National Report on Medicines use in Italy

Year 2015

Agenzia Italiana del Farmaco
AIFA

Dear Readers,

this is an extract/adaptation of 2015 OsMed Report.

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

The English version of the document was edited by F. Mammarella and L.A.A. Muscolo.

Revision by A. Monaco

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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, R. Massimi* – Italian Medicines Agency (AIFA), Rome

- Italian Medicines Agency (AIFA), Rome

  OsMed Coordination Office: *L.A.A. Muscolo, E. Pieroni, M. Sacconi, D. Settesoldi*

  HTA in the pharmaceutical sector Office: G. Altamura, D. Caiazza; A. Cangini, S. De Vito, A. Di Vito, E. Fabrizi R. Marini, M. Petrelli

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

  Research and Clinical Trials Office: *F. Barchetti, I. Pagano; S. Petraglia*

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

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

  Press and Communications Office: *I. Comessatti*

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

- Italian Society of General Medicine, Firenze
  G. Bettoncelli, O. Brignoli, C. Cricelli S.E. Giustini, F. Lapi, P. Lora Aprile, F. Mazzoleni, G. Medea, D. Parretti, A. Rossi, E. Ubaldi, C. Piccinni (Università di Bologna)

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

- Università di Verona
  U. Moretti

Contributions

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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)

3. Azienda Sanitaria Locale di Biella (Regione Piemonte) Referenti: S. Scarpetta, P. Bertone;

4. Azienda Sanitaria Locale di Vercelli (Regione Piemonte) Referenti: C. Serpieri, A. Pasqualucci, P. Enrione, F. Milano, A. Pisterna;

5. ATS Bergamo (Regione Lombardia) Referenti: M. Gambera, R. Piccinelli, M. Frigeni, S. Sonzogni;

6. ATS Brescia (Regione Lombardia) Referenti: C. Scarcella;

7. ATS Brianza - Lecco (Regione Lombardia) Referenti: V. Valsecchi, P. De Luca, E. Scopinaro;

8. ATS Brianza - Monza e Brianza (Regione Lombardia) Referenti: L. Cavalieri d'Oro, M. Rognoni, P. Zarinelli, E. Merlo;

9. ATS Pavia (Regione Lombardia) Referenti: S. Migliazza, M. Dellagiovanna, C. Cerra;

10. ATS Insubria - Varese (Regione Lombardia) Referenti: E. O. Leoni, E. Pini, C. Oria, M. Papagni, G. Nosetti, E. Caldiroli, G. Rulli;

11. Provincia Autonoma di Bolzano (Regione Trentino-Alto Adige) Referente: V. Moser;

12. Azienda Provinciale per i Servizi Sanitari - Provincia Autonoma di Trento (Regione Trentino-Alto Adige) Referenti: R. Roni, A. Polverino;

13. Azienda Sanitaria della Regione Veneto (Regione Veneto) Referenti: G. Scroccaro, V. Fantelli, V. Biasi, L. Gubian, M. Brattina, M. Saugo, C. Iannarilli;

14. Azienda ULSS 20 di Verona (Regione Veneto) Referenti: D. Signorelli, L. Mezzalira, M. Andretta, L. Trentin;

15. Azienda Sanitaria Universitaria Integrata di Trieste (Regione Aut. Friuli Venezia Giulia) Referenti: S. Palcic;

16. Azienda Sanitaria Universitaria Integrata di Udine (Regione Aut. Friuli Venezia Giulia) Referenti: C. Cattaruzzi, L. Marcuzzo;

17. Azienda per l'Assistenza Sanitaria n. 5 "Friuli Occidentale" (Regione Aut. Friuli Venezia Giulia) Referenti: B. Basso, F.V. Rosa;

18. Azienda Sanitaria n. 1 Imperiese (Regione Liguria) Referenti: M. Saglietto, S. Delucis, M. Prioli;

19. Azienda Sanitaria n. 3 Genovese (Regione Liguria) Referenti: A. Coccini, F. Sanfelici;

20. Azienda Unità Sanitaria Locale Piacenza (Regione Emilia Romagna) Referente: S. Radici;

21. 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;

22. Azienda Unità Sanitaria Locale di Bologna (Regione Emilia-Romagna) Referenti: M. Morini, M Borsari, A. Danielli;

23. USL Toscana Nord Ovest - Massa e Carrara (Regione Toscana) Referenti: M. Dal Maso, B. Marsiglia;

24. USL Toscana Sud Est - Siena (Regione Toscana) Referente: S. Dei; G. Gasperini;

25. USL Toscana Sud Est - Arezzo (Regione Toscana) Referente: B. Vujovic;

26. USL Toscana Sud Est - Grosseto (Regione Toscana) Referenti: M. Pisani, P. Bonini, F. Lena;

27. Agenzia Regionale Sanitaria Marche (Regione Marche) Referenti: P. Aletti, A. Marcobelli, S. Sagratella;

28. Azienda USL Umbria n.2 (Regione Umbria) Referenti: I. Fiaschini, F. Bartolini;

29. Azienda USL Roma A (Regione Lazio) Referenti: G. Riccioni, A. Barbato;

30. Azienda USL Roma D (Regione Lazio) Referenti: R. Di Turi, A. Blasi, E. Pagnozzi;

31. Azienda USL Roma F (Regione Lazio) Referenti: G. Quintavalle, L. Ubertazzo;

32. Azienda Sanitaria Locale di Frosinone (Regione Lazio) Referenti: F. Ferrante, S. Crescenzi, L. Marziale, P. Venditti, C. Bianchi, L. Quaresima, R.M. Folcarelli;

33. Azienda USL Latina (Regione Lazio) Referenti: L. Accusani; L. Arenare;

34. Regione Abruzzo Centro Regionale Farmacovigilanza (Regione Abruzzo) Referenti: G. C. Carla Sorrentino, S. Melena;

35. Azienda Sanitaria Locale n. 2 - Lanciano Vasto Chieti (Regione Abruzzo) Referenti: P. Flacco, V. Orsatti, R. Borgia, P. D'Ovidio, M. Galante, C. Sbaraglia, R. Lisio, F. Salvatore (Regione Abruzzo);

36. Azienda Sanitaria Locale Teramo (Regione Abruzzo) Referenti: I. Senesi, R. Baci;

37. Azienda Sanitaria Regionale del Molise (Regione Molise) Direzione Generale per la Salute - Servizio Programmazione e Assistenza Farmaceutica - Referenti: A. Lavalle, G. Trofa, S. Gentile;

38. Azienda Sanitaria Locale di Caserta (Regione Campania) Referenti: M. Ignozzi, A. Di Giorgio, C. Pagliaro, C. Troncone e D.U. Tari;

39. Azienda Sanitaria Locale Napoli 3 Sud (Regione Campania) Referenti: E. Nava, A. Vercellone, R. Castaldo, R. Pagnotta;

40. Azienda Sanitaria Locale di Potenza (Regione Basilicata) Referenti: G. Motola, C. Granieri;

41. Azienda Sanitaria Locale BAT (Regione Puglia) Referenti: O. Narracci, D. Ancona, V. Angiulli, A. Loglisci, D. Bevilacqua;

42. Azienda Sanitaria Locale Lecce (Regione Puglia) Referenti: S. Melli, A. Sanguedolce, C. Montinari;

43. Azienda Sanitaria Locale Foggia (Regione Puglia) Referenti: V. Piazzolla;

44. Azienda Sanitaria Locale Taranto (Regione Puglia) Referenti: S. Rossi, A. Chiari, M. Leone, R. Moscogiuri, E. Ferri, S. Minerba;

45. Regione Calabria Dipartimento Tutela Salute (Regione Calabria) Referenti: R. Fatarella, G. Brancati, R., M.R. Maione, L. Florio, A.E. De Francesco;

46. Azienda Sanitaria Provinciale di Cosenza (Regione Calabria) Referenti: M. Vulnera, L. Florio;

47. Azienda Sanitaria Provinciale di Reggio Calabria (Regione Calabria) Referente: D. Costantino;

48. Azienda Sanitaria Provinciale di Catanzaro (Regione Calabria) Referente: M. Maione;

49. Assessorato Regionale della Salute Regione Sicilia (Regione Sicilia) Referenti: B. Gucciardi, G. Chiaro, C. La Cavera, P. Cananzi;

50. Azienda Sanitaria Provinciale di Catania (Regione Sicilia) Referenti: F. Rapisarda, P.L. Lazzaro;

51. Azienda Sanitaria Provinciale di Palermo (Regione Sicilia) Referenti: M. Pastorello;

52. ASL Cagliari (Regione Sardegna) Referenti: P. Sanna, M. Marcias, F. Lombardo;

53. ASL Sassari (Regione Sardegna) Referente: A. Sussarellu; Thanks to I. Cricelli, A. Pasqua, S. Pecchioli, M. Simonetti. E. Bianchini, E. Cerpolini, F. Palladino (Helath Search/CSD Longitudinal Patient Database) for the elaboration of General Medicine prescribing data.

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Executive Summary

Section 1. Pharmaceutical care regulation in Italy

Throughout 2015, AIFA's European Assessment Office released 647 pharmaceutical marketing authorizations, mostly approved through mutual recognition or centralized authorization procedures. In addition, the Agency received 644 medicines marketing applications concerning new active ingredients. Throughout the year, over 16.000 pharmaceutical packages have been consumed, of which 60% reimbursed by the National Health Service (NHS). In 2015, significant pharmaceutical regulations were issued in Italy, including interventions to contain pharmaceutical expenditure. These interventions include payback procedures to contain pharmaceutical expenditure ceilings' when the threshold is exceeded.

Section 3. Data sources and methods

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

Section 4. Medicines appropriateness: prescription and use profiles

A pharmaceutical prescription is deemed appropriate when issued within the clinical indications for which the product's efficacy has been tested and according to its appropriate use (in terms of dose and treatment duration).
Any monitoring activity regarding pharmaceuticals consumption should be implemented according to parameters identified for its appropriateness of use. For this reason, suitable indicators have been identified, allowing to converge both physicians' prescription choices and medicines' utilization by patients. In addition to epidemiological data on the main chronic diseases in Italy, section 4 contains all indicators related to prescriptions from 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, psoriasis, atrial fibrillation and deep vein thrombosis), the economic impact on pharmaceutical expenditure by means of the variation of the indicators.

Section 5. General characteristics of pharmaceutical use in Italy

Throughout 2015, the total amount of public and private pharmaceutical expenditure was €28,9 billion, 76,3% of which is reimbursed by the NHS; the average pharmaceutical expenditure per italian citizen was €476.
Moreover, the total amount of public and private outpatient pharmaceutical expenditure increased by +8,9% over the previous year and amounted to €21.778 million.
In more details, the total NHS pharmaceutical expenditure, corresponding to the total amount of NHS outpatient pharmaceutical expenditure and Class A medicines distributed through the direct distribution channel expenditure, amounted to €13.398 billion, which matches 61,5% of total outpatient expenditure. An increase of 13,1% over the previous year was recorded, mainly due to an increase of pharmaceutical Direct distribution expenditure (+51,4%), countervailed by a reduction of net NHS outpatient pharmaceutical expenditure (-1,4%).
The private expenditure (out of citizens' pocket) increases of +2,9% compared to 2014. More specifically the private expenditure accounts for the total amount of:

1. regional ticket co-payment, a fixed prescription fee (corresponding to a fixed cost linked to the medical prescription and/or to the number of pharmaceutical packages prescribed)
2. another ticket co-payment resulting from the balance between the price of originator products, whose patent expired, and the reference price of the generic product reimbursed by the NHS
3. out of pocket expenditure coming from Class A and Class C medicines privately purchased by the citizens

Major influence factors are represented by the increase in both private purchase of class A medicines (+3,1%), Class C medicines expenditure (+2,1%) as well as OTC medicines (+4,7%) and co-payment share (+1,4%) 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 up to €1.521 million, corresponding to €25,0 per capita.
During 2015, approximately 1.114,9 doses per thousand inhabitants were consumed daily (hereinafter DDD/1000 inhabitants daily), corresponding to an increase of +1,7% over the previous year. Consumption in terms of number of packages decreased by -0,2% (over 1 billion packs in 2015, corresponding to 18,6 packs per capita).
Concerning total public and private outpatient consumption, 1,9 billion packages were dispensed, recording an increase of +0,1% over the previous year. This trend is mainly driven by the increase in the consumption of Class A medicines privately purchased by citizens (+2,1%) and OTC (+0,8%) as well as a reduction in the consumption of reimbursed medicines (-0,2%), and Class C medicines (-0,8%).
Looking at the main components of the pharmaceutical expenditure throughout the years, a slight increase in consumption [quantity effect (DDD): +1,7%], together with a price reduction (price effect: -1,8%) and a mild shift towards lower price medicine prescriptions (negative mix effect: -1,0%) were registered. In 2015 pharmaceuticals' expenditure by

public health facilities amounted to €11,2 billion (€184,3 per capita), generating an increase of +24,5% compared to 2014.
Pharmaceuticals expenditure and consumption are influenced by patient age. 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 50%, 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 moved to third position in terms of total (public and private) pharmaceutical expenditure (€4.079 million) and in terms of pharmaceutical consumption (534,3 DDD/1000 inhabitants daily). For the first time anti-infective for systemic use show the highest expenditure (€4.402 million) among all the pharmaceuticals in 2015. Antineoplastic and immunomodulators are located in second position among categories with highest impact on total expenditure (€4.213 million) and in first place in terms of public expenditure. Other therapeutic categories significantly impacting on expenditure were: gastrointestinal tract and metabolism medicines (€3.856 million) and central nervous system medicines (€3.313 million). Statins (among cardiovascular system medicines), proton-pump inhibitor products (among the tract and metabolism medicines) and other antiepileptic drugs (among the central nervous system medicines) were the categories with the greatest impact on the NHS pharmaceutical expenditure. Furthermore, during 2015 monoclonal antibodies and hepatitis C medicines represented the categories with major impact on expenditure and consumption of pharmaceuticals purchased by public utilities.

Section 7. Detailed analyses on pharmaceutical expenditure and consumption, concerning therapeutic categories and active ingredients

Section 8. Adverse drug reactions monitoring

Pharmaceutical consumption monitoring is closely related to pharmacovigilance activities, which are focused on assessing the pharmaceutical safety profile after marketing authorization. During 2015 the number of reports included in the National Network of Pharmacovigilance (RNF) was 49.655, corresponding to a reporting rate of 817 per million inhabitants, a higher ratio than the ones registered in other European Union Countries with a strong tradition in pharmacovigilance. This ratio is also 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 slightly reducing, leading to a -2,9% variation compared to reports collected in 2014.
Most of the reports in 2015 concerned antineoplastics (25,1%), antimicrobials (14,8%), blood medicines (14,5%) and central nervous system products (14,3%).
The AIFA, in collaboration with departments of pharmacovigilance of local health units (LHUs), continued a periodic analysis of the ADR reports contained not only within the RNF

database, but also in Eudravigilance database, with a meticulous focus to the active substances for which Italy has been appointed Lead Member State for Europe. In addition, in 2015 Italy has paid particular attention to activities aimed at ensuring greater transparency and timeliness on Pharmacovigilance issues, as required by new regulations.
These results confirm that efforts made over the past years to increase the sensitivity of health care workers and patients towards the pharmacovigilance system were effective. In this context cooperation between all stakeholders is essential, ensuring a steady monitoring of the pharmaceutical safety profile, with the overall objective of promoting the preservation of public health.

SECTION 1
PHARMACEUTICAL CARE REGULATION IN ITALY

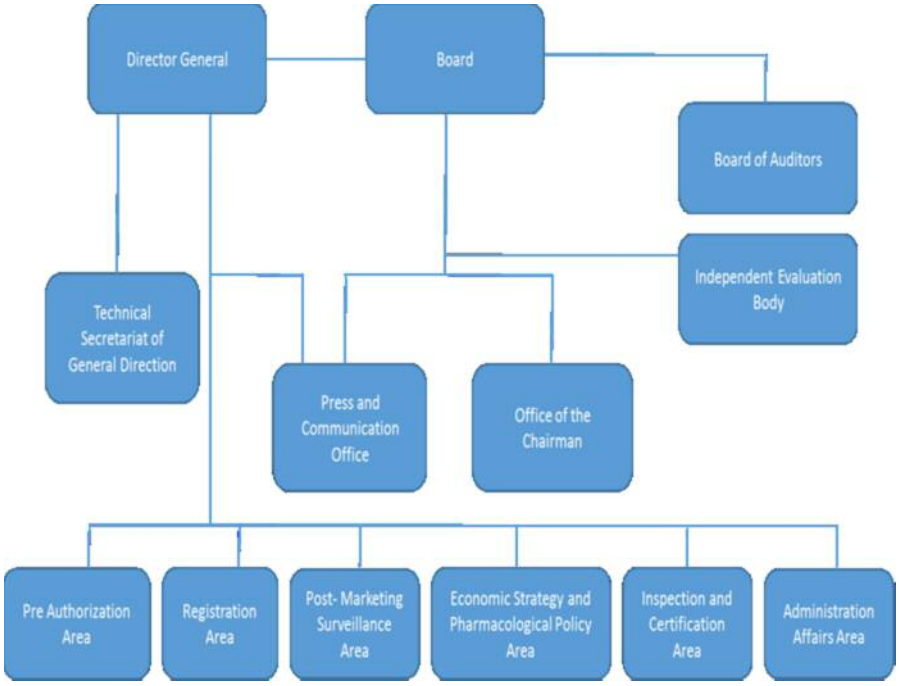
1.1 The Italian Medicines Agency

Since 2004, in Italy the national authority responsible for the regulatory activity on pharmaceuticals is the Italian Medicines Agency (AIFA, www.agenziafarmaco.it). AIFA's activity consists of the following tasks:

1. improving human health care through pharmaceutical products
2. guaranteeing the economic balance 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.

During 2014 the Regulation outlining AIFA's organisation was reviewed and published on the Official Journal n.22 on January 28, 2015.
The Figure 1.1 reports the organization laid down by the new Regulation with its different Areas.

Figure 1.1 Organization of the Italian Medicines Agency



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) that assesses the therapeutic value of human pharmaceutical products due to obtain marketing authorization; 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) that 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. 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).
The number 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 Market Authorization 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 it 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 purchase 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 directly to patients, even if available in pharmacies, but can be provided to specialists only, who can 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 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.

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 authorization: *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 the 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, by community pharmacies, by virtue of specific agreements between pharmacist and local health unit (so called *per conto* distribution), for subjects with chronic diseases requiring a continuative pharmaceutical care (Article n. 8 of Law n. 405 of 2001, as amended and integrations).

Pharmaceutical hospital care refers specifically to medicines administered within NHS health facilities. However, for the specific purpose of the costs monitoring, the pharmaceutical hospital expenditure includes both the in-patient pharmaceutical consumption and the *direct* and *per conto* distribution channels of Class A medicines, in line with Law n. 135 of 2012 and its amendments.

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

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

Class	Prescription System	N. AIC	% per Class	% on total
A	RR	7.690	86,9	47,3
	RNR	451	5,1	2,8
	RRL	340	3,8	2,1
	RNRL	284	3,2	1,7
	SOP	40	0,5	0,2
	RMS	38	0,4	0,2
	OSP	3	0,0	0,0
Total Class A		**8.846**	**100,0**	**54,4**
C	RR	2.788	47,2	17,2
	OTC	1.027	17,4	6,3
	SOP	858	14,5	5,3
	OSP	819	13,9	5,0
	RNR	197	3,3	1,2
	RNRL	126	2,1	0,8
	USPL	62	1,0	0,4
	RRL	19	0,3	0,1
	RMS	10	0,2	0,1
Total Class C		**5.906**	**100,0**	**36,4**
H	OSP	1.141	76,3	7,0
	RLNR	233	15,6	1,4
	RRL	57	3,8	0,4
	RR	55	3,7	0,3
	RNR	4	0,3	0,0
	USPL	4	0,3	0,0
	SOP	1	0,1	0,0
Total Class H	**TOTAL CLASS**	**1.495**	**100,0**	**9,2**
Total		**16.247**		**100,0**

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 1,82% discount to be applied at the expense of pharmacies in favor of the NHS. This discount pertains to both off-patent and patented medicines, while it is not applied to:

- rural pharmacies with national subsidy (pharmacies located in towns with less than (under) 3.000 inhabitants) and sales volumes below €387.342,67, VAT excluded, per year;
- rural and urban pharmacies, without national subsidy, 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 modified and converted into Law n. 122 of 2010, distribution margins of generics are calculated as indicated: 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, 2013, 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 subsidy**		**Rate for rural pharmacies with national subsidy**	
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 established through a negotiation procedure between AIFA and pharmaceutical companies, in accordance with methods and criteria previously adopted only for medicines approved with European procedures.
During negotiations, 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.

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 binding opinions on therapeutic value of medicines, provision systems for medicinal products and on innovativeness;
3. CPR assesses the dossier and then meets the pharmaceutical company for the negotiation procedure;
4. result of the negotiation is submitted to the Board of Directors for a final evaluation.

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

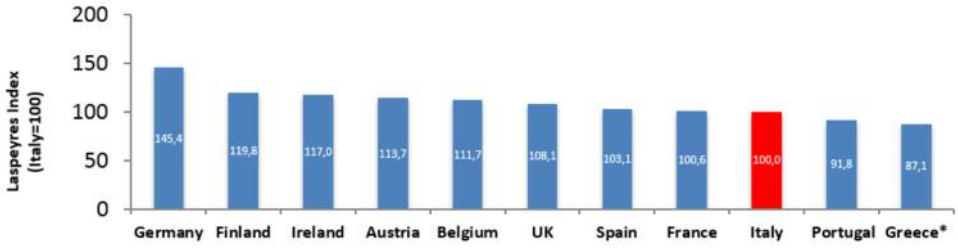
Law Decree n. 69 of June 21, 2013 (converted with amendments to Law n. 98 of August 9, 2013) establishes as a priority the assessment of orphan drugs and medicines with exceptional therapeutic value and considered of social relevance, compared to other pending procedures, and sets a 100-day time limit for the assessment of these products. In addition, the pharmaceutical company of an orphan medication can benefit from the opportunity to submit the pricing and reimbursement dossier of that product to AIFA before receiving marketing authorization by European Commission.

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; these prices are notified to AIFA, but 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 2015 (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, regulates the possibility by the regions to introduce or increase citizens' co-payment, by introducing or increasing a 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 those Regions undergoing repayment plan, but later it was applied across almost all the country.
However, total citizens' co-payment is due also to the payment of the difference in price between a medicine and the reference medicine with the lowest price (Reference price). Since December 1, 2001 AIFA provides a monthly publication of the so called Transparency List (*Lista di trasparenza AIFA*). The transparency list contains the list of all off-patent medicines that can be produced as generics and allows to identify the reference price for all substitutable packages. Specifically, in cases in which there are two or more medicines with the same active ingredient, administration route, pharmaceutical formulation and number of standard units, only the one with the lowest price is completely reimbursed by the NHS. Law n. 122 of July 30, 2010, as amended an integrated, describes the reduction of reference prices of pharmaceutical products listed in the Transparency Lists, on the basis of a comparison with EU generics prices (Germany, UK, France and Spain).
The Article 5, paragraph 4 of Law n. 222 of 2007, imposes obligation for the regions to reduce pharmaceutical expenditure. The regions are indeed required to adopt measures for pharmaceutical expenditure containment. The amount of the expenditure containment shall correspond to at least 30% of the total NHS pharmaceutical expenditure deficit. The implementation of these measures represents a necessary condition for the regions' access to Government's additional financing.
At National level, the total co-payment expenditure is €1,5 billion (14% of the NHS pharmaceutical expenditure). During 2015 the per capita co-payment expenditure was €25 (+2,5% if compared to the previous year). The 34,5% of this value derives from the regional co-payment while the residual 65,5% originates from the difference between the off-patent medications price and the reference one (lowest price) reported in AIFA's Transparency List.

1.7 Off patent medicines

In Italy, the off patent medicines' regulation has experienced a significant boost, since year 2000, this was mainly due to enacted legislative measures. The Transparency List has indeed been introduced in the same year (Article 85, paragraph 28 of Law n. 338/2000). The Transparency List collects lists of off patent products with respective reimburse prices 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;

- the price of pharmaceutical package with the lowest price among those considered equivalent and reciprocally substitutable, has to be considered the reference price covered by 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 according the real availability of generics within the own regional distribution network.

In Italy the Complementary Protection Certificate (*Certificato Complementare di Protezione*, CCP) was introduced in 1991, allowing the extension of the pharmaceutical patent protection of additional 18 years, thus it extends exclusive use rights of a molecule to a maximum of 38 years.
Furthermore, EC Regulation n. 1768/1992, modified with EC Regulation n.469/2009, outdated *de facto* the previous national legislation on the CCP by the introduction of the Supplementary Protection Certificate (Certificato Protettivo Supplementare, SPC) that provides a 5-year protection after the patent expiration. 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, in Italy, savings resulting from the loss of patent protection had been postponed due to the impossibility of marketing generics already available in other European countries.
In order to mitigate the mentioned negative effects, a progressive adaptation measure was introduced (according to the Law n. 112/2002), 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. 39/2009 (converted with amendments in the Law n. 77, June 24, 2009), legal provisions regulating economic aspects of the pharmaceutical market were introduced in Italy. These can be described as follows:

1. 12% reduction of generics retail price;
2. 1,4% reduction (on pharmaceutical gross expenditure) of pharmacists' wage in favour of the NHS. This action was to regain extra discounts granted to pharmaceutical companies in 2008;
3. reduction to 58,65% of distribution chain margins on generics for pharmaceutical companies. The 8% to the previous value of 66,65% is redistributed between wholesalers and pharmacies (after that margins of pharmacies and wholesalers have been modified by Law n. 122 of 2010 -see section 1.4);
4. off patent medicinal product marketing authorisation holders (MAH) can reduce the 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 with cost ≤€5
- €1 for those medicines with cost between €5 and €10

- €1,5 for those medicines with cost >€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– generics 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, in line with prices in force in other European Union countries.

A description of the new methodology to assign reference price 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 of the SPC. Active ingredients that lost patent protection during 2015, 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 2015 or new active ingredient packages which had previously lost their patent protections and which were included in AIFA's Transparency Lists.

Active ingredient	Price reduction effect	Price reduction
Active ingredients or new packages that lost patent protection before 01/12/2014		
Aceclofenac 40 tab 100 mg	15/05/2015	45%
Folic acid 20 tab 5 mg	15/02/2015	25%
Folic acid 28 tab 5 mg	15/04/2015	25%
Desmopressin	15/07/2015	32%
Duloxetine	15/09/2015	65%
Eplerenone	15/09/2015	22%
Oxcarbazepine	15/02/2015	32%
Prednisone	15/02/2015	22%
Pregabalin (with the exception of indication for the neuropathic pain that expires on February 16, 2017)	15/09/2015	65%
Quetiapine 60 tab retard 150 mg	15/07/2015	57%
Active ingredients that lost patent protection between 01/12/2014 and 01/12/2015		
Etanercept	-	-
Bendamustine	-	
Stronzium ranelate	-	-

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 2016

Active ingredient	Marketing launch	Reimbursement class	Price reduction
Active ingredients or new packages that lost patent protection before 01/12/2015			
Rasagiline tartrate	22/04/2016	A	48%
Aripiprazole	19/01/2016	A	70%
Brinzolamide	29/10/2015	A	45%
Levodopa/carbidopa/entacapone	15/04/2016	A	47,5%
Perindopril+indapamide 30 tab 8 mg/2.5 mg	15/03/2016	A	30%
Zofenopril and hydrochlorothiazide	15/09/2015	A	33%
Active ingredient	**Patent expiration**	**Reimbursed class**	**Price reduction**
Active ingredients going to lose patent protection between 01/12/2015 and 01/12/2016			
Linezolid	15/03/2016	A	47,5%
Eletriptan	15/03/2016	A	47,5%
Frovatriptan	15/12/2015	A	45%

Legal provisions that govern medical prescriptions of off-patent medicines and of NHS reimbursed pharmacological products underwent a several amendments over the years. In fact, general practitioners (GPs) received indication to report 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 of 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 implementation of these legal provisions, AIFA provides, on a monthly basis, lists of Class A and H pharmaceutical products. These lists are published on AIFA's website and report generics 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 aim to fast-track generics 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) introduces the possibility to grant that a generic product can automatically be included in a certain reimbursement class, without undergoing a price negotiation, in cases where the price proposed by the pharmaceutical 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 on the basis of the expected sale volumes (Table 1.7.3).
Subsequently, this decree was invalidated by the Regional Administrative Court (TAR) of Lazio, section Quater III, n. 3803/2014, as regards 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 any distinction amongst 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, biosimilar products represent an area of increasing importance. 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 main criteria to characterise the biological and biosimilar medicines
2. EU regulatory background on biosimilar medicines
3. biosimilar medicines to improve the economic sustainability of the NHS.

The document can be downloaded at the following link:
http://www.agenziafarmaco.gov.it/sites/default/files/AIFA_POSITION_PAPER_FARMACI_BIOSIMILARI.pdf).
This Position Paper clarified the AIFA's position with regards to the substitution of off patented biological medicines with biosimilars, and provides both elements concerning economic sustainability and considerations on health protection.

Following the publication of AIFA's position paper, AIFA received several requests of clarification on biosimilars use. Thus AIFA, in May 2014, conduct a further public consultation, and nowadays the assessment of receiving comments is ongoing. This activity will lead to the release of the updated version of the position paper.
Concerning biotech medicines the Decree Law n. 78/2015 (Decreto Enti Locali) converted with amendments by Law n.125/2015, established that AIFA starts a new price and reimbursement procedure with the holder of the biotech product, when a new assignment price procedure for biosimilars or equivalents of that product doesn't start after the patent's expiration of the active ingredient of the biotech product. This happens to reduce the price reimbursed by the NHS.

1.8 Innovative medicines

The assessment of pharmaceutical innovation is a complex and dynamic process. The complexity rises from the heterogeneity of available treatment options as well as of the variable perception of priorities and expectations towards a new medicine in relation to health and social context. The pharmaceutical innovation evaluation should systematically take into account 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 European level, Italy was among the first countries adopting a complex system of regulations for the assessment and patient access to innovative medicines. Above all, 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 Decree n. 159/2007, (converted into Law n. 222 of 2012, 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%), following the AIFA Resolution of September 27, 2006
- concerning several aspects related to pharmaceutical expenditure, innovative medicines are not subject to any budget constraints and benefits from a solely dedicated Innovation Resource Fund, whose value is set at the beginning of the year. In case of National pharmaceutical expenditure ceiling exceeding (please, see section n. 1.10), and in case of innovative medicines expenditure exceeding the Innovation Fund's value, then innovative medicines do not participate to the payback mechanism, which is conversely distributed among Marketing Authorization Holders in proportion to their sales volumes for on patent non innovative medicines.

Provisions of Law n. 159 of 2007 (converted into Law n. 222 of 2012), 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, are set both in the outpatient sector (20%) and in the inpatient sector (80%) (as a maximum quota).

Law n. 190/2014 ("Stability Act" of 2015) introduced significant changes regarding the financing of innovative medicines. First of all, the establishment of an experimental financial fund for the period 2015-2016 for the reimbursement of innovative medicines and amounting up to €1 billion (€500 million for 2015 + €500 million for 2016) 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 an innovative product exceeds €300 million, then the Marketing Authorization Holder of the innovative medicinal product is required to pay back up to 20% of the breakthrough value (article 1, paragraph 595).

Law n. 208 of 28 December 2015 ("Stability Act" on 2016) provided that, in case of outpatient expenditure ceiling excess, innovative medicines overcoming €300 million annual sales volume must participate with a payback up to 20% of the breakthrough value.

In order to assess the innovation degree of new pharmaceutical products entering the Italian market, the CTS has defined a set of criteria (approved in the course of the meeting held on July 10, 2007). 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 in issuing the place in therapy and the degree of innovation of a pharmaceutical product, both from a scientific and a therapeutic point of view. In fact, the concept of innovation for a medicine was widened and its evaluation was more detailed. For this reason, the Agency decided to re-engineering the Commissions' preliminary activities and the methods for Members' participation to decisions concerning innovation assessments. These methods converged 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.

This tool aims at ensuring homogeneity of nationwide access to medicinal products appraised as innovative and thus considered a priority for the public health safeguard.

Despite this, the State-Regions Agreement dated November 18, 2010 (O.J. n. 6 of January 1, 2011) provided the publication of a list of innovative medicines by AIFA and urgent inclusion of innovative medicines in the therapeutic regional hospital formularies. The agreement also included 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 Act of 2015) AIFA provides, in support of the Ministry of Health and the Regions, evaluations of Health Technology Assessment with particular reference to innovative medicines (Art. N.1, paragraph 588). To allow access to innovative treatments, while ensuring the sustainability of NHS, the Stability Act of 2016 has committed AIFA to prepare a strategic plan on a year basis.

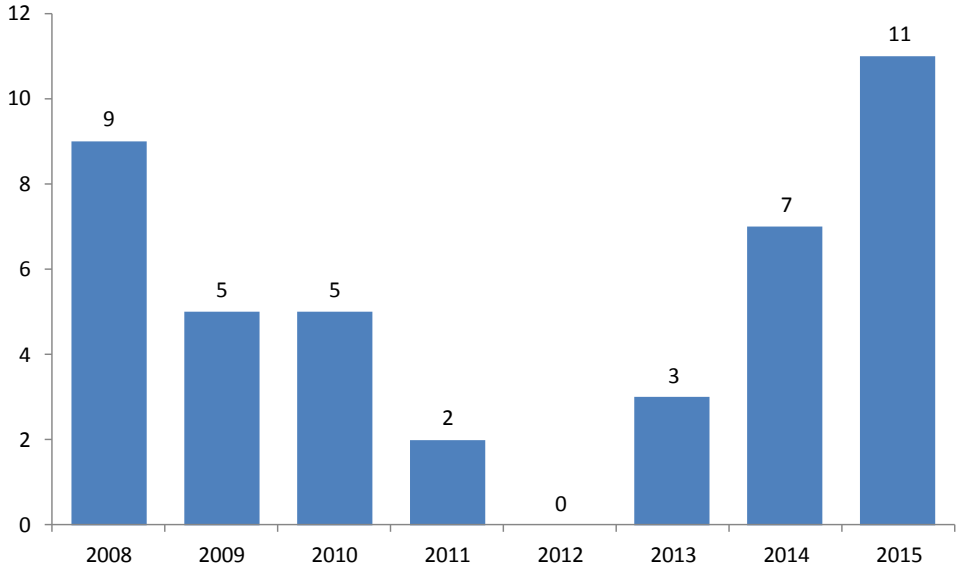
Even though the concept of innovation appears a general connotation, recalling the State-Regions Agreement rather than Law n. 159 of 2007 (converted in Law n. 222 of 2007and

Law n. 135 of 2012), it implies significant differences from a juridical point of view. As mentioned previously, the status of innovative medicine entails a variety of economic benefits, defined by laws mentioned above, 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 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. 159 of 2007 converted in Law n. 222 of 2007 and, Law n. 95 of 2012 and converted in Law n. 135 of 2012). 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.

Table 1.8.1 List of innovative medicines updated by CTS in 2015 in accordance with Art. 1, paragraph 1 of State-Regions Agreement of November 18, 2010

ATC IV	Brand name	Active ingredient	Reimbursement class	Therapeutic innovation	CTS decision date	O.J. date (Validity date)	Qualification expiry date
L01XC	YERVOY	Ipilimumab	H	Relevant	30/10/2012	09/03/2013	08/03/2016
L02BX	ZYTIGA	Abiraterone	H	Potencial	15/11/2012	06/04/2013	05/04/2016
M09AB	XIAPEX	Collagenase of clostridium histolyticum	H	Potencial	06/03/2013	14/03/2013	13/03/2016
L01XC	ADCETRIS	Brentuximab vedotin	H	Potencial	02/12/2013	08/07/2014	07/07/2017
L01XC	PERJETA	Pertuzumab	H	Relevant	02/12/2013	08/07/2014	07/07/2017
L04AX	REVLIMID	Lenalidomide	H	Potencial	13/02/2014	30/09/2014	29/09/2017
J05AX	TIVICAY	Dolutegravir	H	Potencial	10/03/2014	02/11/2014	01/11/2017
J04AK	SIRTURO	Bedaquilina	H	Potencial	11/03/2014	01/10/2014	30/09/2017
L01XC	KADCYLA	Trastuzumab emtansine	H	Potencial	07/04/2014	11/10/2014	10/10/2017
L01CD	ABRAXANE	Nab paclitaxel	H	Relevant	07/04/2014	21/02/2015	20/02/2018
J05AX	SOVALDI	Sofosbuvir	A	Relevant	15/05/2014	20/12/2014	19/12/2017
L01XE	XALKORI	Crizotinib	H	Potencial	09/06/2014	11/04/2015	10/04/2018
J05AE	OLYSIO	Simeprevir	A	Potencial	10/11/2014	24/02/2015	23/02/2018
J05AX	DAKLINZA	Daclatasvir	A	YES	16/02/2015	05/05/2015	04/05/2018
R07AX	KALYDECO	Ivacaftor	A	YES	16/02/2015	05/05/2015	04/05/2018
J05AX	HARVONI	Ledipasvir/ Sofosbuvir	A	YES	24/03/2015	14/05/2015	13/05/2018
J05AX	VIEKIRAX	Ombitasvir/ Paritaprevir/ Ritonavir	A	Relevant	21/01/2015	24/05/2015	23/05/2018
J05AX	EXVIERA	Dasabuvir	A	Relevant	21/01/2015	24/05/2015	23/05/2018
V10XX	XOFIGO	Radium-223 dichloride	H	Potencial	13/05/2014	11/06/2015	10/06/2018
L04AX	IMNOVID	Pomalidomide	H	YES	18/02/2015	20/08/2015	19/08/2018
L01XX	ZYDELIG	Idelalisib	H	YES	18/02/2015	11/09/2015	10/09/2018
L01XE	IMBRUVICA	Ibrutinib	H	YES	13/07/2015	05/01/2016	04/01/2019

Figure 1.8.1. Number of innovative medicines: a comparison between the years 2008-2015 *



* It was considered the date of the O.J. publication. The lists of innovative medicines are referred to those published by AIFA.

Figure 1.8.2. Distribution of innovative medicines by ATC level during 2008-2015

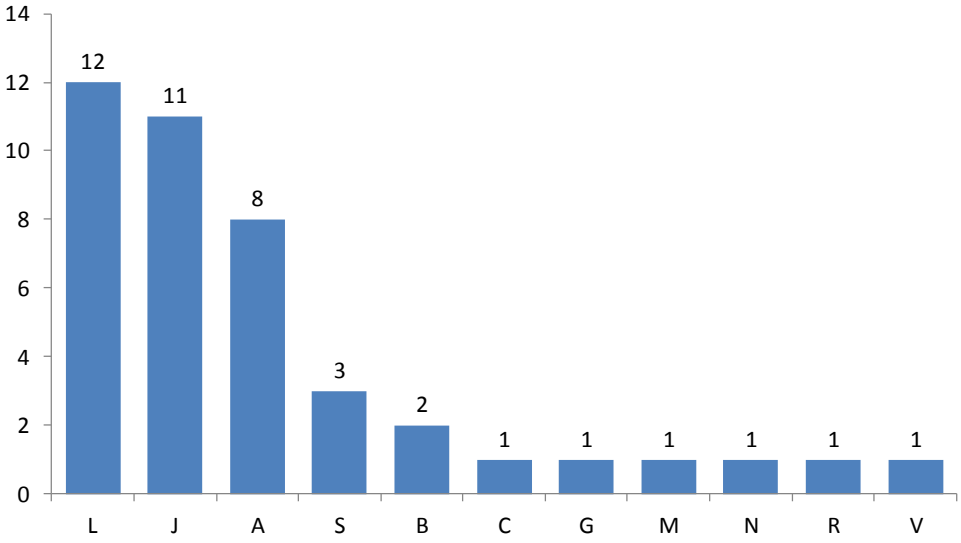
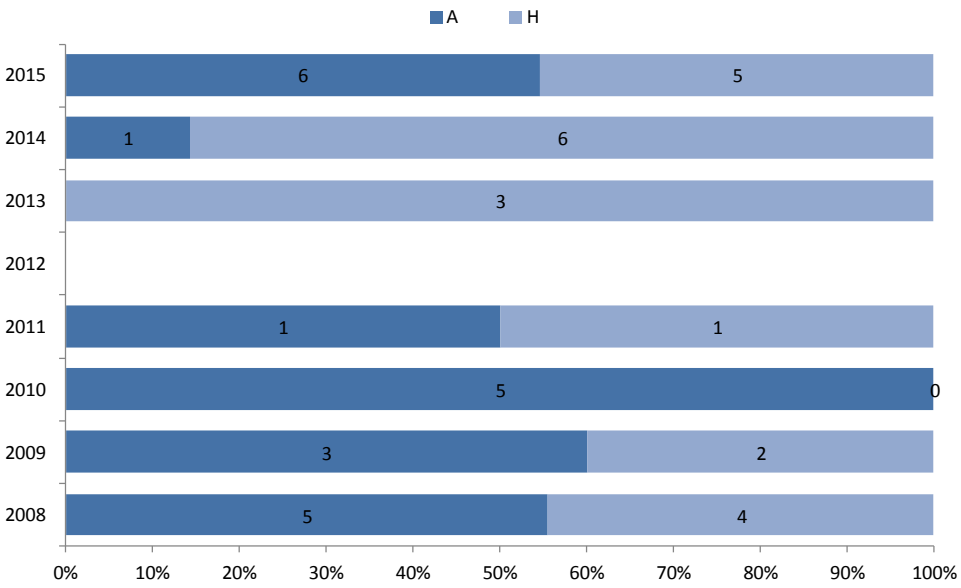


Figure 1.8.3. Innovative medicine sorted by class of reimbursement during 2008-2015



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 on December 27, 2013 – Stability Act on 2014). To date, more than seven thousand rare diseases have been discovered, therefore they represent a significant social issue, involving million of people: according to estimates, patients affected in Europe are over thirty million, thereof 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 Committee of Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) grants the orphan status. The marketing authorisation (MA) of an orphan drug is achieved through a centralised procedure. In some cases, in order to accelerate the marketing of an orphan product, a medicine may be granted an authorisation, even though the clinical trials have not been completed yet. 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 unmet medical needs
- The benefits in terms of public health impact and immediate availability outweighing the risks of incomplete evidence of efficacy

Generally, once the efficacy and safety profile evaluation is completed, the Committee for Medicinal Products for Human Use (CHMP) issues a favourable opinion to grant the authorisation, and afterwards the European Commission formally issues the marketing 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 due to a requirement for the applicant to introduce specific procedures, particularly concerning the safety profile 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. Expressly, the Stability Act has introduced a mechanism of economic protection for orphan medicinal product marketing authorization holders (MAHs). When the national pharmaceutical expenditure ceiling is exceeded, orphan medicinal products' MAHs are excluded from the payback mechanism, which is conversely distributed among all other 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 includes:

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 (including orphan drugs, whose 10 year market exclusivity expired) and Article 8 of Regulation of December 31, 2013

2. medicines, referring to paragraph 1, are included in the list only if they hold a marketing authorisation in Italy. The following are thus excluded:

a. orphan medicinal products not reimbursed by the NHS as referred to letter c) and c bis) of Article 8, paragraph 10, of Law n. 537 of December 24, 1993
b. orphan drug packages reimbursed by the NHS, as referred to 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 authorisation was then suspended or withdrawn as of December 31, 2013
d. any medicinal product initially inserted in the Community Register of orphan medicinal products for human use and which have lost the orphan designation, as a result of the Marketing Authorisation 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 authorisation 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 rather excluded:

a. any product authorised for the treatment of non - rare diseases or non rare conditions
b. products authorized for the treatment of rare diseases or conditions, for which MAHs had not submitted as on 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.

