The discharge date, in case of a hospitalization for fracture, or the last prescription of corticosteroids (the last date in case of hospitalization and treatment) is the index date.
The presence of a therapy with medicines for osteoporosis has been evaluated with regard to 365 days following the index date.

N: Number of patients aged 18 years or older who have a vertebral or hip fracture, or assume corticosteroids

**Percentage of patients in treatment with osteoporosis medications, but without a previous vertebral or hip fracture, or a previous therapy with corticosteroids (Indicator H-DB 5.2)**

The number of patients aged 18 years or older in treatment with medicines for the osteoporosis amounts to 294.319 in 2013.
The percentage of patients receiving an osteoporotic treatment but without a vertebral or hip fracture, or a corticosteroid therapy amounts to 95,9% in 2013; this value is slightly decreased compared to the previous year (-2,5% in 2013 compared to 2012). If the absence of vertebral or hip fracture and of a corticosteroid therapy is evaluated starting from January 1, 2009, the percentage in 2013 amounts to 93,1%.,. There are no significant differences across Italy (Northern Italy 94,1%; Central Italy 95,8%; Southern Italy 97,7%), neither among new users and old users (95,1% vs 96,2%). Treatment with osteoporosis medications without a vertebral or hip fracture, or a therapy with corticosteroids appears more frequent in females (96,3% compared to 90,8% of males) and is higher among younger patients (100,0% in age group ≤45 years, 96,7% in age group 46-65 years, 96,3% in age group 66-75 years and 95,1% in age group ≥75 years).

**Table 4.4.31.** Number of patients in treatment with osteoporosis medications, but without a previous vertebral or hip fracture, or a previous therapy with corticosteroids [numerator]/Total number of patients in treatment with osteoporosis medications [denominator]

| | 2013 N:294.319 | | 2012 N:302.960 | | 2011 N:311.718 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 95,9 | -2,5 | 95.9 | -0.1 | 95,9 | / |
| Geographic distribution | | | | | | |
| North | 94,1 | -4,2 | 94.2 | -0.2 | 94,4 | / |
| Centre | 95,8 | -2,0 | 95.5 | -0.2 | 95,7 | / |
| South | 97,7 | -1,2 | 97.6 | 0.1 | 97,6 | / |
| Gender | | | | | | |
| Male | 90,8 | -7,4 | 91.0 | -0.5 | 91,4 | / |
| Female | 96,3 | -2,2 | 96.2 | 0.0 | 96,3 | / |
| Age group | | | | | | |
| ≤45 | 100,0 | 0,0 | 100.0 | 0.0 | 100,0 | / |
| 46-65 | 96,7 | -2,9 | 96.7 | -0.3 | 97,0 | / |
| 66-75 | 96,3 | -2,5 | 96.2 | -0.2 | 96,4 | / |
| >75 | 95,1 | -2,3 | 95.1 | 0.2 | 94,8 | / |
| Treatment status | | | | | | |
| New users | 95,1 | -2,1 | 95.0 | -0.6 | 95,5 | / |
| Old users | 96,2 | -2,7 | 96.2 | 0.0 | 96,2 | / |
| From 01-January-2009 | 93,1 | | 93.7 | | 94,5 | / |

The presence of a therapy for osteoporosis has been evaluated with regard to the reporting year.
The date of the first prescription in the index date. The absence of a vertebral or hip fracture or of a therapy with corticosteroids is evaluated with regard to 365 days prior to the index date.

N: number of patients aged 18 years or older in treatment with medicines for osteoporosis

**Percentage of patients in treatment with osteoporosis medications in combination with calcium or vitamin D (Indicator H-DB 5.3)**

The number of patients aged 18 years or older in treatment with medicines for osteoporosis amounts to 294.319 in 2013.
The percentage of subjects in treatment with calcium or vitamin D in combination with osteoporosis medications amounts to 54,2% in 2013; this value is slightly increased compared to previous years (+3,8% in 2013 compared to 2012 and +3,7% in 2012 compared to 2011). The percentage is higher in Northern (57,5%) and Central (53,8%) Italy compared to Southern (51,4%) Italy, among females (54,5% compared to 50,1% of males), in the 46-75 year age range (48,8% in age group ≤45 years, 56,0% in age group 46-65 years, 56,3% in age group 66-75 years and 51,8% in age group ≥75 years ) and in old users (55,0% compared to 52,1% of new users).

**Table 4.4.32.** Number of patient in treatment with calcium or vitamin D in combination with osteoporosis medications [numerator]/Total number of patients in treatment with osteoporosis medications [denominator]

| | 2013 N:294.319 | | 2012 N:302.960 | | 2011 N:311.718 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 54,2 | 3,8 | 52,2 | 3,7 | 50,4 | / |
| Geographic distribution | | | | | | |
| North | 57,5 | 3,5 | 55,6 | 2,8 | 54,1 | / |
| Centre | 53,8 | 4,2 | 51,6 | 3,7 | 49,8 | / |
| South | 51,4 | 3,9 | 49,4 | 4,9 | 47,2 | / |
| Gender | | | | | | |
| Male | 50,1 | 4,9 | 47,8 | 2,3 | 46,7 | / |
| Female | 54,5 | 3,8 | 52,5 | 3,8 | 50,6 | / |
| Age group | | | | | | |
| ≤45 | 48,8 | 2,8 | 47,5 | 0,8 | 47,1 | / |
| 46-65 | 56,0 | 4,0 | 53,9 | 3,4 | 52,1 | / |
| 66-75 | 56,3 | 3,8 | 54,3 | 4,4 | 52,0 | / |
| >75 | 51,8 | 4,1 | 49,7 | 3,4 | 48,1 | / |
| Treatment status | | | | | | |
| New users | 52,1 | 4,4 | 49,9 | 2,5 | 48,7 | / |
| Old users | 55,0 | 3,6 | 53,1 | 3,5 | 51,3 | / |

N: number of patients aged 18 years or older in treatment with medicines for osteoporosis

**Percentage of adherent patients in treatment with osteoporosis medications (Indicator H-DB 4.4)**

The number of patients aged 18 years or older in treatment with medicines for osteoporosis amounts to 291.322 in 2012.
The percentage of adherent subjects amounts to 46,3% in 2012; this value is increased compared to the previous year (+2,4% in 2012 compared to 2011) and is higher in Northern (50,1%) and Central Regions (48,1) compared to Southern Regions (42,2%). The adherence is higher in females (46,9% compared to 38,9% of males), in older subjects (the highest value amounts to 47,8% in the age-group 66-75 years) and in old users (54,0% compared to 26,2% of new users). Excluding occasional users from the analysis, the percentage of adherent patients in treatment with medicines for osteoporosis amounts to 55,2% in 2012,.

**Table 4.4.33.** Number of adherent patients in treatment with osteoporosis medications [numerator]/Total number of patients in treatment with osteoporosis medications [denominator]

| | 2012 N:291.322 | | 2011 N:299.287 | | 2010 N:290.480 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 46,3 | 2,4 | 45,2 | -4,6 | 47,4 | / |
| Geographic distribution | | | | | | |
| North | 50,1 | -0,4 | 50,3 | -2,5 | 51,5 | / |
| Centre | 48,1 | -0,6 | 48,4 | -1,2 | 49,0 | / |
| South | 42,2 | 7,9 | 39,1 | -10,0 | 43,4 | / |
| Gender | | | | | | |
| Male | 38,9 | 1,2 | 38,5 | -1,7 | 39,1 | / |
| Female | 46,9 | 2,4 | 45,7 | -4,9 | 48,1 | / |
| Age group | | | | | | |
| ≤45 | 28,0 | 3,2 | 27,2 | -4,5 | 28,4 | / |
| 46-65 | 43,3 | 2,2 | 42,4 | -4,7 | 44,5 | / |
| 66-75 | 47,8 | 2,2 | 46,8 | -5,2 | 49,3 | / |
| >75 | 47,2 | 2,2 | 46,2 | -4,3 | 48,3 | / |
| Treatment status | | | | | | |
| New users | 26,2 | -16,4 | 31,4 | 5,6 | 29,7 | / |
| Old users | 54,0 | 1,9 | 53,0 | -6,2 | 56,5 | / |
| TOTAL without occasional users | 55,2 | 2,4 | 53,8 | -4,9 | 56,6 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of patients aged 18 years or older in treatment with medicines for osteoporosis

**Percentage of occasional patients in treatment with osteoporosis medications (Indicator H-DB 5.5)**

The number of patients aged 18 years or older in treatment with osteoporosis medications amounts to 291.322 in 2012.
The percentage of occasional subjects amounts to 16,0% in 2012; this value appears substantially unchanged compared to the previous year (+0,2% in 2012 compared to 2011), is higher in Central (15,4%) and Southern (18,2%) Italy compared to Northern regions (13,9%) and in males (26,7% compared to 15,2% of females). The prevalence of non- adherent patients is higher in younger age-group (34,5% in age group ≤45 years, 18,1% in age group 46-65 years, 14,6% in age group 66-75 years and 15,6% in age group ≥75 years ) and in new users (37,3% compared to 7,9% old users).

**Table 4.4.34.** Number of occasional patients in treatment with osteoporosis medications [numerator]/Total number of patients in treatment with osteoporosis medications [denominator]

| | 2012 N:291.322 | | 2011 N:299.287 | | 2010 N:290.480 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 16,0 | 0,2 | 16,0 | -1,3 | 16,2 | / |
| Geographic distribution | | | | | | |
| North | 13,9 | -2,5 | 14,3 | -0,8 | 14,4 | / |
| Centre | 15,4 | -1,9 | 15,7 | -0,9 | 15,8 | / |
| South e Islands | 18,2 | 2,4 | 17,8 | -0,6 | 17,9 | / |
| Gender | | | | | | |
| Male | 26,7 | 0,2 | 26,7 | -0,6 | 26,8 | / |
| Female | 15,2 | 0,3 | 15,2 | -1,2 | 15,4 | / |
| Age group | | | | | | |
| ≤45 | 34,5 | -9,8 | 38,3 | 4,5 | 36,6 | / |
| 46-65 | 18,1 | 2,5 | 17,7 | -2,6 | 18,1 | / |
| 66-75 | 14,6 | 1,0 | 14,4 | 0,3 | 14,4 | / |
| >75 | 15,6 | -0,6 | 15,7 | -1,5 | 15,9 | / |
| Treatment status | | | | | | |
| New users | 37,3 | 4,0 | 35,9 | 5,8 | 33,9 | / |
| Old users | 7,9 | 7,2 | 7,4 | 3,5 | 7,1 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of patients aged 18 years or older in treatment with osteoporosis medications

**Economic impact of indicators**

The improvement of indicators described in this section is associated with an improvement of health status and with a reduction of patient care overall cost (as they have been designed according to therapeutic standards of efficacy). They can impact on pharmaceutical expenditure in different ways, depending on the features of the single indicators. (Table 4.4.35).

**Table 4.4.35.** Pharmaceutical expenditure for osteoporosis elasticity in relation to an improvement of related indicators

| Indicator | % Overall expenditure variation per 1% variation of Indicator | Overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-5.1 | +0,14% | € 583.061 |
| H.DB-5.2 | -0,99% | € -4.265.789 |
| H.DB-5.3 | +0,26% | € 1.105.288 |
| H.DB-5.4 | +0,73% | € 3.135.241 |
| H.DB-5.5 | -0,18% | € -778.817 |

The savings resulting from a reduced number of non- adherent users and of patients in treatment without fracture risk factors (e.g. a previous hip or vertebral fracture or/and a treatment with corticosteroids), to be achieved through a better selection of patients, could allow, for example, a reinvestment in policies to improve adherence, to promote larger consumption of calcium and vitamin D and of high-efficacy medications (more expensive) for patients with a high fracture risk (e.g. patients with a previous fracture).

**Indicators for antidepressants**

- Percentage of patients in treatment with SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors) after a second failure of treatment with SSRI class drugs (Selective Serotonin Reuptake Inhibitors) (Indicator H-DB 6.1)

- Percentage of adherent patients to a treatment with antidepressants (Indicator H-DB 6.2)

- Percentage of occasional patients to a treatment with antidepressants (Indicator H-DB 6.3).

*Methodology*

The following antidepressants have been taken into account for the analysis:

- Antidepressants ATC CODE N06A, excluding trazodone (ATC CODE: N06AX05) and mirtazapine (ATC CODE: N06AX11) used as hypnotics when supplied at low-doses; these have at high doses, these produce anti-depressive effects, but are rarely used in clinical practice. Selective Serotonin Reuptake Inhibitors (SSRI): antidepressants (ATC CODE: N06AB) and venlafaxine <150 mg (ATC CODE: N06AX16)
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRI): venlafaxine ≥150 mg ATC CODE N06AX16 and duloxetine: (ATC CODE: N06AX21).

Furthermore, the combination of the above mentioned antidepressants with the following medications has been evaluated: antipsychotics (ATC CODE:N05A) and/or mood stabilizers (ATC CODE: N03A) to identify subjects with other psychiatric diseases.

Patients in treatment with antidepressants have been categorized as new users or old users in relation to the absence or presence of at least one prescription for antidepressants within the 12 months prior to the first prescription of the reporting year.
Patients in treatment with antidepressants have been categorized as non- adherent users and adherent users depending on the therapeutic coverage percentage ( <20% or ≥80%, respectively) of the observation period (12 months following the first prescription).

The therapeutic coverage has been calculated considering all DDDs (defined daily doses) prescribed within 12 months following the first antidepressants prescription. The presence, in the same prescription, of different types of antidepressants and/or the consumption, either together or separately, of at least two antidepressants for the same

indication, have been considered as a free-dose combination therapy. The therapeutic coverage has been compared with the observation period and multiplied by 100.
For each medicine , the exposition time(being the period between the first and last prescription for a specific time range), has been calculated.

*Cohort of patients in analysis*

The number of patients aged 18 years or older in treatment with antidepressants amounts to 857.922 (Table 4.4.36) in 2013. The prevalence of treatment with antidepressants amounts to 6,5% of the study sample (6,8% in Northern Italy, 6,6% in Central Italy and 5,9% in Southern Italy). This value is higher in females (8,7% compared to 4,1% of males) and varies with age (2,8% in age group ≤45 years, 6,9% in age group 46-65 years, 10,6% in age group 66-75 years and 14,7% in the age group ≥75 years). There are no significant differences among the reporting years taken into account.

**Table 4.4.36.** Distribution of patients in treatment with antidepressants

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % SS | Var.% | N | % SS | Var.% | N | % SS | Var.% |
| TOTAL | 857.922 | 6,5 | 0,7 | 852.311 | 6,4 | 0,7 | 846.743 | 6,4 | / |
| Geographic distribution | | | | | | | | | |
| North | 421.452 | 6,8 | 0,5 | 419.403 | 6,8 | 0,1 | 419.090 | 6,8 | / |
| Centre | 182.106 | 6,6 | 0,5 | 181.212 | 6,6 | 0,0 | 181.255 | 6,6 | / |
| South | 254.364 | 5,9 | 1,1 | 251.696 | 5,9 | 2,2 | 246.398 | 5,8 | / |
| Gender | | | | | | | | | |
| Male | 264.702 | 4,1 | 1,5 | 260.776 | 4,1 | 1,3 | 257.443 | 4,0 | / |
| Female | 593.220 | 8,7 | 0,3 | 591.535 | 8,7 | 0,4 | 589.300 | 8,7 | / |
| Age group | | | | | | | | | |
| ≤45 | 165.446 | 2,8 | -4,8 | 173.735 | 3,0 | -5,1 | 183.025 | 3,2 | / |
| 46-65 | 299.889 | 6,9 | -0,1 | 300.182 | 7,0 | -0,1 | 300.493 | 7,0 | / |
| 66-75 | 170.323 | 10,6 | 2,1 | 166.869 | 10,4 | 3,8 | 160.786 | 10,1 | / |
| >75 | 222.264 | 14,7 | 5,1 | 211.525 | 14,0 | 4,5 | 202.439 | 13,5 | / |
| Mean age | 61.9 ± 17.2 | | | 61.4 ± 17.2 | | | 60.8 ± 17.2 | | |

N: number of patients aged 18 years or older in treatment with antidepressants
SS: study sample

*Results and considerations*

**Percentage of patients in treatment with SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors) after a second attempt with two different SSRIs (Selective Serotonin Reuptake Inhibitors) (Indicator H-DB 6.1)**

The number of patients aged 18 years or older in treatment with SSRIs, with at least 3 changes in therapy, the second of which is towards a different SSRI, amounts to 6.232 in 2012.
The percentage of patients that at the third change of therapy shift to a SNRI class drug amounts to 19,3%; this value is slightly decreased compared to the previous year (-1,3% in 2012 compared to 2011). Moreover, this percentage is slightly higher in Northern Regions (21,4%) compared to Central (15,2%) and Southern (19,4%) Italy, in females (19,6% compared to 18,4% of males) and in old users (20,1% compared to 18,1% in new users) and does not vary significantly by age (17,4% in ≤45 years age group, 21,4% in age group 46-65 years, 20,0% in age group 66-75 years, 17,1% in age group ≥75 years). There are no significant differences among the reporting years taken into account.

**Table 4.4.37.** Number of patients in treatment with SNRI after a second attempt with two different SSRIs (Selective Serotonin Reuptake Inhibitors) [numerator]/Total number of patients in treatment with antidepressants after a second attempt with two different SSRIs (Selective Serotonin Reuptake Inhibitors) [denominator]

| | 2012 N = 6.232 | | 2011 N = 6.948 | | 2010 N = 7.134 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 19,3 | -1,3 | 19,5 | -3,3 | 20,2 | / |
| Geographic distribution | | | | | | |
| North | 21,4 | -0,1 | 21,4 | -8,5 | 23,4 | / |
| Centre | 15,2 | -4,8 | 15,9 | -3,5 | 16,5 | / |
| South | 19,4 | -0,9 | 19,6 | 3,3 | 19,0 | / |
| Gender | | | | | | |
| Male | 18,4 | -11,1 | 20,7 | -2,8 | 21,3 | / |
| Female | 19,6 | 3,3 | 19,0 | -3,6 | 19,7 | / |
| Age group | | | | | | |
| ≤45 | 17,4 | -10,8 | 19,5 | 0,0 | 19,5 | / |
| 46-65 | 21,4 | 4,5 | 20,5 | -4,3 | 21,4 | / |
| 66-75 | 20,0 | -2,9 | 20,6 | -7,7 | 22,3 | / |
| >75 | 17,1 | 1,2 | 16,9 | 0,8 | 16,8 | / |
| Treatment status | | | | | | |
| New users | 18,1 | 1,5 | 17,8 | -4,9 | 18,8 | / |
| Old users | 20,1 | -4,9 | 21,2 | -0,9 | 21,3 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: subjects aged 18 years or older in treatment with SSRI, with at least 3 changes of therapy, of which the second toward a different SSRI

**Percentage of adherent patients in treatment with antidepressants (Indicator H-DB 6.2)**

The number of patients aged 18 years or older in treatment with antidepressants taken into account amounts to 852.311 in 2012.
The percentage of adherent patients amounts to 38,4%; this value in slightly higher compared to previous years (+2,9% in 2012 compared to 2011, +0,7% in 2011 compared to 2010). The adherence is lower in Southern Italy (34,5%) compared to Northern 40,2% and to Central 39,8% Italy and among males (37,4% compared to 38,8% of females). The adherence improves with age (33,6% in the age group ≤45 years, 37,8% in the age group 46-65 years, 40,4% in the age group 66-75 years, 41,6% in the age group ≥75 years ) and is higher in old users compared to new ones (49,6% vs 16,9%). Excluding occasional subjects, the percentage of patients adherent to the treatment with antidepressants is 50,9% in the year 2012.. If we consider as adherent subjects those patients who have a therapeutic coverage ≥50%, the adherence rises to 55,9%. When patients affected jointly by other psychiatric diseases are excluded, the adherence amounts to 34,3%.

**Table 4.4.38.** Number of adherent patients to a treatment with antidepressants [numerator]/Total number of patients in treatment with antidepressants [denominator]

| | 2012 N = 852.311 | | 2011 N = 846.743 | | 2010 N = 815.562 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 38,4 | 2,9 | 37,3 | 0,7 | 37,1 | / |
| Geographic distribution | | | | | | |
| North | 40,2 | 2,1 | 39,3 | 1,0 | 38,9 | / |
| Centre | 39,8 | 1,0 | 39,4 | 1,1 | 39,0 | / |
| South | 34,5 | 6,4 | 32,4 | -2,0 | 33,1 | / |
| Gender | | | | | | |
| Male | 37,4 | 2,6 | 36,5 | 0,8 | 36,2 | / |
| Female | 38,8 | 3,0 | 37,7 | 0,7 | 37,4 | / |
| Age group | | | | | | |
| ≤45 | 33,6 | 2,3 | 32,9 | 0,4 | 32,7 | / |
| 46-65 | 37,8 | 3,1 | 36,6 | 0,8 | 36,4 | / |
| 66-75 | 40,4 | 2,5 | 39,4 | -0,2 | 39,5 | / |
| >75 | 41,6 | 2,1 | 40,7 | 0,3 | 40,6 | / |
| Treatment status | | | | | | |
| New users | 16,9 | -1,5 | 17,1 | -6,1 | 18,2 | / |
| Old users | 49,6 | 1,7 | 48,7 | 0,1 | 48,7 | / |
| Cut off 50%* | 55,9 | 2,0 | 54,8 | 1,2 | 54,2 | / |
| Total without occasional patients° | 50,9 | 1,4 | 50,2 | -0,2 | 50,3 | / |
| Total without patients with other psychiatric diseases^ | 34,3 | 1,5 | 33,8 | 3,8 | 32,6 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of patients aged 18 years or older in treatment with antidepressants taken into account
*Adherent patients are defined, in this case, those patients with a therapeutic coverage ≥50%

**Percentage of occasional patients in treatment with antidepressants (Indicator H-DB 6.3)**

The number of Patients aged 18 years or older in treatment with antidepressants amounts to 852.311 in 2012.
The percentage of occasional subjects amounts to 24,5%; this value is slightly decreased compared to previous years (-4,3% in 2012 compared to 2011; -2,6% in 2011 compared to 2010). The percentage of occasional subjects is higher in Southern Italy (28,8%) compared to Northern and Central (22,6%) Italy and in males (26,1% compared to 23,7% in females). The low adherence is higher in younger age-groups (29,4% in age group ≤45 years, 24,7% in age group 46-65 years, 22,7% in age group 66-75 years and 21,5% in age group ≥75 years), in new users (51,5% compared to 10,5% of old ones). The prevalence of low adherence amounts to 27,0%, excluding patients also affected by other psychiatric diseases.

**Table 4.4.39** Number of occasional patients in treatment with antidepressants [numerator]/ Total number of patients in treatment with antidepressants [denominator]

| | 2012 N = 852.311 | | 2011 N = 846.743 | | 2010 N = 815.562 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 24,5 | -4,3 | 25,6 | -2,6 | 26,3 | / |
| Geographic distribution | | | | | | |
| North | 22,6 | -4,5 | 23,7 | -1,3 | 24,0 | / |
| Centre | 22,6 | -3,9 | 23,5 | -0,1 | 23,6 | / |
| South | 28,8 | -4,6 | 30,2 | -3,3 | 31,2 | / |
| Gender | | | | | | |
| Male | 26,1 | -3,9 | 27,2 | -2,3 | 27,8 | / |
| Female | 23,7 | -4,5 | 24,9 | -2,7 | 25,6 | / |
| Age group | | | | | | |
| ≤45 | 29,4 | -3,3 | 30,4 | -1,6 | 30,9 | / |
| 46-65 | 24,7 | -4,8 | 25,9 | -2,9 | 26,7 | / |
| 66-75 | 22,7 | -4,1 | 23,6 | -2,0 | 24,1 | / |
| >75 | 21,5 | -3,3 | 22,2 | -1,1 | 22,5 | / |
| Treatment status | | | | | | |
| New users | 51,5 | -0,6 | 51,8 | 2,1 | 50,7 | / |
| Old users | 10,5 | -3,8 | 10,9 | -2,5 | 11,2 | / |
| TOTAL without patients with other psychiatric diseases | 27,0 | -4,2 | 28,2 | -4,0 | 29,3 | / |

This indicator has not been calculated in all LHUs in relation to the impossibility of an extra-site data management.
Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of patients aged 18 or older in treatment with antidepressants

***Economic impact of indicators***

The improvement of indicators described in this section is associated with an improvement of health status and with a reduction of patient care overall cost (since they have been designed according to therapeutic standards of efficacy). These can impact on pharmaceutical expenditure in different way depending on the features of the single indicators. (Table 4.4.40).

**Table 4.4.40.** Pharmaceutical expenditure elasticity for antidepressants in relation to the improvement of related indicators

| Indicator | % Overall expenditure variation per 1% variation of Indicator | Overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-6.1 | +0,01% | € 40.641 |
| H.DB-6.2 | +1,28% | € 6.341.575 |
| H.DB-6.3 | -0,15% | € -717.627 |

The savings resulting from a reduction of the number of occasional users to be achieved through a better selection of patients and from improvements in antidepressants' use could allow, for example, a reinvestment in policies to improve adherence and encourage major use of high-efficacy (and more expensive) medications for complex patients.

**Indicators for medicines used for the treatment of ulcer and esophagitis**

Percentage of patients in treatment with proton pomp inhibitors who do not meet AIFA reimbursement criteria (AIFA Note 1 or AIFA Note 48) (Indicator H-DB 7.1)

*Methodology*

For the purpose of this analysis the following proton pump inhibitors (ATC CODE: A02BC) have been taken into account. These medicines have been categorized in two class:

- Agents reimbursed according to AIFA Note 1: esomeprazole (ATC CODE: A02BC05), lansoprazole (ATC CODE: A02BC03), omeprazole (ATC CODE: A02BC01) and pantoprazole (ATC CODE: A02BC02)

- Agents reimbursed according to AIFA Note 48: esomeprazole (ATC CODE: A02BC05), lansoprazole (ATC CODE: A02BC03), omeprazole (ATC CODE: A02BC01), pantoprazole (ATC CODE: A02BC02), rabeprazole (ATC CODE: A02BC04).

According to reimbursement criteria set by AIFA Note 1, the presence of at least one of the following criteria within the 12 months prior to the first prescription of the reporting year has been taken into account:

- chronic treatment with anti-inflammatory and antirheumatic products, non-steroids: at least 3 prescriptions of anti-inflammatory and antirheumatic products, non-steroids (ATC CODE: M01A);
- therapy with low doses of acetylsalicylic acid: at least 3 prescriptions of acetylsalicylic acid (ATC CODE: B01AC06);

and at least one of the following risk factors:

- digestive hemorrhage or of peptic ulcer not resolved with eradicating therapy : at least one hospitalization with diagnosis of esophageal varices associated with bleeding (ICD-9 CODE: 456.0); hemorrhage of rectum and anus (ICD-9 CODE: 569.3); or hematemesis (ICD-9 code: 578.0); hemorrhage of gastrointestinal tract, unspecified (ICD-9 CODE: 578.9); gastric and duodenal ulcer (ICD-9 CODE: 531-534) within 12 months prior to the first prescription;
- concomitant therapy with anticoagulants: at least one prescription of antithrombotic agents, with the exclusion of heparin (ATC CODE: B01A) and/or corticosteroids for systemic use (ATC CODE: H02) in the two months preceding or following the first prescription;
- older age: patients over 65 years old.

In relation to the presence of reimbursement criteria set in AIFA Note 2 and AIFA Note 48, the following condition has been assessed:

- treatment duration of four consecutive weeks.

Patients in treatment with proton pump inhibitors have been categorized as new users or old users in relation to absence or presence of at least one prescription for proton pump inhibitors within 12 months prior to the first prescription of the reporting year.

The therapeutic coverage has been calculated considering all DDDs (defined daily doses) prescribed within 12 months following the first proton pomp inhibitors prescription in the reporting year. For each patient, the algorithm considers the number of prescriptions issued in the reporting period, and, according to the total amount of drug dispensed, the therapeutic coverage periods are identified.

Moreover, patients in treatment with proton pump inhibitors have been categorized as patients without or with a previous hospitalization in relation to the absence or presence, respectively, of at least one hospitalization (for any reason) in the 12 months prior to the first prescription of the reporting year (index date).

*Cohort of Patients in analysis*

The number of patients aged 18 years or older in treatment with proton pump inhibitors amounts to 2.873.500 in 2013 (table 4.4.41). The prevalence of treatment with proton pump inhibitors amounts to 21,6% of the study sample (17,9% in Northern Italy, 22,1% in Central Italy and 26,8% in Southern Italy). This value is higher in females (24,0% compared to 19,1% of males) and increases with age (7,6% in age group ≤45 years, 21,3% in age group 46-65 years, 42,0% in age group 66-75 years, 54,9% in age group ≥75 years).

