National Report on Medicines use in Italy

Year 2014

Agenzia Italiana del Farmaco
AIFA

Dear Readers,

this is an extract/adaptation of 2014 OsMed Report.

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

The English version of the document has been edited by F. Mammarella and L.A.A. Muscolo.
Revision by G. Viceconte, S. De Vito,A. Cangini and S. Montilla,. Graphics by I. Comessatti **.**

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Italian Medicines Agency

General Director: *L. Pani*

Working group of the National Observatory for medicines use monitoring who worked at this Report:

Coordination: *P. Russo* – Italian Medicines Agency (AIFA), Rome

- Italian Medicines Agency (AIFA), Rome

  OsMed Coordination Office: *R. Massimi, L.A.A.Muscolo, M. Sacconi, D. Settesoldi*

  HTA in the pharmaceutical sector Office: G. Altamura, A. Cangini, S. De Vito, A. Di Vito, R. Marini, M. Petrelli, M.P. Trotta

  Pharmacovigilance Office: *R. Bertini Malgarini, G. Pimpinella, L. Sottosanti*

  Research and Clinical Trials Office: *F. Barchetti*

  Registries Unit for medicines protocols monitoring: *G. Murri, E. Xoxi*

  European Assessment Office: *M. Caleno, M. Evandri, P. Foggi, D. Melchiorri*

  General Diector's Technical Secretary: *M.Marangi*

  Press and Communications Office: *A. Gasparini, I. Comessatti*

  Datawarehousing activities, statistical analysis and quality control: *D. Barbato, E.Fabrizi, F. Fortinguerra, F. Mammarella, A. Pierantozzi, R. Scarpellino, M. Troilo*

  Registry of medicines: *M. Di Barbora*

- Ministry of Health – General Direction of informatics and statistic Health System, Rome
  C. Biffoli, M.C. Brutti, R. Ugenti

- National Agency for Regional Health Services (AgeNaS), Rome
  F. Bevere, E. Pieroni

- Italian Society of General Medicine, Firenze
  O. Brignoli, C. Cricelli, F. Lapi, C. Piccinni (Università di Bologna)

- Clicon S.r.l., Ravenna
  V.Blini, S. Buda,S. Crovato, E. Degli Esposti, L. Degli Esposti,D. Paoli, D. Sangiorgi, S. Saragoni, C. Veronesi, V. Blini, E. Degli Esposti,

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*

1. Azienda USL della Valle d'Aosta (Regione Valle D'Aosta) Referenti: S.Bettoni, S.Grumolato, J.Luboz;
2. Regione Piemonte Direzione Sanità (Regione Piemonte) Referente: D.Nigro;
3. Azienda Sanitaria Locale di Asti (Regione Piemonte) Referenti: I. Grossi, S. Martinetti, P.Mero, L.Raeli;
4. ASL Pavia (Regione Lombardia) Referenti: S. Migliazza, M. Dellagiovanna, C. Cerra;
5. Azienda Sanitaria Locale della Provincia di Bergamo (Regione Lombardia) Referenti: M. Gambera, R. Piccinelli, M. Zambetti;
6. Azienda Sanitaria Locale della Provincia di Lecco (Regione Lombardia) Referenti: V. Valsecchi, P. DeLuca, E. Scopinaro, D. Moltoni;
7. Azienda Sanitaria Locale della Provincia di Varese (Regione Lombardia) Referenti: E. Pini, O. Leoni, C. Oria, M. Papagni, G. Nosetti, E. Caldiroli;
8. Provincia Autonoma di Bolzano (Regione Trentino-Alto Adige) Referente: V. Moser;
9. Azienda Provinciale per i Servizi Sanitari - Provincia Autonoma di Trento (Regione Trentino-Alto Adige) Referenti: R. Roni, A. Polverino;
10. Azienda Sanitaria della Regione Veneto (Regione Veneto) Referenti: G. Scroccaro, V. Fantelli, S. Amadei, L. Gubian, M. Brattina, M. Saugo;
11. Azienda ULSS 20 di Verona (Regione Veneto) Referenti: A. Ferro, L. Mezzalira, M.Andretta, L. Trentin;
12. Azienda per l'Assistenza Sanitaria n. 1 Triestina (Regione Aut. Friuli Venezia Giulia) Referenti: S. Palcic;
13. Azienda per l'Assistenza Sanitaria n. 4 "Friuli Centrale" (Regione Aut. Friuli Venezia Giulia) Referenti: C. Cattaruzzi, L. Marcuzzo;
14. Azienda per l'Assistenza Sanitaria n. 5 "Friuli Occidentale" (Regione Aut. Friuli Venezia Giulia) Referenti: F.V. Rosa, B. Basso;
15. Azienda Sanitaria n° 1 Imperiese (Regione Liguria) Referenti: M. Saglietto, S. Delucis, M. Prioli;
16. Azienda Sanitaria n. 3 Genovese (Regione Liguria) Referenti: A. Coccini, M. Ghia, F. Sanfelici;

17. Azienda Unità Sanitaria Locale Piacenza (Regione Emilia Romagna) Referente: S. Radici;
18. Azienda Unità Sanitaria Locale di Ferrara e Azienda Ospedaliera Universitaria S. Anna di Ferrara (Regione Emilia Romagna) Referenti: P. Scanavacca, A. Campi, S. Bianchi, A. Verzola, N.Napoli;
19. Azienda Unità Sanitaria Locale di Bologna (Regione Emilia-Romagna) Referenti: M. Morini, M Borsari, A. Danielli;
20. Azienda USL 1 Massa e Carrara (Regione Toscana) Referenti: M. Dal Maso, B. Marsiglia;
21. Azienda USL 8 Arezzo (Regione Toscana) Referente: B. Vujovic;
22. Azienda USL 9 Grosseto (Regione Toscana) Referenti: M. Pisani, P. Bonini, F. Lena;
23. Agenzia Regionale Sanitaria Marche (Regione Marche) Referenti: P. Aletti, A. Marcobelli, S.Sagratella;
24. Azienda USL Umbria n.2 (Regione Umbria) Referenti: S. Fratini, F. Bartolini;
25. Azienda USL Roma A (Regione Lazio) Referenti: G. Riccioni, A. Barbato;
26. Azienda USL Roma D (Regione Lazio) Referenti: R. Di Turi, A. Blasi, E. Pagnozzi;
27. Azienda USL Roma F (Regione Lazio) Referenti: G. Quintavalle, P. D'Avenia, M.C. De Matthaeis;
28. Azienda Sanitaria Locale di Frosinone (Regione Lazio) Referenti: F. Ferrante, S. Crescenzi, L.Marziale, P.Venditti, C.Bianchi, L.Quaresima;
29. Azienda Sanitaria Locale Teramo (Regione Abruzzo) Referenti: I. Senesi, R. Baci, I. De Carlo;
30. Azienda Sanitaria Regionale del Molise (Regione Molise) Direzione Generale per la Salute - Servizio Programmazione e Assistenza Farmaceutica - Referenti: A. Lavalle, G. Trofa;
31. Azienda Sanitaria Locale di Caserta (Regione Campania) Referenti: C.Linguiti, G.Farina, C.Pagliaro, C.Troncone, MG Tari;
32. Azienda Sanitaria Locale di Potenza (Regione Basilicata) Referenti: G. Motola, C. Granieri;
33. Azienda Sanitaria Locale BAT (Regione Puglia) Referenti: O. Narracci, D. Ancona, M. Cammarrota;
34. Azienda Sanitaria Locale Lecce (Regione Puglia) Referenti: G.Gorgoni, A.Sanguedolce, C.Montinari;
35. Regione Calabria Dipartimento Tutela Salute (Regione Calabria) Referenti: B. Zito, G. Brancati, R. Cosentino, M.R. Maione, L. Florio, A.E. De Francesco.

36. Azienda Sanitaria Provinciale di Cosenza (Regione Calabria) Referenti: M. Vulnera, L. Florio, F. La Viola;
37. Azienda Sanitaria Provinciale di Reggio Calabria (Regione Calabria) Referente: D. Costantino;
38. Azienda Sanitaria Provinciale di Catania (Regione Sicilia) Referenti: F. Rapisarda, P.L. Lazzaro;
39. Azienda Sanitaria Provinciale di Palermo (Regione Sicilia) Referenti: M. Pastorello, M. Parelli, M. Visconti, I. Uomo;
40. ASL Cagliari (Regione Sardegna) Referenti: P. Sanna, F. Lombardo.
41. ASL Sassari (Regione Sardegna) Referente: A.Sussarellu.

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Executive Summary

Section 1. Pharmaceutical care regulation in Italy

Throughout 2014, AIFA's Evaluation & Assessment Unit and European Assessment Unit released 621 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, of which 60% reimbursed by the National Health Service (NHS). All through 2014, significant pharmaceutical regulations were issued in Italy, with interventions ranging from authorization and reimbursement of medicines, to provisions on pharmacovigilance and administration of 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 deemed 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 medicines' 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. Finally, the Report introduces the monitoring of pharmaceutical utilization profiles, according to the patients' geographical, demographic and clinical characteristics, as well as adherence to treatment. The reader will be able to identify, for the different therapeutic areas (hypertension, hypercholesterolemia, diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, depression, peptic ulcers, esophagitis, anemic conditions, rheumatoid arthritis and psoriasis), the economic impact on pharmaceutical expenditure through variation in the indicators.

Section 5. General characteristic of pharmaceutical use in Italy

Throughout 2014, the total amount of public and private pharmaceutical expenditure was €26,6 billion, of which 75% reimbursed by the NHS. The average pharmaceutical expenditure per Italian citizen was €438.
Moreover, the total amount of public and private outpatient pharmaceutical expenditure decreased by -0,1% over the previous year and amounted to €20.009 million.
In more detail, the total NHS pharmaceutical expenditure, including the NHS outpatient pharmaceutical expenditure and the expenditure of Class A medicines distributed through the direct distribution channel, amounted to €11.848 billion. A slight decrease -2,2% over the previous year was recorded, mainly due to an increase of pharmaceutical direct distribution expenditure (+8,2%), countervailed by a reduction of the net NHS pharmaceutical expenditure (-3%).
The private expenditure borne by citizens – that is, the co-payment amount [fixed prescription fees defined as "tickets" - corresponding to a fixed amount per prescription and/or per package - and the difference between the price of originator products whose patent expired and the reference price reimbursed by NHS] and privately purchased Class A and Class C medicines registered a decrease of -0,1% compared to 2013. Major influence factors are represented by the decrease in both private purchase of class A medicines (-1,9%), and in Class C medicines expenditure (-1,6%), whereas the expenditure for OTC medicines (+0,2%) and co-payment share (+4,5%) registered an increase.
Total co-payment expenditure, consisting of the aforementioned "tickets" and the difference between the price of products whose patents expired and the reference price, amounts to €1.500 million, corresponding to €24,7 per capita.
During 2014, approximately 1.039,4 doses per thousand inhabitants were consumed daily, recording an increase of +0,7% over the previous year. The consumption boost in terms of number of packages was +1,5% (over 1 billion packs in 2014, corresponding to 18,7 packs per capita).

As regards total public and private outpatient consumption, 1,9 billion packages were dispensed, recording an increase of +0,7% over the previous year. This trend is mainly driven by the consumption increase of Class A medicines privately purchased by citizens (+3,6%), and reimbursed medicines consumption (+1,5%), while a reduction in the consumption of Class C medicines (-1,6%) was registered.
Looking at the main components of the pharmaceutical expenditure throughout the years, a slight increase in consumption [quantity effect (DDD): +2,5%], together with a price reduction (price effect: -3,3%) and a mild shift towards lower price medicine prescriptions (negative mix effect: -1,0%) were registered. Expenditure for public health facilities' purchases amounted to €9 billion (€148 per capita), recording an increase of 4,8% compared to 2013.
Pharmaceutical expenditure and consumption are conditioned by patient age groups. For patients aged 64 years and over, a per capita NHS expenditure up to 3 times higher than the national average and almost six times higher than the lower age groups was revealed. The overall prevalence of use was 55%, recording the highest levels in children and in the

elderly population: half of the children and almost 90% of the population over 74 years of age received at least one prescription during the year.

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

Cardiovascular medicines placed themselves at the highest positions in terms of total (public and private) pharmaceutical expenditure (€4087 billion) and in terms of pharmaceutical consumption (536 DDD/1000 inhab. daily). For the first time antineoplastic and immunomodulators are located in second position among categories with highest impact on total expenditure (€3.934 million) and in first place in terms of public expenditure. Other therapeutic categories significantly impacting on expenditure were: gastrointestinal tract and metabolism medicines (€3.771 billion) and central nervous system medicines (€3.228 million). 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 2014 monoclonal antibodies represented the categories with major impact on expenditure and consumption of pharmaceuticals purchased by public utilities.

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 authorisation. During 2014 the number of reports included in the National Network of Pharmacovigilance (RNF) was 51.204, corresponding to a reporting rate of 842 per million population, higher than the ones registered in other European Union countries with a strong tradition in pharmacovigilance and above the WHO gold standard which sets at 300 per million the number of reports necessary to define a pharmacovigilance system as effective. The number of reports is growing, revealing a +25% variation compared to data referring to 2013.
Most of the reports in 2014 concerned antineoplastics (17%), vaccines (14%) antimicrobials (13%), central nervous system products (12%), and blood medicines (11%).
These results confirm that efforts made over the past years to increase the sensitivity of 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 in Italy for the regulatory activity on pharmaceuticals is the Italian Medicines Agency (AIFA) (www.agenziafarmaco.gov.it). AIFA's mission consists of the following tasks:

1. improving human health care through pharmaceutical products
2. guaranteeing the economic equilibrium of the system by respecting yearly 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 relations with 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 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 belonging to the 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 Guidelines on clinical trials, as well as clinical research for non-commercial purpose and dissemination of pharmaceutical independent information. Moreover, it supervises the accuracy of public and private clinical trials and also controls promotional activity on pharmaceuticals conducted by companies. Furthermore, it coordinates and supports, drawing on 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 guidelines for good clinical practice, as well as 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 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 manages rapid alert quality reports as well as post marketing controls, national and international warnings relating to quality flaws batch withdrawals and requisitions, medicine shortages and suspension of marketing authorization.

• **Medical Scientific Information Office** provides pharmaceutical information/training addressed to healthcare professionals, together with 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 Health 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:

• **Authorisation 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 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 compliance with Good Manufacturing Practice (GMP) on the production of medicines, medical gases and raw materials intended for production of medicines. It also performs inspections at 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, carrying 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)

During 2014 the Regulation outlining AIFA's organisation, its administration and staff was reviewed and published on the O.J. n.22 on January 28, 2015.

The regulation concerning AIFA's Advisory Committees, ratified by AIFA's Board of Directors n. 27 on 18.12.2009 and amended with AIFA Resolution n.7 on January 20, 2014, was also reviewed .

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

Technical Scientific Committee (CTS) assesses the therapeutic value of human pharmaceutical products due to obtain marketing authorisation; it provides opinions on clinical trials and on results of pharmacovigilance activities; it delivers binding opinions on the therapeutic value of medicines by defining the place in therapy (the role of the medicine in its specific therapeutic context); it expresses binding opinions on the innovativeness and on the provision systems for medicinal products, by giving specific recommendations on their distribution and provision, and by defining their classification for the purpose of reimbursement. Moreover, it provides technical opinions concerning the definition of therapeutic plans and the opportunity for a medicine to be included into the PHT list of products. It also identifies the technical parameters for possible application of managed entry agreements (MEAs).

Pricing & Reimbursement Committee (CPR) carries out the negotiation activity with pharmaceutical companies for the setting of prices of human medicinal products reimbursed by the National Health Service. This Committee establishes the preliminary steps for the negotiation according to the dossier provided by the applicant and the criteria set by the CTS concerning place in the therapy, innovativeness and provision of the medicinal product. In addition, it endorses the outcome of the negotiation held with the manufacturer, including the pricing decision, reimbursement conditions and provision methods of the medicine. After two years of negotiation, the CPR reassesses the product, to ensure conditions of eligibility and price are efficient, according to economic considerations, as well as evaluations on the cost/benefit, cost/utility and the budget impact profile. The Committee also provides advices on containment of pharmaceutical expenditure ceilings, and it periodically monitors the ceiling itself. Moreover, it provides opinions regarding the eligibility conditions and the price of medicines at the expiration of the negotiation agreement.

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 competence is ascribed to 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 are 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 Class 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, as amended and integrated) are defined as over-the-counter (OTC). These products can be dispensed without prescription and can be promoted directly by pharmaceutical companies.
With ministerial decree dated April, 18, 2012, (implementation of regulations of Art. 32, paragraph 1, Legislative Decree n. December 6, 2011 as amended and integrated) AIFA has updated the delivery method of C–medications. The decree established medications for which the medical prescription obligation had to persist and those for which the delivery method was converted in C-SOP, allowing, in this way, the distribution in other settings besides conventional Pharmacies, such as malls and Para-Pharmacies. The ministerial decree of April, 18, 2012 was then updated, implementing the list of C-SOP medicines with medications reclassified as C-SOP by CTS (Ministerial Decree of November 15, 2012 and following amendments).
A list of C-SOP medications approved within December 2014, including those medications approved by CTS, is provided in table 1.3.1

Moreover, Legislative Decree n. 158 of September, 2012 modified with amendments, into Law n. 189 of November 8, 2012 (so-called “Decreto Balduzzi”), established that medications granted MA through centralized or mutual recognition or decentralized, or national procedure as well as of parallel import, are automatically classified in the new group of “C- without negotiation” (C-NN). The pharmaceutical company has the opportunity to request, at a later stage, reimbursement from the NHS and price negotiation, the latter of which is allowed only after the submission of a specific dossier according to CIPE indications (CIPE deliberation n.3 February 1, 2001).

When a pharmaceutical company submits to AIFA the pricing and reimbursement dossier, competent offices and advisory committees conduct a preliminary assessment to evaluate and establish reimbursement class of the pharmaceutical product. At the end of the decision making process, once the Pricing & Reimbursement Committee (CPR) has concluded the negotiation procedure, the final decision concerning reimbursement 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 April 24, 2006 and following amendments), 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 hospitals or analogous healthcare facilities (OSP)
   3) medicines to be used/administered exclusively by specialists (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), as the procurement of the medicine requires the issuing of a new prescription. The validity is of thirty days and is restricted to the number of packages indicated (in case of compounding preparations not including narcotics, the prescription has a three months validity). A peculiar case is represented by the isotretinoin, whose prescription and delivery is allowed only within teratogenic risk prevention programs and with a seven-day validity RNR prescription .
The RRL and RNRL prescriptions are used for medicines dispensable only by specific healthcare facilities' and/or specialists. These include:

a) medicines for exclusive hospital use (Art. 92, Legislative decree n. 219/2006)

b) medicines provided only if prescribed by a specific specialist or hospital (Art. 93, Legislative decree n. 219/2006)

c) medicines for exclusive use of specialist and care settings (Art. 94, Legislative decree n. 219/2006)

There are some medicines that cannot be sold to citizen, even if available in pharmacies, but can be provided to specialists only, who can moreover purchase them directly 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 supply systems , OSP1 and OSP2, were abrogated and a new system came into effect starting from February 16, 2010.
Medicines previously defined as OSP1 became OSP (see above), without additional changes. The OSP2 system supply was modified into RR, RNR, RRL or RNRL. At a later stage, in accordance with 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 for the purpose of ensuring hospital-community continuity of care.

Table 1.3.1. Number, class and prescription system of authorised and marketed medicines during 2014

Class	Prescription System	N. AIC	% per Class	% on total
A	RR	7.272,0	89,0	47,7
	RNR	326,0	4,0	2,1
	RNRL	227,0	2,8	1,5
	RRL	168,0	2,1	1,1
	OSP	86,0	1,1	0,6
	RMS	62,0	0,8	0,4
	SOP	25,0	0,3	0,2
	USPL	4,0	0,0	0,0
Total Class A		**8.170,0**	**100,0**	**53,6**
C	RR	2.861,0	50,7	18,8
	OTC	902,0	16,0	5,9
	SOP	809,0	14,3	5,3
	OSP	795,0	14,1	5,2
	RNR	158,0	2,8	1,0
	USPL	71,0	1,3	0,5
	RNRL	31,0	0,5	0,2
	RRL	10,0	0,2	0,1
	RMS	9,0	0,2	0,1
Total Class C		**5.646,0**	**100,0**	**37,1**
H	OSP	1.090,0	77,0	7,2
	RR	132,0	9,3	0,9
	RLNR	118,0	8,3	0,8
	RRL	38,0	2,7	0,2
	RNR	32,0	2,3	0,2
	USPL	5,0	0,4	0,0
Total Class H	**TOTAL CLASS**	**1.415,0**	**100,0**	**9,3**
Total		15.231,0		100,0

The supply of NHS reimbursed medicines in Italy varies according to the type of prescription and use (primary and secondary care).
Specifically, outpatient pharmaceutical consumption occurs through GPs' and pediatricians' medical prescriptions or medical Specialists, who work within a hospital and prescribe medicines requiring a special authorisation: *Piano Terapeutico – PT*. The pharmaceutical products' distribution occurs either through the standard distribution or the direct distribution channel .

Standard distribution refers to the supply of medicines prescribed by GPs, Pediatricians and NHS specialists by public and private community pharmacies. Direct distribution instead provides for the supply to patients either 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 conclusion 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, as amended and integrations).
Pharmaceutical hospital care refers specifically to the administration of medicines within NHS health facilities. However, pharmaceutical hospital expenditure monitoring refers toin-patient pharmaceutical consumption including the *direct* and *per conto* distribution channels of Class A medicines, in accordance with Law n. 135 of 2012 and its amendments.

Table 1.3.1 reports number, class and prescription system of medicines authorised and marketed in Italy within December 31, 2014.

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, as amended and integrated, establishes an additional 2,25% discount to be applied at the expense of pharmaciesin favor of the NHS. This discount pertains to 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, net VAT, per year;
- rural and urban pharmacies, without national assistance, and sales volumes below €258.228,45, net VAT, per year.

Moreover, pharmaceutical companies are required to remit to Regions an additional discount of 1,83% of the retail price, net VAT.
According to Law Decree n. 39 of April 28, 2009, as amended and integrated, distribution margins of generics are calculated as follows: 58,65% for pharmaceutical companies, 6,65% for wholesalers and 26,70% for pharmacist. In addition, a remaining 8% is shared between pharmacists and wholesalers, according to market agreements.
The pharmacies' discounts in favor of the NHS, starting from January 1, 2014, are reported in table 1.4.1.

Table 1.4.1 Discounts applied to pharmacies 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, prices of all medicines reimbursed by the NHS are set through negotiation procedure between AIFA and pharmaceutical companies, following methods and criteria previously adopted for medicines approved under European procedures only.
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, the pricing and reimbursement process occurs in four stages, which can be summarized as follows:

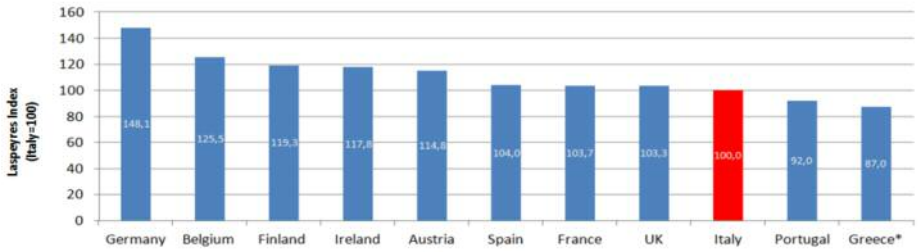
1. pharmaceutical company applies for the pricing and reimbursement procedure by submitting the dossier to AIFA;
2. CTS provides its judgment concerning the reimbursement condition according to clinical-therapeutic evaluations;
3. CPR evaluates the dossier and then meets the pharmaceutical company for 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 the assessment of orphan drugs and medicines with

exceptional therapeutic value and considered of social relevance, compared to other pending procedures, and sets a 100 day time limit for the assessment of these products . The Committees may be convened in extraordinary sessions in order to ensure the time limit for the procedure is respected. 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 prices of Class C pharmaceutical, which are then notified to AIFA without 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). In 2014, the price level of pharmaceuticals in Italy was estimated to be the lowest in Europe.
Figure 1.5.1 compares pharmaceutical prices, including medicines dispensed by hospitals, across different EU Countries. Results reveal that most European Countries, with the exceptions of Portugal and Greece, have higher average prices than Italy (Reference = 100), with a minimum of +3,3% in UK and a maximum of +48,1% in Germany.

Figure 1.5.1. Prices across European Countries in 2014 (Laspeyres index has been applied to ex-factory prices) *



*without hospital data

1.6 Citizens co-payment

Law n. 405 of 2001, as amended and integrated, provides for the possibility for Regions to introduce or increase citizens co-payment, by introducing or increasing per-medical prescription or per-package co-payment (*ticket*), in order to reduce possible Regional budget deficits. This financial measure was originally implemented only in Regions undergoing repayment plan and later applied across almost all the Country.

However, citizens' co-payment also derives from the payment of the difference between the price of the purchased medicine and the one of the reference medicine (i.e. the lowest price) and from cost-sharing mechanisms for off patent medicines. Since December 1, 2001 AIFA has provided a monthly publication of the Transparency List (*Liste di trasparenza AIFA*), in order to identify a unique reference price for all substitutable packages. Specifically, in cases in which there are two medicines with the same active ingredient, administration route, pharmaceutical formulation and number of standard units, only the one with the lowest price is reimbursed by the NHS.. Law n. 122 of July 30, 2010, as amended an integrated, provides for the reduction of pharmaceutical reference prices of products contained in the Transparency Lists, on the basis of a comparison with EU generics prices (Germany, UK, France and Spain).
In accordance with Article 5, paragraph 4 of Law n. 222 of 2007, the option for Regions to reduce pharmaceutical expenditure became an obligation. Regions are indeed required to adopt measures for pharmaceutical expenditure containment. The expenditure containment amount shall correspond to at least 30% of the total NHS pharmaceutical expenditure deficit. The implementation of these measures represents a necessary condition for the purpose of access for Regions to additional financing from the Government.
At National level, the total co-payment expenditure amounted to €1,5 billion, 13,7% of the NHS pharmaceutical expenditure. During 2014 the per capita co-payment expenditure was €24,7, with +2,6% increase compared to the previous year, 36,4% of which derives from regional co-payment while the remaining 63,6% originates from the difference between the price of off patent medication 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 legislative measures enacted starting in year 2000. The previously mentioned Transparency List has indeed been introduced with Article 85, paragraph 28 of Law n. 338, 2000. These lists gather the off patent products together with the corresponding NHS price, which are published on the AIFA website on a monthly basis.
Several aspects concerning off patent medicines were clarified and strengthened with the adoption of Law n. 405 of 2001, as amended and integrated. The key points outlined by 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) are considered reciprocally replaceable at the expiration of the patent protection date
- 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 patients (with the exception of war disablement pension holders)
- Regions are given the opportunity to take appropriate measures on generic medicines based on their current availability within the regional distribution network

It should be mentioned that in 1991, the Complementary Protection Certificate (*Certificato Complementare di Protezione*, CCP) was introduced, allowing the extension of the pharmaceutical patent protection of an additional 18 years, thus extending the possible total period for exclusivity rights of a molecule to a maximum of 38 years.
Furthermore, EC Regulation no 1768 of 1992, modified with EC Regulation no 469/2009, 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 corresponding 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 2004 was set.
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. 12% reduction of generic medicines' 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. Reduction of 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 for those medicines whose cost is ≤€5
- €1 for those medicines whose cost is between €5 and €10
- €1,5 for those medicines whose cost is >€10 (this provision was subsequently abrogated 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, as amended and integrated, 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 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).

The "Balduzzi decree" (Legislative Decree n. 158 on September 2012 which was modified, with amendments, into Law n. 189 of November 8, 2012), established that off patent medicines cannot be reimbursed by the NHS prior to the expiration date of the patent or the SPC, in accordance with law. Active ingredients that lost patent protection during 2014, or new active ingredient packages which had previously lost their patent protections and which were included in AIFA's lists of transparency are listed in Table 1.7.1.

Table 1.7.1. Active ingredients which have lost patent protections in 2014 or new active ingredient packages which had previously lost their patent protections and which were included in AIFA's lists of transparency

Active ingredient	Price reduction effect	Price reduction
Active ingredients or new packages that lost patent protection before 2013/12/1		
Efavirenz	02/12/2013	35%
Atosiban	04/09/2014	30%
Omega 3 fatty acid	16/06/2014	37%
Metoclopramide	15/07/2014	33%
Lymecycline	17/02/2014	45%
Capecitabine	04/12/2013	60%
Active ingredients that lost patent protection between 2013/12/1 and 2014/12/1		
Memantine	15/11/2013	47,5%
Escitalopram	16/06/2014	65%
Moxifloxacina	15/07/2014	55%
Telmisartan/ Hydrochlorothiazide	27/06/2013	60%
Telmisartan	10/12/2013	70%

Table 1.7.2. List of Class A and H active ingredients losing their patent protection and expected to be marketed as generic products in 2015

Active ingredient	Marketing launch	Reimbursement class	Price reduction
Active ingredients or new packages that lost patent protection before 2014/12/1			
Sildenafil	15/12/2014-	A	64%
Ciclosporin	15/04/2015-	A	55%
Active ingredient	**Patent expiration**	**Reimbursed class**	**Price reduction**
Active ingredients going to lose patent protection between 2014/12/1 and 2015/12/1			
Almotriptan	29/03/2015	A	47,5%
Paracalcitol	09/03/2015	A	47,5%
Sevelamer	28/01/2015	A	45%
Celecoxib	03/12/2014	A	50%
Infliximab	20/02/2015	H	-

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).

Subsequently, this decree was invalidated by the Lazio Regional Administrative Court (TAR) judgment, section Quater III, n. 3803/2014, with respect to the method of calculation of the price reduction, which was based on the average value of the NHS expenditure of medicinal products covered by patent protection, without making any distinction between specific packages.

For this reason, AIFA's Pricing and Reimbursement Committee deemed that negotiations of new prices of generic or biosimilar products should take place according to the procedure in force before the invalidation of the referred DM (AIFA press release on 02.12.2014).
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. Main points discussed are:
1. definition and criteria to characterise the biological and biosimilar medicines
2. background of EU regulatory requirements on biosimilar medicines
3. biosimilar medicines' role and 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 mainly depends on the continuous evolution of scientific knowledge and 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 to innovative medicines. In particular, the definition of pharmaceutical innovation 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, whose value is set at the beginning of the year. In the case of expenditure exceeding the national pharmaceutical expenditure ceiling (see next section 1.10), if expenditure for innovative medicines exceeds the Innovation Fund's value , 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.

Provisions of Law n. 222 of 2007, initially intended for the outpatient setting only, were subsequently extended to cover 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, respectively at 20% and 80% (as a maximum quota).

Law n. 190/2014 (Stability Law on 2015) introduced significant changes as regards financing of innovative medicines. First of all, the establishment of a financial fund for the period 2015- 2016 for the reimbursement of innovative medicines and amounting to €1 billion, was foreseen, (article 1, paragraph 593. The legislation also introduced a safeguard limit concerning economic benefits arising from the innovative medicine designation , according to which, if the sales volume of the innovative product exceeds €300 million, then the marketing authorization holder of the medicinal product is required to payback 20% of the breakthrough value (article 1, paragraph 595).

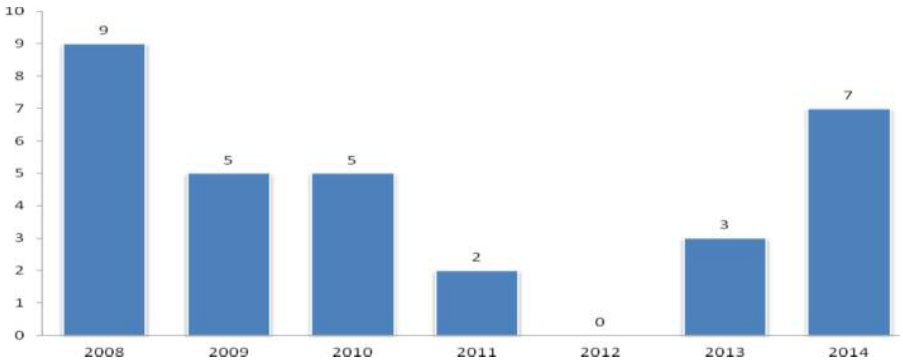
In order to define and assess pharmaceutical innovation of new pharmaceutical products entering the Italian market, the CTS has set forth criteria (approved in the course of the meeting held on July 10 of 2007) to be met to determine the degree of innovation of a product. This evaluation initially considered 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 the place in therapy and 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 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.

The algorithm was completed and presented to the CTS at the meeting held on March 3 2015. Currently a testing phase of the algorithm concerning authorized or pending authorization medicines has begun.
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).
Following Law n. 190/2014 (Stability Law on 2015) AIFA provides, in support of the Ministry of Health and the Regions, evaluations of Health Technology Assessment with particular reference to innovative medicines.
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, it determines 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 in 2014 in accordance with Art. 1, paragraph 1 of State-Regions Agreement of November, 18 2010

ATC	Active ingredient	Grade of innovatineness	Reimbursement class	CTS opinion	Outpatient innovativeness fund L.222/2007	Inpatient innovativeness fund L.135/2012	Deadline
L01XC	YERVOY	Ipilimumab	H	Significant	30/10/2012	09/03/2013	08/03/2016
L02BX	ZYTIGA	Abiraterone	H	Potential	15/11/2012	06/04/2013	05/04/2016
M09AB	XIAPEX	Clostridium histolyticum collagenase	H	Potential	06/03/2013	14/03/2013	13/03/2016
L01XC	ADCETRIS	Brentuximab vedotin	H	Potential	02/12/2013	08/07/2014	07/07/2017
L01XC	PERJETA	Pertuzumab	H	Significant	02/12/2013	08/07/2014	07/07/2017
L04AX	REVLIMID	Lenalidomide	H	Potential	13/02/2014	30/09/2014	29/09/2017
J05AX	TIVICAY	Dolutegravir	H	Potential	10/03/2014	02/11/2014	01/11/2017
J04AK	SIRTURO	Bedaquiline	H	Potential	11/03/2014	01/10/2014	30/09/2017
L01XC	KADCYLA	Trastuzumab emtansine	H	Potential	07/04/2014	11/10/2014	10/10/2017
L01CD	ABRAXANE	Nab paclitaxel	H	Significant	07/04/2014	21/02/2015	20/02/2018
J05AB	SOVALDI	Sofosbuvir	A	Significant	15/05/2014	20/12/2014	19/12/2017
J05AE	XALKORI	Crizotinib	H	Potential	09/06/2014	11/04/2015	10/04/2018
J05AX	OLYSIO	Simeprevir	A	Potential	10/11/2014	24/02/2015	23/02/2018

Figure 1.8.1 . Number of innovative medicines: a comparison between the years 2008-2014 *



* It was considered the date of the O.J. publication. The lists of innovative medicines published by AIFA were used.

Figure 1.8.2. Distribution of innovative medicines for the ATC level in the period 2008-2014

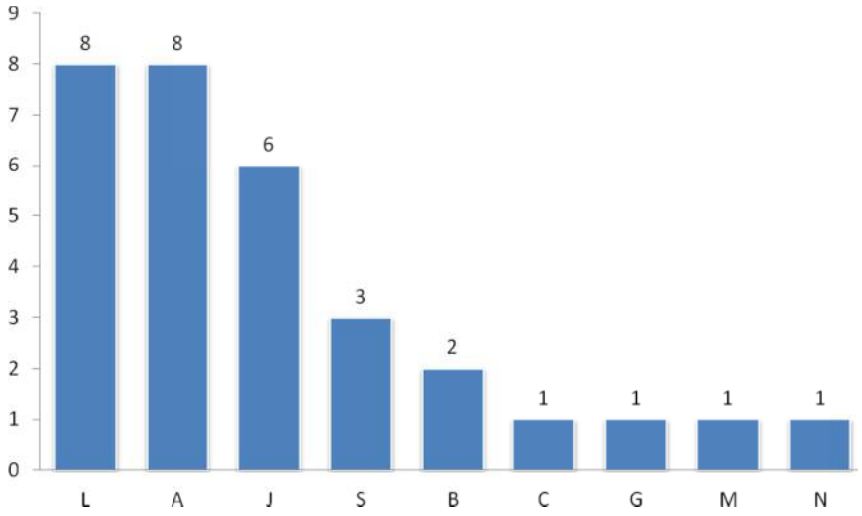
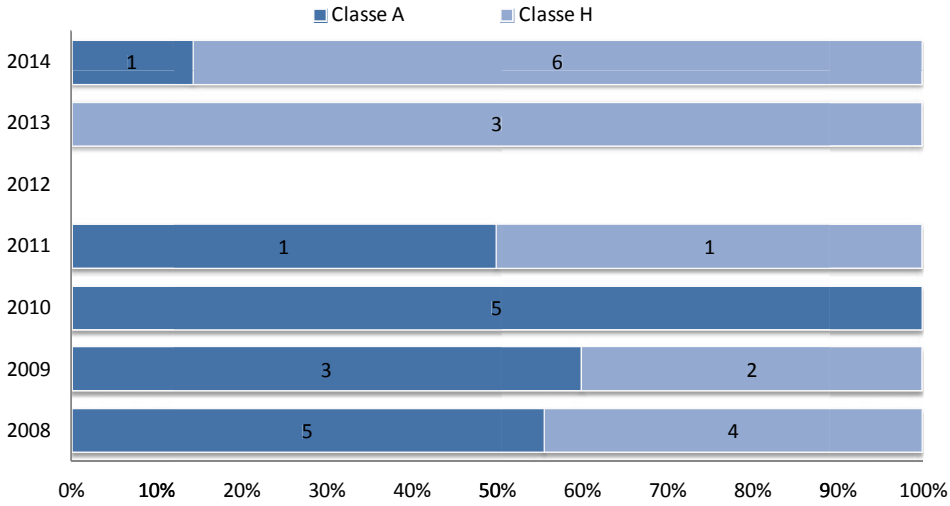


Figure 1.8.3. Distribution of new drug class of eligibility in the period 2008-2014



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 foreseen in the hospital pharmaceutical expenditure regulation(Article 15, paragraph 8, letters i and i-bis of Law n. 135 of 2012, amended by Law n. 147 of December 27, 2013). To date, more than seven thousand rare diseases have been discovered, therefore representing a significant social issue, involving millions of people: according to estimates, patients affected in Europe are over thirty million, of which 2-3 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 define criteria and procedures for orphan drug designation, and provide for awards and incentives. The orphan status is granted by the Committee of Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA). The marketing authorization (MA) of an orphan 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 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

In order to facilitate orphan drugs access, several regulations were issued. In particular, the Stability Law has introduced a mechanism of economic protection for orphan medicinal product marketing authorization holders. Indeed when 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 pharmaceutical 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 which have 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 rare diseases or conditions, for which MAHs had not submitted as of 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, patient access is ensured through 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 are available;
- medicines intended for different therapeutic indications 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 the basis of a documented request of patients associations, scientific societies, health facilities, and universities' or following recommendation of the CTS.
Following the entry into force of Law n.79 of 2014, the supply of medicines within Law n. 648/96 (100% reimbursement by the NHS) both when other therapeutic alternatives are available, and when medicines are used for a therapeutic indication different from that authorized one, according to affordability and appropriateness parameters, is allowed. Adempas constitutes an example of orphan drug that has benefited from this provision.

