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Italian Blood System 2018: demand for plasma-derived medicinal products. Volume 2

F. Candura, M.L. Salvatori, M.S. Massari, G. Calizzani, S. Profili,
C. Chelucci, C. Brutti, C. Biffoli, S. Pupella, G.M. Liumbruno, V. De Angelis



EPIDEMIOLOGIA
E SANITÀ PUBBLICA

ISTITUTO SUPERIORE DI SANITÀ

**Italian Blood System 2018:
demand for plasma-derived medicinal products.
Volume 2**

Fabio Candura (a), Maria Lavinia Salvatori (a),
Maria Simona Massari (a), Gabriele Calizzani (a), Samantha Profili (a),
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With the aim of fulfilling the task assigned it pursuant to national regulations regarding coordinating and providing technical support to the planning of self-sufficiency in blood components and plasma-derived medicinal products at regional and national level, the Italian National Blood Centre has conducted an analysis in collaboration with the Information and Statistics Department of the Italian Health Ministry. The analysis of the demand for plasma-derived medicinal products and recombinant therapies included the assessment of self-sufficiency levels achieved and the costs sustained by the Italian National Health Service for the provision of these products. The content of this document, an update of the data for the year 2017 published in the Rapporto ISTISAN 20/13, was obtained by conducting a comparative analysis of the available data sources. The document is also an invaluable tool for planning self-sufficiency at national level.

Key words: Plasma-derived medicinal products; Demand; Self-sufficiency; Expenditure

Istituto Superiore di Sanità

Sistema trasfusionale italiano 2018: analisi della domanda dei medicinali plasmaderivati. Volume 2.

Fabio Candura, Maria Lavinia Salvatori, Maria Simona Massari, Gabriele Calizzani, Samantha Profili, Cristiana Chelucci, Chiara Brutti, Claudia Biffoli, Simonetta Pupella, Giancarlo Maria Liunbruno, Vincenzo De Angelis
2020, vii, 138 p. Rapporti ISTISAN 20/23 (in inglese)

Al fine di adempiere ai compiti ad esso assegnati dalla normativa vigente in materia di coordinamento e supporto tecnico alla programmazione dell'autosufficienza regionale e nazionale di emocomponenti e medicinali plasmaderivati, il Centro Nazionale Sangue ha effettuato, in collaborazione con l'Ufficio IV della Direzione Generale del Sistema Informativo e Statistico Sanitario del Ministero della Salute, l'analisi della domanda dei prodotti medicinali plasmaderivati e delle alternative terapeutiche di natura ricombinante, le valutazioni dei livelli di autosufficienza regionale e nazionale e la stima della spesa farmaceutica a carico del Servizio Sanitario Nazionale. Il confronto delle diverse fonti dati disponibili ha consentito l'elaborazione del presente documento che riporta l'aggiornamento relativo all'anno 2017 dei dati sull'argomento pubblicati nel Rapporto ISTISAN 20/13 e che si configura come uno strumento fondamentale per la programmazione dell'autosufficienza nazionale.

Parole chiave: Medicinali plasmaderivati; Domanda; Autosufficienza; Spesa

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ACRONYMS AND ABBREVIATIONS

3F-PCCs	3-Factor Prothrombin Complex Concentrates
4F-PCCs	4-Factor Prothrombin Complex Concentrates
AIC	<i>Autorizzazione di Immissione in Commercio</i> (Marketing Authorisation)
AIFA	<i>Agenzia Italiana del Farmaco</i> (Italian Medicines Agency)
AP	Autonomous Province
aPCCs	Activated Prothrombin Complex Concentrates
AT	AntiThrombin
ATC	Anatomical Therapeutic Chemical classification system
BE/s	Blood Establishment/s
BCU/s	Blood Collection Unit/s
BHK	Baby Hamster Kidney fibroblasts
BZ	Bolzano
CHO	Chinese Hamster Ovary cells
CMV	CytoMegaloVirus
CNS	<i>Centro Nazionale Sangue</i>
DL	<i>Decreto Legge</i> (Decree Law)
DL.vo	<i>Decreto Legislativo</i> (Legislative Decree)
DM	<i>Decreto Ministeriale</i> (Ministerial Decree of the Ministry of Health)
ELC	Essential Levels of Care
ER	Emilia-Romagna
F	Factor
pdFVII	Plasma-derived factor VII
pdFVIII	Plasma-derived factor VIII
pdFIX	Plasma-derived factor IX
Friuli-V. Giulia	Friuli-Venezia Giulia
FU/s	FEIBA Unit/s
FVG	Friuli-Venezia Giulia
IG	ImmunoGlobulin
ISTAT	<i>Istituto Italiano di Statistica</i> (Italian National Statistics Institute)
IU/s	International Unit/s
IVIG	IntraVenous ImmunoGlobulin
LHCs	Local Health Centres
LPS	Lombardy-Piedmont-Sardinia Agreement
Min	Ministry
MoH	Ministry of Health
NAIP	<i>Nuovo Accordo Interregionale per la Plasmaderivazione</i> (New Interregional Agreement for plasma-derived medicinal products)
NHS	National Health Service
NSIS	<i>Nuovo Sistema Informativo Sanitario</i> (New Health Information System)
PDMP/s	Plasma-Derived Medicinal Product/s
rFVIIa	Recombinant activated Factor VII
rFVIII	Recombinant Factor VIII
rFIX	Recombinant Factor IX
S/D	Solvent / Detergent (plasma)
SC/IM	SubCutaneous/IntraMuscular
ST/s	Transfusion Service/s
UdR	Collection Units run by Donor Associations
VAT	Value Added Tax
vWF	von Willebrand Factor
WHO	World Health Organisation

PRESENTATION

Plasma-derived medicinal products (PDMPs) represent a heterogeneous class of medicines whose common characteristic is their origin from human plasma and a complex and highly regulated manufacturing process. These products are critical in the treatment of a variety of diseases and the survival of patients suffering from different life-threatening diseases is strictly dependent from a regular availability of PMPDs. Achievement of self-sufficiency in plasma products from voluntary non remunerated healthy donors has been advocated by the Italian legislation and PDMPs from plasma collected by the Italian public transfusion system can be only supplied by authorised third-party companies fractionating national plasma in the framework of contract manufacturing agreements. Nevertheless, at the moment, self-sufficiency is far from being achieved. The fractionation of national plasma covers the internal demand for albumin for around 70% and that for immunoglobulins for around 60%, the remaining part relies on the market provision together with a variety of other plasma proteins. Therefore, it is of utmost importance to have a deep and complete picture of the demand and the use of these products in the country, in order to modulate plasma collection and to promote the policies for an appropriate utilisation of plasma products, with the aim of satisfying clinical needs through national plasma.

This is the sixth report of the Italian demand for PDMPs; it offers an exhaustive study and understanding of the national provision of these products and, together with the previous reports, clearly depicts the results of the national efforts toward self-sufficiency during these last years. Moreover, it offers a strategic and effective tool aimed at building up a system capable of guaranteeing and maintaining a proper utilisation of national plasma, an ethical exploitation of donations, an appropriate clinical use of plasma products and an adequate provision of medicines to patients. Without such data, planning for a rational and cost-effective national plasma program would be simply impossible.

This report is dedicated to the memory of dr. Gabriele Calizzani, who passed away just before the publication; he first conceived the idea of an annual report on the national demand for PDMPs and he was among the main contributors to all the editions until the present one; his passionate work is gratefully acknowledged.

Vincenzo De Angelis
Director of the Italian National Blood Centre

INTRODUCTION

Plasma-derived Medicinal Products (PDMPs) are pharmaceutical specialties produced through the industrial processing of plasma that is the liquid component of the blood collected from voluntary donors through apheresis or recovered from whole blood by centrifugation. PDMPs play a key, and sometimes irreplaceable, role in the treatment of many acute and chronic clinical conditions (1).

Given their biological nature, the quality and safety of PDMPs are based on the controls carried out on the raw material – “plasma” – and on its origin, as well as on the industrial manufacturing processes, which include removal and viral inactivation steps (2).

In Italy, plasma comes exclusively from the voluntary, anonymous and unremunerated donations of mainly periodic donors. Regions and Autonomous Provinces (APs) (hereinafter Regions), individually or in association, supply the plasma collected by Blood Establishments (BEs), to the Company(s) holder(s) of the agreements for the industrial transformation of plasma for the production of PDMPs. The contract with companies, which operate as service providers, is considered a “third party processing” method, the acquisition of which by the Regions is implemented by means of a tender procedure in accordance with current legislation (3).

In June 2017, the New Interregional Agreement for Plasma-Derived Medicinal Products (*Nuovo Accordo Interregionale per la Plasmaderivazione*, NAIP), led by the Veneto Region, started to send plasma for fractionation to CSL Behring, the company that won the tender launched in 2015 pursuant to Law 219/2005 (4), whose contract provides for the production of the following PDMPs: albumin, normal human immunoglobulins for intravenous use (IntraVenous ImmunoGlobulin, IVIG), subcutaneous (SC)/ intramuscular (IM) immunoglobulins (IG), factor VIII concentrates of plasma origin (pdFVIII), pdFVIII and von Willebrand factor (vWF) in combination concentrates (pdFVIII/vWF), and fibrinogen. In 2018, the distribution of PDMPs manufactured by CSL Behring and returned to NAIP Regions was recorded for the first time.

Pending the launching of other tenders for the assignment of the plasma toll-fractionation service, the other Regions were still affiliated exclusively with the company Kedrion SpA (hereinafter Kedrion), whose contract provided for the production of the following PDMPs: albumin, IVIG, Anti-Thrombin (AT), pdFVIII, plasma-derived Factor IX concentrates (pdFIX), and 3-factor Prothrombin Complex Concentrates (3F-PCCs).

In consideration of the clinical interest and their impact on pharmaceutical expenditure, the report describes the demand for other PDMPs and for the recombinant medicinal products used for the treatment of congenital and acquired bleeding disorders distributed through commercial channels, with a particular concern to long-acting and innovative haemostatic products.

For each of the PDMPs whose supply is included in the contracts between the Regions and the fractionators (Kedrion and CSL Behring), the level of regional and national self-sufficiencies is estimated.

Finally, the pharmaceutical expenditure incurred by the National Health Service (NHS) for procurement on the market is described, regardless of whether it is or not the portion of the NHS demand not covered by toll fractionation agreements.

The report, after a description of data sources and the methodology used, analyses the demand for each active ingredient, the level of self-sufficiency in the PDMPs produced by toll fractionation, and pharmaceutical expenditure.

It is divided into four analytical sections:

- *Part A*
The demand for PDMPs currently provided by toll fractionation agreements.
- *Part B*
The demand for PDMPs.
- *Part C*
National and Regional PDMP self-sufficiency.
- *Part D*
Pharmaceutical expenditure for plasma-derived and recombinant medicinal products.

SOURCES AND METHODOLOGY

Data sources

Drug traceability flow

Since January 2005, the medicinal products traceability database (5) has been updated daily with data gathered from the delivery notes of drugs belonging to each reimbursement and dispensation regime. Every actor involved in their production and distribution – production sites, warehouses and wholesalers, pharmacies, hospitals etc. – is assigned a unique identifying code and each single package is tracked through a marketing authorisation code (*Autorizzazione all’Immissione in Commercio*, AIC code) during every step of the entire supply chain process (Figure 1).

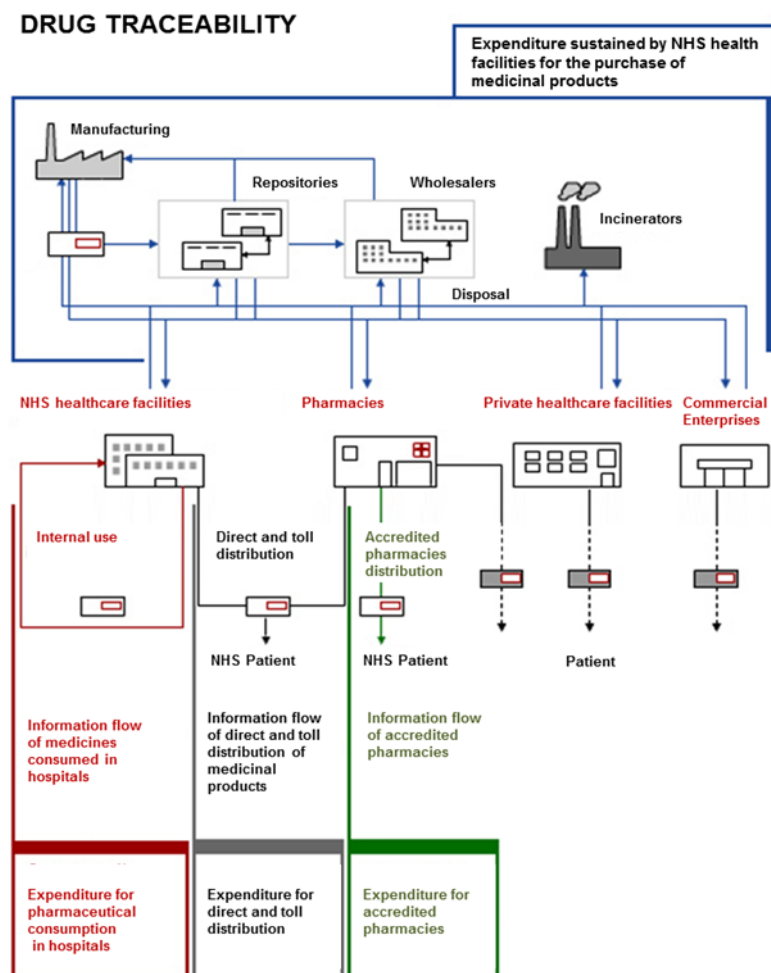


Figure 1. The drug traceability system in Italy (adapted by the CNS on data from www.salute.gov.it)

Pursuant to Italian law, if the final receiver is a public entity (hospital pharmacy, public healthcare facility, etc.), also the payment due is detected along with the quantity of the product in order to monitor pharmaceutical expenditure. Thus, the drug traceability system keeps track of all medicinal product movements identified by the AIC code and quantified by the number of packages, from one logistics site to another (see details below dotted horizontal line in Figure 1) without considering any final user.

Therefore, the drug traceability system is suitable to quantify the total demand for PDMPs because it takes into account the quantities distributed to both public and private health facilities, and to pharmacies regardless of the dispensation regime, and whether or not charged to the Italian NHS.

Information flow of accredited pharmacies

The “Health Card” project (Law 326/2003) (6), established the information flow that records all data related to prescription drugs with the aim of monitoring the pharmaceutical services funded by the NHS and provided by public pharmacies.

This dispensation regime concerns the medicinal products included in the Essential Levels of Care (ELC).

This information flow is the most suitable for calculating the demand for PDMPs provided through public pharmacies and it is managed and supplied by the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) (Figure 2).

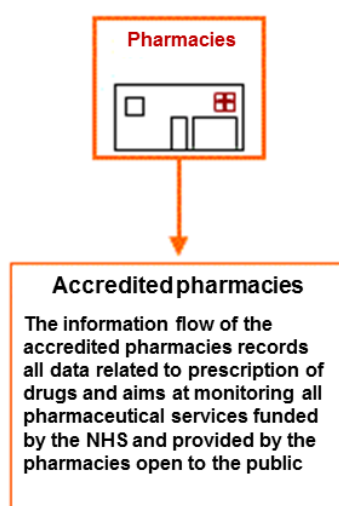


Figure 2. Scope of the information flow of accredited pharmacies (adapted by the CNS on data from www.salute.gov.it)

Information flow of the direct provision of medicinal products

The institutional information flow of the direct provision of medicinal products records the home utilisation of medicinal products distributed by public healthcare facilities; direct provision can also occur through specific agreements with public pharmacies (toll distribution).

- This information flow, established by DM of 31 July 2007 (7), considers:
- medicinal products given to the patient to be utilised at home;

- medicinal products provided directly by healthcare facilities after hospital discharge or medical examination;
- medicinal products provided to chronic patients within disease-specific therapeutic plans and to patients for home care;
- medicinal products distributed to prison facilities;
- medicinal products provided by public and private pharmacies on behalf of local health centres (LHCs) (toll distribution).

The medicinal products considered in this information flow are all drugs with an AIC (MA), regardless of the class of reimbursement (A-C-H), magistral formulations, officinal formulas and foreign medicines not authorised to be sold in Italy and used pursuant to DM of 11 February 1997 (8). In the latter cases, the pharmaceutical performance is identified through the Anatomical Therapeutic Chemical (ATC) classification system, (see dedicated paragraph).

This information flow consists of the following details that are submitted monthly to the MoH: providing facility, prescription barcode (which through the prescription pad database can be traced to the prescriber), patient, medicinal product code, date of delivery, quantity delivered and related expenditure. Until 2009, only the costs, and not the related quantities, were recorded.

The institutional information flow of the direct provision of medicinal products, shown in Figure 3, records the medicinal product delivery on a nominal basis.

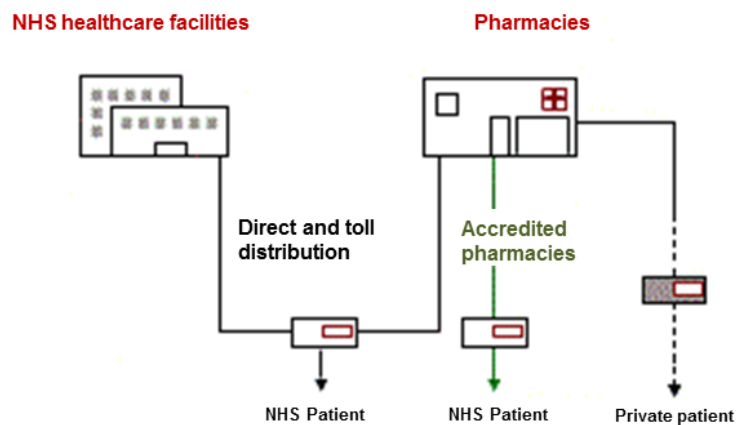


Figure 3. Medicinal products information flow
(adapted by the CNS on data from www.salute.gov.it)

This information flow is the most suitable for quantifying the NHS's demand for PDMPs, provided through the direct distribution channel. The information recorded by this flow makes it possible to assess the appropriateness of the prescription and the appropriateness of the total number of medicinal products consumed by patients, as well as to compare the drug acquisition costs incurred by single health facilities, thus allowing an indirect evaluation of the purchase tenders.

Information flow of medicines consumed in hospitals

In order to monitor the consumption of medicinal products in hospitals, the information flow takes into consideration the medicinal products utilised by public healthcare facilities.

These include all medicinal products with an AIC code, regardless of their reimbursement class (A, C, H), masterly formulations, medicinal formulas and foreign medicines not authorised to be sold in Italy and used in accordance with DM of 11 February 1997 (8). In the latter cases, pharmaceutical performance is identified by the ATC code.

The information flow includes the following details submitted monthly to the MoH: providing facility, receiving operating unit, recipient activity regime, drug code, disbursement date, quantity delivered and related expenditure.

The movement of toll-manufactured PDMPs is not associated with a purchase cost; however, an estimate of the aforementioned costs can be made through the exchange fees defined in the State-Regions Agreement of 20 October 2015 (9).

Therefore to monitor the consumption of medicinal products in hospitals, the information flow detects the internal movements of drugs purchased or made available for use by healthcare facilities directly managed by the Italian NHS, with the exception of those delivered through direct distribution. The hospital information flow records the movements of single packages to the operating units, as shown in Figure 4. This flow is the most suitable for quantifying the consumption of those PDMPs whose costs are covered by the NHS and which are used during hospitalisation or outpatient regimens.

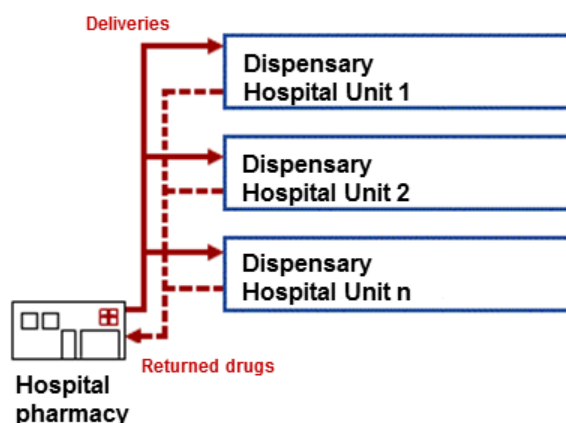


Figure 4. Information flow of medicines consumed in hospitals (adapted by the CNS on data from www.salute.gov.it)

Data on plasma-derived medicinal products produced from Italian plasma

The Italian National Blood Centre (Centro Nazionale Sangue, CNS) receives the data regarding PDMPs distributed by Kedrion and CSL Behring on behalf of the Regions from the aforesaid companies themselves as part of their toll-manufacturing contracts. These figures go to form the database for the analysis of PDMP production from national plasma.

Data on plasma-derived medicinal products subject to import procedures

Data related to the PDMPs imported by Italy due to a national shortage, registered abroad and subject to import procedures pursuant to DM of 11 February 1997 (8), and DM of 11 May 2001 (10), are provided by the Product Quality Office of the AIFA.

Data processing and the ATC drug classification system

For this report, different data sources were accessed to detect the number of packages – by reference year and by unique AIC codes – and to identify quantities of active ingredients of distributed PDMPs. The individual AIC codes were traced back to the relevant active ingredient and to the related ATC code.

The ATC system is a drug classification system managed by the Nordic Council on Medicine and the Collaborating Centre for Drug Statistics Methodology of the World Health Organisation (WHO) in Oslo, Norway (www.whooc.no).

Under the ATC system, drugs are classified in different groups according to the target organ, their mechanism of action and chemical and therapeutic properties. The main groups of the ATC system are further divided into 5 hierarchical levels, shown in Table 1.

Table 1. ATC classification system

Level	Description	Note
I	anatomical main group	consists of one letter
II	therapeutic main group	consists of two digits
III	therapeutic subgroup	consists of one letter
IV	chemical/therapeutic subgroup	consists of one letter
V	chemical subgroup	consists of two digits

For example, the classification of FVIII and von Willebrand Factor (vWF) in combination is B02BD06 and is based on the composition as shown in Table 2.

Table 2. ATC classification system of FVIII and von Willebrand Factor (vWF) in combination

Level	Description
B	Blood and Blood forming organs
B02	Antihaemorrhagics
B02B	Vitamin K and other haemostatics
B02BD	Blood coagulation factors
B02BD06	von Willebrand factor and coagulation factor VIII in combination

The ATC classification system is based on the principle of assigning a unique code to individual pharmaceutical products (AIC code).

Medicinal products are therefore classified according to their main therapeutic use. A medicinal product, however, can be used for two or more therapeutic indications of equal importance with different classification possibilities.

When a drug is available in two or more dosages or pharmaceutical forms for different therapeutic uses, the classification is determined on the basis of the actual therapeutic use. Finally, preparations that cannot be uniquely classified in a particular group are coded in the fourth level with the letter X.

Therefore, the ATC classification makes it possible to perform a progressively more detailed identification of all drugs and substances for therapeutic use and, indirectly, through the analysis of active ingredients or of the prescribed therapeutic groups, it makes it possible to formulate hypotheses on the incidence of specified pathologies or prevalence in the general population (11).

When a medicinal product is placed on the market, the AIFA assigns it an AIC code. Based on the active ingredient and the therapeutic indications, it is possible to associate an ATC code and the quantity of active ingredient contained (expressed in specific units of measurement: mg, IU, g, etc.) to it.

In order to make aggregate data comparable at regional level, the absolute quantities are standardised for the resident population as of 1 January of each year in question taken from the Italian National Statistics Institute (Istituto Italiano di STATistica - ISTAT) figures (12) (Table 3).

Table 3. Resident population by Region and Autonomous Province, 2017-2018 (adapted by the CNS on data from ISTAT, 31/8/2019)

Region	2017	2018
Abruzzo	1,322,247	1,315,196
Aosta Valley	126,883	126,202
AP Bolzano	524,256	527,750
AP Trento	538,604	539,898
Apulia	4,063,888	4,048,242
Basilicata	570,365	567,118
Calabria	1,965,128	1,956,687
Campania	5,839,084	5,826,860
Emilia-Romagna	4,448,841	4,452,629
Friuli-Venezia Giulia	1,217,872	1,215,538
Latium	5,898,124	5,896,693
Liguria	1,565,307	1,556,981
Lombardy	10,019,166	10,036,258
Marche	1,538,055	1,531,753
Molise	310,449	308,493
Piedmont	4,392,526	4,375,865
Sardinia	1,653,135	1,648,176
Sicily	5,056,641	5,026,989
Tuscany	3,742,437	3,736,968
Umbria	888,908	884,640
Veneto	4,907,529	4,905,037
Italy	60,589,445	60,483,973

AP: Autonomous Province

Active ingredients and measurement units

In order to quantify the demand for PDMPs, measurement units used for each active ingredient are shown in Table 4.

As regards local haemostatics and combinations (ATC B02BC and B02BC30), the various commercial products are composed of a mixture of different active ingredients, the related data of which are expressed in millilitres, with the exception of formulations where the number of sponges utilised are provided per year.

Table 4. Active ingredients, ATC codes and measurement units

Active ingredient	ATC Code	Measurement unit
Albumin	B05AA01	g
Normal human Immunoglobulins for extravascular administration	J06BA01	g
Normal human Immunoglobulins for intravascular administration	J06BA02	g
Antithrombin	B01AB02	IU
Plasma-derived and recombinant coagulation factor VIII	B02BD02	IU
von Willebrand factor and coagulation factor VIII in combination	B02BD06	IU
von Willebrand factor	B02BD10	IU
Emicizumab	B02BX06	mg
Plasma-derived coagulation factor IX	B02BD04	IU
Recombinant coagulation factor IX	B02BD04	IU
3-factor prothrombin complex concentrates	B02BD	IU
4-factor prothrombin complex concentrates	B02BD01	IU
Hepatitis B immunoglobulins	J06BB04	IU
Tetanus immunoglobulins	J06BB02	IU
Anti-D (Rh) immunoglobulin	J06BB01	IU
Cytomegalovirus immunoglobulins	J06BB09	IU
Varicella/zoster immunoglobulins	J06BB03	IU
Rabies immunoglobulins	J06BB05	IU
Local haemostatics and combinations	B02BC	mL/sponges
	B02BC30	
Plasma-derived coagulation factor VII	B02BD05	IU
Activated recombinant factor VII	B02BD08	mg
Activated prothrombin complex concentrates	B02BD03	FU
Human fibrinogen	B02BB01	g
Alfa-1 antitrypsin	B02AB02	mg
Plasma-derived C1-inhibitor	B06AC01	IU
Coagulation factor X	B02BD13	IU
Coagulation factor XI	B02BD	IU
Plasma-derived coagulation factor XIII	B02BD07	IU
Recombinant coagulation factor XIII	B02BD11	IU
Protein C	B01AD12	IU
Other plasma proteins fractions	B05AA02	mL

Self-sufficiency and pharmaceutical expenditure

For every PDMP included in the agreements between the Regions and their affiliated Companies (Kedrion and CSL Behring), the degree of self-sufficiency achieved was assessed by comparing the actual supply with NHS demand. In this report, productive capacity (or potential supply) means the theoretic quantity of PDMPs derivable from the plasma sent by each Region for fractionation from July 2017 to June 2018. By contrast, effective supply (or toll fractionation) means the quantity of PDMPs *de facto* distributed by Kedrion and CSL Behring to each Region during the 2018 calendar year. Data related to the productive capacity and effective supply are provided by the companies themselves. Both productive capacity and effective supply are strictly influenced by the quantity and quality of plasma sent by the Regions, industrial yields and planning.

Total demand refers to the regional PDMP utilisation considering all distribution channels (public and private healthcare facilities, pharmacies, etc.). NHS demand means the share of the total demand funded by the NHS.

Potential self-sufficiency means the percent ratio between the productive capacity and NHS demand. Effective self-sufficiency means the percent ratio between the effective supply and NHS demand.

In the dedicated chapter, pharmaceutical expenditure is defined as the expenditure for the supply of PDMPs covered by the NHS through public health facilities and pharmacies. As far as the first channel is concerned, the aggregate purchase cost of PDMPs incurred by public facilities was detected and quantified by means of the traceability information flow. The quantities and the monetary value of PDMPs delivered to public pharmacies were calculated by using the price in force on 31/12/2018, and applying any eventual discounts provided for by Law 662/1996 (13), amended by Law 122/2010 (14).

For albumin, IVIG and pdFVIII, as identified by Italian law as the main drivers of the toll fractionation, the average cost per unit purchased on the market, and the average cost per unit purchased through public health facilities and pharmacies are specified in summary tables, to which the related percentages of the demand and expenditure paid through the same distribution channels are added.

For toll-fractionated medicinal products, it is not possible to provide an estimate of the related expenditure, but only the total amount paid by the Regions for plasma processing services not including the costs they sustained for the production of plasma as “raw material”.

PART A
Plasma-derived medicinal products
from toll fractionation

ALBUMIN (ATC B05AA01)

Albumin is a plasma protein produced from liver cells and accounts for about 60% of all plasma proteins. Its concentration in the blood (referred to as albuminaemia) can range between 3.5 and 5.0 g / dL. Lower albuminaemia values are mainly due to a reduced production of albumin by the liver. The ability to synthesise proteins by the hepatocyte is compromised in severe liver diseases (15,16). Table 5 shows the brand names of drugs containing albumin currently on the market in Italy and the amount of active ingredient they contain expressed in grams.