In order to increase orphan drugs nationwide availability, the so-called Balduzzi Law (Law n. 189 of 2012, Article 12, paragraph 3) provides for the possibility for marketing authorisation holders to apply AIFA for pricing & reimbursement procedures as soon as the CHMP positive opinion is released and therefore, before the marketing authorisation 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, the access to treatment for patients suffering from a rare disease is guaranteed by means of various legislative instruments. The centralised procedure represents the standard access way; whenever an orphan drug has no marketing authorisation, patient access is ensured through the following rules:

- Law n. 648 of 1996, allowing the use of a medicine on a national basis
- Law n. 326 of 2003, Article 48 (also known as 5% AIFA Fund) and the Ministerial Decree of May 8, 2003 (also known as the “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. 648/1996

This regulation allows the administration of certain medicines reimbursed by the NHS, in order to cure clinical conditions for which no alternative therapeutic option are available

(see Table 1.9.1). In order to include a medicine into Law n. 648 list, one of the following conditions must be met:

- innovative medicines holding a marketing authorisation gained in any European Country, but not in Italy;
- medicinal products not authorised yet, but undergoing clinical trials, and for which results concerning phase two clinical studies are available;
- medicines authorised for a different therapeutic indication compared to the one already authorised in Italy, and which underwent a phase two clinical trial.

The inclusion of a pharmaceutical product into Law n. 648 list is performed by AIFA on the basis of a documented request from: patients' associations, scientific societies, health facilities, and universities' or following CTS recommendations. Orphan drugs' list included within Law n. 648/1996 can be downloaded from the AIFA website at the following link: http://www.agenziafarmaco.gov.it/it/content/legge-64896.
Following the entry into force of Law n.79 of 2014, it was established that, the provision of medicines within Law n. 648/96 list (100% reimbursement by the NHS) is allowed even when other therapeutic alternatives are available, and when medicines are used for a therapeutic indication different from that authorised one, according to affordability and appropriateness parameters. Adempas constitutes an example of an orphan drug that has benefited from this provision.

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

50% of the AIFA Fund is allocated to finance the purchase of orphan drugs intended for the treatment of rare diseases and medicinal products not authorised yet, but representing a chance to treat serious conditions (i). The remaining 50% of the fund is used to carry on scientific researches on the use of pharmaceutical products (ii; i.e. comparative trials on medicines aimed at demonstrating their additional therapeutic value, or studies aimed at demonstrating the appropriateness use of medicines, or focusing on scientific information). This fund is financed by 5% of pharmaceutical companies' annual expenditure from 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 2015, this fund amounted approximately to €17,8 million.
As regards the purchase of the mentioned pharmaceutical products (i), requests to access the fund are submitted to AIFA, through the regions, by local reference centers or designated structures treating patients affected by a rare disease.
The following documents are required in order to access the fund: a formal request, possibly supporting scientific literature papers as well as 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 treatment cycles, 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 a proof of costs incurred for the patient's treatment, AIFA reimburses the invoices submitted. In 2015 the total expenditure for patients accessing the AIFA Fund amounted to €1.108.530 (see Table 1.9.1).

The remaining 50% of the Fund is dedicated to independent research on the use of medicines (ii).

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. In this direction, 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 authorisation for access to experimental medicines, it being understood that the pharmaceutical company shall provide a declaration of willingness to supply the medicine free of charge. 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. 94/1998, Art. 3, paragraph 2 , the so - called Legge Di Bella

This legislation allows the medical prescription of an off label medicine; the prescription of an off label medicine is granted under the responsibility of the prescribing physician and followed by an informed consent of the patient, when the patient cannot be effectively treated with available treatments approved for that same therapeutic indication. Documents on the use of a medicine, in addition to positive results coming from successfully concluded phase two clinical trials, are required for such a prescription to be issued.

Table 1.9.1. Number of patients accessing to 5% AIFA Fund during 2015

Orphan drug	Therapeutic indication	N. Patient	Treatment time	€
Teduglutide (Revestive)	Revestive is used to treat adults with short bowel syndrome. Patients need to be in a stable condition after a period of bowel adaptation following the surgery.	2	6 months	235.000
Carfilzomib (Kyprolis)	Treatment in combination with lenalidomide and dexamethasone in adults with multiple myeloma who have received at least one prior therapy.	1	2 cycles	14.400
Carfilzomib (Kyprolis)	Treatment in combination with lenalidomide and dexamethasone in adults with multiple myeloma who have received at least one prior therapy.	1	18 cycles	129.600
Temocillin (Negaban)	Treatment of cystic fibrosis with Burkholderia cepacia lungs infection.	1	15 days	2.970
Blinatumomab (Blincyto)	Treatment of B precursor acute lymphoblastic leukaemia (ALL), in relapsed or refractory cells negative for the Philadelphia chromosome.	1	1 cycle (28 days)	80.000
Sebelipase alfa (Kanuma)	Long term enzyme replacement therapy (ERT) in all ages patients of suffering from a deficiency of the lysosomal acid lipase (LAL).	1	6 months	431.040
Sebelipase alfa (Kanuma)	Long term enzyme replacement therapy (ERT) in all ages patients of suffering from a deficiency of the lysosomal acid lipase (LAL).	1	6 months	215.520

Table 1.9.2. Orphan drugs used during 2015, following Law Decree of 8/5/2003

Orphan drug	Therapeutic indication	MAH	N. patients	Medicine regulatory status
Everolimus Votubia ®	Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)	Novartis	35	Compassionate use program started in 2012. Pending M.A.H. in Italy
Nintedanib Ovef ®	IPF	Boehringer-Ingelheim pharmaceuticals	18	Compassionate use program started in 2014. Pending M.A.H. in Italy
Lenvatinib	Treatment of differentiated thyroid carcinoma, progressive, and refractory to radioactive iodine	EISAI	24	Compassionate use program started in 2014. Pending M.A.H. in Italy
Midostaurin (PKC412)	Treatment of mastocytosis	Novartis	24	Medicine under clinical development.
Daratumumab	Multiple myeloma	Janssen - Cilag	10	Compassionate use program started in 2015. Pending M.A.H. in Italy
Siltuximab	Castleman's disease	Janssen-Cilag	2	Compassionate use program started in 2013. Pending M.A.H. in Italy
Lumacaftor/Ivacaftor	CF in patients aged 12 years or above for the F508 mutation of the CFTR gene	Vertex Pharmaceuticals	100	Compassionate use program started in 2015. Pending M.A.H. in Italy
Pitolisant	Narcolepsy with or without cataplexy	Bioprojet Pharma	20	Compassionate use program started in 2015
Blinatumumab	LLA r/r Ph-	Amgen	10	Compassionate use program started in 2014/2015. Pending M.A.H. in Italy
Blinatumumab	LLA MRD+	Amgen	10	Compassionate use program started in 2014/2015 at international level. Indication in clinical development
Blinatumumab	LLA r/r in pediatric patients	Amgen	8	Compassionate use program started in 2014/2015 at international level. Indication in clinical development
Blinatumumab	LLA r/r Ph+	Amgen	7	Compassionate use program started in 2014/2015 at international level. Indication in clinical development

Orphan drug	Therapeutic indication	MAH	N. patients	Medicine regulatory status
Carfilzomib/Desamet ason	Multiple myeloma r/r	Amgen	38	Compassionate use program started in 2015. Under clinical trial

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

Requirement	Law n. 648/1996	Law n. 326/2003	M.D. of May 8, 2003	Law n. 94/1998
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

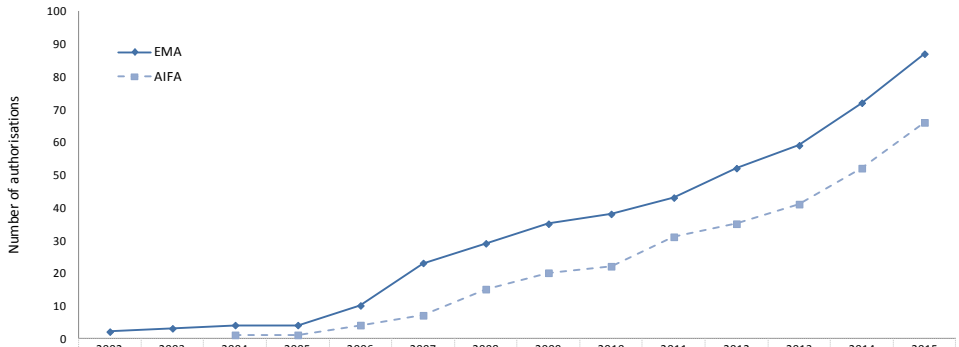
Orphan drug expenditure and consumption in Italy

2015 has been a record year for the European Medicines Agency due to the high number of human use medicine authorisations (93) of which at least 21 concern orphan drugs for the treatment of rare diseases[1]. Orphan drugs showed main indication within the oncology, metabolic (including enzyme replacement therapies) and central nervous system therapeutic areas.
Furthermore, among 87 EMA authorised orphan drugs within December, 31st 2015, 66 of them, including 13 products classified as C-nn (medicines not negotiated yet and for that reason classified as C class) were approved by AIFA and marketed in Italy. In more details of those 21 not authorised in Italy yet, 11 products did not conclude the approval process,

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/04/WC500204174.pdf

therefore pending for C-nn classification; 2 pricing & reimbursement applications have never been submitted by the Companies. Finally, 8 more products, which have never been authorised, but available to patients due to alternative channels encouraged by the Italian Medicines Agency (e.g. Law n. 648, Law n. 326/2003, etc...).

Figure 1.9.1. A comparison between medicines authorised by the European Medicines Agency (EMA) and approved by the Italian medicines Agency (AIFA)



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
EMA	2	3	4	4	10	23	29	35	38	43	52	59	72	87
AIFA			1	1	4	7	15	20	22	31	35	41	52	66

Orphan drugs authorised by EMA	87 (100%)
Orphan drugs authorised by AIFA	66 (76%)
Orphan drugs pending for Cnn	11 (13%)
No application for P&R	2 (2%)
Orphan drugs distributed through (Law n.648, 5% AIFA Fund)	8 (9%)

Moreover, according to criteria approved by the Board of Directors of AIFA, the list of orphan drugs reimbursed by the Italian Health System increases from 66 to 89, due to the inclusion of orphan-like products, as well as the addition of orphan drugs, to whom market exclusivity granted by the EMA expired. For that reason, they have been removed from the Community register.

Between years 2013-2015 expenditure and consumption data concerning orphan drugs have been analysed on the basis of the new lists approved by the AIFA's Board of Directors (Resolution n. 10 of February 27, 2014). Because of the use of these new lists, data resulting from current analyses are not comparable with those referring to previous years. During 2015, orphan drugs expenditure, (inpatient + outpatient settings), amounted to €1,2 billion, corresponding to 5,5% of the total pharmaceutical expenditure. The share of

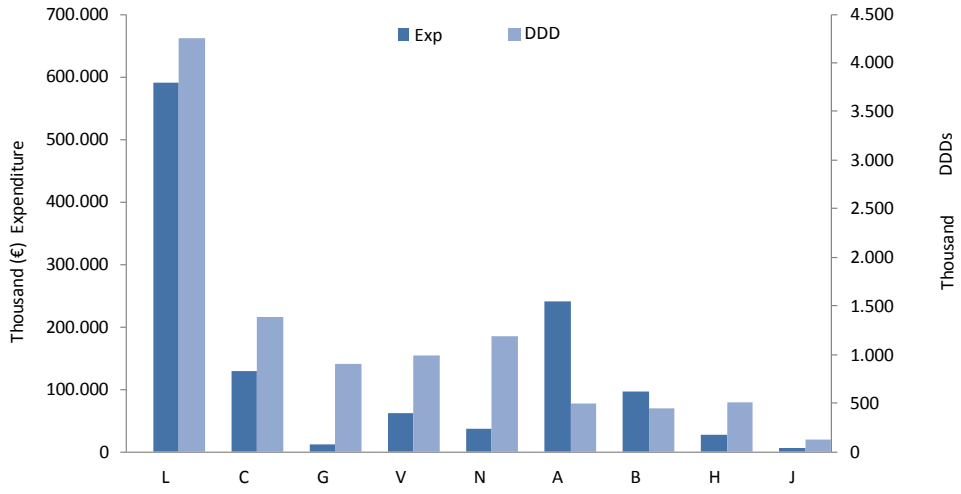
not reimbursed orphan drugs, calculated on total orphan drugs' expenditure (reimbursed + not reimbursed) is 0,85% (it was 0,11% in 2014).
In terms of DDDs, orphan drugs consumption (analysed in both settings) amounts to 10,3 million DDDs during 2015, corresponding to 0,04% of the total pharmaceutical consumption. Above all, the share in consumption of not reimbursed orphan drugs over total consumption of orphan drugs (reimbursed + not reimbursed by the NHS) is increasing up to 1,5% (it was 0,0007% in 2014).
For what concerns therapeutic classes, 49% of orphan drugs' expenditure concerned antineoplastic agents and immuno-modulators, followed by gastrointestinal tract and metabolism medicines (20%), and, finally, cardiovascular system medicines (11%).
On the other hand, 41% of orphan drugs' consumption was covered by antineoplastic agents and immuno-modulators, followed by cardiovascular system medicines (13%) and nervous system medicines (11%) (Table 1.9.6 and Figure 1.9.1).

Table 1.9.5. Trend of orphan drugs expenditure and consumption, years 2010-2015*

YEAR	2010	2011	2012	2013*	2014*	2015*
Orphan drug expenditure	657 (Mln)	800 (Mln)	671 (Mln)	917 (Mln)	1.060 (Mln)	1.212 (Mln)
% Share of orphan drug exp on total pharmaceutical exp	3,50%	4,20%	3,50%	4,67	5,31	5,49
Orphan drug consumption (DDD)	6,6 (Mln)	7,5 (Mln)	5,9 (Mln)	7,5 (Mln)	8,5 (Mln)	10,3 (Mln)
% Share of orphan drug DDDs on total pharmaceutical DDDs	0,03%	0,03%	0,02%	0,03	0,03	0,04

*2013-2014 and 2015 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 total inpatient and outpatient settings

Figure 1.9.2. Orphan drugs expenditure and consumption by ATC I° level, year 2015



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

Five active ingredients with major impact on expenditure are: lenalidomide (13,6%), bosentan (7,8%), eculizumab (6,4%), dasatinib (5,3%) and nilotinib (5,1%). Together they accounted for 38,2% of total orphan drugs' expenditure. According to consumption data, almost half of doses consumed (45,4%) is composed by the following active ingredients: lenalidomide (10,2%), bosentan (9,8%), deferasirox (9,5%), sildenafil (8,7%) and levodopa with decarboxylase inhibitor (7,2%).

1.10 The management of pharmaceutical expenditure

The management of pharmaceutical expenditure involves several financial measures aimed at balancing NHS pharmaceutical expenditure and the financial resources available (i.e. planned expenditure). This task is considered highly relevant for AIFA's mission, since the pharmaceutical expenditure management accounts for the equilibrium of the economic system. Any action intended to the appropriate use of medicines or any action intended to restrain regional expenditure (e.g. prices granted through local tenders lowering current ones) contributes to expenditure regulation. In this context, the activity of the CPR-CTS represents a significant tool to rule pharmaceutical expenditure, particularly in the context of price negotiations with pharmaceutical companies and when

defining reimbursed indications. Regions and/or Health Local Units (HLUs) 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 Law n.222 of 2007 and most recent Law n.135 of 2012, the control of pharmaceutical expenditure is obtained through a set of measures, notably the outpatient and inpatient pharmaceutical expenditure ceilings, the pharmaceutical expenditure monitoring, the fixed maximum budget ceilings for companies and the payback mechanism when budget is exceeded. In 2015, the outpatient pharmaceutical expenditure ceiling was set at 11,35% of the National Health Fund (Article 15, paragraph 3, of Law Decree n. 95 on July 6, 2012, followed by Law n.135 of August 7, 2012). This issue implies that the total NHS pharmaceutical expenditure, including costs of tickets paid by citizens (and excluding citizen reference price system co-payment, as provided by 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 the Direct distribution (including *per conto* distribution and First cycle therapy distribution), should be limited to €12.335 million. This threshold was determined excluding amounts paid by pharmaceutical companies as payback measures. In 2015, outpatient expenditure monitoring data revealed €12.666 million expenditure, with an overall deficit of €+331 million compared to the planned ceiling amounting up to €12.402 million. The outpatient pharmaceutical expenditure has increased compared to the previous year (€12.217 million).

As a result of €49,8 million breakthrough concerning both inpatient and outpatient expenditure in 2014, AIFA determined through a Resolution dated October 30, 2014 a payback mechanism for pharmaceutical companies. Afterward Lazio Regional Administrative Court ordered the cancellation of the payback to the outpatient pharmaceutical expenditure as well as the AIFA Resolution n. 1238/2014. Moreover, the Stability Act of 2016 (Law n. 208 of 28 December 2015) at paragraph n. 702 provided that, for the years 2013 and 2014, the Regions could enrol in their 2015 regional budget 90% of the amount they owed as payback of the breakthrough of the ceilings by pharmaceutical companies. In Table 1.10.1 it is shown the trend of the main parameters regarding the pharmaceutical expenditure in recent years. Because of the effects linked to the dispute with the rules of budget allocation's procedure, which must take into account the data of the previous year, it was not possible to attribute the 2015 budget.

Table 1.10.1 Trend of main parameters intended to manage outpatient NHS pharmaceutical expenditure during 2012-2016

Outpatient setting	2012	2013	2014	2015	2016***
Ceiling	13,10%	11,35%	11,35%	11,35%	11,35%
Pharmaceutical company budget *	13.358,8	12,184,7	12.108,8	NA	NA
% difference of outpatient pharmaceutical expenditure vs previous years**	5,19%	-0,88%	2,49%	NA	NA
Absolute difference vs budget **	685,0	-106,6	296,7	NA	NA
Fund of innovativeness	75,1	18,9	109,1	NA	NA
Innovative medicine ceiling	23,8	63,9	34,7****	NA	NA
Programmed expenditure	13.069,9	12.127,6	12.216,69	NA	NA
% share on National Health Fund (FSN)	12,20%	11,40%	11,18%	NA	NA
Not allocated resources	-968,7	0,0	-185,2	NA	NA
Breakthrough ceiling	0,0	49,8	0,0	NA	NA

Note: value expressed in 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 latter determines that in case of a failure in respecting 3,5% expenditure ceiling, the marketing authorization holder is responsible for 50% of the national overcoming while the remaining 50% is paid-back by the 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 Decree of the Minister of Health of July 15, 2004. In this context, the amount of the hospital pharmaceutical expenditure is calculated excluding the expenditure for Class A pharmaceuticals supplied through the Direct distribution channel as well as the pharmaceutical companies' pay-back (according to Article 15, paragraph 6 of Law n.135 of 2012). Furthermore, for the purpose of balancing overcoming of the expenditure ceiling at national level, inpatient 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).

Table 1.10.2. Trend of main parameters intended to manage inpatient NHS pharmaceutical expenditure during 2012-2016

Inpatient setting	2012	2013	2014	2015	2016***
Ceiling	2,40%	3,50%	3,50%	3,50%	3,50%
Pharmaceutical company budget *		4.460,80	4.178,60	NA	NA
% difference of outpatient pharmaceutical expenditure vs previous years**		-17,60%	-8,65%	NA	NA
Absolute difference vs budget**		-736,2	-353,1	NA	NA
Fund of innovatives		153,2	107,8	NA	NA
Innovative medicines ceiling		60,8	83,8	NA	NA
Programmed expenditure	5.170,60	4.497,60	4.874,20	NA	NA
% share on National Health Fund (FSN)	4,82%	4,23%	4,46%	NA	NA
Not allocated resources	0	0	0	NA	NA
Ceiling exceedance	2.598,70	773,2	1049,8	NA	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 modification, from temporary budget

Following a €1.049,8 million breakthrough in the inpatient pharmaceutical expenditure ceiling set for 2014, €524,9 million payback by the pharmaceutical companies has been established. Hospital pharmaceutical expenditure has increased compared to the previous years. Similarly, to the breakthrough of the outpatient pharmaceutical expenditure ceiling, paragraph n.702 of the Stability Act on 2016 has allowed Regions to enrol in their 2015 regional budget 90% of the amount they owed as a payback, coming from the breakthrough of the 2014 inpatient ceilings by the pharmaceutical companies. In Table 1.10.2 it is shown the trend of the main parameters regarding the pharmaceutical expenditure in recent years. Due to the effects linked to the dispute with the rules of budget allocation's procedure, which must take into account the data of the previous year, it was not possible to attribute 2015 budget. Finally, during 2015, AIFA carried out several payback mechanisms regarding the outpatient pharmaceutical expenditure for the second half of 2014 and first half of 2015 and launched 5% payback related to the 2015 inpatient pharmaceutical expenditure. Pursuant to AIFA Determination n.1529 of November 26, 2015 (published on the Official Journal n.279 on November 20, 2015), subsequently amended with the AIFA Determination n.1665 of December 17, 2015, the payback procedure for the years 2015-2016 and 2017 was adjusted, according to the renegotiation of the prices of medicines reimbursed by the NHS, on the basis of the groupings of medicines therapeutically equivalent.

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 manage "administrative databases", which represent important sources of medicines consumption, health outcomes and hospidalization data, 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 provision, in order to meet the different needs of the administration. This system allows to collect all information available for each subject, in respect of privacy laws 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 provided healthcare services. Main dataflows concern demographic registries, deaths records, community pharmaceutical flow, *direct* and *indirect* distribution flow, hospital discharge records (*SDO – Scheda di Dimissione Ospedaliera*), outpatient specialist care, "previous Article 26" rehabilitation services and integrated home-care services.
More specifically:

- 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 indirect 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 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); type of admission (e.g. day-hospital, ordinary); 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 dataflow originates from laboratories, and it is available only for some LHUs. It provides patients biographical data and information regarding laboratory exams such as request and execution date, code and description, results and units of measurement. Improvements of this flow could be obtained through 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 indicators developed in the Health-DB project. Health-DB is a business intelligence tool with data warehouse and dashboard functions.

- 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.

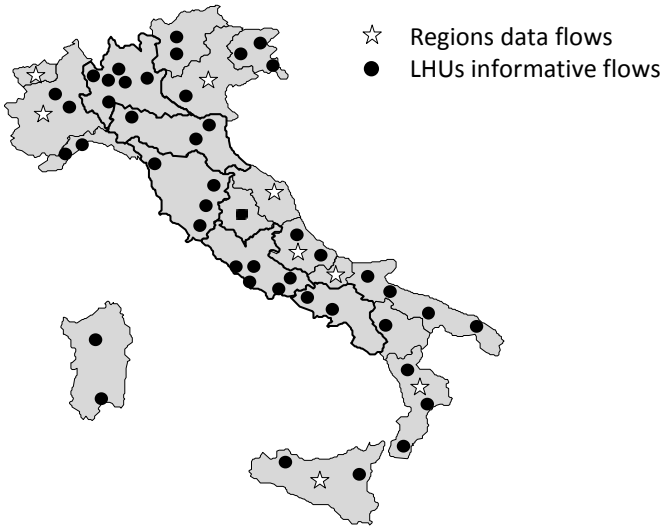
- The dashboard is based on a set of performance indicators designed to evaluate the compliance of medical prescriptions to therapeutic care standards (based on scientific evidence, guidelines, Ministerial notes, treatment plans). These indicators can be calculated in relation to specific aspects (e.g. 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 special centres. Since 1996, CliCon has conducted analysis in several therapeutic areas in partnership with a number of LHUs and Regions, taking into account community and hospital pharmaceutical consumptions as well as medical devices use.
This database, actually includes about 39 million health-assisted individuals (about 63,8% of the whole Italian population) distributed throughout the Country: North (67,6%), Center (45,8%) and South (68,9%). In particular, 48 Institutions are currently involved in the database feeding: 40 LHUs and 8 Regions. The average age of LHUs' and Regions' sample is 43,8 years versus 43,7 years of the Italian population. The percentage of males is estimated to 48,5%, in accordance with the national data. (Figure 3.6.1). The average age of LHUs' and Regions' sample is 43,8 years *versus* 43,7 years of the Italian population. The percentage of males is estimated to 48,5%, in accordance with the national data.

[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 2015 OsMed Report



For each LHU and 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 of 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 were combined through a data linkage procedure on the patient identification code (e.g. using the tax identification code) associating them with 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
- Rheumatoid arthritis
- Psoriasis
- Atrial fibrillation
- Deep vein thrombosis

Outpatient pharmaco-utilization data are 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 a management control activity. In this context, 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 traceability of prescription 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 regard to:

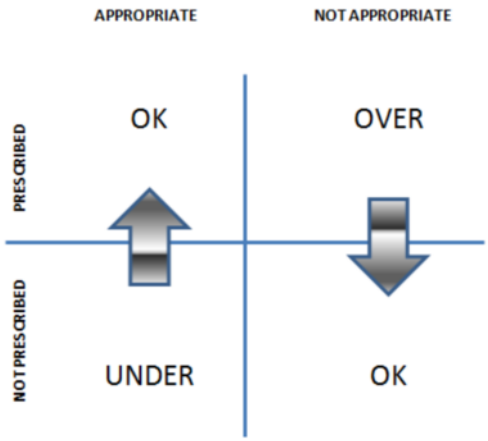
1. *therapeutic appropriateness (individual and collective*): each indicator has been selected based on the assumption that its increase is closely associated with an improvement in the patient's health status and in a more efficient allocation of resources. For example, prescription compliance with 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*: indicators have been selected so that an improvement of the measured parameter results in a better health status (e.g. decrease of exacerbations, hospitalizations) and in a reduction of overall costs for patients care. Due to a fixed budget, the Italian NHS is not able to handle an uncontrolled growth of pharmaceutical expenditure in the short run.

   These indicators are helpful to optimize the pharmaceutical expenditure, identifying area of under or over prescription as well as areas of appropriate or inappropriate prescription (Figure 3.6.3).

Health-DB project indicators undergo a continuous development and improvement process 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 as amended), patient ID codes are anonymized by LHUs, in site, so that CliCon cannot retrieve the patient identity. CliCon, by signing a specific agreement with each LHU, becomes responsible for the data analysis. All results are produced only in an aggregated form.

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 comorbid patients 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 2015) (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 begin a fixed-dose combination therapy with antihypertensive medicines 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) distinct 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 a 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 6.188.245 in 2015 (N) (Table 4.4.1). The prevalence of subjects in treatment with antihypertensive agents amounts to 28,0% of the overall study sample (27,0% in Northern, 27,4% in Center and 30,0% in Southern of Italy). The prevalence of subjects in treatment with antihypertensive medicines increases with age (3,2% in the age group ≤45 years, 28,4% in the age group 46-65 years, 61,8% in the age group 66-75 years and 77,6% in the age group >75 years) and over the years (+4,3% in 2015 compared to 2014 and +2,9% in 2014 compared to 2013).

Table 4.3.1. Distribution of patients in treatment with antihypertensive medicines

	2015			2014			2013		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**6.188.245**	**28,0**	**4,3**	**5.930.693**	**26,8**	**2,9**	**5.761.764**	**26,6**	**/**
Geographic distribution									
North	3.269.435	27,0	4,2	3.136.842	25,9	2,0	3.074.874	25,9	/
Center	894.304	27,4	6,4	840.765	25,8	5,8	794.974	24,8	/
South	2.024.506	30,0	3,7	1.953.086	28,9	3,2	1.891.916	28,6	/
Gender									
Male	2.849.209	26,5	5,0	2.714.810	25,3	3,4	2.624.781	24,9	/
Female	3.339.036	29,4	3,8	3.215.883	28,3	2,5	3.136.983	28,1	/
Age group									
≤45	299.779	3,2	-2,9	308.883	3,3	-0,2	309.505	3,4	/
46-65	2.106.902	28,4	1,2	2.082.726	28,1	0,9	2.065.117	28,4	/
66-75	1.724.770	61,8	2,7	1.679.881	60,2	2,4	1.640.533	59,9	/
>75	2.056.794	77,6	10,6	1.859.203	70,1	6,4	1.746.609	67,1	/
Mean age	68.5 ± 13.2			67.9 ± 13.1			67.7 ± 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 1.108.961 in 2015.
The percentage of comorbid patients treated with medicines acting on renin-angiotensin system amouned to 82,3% in 2015, a percentage slightly lower compared to the previous year (-1,6% in 2015 compared to 2014). This percentage appears slightly higher in Southern Italy (84,7%) than in Northern and Central regions of the country (80,7% and 81,4% respectively) and in males compared to females (83,4% vs 81,2%).
The percentage of comorbid patients in treatment with renin-angiotensin system inhibitors amounts to 74,6% in the age group ≤45 years, 84,0% in the age group 46-65 years, 85,1% in the age group 66-75 years and 79,4% in the age group >75 years. This percentage is lower in new users than in already treated ones (59,7% and 83,6% 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]

	2015 N = 1.108.961		2014 N = 1.046.277		2013 N = 1.001.374	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**82,3**	**-1,6**	**83,6**	**82,3**	**-1,6**	**83,6**
Geographic distribution						
North	80,7	-2,0	82,3	80,7	-2,0	82,3
Center	81,4	-1,4	82,6	81,4	-1,4	82,6
South	84,7	-1,1	85,6	84,7	-1,1	85,6
Gender						
Male	83,4	-1,4	84,6	83,4	-1,4	84,6
Female	81,2	-1,7	82,6	81,2	-1,7	82,6
Age group						
≤45	74,6	-1,2	75,5	74,6	-1,2	75,5
46-65	84,0	-0,8	84,7	84,0	-0,8	84,7
66-75	85,1	-0,9	85,9	85,1	-0,9	85,9
>75	79,4	-2,3	81,2	79,4	-2,3	81,2
Treatment status						
New users	59,7	-3,0	61,5	59,7	-3,0	61,5
Old users	83,6	-1,6	84,9	83,6	-1,6	84,9

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

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

The number of subjects aged 18 years or older taking angiotensin II antagonists in monotherapy amounts to 2.334.942 in 2015.
The percentage of patients receiving off-patent angiotensin II antagonists in December 2015 amounts to 75,8%; this value decreased compared to previous years (-2,2% in 2015 compared to 2014 and -1,8% in 2014 compared to 2013). This data is slightly higher in Northern (77,1%) and in Central (78,8%) Italy compared to Southern (73,0%) areas of the Country and in females compared to males (76,8% and 74,6% respectively). The percentage of patients treated with off-patent angiotensin II antagonists in december 2015 was 66,1% in ≤45 age group, 71,7% in 46-65 age group, 76,7% in 66-75 age group and 80,1% in age group >75 years and was lower among new users compared to already treated ones (67,0% vs 77,0%).

Table 4.3.3. Number of subjects who assume in monotherapy angiotensin II antagonists with patent expired in December 2015* [numerator]/Total number of patients receiving angiotensin II antagonists in monotherapy [denominator]

	2015 N = 2.334.942		**2014 N = 2.257.689**		**2013 N = 2.205.019**	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**75,8**	**-2,2**	**77,5**	**-1,8**	**78,9**	**/**
Geographic distribution						
North	77,1	-1,9	78,6	-1,4	79,7	/
Center	78,8	-1,6	80,1	-1,8	81,5	/
South	73,0	-2,9	75,1	-2,3	76,9	/
Gender						
Male	74,6	-2,5	76,5	-2,0	78,1	/
Female	76,8	-1,9	78,3	-1,6	79,5	/
Age group						
≤45	66,1	-4,0	68,9	-2,9	71,0	/
46-65	71,7	-3,0	74,0	-2,4	75,8	/
66-75	76,7	-2,2	78,5	-1,8	79,9	/
>75	80,1	-1,7	81,5	-1,3	82,7	/
Treatment status						
New users	67,0	-3,4	69,4	-6,8	74,5	/
Old users	77,0	-2,1	78,7	-1,1	79,6	/

N: number of subjects aged 18 years or older that assume angiotensin II antagonists in monotherapy
*List of angiotensin II antagonists with patent expired in December 2015 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 5.803.222 in 2015.
The percentage of adherent subjects in treatment with antihypertensive medicines amounts to 58,1%, in 2015 (+1,8% in 2015 compared to 2014). This value is slightly higher in Northern (58.1%) and in Southern (59,4%) than in Center (54,4%) Italy. The adherence is higher in males (59,9% vs 56,6% of females), in older subjects (62,9%, is in the age groups 66-75 years and 63,1% in over 75 years group), in already treated patients (62,7% compared to 24,3% of new users) and in comorbid users (the adherence of subjects with a previous CV event or diabetes amounts to 69,5% vs 55,7% 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 61,5% in 2015.

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

	2015 N = 5.803.222		2014 N = 5.642.654		2013 N = 5.492.285	
	%	Var. %	%	Ver. %	%	Var. %
TOTAL	**58,1**	**1,8**	**57,0**	**2,8**	**55,4**	**/**
Geographic distribution						
North	58,1	2,4	56,8	1,8	55,8	/
Center	54,4	7,5	50,6	-9,7	56,0	/
South	59,4	-0,5	59,7	9,2	54,7	/
Gender						
Male	59,9	1,8	58,8	2,3	57,5	/
Female	56,6	1,9	55,5	3,2	53,8	/
Age group						
≤45	34,8	0,7	34,6	4,3	33,1	/
46-65	53,1	1,0	52,5	2,9	51,1	/
66-75	62,9	1,9	61,8	2,2	60,4	/
>75	63,1	2,1	61,8	2,6	60,3	/
Treatment status						
New users	24,3	-5,1	25,7	8,4	23,7	/
Old users	62,7	2,0	61,4	2,7	59,8	/
Comorbidity status						
Without previous CV event or diabetes	55,7	1,8	54,7	3,0	53,1	/
With previous CV event or diabetes	69,5	1,6	68,4	2,1	67,0	/
TOTAL without occasional users	61,5	1,9	60,3	2,4	58,9	

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data were available up until December 31 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 5.803.222 in 2015. The percentage of occasional subjects in treatment with anti-hypertensive medicines amounts to 5,5%; this value increases slightly compared to the previous year (+0,5% in 2015 compared to 2014). The percentage of occasional users is higher in Central (6,2%) and Southern (6,8%) Italy compared to Northern (4,6%) regions of the Country and is slightly higher in females (6,0% vs 5,0% of males). This percentage is higher in younger age groups (20,5% in the age group ≤45 years, 6,8% in the age group 46-65 years, 3,6% in the age group 66-75 years and 3,4% in the age group >75 years), in new users (32,1% vs 1,9% of old users) and in the subjects without a previous CV event or diabetes (6,1% vs 2,6% 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]

	2015 N = 5.803.222		**2014** N = 5.642.654		**2013** N = 5.492.285	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**5,5**	**0,5**	**5,5**	**-6,9**	**5,9**	**/**
Geographic distribution						
North	4,6	-4,4	4,8	-1,4	4,9	/
Center	6,2	6,3	5,8	-1,4	5,9	/
South	6,8	4,2	6,5	-14,4	7,6	/
Gender						
Male	5,0	0,2	5,0	-6,4	5,3	/
Female	6,0	0,8	5,9	-7,4	6,4	/
Age group						
≤45	20,5	1,7	20,2	-5,1	21,3	/
46-65	6,8	3,3	6,6	-5,1	6,9	/
66-75	3,6	0,9	3,5	-6,6	3,8	/
>75	3,4	-2,3	3,5	-8,9	3,8	/
Treatment status						
New users	32,1	3,1	31,1	-7,1	33,5	/
Old users	1,9	0,5	1,9	-10,0	2,1	/
Comorbidity status						
Without previous CV event or diabetes	6,1	0,8	6,1	-6,6	6,5	/
With previous CV event or diabetes	2,6	-0,8	2,6	-10,4	2,9	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data were available up until December 31 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 149.177 in 2015.
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 82,3% in 2015. This value decreases compared to the previous year (-2,7% in 2015 compared to 2014). The percentage is higher in Central (83,2%) and Southern (84,9%) Italy than in Northern (79,7%) regions, as well as in females (83,1% vs 81,6% of males). This percentage decreases slightly with the age of patients (87,5% in the age group ≤45 years, 83,5% in the age group 46-65 years, 80,9% in the age group 66-75 years and 80,4% in over 75 years). The 77,4% 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]*

	2015 N = 149.177		2014 N = 144.486		2013 N = 109.888	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**82,3**	**-2,7**	**84,6**	**-1,9**	**86,3**	**/**
Geographic distribution						
North	79,7	-4,0	83,0	-1,2	84,0	/
Center	83,2	-0,9	84,0	-0,8	84,7	/
South	84,9	-1,6	86,3	-3,1	89,1	/
Gender						
Male	81,6	-2,9	84,1	-1,8	85,6	/
Female	83,1	-2,3	85,1	-2,1	87,0	/
Age group						
≤45	87,5	-2,1	89,3	-1,8	91,0	/
46-65	83,5	-2,7	85,9	-1,9	87,6	/
66-75	80,9	-2,6	83,1	-1,9	84,7	/
>75	80,4	-2,7	82,6	-2,0	84,3	/
Treatment status						
New users	100,0	0,0	100,0	0,0	100,0	/
Old users	77,4	-4,1	80,7	-2,3	82,6	/

N: number of subjects analyzed 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 analyzed aged 18 years or older in treatment with calcium channel blockers in free combination with another antihypertensive agent amounts to 267.895 in 2015. The percentage of patients in free combination, who did not shift to a fixed-dose combination therapy, amounts to 98,4%; this value decreased slightly compared to the previous year (-0,2% in 2015 compared to 2014). There are no significant differences across Italy (North 98,6%; Center 98,2%; South 97,9%), in males compared to females (98,3% vs 98,5%) or among age groups of patients (98,0% in the age group ≤45 years and in the age group 46-65 years, 98,2% in the age group 66-75 years and 98,8% 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]

	2015 N = 267.895		2014 N = 261.020		2013 N = 243.764	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**98,4**	**-0,2**	**98,5**	**-0,3**	**98,9**	**/**
Geographical distribution						
North	98,6	-0,2	98,8	-0,2	99,0	/
Center	98,2	-0,1	98,3	-0,4	98,7	/
South	97,9	-0,3	98,2	-0,5	98,7	/
Gender						
Male	98,3	-0,2	98,5	-0,4	98,8	/
Female	98,5	-0,2	98,6	-0,3	98,9	/
Age group						
≤45	98,0	0,1	97,9	-0,7	98,6	/
46-65	98,0	-0,1	98,1	-0,6	98,7	/
66-75	98,2	-0,3	98,6	-0,3	98,8	/
>75	98,8	-0,2	98,9	-0,2	99,1	/
Treatment status						
New users	98,4	-0,9	99,2	-0,1	99,3	/
Old users	98,4	-0,1	98,5	-0,4	98,9	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator
H.DB-1.1	+0,06%	€ 1.357.048
H.DB-1.2	-0,42%	€ -8.993.635
H.DB-1.3	+0,54%	€ 11.519.248
H.DB-1.4	-0,14%	€ -3.035.514
H.DB-1.5	-0,04%	€ -828.903
H.DB-1.6	+0,05%	€ 1.045.290

°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 over 80 in treatment with statins without a previous CV event or diabetes (Indicator H-DB 2.2.1)
- 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 analyzed 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 analyzed aged 18 years or older in treatment with statins amounts to 2.550.040 in 2015 (Table 4.4.1). The prevalence of the treatment with statins amounts to 11,5% of the study sample (10,8% in Northern, 12,4% 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, 10,36% in age group 46-65 years, 30,7% in age group 66-75 years and 31,8% in the group ≥75 years) and over the years (+3,2% in 2015 compared to 2014 and +4,1% in 2014 compared to 2013).

Table 4.4.1. Distribution of patients in treatment with statins

	2015			2014			2013		
	N	% SS	Var.%	N	% SS	Var.%	N	% SS	Var.%
TOTAL	**2.550.040**	**11,5**	**3,2**	**2.469.987**	**11,2**	**4,1**	**2.373.677**	**10,9**	**/**
Geographic distribution									
North	1.302.398	10,8	3,7	1.256.138	10,4	2,6	1.224.032	10,3	/
Center	402.997	12,4	4,2	386.848	11,9	6,8	362.257	11,3	/
South	844.645	12,5	2,1	827.001	12,3	5,0	787.388	11,9	/
Gender									
Male	1.251.999	11,7	3,7	1.207.045	11,2	4,1	1.159.582	11,0	/
Female	1.298.041	11,4	2,8	1.262.942	11,1	4,0	1.214.095	10,9	/
Age group									
≤45	63.607	0,7	-5,2	67.105	0,7	-1,2	67.934	0,7	/
46-65	785.055	10,6	-0,3	787.053	10,6	0,5	782.909	10,8	/
66-75	857.354	30,7	2,3	838.441	30,0	3,5	809.819	29,6	/
>75	844.024	31,8	8,6	777.388	29,3	9,0	713.015	27,4	/
Mean age	69.6 ± 11.3			69.2 ± 11.3			68.9 ± 11.3		

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 1.385.824 in 2015.
The percentage of patients with a previous CV event or diabetes treated with statins amounts to 56,0%, this value is slightly increased compared to the previous years (+0,6% in 2015 compared to 2014). The percentage of subjects in treatment with statins is slightly higher in southern regions: North (55,8%), Center (56,0%) and South (56,3%) of the Country and in males (58,1% vs 53,7% 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 (64,3%).