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 2014, the Fund amounted approximately to €15,5 million.
as regards 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 reimburses the invoices submitted. In 2014, the total expenditure for patients accessing the AIFA Fund amounted to €239.895.

The remaining 50% of the Fund is dedicated to 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, specific topics covered 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 for rare diseases. Moreover, in 2008 AIFA contributed to the activity set forth by the Ministry of Health, with a €3.000.000 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 the considerable medical advances made 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 shall provide a 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 rare diseases, 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.

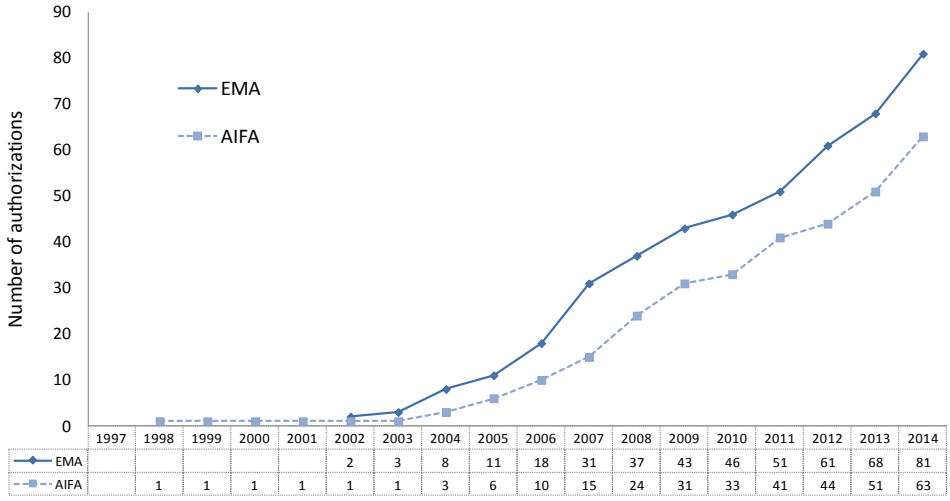
Table 1.9.5. Synoptic table regarding main requirements on orphan drug access according to Italian regulations

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

Year 2014 has been a record year for the European Medicines Agency due to the high number of human use medicine authorisations, that is, 82, of which at least 17 regarding new chemical entities for the treatment of rare diseases. The first treatment for Duchenne muscular dystrophy (Translarna, containing Ataluren molecule) and the first treatment for erythropoietic protoporphyria (Scenesse, containing Afamelanotide molecule), a rare genetic disease that involves intolerance to light, were approved. Orphan drugs are mainly concentrated within the therapeutic areas of oncology, metabolic and central nervous system.
In particular, among the 81 EMA authorized orphan drugs within December, 31 2014, 63 were approved by AIFA. In more detailsof those not yet authorized in Italy, some did not conclude the approval process; for others applications for reimbursement and negotiation procedures have not been submitted; others are in any case accessible through other systems made available to patients by the Italian Medicines Agency.

Figure 1.9.1. A comparison between medicines authorised by the EMA and approved by the AIFA



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
EMA						2	3	8	11	18	31	37	43	46	51	61	68	81
AIFA		1	1	1	1	1	1	3	6	10	15	24	31	33	41	44	51	63

Orphan drugs authorised by the EMA	81	Inc %
Orphan drugs authorised by the AIFA	63	78%
Medicines pending for the Cnn class	7	9%
No P&R applications	6	7%
Orphan drugs distributed by other channels (L.n.648, 5% Fund)	5	6%

Expenditure and consumption data for the year 2014 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 2014, orphan drugs expenditure, inclusive of purchases made by public health facilities, amounted to €1 billion, corresponding to 5,3% of the total pharmaceutical expenditure. In terms of DDDs, , consumption for the same period amounted to 8,5 million DDDs. In particular, 47% of the expenditure concerned antineoplastic agents and immuno-modulators, followed by gastrointestinal tract and metabolism medicines (21%), and, finally, cardiovascular system medicines (10%).

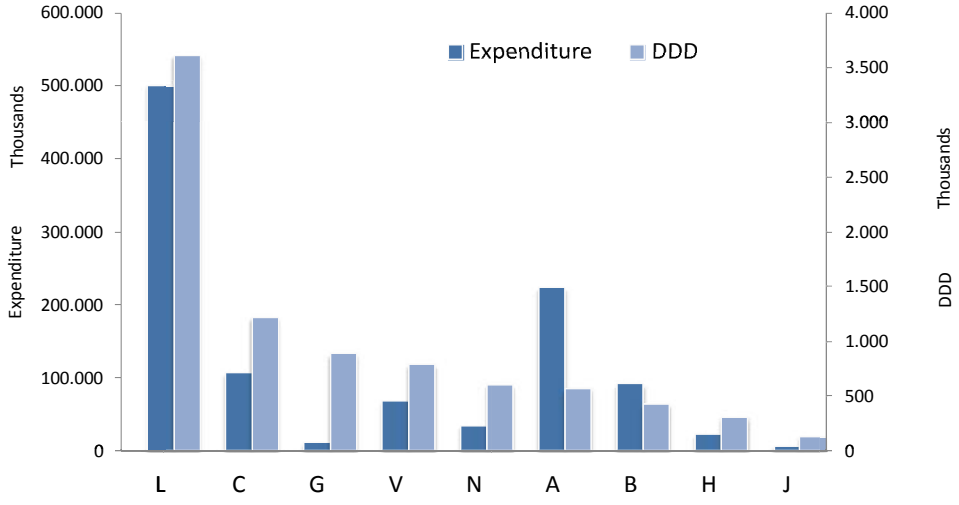
42% of the consumption of these drugs was absorbed by antineoplastic agents and immuno-modulators, followed by cardiovascular system medicines (14%) and medicines of the genito-urinary system (10%) (Table 1.9.6 and Figure 1.9.1).

Table 1.9.6. Trend of orphan drugs expenditure and consumption, years 2009-2014*

YEAR	2009	2010	2011	2012	2013*	2014*
Orphan drug expenditure	507 (Mln)	657 (Mln)	800 (Mln)	671 (Mln)	917 (Mln)	1.060 (Mln)
% share of orphan drug Exp. on total pharmaceutical expenditure	2,7%	3,5%	4,2%	3,5%	4,67	5,31
Orphan drug DDD-consumption	5,3 (Mln)	6,6 (Mln)	7,5 (Mln)	5,9 (Mln)	7,5 (Mln)	8,5 (Mln)
% share of orphan drug consumption on pharmaceutical consumption	0,02%	0,03%	0,03%	0,02%	0,03	0,03

*2013 and 2014 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 1.9.2. Orphan drugs expenditure and consumption by ATC I level, year 2014



Active ingredients with major impact on expenditure are the following: lenalidomide (14,0%), bosentan (9%), eculizumab (7%), deferasirox (6%) and nilotinib (6,0%), that together accounted for 41,2% of total orphan drug expenditure. With regards to consumption, almost half (48,6%) of delivered DDDs are represented by the following active ingredients: bosentan (13%), lenalidomide (11%), sildenafil (10%), deferasirox (9%) and anagrelide (6%).

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 provision of pharmaceuticals to the financial resources available (i.e. planned expenditure). This task is considered highly relevant for AIFA's mission, as pharmaceutical expenditure management ensures equilibrium of the economic system. 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 2014, the outpatient pharmaceutical expenditure ceiling 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 costs of tickets paid by citizens (and excluding citizen reference price system co-payment, as provided for in 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. This threshold was determined excluding amounts paid by pharmaceutical companies as pay back. In 2014, NHS expenditure monitoring data revealed a €12.217million expenditure, with an overall deficit of €-182,2 million compared to the planned ceilingamounting to €12.402 million . The NHS outpatient pharmaceutical expenditure increased compared to the previous year (€12.128 million.

As a result of the €49,8 million breakthrough spending in in 2013, AIFA determined through a Resolution dated October 30, 2014 (Official Journal n . 254 of 31/10/2014) a payback amount of €23,5 (in addition to the €20,6 million payback resulting from breaches of ceilings set for single pharmaceutical productsubject to verification as of 31-12-2013). A further€5,6 million payment, concerning outpatient NHS medicines only, at the expense of pharmacists and wholesalers was set , according to AIFA Resolution dated February 9,

2007,., which provides for temporary price discount for such products which passes from 0,64% to 0,74% of the retail price VAT included (until May 1, 2015). These measures are currently being discussed by administrative courts.

Table 1.10.1 Trend of main parameters intended to manage NHS pharmaceutical expenditure during 2011-2015

Outpatient setting	**2011**	**2012**	**2013**	**2014**	**2015*** **
Ceiling	13,30%	13,10%	11,35%	11,35%	11,35%
Pharmaceutical company budget *	13.950,7	13.358,8	12,184,7	12.108,8	NA
% difference of outpatient pharmaceutical expenditure vs previous years**	1,33%	5,19%	-0,88%	2,49%	NA
Absolute difference vs budget **	182,6	685,0	-106,6	296,7	NA
Fund of innovativeness	98,2	75,1	18,9	109,1	NA
Innovative medicine ceiling	0,4	23,8	63,9	34,7*** *	NA
Programmed expenditure	14.005,8	13.069,9	12.127,6	12.216,69	NA
% share on National Health Fund (FSN)	13,18%	12,20%	11,40%	11,18%	NA
Not allocated resources	-127,4	-968,7	0,0	-185,2	NA
Breakthrough ceiling	0,0	0,0	49,8	0,0	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 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 expenditure for Class A (reimbursed) pharmaceuticals supplied through direct distribution, 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 national level, hospital pharmaceutical expenditure attributable to pharmaceutical

companies is calculated by deducting the expenses originating from 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).
Following the €773,2 millio breakthrough in the inpatient pharmaceutical expenditure ceiling set for 2013, by the, a €368,9 million payback from pharmaceutical companies has been fixed through . AIFA Resolution of October 30, 2014 (Official Journal n . 254 of 31/10 / 2014) at 3,5% of the National Health Fund (FSN). These measures are currently under examination by administrative courts .
Finally, following regulatory changes introduced throughout 2014, the hospital pharmaceutical expenditure fund for year 2014 was set at €3.824 billion (Table 1.10.2).

Table 1.10.2. Main parameters of hospital pharmaceutical expenditure management in the period 2011-2015

Inpatient setting	**2011**	**2012**	**2013**	**2014**	**2015*** **
Ceiling	2,40%	2,40%	3,50%	3,50%	3,50%
Pharmaceutical company budget *			4.460,8	4.178,6	NA
% difference of outpatient pharmaceutical expenditure vs previous years**			-17,6%	-8,65%	NA
Absolute difference vs budget**			-736,2	-353,1	NA
Innovativeness Fund			153,2	107,8	NA
Innovative medicines ceiling			60,8	83,8	NA
Programmed expenditure	4.979,6	5.170,6	4.497,6	4.874,2	NA
% share on National Health Fund (FSN)	4,69%	4,82%	4,23%	4,46%	NA
Not allocated resources	0,0	0,0	0,0	0	NA
Ceiling exceedance	2.429,2	2.598,7	773,2	1049,8	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 2014, hospital pharmaceutical expenditure monitoring revealed a €4.909,2 billion expenditure, with an overall deficit of €+1,084.8 million, compared to the planned pharmaceutical expenditure (€3.824,4 million) set at 3,5% of the FSN. Hospital pharmaceutical expenditure increased compared to the previous .

SECTION 3
DATA SOURCE AND METHODS

3.6 NHS reimbursed medicines use per individual patient[7]

Local Health Units (LHUs - Azienda Sanitaria Locale - ASL) are public entities responsible for delivering pharmaceutical care at local level.
LHUs provide themselves with information flows, so-called "administrative databases", which represent important sources of health and functional information, allowing, for instance, the identification and description of medicines use profiles in daily clinical practice.[8,9,10]
Within administrative databases, information is recorded according to patient ID code and date of the services rendered, in order to meet the 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 flows only include NHS covered services. Main flows concern demographic registries, 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 detail:

- 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 corresponding to that originating from community pharmaceutical distribution flow (see above) but, unlike the latter, it allows to identify medicines dispensed by NHS hospitals for outpatients use.

[7] This section is edited by Clicon S.r.l..
[8] Birnbaum HG, Cremieux PY, Greenberg PE, et al. Using healthcare claims data for outcome research and pharmacoeconomic analyses. Pharmacoeconomics 1999; 16: 1-8.
[9] Motheral BR, Fairman KA. The use of claims databases for outcome research: rational challenges and strategies. Clin Ther 1997; 19: 346-66.
[10] 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; primary 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, laboratory exams and instrumental diagnostics exams 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 and by NHS health facilities as part of the state-run healthcare. 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 significant 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 includes main phases of the care process: multidimensional assessment and follow-up, definition of an individualized care program, taking 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. This information flow is however available for some LHUs only. 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 the integration with clinical data concerning the supply of sanitary services.

Use indicators and methodology of analysis

Within this Report, CliCon, in partnership with AIFA and a selection of LHUs, calculated some of the indicators developed in the Health-DB project. 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) and 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 monitoring the compliance of prescribing methods with therapeutic care standards and in assessing the effects of measures implemented to improve adherence to these standards.

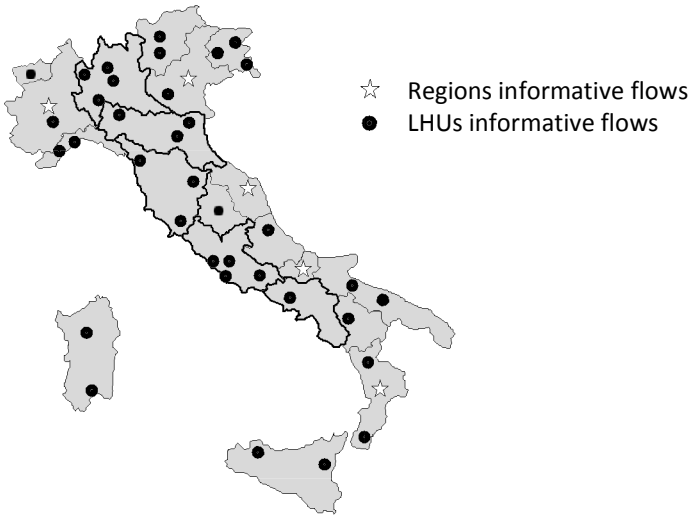
CliCon is a company specialized in the planning/design and implementation of pharmacoutilization and outcome analysis based on clinical and administrative databases, in collaboration with LHUs, GPs and specialist Centres. Since 1996, CliCon has conducted analysis in various therapeutic areas in partnership with several LHUs and Regions, taking 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 LHUs and Regions. This database includes about 30 million subjects (about 49,2% of the Italian population) distributed throughout the Country: North (62,1%), Center (36,8%) and South (39,7%)[11]**.** In particular, 41 Institutions are currently involved in the database feeding: 36 LHUs and 5 Regions, covering the whole Country. (Figure 3.6.1).

The average age of LHUs' and Regions' sample is 44,0 years *versus* 43,7 years of the Italian population. The percentage of males is estimated to 48,5%, in accordance with the national data available.

[11] Percentages were calculated with reference to the geographical area covered.

Figure 3.6.1. Geographic representation of LHUs and Regions sample that contributed to 2014 OsMed Report



For each LHUand Region involved, 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
- outpatient specialist care

For some LHUs, the flow originating from laboratories was also acquired.

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), date and value of laboratory test (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) leading to the identification of a chronological and detailed profile for each single patient (patient analytics). This procedure was performed, in site, by LHU and Region 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
- Rheumathoid arthritis
- Psoriasis

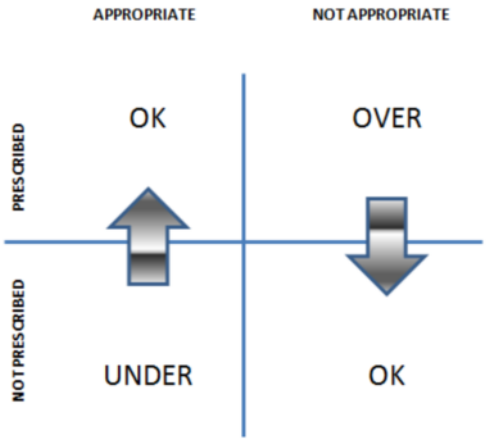
Outpatient harmacoutilization data was analyzed for all therapeutic areas and for all distribution methods (conventional, *per conto* and direct distribution). Increased awareness of the overall expenditure volumes by therapeutic category and patient use (compared to standard), is essential for management 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 (and 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 methods 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 new 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.
Having a fixed budget, the Italian NHS is not able to handle uncontrolled growth of pharmaceutical expenditure in the short run.. Indicators have therefore been designed to identify areas of under spending (e.g. therapeutic discontinuity in chronic treatments) and overspending (e.g. use of unnecessary potent and expensive medicines for patients with mild disease) (Figure 3.6.3), with the aim of being "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 should be considered.
Health-DB project indicators undergo continuous development and improvement as results of several factors, such as enhancement of the logical framework and the acquisition of new information coming, for instance, from other flows.

Figure 3.6.3. The utility of indicators in rationalizing pharmaceutical expenditure



Data ownership and treatment

According to the privacy legislation (Legislative Decree n. 196 of 2003 and following amendments), patient ID code are anonymized by LHUs, in site, so that CliCon cannot retrieve the patient ID code. CliCon, by signing a specific agreement with each LHU, 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 depend 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 the previous four years, in order to allow a "self-consistent" reading of the Report.

SECTION 4

THERAPEUTIC APPROPRIATENESS: PRESCRIPTION AND USE PROFILES

4.3 Medicines use and treatment adherence profiles in arterial hypertension[8]

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 2014) (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 started 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) distincted 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 under treatment have been categorized as patients having experienced a previous cardio-cerebral vascular event or diabetes and 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)

[8]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 analyzed 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)

- 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 the absence or the 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 4.607.442 in 2014 (N) (Table 4.4.1). The prevalence of subjects in treatment with antihypertensive agents amounts to 27,7% of the overall study sample (26,8% in Northern, 28,1% in Center and 30,1% in Southern of Italy). The prevalence of subjects in treatment with antihypertensive medicines increases with age (3,1% in the age group ≤45 years, 27,8% in the age group 46-65 years, 62,0% in the age group 66-75 years and 80,0% in the age group >75 years) and over the years (+2,9% in 2014 compared to 2013 and +2,4% in 2013 compared to 2012).

Table 4.3.1. Distribution of patients in treatment with antihypertensive medicines

	2014			2013			2012		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**4.607.442**	**27,7**	**2,9**	**4.479.294**	**27,4**	**2,4**	**4.374.662**	**26,9**	**/**
Geographic distribution									
North	2.683.269	26,8	1,9	2.632.972	26,8	1,8	2.585.625	26,4	/
Centre	989.154	28,1	4,0	950.977	27,5	1,8	933.709	27,1	/
South	935.019	30,1	4,4	895.345	29,3	4,7	855.328	28,1	/
Gender									
Male	2.116.609	26,2	3,3	2.048.006	25,8	2,9	1.990.642	25,2	/
Female	2.490.833	29,1	2,4	2.431.288	28,9	2,0	2.384.020	28,5	/
Age group									
≤45	220.241	3,1	-3,0	227.011	3,3	-1,5	230.550	3,3	/
46-65	1.538.727	27,8	-0,4	1.545.613	28,4	0,2	1.542.216	28,5	/
66-75	1.289.965	62,0	1,7	1.268.331	62,1	2,5	1.237.872	60,9	/
>75	1.558.509	80,0	8,4	1.438.339	75,2	5,4	1.364.024	71,7	/
Mean age	68.7 ± 13.2			68.2 ± 13.1			68.0 ± 13.1		

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 819.324 in 2014.
The percentage of comorbid patients treated with medicines acting on renin-angiotensin system amounts to 82,5% in 2014, a percentage slightly lower compared to the previous year (-1,3% in 2014 compared to 2013). This percentage appears slightly higher in Southern Italy (85,1%) than in Northern and Central regions of the country (81,9% and 81,3% respectively) and in males compared to females (83,7% vs 81,3%).
The percentage of comorbid patients in treatment with renin-angiotensin system inhibitors amounts to 75,2% in the age group ≤45 years, 84,3% in the age group 46-65 years, 85,3% in the age group 66-75 years and 79,7% in the age group >75 years. This percentage is lower in new users than in already treated ones (59,9% and 83,9% respectively).

Table 4.3.2. Number of comorbid patients in treatment with renin-angiotensin-aldosterone system inhibitors [numerator]/Total number of comorbid patients in treatment with antihypertensive medicines [denominator]

	2014 N = 819.324		**2013 N = 781.397**		**2012 N = 755.102**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**82,5**	**-1,3**	**83,6**	**-0,6**	**84,1**	**/**
Geographic distribution						
North	81,9	-1,2	82,9	-0,5	83,3	/
Centre	81,3	-1,6	82,6	-1,0	83,5	/
South	85,1	-1,1	86,1	-0,7	86,7	/
Gender						
Male	83,7	-1,2	84,7	-0,6	85,2	/
Female	81,3	-1,3	82,4	-0,7	83,0	/
Age group						
≤45	75,2	-1,2	76,1	-1,5	77,3	/
46-65	84,3	-0,7	84,9	-0,5	85,3	/
66-75	85,3	-0,7	85,9	-0,4	86,2	/
>75	79,7	-1,8	81,2	-0,8	81,8	/
Treatment status						
New users	59,9	-3,9	62,3	-2,1	63,7	/
Old users	83,9	-1,2	84,9	-0,6	85,5	/

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 1.702.879 in 2014.
The percentage of patients receiving off-patent angiotensin II antagonists in December 2014 amounts to 78,5% ; this value decreased compared to previous years (-1,3% in 2014 compared to 2013 and -1,1% in 2013 compared to 2012). This data is slightly higher in Central Italy (80,5%) compared to Northern (78,9%) and to Southern (76,0%) areas of the country and in females compared to males (79,3% and 77,6% respectively). The percentage of patients treated with off-patent angiotensin II antagonists in December 2014 was 69,9% in ≤45 age group, 74,9% in 46-65 age group, 79,4% in 66-75 age group and 82,4% in age group >75 years and was lower among new users compared to already treated ones (71,5% vs 79,5%).

Table 4.3.3. Number of subjects who assume off-patent angiotensin II antagonists in monotherapy in December 2014* [numerator]/Total number of patients receiving angiotensin II antagonists in monotherapy [denominator]

	2014 N = 1.702.879		**2013 N = 1.671.223**	**2012 N = 1.621.192**		
	%	Var. %	%	%	Var. %	%
TOTAL	**78,5**	**-1,3**	**79,5**	**78,5**	**-1,3**	**79,5**
Geographic distribution						
North	78,9	-1,1	79,8	78,9	-1,1	79,8
Centre	80,5	-1,5	81,7	80,5	-1,5	81,7
South	76,0	-1,5	77,1	76,0	-1,5	77,1
Gender						
Male	77,6	-1,5	78,8	77,6	-1,5	78,8
Female	79,3	-1,1	80,2	79,3	-1,1	80,2
Age group						
≤45	69,9	-2,0	71,4	69,9	-2,0	71,4
46-65	74,9	-1,9	76,4	74,9	-1,9	76,4
66-75	79,4	-1,4	80,5	79,4	-1,4	80,5
>75	82,4	-0,9	83,2	82,4	-0,9	83,2
Treatment status						
New users	71,5	-3,3	74,0	71,5	-3,3	74,0
Old users	79,5	-1,0	80,4	79,5	-1,0	80,4

N: number of subjects aged 18 years or older that assume angiotensin II antagonists in monotherapy
*List of off-patent angiotensin II antagonists taken in account: losartan: ATC CODE C09CA01, C09DA01; valsartan: ATC CODE C09CA03, C09DA03; irbesartan: C09CA04, C09DA04; candesartan: ATC CODE C09CA06, C09DA06; telmisartan: ATC CODE C09CA07, C09DA07.

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 4.354.334 in 2014.
The percentage of adherent subjects in treatment with antihypertensive medicines amounts to 55,5%, in 2014 (+0,2% in 2014 compared to 2013). This value is slightly higher in Northern (56.8%), than in Center (50,4%) and in Southern (56,2%) Italy. The adherence is higher in males (57,4% vs 53,9% of females), in older subjects (the higher level, 60,1%, is in the age groups 66-75 years and over 75 years), in already treated patients (59,7% compared to 24,0% of new users) and in comorbid users (the adherence of subjects with a previous CV event or diabetes amounts to 66,6% vs 53,2% 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 58,8% in 2014.

Table 4.3.4. Number of adherent patients in treatment with antihypertensive medicines [numerator]/Total number of patients in treatment with antihypertensive agents [denominator]

	2014 N = 4.354.334		2013 N = 4.253.410		2012 N = 4.163.262	
	%	Var. %	%	%	Var. %	%
TOTAL	**55,5**	**0,2**	**55,3**	**1,3**	**54,7**	**/**
Geographic distribution						
North	56,8	1,7	55,8	0,9	55,3	/
Centre	50,4	-7,7	54,6	0,4	54,4	/
South	56,2	3,0	54,5	3,4	52,7	/
Gender						
Male	57,4	-0,1	57,4	1,1	56,8	/
Female	53,9	0,5	53,6	1,3	52,9	/
Age group						
≤45	33,1	0,7	32,8	2,4	32,1	/
46-65	50,6	-0,4	50,8	0,8	50,4	/
66-75	60,1	-0,1	60,2	0,8	59,7	/
>75	60,1	0,4	59,8	1,1	59,2	/
Treatment status						
New users	24,0	2,1	23,5	0,2	23,4	/
Old users	59,7	0,0	59,7	1,0	59,1	/
Comorbidity status						
Without previous CV event or diabetes	53,2	0,3	53,0	1,3	52,3	/
With previous CV event or diabetes	66,6	-0,5	66,9	0,9	66,3	/
TOTAL without occasional users	58,8	0,0	58,8	1,0	58,2	

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data were available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).
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 4.354.334 in 2014. The percentage of occasional subjects in treatment with anti-hypertensive medicines amounts to 5,7%; this value decreased slightly compared to the previous year (-3,1% in 2014 compared to 2013). The percentage of occasional users is higher in Southern Italy (7,3%) compared to Northern (5,0%) and to Central (6,2%) regions of the Country and is slightly higher in females (6,2% vs 5,1% of males). This percentage is higher in younger age groups (20,7% in the age group ≤45 years, 6,9% in the age group 46-65 years, 3,7% in the age group 66-75 years and 3,8% in the age group >75 years), in new users (33,1% vs 2,0% of old users) and in the subjects without a previous CV event or diabetes (6,3% vs 2,8% of subjects with a previous CV event or diabetes).

Table 4.3.5. Number of occasional patients in treatment with antihypertensive medicines [numerator] / Total number of patients in treatment with antihypertensive medications [denominator]

	2014 N = 4.354.334		2013 N = 4.253.410		2012 N = 4.163.262	
	%	Var. %	%	%	Var. %	%
TOTAL	**5,7**	**-3,1**	**5,9**	**-3,1**	**6,1**	**/**
Geographic distribution						
North	5,0	-2,2	5,1	-1,7	5,2	/
Centre	6,2	-2,8	6,4	-3,3	6,6	/
South	7,3	-6,0	7,7	-6,5	8,3	/
Gender						
Male	5,1	-2,1	5,3	-3,0	5,4	/
Female	6,2	-3,6	6,4	-3,3	6,6	/
Age group						
≤45	20,7	-1,8	21,1	-2,8	21,7	/
46-65	6,9	-0,9	7,0	-2,1	7,1	/
66-75	3,7	-3,1	3,8	-1,5	3,9	/
>75	3,8	-4,5	4,0	-1,2	4,0	/
Treatment status						
New users	33,1	-0,7	33,3	-1,0	33,7	/
Old users	2,0	-5,1	2,1	-0,9	2,2	/
Comorbidity status						
Without previous CV event or diabetes	6,3	-2,9	6,5	-3,3	6,7	/
With previous CV event or diabetes	2,8	-4,8	2,9	-0,3	3,0	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data were available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).
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 101.572 in 2014.
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 is 84,4% in 2014. This value decreased compared to the previous year (-1,2% in 2014 compared to 2013). The percentage is higher in Southern Italy (87,2%) than in Northern (83,3%) and Central (83,9%) Italy, as well as in females (85,0% vs 83,9% of males). This percentage decreases slightly with the age of patients (89,2% in the age group ≤45 years, 85,8% in the age group 46-65 years, 83,0% in the age group 66-75 years and 82,6% in over 75 years). 80,6% of old users have never taken the same active ingredients either in free combination or fixed-dose combination or in monotherapy.

Table 4.3.6. 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]*

	2014 N = 101.572		2013 N = 80.627		2012 N = 107.028	
	%	Var. %	%	%	Var. %	%
TOTAL	**84,4**	**-1,2**	**85,5**	**6,2**	**80,5**	**/**
Geographic distribution						
North	83,3	-0,9	84,1	6,1	79,2	/
Centre	83,9	-1,2	84,9	5,4	80,5	/
South	87,2	-1,7	88,7	7,1	82,9	/
Gender						
Male	83,9	-0,9	84,7	6,2	79,8	/
Female	85,0	-1,5	86,2	6,3	81,1	/
Age group						
≤45	89,2	-0,8	89,9	6,3	84,6	/
46-65	85,8	-1,3	86,9	6,8	81,4	/
66-75	83,0	-1,1	83,9	6,1	79,1	/
>75	82,6	-1,2	83,6	5,2	79,5	/
Treatment status						
New users	100,0	0,0	100,0	0,0	100,0	/
Old users	80,6	-1,5	81,9	6,2	77,1	/

N: number of subjects analysed 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 analysed aged 18 years or older in treatment with calcium channel blockers in free combination with another antihypertensive agent amounts to 97.784 in 2014. The percentage of patients in free combination, who did not shift to a fixed-dose combination therapy, amounts to 97,2%; this value decreased slightly compared to the previous year (-0,5% in 2014 compared to 2013). There are no significant differences across Italy (North 97,3%; Center 96,8%; South 97,2%), in males compared to females (96,9% vs 97,6%) or in new users compared to old users (98,0% vs 97,2%). This percentage rises slightly with the age of patients (95,1% in the age group ≤45 years, 96,4% in the age group 46-65 years, 97,2% in the age group 66-75 years and 97,9% in the age group over 75 years).

Table 4.3.7. Number of patients in treatment with calcium channel blocker in free combination with another antihypertensive agent who did not shift to a fixed-dose combination therapy [numerator]*/Total number of patients receiving a fixed-dose combination therapy with calcium channel blockers [denominator]

	2014		2013		2012	
	N = 97.784		N = 89.906		N = 90.114	
	%	Var. %	%	%	Var. %	%
TOTAL	**97,2**	**-0,5**	**97,6**	**2,0**	**95,8**	**/**
Geographical distribution						
North	97,3	-0,4	97,7	1,9	95,9	/
Centre	96,8	-0,6	97,4	1,8	95,6	/
South	97,2	-0,5	97,7	2,3	95,6	/
Gender						
Male	96,9	-0,5	97,4	2,1	95,4	/
Female	97,6	-0,4	97,9	1,8	96,2	/
Age group						
≤45	95,1	-1,8	96,8	2,5	94,4	/
46-65	96,4	-1,0	97,4	2,2	95,3	/
66-75	97,2	-0,3	97,5	2,0	95,6	/
>75	97,9	-0,1	98,0	1,6	96,4	/
Treatment status						
New users	98,0	0,3	97,8	1,5	96,3	/
Old users	97,2	-0,5	97,6	2,0	95,7	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

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 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 4.4.8).

Table 4.3.8. 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	+0,12%	€ 2.508.046
H.DB-1.2	-0,27%	€ -5.729.883
H.DB-1.3	+0,63%	€ 13.604.595
H.DB-1.4	-0,15%	€ -3.163.788
H.DB-1.5	-0,02%	€ -469.983
H.DB-1.6	+0,02%	€ 357.621

°This value includes all NHS reimbursed pharmaceutical expenditure (standard distribution and medicines purchased by Hospitals)

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

4.4 Medicines use and treatment adherence profiles in hypercholesterolemia.

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 analysed have been categorized as patients with or without comorbidity in relation to the presence of at least one of the following diagnosis and/or procedures:

- Diabetes: at least two prescriptions of anti-diabetic medicines or a 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 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).

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 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 classes of lipid lowering agents and/or the consumption of at least two different classes of lipid lowering agents, have been considered as a 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 analysed aged 18 years or older in treatment with statins amounts to 1.860.754 in 2014 (Table 4.4.1). The prevalence of the treatment with statins amounts to 11,2% of the study sample (10,5% in Northern, 11,8% in Central and 12,5% in Southern Italy). The prevalence of statins treatment increases with the patients' age (0,7% in age group ≤45 years, 10,3% in age group 46-65 years, 30,3% in age group 66-75 years and 31,5% in the group ≥75 years) and over the years (+2,6% in 2014 compared to 2013 and +4,6% in 2013 compared to 2012).

Table 4.4.1. Distribution of patients in treatment with statins

	2014			2013			2012		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**1.860.754**	**11,2**	**2,6**	**1.814.434**	**11,1**	**4,6**	**1.734.768**	**10,7**	**/**
Geographic distribution									
North	1.056.149	10,5	2,3	1.032.337	10,5	4,8	985.150	10,1	/
Centre	416.393	11,8	2,1	408.010	11,8	3,4	394.740	11,5	/
South	388.212	12,5	3,8	374.087	12,3	5,4	354.878	11,7	/
Gender									
Male	912.400	11,3	2,7	888.073	11,2	4,7	847.814	10,7	/
Female	948.354	11,1	2,4	926.361	11,0	4,4	886.954	10,6	/
Age group									
≤45	47.110	0,7	-4,5	49.311	0,7	-3,0	50.822	0,7	/
46-65	569.461	10,3	-1,5	577.981	10,6	0,6	574.395	10,6	/
66-75	630.050	30,3	1,9	618.343	30,3	4,7	590.362	29,1	/
>75	614.133	31,5	8,0	568.799	29,7	9,6	519.189	27,3	/
Mean age	69.7 ± 11.3			69.3 ± 11.2			68.9 ± 11.2		

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 1.019.866 in 2014.
The percentage of patients with a previous CV event or diabetes treated with statins amounts to 54,9%, this value is slightly decreased compared to previous years (-0,3% in 2014 compared to 2013. The percentage of subjects in treatment with statins is similar across Italy: North (55,2%), Center (54,9%) and South (54,1%) of the country with a prevalence in males (57,0% vs 52% in females). Age seems to significantly affect the use of statins: the higher percentage of patients in treatment with statins is in the age group 66 - 75 years (63,4%).

Table 4.4.2. 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]

	2014 N = 1.019.866		**2013 N = 989.932**		**2012 N = 961.924**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**54,9**	**-0,3**	**55,0**	**1,9**	**54,0**	**/**
Geographic distribution						
North	55,2	0,0	55,2	2,5	53,9	/
Centre	54,9	0,1	54,8	1,4	54,1	/
South	54,1	-1,4	54,9	0,8	54,4	/
Gender						
Male	57,0	-0,2	57,2	1,9	56,1	/
Female	52,4	-0,4	52,6	1,7	51,7	/
Age group						
≤45	22,6	-5,1	23,8	0,2	23,8	/
46-65	55,6	-1,4	56,3	0,7	55,9	/
66-75	63,4	-0,1	63,5	1,8	62,3	/
>75	50,9	0,8	50,5	3,2	48,9	/
Follow-up until 31-December 2013	54,9		58,6		60,7	

Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

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

The number of subjects analysed aged 18 years or older in treatment with statins amounts to 1.860.754 in 2014.
The percentage of patients treated with statins without a previous CV event or diabetes amounts to 77,1% in 2014; this value decreased slightly compared to previous years (-0,4% in 2014 compared to 2013). This percentage becomes 72,5% when the starting date of the evaluation period for previous CV event or diabetes is starts from January 1, 2009.
The percentage of patients treated with statins is slightly higher in Central Italy (78,4%) than in Northern (77,5%) and in Southern (74,7%) Italy and in females (79,6% vs 74,6% 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 (87,0%). The number of new user is higher than the one of old users (83,3% vs 75,6%).

Table 4.4.3. 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]

	2014 N = 1.860.754		**2013 N = 1.814.434**		**2012 N = 1.734.768**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**77,1**	**-0,4**	**77,4**	**-0,5**	**77,8**	**/**
Geographic distribution						
North	77,5	-0,5	77,9	-0,3	78,1	/
Centre	78,4	0,0	78,4	-0,6	78,8	/
South	74,7	-0,4	75,0	-0,9	75,7	/
Gender						
Male	74,6	-0,5	75,0	-0,6	75,4	/
Female	79,6	-0,2	79,7	-0,3	80,0	/
Age group						
≤45	87,0	0,0	87,0	-0,2	87,1	/
46-65	78,8	-0,1	78,8	-0,1	78,9	/
66-75	75,2	-0,4	75,5	-0,6	76,0	/
>75	76,8	-0,5	77,2	-0,6	77,7	/
Treatment status						
New users	83,3	-1,4	84,5	-0,3	84,7	/
Old users	75,6	-0,4	75,9	-0,3	76,1	/
Assessment from 01-January-2009°	72,5		73,7		75,0	

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 analysed aged 18 years or older in treatment with statins without a previous CV event or diabetes amounts to 1.435.254 in 2014.
The percentage of patient without a previous CV event or diabetes treated with low-intensity statins throughout 2014 amounts to 39,6%; this value is lower compared to previous years (-4,4% in 2014 compared to 2013 and -5,8% in 2013 compared to 2012). The percentage of patients in treatment with low-intensity is slightly higher in Central Italy (43,4%) than in Northern (39,1%) and Southern (36,8%) Italy, in females (43,5% vs 35,3% of males), in the elderly (33,6% in the age group ≤45 years, 35,6%, in the age group 46-65 years, 39,7% in the age group 66-75 years and 43,8% in the age group >75 years) and in new users (40,8% vs 39,3% of old users group).

Table 4.4.4. Number of patients 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]

	2014 N = 1.435.254		**2013** N = 1.404.442		**2012** N = 1.349.172	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**39,6**	**-4,4**	**41,4**	**-5,8**	**44,0**	**/**
Geographical distribution						
North	39,1	-5,1	41,2	-6,2	43,9	/
Centre	43,4	-4,7	45,6	-5,9	48,5	/
South	36,8	-1,4	37,3	-3,9	38,8	/
Gender						
Male	35,3	-5,4	37,4	-7,0	40,2	/
Female	43,5	-3,6	45,1	-4,8	47,4	/
Age group						
≤45	33,6	-4,0	35,0	-8,6	38,2	/
46-65	35,6	-5,0	37,5	-7,2	40,4	/
66-75	39,7	-4,8	41,8	-5,7	44,3	/
>75	43,8	-4,2	45,7	-5,1	48,2	/
Treatment status						
New users	40,8	-1,9	41,6	-15,0	48,9	/
Old users	39,3	-5,1	41,4	-2,9	42,6	/

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 analysed aged 18 years or older with a previous CV event or diabetes and in treatment with statins amounts to 425.500 in 2014.
The percentage of patients, with a previous CV event or diabetes, in treatment with high-intensity statins amounts to 64,4% in 2014; this value increased slightly compared to previous years (+2,5% in 2014 compared to 2013 and +3,5% in 2013 compared to 2012). 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 higher in males (67,0% vs 61,3% in females) and in younger age groups (68,7% in the age group ≤45 years, 68,0% in the age group 46-65 years, 64,7% in the age group 66-75 years and 60,8% in the age group >75 years). There are no significant differences between new users and old users.