**Table 4.4.41.** Distribution of patients in treatment with proton pump inhibitors

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % SS | Var.% | N | % SS | Var.% | N | % SS | Var.% |
| TOTAL | 2.873.500 | 21,6 | 3,6 | 2.772.873 | 21,0 | 5,1 | 2.637.916 | 20,1 | / |
| Geographic distribution | | | | | | | | | |
| North | 1.104.456 | 17,9 | 4,0 | 1.062.169 | 17,3 | 4,4 | 1.017.225 | 16,6 | / |
| Centre | 612.931 | 22,1 | 4,9 | 584.458 | 21,1 | 4,2 | 561.152 | 20,4 | / |
| South | 1.156.113 | 26,8 | 2,7 | 1.126.246 | 26,2 | 6,3 | 1.059.539 | 24,8 | / |
| Gender | | | | | | | | | |
| Male | 1.230.582 | 19,1 | 3,9 | 1.184.457 | 18,5 | 5,5 | 1.122.704 | 17,6 | / |
| Female | 1.642.918 | 24,0 | 3,4 | 1.588.416 | 23,3 | 4,8 | 1.515.212 | 22,4 | / |
| Age group | | | | | | | | | |
| ≤45 | 440.695 | 7,6 | -2,6 | 452.566 | 7,8 | -1,8 | 461.056 | 8,0 | / |
| 46-65 | 925.643 | 21,3 | 1,6 | 911.383 | 21,1 | 3,0 | 885.053 | 20,6 | / |
| 66-75 | 676.034 | 42,0 | 5,4 | 641.230 | 40,0 | 8,9 | 588.822 | 36,9 | / |
| >75 | 831.128 | 54,9 | 8,3 | 767.694 | 51,0 | 9,2 | 702.985 | 46,9 | / |
| Mean age | 64.2 ± 16.7 | | | 63.6 ± 16.8 | | | 62.9 ± 16.9 | | |

N: number of patients aged 18 years or older in treatment with proton pomp inhibitors
SS: study sample

*Output of the Indicators and considerations*

**Percentage of patients in treatment with proton pomp inhibitors who don't meet AIFA reimbursement criteria (AIFA Note 1 or AIFA Note 48) (Indicator H-DB 7.1)**

The number of patients aged 18 years or older in treatment with proton pump inhibitors amounts to 2.772.873 in 2012.
The percentage of patients in treatment with proton pomp inhibitors without fitting AIFA reimbursement criteria (AIFA Note 1 or AIFA note 48) amounts to 46,5%; this value is increased compared to the previous year (+5,5% in 2012 compared to 2011). The percentage is higher in Southern Italy (50,9%) compared to Northern (46,5%) and to Central (38,3%) Italy, in younger patients (72,3% in age group ≤45 years, 57,7% in age group 46-65 years, 35,1% in age group 66-75 years, 27,6% in age group ≥75 years), in new users (66,5% compared to 34,1% of old users) and in patients without a previous hospitalization (48,1% compared to 39,0% of patients with a previous hospitalization). No differences have been observed among males and females (46,7% vs 46,3%).

**Table 4.4.42.** Percentage of patients in treatment with proton pomp inhibitors who do not meet AIFA reimbursement criteria (AIFA Note 1 or AIFA Note 48) [numerator]/Total number of patients in treatment with inhibitors medicines of the protonic pomp inhibitor [denominator]

| | 2012 N = 2.772.873 | | 2011 N = 2.637.916 | | 2010 N = 2.261.788 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 46,5 | 5,5 | 44,1 | -1,1 | 44,6 | / |
| Geographic distribution | | | | | | |
| North | 46,5 | 6,1 | 43,8 | 2,0 | 43,0 | / |
| Centre | 38,3 | -5,3 | 40,4 | 0,5 | 40,2 | / |
| South | 50,9 | 9,8 | 46,3 | -3,5 | 48,0 | / |
| Gender | | | | | | |
| Male | 46,9 | 5,4 | 44,5 | -1,4 | 45,1 | / |
| Female | 46,3 | 5,6 | 43,8 | -0,9 | 44,3 | / |
| Age group | | | | | | |
| ≤45 | 72,3 | 5,2 | 68,7 | -0,4 | 69,0 | / |
| 46-65 | 57,7 | 8,9 | 53,0 | -2,2 | 54,2 | / |
| 66-75 | 35,1 | 7,1 | 32,8 | 2,4 | 32,0 | / |
| >75 | 27,6 | 5,5 | 26,2 | 3,7 | 25,3 | / |
| Treatment status | | | | | | |
| New users | 66,5 | 6,9 | 62,2 | -2,6 | 63,8 | / |
| Old users | 34,1 | 17,6 | 29,0 | -4,2 | 30,2 | / |
| Hospitalization history | | | | | | |
| Without a previous hospitalization | 48,1 | 4,1 | 46,2 | -1,3 | 46,8 | / |
| With a previous hospitalization | 39,0 | 13,6 | 34,3 | -2,5 | 35,2 | / |

This indicator has not been calculated in all LHUs, as a result of impossibility of extra-site data management. Since data was available up until December 31 2013, the last reporting year is 2012 (in order to have one full observation year also for subjects included in December 2012).

N: number of patients aged 18 years or older in treatment with proton pump inhibitors

***Economic impact of indicators***

The improvement of indicators described in this section is associated with an improvement of health status and with a reduction of patient care overall cost (since they have been designed according to therapeutic standards of efficacy). They can impact on pharmaceutical expenditure in different ways depending on the features of the single indicator. (Table 4.4.43).

**Table 4.4.43.** Pharmaceutical expenditure elasticity for proton pomp inhibitors in relation to the improvement of related indicators.

| Indicator | % overall expenditure variation per 1% variation of Indicator | overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-7.1 | -0,62% | € -5.782.934 |

The saving resulting from a reduction of patients in treatment with protonic pomp inhibitors without meeting AIFA reimbursement criteria (Note 1 or Note 48) could allow a reinvestment in other fields of pharmaceutical care.

**Indicators for antianemic preparation- Percentage of patients starting a new cycle of therapy with biosimilars of epoetin alpha (Indicator H-DB 8.1)**

*Calculation methodology*

For the purpose of this analysis, both the originator product (Eprex ATC CODE B03XA01) and epoetin alpha biosimilars (Binocrit, Abseamed, Retacrit: ATC CODE B03XA01) have been considered.
Patients starting a new cycle of treatment with epoetin alpha biosimilars have been identified in relation to the absence of an epoetin alpha prescription within the six months prior to the first prescription of the reporting year (new users).
New users have been also categorized as patients with or without a previous cycles of therapy in the last year in relation to the presence or absence of at least one prescription of epoetin alpha in 12 months preceding the first prescription of the reporting year.

*Cohort of Patients in analysis*

The number of patients aged 18 years or older in treatment with epoetins alpha amounts to 12.978 in 2013 (Table 4.4.44). The prevalence of treatment with epoetin alpha amounts to 1,0‰ of the study sample. This data increases with the age of patients (0,6‰ in the age group 46-65, 1,9‰ in the age group 66-75 and 4,4‰ in the age group ≥75 years).

**Table 4.4.44.** Distribution of patients in treatment with epoetin alpha

| | 2013 | | | 2012 | | | 2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | ‰ SS | Var.% | N | ‰ SS | Var.% | N | ‰ SS | Var.% |
| TOTAL | 12.978 | 1,0 | 28,3 | 10.117 | 0,8 | 11,4 | 9.080 | 0,7 | / |
| Geographic distribution | | | | | | | | | |
| North | 4.310 | 0,7 | 34,6 | 3.203 | 0,5 | 12,7 | 2.841 | 0,5 | / |
| Centre | 3.260 | 1,2 | 20,7 | 2.701 | 1,0 | 8,5 | 2.489 | 0,9 | / |
| South | 5.408 | 1,3 | 28,4 | 4.213 | 1,0 | 12,3 | 3.750 | 0,9 | / |
| Gender | | | | | | | | | |
| Male | 6.495 | 1,0 | 32,6 | 4.900 | 0,8 | 12,5 | 4.357 | 0,7 | / |
| Female | 6.483 | 0,9 | 24,3 | 5.217 | 0,8 | 10,5 | 4.723 | 0,7 | / |
| Age group | | | | | | | | | |
| ≤45 | 692 | 0,1 | 12,2 | 617 | 0,1 | -1,1 | 624 | 0,1 | / |
| 46-65 | 2.576 | 0,6 | 18,8 | 2.168 | 0,5 | 8,3 | 2.001 | 0,5 | / |
| 66-75 | 3.026 | 1,9 | 29,1 | 2.344 | 1,5 | 9,8 | 2.135 | 1,3 | / |
| >75 | 6.684 | 4,4 | 34,0 | 4.988 | 3,3 | 15,5 | 4.320 | 2,9 | / |
| Mean age | 73.0 ± 14.2 | | | 72.1 ± 14.3 | | | 71.3 ± 14.6 | | |

N: number of patients aged 18 years or older in treatment with epoetin alpha
SS: study sample

*Results and considerations*

**Percentage of patients who start a new cycle of therapy with biosimilars of epoetin alfa (Indicator H-DB 8.1)**

The number of patients aged 18 years or older initiating a new cycle of treatment with epoetins alpha amounts to 8.341 in 2013.
The percentage of patients starting a new cycle of therapy with epoetin alpha biosimilars amounts to 41,0%; this value is increased compared to previous years (+71,6% in 2013 compared to 2012; +87,9% in 2011 compared to 2010). There is a certain variability across Italy (Northern 42,7%; Central 34,0%; Southern 43,4%), while no remarkable differences according to the gender (41,7% in males and 40,3% in females) have been observed. This percentage changes with age of patients (45,2% in age group ≤45 years, 42,4% in age group 46-65 years, 44,5% in age group 66-75 years, 37,9% in age group ≥75 years). The percentage of patients who start the first cycle of treatment with alpha epoetin biosimilars amounts to 43,0%, while the percentage of patients in treatment but with a history of a previous cycle of therapy amounts to 20,6%.

**Table 4.4.45.** Number of patient with a new cycle of therapy with epoetin alpha biosimilars [numerator]/Total number of patients with a new cycle of therapy with epoetin alpha [denominator]

| | 2013 N = 8.341 | | 2012 N = 6.260 | | 2011 N = 6.270 | |
|---|---|---|---|---|---|---|
| | % | Var.% | % | Var.% | % | Var.% |
| TOTAL | 41,0 | 71,6 | 23,9 | 87,9 | 12,7 | / |
| Geographical distribution | | | | | | |
| North | 42,7 | 64,2 | 26,0 | 368,2 | 5,6 | / |
| Centre | 34,0 | 19,2 | 28,5 | 107,6 | 13,7 | / |
| South | 43,4 | 123,9 | 19,4 | 13,5 | 17,1 | / |
| Gender | | | | | | |
| Male | 41,7 | 78,4 | 23,4 | 93,2 | 12,1 | / |
| Female | 40,3 | 65,1 | 24,4 | 83,7 | 13,3 | / |
| Age group | | | | | | |
| ≤45 | 45,2 | 173,6 | 16,5 | 51,5 | 10,9 | / |
| 46-65 | 42,4 | 93,3 | 21,9 | 88,8 | 11,6 | / |
| 66-75 | 44,5 | 60,7 | 27,7 | 108,0 | 13,3 | / |
| >75 | 37,9 | 58,5 | 23,9 | 80,5 | 13,3 | / |
| New therapy cycles within previous 12 months status | | | | | | |
| Without previous therapy cycles | 42,4 | 69,6 | 25,0 | 93,3 | 12,9 | / |
| With previous therapy cycles | 18,9 | 73,3 | 10,9 | 74,3 | 6,3 | / |
| New therapy cycles from 01-January-2009° | | | | | | |
| Without previous therapy cycles | 43,0 | 69,7 | 25,3 | 95,8 | 12,9 | / |
| With previous therapy cycles | 20,6 | 72,4 | 12,0 | 73,3 | 6,9 | / |

N: number of patients aged 18 years or older who begin a new cycle of treatment with epoetin alpha taken into account

***Economic impact of indicators***

The improvement of the indicator described in this section is associated with an improvement of health status and with a reduction of patient care overall cost (since these indicators have been designed according to therapeutic standards of efficacy). They can impact on pharmaceutical expenditure in different ways depending on the features of the single indicator. (Table 4.4.46).

**Table 4.4.46.** Pharmaceutical expenditure elasticity for anti-anemic preparations in relation to the improvement of related indicators

| Indicator | % overall expenditure variation per 1% variation of Indicator | overall expenditure variation per 1% variation of Indicator |
|---|---|---|
| H.DB-8.1 | -0,28 | € -447.737 |

A preferential use of epoetin alpha biosimilars in patients initiating a new therapeutic cycle could reduce pharmaceutical expenditure for epoetin alpha. These savings could allow, for example, reinvestment in other pharmaceutical care areas.

**Acronyms**

CV = cardiovascular
ESC = European society of cardiology
ESH = European society of hypertension
GFR = glomerular filtration rate
HMG-CoA = hydroxymethylglutaryl-CoA reductase
LDL = low density lipoprotein
HbA1c = glycosylated hemoglobin
COPD = chronic obstructive pulmonary disease
ICS = inhaled corticosteroids
LABA = long-acting beta-adrenoceptor agonist
LAMA = long-acting antimuscarinic agent
SNRI = serotonin and norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor

## SECTION 5

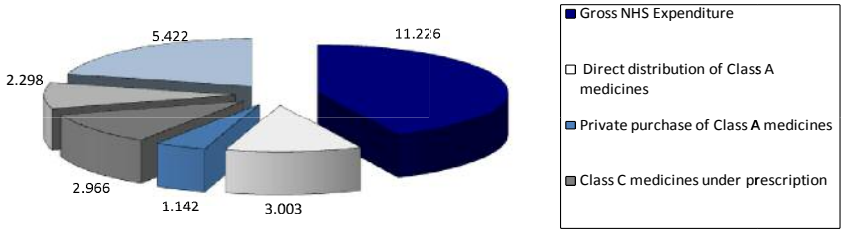
# GENERAL CHARACTERISTICS OF PHARMACEUTICAL USE IN ITALY

Pharmaceutical expenditure represents a significant part of health care spending ( 1,7% of the national Gross Domestic Product (GDP) throughout 2013). The total pharmaceutical expenditure (concerning both public and private expenses) amounted to 26,1 billion euros in Italy, whereof nearly 75,4% was reimbursed by the National Health Service. Reimbursed medicines were supplied to the public through both public and private pharmacy channels (i.e. 43,1%; Table 5.1). Pharmaceutical expenditure in charge of citizens amounted to 6.406 million euros, consisting primarily of Class C (non-reimbursed) medicines requiring a medical prescription (11,4% of total expenditure).

**Table 5.1.** Pharmaceutical expenditure breakdown in 2013 (Table and Figure)

| | Expenditure | % |
|---|---|---|
| Gross NHS outpatient expenditure | 11.226 | 43,1 |
| Class A medicines dispensed by the Direct distribution | 3.003 | 11,5 |
| Out of pocket Class A medicines | 1.142 | 4,4 |
| Class C medicines under prescription | 2.966 | 11,4 |
| OTC medicines | 2.298 | 8,8 |
| Health Public Facilities (Health Local Unit, Public Hospital, Nursing Home; Penitentiary, etc.)* | 5.422 | 20,8 |
| **Total** | **26.057** | **100,0** |

*excluding expenditure for Class A medicines dispensed by the Direct distribution




## 5.1 Outpatient medicines consumption and expenditure

Throughout 2013, the total pharmaceutical expenditure, concerning both public and private settings, amounted to 19.708 billion euros, increasing by +1,7% compared to the previous year (Table 5.1.3).

Outpatient pharmaceutical expenditure in charge of the NHS is composed by medicines provided under the national health care agreement (table 5.1.2 and figure 5.1.2), and by

Class A (reimbursed) medicines provided through direct distribution through public healthcare facilities. The NHS expenditure amounted to 11.866 billion euros (199 euros per capita), which represents 60,2% of outpatient pharmaceutical expenditure. Compared to 2012, a slight increase (+0,4%) in pharmaceutical expenditure was observed primarily due to the increase in spending for Class A (reimbursed) medicines supplied through direct distribution (+5,9%), while a decrease of the NHS outpatient pharmaceutical expenditure was recorded (-1,4%).

Pharmaceutical expenditure in charge of citizens (Table 5.1.3), including cost-sharing (regional co-payments and co-payment resulting from the difference between the price of the purchased product and that of the reference medicine), together with expenses for privately purchased Class A , and Class C medicines, was 7.842 million euros, increasing by +3,8% compared to 2012.

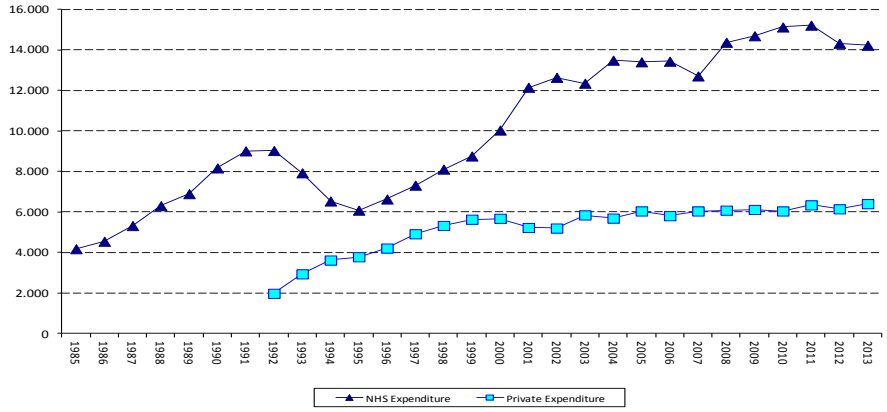
This increase in sales is mainly ascribable to the rise in private purchase of Class A medicines (+11,2%), as well as to the increase in expenditure for self-medication medicines (+8,1%) and co-payment borne by citizens (+2,1%), while a slight decrease of expenditure for Class C medicines requiring prescription was recorded (-1,1%).

The co-payment borne by the citizen (Table 5.1.2 and 5.1.3) amounted to 1.436 million euros (24,1 euros per capita), impacting on the gross NHS pharmaceutical expenditure by 12,8 %. Compared to 2012, the increase of the co-payment mainly resulted from the boost in shares exceeding the reference price of off-patent medicines (+5,5%), while a reduction in co-payment expenditure ( ticket per prescription and package) was registered (-2,7%).

Concerning consumption part of the state-run healthcare, an upward trend in the use of medicine reimbursed by the NHS was observed, even if at a slower pace than in the previous years, mainly because of those medicines supplied through alternative distribution channels (i.e. direct distribution by the public health facilities). During 2013, an average 1.031,5 doses of Class A medicines reimbursed by the NHS per 1,000 inhabitants (Table 5.1.4) were consumed every day (in 2012 the doses amounted to 1.006,6), corresponding to over 1 billion packages dispensed (18,7 packs per capita), with an +2,5% increase compared to 2012 (+2,2%).

Major components (i.e. quantity effect, price effect and mix effect) of variations in the gross NHS outpatient pharmaceutical expenditure observed in 2013, compared to the previous year, highlight a decremental effect on expenditure, as a result of increased consumption of prescribed medicines (+2,7 in terms of defined daily doses, DDDs), decrease in average prices (-4,2%) (due to a rise in the use of off patent medicines and the strengthening of medicines delivered through alternative distribution channels) and, finally, variation of the consumption mix in favour of medicines with lower unitary price (positive mix effect: -0,8%) (Figure 5.1.3).

**Figure and Table 5.1.1.** Outpatient pharmaceutical expenditure during 1985 – 2013




| | Gross NHS expenditure *(million)* | Class A medicines by direct distribution *(million)* | NHS expenditure* *(million)* | Private expenditure *(million)* |
|---|---|---|---|---|
| 1985 | 4.182 | | 4.182 | |
| 1986 | 4.553 | | 4.553 | |
| 1987 | 5.324 | | 5.324 | |
| 1988 | 6.306 | | 6.306 | |
| 1989 | 6.900 | | 6.900 | |
| 1990 | 8.171 | | 8.171 | |
| 1991 | 9.011 | | 9.011 | |
| 1992 | 9.030 | | 9.030 | 1.982 |
| 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 |
| 2012 | 11.488 | 2.837 | 14.325 | 6.160 |
| **2013** | **11.226** | **3.003** | **14.229** | **6.406** |

*including NHS pharmaceutical expenditure and Class A medicine expenditure dispensed through Direct distribution; Source: OsMed data and Data from the Ministry of Economy and IMS Health

**Table 5.1.2.** Outpatient pharmaceutical expenditure: 2009-2013 comparasion

| | | 2009 (million) | 2010 (million) | 2011 (million) | 2012 (million) | 2013 (million) | Δ % 10/09 | Δ % 11/10 | Δ % 12/11 | Δ % 13/12 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1+2+3+4 | Gross pharmaceutical expenditure | 12.928 | 12.985 | 12.387 | 11.488 | 11.226 | 0,4 | -4,6 | -7,3 | -2,3 |
| 1+2 | Citizen co-payment | 862 | 998 | 1.337 | 1.406 | 1.436 | 15,7 | 34,0 | 5,2 | 2,1 |
| 1 | Sharing per prescription | 426 | 449 | 577 | 573 | 558 | 5,5 | 28,5 | -0,7 | -2,7 |
| 2 | Reference price share | 436 | 549 | 760 | 833 | 878 | 25,8 | 38,5 | 9,6 | 5,5 |
| 3 | Discount^ | 872 | 1.016 | 1.028 | 1.096 | 927 | 16,5 | 1,1 | 6,6 | -15,4 |
| 4 | Net NHS expenditure | 11.193 | 10.971 | 10.023 | 8.986 | 8.863 | -2,0 | -8,6 | -10,3 | -1,4 |
| 5 | Class A direct distribution° | 1.767 | 2.144 | 2.832 | 2.837 | 3.003 | 21,3 | 32,1 | 0,2 | 5,9 |
| **4+5** | **Outpatient expenditure** | **12.960** | **13.115** | **12.855** | **11.823** | **11.866** | **1,2** | **-2,0** | **-8,0** | **0,4** |

^ 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 n. 135 of 2012 and charged to Industries, both discount following AIFA resolution of December 30, 2005, and the pay-back on the NHS expenditure as per Art. 11, paragraph 6, Law n. 122 of 2010, temporarily modified by Law n.135 of 2012.
° Direct distribution expenditure of class A medicines, including 40% of inpatient pharmaceutical expenditure (for those Regions missing data) following Law n. 222 of 2007. Source: OsMed analysis calculated on the Ministry of Health, Age.Na.S. and IMS Health data

**Table and Figure 5.1.3.** Comparison of public and private outpatient expenditure (2009-2013)

| | | 2009 (million) | 2010 (million) | 2011 (million) | 2012 (million) | 2013 (million) | Δ% 10/09 | Δ% 11/10 | Δ% 12/11 | Δ% 13/12 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Net NHS expenditure | 11.193 | 10.971 | 10.023 | 8.986 | 8.863 | -2,0 | -8,6 | -10,3 | -1,4 |
| 2 | Class A medicines by Direct distribution | 1.767 | 2.144 | 2.832 | 2.837 | 3.003 | 21,3 | 32,1 | 0,2 | 5,9 |
| 1+2 | Total public expenditure | 12.960 | 13.115 | 12.855 | 11.823 | 11.866 | 1,2 | -2,0 | -8,0 | 0,4 |
| 3 | Citizen co-payment | 862 | 998 | 1.337 | 1.406 | 1.436 | 15,8 | 34,0 | 5,2 | 2,1 |
| 4 | Class A medicines paid by citizen* | 829 | 848 | 1.026 | 1.027 | 1.142 | 2,3 | 21,0 | 0,1 | 11,2 |
| 5 | Class C medicine under prescription | 3.154 | 3.093 | 3.207 | 3.000 | 2.966 | -1,9 | 3,7 | -6,5 | -1,1 |
| 6 | OTC medicines | 2.140 | 2.105 | 2.113 | 2.125 | 2.298 | -1,6 | 0,4 | 0,6 | 8,1 |
| 3+4+5+6 | Total private expenditure | 6.985 | 7.044 | 7.683 | 7.558 | 7.842 | 0,8 | 9,1 | -1,6 | 3,8 |
| | Total pharmaceutical expenditure | 19.945 | 20.159 | 20.538 | 19.381 | 19.708 | 1,1 | 1,9 | -5,6 | 1,7 |
| | **Share (%) borne NHS** | **65,0** | **65,1** | **62,6** | **61,0** | **60,2** | | | | |

***** data concerning private expenditure for medicines reimbursed by the NHS is calculated by the resulted difference between the total expenditure (estimated by IMS) and the expenditure paid by the NHS (obtained from OsMed data). Source: Based on data from IMS Health OsMed (for data of private spending).

**Figure 5.1.2.** Outpatient pharmaceutical consumption: a comparison between 2009-2013

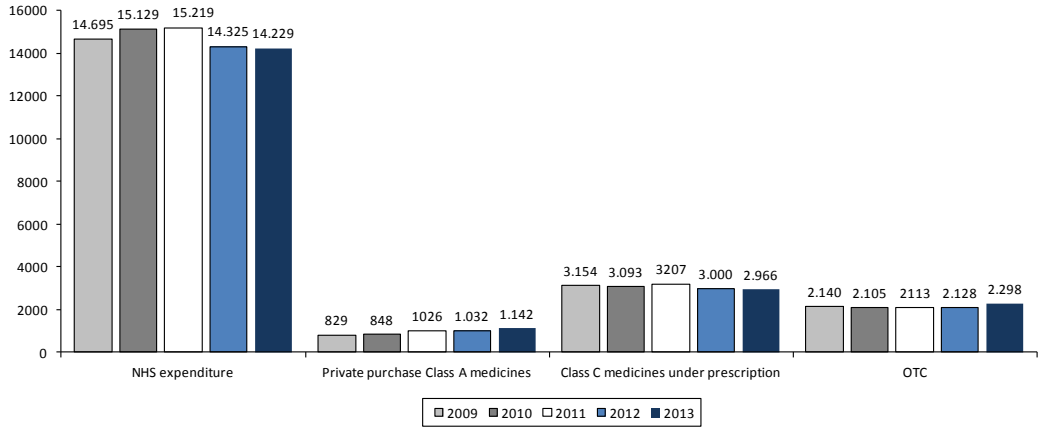
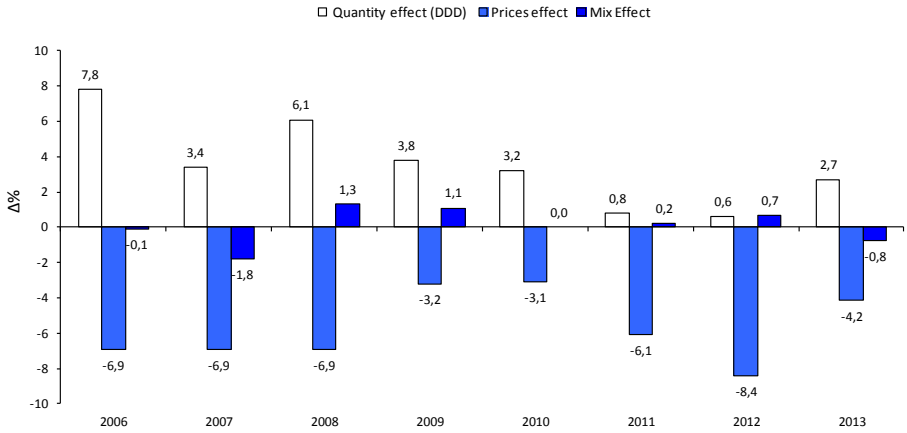



**Table and Figure 5.1.4.** Public and private outpatient pharmaceutical consumption: a comparison between 2009-2013

| | | 2009 | 2010 | 2011 | 2012 | 2013 | Δ % | Δ % | Δ % | Δ % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *million^* | *million* | *million^* | *million^* | *million^* | 10/09 | 11/10 | 12/11 | 13/12 |
| | Prescriptions # | 572 | 587 | 590 | 593 | 608 | 2,6 | 0,5 | 0,5 | 2,5 |
| | N. Packages | | | | | | | | | |
| 1 | NHS consumption | 1.054 | 1.080 | 1.089 | 1.095 | 1.119 | 2,5 | 0,8 | 0,6 | 2,2 |
| 2 | Class A medicines paid by citizen* | 112 | 123 | 146 | 170 | 183 | 10,1 | 18,7 | 16,4 | 7,6 |
| 3 | Class A medicines by direct distribution | NA | NA | NA | NA | NA | | | | |
| 1+2+3 | Total class A medicines | 1.166 | 1.203 | 1.235 | 1.265 | 1.302 | 3,2 | 2,7 | 2,4 | 2,9 |
| 4 | Class C medicines under prescription | 288 | 283 | 284 | 267 | 252 | -1,7 | 0,4 | -6,0 | -5,6 |
| 5 | OTC | 325 | 308 | 300 | 280 | 288 | -5,3 | -2,6 | -6,7 | 2,9 |
| 4+5 | Total class C medicines | 613 | 591 | 584 | 547 | 540 | -3,6 | -1,2 | -6,3 | -1,3 |
| 1+2+3+4+5 | Total packages | 1.779 | 1.794 | 1.819 | 1.812 | 1.842 | 0,9 | 1,4 | -0,4 | 1,7 |
| | DDD/1.000 inhab. die # | 934 | 956 | 963 | 1.006,6 | 1.031,5 | 2,4 | 0,7 | 4,5 | 2,5 |

NA: not available data
#concerning (class A) NHS reimbursed medicines
*data concerning NHS medicines privately purchased by the citizen is calculated by deducting the NHS expenditure (OsMed data) from the total expenditure (IMS estimate)
^prescriptions and packages amount is expressed by million units
Source: IMS data analysed by OsMed (concerning out of pocket expenditure)

**Figure 5.1.3**. Trend of Class A reimbursed medicines expenditure: consumption effect, prices effect and mix effect, during 2006-2013




## 5.2 Medicines purchased by public health facilities

During 2013 the expenditure for medicines purchased by public health facilities (hospitals, health local units, etc.) amounted to approximately 8,4 euros billion (141,2 euros per capita; Table 5.2.1). This expenditure represents 32% of the total public and private spending on pharmaceuticals (Table 5.1; i.e. 3.003 +5.422 billion euros) and registers an increase by 6,2% compared to 2012. In terms of pharmaceutical consumption (DDDs), a decrease by -13,8%, was registered, with an average 150,6 daily doses per 1.000 inhabitants (hereinafter DDD/1000 inhab. die). In this regard, it should be underlined that the definition of medicines purchased by the public health facilities in terms of DDDs, even if allowing a useful parameterization of the consumption at different levels (geographical and temporal), it does not represents the actual dose of a medicine administered to the patient. Although this assumption remains valid even when the DDD is used to parameterise outpatient medicines' consumption (e.g. in the paediatric population, etc.), it gains increasing validity in inpatient settings (where the dose is most likely to vary as a result of the different healthcare needs).