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]

	2015 N = 1.385.824		**2014** N = 1.348.319		**2013** N = 1.311.725	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**56,0**	**0,6**	**55,7**	**1,0**	**55,1**	**/**
Geographic distribution						
North	55,8	0,6	55,5	0,2	55,4	/
Center	56,0	-0,2	56,1	1,3	55,4	/
South	56,3	1,1	55,7	2,0	54,6	/
Gender						
Male	58,1	0,8	57,7	0,9	57,1	/
Female	53,7	0,5	53,4	1,1	52,8	/
Age group						
≤45	22,9	-0,3	22,9	-0,1	23,0	/
46-65	56,2	-0,5	56,5	0,0	56,5	/
66-75	64,3	0,7	63,9	0,9	63,4	/
>75	52,6	1,6	51,8	2,1	50,7	/
Follow-up until 31-December 2013	56,0		59,3		61,5	

Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).

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

The number of subjects analyzed aged 18 years or older in treatment with statins amounts to 2.550.040 in 2014.
The percentage of patients treated with statins without a previous CV event or diabetes amounts to 76,4% in 2016; this value decreases slightly compared to the previous years (-0,3% in 2015 compared to 2014). This percentage becomes 71,3% when the starting date of the evaluation period for previous CV event or diabetes starts from January 1, 2009. The percentage of patients treated with statins is slightly higher in Northern (77,5%) and Central Italy (78,1%) than in Southern (73,8%) Italy and in females (78,6% vs 74,0% of males).
Age seems to affect significantly the statins use: the higher percentage of patients in treatment and without a previous CV event or diabetes is in the age group ≤45 years (87,3%). The number of new users is higher than old users (84,4% vs 74,8%).

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]

	2015 N = 2.550.040		**2014** N = 2.469.987		**2013** N = 2.373.677	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**76,4**	**-0,3**	**76,6**	**-0,4**	**76,9**	**/**
Geographic distribution						
North	77,5	0,1	77,4	-0,6	77,9	/
Center	78,1	-1,0	78,9	0,5	78,5	/
South	73,8	-0,5	74,2	-0,4	74,5	/
Gender						
Male	74,0	-0,4	74,3	-0,6	74,7	/
Female	78,6	-0,1	78,7	-0,2	78,9	/
Age group						
≤45	87,3	0,0	87,2	0,0	87,3	/
46-65	78,5	0,1	78,4	0,0	78,4	/
66-75	74,2	-0,3	74,4	-0,4	74,7	/
>75	75,8	-0,5	76,1	-0,6	76,6	/
Treatment status						
New users	84,4	-0,1	84,5	0,4	84,1	/
Old users	74,8	-0,2	74,9	-0,4	75,2	/
Assessment from 01-January-2009°	71,3		72,3		73,3	

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

Percentage of patients over 80 in treatment with statins without a previous CV event or diabetes (Indicator H-DB 2.2.1)

The number of patients analyzed aged over 80 in treatment with statins without a previous CV event or diabetes amounts to 510.437 in 2015.
The percentage of over 80 patients without a previous CV event or diabetes in treatment with statins amounts to 76,6% in 2015; this value is slightly lower compared to the previous years (-0,7% in 2015 compared to 2014). The percentage of over 80 in treatment with statins is slightly higher in Northern (78,2%) and Central (78,0%) Italy than in Southern (72,7,8%) Italy, in females (77,5% vs 75,2% of males). The number of elderly new users treated with statins without a previous CV event or diabetes is higher than in old users (82,4% vs 75,8% of old users group).

Table 4.4.4. Number of patients over 80 in treatment with statins without a previous CV event or diabetes [numerator]/Total number of patients over 80 in treatment with statins [denominator].

	2015 N = 510.437		**2014 N = 465.585**		**2013 N = 422.321**	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**76,6**	**-0,7**	**77,1**	**-0,6**	**77,5**	**/**
Geographic distribution						
North	78,2	-0,4	78,5	-0,6	79,0	/
Center	78,0	-1,3	79,0	0,0	79,0	/
South	72,7	-0,9	73,3	-0,8	73,9	/
Gender						
Male	75,2	-0,8	75,8	-0,8	76,4	/
Female	77,5	-0,6	77,9	-0,4	78,2	/
Treatment status						
New users	82,4	-0,6	82,8	0,2	82,7	/
Old users	75,8	-0,6	76,3	-0,6	76,7	/

N: number of subjects over 80 in analysis, 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 analyzed aged 18 years or older in treatment with statins without a previous CV event or diabetes amounted to 1.947.589 in 2015.
The percentage of patients without a previous CV event or diabetes treated with low-intensity statins amounts to 39,0% in 2015; this value is lower compared to the previous years (-3,8% in 2015 compared to 2014 and -4,2% in 2014 compared to 2013). The percentage of patients in treatment with low-intensity is slightly higher in Central Italy (42,4%) than in Northern (37,8%) and Southern (39,0%) Italy, in females (43,1% vs 34,4% of males), in the elderly (33,6% in the age group ≤45 years, 35,4%, in the age group 46-65 years, 39,0% in the age group 66-75 years and 42,8% in the age group >75 years), there are no significant differences between new users and old users (39,0% vs 38,9%). The percentage of patients without a previous CV event or diabetes, treated with off-patent statins amounts to 79,9%.

Table 4.4.5. 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]

	2015 N = 1.947.589		2014 N = 1.891.190		2013 N = 1.824.328	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**39,0**	**-3,8**	**40,5**	**-4,2**	**42,3**	**/**
Geographical distribution						
North	37,8	-5,4	40,0	-5,0	42,1	/
Center	42,4	-3,4	43,9	-4,8	46,2	/
South	39,0	-1,5	39,6	-2,5	40,6	/
Gender						
Male	34,4	-4,9	36,2	-5,2	38,2	/
Female	43,1	-3,0	44,4	-3,4	46,0	/
Age group						
≤45	33,6	-4,4	35,1	-4,1	36,6	/
46-65	35,4	-4,3	37,0	-4,5	38,7	/
66-75	39,0	-4,1	40,7	-4,6	42,7	/
>75	42,8	-3,9	44,5	-4,2	46,4	/
Treatment status						
New users	39,0	-5,5	41,3	-4,4	43,2	/
Old users	38,9	-3,4	40,3	-4,1	42,0	/
Off-patent statins ^	79,9	1,9	78,3	2,1	76,7	/

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 (ATC CODE C10AA01), lovastatin (ATC CODE C10AA02), pravastatin (ATC CODE C10AA03), fluvastatin (ATC CODE C10AA04).
^Off-patent statins: simvastatin (ATC CODE C10AA01), lovastatin (ATC CODE C10AA02), pravastatin (ATC CODE C10AA03), fluvastatin (ATC CODE C10AA04) and atorvastatin (ATC CODE C10AA05).

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 analyzed aged 18 years or older with a previous CV event or diabetes and in treatment with statins amounted to 602.451 in 2015.
The percentage of patients, with a previous CV event or diabetes, in treatment with high-intensity statins, amounts to 64,8% in 2015; this value is slightly increased compared to previous years (+2,2% in 2015 compared to 2014 and +2,6% in 2014 compared to 2013). The percentage of subjects in treatment with high-intensity-statins is slightly lower in Central Italy (61,9%) than in Northern and Southern Italy (64,9% and 65,8% respectively). This percentage is higher in males (67,5% vs 61,6% in females), in younger age groups (67,2% in the age group ≤45 years, 67,8% in the age group 46-65 years, 65,3% in the age group 66-75 years and 61,7% in the age group >75 years), and in new users (39,0% vs 38,9% in old users). The percentage of patients without a previous CV event or diabetes, treated with patented statins amounts to 21,1%.

Table 4.4.6. 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]

	2015 N = 602.451		2014 N = 578.797		2013 N = 549.349	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**64,8**	**2,2**	**63,4**	**2,6**	**61,8**	**/**
Geographic distribution						
North	64,9	2,8	63,1	2,9	61,4	/
Center	61,9	2,9	60,2	3,2	58,3	/
South	65,8	1,2	65,0	2,0	63,7	/
Gender						
Male	67,5	2,2	66,1	2,8	64,3	/
Female	61,6	2,1	60,3	2,4	58,9	/
Age group						
≤45	67,2	1,1	66,5	2,1	65,1	/
46-65	67,8	2,0	66,5	2,1	65,1	/
66-75	65,3	2,6	63,6	2,9	61,8	/
>75	61,7	2,5	60,2	3,4	58,2	/
Treatment status						
New users	65,8	3,5	63,6	3,5	61,5	/
Old users	64,7	2,0	63,4	2,5	61,8	/
Patented statins^	21,1	-7,5	22,8	-6,2	24,3	/

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 (ATC CODE C10AA05), rosuvastatin (ATC CODE C10AA07), simvastatin and ezetimibe (ATC CODE C10BA02)
^Patented statins: rosuvastatin (ATC CODE C10AA07), simvastatin and ezetimibe (ATC CODE C10BA02).

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

The number of subjects analyzed aged 18 years and older in treatment with statins amounted to 2.420.164 in 2015.
The percentage of subjects adhering to treatment with statins amounts to 45,8%; this value is slightly increased on the previous year (+0,8% in 2015 compared to 2014). The percentage of adherence is higher in Northern Italy (48,9%) compared to Central (39,5%) and Southern (43,7,3%) Italy and in males (49,1% vs 42,6% of females). The highest adherence level has been observed in the age group 66-75 years (49,0%) compared to 28,1% registered in ≤45 years age group, to 43,0% in 46-65 years age group and to 46,7% in > 75 years age group, and in old users (50,3% vs 24,5% of new users). The adherence to the treatment with statins changes in relation to subject's clinical status (51,5% in subjects with a previous CV event or diabetes and 44,1% in subjects without a previous CV event or diabetes).
Excluding occasional users, the percentage of adherent patients amounts to 49,7%.

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

	2015 N = 2.420.164		2014 N = 2.328.163		2013 N = 2.215.947	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**45,8**	**0,8**	**45,5**	**4,3**	**43,6**	**/**
Geographic distribution						
North	48,9	1,9	48,0	1,4	47,3	/
Center	39,5	7,1	36,8	-8,8	40,4	/
South	43,7	-2,9	45,0	14,9	39,2	/
Gender						
Male	49,1	1,0	48,6	3,3	47,0	/
Female	42,6	0,4	42,5	5,3	40,3	/
Age group						
≤45	28,1	-1,3	28,4	4,9	27,1	/
46-65	43,0	-0,5	43,2	3,7	41,7	/
66-75	49,0	1,1	48,5	4,1	46,6	/
>75	46,7	1,3	46,1	4,5	44,1	/
Treatment status						
New users	24,5	-5,1	25,8	2,2	25,2	/
Old users	50,3	0,8	49,9	3,8	48,1	/
Comorbidity status						
Without previous CV event or diabetes	44,1	0,6	43,8	4,2	42,1	/
With previous CV event or diabetes	51,5	1,1	50,9	4,5	48,7	/
TOTAL without occasional users	49,7	0,7	49,3	3,3	47,7	/

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, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 analyzed aged 18 years and older in treatment with statins amounted to 2.420.164 in 2015. The percentage of occasional users amounts to 7,8%; this value is decreased compared to the previous year (-0,3% in 2015 compared to 2014). The percentage of occasional users is higher in Central (8,6%) and in Southern (10,6%) Italy compared to Northern (5,8%) Italy and is slightly higher in females (8,4% compared to 7,2% of males). Poor adherence (occasional users) is higher in younger age groups (21,5% in the age group ≤45 years, 9,5% in the age group 46-65 years, 6,2% in the age group 66-75 years and 6,8% in the age group >75 years), in new users (28,4% compared to 3,5% of old users) and in subjects without a previous CV event or diabetes (8,6% compared to 5,2% of subjects with a previous CV event or diabetes).

Table 4.4.8. Number of occasional patients in treatment with statins [numerator] / Total number of patients in treatment with statins [denominator].

	2015 N = 2.420.164		2014 N = 2.328.163		2013 N = 2.215.947	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**7,8**	**-0,3**	**7,9**	**-9,4**	**8,7**	**/**
Geographic distribution						
North	5,8	-4,4	6,1	-1,2	6,2	/
Center	8,6	-2,4	8,8	-3,5	9,1	/
South	10,6	3,5	10,2	-17,4	12,4	/
Gender						
Male	7,2	-0,8	7,3	-9,5	8,0	/
Female	8,4	0,1	8,4	-9,4	9,3	/
Age group						
≤45	21,5	2,8	20,9	-6,5	22,3	/
46-65	9,5	3,1	9,2	-6,9	9,9	/
66-75	6,2	-1,4	6,3	-9,3	6,9	/
>75	6,8	-2,4	6,9	-11,8	7,9	/
Treatment status						
New users	28,4	3,7	27,4	-4,9	28,8	/
Old users	3,5	1,7	3,4	-9,0	3,8	/
Comorbidity status						
Without previous CV event or diabetes	8,6	-0,1	8,6	-8,9	9,5	/
With previous CV event or diabetes	5,2	-0,4	5,3	-12,0	6,0	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 4.4.9. Pharmaceutical expenditure flexibility for statins with regard to the improvement of related indicators

Indicator	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator
H.DB-2.1	+0,53%	€ 4.280.410
H.DB-2.2	-0,96%	€ -7.724.306
H.DB-2.2.1	-0,14%	€ -1.153.730
H.DB-2.3	-0,51%	€ -4.140.463
H.DB-2.4	+0,18%	€ 1.452.657
H.DB-2.5	+0,47%	€ 3.824.555
H.DB-2.6	-0,17%	€ -1.362.378

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 a 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), thiazolidinedione (ATC CODE A10BG), dipeptidyl peptidase 4 inhibitors (DPP-IV inhibitors ATC CODE A10BH), other blood glucose lowering agents, with the exclusion insulins (ATC CODE A10BX).
The subjects analyzed have been categorized as patients with a previous cardio-cerebral vascular event or diabetes, and as 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 961/2013, November 4, 2013

- 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) during 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
- no 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 amounted to 1.185.497 in 2015 (Table 4.5.1). The prevalence of the treatment with hypoglycemic agents amounts to 5,4% of the study sample (4,6% in Northern Italy, 5,6% in Central and 6,6% in Southern Italy). The prevalence of treatment with anti-diabetic agents increases with age (0,4% in the age group ≤45 years, 4,9% in the age group 46-65 years, 13,8% in the age group 66-75 years and 14,9% in the age group >75 years) and over the years (+3,7% in 2015 compared to 2014 and +2,6% in 2014 compared to 2013).

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

	2015			2014			2013		
	N	% SS	Var. %	N	% SS	Var. %	N	% SS	Var. %
TOTAL	**1.185.497**	**5,4**	**3,7**	**1.143.185**	**5,2**	**2,6**	**1.114.651**	**5,1**	**/**
Geographic distribution									
North	557.616	4,6	3,4	539.384	4,5	1,7	530.387	4,5	/
Center	181.863	5,6	6,8	170.284	5,2	5,7	161.070	5,0	/
South	446.018	6,6	2,9	433.517	6,4	2,4	423.194	6,4	/
Gender									
Male	620.589	5,8	4,2	595.294	5,5	3,0	578.024	5,5	/
Female	564.908	5,0	3,1	547.891	4,8	2,1	536.627	4,8	/
Age group									
≤45	40.619	0,4	-3,2	41.959	0,5	0,6	41.701	0,5	/
46-65	362.685	4,9	-0,7	365.372	4,9	-0,9	368.793	5,1	/
66-75	386.367	13,8	2,5	377.071	13,5	2,4	368.370	13,4	/
>75	395.826	14,9	10,3	358.783	13,5	6,8	335.787	12,9	/
Mean age	69.4 ± 12.1			68.9 ± 12.0			68.6 ± 11.9		

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 amounted to 1.115.527 in 2015.
The percentage of adherent patients amounted to 63,6%; this value decreases slightly compared to the previous year (-0,7% in 2015 compared to 2014). The percentage of adherent patients is higher in the north of the country (66,2%) compared to Southern Italy (61,4%) to Center (59,4%) of Italy. This value is higher in males than in females (65,1% vs 62,0% respectively). The adherence is higher in old users (69,2% vs 29,0% of new users) and in patients without a previous CV event compared to patients with a previous CV event (63,8% vs 60,7%). The adherence improves with age (45,7% in the age group ≤45 years, 65,8% in the age group 46-65 years, 67,5% in the age group 66-75 years and 59,5% in the age group >75 years). With the exclusion of occasional users, the percentage of adherent patients amounted to 68,3% in 2015.

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]

	2015 N = 1.115.527		2014 N = 1.089.145		2013 N = 1.053.670	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**63,6**	**-0,7**	**64,1**	**1,7**	**63,0**	**/**
Geographic distribution						
North	66,2	-0,3	66,4	0,4	66,1	/
Center	59,4	-1,0	60,0	-5,0	63,2	/
South	61,8	-1,2	62,6	5,7	59,2	/
Gender						
Male	65,1	-0,5	65,5	1,8	64,3	/
Female	62,0	-1,1	62,7	1,6	61,7	/
Age group						
≤45	45,7	-2,7	47,0	4,0	45,2	/
46-65	65,8	-0,6	66,2	1,9	64,9	/
66-75	67,5	-0,4	67,7	1,6	66,7	/
>75	59,5	-0,9	60,0	1,5	59,1	/
Treatment status						
New users	29,0	-7,4	31,3	9,4	28,6	/
Old users	69,2	-1,0	69,8	1,2	69,0	/
Comorbidity status						
Without previous CV event or diabetes	63,8	-0,7	64,2	1,7	63,1	/
With previous CV event or diabetes	60,7	-2,5	62,3	1,6	61,3	/
TOTAL without occasional users	68,3	-0,6	68,7	1,2	67,9	

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, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).

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 amounted to 1.202 in 2015.
The percentage of patients in treatment with DPP-IV inhibitors who don't meet DPP-IV inhibitors reimbursement criteria amounts to 24,1%; this value appears increased compared to the previous year (+10,9% in 2015 compared to 2014). There are no differences between males and females (24,0% vs 24,3% respectively). The percentage is higher in younger subjects (30,3% in the age group ≤45 years, 23,8% in the age group 46-65 years, 25,4% in the age group 66-75 years and 22,4% in the age group >75 years). In 2015 the percentage of patients in treatment with DPP-IV inhibitors who don't meet DPP-IV inhibitors reimbursement criteria amounts to 10,2% of old users, and to 41,0% of new 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]

	2015 N = 1.202		2014 N = 1.315		2013 N = 1.279	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**24,1**	**10,9**	**21,7**	**-33,5**	**32,7**	**/**
Gender						
Male	24,0	6,9	22,4	-27,1	30,8	/
Female	24,3	16,0	21,0	-40,0	34,9	/
Age group						
≤45	30,3	-18,4	37,1	-21,8	47,5	/
46-65	23,8	7,7	22,1	-36,3	34,7	/
66-75	25,4	34,2	18,9	-44,1	33,9	/
>75	22,4	-6,0	23,8	3,9	22,9	/
DPP-IV inhibitors treatment status						
Treatment beginning	41,0	-13,1	47,2	-19,0	58,2	/
Treatment continuation	10,2	29,3	7,9	-42,3	13,6	/

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

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 2.562 in 2015.
The percentage of patients who meet DPP-IV inhibitors reimbursement criteria but are not in treatment with DPP-IV inhibitors amounts to 64,4% in 2015; this value decreased compared to the previous year (+3,2% in 2015 compared to 2014). There are no differences between males and females (66,6% vs 62,4% respectively); the percentage is higher in younger and in older patients (72,9% in the age group ≤45 years, 63,0% in the age group 46-65 years, 63,0% in the age group 66-75 years and 71,9% higher to 75 years). As regard the therapy previously taken: 80,5% of subjects assumed a monotherapy with metformin; 75,5% of patients metformin and sulfonamides in association; 73,6% of patients metformin and thiazolidinedione in association; 72,2% of patients metformin, sulfonamide and thiazolidinedione in association; 81,7% of patients assumed a monotherapy with sulfonamide; 21,2% of patients assumed other agents in association, also with DPP-IV inhibitors and 95,6% of subjects didn't assume any antidiabetic agents taken into account. After excluding from the analysis old DPP-IV inhibitors users with reimbursement criteria, the percentage of patients with DPP-IV inhibitors reimbursement criteria and without a DPP-IV inhibitor therapy amounts to of 82,7% in 2015.

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 meet DPP-IV inhibitors reimbursement criteria [denominator]

	2015 N = 2.562		2014 N = 2.739		2013 N = 2.527	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**64,4**	**3,2**	**62,4**	**-5,3**	**65,9**	**/**
Gender						
Male	62,4	1,4	61,5	-0,9	62,1	/
Female	66,6	5,0	63,5	-9,0	69,8	/
Age group						
≤45	72,9	-2,7	75,0	-4,8	78,8	/
46-65	55,4	0,6	55,0	-2,3	56,4	/
66-75	63,0	7,8	58,4	-5,7	62,0	/
>75	71,9	-1,6	73,0	-6,4	78,0	/
Therapy						
Monotherapy with metformin	80,5	-4,6	84,4	-2,2	86,3	/
Metformin and sulfonamides	75,7	-7,5	81,8	-4,9	86,0	/
Metformin and thiazolidinedione	73,6	-2,4	75,4	2,2	73,8	/
Metformin, sulfonamide and thiazolidinedione	72,2	-0,1	72,3	3,8	69,7	/
Monotherapy with sulfonamide	81,7	-8,2	89,0	3,3	86,2	/
Other combination therapy	21,2	9,9	19,3	7,6	18,0	/
No anti-diabetic therapy	95,6	-1,0	96,6	-0,3	96,8	/
Without old DPP-IV inhibitor users	82,7	-4,4	86,5	-1,0	87,4	/

This indicator has been calculated only for LHUs with a laboratory flow.

The value of the last glycosylated hemoglobin (HbA1c) performed within two months before the beginning of therapy has been taken into account.

N: number of patients aged 18 year or older in treatment with hypoglycemic agents who meet DPP-IV reimbursement criteria

^With regard to the therapy previously assumed by patients with DPP-IV inhibitors reimbursement criteria but not in treatment with DPP-IV inhibitors:

- During 2013 the 27,1% of patients come from a monotherapy with metformin, 25,5% from metformin and sulfonamides in association; 2,7% from metformin and thiazolidinedione in association; 3,7% from metformin, sulfonamide and thiazolidinedione in association; 3,0% from a monotherapy with sulfonamide; 8,6% from other agents in association, also with DPP-IV inhibitors, and 29,4% doesn't come from any antidiabetic therapy.
- During 2014 the 25,6% of patients come from a monotherapy with metformin, 22,6% from metformin and sulfonamides in association; 2,9% from metformin and thiazolidinedione in association; 2,7% from metformin, sulfonamide and thiazolidinedione in association; 3,8% from a monotherapy with sulfonamide; 11,2% from other agents in association, also with DPP-IV inhibitors, and 31,2% doesn't come from any antidiabetic therapy.
- During 2015 the 28,2% of patients come from a monotherapy with metformin, 19,4% from metformin and sulfonamides in association; 3,2% from metformin and thiazolidinedione in association; 2,4% from metformin, sulfonamide and thiazolidinedione in association; 5,2% from a monotherapy with sulfonamide; 10,1% from other agents in association, also with DPP-IV inhibitors, and 31,5% 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 4.5.5).

Table 4.5.5. Pharmaceutical expenditure flexibility for antidiabetic agents with regard to the improvement of related indicators

Indicator	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator°
H.DB-3.1	+0,99%	€ 4.121.578
H.DB-3.2	-0,52%	€ -2.012.309
H.DB-3.3	+1,12%	€ 4.308.061

°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 analyzed 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 analyzed 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 analyzed aged 40 years or older in treatment with medicines for obstructive pulmonary diseases amounted to 1.998.027 in 2015 (Table 4.6.1). The prevalence of treatment with medicines for obstructive pulmonary diseases amounts to 13,0% of the study sample (11,0% in Northern Italy, 14,3% in Central Italy and 15,9% in Southern Italy). The prevalence of the treatment with medicines for obstructive pulmonary diseases increases with age (9,0% in the age group ≤45 years, 10,6% in the age group 46-65 years, 16,4% in the age group 66-75 years and 19,8% in the age group >75 years).

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

	2015			2014			2013		
	N	% SS	Var. %	N	% SS	Var. %	N	% SS	Var. %
TOTAL	**1.998.027**	**13,0**	**5,1**	**1.901.089**	**12,4**	**3,9**	**1.830.610**	**12,1**	**/**
Geographic distribution									
North	926.857	11,0	6,8	867.605	10,3	0,2	865.614	10,5	/
Center	324.022	14,3	9,9	294.906	13,0	8,3	272.204	12,2	/
South	747.148	15,9	1,2	738.578	15,7	6,6	692.792	15,0	/
Gender									
Male	887.494	11,9	5,1	844.300	11,3	3,7	814.212	11,1	/
Female	1.110.533	14,0	5,1	1.056.789	13,4	4,0	1.016.398	13,1	/
Age group									
≤45	228.138	9,0	-1,2	230.904	9,1	2,9	224.408	9,0	/
46-65	786.767	10,6	4,9	750.250	10,1	2,6	730.952	10,0	/
66-75	457.754	16,4	3,6	441.789	15,8	3,8	425.610	15,5	/
>75	525.368	19,8	9,9	478.146	18,0	6,3	449.640	17,3	/
Mean age	64.6 ± 14.3			64.2 ± 14.2			64.1 ± 14.2		

N: number of subjects 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 amounted to 54.086 in 2015.
The percentage of patients in treatment with ICS after the hospital discharge amounted to 59,1%; this value is higher than the previous year (+3,5% in 2015 compared to 2014). Evaluating the presence of a therapy with ICS up until December 31, 2015, the following percentages are: 63,0% in 2015, 66,7% in 2014 and 68,8% in 2013. The percentage of subjects in treatment is slightly lower in southern Italy (55,8%) compared to northern (61,2%) and central Italy (60,2%) and in females (58,2% vs 59,6% in males). This percentage changes with age (40,0% in the age group ≤45 years, 52,8% in age group 46-65 years, 61,9% in age group 66-75 years and 59,7% in age group > 75 years) and is higher in old users than in new users (75,0% vs 29,5% 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]

	2015 N = 54.086		2014 N = 54.774		2013 N = 55.840	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**59,1**	**3,5**	**57,1**	**2,8**	**55,5**	**/**
Geographic distribution						
North	61,2	0,7	60,8	1,9	59,6	/
Center	60,2	5,8	56,9	-2,3	58,3	/
South	55,8	6,9	52,1	6,1	49,2	/
Gender						
Male	59,6	4,0	57,3	1,4	56,5	/
Female	58,2	2,8	56,6	4,8	54,0	/
Age group						
≤45	40,0	23,5	32,4	12,2	28,9	/
46-65	52,8	7,5	49,1	3,6	47,4	/
66-75	61,9	1,0	61,3	3,0	59,5	/
>75	59,7	2,8	58,0	2,1	56,8	/
Treatment status						
New users	29,5	6,7	27,6	4,5	26,4	/
Old users	75,0	0,1	74,9	1,1	74,1	/
Follow-up until 31 Dec 2015	63,0		66,7		68,8	/

Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have a complete one full observation year also for subjects included at in December 2014). 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 amounted to 54.086 in 2015.
The percentage of patients in treatment with LABA and/or LAMA in the period following hospital discharge amounts to 58,3%; this percentage is higher compared to previous years (+4,2% in 2015 compared to 2014; +4,0% in 2014 compared to 2013). Evaluating the presence of a therapy with LABA and/or LAMA up until December 31, 2015, the percentages are: 60,5% in 2015, 61,4% in 2014 and 61,7% in 2013. This percentage is lower in Southern (52,7%) than in Northern (62,2%) and Central (59,4%) Italy, and in females (54,5% compared to 60,9% of males). The presence of the treatment changes with age (30,8% in the age group ≤45 years, 51,7% in the age group 46-65 years, 63,0% in the age group 66-75 years and 58,3% in the age group >75 years) and is higher in old users (75,7% vs 26,2% 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 a hospitalization for COPD [denominator]

	2015 N = 54.086		2014 N = 54.774		2013 N = 55.840	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**58,3**	**4,2**	**56,0**	**4,0**	**53,9**	**/**
Geographic distribution						
North	62,2	0,9	61,6	2,3	60,3	/
Center	59,4	6,5	55,8	-0,5	56,0	/
South	52,7	8,4	48,6	8,3	44,9	/
Gender						
Male	60,9	4,2	58,4	3,4	56,5	/
Female	54,5	3,9	52,4	4,9	50,0	/
Age group						
≤45	30,8	31,6	23,4	21,8	19,2	/
46-65	51,7	11,1	46,5	6,3	43,8	/
66-75	63,0	2,3	61,6	4,4	59,0	/
>75	58,3	2,2	57,0	2,7	55,5	/
Treatment status						
New users	26,2	6,8	24,5	6,9	22,9	/
Old users	75,7	0,7	75,2	2,1	73,7	/
Follow-up until 31 December 2015	60,5		61,4		61,7	/

Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).

The presence of a 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 amounted to 1.660.219 in 2015.
The percentage of subjects in treatment with ICS without exacerbations amounted to 53,3%; this value is slightly lower than in the previous year (-1,9% in 2015 compared to 2014). Evaluating the absence of exacerbations starting from January 1, 2009 the percentages are: 17,9% in 2015, 25,7% in 2014 and 38,7% in 2013. This percentage is higher in Northern Italy (63,4%) than in Central (41,7%) and Southern (40,9%) Italy, in younger subjects (64,6% in the age group ≤45 years, 58,6% in the age group 46-65 years, 47,8% in the age group 66-75 years and 43,8% in the age group >75 years), in new users (61,1% compared to 39,7% of old users) and in males (54,5% vs 52,3% 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]

	2015 N = 1.660.219		**2014 N = 1.594.916**		**2013 N = 1.516.784**	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**53,3**	**-1,9**	**54,3**	**1,5**	**53,5**	**/**
Geographic distribution						
North	63,4	-1,7	64,5	0,8	64,0	/
Center	51,8	3,9	49,9	0,5	49,6	/
South	41,7	-2,8	42,9	2,8	41,7	/
Gender						
Male	54,5	-1,6	55,4	5,4	52,6	/
Female	52,3	-2,1	53,4	-2,2	54,6	/
Age group						
≤45	64,6	-1,5	65,5	1,7	64,4	/
46-65	58,6	-1,4	59,4	1,9	58,3	/
66-75	47,8	-2,2	48,9	1,0	48,4	/
>75	43,8	-1,9	44,6	0,6	44,4	/
Treatment status						
New users	61,1	-1,6	62,1	0,6	61,7	/
Old users	39,7	-2,4	40,7	1,7	40,0	/
From 01-January-2009	17,9		25,7		38,7	/

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, 2015, the last reporting year is 2014 (in order to have one whole observation year also for subjects included in December 2014).
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 1.855.184 in 2015.
The percentage of adherent patients is of 13,8%; this value is slightly lower than in the previous year (-0,2% in 2015 compared to 2014). The adherence is higher in Northern Italy (15,4%) compared to Central (13,6%) and Southern (12,0%) Italy, in males (17,9% vs 10,5% of females), in old users (32,6% vs 2,5% in new users), and in patients with exacerbations (18,0% vs 10,2% of patients without exacerbations). Moreover, the adherence to the treatment improves with age (4,2% in the age group ≤45 years, 7,9% in the age group 46-65 years, 17,1% in the age group 66-75 years, 24,7% in the age group >75 years). With the exclusion from the analysis of occasional users, the percentage of adherent patients amounts to 37,1% in 2015.

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]

	2015 N = 1.855.184		2014 N = 1.792.068		2013 N = 1.707.514	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**13,8**	**-0,2**	**13,8**	**3,1**	**13,4**	**/**
Geographic distribution						
North	15,4	4,3	14,8	-0,2	14,8	/
Center	13,6	0,0	13,6	-7,0	14,6	/
South	12,0	-5,7	12,7	12,4	11,3	/
Gender						
Male	17,9	-0,1	17,9	2,7	17,5	/
Female	10,5	-0,2	10,5	3,9	10,1	/
Age group						
≤45	4,2	-0,7	4,2	2,0	4,1	/
46-65	7,9	0,3	7,9	2,0	7,8	/
66-75	17,1	-1,4	17,3	3,1	16,8	/
>75	24,7	-1,3	25,0	4,3	24,0	/
Treatment status						
New users	2,5	-0,4	2,6	10,0	2,3	/
Old users	32,6	-1,4	33,0	6,2	31,1	/
Exacerbation status						
Without exacerbations	10,2	-0,4	10,2	3,6	9,8	/
With exacerbations	18,0	-1,0	18,2	3,6	17,5	/
Total without occasional users	37,1	0,7	36,8	0,5	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, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 1.855.184 in 2015.
The percentage of occasional users amounts to 62,8%; this value is slightly higher than in the previous year (+0,5% in 2015 compared to 2014). There are no significant differences across Italy (Northern 62,2%; Central 63,8%; Southern 63,1% Italy). The percentage of occasional users is slightly higher in females (66,4% vs 58,1% of males), in new users (81,9% vs 30,9% of old users) and in subjects without exacerbations (68,9% vs 55,7% in patients with exacerbations). The occasional use is higher among younger subjects (76,6% in age group ≤45 years, 70,8% in age group 46-65 years, 57,9% in age group 66-75 years and 47,9% 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]

	2015 N = 1.855.184		**2014** N = 1.792.068		**2013** N = 1.707.514	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**62,8**	**0,5**	**62,5**	**-1,5**	**63,4**	**/**
Geographic distribution						
North	62,2	-1,9	63,4	0,4	63,1	/
Center	63,8	-0,4	64,1	3,4	62,0	/
South	63,1	3,9	60,7	-5,5	64,2	/
Gender						
Male	58,1	0,5	57,9	-1,5	58,7	/
Female	66,4	0,5	66,1	-1,6	67,2	/
Age group						
≤45	76,6	0,6	76,1	-1,0	76,9	/
46-65	70,8	0,3	70,6	-1,1	71,4	/
66-75	57,9	1,0	57,3	-1,6	58,3	/
>75	47,9	1,5	47,2	-3,2	48,8	/
Treatment status						
New users	81,9	0,7	81,4	-1,7	82,7	/
Old users	30,9	1,8	30,3	-7,1	32,6	/
Exacerbation status						
Without exacerbations	68,9	0,5	68,6	-1,3	69,5	/
With exacerbations	55,7	1,0	55,2	-2,2	56,4	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator
H.DB-4.1	+0,07%	€ 681.810
H.DB-4.2	+0,08%	€ 803.896
H.DB-4.3	-0,02%	€ -196.013
H.DB-4.4	+3,30%	€ 33.640.694
H.DB-4.5	-0,17%	€ -1.752.680

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 plus calcium or vitamin D (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 amounted to 403.537 in 2015 (Table 4.7.1). The prevalence of treatment with osteoporosis medicines amounts to 1,8% of the study sample (1,6% in Northern, 2,1% in Central and Southern Italy). This value increases with age (1,2% in the age group 46-65 years, 4,7% in the age group 66-75 years and 6,8% in the age group >75 years) and is decreased compared to the previous year (-2,4% in 2015 compared to 2014).

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

	2015			2014			2013		
	N	% SS	Var. %	N	% SS	Var. %	N	% SS	Var. %
TOTAL	**403.537**	**1,8**	**-2,4**	**413.591**	**1,9**	**-6,3**	**441.437**	**2,0**	/
Geographic distribution									
North	194.326	1,6	-0,3	194.818	1,6	-8,2	212.260	1,8	/
Center	66.939	2,1	2,7	65.152	2,0	-2,3	66.668	2,1	/
South	142.272	2,1	-7,4	153.621	2,3	-5,5	162.509	2,5	/
Gender									
Male	28.981	0,3	2,7	28.230	0,3	-5,0	29.731	0,3	/
Female	374.556	3,3	-2,8	385.361	3,4	-6,4	411.706	3,7	/
Age group									
≤45	3.082	0,0	-7,7	3.338	0,0	-10,8	3.744	0,0	/
46-65	88.044	1,2	-6,4	94.020	1,3	-8,4	102.682	1,4	/
66-75	131.284	4,7	-5,0	138.121	5,0	-7,1	148.599	5,4	/
>75	181.127	6,8	1,7	178.112	6,7	-4,5	186.412	7,2	/
Mean age	72.6 ± 10.2			72.8 ± 10.2			73.1 ± 10.3		

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 amounted to 85.544 in 2015.
The percentage of subjects who received osteoporosis medicines within one year from a vertebral or hip fracture, or a treatment with corticosteroids, amounted to 20,6%; this value is lower than in the previous year (-7,8% in 2015 compared to 2014). Evaluating the presence of a therapy with medicines for osteoporosis up until December 31, 2015 the percentage are: 21,3 in 2015, 25,3% in 2014 and 29,4% in 2013. There are no significant differences across Italy: 20,6% in Northern Italy, 21,1% in Central Italy, 20,5% in Southern Italy. The prevalence of osteoporotic therapy changes with gender (9,8% in males and 26,1% in females) and with age (the highest percentage amounts to 23.5% 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]

	2015 N=85.544		2014 N=82.291		2013 N=73.272	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**20,6**	**-7,8**	**22,4**	**-10,3**	**24,9**	**/**
Geographic distribution						
North	20,6	-10,4	23,0	-9,1	25,3	/
Center	21,1	-4,1	22,0	-10,0	24,4	/
South	20,5	-3,5	21,2	-12,8	24,3	/
Gender						
Male	9,8	-8,7	10,7	-7,7	11,6	/
Female	26,1	-7,1	28,1	-10,7	31,5	/
Age group						
≤45	9,8	-8,7	10,7	-7,7	11,6	/
46-65	18,4	-7,7	20,0	-8,1	21,8	/
66-75	23,5	-9,8	26,0	-9,2	28,7	/
>75	20,0	-6,4	21,4	-12,0	24,3	/
Follow up until 31December 2015	21,3		25,3		29,4	/

Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 amounted to 297.802 in 2015.
The percentage of patients undergoing a treatment for osteoporosis but without a vertebral or hip fracture, and without corticosteroid therapy amounted to 77,6% in 2015; this value is slightly lower than the previous year (-1,1% in 2015 compared to 2014). Evaluating the up the absence of vertebral or hip fracture and of a corticosteroid therapy starting from January 1, 2009, the percentage amounted to 43,5% in 2015. The percentages across the Country are: 76,1% in Northern Italy; 66,0% in Central Italy; 63,4% in Southern Italy, 76,1% in males vs 77,7% in females, and 73,2% in new users vs 79,2% in old users. The presence is higher in younger patients (100,0% in age group ≤45 years, 81,3% in age group 46-65 years, 74,4% in age group 66-75 years and 77,8% 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]

	2015 N=297.802		2014 N=308.070		2013 N=327.213	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**77,6**	**1,1**	**76,8**	**-2,9**	**79,1**	**/**
Geographic distribution						
North	76,1	2,4	74,4	-4,0	77,5	/
Center	66,0	-4,8	69,3	-3,9	72,2	/
South	83,4	2,3	81,5	-1,6	82,8	/
Gender						
Male	76,1	1,6	74,9	-3,0	77,2	/
Female	77,7	1,0	76,9	-2,9	79,2	/
Age group						
≤45	100,0	0,0	100,0	0,0	100,0	/
46-65	81,3	0,5	80,9	-2,1	82,6	/
66-75	74,4	1,3	73,5	-3,8	76,4	/
>75	77,8	1,2	76,8	-2,6	78,9	/
Treatment status						
New users	73,2	6,5	68,7	-4,7	72,1	/
Old users	79,2	-0,7	79,7	-2,3	81,6	/
From 01-January-2009	43,5		48,1		54,0	/

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 plus calcium or vitamin D (Indicator H-DB 5.3)

The number of patients aged 18 years or older in treatment with medicines for osteoporosis amounted to 403.537 in 2015.
The percentage of subjects in treatment with calcium or vitamin D in combination with osteoporosis medications amounts to 61,2% in 2015; this value is slightly higher than in previous years (+4,6% in 2015 compared to 2014 and +5,6% in 2014 compared to 2013). The percentage is higher in Northern (65,2%) and Central (61,0%) Italy compared to Southern (55,7%) Italy, in females (61,5% vs 57,2% of males), in the 46-75 years age range (55,4% in age group ≤45 years, 62,9% in age group 46-65 years, 63,3% in age group 66-75 years and 58,9% in age group >75 years). There are no significant differences between the percentages found in old and new users (61,1% and 61,4% respectively).

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]

	2015 N=403.537		2014 N=413.591		2013 N=441.437	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**61,2**	**4,6**	**58,5**	**5,6**	**55,4**	**/**
Geographic distribution						
North	65,2	3,4	63,1	4,4	60,4	/
Center	61,0	6,4	57,4	8,1	53,1	/
South	55,7	4,8	53,2	6,8	49,8	/
Gender						
Male	57,2	4,7	54,6	7,2	50,9	/
Female	61,5	4,6	58,8	5,5	55,7	/
Age group						
≤45	55,4	4,2	53,2	7,8	49,3	/
46-65	62,9	4,9	59,9	5,3	56,9	/
66-75	63,3	4,6	60,5	5,6	57,3	/
>75	58,9	4,7	56,3	5,9	53,2	/
Treatment status						
New users	61,4	8,2	56,8	7,7	52,7	/
Old users	61,1	3,3	59,2	4,8	56,4	/

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 402.442 in 2015.
The percentage of adherent subjects amounts to 50,1% in 2015; this value is increased compared to the previous year (+5,5% in 2015 compared to 2014) and is higher in Northern Italy (54,6%) compared to Central (46,1%) and Southern Regions (45,7%). The adherence is higher in females (50,6% compared to 43,3% of males), in older subjects (the highest value amounts to 51,4% in the age-group 66-75 years and 51,4% in the age group over 75 years) and in old users (57,8% compared to 29,2% of new users). Excluding occasional users from the analysis, the percentage of adherent patients in treatment with medicines for osteoporosis amounted to 58,3% in 2015.