Table 4.4.5. Number of patients 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]

	2014 N = 425.500		2013 N = 409.992		2012 N = 385.596	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**64,4**	**2,5**	**62,8**	**3,5**	**60,7**	**/**
Geographic distribution						
North	64,2	3,0	62,3	3,6	60,1	/
Centre	61,0	3,1	59,1	4,2	56,7	/
South	68,1	1,0	67,4	2,5	65,8	/
Gender						
Male	67,0	2,6	65,3	3,6	63,0	/
Female	61,3	2,4	59,9	3,4	57,9	/
Age group						
≤45	68,7	2,4	67,1	2,4	65,5	/
46-65	68,0	2,2	66,6	3,2	64,5	/
66-75	64,7	2,7	63,0	4,0	60,6	/
>75	60,8	3,4	58,8	4,1	56,5	/
Treatment status						
New users	64,4	0,7	63,9	12,1	57,0	/
Old users	64,4	2,8	62,6	2,3	61,2	/

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 analysed aged 18 years and older in treatment with statins amounts to 1.768.218 in 2014.
The percentage of subjects adhering to treatment with statins amounts to 43,1%; this value is stable compared to the previous year. The percentage of adheranceis higher in Northern Italy (47,6%) compared to Central (35,2%) and Southern (38,3%) Italy and in males (46,% vs 40,80 of females). The highest adherence level has been observed in the age group 66-75 years (46,1%) compared to 26,2% in ≤45 years, 40,8% in 46-65 years and 43,7% in > 75 years age groups, and in old users (47,2% vs 24,1% of new users). The adherence to the treatment with statins varies in relation to subject's clinical status (48,5% in subjects with a previous CV event or diabetes and 41,6% in subjects without a previous CV event or diabetes).
Excluding occasional users, the percentage of adherent patients amounts to 47,1%.

Table 4.4.6. Number of adherent patients in treatment with statins [numerator]/Total number of patients in treatment with statins [denominator]

	2014 N = 1.768.218		**2013 N = 1.690.168**		**2012 N = 1.597.006**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**43,1**	**0,0**	**43,1**	**3,9**	**41,5**	**/**
Geographic distribution						
North	47,6	0,9	47,2	4,0	45,4	/
Centre	35,2	-8,1	38,4	2,9	37,3	/
South	38,3	5,0	36,5	5,0	34,8	/
Gender						
Male	46,4	-0,5	46,6	3,3	45,1	/
Female	40,0	0,5	39,8	4,5	38,1	/
Age group						
≤45	26,2	-0,6	26,3	2,9	25,6	/
46-65	40,8	-1,0	41,2	2,9	40,0	/
66-75	46,1	0,0	46,1	4,4	44,2	/
>75	43,7	0,4	43,5	3,8	41,9	/
Treatment status						
New users	24,1	-3,7	25,0	0,7	24,8	/
Old users	47,2	-0,5	47,5	3,8	45,7	/
Comorbidity status						
Without previous CV event or diabetes	41,6	0,0	41,5	4,1	39,9	/
With previous CV event or diabetes	48,5	-0,4	48,7	3,0	47,3	/
TOTAL without occasional users	47,1	-0,2	47,2	3,3	45,7	/

This indicator has not been calculated in all LHUs in relation as extra-site data management appeared unfeasible. Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).
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 analysed aged 18 years and older in treatment with statins amounts to 1.768.218 in 2014. The percentage of occasional users amounts to 8,5%; this value decreased compared to previous years (-1,8% in 2014 compared to 2013 and -5,9% in 2013 compared to 2012). The percentage of occasional users is higher in Central (10,0%) and in Southern (12,8%) Italy compared to Northern (6,3%) Italy and is slightly higher in females (9,1% compared to 7,8% of the males). Poor adherence (occasional users) is higher in younger age groups (22,3% in the age group ≤45 years, 9,9% in the age group 46-65 years, 6,8% in the age group 66-75 years and 7,6% in the age group >75 years), in new users (30,1% compared to 3,8% of old users) and in subjects without a previous CV event or diabetes (9,3% compared to 5,6% of subjects with a previous CV event or diabetes).

Table 4.4.7. Number of occasional patients in treatment with statins [numerator] / Total number of patients in treatment with statins [denominator].

	2014		**2013**		**2012**	
	N = 1.768.218		**N = 1.690.168**		**N = 1.597.006**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**8,5**	**-1,8**	**8,6**	**-5,9**	**9,2**	**/**
Geographic distribution						
North	6,3	0,6	6,3	-6,8	6,7	/
Centre	10,0	-0,3	10,1	-4,8	10,6	/
South	12,8	-6,1	13,7	-5,9	14,5	/
Gender						
Male	7,8	-1,6	7,9	-5,2	8,4	/
Female	9,1	-2,0	9,3	-6,5	9,9	/
Age group						
≤45	22,3	-1,4	22,6	-2,0	23,1	/
46-65	9,9	0,9	9,8	-4,7	10,3	/
66-75	6,8	-1,7	6,9	-6,1	7,3	/
>75	7,6	-3,3	7,9	-6,0	8,4	/
Treatment status						
New users	30,1	4,2	28,9	-0,8	29,2	/
Old users	3,8	1,3	3,7	-8,2	4,1	/
Comorbidity status						
Without previous CV event or diabetes	9,3	-1,6	9,4	-5,7	10,0	/
With previous CV event or diabetes	5,6	-2,2	5,8	-5,9	6,1	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).
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 single indicators (Table 4.4.8).

Table 4.4.8. 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%	€ 4.271.862
H.DB-2.2	-0,97%	€ -7.837.936
H.DB-2.3	-0,56%	€ -4.557.664
H.DB-2.4	+0,18%	€ 1.436.022
H.DB-2.5	+0,56%	€ 4.501.201
H.DB-2.6	-0,15%	€ -1.173.028

A preferential use of low-intensity statins in patients without a previous CV event or diabetes should reduce pharmaceutical expenditure for statins, while a preferential use of high-intensity statins in patients with a previous CV event or diabetes should increase the pharmaceutical expenditure for statins, with a negative final balance. In fact, even though low-intensity statins are low-priced, the number of patients needing low-intensity statins is higher than the number of patients needing high-intensity statins. This saving, together with the one achievable through the reduction of occasional users (through a better selection of patients to treat), would moreover allow reinvestment in policies aimed at improving adherence and appropriateness (e.g. high-intensity statins for subjects with a previous CV event or diabetes).

4.5 Medicines use and treatment adherence profiles in diabetes mellitus.

Indicators for hypoglycemic agents

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

- Percentage of patients in treatment with DPP-IV inhibitors who do not meet DPP-IV inhibitors reimbursement criteria[9] (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 considered for the analysis: ATC CODE A10B medicines (e.g. metformin 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 analysed 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 the presence or absence, respectively, 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);

9 More details are attached to AIFA's determination 916/2014 November 4, 2014

- 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).

Subjects in treatment with hypoglycemic agents 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 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 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 following criteria :
  - ✓ HbA1c <7.5% or ≥8,5% HbA1c <9% at the beginning of the treatment
  - ✓ HbA1 ≥9% at the treatment beginning in 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 858.924 in 2014 (Table 4.5.1). The prevalence of the treatment with hypoglycemic agents amounts to 5,2% of the study sample (4,6% in Northern Italy, 5,4% in Central and 6,8% in Southern Italy). The prevalence of treatment with anti-diabetic agents increases with age (0,4% in the age group ≤45 years, 4,8% in the age group 46-65 years, 13,4% in the age group 66-75 years and 14,7% in the age group >75 years) and over the years (+3,0% in 2014 compared to 2013 and +3,4% in 2013 compared to 2012).

Table 4.5.1 Distribution of patients in treatment with anti-diabetic agents

	2014			2013			2012		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**858.924**	**5,2**	**3,0**	**834.069**	**5,1**	**3,4**	**806.787**	**5,0**	**/**
Geographic distribution									
North	457.308	4,6	2,1	447.784	4,6	3,3	433.391	4,4	/
Centre	191.170	5,4	3,7	184.335	5,3	2,2	180.406	5,2	/
South	210.446	6,8	4,2	201.950	6,6	4,6	192.990	6,4	/
Gender									
Male	451.849	5,6	3,4	437.146	5,5	3,8	421.297	5,3	/
Female	407.075	4,8	2,6	396.923	4,7	3,0	385.490	4,6	/
Age group									
≤45	30.647	0,4	-2,1	31.303	0,5	0,6	31.121	0,4	/
46-65	263.256	4,8	-1,6	267.473	4,9	0,0	267.435	4,9	/
66-75	278.087	13,4	2,0	272.591	13,4	3,7	262.881	12,9	/
>75	286.934	14,7	9,2	262.702	13,7	7,1	245.350	12,9	/
Mean age	69.4 ± 12.1			68.9 ± 12.1			68.6 ± 12.0		

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 807.185 in 2014.

The percentage of adherent patients amounts to 62,2%; this value decreased slightly compared to the previous year (-0,4% in 2014 compared to 2013). The percentage of adherent patients is slightly lower in Southern Italy (56,9%) compared to North (65,6%) and to Center (59,2%) of the Country. This value is higher in males than in females (63,7% vs 60,5% respectively). The adherence is higher in old users (67,7% vs 29,8% of new users) and in patients without a previous CV event compared to patients with a previous CV event (62,3% vs 58,9%).The adherence improves with age (44,7% in the age group ≤45 years, 64,1% in the age group 46-65 years, 66,1% in the age group 66-75 years and 58,2% in the age group >75 years). Excluding occasional users, the percentage of adherent patients amounts to 67,0% in 2014.

Table 4.5.2. Number of adherent patients in treatment with anti-diabetic agents [numerator]/Total number of patients in treatment with antidiabetic agents [denominator]

	2014 N = 807.185		2013 N = 780.577		2012 N = 761.936	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**62,2**	**-0,4**	**62,5**	**1,1**	**61,8**	**/**
Geographic distribution						
North	65,6	0,4	65,4	2,1	64,0	/
Centre	59,2	-4,6	62,1	0,4	61,8	/
South	56,9	1,1	56,3	-0,4	56,5	/
Gender						
Male	63,7	-0,1	63,8	1,1	63,1	/
Female	60,5	-0,8	61,0	1,1	60,4	/
Age group						
≤45	44,7	1,5	44,0	5,4	41,7	/
46-65	64,1	-0,1	64,1	1,7	63,1	/
66-75	66,1	-0,3	66,3	1,2	65,6	/
>75	58,2	-0,9	58,8	-0,2	58,8	/
Treatment status						
New users	29,8	5,1	28,3	4,2	27,2	/
Old users	67,7	-1,0	68,4	0,1	68,4	/
Comorbidity status						
Without previous CV event or diabetes	62,3	-0,4	62,6	1,2	61,9	/
With previous CV event or diabetes	58,9	-0,6	59,3	-0,7	59,7	/
TOTAL without occasional users	67,0	-0,4	67,3	0,4	67,0	

This indicator has not been calculated in all LHUs, as an extra-site data management appeared infeasible. Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

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 521 in 2014.
The percentage of patients in treatment with DPP-IV inhibitors who don't meet DPP-IV inhibitors reimbursement criteria amounts to 18,4%; this value decreased compared to the previous year (-48,7% in 2014 compared to 2013). There are no differences between males and females (18,5% vs 18,4% respectively). The percentage is higher in younger subjects (25,0% in the age group ≤45 years, 20,2% in the age group 46-65 years, of 15,9% in the age group 66-75 years and of 19,2% in the age group >75 years). 5,0% of patients in treatment with DPP-IV inhibitors who don't meet DPP-IV inhibitors reimbursement criteria come from a previous DPP-IV inhibitor therapy, while the 54,2% of subjects are new DPP-IV users.

Table 4.5.3. 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]

	2014		2013		2012	
	N = 521		**N = 509**		**N = 412**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**18,4**	**-48,7**	**36,0**	**-12,9**	**41,3**	**/**
Gender						
Male	18,5	-42,1	31,9	-23,6	41,8	/
Female	18,4	-54,3	40,2	-1,2	40,6	/
Age group						
≤45	25,0	-57,5	58,8	17,6	50,0	/
46-65	20,2	-36,0	31,6	-26,4	42,9	/
66-75	15,9	-61,6	41,4	-4,9	43,6	/
>75	19,2	-38,8	31,4	-3,5	32,5	/
DPP-IV inhibitors treatment status						
Treatment beginning	54,2	-6,7	58,1	9,7	53,0	/
Treatment continuation	5,0	-61,9	13,1	-42,8	23,0	/

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 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 2012 among patients who don't present elements of frailty the 34,1% has a HbA1c value <7,5% and the 65,9% 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 36,6% has a HbA1c value <7,5% and the 63,4% has HbA1c value ≥8,5% and <9,0% or ≥9,0% in frail subjects
- during 2014 among patients who don't present elements of frailty the 53,1% has a HbA1c value <7,5% and the 46,9% 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 1.074 in 2014.
The percentage of patients who meet DPP-IV inhibitors reimbursement criteria but are not in treatment with DPP-IV inhibitors amounts to 60,4% in 2014; this value decreased compared to the previous year (-5,9% in 2014 compared to 2013). There are no differences between males and females (60,9% vs 60,0% respectively); the percentage is higher in younger and in older patients (70,0% in the age group ≤45 years, 58,1% in the age group 46-65 years, 56,3% in the age group 66-75 years and 66,2% higher to 75 years). With regards the origin therapy: 92,9% of subjects come from a monotherapy with metformin; 86,9% from metformin and sulfonamides in association; 83,9% from metformin and thiazolidinedione in association; 80,0% from metformin, sulfonamide and thiazolidinedione in association; 95,8% from a monotherapy with sulfonamide; 19,3% from other agents in association, also with DPP-IV inhibitors and 97,2% of subjects doesn't assume any antidiabetic therapy taken into account. 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 90,1% in 2014.

Table 4.5.4. 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]

	2014 N = 1.074		2013 N = 911		2012 N = 808	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**60,4**	**-5,9**	**64,2**	**-8,3**	**70,0**	**/**
Gender						
Male	60,9	-0,8	61,4	-10,5	68,6	/
Female	60,0	-10,6	67,1	-6,3	71,6	/
Age group						
≤45	70,0	-15,6	82,9	-4,8	87,1	/
46-65	58,1	3,5	56,1	-8,3	61,3	/
66-75	56,3	-10,2	62,7	-11,9	71,2	/
>75	66,2	-7,5	71,6	-6,7	76,7	/
Therapy						
Monotherapy with metformin	92,9	10,4	84,1	-3,2	86,9	/
Metformin and sulfonamides	86,9	3,6	83,8	3,1	81,3	/
Metformin and thiazolidinedione	83,9	1,5	82,6	55,5	53,1	/
Metformin, sulfonamide and thiazolidinedione	80,0	29,0	62,0	46,8	42,2	/
Monotherapy with sulfonamide	95,8	18,7	80,8	-6,3	86,2	/
Other combination therapy	19,3	16,7	16,5	-42,9	29,0	/
No anti-diabetic therapy	97,2	1,4	95,8	-0,2	96,0	/
Without patients who continue a previous DPP-IV inhibitors therapy	90,1	7,5	83,8	2,0	82,1	/

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 regards the origin therapy of subjects with DPP-IV inhibitors reimbursement criteria but who don't take DPP-IV inhibitors:

- During 2012 32,6% come from a monotherapy with metformin, 26,1% from metformin and sulfonamides in association; 3% from metformin and thiazolidinedione in association; 3,4% from metformin, sulfonamide and thiazolidinedione in association; 4,4% from a monotherapy with sulfonamide; 9,4% from other agents in association, also with DPP-IV inhibitors, and 21,0% doesn't come from any antidiabetic therapy.
- During 2013 28,9% come from a monotherapy with metformin, 23,9% from metformin and sulfonamides in association; 3,2% from metformin and thiazolidinedione in association; 5,3% from metformin, sulfonamide and thiazolidinedione in association; 3,6% from a monotherapy with sulfonamide; 7,9% from other agents in association, also with DPP-IV inhibitors, and 27,2% doesn't come from any antidiabetic therapy.
- During 2014 26,0% come from a monotherapy with metformin, 21,4% from metformin and sulfonamides in association; 4,0% from metformin and thiazolidinedione in association; 4,9% from metformin, sulfonamide and thiazolidinedione in association; 3,5% from a monotherapy with sulfonamide; 13,7% from other agents in association, also with DPP-IV inhibitors, and 26,3% doesn't come from any antidiabetic therapy.

Economic impact of indicators

The improvement of all indicators described in this section is associated with an improvement of patient' 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	+0,99%	€ 3.824.321
H.DB-3.2	-0.36%	€ -1,387,364
H.DB-3.3	+0.77%	€ 2,981,397

°This value includes all NHS reimbursed pharmaceutical expenditure (standard distribution and medicines purchased by Public Hospitals)

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

4.6 Medicines use and treatment adherence profiles in COPD.

Indicators for obstructive pulmonary diseases medicines

- Percentage of patients with a hospitalization for COPD in treatment with ICS (Indicator H-DB 4.1)
- Percentage of patients with a 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 considered 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 analysed 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 analysed 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.

Cohort of subjects in analysis

The number of subjects analysed aged 40 years or older in treatment with medicines for obstructive pulmonary diseases amounts to 1.348.189 in 2014 (Table 4.6.1). The prevalence of treatment with medicines for obstructive pulmonary diseases amounts to 11,7% of the study sample (10,3% in Northern Italy, 12,7% in Central Italy and 15,1% in Southern Italy). The prevalence of the treatment with medicines for obstructive pulmonary diseases increases with age (8,2% in the age group ≤45 years, 9,2% in the age group 46-65 years, 15,1% in the age group 66-75 years and 18,7% in the age group >75 years).

Table 4.6.1. Distribution of patients in treatment with medicines for obstructive pulmonary diseases

	2014			2013			2012		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**1.348.189**	**11,7**	**-0,2**	**1.351.077**	**12,0**	**5,6**	**1.279.294**	**11,4**	**/**
Geographic distribution									
North	715.309	10,3	-2,6	734.363	10,8	4,9	699.833	10,4	/
Centre	309.656	12,7	1,2	305.986	12,8	4,7	292.155	12,3	/
South	323.224	15,1	4,0	310.728	14,7	8,2	287.306	13,7	/
Gender									
Male	599.781	10,7	0,0	599.948	10,9	5,6	568.306	10,4	/
Female	748.408	12,7	-0,4	751.129	12,9	5,6	710.988	12,3	/
Age group									
≤45	158.055	8,2	-3,3	163.435	8,6	6,2	153.948	8,2	/
46-65	511.686	9,2	-2,6	525.601	9,7	5,9	496.293	9,2	/
66-75	313.612	15,1	0,0	313.721	15,4	4,8	299.316	14,7	/
>75	364.836	18,7	4,7	348.320	18,2	5,6	329.737	17,3	/
Mean age	64.9 ± 14.4			64.4 ± 14.3			64.5 ± 14.2		

N: number of subjects analysed aged 40 years or older in treatment with medicines for obstructive pulmonary diseases, with the exclusion of subjects with a previous hospitalization for asthma and/or a previous treatment with receptor antagonists.
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 44.082 in 2014.
The percentage of patients in treatment with ICS in the period following hospital discharge amounts to 57,9%; this value is slightly higher than the previous year (+0,9% in 2014 compared to 2013). If the presence of a therapy with ICS is evaluated up until December 31, 2014, the following percentages have been registered: 61,4% in 2014, 66,4% in 2013 and 69,4% in 2012. The percentage of subjects in treatment is slightly lower in Southern Italy (53,4%) compared to Northern Italy (63,0%) and Central Italy (54,0%), and in females (57,3% vs 58,3% of males). This percentage changes with age (43,1% in the age group ≤45 years, 53,1% in age group 46-65 years, 62,1% in age group 66-75 years and 57,5% in age group > 75 years) and is higher in old users than in new users (75,0% vs 29,0% of new users).

Table 4.6.2. Number of patients with a hospitalization for COPD in treatment with ICS [numerator]/Total number of patients with a hospitalization for COPD [denominator]

	2014 N = 44.082		2013 N = 45.550		2012 N = 45.710	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**57,9**	**0,9**	**57,4**	**0,8**	**56,9**	**/**
Geographic distribution						
North	63,0	1,3	62,1	0,7	61,7	/
Centre	54,0	-2,8	55,5	1,4	54,8	/
South	53,4	2,8	51,9	0,2	51,8	/
Gender						
Male	58,3	0,2	58,2	0,6	57,8	/
Female	57,3	2,1	56,1	1,0	55,6	/
Age group						
≤45	43,1	8,0	40,0	-14,1	46,5	/
46-65	53,1	2,7	51,7	0,6	51,4	/
66-75	62,1	1,6	61,1	0,7	60,6	/
>75	57,5	0,1	57,4	0,8	57,0	/
Treatment status						
New users	29,0	1,4	28,6	0,7	28,4	/
Old users	75,0	0,2	74,9	-0,8	75,5	/
Follow-up until 31 Dec 2013	61,4		66,4		69,4	/

Since data was available up until December 31, 2014, the last reporting year is 2013 (in order to have a complete one full observation year also for subjects included at in December 2013). The presence of a 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 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 a treatment with leukotriene receptor antagonists.

Percentage of patients with a 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 44.082 in 2014.
The percentage of patients in treatment with LABA and/or LAMA in the period following hospital discharge amounts to 57,1%; this percentage is higher compared to previous years (+2,0% in 2014 compared to 2013; +2,4% in 2013 compared to 2012). If the presence of a therapy with LABA and/or LAMA is evaluated up until December 31, 2014, the percentages are the following: 59,3% in 2014, 61,9% in 2013 and 62,9% in 2012. This percentage is lower in Southern (49,9%) than in Northern (64,0%) and Central (52,9%) Italy, and in females (53,7% compared to 59,4% of males). The presence of a treatment changes with age (31,9% in the age group ≤45 years, 51,2% in the age group 46-65 years, 62,4% in the age group 66-75 years and 56,7% in the age group >75 years) and is more elevated in old users (75,4% vs 26,1% of new users).

Table 4.6.3. Number of patients with a hospitalization for COPD in treatment with LABA and/or LAMA [numerator]/Total number of patients with one hospitalization for COPD [denominator]

	2014 N = 44.082		2013 N = 45.550		2012 N = 45.710	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**57,1**	**2,0**	**56,0**	**2,4**	**54,7**	**/**
Geographic distribution						
North	64,0	1,8	62,9	3,0	61,1	/
Centre	52,9	-2,1	54,0	1,8	53,1	/
South	49,9	4,6	47,7	1,6	46,9	/
Gender						
Male	59,4	1,7	58,4	2,5	57,0	/
Female	53,7	2,5	52,4	2,5	51,1	/
Age group						
≤45	31,9	8,1	29,5	-9,0	32,5	/
46-65	51,2	4,1	49,2	2,7	47,9	/
66-75	62,4	2,9	60,6	3,2	58,8	/
>75	56,7	1,0	56,1	1,7	55,2	/
Treatment status						
New users	26,1	2,2	25,6	3,5	24,7	/
Old users	75,4	1,2	74,5	0,4	74,2	/
Follow-up until 31 December 2014	59,3		61,9		62,9	/

Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

The presence of an 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 1.181.365 in 2014.
The percentage of subjects in treatment with ICS without exacerbations amounts to 55,6%; this value is slightly higher than the previous year (+0,4% in 2014 compared to 2013). This percentage amounts to 17,1% in 2014, 23,5% in 2013 and 35,2% in 2012 if the absence of exacerbations is evaluated starting from January 1, 2009. This percentage is higher in Northern Italy (64,1%) than in Central (49,8%) and Southern (40,9%) Italy, in younger subjects (67,1% in the age group ≤45 years, 61,7% in the age group 46-65 years, 50,1% in the age group 66-75 years and 45,3% in the age group >75 years), in new users (63,4% compared to 42,2% of old users) and in males (56,7% vs 54,8% of females).

Table 4.6.4. Number of patients in treatment with ICS without exacerbations [numerator]/Total number of patients in treatment with ICS [denominator]

	2014 N = 1.181.365		**2013 N = 1.117.423**		**2012 N = 1.127.579**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**55,6**	**0,4**	**55,4**	**-1,9**	**56,5**	**/**
Geographic distribution						
North	64,1	0,8	63,6	0,6	63,3	/
Centre	49,8	0,4	49,6	-8,6	54,3	/
South	40,9	-0,5	41,1	-2,4	42,1	/
Gender						
Male	56,7	0,3	56,5	1,9	55,5	/
Female	54,8	0,4	54,6	-5,7	57,9	/
Age group						
≤45	67,1	1,0	66,5	0,8	65,9	/
46-65	61,7	1,1	61,1	0,5	60,8	/
66-75	50,1	-0,5	50,3	-3,3	52,0	/
>75	45,3	-1,2	45,8	-4,6	48,0	/
Treatment status						
New users	63,4	0,0	63,4	-1,3	64,2	/
Old users	42,2	-0,3	42,3	-0,9	42,7	/
From 01-January-2009	17,1		23,5		35,2	/

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, 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).
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 1.311.215 in 2014.
The percentage of adherent patients is of 13,9%; this value decreased compared to the previous year (-1,4% in 2014 compared to 2013). The adherence is higher in Northern Italy (15,1%) compared to Central (13,9%) and Southern (11,1%) Italy, in males (17,9% vs 10,7% of females), in old users (33,2% compared to 2,5% in new users) and in patients with exacerbations (18,6% compared to 10,2% of patients without exacerbations). Moreover, adherence to the treatment improves with age (4,1% in the age group ≤45 years, 7,6% in the age group 46-65 years, 17,1% in the age group 66-75 years, 25,2% in the age group >75 years), excluding occasional users from the analysis, the percentage of adherent patients amounts to 37,4% in 2014.

Table 4.6.5. 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]

	2014 N = 1.311.215		2013 N = 1.239.069		2012 N = 1.244.323	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**13,9**	**-1,4**	**14,1**	**3,6**	**13,6**	**/**
Geographic distribution						
North	15,1	-1,4	15,3	2,4	14,9	/
Centre	13,9	-6,0	14,8	4,4	14,1	/
South	11,1	5,2	10,5	6,8	9,9	/
Gender						
Male	17,9	-1,1	18,1	3,0	17,6	/
Female	10,7	-1,7	10,8	4,0	10,4	/
Age group						
≤45	4,1	-6,1	4,3	6,4	4,1	/
46-65	7,6	-4,2	7,9	2,7	7,7	/
66-75	17,1	-1,0	17,2	1,0	17,1	/
>75	25,2	0,4	25,1	-1,3	25,4	/
Treatment status						
New users	2,5	-1,4	2,5	4,6	2,4	/
Old users	33,2	1,4	32,7	1,3	32,3	/
Exacerbation status						
Without exacerbations	10,2	-2,3	10,4	3,3	10,1	/
With exacerbations	18,6	-0,6	18,8	3,6	18,1	/
Total without occasional users	37,4	-0,1	37,4	1,8	36,7	/

This indicator has not been calculated in LHUs for which extra-site data management was infeasible.
Since data was available up until December 31, 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).
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 1.311.215 in 2014.
The percentage of occasional users amounts to 62,8%; this value is slightly higher than the previous year (+0,8% in 2014 compared to 2013). There are no significant differences across Italy (Northern 62,6%; Central 62,8%; Southern 63,3%). The percentage of occasional users is slightly higher in females (66,5% vs 58,1% of males), in new users (82,4% compared to 29,7% of old users) and in subjects without exacerbations (68,9% compared to 55,1% in patients with exacerbations). The occasional use is higher among younger subjects (77,0% in age group ≤45 years, 71,6% in age group 46-65 years, 57,9% in age group 66-75 years and 47,1% in age group >75 years).

Table 4.6.6. 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]

	2014 N = 1.311.215		**2013** N = 1.239.069		**2012** N = 1.244.323	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**62,8**	**0,8**	**62,3**	**-1,0**	**63,0**	**/**
Geographic distribution						
North	62,6	0,8	62,1	-0,5	62,4	/
Centre	62,8	2,7	61,2	-1,6	62,2	/
South	63,3	-0,9	63,9	-1,8	65,1	/
Gender						
Male	58,1	0,8	57,7	-1,1	58,3	/
Female	66,5	0,8	66,0	-1,0	66,7	/
Age group						
≤45	77,0	0,7	76,5	-0,8	77,1	/
46-65	71,6	1,1	70,8	-0,4	71,2	/
66-75	57,9	0,9	57,4	0,0	57,4	/
>75	47,1	-0,2	47,2	1,1	46,7	/
Treatment status						
New users	82,4	0,5	82,0	-0,2	82,2	/
Old users	29,7	-2,9	30,6	-1,0	30,9	/
Exacerbation status						
Without exacerbations	68,9	0,9	68,2	-0,7	68,7	/
With exacerbations	55,1	0,6	54,8	-1,6	55,6	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).
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 4.6.7.).

Table 4.6.7. 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	+0,11%	€ 1.118.279
H.DB-4.2	+0,13%	€ 1.294.464
H.DB-4.3	-0,04%	€ -353.515
H.DB-4.4	+3,45%	€ 34.855.775
H.DB-4.5	-0,15%	€ -1.560.467

The reduction of ICS use for patients without exacerbations could result in savings in 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).

4.7 Medicines use and treatment adherence profiles in osteoporosis.

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 considered 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 into two groups: new users and patients already in treatment (old users) according 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 according to a therapeutic 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 and older in treatment with medicines for osteoporosis amounts to 315.310 in 2014 (Table 4.7.1). The prevalence of treatment with osteoporosis medicines amounts to 1,9% of the study sample (1,7% in Northern, 2,0% in Central and 2,5% in Southern of Italy). This value increases with age (1,2% in the age group 46-65 years, 5,0% in the age group 66-75 years and 7,3% in the age group >75 years) and is lower compared to the previous year (-7,8% in 2014 compared to 2013).

Table 4.7.1. Distribution of patients in treatment with medicines for osteoporosis

	2014			2013			2012		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**315.310**	**1,9**	**-7,8**	**341.844**	**2,1**	**-2,9**	**352.131**	**2,2**	**/**
Geographic distribution									
North	167.566	1,7	-8,7	183.495	1,9	-3,5	190.220	1,9	/
Centre	69.941	2,0	-6,3	74.649	2,2	-3,2	77.086	2,2	/
South	77.803	2,5	-7,0	83.700	2,7	-1,3	84.825	2,8	/
Gender									
Male	22.213	0,3	-5,6	23.519	0,3	-2,6	24.150	0,3	/
Female	293.097	3,4	-7,9	318.325	3,8	-2,9	327.981	3,9	/
Age group									
≤45	2.386	0,0	-14,4	2.787	0,0	-7,0	2.997	0,0	/
46-65	67.938	1,2	-11,3	76.576	1,4	-5,6	81.082	1,5	/
66-75	103.103	5,0	-9,2	113.525	5,6	-3,6	117.799	5,8	/
>75	141.883	7,3	-4,7	148.956	7,8	-0,9	150.253	7,9	/
Mean age	73.2 ± 10.2			72.9 ± 10.2			72.7 ± 10.2		

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 and older in treatment with osteoporosis medications, with vertebral or hip fracture, or who assume corticosteroids amounts to 63.625 in 2014.
The percentage of subjects who received osteoporosis medicines within one year from a vertebral or hip fracture, or a treatment with corticosteroids, amounts to 22,2%; this value is lower than in the previous year (-10,7% in 2014 compared to 2013). If the presence of a therapy with medicines for osteoporosis is evaluated until 31 December 2014, the observed percentages are the following: 22,9 in 2014, 27,8% in 2013 and 32,5% in 2012. There are no significant differences across Italy: 22,8% in Northern Italy, 20,4% in Central Italy, 22,2% in Southern Italy. The prevalence of osteoporotic therapy changes with gender (10,9% in males and 27,7% in females) and with age (the highest percentage amounts to 26.3% in the age group 66-75 years).

Table 4.7.2. Number of patients in treatment with osteoporosis medications, with vertebral or hip fracture, or who assume corticosteroids [numerator]/Total number of patients with hip or vertebral fracture or who assume corticosteroids [denominator]

	2014 N=63.625		2013 N=59.204		2012 N=55.014	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**22,2**	**-10,7**	**24,9**	**-11,4**	**28,1**	**/**
Geographic distribution						
North	22,8	-9,9	25,4	-10,6	28,4	/
Centre	20,4	-12,2	23,3	-11,3	26,2	/
South	22,2	-11,6	25,1	-14,9	29,5	/
Gender						
Male	10,9	-7,7	11,8	-11,9	13,4	/
Female	27,7	-11,1	31,2	-11,2	35,1	/
Age group						
≤45	10,9	-7,7	11,8	-11,9	13,4	/
46-65	20,6	-7,8	22,3	-10,5	24,9	/
66-75	26,3	-9,2	29,0	-10,1	32,2	/
>75	20,8	-12,6	23,8	-12,6	27,3	/
Follow up until 31December 2013	22,9		27,8		32,5	/

Since data was available up until December 31 2014, the last reporting year is 2013 (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 with a vertebral or hip fracture, or who 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 osteoporosis amounts to 130.082 in 2014.
The percentage of patients undergoing treatment for osteoporosis but without a vertebral or hip fracture, and without corticosteroid therapy amounts to 79,3% in 2014; this value is slightly lower than the previous year (-2,4% in 2014 compared to 2013). If the absence of vertebral or hip fracture and of a corticosteroid therapy is evaluated starting from January 1, 2009, the percentage in 2014 amounts to 70,6%. There are no significant differences across Italy (Northern Italy 67,%; Central Italy 68,0%; Southern Italy 86,4%), neither among males and females (78,4% vs 79,4%). Treatment with osteoporosis medications without a vertebral or hip fracture, or a therapy with corticosteroids appears higher in old users compared to new users (96,3% compared to 90,8% of males) and is higher among younger patients (100,0% in age group ≤45 years, 83,0% in age group 46-65 years, 76,1% in age group 66-75 years and 79,4% in age group > 75 years).

Table 4.7.3. 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]

	2014 N=130.082		2013 N=134.024		2012 N=135.181	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**79,3**	**-2,4**	**81,3**	**0,3**	**81,0**	**/**
Geographic distribution						
North	67,4	-2,3	69,0	1,2	68,2	/
Centre	68,0	-11,1	76,5	5,1	72,8	/
South	86,4	-1,7	87,8	-0,4	88,2	/
Gender						
Male	78,4	-8,4	85,7	-0,3	85,9	/
Female	79,4	-1,7	80,7	0,4	80,4	/
Age group						
≤45	100,0	0,0	100,0	0,0	100,0	/
46-65	83,0	-2,0	84,7	-0,1	84,7	/
66-75	76,1	-1,8	77,4	0,7	76,9	/
>75	79,4	-0,5	79,8	0,7	79,3	/
Treatment status						
New users	76,2	0,4	75,9	-1,8	77,3	/
Old users	81,1	-2,8	83,4	1,1	82,5	/
From 01-January-2009	70,6		76,6		81,6	/

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 315.310 in 2014.
The percentage of subjects in treatment with calcium or vitamin D in combination with osteoporosis medications amounts to 58,3% in 2014; this value is slightly higher than in previous years (+3,9% in 2014 compared to 2013 and +3,9% in 2013 compared to 2012). The percentage is higher in Northern (62,9%) and Central (54,6%) Italy compared to Southern (51,4%) Italy, among females (58,5% compared to 55,0% of males), in the 46-75 years age range (53,8% in age group ≤45 years, 59,9% in age group 46-65 years, 60,6% in age group 66-75 years and 55,9% in age group >75 years) and in old users (58,9% compared to 56,2% of new users).

Table 4.7.4. 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]

	2014 N=315.310		2013 N=341.844		2012 N=352.131	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**58,3**	**3,9**	**56,1**	**3,9**	**54,0**	**/**
Geographic distribution						
North	62,9	3,7	60,7	3,8	58,5	/
Centre	54,6	3,5	52,8	3,6	51,0	/
South	51,4	5,2	48,9	4,9	46,6	/
Gender						
Male	55,0	7,0	51,4	3,9	49,4	/
Female	58,5	3,7	56,4	3,9	54,3	/
Age group						
≤45	53,8	7,7	49,9	0,3	49,8	/
46-65	59,9	3,3	58,0	4,1	55,7	/
66-75	60,6	4,0	58,2	4,1	55,9	/
>75	55,9	4,3	53,6	3,8	51,6	/
Treatment status						
New users	56,2	5,6	53,2	4,7	50,9	/
Old users	58,9	3,3	57,1	3,6	55,1	/

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 5.4)

The number of patients aged 18 years or older in treatment with medicines for osteoporosis amounts to 330.289 in 2014.
The percentage of adherent subjects amounts to 46,8% in 2014; this value is lower than in the previous year (-3,4% in 2014 compared to 2013) and is higher in Northern Italy (50,9%) compared to Central (41,3%) and Southern Regions (42,1%). The adherence is higher in females (47,3 compared to 40,9% of males), in older subjects (the highest value amounts to 48,1% in the age-group 66-75 years) and in old users (53,2% compared to 28,5% of new users). Excluding occasional users from the analysis, the percentage of adherent patients in treatment with medicines for osteoporosis amounts to 55,1% in 2014.

Table 4.7.5. Number of adherent patients in treatment with osteoporosis medications [numerator]/Total number of patients in treatment with osteoporosis medications [denominator]

	2014 N=330.289		**2013 N=340.373**		**2012 N=353.791**	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**46,8**	**-3,4**	**48,5**	**-0,5**	**48,7**	**/**
Geographic distribution						
North	50,9	-2,4	52,1	-0,5	52,4	/
Centre	41,3	-10,2	46,0	0,3	45,8	/
South	42,1	-0,2	42,2	-0,9	42,6	/
Gender						
Male	40,9	-1,2	41,4	0,3	41,3	/
Female	47,3	-3,5	49,0	-0,6	49,3	/
Age group						
≤45	29,0	-2,5	29,7	0,7	29,5	/
46-65	43,7	-4,4	45,7	-0,7	46,0	/
66-75	48,1	-3,4	49,8	-1,1	50,3	/
>75	47,8	-3,0	49,3	-0,3	49,4	/
Treatment status						
New users	28,5	2,0	27,9	-0,9	28,1	/
Old users	53,2	-4,3	55,6	-2,0	56,8	/
TOTAL without occasional users	55,1	-3,3	56,9	-0,7	57,3	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

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 330.289 in 2014.
The percentage of occasional subjects amounts to 15,0% in 2014; this value appears slightly higher than the previous year (+0,7% in 2014 compared to 2013), and is higher in Central (16,0%) and Southern (18,3%) Italy compared to Northern Regions (13,1%) and in males (24,8% compared to 14,3% of females). The prevalence of occasional users is higher in younger age-group (34,6% in age group ≤45 years, 17,4% in age group 46-65 years, 13,8% in age group 66-75 years and 14,63% in age group > 75 years) and in new users (36,5% compared to 7,5% old users).