Table 5. Products containing albumin currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	g Manufacturer	NHS class
034611032	ALBUMINA GRIFOLS*1FL 100ML 5%	5 GRIFOLS ITALIA SpA	C
036504025	ALBUREX* INFUS 1FL 100ML 5%	5 CSL BEHRING GmbH	C
039187012	ALBUNORM*1FL 100ML 5% 50G/L	5 OCTAPharma ITALY SpA	C
010317028	ALBUMINA UM.IMMUNO*50ML 20%+S.	10 BAXTER SpA	A
011544020	ALBUMINA BEHRING*IV 50ML20%	10 CSL BEHRING SpA	A
021111024	UMANALBUMIN*INF FL 50ML 200G/L	10 KEDRION SpA	A
022515163	ALBITAL*1FL 50ML SOLUZ 20%+SET	10 KEDRION SpA	A
028989046	PLASBUMIN*EV 1FL 50ML 200G/L	10 GRIFOLS ITALIA SpA	A
029251030	ALBUTEIN*IV FL 50ML 200G/L	10 GRIFOLS ITALIA SpA	A
034611018	ALBUMINA GRIFOLS*1FL 50ML 20%	10 GRIFOLS ITALIA SpA	A
036176016	ALBUMINA LFB*FL 50ML 200MG/ML	10 LFB	A
036504052	ALBUREX*INFUS 1FL 50ML 20%	10 CSL BEHRING GmbH	A
037566054	ALBUMINA BAXTER*FL 50ML 200G/L	10 BAXALTA ITALY Srl	A
038109056	FLEXBUMIN*SAC INF 50ML 200G/L	10 BAXALTA ITALY Srl	A
038747034	OCTALBIN*IV 50ML 200MG/ML	10 OCTAPharma ITALY SpA	A
039073022	ALBIOMIN*FL 50ML 200G/L 20%	10 BIOTEST ITALIA Srl	A
039187063	ALBUNORM*1FL 50ML 20% 200G/L	10 OCTAPharma ITALY SpA	A
042029013	KALBI*FL 50ML 200G/L	10 KEDRION SpA	A
043358011	ALBUMEON*FL 50ML 200G/L 20%	10 CSL BEHRING SpA	A
044549018	PROBUMIN*FL 50 ML 200 G/L	10 GRIFOLS ITALIA SpA	C (nn)
010317042	ALBUMINA UM.IMMUNO*50ML 25%+S.	12.5 BAXTER SpA	A
021111051	UMANALBUMIN*FL 250ML 5%	12.5 KEDRION SpA	C
021111087	UMANALBUMIN*INF FL 50ML 250G/L	12.5 KEDRION SpA	A
022515136	ALBITAL*1FL 50ML 25G/100ML+SET	12.5 KEDRION SpA	A
028989097	PLASBUMIN*EV 1FL 50ML 250G/L	12.5 GRIFOLS ITALIA SpA	A
029251016	ALBUTEIN*IV FL 250ML 50G/L	12.5 GRIFOLS ITALIA SpA	C
029251042	ALBUTEIN*IV FL 50ML 25%	12.5 GRIFOLS ITALIA SpA	A
034611044	ALBUMINA GRIFOLS*1FL 250ML 5%	12.5 GRIFOLS ITALIA SpA	C
034611069	ALBUMINA GRIFOLS*50ML 25G/100M	12.5 GRIFOLS ITALIA SpA	A
036504037	ALBUREX* INFUS 1 FL 250ML 5%	12.5 CSL BEHRING GmbH	C
036504076	ALBUREX*INFUS 1FL 50ML 25%	12.5 CSL BEHRING GmbH	A
037566015	ALBUMINA BAXTER*1FL 250ML 50G/L	12.5 BAXALTA ITALY Srl	C
037566092	ALBUMINA BAXTER*FL 50ML 250G/L	12.5 BAXALTA ITALY Srl	A
038109070	FLEXBUMIN*SAC INF 50ML 250G/L	12.5 BAXALTA ITALY Srl	A
039073010	ALBIOMIN*INF 250ML 50G/L 5%	12.5 BIOTEST ITALIA Srl	C
039187036	ALBUNORM*1FL 250ML 5% 50G/L	12.5 OCTAPharma ITALY SpA	C
039187101	ALBUNORM*1FL 50ML 25% 250G/L	12.5 OCTAPharma ITALY SpA	A
042029025	KALBI*FL 50ML 250G/L+SET	12.5 KEDRION SpA	A
021111101	UMANALBUMIN*EV FL 100ML 200G/L	20 KEDRION SpA	A
028989059	PLASBUMIN*EV 1FL 100ML 200G/L	20 GRIFOLS ITALIA SpA	A
034611020	ALBUMINA GRIFOLS*1FL 100ML 20%	20 GRIFOLS ITALIA SpA	A
036176028	ALBUMINA LFB* FL 100ML 200 MG/ML	20 LFB	C

AIC code	Brand name	g Manufacturer	NHS class
036504064	ALBUREX*INFUS 1FL 100ML 20%	20 CSL BEHRING GmbH	A
037566078	ALBUMINA BAXTER*1FL 100ML 200G	20 BAXALTA ITALY Srl	A
038109068	FLEXBUMIN*SAC INF 100ML 200G/L	20 BAXALTA ITALY Srl	A
038747046	OCTALBIN*IV 100ML 200MG/ML	20 OCTAPHARMA ITALY SpA	A
039073034	ALBIOMIN*INF 100ML 200G/L 20%	20 BIOTEST ITALIA Srl	A
039187087	ALBUNORM*1FL 100ML 20% 200G/L	20 OCTAPHARMA ITALY SpA	A
043358023	ALBUMEON*FL 100ML 200G/L 20%	20 CSL BEHRING SpA	A
044549020	PROBUMIN*FL 100ML 200 G/L	20 GRIFOLS ITALIA SpA	C (nn)
029251028	ALBUTEIN*IV FL 500ML 50G/L	25 GRIFOLS ITALIA SpA	C
034611057	ALBUMINA GRIFOLS*1FL 500ML 5%	25 GRIFOLS ITALIA SpA	C
034611071	ALBUMINA GRIFOLS25G/100ML	25 GRIFOLS ITALIA SpA	H
036504049	ALBUREX* INFUS 1FL 500ML 5%	25 CSL BEHRING GmbH	C
036504088	ALBUREX* INFUS 1FL 100ML 25%	25 CSL BEHRING GmbH	H
037566039	ALBUMINA BAXTER*1FL 500ML 50 G/L	25 BAXALTA ITALY Srl	C
037566116	ALBUMINA BAXTER*1FL100ML 250G/L	25 BAXALTA ITALY Srl	H
038109082	FLEXBUMIN*1SACCA 100ML 250G/L	25 BAXALTA ITALY Srl	H
039187051	ALBUNORM" 1 FL 500ML 5%, 50 G/L	25 OCTAPHARMA ITALY SpA	C
039187113	ALBUNORM* 1 FL 100ML 25%, 250 G/L	25 OCTAPHARMA ITALY SpA	H
039187024	ALBUNORM*10FL 100ML 5% 50G/L	50 OCTAPHARMA ITALY SpA	C
036176030	ALBUMINA 200 MG/ML INF 6*50mL	60 LFB	C
039187075	ALBUNORM* 10FL 50ML 20%, 200 G/L	100 OCTAPHARMA ITALY SpA	H
036176042	ALBUMINA 200 MG/ML INF 6*100mL	120 LFB	C
039187048	ALBUNORM* 10FL 250ML 5%, 50 G/L	125 OCTAPHARMA ITALY SpA	C
039187099	ALBUNORM*10FL 100ML 20%, 200 G/L	200 OCTAPHARMA ITALY SpA	H
038109017	FLEXBUMIN*24SACCHE 50ML 200G/L	240 BAXALTA ITALY Srl	H
038109031	FLEXBUMIN*12SACCHE 100ML200G/L	240 BAXALTA ITALY Srl	H
037566041	ALBUMINA BAXTER*10FL 500ML 50 G/L	250 BAXALTA ITALY Srl	C
037566027	ALBUMINA BAXTER* 24FL 250ML 50 G/L	300 BAXALTA ITALY Srl	C
038109029	FLEXBUMIN*12SACCHE 100ML 250 G/L	300 BAXALTA ITALY Srl	H
038109043	FLEXBUMIN*24SACCHE 50ML 250G/L	300 BAXALTA ITALY Srl	H
037566066	ALBUMINA BAXTER*70FL 50ML 200 G/L	700 BAXALTA ITALY Srl	H
037566104	ALBUMINA BAXTER*70FL 50ML 250 G/L	875 BAXALTA ITALY Srl	H
037566080	ALBUMINA BAXTER*56FL 100ML 200 G/L	1120 BAXALTA ITALY Srl	H
037566128	ALBUMINA BAXTER*56FL 100ML 250 G/L	1400 BAXALTA ITALY Srl	H

Quantification and characterisation of the demand

Table 6 shows the total demand (expressed in grams) and the total standardised demand (expressed in grams per 1,000 population) of albumin¹ for the two-year period 2017-2018 with the variations in percentage, both at national and regional levels.

In 2018, the national demand for this ingredient was about 35,000 kilograms (Table 6), equal to 578 grams per 1,000 population. The two Regions with the highest standardised demand were Campania and Sardinia with standardised volumes of 873 and 866 grams, respectively. The Regions with the lowest demand were the AP of Trento and the AP of Bolzano, with about 337 and 341 grams per 1,000 population, respectively (Figure 5).

In this two-year period, the total standardised demand for albumin showed a constant trend with respect to previous years (-0.9% compared to 2017) (17). The Regions where the increase in albumin utilisation was more evident, measured as a percentage change compared to the Italian mean value, were Molise (+57%), Friuli-Venezia Giulia (+23%) and the AP of Bolzano (+20%).

¹ The data analysed did not consider the use of *Umanserum*TM. This product is classified as human plasma protein (ATC B05AA02, see related chapter) within the ATC system, despite its 90% albumin composition.

By contrast, a decrease was observed in Campania, Lombardy, Sardinia (-8%), and Tuscany and Umbria (-5 and -6%, respectively).

Table 6. Total demand (public and private) and total standardised demand for albumin, expressed in grams and grams per 1,000 population, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	791,568	598.7	830,828	631.7	5.5
Aosta Valley	73,750	581.2	81,970	649.5	11.7
APBolzano	148,960	284.1	179,885	340.9	20.0
APTrento	183,425	340.6	181,903	336.9	-1.1
Apulia	2,088,145	513.8	2,117,368	523.0	1.8
Basilicata	334,825	587.0	356,763	629.1	7.2
Calabria	1,085,958	552.6	1,088,155	556.1	0.6
Campania	5,552,418	950.9	5,084,775	872.6	-8.2
E.-Romagna	2,437,620	547.9	2,546,528	571.9	4.4
Friuli-V. Giulia	378,478	310.8	465,298	382.8	23.2
Latium	3,150,310	534.1	3,227,708	547.4	2.5
Liguria	672,413	429.6	667,428	428.7	-0.2
Lombardy	6,896,345	688.3	6,363,728	634.1	-7.9
Marche	717,305	466.4	743,548	485.4	4.1
Molise	144,963	466.9	225,550	731.1	56.6
Piedmont	1,449,118	329.9	1,502,955	343.5	4.1
Sardinia	1,553,920	940.0	1,428,023	866.4	-7.8
Sicily	3,043,375	601.9	3,340,583	664.5	10.4
Tuscany	1,811,433	484.0	1,710,363	457.7	-5.4
Umbria	516,325	580.9	485,428	548.7	-5.5
Veneto	2,308,243	470.3	2,314,323	471.8	0.3
ITALY	35,338,893	583.3	34,943,103	577.7	-0.9

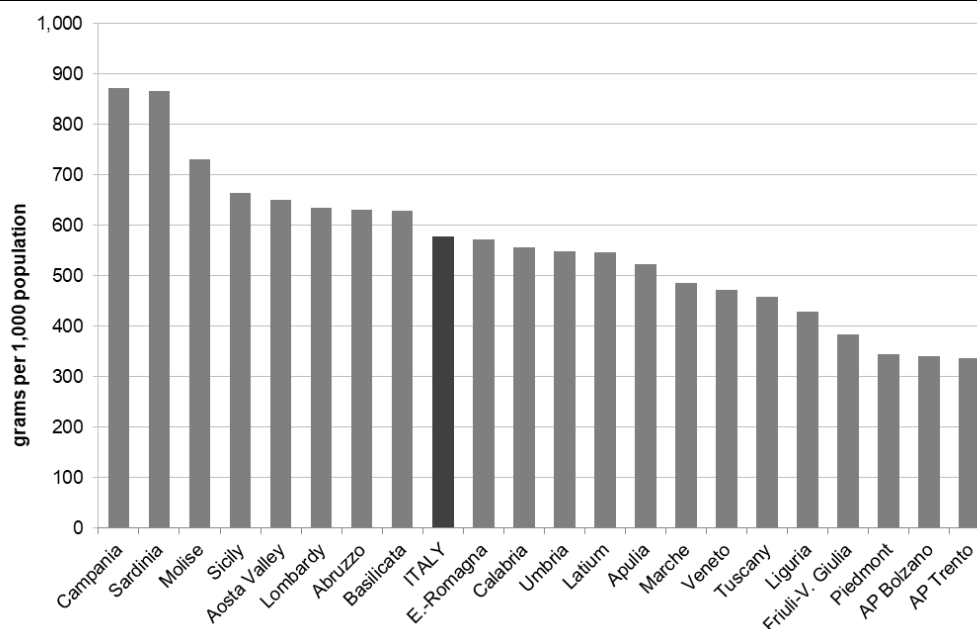


Figure 5. Total and regional demand (public and private) for albumin, expressed in grams per 1,000 population, 2018 (adapted by the CNS on data from the traceability information flow)

Figure 6 highlights the eight Regions with a higher demand compared to national demand. Two of them show significantly higher values (>50%). Figure 7 shows the standardised regional demand for albumin recorded in 2018 per distribution channel (public pharmacies compared to other facilities), as shown by the drug traceability system (17,18). In 2018, about 9% of the national demand – approximately 3,068 kilograms – was distributed through public pharmacies. Pharmacies as a distribution channel were particularly used in Calabria and Campania, where they accounted for 29% and 22% respectively of regional demand, while they were used albeit to a lesser extent in Apulia, Basilicata and Latium with percentages of between 10 and 17% of the total regional demand. As far as the other Regions are concerned, they were rarely used.

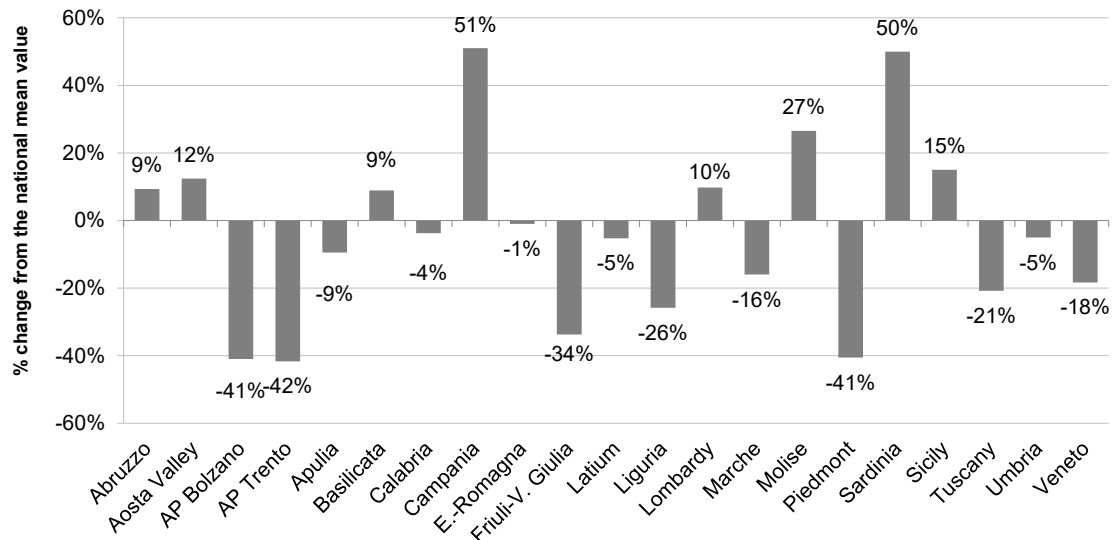


Figure 6. Percentage change from the national mean value of standardised regional demand for human albumin in 2018 (adapted by the CNS on data from the traceability information flow)

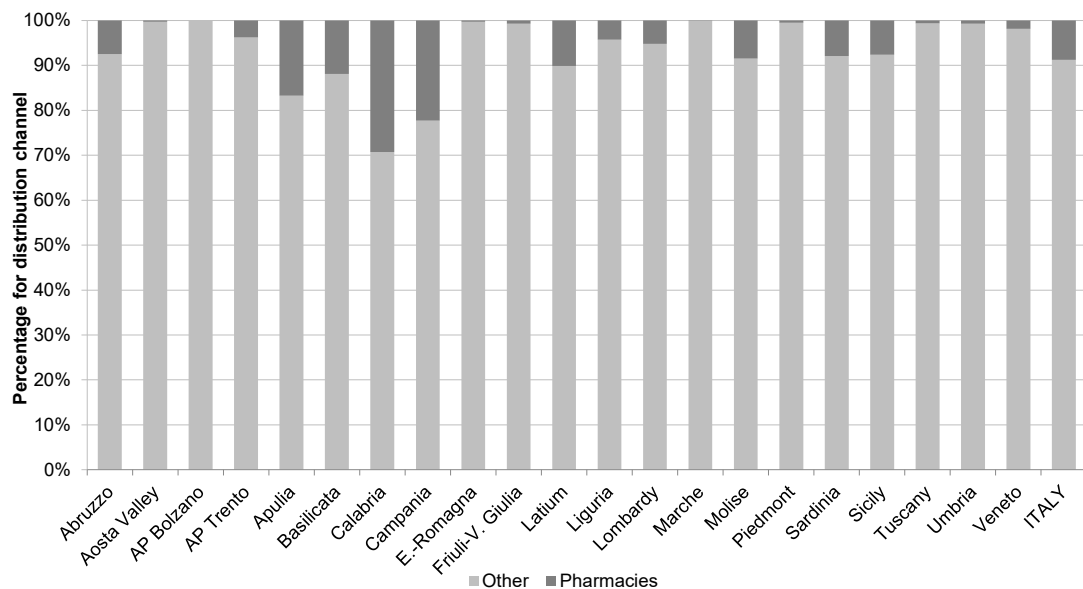


Figure 7. Standardised regional demand for albumin recorded per distribution channel, 2018 (adapted by the CNS on data from the traceability information flow)

NORMAL HUMAN IMMUNOGLOBULINS FOR SUBCUTANEOUS USE (ATC J06BA01) AND FOR INTRAVENOUS USE (ATC J06BA02)

Immunoglobulins (IGs) are used in substitutive immunodeficiency therapy and in the treatment of autoimmune diseases or systemic inflammatory processes. However, in clinical practice they are used much more extensively and their use is not always fully justified by the available evidence in scientific literature. Since 2007, both soluble IG preparations for subcutaneous/intramuscular infusion (SC/IM) and those for intravenous use (IntraVenous, IV) (18) have been available in Italy. IGs, like all other PDMPs, are prepared by using human plasma pools, which guarantees the recipient a higher antibody coverage thanks to a significant idiotypical diversity. The preparations contain structurally and functionally intact IG, with normal half-life and subclass proportions: 95% of monomeric IGG, small amounts of dimers, and variable amounts of IGA and IGM (19). Table 7 shows the names of the drugs containing IG that are currently marketed in Italy and the amount of active ingredient they contain expressed in grams.

Table 7. Products containing normal human immunoglobulins for subcutaneous/ intramuscular and intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	g	Manufacturer	NHS class
Normal human immunoglobulin for subcutaneous/intramuscular use				
036800011	SUBCUVIA*SC IM FL 5ML 160MG/ML	0.8	BAXALTA ITALY Srl	H
036800047	SUBCUVIA*SC IM FL10ML 160MG/ML	1.6	BAXALTA ITALY Srl	H
036800023	SUBCUVIA*SC IM 20FL5ML 160MG/ML	16	BAXALTA ITALY Srl	H
036800035	SUBCUVIA*SC IM 20FL10ML 160MG/ML	32	BAXALTA ITALY Srl	H
Normal human immunoglobulin for subcutaneous use				
040652075	OCTANORM*1FL 6ML 165MG/ML	0.99	OCTAPHARMA ITALY SpA	H
041157013	HIZENTRA*SC 1FL 5ML 200MG/ML	1	CSL BEHRING SpA	H
041157153	HIZENTRA*SC 1SIR 5ML 200MG/ML	1	CSL BEHRING SpA	C(nn)
044244010	CUVITRU*SC 1FL 5ML 200MG/ML	1	BAXALTA ITALY Srl	H
043396011	NAXIGLO*SC FL 10ML 160MG/ML	1.6	KEDRION SpA	H
043398015	KEYCUTE*SC FL 10ML 160MG/ML	1.6	KEDRION SpA	H
040652012	OCTANORM*1FL10ML 165MG/ML	1.65	OCTAPHARMA ITALY SpA	H
040652101	OCTANORM*FL 12ML 165MG/ML	1.98	OCTAPHARMA ITALY SpA	H
041157049	HIZENTRA*SC 1FL 10ML 200MG/ML	2	CSL BEHRING SpA	H
041157177	HIZENTRA*SC 1SIR 10ML 200MG/ML	2	CSL BEHRING SpA	C(nn)
044244022	CUVITRU*SC 1FL 10ML 200MG/ML	2	BAXALTA ITALY Srl	H
042804017	HYQVIA*SC 1FL 25ML+1FL 1,25ML	2.5	BAXALTA ITALY Srl	H
041157076	HIZENTRA*1FL 15ML 200 MG/ML	3	CSL BEHRING SpA	H
040652048	OCTANORM*1FL 20ML 165MG/ML	3.3	OCTAPHARMA ITALY SpA	H
040652137	OCTANORM*FL 24ML 165MG/ML	3.96	OCTAPHARMA ITALY SpA	H
041157102	HIZENTRA*SC 1FL 20ML 200MG/ML	4	CSL BEHRING SpA	H
043396023	NAXIGLO*SC FL 25ML 160MG/ML	4	KEDRION SpA	H
043398027	KEYCUTE*SC FL 25ML 160MG/ML	4	KEDRION SpA	H
044244034	CUVITRU*SC 1FL 20ML 200MG/ML	4	BAXALTA ITALY Srl	H
042804029	HYQVIA*SC 1FL 50ML+1FL 2,5ML	5	BAXALTA ITALY Srl	H
040652164	OCTANORM*FL 48ML 165MG/ML	7.92	OCTAPHARMA ITALY SpA	H
044244046	CUVITRU*SC 1FL 40ML 200MG/ML	8	BAXALTA ITALY Srl	H
040652087	OCTANORM*10FL 6ML 165 MG/ML	9.9	OCTAPHARMA ITALY SpA	H

AIC code	Brand name	g	Manufacturer	NHS class
041157025	HIZENTRA*10FL 5ML 200MG/ML	10	CSL BEHRING SpA	H
041157138	HIZENTRA*SC 1FL 50ML 200MG/ML	10	CSL BEHRING SpA	H
041157165	HIZENTRA*SC 10SIR 5ML 200MG/ML	10	CSL BEHRING SpA	C(nn)
042804031	HYQVIA*SC 1FL 100ML+1FL 5ML	10	BAXALTA ITALY Srl	H
040652024	OCTANORM*10FL 10ML 165MG/ML	16.5	OCTAPHARMA ITALY SpA	H
040652099	OCTANORM*20FL 6ML 165MG/ML	19.8	OCTAPHARMA ITALY SpA	H
040652113	OCTANORM*10FL 12ML 165MG/ML	19.8	OCTAPHARMA ITALY SpA	H
041157037	HIZENTRA*20FL 5ML 200MG/ML	20	CSL BEHRING SpA	H
041157052	HIZENTRA*10FL 10ML 200MG/ML	20	CSL BEHRING SpA	H
041157189	HIZENTRA*SC 10SIR 10ML 200MG/ML	20	CSL BEHRING SpA	C(nn)
042804043	HYQVIA*SC 1FL 200ML+1FL 10ML	20	BAXALTA ITALY Srl	H
041157088	HIZENTRA*10FL 15ML 200MG/ML	30	CSL BEHRING SpA	H
042804056	HYQVIA*SC 1FL 300ML+1FL 15ML	30	BAXALTA ITALY Srl	H
040652036	OCTANORM*20FL 10ML 165MG/ML	33	OCTAPHARMA ITALY SpA	H
040652051	OCTANORM*10FL 20ML 165MG/ML	33	OCTAPHARMA ITALY SpA	H
040652125	OCTANORM*20FL 12ML 165 MG/ML	39.6	OCTAPHARMA ITALY SpA	H
040652149	OCTANORM*10FL 24ML 165 MG/ML	39.6	OCTAPHARMA ITALY SpA	H
041157064	HIZENTRA*20FL 10ML 200MG/ML	40	CSL BEHRING SpA	H
041157114	HIZENTRA*10FL 20ML 200MG/ML	40	CSL BEHRING SpA	H
041157090	HIZENTRA*20FL 15ML 200MG/ML	60	CSL BEHRING SpA	H
040652063	OCTANORM*20FL 20ML 165MG/ML	66	OCTAPHARMA ITALY SpA	H
040652152	OCTANORM* 20FL 24ML 165MG/ML	79.2	OCTAPHARMA ITALY SpA	H
040652176	OCTANORM*10FL 48ML 165MG/ML	79.2	OCTAPHARMA ITALY SpA	H
041157126	HIZENTRA*20FL 20ML 200MG/ML	80	CSL BEHRING SpA	H
041157140	HIZENTRA*10FL 50ML 200MG/ML	100	CSL BEHRING SpA	H
040652188	OCTANORM* 20FL 48ML 165MG/ML	158.4	OCTAPHARMA ITALY SpA	H
Normal human immunoglobulin for intravenous use				
029021019*	PENTAGLOBIN*EV FL 50MG/ML 10ML	0.5	BIOTEST ITALIA Srl	C
029249075	PLITAGAMMA *INF 1 FL 10ML 50MG/ML	0.5	ISTITUTO GRIFOLS SA	H
040267015	FLEBOGAMMA*INF 1FL 10ML 50 MG/ML	0.5	GRIFOLS ITALIA SpA	H
025266141	IGVENA*EV 1FL 20ML 50G/L	1	KEDRION SpA	H
035143054	OCTAGAM*IV 1FL 20ML 50MG/ML	1	OCTAPHARMA ITALY SpA	H
037107012	KIOVIG*EV FL 10ML 100MG/ML	1	BAXTER SpA	H
037240052	INTRATECT*INF FL 50G/L 20ML	1	BIOTEST ITALIA Srl	H
037240090	INTRATECT*INF FL 100G/L 10ML	1	BIOTEST ITALIA Srl	H
037254012	VENITAL*EV FL 20ML 50G/L	1	KEDRION SpA	H
044187019	GLOBIGA*INF 1FL 1G 100MG/ML	1	OCTAPHARMA ITALY SpA	H
037240126	INTRATECT*INF FL100G/L 200ML	2	BIOTEST ITALIA Srl	H
039457015	GAMTEN*INF 1FL 20ML 100MG/ML	2	OCTAPHARMA ITALY SpA	H
043736014	IQYMUNE*FL INF 20ML 100MG/ML	2	LFB	C(nn)
025266154	IGVENA*EV 1FL 50ML 50G/L+SET	2.5	KEDRION SpA	H
029021033*	PENTAGLOBIN*EV 1FL 50MG/ML50ML	2.5	BIOTEST ITALIA Srl	C
029249048	PLITAGAMMA*50ML(2,5G)5%+SET	2.5	GRIFOLS ITALIA SpA	H
035143015	OCTAGAM*IV FL 50ML 5%	2.5	OCTAPHARMA ITALY SpA	H
037107024	KIOVIG*EV FL 25ML 100MG/ML	2.5	BAXTER SpA	H
037240064	INTRATECT*INF FL 50G/L 50ML	2.5	BIOTEST ITALIA Srl	H
037240138	INTRATECT*INF FL100 G/L 25ML	2.5	BIOTEST ITALIA Srl	H
037254024	VENITAL*EV FL 50ML 50G/L+SET	2.5	KEDRION SpA	H
039712043	PRIVIGEN*EV 1FL 25ML 100MG/ML	2.5	CSL BEHRING SpA	H
040267027	FLEBOGAMMA DIF*FL 50ML 50MG/ML	2.5	GRIFOLS ITALIA SpA	H
044187021	GLOBIGA*INF 1FL 2,5G 100MG/ML	2.5	OCTAPHARMA ITALY SpA	H
033240033	GAMMAGARD*EV 1FL 50MG/ML 96ML	4.8	BAXTER SpA	H
025266166	IGVENA*EV 1FL 100ML 50G/L+SET	5	KEDRION SpA	H
029021045*	PENTAGLOBIN*EV 1FL 50MG/ML100ML	5	BIOTEST ITALIA Srl	C

AIC code	Brand name	g	Manufacturer	NHS class
029249051	PLITAGAMMA*100ML(5G)5%+SET	5	GRIFOLS ITALIA SpA	H
035143027	OCTAGAM*IV FL 100ML 5%	5	OCTAPHARMA ITALY SpA	H
037107036	KIOVIG*EV FL 50ML 100MG/ML	5	BAXTER SpA	H
037240076	INTRATECT*INF FL 50G/L 100ML	5	BIOTEST ITALIA Srl	H
037240102	INTRATECT*INF FL 100G/L 50ML	5	BIOTEST ITALIA Srl	H
037253034	KEYVEN*EV FL 100ML 50G/L+SET	5	KEDRION SpA	H
037254036	VENITAL*EV FL 100ML 50G/L+SET	5	KEDRION SpA	H
039457027	GAMTEN*INF 1FL 50ML 100MG/ML	5	OCTAPHARMA ITALY SpA	H
039712017	PRIVIGEN*EV 1FL 50ML 100MG/ML	5	CSL BEHRING SpA	H
040267039	FLEBOGAMMA DIF*FL 100ML 5G	5	GRIFOLS ITALIA SpA	H
040267066	FLEBOGAMMA DIF*EV 50ML 5G	5	GRIFOLS ITALIA SpA	H
043736026	IQYMUNE*FL INF 50ML 100MG/ML	5	LFB	C(nn)
044187033	GLOBIGA*INF 1FL 5G 100MG/ML	5	OCTAPHARMA ITALY SpA	H
039457054	GAMTEN*INFUS 1FL 60ML 100MG/ML	6	OCTAPHARMA ITALY SpA	C(nn)
044187045	GLOBIGA*INF 1FL 6G 100MG/ML	6	OCTAPHARMA ITALY SpA	H
033240045	GAMMAGARD*EV 1FL 50MG/ML 192ML	9.6	BAXTER SpA	H
025266178	IGVENA*EV 1FL 200ML 50G/L+SET	10	KEDRION SpA	H
029249063	PLITAGAMMA*200ML(10G)5%+SET	10	GRIFOLS ITALIA SpA	H
035143039	OCTAGAM*IV FL 200ML 5%	10	OCTAPHARMA ITALY SpA	H
037107048	KIOVIG*EV FL 100ML 100MG/ML	10	BAXTER SpA	H
037240088	INTRATECT*INF FL 50G/L 200ML	10	BIOTEST ITALIA Srl	H
037240114	INTRATECT*INF FL100G/L 100ML	10	BIOTEST ITALIA Srl	H
037253046	KEYVEN*EV FL 200ML 50G/L+SET	10	KEDRION SpA	H
037254048	VENITAL*EV FL 200ML 50G/L+SET	10	KEDRION SpA	H
039457039	GAMTEN*INF 1FL100ML 100MG/ML	10	OCTAPHARMA ITALY SpA	H
039712029	PRIVIGEN*EV 1FL 100ML 100MG/ML	10	CSL BEHRING SpA	H
040267041	FLEBOGAMMA DIF*FL 200ML 10G	10	GRIFOLS ITALIA SpA	H
040267078	FLEBOGAMMA DIF*EV 100ML 10G	10	GRIFOLS ITALIA SpA	H
043736038	IQYMUNE*FL INF100ML 100MG/ML	10	LFB	C(nn)
044187058	GLOBIGA*INF 1FL 10G 100MG/ML	10	OCTAPHARMA ITALY SpA	H
029249087	PLITAGAMMA*INF 1 FL 400ML 50MG/ML	20	ISTITUTO GRIFOLS SA	H
035143066	OCTAGAM*IV 2FL 200ML 50MG/ML	20	OCTAPHARMA ITALY SpA	H
037107051	KIOVIG*EV FL 200ML 100MG/ML	20	BAXTER SpA	H
039457041	GAMTEN*INF 1 FL 200ML 100MG/ML	20	OCTAPHARMA ITALY SpA	H
039712031	PRIVIGEN*EV 1FL 200ML 100MG/ML	20	CSL BEHRING SpA	H
040267054	FLEBOGAMMA DIF*FL 400ML 20G	20	GRIFOLS ITALIA SpA	H
040267080	FLEBOGAMMA DIF*EV 200ML 20G	20	GRIFOLS ITALIA SpA	H
043736040	IQYMUNE*FL INF 200ML 100MG/ML	20	LFB	C(nn)
044187072	GLOBIGA*INF 1FL 20G 100MG/ML	20	OCTAPHARMA ITALY SpA	H
035143041	OCTAGAM*IV FL 500ML 5%	25	OCTAPHARMA ITALY SpA	H
035143078	OCTAGAM*IV 3 FL 200ML 50MG/ML	30	OCTAPHARMA ITALY SpA	H
037107063	KIOVIG*EV FL 300ML 100MG/ML	30	BAXTER SpA	H
037240140	INTRATECT* INF 3FL 200ML 50G/L	30	BIOTEST ITALIA Srl	C
037240153	INTRATECT*INF 3FL 100ML 100G/L	30	BIOTEST ITALIA Srl	C
039457066	GAMTEN*INF 3FL 100ML 100MG/ML	30	OCTAPHARMA ITALY SpA	C(nn)
039712056	PRIVIGEN*EV 3FL 100ML 100MG/ML	30	CSL BEHRING GMBH	C
044187060	GLOBIGA*INF 3FL 10G 100MG/ML	30	OCTAPHARMA ITALY SpA	C(nn)
044187096	GLOBIGA*INF 1FL 30G 100MG/ML	30	OCTAPHARMA ITALY SpA	H
039712070	PRIVIGEN*EV 1FL 400ML 100MG/ML	40	CSL BEHRING GMBH	C(nn)
037240165	INTRATECT* INF 3FL 200ML 100 G/L	60	BIOTEST ITALIA Srl	C
039457078	GAMTEN*INF 3FL 200ML 100MG/ML	60	OCTAPHARMA ITALY SpA	C(nn)
039712068	PRIVIGEN*EV 3FL 200ML 100MG/ML	60	CSL BEHRING GMBH	C
044187084	GLOBIGA*INF 3FL 20G 100MG/ML	60	OCTAPHARMA ITALY SpA	C(nn)

* Normal human immunoglobulins for intravenous use with high titers of IgM indicated as support therapy along with antibiotics for serious bacterial infections and as replacement therapy in immunodepressed patients.