The composition of public health facilities expenditure is based on the actual delivery of medicines to the patient, as detected by the flow fuelled by Regions. Expenditure concerning direct distribution of medicines by public health facilities and home care consumption is significantly higher than pharmaceutical expenditure relating to the hospital care consumption. In fact, during 2013 direct distribution expenditure amounted to 5.225 billion euros, concerning mainly Class A reimbursed medicines (3.002 million euros), and a residual share of Class C (medicines not reimbursed by the NHS) and hospital-only(Class H) medicines (2.223 million euros).

Inpatient pharmaceutical expenditure amounted to 2.811 billion euros and was composed for 70% of Class H medicines. In particular, during 2013 an increase in expenditure for

Class A medicines supplied through direct distribution was observed (Table 5.2.1), while a reduction of pharmaceutical expenditure within inpatient settings was recorded (Figure 5.2.1 and 5.2.2).
It should be noted that differences between pharmaceutical expenditure resulting from Regional flows, in addition to expenditure for medicines administered within hospital settings, and the economic value of pharmaceuticals purchased by public health facilities, is to be attributed to the following aspects: a) a temporary mismatch between pharmaceutical provision to hospitals and distribution of the product within inner wards or to patients (difference between sell-in and sell-out), b) the incomplete transfer of data expenditure by the Regions.

**Table 5.2.1**: Expenditure and consumption of medicines purchased by public health facilities at the national level, 2013

| | Per capita NHS expenditure | | DDD/1.000 inhab. die | |
|---|---|---|---|---|
| | € | Δ % | € | Δ % |
| **ITALY** | 141,2 | 69,2 | 150,6 | -13,8 |

**Figure 5.2.1.** Direct distribution pharmaceutical expenditure by reimbursement class, years 2011 - 2013

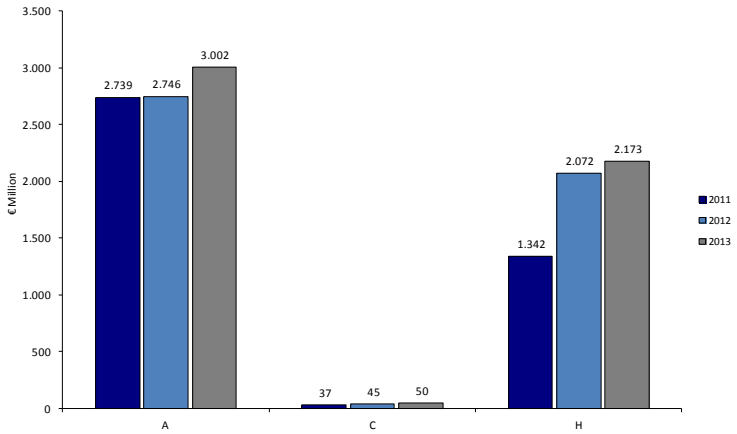
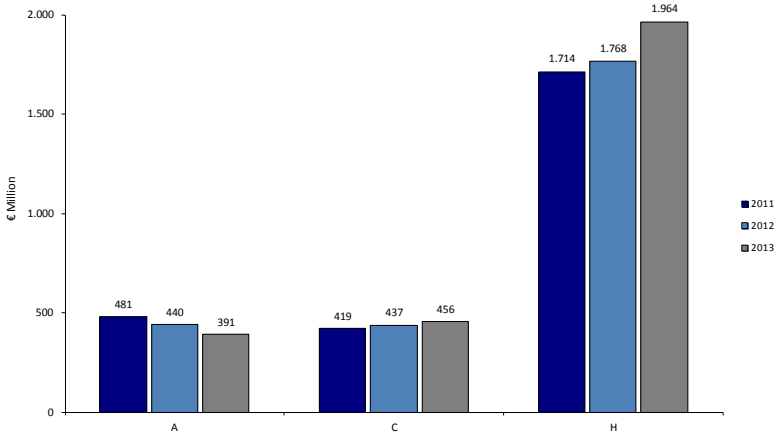


**Figure 5.2.2.** Inpatient pharmaceutical expenditure by reimbursement class , years 2011 – 2013




## 5.3 Pharmaceutical consumption by age and gender

The variability in pharmaceutical expenditure and consumption is primarily dependent on changes in the epidemiological profiles overtime, as well as on the variety of healthcare condition settings and the different prescribing attitudes of physicians. In addition, pharmaceutical consumption is significantly concentrated in specific population groups, according to age, gender and type of disease. For the purpose of this analysis, data on individual NHS patients collected by 32 Health Local Units (HLUs), distributed across the country, was examined. The number of patients referring to the HLUs has been estimated to approximately 18 million patients, with an average age and a male/female ratio corresponding to national average data.

Overall, the average pharmaceutical expenditure and consumption is highly dependent on the age group. Gender, appears to have little influence on general pharmaceutical consumption, if compared to age. For a detailed analysis on settings in which gender differences mostly impact on consumption, please see section 6.

The population group aged above 65 years highlights a per capita pharmaceutical expenditure 3 times higher than the national average. Moreover, it was observed that for each individual belonging to this age group, the NHS bears a pharmaceutical expenditure 6 times higher than the average expenditure for individuals belonging to younger age groups. This result is an effect of the prevalence of average pharmaceutical consumption by the elderly, which shifts from approximately 50% in the adult population group to almost 90% in age groups over 74 years (see Figure 5.3.1); in other words, almost all individuals aged 74 years or oldertakes at least one medicine. Gender differences are detectable in the age group 15-64 years, where female prevalence of use appears higher than in males, with an absolute deviation of 8% (see Figure 5.3.1). A major prevalence of pharmaceutical consumption was also observed in children (0-4 years old) if compared to

the 15-44 years population group (especially among males): about half of the children received at least one medical prescription during the year. The overall prevalence of pharmaceutical consumption was approximately 57% (53,6% in males and 60,7% in females).

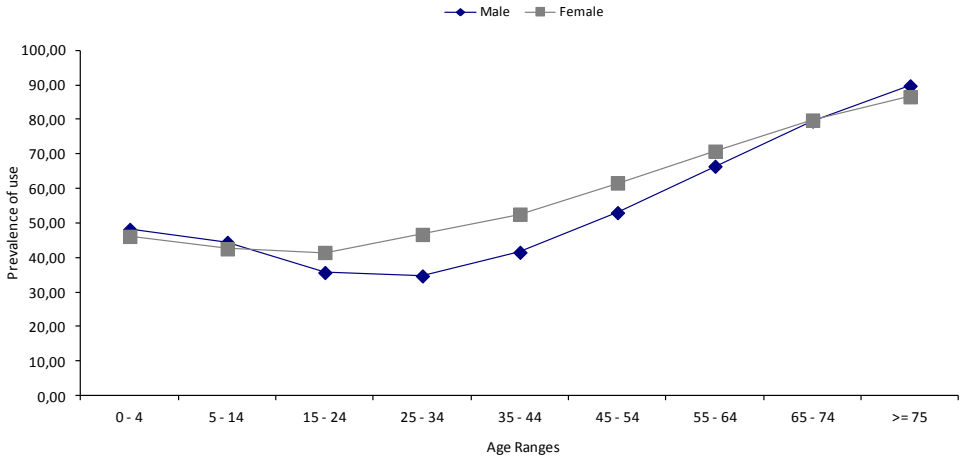
The population aged 65 and over absorbed almost 60% of the total pharmaceutical expenditure (without including inpatient pharmaceutical expenditure) and more than 65% of the total DDDs (see Table 5.3.1). In terms of consumption, a 65 year old patient consumes an average of 2,7 DDDs per day, while a 74 year old patient consumes an average of 3,7 DDDs per day (see Table 5.3.1 and figure 5.3.2). It should be mentioned that the average total pharmaceutical consumption (amounting to 1.049,8 DDDs per 1.000 inhabitants per day) and the estimated209 euros per capita gross expenditure appear to be slightly different when compared to the same parameters calculated on national-level aggregated data . Nevertheless, the 18 million patients population taken into account in this analysis seems sufficient to outline national epidemiological profiles by age and gender, as well as the distribution of per capita expenditure and the average pharmaceutical consumption.

**Table 5.3.1.** Outpatient pharmaceutical expenditure and consumption by age^ 2013

| Age Range | Gross per capita expenditure | | | % share on total expenditure | DDD/1000 inhab. die | | | % share on total consumption |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | | Male | Female | Total | |
| 0 - 4 | 30,0 | 25,0 | 27,5 | 0,61 | 78,8 | 67,6 | 73,4 | 0,32 |
| 5 - 14 | 38,3 | 30,9 | 34,6 | 1,55 | 74,4 | 63,2 | 68,8 | 0,62 |
| 15 - 24 | 37,4 | 31,5 | 34,5 | 1,65 | 85,6 | 119,6 | 102,0 | 0,97 |
| 25 - 34 | 48,6 | 52,8 | 50,7 | 2,85 | 125,7 | 227,8 | 176,4 | 1,98 |
| 35 - 44 | 73,0 | 87,0 | 79,8 | 5,83 | 256,8 | 353,7 | 305,0 | 4,44 |
| 45 - 54 | 140,9 | 148,4 | 144,6 | 10,49 | 646,5 | 667,4 | 657,0 | 9,49 |
| 55 - 64 | 288,2 | 271,5 | 279,5 | 16,69 | 1.501,2 | 1.329,8 | 1.413,2 | 16,80 |
| 65 - 74 | 523,7 | 480,0 | 500,4 | 25,12 | 2.875,7 | 2.500,5 | 2.676,8 | 26,75 |
| >= 75 | 756,7 | 630,9 | 679,3 | 35,20 | 4.115,2 | 3.513,0 | 3.743,8 | 38,63 |
| **Overall** | 202,5 | 215,3 | 209,0 | 100,00 | 1.008,7 | 1.088,9 | 1.049,8 | 100,00 |

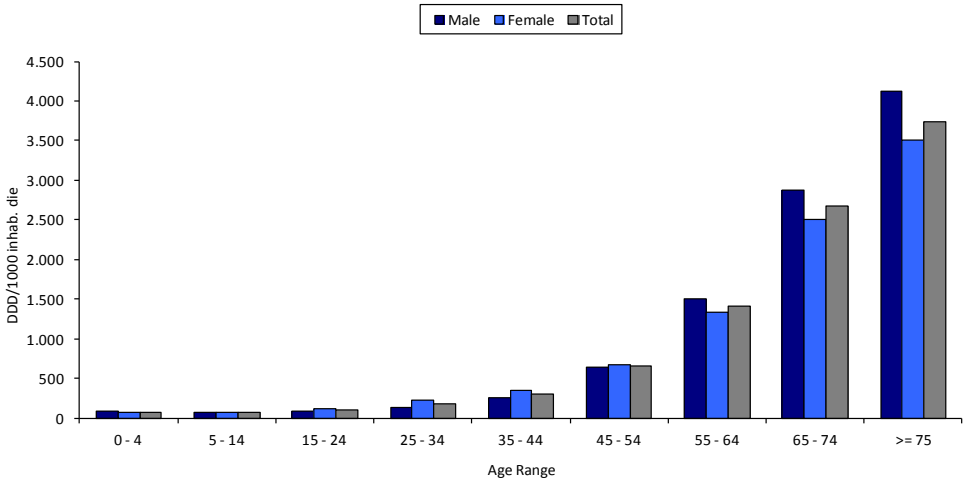
^excluding inpatient consumption

**Figure 5.3.1**. Prevalence of use by age and gender in the outpatient setting^ 2013




^ excluding inpatient consumption

**Figure 5.3.2.** Outpatient consumption^ (DDD/1000 inhab. die) by age and gender 2013




^ excluding inpatient consumption

## 5.4 Pharmaceutical consumption on a monthly basis

Figure 5.4.1 illustrates the consumption trend of reimbursed medicines (class A), (expressed in days of therapy) for the period 2004-2013. Throughout the last decade, pharmaceutical consumption registered a persistent upward trend and increased from 764 DDD/1000 inhabitants per day in 2004 to 1.031,5 DDD/1000 inhabitants per day in 2013, thus, an increase of +35%.

Pharmaceutical consumption, in addition to the rising trend, is related to seasonal variations, as proved by the peaks in consumption of pharmaceuticals visible on a monthly basis (see Figure 5.4.1). As a result of this periodicity, consumption levels registered in the first half of 2013 were higher than the annual average of 2,5%, as opposed to the second half of the year, where the consumption was below 2,5%. In particular, in August the consumption was 15% lower than average. Notoriously, systemic antimicrobial medicines and respiratory medicines are the therapeutic categories on which seasonality of consumption impacts mostly.

Figure 5.4.2 illustrates the consumption trend of non-reimbursed medicines (Class C) starting from January 2004. This trend could be affected by regulatory decisions according to which pharmaceuticals and recognized or not the status of reimbursed medicine.. Starting from 2004, a tendential downwards trend in consumption of Class C medicines was observed; the tendency varied indeed from 242 DDD/1000 inhabitants per day in 2004 to 199,8 DDD/1000 inhabitants per day in 2013. The highest average consumption was recorded in January (+13% compared to the annual average), whilst the lowest levels of consumption were observed in August (-18% compared to annual average). The high levels registered in correspondence with transition months (autumn) mainly result from vaccines consumption. Moreover, the peaks corresponding to the first three months of the year are ascribable to the higher consumption of respiratory system medicines, whose consumption appears doubled if compared to summer months.

Figure 5.4.3 shows the consumption trend of medicines purchased by public health facilities in the period 2006-2013. In particular, an overall growing trend in consumption was registered, with an increase from 100,6 DDD/1000 inhabitants per day during 2011 to 150,6 DDD/1000 inhabitants per day in 2013, even though a reduction was observed of -13,8% in the last year. During 2013, the lowest consumption level was observed in August (-36%) and December (-25%), while July (+26%) and January (+22%) registered higher levels of consumption.

In order to correctly interpret monthly consumption trends , expressed as DDD/1000 inhabitants per day, of medicines purchased by public health facilities (as opposed to annual trends), it should be noted that these are influenced by the purchasing procedures of facilities themselves, and thus cannot be strictly interpreted in terms of monthly patient consumption . In support of this statement, strong irregularities in monthly purchasing patterns by the public health facilities during the last six years are observable.

**Figure 5.4.1.** Trend of Class A reimbursed medicines consumption (DDD/1000 inhab. die), 2004-2013

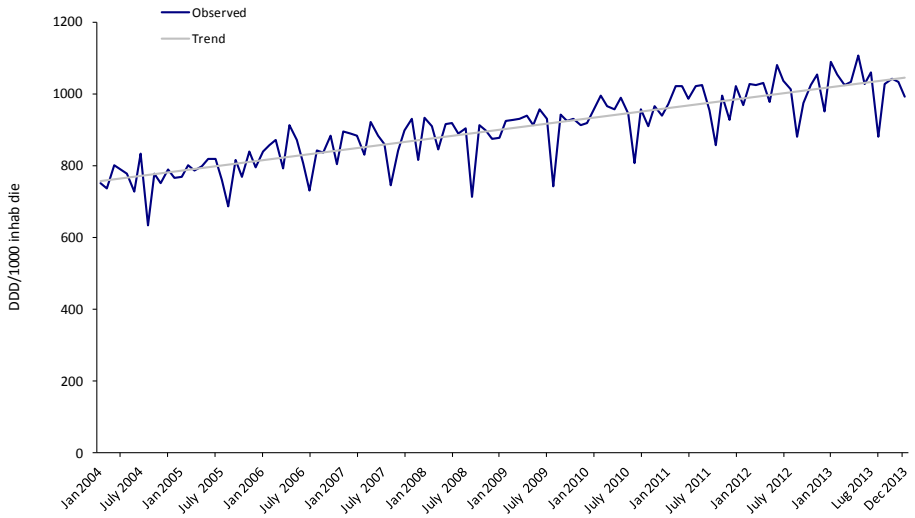



**Figure 5.4.2.** Trend of Class C medicines under prescription consumption (DDD/1000 inhab. die), 2004-2013

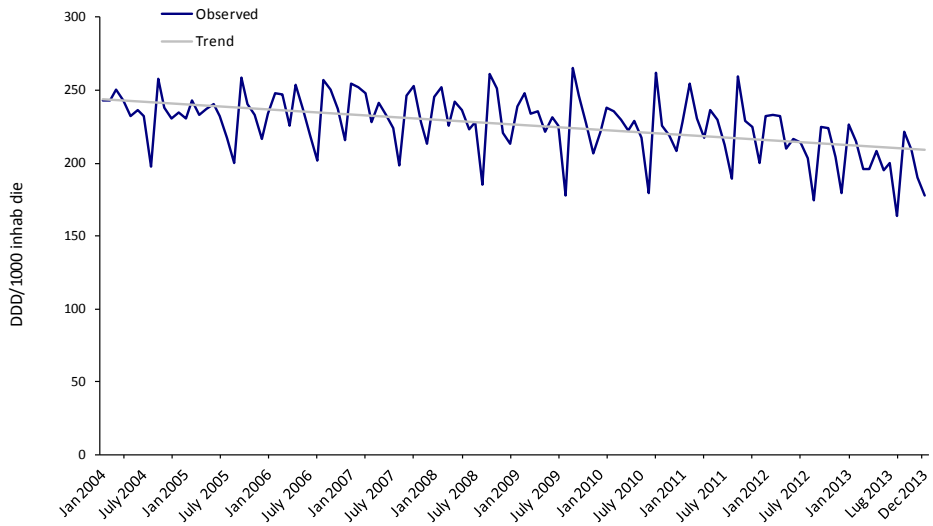
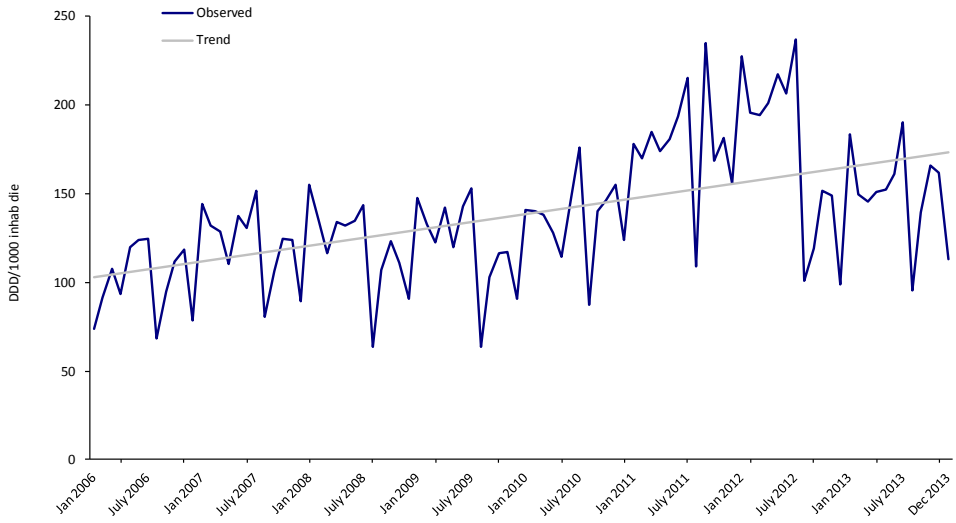


**Figure 5.4.3.** Trend of consumption of medicines purchased by the public health facilities (DDD/1000 inhab. die), 2006-2013




## 5.5 Trend of pharmaceutical prices

Data shown in Figure 5.5.1 represents the average price weighted per package and per DDD of Class A reimbursed medicine between January 2004 and December 2013. The time series reveals a descendent trend for both prices, especially since 2004-2005 and 2011-2012. This reduction was mainly driven by price reduction manoeuvres implemented at National level starting from 2004 and by the economic effect resulting from Resolution of April 8, 2011;these measures determined a reduction of the reference prices of medicines included in the Transparency List (*liste di Trasparenza)* on the basis of a comparison between the prices of generics in Italy and the same packages marketed in Germany, UK, France and Spain.

Figure 5.5.2 shows the average price trend, weighted per package and per DDD, of Class C (not-reimbursed) medicines requiring medical prescription, for the period between 2004 and 2013. Looking at the monthly time series data , the performance of the two indexes show a steady growth, rising from 9,8 euros per package (0,6 euros per DDD) in 2004 to 11,8 euros per package (0,7 euros per DDD) in 2013, that is an increase +20,4% (and +16,6% price per DDD) over a ten year period.

Figure 5.5.3 illustrates the performance of the average price, weighted per package and per DDD, of medicines purchased by the public health facilities for the period between 2004 and 2013. Averages prices increase from 2006 to 2010, appear stable in the period between 2011 and 2012, and experience a further increase in 2013 (+14,1% price per pack and +19,1% in DDD). As mentioned previously, the average price of medicines purchased

by public health facilities is greatly influenced both by purchasing procedures and by the average price of the medicines mix purchased from time to time.

**Figure 5.5.1**. Average price trend of Class A reimbursed medicines, 2004-2013

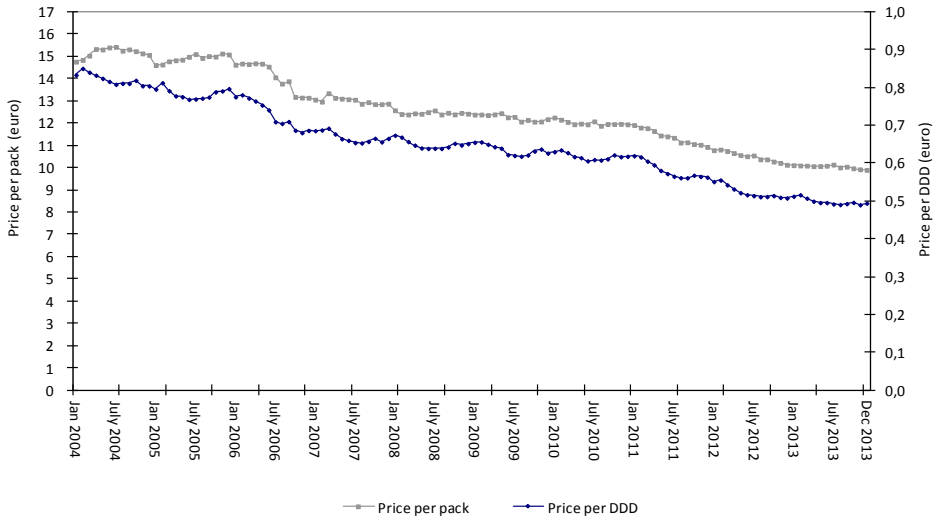



**Figure 5.5.2.** Average price trend of Class C medicines requiring prescription, 2004-2013

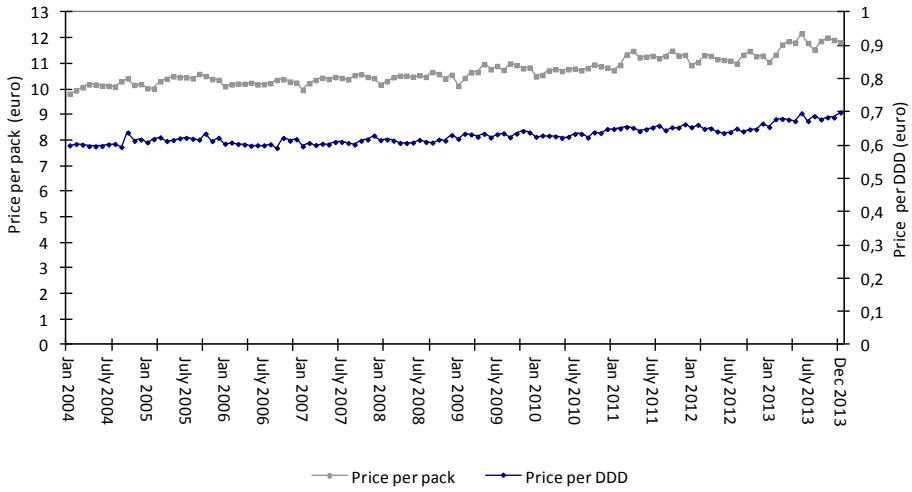
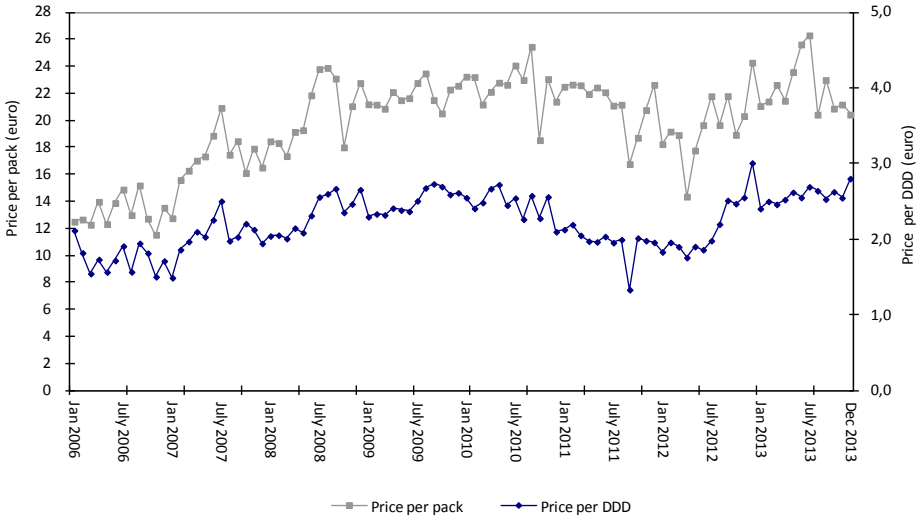


**Figure 5.5.3.** Average price trend of medicines purchased by health public facilities, 2006-2013



## SECTION 6

# CONSUMPTION AND EXPENDITURE BY THERAPEUTIC CLASS AND EPIDEMIOLOGICAL DATA

**Table 6.1.** Pharmaceutical expenditure by ATC I level and class of reimbursement in 2013

| Therapeutic class | Class A-NHSˆ | | Class A medicines privately purchased | | Class C under prescription | | Self-medication SOP and OTC | | Public Health Facilities | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | euro° | %* | euro° | %* | euro° | %* | euro° | %* | euro° | %* | euros° |
| C- Cardiovascular system | 3.604 | 85,9 | 203 | 4,8 | 59 | 1,4 | 142 | 3,4 | 185 | 4,4 | 4.194 |
| A- Alimentary tract and metabolism | 1.947 | 54,1 | 192 | 5,3 | 273 | 7,6 | 644 | 17,9 | 545 | 15,1 | 3.601 |
| L- Antineoplastic agents and immunomodulatating agents | 252 | 7,0 | 23 | 0,6 | 9 | 0,3 | - | - | 3.305 | 92,1 | 3.589 |
| N- Nervous system | 1.398 | 42,7 | 148 | 4,5 | 938 | 28,6 | 253 | 7,7 | 538 | 16,4 | 3.275 |
| J- Antiinfectives for sistemic use | 898 | 33,3 | 138 | 5,1 | 85 | 3,1 | - | - | 1.572 | 58,4 | 2.693 |
| B- Blood and blood forming organs | 576 | 29,9 | 79 | 4,1 | 89 | 4,6 | 16 | 0,8 | 1.166 | 60,6 | 1.926 |
| R- Respiratory system | 1.023 | 58,2 | 118 | 6,7 | 168 | 9,5 | 394 | 22,4 | 55 | 3,1 | 1.758 |
| G- Genito urinary system and sex hormones | 412 | 31,8 | 38 | 2,9 | 659 | 50,9 | 80 | 6,2 | 106 | 8,2 | 1.294 |
| M- Musculo-sketal system | 485 | 37,6 | 175 | 13,6 | 210 | 16,3 | 354 | 27,4 | 67 | 5,2 | 1.291 |
| D- Dermatologicals | 59 | 9,0 | 36 | 5,5 | 245 | 37,2 | 294 | 44,7 | 24 | 3,7 | 657 |
| S- Sensory organs | 215 | 34,7 | 18 | 2,9 | 164 | 26,5 | 120 | 19,4 | 102 | 16,5 | 619 |
| H- Systemic hormonal preparations, excl.sex hormones and insulins | 216 | 38,3 | 51 | 9,1 | 27 | 4,8 | - | - | 270 | 47,8 | 565 |
| V-Various | 106 | 19,1 | <0,1 | <0,1 | 38 | 6,9 | - | - | 488 | 88,5 | 551 |
| P- Antiparasitic products, insecticides and repellents | 12 | 56,9 | 3 | 14,5 | 3 | 16,2 | 1 | 6,8 | 1 | 5,6 | 21 |
| **Total** | **11.202** | **43,0** | **1.142** | **4,4** | **2.966** | **11,4** | **2.298** | **8,8** | **8.425** | **32,4** | **26.034** |

ˆClass A medicine expenditure net of the expenditure of Class C medicine reimbursed to subjects with a lifetime war pension (Act n. 203 of July 19, 2000) (24 million euros)

° Gross expenditure expressed as million euros; *calculated on the category.