Table 4.7.6. Number of occasional patients in treatment with osteoporosis medications [numerator]/Total number of patients in treatment with osteoporosis medications [denominator]

	2014 N=330.289		2013 N=340.373		2012 N=353.791	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**15,0**	**0,7**	**14,9**	**-1,1**	**15,0**	**/**
Geographic distribution						
North	13,1	0,8	13,0	-2,1	13,3	/
Centre	16,0	3,2	15,5	-2,3	15,9	/
South e Islands	18,3	-1,3	18,6	0,9	18,4	/
Gender						
Male	24,8	0,0	24,8	-2,7	25,5	/
Female	14,3	0,8	14,2	-0,7	14,3	/
Age group						
≤45	34,6	8,2	32,0	-11,1	36,0	/
46-65	17,4	3,1	16,9	1,0	16,7	/
66-75	13,8	1,2	13,7	0,4	13,6	/
>75	14,3	-1,1	14,5	-2,1	14,8	/
Treatment status						
New users	36,5	1,5	35,9	0,2	35,9	/
Old users	7,5	2,3	7,3	6,3	6,9	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

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 4.7.7).

Table 4.7.7. 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	+0,17%	€ 660.920
H.DB-5.2	-1,10%	€ -4.276.541
H.DB-5.3	+0,26%	€ 1.010.819
H.DB-5.4	+0,42%	€ 1.632.861
H.DB-5.5	-0,20%	€ -777.553

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, reinvestment in policies aiming at improving adherence, promoting larger consumption of both calcium and vitamin D and of high-efficacy medications (more expensive) in patients with a high fracture risk (e.g. patients with a previous fracture).

4.8 Medicines use and treatment adherence profiles in depression.

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 treatment with antidepressants (Indicator H-DB 6.2)

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

Methodology

The following antidepressants have been considered 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; 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 possible 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 and 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 the 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 1.052.009 (Table 4.8.1) in 2014. The prevalence of treatment with antidepressants amounts to 6,3% of the study sample (6,3% in Northern and in Central Italy and 6,4% in Southern Italy). This value is higher in females (8,6% compared to 4,0% of males) and increases with age (2,7% in age group ≤45 years, 6,6% in age group 46-65 years, 10,1% in age group 66-75 years and 14,4% in the age group >75 years). The prevalence of treatment is higher compared to the previous year (+1,4% in 2014 compared to 2013).

Table 4.8.1. Distribution of patients in treatment with antidepressants

	2014			2013			2012		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**1.052.009**	**6,3**	**1,4**	**1.037.043**	**6,3**	**1,5**	**1.021.219**	**6,3**	**/**
Geographic distribution									
North	631.262	6,3	-0,1	632.206	6,4	1,4	623.266	6,4	/
Centre	222.039	6,3	4,0	213.411	6,2	-0,1	213.654	6,2	/
South	198.708	6,4	3,8	191.426	6,3	3,9	184.299	6,1	/
Gender									
Male	319.504	4,0	2,0	313.112	3,9	2,2	306.323	3,9	/
Female	732.505	8,6	1,2	723.931	8,6	1,3	714.896	8,5	/
Age group									
≤45	194.313	2,7	-2,7	199.710	2,9	-3,0	205.864	3,0	/
46-65	366.937	6,6	0,7	364.439	6,7	0,8	361.696	6,7	/
66-75	209.477	10,1	1,2	207.000	10,1	2,6	201.691	9,9	/
>75	281.282	14,4	5,8	265.894	13,9	5,5	251.968	13,2	/
Mean age	62.2 ± 17.1			61.8 ± 17.1			61.3 ± 17.1		

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 failure of 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 towards a different SSRI, amounts to 6.762 in 2014.
The percentage of patients that at the third change of therapy shift to a SNRI class drug amounts to 18,9%; this value is lower than the previous year (-4,5% in 2014 compared to 2013). This percentage is slightly higher in Northern Regions (21,0%) compared to Central (13,9%) and Southern (19,0%) Italy and in patients already in treatment (old users) (20,1% compared to 17,4% of new users). There are no differences between males and females and no correlation between age and shift to SNRI (17,3% in ≤45 years age group, 20,1% in age group 46-65 years, 20,2% in age group 66-75 years, 17,4% in age group > 75 years).

Table 4.8.2. Number of patients in treatment with SNRI after a second failure of SSRIs (Selective Serotonin Reuptake Inhibitors) [numerator]/Total number of patients in treatment with antidepressants after a second a failure of SSRIs (Selective Serotonin Reuptake Inhibitors) [denominator]

	2014 N = 6.762		2013 N = 7.025		2012 N = 8.034	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**18,9**	**-4,5**	**19,8**	**-1,4**	**20,1**	**/**
Geographic distribution						
North	21,0	-5,7	22,3	0,5	22,2	/
Centre	13,9	-13,4	16,1	-2,6	16,5	/
South	19,0	7,9	17,6	-5,3	18,6	/
Gender						
Male	18,9	-1,4	19,2	-12,6	22,0	/
Female	18,9	-5,8	20,1	3,8	19,4	/
Age group						
≤45	17,3	-5,6	18,3	-4,8	19,2	/
46-65	20,1	-7,0	21,6	-0,3	21,7	/
66-75	20,2	-4,8	21,2	1,2	21,0	/
>75	17,4	0,6	17,3	-2,2	17,7	/
Treatment status						
New users	17,4	-10,6	19,5	2,7	19,0	/
Old users	20,1	-0,2	20,1	-4,5	21,1	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

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 in 2014 amounts to 1.037.043.
The percentage of adherent patients amounts to 38,4%; this value in slightly higher than previous years (0,7% in 2014 compared to 2013, +1,7% in 2013 compared to 2012). The adherence is lower in Southern Italy (35,3%) compared to Northern (39,8%) and to Central (36,9%) Italy and among males (37,6% compared to 38,7% of females). The adherence improves with age (32,9% in the age group ≤45 years, 37,5% in the age group 46-65 years, 40,8% in the age group 66-75 years, 41,9% in the age group > 75 years) and is higher in old users (patients already in treatment) compared to new ones (48,9% vs 16,6%). Excluding occasional subjects, the percentage of patients adherent to the treatment with antidepressants is 50,6% in the year 2014. If we consider as adherent subjects those patients who have a therapeutic coverage ≥50%, the adherence rises to 55,6%. The adherence amounts to 35,9% when patients also affected by other psychiatric diseases are excluded.

Table 4.8.3. Number of adherent patients to a treatment with antidepressants [numerator]/Total number of patients in treatment with antidepressants [denominator]

	2014 N = 1.037.043		2013 N = 1.021.219		2012 N = 1.016.078	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**38,4**	**0,7**	**38,1**	**1,7**	**37,5**	**/**
Geographic distribution						
North	39,8	0,8	39,5	1,7	38,9	/
Centre	36,9	-3,7	38,3	0,0	38,3	/
South	35,3	6,3	33,2	4,2	31,9	/
Gender						
Male	37,6	0,6	37,4	1,6	36,8	/
Female	38,7	0,8	38,4	1,7	37,8	/
Age group						
≤45	32,9	0,1	32,9	0,4	32,8	/
46-65	37,5	0,6	37,2	1,6	36,7	/
66-75	40,8	1,1	40,4	1,8	39,6	/
>75	41,9	0,1	41,9	1,4	41,3	/
Treatment status						
New users	16,6	0,8	16,5	-2,2	16,9	/
Old users	48,9	0,0	48,9	0,6	48,6	/
Cut off 50%*	55,6	0,2	55,5	1,5	54,7	/
Total without occasional patients	50,6	0,2	50,5	0,8	50,1	/
Total without patients with other psychiatric diseases^	35,9	-0,3	36,1	1,8	35,4	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

N: number of patients aged 18 years or older in treatment with antidepressants taken into account
* In this case, patients with a therapeutic coverage ≥50% are defined as adherent patients.
^Patients with, at least, one prescription of antipsychotics (ATC CODE N05A) and/or mood stabilizers (ATC CODE N03A) within the year before the index date.

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 1.037.043 in 2014.
The percentage of occasional subjects amounts to 24,0%; this value is slightly lower than previous years (-1,6% in 2014 compared to 2013; -2,5% in 2013 compared to 2012). The percentage of occasional subjects is higher in Southern Italy (28,5%) compared to Northern (22,8%) and Central (23,5%) Italy and in males (25,8% compared to 23,3% in females). Occasional use is higher in younger age-groups (30,0% in age group ≤45 years, 24,5% in age group 46-65 years, 22,0% in age group 66-75 years and 20,5% in age group >75 years), in new users (51,9% compared to 10,6% of patients already in treatment). Occasional use amounts to 25,2% when patients also affected by other psychiatric diseases are excluded.

Table 4.8.4 Number of occasional patients in treatment with antidepressants [numerator]/ Total number of patients in treatment with antidepressants [denominator]

	2014 N = 1.037.043		2013 N = 1.021.219		2012 N = 1.016.078	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**24,0**	**-1,6**	**24,4**	**-2,5**	**25,1**	**/**
Geographic distribution						
North	22,8	-0,9	23,1	-2,4	23,6	/
Centre	23,5	-1,4	23,9	-0,7	24,0	/
South	28,5	-4,0	29,7	-4,6	31,1	/
Gender						
Male	25,8	-1,0	26,0	-1,7	26,5	/
Female	23,3	-1,9	23,8	-2,9	24,5	/
Age group						
≤45	30,0	-0,1	30,1	0,0	30,1	/
46-65	24,5	-1,3	24,8	-2,3	25,4	/
66-75	22,0	-1,6	22,3	-4,0	23,2	/
>75	20,5	-2,0	20,9	-2,6	21,5	/
Treatment status						
New users	51,9	-0,1	51,9	0,5	51,7	/
Old users	10,6	-1,1	10,7	-0,2	10,7	/
TOTAL without patients with other psychiatric diseases^	25,2	-1,4	25,6	-2,9	26,3	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

N: number of patients aged 18 or older in treatment with antidepressants
^Patients with, at least, one prescription of antipsychotics (ATC CODE N05A) and/or mood stabilizers (ATC CODE N03A) within the year before the index date.

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 4.8.5. 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%	€ 30.087
H.DB-6.2	+1,08%	€ 4.999.403
H.DB-6.3	-0,15%	€ -685.531

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, reinvestment in policies to improve adherence and encourage major use of high-efficacy (and more expensive) medications for complex patients.

4.9 Medicines use and treatment adherence profiles in ulcer and esophagitis

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's 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 into 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 conditions within the 12 months prior to the first prescription of the reporting year has been considered:

- 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 of 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 identifies, according to the total amount of drug dispensed, the therapeutic coverage periods.

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 3.441.780 in 2014 (table 4.9.1). The prevalence of treatment with proton pump inhibitors amounts to 20,7% of the study sample (17,7% in Northern Italy, 22,1% in Central Italy and 28,6% in Southern Italy). This value is higher in females (23,0% compared to 18,2% of males) and increases with age (7,1% in age group ≤45 years, 19,6% in age group 46-65 years, 39,5% in age group 66-75 years, 53,1% in age group >75 years).

Table 4.9.1. Distribution of patients in treatment with proton pump inhibitors

	2014			2013			2012		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**3.441.780**	**20,7**	**1,9**	**3.377.781**	**20,7**	**4,5**	**3.232.507**	**19,9**	**/**
Geographic distribution									
North	1.773.287	17,7	-0,1	1.774.261	18,0	4,2	1.702.432	17,4	/
Centre	777.970	22,1	5,3	738.846	21,4	3,0	717.167	20,8	/
South	890.523	28,6	3,0	864.674	28,3	6,4	812.908	26,8	/
Gender									
Male	1.471.871	18,2	2,2	1.439.979	18,1	4,7	1.375.661	17,4	/
Female	1.969.909	23,0	1,7	1.937.802	23,0	4,4	1.856.846	22,2	/
Age group									
≤45	501.098	7,1	-3,6	520.069	7,5	0,0	520.204	7,5	/
46-65	1.086.926	19,6	-0,5	1.092.673	20,1	2,8	1.062.732	19,6	/
66-75	820.532	39,5	2,5	800.405	39,2	5,4	759.448	37,4	/
>75	1.033.224	53,1	7,1	964.634	50,4	8,4	890.123	46,8	/
Mean age	64.7 ± 16.6			64.1 ± 16.7			63.7 ± 16.7		

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 3.377.781 in 2014.
The percentage of patients in treatment with proton pomp inhibitors without meeting AIFA reimbursement criteria (AIFA Note 1 or AIFA note 48) amounts to 43,2%; this value is lower than the previous year (-7,2% in 2014 compared to 2013). The percentage is higher in Northern Italy (48,1%) compared to Central (37,1%) and to Southern (38,4%) Italy, in younger patients (69,2% in age group ≤45 years, 54,3% in age group 46-65 years, 32,3% in age group 66-75 years, 25,7% in age group >75 years), in new users (66,5% compared to 29,5% of old users) and in patients without a previous hospitalization (45,3% compared to 33,6% of patients with a previous hospitalization). No differences have been observed among males and females (43,3% vs 43,2%). The percentage of patients with a < 4 weeks treatment length amounts to 23,3%.

Table 4.9.2. Percentage of patients in treatment with proton pomp inhibitors who do not meet AIFA's 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]

	2014 N = 3.377.781		**2013** N = 3.232.507		**2012** N = 3.080.925	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**43,2**	**-7,2**	**46,6**	**4,4**	**44,6**	**/**
Geographic distribution						
North	48,1	0,1	48,1	4,8	45,9	/
Centre	37,1	-2,4	38,0	-4,6	39,8	/
South	38,4	-24,8	51,0	10,2	46,3	/
Gender						
Male	43,3	-7,7	46,9	4,2	45,0	/
Female	43,2	-6,8	46,3	4,5	44,3	/
Age group						
≤45	69,2	-4,0	72,1	4,0	69,4	/
46-65	54,3	-6,0	57,7	6,8	54,1	/
66-75	32,3	-8,1	35,1	6,1	33,1	/
>75	25,7	-8,3	28,0	5,5	26,6	/
Treatment status						
New users	66,7	-0,9	67,3	4,4	64,4	/
Old users	29,5	-12,0	33,6	11,5	30,1	/
Hospitalization history	23,3	-15,0	27,4	22,3	22,4	/
Without a previous hospitalization						
With a previous hospitalization	45,3	-7,1	48,8	3,5	47,1	/

This indicator has not been calculated in all LHUs, as extra-site data management appeared unfeasible. Since data was available up until December 31, 2014, the last reporting year is 2013 (in order to have one full observation year also for subjects included in December 2013).

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 4.9.3).

Table 4.9.3. 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	-0,52%	€ -5.022.114

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

4.10 Medicines use and treatment adherence profiles in anemia

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 14.863 in 2014 (Table 4.10.1). The prevalence of treatment with epoetin alpha amounts to 0,9‰ of the study sample. This data increases with the age of patients (0,1‰ in the age group ≤ 45 years, 0,5‰ in the age group 46-65 years, 1,7‰ in the age group 66-75 years and 4,2‰ in the age group >75 years).

Table 4.10.1. Distribution of patients in treatment with epoetin alpha

	2014			2013			2012		
	N	‰ SS	Var.%	N	‰ SS	Var.%	N	‰ SS	Var.%
TOTAL	**14.863**	**0,9**	**33,4**	**11.141**	**0,7**	**13,9**	**9.782**	**0,6**	**/**
Geographic distribution									
North	8.261	0,8	36,0	6.073	0,6	24,1	4.892	0,5	/
Centre	4.112	1,2	43,6	2.864	0,8	-2,4	2.933	0,9	/
South	2.490	0,8	13,0	2.204	0,7	12,6	1.957	0,6	/
Gender									
Male	7.635	0,9	35,7	5.628	0,7	16,5	4.830	0,6	/
Female	7.228	0,8	31,1	5.513	0,7	11,3	4.952	0,6	/
Age group									
≤45	604	0,1	5,6	572	0,1	0,0	572	0,1	/
46-65	2.659	0,5	16,6	2.280	0,4	8,4	2.103	0,4	/
66-75	3.466	1,7	29,4	2.679	1,3	14,1	2.348	1,2	/
>75	8.134	4,2	45,0	5.610	2,9	17,9	4.759	2,5	/
Mean age	74.0 ± 13.5			72.6 ± 14.0			72.0 ± 14.1		

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 9.794 in 2014.
The percentage of patients starting a new cycle of therapy with epoetin alpha biosimilars amounts to 59,9%; this value is higher than in previous years (+54,6% in 2014 compared to 2013). There is a certain variability across Italy (Northern 56,5%; Central 47,6%; Southern 67,5%), with a percentage slightly higher in females (56,5% vs 55,2% in males). 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 58,1%, while the percentage of patients who start a new cycle of theraphy with biosimilar of epoetin alfa and have a history of a previous cycle of therapy amounts to 33,2%.

Table 4.10.2. 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]

	2014 N = 9.794		2013 N = 7.162		2012 N = 6.238	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**55,9**	**54,6**	**36,2**	**93,7**	**18,7**	**/**
Geographical distribution						
North	56,5	30,1	43,4	121,9	19,6	/
Centre	47,6	58,7	30,0	22,8	24,5	/
South	67,5	167,4	25,2	178,6	9,1	/
Gender						
Male	55,2	54,0	35,9	95,3	18,4	/
Female	56,7	55,2	36,5	92,2	19,0	/
Age group						
≤45	42,3	71,2	24,7	114,3	11,5	/
46-65	50,6	55,1	32,6	68,0	19,4	/
66-75	58,1	46,8	39,6	82,8	21,6	/
>75	58,2	54,8	37,6	110,9	17,8	/
New therapy cycles within previous 12 months status						
Without previous therapy cycles	57,1	54,0	37,1	89,7	19,6	/
With previous therapy cycles	31,7	64,1	19,3	144,4	7,9	/
New therapy cycles from 01-January-2009°						
Without previous therapy cycles	58,1	51,7	38,3	88,9	20,3	/
With previous therapy cycles	33,2	71,8	19,3	134,6	8,2	/

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 4.10.3).

Table 4.10.3. 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	-0,09	€ -145.633

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.

4.11 Medicines use and treatment adherence profiles in rheumatoid arthritis

- Percentage of patients with rheumatoid arthritis initiating treatment with biological medication without previous use of classic DMARDS for at least 3 months (Indicator H-DB 9.1);
- Percentage of patients with rheumatoid arthritis in treatment with biological medication not in combination with MTX (Indicator H-DB 9.2)

Calculation methodology

For the purpose of this analysis the following biological medications have been considered: abatacept ATC CODE L04AA24; etanercept ATC CODE L04AB01; infliximab ATC CODE L04AB02; adalimumab ATC CODE L04AB04; certolizumab pegol ATC CODE L04AB05; golimumab ATC CODE L04AB06; tocilizumab ATC CODE L04AC07; rituximab ATC CODE L01XC02; anakinra ATC CODE L04AC03.
All patients with rheumatoid arthritis (ICD-9 CODE 714 or MEDICAL EXONERATION CODE 006) have been considered for the analysis, while patients with following concomitant diagnosis have been excluded: ankylosing spondylitis (ICD-9 CODE 720.0 or MEDICAL EXONERATION CODE 054), psoriatic arthropathy (ICD-9 CODE 696.0 or MEDICAL EXONERATION CODE 045.696.0), psoriasis (ICD-9 CODE 696.1 or MEDICAL EXONERATION CODE 045.696.1), regional enteritis of small intestine (Crohn's disease) (ICD-9 CODE 555 or MEDICAL EXONERATION CODE 009), ulcerative enterocolitis (ICD-9 CODE 556 or MEDICAL EXONERATION CODE 009).
Subjects analysed have been classified as subjects with a previous treatment with Disease Modifying Antirheumatic Drugs (DMARDs) if they have received treatment of at least 3 months with methotrexate (MTX, ATC CODE L01BA01), leflunomide (ATC CODE L04AA13), sulfasalazine (ATC CODE A07EC01), azathioprine (ATC CODE L04AX01), chloroquine (ATC CODE P01BA01), hydroxychloroquine (ATC CODE P01BA02), ciclosporin (ATC CODE L04AD01), sodium aurothiomalate (ATC CODE M01CB01), auranofin (ATC CODE M01CB03)
Subjects in treatment with biological medications have been classified as new users or already in treatment (old users) in relation to the absence or presence, respectively, of at least one prescription of biological medications within the 12 months preceding the index date (date of the first prescription of the reporting year).

Cohort of Patients in analysis

The number of patients aged 18 years or older with rheumatoid arthritis and in treatment with biological medications amounts to 3.983 in 2014 (Table 4.11.1). The prevalence of subjects with rheumatoid arthritis in treatment with biological medication amounts to 0,3‰ of the study sample. These values increase slightly with the age of patients (0,5‰ in the age group 46-65, 0,6‰ in the age group 66-75 and 0,2‰ in the age group >75 years).

Table 4.11.1. Distribution of patients with rheumatoid arthritis in treatment with biological medications

	2014			2013			2012		
	N	‰ SS*	Var.%	N	‰ SS*	Var.%	N	‰ SS*	Var.%
TOTAL	**3.983**	**0,3**	**3,3**	**3.855**	**0,3**	**17,1**	**3.291**	**0,3**	**/**
Geographic distribution									
North	3.031	0,4	7,9	2.810	0,4	14,2	2.460	0,4	/
Centre	849	0,3	17,8	721	0,3	9,1	661	0,3	/
South	103	0,0	-68,2	324	0,1	90,6	170	0,1	/
Gender									
Male	784	0,1	1,3	774	0,1	18,9	651	0,1	/
Female	3.199	0,5	3,8	3.081	0,5	16,7	2.640	0,4	/
Age group									
≤45	720	0,1	2,3	704	0,1	14,1	617	0,1	/
46-65	1.978	0,5	-0,7	1.991	0,5	15,6	1.722	0,4	/
66-75	946	0,6	9,6	863	0,6	20,5	716	0,5	/
>75	339	0,2	14,1	297	0,2	25,8	236	0,2	/
Mean age	57.9 ± 13.7			57.6 ± 13.5			57.3 ± 13.5		

*The prevalence has been calculated on 1000 residents and was calculated only for LHUs with available data of medical exoneration codes.
N: number of patients aged 18 years or older with rheumatoid arthritis in treatment with biological medications.
SS: study sample

Results and considerations

- Percentage of patients with rheumatoid arthritis initiating treatment with biological medications without previous use of classic DMARDS for at least 3 months (Indicator H-DB 9.1)

The number of patients aged 18 years or older with rheumatoid arthritis who initiate treatment with biological medications amounts to 871 in 2014.
The percentage of patients with rheumatoid arthritis initiating treatment with biological medications without previous use of DMARDS for at least 3 months amounts to 73,2%; this value is lower than the previous year (-1,0% in 2014 compared to 2013). There is a certain variability across Italy (Northern 72,1%; Central 77,2%; Southern 85,7%), with a higher percentage in males (77,1% vs 72,3% of females). This percentage changes with according to the age of patients (77,7% in age group ≤45 years, 67,8% in age group 46-65 years, 79,0% in age group 66-75 years, 81,7% in age group >75 years).

Table 4.11.2. Percentage of patients with rheumatoid arthritis initiating treatment with biological medications without previous use of classic DMARDS for at least 3 months [numerator]/Total number of patients with rheumatoid arthritis initiating treatment with biological medications [denominator]

	2014 N = 871		2013 N = 920		2012 N = 806	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**73,2**	**-1,0**	**74,0**	**3,5**	**71,5**	**/**
Geographical distribution						
North	72,1	3,6	69,6	4,9	66,3	/
Centre	77,2	1,0	76,4	5,3	72,6	/
South	85,7	-6,1	91,3	7,5	84,9	/
Gender						
Male	77,1	-0,7	77,7	13,7	68,3	/
Female	72,3	-0,9	73,0	0,8	72,4	/
Age group						
≤45	77,7	3,7	74,9	-0,2	75,0	/
46-65	67,8	-6,6	72,6	3,5	70,2	/
66-75	79,0	2,0	77,4	11,5	69,4	/
>75	81,7	14,3	71,4	-12,3	81,5	/

This indicator has been calculated only for LHUs with available data of medical exoneration code.
This indicator has been not calculated for those LHUs for which an extra-site data management was unfeasible.
The presence of a biological therapy is evaluated for the reporting year.
N: number of patients aged 18 years or older with rheumatoid arthritis initiating treatment with biological medications. The diagnosis of rheumatoid arthritis was derived from the presence of the medical exoneration code 006.

- Percentage of patients with rheumatoid arthritis in treatment with biological medications not in combination with MTX (Indicator H-DB 9.2)

The number of patients aged 18 years or older with rheumatoid arthritis who initiating treatment with biological medications amounts to 3.855 in 2014.
The percentage of patients with rheumatoid arthritis in treatment with biological medications not in combination with MTX amounts to 56,5%; this value increased compared to the previous year (+6,8% in 2014 compared to 2013). There is a certain variability across Italy (Northern 55,9%; Central 60,1%; Southern 53,7%), while no remarkable differences according to the gender have been observed (57,5% in males and 56,3% in females). This percentage changes with age of patients (65,1% in age group ≤45 years, 54,7% in age group 46-65 years, 54,8% in age group 66-75 years, 53,2% in age group >75 years). The percentage of new users is higher than the one of old users (62,9% vs 54,5%).

Table 4.11.3. Number of patients with rheumatoid arthritis in treatment with biological medications not in combination with MTX [numerator]/Total number of patients with rheumatoid arthritis in treatment with biological medications [denominator]

	2014 N = 3.855		2013 N = 3.291		2012 N = 2.788	
	%	Var.%	%	Var.%	%	Var.%
TOTAL	**56,5**	**6,8**	**52,9**	**-1,4**	**53,7**	**/**
Geographical distribution						
North	55,9	9,6	51,0	-0,8	51,4	/
Centre	60,1	6,7	56,3	-4,1	58,7	/
South	53,7	-7,8	58,2	-7,1	62,7	/
Gender						
Male	57,5	-0,1	57,6	1,1	56,9	/
Female	56,3	8,7	51,8	-2,2	53,0	/
Age group						
≤45	65,1	1,0	64,4	-0,7	64,8	/
46-65	54,7	8,3	50,6	-1,7	51,4	/
66-75	54,8	8,0	50,7	-2,1	51,8	/
>75	53,2	12,0	47,5	6,7	44,5	/
Treatment status						
New users	62,9	14,9	54,8	-7,4	59,2	/
Old users	54,5	4,0	52,4	0,9	52,0	/

This indicator has been calculated only for those LHUs with available data on medical exoneration code.
This indicator has been not calculated for those LHUs for which an extra-site data management was unfeasible.
The presence of a biological therapy is evaluated for the reporting year.
N: number of patients aged 18 years or older with rheumatoid arthritis who begin a treatment with biological medications. The diagnosis of rheumatoid arthritis was derived from the presence of the medical exoneration code 006.

4.12 Medicines use and treatment adherence profiles in psoriasis

- Percentage of patients with psoriasis initiating traditional systemic medications without previous use of topic medications (Indicator H-DB 10.1);
- Percentage of patients with psoriasis initiating biological medication without previous use of methotrexate or cyclosporine for at least 3 months (Indicator H-DB 10.2).

Calculation methodology

For the purpose of this analysis, the following biological medications have been considered: adalimumab (ATC CODE L04AB04), etanercept (ATC CODE L04AB01); infliximab (ATC CODE L04AB02); ustekinumab (ATC CODE L04AC05).
All patients with psoriasis (ICD-9 CODE 696.1 or MEDICAL EXONERATION CODE 045.696.1) have been considered for the analysis, while patients with the following concomitant diagnosis have been excluded: rheumatoid arthritis (ICD-9 CODE 714 or MEDICAL EXONERATION CODE 006); ankylosing spondylitis (ICD-9 CODE 720.0 or MEDICAL EXONERATION CODE 054), psoriatic arthropathy (ICD-9 CODE 696.0 or MEDICAL EXONERATION CODE 045.696.0), regional enteritis of small intestine (Crohn's disease) (ICD-9 CODE 555 or MEDICAL EXONERATION CODE 009), ulcerative enterocolititis (ICD-9 CODE 556 or MEDICAL EXONERATION CODE 009).
Subjects analyseed have been classified as:
- subjects with a previous treatment with traditional systemic medications in presence of treatment with methotrexate (MTX, ATC CODE L01BA01), cyclosporine (ATC CODE L04AD01), acitretin (ATC CODE D05BB02).
- subjects with a previous treatment with topic medications in presence of a previous treatment with antipsoriatics for topical use (ATC CODE D05A) or topical dermatological corticosteroids (ATC CODE D07).

Cohort of Patients in analysis

The number of patients aged 18 years or older with psoriasis and in treatment with biological medication amounts to 1.330 in 2014 (Table 4.12.1). The prevalence of treatment with biological medications amounts to 0,1‰ of the study sample. This prevalence amounts to 0,1‰ in age group ≤45 years, 0,2‰ in age group 46-65 years and 0,1‰ in age group 66-75 years.

Table 4.12.1. Distribution of patients with psoriasis in treatment with biological medications

	2014			2013			2012		
	N	‰ SS*	Var.%	N	‰ SS*	Var.%	N	‰ SS*	Var.%
TOTAL	**1.330**	**0,1**	**-16,8**	**1.598**	**0,1**	**46,6**	**1.090**	**0,1**	**/**
Geographic distribution									
North	830	0,1	9,8	756	0,1	35,0	560	0,1	/
Centre	429	0,2	23,3	348	0,1	7,1	325	0,1	/
South	71	0,0	-85,6	494	0,2	141,0	205	0,1	/
Gender									
Male	880	0,2	-15,2	1.038	0,2	45,6	713	0,1	/
Female	450	0,1	-19,6	560	0,1	48,5	377	0,1	/
Age group									
≤45	387	0,1	-21,3	492	0,1	49,5	329	0,1	/
46-65	673	0,2	-20,3	844	0,2	42,3	593	0,2	/
66-75	203	0,1	6,3	191	0,1	51,6	126	0,1	/
>75	67	0,0	-5,6	71	0,1	69,0	42	0,0	/
Mean age	53.6 ± 13.5			52.4 ± 13.5			52.4 ± 13.0		

* The prevalence has been calculated on 1000 residents and only for LHUs with available data on medical exoneration codes.
N: number of patients aged 18 years or older with psoriasis in treatment with biological medications. The diagnosis of psoriasis was derived from the presence of the medical exoneration code 045.696.1.
SS: study sample.

Results and considerations

Percentage of patients with psoriasis who begin traditional systemic medications without a previous use of topic medications (Indicator H-DB 10.1)

The number of patients aged 18 years or older with psoriasis initiating traditional systemic medications amounts to 551 in 2014.
The percentage of patients with psoriasis initiating traditional systemic medications without a previous use of topic medications amounts to 38,7%; this value is higher than the previous year (+15,5% in 2014 compared to 2013). There is a certain variability across Italy (Northern 36,3%; Central 48,7%; Southern 31,1%), and a higher percentage is observed in females compared to males (45,5% vs 34,8%). The value changes with age of patients (33,8% in age group ≤45 years, 41,3% in age group 46-65 years, 39,2% in age group 66-75 years, 38,2% in age group >75 years).

Table 4.12.2. Number of patients with psoriasis initiating traditional systemic medications without previous use of topic medications [numerator]/Total number of patients with psoriasis initiating traditional systemic medications [denominator].

	2014 N = 551		2013 N = 487		2012 N = 739	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**38,7**	**15,5**	**33,5**	**-29,9**	**47,8**	**/**
Geographical distribution						
North	36,3	16,1	31,3	-39,2	51,4	/
Centre	48,7	14,4	42,5	16,6	36,5	/
South	31,1	-2,5	31,9	-18,8	39,3	/
Gender						
Male	34,8	10,9	31,3	-32,1	46,2	/
Female	45,5	24,8	36,5	-28,2	50,8	/
Age group						
≤45	33,8	-6,6	36,2	-17,4	43,8	/
46-65	41,3	16,4	35,5	-29,5	50,3	/
66-75	39,2	56,7	25,0	-51,6	51,7	/
>75	38,2	19,2	32,1	-17,2	38,8	/

This indicator has been calculated only for LHUs with available medical exonerations data.
The presence of a traditional systemic medications' therapy is evaluated for the reporting year.
N: number of patients aged 18 years or older with psoriasis who begin a treatment with traditional systemic medications. The diagnosis of psoriasis was derived from the presence of the medical exoneration code 045.696.1.

Percentage of patients with psoriasis initiating biological medications without previous use of methotrexate or cyclosporine for at least 3 months (Indicator H-DB 10.2)

The number of patients aged 18 years or older with psoriasis initiating biological medications amounts to 379 in 2014.
The percentage of patients with psoriasis initiating biological medications withoutprevious use of methotrexate or cyclosporine for at least 3 months amounts to 86,3%; this value is lower thanthe previous year (-0,8% in 2014 compared to 2013). There is a certain variability across Italy (Northern 88,7%; Central 81,3%; Southern 94,4%), and a higher percentage is observed in females compared to males (87,2% vs 85,8%). The percentage changes with age of patients (78,3% in age group ≤45 years, 91,7% in age group 46-65 years, 87,0% in age group 66-75 years, 86,7% in age group >75 years).

Table 4.12.3. Number of patients with psoriasis initiating biological medications without previous use of methotrexate or cyclosporine for at least 3 months [numerator]/Total number of patients with psoriasis initiating biological medications [denominator]

	2014 N = 379		2013 N = 623		2012 N = 426	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**86,3**	**-0,8**	**87,0**	**-3,5**	**90,1**	**/**
Geographical distribution						
North	88,7	12,5	78,9	-12,3	89,9	/
Centre	81,3	-7,4	87,8	1,5	86,5	/
South	94,4	2,4	92,2	0,0	92,2	/
Gender						
Male	85,8	-1,7	87,3	-4,4	91,4	/
Female	87,2	0,9	86,4	-2,1	88,3	/
Age group						
≤45	78,3	-5,6	82,9	-8,9	91,0	/
46-65	91,7	3,3	88,8	-0,3	89,1	/
66-75	87,0	-3,1	89,8	-3,8	93,3	/
>75	86,7	-5,8	92,0	3,5	88,9	/

This indicator has been calculated only for LHUs with available data onmedical exoneration codes.
The presence of a biological medications' therapy is evaluated for the reporting year.
N: number of patients aged 18 years or older with psoriasis initiating biological medications. The diagnosis of psoriasis was derived from the presence of the medical exoneration code 045.696.1.

Acronyms

CV = cardiovascular
DMARDS = Disease Modifying Antirheumatic Drugs
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
MTX = methotrexate
SNRI = serotonin and norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor

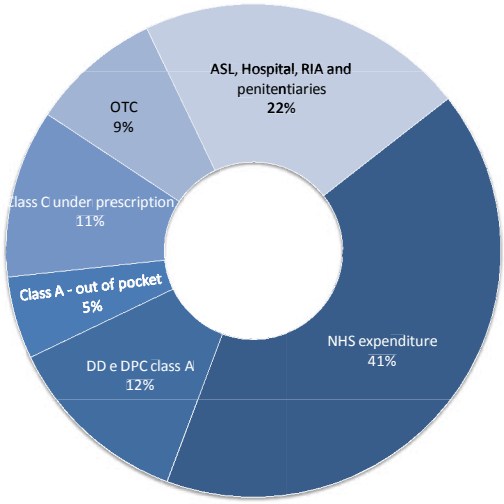
SECTION 5

GENERAL CHARACTERISTICS OF PHARMACEUTICAL USE IN ITALY

Table 5.1.a. Pharmaceutical expenditure breakdown in 2014 compared to 2013 (Table and Figure)

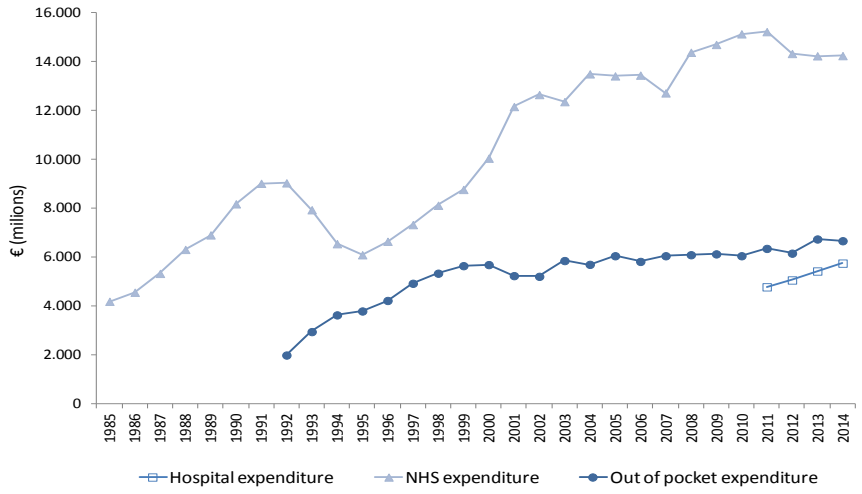
	Expenditure	%	Var % 14-13
Gross NHS outpatient expenditure*	10.988	41,2	-2,1%
Class A medicines dispensed by the Direct distribution	3.249	12,2	8,2%
Out of pocket Class A medicines	1.441	5,4	-1,9%
Class C medicines under prescription	2.937	11,0	-1,6%
OTC medicines	2.283	8,6	0,2%
Health Public Facilities (Health Local Unit, Public Hospital, Nursing Home; Penitentiary, etc.)*	5.745	21,6	6,2%
Total	**26.643**	**100,0**	**1,0%**

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



Pharmaceutical expenditure represents a significant part of health care spending (1,6% of the national Gross Domestic Product (GDP) in 2014). The total national pharmaceutical expenditure (concerning both public and private expenses) amounted to €26,6 billion, increasing by +1% compared to the previous year (**Table 5.1.a.**). 75,0% was reimbursed by the National Health Service. Pharmaceuticals have been supplied mainly through the outpatient channel (41,2%).. Pharmaceutical expenditure in charge of citizens amounted to €6.661 million, consisting primarily of Class C (non-reimbursed) medicines requiring a medical prescription (11,0% of total expenditure).