Quantification and characterisation of the demand

Table 8 shows the total demand (expressed in grams) and the total standardised demand (in grams per 1,000 population) for IGs for the period 2017-2018 and the relative variations in percentage at national and regional levels. The same information is reported for both SC/IM (Table 9) and IV (Table 10) preparations.

In 2018, the total national demand for IGs was 5,933,819 grams, equal to 98.1 grams per 1,000 population (Table 8).

Table 8. Total demand (public and private) and total standardised demand for normal human immunoglobulins for intravenous and subcutaneous/ intramuscular use, expressed in grams and grams per 1,000 population, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	104,627	79.1	119,245	90.7	14.6
Aosta Valley	22,234	175.2	20,623	163.4	-6.7
AP Bolzano	39,369	75.1	44,385	84.1	12.0
AP Trento	32,411	60.2	42,183	78.1	29.8
Apulia	383,616	94.4	451,209	111.5	18.1
Basilicata	32,733	57.4	35,668	62.9	9.6
Calabria	92,110	46.9	118,232	60.4	28.9
Campania	358,867	61.5	408,658	70.1	14.1
E.-Romagna	419,639	94.3	466,126	104.7	11.0
Friuli-V. Giulia	116,621	95.8	137,063	112.8	17.8
Latium	500,964	84.9	597,037	101.2	19.2
Liguria	169,793	108.5	203,291	130.6	20.4
Lombardy	866,654	86.5	865,107	86.2	-0.3
Marche	176,179	114.5	209,528	136.8	19.4
Molise	17,652	56.9	45,757	148.3	160.9
Piedmont	445,952	101.5	497,587	113.7	12.0
Sardinia	73,740	44.6	95,110	57.7	29.4
Sicily	309,856	61.3	335,524	66.7	8.9
Tuscany	713,238	190.6	638,183	170.8	-10.4
Umbria	82,926	93.3	94,805	107.2	14.9
Veneto	445,601	90.8	508,498	103.7	14.2
ITALY	5,404,781	89.2	5,933,819	98.1	10.0

The three Regions with the highest standardised demand per 1,000 population were Tuscany, Aosta Valley and Molise, with around 171, 163 and 148 grams, respectively. The demand was lower in Sardinia, Calabria and Basilicata, where it was between 58 and 63 grams per 1,000 population.

The demand for these PDMPs rose sharply in the two-year period 2017-2018 (+10%), especially for the SC/IM formulations (+21.3%), and there were notable differences from one Region to another. This trend was not observed in Lombardy, where demand remained substantially stable. A decrease occurred in Tuscany and Aosta Valley (-10.4% and -6.7%, respectively).

Figure 8 shows which Regions tended to use more SC/IM formulations and which preferred IV ones. More SC/IM formulations were used in Umbria (32%), Calabria (28%) and Basilicata (27%) while fewer were used in Friuli-Venezia Giulia, Sardinia and in the AP of Bolzano (<7%). At national level, the demand for SC/IM IGs stood at 19% of the total demand for IGs (17% in 2017).

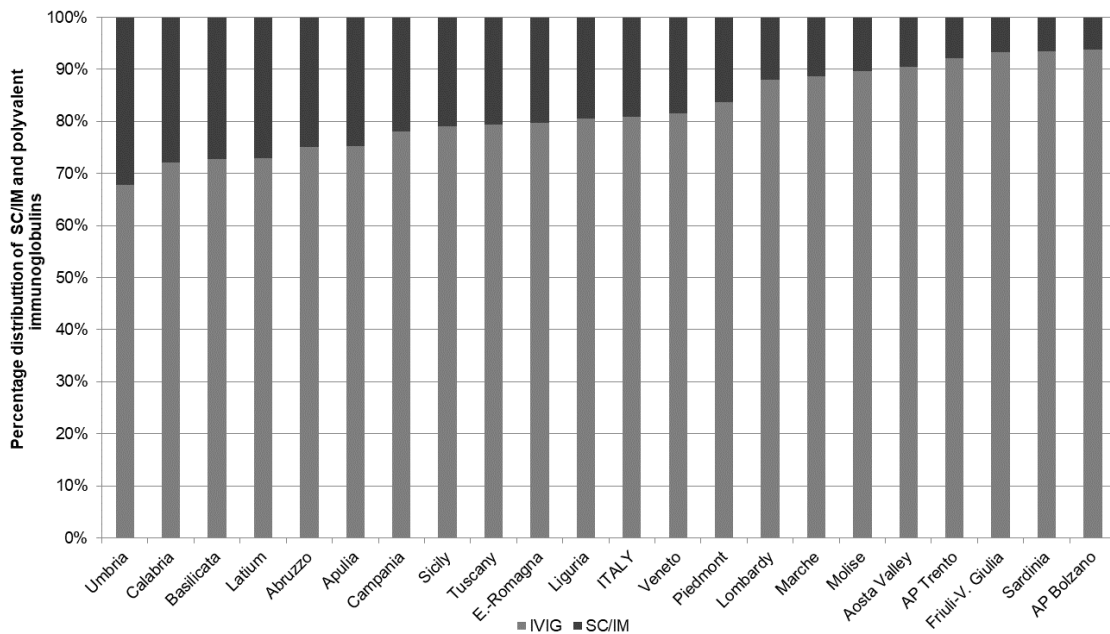


Figure 8. Total standardised demand (public and private) per administration of immunoglobulins (percentage on total), by Region, 2018 (adapted by the CNS on data from the traceability information flow)

Normal human immunoglobulins for subcutaneous use

In 2018, the total demand for SC/IM IGs was about 1,132,275 grams (18.7 grams per 1,000 population), with a 21% increase compared to 2017 (Table 9).

The regional demands were diversified and the highest values, 35.1, 34.4 and 27.6 grams per 1,000 population were respectively recorded in Tuscany, Umbria and Apulia. The lowest values were recorded in Sardinia and AP of Bolzano and were equal to 3.8 and 5.2, respectively (Figure 9).

In Abruzzo, Apulia, Emilia-Romagna, Lazio, Liguria, Tuscany, Umbria and Veneto, a higher total demand compared to national demand was recorded (range: 2-87%) (Figure 10).

Table 9. Total demand (public and private) and total standardised demand for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams and grams per 1,000 population, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	27,292	20.6	29,696	22.6	9.4
Aosta Valley	1,864	14.7	1,944	15.4	4.9
AP Bolzano	2,185	4.2	2,740	5.2	24.6
AP Trento	2,623	4.9	3,293	6.1	25.2
Apulia	92,705	22.8	111,664	27.6	20.9
Basilicata	8,233	14.4	9,683	17.1	18.3
Calabria	26,410	13.4	32,970	16.8	25.4
Campania	75,613	12.9	89,513	15.4	18.6
E.-Romagna	74,503	16.7	94,088	21.1	26.2
Friuli-V. Giulia	4,851	4.0	9,231	7.6	90.7
Latium	114,316	19.4	161,603	27.4	41.4
Liguria	24,977	16.0	39,621	25.4	59.5
Lombardy	94,287	9.4	104,276	10.4	10.4
Marche	22,304	14.5	23,693	15.5	6.7
Molise	3,682	11.9	4,697	15.2	28.4
Piedmont	73,413	16.7	81,344	18.6	11.2
Sardinia	7,042	4.3	6,220	3.8	-11.4
Sicily	61,503	12.2	70,441	14.0	15.2
Tuscany	109,336	29.2	131,107	35.1	20.1
Umbria	23,445	26.4	30,445	34.4	30.5
Veneto	84,413	17.2	94,006	19.2	11.4
ITALY	934,996	15.4	1,132,275	18.7	21.3

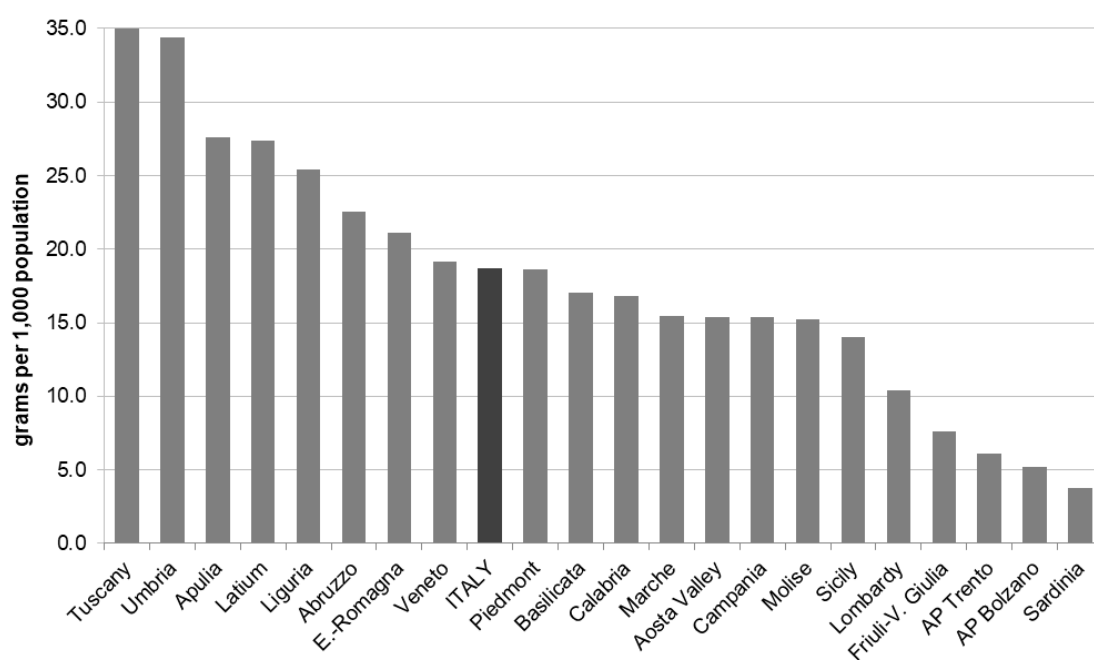


Figure 9. Total and regional demand (public and private) for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams per 1,000 population, 2018 (adapted by the CNS on data from the traceability information flow)

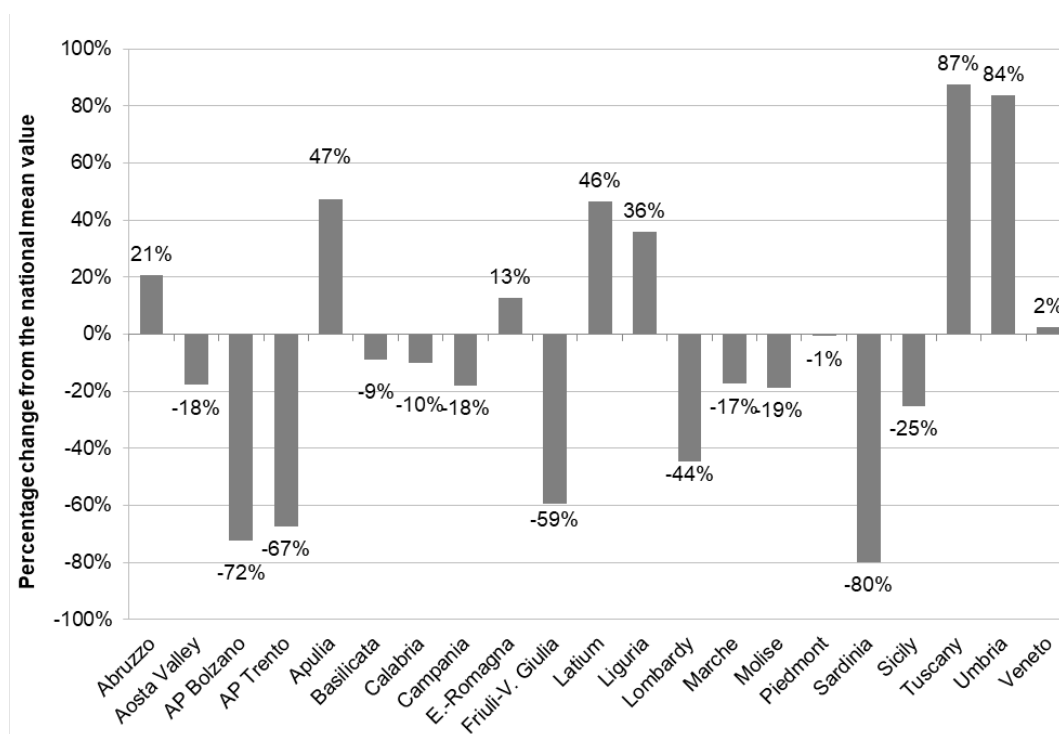


Figure 10. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for subcutaneous/ intramuscular use in 2018 (adapted by the CNS on data from the traceability information flow)

Normal human immunoglobulins for intravenous use

Finally, in Table 10, the total and standardised demands for IG for intravenous use in 2017-2018 are reported.

Also, in this case, a general upward trend (about +7.6%) was observed which however was not confirmed in Aosta Valley, Lombardy, and Tuscany.

Figure 11 shows the standardised regional demand for IVIGs in 2018 as recorded by the drug traceability system.

The highest demand for IVIGs was recorded in Aosta Valley, Tuscany, Molise and Marche with volumes ranging between 121 and 148 grams per 1,000 population (respectively +86%, +71%, +68% and +53% compared to the national mean value - Figure 12).

The lowest standardised demand was observed in Calabria, Basilicata, Sicily and Sardinia, with volumes of between 44 and 54 grams per 1,000 population.

Table 10. Total demand (public and private) and total standardised demand for normal human immunoglobulins for intravenous use, expressed in grams and grams per 1,000 population, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	77,335	58.5	89,549	68.1	16.4
Aosta Valley	20,370	160.5	18,679	148.0	-7.8
AP Bolzano	37,184	70.9	41,645	78.9	11.3
AP Trento	29,788	55.3	38,890	72.0	30.2
Apulia	290,911	71.6	339,545	83.9	17.2
Basilicata	24,500	43.0	25,985	45.8	6.7
Calabria	65,700	33.4	85,262	43.6	30.3
Campania	283,254	48.5	319,145	54.8	12.9
E.-Romagna	345,136	77.6	372,038	83.6	7.7
Friuli-V. Giulia	111,770	91.8	127,833	105.2	14.6
Latium	386,649	65.6	435,434	73.8	12.6
Liguria	144,816	92.5	163,670	105.1	13.6
Lombardy	772,367	77.1	760,831	75.8	-1.7
Marche	153,875	100.0	185,835	121.3	21.3
Molise	13,970	45.0	41,060	133.1	195.8
Piedmont	372,539	84.8	416,243	95.1	12.2
Sardinia	66,698	40.3	88,890	53.9	33.7
Sicily	248,354	49.1	265,083	52.7	7.4
Tuscany	603,902	161.4	507,076	135.7	-15.9
Umbria	59,481	66.9	64,360	72.8	8.7
Veneto	361,188	73.6	414,492	84.5	14.8
ITALY	4,469,785	73.8	4,801,544	79.4	7.6

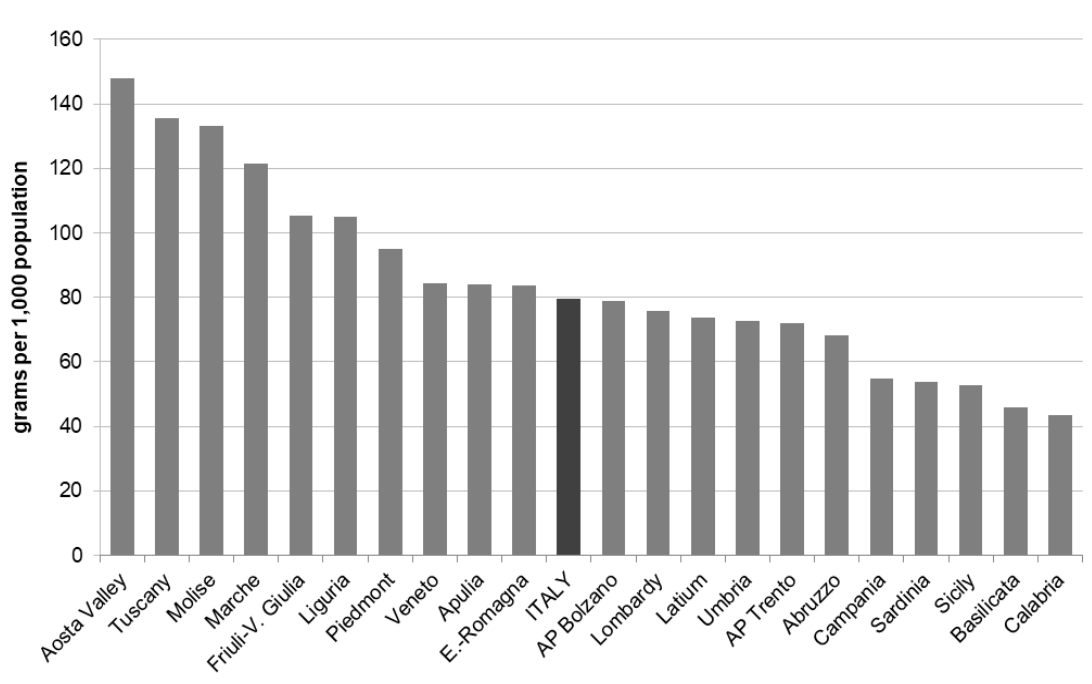


Figure 11. Total and regional demand (public and private) for normal human immunoglobulins for intravenous use, expressed in grams per 1,000 population, 2018 (adapted by the CNS on data from the traceability information flow)

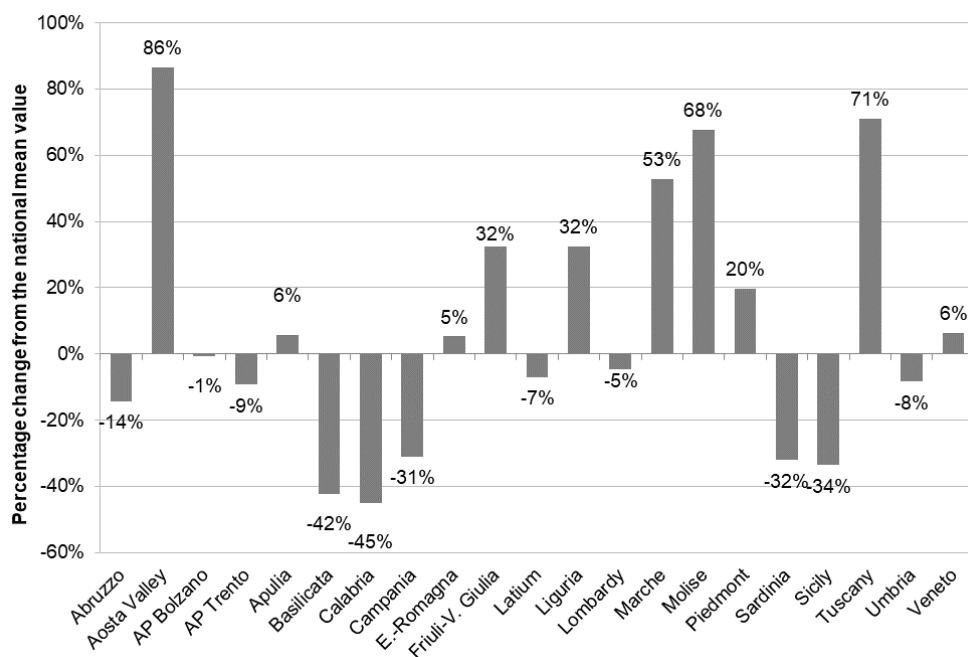


Figure 12. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for intravenous use in 2018 (adapted by the CNS on data from the traceability information flow)

ANTITHROMBIN (ATC B01AB02)

Antithrombin (AT) is a hepatic synthesised glycoprotein present in plasma at a concentration of about 150 µg / mL (19). It is a protease inhibitor, belonging to the serpentine family or serine protease inhibitors. It is the most powerful natural coagulation inhibitor and plays a key role in haemostatic balance. It inhibits the action of all activated coagulation factors, except for FV and FVIII; it has a particular affinity for thrombin and is also called heparin cofactor, as the anticoagulant action of heparin is mediated by AT. It also has anti-inflammatory and anti-aggregating properties mediated by the release of prostacyclines by endothelial cells (20, 21).

Table 11 shows the names of AT drugs currently on the market in Italy and the relative quantity of active ingredient they contain measured in International Units (IUs).

Table 11. Products containing antithrombin currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
025766039	KYBERNIN P*IV FL 500UI+10ML+SET	500	CSL BEHRING SpA	H
027113012	ANTITROMBINA III IMMUNO*FL10ML	500	BAXALTA ITALY Srl	H
029378015	AT III KED*500UI+FL 10ML+SET	500	KEDRION SpA	H
031118019	ATENATIV*IV FL 500UI+FL 10ML	500	OCTAPHARMA ITALY SpA	H
034330035	ANBINEX*FL 500UI+SIR 10ML+SET	500	GRIFOLS ITALIA SpA	H
041800018	ATKED*FL 500UI+FL 20ML+SET	500	KEDRION SpA	H
044565012	ATTERTIUM FL 500UI+SIR 10ML	500	GRIFOLS ITALIA SpA	C(nn)
025766027	KYBERNIN P*IV FL 1000UI+F 20ML	1000	CSL BEHRING SpA	H
027113024	ANTITROMBINA III IMMUNO*FL20ML	1000	BAXALTA ITALY Srl	H
029378027	AT III KED*1000UI+FL 20ML+SET	1000	KEDRION SpA	H
031118021	ATENATIV*IV FL 1000UI+FL 20ML	1000	OCTAPHARMA ITALY SpA	H
034330047	ANBINEX*FL 1000UI+SIR 20ML+SET	1000	GRIFOLS ITALIA SpA	H
041800020	ATKED*FL 1000UI+FL 20ML+SET	1000	KEDRION SpA	H
044565024	ATTERTIUM FL 1000UI+SIR 20ML	1000	GRIFOLS ITALIA SpA	C(nn)
029378039	AT III KED*2000UI+FL 20ML+SET	2000	KEDRION SpA	H
041800032	ATKED*FL 2000UI+FL 20ML+SET	2000	KEDRION SpA	H

Quantification and characterisation of the demand

Table 12 shows the total demand (expressed in IUs) and the total standardised demand (expressed in IUs *per capita*) of AT for the two-year period 2017-2018 with the relative percentage changes at national and at regional levels.

In 2018, total AT demand was 115,386,000 IUs, equal to 1.9 IUs *per capita*, showing a slight downward trend in utilisation compared to the previous years. However, in thirteen Regions there was a significant upward trend in use [range: Abruzzo (+59.9%), Sicily (+2.2%)]. The Region in which the biggest drop in the use of AT was observed was Sardinia (-44%).

Figure 13 shows the regional and national standardised demand for AT in 2018. The Regions with the highest *per capita* demand were Calabria, Molise, Sicilia and Latium, with a demand of 4 IUs for the first and the second, 3.5 IUs for the third and 3.2 IUs for the fourth Region. The lowest demand, between 0.4 and 0.6 IUs *per capita*, was recorded in the AP of Trento, the AP of Bolzano, Umbria and Emilia-Romagna.

Table 12. Total demand (public and private) and total standardised demand for antithrombin, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	1,545,500	1.2	2,458,000	1.9	59.9
Aosta Valley	332,000	2.6	363,000	2.9	9.9
AP Bolzano	202,000	0.4	250,000	0.5	22.9
APTrento	181,000	0.3	200,000	0.4	10.2
Apulia	7,901,500	1.9	6,907,000	1.7	-12.2
Basilicata	1,247,000	2.2	1,556,000	2.7	25.5
Calabria	8,056,500	4.1	7,806,000	4.0	-2.7
Campania	17,307,500	3.0	17,832,000	3.1	3.2
E.-Romagna	2,351,000	0.5	2,826,500	0.6	20.1
Friuli-V. Giulia	3,095,000	2.5	3,253,000	2.7	5.3
Latium	19,128,000	3.2	19,004,500	3.2	-0.6
Liguria	2,170,500	1.4	2,374,000	1.5	10.0
Lombardy	10,721,500	1.1	8,020,500	0.8	-25.3
Marche	2,227,000	1.4	2,665,000	1.7	20.2
Molise	1,194,000	3.8	1,225,500	4.0	3.3
Piedmont	7,597,500	1.7	6,410,500	1.5	-15.3
Sardinia	2,700,500	1.6	1,507,000	0.9	-44.0
Sicily	17,434,000	3.4	17,713,000	3.5	2.2
Tuscany	7,454,000	2.0	6,434,000	1.7	-13.6
Umbria	714,000	0.8	534,000	0.6	-24.8
Veneto	5,459,500	1.1	6,046,500	1.2	10.8
ITALY	119,019,500	2.0	115,386,000	1.9	-2.9

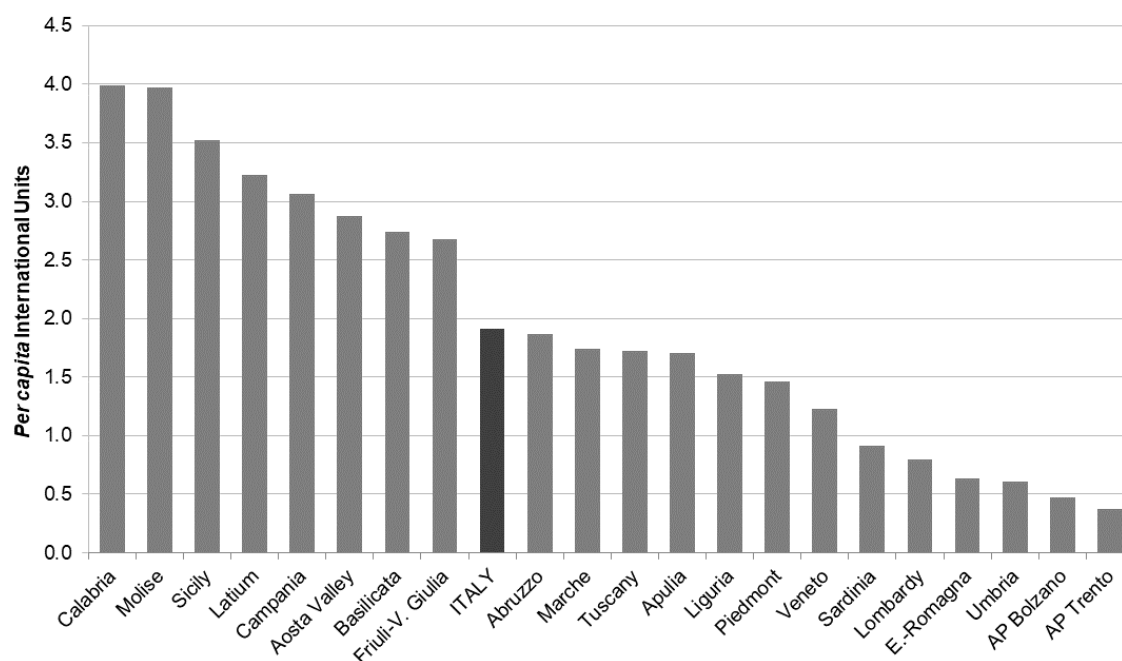


Figure 13. Total and regional demand (public and private) for antithrombin, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

Figure 14 shows the difference between the regional *per capita* percentage and the national mean value for the year 2018.

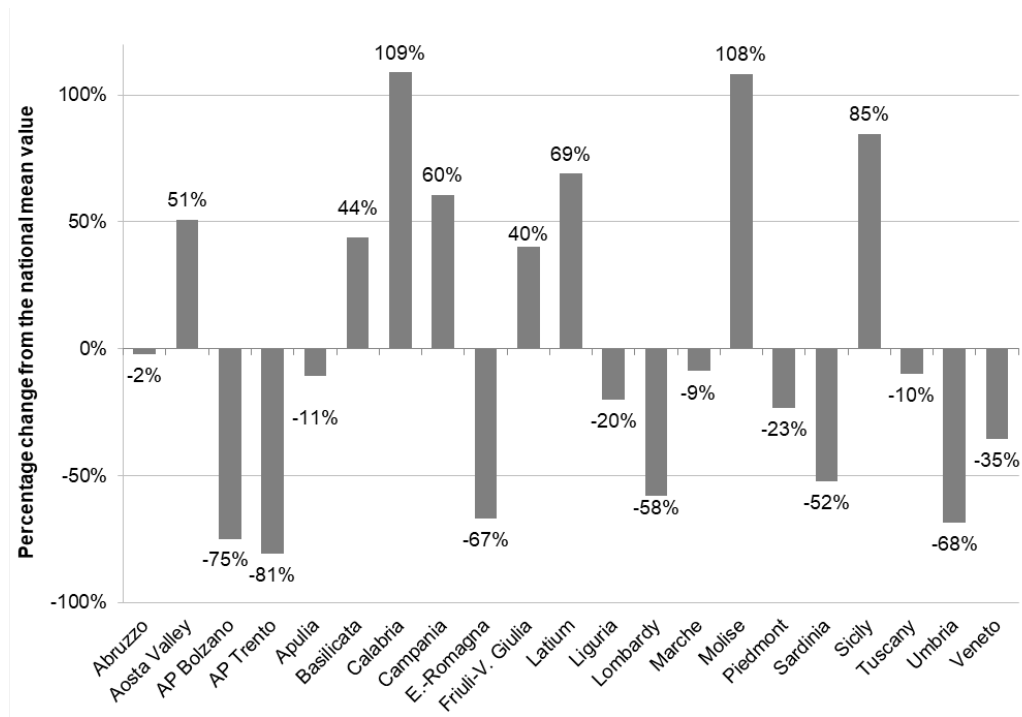


Figure 14. Percentage change from the national mean value of standardised regional demand for antithrombin in 2018 (adapted by the CNS on data from the traceability information flow)

COAGULATION FACTOR VIII (ATC B02BD02), COAGULATION FACTOR VIII AND VON WILLEBRAND FACTOR IN COMBINATION (ATC B02BD06), VON WILLEBRAND FACTOR (ATC B02BD10), RECOMBINANT FACTOR VIII (ATC B02BD02)

Coagulation FVIII is used in the replacement therapy of haemophilia A, a rare, haemorrhagic, hereditary, x-linked or acquired recessive disorder caused by FVIII deficiency. Depending on the level of activity of the circulating FVIII, there are severe forms of haemophilia A (FVIII <1%), moderate (between 1 and 5%) and mild (>5%) (22).