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

	2015 N=402.442		2014 N=430.235		2013 N=443.548	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**50,1**	**5,5**	**47,5**	**0,7**	**47,2**	**/**
Geographic distribution						
North	54,6	7,1	51,0	-1,8	51,9	/
Center	46,1	9,4	42,1	-11,2	47,5	/
South	45,7	2,2	44,8	9,3	40,9	/
Gender						
Male	43,3	4,9	41,3	1,8	40,6	/
Female	50,6	5,5	47,9	0,6	47,6	/
Age group						
≤45	30,0	1,3	29,6	1,1	29,3	/
46-65	46,1	4,4	44,2	0,2	44,1	/
66-75	51,4	5,6	48,7	0,5	48,4	/
>75	51,5	5,8	48,7	0,9	48,3	/
Treatment status						
New users	29,2	0,6	29,0	6,6	27,2	/
Old users	57,8	6,3	54,4	0,1	54,4	/
TOTAL without occasional users	58,3	4,8	55,7	-0,2	55,7	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 402.442 in 2015.
The percentage of occasional subjects amounted to 14,1% in 2015; this value appears slightly decreased compared to the previous year (-3,5% in 2015 compared to 2014), and is higher in Central (15,3,0%) and Southern (16,5%) Italy compared to Northern Regions (12,5%) and in males (22,1% vs 13,6% in females). The prevalence of occasional users is higher in younger age-group (32,0% in age group ≤45 years, 16,6% in age group 46-65 years, 13,3% in age group 66-75 years and 13,2% in age group > 75 years) and in new users (33,5% vs 7,0% in 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]

	2015 N=402.442		2014 N=430.235		2013 N=443.548	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**14,1**	**-3,5**	**14,7**	**-4,7**	**15,4**	**/**
Geographic distribution						
North	12,0	-8,6	13,1	0,4	13,1	/
Center	15,3	0,5	15,2	3,5	14,7	/
South e Islands	16,5	-0,1	16,5	-11,5	18,6	/
Gender						
Male	22,1	-6,6	23,6	-5,6	25,0	/
Female	13,6	-3,2	14,0	-4,6	14,7	/
Age group						
≤45	32,0	-6,7	34,3	1,8	33,7	/
46-65	16,6	-2,9	17,1	-2,5	17,6	/
66-75	13,3	-1,6	13,5	-4,1	14,1	/
>75	13,2	-4,8	13,8	-6,7	14,8	/
Treatment status						
New users	33,5	-2,0	34,2	-6,6	36,6	/
Old users	7,0	-2,9	7,2	-7,6	7,8	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator
H.DB-5.1	+0,17%	€ 700.248
H.DB-5.2	-1,09%	€ -4.489.823
H.DB-5.3	+0,09%	€ 370.719
H.DB-5.4	+0,49%	€ 2.018.361
H.DB-5.5	-0,21%	€ -865.012

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 in treatment with antidepressants (Indicator H-DB 6.2)

- Percentage of occasional patients in 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) in order to identify subjects with other psychiatric disorders.

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 amounted to 1.356.650 (Table 4.8.1) in 2015. The prevalence of treatment with antidepressants amounts to 6,1% of the study sample (6,3% in Northern, 6,4% in Central and 5,7% in Southern Italy). This value is higher in females (8,3% vs 3,9% of males) and increases with age (2,7% in age group ≤45 years, 6,4% in age group 46-65 years, 9,6% in age group 66-75 years and 13,7% in the age group >75 years). The prevalence of treatment is higher compared to the previous year (+1,1 % in 2015 compared to 2014).

Table 4.8.1. Distribution of patients in treatment with antidepressants

	2015			2014			2013		
	N	% SS	Var. %	N	% SS	Var. %	N	% SS	Var. %
TOTAL	**1.356.650**	**6,1**	**1,1**	**1.341.542**	**6,1**	**2,5**	**1.308.848**	**6,0**	**/**
Geographic distribution									
North	763.068	6,3	1,8	749.244	6,2	1,3	739.682	6,2	/
Center	210.221	6,4	3,1	203.843	6,3	4,9	194.234	6,1	/
South	383.361	5,7	-1,3	388.455	5,8	3,6	374.932	5,7	/
Gender									
Male	415.911	3,9	1,5	409.813	3,8	3,0	398.063	3,8	/
Female	940.739	8,3	1,0	931.729	8,2	2,3	910.785	8,2	/
Age group									
≤45	248.139	2,7	-5,0	261.277	2,8	-0,8	263.285	2,9	/
46-65	477.685	6,4	0,2	476.685	6,4	2,1	467.016	6,4	/
66-75	267.833	9,6	1,2	264.577	9,5	2,3	258.746	9,4	/
>75	362.993	13,7	7,1	339.003	12,8	6,0	319.801	12,3	/
Mean age	62.3 ± 17.1			61.6 ± 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 8.196 in 2015.
The percentage of patients that at the third change of therapy shift to a SNRI class drug amounts to 19,7%; this value is increased on the previous year (+5,2% in 2015 compared to 2014). This percentage is higher in Northern Regions (22,6%) compared to Central (15,7%) and Southern (17,6%) Italy and in patients already in treatment (old users) (20,6% compared to 18,6% of new users). There are no differences between males and females and no correlation between age and shift to SNRI (17,0% in ≤45 years age group, 20,7% in age group 46-65 years, 21,2% in age group 66-75 years, 19,3% 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]

	2015 N = 8.196		2014 N = 8.379		2013 N = 8.700	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**19,7**	**5,2**	**18,7**	**-4,8**	**19,7**	**/**
Geographic distribution						
North	22,6	7,6	21,0	-6,1	22,4	/
Center	15,7	14,0	13,7	-11,2	15,5	/
South	17,6	-1,1	17,8	1,0	17,6	/
Gender						
Male	19,4	2,9	18,9	-1,5	19,1	/
Female	19,8	6,2	18,7	-6,2	19,9	/
Age group						
≤45	17,0	5,7	16,0	-13,0	18,4	/
46-65	20,7	1,2	20,5	-5,4	21,7	/
66-75	21,2	7,5	19,7	-2,5	20,2	/
>75	19,3	10,2	17,6	2,6	17,1	/
Treatment status						
New users	18,6	6,8	17,4	-7,4	18,8	/
Old users	20,6	4,2	19,8	-2,9	20,3	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 amounts to 1.341.542 in 2015.
The percentage of adherent patients amounts to 39,6%; this value in slightly higher than previous years (+0,7% in 2015 compared to 2014). The adherence is lower in central Regions (37,4%) compared to Northern (39,8%) and to Southern (36,9%) Italy and in females (40,0% vs 38,8% in males). The adherence increases with age (34,2% in the age group ≤45 years, 38,5% in the age group 46-65 years, 42,0% in the age group 66-75 years, 43,3% in the age group > 75 years) and is higher in old users (patients already in treatment) compared to new users (50,6% vs 17,2%, respectively). Excluding occasional subjects, the percentage of patients adherent to the treatment with antidepressants was 51,6% in 2015. Considering as adherent subjects those patients who have a therapeutic coverage ≥50%, the adherence rises to 56,9%. The adherence amounts to 37,4% when patients with other psychiatric disorders 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]

	2015 N = 1.341.542		2014 N = 1.308.848		2013 N = 1.288.282	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**39,6**	**0,7**	**39,3**	**3,1**	**38,2**	**/**
Geographic distribution						
North	41,0	1,2	40,6	2,3	39,7	/
Center	37,4	3,1	36,2	-8,3	39,5	/
South	38,0	-1,3	38,5	11,6	34,5	/
Gender						
Male	38,8	0,9	38,5	3,1	37,3	/
Female	40,0	0,6	39,7	3,0	38,5	/
Age group						
≤45	34,2	-0,2	34,3	2,7	33,4	/
46-65	38,5	0,4	38,4	2,9	37,3	/
66-75	42,0	1,0	41,6	3,0	40,4	/
>75	43,3	0,8	43,0	2,7	41,8	/
Treatment status						
New users	17,2	-1,6	17,5	4,7	16,7	/
Old users	50,6	0,9	50,2	2,2	49,1	/
Cut off 50%*	56,9	0,4	56,6	2,1	55,5	/
Total without occasional patients	51,6	0,6	51,3	1,6	50,5	/
Total without patients with other psychiatric disorders^	37,4	0,5	37,2	3,4	36,0	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 amounted to 1.341.542 in 2015.
The percentage of occasional patients amounts to 23,3%; this value is slightly lower than in the previous years (-0,5% in 2015 compared to 2014). The percentage of occasional subjects is higher in Southern Italy (26,9%) compared to Northern (21,6%) and Central (22,6%) Italy and in males (24,8% vs 22,6% in females). An occasional use is higher in younger age-groups (29,1% in age group ≤45 years, 23,9% in age group 46-65 years, 21,1% in age group 66-75 years and 19,5% in age group >75 years), in new users (51,1% compared to 9,6% of patients already in treatment). Occasional use amounted to 25,2% when patients with other psychiatric disorders are excluded.

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

	2015 N = 1.341.542		2014 N = 1.308.848		2013 N = 1.288.282	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**23,3**	**-0,5**	**23,4**	**-4,5**	**24,5**	**/**
Geographic distribution						
North	21,6	-2,4	22,1	-2,2	22,6	/
Center	22,6	0,7	22,4	-1,1	22,6	/
South	26,9	2,0	26,3	-9,2	29,0	/
Gender						
Male	24,8	-0,5	24,9	-4,4	26,1	/
Female	22,6	-0,5	22,7	-4,5	23,8	/
Age group						
≤45	29,1	1,1	28,8	-2,9	29,6	/
46-65	23,9	0,3	23,9	-4,0	24,9	/
66-75	21,1	-1,8	21,5	-4,3	22,4	/
>75	19,5	-1,1	19,8	-5,8	21,0	/
Treatment status						
New users	51,1	0,9	50,6	-2,6	52,0	/
Old users	9,6	-2,4	9,9	-5,7	10,5	/
TOTAL without patients with other psychiatric disorders^	24,5	-0,4	24,6	-4,4	25,8	/

This indicator has not been calculated in all LHUs as extra-site data management appeared unfeasible.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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 4.8.5.).

Table 4.8.5. Pharmaceutical expenditure elasticity for antidepressants in relation to the improvement of related indicators

Indicator	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator
H.DB-6.1	+0,01%	€ 23.000
H.DB-6.2	+0,98%	€ 3.979.690
H.DB-6.3	-0,17%	€ -698.126

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

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 n. 1 or AIFA Note n. 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 n. 1: esomeprazole (ATC CODE A02BC05), lansoprazole (ATC CODE A02BC03), omeprazole (ATC CODE A02BC01) and pantoprazole (ATC CODE A02BC02)

- Agents reimbursed according to AIFA Note n. 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 n. 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;
- old age: patients over 65 years old.

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

– treatment length 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 amounted to 3.490.114 in 2015 (table 4.9.1). The prevalence of treatment with proton pump inhibitors amounts to 20,7% of the study sample (17,9% in Northern Italy, 23,7% in Central Italy and 25,4% in Southern Italy). This value is higher in females (23,4% compared to 18,7% of males) and increases with age (6,9% in age group ≤45 years, 20,1% in age group 46-65 years, 40,6% in age group 66-75 years, 52,8% in age group >75 years).

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

	2015			2014			2013		
	N	% SS	Var. %	N	% SS	Var. %	N	% SS	Var. %
TOTAL	**3.490.114**	**21,1**	**-3,6**	**3.621.002**	**21,9**	**3,9**	**3.485.503**	**21,5**	**/**
Geographic distribution									
North	1.666.878	17,9	0,3	1.661.256	17,8	0,9	1.646.032	18,0	/
Center	112.247	23,7	13,9	98.537	20,8	20,0	82.096	17,7	/
South	1.710.989	25,4	-8,1	1.861.209	27,6	5,9	1.757.375	26,5	/
Gender									
Male	1.505.265	18,7	-3,0	1.551.621	19,3	4,2	1.489.622	18,9	/
Female	1.984.849	23,4	-4,1	2.069.381	24,4	3,7	1.995.881	23,9	/
Age group									
≤45	479.456	6,9	-17,1	578.402	8,4	1,3	571.024	8,4	/
46-65	1.117.116	20,1	-7,4	1.205.823	21,7	2,7	1.174.377	21,6	/
66-75	846.505	40,6	-0,9	854.124	40,9	4,2	819.364	40,0	/
>75	1.047.037	52,8	6,6	982.653	49,6	6,7	920.738	47,3	/
Mean age	64.9 ± 16.4			63.5 ± 16.7			63.2 ± 16.6		

N: number of patients aged 18 years or older in treatment with proton pomp inhibitors. Indicator calculated only for those LHUs with a properly completed data concerning AIFA notes
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 n. 1 or AIFA Note n. 48) (Indicator H-DB 7.1)

The number of patients aged 18 years or older in treatment with proton pump inhibitors amounted to 3.621.002 in 2015.
The percentage of patients in treatment with proton pomp inhibitors without meeting AIFA reimbursement criteria (AIFA Note n. 1 or AIFA Note n. 48) amounted to 50,4%; this value is increased compared to the previous year (+4,3% in 2015 compared to 2014). The percentage is higher in Northern Italy (52,1%) 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 length < 4 weeks treatment 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]

	2015 N = 3.621.002		2014 N = 3.485.503		2013 N = 3.338.010	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**50,4**	**4,3**	**48,3**	**-6,8**	**51,8**	**/**
Geographic distribution						
North	52,0	-0,7	52,3	4,3	50,2	/
Center	44,8	61,4	27,8	-6,7	29,8	/
South	49,3	8,3	45,5	-16,6	54,5	/
Gender						
Male	50,9	4,4	48,8	-7,2	52,5	/
Female	50,0	4,3	48,0	-6,6	51,3	/
Age group						
≤45	73,1	4,7	69,8	-7,2	75,2	/
46-65	61,1	4,9	58,2	-6,9	62,5	/
66-75	39,3	5,1	37,4	-5,1	39,4	/
>75	33,5	4,8	32,0	-3,8	33,3	/
Treatment status						
New users	72,6	4,8	69,3	-3,7	71,9	/
Old users	38,0	6,0	35,9	-8,7	39,3	/
Duration of treatment < 4 weeks	34,3	7,7	31,8	-8,3	34,7	/
Hospitalization history						
Without a previous hospitalization	51,7	3,6	49,9	-6,8	53,5	/
With a previous hospitalization	42,9	8,6	39,5	-7,8	42,9	/

This indicator has not been calculated in all LHUs, as extra-site data management appeared unfeasible and without a properly completed data concerning AIFA notes.
Since data was available up until December 31, 2015, the last reporting year is 2014 (in order to have one full observation year also for subjects included in December 2014).
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	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator
H.DB-7.1	-0,63%	€ -5.774.166

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 amounted to 23.183 in 2015 (Table 4.10.1). The prevalence of treatment with epoetin alpha amounted to 1,0‰ 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, 2,0‰ in the age group 66-75 years and 4,9‰ in the age group >75 years).

Table 4.10.1. Distribution of patients in treatment with epoetin alpha

	2015			2014			2013		
	N	‰ SS	Var. %	N	‰ SS	Var. %	N	‰ SS	Var. %
TOTAL	**23.183**	**1,0**	**36,1**	**17.038**	**0,8**	**17,4**	**14.510**	**0,7**	**/**
Geographic distribution									
North	11.286	0,9	36,9	8.246	0,7	18,7	6.949	0,6	/
Center	3.680	1,1	42,7	2.579	0,8	23,9	2.081	0,7	/
South	8.217	1,2	32,3	6.213	0,9	13,4	5.480	0,8	/
Gender									
Male	11.594	1,1	36,1	8.521	0,8	19,0	7.161	0,7	/
Female	11.589	1,0	36,1	8.517	0,8	15,9	7.349	0,7	/
Age group									
≤45	780	0,1	3,0	757	0,1	7,8	702	0,1	/
46-65	3.819	0,5	15,3	3.312	0,4	9,7	3.019	0,4	/
66-75	5.548	2,0	32,6	4.183	1,5	16,0	3.605	1,3	/
>75	13.036	4,9	48,4	8.786	3,3	22,3	7.184	2,8	/
Mean age	74.8 ± 12.9			73.2 ± 13.5			72.5 ± 13.6		

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

Results and considerations

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

The number of patients aged 18 years or older who begin a new cycle of treatment with epoetins alpha amounts to 14.802 in 2015.
The percentage of patients starting a new cycle of therapy with epoetin alpha biosimilars amounts to 68,2%; this value is higher than in previous years (+24,8% in 2015 compared to 2014). There is a certain variability across the Country (74,9% in Northern; 68,0% in Central; 60,3% in Southern of Italy), with a percentage slightly higher in males (68,6% vs 67,8% in females). This percentage changes with age of patients (62,1% in age group ≤45 years, 67,5% in age group 46-65 years, 69,8% in age group 66-75 years, 68,8% in age group >75 years). The percentage of patients who begin the first cycle of treatment with alpha epoetin biosimilars amounts to 70,2%, while the percentage of patients who begin a new cycle of theraphy with biosimilar of epoetin alfa and have a history of a previous cycle of therapy amounts to 49,5%.

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 treatment cycle with epoetin alpha [denominator]

	2015 N = 14.802		2014 N = 10.954		2013 N = 9.414	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**68,2**	**24,8**	**54,7**	**54,0**	**35,5**	**/**
Geographical distribution						
North	74,9	25,8	59,5	31,3	45,4	/
Center	68,0	40,6	48,4	66,3	29,1	/
South	60,3	17,9	51,2	98,5	25,8	/
Gender						
Male	68,6	25,7	54,6	52,3	35,8	/
Female	67,8	23,8	54,8	55,7	35,2	/
Age group						
≤45	62,1	45,3	42,8	62,2	26,4	/
46-65	65,7	34,5	48,8	48,0	33,0	/
66-75	69,8	23,5	56,5	48,9	38,0	/
>75	68,8	19,7	57,5	57,4	36,5	/
Presence of new treatment cycles during the previous 12 months						
Without previous therapy cycles	69,2	24,7	55,5	52,4	36,4	/
With previous therapy cycles	48,6	41,5	34,3	50,0	22,9	/
New therapy cycles from 01-January-2009						
Without previous therapy cycles	70,2	23,5	56,9	51,8	37,5	/
With previous therapy cycles	49,5	41,4	35,0	53,4	22,8	/

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	% Overalll expenditure variation per 1% variation of Indicator	Overall expenditure variation per 1% variation of Indicator
H.DB-8.1	-0,38%	€ -573.570

A preferential use of epoetin alpha biosimilars in patients who start 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 who start a treatment with biological medication without a 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 analyzed 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 5.775 in 2015 (Table 4.11.1). The prevalence of subjects with rheumatoid arthritis in treatment with biological medication amounts to 0,4‰ of the study sample. These values increase slightly with the age of patients until 75 years (0,2‰ in the age group ≤ 45 years; 0,5‰ in the age group 46-65, 0,7‰ in the age group 66-75).

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

	2015			2014			2013		
	N	‰ SS*	Var. %	N	‰ SS*	Var. %	N	‰ SS*	Var. %
TOTAL	**5.775**	**0,4**	**16,4**	**4.961**	**0,3**	**1,2**	**4.904**	**0,3**	**/**
Geographic distribution									
North	4.036	0,5	7,2	3.764	0,4	5,4	3.570	0,4	/
Center	659	0,3	8,2	609	0,3	19,6	509	0,2	/
South	1.080	0,2	83,7	588	0,1	-28,7	825	0,2	/
Gender									
Male	1.184	0,2	18,4	1.000	0,1	0,2	998	0,1	/
Female	4.591	0,6	15,9	3.961	0,5	1,4	3.906	0,5	/
Age group									
≤45	1.060	0,2	10,3	961	0,1	-0,4	965	0,1	/
46-65	2.877	0,5	15,8	2.484	0,5	-2,5	2.547	0,5	/
66-75	1.319	0,7	18,8	1.110	0,6	7,2	1.035	0,5	/
>75	519	0,3	27,8	406	0,2	13,7	357	0,2	/
Mean age	57.6 ± 14.2			57.4 ± 14.1			56.9 ± 14.0		

*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 who begin a 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 initiated treatment with biological medications amounted to 1.424 in 2015.
The percentage of patients with rheumatoid arthritis who begun treatment with biological medications without previous use of DMARDS for at least 3 months amounted to 66,9%; this value is higher than the previous year (+4,0% in 2015 compared to 2014). There is a certain variability across Italy (Northern 59,0%; Central 70,4%; Southern 76,9%), with a higher percentage in males (69,4% vs 66,1% of females). This percentage changes slightly with age of patients (65,2% in age group ≤45 years, 67,3% in age group 46-65 years, 64,4% in age group 66-75 years, 69,1% in age group >75 years).

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

	2015 N = 1.424		2014 N = 1.036		2013 N = 1.113	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**66,9**	**4,0**	**64,3**	**3,1**	**62,4**	**/**
Geographical distribution						
North	59,0	-2,5	60,5	8,0	56,1	/
Center	70,4	-8,9	77,2	9,1	70,8	/
South	76,9	3,9	74,1	-3,7	76,9	/
Gender						
Male	69,4	2,9	67,5	3,7	65,1	/
Female	66,1	4,1	63,5	3,1	61,6	/
Age group						
≤45	65,2	0,8	64,7	4,8	61,8	/
46-65	67,3	6,8	63,1	2,2	61,7	/
66-75	66,4	-1,7	67,6	2,6	65,9	/
>75	69,1	8,9	63,5	7,6	59,0	/

This indicator has been calculated only for LHUs with 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 who begin 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 begun treatment with biological medications amounted to 4.961 in 2015.
The percentage of patients with rheumatoid arthritis in treatment with biological medications not in combination with MTX amounts to 55,9%; this value is slightly decreased compared to the previous year -0,4% in 2015 compared to 2014). There is a certain variability across Italy (Northern 54,9%; Central 58,3%; Southern 59,7%), and between males and females (58,3% and 55,2% respectively). This percentage changes with age of patients (64,3% in age group ≤45 years, 55,3% in age group 46-65 years, 51,9% in age group 66-75 years, 50,2% in age group >75 years), and is higher in new than in old users (62,9% vs 54,5% respectively).

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]

	2015 N = 4.961		2014 N = 4.904		2013 N = 4.368	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**55,9**	**-0,4**	**56,1**	**0,9**	**55,5**	**/**
Geographical distribution						
North	54,9	0,1	54,8	1,6	53,9	/
Center	58,3	-4,3	60,9	6,3	57,3	/
South	59,7	2,0	58,5	-6,1	62,4	/
Gender						
Male	58,3	1,2	57,6	-0,5	57,9	/
Female	55,2	-0,8	55,7	1,3	55,0	/
Age group						
≤45	64,3	-1,8	65,5	1,8	64,3	/
46-65	55,3	2,1	54,1	-0,7	54,5	/
66-75	51,9	-2,0	52,9	3,5	51,1	/
>75	50,2	-5,6	53,2	4,7	50,8	/
Treatment status						
New users	62,3	-1,4	63,2	2,2	61,8	/
Old users	54,2	0,4	54,0	3,3	52,3	/

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 that begun traditional systemic medications without a previous use of topic medications (Indicator H-DB 10.1);
- Percentage of patients with psoriasis who begun biological medication without a 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 analyzed 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 16.219 in 2015 (Table 4.12.1). The prevalence of treatment with biological medications amounts to 1,0‰ of the study sample. This prevalence amounts to 0,5‰ in age group ≤45 years, 1,4‰ in age group 46-65 years and 1,7‰ in age group 66-75 years.

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

	2015			2014			2013		
	N	‰ SS*	Var.%	N	‰ SS*	Var.%	N	‰ SS*	Var.%
TOTAL	**16.219**	**1,0**	**2,3**	**15.860**	**1,0**	**3,2**	**15.367**	**1,0**	**/**
Geographic distribution									
North	8.652	1,0	-0,4	8.684	1,0	4,3	8.328	1,0	/
Center	2.101	0,9	-2,7	2.159	0,9	11,9	1.930	0,8	/
South	5.466	1,1	8,9	5.017	1,0	-1,8	5.109	1,1	/
Gender									
Male	10.083	1,3	2,0	9.882	1,3	3,8	9.521	1,3	/
Female	6.136	0,8	2,6	5.978	0,7	2,3	5.846	0,7	/
Age group									
≤45	3.551	0,5	-3,9	3.695	0,6	-1,1	3.735	0,6	/
46-65	7.559	1,4	2,5	7.375	1,4	1,0	7.299	1,4	/
66-75	3.362	1,7	6,5	3.158	1,6	10,7	2.852	1,5	/
>75	1.747	0,9	7,0	1.632	0,9	10,2	1.481	0,8	/
Mean age	57.0±14.8			56.5±15.0			56.0±14.9		

* The prevalence has been calculated on 1000 residents and only for LHUs with 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 begun 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 who begin traditional systemic medications amounts to 831 in 2015.
The percentage of patients with psoriasis who begun traditional systemic medications without a previous use of topic medications amounts to 37,3%; this value is higher than in the previous year (+15,7% in 2015 compared to 2014). There is a certain variability across the Country (34,4% in Northern, 39,8% in Central, 41,1% in Southern Italy), and a higher percentage is observed in females compared to males (41,1% vs 34,9%, respectively). The value changes with age of patients (44,4% in age group ≤45 years, 39,1% in age group 46-65 years, 26,2% in age group 66-75 years, 34,1% in age group >75 years).

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

	2015 N = 831		2014 N = 828		2013 N = 805	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**37,3**	**15,7**	**32,2**	**9,5**	**29,4**	**/**
Geographical distribution						
North	34,4	8,2	31,8	8,3	29,4	/
Center	39,8	-1,4	40,3	9,1	37,0	/
South	41,1	40,0	29,4	7,7	27,3	/
Gender						
Male	34,9	19,5	29,2	7,5	27,2	/
Female	41,1	10,2	37,3	14,3	32,6	/
Age group						
≤45	44,4	42,1	31,3	-6,6	33,5	/
46-65	39,1	15,9	33,7	13,7	29,6	/
66-75	26,2	-16,7	31,5	34,7	23,4	/
>75	34,1	14,2	29,9	2,6	29,1	/

This indicator has been calculated only for LHUs with data on medical exoneration code.
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 who begin 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 who begun biological medications amounts to 1.086 in 2015.
The percentage of patients with psoriasis who begin biological medications without a previous use of methotrexate or cyclosporine for at least 3 months amounts to 77,3%; this value is higher than in the previous year (+11,5% in 2015 compared to 2014). There is a certain variability across Italy (59,1% in northern, 73,3% in central, 82,9% in southern of the Country), and a higher percentage is observed in males compared to females (78,4% vs 75,3%, respectively). The percentage changes with age of patients (78,0% in age group ≤45 years, 76,3% in age group 46-65 years, 78,7% in age group 66-75 years, 79,1% in age group >75 years).

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

	2015 N = 1.086		2014 N = 550		2013 N = 784	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**77,3**	**11,5**	**69,3**	**-3,7**	**71,9**	**/**
Geographical distribution						
North	59,1	-13,7	68,4	14,8	59,6	/
Center	73,3	3,4	70,8	0,9	70,2	/
South	82,9	19,8	69,2	-13,0	79,5	/
Gender						
Male	78,4	13,6	69,1	-5,1	72,8	/
Female	75,3	8,0	69,7	-1,1	70,5	/
Age group						
≤45	78,0	20,1	65,0	-9,5	71,8	/
46-65	76,3	4,7	72,8	1,6	71,7	/
66-75	78,7	16,3	67,6	-4,4	70,8	/
>75	79,1	13,0	70,0	-12,5	80,0	/

This indicator has been calculated only for LHUs with available data on medical 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 who begin biological medications. The diagnosis of psoriasis was derived from the presence of the medical exoneration code 045.696.1.

4.13 Medicines use and treatment adherence profiles in atrial fibrillation

- Percentage of patients with atrial fibrillation in treatment with a New Oral Anticoagulant (NOA) and with a therapeutic INR value during treatment with classic oral anticoagulants and without alteration of thrombotic and bleeding risk (Indicator H-DB 11.1);
- Percentage of patients with atrial fibrillation without an adequate control of INR during treatment with classic oral anticoagulants and with an alteration of the thrombotic and bleeding not treated with NOA (Indicator H-DB 11.2).

Calculation methodology

For the purpose of this analysis, the following new oral anticoagulant have been considered: dabigatran etexilate (ATC CODE B01AE07), rivaroxaban (ATC CODE B01AF01), apixaban (ATC CODE B01AF02) and classic oral anticoagulant: warfarin (ATC CODE B01AA03).

All patients in treatment with anticoagulants for an indication other than atrial fibrillation, identified by the presence of at least one hospitalization for acute pulmonary heart disease (ICD-9 CODE 415), or phlebitis and thrombophlebitis (ICD-9 CODE 451), or other venous embolism and thrombosis (ICD-9 CODE 453), have been excluded from this analysis.

The following parameters have been considered to identify the presence or the absence of a well controlled INR or of an alteration of thrombotic or bleeding risk:

- the time in therapeutic range (TTR). Its calculation is based on the time with INR of 2.0 to 3.0, during the last 12 months. For each patient the algorithm performs the chronological reading of each INR value and then identifies the temporal frames between two measurements characterized by therapeutic INR values. After that the total time with INR in therapeutic range is compared to the whole observation period and multiplied by 100.

- the risk of stroke assessed by the *CHA_2DS_2-VASc* score:
  C – Heart failure identified by the presence of, at least, one hospitalization with diagnosis of heart failure (ICD-9 CODE 428) or of, at least, one prescription for cardiac therapy (ATC CODE C01) (1 point);
  H - Hypertension identified by the presence of at least one prescription of antihypertensive drugs (ATC CODE C03, C07, C08, C09) (1 point);
  A_2 – Age ≥ 75 years (2 points);
  D – Diabetes mellitus identified by the presence of at least one hospitalization with diagnosis of diabetes mellitus (ICD-9 CODE 250) or the presence of at least of two prescriptions for hypoglycemic agents (ATC CODE A10) (1 point);

S_2 - Stroke or transient ischemic attack (TIA) or thromboembolism history (2 points) identified by the presence of at least one hospitalization with diagnosis of: Subarachnoid hemorrhage (ICD-9 CODE 430), Intracerebral hemorrhage (ICD-9 CODE 431), Other and unspecified intracranial hemorrhage (ICD-9 CODE 432), Occlusion and stenosis of precerebral arteries (ICD-9 CODE 433), Occlusion of cerebral arteries (ICD-9 CODE 434), Transient cerebral ischemia (ICD-9 CODE 435), Acute, but ill-defined, cerebrovascular disease (ICD-9 CODE 436), Other and ill-defined cerebrovascular disease (ICD-9 CODE 437), Late effects of cerebrovascular disease (ICD-9 CODE 438) (2 points);
V - Vascular disease identified by the presence of at least one hospitalization with diagnosis of acute myocardial infarction (ICD-9 CODE 410), Old myocardial infarction (ICD-9 CODE 412), Peripheral vascular disease, unspecified (ICD-9 CODE 443.9), Gangrene (ICD-9 CODE 785.4) or by the presence of at least one prescription of peripheral vasodilators (ATC CODE C04);
A – Age 65-74 years (1 point);
Sc – Sex category: female (1 point).

- the bleeding risk assessed by the HAS-BLED score:
  H – Hypertension identified by the presence of at least one prescription of antihypertensive drugs (ATC CODE C03, C07, C08, C09);
  A – Abnormal renal and liver function identified by the presence of a GFR value < 60 ml/min (parameter calculated by the short MDRD equation) (It is takes into account the last available value in the previous 6 months) (1 point);
  S - Stroke or transient ischemic attack (TIA) or thromboembolism history (1 point);
  B – Prior Major Bleeding or Predisposition to Bleeding (anemia) (2 points) identified by the presence of at least one hospitalization for subarachnoid hemorrhage (ICD-9 CODE 430), gastrointestinal hemorrhage (ICD-9 CODE 578), iron deficiency anemia (ICD-9 CODE 280), other deficiency anemia (ICD-9 CODE 281), hereditary hemolytic anemia (ICD-9 CODE 282), acquired hemolytic anemias (ICD-9 CODE 283), aplastic anemia and other bone marrow failure syndromes (ICD-9 CODE 284), other and unspecified anemia (ICD-9 CODE 285) or by the presence of at least one prescription of antihemorrhagics (ATC CODE B02), or by the presence of at least one Hemoglobin value (Hb) < 11,5 mg/dl (1 point);
  L – Labile INRs: time in therapeutic range (TTR) < 60% (1 point);
  E – Elderly: Age > 65 years (1point);
  Drug – Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) or antiplatelet agents identified by the presence of, at least, one prescription of anti-inflammatory and antirheumatic products, non-steroids (ATC CODE M01A) or of Platelet aggregation inhibitors excluding heparin (ATC CODE B01AC);

On the basis of the above described patients have been categorized as:

- "with" a well controlled INR for a TTR ≥ 70%;
- "without" a well controlled INR for a TTR < 70%;
- "with" a higher thrombotic or bleeding risk, respectively in case of CHA_2DS_2-VASc score ≥ 1 or TTR < 70%, and in case of HAS-BLED score > 3
- "without" an alteration of thrombotic or bleeding risk, respectively in case of CHA_2DS_2-VASc < 1 or HAS-BLED ≤ 3 and TTR ≥ 70%.

Cohort of Patients in analysis

The number of patients aged 18 years or older with atrial fibrillation and in treatment with oral anticoagulants amounts to 6.767 in 2015 (Table 4.13.1). The prevalence of the treatment with oral anticoagulants amounts to 2,3% of the study sample. This prevalence amounts to 0,1% in the age group ≤45 years, 0,8% in the age group 46-65 years, 4,5% in the age group 66-75 years and 11,9% in the age group over 75 years).

Table 4.13.1. Distribution of patients with atrial fibrillation in treatment with anticoagulant *

	2015			2014			2013		
	N	% SS	Var. %	N	% SS	Var. %	N	% SS	Var. %
TOTAL	**6.767**	**2,3**	**15,4**	**5.866**	**2,0**	**/**	**/**	**/**	**/**
Gender									
Male	3.547	2,5	15,6	3.068	2,1	/	/	/	/
Female	3.220	2,1	15,1	2.798	1,8	/	/	/	/
Age group									
≤45	86	0,1	-11,3	97	0,1	/	/	/	/
46-65	754	0,8	4,7	720	0,7	/	/	/	/
66-75	1.682	4,5	11,8	1.504	4,0	/	/	/	/
>75	4.245	11,9	19,7	3.545	9,9	/	/	/	/
Mean Age	76.8 ± 10.4			76.1 ± 10.6					

*This indicator has been calculated only for LHUs with a laboratory flow.
N: number of patients with atrial fibrillation aged 18 years or older in treatment with NAO. Patient in treatment with NOA for an indication other than atrial fibrillation, defined by the presence at least one hospitalization with one of the following ICD-9 CODE 415, 451,453, were excluded from the analysis.
SS: study sample

Results and considerations

Percentage of patients with atrial fibrillation in treatment with a New Oral Anticoagulant (NOA) and with a therapeutic INR value during treatment with classic oral anticoagulants and without alteration of the thrombotic and bleeding risk (Indicator H-DB 11.1)

The number of patients aged 18 years or older with atrial fibrillation in treatment with NAO amounts to 1.736 in 2015.
The percentage of patients with atrial fibrillation in treatment with NAO and concomitant treatment with classic oral anticoagulants and without alteration of the thrombotic and bleeding risk amounts to 6,1%, this value is lower than in the previous year (-6,5% in 2015 compared to 2014). A higher percentage is observed in females compared to males (6,8% vs 5,4%). The percentage changes with age of patients (12,5% in age group ≤45 years, 14,9% in age group 46-65 years, 7,2% in age group 66-75 years, 4,2% in age group >75 years).

This data should be interpreted, taking into account the proportion of patients in treatment with NAO due to real difficulties to undergo regular checks of INR. This option is indeed contemplated in the *web-based* prescription form developed and requested by AIFA for the delivery of this type of medicine.

Table 4.13.2. Number of patients with atrial fibrillation in treatment with a New Oral Anticoagulant (NOA) and with a therapeutic INR value during treatment with classic oral anticoagulants and without alteration of the thrombotic and bleeding risk[^] [numerator], Patients with atrial fibrillation in treatment with NAO [denominator].

	2015 N = 1.736		2014 N = 965		2013 -	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**6,1**	**-6,5**	**6,5**	**/**	**/**	**/**
Gender						
Male	5,4	-26,0	7,4	/	/	/
Female	6,8	21,8	5,6	/	/	/
Age group						
≤45	12,5	-43,7	22,2	/	/	/
46-65	14,9	367,1	3,2	/	/	/
66-75	7,2	4,9	6,9	/	/	/
>75	4,2	-37,0	6,6	/	/	/

This indicator has been calculated only for LHUs with a laboratory flow.
N: number of patients with atrial fibrillation aged 18 years or older in treatment with NAO. Patient in treatment with oral anticoagulants for a clinical indication other than atrial fibrillation have been excluded from this analysis. Exclusion criteria applied: at least one hospitalization for acute pulmonary heart disease (ICD-9 CODE 415), or phlebitis and thrombophlebitis (ICD-9 CODE 451), or other venous embolism and thrombosis (ICD-9 CODE 453).
[§] Patients have been categorized as "with" a well controlled INR for TTR ≥ 70%.
[^] Patients have been categorized as "without" an alteration of thrombotic or bleeding risk, respectively in case of CHA2DS2-VASc score < 1 or HAS-BLED score≤ 3 and a TTR ≥ 70%.

Percentage of patients with atrial fibrillation without an adequate control of INR during treatment with classic oral anticoagulants or with an alteration of the thrombotic or bleeding risk not treated with NOA (Indicator H-DB 11.2).

The number of patients aged 18 years or older with atrial fibrillation in treatment with classic oral anticoagulants without an adequate control of INR or with an alteration of the thrombotic or bleeding risk amounts to 3.977 in 2015

The percentage of patients with atrial fibrillation in treatment with classic oral anticoagulants without an adequate control of INR or with an alteration of the thrombotic or bleeding risk not treated with NOA amounts to 59,0%, this value is lower than in the previous year (-18,4% in 2015 compared to 2014). A higher percentage is observed in females compared to males (59,7% vs 58,4%). The percentage changes with age of patients (70,2% in age group ≤45 years, 64,0% in age group 46-65 years, 54,1% in age group 66-75 years, 59,9% in age group >75 years).

Table 4.13.3. Percentage of patients with atrial fibrillation without an adequate control of INR[§] during treatment with classic oral anticoagulants or with an alteration of the thrombotic and bleeding risk[^] not treated with NOA [numerator]/ Total number of patients with atrial fibrillation and without an adequate control of INR during treatment with classic oral anticoagulants or with an alteration of thrombotic or bleeding risk [denominator].

	2015 N = 3.977		2014 N = 3.254		2013 -	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**59,0**	**-18,4**	**72,3**	**/**	**/**	**/**
Gender						
Male	58,4	-17,9	71,1	/	/	/
Female	59,7	-18,8	73,5	/	/	/
Age group						
≤45	70,2	-17,5	85,1	/	/	/
46-65	64,0	-15,7	75,9	/	/	/
66-75	54,1	-20,0	67,7	/	/	/
>75	59,9	-18,2	73,2	/	/	/

This indicator has been calculated only for LHUs with lab data available.
N: number of patients aged 18 years or older with atrial fibrillation without an adequate control of INR or with an alteration of thrombotic or bleeding risk.
Patient in treatment with oral anticoagulants for a clinical indication other than atrial fibrillation have been excluded from this analysis. Exclusion criteria applied: at least one hospitalization for acute pulmonary heart disease (ICD-9 CODE 415), or phlebitis and thrombophlebitis (ICD-9 CODE 451), or other venous embolism and thrombosis (ICD-9 CODE 453).
§ Patients have been classified as "without" an adequate control of INR in case of a TTR value < 70%;
^Patients have been classified as "with" a thrombotic or bleeding risk in presence of CHA2DS2-VASc score ≥ 1 or HAS-BLED score > 3 or a TTR < 70%.

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 4.13.4).

Table 4.13.4. Pharmaceutical expenditure elasticity for atrial fibrillation in relation to the improvement of related indicators

Indicator	% Overalll expenditure variation per 1% variation of Indicator§	Overall expenditure variation per 1% variation of Indicator[§]
H.DB-11.1	-0,01%	€-12.995
H.DB-11.2	+0,02	€ 37.548

[§]Medicines for atrial fibrillation taken into account: new oral anticoagulant (NOA): Dabigatran etexilate (ATC CODE B01AE07), Rivaroxaban (ATC CODE B01AF01), Apixaban (ATC CODE B01AF02) and classic oral anticoagulants: Warfarin (ATC CODE B01AA03).

The reduction of NOAs use for patients with an adequate control of INR during treatment with classic oral anticoagulants and without an alteration of thrombotic or bleeding risk could lead to a reduction of pharmaceutical expenditure for medicines for atrial fibrillation.

These savings could allow, for example, to widen AIFA's criteria to provide NOAs also to patients with an adequate control of INR during treatment with classic oral anticoagulants or with an alteration of thrombotic or bleeding risk.

4.14 Medicines use and treatment adherence profiles in deep vein thrombosis (low molecular weight heparins - LMWHs)

– Percentage of patients in treatment with LMWH or fondaparinux for more than 45 days (cancer patients excluded) (Indicator H-DB 12.1);

Calculation methodology

For the purpose of this analysis, the following low molecular weight heparins (LMWHs) have been considered: dalteparin (ATC CODE B01AB04), enoxaparin (ATC CODE B01AB05), nadroparin (ATC CODE B01AB06), parnaparin (ATC CODE B01AB07), reviparin (ATC CODE B01AB08), bemiparin (ATC CODE B01AB12), fondaparinux (ATC CODE B01AX05).