Figure and Table 5.1.b. Outpatient pharmaceutical expenditure for the period 1985 – 2014



	Gross outpatient NHS expenditure	Class A medicines by direct distribution	NHS expenditure^	Private expenditure	Inpatient expenditure^^
	(million)	*(million)*	*(million)*	*(million)*	*(million)*
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	4.774
2012	11.488	2.837	14.325	6.152	5.055
2013	11.226	3.003	14.229	6.732	5.421
2014	**10.988**	**3.249**	**14.237**	**6.661**	**5.745**

^including payback and discount and Class A medicine expenditure dispensed through the Direct distribution;
^^including payback and net of Class A medicine expenditure dispensed through the Direct distribution
Source: OsMed data and Data from the Ministry of Economy and IMS Health

5.1 Outpatient pharmaceutical consumption

During 2014 the total pharmaceutical expenditure, composed by public and private expenses, amounted to €20.009 billion, decreasing by -0,1% over the previous year (Table 5.1.2).
The NHS outpatient pharmaceutical expenditure is composed of expenses of medicines reimbursed by the NHS (Table 5.1.1 and Table 5.1.2), including those of reimbursed (Class A) medicines provided through direct distribution. Public pharmaceutical expenditure totalled €11.848 billion (€194,9 per capita), representing 59,2% of total outpatient pharmaceutical expenditure. Compared to 2013, public pharmaceutical expenditure data revealed a slight decrease by -0,2%, as a result of the increased expenses of Class A medicines provided through the direct distribution (+ 8,2%), balanced by the decrease in outpatient pharmaceutical expenditure net of discounts and rebates (-3,0%).
The private pharmaceutical expenditure (Table 5.1.2), 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), and expenses of Class A or C medicines privately purchased by citizens, was €8.161 billion, resulting in a decrease by -0,1% compared to 2013. This reduction is primarily due to the decrease of expenses for privately purchased Class A medicines (-1,9%) and under prescription Class C medicines (-1,6%), balanced by an increase in citizens' cost-sharing (+ 4,5%) and OTC medicines' expenditure (+ 0,2%).Citizen cost-sharing expenditure (Table 5.1.1 and 5.1.2) amounted to €1.500 million (approximately €24,7 per capita), impacting gross pharmaceutical expenditure by 13,7%. Compared to 2013, the increase of the co-payment was mainly determined by the boost in shares exceeding the reference price of off-patent medicines (+8,6%), while a reduction in co-payment expenditure (ticket per prescription and package) was registered (-2,0%).
As regards consumption of 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 previous years, mainly because of the strengthening of alternative distribution channels (i.e. direct distribution by public health facilities). During 2014, in average 1.039,4 doses of Class A medicines reimbursed by the NHS per 1.000 inhabitants were consumed every day (in 2013 the doses amounted to 1.032,3), corresponding to over 1 billion packages dispensed (18,7 packs per capita), with an increase, respectively, of + 0,7% and + 1,5% compared to 2013.
Major components (i.e. quantity effect, price effect and mix effect) of variations in the gross NHS outpatient pharmaceutical expenditure observed in 2014, compared to the previous year, highlight a decremental effect on expenditure, as a result of increased consumption of prescribed medicines (+2,5 in terms of defined daily doses, DDDs), decrease in average prices (-3,3%) (due to a rise in the use of off patent medicines and the strengthening of medicines delivered through alternative distribution channels) and, finally, changes in the consumption mix in favour of medicines with a lower unitary price (positive mix effect: -1,0%) (Figure 5.1.2).

Table 5.1.1. Outpatient pharmaceutical expenditure: 2010-2014 comparison

		2010 (million)	2011 (million)	2012 (million)	2013 (million)	2014 (million)	Δ % 11/10	Δ % 12/11	Δ % 13/12	Δ % 14/13
1+2+3+4	Gross pharmaceutical expenditure	12.985	12.387	11.488	11.226	10.988	-4,6	-7,3	-2,3	-2,1
1+2	Citizen co-payment	998	1.337	1.406	1.436	1.500	34,0	5,2	2,1	4,5
1	Sharing per prescription	453	577	573	558	546	27,5	-0,7	-2,7	-2,0
2	Reference price share	546	760	833	878	954	39,3	9,6	5,5	8,6
3	Discount^	929	1.028	1.096	927	889	10,7	6,6	-15,4	-4,1
4	Net NHS expenditure	11.058	10.023	8.986	8.863	8.598	-9,4	-10,3	-1,4	-3,0
5	Class A direct distribution°	2.144	2.832	2.837	3.003	3.249	32,1	0,2	5,9	8,2
4+5	**Outpatient expenditure**	**13.202**	**12.855**	**11.823**	**11.866**	**11.848**	**-2,6**	**-8,0**	**0,4**	**-0,2**

^ 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 5.1.2. Comparison of public and private outpatient expenditure (2010-2014)

		2010 (million)	2011 (million)	2012 (million)	2013 (million)	2014 (million)	Δ% 11/10	Δ% 12/11	Δ% 13/12	Δ% 14/13
1	Net NHS expenditure	11.058	10.023	8.986	8.863	8.598	-9,4	-10,3	-1,4	-3,0
2	Class A medicines by Direct distribution	2.144	2.832	2.837	3.003	3.249	32,1	0,2	5,9	8,2
1+2	Total public expenditure	13.202	12.855	11.823	11.866	11.848	-2,6	-8,0	0,4	-0,2
3	Citizen co-payment	998	1.337	1.406	1.436	1.500	34,0	5,2	2,1	4,5
4	Class A medicines paid by citizen*	848	1.026	1.027	1.468	1.441	21,0	0,1	43,0	-1,9
5	Class C medicine under prescription	3.093	3.207	3.000	2.985	2.937	3,7	-6,5	-0,5	-1,6
6	OTC medicines	2.105	2.113	2.125	2.278	2.283	0,4	0,6	7,2	0,2
3+4+5+6	Total private expenditure	7.044	7.683	7.558	8.168	8.161	9,1	-1,6	8,1	-0,1
	Total pharmaceutical expenditure	20.246	20.538	19.381	20.035	20.009	1,4	-5,6	3,4	-0,1
	Share (%) borne NHS	**65,2**	**62,6**	**61,0**	**59,2**	**59,2**				

***** 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 5.1.1. Outpatient pharmaceutical consumption: a comparison between 2010-2014

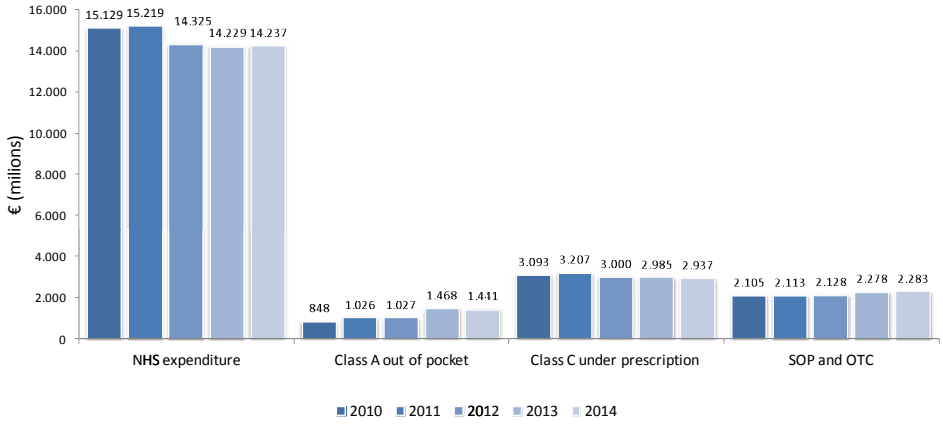


Table 5.1.3. Public and private outpatient pharmaceutical consumption: a comparison between 2010-2014

		2010	2011	2012	2013	2014	Δ %	Δ %	Δ %	Δ %
		*million^*	*million*	*million^*	*million^*	*million^*	11/10	12/11	13/12	14/13
	Prescriptions #	587	590	593	608	609	0,5	0,5	2,5	0,2
	N. Packages									
1	NHS consumption	1.080	1.089	1.095	1.119	1.136	0,8	0,6	2,2	1,5
2	Class A medicines paid by citizen*	123	146	170	213	221	18,7	16,4	25,5	3,6
3	Class A medicines by direct distribution	NA	NA	NA	NA	NA				
1+2+3	Total class A medicines	1.203	1.235	1.265	1.332	1.357	2,7	2,4	5,3	1,9
4	Class C medicines under prescription	283	284	267	254	250	0,4	-6,0	-4,9	-1,6
5	OTC	308	300	280	287	279	-2,6	-6,7	2,6	-2,8
4+5	Total class C medicines	591	584	547	541	529	-1,2	-6,3	-1,1	-2,2
1+2+3+4+5	Total packages	1.794	1.819	1.812	1.873	1.886	1,4	-0,4	3,4	0,7
	DDD/1.000 inhab. die #	956,0	963,0	1.006,6	1.032,3	1.039,4	0,7	4,5	2,6	0,7

NA: not available data

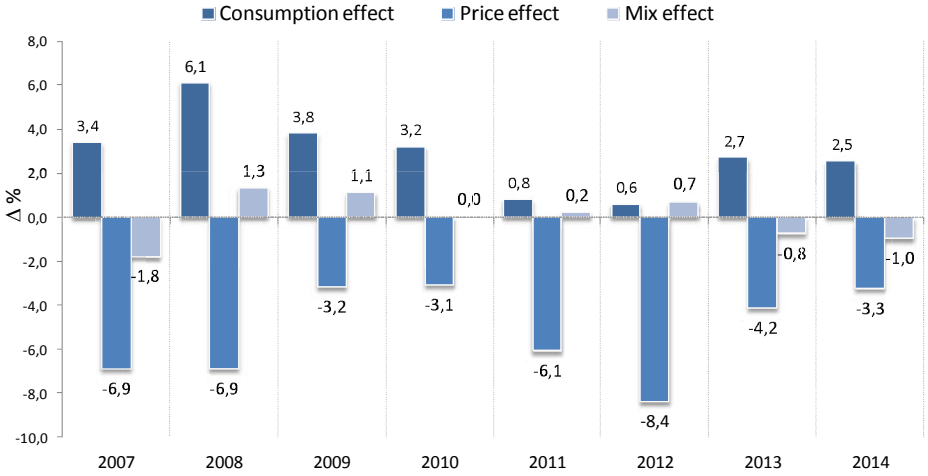
#concerning (class A) NHS reimbursed medicines

*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 5.1.2. Trend of Class A reimbursed medicines expenditure: consumption effect, prices effect and mix effect, during 2007-2014



5.2 Medicines purchased by public health facilities

During 2014 expenditure for medicines purchased by public health facilities (hospitals, health local units, etc) amounted to approximately €9 billion (€141,2 per capita; Table 5.2.1). This share of expenditure represents 34% of the total public and private spending on pharmaceuticals (Table 5.1; i.e. 3.249 €+5.745 billion) and determined an increase by 4,8% compared to 2013. In terms of pharmaceutical consumption (DDDs), an increase by +4,0%%, was registered, with an average 157,0 daily doses per 1.000 inhabitants (hereinafter DDD/1000 inhab. daily). It should be underlined that, even though the definition of medicines purchased by public health facilities in terms of DDDs allows a useful parameterization of consumption at different levels (geographical and temporal), it does not represent 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 flows fuelled by Regions. Expenditure for direct distribution of medicines by public health facilities and home care is significantly higher than expenditure for products supplied in hospital care settings. Indeed during 2014 the direct distribution expenditure amounted to €5.790 billion, concerning mainly Class A reimbursed medicines (€3.250 million), and a residual share of Class C (not reimbursed by the NHS) and Class H (hospital-only) medicines (€2.540 million).

Inpatient pharmaceutical expenditure amounted to €2.904 billion and was composed of 70% Class H medicines. In particular, during 2014 an increase in expenditure for Class A medicines supplied through direct distribution was observed, 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 as 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 patients (difference between sell-in and sell-out), b) the incomplete transfer of expenditure data by Regions.

Table 5.2.1: Expenditure and consumption of medicines purchased by public health facilities at the national level, years 2013-2014

	Per capita NHS expenditure		DDD/1.000 inhab. die	
	€	Δ% 14/13	€	Δ% 14/13
ITALY	148,0	4,8	157,0	4,0

Figure 5.2.1. Direct distribution pharmaceutical expenditure by reimbursement class, years 2011 – 2014

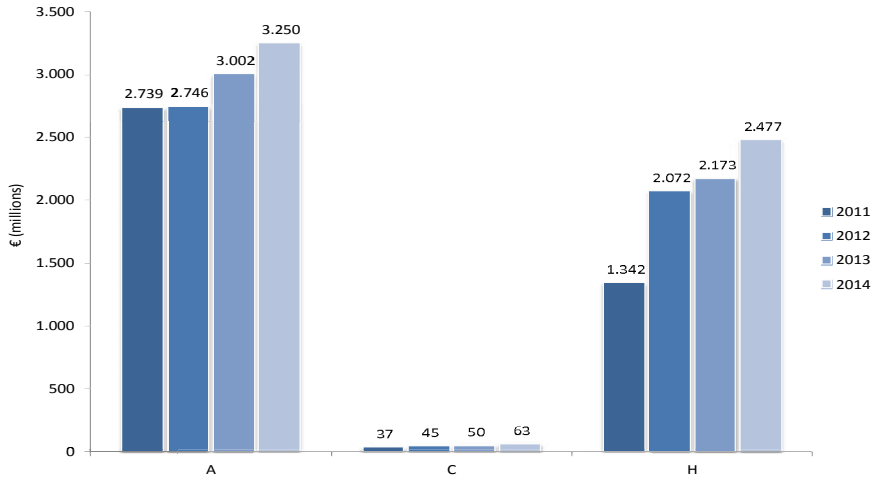
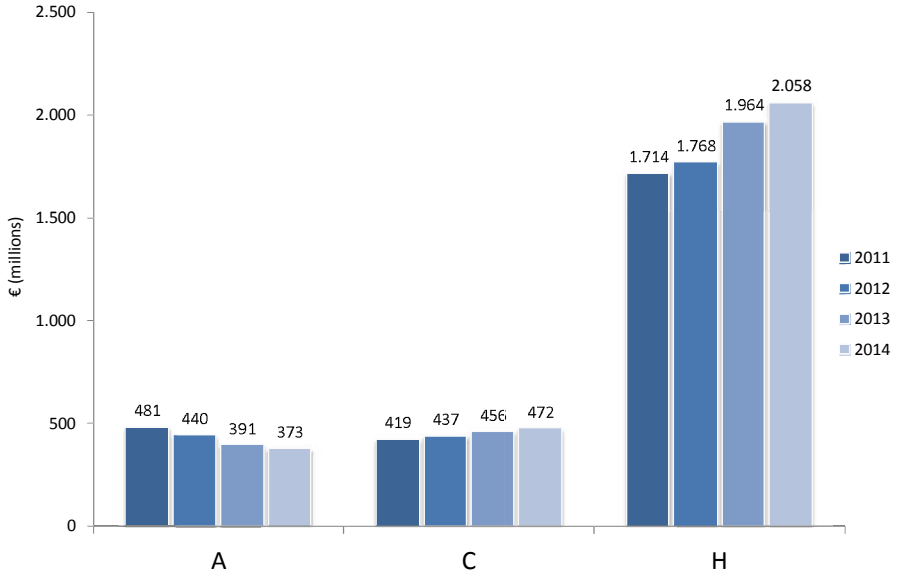


Figure 5.2.2. Inpatient pharmaceutical expenditure by reimbursement class , years 2011 – 2014



5.3 Pharmaceutical consumption by age and gender

Variability in pharmaceutical expenditure and consumption is primarily dependent on changes in epidemiological profiles overtime, variety of healthcare condition settings and 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 36 Health Local Units (HLUs), distributed across the country, was examined. The number of patients referring to HLUs has been estimated to approximately 30 million patients, with an average age and a male/female ratio corresponding to national average data. Data has been readjusted according to the overall national consumption.

Overall, the average pharmaceutical expenditure and consumption is highly dependent on age groups. Compared to age, genderappears to have little influence on general pharmaceutical consumption. For a detailed analysis on settings in which gender differences mostly impact on consumption, please see section 6.
The population in the age group above 64 years highlights a per capita pharmaceutical expenditure 3 times higher than the national average. Moreover, 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 changes in prevalence of average pharmaceutical consumption, 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 older take at least one medicine during the year. Gender differences are detectable in the

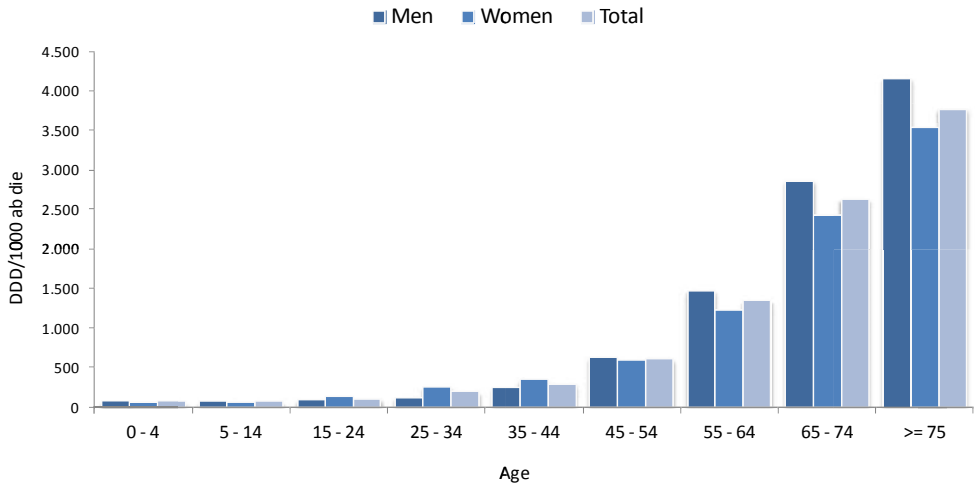
age group 15-64 years, where female prevalence of use appears higher than in males, with an absolute deviation of 9% (see Figure 5.3.1). A major prevalence of pharmaceutical consumption was also observed in children (0-4 years old) if compared to the 15-44 years population group (especially among males): about half of the children received at least one medical prescription during the year. The overall prevalence of pharmaceutical consumption was approximately 55% (51,2% in males and 58,7% in females).
The population aged 64 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 65-74 year old patient consumes an average of 2,6 DDDs per day, while an over 74 year old patient consumes an average of 3,8 DDDs per day (see Table 5.3.1 and figure 5.3.2

Table 5.3.1. Outpatient pharmaceutical expenditure and consumption by age^ 2014

	Gross expenditure (per capita)			% share on total expenditure	DDD/1000 inhab. die			% share on total consumption
Age Range	**Male**	**Female**	**Total**		**Male**	**Female**	**Total**	
0 - 4	23,6	20,4	22,1	0,5	69,2	59,2	64,5	0,3
5 - 14	28,3	23,9	26,3	1,4	68,7	57,3	63,1	0,6
15 - 24	31,1	28,4	29,8	1,6	85,9	124,9	104,8	1,0
25 - 34	38,1	45,3	41,6	2,6	119,3	258,1	188,4	2,1
35 - 44	60,0	72,8	66,4	5,6	241,9	341,0	291,6	4,3
45 - 54	117,5	121,1	119,0	10,3	627,5	600,6	614,0	9,3
55 - 64	244,3	227,3	235,6	16,3	1.467,3	1.223,5	1.342,0	16,1
65 - 74	456,5	408,7	431,1	25,4	2.859,6	2.425,1	2.630,1	26,9
>= 75	672,4	552,3	598,9	36,2	4.150,3	3.535,3	3.772,3	39,5
Overall	**175,6**	**184,9**	**180,4**	**100,0**	**1.008,8**	**1.068,2**	**1.039,4**	**100,0**

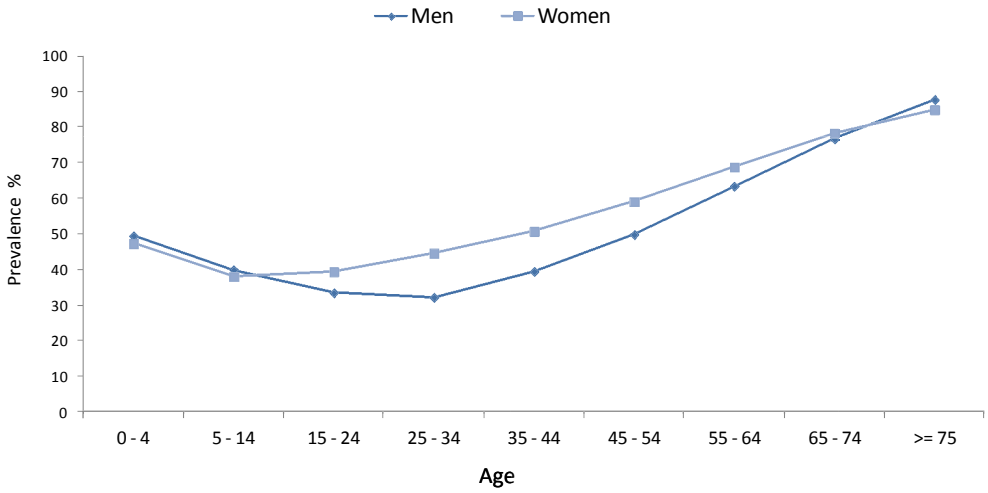
^excluding inpatient consumption

Figure 5.3.1. Prevalence of use by age and gender in the outpatient setting^ 2014



^ excluding inpatient consumption

Figure 5.3.2. Outpatient consumption^ (DDD/1000 inhab. die) by age and gender 2014



^ 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 2004-2014. Throughout the last decade, pharmaceutical consumption registered a persistent upward trend and increased from 763,8 DDD/1000 inhabitants per day in 2004 to 1.039,4 DDD/1000 inhabitants per day in 2014, thus, resulting in a +36% increase.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 2014 were higher than the annual average of +1,3%, as opposed to the second half of the year, where the consumption was below -1,2%. In particular, in August the consumption was 16,5% 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 which over time have determined the granting or not of the status of reimbursed medicine. Starting from 2004, a downwards trend in consumption of Class C medicines was observed; the tendency indeed varied from 236,5 DDD/1000 inhabitants per day in 2004 to 195,8 DDD/1000 inhabitants per day in 2014. The highest average consumption was recorded in February (+9,2% compared to the annual average), whilst the lowest levels of consumption were observed in August (-21,5% compared to annual average). The high levels registered in correspondence with transition months (autumn) mainly result from vaccines consumption. Moreover, 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 2006-2014. In particular, an overall growing trend in consumption was registered, with an increase from 100,6 DDD/1000 inhabitants per day during 2006 to 157,0 DDD/1000 inhabitants per day in 2014. During 2014, the lowest consumption level was observed in August (-44,3%) and December (-18,5%), while July (+29,3%) and January (+17,6%) registered highest 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 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 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), 2004-2014

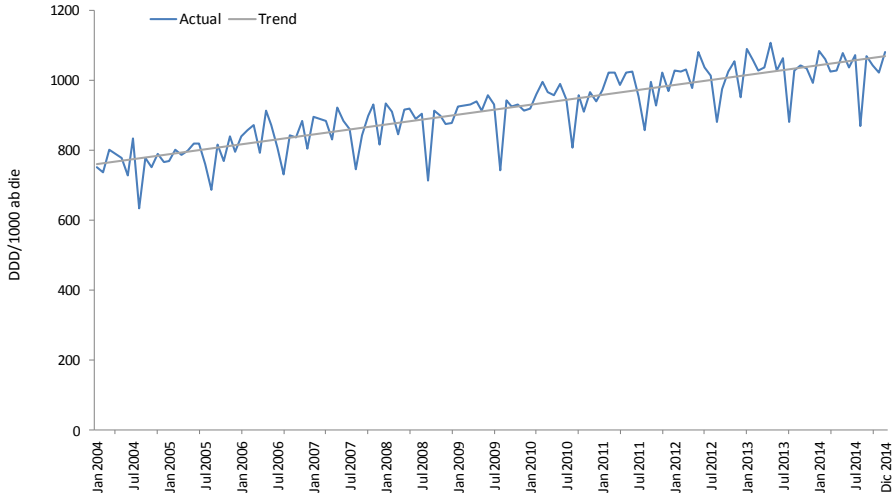


Figure 5.4.2. Trend of Class C medicines under prescription consumption (DDD/1000 inhab. die), 2004-2014

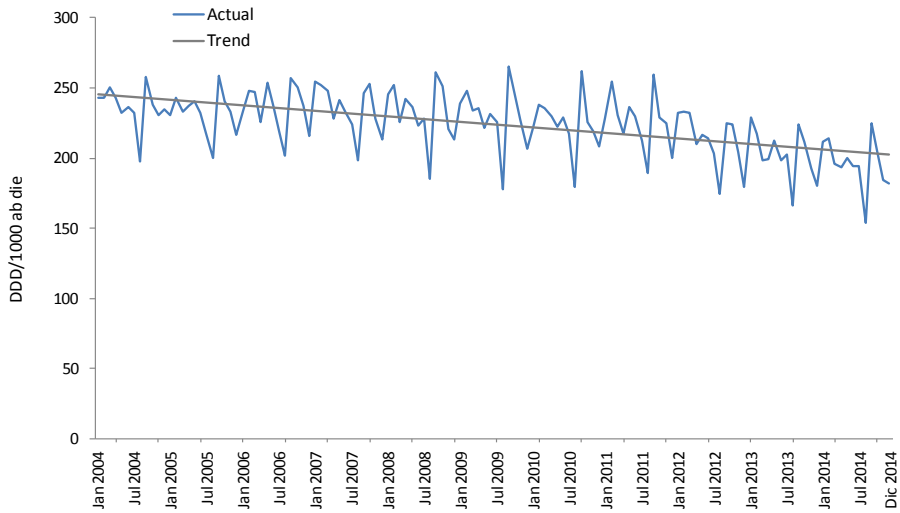
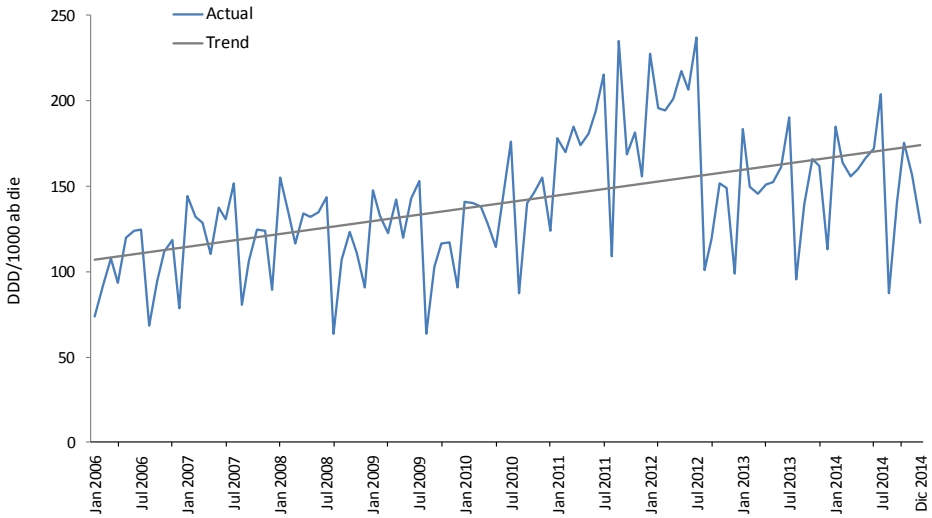


Figure 5.4.3. Trend of consumption of medicines purchased by the public health facilities (DDD/1000 inhab. die), 2006-2014



5.5 Trend of pharmaceutical prices

Data shown in Figure 5.5.1 represent the average price weighted per package and per DDD of Class A reimbursed medicine between January 2004 and December 2014. The time series reveals a descendent trend for both prices, especially starting from 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 2014. Looking at the monthly time series data, trends of the two indexes reveal a steady growth, rising from €10,1 per package (€0,6 per DDD) in 2004 to €11,7 per package (€0,7 per DDD) in 2014, that is, with increase of +15,7% (and +11,4% price per DDD) over a ten year period.

Figure 5.5.3 illustrates the average price performance, weighted per package and per DDD, of medicines purchased by the public health facilities for the period between 2004 and 2014. Averages prices increase from 2006 to 2010, appear stable in the period between 2011 and 2012, and experience a further increase in 2013-2014. 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, 2004-2014

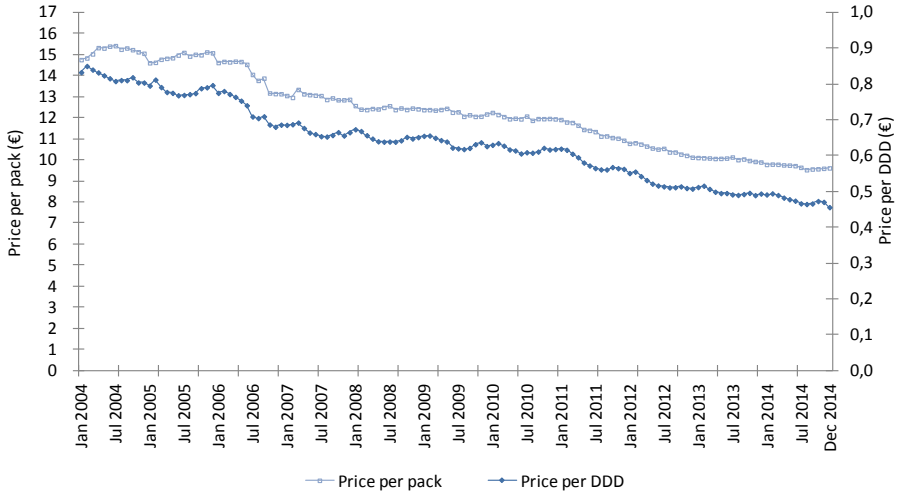


Figure 5.5.2. Average price trend of Class C medicines requiring prescription, 2004-2014

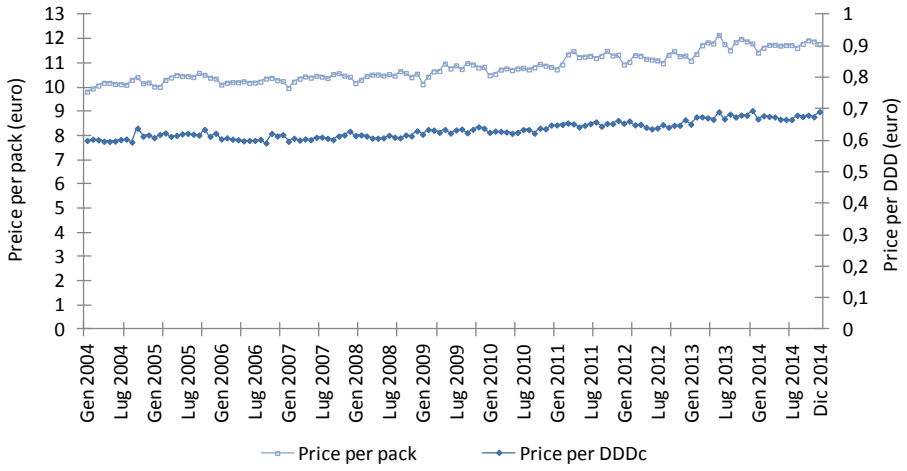
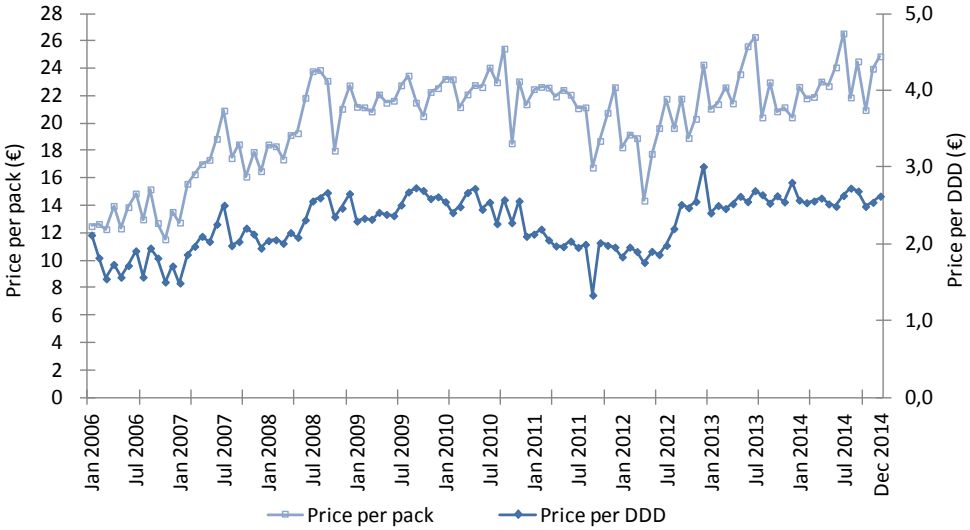


Figure 5.5.3. Average price trend of medicines purchased by health public facilities, 2006-2014



SECTION 6

CONSUMPTION AND EXPENDITURE BY THERAPEUTIC CLASS AND EPIDEMIOLOGICAL DATA

Individual therapeutic categories are analysed in this section. Tables show data concerning private and public pharmaceutical expenditure in a descending order (categories totalling less than €500 million are excluded). Public pharmaceutical expenditure is given by the sum of NHS outpatient pharmaceutical expenditure and inpatient pharmaceutical expenditure.

Table 6.1 shows the composition of public and private pharmaceutical expenditure by classes of reimbursement. Total pharmaceutical expenditure amounted to €26,6 billion, 75% of which reimbursed by the NHS (€11 billion,including €1 billion concerning discounts and rebates, for NHS outpatient pharmaceutical expenditure and €9 billion for inpatient pharmaceutical expenditure. The residual 25% represents expenditure borne by citizens, with €5,2 billion corresponding to medicines not reimbursed by the NHS and €1,4 billion belonging to Class A medicines privately purchased.. Table 6.2 shows medicines consumption distinguishing between medicines provided by the NHS and those privately purchased by citizens. The total amount of medicines consumption in Italy is 1.714 DDDs per 1.000 inhabitants per day,69,8% of which delivered by the NHS, whilst the remaining 30,2% is related to doses of medicines purchased directly by citizens.

Table 6.1. Pharmaceutical expenditure by ATC I level and class of reimbursement in 2014

Therapeutic class	Class A-NHS^		Class A medicines privately purchased		Class C under prescription		Self-medication SOP and OTC		Public Health Facilities		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°
C- Cardiovascular system	3.423	83,8	267	6,5	47	1,1	142	3,5	208	5,1	4.087
L- Antineoplastic and immunomodulatating agents	252	6,4	25	0,6	10	0,2	-	-	3.647	92,7	3.934
A- Alimentary tract and metabolism	1.988	52,7	269	7,1	269	7,1	644	17,1	602	16,0	3.771
N- Nervous system	1.396	43,2	165	5,1	942	29,2	254	7,9	473	14,6	3.228
J- Antiinfectives for sistemic use	887	32,9	156	5,8	81	3,0	-	-	1.573	58,3	2.697
B- Blood and blood forming organs	548	26,6	97	4,7	89	4,3	5	0,2	1.322	64,1	2.061
R- Respiratory system	1.044	59,0	131	7,4	165	9,3	368	20,8	60	3,4	1.768
G- Genito urinary system and sex hormones	421	32,5	41	3,2	642	49,5	80	6,2	112	8,7	1.297
M- Musculo-skeletal system	452	35,4	177	13,9	201	15,7	393	30,8	54	4,2	1.276
D- Dermatologicals	60	9,0	33	5,0	246	37,0	305	45,8	22	3,2	665
V-Various	66	10,6	5	0,9	36	5,9	0	0,0	514	82,6	622
S- Sensory organs	223	35,9	18	2,9	180	29,0	90	14,5	110	17,7	621
H- Systemic hormonal preparations, excl.sex hormones and insulins	191	33,6	52	9,2	28	4,9	-	-	297	52,3	569
P- Antiparasitic products, insecticides and repellents	13	56,9	3	15,8	3	13,6	2	8,0	1	5,8	22
Total	**10.964**	**41,2**	**1.441**	**5,4**	**2.937**	**11,0**	**2.283**	**8,6**	**8.994**	**33,8**	**26.618**

^Class 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)

° 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 2014 (in descending order of expenditure from table 6.1)

Therapeutic class	Class A-NHSˆ		Class A medicines privately purchased		Class C under prescription		Self-medication SOP and OTC		Public Health Facilities		Total
	DDD	%*	DDD	%*	DDD	%*	DDD	%*	DDD	%*	DDD
C- Cardiovascular system	467,6	87,2	41,5	7,7	1,5	0,3	8,5	1,6	16,9	3,1	536,0
L- Antineoplastic and immunomodulatating agents	4,4	31,5	0,5	3,4	0,1	0,4	-	-	9,0	64,7	13,9
A- Alimentary tract and metabolism	152,7	59,8	23,1	9,1	10,0	3,9	42,8	16,8	26,8	10,5	255,5
N- Nervous system	60,5	36,7	8,0	4,9	64,8	39,2	6,4	3,9	25,4	15,4	165,1
J- Antiinfectives for sistemic use	22,6	59,9	5,7	15,1	2,5	6,6			6,9	18,4	37,7
B- Blood and blood forming organs	142,0	52,7	52,8	19,6	37,5	13,9	0,2	0,1	37,1	13,8	269,7
R- Respiratory system	48,3	50,6	10,5	11,0	13,9	14,6	19,5	20,5	3,2	3,3	95,4
G- Genito urinary system and sex hormones	41,9	50,7	5,8	7,0	30,3	36,7	2,8	3,4	1,7	2,1	82,6
M- Musculo-skeletal system	41,2	46,5	22,0	24,8	4,7	5,3	17,6	19,9	3,0	3,4	88,5
D- Dermatologicals	4,2	6,8	4,9	7,9	15,4	25,0	20,1	32,6	17,0	27,6	61,6
V-Various	0,1	1,7	0,2	3,8	1,2	28,4	-	0,2	2,8	65,9	4,2
S- Sensory organs	19,5	37,7	2,3	4,4	13,0	25,1	15,3	29,5	1,7	3,3	51,7
H- Systemic hormonal preparations, excl.sex hormones and insulins	33,7	65,9	11,1	21,7	0,8	1,6	-	-	5,5	10,7	51,2
P- Antiparasitic products, insecticides and repellentsV	0,8	77,3	0,2	15,4	-	3,8	-	1,2	-	2,3	1,0
Total	1.039,4	60,6	188,4	11,0	195,8	11,4	133,3	7,8	157,0	9,2	1.714,0