Products containing FVIII are subdivided in plasma-derived concentrates (pdFVIII) and products obtained with genetic recombination techniques (rFVIII) (23). pdFVIII concentrates are obtained from plasma pools of thousands of donors. FVIII is initially separated from the plasma by cold precipitation (cryoprecipitation) and then further purified with different techniques such as ion exchange and affinity chromatography (24).

The number of FVIII units administered is expressed in IUs, according to the current international WHO standards (25) for human FVIII concentrates. One IU is equivalent to the amount of FVIII in 1 millilitre (mL) of normal human plasma. The calculation of the required dosage is based on empirical evidence that 1 IU of FVIII per kilogram of body weight increases the plasma activity of FVIII by $2.1 \pm 0.4\%$ of normal activity.

Many of the pdFVIII concentrates also contain von Willebrand factor (vWF) with a different ratio compared to the FVIII content: following clinical trials supporting their efficacy, some of these drugs were approved for both the treatment of haemophilia and of von Willebrand disease (26).

The recombinant products obtained with genetic engineering techniques became part of clinical practice in Italy in the 1990s. The recombinant protein is synthesised by inserting the regions encoding the human FVIII gene in Chinese hamster ovary cells (CHO) or in newborn hamster kidney cells (BHK) (23).

Tables 13-15 show the brand names of the preparations containing both plasma-derived and recombinant FVIII currently on the market in Italy and the relative amount of active ingredient contained expressed in IUs.

Table 13. Products containing plasma-derived coagulation factor VIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
033657014	BERIATE*F 250UI+SOLV+SET	250	CSL BEHRING SpA	A
038541013	HAEMOCTIN*FL 250UI+FL 5ML+SIR	250	BIOTEST PHARMA GMBH	A
023564216	EMOCLOT*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
033657026	BERIATE*F 500UI+SOLV+SET	500	CSL BEHRING SpA	A
038541025	HAEMOCTIN*FL 500UI+FL 10ML+SIR	500	BIOTEST PHARMA GMBH	A
041649017	KLOTT*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
023564228	EMOCLOT*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
033657038	BERIATE*F 1000UI+SOLV+S	1000	CSL BEHRING SpA	A
038541037	HAEMOCTIN*FL 1000UI+FL 10ML+SIR	1000	BIOTEST PHARMA GMBH	A
041649029	KLOTT*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
033657040	BERIATE*FL 2000UI+FL 10ML	2000	CSL BEHRING SpA	A

Table 14. Products containing plasma-derived coagulation factor VIII and von Willebrand factor in combination, and von Willebrand factor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
Factor VIII and von Willebrand factor in combination				
033077088	ALPHANATE*INF 1F 250UI+SIR+AD	250	GRIFOLS ITALIA SpA	A
033866043	FANHDI*INF FL 250UI+SIR SOLV+S	250	GRIFOLS ITALIA SpA	A
037148018	TALATE*250UI/190UI+FL5ML+SIR	250	BAXALTA INN.Gmbh	A
040112017	OCTANATE*INIET FL 250UI+FL 5ML	250	OCTAPHARMA ITALY SpA	A
042939013	VONCENTO*250UI/600UI+FL 5ML	250	CSL BEHRING SpA	C(nn)
044564019	PLITATE*INF FL 250UI+SIR SOLV+SET	250	GRIFOLS ITALIA SpA	C(nn)
023308152	EMOWIL*1F 500UI+F 10ML	500	KEDRION SpA	A
026600080	HAEMATEP*FL 500UI+FL 10ML+SET	500	CSL BEHRING SpA	A
033077090	ALPHANATE*INF 1F 500UI+SIR+AD	500	GRIFOLS ITALIA SpA	A
033866056	FANHDI*INF FL 500UI+SIR SOLV+S	500	GRIFOLS ITALIA SpA	A
037148020	TALATE*500UI/375UI+FL10ML+SIR	500	BAXALTA INN. Gmbh	A
039385036	WILATE*FL 500+500UI+FL 5ML+SIR	500	OCTAPHARMA ITALY SpA	A
040112029	OCTANATE*INIET FL 500UI+FL 10ML	500	OCTAPHARMA ITALY SpA	A
040112056	OCTANATE*INIET FL 5ML100UI/ML	500	OCTAPHARMA ITALY SpA	A
042939025	VONCENTO*500UI/1200UI+FL 10ML	500	CSL BEHRING SpA	C(nn)
042939037	VONCENTO*500UI/1200UI+FL 5ML	500	CSL BEHRING SpA	C(nn)
044564021	PLITATE*INF FL 500UI+SIR SOLV+SET	500	GRIFOLS ITALIA SpA	C(nn)
023308188	EMOWIL*1F 1000UI+F 10ML	1000	KEDRION SpA	A
026600078	HAEMATEP*FL 1000UI+FL 15ML+SET	1000	CSL BEHRING SpA	A
033077102	ALPHANATE*INF 1F 1000UI+SIR+AD	1000	GRIFOLS ITALIA SpA	A
033866068	FANHDI*INF FL 1000UI+SIR SOLV+S	1000	GRIFOLS ITALIA SpA	A
037148032	TALATE*1000UI/750UI+FL10ML+SIR	1000	BAXALTA ITALY Srl	A
039385024	WILATE*FL 900+800UI+FL 10ML+SIR	1000	OCTAPHARMA ITALY SpA	A
039385048	WILATE*FL 1000+1000UI+FL 10ML+SI	1000	OCTAPHARMA ITALY SpA	A
040112031	OCTANATE*INIET FL 1000UI+FL 10ML	1000	OCTAPHARMA ITALY SpA	A
040112068	OCTANATE*INIET FL 5ML 200UI/ML	1000	OCTAPHARMA ITALY SpA	A
042939049	VONCENTO*1000UI/2400UI+FL 10ML	1000	CSL BEHRING SpA	C(nn)
044564033	PLITATE*INF FL1000UI+SIR SOLV+SET	1000	GRIFOLS ITALIA SpA	C(nn)
033077114	ALPHANATE*INF 1F 1500UI+SIR+AD	1500	GRIFOLS ITALIA SpA	A
033866070	FANHDI*INF FL1500UI+SIR SOLV+S	1500	GRIFOLS ITALIA SpA	A
044564045	PLITATE*INF FL1500UI+SIRSOLV+SET	1500	GRIFOLS ITALIA SpA	C(nn)
033077126	ALPHANATE *INF 1F 2000 UI+SIR+SET	2000	GRIFOLS ITALIA SpA	C
von Willebrand Factor				
037392026	WILFACTIN* 500UI+FL 5ML	500	LFB	C
037392014	WILFACTIN*1000UI+FL 10ML	1000	LFB	C
037392038	WILFACTIN*2000UI+FL 20ML	2000	LFB	C

Table 15. Products containing recombinant coagulation factor VIII and long-acting recombinant Factor VIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
028687010	RECOMBINATE*FL 250UI+FL 10ML	250	BAXALTA ITALY Srl	A
028687046	RECOMBINATE*FL 250UI+FL 5ML	250	BAXALTA ITALY Srl	A
028687073	RECOMBINATE*FL 250UI+FL 5ML	250	BAXALTA ITALY Srl	A
028687109	RECOMBINATE*FL 250UI+FL 10ML	250	BAXALTA ITALY Srl	A
034421014	REFACTOAF*IV 1FL 250UI+SIR 4ML	250	PFIZER ITALIA Srl	A
034421091	REFACTOAF*IV 1SIR PRER 250UI	250	PFIZER ITALIA Srl	A
034955017	KOGENATE BAYER*250UI+1FL+1KI	250	BAYER SpA	A
034955043	KOGENATE BAYER*FL 250UI+SIR+1KI	250	BAYER SpA	A
034955070	KOGENATE BAYER*EV 250UI+SIR	250	BAYER SpA	A
034956019	HELIXATE NEXGEN*250UI+1FL+1KIT	250	CSL BEHRING SpA	A
036160012	ADVATE*FL 250UI+FL SOLV 5ML	250	BAXTER SpA	A
036160075	ADVATE*FL 250UI+FL SOLV 2ML	250	BAXALTA ITALY Srl	A
036160113	ADVATE*FL 250UI+FL SOLV 5ML	250	BAXALTA ITALY Srl	A
036160176	ADVATE*FL 250UI+FL SOLV 2ML	250	BAXALTA ITALY Srl	A
043153016	NOVOEIGHT*EV FL 250UI+SIR 4ML	250	NOVO NORDISK SpA	A
043534015	NUWIQ*EV FL 250UI+SIR 2,5ML	250	KEDRION SpA	A
044725012	IBLIAS*FL POLV EV 250UI+FL 2,5ML	250	BAYER SpA	A
044726014	KOVALTRY*1FL POLV EV 250UI+SOLV	250	BAYER SpA	A
044726026	KOVALTRY*1FL POLV EV 250UI+SOLV	250	BAYER SpA	A
044726115	KOVALTRY* 1FL POLV EV 250 UI	250	BAYER AG	C(nn)
044726127	KOVALTRY* 1FL POLV EV 250 UI	250	BAYER AG	C(nn)
045255015	AFSTYLA 250UI+FL SOLV 2,5ML+SIR	250	CSL Behring GmbH	A
045273012	VIHUMA*EV 250UI+FL SOLV 2,5ML	250	Octapharma AB	C(nn)
028687022	RECOMBINATE*FL 500UI+FL 10ML	500	BAXALTA ITALY Srl	A
028687059	RECOMBINATE*FL 500UI+FL 5ML	500	BAXALTA ITALY Srl	A
028687085	RECOMBINATE*FL 500UI+FL 5ML	500	BAXALTA ITALY Srl	A
028687111	RECOMBINATE*FL 500UI+FL 10ML	500	BAXALTA ITALY Srl	A
034421026	REFACTOAF*IV 1FL 500UI+SIR 4ML	500	PFIZER ITALIA Srl	A
034421065	REFACTOAF*IV 1SIR PRER 500UI	500	PFIZER ITALIA Srl	A
034955029	KOGENATE BAYER*500UI+1FL+1KIT	500	BAYER SpA	A
034955056	KOGENATE BAYER*FL 500UI+SIR	500	BAYER SpA	A
034955082	KOGENATE BAYER*EV 500UI+SIR	500	BAYER SpA	A
034956021	HELIXATE NEXGEN*500UI+1FL+1KIT	500	CSL BEHRING SpA	A
036160024	ADVATE*FL 500UI+FL SOLV 5ML	500	BAXTER SpA	A
036160087	ADVATE*FL 500UI+FL SOLV 2ML	500	BAXALTA ITALY Srl	A
036160125	ADVATE*FL 500UI+FL SOLV 5ML	500	BAXALTA ITALY Srl	A
036160188	ADVATE*FL 500UI+FL SOLV 2ML	500	BAXALTA ITALY Srl	A
043153028	NOVOEIGHT*EV FL 500UI+SIR 4ML	500	NOVO NORDISK SpA	A
043534027	NUWIQ*EV FL 500UI+SIR 2,5ML	500	KEDRION SpA	A
044725024	IBLIAS*FL POLV EV 500UI+FL 2,5ML	500	BAYER SpA	A
044726038	KOVALTRY*1FL POLV EV 500UI+SOLV	500	BAYER SpA	A
044726040	KOVALTRY*1FL POLV EV 500UI+SOLV	500	BAYER SpA	A
044726139	KOVALTRY*1FL POLV EV 500UI	500	BAYER AG	C(nn)
044726141	KOVALTRY*1FL POLV EV 500UI	500	BAYER AG	C(nn)
045255027	AFSTYLA 500UI+FL SOLV 2,5ML+SIR	500	CSL Behring GmbH	A
045273024	VIHUMA*EV 500UI+FL SOLV 2,5ML	500	Octapharma AB	C(nn)
028687034	RECOMBINATE*FL 1000UI+FL 10ML	1000	BAXALTA ITALY Srl	A
028687061	RECOMBINATE*FL 1000UI+FL 5ML	1000	BAXALTA ITALY Srl	A
028687097	RECOMBINATE*FL 1000UI+FL 5ML	1000	BAXALTA ITALY Srl	A
028687123	RECOMBINATE*FL 1000UI+FL 10ML	1000	BAXALTA ITALY Srl	A
034421038	REFACTO AF*IV 1FL 1000UI+SIR 4ML	1000	PFIZER ITALIA Srl	A
034421077	REFACTO AF*IV 1SIR PRER 1000UI	1000	PFIZER ITALIA Srl	A
034955031	KOGENATE BAYER*1000UI+1FL+1KIT	1000	BAYER SpA	A
034955068	KOGENATE BAYER*FL 1000UI+SIR	1000	BAYER SpA	A

AIC code	Brand name	IU	Manufacturer	NHS class
034955094	KOGENATE BAYER*EV 1000UI+SIR	1000	BAYER SpA	A
034956033	HELIXATE NEXGEN*1000UI+1FL+KIT	1000	CSL BEHRING SpA	A
036160036	ADVATE*FL 1000UI+FL SOLV 5ML	1000	BAXTER SpA	A
036160099	ADVATE*FL 1000UI+FL SOLV 2ML	1000	BAXALTA ITALY Srl	A
036160137	ADVATE*FL 1000UI+FL SOLV 5ML	1000	BAXALTA ITALY Srl	A
036160190	ADVATE*FL 1000UI+FL SOLV 2ML	1000	BAXALTA ITALY Srl	A
043153030	NOVOEIGHT*EV FL 1000UI+SIR 4ML	1000	NOVO NORDISK SpA	A
043534039	NUWIQ*EV FL 1000UI+SIR 2,5ML	1000	KEDRION SpA	A
044725036	IBLIAS*FL POLV EV 1000UI+2,5 ML	1000	BAYER SpA	A
044726053	KOVALTRY*FL POLV EV 1000UI+SOLV	1000	BAYER SpA	A
044726065	KOVALTRY*FL POLV EV 1000UI+SOLV	1000	BAYER SpA	A
044726154	KOVALTRY* 1FL POLV EV 1000 UI	1000	BAYER AG	C(nn)
044726166	KOVALTRY* 1FL POLV EV 1000 UI	1000	BAYER AG	C(nn)
045255039	AFSTYLA 1000UI+FL SOLV 2,5ML+SIR	1000	CSL Behring GmbH	A
045273036	VIHUMA*EV 1000UI+FL SOLV 2,5ML	1000	Octapharma AB	C(nn)
036160048	ADVATE*FL 1500UI+FL SOLV 5ML	1500	BAXTER SpA	A
036160101	ADVATE*FL 1500UI+FL SOLV 2ML	1500	BAXALTA ITALY Srl	A
036160149	ADVATE*FL 1500UI+FL SOLV 5ML	1500	BAXALTA ITALY Srl	A
036160202	ADVATE*FL 1500UI+FL SOLV 2ML	1500	BAXALTA ITALY Srl	A
043153042	NOVOEIGHT*EV FL 1500UI+SIR 4ML	1500	NOVO NORDISK SpA	A
045255041	AFSTYLA 1500UI+FL SOLV 2,5ML+SIR	1500	CSL Behring GmbH	A
034421040	REFACTOAF*IV 1FL 2000UI+SIR 4ML	2000	PFIZER ITALIA Srl	A
034421089	REFACTOAF*IV 1SIR PRER 2000UI	2000	PFIZER ITALIA Srl	A
034955106	KOGENATE BAYER*EV 2000UI+SIR	2000	BAYER SpA	A
034955118	KOGENATE BAYER*EV 2000UI+SIR	2000	BAYER SpA	A
036160051	ADVATE*FL 2000UI+FL SOLV 5ML	2000	BAXTER SpA	A
036160152	ADVATE*FL 2000UI+FL SOLV 5ML	2000	BAXALTA ITALY Srl	A
043153055	NOVOEIGHT*EV FL 2000UI+SIR 4ML	2000	NOVO NORDISK SpA	A
043534041	NUWIQ*EV FL 2000UI+SIR 2,5ML	2000	KEDRION SpA	A
044725048	IBLIAS*FL POLV EV 2000UI+FL 5ML	2000	BAYER SpA	A
044726077	KOVALTRY*FL POLV EV 2000UI+SOLV	2000	BAYER SpA	A
044726089	KOVALTRY*FL POLV EV 2000UI+SOLV	2000	BAYER SpA	A
045255054	AFSTYLA 2000UI+FL SOLV 2,5ML+SIR	2000	CSL Behring GmbH	A
045273048	VIHUMA*EV 2000UI+FL SOLV 2,5ML	2000	Octapharma AB	C(nn)
043534054	NUWIQ*EV FL 2500UI+SIR 2,5ML	2500	OCTAPHARMA AB	C(nn)
045255066	AFSTYLA 2500UI+FL SOLV 2,5ML+SIR	2500	CSL Behring GmbH	A
034421053	REFACTOAF*IV 1SIR PRER 3000UI	3000	PFIZER ITALIA Srl	A
034955120	KOGENATE BAYER*EV 3000UI+SIR	3000	BAYER SpA	A
034955132	KOGENATE BAYER*EV 3000UI+SIR	3000	BAYER SpA	A
034956058	HELIXATE NEXGEN*3000UI+1FL+KIT	3000	CSL BEHRING SpA	A
036160063	ADVATE*FL 3000UI+FL SOLV 5ML	3000	BAXTER SpA	A
036160164	ADVATE*FL 3000UI+FL SOLV 5ML	3000	BAXALTA ITALY Srl	A
043153067	NOVOEIGHT*EV FL 3000UI+SIR 4ML	3000	NOVO NORDISK SpA	A
043534066	NUWIQ*EV FL 3000UI+SIR 2,5ML	3000	OCTAPHARMA AB	C(nn)
044725051	IBLIAS*FL POLV EV 3000UI+FL 5ML	3000	BAYER SpA	A
044726091	KOVALTRY*FL POLV EV 3000UI+SOLV	3000	BAYER SpA	A
044726103	KOVALTRY*FL POLV EV 3000UI+SOLV	3000	BAYER SpA	A
045255078	AFSTYLA 3000UI+FL SOLV 2,5ML+SIR	3000	CSL Behring GmbH	A
043534078	NUWIQ*EV FL 4000UI+SIR 2,5ML	4000	OCTAPHARMA AB	C(nn)
Extended half-life recombinant Factor VIII				
044563017	ELOCTA*IV 1FL 250UI+SIR PRERI	250	SOBI Srl	A
045936010	ADYNOVI*EV 250 UI + FL 2 ML + DISP	250	BAXALTA INN. GmbH	A
045936022	ADYNOVI*EV 250 UI + FL 2 ML + DISP	250	BAXALTA INN. GmbH	A
045936034	ADYNOVI*EV 250 UI + FL 5 ML + DISP	250	BAXALTA INN. GmbH	A
045936046	ADYNOVI*EV 250 UI + FL 5 ML + DISP	250	BAXALTA INN. GmbH	A
044563029	ELOCTA*IV 1FL 500UI+SIR PRERI	500	SOBI Srl	A
045936059	ADYNOVI*EV 500UI + FL 2 ML + DISP	500	BAXALTA INN. GmbH	A

AIC code	Brand name	IU	Manufacturer	NHS class
045936061	ADYNOVI*EV 500UI + FL 2 ML + DISP	500	BAXALTA INN. Gmbh	C(nn)
045936073	ADYNOVI*EV 500UI + FL 5 ML + DISP	500	BAXALTA INN. Gmbh	C(nn)
045936085	ADYNOVI*EV 500UI + FL 5 ML + DISP	500	BAXALTA INN. Gmbh	C(nn)
044563031	ELOCTA*IV 1FL 750UI+SIR PRERI	750	SOBI Srl	A
044563056	ELOCTA*IV 1FL 1000UI+SIR PRERI	1000	SOBI Srl	A
045936097	ADYNOVI*EV 1000 UI + FL 2 ML	1000	BAXALTA INN. Gmbh	C(nn)
045936109	ADYNOVI*EV 1000 UI + FL 2 ML	1000	BAXALTA INN. Gmbh	C(nn)
045936111	ADYNOVI*EV 1000 UI + FL 5 ML	1000	BAXALTA INN. Gmbh	C(nn)
045936123	ADYNOVI*EV 1000 UI + FL 5 ML	1000	BAXALTA INN. Gmbh	C(nn)
044563068	ELOCTA*IV 1FL 1500UI+SIR PRERI	1500	SOBI Srl	A
044563070	ELOCTA*IV 1FL 2000UI+SIR PRERI	2000	SOBI Srl	A
045936135	ADYNOVI*EV 2000 UI + FL 5 ML	2000	BAXALTA INN. Gmbh	C(nn)
045936147	ADYNOVI*EV 2000 UI + FL 5 ML	2000	BAXALTA INN. Gmbh	C(nn)
044563082	ELOCTA*IV 1FL 3000UI+SIR PRERI	3000	SOBI Srl	A

Quantification and characterisation of demand

In Italy, the total demand for both plasma-derived and recombinant formulations FVIII, was equal to 581,459,000 IUs in 2018 (Table 16); of these, about a fifth (20.8% of the total - 121,616,750 IUs) were human plasma-derived (Figure 15). The tendency to use pdFVIII varied significantly from one Region to another ranging from 0.4% in Aosta Valley to 38.2% in Piedmont (Figure 15).

Table 16. Total demand (public and private) and total standardised demand for coagulation factor VIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	11,281,000	8.5	10,392,750	7.9	-7.4
Aosta Valley	1,044,000	8.2	844,000	6.7	-18.7
AP Bolzano	3,638,750	6.9	3,219,500	6.1	-12.1
AP Trento	2,656,000	4.9	3,066,500	5.7	15.2
Apulia	46,748,250	11.5	49,464,250	12.2	6.2
Basilicata	4,382,000	7.7	5,501,000	9.7	26.3
Calabria	21,691,750	11	25,121,750	12.8	16.3
Campania	69,642,250	11.9	72,703,250	12.5	4.6
E.-Romagna	34,958,500	7.9	34,100,000	7.7	-2.5
Friuli-V. Giulia	11,053,000	9.1	7,825,000	6.4	-29.1
Latium	91,786,750	15.6	84,913,500	14.4	-7.5
Liguria	11,318,000	7.2	12,154,500	7.8	8.0
Lombardy	79,375,250	7.9	75,610,250	7.5	-4.9
Marche	11,258,500	7.3	10,459,000	6.8	-6.7
Molise	2,943,000	9.5	3,488,000	11.3	19.3
Piedmont	49,602,000	11.3	45,210,250	10.3	-8.5
Sardinia	11,681,750	7.1	13,950,000	8.5	19.8
Sicily	54,077,750	10.7	49,959,500	9.9	-7.1
Tuscany	24,302,000	6.5	27,082,000	7.2	11.6
Umbria	7,727,000	8.7	7,543,500	8.5	-1.9
Veneto	38,072,000	7.8	38,850,500	7.9	2.1
ITALY	589,239,500	9.7	581,459,000	9.6	-1.1

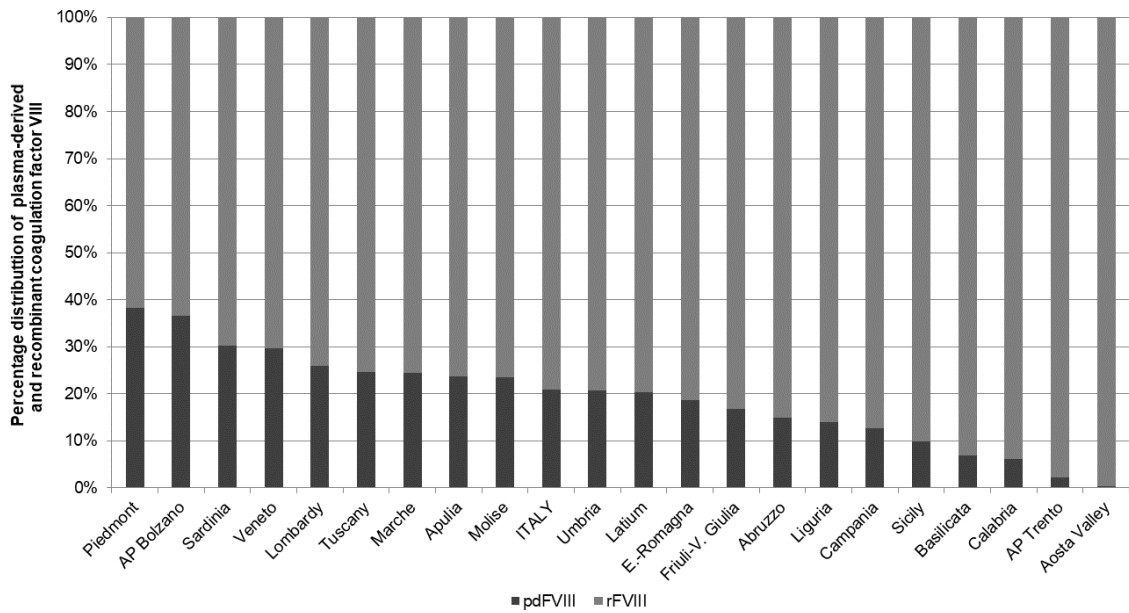


Figure 15. Percentage distribution of plasma-derived and recombinant coagulation factor VIII, by Region, 2018 (adapted by the CNS on data from the traceability information flow)

In 2018, the total FVIII demand *per capita* (plasma-derived and recombinant) was 9.6 IUs showing a stable trend compared to 2017. The regional *per capita* demand showed significant fluctuations ranging from about 5.7 IUs in the AP of Trento to about 14 IUs in Lazio (Figure 16).

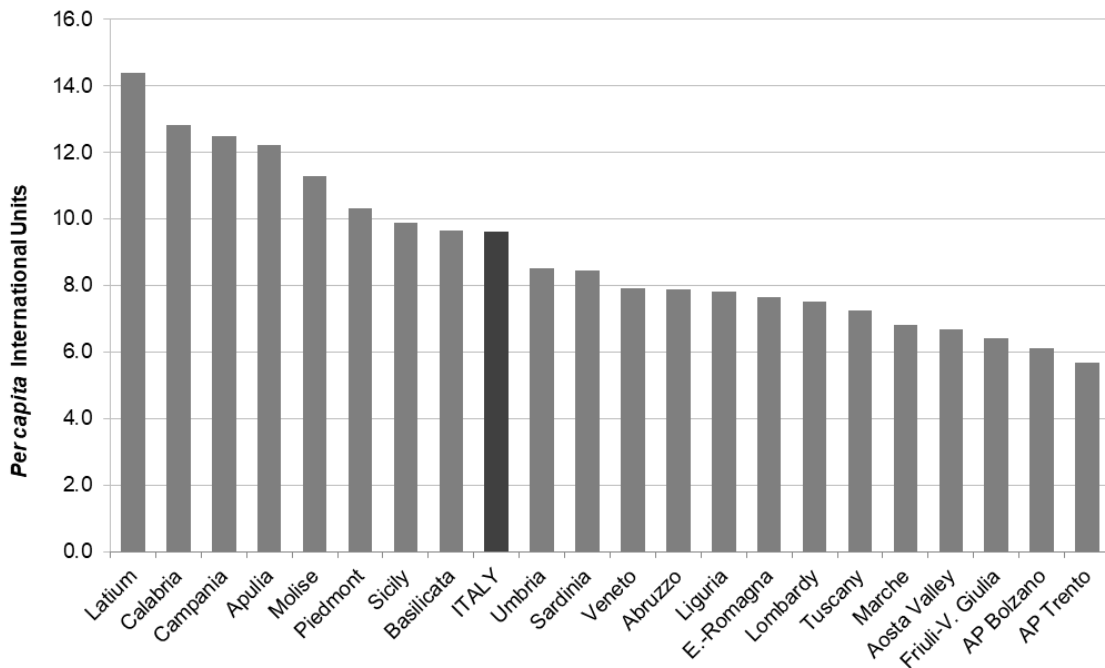


Figure 16. Total and regional demand (public and private) for coagulation factor VIII, expressed in International Units per capita, 2018 (adapted by the CNS on data from the traceability information flow)

The most significant increases in standardised regional demand were observed in Basilicata and Sardinia, where utilisation increased by 26% and 20%, respectively.

It is important to underline that for FVIII, strong fluctuations can occur due to the contingent needs of a few patients (immunotolerance treatment, surgery, severe trauma, etc.). However, seven Regions had a greater demand compared to the national average (Figure 17).

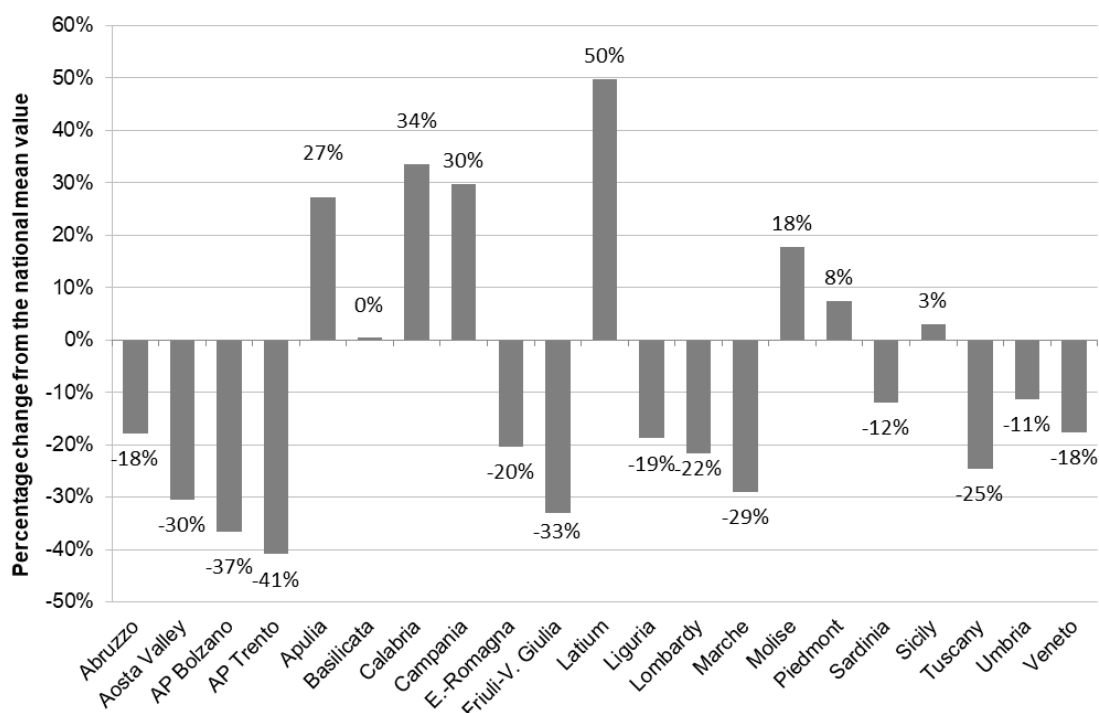


Figure 17. Percentage change from the national mean value of standardised regional demand for coagulation factor VIII in 2018 (adapted by the CNS on data from the traceability information flow)

Plasma-derived Factor VIII (B02BD02), Plasma derived and von Willebrand Factor in combination (B02BD06) and von Willebrand Factor (B02BD10)

In 2018, the national demand for pdFVIII was about 21% - equivalent to 121,616,750 IUs - of the total demand. There was an 8% decrease compared to 2017 and a total standardised demand of 2 IUs *per capita* (Table 17). *Per capita* demand varied significantly with the highest volumes in Piedmont (3.9 IUs *per capita*), Latium and Apulia (2.9 IUs *per capita*); the corresponding percentage change between the aforementioned values and the Italian mean value were of +97%, +45% and +44%, respectively. The lowest volumes (below 1 IU *per capita*) were recorded in Calabria, Basilicata, Aosta Valley and the AP of Trento (Figures 18 and 19). The consumption of pdFVIII drastically decreased in Aosta Valley Region.