Patients with at least one of following clinical conditions during the twelve months preceding the first prescription of LMWH of the reference year (index date):

- Venous thromboembolism (ICD-9 CODE 451.1, 451.11, 451.19, 451.2, 451.81, 451.9, 453.4, 453.40, 453.41, 453.42, 453.8, 453.9)
- Major orthopedic surgery: Revision of hip replacement (ICD-9 CODE 0070, 0071, 0072, 0073), revision of knee replacement (ICD-9 CODE 0080, 0081, 0082, 0083, 0084), Repair of vertebral fracture (ICD-9 CODE 0353), spinal fusion (ICD-9 CODE 8100-8109), arthrodesis (ICD-9 CODE 811, 812), Spinal refusion (ICD-9 CODE 8130-8139), Total/partial hip replacement and revision (ICD-9 CODE 8151-8153), total knee replacement and revision (ICD-9 CODE 8154-8155), total/partial hip replacement of lower limbs joints and revision (ICD-9 8156-8159), percutaneous vertebroplasty (ICD-9 CODE 8165), kyphoplasty (ICD-9 CODE 8166), arthroplasty of hand, fingers and wrist bones (ICD-9 817), total/partial replacement of upper limbs fractures (ICD-9 CODE 8180, 8181, 8183), total elbow replacement (ICD-9 CODE 8184), insertion of spinal device (ICD-9 CODE 8161, 8451, 8458, 8459, 8480-8485), insertion/revision/replacement of spinal discle implants (ICD-9 CODE 8460-8469).

Cancer patients with at least one hospitalization for malignant cancer (ICD-9 CODE 140-209) within the 12 months, before the index date, have been excluded from this analysis.

The following clinical conditions have been taken into account on the basis of Summary of Product Characteristics (SPC):

- Patients in treatment with LMWH or fondaparinux (with the exclusion of cancer patients) for more than 45 days;
- Patients in treatment with LMWH or fondaparinux (with the exclusion of cancer patients) after a major orthopedic surgery for more than 35 days;
- Patients with deep vein thrombosis in treatment with LMWH or fondaparinux (with the exclusion of cancer patients) for more than 10 days;
- Patients in treatment with fondaparinux (with the exclusion of cancer patients) for more than 7 days.

Patients in treatment with LMWH have been classified as “without” previous cycles of treatment or “with” previous cycles of treatment on the basis, respectively, of the absence or presence of at least one LMWH prescription within the 12 months before the index date.

The therapeutic coverage has been calculated, in those cases with a prescription of at least two packages, taking into account all the LMWH dosage units prescribed during the 12 months after the index date (reference period).
For each patient, the algorithm screens the chronological reading of the individual prescription, and based on the amount of prescribed medication, identifies the sequence of pharmacological coverage periods.

Cohort of patients in analysis

The number of patients aged 18 years or older in treatment with LMWH during the reporting year, 2015, amounts to 827.754 (Table 4.14.1). The prevalence of treatment with LMWH amounts to 3,7% of the study sample. This prevalence amounts to 1,7% in the age group ≤45 years, 3,0% in the age group 46-65 years, 6,4% in the age group 66-75 years and 10,1% in the age group over 75 years).

Table 4.14.1. Distribution of patients in treatment with LWMH

	2015			2014			2013		
	N	% SS	Var. %	N	% SS	Var. %	N	% SS	Var. %
TOTAL	**827.754**	**3,7**	**-1,1**	**836.745**	**3,8**	**2,3**	**817.940**	**3,8**	**/**
Geographic distribution									
North	382.398	3,2	-1,9	389.783	3,2	-3,1	402.372	3,4	/
Center	149.539	4,6	3,4	144.675	4,4	19,4	121.209	3,8	/
South	295.817	4,4	-2,1	302.287	4,5	2,7	294.359	4,4	/
Gender									
Male	340.501	3,2	-0,6	342.562	3,2	2,7	333.521	3,2	/
Female	487.253	4,3	-1,4	494.183	4,4	2,0	484.419	4,3	/
Age group									
≤45	160.954	1,7	-5,0	169.385	1,8	-0,2	169.683	1,9	/
46-65	220.490	3,0	-3,2	227.846	3,1	1,4	224.619	3,1	/
66-75	177.753	6,4	-3,4	183.939	6,6	1,7	180.778	6,6	/
>75	268.557	10,1	5,1	255.575	9,6	5,2	242.860	9,3	/
Mean age	64.1 ± 18.4			63.4 ± 18.3			63.1 ± 18.3		

N=patients aged 18 years or older in treatment with LMWH (cancer patients excluded).
SS= study sample

Results and considerations

Percentage of patients in treatment with LMWH or fondaparinux for more than 45 days (cancer patients excluded) (Indicator H-DB 12.1)

The number of patients aged 18 years or older in treatment with LMWH or fondaparinux amounts to 836.745 in 2015.
The percentage of patients in treatment with LMWE or fondaparinux for more than 45 years amounts to 33,7%, this value is lower than in the previous year (-3,7% in 2015 compared to 2014). There is some variability in terms distribution across the Country: Nord 35,6%; Center 26,8%; South 34,7%. There are not significant differences between males and females. The percentage changes with ages of patients (24,8% in age group ≤45 years, 29,4% in age group 46-65 years, 36,1% in age group 66-75 years; 41,9% in age group >75 years), and it is higher in those patients with previous therapy cycles (51,3% compared to 30,7% registered for patients without previous treatment cycles). The subgroup analysis shows that: in the group of patients who had a major orthopedic surgery the percentage of those in treatment with LMWH or fondaparinux for more than 35 days amounts to 48,7%; in the group with deep venous thrombosis the percentage of patients in treatment with LMWH or fondaparinux for more than 10 days amounts to dell'84,4%. Then in the group of patients in treatment with fondaparinux the percentage of those in treatment for more than 7 days amounts to 68,7%.

Table 4.14.2. Number of patients in treatment with LMWH or fondaparinux* for more than 45 days [numerator]/Patients in treatment with LMWH or fondaparinux [denominator].

	2015 N = 836.745		2014 N = 817.940		2013 N = 812.971	
	%	Var. %	%	Var. %	%	Var. %
TOTAL	**33,7**	**-3,7**	**35,0**	**3,5**	**33,9**	**/**
Geographic distribution						
North	35,6	5,5	33,7	-0,5	33,9	/
Center	26,8	-2,8	27,5	-3,4	28,5	/
South	34,7	-13,1	39,9	10,5	36,1	/
Gender						
Male	33,6	-3,6	34,9	3,5	33,7	/
Female	33,8	-3,8	35,2	3,5	34,0	/
Age group						
≤45	24,8	-1,1	25,1	6,2	23,6	/
46-65	29,4	-3,6	30,5	2,3	29,8	/
66-75	36,1	-4,9	38,0	2,5	37,1	/
>75	41,9	-5,0	44,1	2,6	43,0	/
Treatment status in the last 12 months						
Without a previous treatment	30,7	-3,1	31,7	3,9	30,5	/
With a previous treatment	51,3	-5,0	54,0	2,6	52,6	/
Treatment with LMWH or fondaparinux for more than 35 days in patients undergoing a major orthopedic surgery	48,7	-0,6	49,0	0,9	48,6	/
Treatment with LMWH or fondaparinux for more than 10 days in patients with deep venous thrombosis	84,4	-0,6	84,9	-1,2	85,9	/
Treatment with fondaparinux for more than 7 days	68,4	0,1	68,4	5,3	64,9	/

N: patients aged 18 years or older in treatment with LMWH (cancer patients excluded).
*LMWH: Dalteparin (ATC CODE B01AB04), Enoxaparin (ATC CODE B01AB05), Nadroparin (ATC CODE B01AB06), Parnaparin (ATC CODE B01AB07), Reviparin (ATC CODE B01AB08), Bemiparin (ATC CODE B01AB12), Fondaparinux (ATC CODE B01AX05).

Economic impact of indicators

The improvement of the indicator described in this section is associated with an improvement of health outcomes 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 indicator. (Table 4.14.3).

Table 4.14.3. Pharmaceutical expenditure elasticity for deep venous thrombosis in relation to the improvement of the related indicator

Indicator	% Overalll expenditure variation per 1% variation of Indicator[§]	Overall expenditure variation per 1% variation of Indicator[§]
Indicator H-DB 12.1	-0,87%	€ -3.068.820

[§]LMWH taken into account: Dalteparin (ATC CODE B01AB04), Enoxaparin (ATC CODE B01AB05), Nadroparin (ATC CODE B01AB06), Parnaparin (ATC CODE B01AB07), Reviparin (ATC CODE B01AB08), Bemiparin (ATC CODE B01AB12), Fondaparinux (ATC CODE B01AX05).

Acronyms

COPD = chronic obstructive pulmonary disease
CV = cardiovascular
DMARDS = Disease Modifying Antirheumatic Drugs
ESC = European society of cardiology
ESH = European society of hypertension
GFR = glomerular filtration rate
HbA1c = glycosylated hemoglobin
HMG-CoA = hydroxymethylglutaryl-CoA reductase
ICS = inhaled corticosteroids
LABA = long-acting beta-adrenoceptor agonist
LAMA = long-acting antimuscarinic agent
LDL = low density lipoprotein
MTX = methotrexate
MDRD = Modification of Diet in Renal Disease
NOA = new oral anticoagulant
SNRI = serotonin and norepinephrine reuptake inhibitor
SPC = Summary of Product Characteristics
SSRI = selective serotonin reuptake inhibitor
TTR = time in therapeutic range

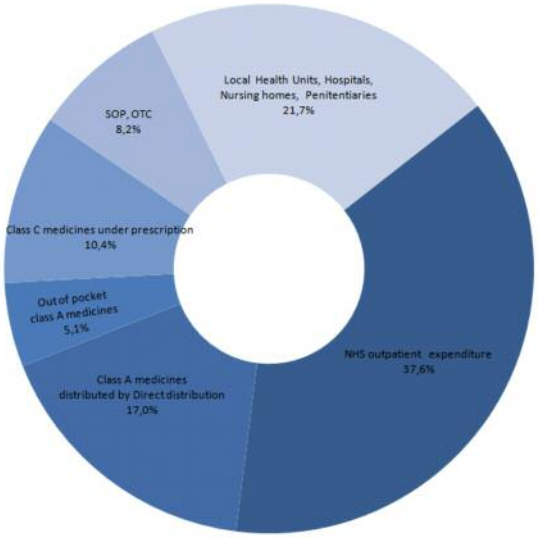
SECTION 5

GENERAL CHARACTERISTICS OF PHARMACEUTICAL USE IN ITALY

Table 5.1.a. Pharmaceutical expenditure breakdown in 2015 compared to 2014 (Table and Figure)

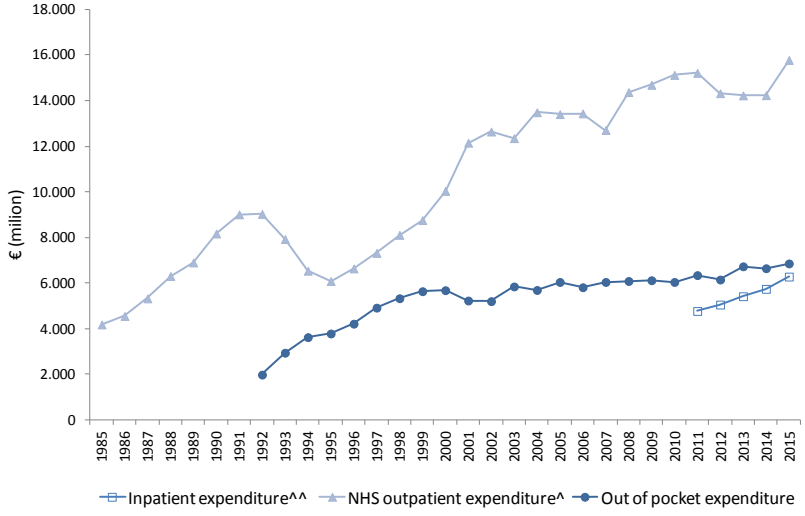
	Expenditure	%	Var % 15-14
Gross NHS outpatient expenditure*	10.863	37,6	-1,1%
Class A medicines dispensed by the Direct distribution	4.921	17,0	51,4%
Out of pocket Class A medicines	1.487	5,1	3,1%
Class C medicines under prescription	2.997	10,4	2,1%
OTC medicines	2.375	8,2	4,7%
Health Public Facilities (Health Local Unit, Public Hospital, Nursing Home; Penitentiary, etc.)*	6.282	21,7	9,4%
Total	**28.926**	**100,0**	**8,6%**

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



Pharmaceutical expenditure represents a significant part of health care expenditure (1,9% of the National Gross Domestic Product (GDP) in 2015). The total National pharmaceutical expenditure (concerning both public and private expenses) amounts up to €28,9 billion, increasing by +8,6% compared to the previous year (Table 5.1.a.). 76,3% is reimbursed by the National Health System. Pharmaceuticals have been supplied mainly through the outpatient channel (community pharmacies, 37,6%). Pharmaceutical expenditure in charge of citizens amounts up to €6.859 million, consisting primarily of Class C (non-reimbursed) medicines requiring a medical prescription (10,4% of total expenditure).

Figure and Table 5.1.b. Outpatient pharmaceutical expenditure for the period 1985 – 2015



	Gross outpatient NHS expenditure (million)	Class A medicines by direct distribution (million)	NHS outpatient expenditure^ (million)	Out of pocket expenditure (million)	Inpatient expenditure^^ (million)
1985	4.182		4.182		
1986	4.553		4.553		
1987	5.324		5.324		
1988	6.306		6.306		
1989	6.900		6.900		
1990	8.171		8.171		
1991	9.011		9.011		
1992	9.030		9.030	1.982	
1993	7.929		7.929	2.942	
1994	6.539		6.539	3.625	
1995	6.087		6.087	3.785	
1996	6.638		6.638	4.216	
1997	7.321		7.321	4.919	
1998	8.113		8.113	5.332	
1999	8.760		8.760	5.640	
2000	10.041		10.041	5.684	
2001	12.154		12.154	5.232	
2002	12.644		12.644	5.204	
2003	12.354		12.354	5.849	
2004	13.491		13.491	5.694	
2005	13.408		13.408	6.046	
2006	13.440		13.440	5.814	
2007	12.712		12.712	6.046	
2008	12.724	1.651	14.375	6.088	
2009	12.928	1.767	14.695	6.122	
2010	12.985	2.144	15.129	6.046	
2011	12.387	2.832	15.219	6.346	4.774
2012	11.488	2.837	14.325	6.152	5.055
2013	11.226	3.003	14.229	6.732	5.421
2014	10.988	3.250	14.238	6.648	6
2015	10.863	4.921	15.784	6.859	6.282

^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 2015 the total pharmaceutical expenditure, including public and private expenses, amounted to €21.778 billion, increasing by +8,9% over the previous year (Table 5.1.2).
The NHS outpatient pharmaceutical expenditure is composed by expenses of medicines reimbursed by the NHS (Table 5.1.1 and Table 5.1.2), including (Class A) medicines provided through the direct distribution. Public pharmaceutical expenditure totalled €13.398 billion (€220,4 per capita), representing 61,5% of total outpatient pharmaceutical expenditure. Compared to 2014, public pharmaceutical expenditure data revealed a significant increase by +13,1%, as a result of the increased expenses of Class A medicines provided through the direct distribution (+ 51,4%), balanced by the decrease in outpatient pharmaceutical expenditure net of discounts and rebates (-1,4%).
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 €8.380 billion, resulting in increase by +2,9% compared to 2014. This growth is primarily due to the increase of expenses for privately purchased Class A medicines +3,1%) and under prescription Class C medicines +2,1%), as well as an increase in citizens' cost-sharing (+1,4%) and OTC medicines' expenditure (+4,7%). Citizens' cost-sharing expenditure (Table 5.1.1 and 5.1.2) amounted to €1.521 million (approximately €25,0 per capita), impacting gross pharmaceutical expenditure by 14,0%. Compared to 2014, the increase of co-payment was mainly determined by the boost in shares exceeding the reference price of off-patent medicines (+5,4%), while a reduction in co-payment expenditure (ticket per prescription/package) was registered (-5,5%).
For what concern the consumption in NHS outpatient sector, a downward trend in the use of medicine reimbursed by the NHS was observed (-0,2%), on the contrary an increase in consumption of class A medicines privately purchased by the citizens (+2,1%) was remarked. During 2015, in average 1.114,9 doses of Class A medicines reimbursed by the NHS per 1.000 inhabitants were consumed every day (in 2014 the doses amounted to 1.096,4), corresponding to over 1 billion packages dispensed (18,6 packs per capita), with an increase of + 1,7% compared to 2014.
Major components (i.e. quantity effect, price effect and mix effect) of variations in the gross NHS outpatient pharmaceutical expenditure observed in 2015, compared to the previous year, highlight a decrease effect on expenditure, as a result of an increased in consumption of prescribed medicines (+1,7% in terms of defined daily doses, DDDs), a decrease in average prices (-1,8%) (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 (negative mix effect: -1,0%) (Figure 5.1.2).

Table 5.1.1. Outpatient pharmaceutical expenditure: a comparison between 2011-2015

		2011 *(million)*	2012 *(million)*	2013 *(million)*	2014 *(million)*	2015 *(million)*	Δ % 12/11	Δ % 13/12	Δ % 14/13	Δ % 15/14
1+2+3+4	Gross pharmaceutical expenditure	12.387	11.488	11.226	10.988	10.863	-7,3	-2,3	-2,1	-1,1
1+2	Citizen co-payment	1.337	1.406	1.436	1.500	1.521	5,2	2,1	4,5	1,4
1	Sharing per prescription	577	573	558	546	516	-0,7	-2,7	-2,0	--5,5
2	Reference price share	760	833	878	954	1.005	9,6	5,5	8,6	5,4
3	Discount^	1.028	1.096	927	889	865	6,6	-15,4	-4,1	-2,7
4	Net NHS expenditure	10.023	8.986	8.863	8.598	8.477	-10,3	-1,4	-3,0	-1,4
5	Class A direct distribution°	2.832	2.837	3.003	3.249	4.921	0,2	5,9	8,2	51,4
4+5	**Outpatient expenditure**	**12.855**	**11.823**	**11.866**	**11.848**	**13.398**	**-8,0**	**0,4**	**-0,2**	**13,1**

^ including discounts per price ranges charged to pharmacies; extra-discounts following AIFA Resolution on June 15, 2012 and Art. 15, paragraph 2 of Law n. 135 on 2012 and charged to Industries, both discounts following AIFA resolution of December 30, 2005, and the pay-back on the NHS expenditure as Art. 11, paragraph 6, Law n. 122 of 2010, temporarily modified by Law n.135 on 2012.

° Direct distribution expenditure of Class A medicines, including 40% inpatient pharmaceutical expenditure (for those Regions missing data) following Law n. 222 on 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 (2011-2015)

		2011	2012	2013	2014	2015	Δ%	Δ%	Δ%	Δ%
		(million)	*(million)*	*(million)*	*(million)*	*(million)*	12/11	13/12	14/13	15/14
1	Net NHS expenditure	10.023	8.986	8.863	8.598	8.4774	-10,3	-1,4	-3,0	-1,4
2	Class A medicines by Direct distribution	2.832	2.837	3.003	3.249	4.921	0,2	5,9	8,2	51,4
1+2	Total public expenditure	12.855	11.823	11.866	11.848	13.398	-8,0	0,4	-0,2	13,1
3	Citizen co-payment	1.337	1.406	1.436	1.500	1.521	5,2	2,1	4,5	1,4
4	Class A medicines paid by citizens*	1.026	1.027	1.468	1.441	1.487	0,1	43,0	-1,9	3,1
5	Class C medicine under prescription	3.207	3.000	2.985	2.937	2.997	-6,5	-0,5	-1,6	2,1
6	OTC medicines	2.113	2.125	2.278	2.283	2.375	0,6	7,2	0,2	4,7
3+4+5+6	Total private expenditure	7.683	7.558	8.168	8.161	8.380	-1,6	8,1	-0,1	2,9
	Total pharmaceutical expenditure	20.538	19.381	20.035	20.009	21.778	-5,6	3,4	-0,1	8,9
	Share (%) borne by the NHS	**62,6**	**61,0**	**59,2**	**59,3**	**61,5**				

***** 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 IMS Health data and OsMed data.

Figure 5.1.1. Outpatient pharmaceutical consumption: a comparison between 2011-2015

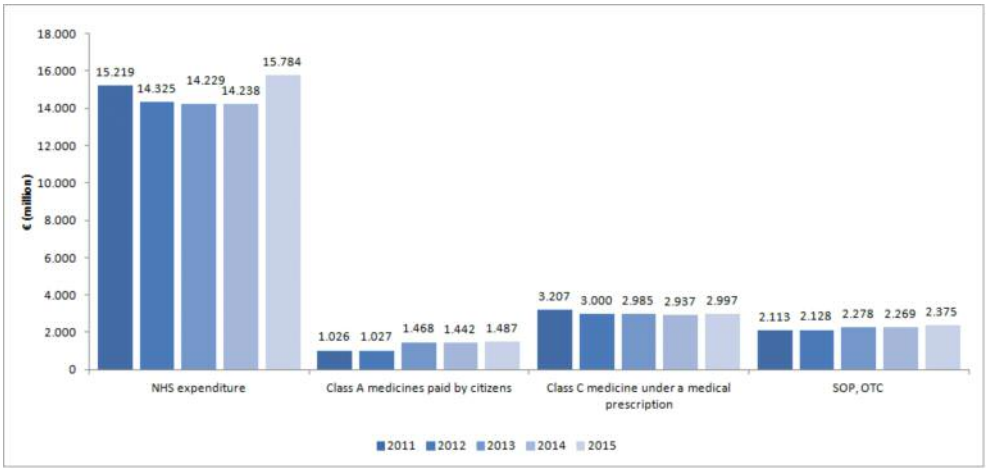


Table 5.1.3. Public and private outpatient pharmaceutical consumption: a comparison between 2011-2015

		2011 (milioni)	2012 (milioni)	2013 (milioni)	2014 (milioni)	2015 (milioni)	Δ% 12/11	Δ% 13/12	Δ% 14/13	Δ% 15/14
	Prescriptions #	590	593	608	609	596	0,5	2,5	0,2	-2,2
	N. Packages									
1	NHS consumption	1.089	1.095	1.119	1.136	1.133	0,6	2,2	1,5	-0,2
2	Class A medicines paid by citizen*	146	170	213	221	225	16,4	25,5	3,4	2,1
3	Class A medicines by direct	ND	ND	ND	ND	ND				
1+2+3	Total class A medicines	1.235	1.265	1.332	1.356	1.358	2,4	5,3	1,8	0,2
4	Class C medicines under prescription	284	267	254	250	248	-6,0	-4,9	-1,6	-0,8
5	OTC	300	280	287	277	280	-6,7	2,6	-3,4	0,8
4+5	Total class C medicines	584	547	541	527	528	-6,3	-1,1	-2,5	0,1
1+2+3+4+5	Total packages	1.819	1.812	1.873	1.884	1.886	-0,4	3,4	0,5	0,1
	DDD/1.000 inhab. die#	963,0	1.006,6	1.032,3	1.096,4	1.114,9	4,5	2,6	6,2	1,7

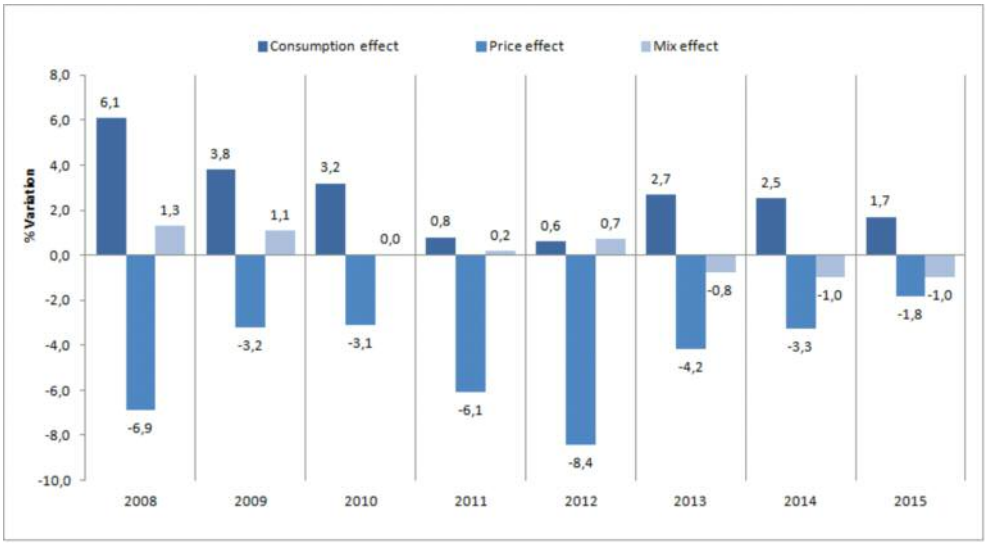
#concerning (class A) NHS reimbursed medicines

***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 2008-2015



5.2 Medicines purchased by public health facilities

During 2015 expenditure for medicines purchased by public health facilities (hospitals, health local units, etc) amounted to approximately €11,2 billion (€184,3 per capita; Table 5.2.1). This share of expenditure represents 38,7% of the total public and private expenditure on pharmaceuticals (Table 5.1; i.e. €4.921 + €6.282 billion) and determined an increase by +24,5% compared to 2014. In terms of pharmaceutical consumption (DDDs), an increase by +2,2% was registered, with an average of 154,1 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 an 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 is valid even when the DDD is used to parameterise outpatient medicines' consumption (e.g. in the paediatric population, etc.), it's even more realistic in the 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 fed by the Regions. Expenditure regarding the 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 2015 the direct distribution expenditure amounted up to €7.786 billion, concerning mainly Class A reimbursed medicines (€4.921 million), and a residual share of Class C (not reimbursed by the NHS) and Class H (hospital use only) medicines (€2.866 million).

Inpatient pharmaceutical expenditure amounted to €2.996 billion and was composed of 70% Class H medicines. Particularly during 2015 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).
Notably 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, are 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 national level, years 2014-2015

	Per capita NHS expenditure		DDD/1.000 inhab. Die	
	€	Δ% 15/14	€	Δ% 15/14
ITALY	184,3	24,5	154,1	2,2

Figure 5.2.1. Direct distribution pharmaceutical expenditure by reimbursement class, years 2011 – 2015

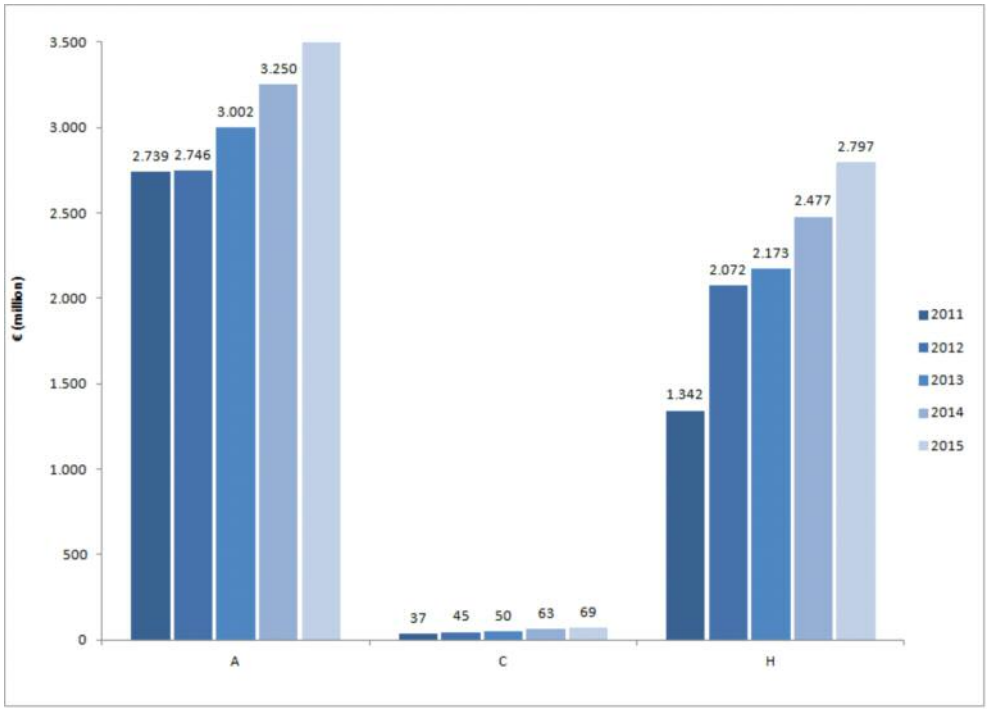
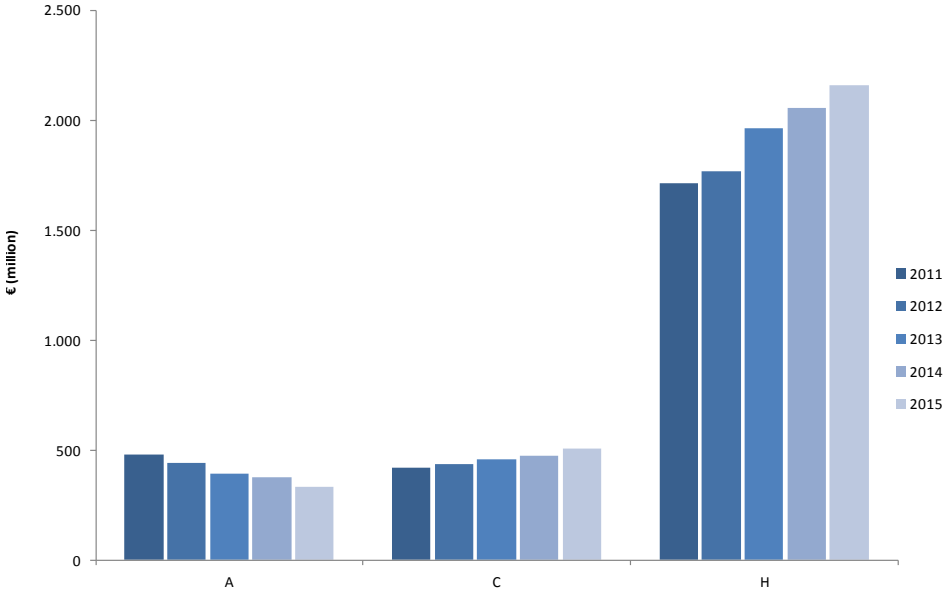


Figure 5.2.2. Inpatient pharmaceutical expenditure by reimbursement class , years 2011 – 2015



5.3 Pharmaceutical consumption by age and gender

The 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. According to these analyses, data were examined on individual NHS patients and collected by 406 Health Local Units (HLUs) and 8 regions which are distributed across the Country. The number of patients referring to HLUs has been estimated to approximately 38,7 million patients, with an average age and a male/female ratio corresponding to national average data. Data have been readjusted according to the overall national consumption.

Overall, the average pharmaceutical expenditure and consumption is highly dependent on age groups. Age and gender items appear 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 10% (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 63,4% (58,9% in males and 67,5% 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 years old patient consumes an average of 2,8 DDDs per day, while an over 74 years old patient consumes an average of 4,1 DDDs per day (see Table 5.3.1 and figure 5.3.2).

Table 5.3.1 Outpatient pharmaceutical expenditure and consumption by age, year 2015

Age range	Gross expenditure (per capita)				DDD/1000 inhab die			
	Male	Female	Total	% share on total expenditure	Male	Female	Total	% share on total consumption
0 - 4	24,3	21,1	22,7	0,6	93,1	82,2	87,8	0,4
5 - 14	27,0	22,8	25,0	1,3	70,7	60,6	65,9	0,6
15 - 24	31,2	30,8	30,9	1,7	91,1	126,3	108,4	0,9
25 - 34	39,8	50,1	44,9	2,8	122,8	223,4	172,9	1,8
35 - 44	60,5	74,9	67,6	5,8	244,2	339,0	291,2	4,0
45 - 54	120,0	125,1	122,5	10,7	633,7	707,9	670,9	9,4
55 - 64	254,3	234,3	244,0	17,1	1.506,7	1.473,8	1.489,9	16,7
65 - 74	455,9	402,3	427,6	25,7	2.879,6	2.684,1	2.776,1	26,7
>= 75	638,5	516,3	563,1	34,3	4.364,5	3.867,4	4.058,3	39,6
	174,7	**182,5**	**178,7**	**100,0**	**1.039,6**	**1.188,2**	**1.115,9**	**100,0**

Figure 5.3.1. Prevalence of use by age and gender in the outpatient setting, year 2015

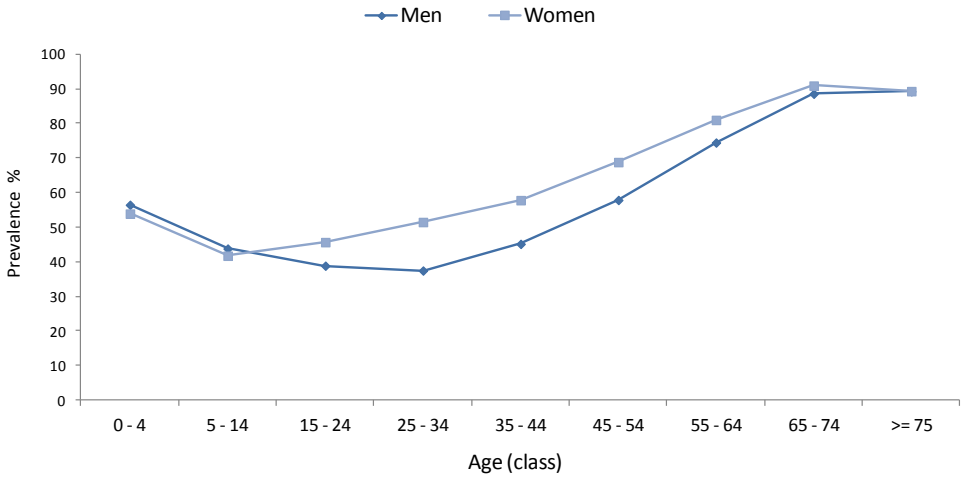
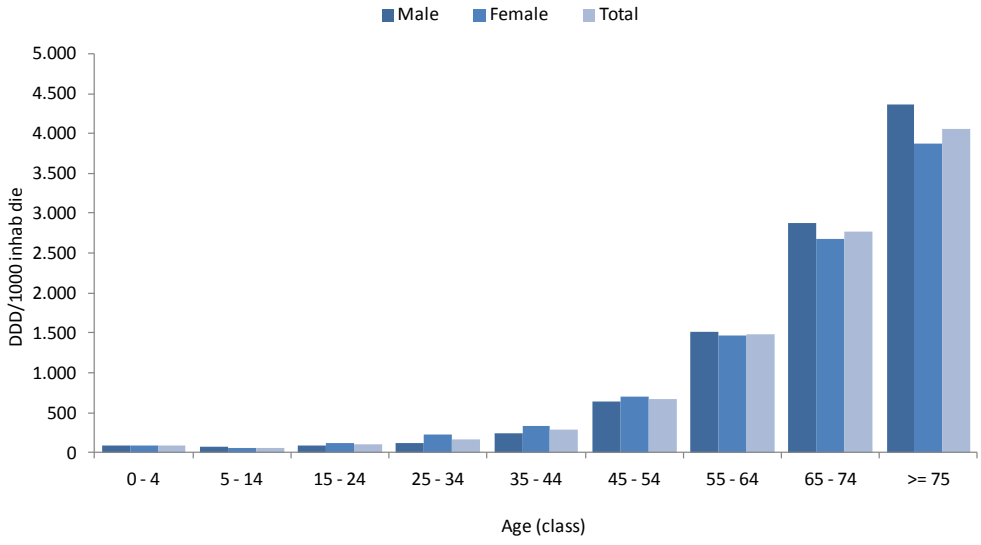


Figure 5.3.2. Outpatient consumption (DDD/1000 inhab. die) by age and gender, year 2015



5.4 Pharmaceutical consumption on a monthly basis

Figure 5.4.1 shows (Class A) reimbursed medicines consumption trend (consumption is expressed as days of therapy) according to the period 2004-2015. Throughout the last

eleven years, pharmaceutical consumption registered a persistent upward trend and increased from 763,8 DDD/1000 inhabitants per day in 2004 up to 1.114,9 DDD/1000 inhabitants per day in 2015, thus, resulting in a +46% increase. Pharmaceutical consumption, in addition to the rising trend is connected with seasonal variations, and this is proved by the peaks in consumption of pharmaceuticals detectable on a monthly basis (see Figure 5.4.1). As a result of this periodicity, consumption levels registered in the first half of 2015 were higher than the annual average of +3,1%, as opposed to the second half of the year, where the consumption was below -3,0%. In more details, during August the use of pharmaceutical doses was 18,6% lower than the average consumption. Generally, systemic antimicrobial medicines and respiratory medicines are the therapeutic categories on which seasonality of consumption impacts mostly.

Figure 5.4.2 shows (Class C) non-reimbursed medicines consumption trend since 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 up to 193,0 DDD/1000 inhabitants per day in 2015. The highest average consumption was recorded in September (214,8 DDD/1000 inhabitants per day) and February (213,7 DDD/1000 inhabitants per day), whilst the lowest levels of consumption were observed in August (151,1 DDD/1000 inhabitants per day). Transition months (autumn) registered high levels in consumption, mainly due to the use of vaccines' doses. Moreover, peaks corresponding to the first three months of the year are attributed to higher consumption of doses due to respiratory system medicines, whose consumption appears doubled when compared to summer months.

Figure 5.4.3 shows medicines purchased by public health facilities consumption trend in the period 2006-2015. In details, an overall growing trend in consumption was registered, following an increase from 100,6 DDD/1000 inhabitants per day during 2006 up to 154,1 DDD/1000 inhabitants per day in 2015. During 2015, the lowest level in consumption was observed in August (-44,6%) and December (-21,8%), while October (+27,6%) and July (+23,8%) registered the highest levels in consumption.

For a correct interpretation of monthly consumption trends (consumption expressed as DDD/1000 inhabitants per day) regarding medicines purchased by public health facilities compared to annual consumption trends, it should be noted that, these trends are influenced by purchasing procedures carried out by public health facilities themselves, and thus trends cannot be strictly interpreted in terms of monthly patient consumption. Moreover, strong irregularities in monthly purchasing patterns by public health facilities during the last six years are registered.

Figure 5.4.1. Consumption trend of Class A medicines reimbursed by the NHS (DDD/1000 inhabitants die), years 2004-2015

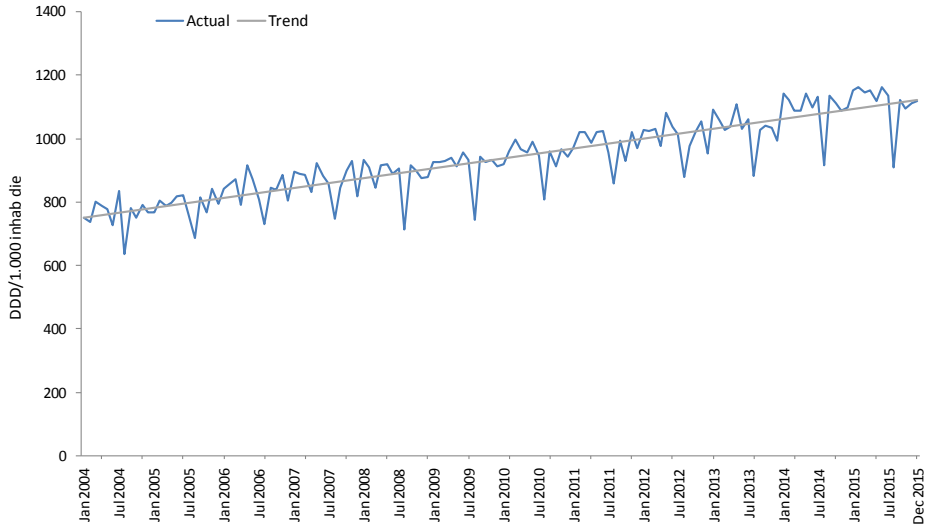


Figure 5.4.2. Consumption trend of Class C medicines under prescription (DDD/1000 inhab die), years 2004-2015

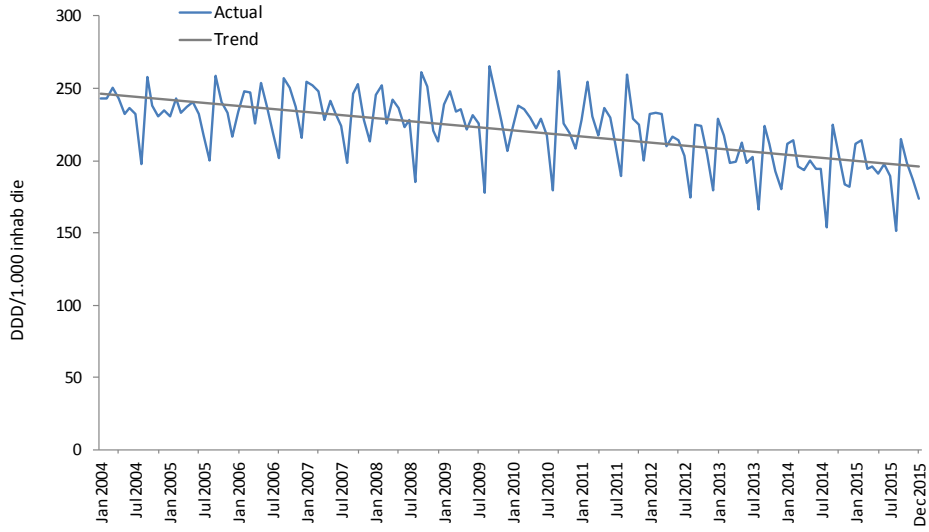
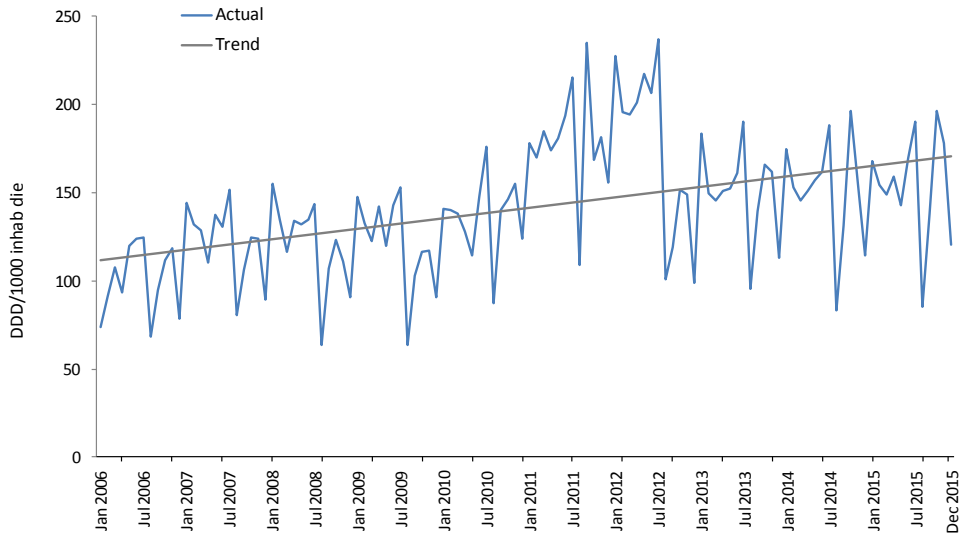


Figure 5.4.3. Consumption trend of medicines purchased by public health facilities (DDD/1000 inhabitants die), years 2006-2015



5.5 Trend of pharmaceutical prices

Data shown in Figure 5.5.1 represent the average price, weighted per package and weighted per DDD, concerning Class A medicine reimbursed by the NHS in the period between January 2004 and December 2015. The time series reveal a decreasing trend for both prices, primarily at the beginning of 2004-2005 and 2011-2012 periods. This decline was mostly driven by price reduction manoeuvres implemented at National level at the beginning of 2004 and by the economic effect resulting from Resolution on April 8, 2011. These procedures resulted in a drop of the reference prices of medicines included in the Transparency List (*liste di Trasparenza)* on the basis of a comparison carried out between the prices of generic medicines in Italy and the same pharmaceutical packages marketed in Germany, UK, France and Spain.