*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 2014

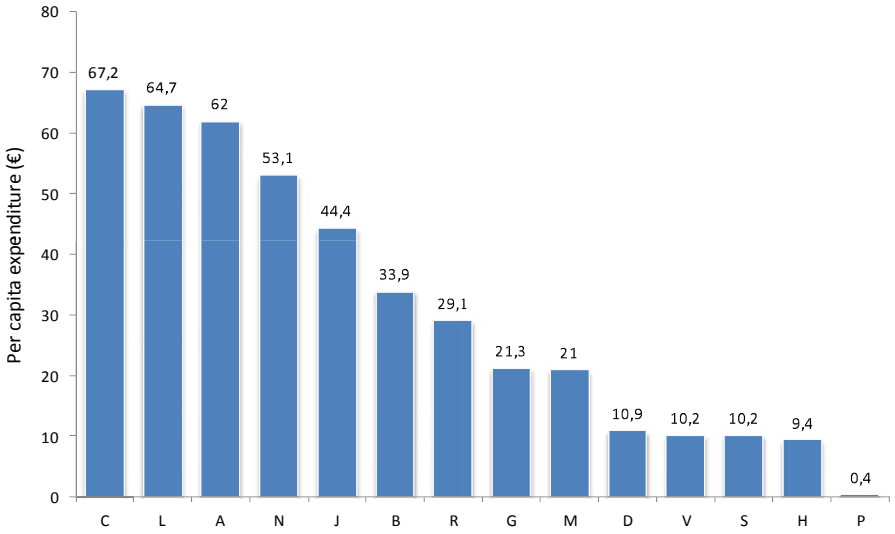


Table 6.3. European comparison of outpatient* expenditure by ATC I level in 2014

ATC	Italy	Austria	Belgium	Finland	France	Germany	Greece	Ireland	Portugal	Spain	Uk
C - Cardiovascular system	22,8	16,0	16,0	11,1	14,5	9,4	29,0	10,9	25,9	17,0	10,4
A -Alimentary tract and metabolism	18,3	14,3	13,0	19,7	13,2	13,3	17,5	19,2	19,3	17,0	17,8
N -Nervous system	14,4	15,3	16,9	16,5	14,3	13,7	15,3	20,0	16,6	20,4	25,6
R -Respiratory system	12,1	10,6	12,9	12,2	10,2	9,7	9,9	11,8	9,6	14,7	18,8
G -Genito urinary system, sex hormones	7,0	4,0	5,4	6,8	4,1	4,1	3,1	4,5	6,6	7,8	5,7
J -Antiinfectives for sistemic use	6,6	11,9	10,5	3,5	11,1	9,8	7,0	3,5	5,6	3,3	2,4
M -Musculo-skeletal system	5,3	4,5	3,9	3,7	3,6	3,6	4,2	3,3	6,2	4,6	2,2
D -Dermatologicals	4,2	3,2	2,9	2,6	2,8	3,1	2,4	3,3	2,9	3,2	5,9
S -Sensory organs	3,4	1,0	1,3	2,3	4,1	2,8	2,0	1,8	2,2	2,8	2,6
B -Blood and blood forming organs	3,2	6,0	5,5	6,5	7,9	10,0	5,8	3,3	3,6	4,0	2,7
H -Systemic hormonal preparations, etc	1,2	1,5	1,9	1,7	2,1	1,8	1,5	1,8	0,7	1,6	3,1
L -Antineoplastic and immunomodulating agent	1,1	10,5	9,3	13,2	11,2	15,8	1,8	14,5	0,4	2,9	2,4
V -Various	0,4	1,1	0,3	0,2	0,6	2,7	0,4	1,9	0,2	0,5	0,2
P Antiparasitic products	0,1	0,1	0,2	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 andself-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 2014

Active ingredient	Italy	Austria	Belgium	Finland	France	Germany	Greece	Ireland	Portugal	Spain	Uk
N - Paracetamol	1	36	2	10	1	61	10	3	7	4	5
R - Fluticasone	2	10	12	3	6	30	15	4	10	2	1
C - Olmesartan	3	19	23	251	30	36	8	41	6	6	210
A - Pantoprazole	4	8	8	52	79	17	26	59	57	33	442
C - Rosuvastatin	5	35	3	64	7	602	12	22	5	25	39
R - Salmeterol	6	13	18	11	9	37	19	6	12	3	2
C - Simvastatin	7	11	14	19	14	29	5	50	8	37	41
A - Lansoprazole	8	115	325	164	118	926	86	36	86	91	56
J - Amoxicillin	9	57	26	69	32	150	27	56	19	26	73
R - Beclometasone	10	71	52	129	42	53	72	93	516	56	11

*The expenditure value covers 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 also includes fixed combinations

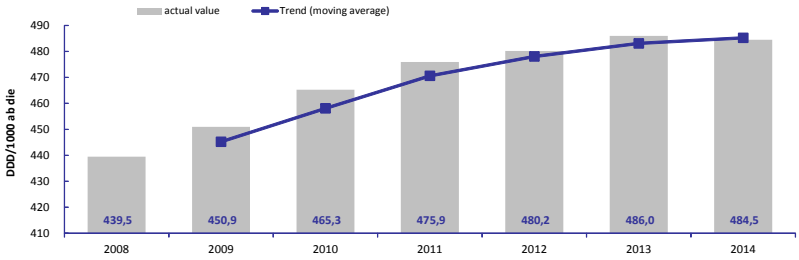
Source: AIFA analysis on IMS/MIDAS data

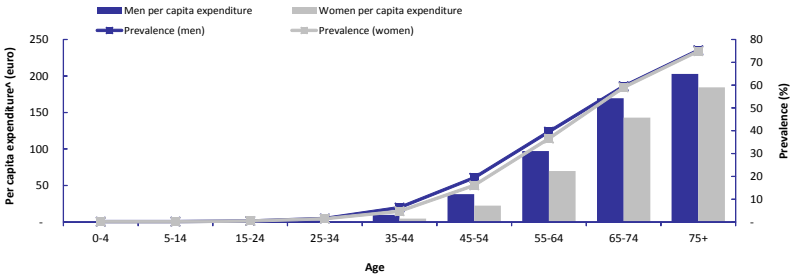
6.1 Cardiovascular System

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
CARDIOVASCULAR

NHS expenditure, milion €* (% on the total)	**3.631,0**	**(18,2)**
Δ % 2014/2013		-4,2
Per capita gross expenditure, range among regions	45	71,1
DDD/1000 ab die (% sul totale)	**484,5**	**(40,5)**
Δ % 2014/2013		-0,3
Range regionale DDD/1000 ab die:	385,9	555,6

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,3	0,3	0,3
5-14	0,1	0,1	0,1	0,9	0,8	0,8
15-24	0,3	0,3	0,3	3,5	2,1	2,8
25-34	1,8	1,0	1,3	14,8	7,9	11,4
35-44	9,8	4,7	7,2	79,1	40,3	59,7
45-54	38,2	22,4	30,2	310,7	186,5	248,1
55-64	97,2	69,9	83,2	798,5	555,6	673,9
65-74	169,6	143,0	155,6	1.432,5	1.138,9	1.277,5
75+	202,9	184,4	191,6	1.887,9	1.656,9	1.745,9

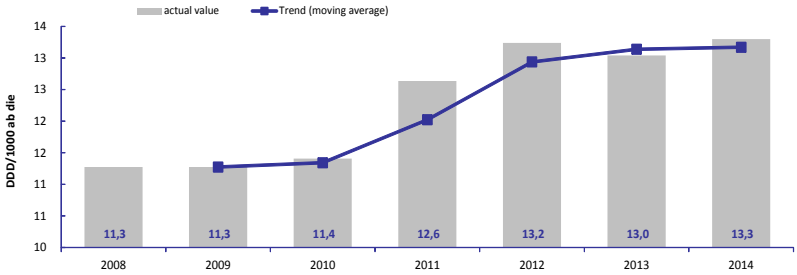
^with the exclusion of medicinal products administered in hospitals

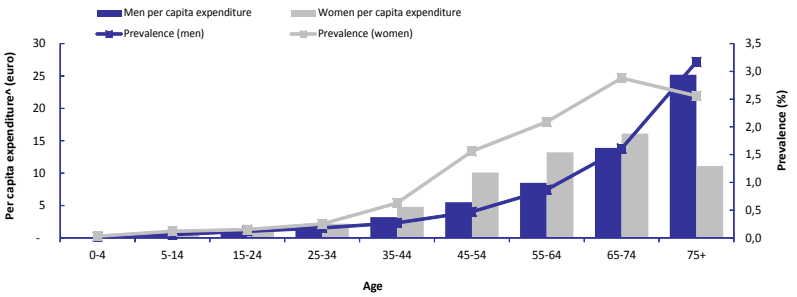
6.2 Antineoplastic and immunomodulating agents

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
LDRUGS ANTINEOPLASTIC AND IMMUNOMODULATING

NHS expenditure, million €* (% on the total)	**3.899,0**	**(19,5)**
Δ % 2014/2013		9,6
Per capita gross expenditure, range among regions	45,2	84,1
DDD/1000 ab die (% sul totale)	**13,3**	**(1,1)**
Δ % 2014/2013		2,0
Range regionale DDD/1000 ab die:	11,4	15,5

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,1	0,1	0,1	0,0	0,0	0,0
5-14	0,4	0,9	0,7	0,2	0,5	0,3
15-24	1,2	1,1	1,2	0,5	0,5	0,5
25-34	2,0	2,2	2,1	0,8	1,1	0,9
35-44	3,2	4,8	4,1	1,0	4,3	2,7
45-54	5,5	10,1	7,8	1,8	11,8	6,9
55-64	8,5	13,2	10,9	3,6	12,3	8,1
65-74	13,9	16,1	15,1	9,7	16,6	13,3
75+	25,2	11,1	16,6	30,4	13,9	20,3

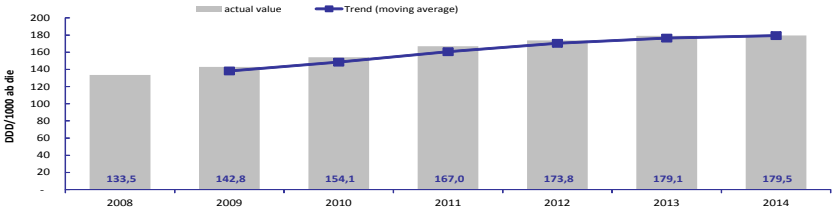
^with the exclusion of medicinal products administered in hospitals

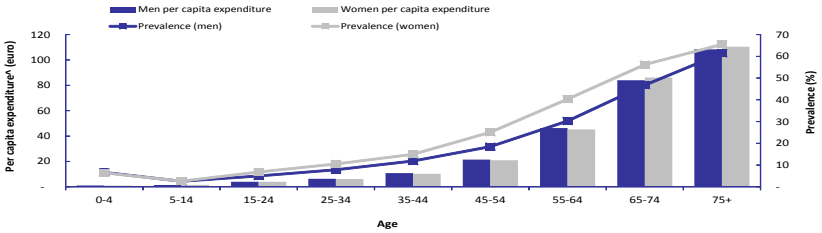
6.3 Alimentary Tract And Metabolism

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
GASTROINTESTINAL SYSTEM AND METABOLISM

NHS expenditure, milion €* (% on the total)	**2.590,0**	**(13)**
Δ % 2014/2013		3,9
Per capita gross expenditure, range among regions	26,8	55,1
DDD/1000 inhab die (% on the total)	**179,5**	**(15)**
Δ % 2014/2013		0,2
DDD/1000 inhab die, range among regions:	127,3	221,3

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	1,1	1,0	1,1	1,9	1,8	1,9
5-14	1,5	1,6	1,5	3,5	3,5	3,5
15-24	4,0	4,0	4,0	10,9	12,1	11,5
25-34	6,3	6,1	6,3	21,1	22,1	21,5
35-44	10,8	10,2	10,5	40,9	40,7	40,8
45-54	21,5	21,0	21,3	93,6	89,4	91,5
55-64	46,3	45,3	45,8	219,7	203,4	211,3
65-74	84,0	86,1	85,1	414,4	398,0	405,8
75+	108,4	110,4	109,7	537,7	524,6	529,6

^with the exclusion of medicinal products administered in hospitals

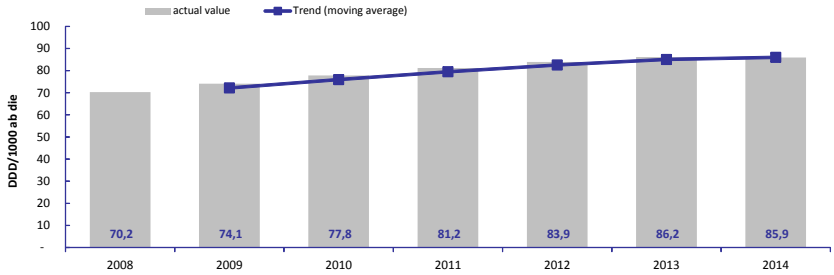
6.4 Nervous system

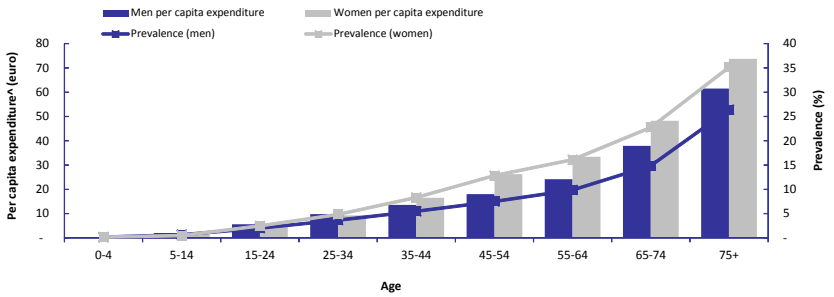
MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

CENTRAL NERVOUS SYSTEM

NHS expenditure, milion €* (% on the total)	**1.868,0**	**(9,4)**
Δ % 2014/2013		-3,5
Per capita gross expenditure, range among regions	27,1	38,3
DDD/1000 inhab die (% on the total)	**85,9**	**(7,2)**
Δ % 2014/2013		-0,3
DDD/1000 inhab die, range among regions:	70,2	108,7

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,3	0,3	0,3	0,6	0,5	0,5
5-14	2,0	1,5	1,8	3,4	2,5	2,9
15-24	5,6	5,2	5,4	12,4	11,6	12,1
25-34	9,8	9,3	9,6	24,2	23,8	24,0
35-44	13,6	16,5	15,0	35,8	43,9	39,9
45-54	18,0	26,3	22,3	65,7	73,0	69,4
55-64	24,2	33,4	28,9	82,6	95,9	89,4
65-74	37,9	48,2	43,3	157,5	221,7	191,4
75+	61,5	73,7	68,9	198,3	294,2	257,3

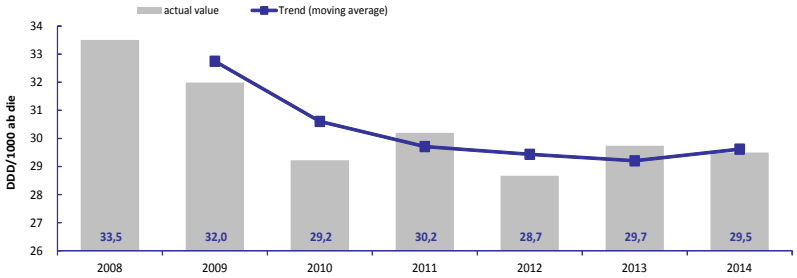
^with the exclusion of medicinal products administered in hospitals

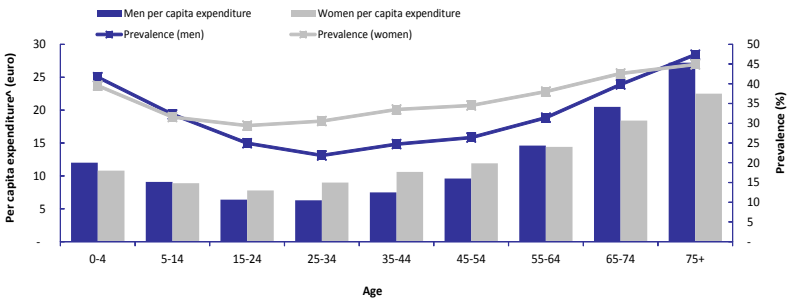
6.5 Antiinfectives for sistemic use

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
ANTIMICROBIALS GENERAL FOR SYSTEMIC

NHS expenditure, milion €* (% on the total)	**2.460,0**	**(12,3)**
Δ % 2014/2013		-0,4
Per capita gross expenditure, range among regions	28,2	50,9
DDD/1000 ab die (% sul totale)	**29,5**	**(2,5)**
Δ % 2014/2013		-0,8
Range regionale DDD/1000 ab die:	20,6	38,4

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	12,0	10,8	11,4	21,5	19,2	20,4
5-14	9,1	8,9	9,0	17,7	16,8	17,2
15-24	6,4	7,8	7,1	13,5	15,2	14,3
25-34	6,3	9,0	7,6	11,8	16,7	14,2
35-44	7,5	10,6	9,0	13,9	19,0	16,4
45-54	9,6	11,9	10,6	15,5	20,1	17,8
55-64	14,6	14,4	14,5	20,3	23,4	21,9
65-74	20,5	18,4	19,4	28,8	27,8	28,3
75+	27,2	22,5	24,4	34,5	28,8	31,0

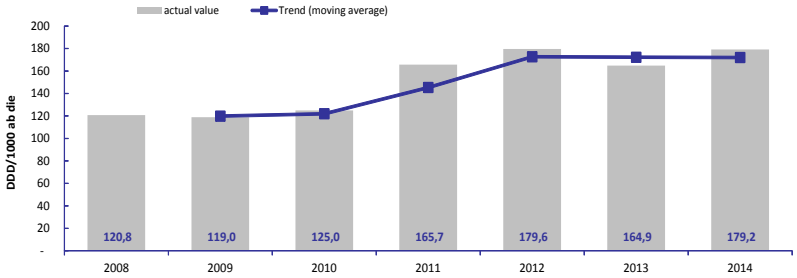
^with the exclusion of medicinal products administered in hospitals

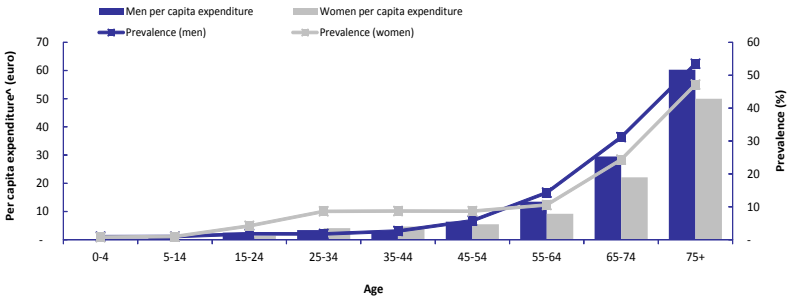
6.6 Blood and blood forming organs

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

NHS expenditure, milion €* (% on the total)	**1.870,0**	**(9,4)**
Δ % 2014/2013		7,3
Per capita gross expenditure, range among regions	20,1	50,1
DDD/1000 ab die (% sul totale)	**179,2**	**(15)**
Δ % 2014/2013		8,7
Range regionale DDD/1000 ab die:	141,6	240,5

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,2	0,1	0,1	1,9	1,4	1,7
5-14	1,3	0,3	0,9	3,9	4,4	4,2
15-24	2,5	1,4	2,0	8,1	36,0	21,6
25-34	3,4	4,1	3,7	10,5	109,0	59,5
35-44	3,1	4,7	4,0	19,8	84,3	52,0
45-54	6,4	5,5	5,9	55,2	67,9	61,6
55-64	13,5	9,2	11,3	151,9	98,8	124,6
65-74	29,5	22,1	25,6	358,7	259,1	306,1
75+	60,3	50,0	53,9	673,4	579,1	615,4

^with the exclusion of medicinal products administered in hospitals

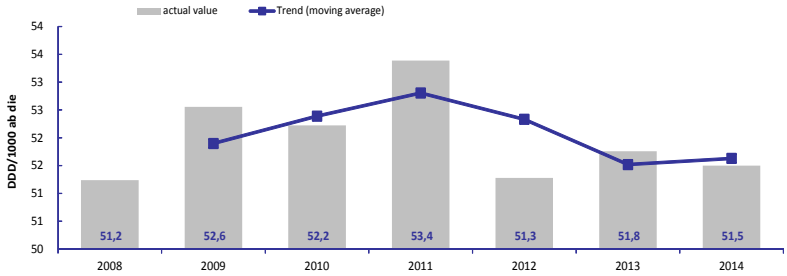
6.7 Respiratory system

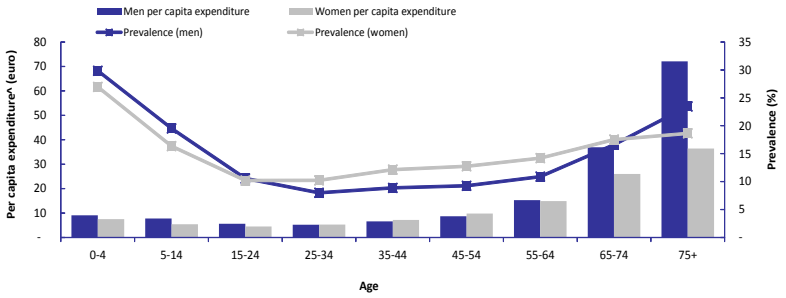
MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

RESPIRATORY SYSTEM

NHS expenditure, milion €* (% on the total)	**1.104,0**	**(5,5)**
Δ % 2014/2013		2,5
Per capita gross expenditure, range among regions	14,4	23,7
DDD/1000 ab die (% sul totale)	**51,5**	**(4,3)**
Δ % 2014/2013		-0,5
Range regionale DDD/1000 ab die:	36,9	71,4

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	9,1	7,5	8,3	39,5	33,0	36,4
5-14	7,8	5,4	6,6	33,5	23,7	28,7
15-24	5,6	4,5	5,0	25,7	20,8	23,3
25-34	5,2	5,3	5,2	19,6	21,1	20,4
35-44	6,6	7,2	6,9	22,4	26,8	24,7
45-54	8,7	9,8	9,2	26,4	33,5	30,0
55-64	15,3	14,9	15,1	38,8	43,4	41,1
65-74	36,9	26,0	31,2	83,0	67,5	74,8
75+	72,1	36,4	50,2	160,1	90,6	117,4

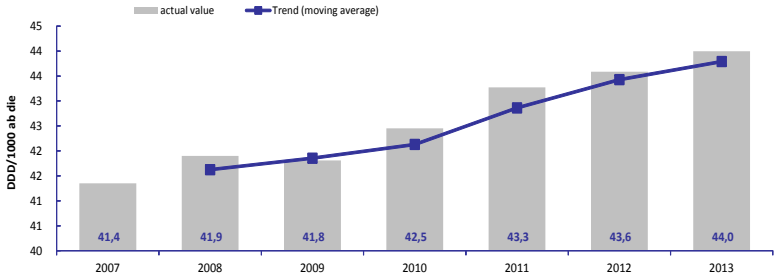
^with the exclusion of medicinal products administered in hospitals

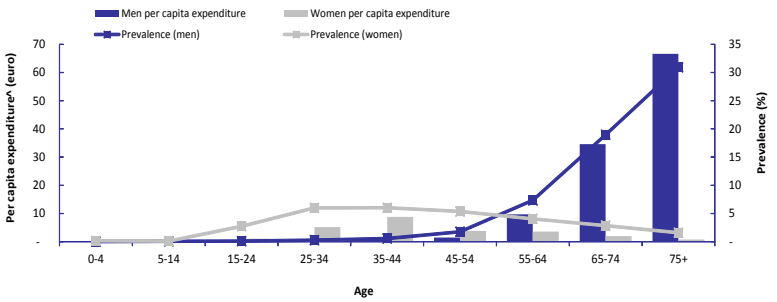
6.8 Genito urinary system and sex hormones

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
GENITO-URINARY SYSTEM AND SEX HORMONES

NHS expenditure, milion €* (% on the total)	**518,4**	**(2,6)**
Δ % 2013/2012		3,3
Per capita gross expenditure, range among regions	7,3	10
DDD/1000 ab die (% sul totale)	**44,0**	**(3,7)**
Δ % 2013/2012		0,9
Range regionale DDD/1000 ab die:	38,2	54,4

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,0	0,1	0,1
5-14	0,0	0,0	0,0	0,1	0,2	0,2
15-24	0,2	1,1	0,7	0,5	13,2	6,6
25-34	0,5	5,2	2,9	0,9	29,3	15,1
35-44	0,9	8,8	4,8	2,1	34,0	18,0
45-54	1,5	3,8	2,6	9,5	33,6	21,6
55-64	9,7	3,6	6,6	61,4	36,0	48,4
65-74	34,6	2,0	17,3	201,9	23,1	107,5
75+	66,6	0,8	26,1	358,1	8,8	143,2

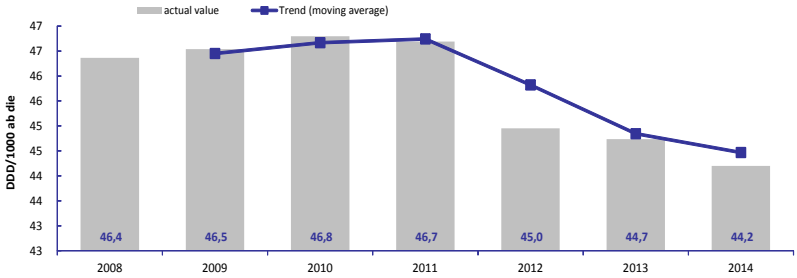
^with the exclusion of medicinal products administered in hospitals

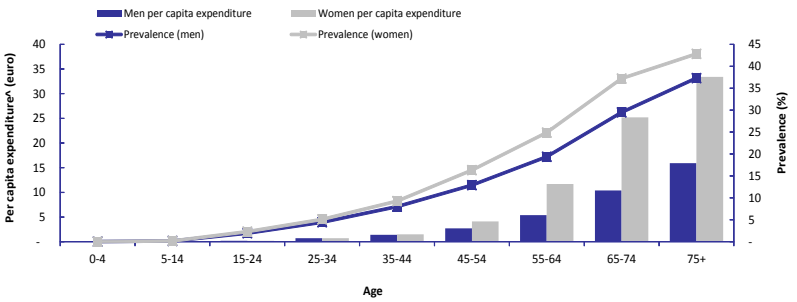
6.9 Musculo-skeletal system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
SKELETAL MUSCLE SYSTEM

NHS expenditure, milion €* (% on the total)	**506,0**	**(2,5)**
Δ % 2014/2013		-8,4
Per capita gross expenditure, range among regions	5,5	13,1
DDD/1000 ab die (% sul totale)	**44,2**	**(3,7)**
Δ % 2014/2013		-1,2
Range regionale DDD/1000 ab die:	30,9	69

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,0	0,0	0,0
5-14	0,0	0,0	0,0	0,2	0,2	0,2
15-24	0,2	0,2	0,2	1,8	1,9	1,8
25-34	0,7	0,7	0,7	4,5	4,8	4,7
35-44	1,4	1,5	1,4	9,2	10,4	9,8
45-54	2,7	4,1	3,4	18,6	24,0	21,3
55-64	5,4	11,7	8,7	36,4	59,0	48,0
65-74	10,4	25,2	18,2	72,5	122,7	99,0
75+	15,9	33,4	26,7	108,7	166,7	144,4

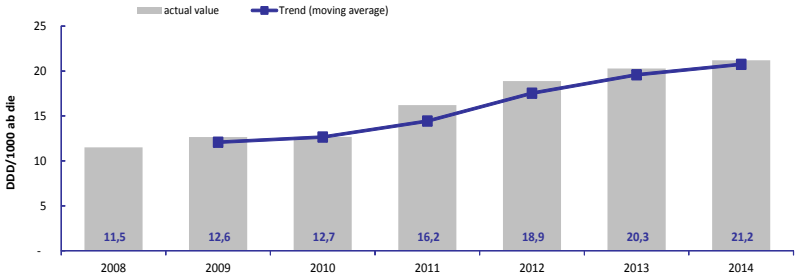
^with the exclusion of medicinal products administered in hospitals

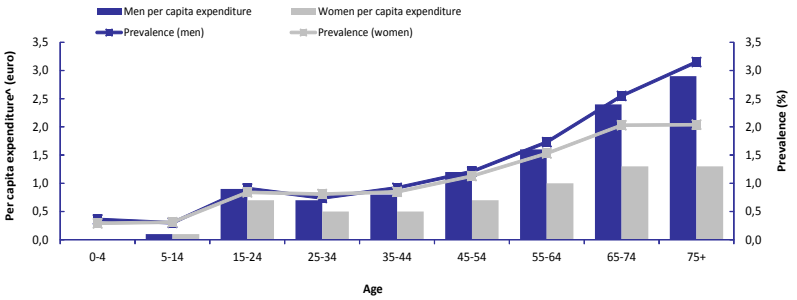
6.10 Dermatologicals

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
DERMATOLOGICAL

NHS expenditure, milion €* (% on the total)	**82,0**	**(0,4)**
Δ % 2014/2013		-2,1
Per capita gross expenditure, range among regions	1,1	1,7
DDD/1000 ab die (% sul totale)	**21,2**	**(1,8)**
Δ % 2014/2013		4,5
Range regionale DDD/1000 ab die:	13,1	132,6

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,3	0,2	0,2
5-14	0,1	0,1	0,1	0,5	0,5	0,5
15-24	0,9	0,7	0,8	2,4	2,0	2,3
25-34	0,7	0,5	0,5	2,6	2,0	2,3
35-44	0,8	0,5	0,7	3,6	2,3	2,9
45-54	1,2	0,7	0,9	5,1	3,0	4,1
55-64	1,6	1,0	1,3	7,2	4,3	5,7
65-74	2,4	1,3	1,8	9,9	5,9	7,8
75+	2,9	1,3	1,9	11,3	5,7	7,9

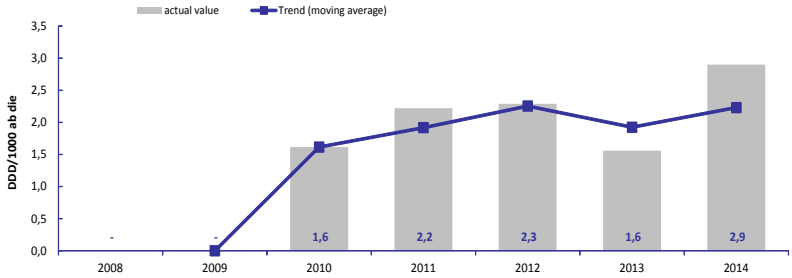
^with the exclusion of medicinal products administered in hospitals

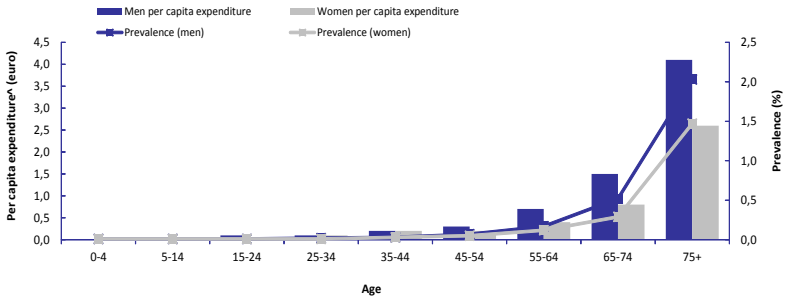
6.11 Various

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
VARIOUS

NHS expenditure, milion €* (% on the total)	**580,0**	**(2,9)**
Δ % 2014/2013		-2,2
Per capita gross expenditure, range among regions	5,8	15,9
DDD/1000 ab die (% sul totale)	**2,9**	**(0,2)**
Δ % 2014/2013		85,8
Range regionale DDD/1000 ab die:	1,2	5,5

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,0	0,0	0,0
5-14	0,0	0,0	0,0	0,0	0,0	0,0
15-24	0,1	0,0	0,0	0,0	0,0	0,0
25-34	0,1	0,1	0,1	0,0	0,0	0,0
35-44	0,2	0,2	0,2	0,1	0,0	0,1
45-54	0,3	0,2	0,2	0,1	0,1	0,1
55-64	0,7	0,4	0,5	0,2	0,1	0,2
65-74	1,5	0,8	1,1	0,5	0,2	0,3
75+	4,1	2,6	3,2	1,0	0,5	0,7

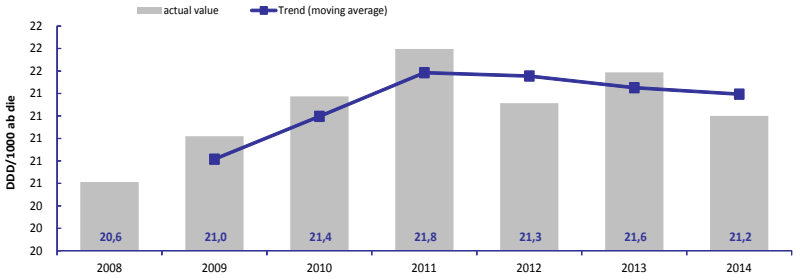
^with the exclusion of medicinal products administered in hospitals

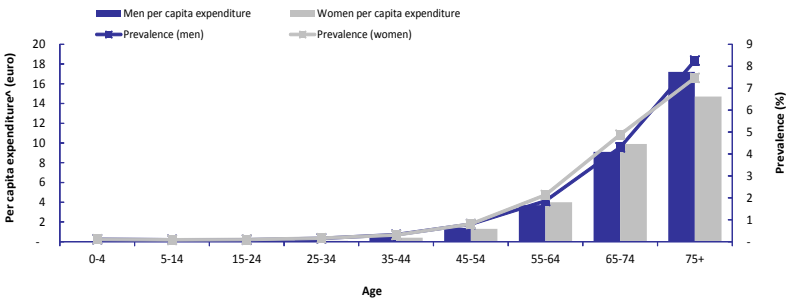
6.12 Sensory organs

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE
SENSE ORGANS

NHS expenditure, milion €* (% on the total)	**332,0**	**(1,7)**
Δ % 2014/2013		4,8
Per capita gross expenditure, range among regions	4,4	7,1
DDD/1000 ab die (% sul totale)	**21,2**	**(1,8)**
Δ % 2014/2013		-1,8
Range regionale DDD/1000 ab die:	16,7	29

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,1	0,1	0,1
5-14	0,0	0,0	0,0	0,2	0,2	0,2
15-24	0,1	0,1	0,1	0,6	0,5	0,6
25-34	0,2	0,1	0,2	1,1	0,9	1,0
35-44	0,5	0,4	0,4	2,8	2,1	2,5
45-54	1,4	1,3	1,3	7,9	7,2	7,5
55-64	3,7	4,0	3,8	20,1	21,5	20,8
65-74	9,1	9,9	9,4	49,0	54,0	51,6
75+	17,2	14,7	15,7	94,9	83,0	87,6

^with the exclusion of medicinal products administered in hospitals

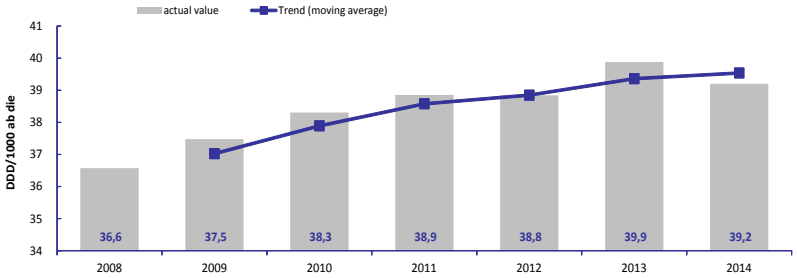
6.13 Systemic hormonal preparations, excl.sex hormones and insulins

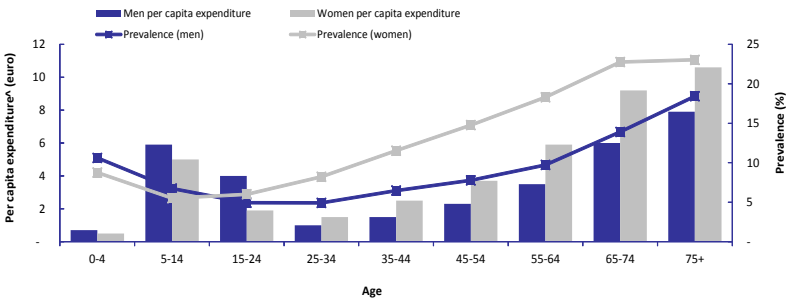
MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

SYSTEMIC HORMONAL PREPARATIONS, EXCLUDING SEX HORMONES

NHS expenditure, milion €* (% on the total)	**488,0**	**(2,4)**
Δ % 2014/2013		0,3
Per capita gross expenditure, range among regions	6,9	10,3
DDD/1000 ab die (% sul totale)	**39,2**	**(3,3)**
Δ % 2014/2013		-1,7
Range regionale DDD/1000 ab die:	27,7	48,7

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2014

	Per capita expenditure			DDD/1000 ab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,7	0,5	0,7	3,0	2,5	2,8
5-14	5,9	5,0	5,5	4,4	3,8	4,2
15-24	4,0	1,9	2,9	5,9	8,8	7,3
25-34	1,0	1,5	1,3	7,3	18,8	13,1
35-44	1,5	2,5	2,0	11,0	32,0	21,5
45-54	2,3	3,7	3,1	17,1	49,3	33,3
55-64	3,5	5,9	4,7	26,0	67,9	47,4
65-74	6,0	9,2	7,7	40,3	87,1	65,0
75+	7,9	10,6	9,7	52,9	80,4	69,8

^with the exclusion of medicinal products administered in hospitals

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

ATC I level	Subgroups	Per capita gross expenditure	DDD/1.000 inhab die	Δ% 14-13				Δ%
				Exp	DDD	Packagei	Mix	DDD average cost
Italia		**180,4**	**1.039,4**	**-2,1**	**2,5**	**-3,3**	**-1,0**	**-4,5**
Cardiovascular System		**56,3**	**467,6**	**-4,9**	**1,6**	**-6,1**	**-0,3**	**-6,4**
HMG CoA reductase inhibitors		10,6	65,9	0,7	5,4	-0,6	-3,9	-4,5
Angiotensin II antagonists and diuretics		6,6	39,4	-20,8	0,0	-21,5	0,9	-20,8
Angiotensin II antagonists, plain		6,0	55,6	-16,0	1,8	-17,9	0,5	-17,5
Dihydropyridine derivatives		4,7	52,8	-0,5	-0,1	-0,3	0,0	-0,3
ACE inhibitors, plain		4,5	88,6	-0,7	0,8	-0,2	-1,3	-1,5
Beta blocking agents, selective		3,7	35,3	6,7	3,1	-0,1	3,6	3,5
ACE inhibitors and diuretics		3,6	24,8	-1,5	-1,8	-0,1	0,4	0,3
Other lipid modifying agents		2,9	4,9	-17,7	-7,8	-9,1	-1,7	-10,7
HMG CoA reductase inhibitors in combination with other lipid modifying agents		2,6	3,5	4,6	4,6	0,0	0,0	0,0
Organic nitrates		1,5	13,9	-9,2	-8,8	-0,4	0,0	-0,4
ACE inhibitors and calcium channel blockers		1,2	6,6	36,0	35,4	0,0	0,5	0,5
Alpha-adrenoreceptor antagonists		1,2	7,6	1,0	1,0	-0,2	0,2	0,0
Angiotensin II antagonists and calcium channel blockers		0,9	2,8	14,5	22,1	-6,0	-0,2	-6,2
Antiarrhythmics, class Ic		0,9	4,6	4,0	0,5	-0,1	3,5	3,5
Sulfonamides, plain		0,9	25,3	3,2	3,9	0,0	-0,6	-0,7
Alpha and beta blocking agents		0,7	4,0	-3,2	-3,0	-2,5	2,3	-0,2
Aldosterone antagonists		0,5	3,8	13,0	4,1	0,0	8,6	8,6
Beta blocking agents, selective, and thiazides		0,5	3,8	33,9	27,3	3,5	1,6	5,1
Fibrates		0,4	2,5	2,8	7,7	-0,1	-4,5	-4,6
Imidazoline receptor agonists		0,3	2,0	-2,7	-3,1	0,0	0,4	0,4
Benzothiazepine derivatives		0,3	1,7	-9,5	-7,2	-2,1	-0,4	-2,5
Antiarrhythmics, class III		0,3	3,0	-2,5	0,7	-0,6	-2,6	-3,3
Other cardiac preparations		0,2	0,2	-39,9	-38,3	-12,1	10,9	-2,5
Phenylalkylamine derivatives		0,2	1,8	-7,0	-7,1	-0,2	0,3	0,1
Low-ceiling diuretics and potassium-sparing agents		0,2	3,2	-4,1	-4,0	0,0	-0,1	-0,1
Beta blocking agents, selective, and other diuretics		0,2	2,5	-4,2	-4,4	-1,5	1,7	0,2
Renin-inhibitors		0,2	0,5	-15,2	-14,4	-1,8	0,9	-0,9
Beta blocking agents, non-selective		0,2	1,7	-2,4	-0,9	-0,4	-1,2	-1,6
High-ceiling diuretics and potassium-sparing agents		0,1	0,7	-0,5	-0,6	0,0	0,1	0,1
Digitalis glycosides		0,1	2,5	-8,5	-10,0	-1,2	2,9	1,7
Sulfonamides, plain		0,1	1,5	-3,4	-3,6	0,0	0,2	0,2
Alimentary Tract and Metabolism		**32,7**	**152,7**	**2,1**	**2,1**	**-0,6**	**0,7**	**0,0**
Proton pump inhibitors		15,5	75,8	4,2	4,3	-0,2	0,0	-0,2
Insulins and analogues for injection, fast-acting		3,7	7,5	3,9	3,3	0,0	0,6	0,6
Vitamin D and analogues		2,0	3,2	28,1	10,4	-3,6	20,4	16,0
Aminosalicylic acid and similar agents		1,6	4,1	6,2	6,0	-0,2	0,4	0,2