The national trend decreased in many Italian Regions (from -93.6% to -3.8%), with the exception of Abruzzo, the AP of Bolzano, the AP of Trento, Apulia, Liguria, Marche, Molise, Sardinia, Tuscany and Veneto, where there were increases of between 0.7% and 93%.

Table 17. Total demand (public and private) and total standardised demand for plasma-derived coagulation factor VIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	977,000	0.7	1,560,000	1.2	60.5
Aosta Valley	47,000	0.4	3,000	0.0	-93.6
AP Bolzano	1,048,000	2	1,180,000	2.2	11.8
AP Trento	61,500	0.1	67,000	0.1	8.7
Apulia	11,489,000	2.8	11,731,500	2.9	2.5
Basilicata	390,000	0.7	402,000	0.7	3.7
Calabria	1,629,500	0.8	1,531,000	0.8	-5.6
Campania	9,854,000	1.7	9,242,000	1.6	-6.0
E.-Romagna	6,639,000	1.5	6,389,750	1.4	-3.8
Friuli-V. Giulia	2,024,000	1.7	1,313,500	1.1	-35.0
Latium	21,569,500	3.7	17,220,000	2.9	-20.1
Liguria	1,692,000	1.1	1,694,000	1.1	0.7
Lombardy	24,329,500	2.4	19,623,000	2.0	-19.5
Marche	2,547,000	1.7	2,565,000	1.7	1.1
Molise	593,000	1.9	819,000	2.7	39.0
Piedmont	19,078,000	4.3	17,268,500	3.9	-9.1
Sardinia	2,193,000	1.3	4,213,000	2.6	92.7
Sicily	7,543,000	1.5	5,049,000	1.0	-32.7
Tuscany	6,387,000	1.7	6,672,000	1.8	4.6
Umbria	1,775,000	2	1,567,000	1.8	-11.3
Veneto	10,167,500	2.1	11,506,500	2.3	13.2
ITALY	132,033,500	2.2	121,616,750	2.0	-7.7

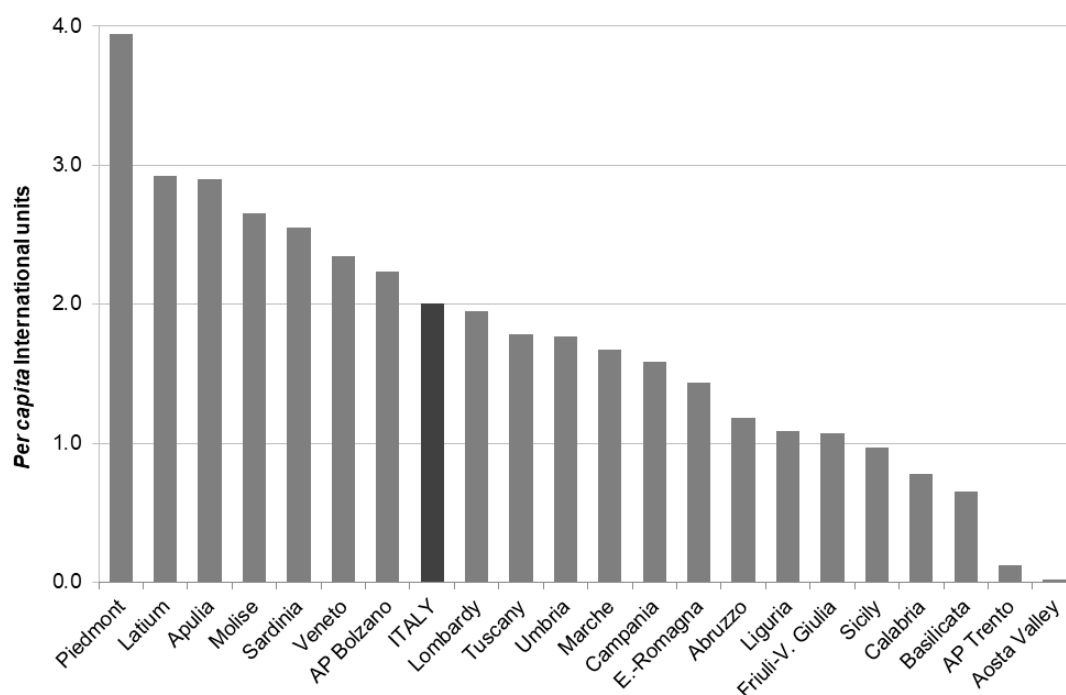


Figure 18. Total and regional demand (public and private) for plasma-derived coagulation factor VIII, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

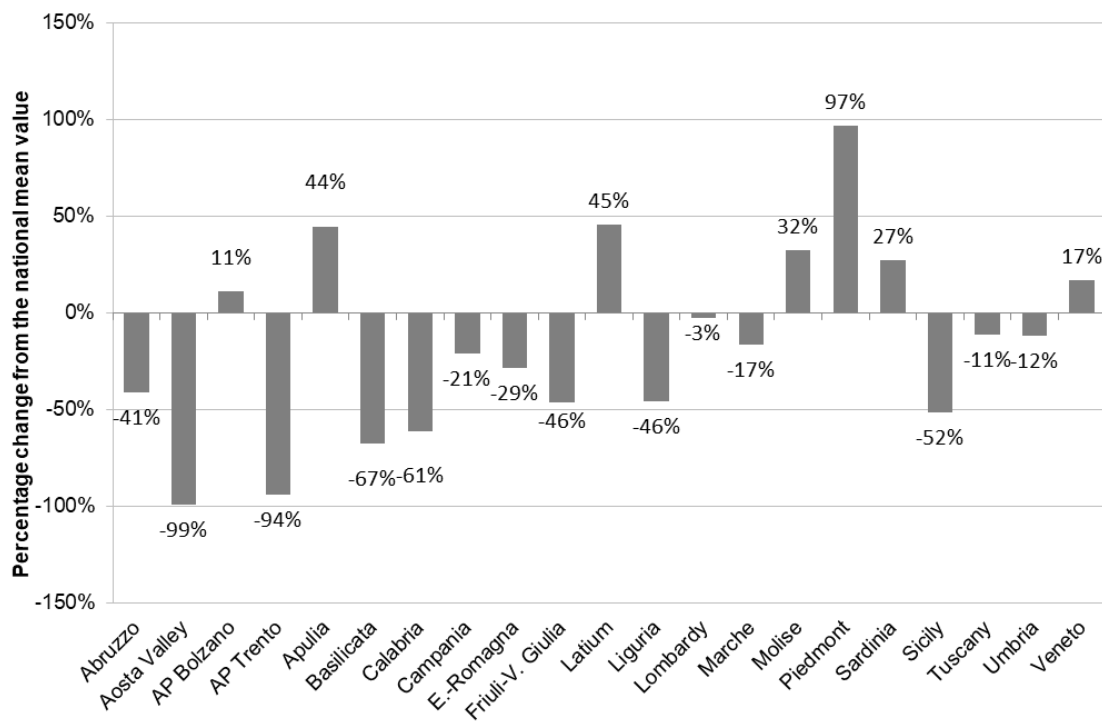


Figure 19. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation factor VIII in 2018 (adapted by the CNS on data from the traceability information flow)

Plasma-derived Factor VIII (B02BD02)

In 2018, the total demand for plasma-derived FVIII was 69,836,000 IUs. The mean national demand *per capita* was about 1.2 IUs, with a range between Regions of 0.1 IUs and 2.7 IUs (Table 18). The Regions with the highest *per capita* utilisation of pdFVIII were Piedmont (2.7 IUs), Molise (2.0 IUs) and Veneto (1.9 IUs).

The lowest utilisation was observed in Basilicata and Sicily (0.1 IUs and 0.2 IUs *per capita* respectively), while Abruzzo and the AP of Trento had a *per capita* utilisation near to the null value. No consumption was recorded in Aosta Valley.

Figure 20 shows the percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination by Region.

Table 18. Total demand (public and private) and total standardised demand for plasma-derived coagulation FVIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	17,000	0.0	43,000	0.0	154.3
Aosta Valley	47,000	0.4	-	-	-100.0
AP Bolzano	318,000	0.6	330,000	0.6	3.1
AP Trento	12,000	0.0	13,000	0.0	8.1
Apulia	4,403,000	1.1	5,046,000	1.2	15.0
Basilicata	33,000	0.1	85,000	0.1	159.1
Calabria	896,000	0.5	777,000	0.4	-12.9
Campania	4,994,000	0.9	5,130,000	0.9	2.9
E.-Romagna	3,692,000	0.8	2,053,000	0.5	-44.4
Friuli-V. Giulia	1,153,000	0.9	911,000	0.7	-20.8
Latium	9,088,000	1.5	8,765,000	1.5	-3.5
Liguria	1,152,000	0.7	864,000	0.6	-24.6
Lombardy	17,873,000	1.8	14,212,000	1.4	-20.6
Marche	2,039,000	1.3	1,835,000	1.2	-9.6
Molise	288,000	0.9	608,000	2.0	112.4
Piedmont	11,305,000	2.6	11,613,000	2.7	3.1
Sardinia	634,000	0.4	2,738,000	1.7	333.2
Sicily	1,918,000	0.4	811,000	0.2	-57.5
Tuscany	4,353,000	1.2	4,317,000	1.2	-0.7
Umbria	724,000	0.8	534,000	0.6	-25.9
Veneto	7,204,000	1.5	9,151,000	1.9	27.1
ITALY	72,143,000	1.2	69,836,000	1.2	-3.0

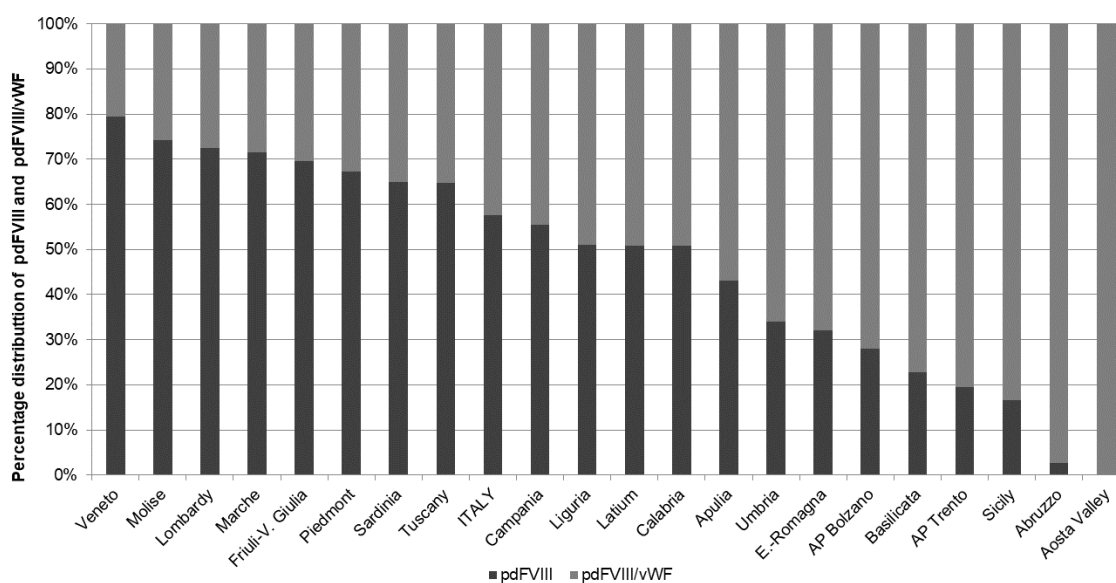


Figure 20. Percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination, by Region, 2018 (adapted by the CNS on data from the traceability information flow)

Coagulation Factor VIII and von Willebrand Factor in combination (ATC B02BD06) and von Willebrand Factor (ATC B02BD10)

In 2018, the national demand for FVIII and von Willebrand Factor in combination was 51,780,750, about 43% of the total demand for pdFVIII. The mean national demand *per capita* was 0.9 IUs, with a range between Regions of 0.1 IUs (AP of Trento) and 1.7 IUs (Apulia) (Table 19).

Table 19. Total demand (public and private) and total standardised demand for FVIII and von Willebrand Factor in combination, expressed in International Units and International Units *per capit*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	960,000	0.7	1,517,000	1.2	58.9
Aosta Valley	-	-	3,000	0.0	100.0
AP Bolzano	730,000	1.4	850,000	1.6	15.7
AP Trento	49,500	0.1	54,000	0.1	8.8
Apulia	7,086,000	1.7	6,685,500	1.7	-5.3
Basilicata	357,000	0.6	317,000	0.6	-10.7
Calabria	733,500	0.4	754,000	0.4	3.2
Campania	4,860,000	0.8	4,112,000	0.7	-15.2
E.-Romagna	2,947,000	0.7	4,336,750	1.0	47.0
Friuli-V. Giulia	871,000	0.7	402,500	0.3	-53.7
Latium	12,481,500	2.1	8,455,000	1.4	-32.2
Liguria	540,000	0.3	830,000	0.5	54.5
Lombardy	6,456,500	0.6	5,411,000	0.5	-16.3
Marche	508,000	0.3	730,000	0.5	44.3
Molise	305,000	1	211,000	0.7	-30.4
Piedmont	7,773,000	1.8	5,655,500	1.3	-27.0
Sardinia	1,559,000	0.9	1,475,000	0.9	-5.1
Sicily	5,625,000	1.1	4,238,000	0.8	-24.2
Tuscany	2,034,000	0.5	2,355,000	0.6	16.0
Umbria	1,051,000	1.2	1,033,000	1.2	-1.2
Veneto	2,963,500	0.6	2,355,500	0.5	-20.5
ITALY	59,890,500	1	51,780,750	0.9	-13.4

The Regions with the highest *per capita* utilisation of FVIII and von Willebrand Factor in combination were Apulia (1.7 IUs), the AP of Bolzano (1.6 IUs) and Latium (1.4 IUs).

The lowest utilisation – between 0.4 and 0.1 IUs *per capita* – was observed in Calabria, Friuli Venezia Giulia and the AP of Trento. In Aosta Valley consumption was near to the null value (Figure 21).

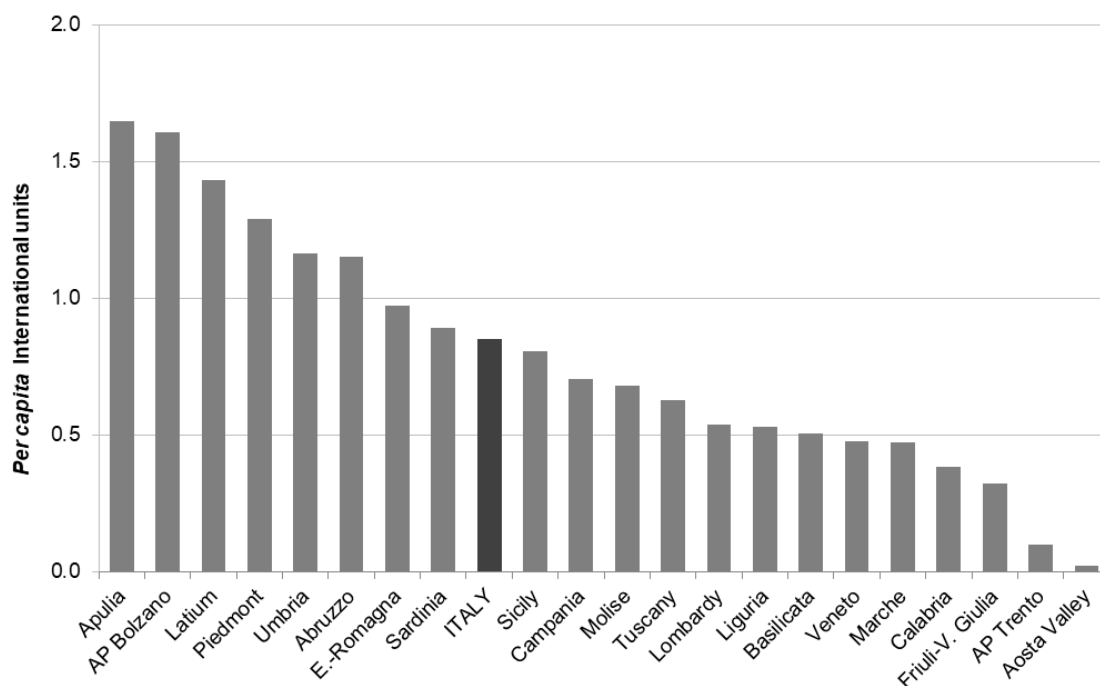


Figure 21. Total and regional demand (public and private) for pdFVIII and von Willebrand Factor in combination, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

Recombinant Factor VIII (B02BD02)

In 2018, the total demand for rFVIII was 459,842,250 IUs, a stable trend (+0.8%) compared to 2017. The mean national demand *per capita* was about 7.6 IUs, with a range between Regions of 3.9 IUs and 12.1 IUs (Table 20).

The Regions in which the highest *per capita* utilisation of rFVIII was observed were Calabria (12.1 IUs), Latium (11.5 IUs) and Campania (10.9 IUs) (Figure 22), with a percentage change compared to the Italian mean value of + 59%, + 51% and +43%, respectively (Figure 23).

The lowest utilisation – between 3.9 and 5.5 IUs *per capita* – was observed in the AP of Bolzano, Marche, Friuli-V. Giulia and Tuscany.

Table 20. Total demand (public and private) and total standardised demand for recombinant coagulation factor VIII, expressed in International Units and International Units per capita, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017- 2018
	IU	IU per capita	IU	IU per capita	
Abruzzo	10,304,000	7.8	8,832,750	6.7	-13.8
Aosta Valley	997,000	7.9	841,000	6.7	-15.2
AP Bolzano	2,590,750	4.9	2,039,500	3.9	-21.8
AP Trento	2,594,500	4.8	2,999,500	5.6	15.3
Apulia	35,259,250	8.7	37,732,750	9.3	7.4
Basilicata	3,992,000	7.0	5,099,000	9.0	28.5
Calabria	20,062,250	10.2	23,590,750	12.1	18.1
Campania	59,788,250	10.2	63,461,250	10.9	6.4
E.-Romagna	28,319,500	6.4	27,710,250	6.2	-2.2
Friuli-V. Giulia	9,029,000	7.4	6,511,500	5.4	-27.7
Latium	70,217,250	11.9	67,693,500	11.5	-3.6
Liguria	9,626,000	6.1	10,460,500	6.7	9.3
Lombardy	55,045,750	5.5	55,987,250	5.6	1.5
Marche	8,711,500	5.7	7,894,000	5.2	-9.0
Molise	2,350,000	7.6	2,669,000	8.7	14.3
Piedmont	30,524,000	6.9	27,941,750	6.4	-8.1
Sardinia	9,488,750	5.7	9,737,000	5.9	2.9
Sicily	46,534,750	9.2	44,910,500	8.9	-2.9
Tuscany	17,915,000	4.8	20,410,000	5.5	14.1
Umbria	5,952,000	6.7	5,976,500	6.8	0.9
Veneto	27,904,500	5.7	27,344,000	5.6	-2.0
ITALY	457,206,000	7.5	459,842,250	7.6	0.8

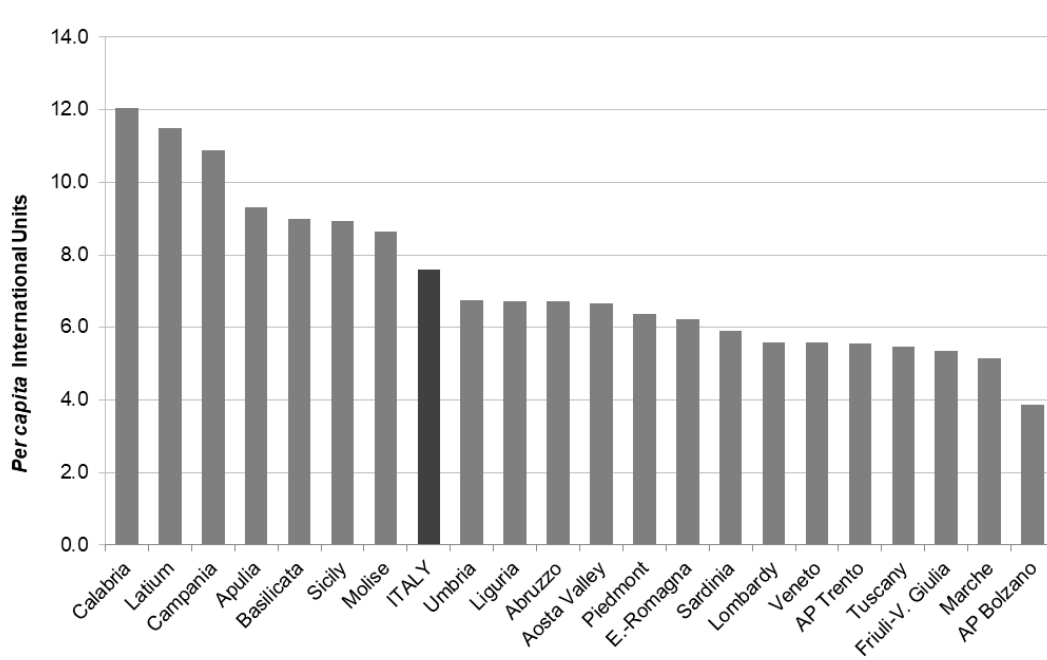


Figure 22. Total and regional demand (public and private) for recombinant coagulation factor VIII, expressed in International Units per capita, 2018 (adapted by the CNS on data from the traceability information flow)

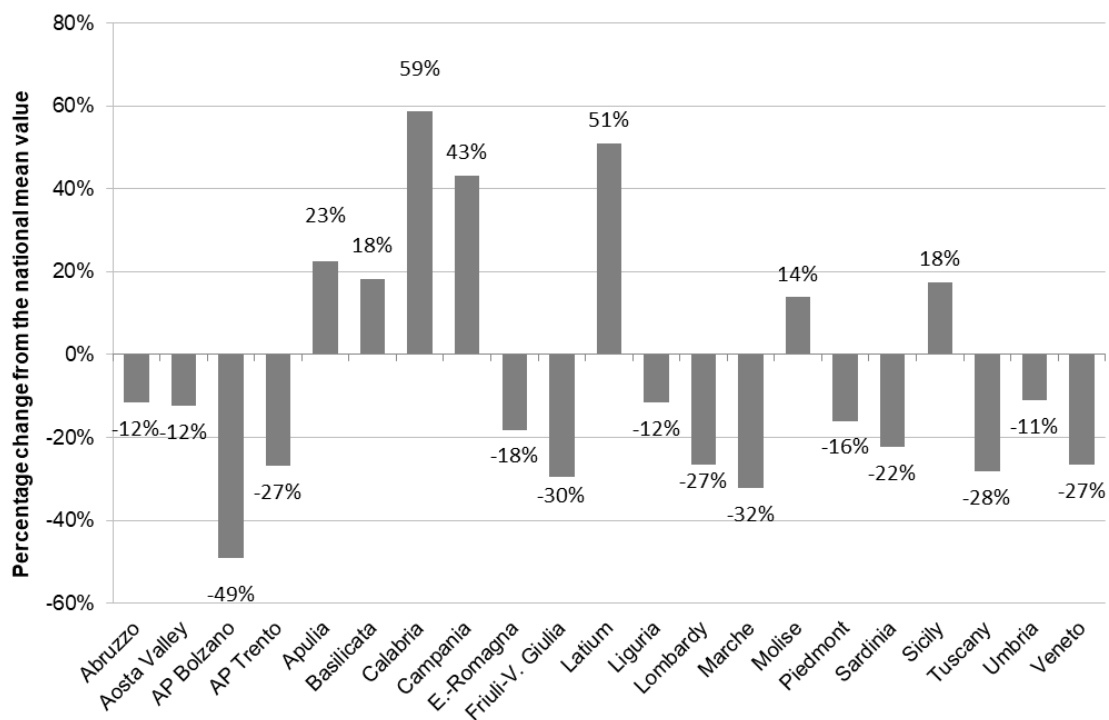


Figure 23. Percentage change from the national mean value of standardised regional demand for recombinant coagulation factor VIII in 2018 (adapted by the CNS on data from the traceability information flow)

Extended half-life Recombinant Factor VIII

Part of the total demand for rFVIII is represented by drugs containing extended half-life molecules. In 2018, the demand for these products was equal to 52,355,500 IUs, about 11% of the total demand for rFVIII.

The national demand *per capita* was about 0.9 IUs, with a range between Regions of 0.2 IUs in the AP of Bolzano and 2.1 IUs in Liguria. In Aosta Valley, Basilicata and Molise no demand was recorded (Table 21).

Table 21. Total demand (public and private) and total standardised demand for long-acting recombinant coagulation factor VIII, expressed in International Units and International Units *per capita* (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	225,000	0.2	908,250	0.7	306
Aosta Valley	0	-	0	-	NA
AP Bolzano	0	-	90,000	0.2	NA
AP Trento	0	-	-	-	NA
Apulia	258,000	0.1	1,522,000	0.4	492
Basilicata	0	-	-	-	NA
Calabria	626,000	0.3	2,907,000	1.5	366
Campania	1,514,000	0.3	6,511,750	1.1	331
E.-Romagna	805,000	0.2	5,710,000	1.3	609
Friuli-V. Giulia	86,000	0.1	462,500	0.4	439
Latium	879,000	0.1	6,454,500	1.1	634
Liguria	1,181,000	0.8	3,248,000	2.1	176
Lombardy	2,519,000	0.3	9,063,500	0.9	259
Marche	168,000	0.1	456,000	0.3	173
Molise	0	-	-	-	NA
Piedmont	1,357,000	0.3	6,215,500	1.4	360
Sardinia	100,000	0.1	552,000	0.3	454
Sicily	560,000	0.1	2,040,000	0.4	266
Tuscany	758,000	0.2	2,782,500	0.7	268
Umbria	0	-	438,000	0.5	NA
Veneto	1,017,000	0.2	2,994,000	0.6	195
ITALY	11,828,000	0.2	52,355,500	0.9	343

EMICIZUMAB (ATC B02BX06)

Emicizumab is a humanised monoclonal modified immunoglobulin G4 (IgG4) antibody produced using recombinant DNA technology in mammalian Chinese Hamster Ovary (CHO) cells.

Emicizumab is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital FVIII deficiency) with FVIII inhibitors. Inhibitors are the most serious complications of the treatment of severe haemophilia A due to the development of alloantibodies against exogenous FVIII. They make factor replacement therapy ineffective, exposing patients to a remarkably high risk of morbidity and mortality. Emicizumab is also indicated in patients with severe haemophilia A (congenital FVIII deficiency, FVIII <1%) without FVIII inhibitors. Emicizumab can be used in all age groups and is administered for subcutaneous use only (27).

Besides the well-known bypassing agents, activated Prothrombin Complex Concentrates (aPCCs) and recombinant activated Factor VII (rFVIIa) used to treat or prevent bleeding in haemophilia patients with inhibitors, Emicizumab is a monoclonal antibody which has been designed to do the work that FVIII normally does – bringing together 2 clotting factors (IXa and X) as part of a chain of reactions needed for blood to clot.

Table 22 shows the brand names of preparations containing emicizumab currently marketed in Italy and the related amount of active ingredient contained expressed in milligrams (mg).

Table 22. Products containing emicizuma currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AICcode	Brand name	mg	Manufacturer	NHS class
046130011	HEMLIBRA*SC1 FL 1ML 30 MG/ML -	30	ROCHE GMBH	A
046130023	HEMLIBRA*SC 1FL 0.4 ML 150MG/ML	60	ROCHE GMBH	A
046130035	HEMLIBRA *SC 1 FL 0.7 ML 150MG/ML	105	ROCHE GMBH	A
046130047	HEMLIBRA*SC 1FL 1ML 150 MG/ML	150	ROCHE GMBH	A

Quantification and characterisation of the demand

Table 23 shows the total and per 1,000 population demand for drugs containing emicizumab for the year 2018, at national and regional levels.

The total national demand for emicizumab formulation for the year 2018 was 26,235 mg.

The national demand (mg per 1,000 population) was about 0.4 IUs, but not all Regions recorded emicizumab consumption (Table 23).

The standardised demand for emicizumab ranged from a minimum of 0.3 mg in Tuscany and Piedmont to a maximum of 1.7 mg in Umbria (Figure 24).