Source: OsMed flow, Traceability flow and IMS Health data analysed by OsMed

**Table 6.2.** Pharmaceutical consumption by ATC I level and class of reimbursement (DDDs/1000 inhabitants die) in 2013 (in descending order of expenditure from table 6.1)

| Therapeutic class | Classe A-NHS | | Class A private purchase | | Class C under prescription | | Self-medication SOP and OTC | | Public Health Facilities | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | units | %* | units | %* | units | %* | units | %* | units | %* | units |
| C- Cardiovascular system | 468,0 | 89,2 | 28,9 | 5,5 | 2,0 | 0,4 | 8,8 | 1,7 | 17,0 | 3,2 | 524,7 |
| A- Alimentary tract and metabolism | 152,2 | 60,7 | 15,3 | 6,1 | 10,3 | 4,1 | 46,1 | 18,4 | 26,8 | 10,7 | 250,8 |
| L- Antineoplastic and immunomodulating agents | 4,6 | 33,1 | 0,4 | 2,9 | 0,1 | 0,4 | - | - | 8,8 | 63,6 | 13,8 |
| N- Nervous system | 60,4 | 36,8 | 6,6 | 4,0 | 65,4 | 39,9 | 6,6 | 4,0 | 25,0 | 15,2 | 164,0 |
| J- Antiinfectives for sistemic use | 23,2 | 61,6 | 5,4 | 14,4 | 2,7 | 7,1 | - | - | 6,4 | 17,0 | 37,7 |
| B- Blood and blood forming organs | 130,8 | 52,6 | 43,9 | 17,7 | 39,6 | 15,9 | 0,5 | 0,2 | 34,0 | 13,7 | 248,8 |
| R- Respiratory system | 48,5 | 50,2 | 10,0 | 10,4 | 13,9 | 14,3 | 21,1 | 21,8 | 3,2 | 3,3 | 96,7 |
| G- Genito urinary system and sex hormones | 42,3 | 50,7 | 5,6 | 6,7 | 30,9 | 37,1 | 2,9 | 3,5 | 1,7 | 2,0 | 83,4 |
| M- Musculo-sketal system | 42,4 | 47,7 | 21,9 | 24,7 | 5,2 | 5,8 | 16,8 | 19,0 | 2,5 | 2,8 | 88,8 |
| D- Dermatologicals | 4,3 | 7,0 | 5,6 | 9,1 | 15,3 | 24,7 | 20,7 | 33,4 | 16,0 | 25,8 | 61,9 |
| S- Sensory organs | 19,5 | 36,0 | 2,3 | 4,3 | 12,4 | 22,7 | 18,1 | 33,3 | 2,0 | 3,7 | 54,3 |
| H- Systemic hormonal preparations, excl.sex hormones and insulins | 34,4 | 68,2 | 9,7 | 19,2 | 0,9 | 1,7 | - | - | 5,5 | 10,9 | 50,5 |
| V- Various | 0,1 | 2,3 | 0,1 | 3,4 | 1,2 | 37,1 | <0,1 | 0,3 | 1,9 | 57,0 | 3,4 |
| P- Antiparasitic products, insecticides and repellents | 0,8 | 77,1 | 0,1 | 14,2 | <0,1 | 4,7 | <0,1 | 1,5 | <0,1 | 2,5 | 1,0 |
| **Total** | **1.031,5** | **61,4** | **156,1** | **9,3** | **199,8** | **11,9** | **141,6** | **8,4** | **150,6** | **9,0** | **1.679,7** |

*calculated on the category

Source: OsMed flow, Traceability flow and IMS Health data analysed by OsMed

**Figure 6.1.** Per capita total pharmaceutical expenditure by ATC I level in 2013

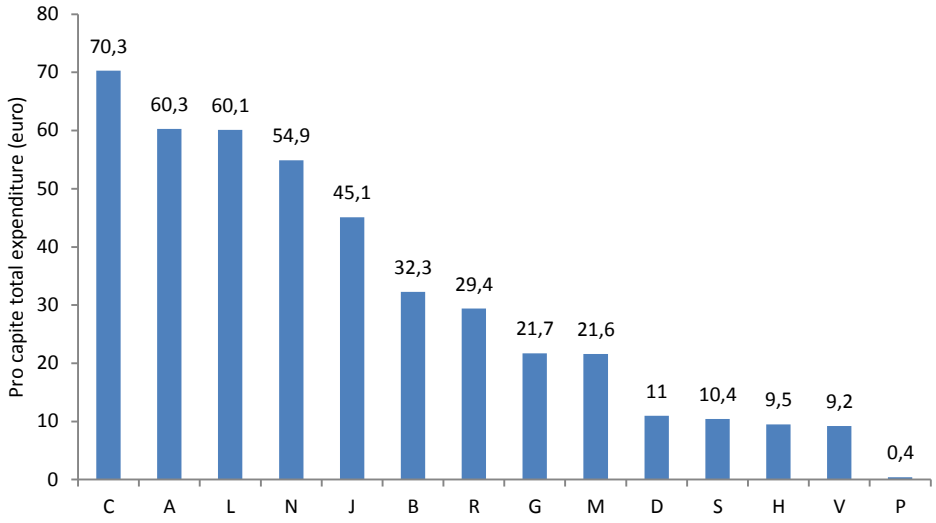



**Table 6.3.** European comparison of outpatient* expenditure by ATC I level in 2013

| ATC | Italy | Austria | Belgium | Finland | France | Germany | Greece | Ireland | Portugal | Spain | Uk |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C - Cardiovascular system | 23,8 | 16,8 | 17,4 | 11,0 | 15,6 | 10,6 | 29,9 | 13,5 | 26,6 | 17,9 | 10,8 |
| A -Alimentary tract and metabolism | 17,7 | 14,4 | 12,5 | 19,3 | 13,0 | 13,4 | 16,9 | 20,1 | 18,5 | 16,4 | 17,2 |
| N -Nervous system | 14,4 | 16,0 | 16,9 | 17,1 | 14,5 | 13,9 | 15,5 | 19,6 | 16,9 | 20,3 | 25,1 |
| R -Respiratory system | 11,5 | 10,9 | 13,7 | 12,4 | 10,5 | 10,4 | 9,7 | 11,4 | 9,9 | 14,5 | 19,2 |
| G -Genito urinary system, sex hormones | 6,9 | 4,3 | 5,5 | 7,0 | 4,1 | 4,4 | 2,9 | 4,6 | 6,5 | 7,9 | 6,1 |
| J -Antiinfectives for sistemic use | 6,7 | 10,0 | 10,3 | 3,6 | 11,0 | 8,5 | 6,6 | 3,4 | 5,4 | 3,4 | 2,5 |
| M -Musculo-sketal system | 5,3 | 4,7 | 3,6 | 3,5 | 3,7 | 3,7 | 4,4 | 3,1 | 6,6 | 4,9 | 2,4 |
| D -Dermatologicals | 4,0 | 3,1 | 2,7 | 2,6 | 2,8 | 3,1 | 2,3 | 3,1 | 2,9 | 3,2 | 6,0 |
| S -Sensory organs | 3,4 | 1,0 | 1,3 | 2,1 | 3,9 | 2,7 | 2,0 | 1,7 | 2,3 | 2,8 | 2,7 |
| B -Blood and blood forming organs | 3,3 | 5,5 | 4,9 | 6,5 | 7,9 | 9,2 | 5,8 | 3,0 | 3,0 | 3,8 | 2,2 |
| H -Systemic hormonal preparations, etc | 1,3 | 1,5 | 1,9 | 1,6 | 2,0 | 1,8 | 1,5 | 1,6 | 0,6 | 1,6 | 2,7 |
| L -Antineoplastic + immunomodulator agent | 1,2 | 10,6 | 8,8 | 12,8 | 10,3 | 15,4 | 2,0 | 13,2 | 0,4 | 2,9 | 2,4 |
| V -Various | 0,5 | 1,1 | 0,3 | 0,2 | 0,5 | 2,7 | 0,4 | 1,3 | 0,2 | 0,5 | 0,2 |
| P Antiparasitic products | 0,1 | 0,1 | 0,3 | 0,2 | 0,3 | 0,2 | 0,1 | 0,3 | 0,2 | 0,1 | 0,3 |

*The expenditure value covers Class A-reimbursed medicines (public + private) together with Class C medicines under prescription and self-medication medicines (SOP and OTC )
Source: AIFA analysis on IMS/MIDAS data

**Table 6.4.** European comparison of top ten active ingredients in Italy: ranked by outpatient* expenditure in 2013

| Active ingredient | Italy | Austria | Belgium | Finland | France | Germany | Greece | Ireland | Portugal | Spain | Uk |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N - Paracetamol | 1 | 36 | 2 | 12 | 1 | 53 | 12 | 4 | 8 | 4 | 5 |
| R - Fluticasone | 2 | 8 | 6 | 2 | 6 | 27 | 11 | 5 | 10 | 2 | 1 |
| C - Rosuvastatin | 3 | 35 | 3 | 67 | 5 | 590 | 16 | 12 | 4 | 25 | 42 |
| C - Olmesartan | 4 | 22 | 25 | 236 | 34 | 21 | 9 | 49 | 6 | 6 | 198 |
| R - Salmeterol | 5 | 10 | 11 | 9 | 9 | 32 | 19 | 8 | 11 | 3 | 2 |
| A - Pantoprazole | 6 | 6 | 16 | 69 | 83 | 16 | 25 | 36 | 66 | 35 | 423 |
| C - Simvastatin | 7 | 7 | 13 | 31 | 13 | 23 | 2 | 41 | 9 | 46 | 34 |
| A - Lansoprazole | 8 | 99 | 318 | 176 | 102 | 846 | 85 | 29 | 88 | 80 | 57 |
| J - Amoxicillin | 9 | 53 | 24 | 60 | 32 | 132 | 32 | 50 | 23 | 28 | 75 |
| R - Beclometasone | 10 | 91 | 67 | 138 | 40 | 54 | 78 | 90 | 497 | 76 | 11 |

*The expenditure value covers with Class A-reimbursed medicines (public + private) plus Class C medicines under prescription and self-medication medicines (SOP and OTC). Data concerning a number of compounds include also fixed combinations

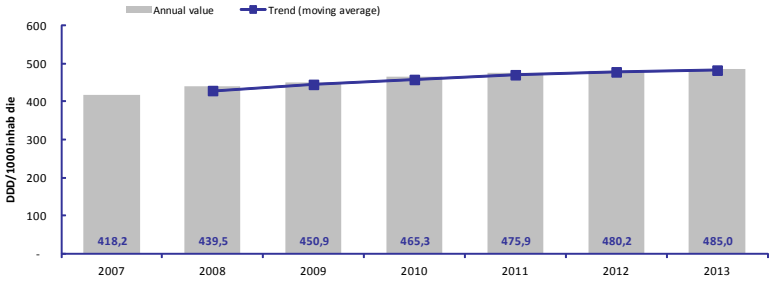
Source: AIFA analysis on IMS/MIDAS data

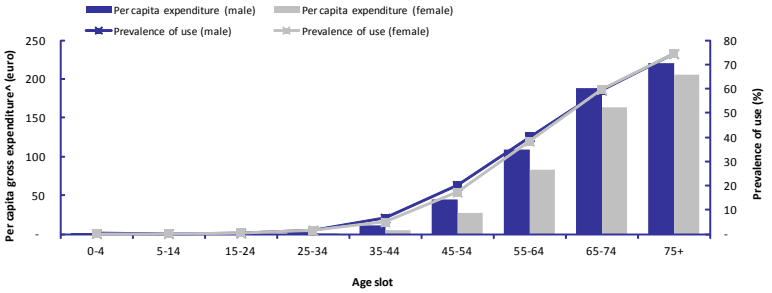
## 6.1 Cardiovascular System

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
CARDIOVASCULAR SYSTEM

| | | |
|---|---|---|
| **NHS expenditure* in milion € (% on the total)** | **3.789,0** | **(19,3)** |
| Δ % 2013/2012 | | -4,8 |
| Range regionale spesa lorda pro capite (€): | 47,5 | 74,1 |
| **DDD/1000 ab die (% sul totale)** | **485,0** | **(41)** |
| Δ % 2013/2012 | | 1,0 |
| Range regionale DDD/1000 ab die: | 382,5 | 567 |

*Spesa convenzionata e spesa per farmaci acquistati dalle strutture sanitarie pubbliche




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 0,1 | 0,1 | 0,1 | 0,5 | 0,8 | 0,7 |
| 5-14 | 0,1 | 0,1 | 0,1 | 0,9 | 0,7 | 0,8 |
| 15-24 | 0,4 | 0,3 | 0,3 | 3,3 | 2,1 | 2,7 |
| 25-34 | 2,0 | 1,1 | 1,5 | 14,7 | 8,1 | 11,4 |
| 35-44 | 11,2 | 5,4 | 8,3 | 81,5 | 42,4 | 61,9 |
| 45-54 | 44,1 | 26,7 | 35,3 | 323,1 | 202,6 | 262,2 |
| 55-64 | 109,5 | 82,5 | 95,6 | 818,9 | 600,5 | 706,8 |
| 65-74 | 188,1 | 163,6 | 175,1 | 1.461,7 | 1.212,6 | 1.329,7 |
| 75+ | 220,5 | 205,4 | 211,2 | 1.883,4 | 1.693,0 | 1.766,0 |

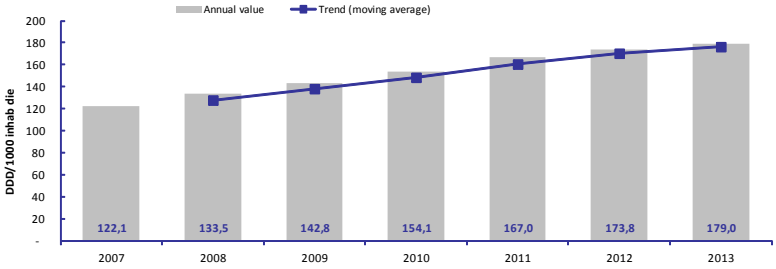
^with the exclusion of medicinal products administered in hospitals

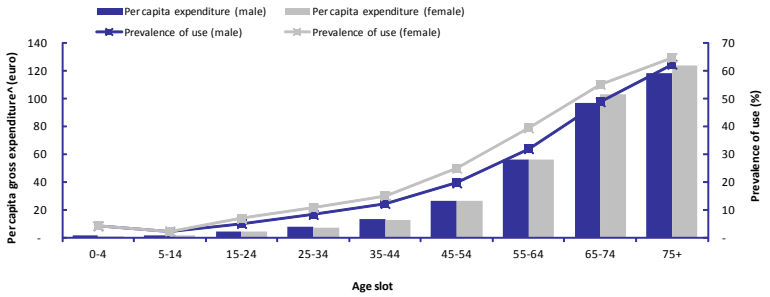
## 6.2 Alimentary Tract And Metabolism

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
ALIMENTARY TRACT AND METABOLISM

| | | |
|---|---|---|
| **NHS expenditure, milion €* (% on the total)** | **2.492,0** | **(12,7)** |
| Δ % 2013/2012 | | 5,1 |
| Per capita gross expenditure, range among | 26 | 58,6 |
| **DDD/1000 inhab die (% on the total)** | **179,0** | **(15,1)** |
| Δ % 2013/2012 | | 3,0 |
| DDD/1000 inhab die, range among regions: | 124,8 | 230,1 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 1,1 | 1,0 | 1,1 | 2,0 | 2,0 | 2,0 |
| 5-14 | 1,6 | 1,7 | 1,6 | 3,7 | 3,6 | 3,6 |
| 15-24 | 4,3 | 4,4 | 4,4 | 11,5 | 12,6 | 12,1 |
| 25-34 | 7,4 | 7,2 | 7,3 | 23,5 | 24,6 | 24,1 |
| 35-44 | 13,0 | 12,3 | 12,6 | 46,3 | 46,2 | 46,2 |
| 45-54 | 26,5 | 26,1 | 26,3 | 105,0 | 102,9 | 104,0 |
| 55-64 | 55,7 | 55,8 | 55,7 | 238,7 | 227,2 | 232,8 |
| 65-74 | 96,7 | 102,6 | 99,8 | 440,6 | 432,1 | 436,1 |
| 75+ | 117,8 | 123,3 | 121,2 | 552,1 | 542,3 | 546,0 |

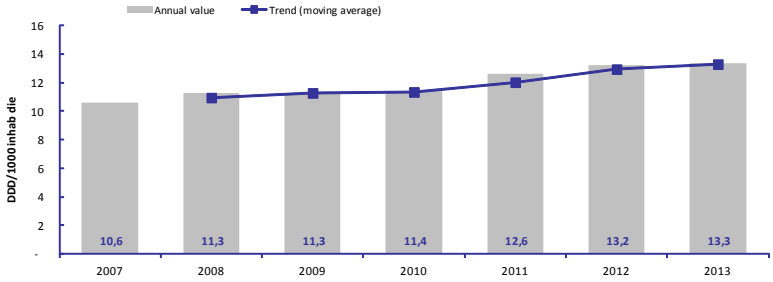
^with the exclusion of medicinal products administered in hospitals

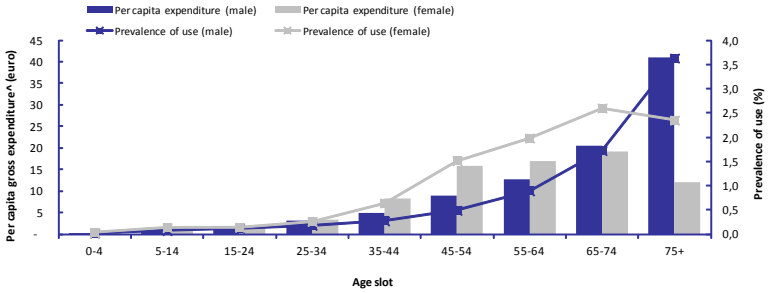
## 6.3 Antineoplastic and immunomodulating agents

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **3.557,0** | **(18,1)** |
| Δ % 2013/2012 | | 8,0 |
| Per capita gross expenditure range among | 45 | 78,3 |
| **DDD/1000 ab die (% sul totale)** | **13,3** | **(1,1)** |
| Δ % 2013/2012 | | 0,8 |
| DDD/1000 inhab die range among regions: | 11 | 15,5 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 0,1 | 0,1 | 0,1 | 0,1 | 0,1 | 0,1 |
| 5-14 | 0,6 | 1,5 | 1,0 | 0,3 | 1,0 | 0,6 |
| 15-24 | 1,7 | 1,6 | 1,6 | 0,7 | 0,7 | 0,7 |
| 25-34 | 3,2 | 3,4 | 3,3 | 1,1 | 1,6 | 1,4 |
| 35-44 | 4,8 | 8,2 | 6,5 | 1,6 | 5,7 | 3,6 |
| 45-54 | 9,0 | 15,8 | 12,4 | 2,7 | 13,8 | 8,3 |
| 55-64 | 12,7 | 16,9 | 14,8 | 5,4 | 12,9 | 9,2 |
| 65-74 | 20,4 | 19,1 | 19,7 | 14,2 | 16,5 | 15,4 |
| 75+ | 41,0 | 12,1 | 23,2 | 44,5 | 14,4 | 26,0 |

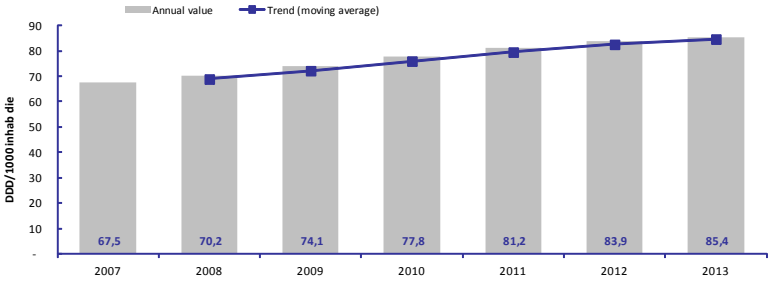
^with the exclusion of medicinal products administered in hospitals

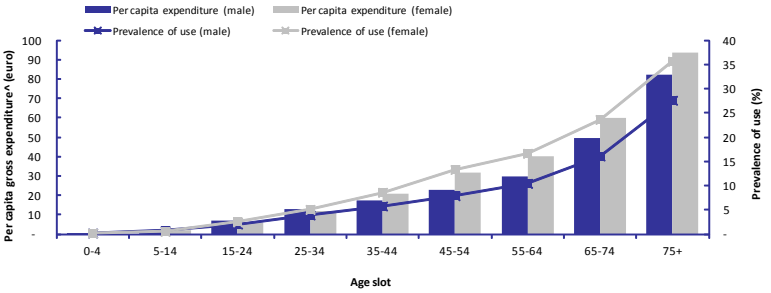
## 6.4 Nervous system

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
NERVOUS SYSTEM

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **1.935,0** | **(9,9)** |
| Δ % 2013/2012 | | -2,2 |
| Per capita gross expenditure range among | 28,3 | 41,8 |
| **DDD/1000 ab die (% sul totale)** | **85,4** | **(7,2)** |
| Δ % 2013/2012 | | 1,7 |
| DDD/1000 inhab die range among regions: | 67,8 | 109 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 0,4 | 0,4 | 0,4 | 0,7 | 0,6 | 0,6 |
| 5-14 | 2,2 | 1,8 | 2,0 | 3,7 | 2,8 | 3,3 |
| 15-24 | 6,9 | 6,1 | 6,5 | 13,2 | 12,0 | 12,6 |
| 25-34 | 12,8 | 11,8 | 12,3 | 27,2 | 25,9 | 26,5 |
| 35-44 | 17,2 | 20,9 | 19,0 | 39,9 | 48,2 | 44,0 |
| 45-54 | 22,6 | 31,8 | 27,2 | 52,6 | 79,1 | 66,0 |
| 55-64 | 29,9 | 40,0 | 35,1 | 65,4 | 102,9 | 84,7 |
| 65-74 | 49,5 | 59,9 | 55,0 | 101,4 | 147,2 | 125,7 |
| 75+ | 82,4 | 93,5 | 89,3 | 172,8 | 221,6 | 202,9 |

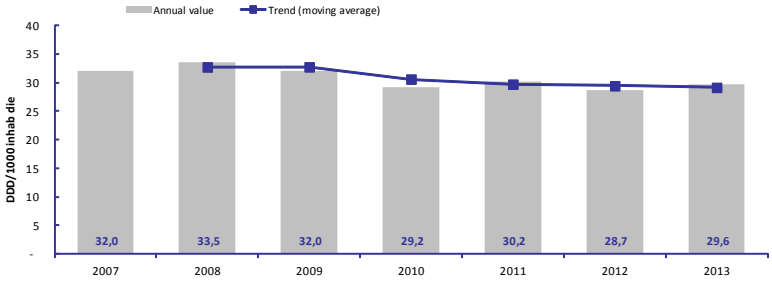
^with the exclusion of medicinal products administered in hospitals

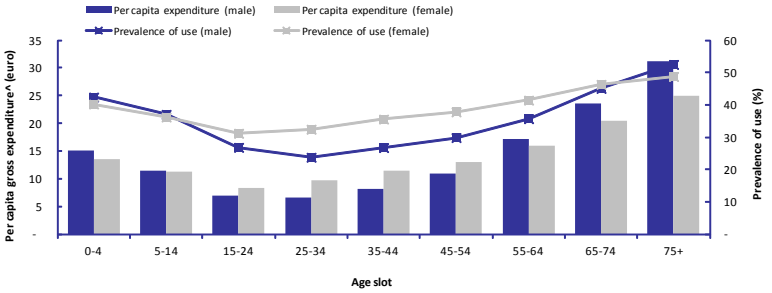
## 6.5 Antiinfectives for sistemic use

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
ANTIINFECTIVES FOR SYSTEMIC USE

| | | |
|---|---|---|
| **Spesa pubblica* in milioni di € (% sul totale)** | **2.470,0** | **(12,6)** |
| Δ % 2013/2012 | | 1,8 |
| Range regionale spesa lorda pro capite (€): | 29,1 | 51,2 |
| **DDD/1000 ab die (% sul totale)** | **29,6** | **(2,5)** |
| Δ % 2013/2012 | | 3,4 |
| Range regionale DDD/1000 ab die: | 21,6 | 38,4 |

*Spesa convenzionata e spesa per farmaci acquistati dalle strutture sanitarie pubbliche




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 15,1 | 13,6 | 14,3 | 24,1 | 21,4 | 22,8 |
| 5-14 | 11,5 | 11,3 | 11,4 | 20,2 | 19,3 | 19,7 |
| 15-24 | 6,9 | 8,3 | 7,6 | 13,7 | 15,3 | 14,4 |
| 25-34 | 6,6 | 9,7 | 8,2 | 12,1 | 16,8 | 14,4 |
| 35-44 | 8,2 | 11,4 | 9,8 | 14,4 | 19,5 | 16,9 |
| 45-54 | 10,9 | 13,0 | 12,0 | 16,6 | 21,2 | 18,9 |
| 55-64 | 17,1 | 16,0 | 16,5 | 21,9 | 24,5 | 23,2 |
| 65-74 | 23,6 | 20,4 | 21,9 | 30,9 | 29,1 | 30,0 |
| 75+ | 31,2 | 25,0 | 27,4 | 36,1 | 29,9 | 32,2 |

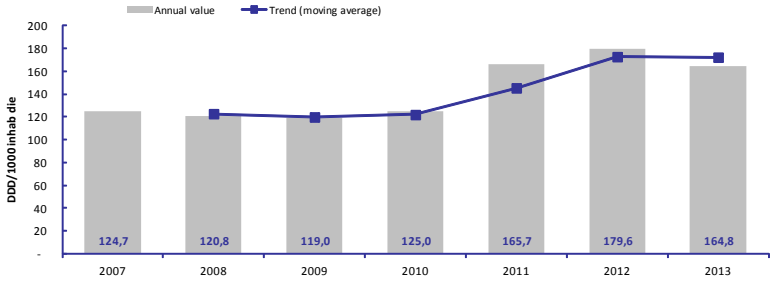
^with the exclusion of medicinal products administered in hospitals