ATC I level	Subgroups	Per capita gross expenditure	DDD/1.000 inhab die	Δ% 14-13				Δ%
				Exp	DDD	Packagei	Mix	DDD average cost
Antibiotics		1,5	2,0	4,7	4,6	0,0	0,0	0,0
Biguanides		1,3	19,9	4,2	4,6	-0,1	-0,2	-0,3
Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)		0,8	2,1	4,1	2,0	-0,3	2,4	2,1
Combinations of oral blood glucose lowering drugs		0,7	5,0	-27,7	-17,7	-2,5	-9,9	-12,2
Bile acid preparations		0,6	2,1	3,0	4,3	-1,0	-0,2	-1,2
Other blood glucose lowering drugs, excl. insulins		0,6	3,9	-15,7	-1,5	-3,3	-11,5	-14,4
Sulfonamides, urea derivatives		0,6	11,0	10,4	-1,0	-0,1	11,7	11,5
Calcium, combinations with vitamin D and/or other drugs		0,5	5,7	-3,5	-4,2	-1,0	1,8	0,8
Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting		0,4	0,9	-13,3	-13,8	0,0	0,6	0,6
Combinations and complexes of aluminium, calcium and magnesium compounds		0,4	1,8	10,3	9,7	0,0	0,7	0,6
H2-receptor antagonists		0,4	2,3	-1,4	-0,9	-0,6	0,1	-0,5
Insulins and analogues for injection, long-acting		0,3	0,4	-51,1	-51,1	-1,9	1,9	0,0
Corticosteroids acting locally		0,3	0,4	4,2	3,7	0,0	0,5	0,5
Alpha glucosidase inhibitors		0,2	0,7	3,7	7,4	0,0	-3,5	-3,5
Serotonin (5HT3) antagonists		0,2	0,0	-2,4	-1,6	-2,4	1,6	-0,9
Insulins and analogues for injection, intermediate-acting		0,2	0,4	-10,4	-12,5	-0,1	2,5	2,4
Enzyme preparations		0,2	0,5	15,8	14,6	-3,8	5,2	1,1
Dipeptidyl peptidase 4 (DPP-4) inhibitors		0,2	0,2	-38,2	-39,0	-5,4	7,1	1,4
Osmotically acting laxatives		0,1	1,2	4,6	4,8	0,0	-0,2	-0,2
Calcium		0,1	0,6	2,2	2,3	0,0	0,0	-0,1
Thiazolidinediones		0,1	0,3	-4,2	25,7	-18,7	-6,3	-23,8
Potassium		0,1	0,3	8,3	8,3	0,0	0,0	0,0
Nervous System		**23,0**	**60,5**	**-0,3**	**1,9**	**-4,8**	**2,7**	**-2,2**
Other antiepileptics		4,5	4,4	8,1	8,0	-0,5	0,7	0,1
Selective serotonin reuptake inhibitors		4,1	27,9	-12,9	1,6	-13,6	-0,8	-14,2
Other antidepressants		3,3	8,3	3,5	4,1	-0,5	0,0	-0,5
Natural opium alkaloids		1,6	2,1	11,4	2,0	0,0	9,3	9,3
Selective serotonin (5HT1) agonists		1,3	0,8	-10,2	1,9	-11,7	-0,1	-11,8
Dopamine agonists		1,3	1,2	-5,6	-7,4	-2,8	4,8	1,9
Phenylpiperidine derivatives		1,1	0,6	9,3	5,0	-0,8	4,9	4,1
Other opioids		0,9	1,0	21,9	8,0	-0,2	13,1	12,9
Fatty acid derivatives		0,9	2,1	4,8	4,6	-0,3	0,5	0,2
Monoamine oxidase B inhibitors		0,8	1,1	8,5	12,4	0,0	-3,4	-3,4
Dopa and dopa derivatives		0,6	1,9	-1,9	2,5	-1,9	-2,3	-4,2
Diazepines, oxazepines, thiazepines and oxepines		0,6	0,8	-5,7	-2,1	-6,1	2,6	-3,6
Carboxamide derivatives		0,5	2,0	-0,3	-1,2	0,0	1,0	1,0
Other antipsychotics		0,2	0,2	-22,9	-17,0	-8,1	1,1	-7,1
Non-selective monoamine reuptake inhibitors		0,2	1,1	10,2	0,3	8,3	1,4	9,9
Amides		0,1	0,1	>100	>100	-2,1	-0,3	-2,4
Oripavine derivatives		0,1	0,1	-5,3	-5,2	0,0	-0,1	-0,1

ATC I level	Subgroups	Per capita gross expenditure	DDD/1.000 inhab die	Δ% 14-13				Δ%
				Exp	DDD	Packagei	Mix	DDD average cost
Anticholinesterases		0,1	0,3	-34,2	-11,7	-12,6	-14,8	-25,5
Other nervous system drugs		0,1	0,0	14,1	12,4	-0,5	2,1	1,6
Benzamides		0,1	0,1	-3,6	-3,5	-0,1	-0,1	-0,2
Anticholinesterases		0,1	0,2	0,8	2,6	0,0	-1,7	-1,7
Barbiturates and derivatives		0,1	1,8	-3,3	-3,7	0,0	0,4	0,4
Benzodiazepine derivatives		0,1	0,3	0,9	0,7	0,0	0,2	0,2
Lithium		0,1	0,3	2,6	2,5	0,0	0,1	0,1
Butyrophenone derivatives		0,1	0,5	-8,9	-9,7	-3,2	4,3	0,9
Other anti-dementia drugs		0,1	0,1	-70,2	-22,2	-58,7	-7,4	-61,7
Respiratory System		**17,2**	**48,3**	**2,1**	**1,3**	**-0,6**	**1,4**	**0,7**
Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics		8,0	10,3	3,2	3,7	0,0	-0,5	-0,5
Anticholinergics		3,3	7,0	9,3	8,0	0,1	1,2	1,2
Glucocorticoids		2,6	10,1	-2,7	-2,7	-0,1	0,2	0,1
Selective beta-2-adrenoreceptor agonists		1,2	5,7	-3,2	-2,1	-0,3	-0,8	-1,1
Other antihistamines for systemic use		0,8	6,4	4,6	4,7	-0,1	0,0	-0,1
Leukotriene receptor antagonists		0,5	2,1	-13,5	1,4	-12,9	-2,0	-14,7
Piperazine derivatives		0,4	4,2	2,5	3,0	-0,1	-0,4	-0,5
Adrenergics in combination with anticholinergics		0,2	1,4	-2,7	-4,1	-0,1	1,5	1,5
Xanthines		0,1	0,8	-17,1	-19,0	-11,6	15,8	2,3
Antiinfectives for Systemic Use		**14,6**	**22,6**	**-1,3**	**-1,2**	**-0,9**	**0,8**	**-0,1**
Third-generation cephalosporins		3,2	1,8	-2,3	-1,9	-0,4	0,0	-0,4
Combinations of penicillins, incl. beta-lactamase inhibitors		3,2	9,0	0,4	0,7	-0,7	0,3	-0,3
Fluoroquinolones		2,5	3,1	-0,8	0,1	-0,7	-0,3	-0,9
Macrolides		1,8	4,0	-2,1	-0,6	-2,1	0,5	-1,5
Triazole derivatives		1,2	0,8	1,2	0,2	-1,5	2,6	1,0
Other antibacterials		0,6	0,4	5,0	4,7	-0,1	0,4	0,3
Nucleosides and nucleotides excl. reverse transcriptase inhibitors		0,6	0,2	-0,5	1,8	-1,2	-1,1	-2,3
Specific immunoglobulins		0,5	0,0	-4,0	-6,6	-1,6	4,4	2,7
Penicillins with extended spectrum		0,3	2,2	-9,5	-8,8	-0,2	-0,5	-0,7
Second-generation cephalosporins		0,2	0,3	-12,0	-11,3	-2,7	2,0	-0,8
Glycopeptide antibacterials		0,1	0,0	-3,4	-3,4	-0,2	0,2	0,0
Other aminoglycosides		0,1	0,0	-0,5	1,7	-1,0	-1,2	-2,2
Tetracyclines		0,1	0,3	-3,4	-1,9	0,0	-1,5	-1,5
Lincosamides		0,1	0,0	-0,3	9,2	-0,3	-8,4	-8,7
Combinations of sulfonamides and trimethoprim, incl. derivatives		0,1	0,2	0,5	0,5	-0,1	0,0	-0,1
Blood and Blood Forming Organs		**9,0**	**142,0**	**-4,8**	**10,6**	**-3,3**	**-11,0**	**-13,9**
Heparin group		3,9	4,0	-3,5	-3,1	-0,3	-0,1	-0,4
Platelet aggregation inhibitors excl. heparin		3,0	60,9	-9,7	-5,5	-5,2	0,8	-4,4
Folic acid and derivatives		0,4	61,1	17,5	37,0	0,0	-14,2	-14,2
Iron bivalent, oral preparations		0,3	3,4	7,5	6,4	0,0	1,1	1,0
Vitamin K antagonists		0,3	6,3	-3,1	-2,8	0,0	-0,3	-0,3
Blood substitutes and plasma protein fractions		0,2	0,0	-4,6	-4,6	-4,5	4,7	0,0
Other antianemic preparations		0,2	0,0	-17,8	-15,4	-14,0	12,9	-2,9

ATC I level	Subgroups	Per capita gross expenditure	DDD/1.000 inhab die	Δ% 14-13				Δ%
				Exp	DDD	Packagei	Mix	DDD average cost
Solutions affecting the electrolyte balance		0,2	0,3	0,5	0,3	-0,1	0,3	0,2
Blood coagulation factors		0,1	0,0	-35,1	-28,1	-42,6	57,2	-9,8
Direct factor Xa inhibitors		0,1	0,1	>100	>100	-11,0	1,4	-9,8
Amino acids		0,1	0,1	-4,0	-2,6	0,0	-1,4	-1,4
Other antithrombotic agents		0,1	0,0	-32,4	-32,3	-1,5	1,4	-0,1
Musculo-Skeletal System		**7,4**	**41,2**	**-6,9**	**-0,9**	**-2,3**	**-3,8**	**-6,0**
Bisphosphonates		1,5	6,8	0,7	3,5	-1,0	-1,6	-2,7
Coxibs		1,5	4,7	-1,0	-0,9	-0,7	0,7	0,0
Bisphosphonates, combinations		1,1	3,5	7,9	7,2	0,7	0,0	0,7
Propionic acid derivatives		0,9	7,5	-0,5	0,4	-0,1	-0,7	-0,9
Acetic acid derivatives and related substances		0,9	5,4	-1,4	-1,1	0,0	-0,3	-0,3
Preparations inhibiting uric acid production		0,8	8,0	15,4	7,6	-5,7	13,7	7,3
Other antiinflammatory and antirheumatic agents, non-steroids		0,2	2,8	-7,5	-6,9	-1,6	1,0	-0,6
Oxicams		0,2	1,3	-4,7	-4,6	-0,3	0,2	-0,1
Other drugs affecting bone structure and mineralization		0,1	0,1	-88,5	-87,9	-15,2	12,2	-4,9
Other centrally acting agents		0,1	0,5	2,6	0,9	0,0	1,6	1,6
Genito Urinary System and Sex Hormones		**6,9**	**41,9**	**2,4**	**0,8**	**-2,3**	**3,9**	**1,6**
Testosterone-5-alpha reductase inhibitors		2,8	9,0	7,1	6,2	-1,2	2,0	0,8
Alpha-adrenoreceptor antagonists		2,6	22,0	7,4	5,4	-0,1	2,0	1,9
Gonadotropins		0,3	0,1	-24,8	-64,6	-10,0	136,3	112,8
Prolactine inhibitors		0,2	0,1	-2,4	-4,6	-1,1	3,6	2,4
Other estrogens		0,1	0,7	-25,9	-1,5	-24,9	0,2	-24,7
Progestogens and estrogens, fixed combinations		0,1	2,9	-9,3	-8,4	-0,5	-0,5	-1,0
Natural and semisynthetic estrogens, plain		0,1	2,0	-15,0	-22,5	-12,7	25,7	9,7
Pregnen (4) derivatives		0,1	1,2	0,6	-1,1	0,0	1,7	1,7
Antineoplastic and Immunomodulating Agents		**4,2**	**4,4**	**0,1**	**3,2**	**-1,0**	**-2,1**	**-3,0**
Aromatase inhibitors		1,5	2,0	6,4	7,4	-1,1	0,2	-0,9
Calcineurin inhibitors		1,1	0,3	-0,3	-0,1	-0,3	0,1	-0,2
Folic acid analogues		0,7	0,1	6,7	5,9	0,0	0,8	0,8
Other antineoplastic agents		0,1	0,2	6,8	4,7	-0,3	2,3	2,0
Anti-androgens		0,1	0,3	-8,1	-6,2	-4,9	3,0	-2,0
Other immunosuppressants		0,1	0,4	3,2	3,2	0,0	0,0	0,0
Anti-estrogens		0,1	0,9	0,7	2,8	-0,3	-1,8	-2,1
Colony stimulating factors		0,1	0,0	-40,3	-45,2	-4,5	14,1	9,0
Selective immunosuppressants		0,1	0,0	-29,8	-19,2	-5,4	-8,2	-13,2
Gonadotropin releasing hormone analogues		0,1	0,0	-17,9	-15,7	-40,9	64,9	-2,5
Interferons		0,1	0,0	-44,3	-35,9	-9,4	-4,1	-13,0
Progestogens		0,1	0,1	-6,8	-6,5	-1,0	0,7	-0,4
Nitrogen mustard analogues		0,1	0,0	>100	-7,6	>100	-2,3	>100
Sensory Organs		**3,7**	**19,5**	**3,7**	**1,5**	**0,2**	**2,0**	**2,1**
Beta blocking agents1)		2,0	11,0	4,1	1,2	-0,2	3,0	2,9
Prostaglandin analogues1)		1,3	5,5	3,5	2,0	0,8	0,6	1,4
Carbonic anhydrase inhibitors		0,3	1,4	2,9	3,0	-0,1	0,0	-0,1
Sympathomimetics in glaucoma therapy1)		0,1	1,2	-0,6	-0,9	-0,9	1,2	0,3
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins		**3,1**	**33,7**	**-11,8**	**-0,2**	**-4,2**	**-7,8**	**-11,6**

ATC I level	Subgroups	Per capita gross expenditure	DDD/1.000 inhab die	Δ% 14-13				Δ%
				Exp	DDD	Packagei	Mix	DDD average cost
Glucocorticoids		1,4	12,9	2,7	3,5	-0,6	-0,2	-0,8
Thyroid hormones		0,8	19,2	-6,3	-2,3	-7,8	4,0	-4,1
Parathyroid hormones and analogues		0,4	0,1	-39,6	-39,6	-5,7	6,1	0,0
Somatropin and somatropin agonists		0,2	0,0	-21,5	-19,8	-4,7	2,7	-2,1
Vasopressin and analogues		0,1	0,1	4,9	4,3	-0,2	0,9	0,6
Other anti-parathyroid agents		0,1	0,0	-13,7	-30,4	-3,3	28,1	23,9
Somatostatin and analogues		0,1	0,0	-56,6	-57,2	-13,8	17,6	1,4
Sulfur-containing imidazole derivatives		0,1	1,4	-0,2	-0,2	0,0	0,0	0,0
Various		**1,1**	**0,1**	**-37,5**	**-5,4**	**-5,8**	**-8,3**	**-33,9**
Medical gases		1,0		-39,2				
Drugs for treatment of hyperkalemia and hyperphosphatemia		0,1	0,1	-21,1	-4,3	-5,6	-12,6	-17,5
Dermatologicals		**1,0**	**4,2**	**1,6**	**-1,5**	**-2,0**	**5,3**	**3,2**
Other antipsoriatics for topical use		0,6	2,0	-4,4	-4,6	-1,8	2,0	0,1
Corticosteroids, potent (group III)		0,1	0,7	-0,9	-2,4	-9,1	11,7	1,5
Antifungals for systemic use		0,1	0,2	-6,2	-6,8	-0,1	0,8	0,7
Retinoids for treatment of acne		0,1	0,1	4,0	4,0	-0,1	0,1	0,0
Corticosteroids, very potent (group IV)		0,1	1,1	5,1	3,8	0,0	1,2	1,2

* 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, a number of therapeutic groups were included in descending order of expenditure, up to a per capita value of €0,10)

ATC I level	Subgroups	Per capita gross expenditure	%	Δ% 14-13	DDD/1000 inhab die	%	Δ% 14-13
Antineoplastic and Immunomodulating Agents		**60,0**		**8,4**	**9,0**		**2,3**
Monoclonal antibodies		12,4	20,7	11,5	0,7	7,3	2,4
Tumor necrosis factor alpha (TNF-) inhibitors		10,2	17,0	4,6	0,9	10,2	5,7
Protein kinase inhibitors		9,8	16,3	14,7	0,3	2,9	8,1
Selective immunosuppressants		5,5	9,1	21,6	0,6	6,6	5,8
Interferons		4,4	7,4	-9,3	0,9	10,1	-5,8
Other immunosuppressants		2,8	4,7	23,7	0,1	1,0	13,7
Other antineoplastic agents		2,0	3,3	8,9	0,2	2,2	4,3
Gonadotropin releasing hormone analogues		1,8	3,0	-1,7	2,0	21,9	-1,9
Interleukin inhibitors		1,4	2,3	21,6	0,1	1,2	22,8
Colony stimulating factors		1,3	2,2	-9,3	0,1	1,1	-1,3
Other immunostimulants		1,3	2,1	9,0	0,1	1,3	8,6
Folic acid analogues		1,3	2,1	1,2	0,1	1,1	-7,5
Pyrimidine analogues		1,1	1,8	-20,6	0,3	3,9	-3,6
Other hormone antagonists and related agents		1,0	1,7	>100	0,1	0,8	91,0
Calcineurin inhibitors		0,7	1,1	-9,5	0,3	3,3	3,2
Taxanes		0,5	0,9	4,8	0,2	1,8	12,8
Anthracyclines and related substances		0,5	0,9	-3,3	0,1	1,3	-6,8
Anti-estrogens		0,4	0,7	2,0	0,2	2,7	-3,1
Nitrogen mustard analogues		0,4	0,6	32,3	0,1	0,7	19,3
Other plant alkaloids and natural products		0,3	0,5	10,5	0,0	0,0	9,8
Vinca alkaloids and analogues		0,2	0,3	-1,0	0,0	0,3	-5,9
Anti-androgens		0,1	0,2	2,4	0,9	10,0	12,8
Other alkylating agents		0,1	0,2	-26,0	0,0	0,1	41,2
Purine analogues		0,1	0,2	-6,7	0,0	0,0	-1,1
Platinum compounds		0,1	0,2	-33,9	0,2	2,4	1,0
Antiinfectives for Systemic Use		**25,9**		**-1,8**	**6,9**		**8,2**
Antivirals for treatment of HIV infections, combinations		5,7	22,1	-1,4	1,0	14,5	-2,2
Protease inhibitors		3,3	12,9	0,5	0,5	7,8	0,6
Nucleoside and nucleotide reverse transcriptase inhibitors		2,1	8,0	-2,1	0,6	9,0	0,2
Bacterial and viral vaccines, combined		1,4	5,4	-6,4	0,1	1,3	-9,6
Pneumococcal vaccines		1,4	5,3	-3,9	0,1	1,2	-4,9
Other antivirals		1,2	4,6	12,7	0,2	2,6	18,2
Immunoglobulins, normal human		1,2	4,5	7,2	0,1	1,3	32,0
Other antimycotics for systemic use		1,1	4,1	19,1	0,0	0,1	17,8
Other antibacterials		0,9	3,6	15,3	0,0	0,5	13,9
Specific immunoglobulins		0,8	3,0	-9,9	0,0	0,3	-4,5
Glycopeptide antibacterials		0,7	2,6	-5,5	0,1	0,9	3,7
Influenza vaccines		0,6	2,5	-21,2	1,2	17,1	>100
Triazole derivatives		0,6	2,4	-2,7	0,1	1,5	-0,7
Non-nucleoside reverse transcriptase inhibitors		0,6	2,3	-12,1	0,3	4,3	23,7
Carbapenems		0,5	1,9	-5,0	0,1	1,4	20,3
Antibiotics		0,5	1,8	3,6	0,0	0,2	-2,3
Combinations of penicillins, incl. beta-lactamase inhibitors		0,4	1,5	-12,0	0,7	10,8	-2,7
Papillomavirus vaccines		0,4	1,5	-41,0	0,0	0,4	-26,1
Tetracyclines		0,4	1,4	0,6	0,0	0,4	21,9
Measles vaccines		0,3	1,2	-12,7	0,0	0,7	-11,9
Nucleosides and nucleotides excl. reverse transcriptase inhibitors		0,3	1,2	24,6	0,2	2,3	-5,9

ATC I level	Subgroups	Per capita gross expenditure	%	Δ% 14-13	DDD/1000 inhab die	%	Δ% 14-13
Meningococcal vaccines		0,2	0,9	24,5	0,0	0,5	-5,8
Polymyxins		0,2	0,7	6,3	0,0	0,3	3,2
Third-generation cephalosporins		0,2	0,7	-18,2	0,3	3,7	-6,0
Other aminoglycosides		0,1	0,5	-10,3	0,1	0,8	-6,3
Varicella zoster vaccines		0,1	0,4	-20,0	0,0	0,1	-16,8
Hepatitis vaccines		0,1	0,4	3,7	0,0	0,2	-1,0
Fluoroquinolones		0,1	0,4	-26,1	0,4	5,9	-4,7
Blood and Blood Forming Organs		**21,7**		**11,3**	**37,1**		**9,3**
Blood coagulation factors		7,3	33,5	13,8	0,0	0,1	22,2
Other antianemic preparations		4,5	20,5	-4,1	2,9	7,8	5,0
Heparin group		2,1	9,9	2,0	6,3	16,9	5,2
Platelet aggregation inhibitors excl. heparin		1,9	8,7	13,8	7,2	19,5	26,6
Solutions affecting the electrolyte balance		1,1	4,9	9,2	6,8	18,4	-19,1
Solutions for parenteral nutrition		0,8	3,8	9,7	0,7	1,9	-11,0
Direct thrombin inhibitors		0,8	3,5	>100	1,0	2,7	>100
Direct factor Xa inhibitors		0,7	3,0	>100	1,5	4,1	>100
Blood substitutes and plasma protein fractions		0,5	2,1	-13,5	0,1	0,2	-59,9
Other systemic hemostatics		0,4	1,9	9,3	0,0	0,0	9,5
Local hemostatics		0,3	1,5	-1,8	0,0	0,0	-6,1
Hypertonic solutions		0,3	1,3	14,1	0,1	0,2	8,8
Enzymes		0,2	1,1	5,1	0,0	0,0	2,2
Drugs used in hereditary angioedema		0,2	0,9	21,5	0,0	0,0	21,4
Other antithrombotic agents		0,2	0,8	-8,5	0,3	0,8	15,4
Isotonic solutions		0,2	0,8	-9,1	0,1	0,1	-6,7
Proteinase inhibitors		0,1	0,7	-2,1	0,0	0,0	-7,4
Alimentary Tract and Metabolism		**9,9**		**8,4**	**26,8**		**0,0**
Enzymes		3,3	33,6	10,5	0,0	0,0	15,8
Insulins and analogues for injection, long-acting		2,1	21,4	15,5	4,7	17,6	15,8
Combinations of oral blood glucose lowering drugs		1,3	13,3	20,5	3,0	11,3	18,8
Other blood glucose lowering drugs, excl. insulins		0,7	6,7	1,2	0,8	3,1	1,4
Dipeptidyl peptidase 4 (DPP-4) inhibitors		0,7	6,7	6,0	1,2	4,6	6,2
Proton pump inhibitors		0,3	3,1	-16,9	4,3	16,0	4,0
Various alimentary tract and metabolism products		0,3	2,7	9,3	0,0	0,0	5,7
Insulins and analogues for injection, fast-acting		0,2	1,9	1,8	0,7	2,7	1,9
Serotonin (5HT3) antagonists		0,2	1,7	-6,6	0,1	0,3	3,5
Multivitamins, plain		0,1	1,1	44,9	0,1	0,3	-0,8
Various		**8,5**		**3,5**	**2,8**		**90,7**
Medical gases		3,8	45,0	4,2			
Iron chelating agents		1,3	15,1	-2,5	0,1	2,3	-0,0
Watersoluble, nephrotropic, low osmolar X-ray contrast media		1,1	13,1	-5,0	0,1	2,2	-4,1
Drugs for treatment of hyperkalemia and hyperphosphatemia		0,5	6,0	4,8	0,2	8,0	4,8
Paramagnetic contrast media		0,3	4,0	0,1	0,0	0,7	1,3
Antidotes		0,2	2,7	27,2	0,1	4,6	-9,9
Other diagnostic radiopharmaceuticals for tumour detection		0,2	2,0	38,6	0,0	0,1	7,1
Technetium (99mTc) compounds		0,2	1,8	99,0	0,0	0,0	68,8
Tests for thyreoidea function		0,1	1,7	-2,5	0,0	0,0	-0,7
Detoxifying agents for antineoplastic treatment		0,1	1,6	1,9	0,2	8,6	5,7
Iodine (123I) compounds		0,1	1,6	9,2	0,0	0,0	9,2
Nervous System		**7,8**		**-13,7**	**25,4**		**1,7**
Other antipsychotics		1,8	23,0	-13,5	1,4	5,4	-8,9
Diazepines, oxazepines, thiazepines and oxepines		1,1	14,3	-5,1	3,5	13,8	17,2
Dopa and dopa derivatives		0,6	7,4	4,7	0,4	1,6	1,4
Anticholinesterases		0,6	7,2	-9,5	1,8	7,2	54,8
Drugs used in opioid dependence		0,5	6,7	-6,8	3,1	12,1	6,9
Other antiepileptics		0,4	5,5	2,7	0,7	2,7	11,4

ATC I level	Subgroups	Per capita gross expenditure	%	Δ% 14-13	DDD/1000 inhab die	%	Δ% 14-13
Halogenated hydrocarbons		0,3	4,1	-5,2	0,0	0,0	22,3
Amides		0,3	4,0	-69,1	3,9	15,2	-23,9
Other nervous system drugs		0,3	3,5	38,1	0,1	0,3	2,0
Other anti-dementia drugs		0,2	3,2	-56,4	0,7	2,7	14,7
Other general anesthetics		0,2	2,2	-9,8	0,2	0,7	-3,8
Anilides		0,2	2,1	-21,5	0,9	3,6	121,8
Opioid anesthetics		0,1	1,6	16,0	0,2	0,9	-7,9
Indole derivatives		0,1	1,6	>100	0,0	0,1	-21,8
Drugs used in alcohol dependence		0,1	1,5	9,8	0,2	0,9	-44,0
Dopamine agonists		0,1	1,4	92,5	0,2	0,8	89,1
NERVOUS SYSTEM		0,1	1,3	>100	0,0	0,1	>100
Systemic Hormonal Preparations, excl. Sex Hormones and Insulins		**4,9**		**8,1**	**5,5**		**0,0**
Somatropin and somatropin agonists		1,6	32,5	6,7	0,2	4,4	-2,5
Somatostatin and analogues		1,2	25,4	3,1	0,2	3,0	4,6
Other anti-parathyroid agents		0,9	17,7	5,8	0,3	4,8	5,2
Parathyroid hormones and analogues		0,5	9,4	49,5	0,1	1,8	49,3
Other anterior pituitary lobe hormones and analogues		0,3	6,9	4,4	0,0	0,2	4,3
Glucocorticoids		0,3	6,6	7,4	4,2	76,7	-1,8
Cardiovascular System		**3,4**		**10,1**	**16,9**		**-0,5**
Other antihypertensives		1,7	51,1	3,3	0,1	0,3	5,6
Other cardiac preparations		1,1	31,1	49,0	1,6	9,7	53,2
Adrenergic and dopaminergic agents		0,1	3,0	-53,9	0,9	5,0	-42,8
Genito Urinary System and Sex Hormones		**1,8**		**3,8**	**1,7**		**2,2**
Gonadotropins		1,2	64,4	3,1	0,2	11,4	2,7
Drugs used in erectile dysfunction		0,3	15,0	10,4	0,1	5,4	14,7
Prostaglandins		0,1	6,6	2,2	0,1	3,0	5,0
Other gynecologicals		0,1	5,8	0,5	0,0	0,1	1,3
Sensory Organs		**1,8**		**5,3**	**1,7**		**-15,9**
Antineovascularisation agents		1,5	83,7	3,9	0,2	11,5	31,1
Corticosteroids, plain		0,2	9,0	41,6	0,0	0,8	1,8
Respiratory System		**1,0**		**7,9**	**3,2**		**-1,0**
Other systemic drugs for obstructive airway diseases		0,4	36,5	23,0	0,0	1,4	30,6
Mucolytics		0,2	16,3	1,9	0,2	7,6	-4,4
Anticholinergics		0,1	11,9	-9,0	0,9	28,1	-1,7
Musculo-Skeletal System		**0,9**		**-20,8**	**3,0**		**24,2**
Other drugs affecting bone structure and mineralization		0,3	31,4	216,5	0,9	31,0	251,9
Other muscle relaxants, peripherally acting agents		0,2	20,1	-1,7	0,0	0,1	1,7
Bisphosphonates		0,1	15,6	-74,2	0,1	3,7	-5,7
Other quaternary ammonium compounds		0,1	13,0	-21,6	0,1	3,5	-1,2

* The analysis does not include 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 the NHS in 2014 is included in the following tables.

Table 7.2.19. First thirty active ingredients in terms of outpatient NHS expenditure: comparison 2009-2014

ATC	Active ingredient	Exp (million)	%	Rank 2014	Rank 2013	Rank 2012	Rank 2011	Rank 2010
A	Pantoprazole	294	2,7	1	3	5	7	10
C	Rosuvastatin	287	2,6	2	1	1	2	2
R	Salmeterol and fluticasone	284	2,6	3	2	2	3	3
A	Lansoprazole	252	2,3	4	4	3	4	4
A	Omeprazole	204	1,9	5	5	7	8	8
C	Atorvastatin	186	1,7	6	10	4	1	1
J	Amoxicillin and enzyme inhibitor	183	1,7	7	6	8	9	11
A	Esomeprazole	164	1,5	8	12	15	14	5
C	Simvastatin and ezetimibe	159	1,4	9	13	13	16	19
B	Enoxaparin	154	1,4	10	11	10	13	18
R	Tiotropium bromide	146	1,3	11	9	9	12	13
G	Dutasteride	138	1,3	12	17	18	31	38
C	Olmesartan medoxomil	137	1,3	13	14	16	18	22
C	Ramipril	125	1,1	14	19	17	21	23
C	Olmesartan medoxomil and diuretics	125	1,1	15	18	20	29	35
N	Pregabalin	123	1,1	16	20	24	34	41
C	Omega-3-triglycerides incl. other esters and acids	123	1,1	17	7	6	5	7
C	Simvastatin	112	1	18	21	19	19	17
R	Formoterol and beclometasone	108	1	19	8	11	11	12
N	Duloxetine	107	1	20	25	27	36	33
C	Bisoprolol	106	1	21	30	38	-	-
A	Colecalciferol	100	0,9	22	41	-	-	-
C	Amlodipine	98	0,9	23	28	29	22	16
S	Timolol, combinations	95	0,9	24	31	32	37	29
A	Mesalazine	94	0,9	25	33	-	-	-
A	Insulin aspart	93	0,9	26	24	23	-	-
N	Escitalopram	93	0,9	27	15	14	17	20
A	Insulin lispro	92	0,8	28	22	-	-	-
J	Ceftriaxone	92	0,8	29	32	35	-	-
A	Rifaximin	86	0,8	30	35			
	Total	**4.359**	**39,8**					
	Total Class A-NHS expenditure	**10.964**						

Table 7.2.20. First thirty active ingredients in terms of outpatient NHS consumption: comparison 2009-2014

ATC	Active ingredient	DDD/1000 inhab die	%	Rank 2014	Rank 2013	Rank 2012	Rank 2011	Rank 2010
B	Folic acid	61,1	5,8	1	3	3	-	-
C	Ramipril	59,8	5,8	2	1	1	1	2
B	Acetylsalicylic acid	52,0	5	3	2	2	2	1
C	Atorvastatin	31,4	3	4	4	5	6	7
C	Amlodipine	27,2	2,6	5	5	4	3	3
C	Furosemide	24,0	2,4	6	6	6	4	4
A	Lansoprazole	20,3	2	7	7	7	5	5
A	Pantoprazole	20,2	2	8	11	11	13	19
A	Metformin	19,9	2	9	10	10	9	8
A	Omeprazole	19,7	1,8	10	9	9	8	9
H	Levothyroxine sodium	19,1	1,8	11	8	8	7	6
C	Simvastatin	15,4	1,4	12	12	13	11	13
C	Valsartan	14,5	1,4	13	14	14	15	14
C	Rosuvastatin	13,9	1,4	14	13	12	10	12
C	Nebivolol	13,4	1,2	15	15	16	16	17
A	Esomeprazole	13,2	1,2	16	17	19	25	33
C	Enalapril	11,9	1,2	17	16	15	12	10
C	Valsartan and diuretics	11,2	1	18	18	18	17	16
C	Glyceryl trinitrate	10,2	1	19	19	17	14	11
C	Atenolol	10,0	1	20	20	20	19	18
C	Lercanidipine	9,3	0,8	21	21	21	20	21
G	Tamsulosin	9,2	0,8	22	24	24	22	23
C	Telmisartan	9,1	0,8	23	22	23	23	24
J	Amoxicillin and enzyme inhibitor	9,0	0,8	24	25	25	24	27
C	Irbesartan	8,9	0,8	25	23	22	21	20
C	Bisoprolol	8,0	0,8	26	32	-	-	-
C	Ramipril and diuretics	7,9	0,8	27	26	27	27	29
C	Candesartan	7,8	0,8	28	27	26	26	25
N	Paroxetine	7,8	0,8	29	28	29	31	32
C	Losartan	7,7	0,8	30	29	28	34	40
	Total	**553,0**	**53,2**					
	Total Class A DDD	**1.039,4**						

Table 7.2.21. Outpatient NHS consumption and expenditure for the year 2014: most frequently prescribed active ingredients for ATC level 1 categories (up to 75% of the expenditure within the therapeutic category

Subgroup/ Active ingredient	Per capita gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Cardiovascular System	**56,3**		**-6,7**	**467,6**		**-0,3**
Rosuvastatin	**4,7**	**8,4**	**-7,7**	**13,9**	**3,0**	**-7,5**
Atorvastatin	3,1	5,4	12,2	31,4	6,7	13,8
Simvastatin and ezetimibe	2,6	4,6	2,7	3,5	0,7	2,7
Olmesartan medoxomil	2,3	4,0	-3,7	7,3	1,6	4,8
Ramipril	2,1	3,7	1,8	59,8	12,8	1,9
Olmesartan medoxomil and diuretics	2,1	3,6	-1,3	6,6	1,4	6,1
Omega-3-triglycerides incl. other esters and acids	2,0	3,6	-31,6	3,5	0,7	-20,3
Simvastatin	1,8	3,3	-2,0	15,4	3,3	-2,0
Bisoprolol	1,7	3,1	10,8	8,0	1,7	8,5
Amlodipine	1,6	2,9	-1,2	27,2	5,8	-1,0
Valsartan and diuretics	1,3	2,3	-3,6	11,2	2,4	-2,1
Nebivolol	1,3	2,3	1,8	13,4	2,9	2,3
Doxazosin	1,2	2,2	-0,8	7,5	1,6	-0,8
Glyceryl trinitrate	1,2	2,2	-10,7	10,2	2,2	-10,4
Telmisartan and diuretics	1,0	1,8	-26,6	4,7	1,0	-1,3
Olmesartan medoxomil and amlodipine	0,9	1,7	12,5	2,8	0,6	19,9
Valsartan	0,9	1,7	0,7	14,5	3,1	1,3
Ezetimibe	0,9	1,6	37,5	1,4	0,3	37,5
Zofenopril and diuretics	0,9	1,6	3,0	3,8	0,8	3,0
Losartan	0,9	1,5	-1,0	7,7	1,7	0,0
Barnidipine	0,8	1,5	3,9	4,5	1,0	4,7
Irbesartan and diuretics	0,8	1,4	-62,7	6,8	1,4	-5,8
Lercanidipine	0,8	1,4	-1,4	9,3	2,0	-1,2
Ramipril and diuretics	0,8	1,4	-2,2	7,9	1,7	-1,1
Irbesartan	0,7	1,3	-3,6	8,9	1,9	-2,9
Perindopril and amlodipine	0,7	1,3	37,4	3,9	0,8	37,4
Carvedilol	0,7	1,3	-4,9	4,0	0,8	-4,7
Furosemide	0,7	1,3	2,5	24,0	5,1	2,3
Losartan and diuretics	0,7	1,2	-4,7	5,9	1,3	-4,5
Enalapril	0,7	1,2	-6,1	11,9	2,5	-6,1
Telmisartan	0,7	1,2	-63,2	9,1	1,9	-1,8
Alimentary tract and Metabolism	**32,7**		**0,3**	**152,7**		**0,3**
Pantoprazole	4,8	14,8	9,2	20,2	13,2	9,8
Lansoprazole	4,1	12,7	-5,5	20,3	13,3	-5,0