Table 23. Total demand (public and private) and total standardised demand for emicizumab expressed in mg and mg per 1,000 population for the year 2018 (adapted by the CNS on data from the traceability information flow)

Region	2018	
	mg	mg per 1,000 pop
Abruzzo	-	-
Aosta Valley	-	-
AP Bolzano	-	-
AP Trento	-	-
Apulia	-	-
Basilicata	-	-
Calabria	-	-
Campania	4,650	0.8
E.-Romagna	1,620	0.4
Friuli-V. Giulia	-	-
Latium	-	-
Liguria	-	-
Lombardy	8,820	0.9
Marche	-	-
Molise	-	-
Piedmont	1,470	0.3
Sardinia	-	-
Sicily	-	-
Tuscany	960	0.3
Umbria	1,500	1.7
Veneto	7,215	1.5
ITALY	26,235	0.4

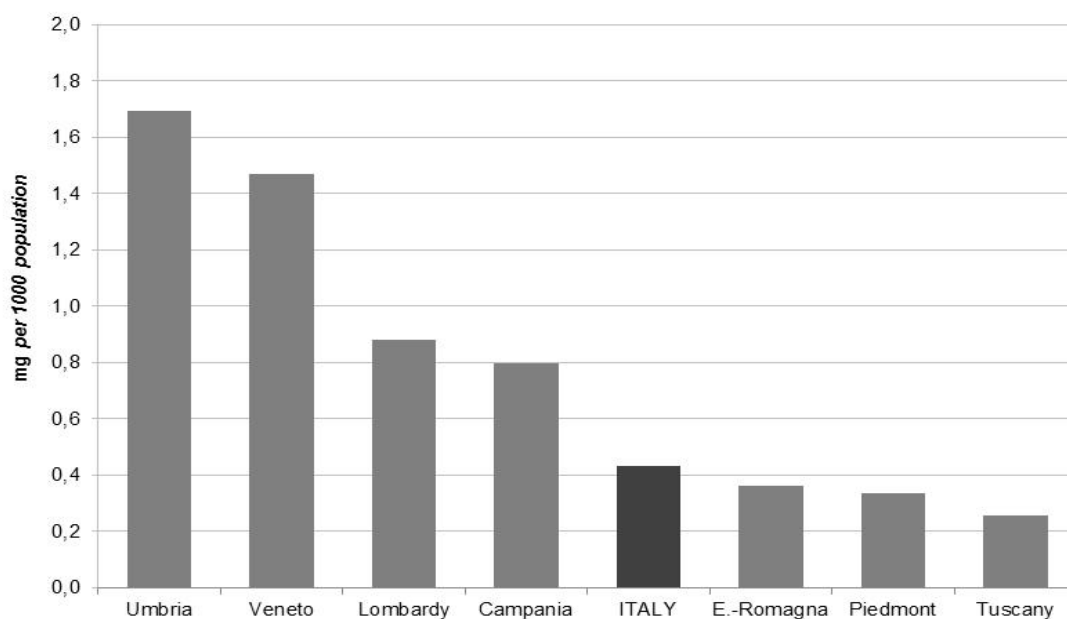


Figure 24. Total and regional demand (public and private) for Emicizumab expressed in mg per 1,000 population 2018 (adapted by the CNS on data from the traceability information flow)

COAGULATION FACTOR IX (ATC B02BD04), RECOMBINANT COAGULATION FACTOR IX (ATC B02BD04)

Coagulation FIX is used in the replacement therapy of haemophilia B, also called Christmas disease, a rare, haemorrhagic, hereditary, x-linked or acquired recessive disorder, with an estimated prevalence of 2-3/100,000 male subjects (28) and caused by a FIX deficiency. Depending on the level of activity of the circulating factor, there are severe forms of haemophilia B (FIX <1%), moderately severe (between 1 and 5%) and mild (> 5%) (29). FIX coagulation concentrates are divided in plasma-derived concentrates and products obtained with genetic recombination techniques (29). Tables 24 and 25 show the brand names of preparations containing pdFIX and rFIX currently marketed in Italy and the related amount of active ingredient contained and expressed in IUs.

Table 24. Products containing plasma-derived coagulation factor IX currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
025841089	AIMAFIX*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
028142026	MONONINE*EV F 500UI+F 5ML+KIT	500	CSL BEHRING SpA	A
029250065	ALPHANINE*EV 500UI+SIR 10ML+A	500	GRIFOLS ITALIA SpA	A
039072020	HAEMOBIONINE*1FL 500UI	500	BIOTEST ITALIA Srl	A
040092013	OCTANINE*FL 500UI+FL 5ML	500	OCTAPHARMA ITALY SpA	A
041799026	IXED*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
038324024	FIXNOVE*FL 600UI+FL 10ML	600	BAXALTA ITALY Srl	A
025841103	AIMAFIX*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
028142038	MONONINE*EV F 1000UI	1000	CSL BEHRING SpA	A
029250077	ALPHANINE "1000 UI/10 ML	1000	GRIFOLS ITALIA SpA	A
039072032	HAEMOBIONINE*1FL 1000UI	1000	BIOTEST ITALIA Srl	A
040092025	OCTANINE*FL 1000UI+FL	1000	OCTAPHARMA ITALY SpA	A
041799038	IXED*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
038324036	FIXNOVE*FL 1200UI+FL 10ML	1200	BAXALTA ITALY Srl	A
029250089	ALPHANINE "1500 UI/10 ML	1500	GRIFOLS ITALIA SpA	A

Table 25. Products containing recombinant coagulation factor IX and long-acting recombinant Factor IX currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
033535016	BENEFIX*IV 1FL 250UI	250	PFIZER ITALIA Srl	A
033535042	BENEFIX*IV 1FL 250UI+SIR 5ML+SE	250	PFIZER ITALIA Srl	A
043796010	RIXUBIS*IV 1FL 250UI 5ML	250	BAXTER SpA	C(nn)
033535028	BENEFIX*IV 1FL 500UI	500	PFIZER ITALIA Srl	A
033535055	BENEFIX*IV 1FL 500UI+SIR 5ML+SE	500	PFIZER ITALIA Srl	A
043796022	RIXUBIS*IV 1FL 500UI 5ML	500	BAXTER SpA	C(nn)
033535030	BENEFIX*IV 1FL 1000UI	1000	PFIZER ITALIA Srl	A
033535067	BENEFIX*IV 1FL 1000UI+SIR 5ML+S	1000	PFIZER ITALIA Srl	A
043796034	RIXUBIS*IV 1FL 1000UI 5ML	1000	BAXTER SpA	C(nn)
033535093	BENEFIX*IV 1FL 1500UI+SIR5ML+S	1500	PFIZER EUROPE MA EEIG	A
033535079	BENEFIX*IV 1FL 2000UI+SIR 5ML+S	2000	PFIZER ITALIA Srl	A
043796046	RIXUBIS*IV 1FL 2000UI 5ML	2000	BAXTER SpA	C(nn)
033535081	BENEFIX*IV 1FL 3000UI+SIR 5ML+S	3000	PFIZER ITALIA Srl	A
043796059	RIXUBIS*IV 1FL 3000UI 5ML	3000	BAXTER SpA	C(nn)

AIC code	Brand name	IU	Manufacturer	NHS class
Extended half-life recombinant Factor IX				
044888016	ALPROLIX*1FL 250UI+1SIR 5ML	250	SOBI Srl	A
044891012	IDELVION*EV FL 250UI+FL 2,5ML	250	CSL BEHRING SpA	A
044888028	ALPROLIX*1FL 500UI+1SIR 5ML	500	SOBI Srl	A
044891024	IDELVION*EV FL 500UI+FL 2,5ML	500	CSL BEHRING SpA	A
045488018	REFIXIA*EV FL 500 UI+ FL 4 ML+SIR	500	NOVO NORDISK A/S	C
044888030	ALPROLIX*1FL 1000UI+1SIR 5ML	1000	SOBI Srl	A
044891036	IDELVION*EV FL 1000UI+FL 2,5ML	1000	CSL BEHRING SpA	A
045488020	REFIXIA*EV FL 1000UI+ FL 4ML+SIR	1000	NOVO NORDISK A/S	C
045488032	REFIXIA*EV FL 2000 UI+FL 4ML+SIR	1500	NOVO NORDISK A/S	C
044888042	ALPROLIX*1FL 2000UI+1SIR 5ML	2000	SOBI Srl	A
044891048	IDELVION*EV FL 2000UI+FL 2,5ML	2000	CSL BEHRING SpA	A
044888055	ALPROLIX*1FL 3000UI+1SIR 5ML	3000	SOBI Srl	A

Quantification and characterisation of the demand

Table 26 shows the total and *per capita* demand for plasma-derived and recombinant FIX for the two-year period 2017-2018, at national and regional levels.

Table 26. Total demand (public and private) and total standardised demand for coagulation factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017- 2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,630,000	2.0	2,119,000	1.6	-19.0
Aosta Valley	-	-	-	-	NA
APBolzano	36,000	0.1	21,000	0.0	-42.1
APTrento	537,500	1.0	461,000	0.9	-14.4
Apulia	6,757,500	1.7	6,351,000	1.6	-5.7
Basilicata	141,750	0.2	299,750	0.5	112.7
Calabria	1,436,500	0.7	1,123,250	0.6	-21.5
Campania	8,228,000	1.4	7,550,000	1.3	-8.0
E.-Romagna	5,128,750	1.2	3,962,250	0.9	-22.8
Friuli-V. Giulia	1,193,000	1.0	1,052,000	0.9	-11.6
Latium	5,058,100	0.9	4,674,500	0.8	-7.6
Liguria	2,821,000	1.8	1,957,000	1.3	-30.3
Lombardy	10,617,750	1.1	6,944,250	0.7	-34.7
Marche	1,922,500	1.2	1,878,000	1.2	-1.9
Molise	-	-	-	-	NA
Piedmont	3,888,750	0.9	4,165,250	1.0	7.5
Sardinia	9,000	0.0	44,000	0.0	390.4
Sicily	4,559,000	0.9	3,904,500	0.8	-13.9
Tuscany	8,271,300	2.2	6,484,000	1.7	-21.5
Umbria	477,000	0.5	278,000	0.3	-41.4
Veneto	3,811,750	0.8	3,788,500	0.8	-0.6
ITALY	67,525,150	1.1	57,057,250	0.9	-15.4

* The values inserted as "0.0" do not identify the absence of quantities distributed, but consumption that would have required an excessive number of decimals to be quantified.

The total demand for FIX formulations recorded in 2018 was 57,057,250 IUs (Table 26); about 13% of the aforementioned amount (7,174,500 IUs) was plasma-derived. There was a decreasing demand for both pdFIX and rFIX; pdFIX demand drastically dropped (-43%) while rFIX demand showed a slight decrease (-9%).

In 2018, the standardised demand for plasma-derived and recombinant FIX was 0.9 IUs *per capita*, with significantly different regional trends. These ranged from a minimum – close to zero – in Aosta Valley, Molise, Sardinia and the AP of Bolzano (-100% and -96% percentage change compared to the Italian mean value, respectively for the first two and for the others), to a maximum in Tuscany and Abruzzo with 1.7 IUs and 1.6 IUs *per capita* (+84%, +71% percentage change compared to the national mean value, respectively) (Figures 25 and 26).

Almost all Regions showed a decreasing demand (percentage range: -0.6 to -42.1) (Table 26). In the AP of Bolzano, the AP of Trento, Campania, Liguria, and Sardinia, rFIX was used almost exclusively, while in Sicily, Latium, Calabria, Apulia, Basilicata, Abruzzo, Lombardy, Toscana and E.-Romagna, the rFIX demand reached volumes of above 80% (Figure 27).

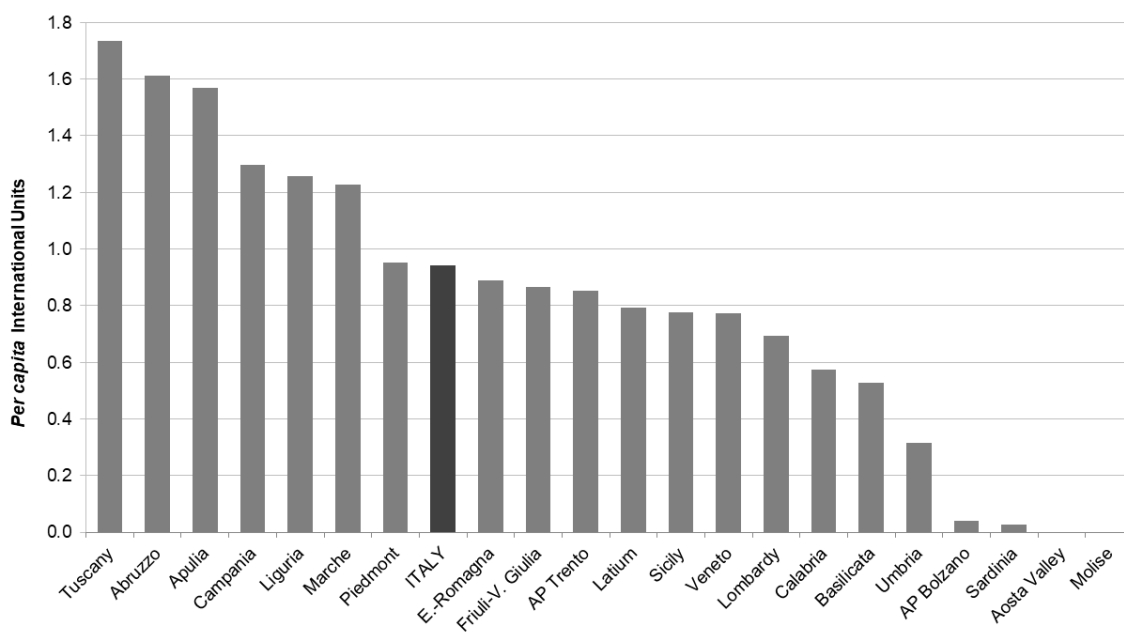


Figure 25. Total and regional demand (public and private) for coagulation factor IX, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

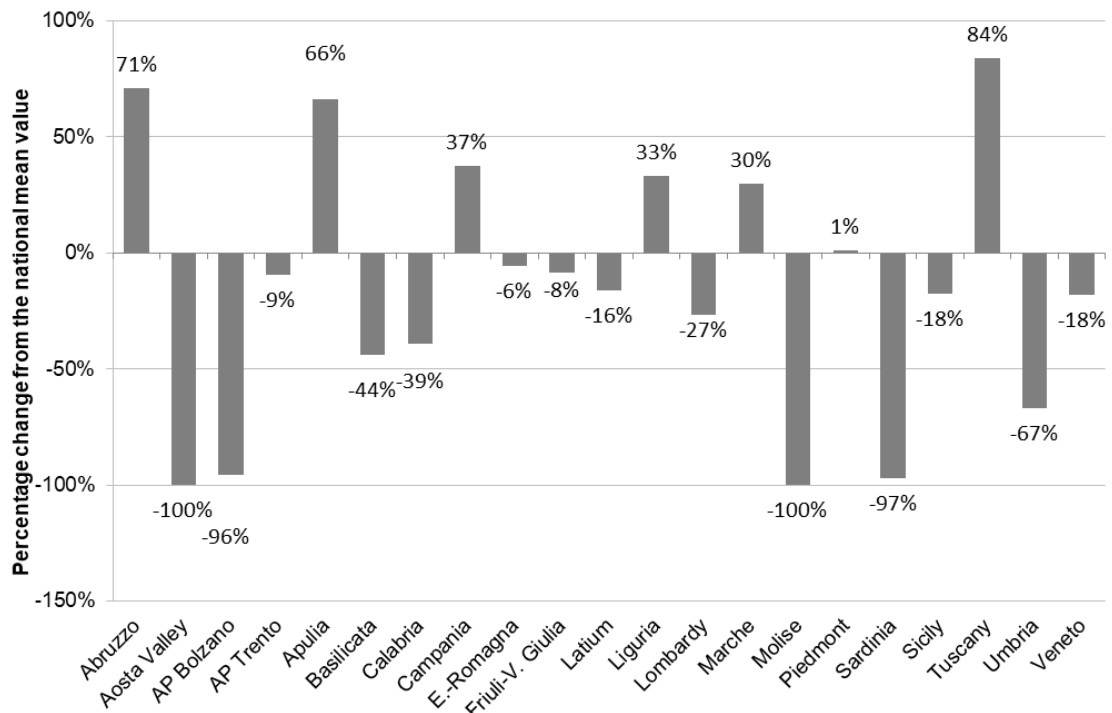


Figure 26. Percentage change from the national mean value of standardised regional demand for coagulation factor IX (International Units *per capita*) in 2018 (adapted by the CNS on data from the traceability information flow)

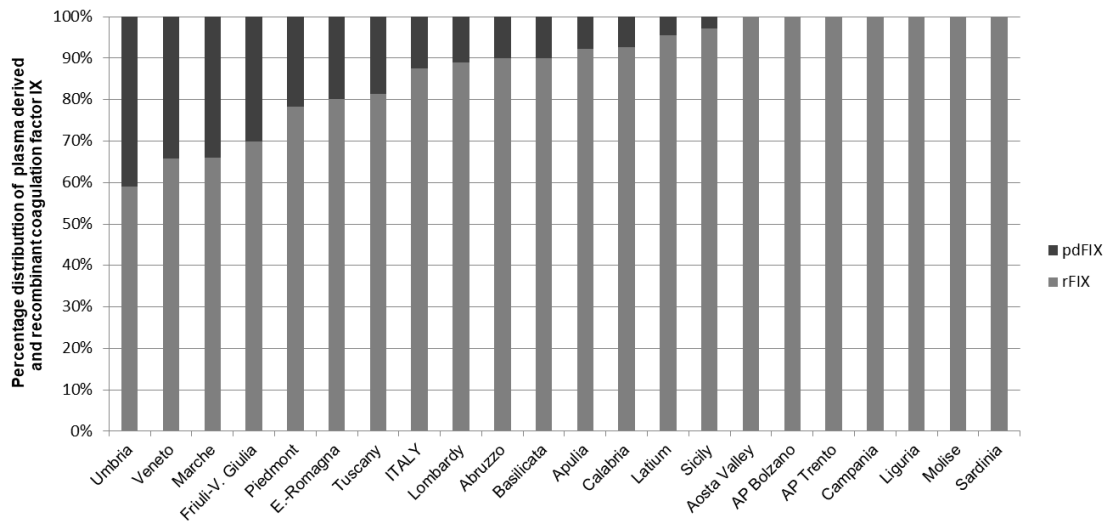


Figure 27. Distribution expressed in % of factor IX per type, by Region, 2018 (adapted by the CNS on data from the traceability information flow)

Plasma-derived Factor IX

In 2018, the total demand for pdFIX (expressed in absolute values and *per capita* volumes), was 7,174,500 IUs, equal to 0.1 IU *per capita*, a 43% decrease compared to 2017 (Table 27).

Table 27. Total demand (public and private) and total standardised demand for plasma-derived coagulation factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	609,000	0.5	214,000	0.2	-64.7
Aosta Valley	-	-	-	0.0	NA
AP Bolzano	32,000	0.1	-	0.0	-100.0
AP Trento	-	-	-	0.0	NA
Apulia	1,263,000	0.3	489,000	0.1	-61.1
Basilicata	20,000	0.0	30,000	0.1	50.9
Calabria	43,000	0.0	82,000	0.0	91.5
Campania	5,000	0.0	-	0.0	-100.0
E.-Romagna	1,547,000	0.3	787,000	0.2	-49.2
Friuli-V.Giulia	270,000	0.2	316,000	0.3	17.3
Latium	248,600	0.0	205,500	0.0	-17.3
Liguria	448,000	0.3	-	0.0	-100.0
Lombardy	2,766,000	0.3	771,000	0.1	-72.2
Marche	687,000	0.4	640,000	0.4	-6.5
Molise	-	-	-	0.0	NA
Piedmont	1,773,000	0.4	905,000	0.2	-48.8
Sardinia	-	-	-	0.0	NA
Sicily	124,000	0.0	114,000	0.0	-7.5
Tuscany	1,130,800	0.3	1,212,000	0.3	7.3
Umbria	244,000	0.3	114,000	0.1	-53.1
Veneto	1,428,000	0.3	1,295,000	0.3	-9.3
ITALY	12,638,400	0.2	7,174,500	0.1	-43.1

* The amounts of pdFIX contained in Factor X P Behring® are not included (see Table 57).

The Regions with the highest *per capita* demand for pdFIX were Marche (0.4 IUs) and Tuscany, Veneto and Friuli-V.Giulia (0.3 IUs), almost three times the demand recorded at national level; while in Lombardy, Basilicata, Calabria, Latium, and Sicily *per capita* volumes were close to zero (Figures 28 and 29). In some Regions, there was no reported utilisation of pdFIX.

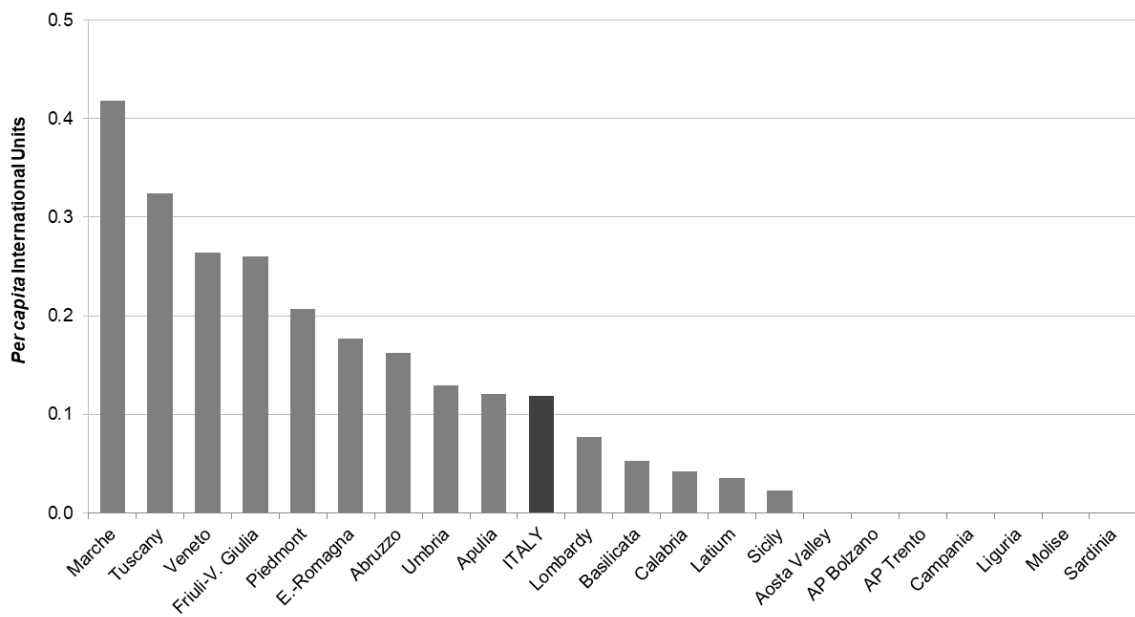


Figure 28. Total and regional demand (public and private) for plasma-derived coagulation factor IX, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

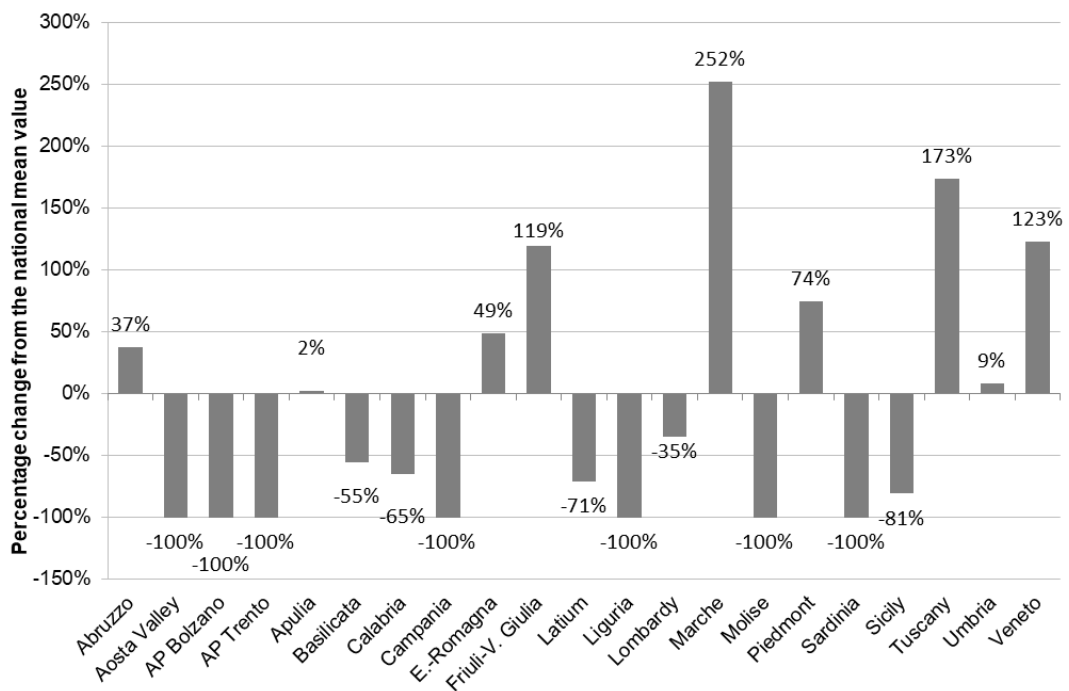


Figure 29. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation factor IX in 2018 (adapted by the CNS on data from the traceability information flow)

Recombinant Factor IX

The total demand for rFIX decreased by 9% in the period 2017-2018, with a volume of 49,882,750 IUs in 2018 alone, equal to 0.8 IU *per capita* (Table 28).

Table 28. Total demand (public and private) and total standardised demand for recombinant coagulation factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,021,000	1.5	1,905,000	1.4	-5.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	4,000	0.0	21,000	0.0	421.5
AP Trento	537,500	1.0	461,000	0.9	-14.4
Apulia	5,494,500	1.4	5,862,000	1.4	7.1
Basilicata	121,750	0.2	269,750	0.5	122.8
Calabria	1,393,500	0.7	1,041,250	0.5	-25.0
Campania	8,223,000	1.4	7,550,000	1.3	-8.0
E.-Romagna	3,581,750	0.8	3,175,250	0.7	-11.4
Friuli-V. Giulia	923,000	0.8	736,000	0.6	-20.1
Latium	4,809,500	0.8	4,469,000	0.8	-7.1
Liguria	2,373,000	1.5	1,957,000	1.3	-17.1
Lombardy	7,851,750	0.8	6,173,250	0.6	-21.5
Marche	1,235,500	0.8	1,238,000	0.8	0.6
Molise	-	-	-	-	NA
Piedmont	2,115,750	0.5	3,260,250	0.7	54.7
Sardinia	9,000	0.0	44,000	0.0	390.4
Sicily	4,435,000	0.9	3,790,500	0.8	-14.0
Tuscany	7,140,500	1.9	5,272,000	1.4	-26.1
Umbria	233,000	0.3	164,000	0.2	-29.3
Veneto	2,383,750	0.5	2,493,500	0.5	4.7
ITALY	54,886,750	0.9	49,882,750	0.8	-9.0

The Regions with the highest *per capita* demand of rFIX (Figure 30) were Abruzzo, Apulia Tuscany, Campania and Liguria with 1.4 IUs (Abruzzo, Apulia and Tuscany); 1.3 IUs (Campania and Liguria), respectively (+76%, +76%, +71%, +57% and +52% percentage change compared to the Italian mean value) (Figure 31).

In Aosta Valley and Molise there was no reported consumption of rFIX in 2018.

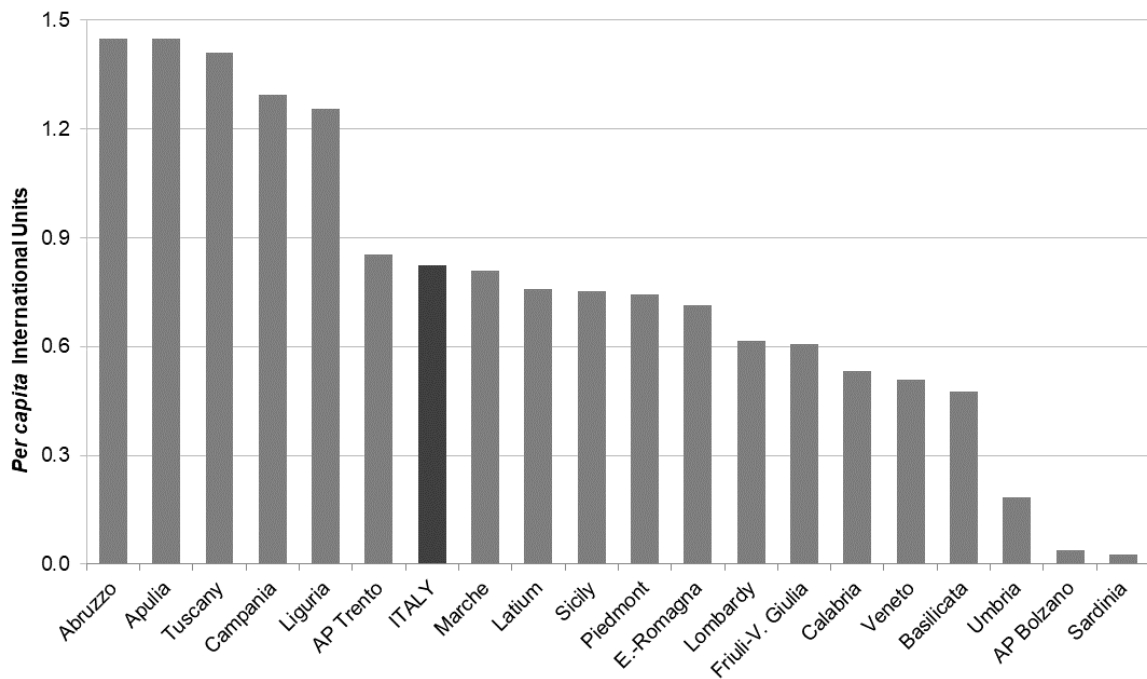


Figure 30. Total and regional demand (public and private) for recombinant coagulation factor IX, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

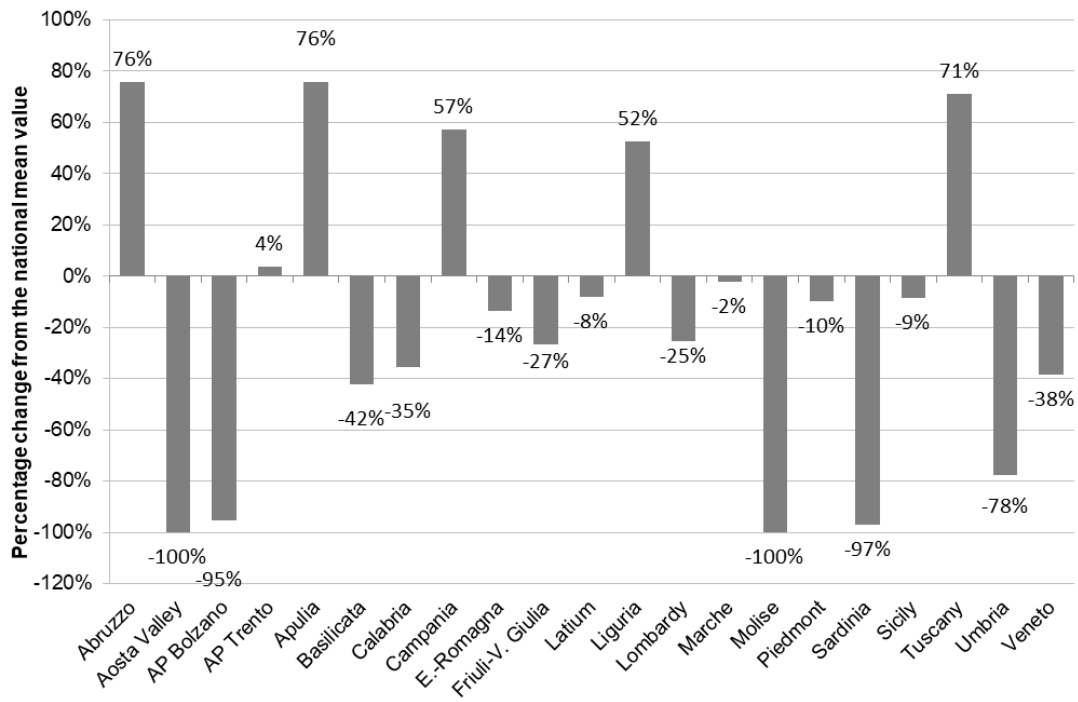


Figure 31. Percentage change from the national mean value of standardised regional demand for recombinant coagulation factor IX in 2018 (adapted by the CNS on data from the traceability information flow)

Extended half-life recombinant Factor IX

Of 49 million IUs about rFIX demand, long-acting recombinant Factor IX molecules recorded a total demand of 23,187,000 IUs, about 46% of the total (Table 29).