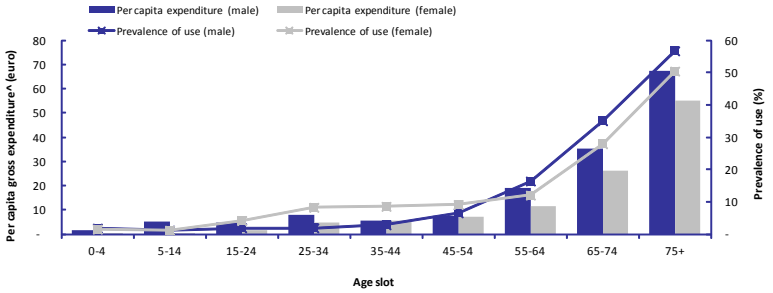
## 6.6 Blood and blood forming organs

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
BLOOD AND FORMING ORGANS

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **1.742,0** | **(8,9)** |
| Δ % 2013/2012 | | -1,4 |
| Per capita gross expenditure range among | 17,9 | 40 |
| **DDD/1000 ab die (% sul totale)** | **164,8** | **(13,9)** |
| Δ % 2013/2012 | | -8,3 |
| DDD/1000 inhab die range among regions: | 124,8 | 214,8 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 1,7 | 0,3 | 1,0 | 2,6 | 1,9 | 2,3 |
| 5-14 | 5,0 | 0,3 | 2,7 | 3,3 | 3,7 | 3,5 |
| 15-24 | 4,8 | 1,7 | 3,3 | 7,0 | 26,3 | 16,4 |
| 25-34 | 8,0 | 4,7 | 6,4 | 8,6 | 62,1 | 35,3 |
| 35-44 | 5,6 | 5,7 | 5,6 | 17,6 | 64,5 | 41,1 |
| 45-54 | 7,6 | 7,3 | 7,5 | 53,0 | 65,9 | 59,5 |
| 55-64 | 19,0 | 11,6 | 15,2 | 146,0 | 93,6 | 119,1 |
| 65-74 | 35,4 | 26,2 | 30,5 | 342,9 | 248,7 | 293,0 |
| 75+ | 67,5 | 55,0 | 59,8 | 618,3 | 531,9 | 565,0 |

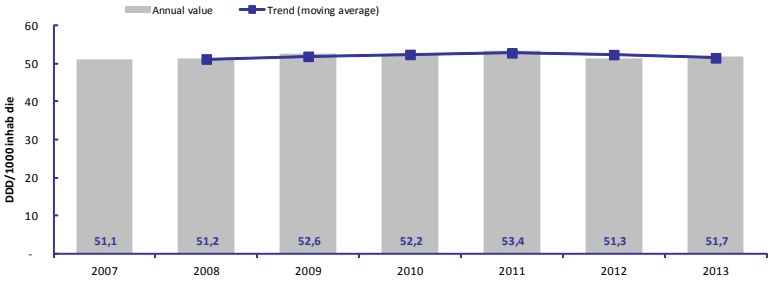
^with the exclusion of medicinal products administered in hospitals

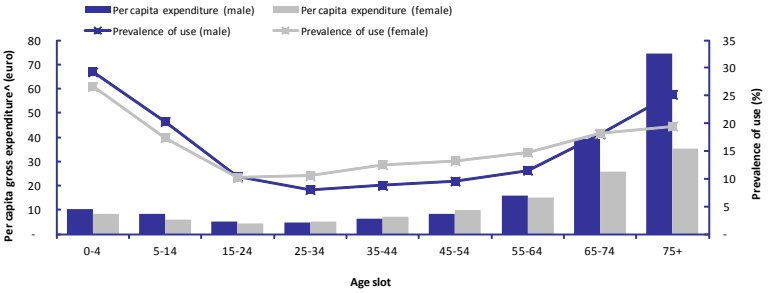
## 6.7 Respiratory system

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
RESPIRATORY SYSTEM

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **1.077,0** | **(5,5)** |
| Δ % 2013/2012 | | -3,0 |
| Per capita gross expenditure range among | 14,4 | 22,8 |
| **DDD/1000 ab die (% sul totale)** | **51,7** | **(4,4)** |
| Δ % 2013/2012 | | 0,9 |
| DDD/1000 inhab die range among regions: | 37,8 | 69,8 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 10,1 | 8,3 | 9,2 | 41,6 | 34,7 | 38,2 |
| 5-14 | 8,4 | 5,9 | 7,2 | 34,0 | 24,5 | 29,4 |
| 15-24 | 5,2 | 4,3 | 4,8 | 22,8 | 19,3 | 21,1 |
| 25-34 | 4,9 | 5,2 | 5,0 | 18,3 | 20,3 | 19,3 |
| 35-44 | 6,3 | 7,2 | 6,8 | 21,1 | 26,5 | 23,8 |
| 45-54 | 8,5 | 10,0 | 9,2 | 25,5 | 33,4 | 29,5 |
| 55-64 | 15,7 | 15,2 | 15,5 | 39,6 | 43,5 | 41,6 |
| 65-74 | 39,3 | 25,8 | 32,1 | 88,8 | 67,7 | 77,6 |
| 75+ | 74,6 | 35,1 | 50,2 | 168,6 | 89,4 | 119,8 |

^with the exclusion of medicinal products administered in hospitals

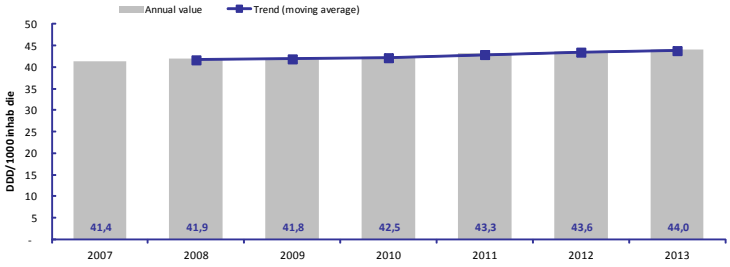
## 6.8 Genito urinary system and sex hormones

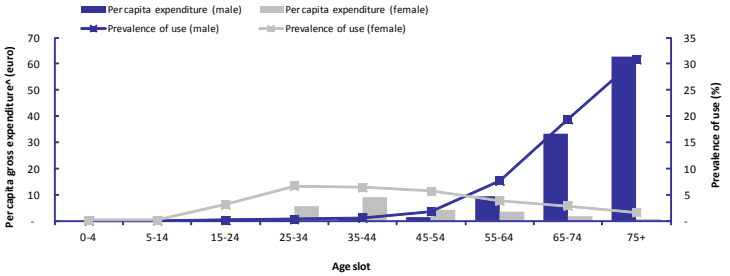
**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**

GENITO URINARY SYSTEM AND SEX HORMONES

| | | |
|---|---|---|
| **Spesa pubblica* in milioni di € (% sul totale)** | **518,0** | **(2,6)** |
| Δ % 2013/2012 | | 3,2 |
| Range regionale spesa lorda pro capite (€): | 7,1 | 10 |
| **DDD/1000 ab die (% sul totale)** | **44,0** | **(3,7)** |
| Δ % 2013/2012 | | 0,8 |
| Range regionale DDD/1000 ab die: | 35,3 | 55,6 |

*Spesa convenzionata e spesa per farmaci acquistati dalle strutture sanitarie pubbliche




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 0,0 | 0,0 | 0,0 | 0,1 | 0,1 | 0,1 |
| 5-14 | 0,0 | 0,0 | 0,0 | 0,1 | 0,3 | 0,2 |
| 15-24 | 0,2 | 1,2 | 0,7 | 0,5 | 14,6 | 7,4 |
| 25-34 | 0,5 | 5,5 | 3,0 | 0,9 | 32,5 | 16,6 |
| 35-44 | 0,7 | 9,1 | 4,9 | 1,9 | 36,1 | 19,0 |
| 45-54 | 1,4 | 4,0 | 2,7 | 8,6 | 32,8 | 20,8 |
| 55-64 | 9,3 | 3,4 | 6,3 | 58,6 | 25,6 | 41,6 |
| 65-74 | 33,1 | 1,7 | 16,5 | 193,2 | 15,2 | 98,8 |
| 75+ | 62,7 | 0,7 | 24,5 | 334,9 | 6,4 | 132,3 |

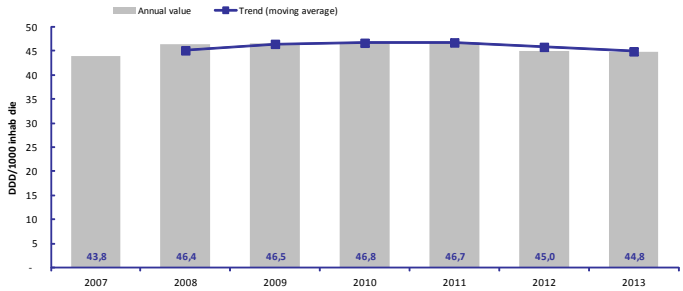
^with the exclusion of medicinal products administered in hospitals

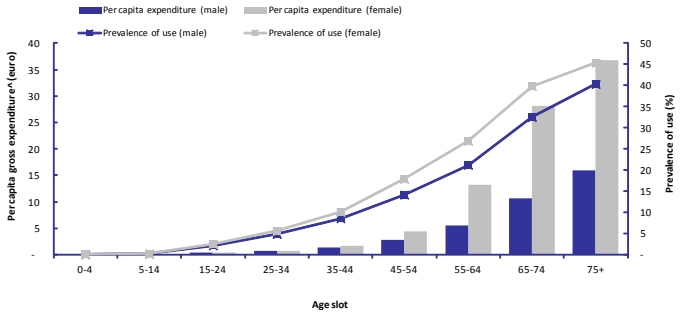
## 6.9 Musculo-sketal system

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
MUSCULO-SKELETAL SYSTEM

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **552,0** | **(2,8)** |
| Δ % 2013/2012 | | -6,9 |
| Per capita gross expenditure range among | 6,6 | 13,6 |
| **DDD/1000 ab die (% sul totale)** | **44,8** | **(3,8)** |
| Δ % 2013/2012 | | -0,3 |
| DDD/1000 inhab die range among regions: | 30,8 | 68,3 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 0,0 | 0,0 | 0,0 | 0,0 | 0,1 | 0,1 |
| 5-14 | 0,0 | 0,0 | 0,0 | 0,2 | 0,2 | 0,2 |
| 15-24 | 0,3 | 0,3 | 0,3 | 1,7 | 1,9 | 1,8 |
| 25-34 | 0,7 | 0,7 | 0,7 | 4,4 | 4,8 | 4,6 |
| 35-44 | 1,4 | 1,6 | 1,5 | 9,1 | 10,3 | 9,7 |
| 45-54 | 2,8 | 4,4 | 3,6 | 18,7 | 24,3 | 21,5 |
| 55-64 | 5,5 | 13,2 | 9,4 | 36,2 | 59,3 | 48,1 |
| 65-74 | 10,7 | 28,2 | 20,0 | 72,7 | 122,5 | 99,1 |
| 75+ | 16,0 | 36,8 | 28,8 | 107,5 | 163,9 | 142,3 |

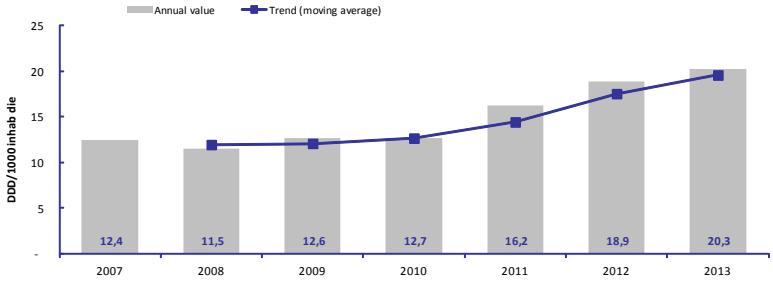
^with the exclusion of medicinal products administered in hospitals

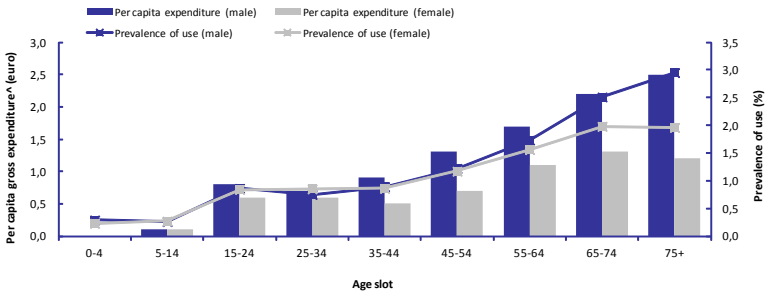
## 6.10 Dermatologicals

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
DERMATOLOGICALS

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **83,0** | **(0,4)** |
| Δ % 2013/2012 | | 4,5 |
| Per capita gross expenditure range among | 1,1 | 1,7 |
| **DDD/1000 ab die (% sul totale)** | **20,3** | **(1,7)** |
| Δ % 2013/2012 | | 7,5 |
| DDD/1000 inhab die range among regions: | 13,3 | 164,1 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 0,0 | 0,0 | 0,0 | 0,3 | 0,2 | 0,3 |
| 5-14 | 0,1 | 0,1 | 0,1 | 0,4 | 0,4 | 0,4 |
| 15-24 | 0,8 | 0,6 | 0,7 | 2,3 | 1,9 | 2,1 |
| 25-34 | 0,7 | 0,6 | 0,6 | 2,6 | 2,1 | 2,3 |
| 35-44 | 0,9 | 0,5 | 0,7 | 3,5 | 2,1 | 2,8 |
| 45-54 | 1,3 | 0,7 | 1,0 | 5,0 | 2,9 | 4,0 |
| 55-64 | 1,7 | 1,1 | 1,4 | 6,7 | 4,3 | 5,5 |
| 65-74 | 2,2 | 1,3 | 1,7 | 9,3 | 5,5 | 7,3 |
| 75+ | 2,5 | 1,2 | 1,7 | 10,5 | 5,5 | 7,4 |

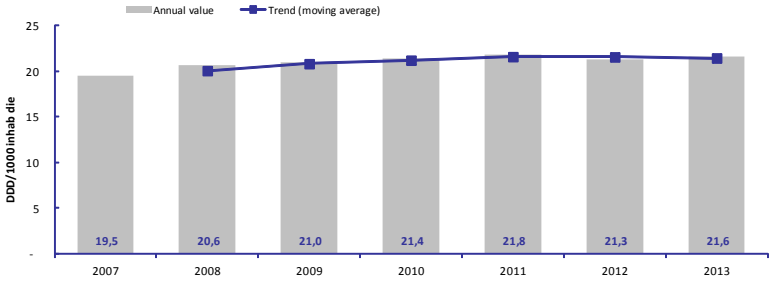
^with the exclusion of medicinal products administered in hospitals

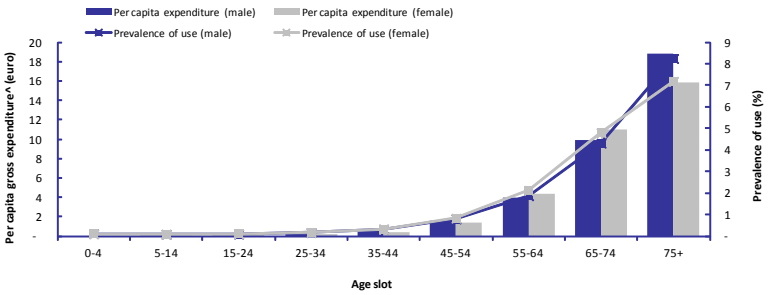
## 6.11 Sensory organs

**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**
SENSORY ORGANS

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **317,0** | **(1,6)** |
| Δ % 2013/2012 | | 13,8 |
| Per capita gross expenditure range among | 4,2 | 7 |
| **DDD/1000 ab die (% sul totale)** | **21,6** | **(1,8)** |
| Δ % 2013/2012 | | 1,2 |
| DDD/1000 inhab die range among regions: | 16,1 | 29,1 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 0,0 | 0,0 | 0,0 | 0,2 | 0,2 | 0,2 |
| 5-14 | 0,1 | 0,1 | 0,1 | 0,3 | 0,3 | 0,3 |
| 15-24 | 0,1 | 0,1 | 0,1 | 0,6 | 0,5 | 0,5 |
| 25-34 | 0,2 | 0,2 | 0,2 | 1,4 | 1,1 | 1,2 |
| 35-44 | 0,6 | 0,4 | 0,5 | 3,3 | 2,6 | 2,9 |
| 45-54 | 1,6 | 1,4 | 1,5 | 9,3 | 8,7 | 9,0 |
| 55-64 | 4,0 | 4,4 | 4,2 | 23,3 | 25,9 | 24,6 |
| 65-74 | 9,9 | 11,0 | 10,5 | 56,2 | 64,2 | 60,4 |
| 75+ | 18,8 | 15,8 | 17,0 | 106,5 | 92,2 | 97,7 |

^with the exclusion of medicinal products administered in hospitals

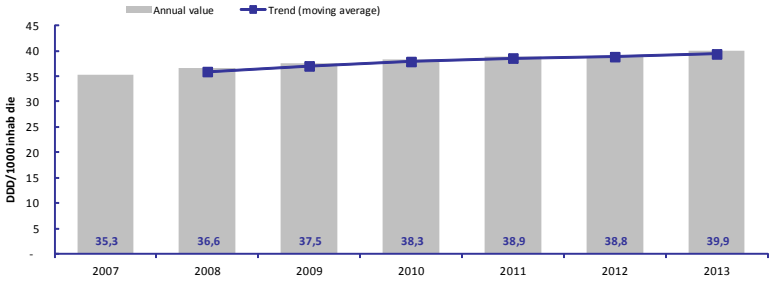
## 6.12 Systemic hormonal preparations, excl.sex hormones and insulins

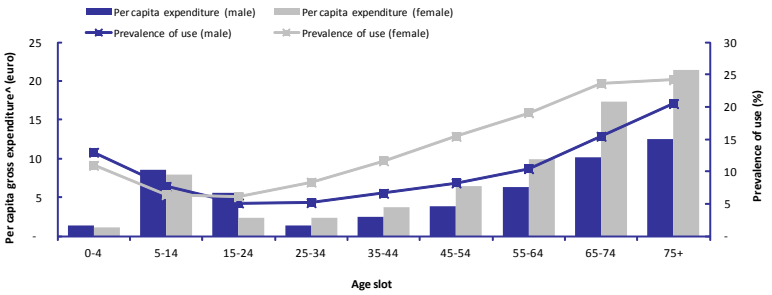
**MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE**

SYSTEMIC HORMONAL PREPARATIONS, EXCLUDING SEX HORMONES AND INSULINS

| | | |
|---|---|---|
| **Milion € NHS expenditure* (% on the total)** | **486,0** | **(2,5)** |
| Δ % 2013/2012 | | 0,2 |
| Per capita gross expenditure range among | 6,8 | 10 |
| **DDD/1000 ab die (% sul totale)** | **39,9** | **(3,4)** |
| Δ % 2013/2012 | | 2,8 |
| DDD/1000 inhab die range among regions: | 30,3 | 48,4 |

*Outpatient and inpatient NHS expenditure




**Expenditure and consumption distribution by age^ 2013**

| | Per capita expenditure | | | DDD/1000 inhab die | | |
|---|---|---|---|---|---|---|
| **Age slot** | **male** | **female** | **total** | **male** | **female** | **total** |
| 0-4 | 1,3 | 1,1 | 1,2 | 6,5 | 5,4 | 5,9 |
| 5-14 | 8,5 | 7,9 | 8,2 | 7,1 | 6,2 | 6,6 |
| 15-24 | 5,6 | 2,4 | 4,0 | 8,2 | 12,0 | 10,0 |
| 25-34 | 1,3 | 2,3 | 1,8 | 10,6 | 27,1 | 18,8 |
| 35-44 | 2,5 | 3,7 | 3,1 | 16,2 | 48,2 | 32,2 |
| 45-54 | 3,8 | 6,4 | 5,1 | 25,6 | 77,6 | 51,8 |
| 55-64 | 6,3 | 9,9 | 8,2 | 39,2 | 106,2 | 73,6 |
| 65-74 | 10,2 | 17,3 | 13,9 | 61,3 | 134,5 | 100,1 |
| 75+ | 12,5 | 21,4 | 18,0 | 76,5 | 118,2 | 102,2 |

^with the exclusion of medicinal products administered in hospitals

**Table 6.5.** Consumption, price, and mix effect of Class A NHS pharmaceutical expenditure (for each ATC I level category associated to a level of expenditure exceeding 50 million euros, a number of therapeutic groups were included in descending order of expenditure, up to the value of 0,10 euro per capita)

| ATC I level | Subgroups | Per capita gross expenditure | DDD/1.000 inhab. die | Δ% 13-12 | | | | Δ% Average cost DDD |
|---|---|---|---|---|---|---|---|---|
| | | | | EXp | DDD | Price | Mix | |
| **Italy** | | **187,7** | **1.031,5** | **-2,3** | **2,7** | **-4,2** | **-0,8** | **-4,9** |
| **CARDIOVASCULAR SYSTEM** | | **60,4** | **468,0** | **-5,5** | **1,1** | **-5,6** | **-1,0** | **-6,6** |
| HMG CoA reductase inhibitors | | 10,7 | 63,6 | -13,3 | 5,6 | -12,9 | -5,7 | -17,9 |
| Angiotensin II antagonists and diuretics | | 8,4 | 40,1 | -6,7 | 1,0 | -7,3 | -0,4 | -7,6 |
| Angiotensin II antagonists, plain | | 7,3 | 55,6 | -14,0 | 2,1 | -15,4 | -0,3 | -15,7 |
| Dihydropyridine derivatives | | 4,8 | 53,9 | -2,5 | -0,7 | -0,6 | -1,3 | -1,9 |
| ACE inhibitors, plain | | 4,6 | 88,6 | -2,4 | 0,3 | -0,3 | -2,3 | -2,6 |
| ACE inhibitors and diuretics | | 3,7 | 25,8 | -2,5 | -2,4 | -0,2 | 0,1 | -0,1 |
| Other lipid modifying agents | | 3,6 | 5,4 | -10,2 | -10,0 | 0,2 | -0,5 | -0,3 |
| Beta blocking agents, selective | | 3,6 | 34,9 | 5,3 | 2,4 | -0,4 | 3,2 | 2,8 |
| HMG CoA reductase inhibitors in combination with other lipid modifying agents | | 2,5 | 3,4 | 7,1 | 7,1 | -0,0 | 0,0 | 0,0 |
| Organic nitrates | | 1,7 | 15,5 | -9,5 | -8,4 | -0,0 | -1,1 | -1,1 |
| Alpha-adrenoreceptor antagonists | | 1,3 | 7,6 | -0,9 | -0,1 | -0,2 | -0,5 | -0,7 |
| ACE inhibitors and calcium channel blockers | | 0,9 | 5,0 | 62,7 | 56,9 | 2,8 | 0,9 | 3,7 |
| Antiarrhythmics, class Ic | | 0,9 | 4,6 | 3,1 | 0,3 | -0,1 | 2,9 | 2,8 |
| Sulfonamides, plain | | 0,8 | 24,8 | 1,3 | 2,3 | -0,0 | -0,9 | -0,9 |
| Angiotensin II antagonists and calcium channel blockers | | 0,8 | 2,3 | 0,6 | -2,4 | 2,9 | 0,1 | 3,0 |
| Alpha and beta blocking agents | | 0,8 | 4,2 | -3,5 | -2,8 | -0,2 | -0,6 | -0,7 |
| Aldosterone antagonists | | 0,5 | 3,7 | 3,9 | 2,3 | -0,0 | 1,6 | 1,6 |
| Other cardiac preparations | | 0,4 | 0,3 | 13,0 | 8,6 | -0,2 | 4,3 | 4,1 |
| Fibrates | | 0,4 | 2,4 | 4,9 | 6,4 | -0,5 | -0,9 | -1,4 |
| Beta blocking agents, selective, and thiazides | | 0,4 | 3,1 | 28,9 | 27,3 | -0,8 | 2,1 | 1,2 |
| Benzothiazepine derivatives | | 0,3 | 1,8 | -8,2 | -7,7 | -0,0 | -0,6 | -0,6 |
| Imidazoline receptor agonists | | 0,3 | 2,1 | -4,7 | -4,8 | -0,0 | 0,2 | 0,2 |
| Antiarrhythmics, class III | | 0,3 | 3,0 | -5,1 | -0,9 | -0,6 | -3,6 | -4,3 |
| Phenylalkylamine derivatives | | 0,2 | 2,0 | -7,4 | -7,2 | -0,1 | -0,1 | -0,2 |
| Renin-inhibitors | | 0,2 | 0,6 | 45,0 | 32,1 | 3,1 | 6,4 | 9,8 |
| Beta blocking agents, selective, and other diuretics | | 0,2 | 2,6 | -5,1 | -4,9 | -0,1 | -0,1 | -0,3 |
| Low-ceiling diuretics and potassium-sparing agents | | 0,2 | 3,4 | -4,6 | -4,5 | -0,0 | -0,1 | -0,1 |
| Beta blocking agents, non-selective | | 0,2 | 1,7 | -0,3 | 0,2 | -0,0 | -0,5 | -0,5 |
| Digitalis glycosides | | 0,1 | 2,8 | -9,5 | -10,7 | -0,2 | 1,5 | 1,3 |
| High-ceiling diuretics and potassium-sparing agents | | 0,1 | 0,7 | -1,9 | -1,8 | -0,0 | -0,1 | -0,1 |
| **ALIMENTARY TRACT AND METABOLISM** | | **32,6** | **152,2** | **2,1** | **2,9** | **-2,6** | **2,0** | **-0,7** |
| Proton pump inhibitors | | 15,2 | 74,0 | 1,6 | 6,5 | -3,9 | -0,7 | -4,6 |
| Insulins and analogues for injection, fast-acting | | 3,6 | 7,4 | 3,1 | 2,2 | -0,3 | 1,2 | 0,9 |

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| ATC I level | Subgroups | Per capita gross expenditure | DDD/1.000 inhab. die | Δ% 13-12 | | | | Δ% Average cost DDD |
|---|---|---|---|---|---|---|---|---|
| | | | | EXp | DDD | Price | Mix | |
| Vitamin D and analogues | | 1,6 | 2,9 | 37,6 | 17,4 | -0,3 | 17,5 | 17,1 |
| Aminosalicylic acid and similar agents | | 1,6 | 4,0 | 4,9 | 5,0 | -0,2 | 0,1 | -0,1 |
| Antibiotics | | 1,5 | 2,0 | 16,4 | 5,8 | -10,8 | 23,3 | 10,0 |
| Biguanides | | 1,3 | 19,4 | 1,9 | 3,7 | -0,2 | -1,5 | -1,7 |
| Combinations of oral blood glucose lowering drugs | | 0,9 | 6,2 | -12,9 | -14,2 | 0,2 | 1,3 | 1,5 |
| Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) | | 0,8 | 2,1 | 5,8 | 4,5 | -0,1 | 1,3 | 1,2 |
| Other blood glucose lowering drugs, excl. insulins | | 0,7 | 4,0 | -7,0 | 0,1 | 0,3 | -7,4 | -7,1 |
| Insulins and analogues for injection, long-acting | | 0,7 | 0,9 | -13,6 | -13,6 | -0,7 | 0,7 | -0,0 |
| Bile acid preparations | | 0,6 | 2,1 | 3,3 | 4,6 | -0,6 | -0,7 | -1,2 |
| Calcium, combinations with vitamin D and/or other drugs | | 0,5 | 6,0 | -3,2 | -3,6 | -0,4 | 0,9 | 0,4 |
| Sulfonamides, urea derivatives | | 0,5 | 11,3 | -3,8 | -4,6 | -0,2 | 1,0 | 0,8 |
| Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting | | 0,5 | 1,0 | -12,5 | -13,4 | -0,1 | 1,1 | 1,0 |
| H2-receptor antagonists | | 0,4 | 2,4 | -3,3 | -1,2 | -1,9 | -0,3 | -2,2 |
| Combinations and complexes of aluminium, calcium and magnesium compounds | | 0,4 | 1,6 | 1,0 | 1,2 | -0,1 | -0,1 | -0,2 |
| Corticosteroids acting locally | | 0,3 | 0,4 | 1,5 | 2,6 | -0,0 | -1,0 | -1,0 |
| Dipeptidyl peptidase 4 (DPP-4) inhibitors | | 0,2 | 0,3 | -3,0 | -11,4 | 1,3 | 8,1 | 9,5 |
| Insulins and analogues for injection, intermediate-acting | | 0,2 | 0,5 | -9,6 | -12,9 | -1,2 | 5,1 | 3,8 |
| Serotonin (5HT3) antagonists | | 0,2 | <0,1 | -9,5 | -3,9 | -3,4 | -2,6 | -5,8 |
| Alpha glucosidase inhibitors | | 0,2 | 0,6 | 9,0 | 10,5 | -0,0 | -1,3 | -1,4 |
| Enzyme preparations | | 0,1 | 0,5 | 13,0 | 5,3 | -7,2 | 15,7 | 7,3 |
| Osmotically acting laxatives | | 0,1 | 1,2 | 5,3 | 6,0 | -0,1 | -0,6 | -0,7 |
| Calcium | | 0,1 | 0,5 | 0,3 | 1,5 | -1,3 | 0,1 | -1,2 |
| **NERVOUS SYSTEM** | | **23,4** | **60,4** | **-2,0** | **2,1** | **-5,9** | **2,0** | **-4,0** |
| Selective serotonin reuptake inhibitors | | 4,8 | 28,0 | -2,2 | 0,9 | -2,1 | -0,9 | -3,0 |
| Other antiepileptics | | 4,2 | 4,2 | -14,3 | 6,1 | -19,2 | 0,0 | -19,2 |
| Other antidepressants | | 3,2 | 8,1 | 3,2 | 3,5 | -0,1 | -0,2 | -0,3 |
| Selective serotonin (5HT1) agonists | | 1,5 | 0,8 | -3,2 | 2,5 | -5,2 | -0,4 | -5,6 |
| Natural opium alkaloids | | 1,4 | 2,1 | 15,6 | 13,6 | -1,7 | 3,5 | 1,7 |
| Dopamine agonists | | 1,4 | 1,4 | -4,9 | -0,0 | -7,7 | 3,0 | -4,9 |
| Phenylpiperidine derivatives | | 1,0 | 0,5 | 11,2 | 5,7 | -0,3 | 5,5 | 5,2 |
| Fatty acid derivatives | | 0,9 | 2,1 | 4,5 | 4,3 | -0,1 | 0,3 | 0,2 |
| Other opioids | | 0,8 | 0,9 | 24,7 | 5,8 | 1,1 | 16,7 | 17,9 |
| Monoamine oxidase B inhibitors | | 0,7 | 1,0 | 9,6 | 14,4 | -0,0 | -4,3 | -4,3 |
| Dopa and dopa derivatives | | 0,7 | 1,9 | -3,0 | 1,5 | -1,1 | -3,4 | -4,5 |
| Diazepines, oxazepines, thiazepines and oxepines | | 0,6 | 0,8 | -7,3 | 6,8 | -9,0 | -4,5 | -13,1 |
| Carboxamide derivatives | | 0,6 | 2,1 | -3,1 | -2,0 | -1,4 | 0,2 | -1,2 |
| Other antipsychotics | | 0,3 | 0,2 | -3,3 | 4,3 | -4,9 | -2,5 | -7,3 |
| Anticholinesterases | | 0,2 | 0,3 | -26,7 | 2,5 | -15,3 | -15,6 | -28,5 |
| Other anti-dementia drugs | | 0,2 | 0,1 | -13,0 | -10,7 | -5,5 | 3,1 | -2,5 |