Subgroup/ Active ingredient	Per capita gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Omeprazole	3,4	10,3	-0,1	19,7	12,9	0,5
Esomeprazole	2,7	8,2	5,8	13,2	8,6	6,0
Colecalciferol	1,6	5,0	33,9	1,3	0,9	26,9
Mesalazine	1,5	4,7	4,5	3,8	2,5	4,4
Insulin aspart	1,5	4,7	1,5	3,0	2,0	1,5
Insulin lispro	1,5	4,6	2,8	3,0	1,9	2,8
Rifaximin	1,4	4,3	2,7	1,9	1,2	2,7
Metformin	1,3	4,1	2,3	19,9	13,0	2,7
Alginic acid	0,8	2,4	4,1	1,8	1,2	3,7
Nervous System	**23,0**		**-1,9**	**60,5**		**0,1**
Pregabalin	2,0	8,8	6,6	1,5	2,5	6,1
Duloxetine	1,8	7,7	1,7	2,6	4,3	2,3
Escitalopram	1,5	6,7	-30,9	7,1	11,8	-1,7
Paroxetine	1,2	5,3	0,1	7,8	12,8	0,1
Levetiracetam	1,1	4,9	8,6	1,5	2,4	9,2
Fentanyl	1,1	4,8	7,3	0,6	0,9	3,1
Oxycodone, combinations	0,9	4,0	25,4	0,6	0,9	15,8
Valproic acid	0,9	3,7	3,2	2,1	3,4	2,8
Venlafaxine	0,8	3,3	0,6	3,3	5,4	0,9
Rasagiline	0,7	3,0	5,8	0,4	0,6	5,8
Sertraline	0,6	2,8	3,0	6,7	11,1	3,6
Rotigotine	0,6	2,7	7,5	0,3	0,5	7,7
Tapentadol	0,6	2,5	37,5	0,2	0,4	37,8
Citalopram	0,5	2,1	-3,8	4,5	7,4	-3,3
Levodopa and decarboxylase inhibitor	0,4	2,0	1,4	1,6	2,6	1,5
Pramipexole	0,4	1,9	-22,2	0,4	0,7	-20,9
Lamotrigine	0,3	1,5	1,6	0,5	0,9	2,1
Codeine, combinations excl. psycholeptics	0,3	1,5	-6,2	1,3	2,1	-4,3
Tramadol	0,3	1,5	-2,1	0,7	1,2	-1,9
Almotriptan	0,3	1,4	1,0	0,2	0,3	1,0
Gabapentin	0,3	1,3	1,6	0,4	0,7	1,5
Topiramate	0,3	1,3	-7,8	0,3	0,5	-2,0
Mirtazapine	0,3	1,3	0,4	1,4	2,3	2,4
Respiratory System	**17,2**		**0,2**	**48,3**		**-0,5**
Salmeterol and fluticasone	4,7	27,2	-2,3	5,6	11,7	-2,2
Tiotropium bromide	2,4	14,0	-12,3	3,9	8,1	-12,3
Formoterol and beclometasone	1,8	10,3	9,6	2,7	5,6	9,9
Beclometasone	1,4	8,0	-3,1	6,4	13,2	-2,9

Subgroup/ Active ingredient	Per capita gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Formoterol and budesonide	1,2	6,8	-4,7	1,3	2,7	-5,1
Montelukast	0,5	3,1	-14,9	2,1	4,4	-0,2
Glycopyrronium bromide	0,5	2,8	234,7	0,8	1,7	233,3
Fluticasone	0,4	2,5	-4,1	1,0	2,1	-4,6
Indacaterol	0,4	2,5	5,2	1,1	2,3	4,7
Antiinfectives for Systemic use	**14,6**		**-3,0**	**22,6**		**-3,0**
Amoxicillin and enzyme inhibitor	3,0	20,6	-1,4	9,0	39,8	-1,1
Ceftriaxone	1,5	10,4	0,6	0,4	1,6	-0,1
Ciprofloxacin	1,1	7,4	2,5	1,1	4,7	2,2
Clarithromycin	0,9	6,5	-5,0	2,6	11,4	-2,4
Fluconazole	0,9	6,4	0,7	0,4	2,0	1,0
Levofloxacin	0,9	6,2	-0,8	1,7	7,3	-0,6
Cefixime	0,9	6,0	-1,5	1,0	4,5	-0,6
Azithromycin	0,7	4,8	-1,4	1,3	5,7	-1,4
Fosfomycin	0,6	4,1	3,2	0,4	1,6	2,8
Hepatitis B immunoglobulin	0,4	3,0	-5,2	0,0	0,0	-5,4
Blood and Blood forming Organs	**9,0**		**-6,5**	**142,0**		**8,6**
Enoxaparin	2,5	28,1	-1,5	2,7	1,9	-1,2
Acetylsalicylic acid	1,4	15,6	-14,8	52,0	36,6	-7,0
Nadroparin	0,9	10,3	-8,8	0,9	0,6	-8,6
Clopidogrel	0,7	8,2	-3,9	3,3	2,4	0,8
Ticlopidine	0,4	4,6	-13,5	4,6	3,2	-13,7
Folic acid	0,4	4,3	15,4	61,1	43,0	34,5
Parnaparin	0,3	3,2	-5,9	0,3	0,2	-5,8
Combinations	0,3	3,0	-1,1	0,9	0,6	-1,5
Musculo-Skeletal System	**7,4**		**-8,6**	**41,2**		**-2,7**
Etoricoxib	1,2	16,1	2,4	3,8	9,1	1,6
Alendronic acid and colecalciferol	1,1	15,4	6,0	3,5	8,4	5,3
Alendronic acid	0,6	8,2	4,6	2,8	6,9	5,4
Diclofenac	0,6	8,0	-1,8	4,1	9,8	-1,9
Risedronic acid	0,6	7,5	-5,1	2,8	6,8	-0,5
Febuxostat	0,5	7,2	20,1	1,0	2,5	31,7
Ketoprofen	0,4	6,0	-3,6	4,1	10,0	-2,0
Ibuprofen	0,3	4,5	-1,0	2,1	5,1	-0,6
Allopurinol	0,3	4,0	3,0	6,9	16,9	2,6
Genito Urinary System and Sex Hormones	**6,9**		**0,5**	**41,9**		**-1,0**
Dutasteride	2,3	32,7	7,9	6,3	15,1	7,9
Tamsulosin	1,0	14,1	0,2	9,2	21,9	0,5

Subgroup/ Active ingredient	Per capita gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Alfuzosin	0,7	10,4	0,8	7,5	18,0	0,9
Silodosin	0,6	9,1	29,2	3,4	8,0	29,2
Finasteride	0,6	8,4	-4,3	2,6	6,3	-3,3
Terazosin	0,2	3,1	-6,5	1,7	4,0	-6,4
Antineoplastic and Immunomodulating Agents	**4,2**		**-1,7**	**4,4**		**1,4**
Ciclosporin	1,0	24,2	-2,1	0,3	5,9	-2,1
Letrozole	0,9	20,5	6,7	1,0	22,8	7,6
Methotrexate	0,7	16,1	4,8	0,1	2,4	4,0
Anastrozole	0,4	10,3	-0,1	0,8	17,9	2,5
Exemestane	0,2	4,5	6,1	0,2	5,1	7,0
Sensory Organs	**3,7**		**1,8**	**19,5**		**-0,3**
Timolol, combinations	1,6	42,5	2,8	6,5	33,1	1,8
Bimatoprost	0,4	11,7	3,9	1,8	9,1	3,7
Travoprost	0,3	8,5	-7,6	1,0	5,4	-7,6
Timolol	0,3	7,8	2,2	3,1	16,1	-2,9
Latanoprost	0,3	7,5	-7,3	1,8	9,2	-5,1
Systemic Hormonal Preparations, excl. Sex Hormones and Insulins	**3,1**		**-13,4**	**33,7**		**-2,0**
Levothyroxine sodium	0,7	23,8	-8,9	19,1	56,7	-4,1
Prednisone	0,6	20,5	2,1	5,8	17,1	1,9
Teriparatide	0,4	12,9	-40,6	0,1	0,2	-40,6
Betamethasone	0,4	11,2	-2,5	2,2	6,5	-0,2
Methylprednisolone	0,2	7,2	1,0	3,5	10,4	1,9
Various	**1,1**		**-38,6**	**0,1**		**-6,8**
Oxygen	1,0	89,5	-40,3			
Dermatologicals	**1,0**		**-0,2**	**4,2**		**-3,3**
Calcipotriol, combinations	0,5	47,0	-6,8	1,5	36,1	-6,8
Terbinafine	0,1	7,7	-7,9	0,1	3,6	-8,7
Calcipotriol	0,1	7,7	-7,7	0,3	7,1	-7,9
Isotretinoin	0,1	6,8	2,1	0,1	3,1	2,1
Tacalcitol	0,1	5,6	1,6	0,1	2,9	5,1
Clobetasol	0,1	5,5	3,4	1,1	26,0	2,0
Antiparasitic Products, Insecticides and Repellents	**0,2**		**1,3**	**0,8**		**3,3**
Hydroxychloroquine	0,1	58,3	3,3	0,6	79,8	3,3
Mefloquine	0,0	17,2	-8,7	0,0	0,9	-8,7

*Expenditure and consumption percentages are calculated on the total of the ATC category
^ Medical gas DDD value is not available

Table 7.2.22. Public health facilities consumption and expenditure in 2014: most frequently prescribed active ingredients for ATC level 1 categories (up to 75% of the expenditure within the therapeutic category

Subgroup/Active ingredient	Per capite gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Antineoplastic and Immunomodulating Agents	**60,0**		**8,4**	**9,0**		**2,3**
Adalimumab	4,1	6,9	7,8	0,3	3,4	7,9
Trastuzumab	4,0	6,7	0,4	0,1	1,5	2,2
Etanercept	3,5	5,9	-4,7	0,3	3,0	-3,0
Rituximab	3,1	5,2	-1,3	0,4	4,4	-1,0
Interferon beta-1a	3,1	5,1	-5,2	0,7	7,7	-2,8
Imatinib	2,9	4,9	-2,3	0,1	1,2	-1,9
Bevacizumab	2,8	4,7	19,0	0,1	1,1	17,0
Lenalidomide	2,4	4,0	12,9	0,0	0,5	8,1
Fingolimod	1,6	2,7	45,8	0,1	0,8	46,5
Infliximab	1,6	2,6	5,7	0,3	2,9	5,7
Bortezomib	1,5	2,4	8,7	0,1	1,3	8,7
Pemetrexed	1,2	2,0	1,4	0,0	0,4	3,1
Natalizumab	1,2	2,0	9,6	0,1	0,6	10,5
Eculizumab	1,2	2,0	16,8	0,0	0,0	15,5
Glatiramer acetate	1,1	1,8	8,9	0,1	1,3	8,6
Everolimus	1,0	1,7	94,9	0,0	0,2	89,1
Nilotinib	1,0	1,6	6,2	0,0	0,2	6,9
Leuprorelin	1,0	1,6	-3,0	1,2	13,5	-1,0
Dasatinib	1,0	1,6	19,7	0,0	0,2	19,5
Abiraterone	0,9	1,5	>100	0,0	0,3	>100
Cetuximab	0,9	1,5	-4,4	0,0	0,2	-4,0
Sunitinib	0,8	1,4	-7,7	0,0	0,1	-3,3
Triptorelin	0,8	1,4	0,7	0,7	8,1	-2,8
Azacitidine	0,8	1,3	27,1	0,0	0,1	10,7
Pegfilgrastim	0,7	1,2	-6,0	0,1	0,7	-5,9
Golimumab	0,7	1,2	37,8	0,1	0,7	37,5
Antiinfectives for Systemic Use	**25,9**		**-1,8**	**6,9**		**8,2**
Tenofovir disoproxil and emtricitabine	2,0	7,8	-7,2	0,4	5,5	-7,6
Emtricitabine, tenofovir disoproxil and efavirenz	1,5	5,6	-13,0	0,2	2,7	-12,1
Pneumococcus, purified polysaccharides antigen conjugated	1,4	5,3	-3,3	0,1	1,2	-3,4
Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B	1,2	4,8	-5,2	0,1	0,9	-7,3
Darunavir	1,1	4,4	17,4	0,2	2,9	30,5
Entecavir	1,1	4,4	9,6	0,2	3,5	9,3

Subgroup/Active ingredient	Per capite gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Lamivudine and abacavir	1,1	4,2	8,9	0,2	3,1	9,9
Atazanavir	1,0	3,9	-11,6	0,2	3,5	-11,6
Raltegravir	0,9	3,5	17,3	0,2	2,3	19,4
Immunoglobulins, normal human, for intravascular adm.	0,7	2,9	-4,0	0,0	0,1	-4,1
Caspofungin	0,7	2,7	18,4	0,0	0,1	16,6
Tenofovir disoproxil	0,7	2,7	0,7	0,2	2,9	0,6
Teicoplanin	0,6	2,5	-6,0	0,0	0,6	-6,1
Influenza, inactivated, split virus or surface antigen	0,6	2,4	-21,8	1,2	17,1	113,9
Linezolid	0,6	2,4	15,2	0,0	0,2	15,0
Emtricitabine, tenofovir disoproxil and rilpivirine	0,5	2,1	>100	0,1	1,0	>100
Telaprevir	0,5	2,1	-10,6	0,0	0,1	-10,6
Amphotericin B	0,5	1,8	3,6	0,0	0,2	-2,3
Immunoglobulins, normal human, for extravascular adm.	0,4	1,6	35,3	0,1	1,2	35,9
Lopinavir and ritonavir	0,4	1,6	-22,3	0,1	1,4	-21,6
Voriconazole	0,4	1,5	-6,4	0,0	0,1	-6,2
Palivizumab	0,4	1,5	-9,3	0,0	0,0	-10,0
Tigecycline	0,4	1,4	-0,2	0,0	0,1	-0,7
Meropenem	0,3	1,3	-4,1	0,1	1,1	26,5
Boceprevir	0,3	1,2	45,8	0,0	0,1	45,0
Blood and Blood Forming Organs	**21,7**		**11,3**	**37,1**		**9,3**
Coagulation factor VIII	4,9	22,7	20,0	0,0	0,1	24,6
Erythropoietin	2,6	12,1	1,2	2,1	5,7	11,5
Darbepoetin alfa	1,7	7,7	-10,4	0,7	1,9	-9,4
Enoxaparin	1,4	6,6	8,0	4,8	12,8	8,9
Eptacog alfa (activated)	1,0	4,5	-14,6	0,0	0,0	-14,1
Electrolytes	1,0	4,4	10,8	6,6	17,8	-19,8
Dabigatran etexilate	0,7	3,2	>100	1,0	2,7	>100
Combinations	0,7	3,0	13,6	0,1	0,4	5,7
Nonacog alfa	0,6	2,7	16,9	0,0	0,0	18,4
Treprostinil	0,5	2,2	18,2	0,0	0,0	28,4
Rivaroxaban	0,5	2,2	>100	1,2	3,1	>100
Factor VIII inhibitor bypassing activity	0,4	1,8	26,2	0,0	0,0	28,6
Ticagrelor	0,4	1,8	71,0	0,4	1,1	71,6
Alimentary Tract and Metabolism	**9,9**		**8,4**	**26,8**		**0,0**
Insulin glargine	1,7	16,8	16,6	3,7	13,8	16,6
Alglucosidase alfa	0,8	8,4	7,8	0,0	0,0	8,3
Imiglucerase	0,7	7,2	10,6	0,0	0,0	10,3

Subgroup/Active ingredient	Per capite gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Agalsidase alfa	0,7	7,0	4,5	0,0	0,0	4,9
Liraglutide	0,6	5,8	5,1	0,6	2,1	0,7
Metformin and sitagliptin	0,5	5,4	7,8	1,1	3,9	6,8
Insulin detemir	0,5	4,6	11,5	1,0	3,8	12,8
Idursulfase	0,4	4,5	6,5	0,0	0,0	7,4
Sitagliptin	0,4	4,4	5,3	0,8	3,0	4,4
Metformin and pioglitazone	0,4	3,8	20,0	1,0	3,9	20,9
Metformin and vildagliptin	0,3	3,1	22,2	0,6	2,1	22,3
Agalsidase beta	0,3	2,7	55,5	0,0	0,0	55,5
Velaglucerase alfa	0,2	1,8	19,1	0,0	0,0	22,5
Various	**8,5**		**3,5**	**2,8**		**90,7**
Oxygen	3,8	44,6	4,1			
Deferasirox	1,1	13,2	-2,6	0,0	1,3	2,3
Iomeprol	0,4	4,8	-1,1	0,0	0,7	0,3
Sevelamer	0,4	4,5	3,9	0,2	5,7	4,0
Iodixanol	0,2	2,6	-12,5	0,0	0,3	-13,3
Iopromide	0,2	2,5	-4,9	0,0	0,4	-0,8
Sugammadex	0,2	2,1	65,6	0,0	0,2	69,6
Fludeoxyglucose (18F)	0,2	1,8	45,9	0,0	0,1	7,5
Nervous System	**7,8**		**-13,7**	**25,4**		**1,7**
Paliperidone	0,8	9,8	61,1	0,4	1,6	48,8
Quetiapine	0,7	9,6	-3,2	1,5	5,7	15,0
Risperidone	0,6	7,9	-11,5	0,7	2,9	6,5
Rivastigmine	0,5	6,5	-6,9	1,2	4,7	>100
Aripiprazole	0,4	5,2	-54,5	0,2	0,9	-57,5
Levodopa and decarboxylase inhibitor	0,3	4,2	14,8	0,2	0,6	4,1
Methadone	0,3	3,5	-6,3	2,2	8,8	-2,7
Sevoflurane	0,3	3,3	-12,5	0,0	0,0	-1,9
Memantine	0,2	3,2	-56,4	0,7	2,7	14,7
Levodopa, decarboxylase inhibitor and COMT inhibitor	0,2	3,1	-6,5	0,2	0,9	-0,1
Olanzapine	0,2	2,7	-21,3	1,6	6,2	23,2
Levetiracetam	0,2	2,6	-5,4	0,3	1,1	4,5
Buprenorphine, combinations	0,2	2,6	-6,1	0,2	0,8	-6,1
Paracetamol	0,2	2,1	-21,2	0,9	3,6	>100
Pregabalin	0,2	2,1	8,0	0,2	0,7	7,0
Tafamidis	0,1	1,9	>100	0,0	0,0	>100
Propofol	0,1	1,6	-11,1	0,2	0,6	-4,1

Subgroup/Active ingredient	Per capite gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Ziprasidone	0,1	1,6	>100	0,0	0,1	-21,8
Levobupivacaine	0,1	1,3	1,9	0,0	0,1	3,0
Drugs used in alcohol dependence	0,1	1,2	5,0	0,1	0,4	-64,4
Systemic Hormonal Preparations, excl. Sex Hormones and Insulins	**4,9**		**8,1**	**5,5**		**0,0**
Somatropin	1,6	32,4	6,7	0,2	4,4	-2,5
Octreotide	0,8	16,9	1,4	0,1	2,1	2,7
Teriparatide	0,5	9,4	49,5	0,1	1,8	49,2
Cinacalcet	0,4	8,9	7,0	0,1	1,6	6,6
Paricalcitol	0,4	8,8	4,5	0,2	3,1	4,5
Cardiovascular System	**3,4**		**10,1**	**16,9**		**-0,5**
Bosentan	1,5	44,3	1,4	0,0	0,3	3,8
Ivabradine	0,6	16,5	44,2	1,2	6,9	54,2
Ranolazine	0,5	13,4	65,9	0,4	2,5	59,8
Ambrisentan	0,2	6,4	10,9	0,0	0,0	12,2
Genito Urinary System and Sex Hormones	**1,8**		**3,8**	**1,7**		**2,2**
Follitropin alfa	0,7	35,7	-3,0	0,1	3,9	2,2
Sildenafil	0,2	10,1	3,1	0,0	2,6	4,6
Human menopausal gonadotrophin	0,2	9,8	2,0	0,1	5,3	2,2
Follitropin beta	0,2	8,4	3,7	0,0	1,0	3,4
Atosiban	0,1	5,8	0,5	0,0	0,0	3,2
Dinoprostone	0,1	4,8	6,3	0,0	2,7	6,7
Tadalafil	0,1	4,3	31,9	0,0	2,5	29,1
Sensory Organs	**1,8**		**5,3**	**1,7**		**-15,9**
Ranibizumab	1,3	72,7	-6,8	0,2	9,4	8,9
Aflibercept	0,2	9,3	>100	0,0	2,1	>100
Respiratory System	**1,0**		**7,9**	**3,2**		**-1,0**
Omalizumab	0,4	35,8	22,8	0,0	0,9	27,9
Dornase alfa (desoxyribonuclease)	0,1	13,3	4,9	0,0	0,5	6,0
Tiotropium bromide	0,1	10,1	-12,1	0,2	7,8	-11,0
Natural phospholipids	0,1	9,0	5,4	0,0	0,0	3,9
Salmeterol and fluticasone	0,1	7,9	-13,3	0,2	7,6	1,2
Musculo-Skeletal System	**0,9**		**-20,8**	**3,0**		**24,2**
Denosumab	0,3	31,3	>100	0,9	30,9	>100
Botulinum toxin	0,2	20,1	-1,7	0,0	0,1	1,7
Zoledronic acid	0,1	12,5	-78,0	0,0	0,3	-10,9
Cisatracurium	0,1	8,5	-31,3	0,1	1,8	-12,3
Baclofen	0,0	3,2	-4,9	0,1	2,9	3,9

Subgroup/Active ingredient	Per capite gross expenditure	%*	Δ % 14-13	DDD/1000 inhab die	%*	Δ % 14-13
Dermatologicals	**0,4**		**-12,9**	**17,0**		**6,5**
Other cicatrizants	0,1	14,5	-5,5	0,4	2,2	2,9
Povidone-iodine	0,0	13,0	-20,2	2,9	16,8	0,8
Silver sulfadiazine	0,0	10,1	-9,5	0,4	2,6	-14,6
Sodium hypochlorite	0,0	9,0	10,4	2,4	14,3	1,5
Imiquimod	0,0	7,9	-37,9	0,0	0,2	-16,1
Hyaluronic acid	0,0	7,5	10,0	0,2	1,2	6,5
Chlorhexidine, combinations	0,0	6,2	19,9	6,3	37,2	22,7
Alitretinoin	0,0	4,9	-13,0	0,0	0,0	-13,1
Gentamicin	0,0	2,7	-13,9	0,6	3,7	3,4
Antiparasitic Products, Insecticides and Repellents	**0,0**		**4,5**	**0,0**		**-2,6**
Atovaquone	0,0	52,4	4,4	0,0	8,1	7,3
Permethrin	0,0	14,3	60,0	0,0	3,3	51,2
Proguanil, combinations	0,0	11,0	-25,5	0,0	1,2	2,1

*Expenditure and consumption percentages are calculated on the total of the ATC category
^ Medical gas DDD value is not available

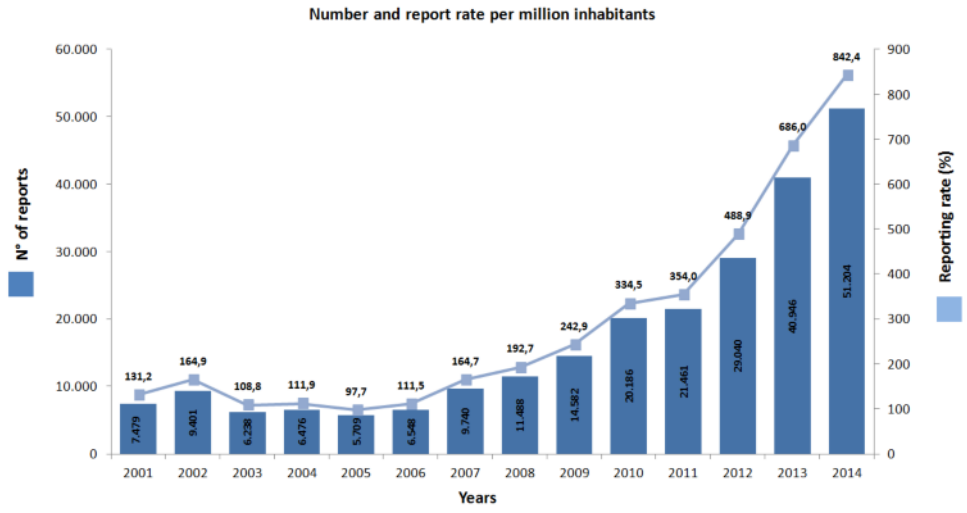
SECTION 8

PHARMACEUTICAL ADVERSE REACTIONS MONITORING

8.1. Reporting flow of suspected adverse reactions in Italy from 2001 to 2014

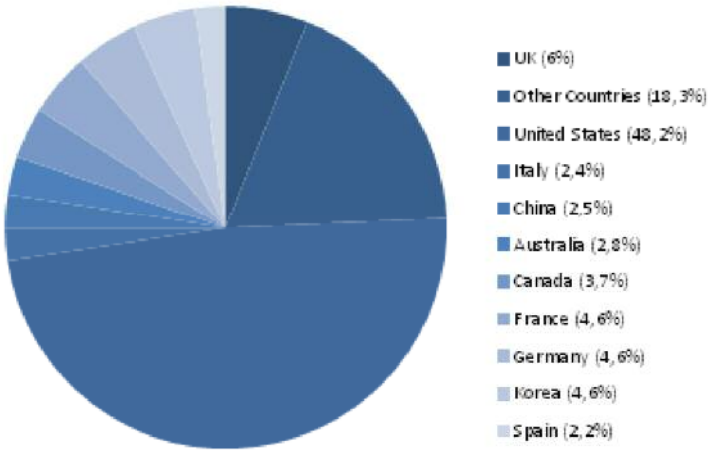
Throughout 2014, 51.204 suspected adverse reaction reports were recorded into the National Pharmacovigilance Network (RNF), an extensive network collecting Italian reports of suspected adverse reactions to medicines. Moreover, 4.105 reports from literature were also received by Pharmaceutical Companies.
In 2015, the increase of spontaneous reporting was confirmed as a trend, with a 25% growth compared to 2013.
The reporting rate was equivalent to 842 per million inhabitants (Figure 8.1.1). On the basis of this result, Italy was recognized by the WHO (World Health Organization) as the eleventh country in the world in terms of highest reporting rates and the fourth at the European level (Source: Uppsala Monitoring Centre (UMC) of the WHO coordinating the international monitoring program on drugs)

Figure 8.1.1 Annual distribution of the number and reporting rate per million inhabitants (2001-2014)



As regards the absolute number of reports, Italy is considered the country contributing the most to the WHO Global Individual Case Safety Report (ICSR) database (Figure 8.1.2) and has been ranked first for quality of reports (source: World Health Organization, Uppsala Monitoring Centre).

Figure 8.1.2. Distribution per Country of the number of reports in the WHO database

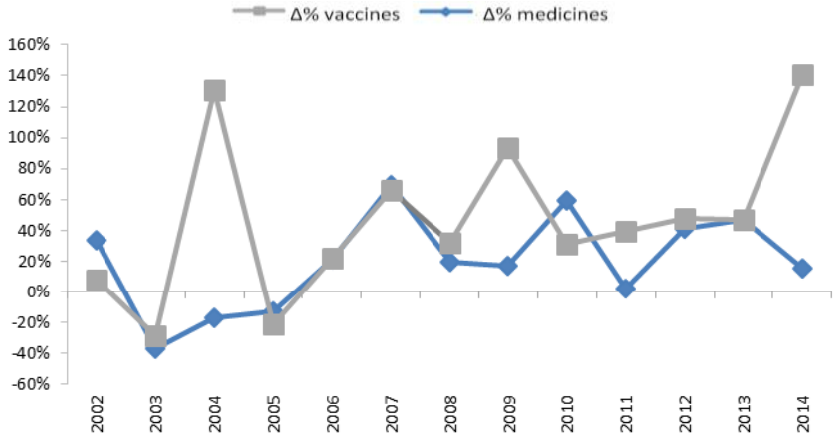


Source: World Health Organisation, Uppsala Monitoring Centre. http://who-umc.org/

Compared to the previous year, the increase in the reporting rate observed in 2014 has concerned mainly ,vaccines (+ 125%) compared to other drugs (+ 15%).

The increase in the number of reports concerning vaccines observed in 2014 is mainly due to the launch of specific active pharmacovigilance projects focused on vaccines (Figure 8.1.3).

Figure 8.1.3. Percentage change in reporting trend for drugs and vaccines compared to the previous year



Similarly to 2013, approximately one third (32%) of the reports received in 2014 was classified as serious, mainly because causing or prolonging hospitalization. With respect to the previous year, there was a significant increase (+ 229%) of reports with undefined seriousness, particularly evident in those from pharmaceutical companies and nurses (Table 8.1.1).

Table 8.1.1. Distribution of reports (absolute number) by severity in 2013 and 2014

DEGREE OF SEVERITY	2013		2014	
	N.	%	N.	%
Other than severe	**27.726**	**68%**	**33.283**	**65%**
Unspecified severity	**472**	**1%**	**1.555**	**3%**
Severe	**12.748**	**31%**	**16.366**	**32%**
Hospitalization or prolongation of hospitalization	8.286	20,2%	9.534	18,6%
Other than condition clinically relevant	3.266	8,0%	5.552	10,8%
Life-threatening	786	1,9%	804	1,6%
Death	251	0,6%	276	0,5%
Severe or permanent disability	152	0,4%	194	0,4%
Congenital anomalies / deficit of newborn	7	0,0%	6	0,0%
Total	**40.946**	**100%**	**51.204**	**100%**

As regards the reporting source, 46% of the reports were submitted from hospital doctors, followed by pharmacists (18%) and specialists (14%). Conversely, few reports were received from general practitioners (only 7% of the total reports in 2014). (Table 8.1.2).
The high percentage of reports received from pharmacists could be related to the implementation in recent years of active pharmacovigilance projects. Most reports were obtained from hospital pharmacists involved in these projects.
A considerable increase (+ 491%) of the reports coming from pharmaceutical companies was also observed, as a result of the new pharmacovigilance legislation, requiring companies to regularly screen internet or digital media for potential reports of suspected adverse reactions to be notified to the regulatory authorities.
In general, an increase in reports coming from almost all sources, excluding pediatricians (-16%), patients (-84%) and dentists (-31%), was registered.
The decrease in patients reporting is probably due to the end of the Pharmacovigilance multi-level regional project, funded by the Italian Medicines Agency with the aim to facilitate spontaneous reporting and to increase awareness on spontaneous reporting.
This result confirms that pharmacovigilance activity requires continuous and enduring incentive to maintain results achieved

Table 8.1.2. Distribution of reports (number of reports and percentage) for primary source in 2013 and 2014

Source of reports	2013		2014		Δ% 14-13
	N.	%	N.	%	
Hospital doctors	21.356	52%	23.803	46%	11%
Pharmacists	6.492	16%	9.227	18%	42%
Specialists	3.693	9%	7.129	14%	93%
General practitioner	3.037	7%	3.415	7%	12%
Others	1.733	4%	2.213	4%	28%
Pharmaceutical company	372	1%	2.199	4%	491%
Nurse	1.182	3%	1.651	3%	40%
Not specified	2	0%	512	1%	>100%
Pediatrician	438	1%	367	1%	-16%
Patient	2.313	6%	365	1%	-84%
Poison control centres	302	1%	302	1%	0%
Dentist	16	0%	11	0%	-31%
Armed forces	10	0%	10	0%	0%
Total	**40.946**	**100%**	**51.204**	**100%**	

In 2014, an increase in the number of reports for all categories of medicines was observed. The highest number of reports concerned medicines belonging to the following ATC classes: antineoplastics, antimicrobials, central nervous system and blood.
The high number of reports for antineoplastics could be related to the high toxicity levels of these products and to the establishment of registries by AIFA, requiring health care professionals to record clinical and safety data during therapy.

The reports for vaccines increased particularly, because of the launch in 2014 of specific active pharmacovigilance projects , focused especially on vaccines. In addition to vaccines, major increases were recorded for the antineoplastic and blood drugs. (Table 8.1.3).

Table 8.1.3. Distribution of reports (number of reports and percentage) for ATC class in 2013 and 2014

ATC	ATC description	2013		2014		Δ % 14-13
		N.	%	N.	%	
L	Antineoplastic and immunomodulating agents	7.328	16%	9.331	17%	27%
J07	Vaccines	3.577	8%	8.182	14%	129%
J	Antimicrobials for systemic use	6.553	15%	7.380	13%	13%
N	Central Nervous System	6.379	14%	7.003	12%	10%
B	Blood and blood forming organs	5.012	11%	6.463	11%	29%
C	Cardiovascular system	4.223	9%	4.415	8%	5%
M	Musculoskeletal system	3.193	7%	3.367	6%	5%
ATC not specified		2.720	6%	3.249	6%	19%
A	Alimentary tract and metabolism	2.098	5%	2.474	4%	18%
V	Various	1.452	3%	1.637	3%	13%
H	Respiratory system	659	1%	851	2%	29%
R	Genitourinary system and sex hormones	746	2%	798	1%	7%
G	Systemic hormonal preparations, excluding sex hormones and insulins	675	1%	698	1%	3%
D	Sensory organs	177	0%	285	1%	61%
S	Dermatologicals	193	0%	271	0%	40%
P	Antiparasitic products, insecticides and repellents	92	0%	95	0%	3%
Total		**45.077**	**100%**	**56.499**	**100%**	**25%**

Note: The total number of reports for single ATC doesn't match with the total number of reports since each report form may contain more than one medicine .

If we consider the adverse reaction classification by system organ class, most of them were cutaneous, followed by those involving general disorders, administration site conditions and gastrointestinal diseases.

The increase of adverse reactions belonging to the SOC of general disorders and administration site conditions (+ 64 % vs 2013) and Psychiatric Disorders (+ 66 % vs 2013) is probably due to the increase of reports for vaccines. Other organs and systems were involved with a rate below 10 %. (Table 8.1.4.)

Table 8.1.4. Distribution of ADR for ATC class by System Organ Classes in 2013 and 2014 (SOCs) (number of reports and percentage)

System Organ Classes (SOCs)	2013		2014	
	N.	%	N.	%
Skin and subcutaneous tissue disorders	11.809	19%	14.131	18%
General disorders and administration site conditions	8.505	14%	13.964	18%
Gastrointestinal disorders	8.578	14%	9.656	12%
Nervous system disorders	5.960	10%	7.413	9%
Respiratory, thoracic and mediastinal disorders	4.441	7%	5.127	6%
Psychiatric disorders	2.746	4%	4.551	6%
Blood and lymphatic system disorders	2.688	4%	3.092	4%
Vascular disorders	2.489	4%	2.841	4%
Metabolism and nutrition disorders	1.806	3%	2.495	3%
Musculoskeletal and connective tissue disorders	2.077	3%	2.443	3%
Investigations	2.100	3%	2.342	3%
Cardiac disorders	1.467	2%	1.776	2%
Infections and infestations	929	2%	1.771	2%
Injury, poisoning and procedural complications	1.089	2%	1.624	2%
Eye disorders	1.095	2%	1.319	2%
Renal and urinary disorders	1.044	2%	1.127	1%
Immune system disorders	919	1%	1.080	1%
Ear and labyrinth disorders	873	1%	904	1%
Hepatobiliary disorders	468	1%	562	1%
Reproductive system and breast disorders System Organ Classes (SOCs)	379	1%	461	1%
Benign, malignant and unspecified (including cysts and polyps) tumor	159	0%	219	0%
Endocrine disorders	132	0%	130	0%
Surgical and medical procedures	60	0%	60	0%
Pregnancy, puerperium and perinatal conditions	30	0%	36	0%
Congenital, familial and genetic disorders	26	0%	33	0%
Social circumstances	14	0%	16	0%
Total	**61.883**	**100%**	**79.173**	**100%**

Note: The total number of ADR reported in the table doesn't match with the total number of reports as each report form may contain more than one ADR.

The active ingredients with the highest number of adverse reactions reports (> 1000 reports) were warfarin, and the associations amoxicillin plus clavulanic acid and acetylsalicylic acid (Table 8.1.5).

Table 8.1.5. First thirty active ingredients for the number of reports in 2014 (number of reports)

Rank	Substance	Number of reports	Inc. %	Cum. %
1	Warfarin	2.397	4,6%	4,6%
2	Amoxicilline / Clavulanic Acid	2.283	4,4%	9,0%
3	Acetilsalicilic Acid	1.379	2,6%	11,6%
4	Ketoprofen	879	1,7%	13,3%
5	Amoxicilline	794	1,5%	14,8%
6	Clopidogrel	758	1,4%	16,3%
7	Dabigatran	723	1,4%	17,6%
8	Levofloxacine	702	1,3%	19,0%
9	Insulin	701	1,3%	20,3%
10	Oxaliplatin	668	1,3%	21,6%
11	Ribavirin	652	1,2%	22,8%
12	Ibuprofen	633	1,2%	24,0%
13	Alpha Interferon	616	1,2%	25,2%
14	Paracetamol	611	1,2%	26,4%
15	Ceftriaxone	548	1,0%	27,4%
16	Fluorouracile	527	1,0%	28,5%
17	Paclitaxel	522	1,0%	29,4%
18	Iomeprol	499	1,0%	30,4%
19	Diclofenac	453	0,9%	31,3%
20	Claritromicine	435	0,8%	32,1%
21	Ciprofloxacine	413	0,8%	32,9%
22	Docetaxel	381	0,7%	33,6%
23	Ramipril	370	0,7%	34,3%
24	Furosemide	364	0,7%	35,0%
25	Paracetamol/Codeine	362	0,7%	35,7%
26	Quetiapine	362	0,7%	36,4%
27	Carboplatin	356	0,7%	37,1%
28	Telaprevir	349	0,7%	37,8%
29	Everolimus	341	0,7%	38,4%
30	Metformin	328	0,6%	39,0%

The active ingredients listed in Table 8.1.6 correspond to those for which a large number of reports (absolute value) has been reported and for whom an evident increase in reports with respect to the previous year was observed.

Table 8.1.6. Active ingredients with significant increase in reports over the previous year

Active ingredients	Number of Reports 2013	Number of reports 2014	Δ % 2014 -2013
Apixaban	1	95	9400%
Delta-9-Tetrahydrocannabinol / Cannabidiol	2	73	3550%
Rivaroxaban	7	241	3343%
Pirfenidone	16	123	669%
Varicella virus vaccine live	237	1.585	569%
Teriparatide	30	181	503%
Glatiramer	25	129	416%
Denosumab	21	85	305%
Measles / Mumps / Rubella virus Vaccine	548	2.184	299%
Measles / Mumps / Rubella/ Varicella virus Vaccine	309	1.214	293%
Dabigatran	206	723	251%

The significant growth of reporting activcity in Italy in recent years proves an increased awareness in the field of pharmacovigilance.
AIFA, in collaboration with Regional Centres of Pharmacovigilance, has continued the systematic analysis of reports within the national Pharmacovigilance Network and in the EudraVigilance database, especially of the active substances for which Italy has been appointed Reference Member State in the EU.
Furthermore, in 2013,particular attention was paid towards activities aimed at ensuring greater transparency and timeliness of information , as required by new pharmacovigilance regulations. Indeed, 90 safety communications have been published in the AIFA web portal.
Data show that the pharmacovigilance system is able to work proactively in order to implement measures to minimize the risks of medicines during their entire life cycle.
Much progress has been made in recent years even though some aspects, such as a simplification of the process of spontaneous reporting, require improvements.
An essential element of the pharmacovigilance system is that it should not be perceived as a bureaucratic requirement by patients/citizens and by health professionals, but as a useful tool to improve knowledge on the safe use of medicines. For this purpose, a close cooperation between all parties involved should be established, with the understanding that all information provided is carefully assessed and that regulatory actions are determined based on data analysis.
A good pharmacovigilance system is likely to result in significant economic benefits to the healthcare system, as ADRs result in increased costs due to hospitalization, prolongation of hospital stay, additional clinical investigations in serious cases and may lead to prescribing cascade when new medications are prescribed for conditions that are a consequence of other ADRs.