The mean national demand *per capita* was about 0.4 IU, with a range between Regions of 0.1 IU and 1 IU.

Table 29. Total demand (public and private) and total standardised demand for long-acting recombinant coagulation factor IX, expressed in International Units and International Units *per capita* (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	32,000	0.0	969,500	0.7	2,946
Aosta Valley	0	0.0	-	0.0	NA
AP Bolzano	0	0.0	10,000	0.0	NA
AP Trento	0	0.0	-	0.0	NA
Apulia	1,419,000	0.3	2,969,500	0.7	110
Basilicata	12,000	0.0	74,750	0.1	526
Calabria	282,000	0.1	408,250	0.2	45
Campania	50,500	0.0	1,309,000	0.2	2,498
E.-Romagna	897,000	0.2	1,957,000	0.4	118
Friuli-V. Giulia	160,000	0.1	448,000	0.4	181
Latium	592,500	0.1	1,626,500	0.3	175
Liguria	662,000	0.4	1,488,000	1	126
Lombardy	1,966,250	0.2	4,207,750	0.4	114
Marche	239,500	0.2	587,500	0.4	146
Molise	-	0.0	-	0.0	NA
Piedmont	458,750	0.1	2,448,750	0.6	436
Sardinia	0	0.0	-	0.0	NA
Sicily	537,000	0.1	1,141,500	0.2	114
Tuscany	651,500	0.2	2,639,500	0.7	306
Umbria	76,000	0.1	137,000	0.2	81
Veneto	443,750	0.1	764,500	0.2	72
ITALY	8,479,750	0.1	23,187,000	0.4	174

3-FACTOR PROTHROMBIN COMPLEX CONCENTRATES (ATC B02BD) AND 4-FACTOR PROTHROMBIN COMPLEX CONCENTRATES (ATC B02BD01)

Prothrombin Complex Concentrates (PCCs) are plasma-derived therapeutic drugs useful for the urgent temporary reversal of prothrombin complex factors deficiency (19).

Three or four-factor PCCs can be obtained through different production processes. 3F-PCCs contain Factor II (FII), Factor IX (FIX) and Factor X (FX), and 4F-PCCs contain FII, FVII, FIX, and FX with pro-coagulant action, as well as natural and physiological coagulation inhibitors such as protein C, protein S and traces of protein, heparin and vitronectin (30).

As with all the other PDMPs, PCCs undergo viral inactivation, which can be physical (heat), chemical (solvent-detergent use) and virus removal by nanofiltration (31).

Tables 30 and 31 show the brand names of preparations containing 3F-PCCs and 4F-PCCs currently on the market in Italy and their relative amount of active ingredient contained expressed in IUs.

Table 30. Products containing 3-factor prothrombin complex concentrates currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AICcode	Brand name	IU	Manufacturer	NHS class
023309103	UMANCOMPLEX D.I.*FL 500UI+F20M	500	KEDRION SpA	A
041850013	KEDCOM*FL 500UI+FL 20ML+SET	500	KEDRION SpA	H
023288032	PROTROMPLEX TIM3*F 600UI+20ML	600	BAXTER AG	A

Table 31. Products containing 4-factor prothrombin complex concentrates currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AICcode	Brand name	IU	Manufacturer	NHS class
038844015	CONFIDEX*500UI+1FL SOLV 20ML	500	CSL BEHRING GMBH	H
039240015	PRONATIV*500UI+FL SOLV 20ML	500	OCTAPHARMA ITALY	H
043304017	PROPLEX*FL 600UI/20ML+FL SOLV	600	BAXALTA ITALY Srl	H
038844027	CONFIDEX 1000*FL POLV+FL 40ML	1000	CSL BEHRING SpA	H
039240027	PRONATIV*1000UI+FL SOLV 20ML	1000	OCTAPHARMA ITALY	H

Quantification and characterisation of the demand

Table 32 shows the total demand and standardised demand (expressed in IUs *per capita*) for 3F-PCCs in the two-year period 2017-2018, at both national and regional level.

In 2018, there was a total demand comparable to that of 2017; it stood at 37,793,100 IUs, equal to 0.6 IU *per capita*. There were considerable differences in the use of 3F-PCCs from one Region to another with standardised values ranging from 0.3 IU (Abruzzo and Latium) to 1.1 IUs (AP Bolzano), with a percentage change compared to the Italian mean value of over 50% in Liguria, E.-Romagna and the AP of Bolzano (+53%, +60%, +80% respectively) (Figures 32 and 33).

Table 32. Total demand (public and private) and total standardised demand for 3 factor-prothrombin complex concentrates, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	463,500	0.4	448,500	0.3	-2.7
Aosta Valley	150,000	1.2	96,000	0.8	-35.7
AP Bolzano	512,000	1.0	592,000	1.1	14.9
AP Trento	471,000	0.9	451,500	0.8	-4.4
Apulia	1,795,000	0.4	2,033,500	0.5	13.7
Basilicata	189,000	0.3	190,000	0.3	1.1
Calabria	1,094,500	0.6	487,500	0.2	-55.3
Campania	2,289,900	0.4	2,962,000	0.5	29.6
E.-Romagna	4,541,000	1.0	4,448,500	1.0	-2.1
Friuli-V. Giulia	1,137,000	0.9	1,097,500	0.9	-3.3
Latium	1,693,000	0.3	1,702,000	0.3	0.6
Liguria	1,016,500	0.6	1,491,000	1.0	47.5
Lombardy	5,854,400	0.6	5,483,800	0.5	-6.5
Marche	1,358,000	0.9	742,000	0.5	-45.1
Molise	211,000	0.7	250,000	0.8	19.2
Piedmont	2,649,000	0.6	2,778,000	0.6	5.3
Sardinia	1,140,000	0.7	1,110,800	0.7	-2.3
Sicily	3,022,800	0.6	3,459,500	0.7	15.1
Tuscany	3,205,000	0.9	3,303,500	0.9	3.2
Umbria	519,500	0.6	555,000	0.6	7.3
Veneto	3,984,500	0.8	4,110,500	0.8	3.2
ITALY	37,296,600	0.6	37,793,100	0.6	1.5

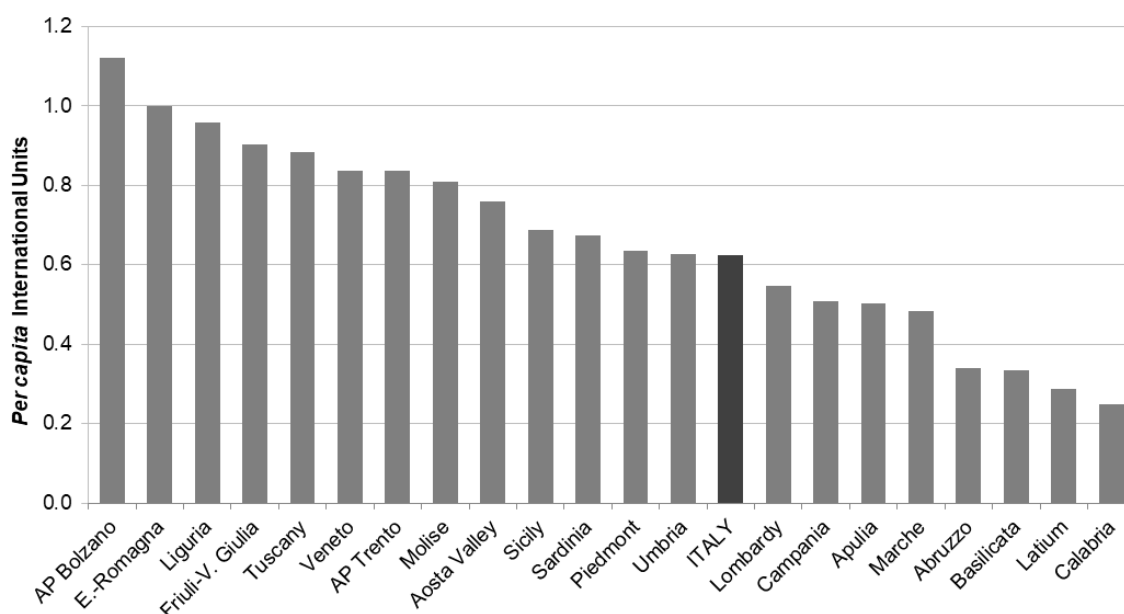


Figure 32. Total and regional demand (public and private) for 3-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

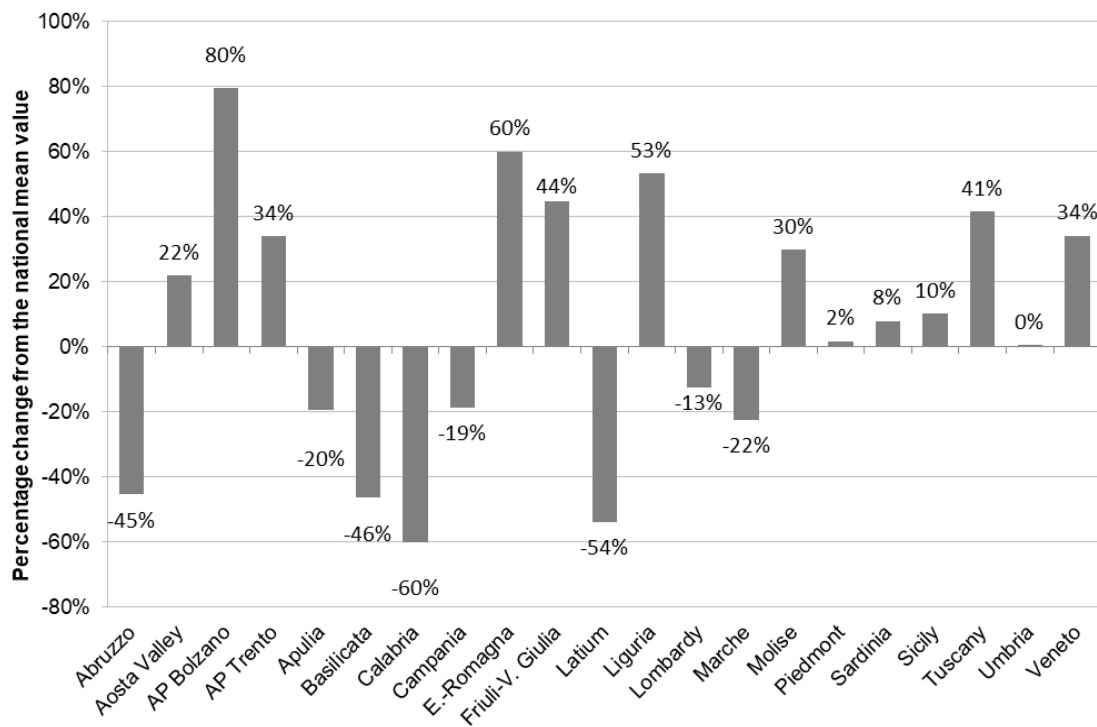


Figure 33. Percentage change from the national mean value of standardised regional demand for 3-factor prothrombin complex concentrates in 2018 (adapted by the CNS on data from the traceability information flow)

In 2018, the national demand for 4F-PCCs was 9,028,000 IUs, equal to 19% of the overall demand for PCCs, with a standardised demand of 0.1 IU *per capita* and a 2.6% increase compared to the previous year (Table 33).

Also for this PDMP, there were considerable differences regarding utilisation from one Region to another. Almost all Regions recorded an increasing demand, in some cases very significant (AP of Trento, Friuli-Venezia Giulia and Umbria).

The Region with the highest demand in 2018 was the AP of Bolzano with 1.1 IUs *per capita*, followed by Sardinia with 0.4, and Abruzzo, Basilicata, Emilia-Romagna, and Latium with 0.3 IU *per capita* (Figure 34).

Figure 35 shows percentage changes compared to the Italian mean values of the standardised regional demand for 4F-PCCs as recorded by the drug traceability system in 2018.

Table 33. Total demand (public and private) and total standardised demand for 4-factor prothrombin complex concentrates, expressed in International Units and International Units *per capita*, and variations in percentage between 2017-2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	264,000	0.2	385,500	0.3	46.8
Aosta Valley	-	-	-	-	NA
AP Bolzano	607,000	1.2	569,000	1.1	-6.9
AP Trento	1,500	0.0	25,500	0.0	1595.9
Apulia	246,000	0.1	164,000	0.0	-33.1
Basilicata	232,000	0.4	147,000	0.3	-36.3
Calabria	542,500	0.3	316,500	0.2	-41.4
Campania	999,000	0.2	1,211,000	0.2	21.5
E.-Romagna	1,074,000	0.2	1,134,000	0.3	5.5
Friuli-V. Giulia	73,500	0.1	122,000	0.1	66.3
Latium	1,305,500	0.2	1,651,000	0.3	26.5
Liguria	105,500	0.1	128,500	0.1	22.5
Lombardy	670,000	0.1	832,000	0.1	24.0
Marche	113,500	0.1	113,500	0.1	0.4
Molise	76,000	0.2	62,000	0.2	-17.9
Piedmont	402,500	0.1	647,500	0.1	61.5
Sardinia	616,500	0.4	670,000	0.4	9.0
Sicily	655,500	0.1	534,000	0.1	-18.1
Tuscany	706,500	0.2	128,000	0.0	-81.9
Umbria	26,500	0.0	54,500	0.1	106.7
Veneto	93,000	0.0	132,500	0.0	42.5
ITALY	8,810,500	0.1	9,028,000	0.1	2.6

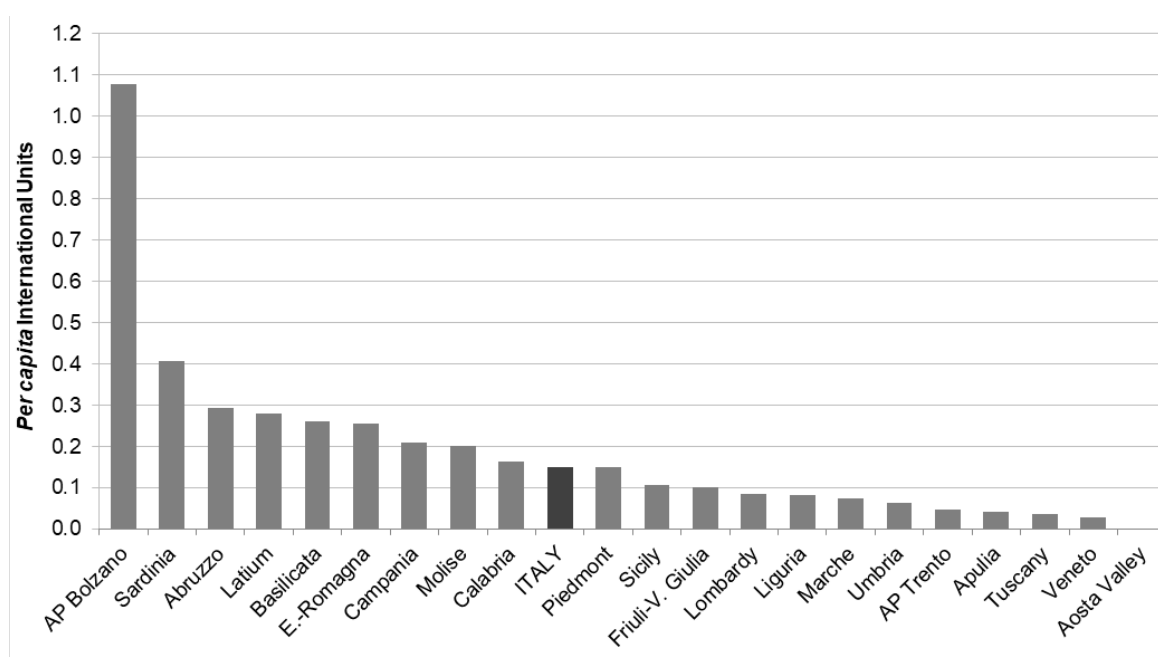


Figure 34. Total and regional demand (public and private) for 4-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2018 (adapted by the CNS on data from the traceability information flow)

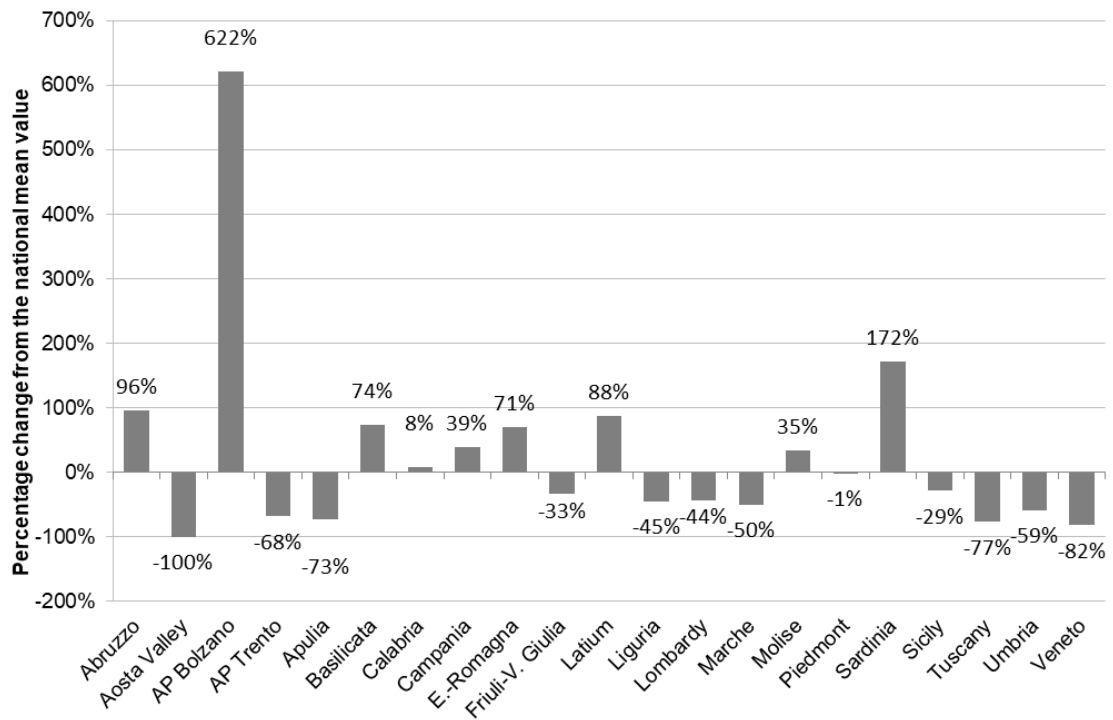


Figure 35. Percentage change from the national mean value of standardised regional demand for 4-factor prothrombin complex concentrates in 2018 (adapted by the CNS on data from the traceability information flow)

FIBRINOGEN (ATC B02BB01)

Fibrinogen is one of the most abundant coagulation factors in plasma, in which it has a mean concentration of about 2-4 g/L. It is converted into fibrin by thrombin and is the main component of the coagulation phase.

Fibrin, therefore, can be considered both a structural protein and a coagulation factor. In order to provide adequate structural support, the plasma concentration of fibrinogen must be relatively high. A deficiency of fibrinogen therefore implies a lower capacity of the blood to coagulate, with a consequent increase in the tendency to bleeding (32).

The utilisation of fibrinogen is indicated in the following clinical conditions: i. hypofibrinogenaemia or congenital afibrinogenaemia; ii. congenital dysfibrinogenaemia with a tendency to haemorrhage; iii. occasionally in acquired hypofibrinogenaemia, but only after carefully evaluating other therapeutic options (33) (fresh frozen plasma and cryoprecipitate).

Table 34 shows the brand names of medicinal products containing fibrinogen currently available on the Italian market and the amount of active ingredient they contain expressed in grams (g).

Table 34. Products containing fibrinogen currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	g	Manufacturer	NHS class
*E00178010	HAEMOCOMPLETTANP 1F 1G	1	CSL BEHRING SpA	H
040170019	RIASTAP FL POLV 1G 20MG/ML	1	CSL BEHRING SpA	C(nn)
044380018	FIBRICLOTTE*FL POLV 1,5G 100ML	1,5	LFB	C(nn)

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

Table 35 shows the total demand and the total standardised demand (g per 1,000 population) for fibrinogen over the two-year period 2017-2018 at regional and national level.

In 2018, total fibrinogen demand showed a significant increase (+12%) compared to the previous year. Its volume of 37,121 g, with a standardised demand of 0.6 g per 1,000 population, confirmed the rapid upward trend. The increase was mainly linked to the imported product, which covered about 90% of total demand. All Regions, with the exception of Molise and Piedmont contributed to this growth in varying degrees (Table 35).

Figure 36 shows the regional and national standardised demand for fibrinogen in 2018. The Regions with the highest per 1,000 population demand were AP of Bolzano and Umbria (1.2 g), and Abruzzo (1.1 g). The lowest demand, between 0.2 and 0.4 g per 1,000 population, was recorded in Molise, Piedmont and Aosta Valley.

Table 35. Total demand (public and private) and total standardised demand for fibrinogen, expressed in grams and grams per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2017		2018		% Var 2017-2018
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,174	0.9	1,461	1.1	25.1
Aosta Valley	35	0.3	46	0.4	32.1
AP Bolzano	862	1.6	641	1.2	-26.1
AP Trento	243	0.5	307	0.6	26.0
Apulia	1,848	0.5	2,141	0.5	16.3
Basilicata	196	0.3	250	0.4	28.3
Calabria	1,601	0.8	1,446	0.7	-9.3
Campania	3,442	0.6	4,785	0.8	39.3
E.-Romagna	3,324	0.7	3,391	0.8	1.9
Friuli-V. Giulia	612	0.5	505	0.4	-17.3
Latium	3,429	0.6	3,919	0.7	14.3
Liguria	383	0.2	589	0.4	54.6
Lombardy	3,772	0.4	3,915	0.4	3.6
Marche	593	0.4	956	0.6	61.9
Molise	48	0.2	47	0.2	-1.5
Piedmont	895	0.2	1,287	0.3	44.3
Sardinia	1,578	1.0	1,654	1.0	5.1
Sicily	1,668	0.3	1,984	0.4	19.6
Tuscany	2,203	0.6	2,502	0.7	13.7
Umbria	1,063	1.2	1,069	1.2	1.0
Veneto	4,175	0.9	4,226	0.9	1.3
ITALY	33,144	0.5	37,121	0.6	12.2

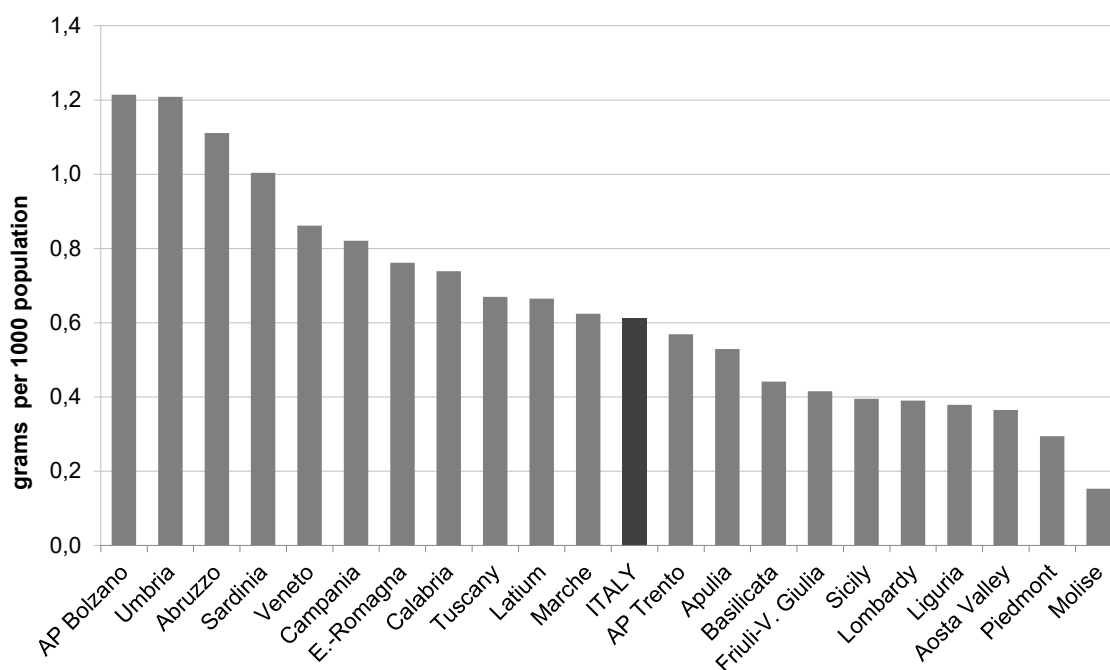


Figure 36. Total and regional demand (public and private) for fibrinogen, expressed in grams per 1,000 population, 2018 (adapted by the CNS on data from the traceability information flow)

PART B
Other plasma-derived medicinal products

HEPATITIS B IMMUNOGLOBULINS FOR INTRAVENOUS AND SUBCUTANEOUS USE (ATC J06BB04)

The tables below show the brand names of medicinal products containing hepatitis B immunoglobulins for intravenous (IV) (Table 36) and subcutaneous (SC) / intramuscular (IM) use (Table 37) currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 36. Products containing hepatitis B immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
035561012	NEOHEPATECT*IV 1F 100UI 2ML	100	BIOTEST PHARMA GMBH	H
026415048	VENBIG*1F 500UI+F 10ML+SET	500	KEDRION SpA	H
035561024	NEOHEPATECT*IV 1F 500UI 10ML	500	BIOTEST PHARMA GMBH	H
038059010	KEYVENB"500UI/10ML+SET	500	KEDRION SpA	H
038059034	KEYVENB"50UI/ML" F. CON 500UI	500	KEDRION SpA	H
041985019	VEBIKED"50UI/ML" FL CON 500UI	500	KEDRION SpA	C(nn)
038445019	NIULIVA*250 IU/ML 1SIR 2.4 ML	600	GRIFOLS ITALIA SpA	H
038445021	NIULIVA*INF 1SIR 4ML"250IU/ML	1000	ISTITUTO GRIFOLS S.A.	H
035561036	NEOHEPATECT*IV FL 2000UI 40ML	2000	BIOTEST PHARMA GMBH	H
026415051	VENBIG*F 2500UI/50ML+F 45ML+SET	2500	KEDRION SpA	H
038059022	KEYVENB"2500UI/45ML+SET	2500	KEDRION SpA	H
038059046	KEYVENB"50UI/ML" F 2500UI	2500	KEDRION SpA	H
041985021	VEBIKED"50UI/ML" FL 2500UI+SET	2500	KEDRION SpA	C(nn)
035561048	NEOHEPATECT*IV FL 5000UI 100ML	5000	BIOTEST ITALIA Srl	H
038445033	NIULIVA*INF 1FL 20ML 250IU/ML	5000	GRIFOLS ITALIA SpA	H
038445045	NIULIVA"250IU/ML" 1F. 40ML	10000	ISTITUTO GRIFOLS S.A.	H

Table 37. Products containing hepatitis B immunoglobulins for subcutaneous/intramuscular use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
023782028	UMAN BIG "180 UI/1ML SOLUZ. INIET"	180	KEDRION SpA	A
025653015	IMMUNOHBS*IM 1F 1ML 180UI	180	KEDRION SpA	A
042002016	KEDHBS 180 UI/1ML - 1FL 1ML	180	KEDRION SpA	A
023782016	UMANBIG*IM 1FL 3ML 540UI	540	KEDRION SpA	A
025653027	IMMUNOHBS*IM 1F 3ML 540UI	540	KEDRION SpA	A
042002028	KEDHBS 540 UI/3ML - 1FL 3ML	540	KEDRION SpA	A
035320011	IGANTIBE*IM 1F 3ML 600UI/3ML	600	ISTITUTO GRIFOLS S.A.	A
025653054	IMMUNOHBS*IM 1SIR 1000UI 3ML	1000	KEDRION SpA	A
035320023	IGANTIBE*IM 1F 5ML 1000UI/5ML	1000	ISTITUTO GRIFOLS S.A.	A
042002030	KEDHBS 1000 UI/3ML 1SIR 3ML	1000	KEDRION SpA	A
039644012	ZUTECTRA*SC 5SIR 1ML 500UI	2500	BIOTEST PHARMA GMBH	A

Quantification of the demand

Tables 38 and 39 show respectively the total demand and the total standardised demand (expressed in IUs *per capita*) of hepatitis B IG formulations for IV and for SC/IM use for the two-

year period 2017-2018, at national and at regional level. The national demand for hepatitis B IGs for IV use, showed a downward trend (-22.3%), unlike that observed in the previous year (34) The total demand in 2018 was almost 18 million IUs (0.3 IU *per capita*) (Table 38).

Table 38. Total demand (public and private) and total standardised demand for hepatitis B immunoglobulins for intravenous use, expressed in International Units and International Units *per capita*, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	64,000	0.0	36,000	0.0	-43.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	2,760,000	0.7	2,819,000	0.7	2.5
Basilicata	1,000	0.0	3,000	0.0	201.7
Calabria	272,000	0.1	225,200	0.1	-16.8
Campania	7,258,000	1.2	5,622,800	1.0	-22.4
E.-Romagna	2,378,500	0.5	2,011,000	0.5	-15.5
Friuli-V. Giulia	310,000	0.3	42,500	0.0	-86.3
Latium	592,000	0.1	923,000	0.2	55.9
Liguria	45,000	0.0	44,000	0.0	-1.7
Lombardy	1,771,000	0.2	1,309,000	0.1	-26.2
Marche	737,000	0.5	228,500	0.1	-68.9
Molise	20,000	0.1	18,000	0.1	-9.4
Piedmont	852,500	0.2	860,000	0.2	1.3
Sardinia	789,000	0.5	354,000	0.2	-55.0
Sicily	296,100	0.1	439,000	0.1	49.1
Tuscany	1,445,500	0.4	940,000	0.3	-34.9
Umbria	-	-	8,000	0.0	NA
Veneto	3,455,500	0.7	2,002,500	0.4	-42.0
ITALY	23,047,100	0.4	17,885,500	0.3	-22.3

Campania continued to be the Region with the highest demand (1 IU *per capita*), equal to one third of the national demand, followed by Apulia, E.-Romagna and Veneto.

On the other hand, the national demand for hepatitis B IGs for SC/IM use confirmed a downward trend (-10.2%) compared to the demand recorded in 2017; total consumption in 2018 was almost 58 million IUs (1 IU *per capita*) (Table 39) and accounted for 76% of the total demand for hepatitis B IGs.

Table 39. Total demand (public and private) and total standardised demand for hepatitis B immunoglobulins for subcutaneous/intramuscular use, expressed in International Units and International Units *per capita*, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow).