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| ATC I level | Subgroups | Per capita gross expenditure | DDD/1.000 inhab. die | Δ% 13-12 | | | | Δ% Average cost DDD |
|---|---|---|---|---|---|---|---|---|
| | | | | EXp | DDD | Price | Mix | |
| Non-selective monoamine reuptake inhibitors | | 0,2 | 1,1 | 0,8 | -1,2 | 1,8 | 0,3 | 2,0 |
| Oripavine derivatives | | 0,1 | 0,1 | -6,7 | -6,7 | -0,1 | 0,1 | 0,0 |
| **RESPIRATORY SYSTEM** | | **17,1** | **48,5** | **-3,4** | **1,1** | **-5,3** | **0,9** | **-4,4** |
| Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics | | 7,9 | 10,1 | 2,1 | 1,9 | -0,0 | 0,2 | 0,2 |
| Anticholinergics | | 3,1 | 6,6 | 6,8 | 5,8 | -0,0 | 1,0 | 1,0 |
| Glucocorticoids | | 2,7 | 10,6 | 2,4 | 2,7 | -0,1 | -0,2 | -0,3 |
| Selective beta-2-adrenoreceptor agonists | | 1,3 | 5,9 | 0,5 | -0,1 | -0,1 | 0,8 | 0,7 |
| Other antihistamines for systemic use | | 0,8 | 6,2 | -17,6 | -1,3 | -14,8 | -2,0 | -16,5 |
| Leukotriene receptor antagonists | | 0,6 | 2,1 | -57,0 | -2,5 | -53,4 | -5,4 | -55,9 |
| Piperazine derivatives | | 0,4 | 4,2 | -4,1 | -1,0 | -0,9 | -2,3 | -3,2 |
| Adrenergics in combination with anticholinergics | | 0,2 | 1,5 | -0,2 | -0,3 | -0,0 | 0,1 | 0,1 |
| Xanthines | | 0,1 | 1,0 | -8,6 | -11,2 | -0,1 | 3,0 | 2,9 |
| **ANTIINFECTIVES FOR SYSTEMIC USE** | | **15,0** | **23,2** | **1,6** | **3,9** | **-0,9** | **-1,4** | **-2,3** |
| Third-generation cephalosporins | | 3,4 | 1,9 | 4,1 | 6,7 | -0,7 | -1,7 | -2,4 |
| Combinations of penicillins, incl. beta-lactamase inhibitors | | 3,2 | 9,1 | 5,8 | 7,7 | -1,0 | -0,9 | -1,8 |
| Fluoroquinolones | | 2,5 | 3,2 | 1,4 | 2,9 | -0,4 | -1,0 | -1,4 |
| Macrolides | | 1,9 | 4,1 | -0,3 | 2,3 | -2,0 | -0,5 | -2,5 |
| Triazole derivatives | | 1,2 | 0,8 | -0,0 | -0,2 | -0,6 | 0,8 | 0,1 |
| Other antibacterials | | 0,6 | 0,3 | 4,8 | 5,8 | -0,0 | -0,9 | -0,9 |
| Nucleosides and nucleotides excl. reverse transcriptase inhibitors | | 0,6 | 0,2 | -0,9 | 2,6 | -1,7 | -1,7 | -3,4 |
| Specific immunoglobulins | | 0,5 | 0,0 | -12,8 | -7,1 | -0,3 | -5,8 | -6,1 |
| Penicillins with extended spectrum | | 0,4 | 2,5 | -4,9 | -3,0 | -1,6 | -0,3 | -1,9 |
| Second-generation cephalosporins | | 0,2 | 0,3 | -5,2 | -5,0 | -0,8 | 0,5 | -0,3 |
| Glycopeptide antibacterials | | 0,2 | <0,1 | -2,0 | -2,0 | -0,6 | 0,6 | 0,0 |
| **BLOOD AND BLOOD FORMING ORGANS** | | **9,6** | **130,8** | **-2,9** | **10,9** | **-2,7** | **-9,9** | **-12,4** |
| Heparin group | | 4,1 | 4,2 | -7,0 | -7,5 | -0,8 | 1,3 | 0,5 |
| Platelet aggregation inhibitors excl. heparin | | 3,4 | 65,7 | 7,3 | -0,1 | -1,4 | 8,9 | 7,3 |
| Folic acid and derivatives | | 0,3 | 45,4 | 20,1 | 36,5 | 0,0 | -12,0 | -12,0 |
| Iron bivalent, oral preparations | | 0,3 | 3,2 | 3,9 | 1,3 | -0,0 | 2,6 | 2,6 |
| Vitamin K antagonists | | 0,3 | 6,6 | 2,7 | 2,8 | -0,0 | -0,2 | -0,2 |
| Blood substitutes and plasma protein fractions | | 0,3 | <0,1 | -11,7 | -11,7 | -3,5 | 3,5 | -0,1 |
| Other antianemic preparations | | 0,2 | <0,1 | -35,7 | -33,8 | -18,6 | 19,3 | -2,9 |
| Blood coagulation factors | | 0,2 | <0,1 | -30,0 | -46,0 | -35,6 | 101,2 | 29,5 |
| Solutions affecting the electrolyte balance | | 0,2 | 0,3 | 0,5 | 0,3 | -0,1 | 0,2 | 0,1 |
| Other antithrombotic agents | | 0,1 | <0,1 | -27,3 | -27,3 | -5,2 | 5,4 | -0,0 |
| **MUSCULO-SKELETAL SYSTEM** | | **8,1** | **42,4** | **-4,2** | **-0,3** | **-3,0** | **-0,9** | **-3,9** |
| Bisphosphonates | | 1,5 | 6,7 | -13,3 | -2,6 | -9,3 | -1,9 | -10,9 |
| Coxibs | | 1,5 | 4,9 | 6,2 | 5,8 | -0,0 | 0,4 | 0,4 |
| Bisphosphonates, combinations | | 1,1 | 3,3 | 4,4 | 4,5 | 0,0 | -0,1 | -0,1 |
| Propionic acid derivatives | | 1,0 | 7,7 | -0,7 | 1,6 | -0,7 | -1,6 | -2,3 |
| Acetic acid derivatives and related | | 0,9 | 5,6 | -0,7 | -0,4 | -0,1 | -0,1 | -0,3 |

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| ATC I level | Subgroups | Per capita gross expenditure | DDD/1.000 inhab. die | Δ% 13-12 | | | | Δ% Average cost DDD |
|---|---|---|---|---|---|---|---|---|
| | | | | EXp | DDD | Price | Mix | |
| substances | | | | | | | | |
| Other drugs affecting bone structure and mineralization | | 0,8 | 1,3 | -29,5 | -26,9 | -5,7 | 2,2 | -3,6 |
| Preparations inhibiting uric acid production | | 0,7 | 7,6 | 27,0 | 8,0 | -1,8 | 19,8 | 17,6 |
| Other antiinflammatory and antirheumatic agents, non-steroids | | 0,3 | 3,1 | -14,3 | -12,8 | -1,3 | -0,4 | -1,7 |
| Oxicams | | 0,2 | 1,4 | -7,0 | -7,6 | -0,6 | 1,3 | 0,7 |
| **GENITO URINARY SYSTEM AND SEX HORMONES** | | **6,9** | **42,3** | **3,0** | **1,2** | **-0,6** | **2,3** | **1,7** |
| Testosterone-5-alpha reductase inhibitors | | 2,7 | 8,6 | 6,7 | 5,6 | -0,1 | 1,1 | 1,0 |
| Alpha-adrenoreceptor antagonists | | 2,4 | 21,3 | 5,9 | 3,9 | 0,2 | 1,7 | 1,9 |
| Gonadotropins | | 0,4 | 0,2 | -12,8 | -21,8 | -8,4 | 21,7 | 11,5 |
| Other estrogens | | 0,2 | 0,7 | -1,7 | -1,7 | -0,0 | 0,0 | -0,0 |
| Progestogens and estrogens, fixed combinations | | 0,2 | 3,2 | -7,5 | -6,3 | -0,4 | -0,9 | -1,2 |
| Prolactine inhibitors | | 0,2 | 0,1 | 1,9 | 0,3 | -0,3 | 2,0 | 1,6 |
| Natural and semisynthetic estrogens, plain | | 0,2 | 2,7 | -6,3 | -5,5 | -0,7 | -0,2 | -0,9 |
| Pregnen (4) derivatives | | 0,1 | 1,3 | -1,8 | -0,9 | -0,1 | -0,7 | -0,8 |
| Antiandrogens, plain | | 0,1 | 0,2 | -4,7 | -3,7 | -0,1 | -0,9 | -1,0 |
| Progestogens and estrogens, fixed combinations | | 0,1 | 0,6 | 2,9 | 0,9 | -0,0 | 2,0 | 2,0 |
| **ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS** | | **4,2** | **4,6** | **-3,1** | **3,4** | **-3,1** | **-3,3** | **-6,3** |
| ARometase inhibitors | | 1,4 | 1,9 | 4,3 | 5,9 | -0,8 | -0,7 | -1,5 |
| Calcineurin inhibitors | | 1,1 | 0,3 | -2,9 | -2,3 | -1,1 | 0,5 | -0,6 |
| Folic acid analogues | | 0,6 | 0,4 | 3,8 | 12,3 | -1,9 | -5,7 | -7,6 |
| Colony stimulating factors | | 0,2 | <0,1 | -31,5 | -36,8 | -5,5 | 14,7 | 8,5 |
| Anti-androgens | | 0,1 | 0,3 | 6,1 | 8,1 | -6,3 | 4,8 | -1,9 |
| Other antineoplastic agents | | 0,1 | 0,2 | -6,1 | 2,4 | -1,0 | -7,4 | -8,3 |
| Selective immunosuppressants | | 0,1 | 0,1 | -11,6 | -3,6 | -6,3 | -2,2 | -8,4 |
| Other immunosuppressants | | 0,1 | 0,3 | 3,0 | 3,2 | -0,2 | 0,0 | -0,2 |
| Interferons | | 0,1 | <0,1 | -32,7 | -29,1 | -16,5 | 13,6 | -5,1 |
| Anti-estrogens | | 0,1 | 0,9 | -17,1 | 0,4 | -15,1 | -2,8 | -17,4 |
| **SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS** | | **3,6** | **34,4** | **-6,0** | **3,5** | **-5,7** | **-3,8** | **-9,2** |
| Glucocorticoids | | 1,4 | 12,7 | 5,1 | 5,3 | -0,8 | 0,6 | -0,2 |
| Thyroid hormones | | 0,8 | 20,0 | 6,3 | 3,1 | -1,0 | 4,2 | 3,1 |
| Parathyroid hormones and analogues | | 0,7 | 0,1 | -26,2 | -29,2 | -16,4 | 24,7 | 4,2 |
| Somatropin and somatropin agonists | | 0,2 | <0,1 | -17,0 | -14,2 | -6,4 | 3,5 | -3,2 |
| Somatostatin and analogues | | 0,2 | <0,1 | -22,6 | -23,0 | -11,1 | 13,1 | 0,5 |
| Vasopressin and analogues | | 0,1 | 0,1 | 2,8 | 2,0 | -0,3 | 1,2 | 0,8 |
| **SENSORY ORGANS** | | **3,6** | **19,5** | **1,4** | **1,5** | **-2,1** | **2,1** | **-0,1** |
| Beta blocking agents1) | | 2,0 | 11,1 | -0,1 | 0,1 | -3,4 | 3,4 | -0,2 |
| Prostaglandin analogues1) | | 1,3 | 5,5 | 4,8 | 4,9 | -0,3 | 0,1 | -0,1 |
| Carbonic anhydrase inhibitors | | 0,3 | 1,4 | 1,3 | 1,7 | -0,2 | -0,2 | -0,4 |
| **VARIOUS** | | **1,8** | **0,1** | **1,1** | **-1,8** | **-4,1** | **-10,9** | **3,0** |
| Medical gases | | 1,6 | | 3,0 | | | | |
| Drugs for treatment of hyperkalemia and | | 0,1 | 0,1 | -16,7 | -1,4 | -4,3 | -11,7 | -15,5 |

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| ATC I level | Subgroups | Per capita gross expenditure | DDD/1.000 inhab. die | Δ% 13-12 | | | | Δ% Average cost DDD |
|---|---|---|---|---|---|---|---|---|
| | | | | EXp | DDD | Price | Mix | |
| Hyperphosphatemia | | | | | | | | |
| **DERMATOLOGICALS** | | **1,0** | **4,3** | **3,4** | **3,9** | **-0,5** | **0,1** | **-0,4** |
| Other antipsoriatics for topical use | | 0,6 | 2,1 | 5,4 | 5,7 | -0,3 | -0,1 | -0,4 |
| **ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS** | | **0,2** | **0,8** | **2,8** | **4,4** | **-0,0** | **-1,5** | **-1,5** |
| Aminoquinolines | | 0,1 | 0,6 | 4,1 | 3,8 | -0,0 | 0,3 | 0,3 |

* The analysis does not include the parameters related to the consumption of medical gases.

**Table 6.6. Expenditure and consumption of medicines purchased by Public health facilities by ATC I level** (for each ATC I level category associated to a level of expenditure exceeding 50 million euros , a number of therapeutic groups were included in descending order of expenditure, up to the value of 0,10 euro per capita)

| ATC I level | Subgroups | Per capita NHS EXp | % | Δ% 13-12 | DDD/1000 inhab. die | % | Δ% 13-12 |
|---|---|---|---|---|---|---|---|
| **L** | **ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS** | **55,4** | | **8,4** | **8,8** | | **-0,4** |
| L01XC | Monoclonal antibodies | 11,1 | 20,1 | 8,5 | 0,6 | 7,3 | 5,3 |
| L04AB | Tumor necrosis factor alpha (TNF-) inhibitors | 9,7 | 17,6 | 6,2 | 0,9 | 9,9 | 9,9 |
| L01XE | Protein kinase inhibitors | 8,5 | 15,4 | 12,1 | 0,2 | 2,7 | 6,3 |
| L03AB | Interferons | 4,9 | 8,8 | 3,2 | 1,0 | 11,0 | 3,5 |
| L04AA | Selective immunosuppressants | 4,5 | 8,1 | 30,2 | 0,6 | 6,4 | 10,4 |
| L04AX | Other immunosuppressants | 2,3 | 4,1 | -0,4 | 0,1 | 0,9 | 6,7 |
| L02AE | Gonadotropin releasing hormone analogues | 1,8 | 3,3 | 1,0 | 2,0 | 22,9 | 3,5 |
| **J** | **ANTIINFECTIVES FOR SYSTEMIC USE** | **26,3** | | **1,4** | **6,4** | | **2,2** |
| J05AR | Antivirals for treatment of HIV infections, combinations | 5,8 | 22,1 | 15,5 | 1,0 | 16,0 | 18,0 |
| J05AE | Protease inhibitors | 3,3 | 12,6 | 10,7 | 0,5 | 8,4 | -16,7 |
| J05AF | Nucleoside and nucleotide reverse transcriptase inhibitors | 2,1 | 8,0 | 2,7 | 0,6 | 9,7 | 1,9 |
| J07CA | Bacterial and viral vaccines, combined | 1,5 | 5,7 | 6,3 | 0,1 | 1,5 | -0,9 |
| J07AL | Pneumococcal vaccines | 1,4 | 5,5 | 6,4 | 0,1 | 1,4 | 3,4 |
| J06BA | Immunoglobulins, normal human | 1,1 | 4,1 | 14,9 | 0,1 | 1,1 | 59,4 |
| J05AX | Other antivirals | 1,1 | 4,0 | 13,1 | 0,2 | 2,4 | 18,8 |
| J02AX | Other antimycotics for systemic use | 0,9 | 3,4 | 22,3 | <0,1 | 0,1 | 18,9 |
| J06BB | Specific immunoglobulins | 0,8 | 3,2 | 16,0 | <0,1 | 0,3 | 27,7 |
| J01XX | Other antibacterials | 0,8 | 3,1 | -25,2 | <0,1 | 0,5 | 10,6 |
| J07BB | Influenza vaccines | 0,8 | 3,1 | 42,5 | 0,6 | 8,6 | 16,6 |
| J01XA | Glycopeptide antibacterials | 0,7 | 2,7 | -7,2 | 0,1 | 0,9 | -16,8 |
| **B** | **BLOOD AND BLOOD FORMING ORGANS** | **19,5** | | **-1,1** | **34,0** | | **-44,7** |
| B02BD | Blood coagulation factors | 6,4 | 32,8 | -3,3 | <0,1 | 0,1 | 4,9 |
| B03XA | Other antianemic preparations | 4,7 | 23,8 | -15,3 | 2,8 | 8,1 | -0,7 |
| B01AB | Heparin group | 2,1 | 10,7 | 12,1 | 6,0 | 17,6 | 8,1 |
| B01AC | Platelet aggregation inhibitors excl. heparin | 1,7 | 8,5 | 29,8 | 5,7 | 16,8 | 21,1 |
| **A** | **ALIMENTARY TRACT AND METABOLISM** | **9,1** | | **16,7** | **26,8** | | **5,0** |
| A16AB | Enzymes | 3,0 | 32,9 | 10,4 | <0,1 | 0,0 | 16,0 |
| A10AE | Insulins and analogues for injection, long-acting | 1,8 | 20,1 | 14,9 | 4,1 | 15,2 | 15,1 |
| A10BD | Combinations of oral blood glucose lowering drugs | 1,1 | 12,0 | 40,2 | 2,5 | 9,5 | 28,3 |
| A10BX | Other blood glucose lowering drugs, excl. insulins | 0,7 | 7,2 | 29,9 | 0,8 | 3,1 | 24,5 |
| A10BH | Dipeptidyl peptidase 4 (DPP-4) inhibitors | 0,6 | 6,8 | 49,0 | 1,2 | 4,3 | 35,8 |
| **N** | **NERVOUS SYSTEM** | **9,0** | | **-3,2** | **25,0** | | **1,4** |
| N05AX | Other antipsychotics | 2,1 | 22,9 | 10,7 | 1,5 | 6,0 | 8,0 |
| N05AH | Diazepines, oxazepines, thiazepines and oxepines | 1,2 | 13,0 | -36,4 | 3,0 | 12,0 | 2,6 |
| N01BB | Amides | 1,0 | 11,3 | 57,7 | 5,1 | 20,3 | -2,6 |

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| ATC I level | Subgroups | Per capita NHS EXp | % | Δ% 13-12 | DDD/1000 inhab. die | % | Δ% 13-12 |
|---|---|---|---|---|---|---|---|
| N06DA | Anticholinesterases | 0,6 | 6,9 | -13,8 | 1,2 | 4,7 | 0,9 |
| N06DX | Other anti-dementia drugs | 0,6 | 6,3 | 22,4 | 0,6 | 2,4 | 26,2 |
| N07BC | Drugs used in opioid dependence | 0,6 | 6,2 | -2,8 | 2,9 | 11,5 | -3,3 |
| N04BA | Dopa and dopa derivatives | 0,5 | 6,1 | 10,9 | 0,4 | 1,6 | 5,5 |
| N03AX | Other antiepileptics | 0,4 | 4,6 | -12,4 | 0,6 | 2,5 | 15,6 |
| **V** | **VARIOUS** | **8,2** | | **31,4** | **1,9** | | **-12,6** |
| V03AN | Medical gases* | 3,7 | 44,7 | 87,1 | | | |
| V03AC | Iron chelating agents | 1,3 | 16,0 | 5,9 | 0,1 | 3,4 | 3,3 |
| V08AB | Water soluble, nephrotropic, low osmolar X-ray contrast media | 1,2 | 14,3 | 0,8 | 0,1 | 3,4 | 0,6 |
| **H** | **SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS** | **4,5** | | **5,2** | **5,5** | | **0,0** |
| H01AC | Somatropin and somatropin agonists | 1,5 | 32,9 | -6,2 | 0,3 | 4,5 | -4,9 |
| H01CB | Somatostatin and analogues | 1,2 | 26,7 | 3,6 | 0,2 | 2,9 | 5,2 |
| H05BX | Other anti-parathyroid agents | 0,8 | 18,1 | 8,3 | 0,2 | 4,5 | 9,9 |
| **C** | **CARDIOVASCULAR SYSTEM** | **3,1** | | **10,6** | **17,0** | | **3,0** |
| C02KX | Other antihypertensives | 1,7 | 54,4 | 5,6 | 0,1 | 0,3 | 4,6 |
| C01EB | Other cardiac preparations | 0,7 | 23,0 | 43,8 | 1,1 | 6,3 | 43,0 |
| **G** | **GENITO URINARY SYSTEM AND SEX HORMONES** | **1,8** | | **3,5** | **1,7** | | **-2,9** |
| G03GA | Gonadotropins | 1,2 | 64,8 | 0,6 | 0,2 | 11,3 | -3,1 |
| G04BE | Drugs used in erectile dysfunction | 0,3 | 14,1 | 10,5 | 0,1 | 4,8 | 15,4 |
| **S** | **SENSORY ORGANS** | **1,7** | | **52,7** | **2,0** | | **0,2** |
| S01LA | Antineovascularisation agents | 1,5 | 84,8 | 58,0 | 0,2 | 7,4 | 116,3 |
| **M** | **MUSCULO-SKELETAL SYSTEM** | **1,1** | | **-23,2** | **2,5** | | **4,3** |
| M05BA | Bisphosphonates | 0,5 | 48,0 | -35,5 | 0,1 | 4,8 | -13,2 |
| M03AX | Other muscle relaxants, peripherally acting agents | 0,2 | 16,2 | 9,3 | <0,1 | 0,1 | 11,2 |
| M03AC | Other quaternary ammonium compounds | 0,1 | 13,1 | -29,4 | 0,1 | 4,4 | 2,6 |
| **R** | **RESPIRATORY SYSTEM** | **0,9** | | **4,5** | **3,2** | | **1,4** |
| R03DX | Other systemic drugs for obstructive airway diseases | 0,3 | 32,0 | 19,9 | <0,1 | 1,1 | 21,8 |
| R05CB | Mucolytics | 0,2 | 17,3 | 1,1 | 0,3 | 7,9 | 1,8 |
| R03BB | Anticholinergics | 0,1 | 14,1 | 5,8 | 0,9 | 28,3 | 4,9 |
| R03AK | Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics | 0,1 | 11,3 | 0,7 | 0,3 | 9,9 | -24,3 |
| **D** | **DERMATOLOGICALS** | **0,4** | | **6,7** | **16,0** | | **8,5** |

* The analysis does not include the parameters related to the consumption of medical gases.

# SECTION 7
# DETAILED ANALYSIS OF PHARMACEUTICAL EXPENDITURE AND CONSUMPTION

## 7.2. Therapeutic categories and active ingredients

An analysis of the most prescribed active ingredients purchased by public health facilities in 2013 is included in the following tables.