Figure 5.5.2 shows the average price trend, weighted per package and per DDD, of Class C medicines requiring a medical prescription (not-reimbursed by the NHS), regarding the period between 2004 and 2015. 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) during 2004 up to €12,1 per package (€0,7 per DDD) during 2015, resulting in an increase +19,0% (and +15,2% price per DDD) over a ten year period.

Figure 5.5.3 shows the average price performance, weighted per package and per DDD, of medicines purchased by public health facilities for the period between 2004 and 2015. Averages prices increase from 2006 to 2010, they appear stable in the period between 2011 and 2012, and finally register a further increase in 2013-2015. As mentioned above,

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

Figure 5.5.1. Average price trend of Class A medicines reimbursed by the NHS, years 2004-2015

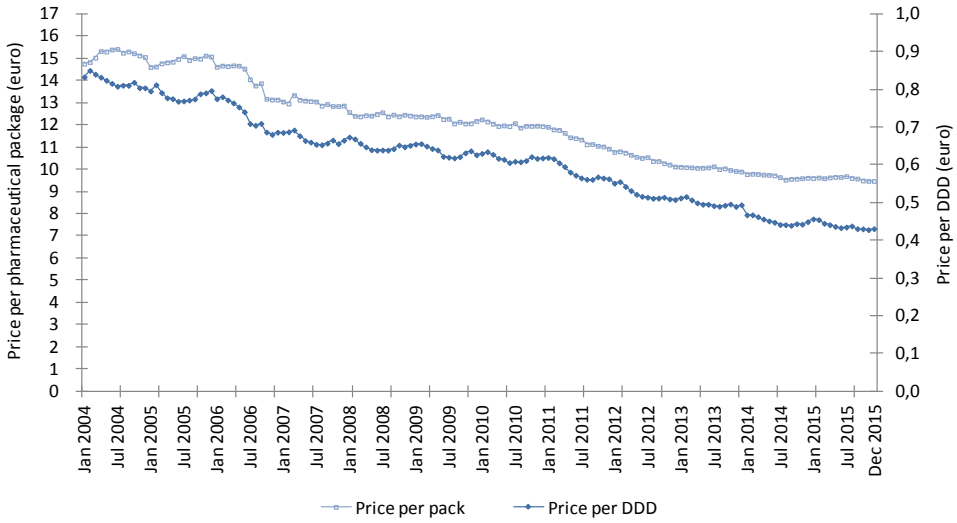


Figure 5.5.2. Average price trend of Class C medicines requiring a medical prescription, 2004-2015

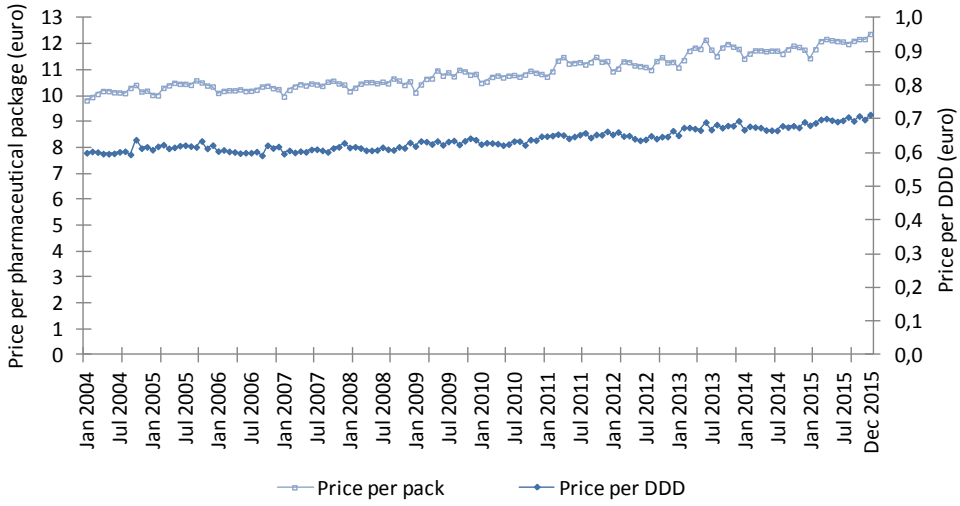
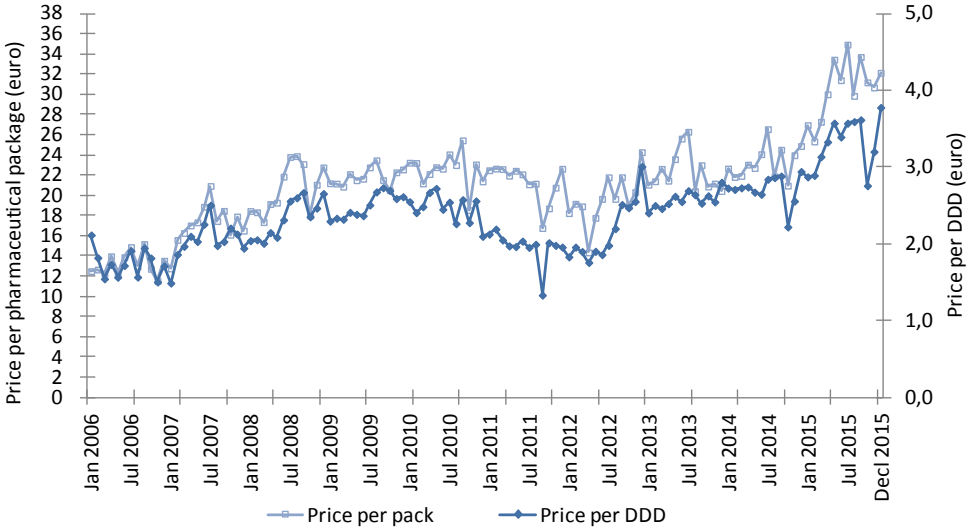


Figure 5.5.3. Average price trend of medicines purchased by health public facilities, 2006-2015



SECTION 6

CONSUMPTION AND EXPENDITURE BY THERAPEUTIC CLASS AND EPIDEMIOLOGICAL DATA

In this section all therapeutic categories will be analysed. Tables below show data concerning private and public pharmaceutical expenditure in decreasing order (categories totalling less than €500 million are excluded). Public pharmaceutical expenditure is the sum of NHS outpatient pharmaceutical expenditure plus inpatient pharmaceutical expenditure.

Table 6.1 shows the composition of public and private pharmaceutical expenditure by classes of reimbursement. Total pharmaceutical expenditure amounted to €28,9 billion, 76,3% of which is reimbursed by the NHS and it is equal to €10,8 billion (including about €1 billion concerning discounts and rebates regarding the distribution chain) plus €11,2 billion on inpatient pharmaceutical expenditure. The residual 23,7% represents the out of pocket expenditure, corresponding to €5,4 billion, plus €1,5 billion related to Class A medicines privately purchased by the citizens.

Table 6.2 shows the consumption of medicines distributed by class of reimbursement. Medicines are distinguished by those provided by the NHS and those privately purchased by the citizens. The total amount of pharmaceutical consumption in Italy is 1.791,9 DDDs per 1.000 inhabitants per day. Thereof 70,8% delivered by the NHS, whilst a remaining 29,2% is related to doses of medicines purchased directly by the citizens.

Table 6.1. Pharmaceutical expenditure by ATC I level and class of reimbursement in 2015

Therapeutic class	Class A medicines reimbursed by the NHS exp^		Class A medicines privately purchased by the citizens		Class C under a medical prescription		Self-medication SOP and OTC medicines		Medicines purchased by Public Health Facilities		Total
	€°	%*	€°	%*	€°	%*	€°	%*	€°	%*	€°
J- Antiinfectives for systemic use	862	19,6	167	3,8	82	1,9	-	-	3.292	74,8	4.402
L- Antineoplastic and immunomodulating agents	253	6,0	27	0,6	11	0,3	-	-	3.923	93,1	4.213
C- Cardiovascular system	3.384	83,0	264	6,5	46	1,1	148	3,6	237	5,8	4.079
A- Alimentary tract and metab	2.004	52,0	287	7,4	245	6,4	657	17,0	664	17,2	3.856
N- Nervous system	1.375	41,5	173	5,2	987	29,8	269	8,1	508	15,3	3.313
B- Blood and blood forming organs	527	24,9	105	4,9	92	4,3	5	0,2	1.393	65,6	2.122
R- Respiratory system	1.045	56,8	142	7,7	173	9,4	399	21,7	79	4,3	1.838
G- Genito urinary system, sex hormones	427	32,6	39	3,0	641	48,9	82	6,3	121	9,2	1.311
M- Musculo-skeletal system	423	33,6	170	13,5	188	15,0	413	32,9	63	5,0	1.257
D- Dermatologicals	57	8,4	27	4,0	267	39,0	312	45,6	21	3,1	684
S- Sensory organs	228	34,8	20	3,1	196	29,9	87	13,3	124	18,9	656
V-Various	65	11,2	5	0,9	36	6,3	0	0,0	473	81,6	580
H- Systemic hormonal prep., excl. sex hormones and insulins	177	31,1	57	10,0	31	5,4	-	-	304	53,5	569
P- Antiparasitic products, insecticides and repellents	12	57,4	4	16,8	2	10,2	2	8,4	2	7,1	22
Total	**10.840**	**37,5**	**1.487**	**5,1**	**2.997**	**10,4**	**2.375**	**8,2**	**11.203**	**38,8**	**28.902**

^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) (€23 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 (DDDs/1000 inhabitants die) by ATC I° level and class of reimbursement in 2015 (expenditure data sorted by a decreasing order referred to table 6.1)

Therapeutic class	Class A medicines reimbursed by the NHS exp^		Class A medicines privately purchased by the citizens		Class C under a medical prescription		Self-medication SOP and OTC medicines		Medicines purchased by Public Health Facilities		Total
	n. packs	%*	n. packs	%*	n. packs	%*	n. packs	%*	n. packs	%*	n. packs
J- Antiinfectives for systemic use	22,1	58,4	6,0	15,9	2,4	6,4	-	-	7,3	19,4	37,8
L- ntineoplastic and immunomodulatating agents	4,8	35,2	0,4	3,2	0,1	0,5	-	-	8,4	61,1	13,8
C- ardiovascular system	465,6	87,1	41,5	7,8	1,5	0,3	9,0	1,7	16,7	3,1	534,3
A- Alimentary tract and metabolism	232,3	66,0	35,4	10,1	8,9	2,5	41,5	11,8	33,8	9,6	351,9
N- Nervous system	61,6	37,1	8,9	5,4	64,8	39,0	6,5	3,9	24,1	14,5	165,9
B- Blood and blood forming organs	144,0	53,5	49,4	18,3	36,1	13,4	0,2	0,1	39,4	14,6	269,2
R- Respiratory system	46,4	49,4	11,0	11,7	13,8	14,7	20,1	21,4	2,7	2,8	93,9
G- Genito urinary system and sex hormones	42,6	51,8	5,7	7,0	29,3	35,5	2,8	3,5	1,9	2,3	82,4
M- Musculo-skeletal system	39,6	45,6	21,6	24,9	4,3	4,9	17,8	20,5	3,6	4,1	86,7
D-Dermatologicals	2,3	4,7	2,6	5,3	17,1	35,0	20,0	41,1	6,7	13,8	48,7
S- Sensory organs	18,7	37,2	2,3	4,6	12,7	25,3	14,7	29,2	1,8	3,6	50,2
V-Various	0,1	3,3	0,2	4,6	1,1	32,8	-	0,2	2,0	59,1	3,4
H- Systemic hormonal preparations, excl.sex hormones and insulins	34,0	64,5	12,1	22,9	0,9	1,7	-	-	5,7	10,9	52,7
P- Antiparasitic products, insecticides and repellents	0,8	75,8	0,2	16,0	-	4,2	-	1,2	-	2,8	1,1
Total	**1.114,9**	**62,2**	**197,2**	**11,0**	**193,0**	**10,8**	**132,7**	**7,4**	**154,1**	**8,6**	**1.791,9**

*calculated on the therapeutic category. Source: OsMed flow, Traceability flow and IMS Health data analysed by OsMed

Figure 6.1. Per capita total pharmaceutical expenditure sorted by ATC I° level in 2015

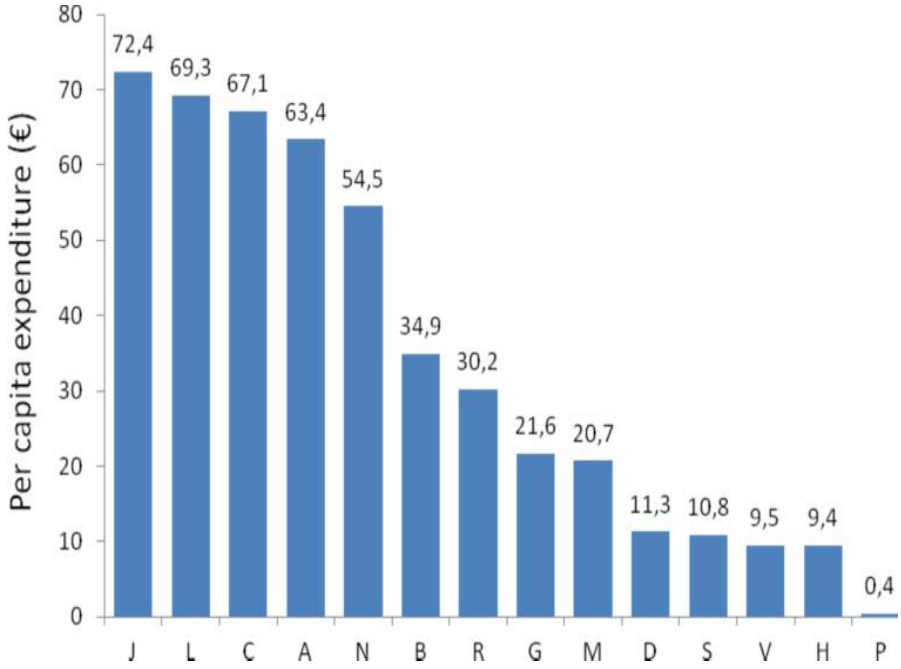


Table 6.3. European comparison on outpatient* expenditure sorted by ATC I level in 2015

ATC I° level	Italy	Austria	Belgium	Finland	France	Germany	Greece	Ireland	Portugal	Spain	Uk
C - Cardiovascular system	22,3	14,9	15,4	11,3	12,9	8,5	27,7	9,5	24,2	16,9	10,1
A -Alimentary tract and metabolism	18,6	13,7	13,2	19,8	13,3	13,0	17,9	19,2	20,0	17,7	18,1
N -Nervous system	14,4	13,7	16,2	15,5	14,0	12,1	14,8	19,1	15,8	19,6	24,6
R -Respiratory system	12,4	10,6	13,4	11,7	10,5	9,9	10,5	12,2	10,8	15,2	17,9
G -Genito urinary system, sex hormones	7,0	3,6	5,3	6,6	4,0	3,9	3,1	4,6	6,4	7,8	5,5
J -Antiinfectives for systemic use	6,5	15,0	10,8	3,7	11,8	13,4	6,8	3,5	5,8	3,2	3,2
M -Musculo-skeletal system	5,1	4,4	4,0	4,0	3,2	3,6	4,2	3,4	5,8	4,4	2,1
D –Dermatologicals	4,2	3,3	2,9	2,7	2,9	3,1	2,5	3,3	2,9	3,1	6,0
S -Sensory organs	3,6	0,9	1,3	2,3	4,3	2,8	2,0	1,9	2,2	2,9	2,7
B -Blood and blood forming organs	3,1	6,3	5,8	6,8	8,0	10,0	6,5	3,4	4,4	4,3	3,4
H -Systemic hormonal preparations, etc	1,2	1,5	1,9	1,7	2,2	1,7	1,6	1,7	0,7	1,6	3,5
L -Antineoplastic, immunomodulating agent	1,1	10,7	9,3	13,8	12,0	15,2	1,8	15,6	0,4	2,8	2,3
V –Various	0,4	1,0	0,3	0,1	0,6	2,7	0,4	2,1	0,2	0,4	0,2
P Antiparasitic products	0,1	0,1	0,2	0,2	0,3	0,2	0,1	0,3	0,3	0,1	0,3

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

Table 6.4. European comparison of top ten active ingredients in Italy: ranked by outpatient* expenditure in 2015

Active ingredient	Italy	Austria	Belgium	Finland	France	Germany	Greece	Ireland	Portugal	Spain	Uk
N – Paracetamol	1	34	2	10	1	61	10	3	7	2	5
C - Olmesartan medoxomil	2	17	19	261	33	62	7	35	6	3	229
A – Pantoprazole	3	9	8	32	73	18	30	108	59	34	433
R – Fluticasone	4	13	15	3	6	36	15	5	9	4	1
C – Rosuvastatin	5	35	3	50	8	610	16	23	5	24	37
C – Simvastatin	6	11	12	16	18	31	5	54	8	36	45
R – Salmeterol	7	18	21	12	10	45	19	6	10	7	2
A – Colecalciferol	8	45	16	36	41	82	61	19	30	31	21
J – Amoxicillin	9	64	24	67	29	157	26	44	22	25	82
C – Ezetimibe	10	48	18	70	9	43	9	22	16	18	39

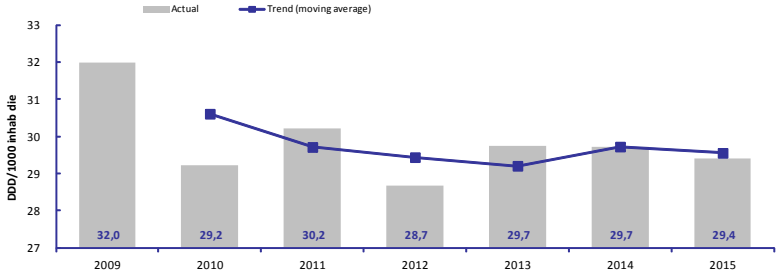
*The expenditure value covers Class A medicines (public + private) plus Class C medicines under prescription and self-medication medicines (SOP and OTC). Data concerning a number of compounds also includes fixed combinations
Source: AIFA analysis on IMS/MIDAS data

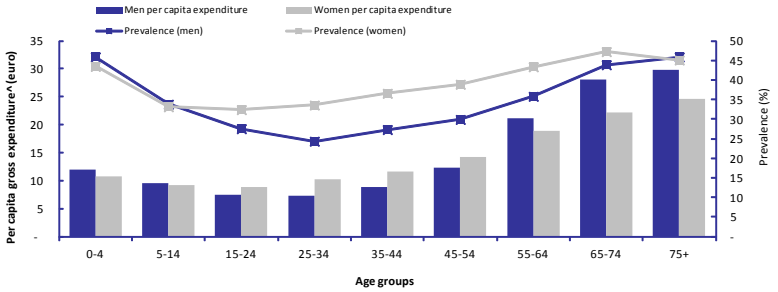
6.1 Anti-infectives for systemic use

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**4.154,0**	**(18,8)**
Δ % 2015/2014		68,8
Per capita gross expenditure, range among	44,2	88,7
DDD/1000 inhab die (% on the total)	**29,4**	**(2,3)**
Δ % 2015/2014		-1,0
DDD/1000 inhab die, range among regions:	21,7	38,6

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	11,9	10,7	11,3	18,9	16,7	17,9
5-14	9,5	9,1	9,3	16,1	15,3	15,8
15-24	7,5	8,8	8,1	13,5	15,0	14,3
25-34	7,3	10,2	8,7	11,8	16,2	14,0
35-44	8,8	11,7	10,2	13,7	18,6	16,2
45-54	12,2	14,2	13,2	16,4	21,1	18,8
55-64	21,1	18,8	20,0	21,6	24,9	23,3
65-74	28,0	22,2	25,0	29,3	28,3	28,8
75+	29,9	24,7	26,7	35,6	29,6	31,9

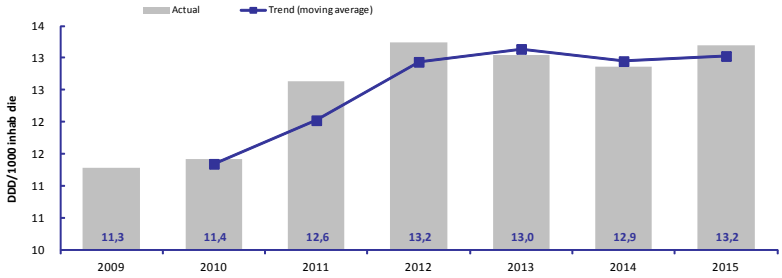
^with the exclusion of medicinal products administered in hospitals

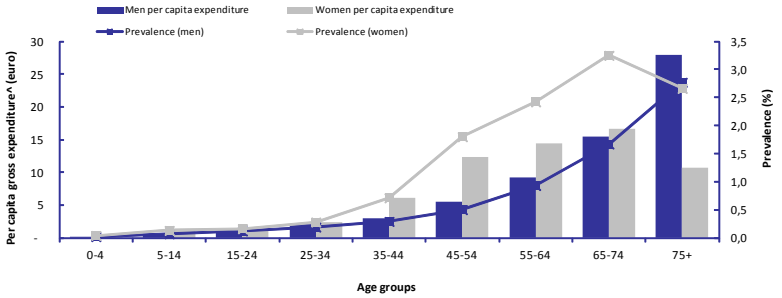
6.2 Antineoplastic and immunomodulating agents

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**4.175,0**	**(18,9)**
Δ % 2015/2014		7,1
Per capita gross expenditure, range among	50,9	89,9
DDD/1000 inhab die (% on the total)	**13,2**	**(1)**
Δ % 2015/2014		2,7
DDD/1000 inhab die, range among regions:	11,1	15,8

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

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

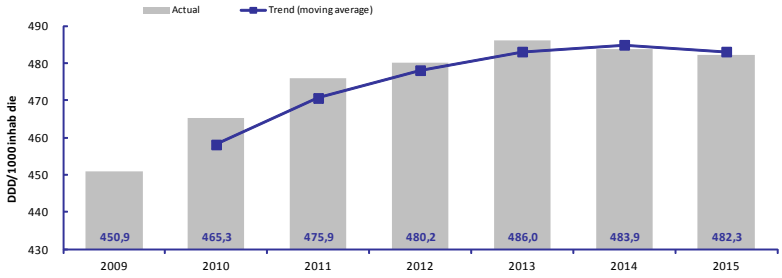
^with the exclusion of medicinal products administered in hospitals

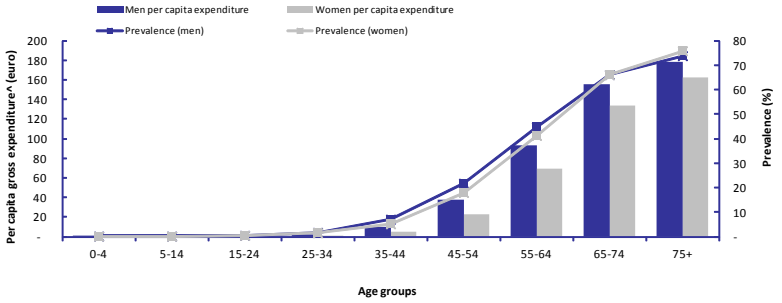
6.3 Cardiovascular System

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**3.621,0**	**(16,4)**
Δ % 2015/2014		-0,3
Per capita gross expenditure, range among	44,8	71,8
DDD/1000 inhab die (% on the total)	**482,3**	**(38)**
Δ % 2015/2014		-0,3
DDD/1000 inhab die, range among regions:	384,8	557,5

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,1	0,1	0,1	0,4	0,3	0,3
5-14	0,1	0,1	0,1	0,9	0,6	0,7
15-24	0,4	0,3	0,4	3,4	2,0	2,8
25-34	2,0	1,1	1,5	14,5	7,5	11,0
35-44	9,7	4,8	7,3	77,9	39,1	58,5
45-54	37,4	22,9	30,1	314,7	189,1	251,4
55-64	93,0	69,6	80,9	812,5	564,3	685,3
65-74	155,3	134,1	144,1	1.439,0	1.141,3	1.281,8
75+	178,2	162,4	168,5	1.955,1	1.691,4	1.792,8

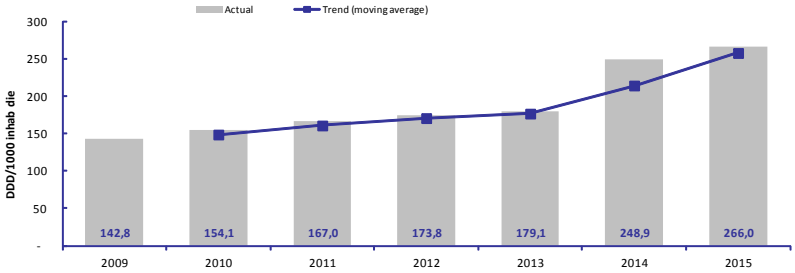
^with the exclusion of medicinal products administered in hospitals

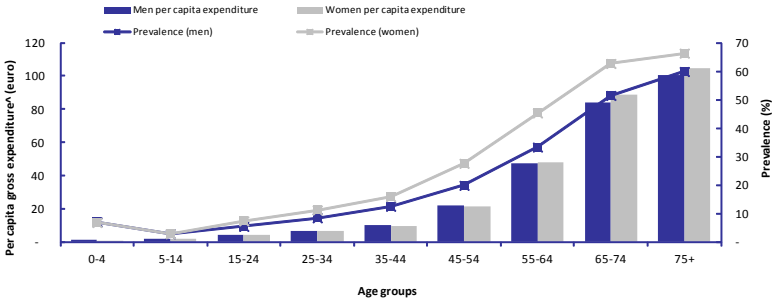
6.4 Alimentary Tract And Metabolism

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**2.667,0**	**(12,1)**
Δ % 2015/2014		3,0
Per capita gross expenditure, range among regions (€):	27,8	57,1
DDD/1000 inhab die (% on the total)	**266,0**	**(21)**
Δ % 2015/2014		6,9
DDD/1000 inhab die, range among regions:	220,4	386,6

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,9	0,9	0,9	34,9	33,2	34,1
5-14	1,5	1,6	1,6	12,5	12,5	12,5
15-24	4,3	4,1	4,2	17,3	22,9	20,0
25-34	6,4	6,3	6,4	25,9	37,2	31,5
35-44	10,3	9,7	10,0	47,7	70,4	59,0
45-54	21,6	21,4	21,5	110,5	197,5	154,4
55-64	47,5	47,6	47,6	252,7	448,4	353,0
65-74	83,8	88,8	86,4	482,1	766,0	632,0
75+	100,5	104,5	103,0	665,2	901,2	810,6

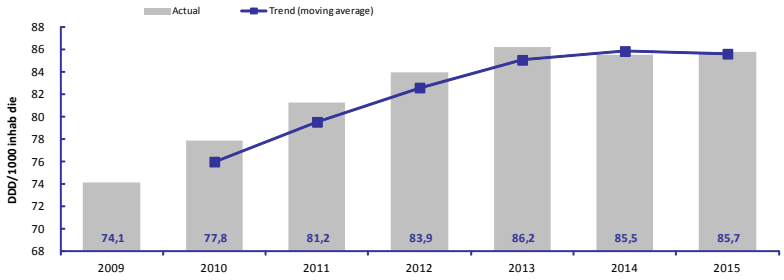
^with the exclusion of medicinal products administered in hospitals

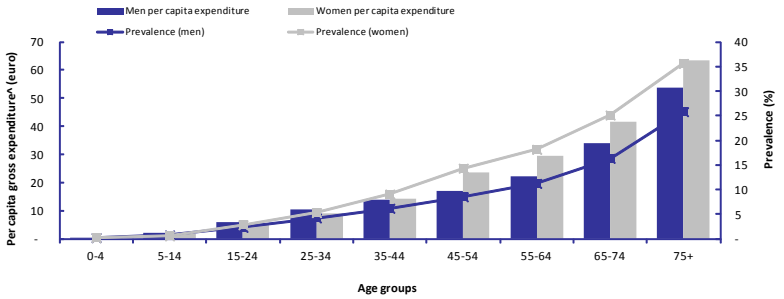
6.5 Nervous system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**1.884,0**	**(8,5)**
Δ % 2015/2014		0,8
Per capita gross expenditure, range among	27,5	37,5
DDD/1000 inhab die (% on the total)	**85,7**	**(6,8)**
Δ % 2015/2014		0,3
DDD/1000 inhab die, range among regions:	69,7	108

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,3	0,3	0,3	0,5	0,4	0,4
5-14	2,0	1,6	1,8	3,4	2,5	3,0
15-24	5,9	5,4	5,6	12,9	12,1	12,6
25-34	10,3	9,0	9,7	25,3	24,0	24,6
35-44	13,8	14,4	14,1	36,2	43,4	39,7
45-54	17,0	23,4	20,2	49,6	75,4	62,6
55-64	22,3	29,3	25,9	62,0	100,7	81,8
65-74	34,0	41,7	38,0	88,9	137,1	114,3
75+	53,6	63,4	59,6	156,6	211,3	190,3

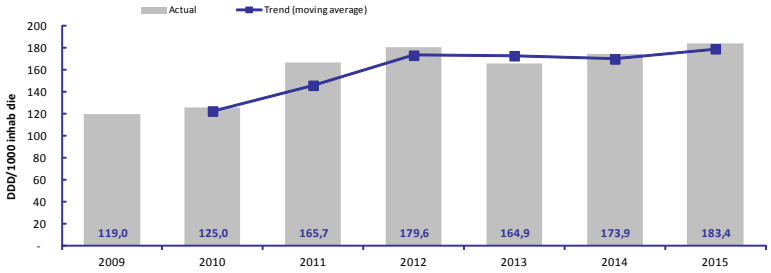
^with the exclusion of medicinal products administered in hospitals

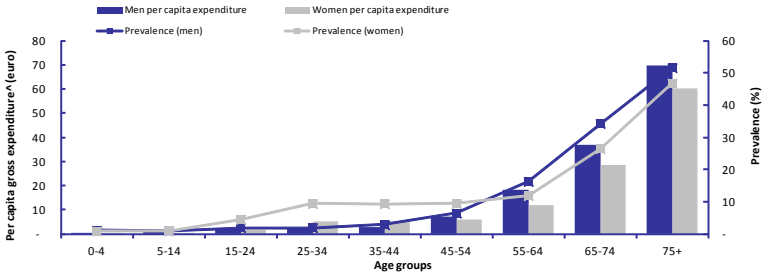
6.6 Blood and blood forming organs

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**1.920,0**	**(8,7)**
Δ % 2015/2014		2,7
Per capita gross expenditure, range among regions (€):	20,4	45,4
DDD/1000 inhab die (% on the total)	**183,4**	**(14,5)**
Δ % 2015/2014		5,5
DDD/1000 inhab die, range among regions:	123,3	257,9

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,1	0,1	0,1	1,7	1,2	1,5
5-14	1,0	0,2	0,6	2,8	3,7	3,2
15-24	1,8	1,7	1,8	7,5	25,7	16,3
25-34	2,4	5,0	3,7	9,7	63,2	36,3
35-44	2,9	5,3	4,1	19,5	60,9	40,2
45-54	7,2	6,1	6,7	56,6	64,5	60,5
55-64	18,1	11,9	14,9	157,9	102,5	129,6
65-74	36,9	28,7	32,6	365,0	256,8	307,8
75+	69,6	60,0	63,7	707,3	596,2	638,8

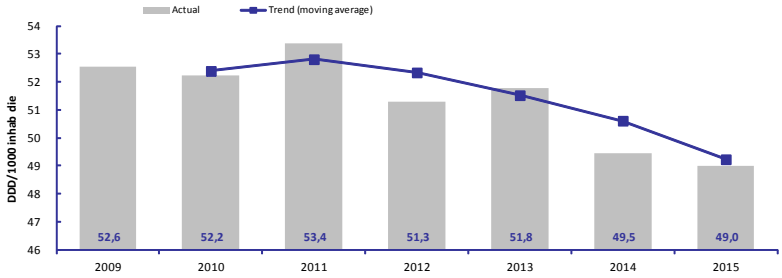
^with the exclusion of medicinal products administered in hospitals

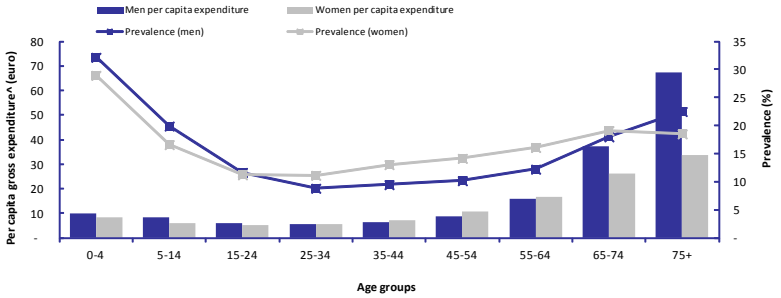
6.7 Respiratory system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**1.124,0**	**(5,1)**
Δ % 2015/2014		1,8
Per capita gross expenditure, range among	14,6	24,4
DDD/1000 inhab die (% on the total)	**49,0**	**(3,9)**
Δ % 2015/2014		-0,9
DDD/1000 inhab die, range among regions:	36,6	68,4

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	10,1	8,4	9,2	33,5	27,7	30,7
5-14	8,2	6,0	7,1	30,0	21,1	25,7
15-24	6,0	5,2	5,5	25,8	21,5	23,8
25-34	5,5	5,7	5,5	20,1	21,3	20,8
35-44	6,3	7,3	6,8	21,6	26,4	24,0
45-54	8,7	10,6	9,7	27,1	35,3	31,2
55-64	16,0	16,6	16,3	40,7	46,6	43,8
65-74	37,2	26,1	31,3	83,3	68,5	75,5
75+	67,3	33,7	46,6	155,5	88,4	114,2

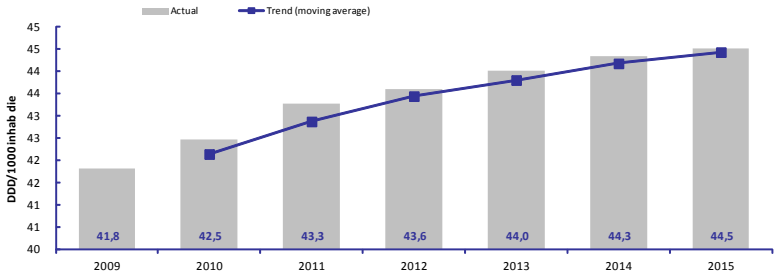
^with the exclusion of medicinal products administered in hospitals

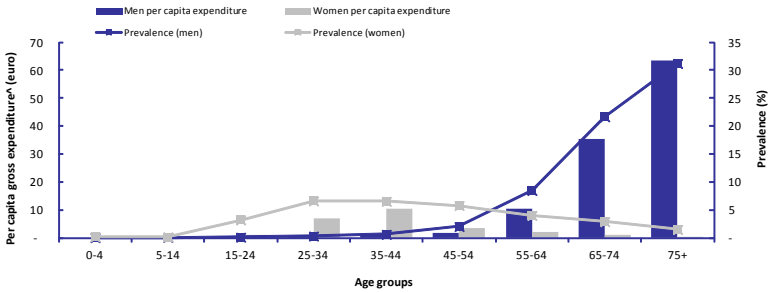
6.8 Genito-urinary system and sex hormones

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**548,0**	**(2,5)**
Δ % 2015/2014		2,7
Per capita gross expenditure, range among	7,3	10,2
DDD/1000 inhab die (% on the total)	**44,5**	**(3,5)**
Δ % 2015/2014		0,4
DDD/1000 inhab die, range among regions:	38,1	54,1

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,0	0,1	0,1
5-14	0,1	0,1	0,1	0,1	0,2	0,2
15-24	0,3	1,1	0,7	0,4	14,2	7,1
25-34	0,9	6,9	3,8	1,0	28,0	14,4
35-44	1,0	10,2	5,6	2,1	32,2	17,0
45-54	1,8	3,5	2,6	10,3	29,8	20,1
55-64	10,4	2,1	6,1	68,0	20,7	43,7
65-74	35,2	1,0	17,1	218,7	11,6	109,3
75+	63,5	0,5	24,7	400,5	5,1	157,0

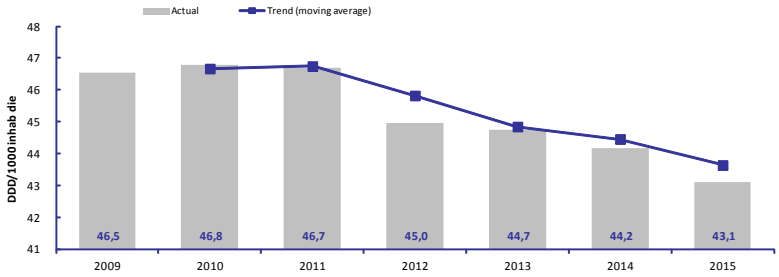
^with the exclusion of medicinal products administered in hospitals

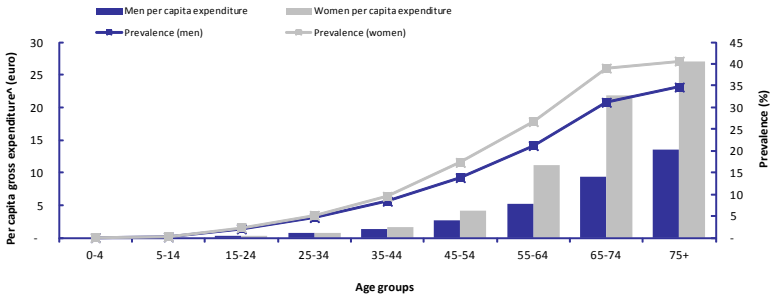
6.9 Musculo-skeletal system

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**486,0**	**(2,2)**
Δ % 2015/2014		-4,0
Per capita gross expenditure, range among	5,4	12,7
DDD/1000 inhab die (% on the total)	**43,1**	**(3,4)**
Δ % 2015/2014		-2,4
DDD/1000 inhab die, range among regions:	31,4	67,3

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab 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	0,3	0,3	0,3	1,7	1,7	1,7
25-34	0,7	0,7	0,7	4,0	4,3	4,2
35-44	1,4	1,6	1,5	8,6	9,3	8,9
45-54	2,7	4,2	3,5	18,4	23,2	20,8
55-64	5,3	11,2	8,3	37,1	56,6	47,1
65-74	9,3	21,9	16,0	71,5	112,9	93,3
75+	13,4	27,1	21,8	109,6	158,5	139,8

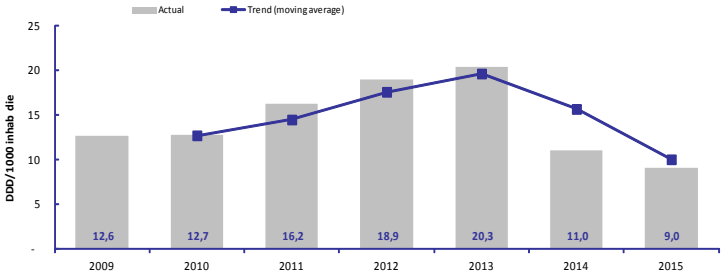
^with the exclusion of medicinal products administered in hospitals

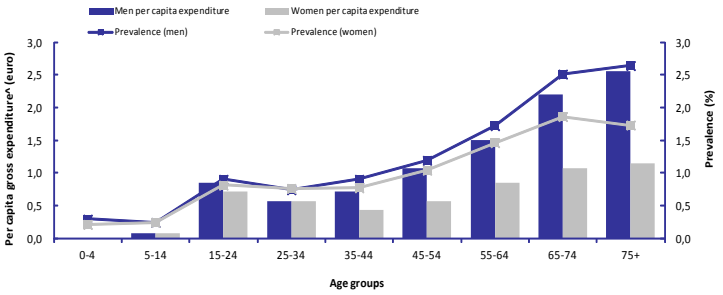
6.10 Dermatologicals

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**78,0**	**(0,4)**
Δ % 2015/2014		-4,0
Per capita gross expenditure, range among	1,1	1,6
DDD/1000 inhab die (% on the total)	**9,0**	**(0,7)**
Δ % 2015/2014		-17,8
DDD/1000 inhab die, range among regions:	5,3	14,8