**Table 7.2.19.** First thirty active ingredients in terms of outpatient NHS expenditure: comparison 2009-2013

| ATC | Active ingredient | EXp (million) | % | Rank 2013 | Rank 2012 | Rank 2011 | Rank 2010 | Rangk 2009 |
|---|---|---|---|---|---|---|---|---|
| C | rosuvastatin | 305 | 2,7 | 1 | 1 | 2 | 2 | 4 |
| R | salmeterol and fluticasone | 286 | 2,5 | 2 | 2 | 3 | 3 | 2 |
| A | pantoprazole | 264 | 2,4 | 3 | 5 | 7 | 10 | 13 |
| A | lansoprazole | 261 | 2,3 | 4 | 3 | 4 | 4 | 3 |
| A | omeprazole | 201 | 1,8 | 5 | 7 | 8 | 8 | 7 |
| J | amoxicillin and enzyme inhibitor | 182 | 1,6 | 6 | 8 | 9 | 11 | 9 |
| C | omega-3-triglycerides incl. other esters and acids | 177 | 1,6 | 7 | 6 | 5 | 7 | 8 |
| R | tiotropium bromide | 164 | 1,5 | 8 | 9 | 12 | 13 | 15 |
| C | atorvastatin | 163 | 1,5 | 9 | 4 | 1 | 1 | 1 |
| B | enoxaparin | 154 | 1,4 | 10 | 10 | 13 | 18 | 22 |
| A | esomeprazole | 152 | 1,4 | 11 | 15 | 14 | 5 | 5 |
| C | simvastatin and ezetimibe | 152 | 1,4 | 12 | 13 | 16 | 19 | 21 |
| C | olmesartan medoxomil | 140 | 1,3 | 13 | 16 | 18 | 22 | 28 |
| N | escitalopram | 133 | 1,2 | 14 | 14 | 17 | 20 | 20 |
| C | irbesartan and diuretics | 130 | 1,2 | 15 | 12 | 10 | 9 | 10 |
| G | dutasteride | 125 | 1,1 | 16 | 18 | 31 | 38 | 47 |
| C | olmesartan medoxomil and diuretics | 124 | 1,1 | 17 | 20 | 29 | 35 | 66 |
| C | ramipril | 121 | 1,1 | 18 | 17 | 21 | 23 | 25 |
| N | pregabalin | 114 | 1,0 | 19 | 24 | 34 | 41 | 56 |
| C | simvastatin | 112 | 1,0 | 20 | 19 | 19 | 17 | 16 |
| C | telmisartan | 108 | 1,0 | 21 | 21 | 25 | 26 | 31 |
| N | duloxetine | 104 | 0,9 | 22 | 27 | 36 | 33 | 44 |
| B | acetylsalicylic acid | 99 | 0,9 | 23 | 25 | 32 | 28 | 32 |
| V | oxygen | 97 | 0,9 | 24 | 30 | 24 | 70 | 771 |
| C | amlodipine | 97 | 0,9 | 25 | 29 | 22 | 16 | 11 |
| R | formoterol and beclometasone | 96 | 0,9 | 26 | 11 | 11 | 12 | 14 |
| C | bisoprolol | 94 | 0,8 | 27 | 38 | - | - | - |
| S | timolol, combinations | 90 | 0,8 | 28 | 32 | 37 | 29 | 39 |
| A | insulin aspart | 90 | 0,8 | 29 | 23 | - | - | - |
| J | ceftriaxone | 90 | 0,8 | 30 | 35 | - | - | - |
| | **Total** | **4.424** | **39,5** | | | | | |
| | **Total Class A-NHS expenditure** | **11.202** | | | | | | |

**Table 7.2.20.** First thirty active ingredients in terms of outpatient NHS consumption: comparison 2009-2013

| ATC | Active ingredient | DDD/1000 Inhab. die | % | Rank 2013 | Rank 2012 | Rank 2011 | Rank 2010 | Rank 2009 |
|---|---|---|---|---|---|---|---|---|
| C | ramipril | 58,7 | 5,6 | 1 | 1 | 1 | 2 | 2 |
| B | acetylsalicylic acid | 55,9 | 5,4 | 2 | 2 | 2 | 1 | 1 |
| B | folic acid | 45,4 | 4,4 | 3 | 3 | - | - | - |
| C | atorvastatin | 27,6 | 2,6 | 4 | 5 | 6 | 7 | 8 |
| C | amlodipine | 27,5 | 2,6 | 5 | 4 | 3 | 3 | 3 |
| C | furosemide | 23,4 | 2,2 | 6 | 6 | 4 | 4 | 4 |
| A | lansoprazole | 21,4 | 2,0 | 7 | 7 | 5 | 5 | 5 |
| H | levothyroxine sodium | 20,0 | 2,0 | 8 | 8 | 7 | 6 | 6 |
| A | omeprazole | 19,6 | 1,8 | 9 | 9 | 8 | 9 | 11 |
| A | metformin | 19,4 | 1,8 | 10 | 10 | 9 | 8 | 10 |
| A | pantoprazole | 18,4 | 1,8 | 11 | 11 | 13 | 19 | 23 |
| C | simvastatin | 15,7 | 1,6 | 12 | 13 | 11 | 13 | 12 |
| C | rosuvastatin | 15,0 | 1,4 | 13 | 12 | 10 | 12 | 13 |
| C | valsartan | 14,3 | 1,4 | 14 | 14 | 15 | 14 | 17 |
| C | nebivolol | 13,1 | 1,2 | 15 | 16 | 16 | 17 | 18 |
| C | enalapril | 12,7 | 1,2 | 16 | 15 | 12 | 10 | 7 |
| A | esomeprazole | 12,4 | 1,2 | 17 | 19 | 25 | 33 | 34 |
| C | valsartan and diuretics | 11,5 | 1,2 | 18 | 18 | 17 | 16 | 16 |
| C | glyceryl trinitrate | 11,3 | 1,0 | 19 | 17 | 14 | 11 | 9 |
| C | atenolol | 10,4 | 1,0 | 20 | 20 | 19 | 18 | 15 |
| C | lercanidipine | 9,5 | 1,0 | 21 | 21 | 20 | 21 | 22 |
| C | telmisartan | 9,3 | 1,0 | 22 | 23 | 23 | 24 | 27 |
| C | irbesartan | 9,2 | 0,8 | 23 | 22 | 21 | 20 | 21 |
| G | tamsulosin | 9,1 | 0,8 | 24 | 24 | 22 | 23 | 26 |
| J | amoxicillin and enzyme inhibitor | 9,1 | 0,8 | 25 | 25 | 24 | 27 | 25 |
| C | ramipril and diuretics | 8,0 | 0,8 | 26 | 27 | 27 | 29 | 30 |
| C | candesartan | 7,9 | 0,8 | 27 | 26 | 26 | 25 | 24 |
| N | paroxetine | 7,7 | 0,8 | 28 | 29 | 31 | 32 | 31 |
| C | losartan | 7,7 | 0,8 | 29 | 28 | 34 | 40 | 46 |
| C | doxazosin | 7,6 | 0,8 | 30 | 30 | 30 | 30 | 28 |
| | **Total** | **538,7** | **52,2** | | | | | |
| | **Total Class A - DDD** | **1.031,5** | | | | | | |

**Table 7.2.21.** ATC level 1 categories, sorted by outpatient NHS consumption and expenditure (up to 75% of the expenditure within the therapeutic category) and grouping the related active ingredients in 2013

| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| **CARDIOVASCULAR SYSTEM** | **60,4** | | **-5,9** | **468,0** | | **0,9** |
| rosuvastatin | 5,1 | 8,5 | -6,5 | 15,0 | 3,2 | -5,9 |
| omega-3-triglycerides incl. other esters and acids | 3,0 | 4,9 | -19,6 | 4,4 | 0,9 | -19,4 |
| atorvastatin | 2,7 | 4,5 | -31,8 | 27,6 | 5,9 | 18,9 |
| simvastatin and ezetimibe | 2,5 | 4,2 | 6,6 | 3,4 | 0,7 | 6,8 |
| olmesartan medoxomil | 2,3 | 3,9 | 6,0 | 6,9 | 1,5 | 9,7 |
| irbesartan and diuretics | 2,2 | 3,6 | -13,9 | 7,2 | 1,5 | -3,8 |
| olmesartan medoxomil and diuretics | 2,1 | 3,4 | 10,9 | 6,2 | 1,3 | 11,2 |
| ramipril | 2,0 | 3,4 | 1,8 | 58,7 | 12,5 | 3,4 |
| simvastatin | 1,9 | 3,1 | -0,8 | 15,7 | 3,4 | 0,7 |
| telmisartan | 1,8 | 3,0 | -1,2 | 9,3 | 2,0 | 1,7 |
| amlodipine | 1,6 | 2,7 | -0,6 | 27,5 | 5,9 | 0,9 |
| bisoprolol | 1,6 | 2,6 | 11,4 | 7,4 | 1,6 | 10,2 |
| telmisartan and diuretics | 1,4 | 2,3 | 3,0 | 4,8 | 1,0 | 3,5 |
| glyceryl trinitrate | 1,4 | 2,3 | -9,7 | 11,3 | 2,4 | -8,4 |
| valsartan and diuretics | 1,4 | 2,3 | -12,6 | 11,5 | 2,5 | 0,9 |
| nebivolol | 1,3 | 2,1 | 2,3 | 13,1 | 2,8 | 3,6 |
| doxazosin | 1,2 | 2,1 | -1,3 | 7,6 | 1,6 | -0,3 |
| valsartan | 0,9 | 1,5 | -11,8 | 14,3 | 3,1 | 4,4 |
| losartan | 0,9 | 1,5 | -0,6 | 7,7 | 1,7 | 1,3 |
| zofenopril and diuretics | 0,9 | 1,4 | 7,6 | 3,7 | 0,8 | 7,9 |
| olmesartan medoxomil and amlodipine | 0,8 | 1,4 | 0,1 | 2,3 | 0,5 | -2,6 |
| barnidipine | 0,8 | 1,3 | -1,4 | 4,3 | 0,9 | 2,4 |
| lercanidipine | 0,8 | 1,3 | -3,0 | 9,5 | 2,0 | -1,4 |
| ramipril and diuretics | 0,8 | 1,3 | -3,1 | 8,0 | 1,7 | -0,1 |
| irbesartan | 0,8 | 1,3 | -53,1 | 9,2 | 2,0 | -2,7 |
| carvedilol | 0,8 | 1,3 | -3,9 | 4,1 | 0,9 | -3,0 |
| losartan and diuretics | 0,7 | 1,2 | -4,0 | 6,2 | 1,3 | -2,9 |
| enalapril | 0,7 | 1,2 | -6,7 | 12,7 | 2,7 | -5,6 |
| furosemide | 0,7 | 1,1 | 1,9 | 23,4 | 5,0 | 2,4 |
| ezetimibe | 0,6 | 1,1 | 81,8 | 1,0 | 0,2 | 77,7 |
| **ALIMENTARY TRACT AND METABOLISM** | **32,6** | | **1,6** | **152,2** | | **2,6** |
| pantoprazole | 4,4 | 13,6 | 12,0 | 18,4 | 12,1 | 14,5 |
| lansoprazole | 4,4 | 13,4 | -2,7 | 21,4 | 14,0 | -1,2 |
| omeprazole | 3,4 | 10,3 | 2,1 | 19,6 | 12,9 | 3,6 |
| esomeprazole | 2,5 | 7,8 | 11,2 | 12,4 | 8,2 | 12,8 |
| insulin aspart | 1,5 | 4,6 | 1,2 | 3,0 | 1,9 | 1,5 |
| mesalazine | 1,5 | 4,5 | 4,6 | 3,7 | 2,4 | 5,0 |
| insulin lispro | 1,5 | 4,5 | 5,0 | 2,9 | 1,9 | 5,3 |
| rifaximin | 1,4 | 4,2 | 16,9 | 1,8 | 1,2 | 5,7 |
| metformin | 1,3 | 4,0 | 1,4 | 19,4 | 12,7 | 3,4 |
| colecalciferol | 1,2 | 3,8 | 48,9 | 1,0 | 0,7 | 30,8 |
| alginic acid | 0,7 | 2,3 | 6,4 | 1,8 | 1,2 | 6,3 |
| ursodeoxycholic acid | 0,6 | 1,9 | 2,4 | 2,0 | 1,3 | 4,1 |
| insulin glargine | 0,5 | 1,7 | -12,8 | 0,7 | 0,5 | -12,6 |

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| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| **NERVOUS SYSTEM** | **23,4** | | **-2,5** | **60,4** | | **1,9** |
| escitalopram | 2,2 | 9,5 | -5,1 | 7,3 | 12,0 | -0,7 |
| pregabalin | 1,9 | 8,1 | 6,9 | 1,4 | 2,4 | 6,9 |
| duloxetine | 1,7 | 7,4 | 4,0 | 2,5 | 4,2 | 4,5 |
| paroxetine | 1,2 | 5,2 | 0,6 | 7,7 | 12,8 | 1,4 |
| levetiracetam | 1,0 | 4,5 | -38,0 | 1,3 | 2,2 | 9,1 |
| fentanyl | 1,0 | 4,4 | 10,7 | 0,5 | 0,9 | 5,5 |
| valproic acid | 0,8 | 3,5 | 4,3 | 2,0 | 3,3 | 4,2 |
| venlafaxine | 0,7 | 3,2 | 1,2 | 3,2 | 5,3 | 2,7 |
| oxycodone, combinations | 0,7 | 3,2 | 37,4 | 0,5 | 0,8 | 22,7 |
| rasagiline | 0,7 | 2,8 | 8,1 | 0,4 | 0,6 | 8,4 |
| sertraline | 0,6 | 2,7 | 2,5 | 6,5 | 10,7 | 5,0 |
| rotigotine | 0,6 | 2,5 | 12,0 | 0,3 | 0,5 | 12,9 |
| pramipexole | 0,6 | 2,4 | -5,6 | 0,6 | 0,9 | -6,2 |
| citalopram | 0,5 | 2,1 | -5,0 | 4,6 | 7,6 | -3,2 |
| levodopa and decarboxylase inhibitor | 0,4 | 1,9 | 0,5 | 1,5 | 2,6 | 1,9 |
| tapentadol | 0,4 | 1,8 | 61,0 | 0,2 | 0,3 | 58,0 |
| rizatriptan | 0,4 | 1,7 | -11,4 | 0,2 | 0,3 | 5,4 |
| codeine, combinations excl. psycholeptics | 0,4 | 1,5 | 5,3 | 1,3 | 2,2 | 14,4 |
| lamotrigine | 0,3 | 1,5 | 0,3 | 0,5 | 0,9 | 1,2 |
| tramadol | 0,3 | 1,5 | -3,0 | 0,7 | 1,2 | -2,5 |
| topiramate | 0,3 | 1,4 | -43,9 | 0,3 | 0,6 | -2,2 |
| almotriptan | 0,3 | 1,3 | 2,0 | 0,2 | 0,3 | 2,3 |
| gabapentin | 0,3 | 1,3 | 0,0 | 0,4 | 0,6 | 0,6 |
| **RESPIRATORY SYSTEM** | **17,1** | | **-3,8** | **48,5** | | **0,8** |
| salmeterol and fluticasone | 4,8 | 27,9 | 0,0 | 5,8 | 11,9 | 0,2 |
| tiotropium bromide | 2,7 | 16,0 | -2,7 | 4,4 | 9,1 | -2,5 |
| formoterol and beclometasone | 1,6 | 9,4 | 9,8 | 2,5 | 5,1 | 10,2 |
| beclometasone | 1,4 | 8,3 | 5,6 | 6,6 | 13,5 | 6,2 |
| formoterol and budesonide | 1,2 | 7,2 | -3,8 | 1,4 | 2,9 | -3,6 |
| montelukast | 0,6 | 3,6 | -57,7 | 2,1 | 4,3 | -2,6 |
| fluticasone | 0,4 | 2,6 | -1,5 | 1,1 | 2,2 | -1,6 |
| **ANTIINFECTIVES FOR SYSTEMIC USE** | **15,0** | | **1,1** | **23,2** | | **3,7** |
| amoxicillin and enzyme inhibitor | 3,0 | 20,2 | 5,6 | 9,1 | 39,1 | 7,5 |
| ceftriaxone | 1,5 | 10,0 | 1,6 | 0,4 | 1,5 | 2,8 |
| ciprofloxacin | 1,1 | 7,0 | 5,3 | 1,0 | 4,5 | 5,5 |
| clarithromycin | 1,0 | 6,6 | -3,8 | 2,6 | 11,4 | 0,6 |
| fluconazole | 0,9 | 6,2 | 1,2 | 0,4 | 1,9 | 2,6 |
| levofloxacin | 0,9 | 6,1 | 1,0 | 1,7 | 7,2 | 4,3 |
| cefixime | 0,9 | 5,9 | 5,8 | 1,0 | 4,4 | 7,5 |
| azithromycin | 0,7 | 4,7 | 4,0 | 1,3 | 5,6 | 5,3 |
| fosfomycin | 0,6 | 3,8 | 4,2 | 0,3 | 1,5 | 5,5 |
| hepatitis B immunoglobulin | 0,5 | 3,1 | -14,2 | 0,0 | 0,0 | -13,0 |
| prulifloxacin | 0,4 | 2,4 | -4,6 | 0,2 | 1,0 | -4,3 |
| **BLOOD AND BLOOD FORMING ORGANS** | **9,6** | | **-3,3** | **130,8** | | **10,6** |
| enoxaparin | 2,6 | 26,7 | -6,4 | 2,7 | 2,1 | -6,2 |
| acetylsalicylic acid | 1,7 | 17,1 | -4,4 | 55,9 | 42,8 | -1,2 |
| nadroparin | 1,0 | 10,5 | -0,9 | 0,9 | 0,7 | -0,6 |
| clopidogrel | 0,8 | 7,9 | 30,6 | 3,3 | 2,5 | 31,8 |
| ticlopidine | 0,5 | 5,0 | -13,3 | 5,3 | 4,1 | -11,9 |

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| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| folic acid | 0,3 | 3,5 | 19,5 | 45,4 | 34,7 | 36,2 |
| parnaparin | 0,3 | 3,2 | 17,3 | 0,3 | 0,2 | 17,8 |
| combinations | 0,3 | 2,9 | 45,2 | 0,9 | 0,7 | 40,5 |
| **MUSCULO-SKELETAL SYSTEM** | **8,1** | | **-4,6** | **42,4** | | **-0,5** |
| etoricoxib | 1,2 | 14,4 | 10,7 | 3,7 | 8,7 | 10,4 |
| alendronic acid and colecalciferol | 1,1 | 13,3 | 3,9 | 3,3 | 7,8 | 4,3 |
| strontium ranelate | 0,8 | 9,3 | -32,4 | 1,2 | 2,8 | -29,6 |
| diclofenac | 0,6 | 7,4 | -0,6 | 4,1 | 9,7 | -0,3 |
| risedronic acid | 0,6 | 7,3 | -9,5 | 2,8 | 6,6 | -4,8 |
| alendronic acid | 0,6 | 7,2 | -3,0 | 2,7 | 6,3 | -1,7 |
| ketoprofen | 0,5 | 5,6 | -0,9 | 4,2 | 10,0 | 2,4 |
| febuxostat | 0,4 | 5,5 | 47,7 | 0,8 | 1,9 | 47,9 |
| celecoxib | 0,4 | 4,5 | -7,6 | 1,2 | 2,8 | -7,4 |
| ibuprofen | 0,3 | 4,1 | -3,5 | 2,1 | 5,0 | -1,0 |
| **GENITO URINARY SYSTEM AND SEX HORMONES** | **6,9** | | **2,5** | **42,3** | | **1,0** |
| dutasteride | 2,1 | 30,5 | 10,0 | 5,9 | 13,9 | 10,3 |
| tamsulosin | 1,0 | 14,1 | -1,2 | 9,1 | 21,6 | 0,5 |
| alfuzosin | 0,7 | 10,4 | -1,1 | 7,5 | 17,6 | -0,1 |
| finasteride | 0,6 | 8,8 | -5,1 | 2,7 | 6,4 | -3,7 |
| silodosin | 0,5 | 7,1 | 51,5 | 2,6 | 6,1 | 47,8 |
| terazosin | 0,2 | 3,3 | -7,0 | 1,8 | 4,3 | -5,5 |
| tibolone | 0,2 | 2,9 | -2,2 | 0,7 | 1,7 | -1,9 |
| **ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS** | **4,2** | | **-3,6** | **4,6** | | **3,2** |
| ciclosporin | 1,0 | 24,3 | -2,0 | 0,3 | 5,8 | -1,8 |
| letrozole | 0,8 | 18,9 | 9,1 | 0,9 | 20,2 | 10,5 |
| methotrexate | 0,6 | 15,1 | 3,3 | 0,4 | 7,9 | 12,1 |
| anastrozole | 0,4 | 10,2 | -3,7 | 0,8 | 16,7 | 1,3 |
| exemestane | 0,2 | 4,2 | 0,7 | 0,2 | 4,5 | 1,9 |
| bicalutamide | 0,1 | 3,3 | 6,9 | 0,3 | 5,9 | 9,3 |
| **SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS** | **3,6** | | **-6,5** | **34,4** | | **3,3** |
| levothyroxine sodium | 0,8 | 22,6 | 5,4 | 20,0 | 57,9 | 2,9 |
| teriparatide | 0,7 | 18,9 | -9,4 | 0,1 | 0,3 | -9,1 |
| prednisone | 0,6 | 17,4 | 4,4 | 5,7 | 16,5 | 4,7 |
| betamethasone | 0,4 | 9,9 | 5,9 | 2,2 | 6,3 | 6,7 |
| somatropin | 0,2 | 6,2 | -17,4 | 0,0 | 0,1 | -14,4 |
| methylprednisolone | 0,2 | 6,1 | 2,5 | 3,4 | 10,0 | 4,4 |
| **SENSORY ORGANS** | **3,6** | | **0,9** | **19,5** | | **1,3** |
| timolol, combinations | 1,5 | 42,1 | -1,3 | 6,3 | 32,4 | 2,5 |
| bimatoprost | 0,4 | 11,5 | 8,9 | 1,7 | 8,7 | 9,6 |
| travoprost | 0,3 | 9,3 | -2,8 | 1,1 | 5,8 | -2,5 |
| latanoprost | 0,3 | 8,2 | -9,4 | 1,9 | 9,7 | -3,5 |
| timolol | 0,3 | 7,8 | 0,3 | 3,2 | 16,5 | -4,8 |
| **VARIOUS** | **1,8** | | **0,6** | **0,1** | | **-2,0** |
| oxygen | 1,6 | 91,9 | 2,5 | | | |
| DERMATOLOGICALS | **1,0** | | **2,9** | **4,3** | | **3,7** |
| calcipotriol, combinations | 0,5 | 50,3 | 10,1 | 1,6 | 37,4 | 10,4 |
| terbinafine | 0,1 | 8,4 | -4,6 | 0,2 | 3,8 | -2,9 |

>

| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| calcipotriol | 0,1 | 8,3 | -9,6 | 0,3 | 7,4 | -8,1 |
| isotretinoin | 0,1 | 6,6 | 6,4 | 0,1 | 2,9 | 6,8 |
| tacalcitol | 0,1 | 5,5 | -9,5 | 0,1 | 2,7 | -8,0 |
| ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS | **0,2** | | **2,3** | **0,8** | | **4,2** |
| hydroxychloroquine | 0,1 | 57,2 | 3,9 | 0,6 | 79,8 | 4,2 |
| mefloquine | 0,0 | 19,1 | -6,0 | 0,0 | 1,1 | -5,7 |

*Expenditure and consumption percentages are calculated on the total of the ATC category

^ Medical gas DDD value is not available

**Table 7.2.22.** ATC I level categories, sorted by public health facilities expenditure and consumption and grouping the related active ingredients (up to 75% of the expenditure within the therapeutic category), in 2013

| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| **L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS** | **55,37** | | **8,4** | **8,8** | | **-0,4** |
| L01XC03 trastuzumab | 4,02 | 7,3 | 0,3 | 0,1 | 1,5 | 0,5 |
| L04AB04 adalimumab | 3,83 | 6,9 | 13,3 | 0,3 | 3,2 | 14,4 |
| L04AB01 etanercept | 3,72 | 6,7 | 0,2 | 0,3 | 3,2 | 0,1 |
| L03AB07 interferon beta-1a | 3,25 | 5,9 | 10,4 | 0,7 | 8,1 | 6,1 |
| L01XC02 rituximab | 3,18 | 5,7 | 6,4 | 0,4 | 4,6 | 6,8 |
| L01XE01 imatinib | 2,98 | 5,4 | -1,6 | 0,1 | 1,3 | -1,3 |
| L01XC07 bevacizumab | 2,39 | 4,3 | 15,1 | 0,1 | 0,9 | 7,4 |
| L04AX04 lenalidomide | 2,14 | 3,9 | -2,6 | 0,0 | 0,4 | 7,9 |
| L04AB02 infliximab | 1,50 | 2,7 | -6,4 | 0,2 | 2,8 | 9,8 |
| L01XX32 bortezomib | 1,34 | 2,4 | 14,3 | 0,1 | 1,2 | 14,6 |
| L01BA04 pemetrexed | 1,20 | 2,2 | -5,8 | 0,0 | 0,4 | -1,6 |
| L04AA27 fingolimod | 1,09 | 2,0 | 128,8 | 0,0 | 0,6 | 129,3 |
| L04AA23 natalizumab | 1,08 | 1,9 | 30,5 | 0,1 | 0,6 | 10,4 |
| L04AA25 eculizumab | 1,00 | 1,8 | 14,8 | 0,0 | 0,0 | 14,1 |
| L03AX13 glatiramer acetate | 1,00 | 1,8 | 10,5 | 0,1 | 1,2 | 11,2 |
| L02AE02 leuprorelin | 1,00 | 1,8 | 1,8 | 1,2 | 13,9 | 5,4 |
| L01XC06 cetuximab | 0,94 | 1,7 | -2,3 | 0,0 | 0,2 | -1,9 |
| L01XE08 nilotinib | 0,91 | 1,6 | 32,7 | 0,0 | 0,2 | 34,4 |
| L01XE04 sunitinib | 0,91 | 1,6 | 9,5 | 0,0 | 0,2 | -0,6 |
| L03AB11 peginterferon alfa-2a | 0,85 | 1,5 | -12,9 | 0,1 | 1,0 | -9,3 |
| L02AE04 triptorelin | 0,81 | 1,5 | 0,9 | 0,7 | 8,5 | 1,2 |
| L01XE06 dasatinib | 0,80 | 1,5 | 22,1 | 0,0 | 0,2 | 22,5 |
| L03AA13 pegfilgrastim | 0,79 | 1,4 | -1,2 | 0,1 | 0,7 | 2,5 |
| L01XE05 sorafenib | 0,65 | 1,2 | -4,8 | 0,0 | 0,2 | -5,0 |
| L04AD02 tacrolimus | 0,63 | 1,1 | 23,4 | 0,2 | 2,5 | 10,3 |
| **J ANTIINFECTIVES FOR SYSTEMIC USE** | **26,34** | | **1,4** | **6,4** | | **2,2** |
| J05AR03 tenofovir disoproxil and emtricitabine | 2,19 | 8,3 | -0,7 | 0,4 | 6,4 | -0,4 |
| J05AR06 emtricitabine, tenofovir disoproxil and efavirenz | 1,68 | 6,4 | 1,4 | 0,2 | 3,3 | 1,7 |
| J07AL02 pneumococcus, purified polysaccharides antigen conjugated | 1,41 | 5,4 | 7,7 | 0,1 | 1,3 | 6,8 |

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| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| J07CA09 diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B | 1,30 | 4,9 | 6,1 | 0,1 | 1,1 | -3,4 |
| J05AE08 atazanavir | 1,14 | 4,3 | -4,2 | 0,3 | 4,3 | -1,5 |
| J05AF10 entecavir | 1,03 | 3,9 | 13,6 | 0,2 | 3,5 | 13,2 |
| J05AR02 lamivudine and abacavir | 1,01 | 3,8 | 25,8 | 0,2 | 3,0 | 18,5 |
| J05AE10 darunavir | 0,97 | 3,7 | 22,1 | 0,2 | 2,4 | 23,8 |
| J07BB02 influenza, inactivated, split virus or surface antigen | 0,81 | 3,1 | 42,5 | 0,6 | 8,6 | 16,6 |
| J05AX08 raltegravir | 0,78 | 3,0 | 13,5 | 0,1 | 2,1 | 19,7 |
| J06BA02 immunoglobulins, normal human, for intravascular adm. | 0,77 | 2,9 | 2,2 | 0,0 | 0,1 | 2,5 |
| J01XA02 teicoplanin | 0,69 | 2,6 | -4,8 | 0,0 | 0,7 | -4,5 |
| J05AF07 tenofovir disoproxil | 0,68 | 2,6 | 8,8 | 0,2 | 3,2 | 9,1 |
| J05AE11 telaprevir | 0,60 | 2,3 | | 0,0 | 0,1 | |
| J02AX04 caspofungin | 0,58 | 2,2 | 21,6 | 0,0 | 0,1 | 16,5 |
| J01XX08 linezolid | 0,54 | 2,1 | -37,5 | 0,0 | 0,2 | 1,2 |
| J05AR10 lopinavir and ritonavir | 0,52 | 2,0 | | 0,1 | 1,9 | |
| J02AA01 amphotericin B | 0,44 | 1,7 | 1,0 | 0,0 | 0,2 | 2,4 |
| J06BB16 palivizumab | 0,42 | 1,6 | 1,6 | 0,0 | 0,0 | 2,3 |
| J02AC03 voriconazole | 0,41 | 1,6 | 8,0 | 0,0 | 0,2 | 8,0 |
| J01AA12 tigecycline | 0,36 | 1,4 | -36,3 | 0,0 | 0,1 | 12,1 |
| J01DH02 meropenem | 0,35 | 1,3 | -23,1 | 0,1 | 1,0 | 0,5 |
| J07BM01 papillomavirus (human types 6, 11, 16, 18) | 0,32 | 1,2 | -6,7 | 0,0 | 0,3 | -5,7 |
| J06BB04 hepatitis B immunoglobulin | 0,32 | 1,2 | 42,0 | 0,0 | 0,1 | 48,1 |
| J07BM02 papillomavirus (human types 16, 18) | 0,32 | 1,2 | -0,6 | 0,0 | 0,2 | -10,9 |
| J05AG01 nevirapine | 0,31 | 1,2 | 14,2 | 0,1 | 2,1 | 12,2 |
| **B BLOOD AND BLOOD FORMING ORGANS** | **19,54** | | **-1,1** | **34,0** | | **-44,7** |
| B02BD02 coagulation factor VIII | 4,11 | 21,0 | 1,4 | 0,0 | 0,1 | 4,0 |
| B03XA01 erythropoietin | 2,60 | 13,3 | -17,0 | 1,9 | 5,6 | 1,9 |
| B03XA02 darbepoetin alfa | 1,87 | 9,6 | -12,4 | 0,8 | 2,3 | -5,1 |
| B01AB05 enoxaparin | 1,32 | 6,8 | 19,5 | 4,4 | 12,8 | 22,0 |
| B02BD08 eptacog alfa (activated) | 1,15 | 5,9 | 9,6 | 0,0 | 0,0 | 9,9 |
| B05BB01 electrolytes | 0,87 | 4,5 | 8,0 | 8,3 | 24,3 | -76,2 |
| B05BA10 combinations | 0,58 | 3,0 | -6,6 | 0,1 | 0,4 | -89,8 |
| B02BD09 nonacog alfa | 0,51 | 2,6 | -38,5 | 0,0 | 0,0 | -0,9 |
| B01AC21 treprostinil | 0,41 | 2,1 | 39,2 | 0,0 | 0,0 | 20,4 |
| B05AA01 albumin | 0,37 | 1,9 | 5,1 | 0,0 | 0,1 | -42,4 |
| B02BD03 factor VIII inhibitor bypassing activity | 0,31 | 1,6 | -17,7 | 0,0 | 0,0 | -15,2 |
| B01AB06 nadroparin | 0,29 | 1,5 | 33,9 | 0,7 | 2,0 | 29,7 |
| B01AC04 clopidogrel | 0,26 | 1,3 | 10,8 | 2,6 | 7,7 | 22,5 |
| **A ALIMENTARY TRACT AND METABOLISM** | **9,14** | | **16,7** | **26,8** | | **5,0** |
| A10AE04 insulin glargine | 1,43 | 15,7 | 14,2 | 3,2 | 11,9 | 14,5 |
| A16AB07 alglucosidase alfa | 0,77 | 8,5 | 8,4 | 0,0 | 0,0 | 8,1 |
| A16AB03 agalsidase alfa | 0,66 | 7,2 | 5,3 | 0,0 | 0,0 | 5,8 |
| A16AB02 imiglucerase | 0,64 | 7,0 | 8,0 | 0,0 | 0,0 | 8,2 |
| A10BX07 liraglutide | 0,55 | 6,0 | 46,8 | 0,6 | 2,1 | 46,7 |
| A10BD07 metformin and sitagliptin | 0,49 | 5,4 | 56,6 | 1,0 | 3,7 | 45,4 |
| A16AB09 idursulfase | 0,42 | 4,6 | 7,4 | 0,0 | 0,0 | 9,6 |