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

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

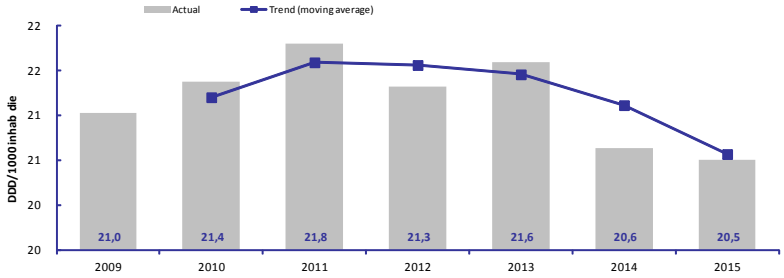
^with the exclusion of medicinal products administered in hospitals

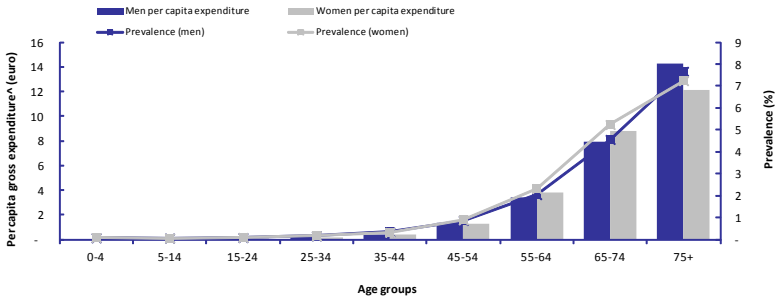
6.11 Sensory organs

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**353,0**	**(1,6)**
Δ % 2015/2014		6,1
Per capita gross expenditure, range among	4,6	7,5
DDD/1000 inhab die (% on the total)	**20,5**	**(1,6)**
Δ % 2015/2014		-0,6
DDD/1000 inhab die, range among regions:	15,4	27,7

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,0	0,0	0,0	0,1	0,1	0,1
5-14	0,1	0,1	0,1	0,2	0,2	0,2
15-24	0,1	0,1	0,1	0,5	0,4	0,4
25-34	0,2	0,1	0,2	1,1	0,9	1,0
35-44	0,4	0,4	0,4	2,6	1,9	2,2
45-54	1,4	1,3	1,3	7,5	6,6	7,0
55-64	3,4	3,8	3,6	19,1	20,0	19,6
65-74	7,9	8,8	8,4	45,9	49,4	47,7
75+	14,2	12,1	12,9	92,7	79,8	84,8

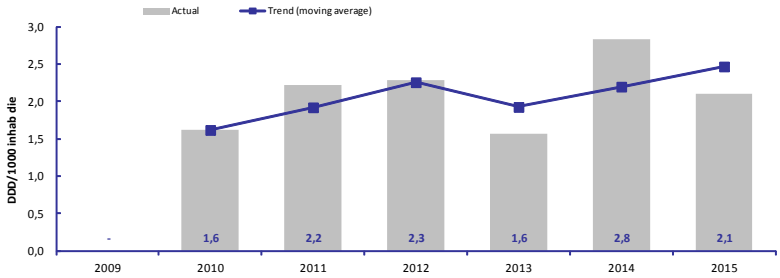
^with the exclusion of medicinal products administered in hospitals

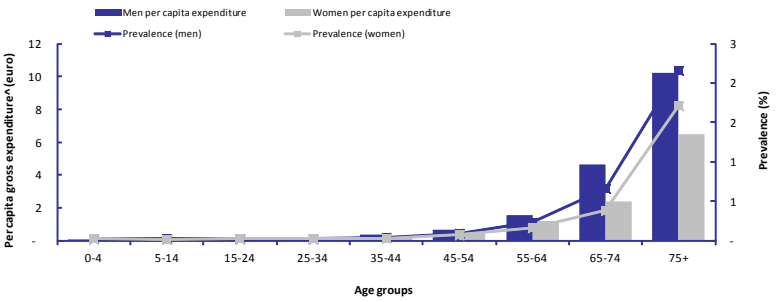
6.12 Various

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**538,0**	**(2,4)**
Δ % 2015/2014		-7,2
Per capita gross expenditure, range among	5,6	13,8
DDD/1000 inhab die (% on the total)	**2,1**	**(0,2)**
Δ % 2015/2014		-25,8
DDD/1000 inhab die, range among regions:	1,1	3,9

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

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

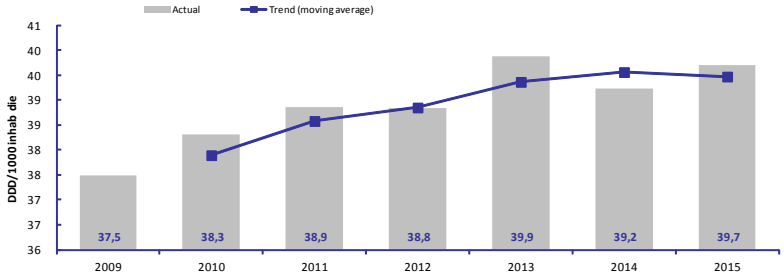
^with the exclusion of medicinal products administered in hospitals

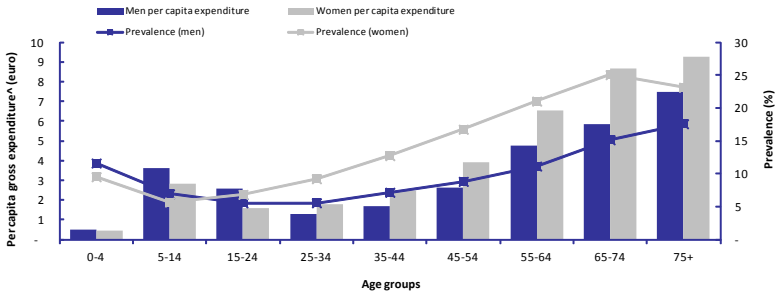
6.13 Systemic hormonal preparations, excl.sex hormones and insulins

MAIN MEASURES CONCERNING EXPENDITURE, CONSUMPTION AND EXPOSURE

NHS expenditure, million €* (% on the total)	**481,0**	**(2,2)**
Δ % 2015/2014		-1,4
Per capita gross expenditure, range among	6,1	10,1
DDD/1000 inhab die (% on the total)	**39,7**	**(3,1)**
Δ % 2015/2014		1,2
DDD/1000 inhab die, range among regions:	27,8	49,4

*Outpatient and inpatient NHS expenditure





Expenditure and consumption by sex and age^2015

	Per capita expenditure			DDD/1000 inhab die		
Age	**men**	**women**	**total**	**men**	**women**	**total**
0-4	0,5	0,4	0,5	2,7	2,1	2,3
5-14	3,6	2,8	3,3	3,9	3,3	3,6
15-24	2,6	1,6	2,1	5,8	8,6	7,1
25-34	1,3	1,8	1,5	7,2	18,2	12,7
35-44	1,7	2,5	2,1	10,9	30,5	20,7
45-54	2,6	3,9	3,3	17,5	50,0	33,8
55-64	4,8	6,5	5,7	26,7	70,3	49,1
65-74	5,8	8,7	7,4	40,8	87,7	65,5
75+	7,5	9,2	8,5	55,3	83,7	72,8

^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	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
ITALY		178,3	1.114,9	-1,1	1,7	-1,9	-0,9	-2,8
C - CARDIOVASCULAR SYSTEM		**55,7**	**465,6**	**-1,2**	**-0,3**	**-1,9**	**1,1**	**-0,9**
HMG CoA reductase inhibitors		10,5	67,6	-1,1	2,6	-0,4	-3,2	-3,6
Angiotensin II antagonists and diuretics		6,1	38,5	-7,3	-2,3	-6,2	1,1	-5,1
Angiotensin II antagonists, plain		6,0	5,5	-0,1	-0,1	-0,9	0,9	-0,0
Dihydropyridine derivatives		4,5	51,5	-4,4	-2,4	-2,1	0,0	-2,0
ACE inhibitors, plain		4,3	87,3	-3,6	-1,5	-1,1	-1,0	-2,1
Beta blocking agents, selective		3,9	35,9	3,8	1,5	-0,8	3,0	2,2
ACE inhibitors and diuretics		3,4	23,8	-5,0	-4,3	-1,1	0,4	-0,7
Other lipid modifying agents		2,9	5,5	0,2	11,7	-8,9	-1,4	-10,3
HMG CoA reductase inhibitors in combination with other lipid modifying agents		2,7	3,6	4,0	2,4	-0,1	1,6	1,5
ACE inhibitors and calcium channel blockers		1,5	8,0	19,4	20,5	-0,0	-0,9	-0,9
Organic nitrates		1,3	12,4	-12,1	-10,8	-1,5	0,1	-1,4
Angiotensin II antagonists and calcium channel blockers		1,2	3,6	30,2	31,6	-1,2	0,1	-1,1
Alpha-adrenoreceptor antagonists		1,2	7,5	-1,1	-1,2	-0,1	0,1	0,0
Antiarrhythmics, class Ic		0,9	4,6	2,9	-0,0	-0,5	3,5	3,0
Sulfonamides, plain		0,9	25,7	1,1	1,7	-0,1	-0,4	-0,5
Alpha and beta blocking agents		0,7	3,8	-5,3	-4,9	-0,0	-0,3	-0,3
Beta blocking agents, selective, and thiazides		0,6	4,4	16,7	15,0	0,6	0,9	1,5

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Aldosterone antagonists		0,5	3,2	-2,5	-0,3	-3,9	1,8	-2,2
Fibrates		0,4	2,5	-0,6	0,5	-0,0	-1,1	-1,1
Imidazoline receptor agonists		0,3	1,9	-8,2	-4,8	-3,8	0,4	-3,5
Antiarrhythmics, class III		0,3	3,0	-2,1	-1,0	-0,1	-1,0	-1,1
Benzothiazepine derivatives		0,3	1,5	-15,0	-8,0	-7,3	-0,4	-7,6
Other cardiac preparations		0,2	0,2	-12,0	-4,3	-4,2	-4,0	-8,0
Phenylalkylamine derivatives		0,2	1,7	-9,4	-8,7	-0,0	-0,8	-0,8
Beta blocking agents, selective, and other diuretics		0,2	2,3	-5,4	-5,5	-0,0	0,1	0,1
Low-ceiling diuretics and potassium-sparing agents		0,2	3,1	-6,6	-6,6	-0,0	0,1	0,1
Beta blocking agents, non-selective		0,1	1,6	-2,3	-2,4	-0,6	0,7	0,1
High-ceiling diuretics and potassium-sparing agents		0,1	0,7	-3,2	-3,3	-0,0	0,0	0,0
Renin-inhibitors		0,1	0,4	-20,3	-19,2	-2,3	1,0	-1,4
Digitalis glycosides		0,1	2,3	-10,5	-10,2	-0,1	-0,2	-0,3
Sulfonamides, plain		0,1	1,5	-4,6	-5,2	-0,0	0,6	0,6
Antiarrhythmics, class Ib		0,1	0,0	91,6	87,6	2,1	0,0	2,1
A - ALIMENTARY TRACT AND METABOLISM		**33,0**	**232,3**	**0,8**	**6,8**	**-0,9**	**-4,7**	**-5,6**
Proton pump inhibitors		14,9	73,6	-3,7	-2,9	-1,1	0,3	-0,8
Insulins and analogues for injection, fast-acting		3,8	7,6	1,5	1,0	-0,0	0,5	0,5
Vitamin D and analogues		2,7	84,9	32,2	27,1	-1,0	5,1	4,0
Aminosalicylic acid and similar agents		1,7	4,3	3,2	3,3	-0,2	0,1	-0,0
Antibiotics		1,5	2,1	0,2	0,7	-0,0	-0,5	-0,5
Biguanides		1,4	20,2	1,1	1,5	-0,2	-0,2	-0,4

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)		0,8	2,6	2,1	1,3	-0,0	0,8	0,8
Bile acid preparations		0,6	2,1	0,5	1,1	-0,2	-0,4	-0,6
Insulins and analogues for injection, long-acting		0,6	0,7	84,2	55,0	-3,5	23,1	18,8
Other blood glucose lowering drugs, excl. insulins		0,6	3,7	-1,4	-5,3	-3,2	7,6	4,1
Sulfonamides, urea derivatives		0,6	10,7	0,9	-2,5	-3,8	7,6	3,5
Combinations of oral blood glucose lowering drugs		0,5	4,1	-19,9	-18,1	-2,3	0,1	-2,2
Calcium, combinations with vitamin D and/or other drugs		0,5	5,3	-6,6	-7,1	-0,0	0,5	0,5
Combinations and complexes of aluminium, calcium and magnesium compounds		0,4	1,8	2,0	2,1	-0,3	0,1	-0,1
Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting		0,4	0,7	-18,0	-18,3	-0,0	0,4	0,3
H2-receptor antagonists		0,4	2,2	-6,2	-4,8	-0,5	-1,0	-1,5
Corticosteroids acting locally		0,3	0,4	-0,1	-1,7	-0,0	1,7	1,6
Serotonin (5HT3) antagonists		0,2	0,0	11,5	-0,2	-0,7	12,6	11,7
Alpha glucosidase inhibitors		0,2	0,7	-0,9	1,2	-0,0	-2,1	-2,1
Enzyme preparations		0,2	0,6	8,2	8,2	-0,0	0,0	0,0
Insulins and analogues for injection, intermediate-acting		0,1	0,3	-16,5	-17,5	-0,0	1,3	1,3
Dipeptidyl peptidase 4 (DPP-4) inhibitors		0,1	0,2	-3,8	2,5	-7,1	1,0	-6,2
Osmotically acting laxatives		0,1	1,2	-0,3	-0,6	-0,0	0,3	0,3
Calcium		0,1	1,4	0,1	-0,0	-0,2	0,3	0,2
Thiazolidinediones		0,1	0,4	12,7	23,3	-9,9	1,4	-8,6

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Potassium		0,1	0,4	4,0	4,0	-0,0	-0,0	-0,0
N - NERVOUS SYSTEM		**22,6**	**61,6**	**-1,3**	**1,6**	**-5,1**	**2,4**	**-2,9**
Other antiepileptics		4,7	4,7	6,1	6,3	-0,3	0,1	-0,2
Selective serotonin reuptake inhibitors		3,5	28,1	-15,4	0,7	-13,6	-2,7	-16,0
Other antidepressants		3,0	8,5	-10,0	1,8	-9,4	-2,4	-11,6
Natural opium alkaloids		1,7	2,0	5,8	-2,0	-0,1	8,0	7,9
Selective serotonin (5HT1) agonists		1,2	0,8	-9,8	-1,3	-9,1	0,4	-8,7
Phenylpiperidine derivatives		1,2	0,6	6,4	1,8	-0,8	5,4	4,5
Dopamine agonists		1,1	1,1	-13,6	-13,7	-6,1	6,7	0,2
Other opioids		1,1	1,0	16,1	4,0	-0,1	11,6	11,6
Fatty acid derivatives		0,9	2,1	1,2	0,9	-0,1	0,5	0,3
Monoamine oxidase B inhibitors		0,8	1,2	5,4	8,0	-0,6	-1,8	-2,4
Diazepines, oxazepines, thiazepines and oxepines		0,8	1,0	27,2	24,7	-6,9	9,5	2,0
Dopa and dopa derivatives		0,7	2,1	9,4	4,4	-0,4	5,2	4,8
Carboxamide derivatives		0,5	1,9	-3,8	-3,2	-0,1	-0,6	-0,7
Other antipsychotics		0,2	0,2	-9,9	5,0	-5,7	-9,0	-14,2
Anticholinesterases		0,2	0,6	48,2	64,2	-11,4	1,8	-9,7
Non-selective monoamine reuptake inhibitors		0,2	1,1	-1,1	-1,0	-0,2	-0,0	-0,2
Amides		0,2	0,1	54,6	52,5	1,4	0,0	1,4
Oripavine derivatives		0,1	0,1	-8,4	-8,1	-0,5	0,0	-0,4
Other anti-dementia drugs		0,1	0,2	83,8	157,0	-10,8	-19,8	-28,5
Other nervous system drugs		0,1	0,0	4,3	4,3	-0,7	0,8	0,0
Benzamides		0,1	0,1	-4,6	-4,4	-1,3	1,1	-0,2

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Anticholinesterases		0,1	0,2	2,1	2,6	-0,0	-0,5	-0,5
Lithium		0,1	0,3	2,5	2,4	0,0	0,1	0,1
Barbiturates and derivatives		0,1	1,7	-3,1	-6,3	2,5	0,9	3,5
Benzodiazepine derivatives		0,1	0,3	-3,2	-3,3	0,0	0,1	0,1
Butyrophenone derivatives		0,1	0,5	-5,2	-5,4	-0,6	0,8	0,2
R - RESPIRATORY SYSTEM		**17,2**	**46,4**	**0,1**	**-0,9**	**-0,6**	**1,6**	**1,0**
Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics		8,0	11,2	0,1	4,0	-1,2	-2,6	-3,8
Anticholinergics		3,5	6,1	4,2	3,7	0,9	-0,3	0,5
Glucocorticoids		2,5	9,8	-2,0	-1,3	-0,1	-0,6	-0,7
Selective beta-2-adrenoreceptor agonists		1,1	5,2	-6,9	-7,0	-2,2	2,4	0,1
Other antihistamines for systemic use		0,8	6,1	-3,8	-4,2	-0,6	0,9	0,4
Leukotriene receptor antagonists		0,5	2,1	-4,5	-2,9	-0,1	-1,6	-1,7
Piperazine derivatives		0,4	4,0	-5,4	-4,9	-0,3	-0,2	-0,5
Adrenergics in combination with anticholinergics		0,3	0,9	44,4	13,4	-0,1	27,4	27,3
Xanthines		0,1	0,7	-11,2	-13,7	-4,3	7,4	2,8
J - ANTIINFECTIVES FOR SYSTEMIC USE		**14,2**	**22,1**	**-2,8**	**-2,9**	**-0,5**	**0,5**	**0,0**
Third-generation cephalosporins		3,2	1,8	-0,7	0,7	-0,4	-1,1	-1,4
Combinations of penicillins, incl. beta-lactamase inhibitors		3,1	8,8	-2,7	-2,2	-0,3	-0,1	-0,4
Fluoroquinolones		2,4	3,1	-3,2	-1,6	-0,5	-1,2	-1,6
Macrolides		1,7	3,9	-4,9	-3,1	-0,4	-1,4	-1,8
Triazole derivatives		1,1	0,7	-6,8	-6,6	-0,4	0,1	-0,3
Other antibacterials		0,6	0,4	0,1	-0,1	-0,0	0,3	0,3

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Nucleosides and nucleotides excl. reverse transcriptase inhibitors		0,6	0,2	6,6	1,8	-1,4	6,2	4,8
Specific immunoglobulins		0,5	0,0	-4,0	-3,1	-1,9	0,9	-1,0
Penicillins with extended spectrum		0,3	2,1	-5,1	-6,4	-0,2	1,7	1,5
Second-generation cephalosporins		0,1	0,2	-16,7	-12,4	-3,2	-1,7	-4,9
Glycopeptide antibacterials		0,1	0,0	-6,4	-6,4	-0,1	0,1	-0,0
Other aminoglycosides		0,1	0,0	-7,2	-8,1	-0,9	1,9	1,0
Tetracyclines		0,1	0,3	-9,0	-6,7	-0,0	-2,5	-2,5
Lincosamides		0,1	0,0	-3,4	0,5	-0,2	-3,7	-3,9
Combinations of sulfonamides and trimethoprim, incl. Derivatives		0,1	0,3	-2,1	-1,9	-0,1	-0,0	-0,1
B - BLOOD AND BLOOD FORMING ORGANS		**8,7**	**144,0**	**-3,8**	**4,9**	**-1,3**	**-7,1**	**-8,3**
Heparin group		3,7	3,8	-5,0	-4,6	-0,4	-0,0	-0,5
Platelet aggregation inhibitors excl. Heparin		3,0	61,4	1,2	0,9	0,9	-0,6	0,4
Folic acid and derivatives		0,4	62,6	7,0	11,0	-0,7	-2,9	-3,6
Iron bivalent, oral preparations		0,3	3,2	-3,5	-4,9	-0,0	1,4	1,4
Vitamin K antagonists		0,2	5,8	-7,0	-6,7	0,0	-0,2	-0,2
Blood substitutes and plasma protein fractions		0,2	0,0	-10,2	-10,2	-2,1	2,1	-0,0
Solutions affecting the electrolyte balance		0,2	0,3	3,6	3,1	-0,1	0,6	0,5
Other antianemic preparations		0,1	0,0	-34,4	-36,6	-17,7	25,8	3,5
Direct factor Xa inhibitors		0,1	0,1	-19,1	-22,7	-1,4	6,2	4,6
Blood coagulation factors		0,1	0,0	-31,6	-36,6	-61,2	177,7	7,8
Amino acids		0,1	0,1	-8,9	-4,8	-0,1	-4,2	-4,3
Vitamin B12 (cyanocobalamin and analogues)		0,1	6,3	14,6	14,3	-0,0	0,3	0,3

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Other antithrombotic agents		0,1	0,0	-35,1	-35,1	-3,9	4,1	0,0
G - GENITO URINARY SYSTEM AND SEX HORMONES		**7,0**	**42,6**	**1,4**	**0,0**	**-0,9**	**2,3**	**1,4**
Testosterone-5-alpha reductase inhibitors		3,0	9,4	5,6	4,7	-0,0	0,9	0,9
Alpha-adrenoreceptor antagonists		2,7	23,4	4,4	2,8	-0,1	1,7	1,5
Prolactine inhibitors		0,2	0,1	2,6	-0,2	-2,0	4,9	2,8
Gonadotropins		0,1	0,0	-51,4	-30,1	-6,9	-25,3	-30,4
Progestogens and estrogens, fixed combinations		0,1	2,6	-10,7	-10,2	-0,0	-0,6	-0,6
Pregnen (4) derivatives		0,1	1,2	-0,8	-5,1	-0,0	4,6	4,6
Other estrogens		0,1	0,7	-18,3	-1,3	-16,1	-1,3	-17,2
Progestogens and estrogens, fixed combinations		0,1	0,6	-1,8	-2,8	-0,0	1,0	1,0
Natural and semisynthetic estrogens, plain		0,1	1,7	-16,0	-18,2	-6,3	9,6	2,7
Antiandrogens, plain		0,1	0,1	-7,6	-6,2	-0,0	-1,4	-1,4
Progestogens and estrogens, sequential preparations		0,1	1,2	-11,8	-11,8	0,0	0,0	0,0
M - MUSCULO-SKELETAL SYSTEM		**7,0**	**39,6**	**-6,5**	**-3,9**	**-2,7**	**-0,1**	**-2,7**
Bisphosphonates		1,4	6,6	-5,7	-3,2	-2,0	-0,6	-2,6
Coxibs		1,3	4,4	-13,1	-6,6	-7,4	0,6	-6,9
Bisphosphonates, combinations		1,1	3,3	-6,5	-6,1	-0,4	0,0	-0,4
Preparations inhibiting uric acid production		0,9	8,4	12,2	5,7	-4,5	11,1	6,1
Propionic acid derivatives		0,9	7,1	-5,4	-5,6	-0,1	0,2	0,2
Acetic acid derivatives and related substances		0,8	5,0	-7,9	-6,9	-0,2	-0,9	-1,0
Other antiinflammatory and antirheumatic agents, non-steroids		0,2	2,5	-10,4	-10,3	-0,6	0,4	-0,1

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Oxicams		0,2	1,2	-9,6	-9,3	-0,6	0,3	-0,3
Other centrally acting agents		0,1	0,5	-0,1	-0,4	0,0	0,3	0,3
L - ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS		**4,2**	**4,8**	**0,1**	**4,2**	**-1,1**	**-3,0**	**-4,0**
Aromatase inhibitors		1,5	2,1	4,7	5,4	-0,1	-0,6	-0,7
Calcineurin inhibitors		1,0	0,3	-5,2	-4,2	-0,4	-0,6	-1,0
Folic acid analogues		0,7	0,4	4,2	1,2	-1,8	4,8	2,9
Anti-androgens		0,2	0,4	39,7	39,3	-2,2	2,5	0,3
Other antineoplastic agents		0,1	0,2	3,5	4,9	-0,3	-1,1	-1,4
Other immunosuppressants		0,1	0,4	-0,6	-0,7	-0,1	0,2	0,1
Anti-estrogens		0,1	0,9	-0,2	1,3	-0,2	-1,3	-1,5
Colony stimulating factors		0,1	0,0	-34,6	-18,6	-5,2	-15,1	-19,6
Nitrogen mustard analogues		0,1	0,0	17,8	-7,3	28,0	-0,8	27,0
Gonadotropin releasing hormone analogues		0,1	0,0	-13,4	1,9	-8,8	-6,7	-15,0
Selective immunosuppressants		0,1	0,0	-34,8	12,5	-9,1	-36,2	-42,1
S - SENSORY ORGANS		**3,8**	**18,7**	**2,5**	**0,2**	**-0,2**	**2,6**	**2,3**
Beta blocking agents1)		2,1	10,1	4,1	-0,0	-0,0	4,1	4,1
Prostaglandin analogues1)		1,3	5,5	1,1	0,3	-0,0	0,8	0,8
Carbonic anhydrase inhibitors		0,3	1,5	0,2	2,8	-2,5	-0,1	-2,6
Sympathomimetics in glaucoma therapy1)		0,1	1,2	0,4	-0,3	-1,1	1,9	0,8
H - SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS		**2,9**	**34,0**	**-7,2**	**0,7**	**-3,0**	**-5,0**	**-7,8**
Glucocorticoids		1,4	13,0	-1,9	0,2	-1,3	-0,8	-2,1
Thyroid hormones		0,8	19,5	5,3	1,5	-0,0	3,8	3,8
Parathyroid hormones and analogues		0,3	0,0	-17,4	-17,4	-5,1	5,4	-0,0

ATC	Subgroups	Per capita gross expenditure	DDD 1000 inhab die	Δ% 15-14				Δ%
				Exp	DDD	Packs	Mix	DDD average cost
Vasopressin and analogues		0,1	0,1	0,2	0,0	-0,2	0,4	0,2
Somatropin and somatropin agonists		0,1	0,0	-60,6	-59,6	-15,1	14,9	-2,4
Sulfur-containing imidazole derivatives		0,1	1,4	-2,4	-2,4	0,0	-0,0	-0,0
V – VARIOUS		**1,1**	**0,1**	**-1,3**	**22,7**	**-8,9**	**4,6**	**-19,5**
Medical gases		0,9		-3,4				
Drugs for treatment of hyperkalemia and hyperphosphatemia		0,1	0,1	11,6	19,3	-10,2	4,2	-6,5
D - DERMATOLOGICALS		**0,9**	**2,3**	**-4,5**	**-6,0**	**-5,4**	**7,4**	**1,6**
Other antipsoriatics for topical use		0,6	1,1	-6,1	-6,6	-0,4	1,0	0,6
Antifungals for systemic use		0,1	0,1	-10,4	-10,8	-0,1	0,6	0,5
Retinoids for treatment of acne		0,1	0,1	0,9	0,8	-0,3	0,3	0,0
Corticosteroids, very potent (group IV)		0,1	0,4	14,7	9,1	-0,0	5,1	5,1
Other chemotherapeutics		0,1	0,0	38,8	38,4	-3,6	4,0	0,3
P - ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS		**0,2**	**0,8**	**-1,0**	**2,6**	**-0,0**	**-3,5**	**-3,5**
Aminoquinolines		0,1	0,7	3,2	3,0	-0,0	0,1	0,1

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

Table 6.6. The 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% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
L - ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	**64,5**		**7,5**	**8,4**		**1,9**
Monoclonal antibodies	15,0	23,3	21,1	0,8	9,3	18,2
Tumor necrosis factor alpha (TNF-) inhibitors	10,7	6,5	4,7	1,0	11,6	5,8
Protein kinase inhibitors	10,1	15,7	3,6	0,3	3,2	5,5
Selective immunosuppressants	6,2	9,6	13,5	0,7	8,0	12,6
Other immunosuppressants	3,4	5,2	19,0	0,1	1,3	18,0
Interferons	3,3	5,2	-24,8	0,7	8,5	-21,1
Other antineoplastic agents	2,1	3,2	4,4	0,2	2,2	-4,5
Gonadotropin releasing hormone analogues	1,8	2,8	-1,7	0,9	11,1	0,6
Other hormone antagonists and related agents	1,7	2,6	66,4	0,1	1,2	40,4
Interleukin inhibitors	1,7	2,6	21,9	0,1	1,7	36,3
Other immunostimulants	1,2	1,9	-3,7	0,1	1,3	-4,5
Folic acid analogues	1,2	1,9	-3,3	0,1	1,3	-3,8
Colony stimulating factors	1,2	1,8	-9,9	0,1	1,2	-2,0
Pyrimidine analogues	1,1	1,6	-0,1	0,4	5,2	25,0
Calcineurin inhibitors	0,7	1,2	8,3	0,3	3,8	7,5
Anthracyclines and related substances	0,5	0,7	-8,2	0,1	1,3	-1,4
Taxanes	0,5	0,7	-14,7	0,2	2,1	8,4
Nitrogen mustard analogues	0,4	0,7	18,3	0,1	1,2	21,8
Anti-estrogens	0,4	0,6	-4,9	0,2	2,5	-12,8
Anti-androgens	0,3	0,5	159,0	0,8	9,1	-14,9

ATC I° level Subgroups	Per capita gross expenditure	%	Δ% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
Other plant alkaloids and natural products	0,3	0,5	2,5	<0,05	0,0	2,4
Vinca alkaloids and analogues	0,2	0,3	5,0	0,0	0,5	-2,0
Other cytotoxic antibiotics	0,1	0,2	6,4	0,1	1,2	2,7
Other alkylating agents	0,1	0,1	-23,5	0,2	2,5	-5,6
Platinum compounds	0,1	0,1	-12,7	0,2	2,7	3,8
Purine analogues	0,1	0,1	-23,1	<0,05	0,0	1,2
Ethylene imines	0,1	0,1	-3,1	<0,05	0,0	-8,0
Alkyl sulfonates	0,1	0,1	-8,0	<0,05	0,1	-4,6
J - ANTIINFECTIVES FOR SYSTEMIC USE	**54,1**		**109,2**	**7,3**		**5,2**
Other antivirals	27,6	50,9	>100	0,4	5,9	141,0
Antivirals for treatment of HIV infections, combinations	5,8	10,8	2,1	1,0	14,0	2,0
Protease inhibitors	4,5	8,3	34,4	0,5	6,8	-4,3
Nucleoside and nucleotide reverse transcriptase inhibitors	2,2	4,0	5,4	0,7	9,2	8,7
Pneumococcal vaccines	1,5	2,7	6,2	0,1	1,2	1,9
Bacterial and viral vaccines, combined	1,3	2,4	-7,6	0,1	1,1	-4,1
Immunoglobulins, normal human	1,2	2,2	3,7	0,1	1,6	28,7
Other antimycotics for systemic use	1,1	2,1	5,9	<0,05	0,1	6,5
Other antibacterials	1,0	1,8	4,1	<0,05	0,5	-0,7
Triazole derivatives	0,8	1,4	23,3	0,1	1,6	11,1
Specific immunoglobulins	0,7	1,3	-5,7	<0,05	0,2	-3,3
Influenza vaccines	0,7	1,3	8,0	1,2	16,5	1,8
Glycopeptide antibacterials	0,7	1,2	-1,9	0,1	0,8	-9,6
Meningococcal vaccines	0,6	1,2	>100	0,1	0,8	59,3
Non-nucleoside reverse transcriptase inhibitors	0,5	1,0	-6,0	0,3	4,0	-1,2
Antibiotics	0,5	0,9	6,1	<0,05	0,2	3,2

ATC I° level Subgroups	Per capita gross expenditure	%	Δ% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
Tetracyclines	0,4	0,7	4,5	<0,05	0,4	-1,0
Combinations of penicillins, incl. beta-lactamase inhibitors	0,4	0,7	-3,4	0,8	10,4	1,9
Measles vaccines	0,4	0,7	11,4	<0,05	0,6	1,1
Papillomavirus vaccines	0,3	0,6	-12,8	<0,05	0,3	-2,3
Carbapenems	0,3	0,6	-36,8	0,1	0,8	-38,0
Polymyxins	0,3	0,5	39,1	<0,05	0,4	23,9
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0,2	0,4	-12,6	0,2	2,6	16,9
Third-generation cephalosporins	0,2	0,4	13,7	0,2	3,4	-3,8
Varicella zoster vaccines	0,1	0,3	28,8	<0,05	0,1	21,9
Other aminoglycosides	0,1	0,2	-18,7	<0,05	0,7	-4,9
Hepatitis vaccines	0,1	0,2	-8,3	<0,05	0,2	-1,8
First-generation cephalosporins	0,1	0,2	14,5	0,1	1,0	-0,8
Fluoroquinolones	0,1	0,2	-19,4	0,4	6,0	7,5
Pertussis vaccines	0,1	0,1	-19,8	<0,05	0,2	-21,2
Macrolides	0,1	0,1	13,9	0,2	2,6	-1,6
Rota virus diarrhea vaccines	0,1	0,1	21,4	<0,05	0,1	28,1
Monobactams	0,1	0,1	30,1	<0,05	0,0	29,9
B - BLOOD AND BLOOD FORMING ORGANS	**22,9**		**5,4**	**39,4**		**7,7**
Blood coagulation factors	7,3	31,8	-0,0	<0,05	0,1	-0,4
Other antianemic preparations	4,2	8,4	-5,7	2,9	7,4	1,3
Heparin group	2,1	9,2	-1,9	6,3	16,1	0,8
Platelet aggregation inhibitors excl. heparin	2,0	8,6	3,3	7,7	19,4	5,8
Direct factor Xa inhibitors	1,9	8,2	187,2	4,4	11,3	192,5
Direct thrombin inhibitors	1,0	4,5	36,1	1,5	3,7	45,3
Solutions for parenteral nutrition	0,9	3,9	7,4	0,6	1,6	-10,5

ATC I° level Subgroups	Per capita gross expenditure	%	Δ% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
Solutions affecting the electrolyte balance	0,7	3,2	-30,4	5,3	13,4	-22,5
Other systemic hemostatics	0,5	2,2	22,0	<0,05	0,1	21,1
Blood substitutes and plasma protein fractions	0,4	1,7	-12,9	0,1	0,1	-5,9
Local hemostatics	0,3	1,4	-0,6	<0,05	0,0	-4,3
Hypertonic solutions	0,3	1,3	8,7	0,1	0,2	25,1
Enzymes	0,2	1,0	0,3	<0,05	0,0	5,1
Drugs used in hereditary angioedema	0,2	1,0	21,5	<0,05	0,0	24,4
Other antithrombotic agents	0,2	1,0	28,6	0,4	1,0	41,6
Proteinase inhibitors	0,2	0,7	7,8	<0,05	0,0	-8,4
Isotonic solutions	0,1	0,7	-10,5	0,1	0,2	42,7
Iron, parenteral preparations	0,1	0,2	130,0	<0,05	0,0	143,0
A - ALIMENTARY TRACT AND METABOLISM	**10,9**		**10,2**	**33,8**		**7,8**
Enzymes	3,6	32,8	7,7	<0,05	0,0	11,4
Insulins and analogues for injection, long-acting	2,3	21,3	9,4	4,9	14,6	4,7
Combinations of oral blood glucose lowering drugs	1,6	4,3	18,0	3,5	10,3	15,1
Dipeptidyl peptidase 4 (DPP-4) inhibitors	0,9	7,9	30,4	1,6	4,7	28,8
Other blood glucose lowering drugs, excl. insulins	0,9	7,8	27,6	1,3	4,0	61,5
Various alimentary tract and metabolism products	0,3	2,9	16,2	<0,05	0,0	-4,9
Proton pump inhibitors	0,2	2,2	-21,2	4,3	12,7	0,1
Insulins and analogues for injection, fast-acting	0,2	1,8	3,9	0,8	2,3	4,0
Serotonin (5HT3) antagonists	0,2	1,5	-5,2	0,1	0,2	-7,5
Multivitamins, plain	0,1	1,2	17,1	0,1	0,2	0,9
Other antiemetics	0,1	0,7	7,0	<0,05	0,0	-7,0
Amino acids and derivatives	0,1	0,7	3,6	0,1	0,2	-5,2
Enemas	0,1	0,7	8,6	6,2	18,3	7,9

ATC I° level Subgroups	Per capita gross expenditure	%	Δ% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
Osmotically acting laxatives	0,1	0,6	1,8	1,1	3,2	-2,7
Enzyme preparations	0,1	0,5	6,9	0,2	0,5	2,1
N - NERVOUS SYSTEM	**8,4**		**7,5**	**24,1**		**-2,7**
Other antipsychotics	2,8	33,0	54,7	1,9	7,8	38,0
Diazepines, oxazepines, thiazepines and oxepines	0,8	9,5	-28,0	3,4	14,0	-3,8
Other nervous system drugs	0,7	8,9	173,4	0,1	0,5	70,2
Dopa and dopa derivatives	0,6	7,0	1,9	0,4	1,6	-8,8
Drugs used in opioid dependence	0,5	6,2	0,2	3,2	13,2	3,7
Other antiepileptics	0,4	5,3	3,4	0,8	3,2	12,9
Anticholinesterases	0,4	4,2	-37,7	1,6	6,7	-10,7
Halogenated hydrocarbons	0,3	3,2	-15,0	<0,05	0,0	-8,0
Amides	0,3	3,2	-14,6	2,6	10,9	-27,6
Other anti-dementia drugs	0,2	1,9	-36,4	0,6	2,5	-12,9
Other general anesthetics	0,1	1,7	-17,0	0,2	0,7	2,2
Dopamine agonists	0,1	1,6	20,5	0,3	1,2	53,6
Anilides	0,1	1,5	-21,9	0,7	2,9	49,9
Drugs used in alcohol dependence	0,1	1,4	0,5	0,2	0,9	-5,6
Other analgesics and antipyretics	0,1	1,3	2,4	<0,05	0,1	7,2
Natural opium alkaloids	0,1	1,2	7,3	0,4	1,8	-4,8
Opioid anesthetics	0,1	0,9	-38,0	0,2	1,0	3,9
Monoamine oxidase B inhibitors	0,1	0,8	0,2	0,1	0,3	0,7
Other antidepressants	0,1	0,6	-2,7	0,6	2,4	8,9
V – VARIOUS*	**7,8**		**-8,0**	**2,0**		**-27,4**
Medical gases	3,4	44,3	-9,4	-	-	-
Iron chelating agents	1,2	14,9	-9,0	0,1	3,5	-3,4

ATC I° level Subgroups	Per capita gross expenditure	%	Δ% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
Watersoluble, nephrotropic, low osmolar X-ray contrast media	1,0	13,0	-8,7	0,1	2,9	-6,7
Drugs for treatment of hyperkalemia and hyperphosphatemia	0,4	4,9	-24,7	0,2	10,5	0,6
Paramagnetic contrast media	0,3	4,4	3,0	<0,05	1,0	1,8
Antidotes	0,3	3,7	26,4	0,1	4,1	-40,9
Detoxifying agents for antineoplastic treatment	0,2	2,0	12,9	0,2	11,0	-2,4
Other diagnostic radiopharmaceuticals for tumour detection	0,1	1,9	-13,3	<0,05	0,1	-39,4
Tests for thyreoidea function	0,1	1,8	-2,5	<0,05	0,1	0,8
Various thyroid diagnostic radiopharmaceuticals	0,1	1,7	2.983,7	<0,05	0,0	1.265,0
Iodine (123I) compounds	0,1	1,7	0,8	<0,05	0,0	4,2
Solvents and diluting agents, incl. irrigating solutions	0,1	0,9	-29,4	1,2	58,6	-37,0
Allergen extracts	0,1	0,7	39,5	0,1	3,7	62,1
Other diagnostic agents	0,1	0,7	-11,3	<0,05	0,6	-5,1
H - SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	**5,0**		**2,2**	**5,7**		**4,0**
Somatropin and somatropin agonists	1,5	30,2	-5,0	0,3	4,5	6,2
Somatostatin and analogues	1,3	26,3	5,8	0,2	3,0	4,2
Other anti-parathyroid agents	0,9	17,4	0,3	0,3	4,8	5,1
Parathyroid hormones and analogues	0,5	10,7	16,6	0,1	2,0	16,5
Other anterior pituitary lobe hormones and analogues	0,4	7,1	4,9	<0,05	0,2	4,3
Glucocorticoids	0,3	6,9	7,2	4,4	76,9	4,2
C - CARDIOVASCULAR SYSTEM	**3,9**		**14,0**	**16,7**		**-0,2**
Other antihypertensives	2,1	54,2	20,9	0,1	0,4	13,9
Other cardiac preparations	1,2	31,4	15,0	1,8	11,0	11,9
Adrenergic and dopaminergic agents	0,1	2,6	1,5	0,5	2,9	-42,2

ATC I° level Subgroups	Per capita gross expenditure	%	Δ% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
Antiarrhythmics, class III	0,1	2,0	2,9	0,3	1,8	-4,6
Other lipid modifying agents	0,1	1,6	391,4	0,1	0,7	1,1
Sulfonamides, plain	0,1	1,6	-15,0	3,7	22,1	1,8
Beta blocking agents, selective	0,1	1,4	-1,5	0,8	4,5	7,6
S - SENSORY ORGANS	**2,0**		**13,3**	**1,8**		**-7,6**
Antineovascularisation agents	1,7	80,8	9,4	0,2	10,9	16,5
Corticosteroids, plain	0,3	12,3	54,0	<0,05	0,5	-6,3
G - GENITO URINARY SYSTEM AND SEX HORMONES	**2,0**		**7,4**	**1,9**		**10,2**
Gonadotropins	1,3	63,6	6,1	0,2	11,1	7,3
Drugs used in erectile dysfunction	0,3	16,0	15,1	0,1	6,3	29,4
Prostaglandins	0,1	5,9	-3,6	0,1	2,6	-2,1
Other gynecologicals	0,1	5,2	-2,7	<0,05	0,1	2,9
R - RESPIRATORY SYSTEM	**1,3**		**32,1**	**2,7**		**-1,2**
Other systemic drugs for obstructive airway diseases	0,4	33,9	22,4	0,1	2,0	17,1
Other respiratory system products	0,2	18,8	>100	<0,05	0,0	-37,0
Mucolytics	0,2	12,8	3,5	0,3	9,5	2,3
Anticholinergics	0,1	10,0	11,2	0,6	20,9	12,0
Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics	0,1	8,2	8,6	0,3	3,0	4,8
Lung surfactants	0,1	6,8	-2,7	<0,05	0,1	-8,9
M - MUSCULO-SKELETAL SYSTEM	**1,0**		**16,7**	**3,6**		**17,6**
Other drugs affecting bone structure and mineralization	0,5	46,3	72,3	1,6	44,9	69,0
Other muscle relaxants, peripherally acting agents	0,2	19,5	13,4	<0,05	0,1	20,9
Other quaternary ammonium compounds	0,1	9,8	-11,6	0,1	3,3	8,4
Bisphosphonates	0,1	8,7	-35,4	0,1	3,1	-0,8
D - DERMATOLOGICALS	0,3		-2,6	6,7		-21,2

ATC I° level Subgroups	Per capita gross expenditure	%	Δ% 15-14	DDD/1000 inhab die	Δ%	Δ% 15-14
Other cicatrizants	0,1	25,8	14,8	0,4	5,5	1,7
P - ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	**0,0**		**20,9**	<0,05		**16,8**

* 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 2015 is included in the following tables.