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| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| A10BH01 sitagliptin | 0,41 | 4,5 | 51,4 | 0,8 | 2,8 | 33,5 |
| A10AE05 insulin detemir | 0,41 | 4,5 | 17,3 | 0,9 | 3,4 | 17,4 |
| A10BD05 metformin and pioglitazone | 0,31 | 3,4 | 7,3 | 0,9 | 3,2 | 8,4 |
| A10BD08 metformin and vildagliptin | 0,25 | 2,7 | 67,2 | 0,5 | 1,7 | 62,7 |
| A02BC02 pantoprazole | 0,18 | 2,0 | 33,2 | 1,5 | 5,4 | 22,7 |
| A16AB04 agalsidase beta | 0,17 | 1,9 | 97,6 | 0,0 | 0,0 | 98,2 |
| A16AB10 velaglucerase alfa | 0,15 | 1,6 | 9,4 | 0,0 | 0,0 | 14,6 |
| A10BH03 saxagliptin | 0,12 | 1,3 | 24,2 | 0,2 | 0,8 | 20,6 |
| **N NERVOUS SYSTEM** | **9,01** | | **-3,2** | **25,0** | | **1,4** |
| N05AX12 aripiprazole | 0,90 | 9,9 | 7,3 | 0,5 | 2,2 | 7,0 |
| N05AH04 quetiapine | 0,77 | 8,6 | -30,0 | 1,3 | 5,1 | 14,0 |
| N05AX08 risperidone | 0,70 | 7,7 | -9,9 | 0,7 | 2,8 | -2,9 |
| N06DX01 memantine | 0,57 | 6,3 | 22,4 | 0,6 | 2,4 | 26,2 |
| N01BB03 mepivacaine | 0,54 | 6,0 | 243,3 | 1,4 | 5,5 | 15,1 |
| N06DA03 rivastigmine | 0,54 | 6,0 | 4,2 | 0,6 | 2,3 | 15,0 |
| N05AX13 paliperidone | 0,47 | 5,2 | 82,9 | 0,3 | 1,1 | 57,5 |
| N07BC02 methadone | 0,29 | 3,3 | -0,3 | 2,3 | 9,2 | 0,7 |
| N01AB08 sevoflurane | 0,29 | 3,3 | -11,9 | 0,0 | 0,0 | -27,8 |
| N04BA02 levodopa and decarboxylase inhibitor | 0,29 | 3,2 | 15,6 | 0,1 | 0,6 | 2,7 |
| N05AH03 olanzapine | 0,26 | 2,9 | -57,4 | 1,3 | 5,1 | -7,9 |
| N04BA03 levodopa, decarboxylase inhibitor and COMT inhibitor | 0,26 | 2,9 | 6,0 | 0,2 | 1,0 | 6,8 |
| N03AX14 levetiracetam | 0,22 | 2,4 | -25,9 | 0,3 | 1,1 | 18,8 |
| N07BC51 buprenorphine, combinations | 0,22 | 2,4 | -4,0 | 0,2 | 0,8 | -3,7 |
| N02BE01 paracetamol | 0,21 | 2,3 | -28,6 | 0,4 | 1,6 | 6,2 |
| N03AX16 pregabalin | 0,15 | 1,6 | 17,3 | 0,2 | 0,7 | 14,1 |
| N01AX10 propofol | 0,14 | 1,5 | -12,4 | 0,2 | 0,7 | -0,9 |
| **V VARIOUS** | **8,18** | | **31,4** | **1,9** | | **-12,6** |
| V03AN01 oxygen | 3,62 | 44,3 | 87,8 | | | |
| V03AC03 deferasirox | 1,14 | 14,0 | 6,9 | 0,0 | 1,8 | 7,2 |
| V08AB10 iomeprol | 0,41 | 5,0 | 3,9 | 0,0 | 1,0 | 1,4 |
| V03AE02 sevelamer | 0,37 | 4,5 | 11,3 | 0,2 | 8,0 | 11,6 |
| V08AB09 iodixanol | 0,25 | 3,0 | -7,3 | 0,0 | 0,5 | -6,2 |
| V08AB05 iopromide | 0,22 | 2,7 | 1,5 | 0,0 | 0,5 | 2,6 |
| V04CJ01 thyrotropin | 0,14 | 1,8 | 14,7 | 0,0 | 0,1 | 17,0 |
| **H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS** | **4,53** | | **5,2** | **5,5** | | **0,0** |
| H01AC01 somatropin | 1,49 | 32,8 | -6,0 | 0,2 | 4,5 | -4,8 |
| H01CB02 octreotide | 0,81 | 18,0 | 1,1 | 0,1 | 2,0 | 3,6 |
| H05BX02 paricalcitol | 0,41 | 9,1 | 6,2 | 0,2 | 3,0 | 9,9 |
| H05BX01 cinacalcet | 0,41 | 9,0 | 10,5 | 0,1 | 1,5 | 10,0 |
| H01CB03 lanreotide | 0,39 | 8,6 | 11,9 | 0,0 | 0,9 | 14,1 |
| **C CARDIOVASCULAR SYSTEM** | **3,11** | | **10,6** | **17,0** | | **3,0** |
| C02KX01 bosentan | 1,49 | 48,1 | 4,6 | 0,0 | 0,3 | 3,4 |
| C01EB17 ivabradine | 0,39 | 12,6 | 42,6 | 0,8 | 4,5 | 41,4 |
| C01EB18 ranolazine | 0,28 | 8,9 | 58,7 | 0,3 | 1,6 | 59,5 |
| C02KX02 ambrisentan | 0,20 | 6,4 | 14,1 | 0,0 | 0,0 | 16,0 |
| **G GENITO URINARY SYSTEM AND SEX HORMONES** | **1,78** | | **3,5** | **1,7** | | **-2,9** |

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| | Per capita gross expenditure | %* | Δ % 13-12 | DDD/1000 inhab. die | %* | Δ % 13-12 |
|---|---|---|---|---|---|---|
| G03GA05 follitropin alfa | 0,68 | 38,2 | -5,6 | 0,1 | 3,9 | -4,8 |
| G04BE03 sildenafil | 0,18 | 10,1 | 3,4 | 0,0 | 2,5 | 4,7 |
| G03GA02 human menopausal gonadotrophin | 0,18 | 10,0 | -1,9 | 0,1 | 5,3 | -3,5 |
| G03GA06 follitropin beta | 0,15 | 8,4 | 25,5 | 0,0 | 1,0 | 13,2 |
| G02CX01 atosiban | 0,11 | 6,0 | 0,3 | 0,0 | 0,0 | 0,7 |
| G02AD02 dinoprostone | 0,08 | 4,7 | 3,0 | 0,0 | 2,5 | 3,5 |
| **S SENSORY ORGANS** | **1,71** | | **52,7** | **2,0** | | **0,2** |
| S01LA04 ranibizumab | 1,41 | 82,1 | 63,2 | 0,1 | 7,2 | 120,7 |
| **M MUSCULO-SKELETAL SYSTEM** | **1,12** | | **-23,2** | **2,5** | | **4,3** |
| M05BA08 zoledronic acid | 0,50 | 45,0 | -36,4 | 0,0 | 0,4 | -0,1 |
| M03AX01 botulinum toxin | 0,18 | 16,2 | 9,3 | 0,0 | 0,1 | 11,2 |
| M03AC11 cisatracurium | 0,11 | 9,8 | -31,8 | 0,1 | 2,5 | 6,8 |
| M05BX04 denosumab | 0,09 | 7,7 | 286,6 | 0,3 | 10,7 | 399,7 |
| **R RESPIRATORY SYSTEM** | **0,91** | | **4,5** | **3,2** | | **1,4** |
| R03DX05 omalizumab | 0,29 | 31,4 | 19,8 | 0,0 | 0,7 | 20,4 |
| R05CB13 dornase alfa (desoxyribonuclease) | 0,12 | 13,6 | 5,9 | 0,0 | 0,5 | 6,5 |
| R03BB04 tiotropium bromide | 0,11 | 12,4 | 5,9 | 0,3 | 8,7 | 5,4 |
| R03AK06 salmeterol and fluticasone | 0,09 | 9,9 | 1,2 | 0,2 | 7,5 | -1,7 |
| R07AA02 natural phospholipids | 0,08 | 9,2 | -14,1 | 0,0 | 0,0 | -14,1 |
| **D DERMATOLOGICALS** | **0,41** | | **6,7** | **16,0** | | **8,5** |
| D08AG02 povidone-iodine | 0,06 | 14,2 | 38,3 | 2,8 | 17,8 | 7,8 |
| D03AX Other cicatrizants | 0,05 | 13,3 | -7,4 | 0,4 | 2,2 | -0,3 |
| D06BB10 imiquimod | 0,05 | 11,1 | 37,7 | 0,0 | 0,3 | 6,0 |
| D06BA01 silver sulfadiazine | 0,04 | 9,7 | -4,2 | 0,5 | 3,3 | -10,8 |
| D08AX07 sodium hypochlorite | 0,03 | 7,1 | -7,2 | 2,4 | 15,0 | -7,3 |
| D03AX05 hyaluronic acid | 0,02 | 5,9 | 7,2 | 0,2 | 1,2 | 7,6 |
| D06AA02 chlortetracycline | 0,02 | 5,2 | 206,8 | 0,1 | 0,4 | -8,5 |
| D11AH04 alitretinoin | 0,02 | 4,9 | 4,5 | 0,0 | 0,0 | 2,1 |
| D08AC52 chlorhexidine, combinations | 0,02 | 4,5 | 14,5 | 5,2 | 32,3 | 30,1 |
| **P ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS** | **0,02** | | **2,6** | **0,0** | | **-2,2** |
| P01AX06 atovaquone | 0,01 | 52,5 | 3,0 | 0,0 | 7,4 | -2,4 |
| P01BB51 proguanil, combinations | 0,00 | 15,4 | 10,9 | 0,0 | 1,1 | 1,3 |
| P03AC04 permethrin | 0,00 | 9,3 | 0,8 | 0,0 | 2,1 | -4,5 |

*Expenditure and consumption percentages are calculated on the total of the ATC category

^ Medical gas DDD value is not available

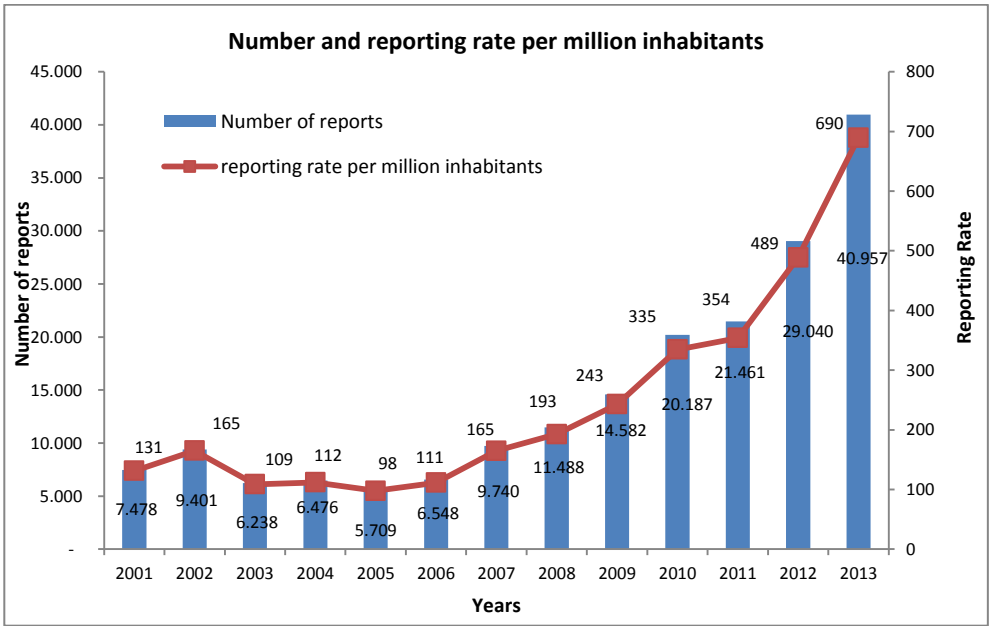
## SECTION 8

# PHARMACEUTICAL ADVERSE REACTIONS MONITORING

## 8.2 Reporting flow of suspected adverse reactions in Italy from 2001 to 2013

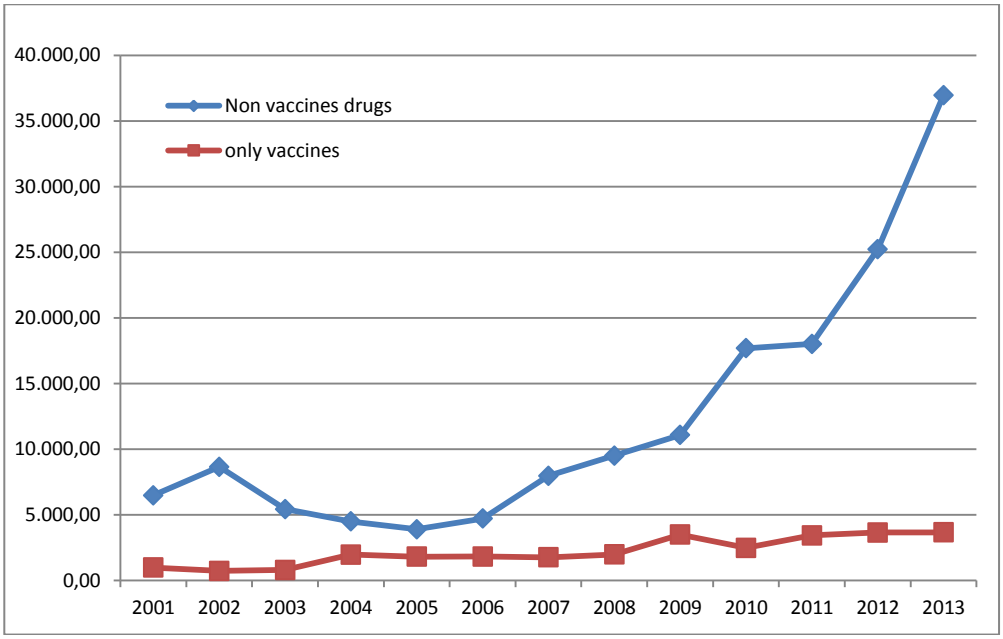
In the period between January 1, 2001 and December 31, 2013, 189.305 suspected adverse reaction reports (excluding literature cases) were recorded into the National Pharmacovigilance Network (RNF), which collects the Italian reports of suspected adverse reactions to medicines.
In 2013, the number of reports included in the RNF was 40.957, equivalent to a reporting rate of 690 per million inhabitants (Figure 8.2.1), higher than the rate of other European countries with a strong tradition in Pharmacovigilance and above the of the World Health Organization (WHO) gold standards which sets at 300 per million the number of reports necessary to define a pharmacovigilance system as effective.

**Figure 8.2.1** Annual distribution of the reporting rate per million population




The increase in reports was observed mainly for non-vaccines medicines (+47%), whilst a fairly stable trend for vaccines reporting was observed, with an increase of +0.2 %, compared to an overall increase of reports of +41%.
In any case, the two situations are very different: with regard to non-vaccine medicines, the increase in the number reports is continuous and fairly consistent; for vaccines, a reporting peak has been observed in 2009 linked to a pandemic and a new increase in 2011 (Figure 8.2.2 ).

**Figure 8.2.2** Trend of vaccines reports (absolute) versus other medicines, 2001-2013




The increase in reports over the last decade may be associated with various interconnected factors, such as increased awareness and sensitivity to Pharmacovigilance issues, funding of active Pharmacovigilance projects and, especially in the last year, to the new definition of ADR which also includes medication errors and medicine misuse.
Similarly to 2012, about one third (31%) of the reports in 2013 was classified as serious, largely because causing or prolonging hospitalization.. With respect to the previous year, an increase of reports of other clinically relevant conditions has been observed, accounting for 26% of serious reports compared to 14 % of the previous year (Table 8.2.1).

**Table 8.2.1** Number of severity reporting, 2012 - 2013

| Severity reporting | 2012 | | 2013 | |
|---|---|---|---|---|
| | N. | % | N. | % |
| Total reports | 29.040 | 100% | 40.957 | 100% |
| Non serious | 20.913 | 72% | 28.225 | 69% |
| **Severe** | **8.127** | **28%** | **12.732** | **31%** |
| Hospitalization (initial or prolonged) | 6.014 | 74% | 8.284 | 65% |
| Clinical relevant conditions | 1.139 | 14% | 3.253 | 26% |
| Life-threatening | 638 | 8% | 784 | 6% |
| Death | 194 | 2% | 251 | 2% |
| Persistent or significant disability/incapacity | 134 | 2% | 153 | 1% |
| Congenital anomaly | 8 | 0% | 7 | 0% |

More than half of the reports were submitted from hospital doctors (52%), followed by pharmacists (16%) and specialists (9%). Reporting by general practitioners in 2013 was still low, with a percentage (7%) even lower than that of the previous year (8%).
Reports from all sources increased, except those from reporters that have been identified with the term "others", mainly corresponding to doctors working in vaccine departments, who recorded a reduction of -14%; This reduction is consistent with the trend observed for reports of suspected adverse reactions to vaccines.
Over the years there has been a growing and significant increase in reports from pharmacists. The increase of reports by pharmacists is certainly positive, but must also be seen in light of the projects of active Pharmacovigilance put in place in recent years. Most of the reports come from hospital pharmacists involved in active Pharmacovigilance projects.
There was also a significant increase (+729%) of the reports coming from pharmaceutical companies, due to the provision of law which states that companies must perform regular screening of the internet or digital media to search for potential reports of suspected adverse reactions to be notified to the regulatory authorities.
The increase in reports from patients (+268%) is particularly interesting and is mainly due to a multi-regional Pharmacovigilance project, funded by the Italian Medicines Agency and addressed to patients, with the aim to facilitate spontaneous reporting and to increase awareness on medicine safety; the Regions that participated to this project recorded the most significant increases in patients' reporting. These results confirm that the Pharmacovigilance activities require continuous stimulation (Table 8.2.3).

**Table 8.2.3** Number of reporting (absolute and percentage) per healthcare profession

| Source | 2012 | | 2013 | | Δ% |
|---|---|---|---|---|---|
| | N. | % | N. | % | 2013-2012 |
| Hospital doctors | 16.444 | 57% | 21.365 | 52% | 30 |
| Pharmacists | 4.035 | 14% | 6.493 | 16% | 61 |
| Specialists | 2.150 | 7% | 3.655 | 9% | 70 |
| General practitioner | 2.417 | 8% | 3.039 | 7% | 26 |
| Patients | Other | 2% | 2.313 | 6% | 268 |
| Others | 2.051 | 7% | 1.769 | 4% | -14 |
| Nurses | 711 | 2% | 1.181 | 3% | 66 |
| Pediatricians | 379 | 1% | 438 | 1% | 16 |
| Marketing Authorisation Holders | 45 | 0% | 373 | 1% | 729 |
| Poison control centers | 159 | 1% | 303 | 1% | 91 |
| Dentists | 13 | 0% | 16 | 0% | 23 |
| Armed forces | 8 | 0% | 10 | 0% | 25 |
| Not specified | 0 | 0% | 2 | 0% | |
| **Total** | **29.040** | **100%** | **40.957** | **100%** | **41** |

Apart from vaccines, that account for about 7% of medicinal products for which a report of suspected adverse reaction has been received, the highest number of reports in 2013 has been recorded for medicines belonging to the ATC class antineoplastics (18%), antimicrobials (16%), central nervous system (15%), blood (12%), cardiovascular system (9%) and the musculoskeletal system (8%). The high number of reports for antineoplastics was attributable, besides from the high levels of toxicity of these products, to record clinical and safety data during therapy. to the establishment of AIFA registries, requiring Health Care professionals

In this context, it should be noted that the overall number of reports for the various ATC classes increased in 2013 compared to 2012. In this respect, changes in legislative provisions on pharmacovigilance, now including direct reporting from patients and pharmaceutical companies, as well as reports for off-label use, should be taken into account.

Considering the therapeutic categories of medicines for which in 2013 more than 1,000 reports were received, a major increase was recorded for those belonging to the cardiovascular ATC (Table 8.2.4).

**Table 8.2.4** Number of reporting (absolute and percentage) per ATC I level, 2012-2013

| ATC (First level) | Anatomical Therapeutic Chemical Classification System | 2012 | | 2013 | | Δ% |
|---|---|---|---|---|---|---|
| | | N. | % | N. | % | 2013-2012 |
| L | Antineoplastic and immunomodulating | 6.631 | 24% | 7.263 | 18% | 10 |
| J | Antimicrobials for systemic use | 4.266 | 16% | 6.397 | 16% | 50 |
| N | Central Nervous System | 3.367 | 12% | 5.893 | 15% | 75 |
| B | Blood and blood forming organs | 3.080 | 11% | 5.004 | 12% | 62 |
| C | Cardiovascular system | 2.091 | 8% | 3.756 | 9% | 80 |
| M | Musculo-skeletal system | 2.200 | 8% | 3.122 | 8% | 42 |
| A | Alimentary tract and metabolism | 1.396 | 5% | 2.056 | 5% | 79 |
| V | Various | 1.156 | 4% | 1.447 | 4% | 47 |
| R | Respiratory system | 515 | 2% | 717 | 2% | 25 |
| G | Genito-urinary system and sex hormones | 329 | 1% | 674 | 2% | 39 |
| H | Systemic hormonal preparations, excluding sex hormones and insulins | 374 | 1% | 659 | 2% | 105 |
| S | Sensory organs | 114 | 0% | 192 | 0% | 76 |
| D | Dermatologicals | 117 | 0% | 172 | 0% | 68 |
| P | Antiparasitic products, insecticides and repellents | 70 | 0% | 93 | 0% | 47 |
| ATC not specified | | 1.535 | 6% | 2.750 | 7% | 33 |
| **Total** | | **27.241** | **100%** | **40.195** | **100%** | **48** |

If we refer to the classification for System Organ Class, most adverse reactions were coetaneous, followed by those related to gastrointestinal disorders, general conditions and nervous system (Table 8.2.5). Other organs and systems were involved with a rate below 10%. The active ingredients with the highest number of adverse reactions reported were warfarin, acetylsalicylic acid and amoxicillin plus clavulanic acid (Table 8.2.6).

**Table 8.2.5** Number of adverse reactions per System Organ Class (SOCs) (absolute and percentage), 2012 - 2013

| System Organ Classes (SOCs) | 2012 | | 2013 | | Δ% |
|---|---|---|---|---|---|
| | N. | % | N. | % | 2013-2012 |
| Skin and subcutaneous tissue disorders | 8.552 | 20% | 11.813 | 19% | 38 |
| Gastrointestinal disorders | 6.007 | 14% | 8.574 | 14% | 43 |
| General disorders and administration site conditions | 6.295 | 15% | 8.570 | 14% | 36 |
| Nervous system disorders | 4.196 | 10% | 5.959 | 10% | 42 |
| Respiratory, thoracic and mediastinal disorders | 3.091 | 7% | 4.440 | 7% | 44 |
| Blood and lymphatic system disorders | 1.833 | 4% | 2.689 | 4% | 47 |
| Psychiatric disorders | 1.440 | 3% | 2.634 | 4% | 83 |
| Vascular disorders | 1.639 | 4% | 2.491 | 4% | 52 |
| nvestigations | 1.362 | 3% | 2.098 | 3% | 54 |
| Musculoskeletal and connective tissue disorders | 1.545 | 4% | 2.082 | 3% | 35 |
| Metabolism and nutrition disorders | 1.138 | 3% | 1.805 | 3% | 59 |
| Cardiac disorders | 1.038 | 2% | 1.468 | 2% | 41 |
| Eye disorders | 862 | 2% | 1.185 | 2% | 37 |
| Injury, poisoning and procedural complications | 545 | 1% | 1.060 | 2% | 94 |
| Renal and urinary disorders | 602 | 1% | 1.043 | 2% | 73 |
| Immune system disorders | 562 | 1% | 916 | 1% | 63 |
| Ear and labyrinth disorders | 574 | 1% | 871 | 1% | 52 |
| Infections and infestations | 660 | 2% | 832 | 1% | 26 |
| Hepatobiliary disorders | 329 | 1% | 468 | 1% | 42 |
| Reproductive system and breast disorders | 235 | 1% | 378 | 1% | 61 |

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| System Organ Classes (SOCs) | 2012 | | 2013 | | Δ% |
|---|---|---|---|---|---|
| | N. | % | N. | % | 2013-2012 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps | 103 | 0% | 159 | 0% | 54 |
| Endocrine disorders | 65 | 0% | 131 | 0% | 102 |
| Surgical and medical procedures | 32 | 0% | 85 | 0% | 166 |
| Pregnancy, puerperium and perinatal conditions | 33 | 0% | 30 | 0% | -9 |
| Congenital, familial and genetic disorders | 34 | 0% | 26 | 0% | -24 |
| Social circumstances | 12 | 0% | 14 | 0% | 17 |
| **Total** | **42.784** | **100%** | **61.821** | **100%** | **44** |

**Table 8.2.6** First 30 active ingredients per reporting in 2013

| Rank | Substance | Number of reports | Inc. % | Cum. % |
|---|---|---|---|---|
| 1 | warfarin | 2.165 | 5,3% | 5,3% |
| 2 | amoxicilline / clavulanic acid | 2.126 | 5,2% | 10,5% |
| 3 | Acetilsalicilic acid | 1.404 | 3,4% | 13,9% |
| 4 | ketoprofen | 840 | 2,1% | 16,0% |
| 5 | amoxicilline | 790 | 1,9% | 17,9% |
| 6 | ibuprofen | 653 | 1,6% | 19,5% |
| 7 | levofloxacine | 650 | 1,6% | 21,1% |
| 8 | oxaliplatin | 645 | 1,6% | 22,6% |
| 9 | paracetamol | 556 | 1,4% | 24,0% |
| 10 | paclitaxel | 526 | 1,3% | 25,3% |
| 11 | ceftriaxone | 504 | 1,2% | 26,5% |
| 12 | fluorouracile | 484 | 1,2% | 27,7% |
| 13 | iomeprol | 470 | 1,1% | 28,8% |
| 14 | clopidogrel | 452 | 1,1% | 29,9% |
| 15 | diclofenac | 451 | 1,1% | 31,0% |
| 16 | claritromicine | 429 | 1,0% | 32,1% |
| 17 | docetaxel | 414 | 1,0% | 33,1% |
| 18 | carboplatin | 403 | 1,0% | 34,1% |
| 19 | ciprofloxacine | 397 | 1,0% | 35,1% |
| 20 | furosemide | 350 | 0,9% | 35,9% |
| 21 | paracetamol/codeine | 350 | 0,9% | 36,8% |
| 22 | nimesulide | 341 | 0,8% | 37,6% |
| 23 | gemcitabine | 330 | 0,8% | 38,4% |
| 24 | ramipril | 327 | 0,8% | 39,2% |
| 25 | insulin | 307 | 0,7% | 40,0% |
| 26 | cisplatin | 304 | 0,7% | 40,7% |
| 27 | quetiapine | 294 | 0,7% | 41,4% |
| 28 | atorvastatin | 289 | 0,7% | 42,1% |
| 29 | ciclofosfamide | 286 | 0,7% | 42,8% |
| 30 | bevacizumab | 285 | 0,7% | 43,5% |
| **Total** | | **40.957** | **100,0%** | |

AIFA, in collaboration with the regional Centres of Pharmacovigilance, has continued the systematic analysis of reports not only contained in National Pharmacovigilance Network, but also those included in EudraVigilance, with particular attention towards active substances for which Italy has been appointed Reference Member State for the EU.
Furthermore, in 2013 particular attention was devoted to activities aimed at ensuring greater transparency and timeliness of information with regards to Pharmacovigilance issues, as required by newly implemented regulations. In fact, 112 safety communications have been published in AIFA's website, with a +40% increase with respect to the previous year.
In conclusion, the significant growth in the number of reports recorded in Italy in recent years (+41% compared to 2012), demonstrates that the efforts made to increase awareness of all stakeholders with respect to Pharmacovigilance allowed to achieve the expected results.