Table 7.2.20. First thirty active ingredients in terms of outpatient NHS expenditure: comparison 2011-2015

ATC	Active ingredient	Exp (million)	%	Rank 2015	Rank 2014	Rank 2013	Rank 2012	Rank 2011
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 7.2.21. First thirty active ingredients in terms of outpatient NHS consumption: comparison 2011-2015

ATC	Active ingredient	DDD/1000 inhab die	%	Rank 2015	Rank 2014	Rank 2013	Rank 2012	Rank 2011
A	Colecalciferol	82,9	7,4	1	1	-	-	-
B	Folic acid	62,6	5,6	2	3	3	3	-
C	Ramipril	60,3	5,4	3	2	1	1	1
B	Acetylsalicylic acid	52,5	4,8	4	4	2	2	2
C	Atorvastatin	34,5	3,0	5	5	4	5	6
C	Amlodipine	26,7	2,4	6	6	5	4	3
C	Furosemide	24,4	2,2	7	7	6	6	4
A	Pantoprazole	20,6	1,8	8	9	11	11	13
A	Metformin	20,2	1,8	9	10	10	10	9
H	Levothyroxine sodium	19,4	1,8	10	12	8	8	7
A	Omeprazole	18,8	1,6	11	11	9	9	8
A	Lansoprazole	18,6	1,6	12	8	7	7	5
C	Simvastatin	15,0	1,4	13	13	12	13	11
C	Valsartan	14,5	1,2	14	14	14	14	15
C	Nebivolol	13,8	1,2	15	16	15	16	16
A	Esomeprazole	13,1	1,2	16	17	17	19	25
C	Rosuvastatin	13,0	1,2	17	15	13	12	10
C	Enalapril	11,1	1,0	18	18	16	15	12
C	Valsartan and diuretics	10,8	1,0	19	19	18	18	17
C	Atenolol	9,5	0,8	20	21	20	20	19
G	Tamsulosin	9,2	0,8	21	23	24	24	22
C	Lercanidipine	9,2	0,8	22	22	21	21	20
C	Glyceryl trinitrate	9,1	0,8	23	20	19	17	14
C	Telmisartan	9,0	0,8	24	24	22	23	23
J	Amoxicillin and enzyme inhibitor	8,8	0,8	25	25	25	25	24
C	Irbesartan	8,7	0,8	26	26	23	22	21
C	Bisoprolol	8,6	0,8	27	27	32	-	-
C	Candesartan	7,8	0,8	28	29	27	26	26
N	Paroxetine	7,8	0,6	29	30	28	29	31
C	Ramipril and diuretics	7,7	0,6	30	28	26	27	27
	Total	**628,2**	**56,4**					
	Total Class A DDD	**1.114,9**						

Table 7.2.22. Outpatient NHS consumption and expenditure for the year 2015: most frequently prescribed active ingredients for ATC level 1 categories (up to 75% of the expenditure within the therapeutic category

	Per capita gross expenditure	%*	Δ % 15-14	DDD/1000 inhab die	%*	Δ % 15-14
C - Cardiovascular System	**55,7**		**-1,2**	**465,6**		**-0,3**
Rosuvastatin	4,4	7,9	-6,6	13,0	2,8	-6,4
Atorvastatin	3,3	6,0	8,4	34,5	7,4	9,7
Simvastatin and ezetimibe	2,7	4,9	4,1	3,6	0,8	4,1
Olmesartan medoxomil	2,4	4,2	4,1	7,7	1,7	5,8
Olmesartan medoxomil and diuretics	2,1	3,8	4,4	6,9	1,5	4,8
Ramipril	2,1	3,7	0,4	60,3	13,0	0,9
Bisoprolol	1,9	3,4	7,8	8,6	1,8	7,8
Simvastatin	1,8	3,2	-2,6	15,0	3,2	-2,5
Omega-3-triglycerides incl. Other esters and acids	1,7	3,1	-14,1	3,6	0,8	3,3
Amlodipine	1,6	2,8	-1,9	26,7	5,7	-1,6
Nebivolol	1,3	2,4	2,2	13,8	3,0	3,1
Valsartan and diuretics	1,2	2,2	-5,9	10,8	2,3	-3,7
Olmesartan medoxomil and amlodipine	1,2	2,2	30,2	3,6	0,8	31,6
Doxazosin	1,2	2,2	-1,1	7,5	1,6	-1,2
Ezetimibe	1,2	2,1	32,8	1,8	0,4	32,8
Glyceryl trinitrate	1,1	1,9	-12,3	9,1	1,9	-10,9
Valsartan	0,9	1,7	-1,2	14,5	3,1	-0,2
Perindopril and amlodipine	0,9	1,6	17,9	4,6	1,0	18,0
Zofenopril and diuretics	0,9	1,6	-1,2	3,8	0,8	1,0
Losartan	0,8	1,5	-2,7	7,6	1,6	-1,3
Barnidipine	0,8	1,5	1,7	4,6	1,0	1,9
Irbesartan and diuretics	0,8	1,4	-4,8	6,5	1,4	-4,3
Lercanidipine	0,8	1,4	-1,3	9,2	2,0	-1,2
Ramipril and diuretics	0,7	1,3	-3,7	7,7	1,7	-2,5
Furosemide	0,7	1,3	1,9	24,4	5,2	1,9
Irbesartan	0,7	1,3	-3,4	8,7	1,9	-3,1
Carvedilol	0,7	1,2	-5,3	3,8	0,8	-5,0
Losartan and diuretics	0,7	1,2	-6,1	5,6	1,2	-5,4
Enalapril	0,6	1,1	-7,2	11,1	2,4	-6,5
Telmisartan and diuretics	0,6	1,1	-37,5	4,7	1,0	-1,8
A - Alimentary Tract and Metabolism	**33,0**		**0,8**	**232,3**		**6,7**
Pantoprazole	4,9	14,8	0,7	20,6	8,9	2,0
Lansoprazole	3,7	11,3	-9,7	18,6	8,0	-8,6
Omeprazole	3,2	9,6	-5,6	18,8	8,1	-4,2
Esomeprazole	2,7	8,1	-0,7	13,1	5,6	-0,8

	Per capita gross expenditure	%*	Δ % 15-14	DDD/1000 inhab die	%*	Δ % 15-14
Colecalciferol	2,3	6,9	38,1	82,9	35,7	27,6
Mesalazine	1,6	4,9	3,4	4,0	1,7	3,4
Insulin lispro	1,6	4,8	3,8	3,1	1,3	3,8
Insulin aspart	1,5	4,6	-0,2	3,0	1,3	-0,2
Rifaximin	1,4	4,3	0,1	1,9	0,8	0,1
Metformin	1,4	4,1	1,1	20,2	8,7	1,5
Alginic acid	0,8	2,4	2,3	2,3	1,0	2,0
N - Nervous System	**22,6**		**-1,5**	**61,6**		**1,5**
Pregabalin	2,1	9,4	5,0	1,6	2,6	5,7
Duloxetine	1,4	6,2	-20,6	2,6	4,3	0,5
Levetiracetam	1,2	5,4	8,3	1,6	2,6	8,7
Paroxetine	1,2	5,3	-2,3	7,8	12,6	0,2
Fentanyl	1,2	5,2	6,4	0,6	0,9	1,8
Oxycodone, combinations	1,1	4,7	14,8	0,6	1,0	8,9
Escitalopram	1,0	4,3	-36,8	7,2	11,7	0,8
Valproic acid	0,9	3,8	1,4	2,1	3,4	0,9
Venlafaxine	0,8	3,3	0,4	3,3	5,3	0,8
Tapentadol	0,7	3,3	28,1	0,3	0,5	28,2
Rasagiline	0,7	3,2	5,2	0,4	0,6	5,6
Rotigotine	0,7	2,9	5,4	0,3	0,5	5,7
Sertraline	0,6	2,8	-2,0	7,0	11,4	4,6
Levodopa and decarboxylase inhibitor	0,5	2,0	2,2	1,6	2,6	2,2
Citalopram	0,5	2,0	-4,1	4,3	7,0	-3,7
Quetiapine	0,4	1,7	52,7	0,3	0,5	56,3
Lamotrigine	0,4	1,6	5,3	0,6	0,9	5,6
Tramadol	0,3	1,4	-4,6	0,7	1,1	-4,5
Codeine, combinations excl. Psycholeptics	0,3	1,4	-6,6	1,2	2,0	-6,2
Gabapentin	0,3	1,4	1,4	0,4	0,6	1,4
Trazodone	0,3	1,4	13,0	0,8	1,4	14,9
Mirtazapine	0,3	1,3	2,5	1,4	2,3	1,7
Topiramate	0,3	1,3	-3,0	0,3	0,5	-0,9
R - Respiratory System	**17,2**		**0,0**	**46,4**		**-0,9**
Salmeterol and fluticasone	4,1	23,6	-13,2	5,0	10,8	-11,3
Tiotropium bromide	2,2	12,7	-8,9	3,5	7,7	-8,7
Formoterol and beclometasone	1,8	10,4	1,3	2,8	5,9	1,9
Beclometasone	1,4	8,1	0,9	6,3	13,6	1,5
Formoterol and budesonide	1,1	6,4	-7,0	1,2	2,7	-7,3
Glycopyrronium bromide	0,7	3,9	41,3	1,1	2,4	37,2
Vilanterol and fluticasone furoate	0,6	3,4	-	1,0	2,1	-

	Per capita gross expenditure	%*	Δ % 15-14	DDD/1000 inhab die	%*	Δ % 15-14
Aclidinium bromide	0,5	3,0	44,8	0,9	1,9	38,2
Montelukast	0,5	2,9	-4,6	2,0	4,4	**-2,9**
Indacaterol	0,4	2,5	-1,9	1,1	2,4	-2,2
J - Antiinfectives for Systemic Use	**14,2**		**-2,9**	**22,1**		**-2,9**
Amoxicillin and enzyme inhibitor	2,9	20,7	-2,3	8,8	39,8	-2,2
Ceftriaxone	1,4	10,2	-4,0	0,3	1,5	-4,3
Ciprofloxacin	1,1	7,7	0,0	1,1	4,8	-0,3
Levofloxacin	0,9	6,4	-0,4	1,7	7,5	0,2
Clarithromycin	0,9	6,3	-5,4	2,5	11,3	-3,4
Fluconazole	0,9	6,2	-5,8	0,4	1,9	-4,4
Cefixime	0,9	6,1	-0,3	1,0	4,6	0,7
Azithromycin	0,7	4,8	-2,9	1,3	5,8	-0,8
Fosfomycin	0,6	4,2	0,1	0,4	1,6	-0,1
Hepatitis B immunoglobulin	0,4	3,0	-4,3	<0,05	<0,05	-4,2
B - Blood and Blood Forming Organs	**8,7**		**-3,8**	**144,0**		**4,9**
Enoxaparin	2,5	28,8	-1,5	2,7	1,9	-1,3
Acetylsalicylic acid	1,4	16,7	2,8	52,5	36,4	0,9
Clopidogrel	0,9	10,1	18,9	4,1	2,9	23,5
Nadroparin	0,8	9,5	-11,0	0,8	0,5	-10,7
Folic acid	0,4	4,8	7,0	62,6	43,5	11,0
Ticlopidine	0,4	4,2	-13,8	3,9	2,7	-13,9
Parnaparin	0,3	3,1	-9,5	0,2	0,2	-9,2
G - Genito Urinary System and Sex Hormones	**7,0**		**1,4**	**42,6**		**<0,05**
dutasteride	2,4	34,8	7,8	6,8	16,0	7,8
tamsulosin	1,0	14,0	0,7	9,2	21,7	0,9
silodosin	0,7	10,6	18,4	4,0	9,3	18,4
alfuzosin	0,7	10,4	0,9	7,6	17,8	1,2
finasteride	0,6	8,0	-3,1	2,5	6,0	-3,0
M - Musculo-Skeletal System	**7,0**		**-6,5**	**39,6**		**-3,9**
Etoricoxib	1,1	16,3	-5,3	3,5	8,9	-6,2
Alendronic acid and colecalciferol	1,1	15,4	-6,5	3,3	8,2	-6,1
Febuxostat	0,6	9,0	17,4	1,3	3,3	25,7
Alendronic acid	0,6	9,0	2,7	3,0	7,6	5,4
Diclofenac	0,6	8,1	-4,5	3,9	9,7	-4,9
Risedronic acid	0,5	7,2	-11,0	2,5	6,4	-9,0
Ketoprofen	0,4	5,8	-8,7	3,8	9,6	-7,8
Ibuprofen	0,3	4,6	-4,2	2,0	5,1	-3,6
L - Antineoplastic and Immunomodulating Agents	**4,2**		**<0,05**	**4,8**		**4,2**
Ciclosporin	1,0	23,1	-4,7	0,2	5,1	-4,3

	Per capita gross expenditure	%*	Δ % 15-14	DDD/1000 inhab die	%*	Δ % 15-14
Letrozole	0,9	21,5	4,8	1,1	21,7	5,7
Methotrexate	0,7	16,7	4,2	0,4	8,4	1,2
Anastrozole	0,4	10,2	-0,9	0,8	16,4	1,4
Exemestane	0,2	5,3	16,6	0,3	5,4	17,9
S - Sensory Organs	**3,8**		**2,5**	**18,7**		**0,2**
Timolol, combinations	1,6	43,8	5,5	6,6	35,5	3,0
Bimatoprost	0,4	11,7	2,7	1,8	9,6	1,9
Travoprost	0,3	8,0	-3,7	1,0	5,4	-3,7
Tafluprost	0,3	7,9	10,5	0,9	5,0	10,5
Timolol	0,3	7,7	1,4	2,4	12,6	-4,8
H - Systemic hormonal preparations, excl. sex hormones and insulins	**2,9**		**-7,2**	**34,0**		**0,7**
Levothyroxine sodium	0,8	27,1	5,7	19,4	57,2	1,5
Prednisone	0,6	21,8	-1,1	5,8	17,2	1,0
Teriparatide	0,3	11,5	-17,4	<0,05	0,1	-17,4
Betamethasone	0,3	11,4	-5,7	2,1	6,3	-1,8
Methylprednisolone	0,2	7,7	-0,7	3,5	10,3	0,0
V - Various	**1,1**		**-1,3**	**0,1**		**22,7**
oxygen	0,9	87,5	-3,4	-		-
D - Dermatologicals	**0,9**		**-4,5**	**2,3**		**-6,0**
Calcipotriol, combinations	0,4	46,4	-5,7	0,7	31,1	-5,7
Calcipotriol	0,1	7,3	-9,8	0,3	11,5	-10,9
Terbinafine	0,1	7,3	-10,4	0,1	5,8	-11,0
Isotretinoin	0,1	7,2	0,9	0,1	5,7	0,8
Clobetasol	0,1	6,7	14,6	0,4	16,6	8,9
Ingenol mebutate	0,1	6,6	38,8	<0,05	0,2	38,4
P - Antiparasitic Products, Insecticides and Repellents	**0,2**		**-1,0**	**0,8**		**2,6**
Hydroxychloroquine	0,1	60,8	3,3	0,7	80,3	3,3
Mefloquine	<0,05	15,3	-12,2	<0,05	0,8	-12,2

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

^ Medical gas DDD value is not available

Table 7.2.23. Public health facilities consumption and expenditure in 2015: most frequently prescribed active ingredients for ATC level 1 categories (up to 75% of the expenditure within the therapeutic category

	Per capite gross expenditure	%*	Δ % 15-14	DDD/1000 inab die	%*	Δ % 15-14
L - Antineoplastic and Immunomodulating Agents	**64,5**		**7,5**	**8,4**		**1,9**
Adalimumab	4,4	6,8	5,7	0,3	3,9	7,1
Trastuzumab	4,3	6,6	5,5	0,2	1,9	21,4
Etanercept	3,6	5,5	0,2	0,3	3,2	0,2
Bevacizumab	3,3	5,1	16,6	0,1	1,4	23,2
Rituximab	3,2	5,0	2,2	0,4	5,3	11,7
Lenalidomide	2,7	4,2	12,2	<0,05	0,6	13,5
Imatinib	2,7	4,2	-7,2	0,1	1,3	-2,7
Interferon beta-1a	2,7	4,2	-12,4	0,6	7,3	-12,2
Fingolimod	1,7	2,7	9,2	0,1	1,0	20,4
Abiraterone	1,6	2,4	70,1	<0,05	0,5	69,8
Infliximab	1,6	2,4	-2,4	0,3	3,1	0,6
Bortezomib	1,4	2,1	-5,8	0,1	1,4	-2,7
Eculizumab	1,3	2,0	9,0	<0,05	0,0	14,4
Natalizumab	1,2	1,9	1,8	0,1	0,7	2,5
Pemetrexed	1,2	1,8	-3,9	<0,05	0,4	-1,9
Dasatinib	1,1	1,6	9,2	<0,05	0,3	8,5
Glatiramer acetate	1,0	1,6	-5,7	0,1	1,3	-4,9
Nilotinib	1,0	1,6	4,7	<0,05	0,2	10,2
Everolimus	1,0	1,5	-3,7	<0,05	0,2	-2,3
Leuprorelin	1,0	1,5	2,6	0,2	2,2	10,8
Trastuzumab emtansine	1,0	1,5	>100	<0,05	0,1	>100
Ipilimumab	0,9	1,4	32,3	0,0	0,1	39,2

	Per capite gross expenditure	%*	Δ % 15-14	DDD/1000 inab die	%*	Δ % 15-14
Golimumab	0,9	1,4	28,7	0,1	1,0	37,5
Pertuzumab	0,9	1,3	>100	<0,05	0,2	>100
Ustekinumab	0,9	1,3	29,4	0,1	1,1	41,6
Azacitidine	0,8	1,2	1,3	<0,05	0,1	4,2
Triptorelin	0,8	1,2	-5,9	0,7	8,6	-0,8
Sunitinib	0,8	1,2	-9,9	<0,05	0,2	-0,6
Cetuximab	0,7	1,1	-18,7	<0,05	0,2	-17,0
Abatacept	0,7	1,0	30,0	<0,05	0,5	23,1
Pegfilgrastim	0,6	1,0	-12,9	0,1	0,6	-13,1
Tacrolimus	0,6	1,0	11,0	0,3	3,1	10,1
Tocilizumab	0,6	0,9	28,4	<0,05	0,5	34,1
Sorafenib	0,5	0,8	-9,4	<0,05	0,1	-3,6
Pirfenidone	0,5	0,7	67,7	<0,05	0,2	64,3
Gefitinib	0,5	0,7	-13,2	<0,05	0,2	-16,4
J - Antiinfectives for Systemic Use	**54,1**		**109,2**	**7,3**		**5,2**
Tenofovir disoproxil and emtricitabine	14,7	27,1	>100	0,1	1,1	>100
Pneumococcus, purified polysaccharides antigen conjugated	7,1	13,2	-	<0,05	0,5	-
Entecavir	2,2	4,0	-	<0,05	0,3	-
Darunavir	2,1	4,0	-	<0,05	0,4	-
Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B	2,0	3,6	-	<0,05	0,3	-

	Per capite gross expenditure	%*	Δ % 15-14	DDD/1000 inab die	%*	Δ % 15-14
Lamivudine and abacavir	1,8	3,4	-9,7	0,3	4,7	-9,7
Emtricitabine, tenofovir disoproxil and efavirenz	1,5	2,7	6,3	0,1	1,1	2,0
Emtricitabine, tenofovir disoproxil and rilpivirine	1,2	2,3	8,9	0,3	3,6	8,4
Atazanavir	1,2	2,2	5,9	0,2	2,6	6,0
Raltegravir	1,2	2,1	-6,2	0,1	0,9	3,0
Tenofovir disoproxil	1,2	2,1	5,3	0,2	3,3	11,6
Immunoglobulins, normal human, for intravascular adm.	1,1	2,1	-23,0	0,2	2,1	-16,6
Caspofungin	1,0	1,9	84,7	0,1	1,9	94,9
Influenza, inactivated, split virus or surface antigen	0,9	1,6	-11,7	0,2	2,9	-11,6
Linezolid	0,8	1,6	-8,0	0,2	2,4	7,7
Teicoplanin	0,8	1,4	9,4	0,2	3,0	9,4
Immunoglobulins, normal human, for extravascular adm.	0,7	1,3	-4,8	<0,05	0,1	0,5
Amphotericin B	0,7	1,3	-0,1	<0,05	0,1	0,1
Tenofovir disoproxil and emtricitabine	0,7	1,3	8,8	1,2	16,5	1,9
Pneumococcus, purified polysaccharides antigen conjugated	0,7	1,2	6,2	<0,05	0,2	6,2
Entecavir	0,6	1,2	-1,9	<0,05	0,6	-2,3
Darunavir	0,5	0,9	19,1	0,1	1,5	31,0
Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B	0,5	0,9	6,1	<0,05	0,2	3,2
B - Blood and Blood Forming Organs	**22,9**		**5,4**	**39,4**		**7,7**
Coagulation factor VIII	4,8	21,0	-2,3	<0,05	0,1	-0,8
Erythropoietin	2,4	10,6	-7,7	2,2	5,6	2,7
Darbepoetin alfa	1,6	7,1	-2,5	0,7	1,7	-2,5
Enoxaparin	1,5	6,4	3,4	4,9	12,5	3,8
Rivaroxaban	1,1	4,8	131,8	2,9	7,3	148,5
Dabigatran etexilate	1,0	4,3	41,9	1,5	3,7	45,3
Eptacog alfa (activated)	1,0	4,2	-1,8	<0,05	0,0	-0,4
Apixaban	0,8	3,4	>100	1,6	4,0	>100
Combinations	0,7	3,2	11,3	0,2	0,4	1,0
Electrolytes	0,7	3,0	-28,5	5,2	13,1	-22,2
Nonacog alfa	0,6	2,7	4,1	<0,05	0,0	2,7
Treprostinil	0,5	2,3	8,9	<0,05	0,0	8,5
Ticagrelor	0,5	2,2	31,1	0,6	1,4	30,7
A - Alimentary Tract and Metabolism	**10,9**		**10,2**	**33,8**		**7,8**
Insulin glargine	1,6	15,0	-1,7	3,6	10,8	-1,7
Alglucosidase alfa	0,9	7,9	4,0	<0,05	0,0	9,0
Imiglucerase	0,8	7,2	10,8	<0,05	0,0	10,7

	Per capite gross expenditure	%*	Δ % 15-14	DDD/1000 inab die	%*	Δ % 15-14
Agalsidase alfa	0,7	6,6	4,5	<0,05	0,0	4,5
Liraglutide	0,6	5,5	4,1	0,6	1,8	4,1
Metformin and sitagliptin	0,6	5,1	5,3	1,1	3,3	5,3
N - Nervous System	**8,4**		**7,5**	**24,1**		**-2,7**
Aripiprazole	1,3	15,8	224,2	0,7	3,0	214,8
Paliperidone	0,9	10,9	19,5	0,5	1,9	14,8
Risperidone	0,5	6,3	-14,1	0,7	3,0	-3,9
Dimethyl fumarate	0,5	6,3	-	<0,05	0,2	-
Quetiapine	0,5	5,7	-36,0	1,3	5,5	-8,6
V - Various	**7,8**		**-8,0**	**2,0**		**-27,4**
Oxygen^	3,4	43,9	-9,5			
Deferasirox	1,0	13,0	-9,3	<0,05	2,2	-0,0
H - Systemic Hormonal Preparations, excl. Sex hormones and insulins	**5,0**		**2,2**	**5,7**		**4,0**
Somatropin	1,5	30,1	-5,0	0,3	4,5	6,2
Octreotide	0,8	16,2	-1,7	0,1	2,0	0,1
Teriparatide	0,5	10,7	16,6	0,1	2,0	16,5
Cinacalcet	0,5	9,9	13,7	0,1	1,8	13,4
C - Cardiovascular System	**3,9**		**14,0**	**16,7**		**-0,2**
Bosentan	1,6	40,0	3,1	<0,05	0,3	-5,7
Ivabradine	0,6	15,6	7,5	1,2	7,3	5,0
Ranolazine	0,6	14,5	23,2	0,6	3,3	30,9
S - Sensory Organs	**2,0**		**13,3**	**1,8**		**-7,6**
Ranibizumab	1,1	56,0	-12,7	0,1	7,5	-8,9
Aflibercept	0,5	23,4	>100	0,1	3,3	>100
G - Genito Urinary System and Sex Hormones	**2,0**		**7,4**	**1,9**		**10,2**
Follitropin Alfa	0,7	35,4	6,3	0,1	3,8	6,4
R - Respiratory System	**1,3**		**32,1**	**2,7**		**-1,2**
M - Musculo-Skeletal System	**1,0**		**16,7**	**3,6**		**17,6**
Denosumab	0,5	46,3	72,5	1,6	44,9	69,2
D - Dermatologicals	**0,3**		**-2,6**	**6,7**		**-21,2**
P - Antiparasitic Products, Insecticides And Repellents	**0,0**		**20,9**	**<0,05**		**16,8**

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

^ Medical gas DDD value is not available

SECTION 8

ADVERSE DRUG REACTIONS MONITORING

8.1 Annual distribution of suspected adverse drug reactions, in Italy, from 2001 to 2015

During 2015, 49.655 suspected Adverse Drug Reaction (ADR) reports were recorded into the National Pharmacovigilance Network (RNF) database. The RNF is an extensive Italian network that collects reports of suspected ADRs. In addition, 3.822 ADR reports, coming from the medical literature, were provided by the pharmaceutical companies, for a total of 53.477 reports

During 2015 the Italian reporting rate amounts to 817 per million inhabitants (Figure 8.1.1), corresponding to an overall percentage reduction (with the exclusion of ADR reports coming from medical literature) decreased by -2,9% on the previous year, with a reduction of -4,7% for vaccines and of -2,6% for other medicines (Table 8.1.1).

Figure 8.1.1 Annual distribution of the number and reporting rate per million inhabitants (2001-2015)

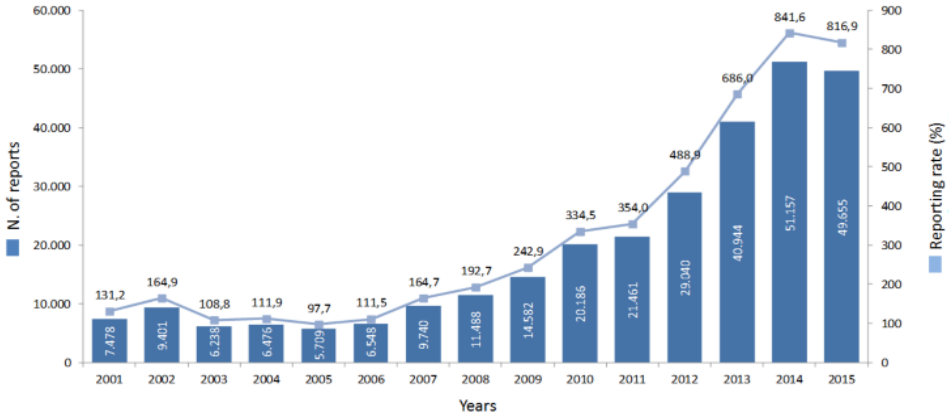


Table 8.1.1. Changes in ADR reports (%) on the previous year

YEARS	Δ% ADR reports (vaccines ADRs excluded)	Δ% ADR reports due to vaccines	Δ% ADR reports
2001			
2002	33,6%	-25,9%	25,7%
2003	-37,2%	8,2%	-33,6%
2004	-17,3%	148,6%	3,8%
2005	-13,4%	-8,4%	-11,8%
2006	21,1%	0,8%	14,7%
2007	69,0%	-3,7%	48,7%
2008	19,1%	12,7%	17,9%
2009	16,6%	76,6%	26,9%
2010	59,7%	-28,7%	38,4%
2011	1,9%	37,8%	6,3%
2012	40,8%	6,6%	35,3%
2013	46,9%	0,2%	41,0%
2014	15,1%	125,2%	24,9%
2015	-2,6%	-4,7%	-2,9%

As observed in the previous years, also in 2015 the highest number of reports was for medications used for adults and older people in line with the aging population that is correlated to multimorbidity and increased consumption of medications.

Data collected through the system of spontaneous reporting is even more important when you consider that the elderly represent an unselected population and often poorly represented in clinical trials which precede the marketing of drugs, for which the acquisition of data from post-marketing becomes essential.
Decrease compared to 2014 reports refer to the drugs used in children (from 1,704 to 1,021). As regards the vaccines the 80% of reports is reported to immunization in the first two years of life. (Table 8.1.2)

Table 8.1.2. Distribution of ADR reports by age group, medication and vaccines.

Age group	ADR reports (vaccines excluded) (N)	%	Vaccines ADR reports (N)	%
not available	1.584	3,8%	24	0,3%
neonates (<1 month)	40	0,1%	4	0,1%
infant (1-23 months)	384	0,9%	6.273	79,5%
children (2-11 years)	1.021	2,4%	681	8,6%
adolescent (12-17 years)	618	1,5%	192	2,4%
adult (18-65 years)	19.418	46,5%	448	5,7%
elderly (>65 years)	18.698	44,8%	270	3,4%
Total	**41.763**	**100,0%**	**7.892**	**100,0%**

The 54% of all reports concerned the female population, this finding is in line with higher consumption of drugs by women than men.
In 2015, similarly to 2014, approximately one third (32%) of received reports was classified as serious and mainly because resulting in or prolonging hospitalisation (Table 8.1.3).
For what concern reactions resulting in death the number is in line with data reported in the scientific literature. In 34% of cases the death was not considered related to the drug or to an unknown cause when a comment/ explanation was available.

Table 8.1.3. ADR reports distribution by severity in 2015

Severity	Severity criterion	Number of reports	%*
Other than serious		31.566	64%
Unspecified		1.990	4%
Serious		16.099	32%
	Other condition medically significant	6.190	38%
	Congenital abnormalities / deficit of new-born	16	0%
	Fatal	344	2%
	Disabling or incapacitating	219	1%
	Result in or prolong hospitalisation	8.571	53%
	Life-threatening	759	5%
Total		**49.655**	**100%**

*Calculated on the total number of reports

The 48% of the reports are from hospital doctors, followed by those from specialists (19%) and pharmacists (13%). Almost all reports coming from "specialists" or "other" refer to vaccines reports compiled by physicians / healthcare professionals working in vaccination centers. There are still few reports from general practitioners accounting for 5% of total reports in 2015, this value is decreased of 18% compared to 2014.
The high percentage of reports from pharmacists should be interpreted taking into account the number of projects of active pharmacovigilance implemented in recent years. Most reports come, in fact, from hospital pharmacists involved such efforts. With regards to the reporting source, it was observed a very high percentage of reports received from patients (+529,2% on 2014). (Table 8.1.4).
The decrease in the number of reports from pharmaceutical companies reporting is probably due to the change in criteria for ADR alerts inclusion in RFN occurred in 2015. In fact, this change removed the possibility to select a pharmaceutical company as an ADR reporter.

Table 8.1.4 Totals number of ADR reports by reporter group in 2015

Reporter group	N. of reports	%*	Δ% 15-14
Hospital doctors	23.773	46%	-0,1%
Medical specialists	9.170	18%	28,7%
Pharmacists	6.315	14%	-31,5%
General practitioners	2.789	7%	-18,3%
Patients	2.303	4%	529,2%
Nurses	1.337	4%	-19,0%
Pharmaceutical companies	448	3%	-79,5%
Poison control centres	215	1%	-28,8%
Paediatricians of free choice	258	1%	-29,5%
Others	3.022	1%	36,6%
Not specified	25	1%	-95,1%
Total	**49.655**	**100%**	

*Calculated on the total number of reports

In 2015, the highest number of reports concerned medicines belonging to the following ATC classes: antineoplastics, antimicrobials, central nervous system and blood.
The high number of ADR reports on antineoplastics medicines could be related to the high toxicity levels of these products and to the establishment of registries by AIFA. These registries, in fact, require that health care professionals record clinical and safety data during therapy (Table 8.1.5).

Table 8.1.5. Distribution of ADR reports for ATC class in 2015 (vaccines ADR reports excluded).

ATC	ATC description	N. of Reports	%*	Δ% 15-14
A	Alimentary tract and metabolism	2.594	6,2%	6,7%
B	Blood and blood forming organs	6.044	14,5%	-6,3%
C	Cardiovascular system	3.332	8,0%	-12,8%
D	Dermatological	216	0,5%	-23,4%
G	Genitourinary system and sex hormones	677	1,6%	-2,9%
H	Systemic hormonal preparations, excluding sex hormones and insulins	910	2,2%	7,1%
J	Antimicrobials for systemic use	6.182	14,8%	-15,7%
L	Antineoplastic and immunomodulating agents	10.489	25,1%	13,3%
M	Musculoskeletal system	2.462	5,9%	-24,8%
N	Central Nervous System	5.953	14,3%	-7,9%
P	Antiparasitic products, insecticides and repellents	96	0,2%	1,1%
R	Respiratory system	625	1,5%	-19,4%
S	Sensory organs	243	0,6%	-10,7%
V	Various	1.554	3,7%	-5,0%

*Calculated on the total number of reports

While the ADRs most frequently reported, according the System Organ Classes (vaccines ADR excluded), are those related to the Skin and subcutaneous tissue disorders class that amount to 10.356 cases, followed by General disorders and administration site conditions class (8.371) and by Gastrointestinal disorders class (8.291) (Table 8.1.6.).

Table 8.1.6. Distribution of ADR by System Organ Classes in 2015 (vaccines ADR reports excluded).

MedDRA System Organ Classes (SOCs)	N. of ADRs	%*	Δ% 15-14
Blood and lymphatic system disorders	2.976	7,1%	1,8%
Cardiac disorders	1.523	3,6%	-10,7%
Congenital, familial and genetic disorders	47	0,1%	42,4%
Ear and labyrinth disorders	787	1,9%	-8,4%
Endocrine disorders	130	0,3%	0,8%
Eye disorders	1.086	2,6%	-13,8%
Gastrointestinal disorders	8.291	19,9%	-9,3%
General disorders and administration site conditions	8.371	20,0%	13,7%
Hepatobiliary disorders	688	1,6%	23,3%
Immune system disorders	1.039	2,5%	-2,7%
Infections and infestations	1.232	2,9%	18,2%
Injury, poisoning and procedural complications	1.664	4,0%	4,0%
Investigations	2.564	6,1%	10,6%
Metabolism and nutrition disorders	2.594	6,2%	12,5%
Musculoskeletal and connective tissue disorders	2.293	5,5%	7,7%
Benign, malignant and unspecified (including cysts and polyps) tumor	398	1,0%	82,6%
Nervous system disorders	5.828	14,0%	-3,9%
Pregnancy, puerperium and perinatal conditions	63	0,2%	80,0%
Psychiatric disorders	3.047	7,3%	-4,8%
Renal and urinary disorders	1.042	2,5%	-6,2%
Reproductive system and breast disorders	460	1,1%	1,3%
Respiratory, thoracic and mediastinal disorders	4.451	10,7%	-2,4%
Skin and subcutaneous tissue disorders	10.356	24,8%	-16,5%
Social circumstances	57	0,1%	280,0%
Surgical and medical procedures	82	0,2%	39,0%
Vascular disorders	2.676	6,4%	1,2%

* Calculated on the total number of reports

The active ingredients with the highest number of adverse reactions reports (> 1000 reports) are: warfarin, combination of amoxicillin plus clavulanic acid and acetylsalicylic acid (Table 8.1.7).

Table 8.1.7. First thirty active ingredients for the number of ADR reports in 2015 (vaccines ADR reports excluded).

Rank	Active ingredients	Number of reports	Inc. %	Δ % 15-14	% Serious reports	Rank 2014
1	Warfarin	2.083	5,0%	-13,1%	49,9%	1
2	Amoxicillin/clavulanic acid	1.606	3,8%	-29,6%	34,3%	2
3	Acetylsalicylic acid	1.270	3,0%	-7,8%	49,1%	3
4	Insulin	1.004	2,4%	43,4%	73,6%	9
5	Ribavirin	749	1,8%	15,1%	38,5%	11
6	Oxaliplatin	741	1,8%	10,9%	34,7%	10
7	Fluorouracil	700	1,7%	32,8%	32,4%	16
8	Paclitaxel	674	1,6%	29,1%	34,0%	17
9	Clopidogrel	623	1,5%	-17,8%	34,8%	6
10	Levofloxacin	575	1,4%	-18,1%	34,3%	8
11	Ketoprofen	548	1,3%	-37,6%	41,2%	4
12	Lenalidomide	547	1,3%	>100%	21,4%	50
13	Dabigatran	533	1,3%	-26,3%	36,4%	7
14	Ibuprofen	493	1,2%	-22,0%	39,1%	12
15	Amoxicillin	472	1,1%	-40,6%	31,8%	5
16	Ceftriaxone	456	1,1%	-16,6%	48,5%	15
17	Interferon Beta	445	1,1%	69,2%	11,5%	41
18	Sofosbuvir	434	1,0%	>100%	45,9%	405
19	Paracetamol	422	1,0%	-30,4%	41,5%	14
20	Metformin	412	1,0%	25,6%	68,2%	30
21	Iomeprol	407	1,0%	-18,4%	17,4%	18
22	Rivaroxaban	401	1,0%	66,4%	43,4%	45
23	Carboplatin	387	0,9%	8,7%	42,6%	27
24	Bevacizumab	383	0,9%	27,7%	42,3%	33
25	Gemcitabine	377	0,9%	49,6%	38,7%	44
26	Diclofenac	375	0,9%	-17,2%	37,9%	19
27	Ciprofloxacin	339	0,8%	-17,9%	31,3%	21
28	Docetaxel	331	0,8%	-13,1%	33,2%	22
29	Ramipril	317	0,8%	-14,3%	30,9%	23
30	Quetiapine	310	0,7%	-14,4%	44,2%	25

In table 8.1.8 are reported active ingredients, with at least 150 reports during 2015, that showed an evident increase compared to the previous year.

Table 8.1.8. Active ingredients with a significant increase in reports in 2015 compared to the previous year (vaccines ADR reports excluded).

Active ingredients	Number of reports 2014	Number of reports 2015	Δ % 2015 -2014	% Serious reports
Dasabuvir	0	174	-	54,6%
Ombitasvir/Paritaprevir/Ritonavir	0	169	-	52,7%
Simeprevir	5	196	>100%	39,8%
Sofosbuvir	18	434	>100%	45,9%
Apixaban	95	281	>100%	46,6%
Lenalidomide	225	547	>100%	21,4%
Pirfenidone	123	249	>100%	12,9%
Trastuzumab	150	298	98,7%	29,9%
Fingolimod	173	303	75,1%	29,7%
Beta Interferon	263	445	69,2%	11,5%
Teriparatide	181	305	68,5%	10,5%
Rivaroxaban	241	401	66,4%	43,4%
Pemetrexed	128	200	56,3%	39,5%
Sunitinib	122	184	50,8%	37,5%
Gemcitabine	252	377	49,6%	38,7%
Insulin	700	1004	43,4%	73,6%
Fluorouracil	527	700	32,8%	32,4%
Paclitaxel	522	674	29,1%	34,0%
Lormetazepam	163	209	28,2%	87,1%
Bevacizumab	300	383	27,7%	42,3%

AIFA, in collaboration with Regional Centres of Pharmacovigilance, has continued the systematic analysis of reports collected in the database of Pharmacovigilance Network and EudraVigilance, paying particular attention on active substances for which Italy has been appointed Reference Member State in the EU.
Furthermore, also in 2015, particular attention was paid towards activities aimed at ensuring greater transparency and timeliness of information, as required by new pharmacovigilance regulations.

Conclusions

Despite a slight decline in the number of reports, in Italy the system of spontaneous reporting is still one of the first in the world in terms of frequency. This enables an effective monitoring of risk profiles of drugs used in Italy. The involvement of Regional Pharmacovigilance Centres and experts in the field of prevention, as regards vaccines, allowed a timely and effective analysis of data collected, and the identification of signals that are presented for debate at European level.

The distribution of ADR reporter groups shows that there are professionals not actively involved in the reporting system (such as general practitioners or paediatricians of free choice) while they may provide very useful information for the study of adverse reactions in specific patient populations. This issue (low spontaneous reporting rate) is common across Europe and AIFA, like other National Centres, together Regions, Regional Centres and Heads of Pharmacovigilance of LHU/Hospitals is working on one hand, to sensitize health care professionals on the topic of pharmacovigilance, and on the other, to facilitate the reporting procedures through innovative ICT tools. In fact, a web-based reporting system dedicated to health professionals and patients/citizens, is currently been developed. In this direction, an increased real-time use of mobile technologies could also lead to a greater involvement of patients/citizens in the system.