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	549,980	0.4	536,880	0.4	-1.9
Aosta Valley	225,980	1.8	255,960	2.0	13.9
AP Bolzano	121,860	0.2	120,200	0.2	-2.0
AP Trento	171,960	0.3	159,460	0.3	-7.5
Apulia	6,000,620	1.5	5,603,440	1.4	-6.3
Basilicata	301,680	0.5	259,100	0.5	-13.6
Calabria	1,218,420	0.6	1,138,320	0.6	-6.2
Campania	18,428,040	3.2	15,581,140	2.7	-15.3
E.-Romagna	3,840,020	0.9	3,518,160	0.8	-8.5
Friuli-V. Giulia	326,700	0.3	245,000	0.2	-24.9
Latium	2,499,800	0.4	2,180,020	0.4	-12.8
Liguria	938,780	0.6	718,180	0.5	-23.1
Lombardy	11,268,900	1.1	10,434,600	1.0	-7.6
Marche	534,340	0.3	447,200	0.3	-16.0
Molise	146,060	0.5	144,900	0.5	-0.2
Piedmont	4,769,380	1.1	4,672,340	1.1	-1.7
Sardinia	3,282,060	2.0	3,492,000	2.1	6.7
Sicily	3,467,560	0.7	2,584,960	0.5	-25.0
Tuscany	3,629,740	1.0	2,969,280	0.8	-18.1
Umbria	245,880	0.3	245,180	0.3	0.2
Veneto	2,608,040	0.5	2,579,860	0.5	-1.0
ITALY	64,575,800	1.1	57,886,180	1.0	-10.2

TETANUS IMMUNOGLOBULINS (ATC J06BB02)

Table 40 shows drugs containing tetanus IGs currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 40. Products containing tetanus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018).

AIC code	Brand name	IU	Manufacturer	NHS class
022488047	TETANUSGAMMA*IM 1SIR 250UI 2ML	250	KEDRION SpA	A
022488062	TETANUSGAMMA*IM SIR 250UI 1ML	250	KEDRION SpA	A
022601088	TETABULIN*IM 1SIR 250UI 1ML	250	BAXTER SpA	A
022635041	GAMMATET P*IM 1F 250UI 1ML	250	CSL BEHRING SpA	A
022635066	GAMMATET P*IM 1SIR 250UI 1ML	250	CSL BEHRING SpA	A
033863010	IGANTET*IM 1SIR 1ML 250UI	250	GRIFOLS ITALIA SpA	A
022488050	TETANUSGAMMA*IM 1SIR 500UI 2ML	500	KEDRION SpA	A
022601090	TETABULIN*IM 1SIR 500UI 2ML	500	BAXTER SpA	A
022635054	GAMMATET P*IM 1F 500UI 2ML	500	CSL BEHRING SpA	A
022635078	GAMMATET P*IM 1SIR 500UI 2ML	500	CSL BEHRING SpA	A
033863022	IGANTET*IM 1SIR 2ML 500UI	500	GRIFOLS ITALIA SpA	A
-*	TETAGAM P 250 IU/1 ml	250	CSL BEHRING SpA	-

*Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

In 2018, the total demand for tetanus IGs decreased by 8% compared to 2017. Total demand was 131,772,250 IUs (2.2 IUs *per capita*) (Table 41).

The Regions with the highest demand, expressed as a standardised volume for the resident population, were Campania (5.1 IUs *per capita*), and Abruzzo and Aosta Valley (3.7 IUs *per capita*). In 2018, the demand decreased – in some cases very significantly - in almost all Regions, with the exception of Aosta Valley (11%), the AP of Trento (46.2%), Campania (42%), and Emilia-Romagna (1%). A significant amount of tetanus IGs was imported under the provisions of DM of 11 February 1997 and DM of 11 May 2001 but no detailed information about the regional distribution was available. They were inserted under the heading “Not Specified Region” and accounted for 2,472,500 IUs.

Table 41. Total demand (public and private) and total standardised demand, expressed in International Units and International Units *per capita*, for tetanus immunoglobulins and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	6,013,250	4.5	4,858,000	3.7	-18.8
Aosta Valley	426,250	3.4	470,500	3.7	11.0
AP Bolzano	888,500	1.7	483,500	0.9	-45.9
AP Trento	503,500	0.9	738,000	1.4	46.2
Apulia	7,959,500	2.0	7,579,750	1.9	-4.4
Basilicata	1,854,000	3.3	1,452,000	2.6	-21.2
Calabria	6,147,000	3.1	5,684,250	2.9	-7.1
Campania	21,153,750	3.6	29,976,750	5.1	42.0
E.-Romagna	7,489,000	1.7	7,566,750	1.7	1.0
Friuli-V. Giulia	1,277,750	1.0	511,500	0.4	-59.9
Latium	11,183,000	1.9	10,599,750	1.8	-5.2
Liguria	4,905,500	3.1	4,673,000	3.0	-4.2
Lombardy	20,886,750	2.1	18,492,500	1.8	-11.6
Marche	5,417,000	3.5	3,952,000	2.6	-26.7
Molise	1,314,500	4.2	649,000	2.1	-50.3
Piedmont	6,748,750	1.5	4,906,000	1.1	-27.0
Sardinia	3,951,250	2.4	3,419,250	2.1	-13.2
Sicily	10,822,500	2.1	9,208,000	1.8	-14.4
Tuscany	14,607,750	3.9	8,562,750	2.3	-41.3
Umbria	2,062,000	2.3	1,732,000	2.0	-15.6
Veneto	5,646,500	1.2	3,784,500	0.8	-32.9
Not specified Region	-		2,472,500	NA	NA
ITALY	141,258,000	2.3	131,772,250	2.2	-0.1

ANTI-D (RH) IMMUNOGLOBULINS (ATC J06BB01)

Table 42 shows the brand names of medicinal products containing the anti-D (Rh) IGs currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 42. Products containing anti-D (Rh) immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
039596010	RHESONATIV*1F 1ML 625UI/ML	625	OCTAPHARMA ITALY SpA	A
022547020	IMMUNORHO*IM 1FL 200MCG+1F 2ML	1000	KEDRION SpA	A
036161014	RHOPHYLAC*1SIR 200 MCG/2ML	1000	CSL BEHRING GmbH	C
039596022	RHESONATIV*1F 2ML 625UI/ML	1250	OCTAPHARMA ITALY SpA	A
022547018	IMMUNORHO*IM 1FL 300MCG+1F 2ML	1500	KEDRION SpA	A
022547044	IMMUNORHO*IM 1SIR 2ML 300MCG	1500	KEDRION SpA	A
033867021	IGAMAD*IM 1SIR 1500UI/2ML	1500	GRIFOLS ITALIA SpA	A
036161026	RHOPHYLAC*1SIR 300MCG/2ML	1500	CSL BEHRING GmbH	C
036161038	RHOPHYLAC*5SIR 300MCG/2ML	7500	CSL BEHRING GmbH	C
039596034	RHESONATIV*10F 2ML 625UI/ML	12500	OCTAPHARMA ITALY SpA	A

Quantification of the demand

The national anti-D (Rh) IGs demand decreased by 4% between 2017 and 2018 and its volume was 117,007,375 IUs in 2018 (1.9 IUs *per capita*), with a maximum in the AP of Trento and a minimum in Tuscany (4.1 and 0.6 IUs *per capita*, respectively) (Table 43).

Table 43. Total demand (public and private) and total standardised demand for anti-D (Rh) immunoglobulins, expressed in International Units and in International Units *per capita* and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,533,500	1.9	2,451,000	1.9	-2.7
Aosta Valley	304,500	2.4	325,500	2.6	7.5
AP Bolzano	2,052,000	3.9	2,113,500	4.0	2.3
AP Trento	1,945,000	3.6	2,195,000	4.1	12.6
Apulia	5,854,500	1.4	6,394,500	1.6	9.6
Basilicata	888,000	1.6	999,000	1.8	13.1
Calabria	2,188,500	1.1	2,346,000	1.2	7.7
Campania	10,202,000	1.7	9,922,000	1.7	-2.5
E.-Romagna	10,664,375	2.4	10,171,750	2.3	-4.7
Friuli-V. Giulia	2,791,500	2.3	3,988,750	3.3	43.2
Latium	11,648,750	2.0	12,868,750	2.2	10.5
Liguria	2,763,000	1.8	3,031,500	1.9	10.3
Lombardy	23,775,000	2.4	24,328,250	2.4	2.2
Marche	2,767,500	1.8	3,145,500	2.1	14.1
Molise	404,750	1.3	392,750	1.3	-2.3

Region	2017		2018		% Var 2017-2018
	IU	IU per capita	IU	UI per capita	
Piedmont	9,108,875	2.1	8,965,625	2.0	-1.2
Sardinia	1,257,000	0.8	1,485,000	0.9	18.5
Sicily	8,428,500	1.7	7,960,500	1.6	-5.0
Tuscany	9,591,875	2.6	2,242,500	0.6	-76.6
Umbria	1,555,500	1.7	1,356,000	1.5	-12.4
Veneto	11,605,500	2.4	10,324,000	2.1	-11.0
ITALY	122,330,125	2.0	117,007,375	1.9	-4.2

CYTOMEGALOVIRUS IMMUNOGLOBULINS (ATC J06BB09)

Table 44 shows the brand names of medicinal products containing cytomegalovirus immunoglobulins (anti-CMV IGs) currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 44. Products containing cytomegalovirus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
026167015	CYTOTECT BIOTEST*EV 10ML 500UI	500	BIOTEST PHARMA GmbH	H
026167027	CYTOTECT BIOTEST*EV 20ML 1000UI	1000	BIOTEST PHARMA GmbH	H
026167041	CYTOTECT BIOTEST*EV 10ML1000UI	1000	BIOTEST PHARMA GmbH	H
026167039	CYTOTECT BIOTEST*EV 50ML 2500UI	2500	BIOTEST PHARMA GmbH	H
026167054	CYTOTECT BIOTEST*EV 50ML5000UI	5000	BIOTEST PHARMA GmbH	H

Quantification of the demand

Table 45 shows the total demand and the total standardised demand (IUs *per capita*) for CMV IGs for the two-year period 2017-2018, at national and regional levels. During the period under examination, the CMV IGs national demand decreased by 9% to a volume of 14,333,000 IUs. However, the national average showed strong fluctuations and trends varied from one Region to another; Veneto was confirmed as the largest user (0.7 IUs *per capita*), followed by Piedmont (0.6 IUs *per capita*), and Emilia-Romagna (0.5 IUs *per capita*).

Table 45. Total demand (public and private) and total standardised demand for cytomegalovirus immunoglobulins products, expressed in International Units and in International Units per capita, and variations in percentages between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU per capita	IU	IU per capita	
Abruzzo	294,000	0.2	313,000	0.2	7.0
Aosta Valley	-	-	-	0.0	NA
AP Bolzano	86,000	0.2	-	0.0	-100.0
AP Trento	5,000	0.0	-	0.0	-100.0
Apulia	293,000	0.1	429,000	0.1	47.0
Basilicata	101,000	0.2	120,000	0.2	19.5
Calabria	10,000	0.0	40,000	0.0	301.7
Campania	529,000	0.1	380,000	0.1	-28.0
E.-Romagna	3,069,000	0.7	2,330,000	0.5	-24.1
Friuli-V. Giulia	685,000	0.6	4,000	0.0	-99.4
Latium	845,000	0.1	1,142,000	0.2	35.2
Liguria	-	-	9,000	0.0	NA
Lombardy	1,664,000	0.2	2,184,000	0.2	31.0
Marche	214,000	0.1	456,000	0.3	114.0
Molise	-	-	-	0.0	NA
Piedmont	2,835,000	0.6	2,466,000	0.6	-12.7

Region	2017		2018		% Var 2017-2018
	IU	IU per capita	IU	IU per capita	
Sardinia	-	-	-	0.0	NA
Sicily	956,000	0.2	535,000	0.1	-43.7
Tuscany	293,000	0.1	257,000	0.1	-12.2
Umbria	49,000	0.1	43,000	0.0	-11.8
Veneto	3,853,000	0.8	3,625,000	0.7	-5.9
ITALY	15,781,000	0.3	14,333,000	0.2	-9.0

VARICELLA/ZOSTER IMMUNOGLOBULINS FOR INTRAVENOUS USE (ATC J06BB03)

Human immunoglobulins with specific anti-human herpesvirus 3 antibodies (varicella-zoster virus 1) (Var IGs) are used in post-exposure prophylaxis of varicella zoster and for the treatment of severe varicella-zoster infections or complications, in immunocompromised patients or infants at risk. These human immunoglobulins are obtained from selected plasma donors with high titers of anti-varicella antibodies (35-37).

Table 46 shows the brand names of medicinal products containing Var IGs currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 46. Products containing specific varicella/zoster immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
026978027*	VARITECT 25 UI/mL 1F 5mL	125	BIOTEST PHARMA GmbH	H
026978015*	VARITECT 25 UI/mL 1F 20mL	500	BIOTEST PHARMA GmbH	H

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

Table 47 shows the total demand and the total standardised demand (IUs per 1,000 population) of Var IGs in the two-year period 2017-2018, at national and regional levels. The national demand for Var IGs showed a slight decrease (-8%). Total demand in 2018 was 179,625 IUs (3.0 IUs per 1,000 population).

Table 47. Total demand (public and private) and total standardised demand for products containing varicella/zoster immunoglobulins for intravenous use, expressed in International Units and International Units per 1,000 population and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the Product Quality and Pharmacrime Office - AIFA)

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	2,125	1.6	1,125	0.9	-46.8
Aosta Valley	-	NA	4,875	38.6	NA
AP Bolzano	-	NA	-	0.0	NA
AP Trento	14,125	26.2	6,000	11.1	-57.6
Apulia	1,500	0.4	3,750	0.9	151.0
Basilicata	500	0.9	-	0.0	-100.0
Calabria	-	NA	125	0.1	NA
Campania	2,875	0.5	6,125	1.1	113.5
Emilia-Romagna	26,625	6.0	27,875	6.3	4.6
Friuli-V. Giulia	18,500	15.2	6,750	5.6	-63.4
Latium	8,125	1.4	13,750	2.3	69.3
Liguria	8,625	5.5	4,500	2.9	-47.5
Lombardy	64,250	6.4	66,625	6.6	3.5

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Marche	22,125	14.4	14,750	9.6	-33.1
Molise	250	0.8	-	0.0	-100.0
Piedmont	1,125	0.3	1,250	0.3	11.5
Sardinia	-	NA	250	0.2	NA
Sicily	1,000	0.2	-	0.0	-100.0
Tuscany	3,875	1.0	5,375	1.4	38.9
Umbria	5,750	6.5	8,000	9.0	39.8
Veneto	14,375	2.9	8,500	1.7	-40.8
ITALY	195,750	3.2	179,625	3.0	-8.1

RABIES IMMUNOGLOBULINS (ATC J06BB05)

Human immunoglobulins with rabies-specific antibodies (rabies IGs) are used for post-exposure prophylaxis in cases of scratches, bites or other injuries caused by rabid or potentially rabid animals. They are obtained from selected plasma donors with high titers of anti-rabies antibodies (38). Table 48 shows the brand names of drugs containing rabies IGs currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 48. Products containing rabies immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
- *	BERIRAB P 150UI/ml 2ml	300	CSL BEHRING GmbH	-
- *	BERIRAB P 150UI/ml 5ml	750	CSL BEHRING GmbH	-

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

In 2018, the total demand for rabies IGs, recorded in ten Regions, showed a significant increase compared to 2017 (+32.6%). The total demand amounted to 111,150 IUs (1.8 IUs per 1,000 population) (Table 49).

Table 49. Total demand (public and private) and total standardised demand for rabies immunoglobulin, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the Product Quality and Pharmacovigilance Office – AIFA)

Region	2017		2018		% Var 2017-2018
	IU	IU per 1.000 pop.	IU	IU per 1.000 pop.	
Abruzzo	-	-	-	-	NA
Aosta Valley	1,500	11.8	-	-	-100.0
AP Bolzano	10,500	20.0	3,450	6.5	-67.4
AP Trento	-	-	3,000	5.6	NA
Apulia	-	-	600	0.1	NA
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	9,000	2.0	10,350	2.3	14.9
Friuli-V. Giulia	10,500	8.6	30,300	24.9	189.1
Latium	-	-	1,500	0.3	NA
Liguria	-	-	-	-	NA
Lombardy	12,000	1.2	22,350	2.2	85.9
Marche	3,750	2.4	1,500	1.0	-59.8
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	10,200	2.7	9,000	2.4	-11.6
Umbria	-	-	-	-	NA
Veneto	26,550	5.4	29,100	5.9	9.7
ITALY	84,000	1.4	111,150	1.8	32.6

LOCAL HAEMOSTATIC AGENTS-COMBINATIONS (ATC B02BC - ATC B02BC30)

Table 50 shows the brand names of drugs containing local haemostatics - combinations currently on the market in Italy and the amount of active ingredient expressed in mL and in the number of gelatin sponges they contain.

Table 50. Products containing local haemostatics-combinations currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	mL	Manufacturer	NHS class
035941018	BERIPLAST P*FL POLV 0,5ML+FL	0.5	CSL BEHRING GmbH	C
035941020	BERIPLAST P*FL POLV 1ML+FL+SET	1	CSL BEHRING GmbH	C
035941032	BERIPLAST P*FL POLV 3ML+FL+SET	3	CSL BEHRING GmbH	C
039546015	ARTISS SOL. ADESIVO TISSUTALE	1	BAXTER SpA	H
025243179	TISSEEL 2ml ADESIVO TISSUTALE	2	BAXTER SpA	H
039546027	ARTISS SOL. ADESIVO TISSUTALE	2	BAXTER SpA	H
039591019	EVICEL*2FL 1ml 90MG/ml+1200UI	2	OMRIX BIOPHARMA	H
042046019	SILKETAL 2,5ml ADESIVO TISSUTALE	2.5	KEDRION SpA	C
044152015	KOLFIB*FL POLV SOLV 2,5ML	2.5	KEDRION SpA	C(nn)
025243181	TISSEEL 4ML ADESIVO TISSUTALE	4	BAXTER SpA	H
039591021	EVICEL*2FL 2ML 90MG/ML+1200UI	4	OMRIX BIOPHARMA	H
039546039	ARTISS SOL. ADESIVO TISSUTALE	5	BAXTER SpA	H
042046021	SILKETAL 5ml ADESIVO TISSUTALE	5	KEDRION SpA	C
044152027	KOLFIB*FL POLV SOLV 5ML	5	KEDRION SpA	C(nn)
025243193	TISSEEL 10ml ADESIVO TISSUTALE	10	BAXTER SpA	H
039591033	EVICEL*2FL 5ml 90MG/ML+1200UI	10	OMRIX BIOPHARMA	H
042046033	SILKETAL 10ml ADESIVO TISSUTALE	10	KEDRION SpA	C
044152039	KOLFIB*FL POLV SOLV 10ML	10	KEDRION SpA	C(nn)
		sponges		
036557015	TACHOSIL*1SPUGNA 9,5CMx4,8CM	1	TAKEDA ITALY SpA	C
036557039	TACHOSIL*1MATRICE 3 CMx2,5 CM	1	TAKEDA GmbH	C
036557054	TACHOSIL*1MATRICE 4,8CMx4,8CM	1	TAKEDA ITALY SpA	C
043011016	EVARREST*1BUST 8,1MG+40UI/CM2	1	OMRIX BIOPHARMA	C
036557027	TACHOSIL*2SPUGNE 4,8CMx4,8CM	2	TAKEDA ITALY SpA	C
043011028	EVARREST*2BUST 8,1MG+40UI/CM2	2	OMRIX BIOPHARMA	C
036557041	TACHOSIL*5MATRICI 3 CM X 2,5 CM	5	TAKEDA GmbH	C

Quantification of the demand

The various products with an ATC code related to local haemostatics-combinations do not always have the same composition, but as they are considered equivalent, the active ingredient is expressed in mL and mL per 1,000 population (Table 51). For the products in the form of “medicated gelatin sponges” that cannot be expressed in mL no standardisation is performed and demand is calculated according to the number of packs sold (Table 52). In 2018, the total demand for local haemostatics-combinations reached a volume of about 39,729 mL (0.7 mL per 1,000 population), a decrease (-47%) compared to the volume of 2017 (Table 51). In 2018, the total demand for local haemostatics-combinations, expressed in number of gelatin sponges, recorded a decrease compared to 2017 (-9.7%). The total demand amounted to 33,819 sponges (Table 52).

Table 51. Total demand (public and private) and total standardised demand for local haemostatics-combinations, expressed in millilitres and in millilitres per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	2,029	1.5	1,521	1.2	-24.6
Aosta Valley	250	2.0	-	-	-100.0
AP Bolzano	532	1.0	437	0.8	-18.4
AP Trento	836	1.6	540	1.0	-35.6
Apulia	5,800	1.4	1,970	0.5	-65.9
Basilicata	1,057	1.9	750	1.3	-28.6
Calabria	1,360	0.7	1,242	0.6	-8.3
Campania	7,698	1.3	4,068	0.7	-47.0
Emilia-Romagna	5,266	1.2	4,062	0.9	-22.9
Friuli-V. Giulia	1,042	0.9	820	0.7	-21.2
Latium	8,010	1.4	2,670	0.5	-66.7
Liguria	1,382	0.9	636	0.4	-53.7
Lombardy	18,917	1.9	5,853	0.6	-69.1
Marche	1,174	0.8	632	0.4	-45.9
Molise	416	1.3	70	0.2	-83.1
Piedmont	3,734	0.9	2,574	0.6	-30.8
Sardinia	948	0.6	1,322	0.8	39.9
Sicily	3,952	0.8	3,233	0.6	-17.7
Tuscany	4,283	1.1	3,416	0.9	-20.1
Umbria	1,196	1.3	372	0.4	-68.7
Veneto	5,778	1.2	3,541	0.7	-38.7
ITALY	75,660	1.2	39,729	0.7	-47.4

Table 52. Total demand (public and private) for local haemostatics-combinations, expressed in number of gelatin sponges, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017	2018	% Var 2017-2018
	sponges	sponges	
Abruzzo	935	1,111	19.5
Aosta Valley	182	248	37.0
AP Bolzano	472	484	1.9
AP Trento	146	132	-9.8
Apulia	2,393	2,110	-11.5
Basilicata	917	1,200	31.6
Calabria	2,158	2,324	8.2
Campania	4,247	3,960	-6.6
Emilia-Romagna	940	1,169	24.3
Friuli-Venezia Giulia	1,305	54	-95.9
Latium	2,505	2,761	10.2
Liguria	429	559	31.0
Lombardy	6,785	6,455	-5.0
Marche	1,049	1,253	19.9
Molise	7	24	245.0
Piedmont	2,844	3,421	20.7
Sardinia	673	764	13.9
Sicily	3,167	2,490	-20.9
Tuscany	2,651	9	-99.7
Umbria	1,127	881	-21.5
Veneto	2,574	2,410	-6.3
ITALY	37,506	33,819	-9.7

COAGULATION FACTOR VII (ATC B02BD05)

Table 53 shows the brand names of medicinal products containing FVII currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 53. Products containing Factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
024748042	PROVERTINUM TIM3*IV FL 600UI	600	BAXTER AG	A

Quantification of the demand

In 2018, the total demand and the total standardised national demand for FVII was approximately 7 million IUs, a 20% increase compared to 2017 (Table 54). This increase was generalised with the exception of Apulia, Molise, Piedmont, Tuscany and Umbria. In 2018, there was no utilisation of FVII in several Regions.

Table 54. Total demand (public and private demand) and total standardised demand for Factor VII expressed in International Units and International Units per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	101,400	76.7	321,600	244.5	218.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	495,000	121.8	351,000	86.7	-28.8
Basilicata	7,200	12.6	57,600	101.6	704.6
Calabria	9,000	4.6	15,600	8.0	74.1
Campania	54,000	9.2	457,800	78.6	749.6
E.-Romagna	196,800	44.2	256,800	57.7	30.4
Friuli-V. Giulia	-	-	-	-	NA
Latium	2,750,400	466.3	2,946,000	499.6	7.1
Liguria	14,400	9.2	15,000	9.6	4.7
Lombardy	1,420,200	141.7	1,738,800	173.3	22.2
Marche	-	-	1,200	0.8	NA
Molise	630,000	2,029.3	570,000	1847.7	-9.0
Piedmont	213,600	48.6	201,600	46.1	-5.3
Sardinia	-	-	-	-	NA
Sicily	51,000	10.1	191,400	38.1	277.5
Tuscany	4,200	1.1	-	-	-100.0
Umbria	2,400	2.7	-	-	-100.0
Veneto	36,600	7.5	38,400	7.8	5.0
ITALY	5,982,000	98.7	7,162,800	118.4	19.9

RECOMBINANT ACTIVATED FACTOR VII (ATC B02BD08)

Table 55 shows the brand names of medicinal products containing rFVIIa currently available on the Italian market and the amount of active ingredient they contain expressed in milligrams (mg).

Table 55. Products containing recombinant activated factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	mg	Manufacturer	NHS class
029447048	NOVOSEVEN*IV 1MG(50KUI)+1,1ML	1	NOVO NORDISK SpA	H
029447087	NOVOSEVEN*IV 1MG(50KUI)+1ML	1	NOVO NORDISK SpA	H
029447012	NOVOSEVEN*IV 1,2MG(60KUI)+2,2ML	1.2	NOVO NORDISK SpA	H
029447051	NOVOSEVEN*IV 2MG(100KUI)+2,1ML	2	NOVO NORDISK SpA	H
029447099	NOVOSEVEN*IV 2MG(100KUI)+2ML	2	NOVO NORDISK SpA	H
029447024	NOVOSEVEN*IV 2,4MG(120 KIU)	2.4	NOVO NORDISK SpA	H
029447036	NOVOSEVEN*IV 4,8 MG(240 KIU)	4.8	NOVO NORDISK SpA	H
029447063	NOVOSEVEN*IV 5MG(250KUI)+5,2ML	5	NOVO NORDISK SpA	H
029447101	NOVOSEVEN*IV 5MG(250KUI)+5ML	5	NOVO NORDISK SpA	H
029447075	NOVOSEVEN*IV8MG (400KUI)+8,1ML	8	NOVO NORDISK SpA	H
029447113	NOVOSEVEN*IV 8MG(400KUI)+8ML	8	NOVO NORDISK SpA	H

Quantification of the demand

Table 56 shows the total demand (mg) and the total standardised demand (mg per 1,000 population) of rFVIIa over the two-year period 2017-2018, at national and regional levels. The total demand for rFVIIa recorded in 2018 was 61,911 mg (1 mg per 1,000 population), -37.3% compared to 2017.

Table 56. Total demand (public and private) and total standardised demand for recombinant activated factor VII expressed in milligrams and in milligrams per 1,000 population and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Abruzzo	1,315	1.0	314	0.2	-76.0
Aosta Valley	13	0.1	10	0.1	-22.7
AP Bolzano	38	0.1	124	0.2	224.2
AP Trento	1	0.0	21	0.0	1995.0
Apulia	11,441	2.8	6,584	1.6	-42.2
Basilicata	152	0.3	137	0.2	-9.4
Calabria	7,652	3.9	6,108	3.1	-19.8
Campania	10,828	1.9	6,479	1.1	-40.0
E.-Romagna	3,895	0.9	3,224	0.7	-17.3
Friuli-V. Giulia	14,292	11.7	22	0.0	-99.8
Latium	4,604	0.8	4,432	0.8	-3.7
Liguria	499	0.3	1,014	0.7	104.3
Lombardy	9,302	0.9	8,936	0.9	-4.1

Region	2017		2018		% Var 2017-2018
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Marche	2,685	1.7	1,237	0.8	-53.7
Molise	76	0.2	74	0.2	-2.0
Piedmont	10,361	2.4	5,696	1.3	-44.8
Sardinia	1,089	0.7	483	0.3	-55.5
Sicily	5,894	1.2	6,922	1.4	18.1
Tuscany	5,979	1.6	-	-	-100.0
Umbria	828	0.9	719	0.8	-12.7
Veneto	8,019	1.6	9,375	1.9	17.0
ITALY	98,963	1.6	61,911	1.0	-37.3

FACTOR VIII INHIBITOR BYPASSING ACTIVITY (ATC B02BD03)

Table 57 shows the brand names of medicinal products containing factor VIII inhibitor bypassing activity currently available on the Italian market and the amount of active ingredient they contain expressed in FEIBA Units (FUs).

Table 57. Products containing factor VIII inhibitor bypassing activity currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	FU	Manufacturer	NHS class
024744043	FEIBA*IV FL 500UI+F 20ML	500	BAXALTAITALYSrl	A
024744068	FEIBA*FL 500UF+BAXJECT II HF	500	BAXALTAITALYSrl	A
024744056	FEIBA TIM3*IV FL 1000UI+F 20ML	1000	BAXTERAG	A
024744070	FEIBA*FL 1000UF+BAXJECT II HF	1000	BAXTERAG	A

Quantification of the demand

Table 58 shows the total demand and the total standardised demand (FUs *per capita*) of factor VIII inhibitor bypassing activity, or aPCCs, over the two-year period 2017-2018 at regional and national levels.

Table 58. Total demand (public and private) and total standardised demand for factor VIII inhibitor bypassing activity, expressed in FEIBA Units and FEIBA Units *per capita*, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	FU	FU <i>per capita</i>	FU	FU <i>per capita</i>	
Abruzzo	1,769,000	1.3	1,687,000	1.3	-4.1
Aosta Valley	-	-	-	-	NA
AP Bolzano	50,000	0.1	16,000	0.0	-68.2
AP Trento	25,000	0.0	131,000	0.2	422.7
Apulia	514,000	0.1	470,000	0.1	-8.2
Basilicata	-	-	-	-	NA
Calabria	1,804,000	0.9	1,604,000	0.8	-10.7
Campania	5,977,000	1.0	6,073,000	1.0	1.8
E.-Romagna	3,774,000	0.8	1,660,000	0.4	-56.1
Friuli-V. Giulia	926,000	0.8	600,000	0.5	-35.1
Latium	1,458,000	0.2	675,000	0.1	-53.7
Liguria	-	-	352,000	0.2	NA
Lombardy	1,770,000	0.2	2,926,000	0.3	65.0
Marche	120,000	0.1	-	-	-100.0
Molise	-	-	-	-	NA
Piedmont	1,456,000	0.3	1,546,000	0.4	6.6
Sardinia	522,000	0.3	356,000	0.2	-31.6
Sicily	1,299,000	0.3	934,000	0.2	-27.7
Tuscany	2,228,000	0.6	-	-	-100.0
Umbria	10,000	0.0	-	-	-100.0
Veneto	751,000	0.2	225,000	0.0	-70.0
ITALY	24,453,000	0.4	19,255,000	0.3	-21.1

In 2018, the national demand for aPCCs showed a significant decrease (-21%) compared to 2017, with wide variations at regional level. Its total volume was 19,255,000 FUs (0.3 FUs *per capita*).

ALPHA-1-PROTEINASE INHIBITOR (ATC B02AB02)

The alpha-1-proteinase inhibitor (also known as alpha-1-antitrypsin or alpha-1-antiproteinase) is normally present in human plasma at concentrations that range from 0.7 to 2.3 g/L. The alpha-1-proteinase inhibitor is also present in some extravascular spaces, in particular the pulmonary alveoli, where it carries out its main function. In fact, it modulates the action of enzymes produced by neutrophils (elastase) thus avoiding damage to lung tissue.

Alpha-1-antitrypsin is indicated for replacement therapy in subjects with inherited deficiency (39).

Table 59 shows the brand names of medicinal products containing alpha-1-proteinase inhibitor currently available on the Italian market and the relative quantity of active ingredient they contain expressed in milligrams (mg).

Table 59. Products containing alpha-1-proteinase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC Code	Brand name	mg	Manufacturer	NHS class
037709019	PROLASTIN*EV 1F 1G/40ML+F40ML	1000	GRIFOLS ITALIA SpA	H
044479018	RESPREEZA*EV 1FL 20ML+SOL 1G	1000	CSL BEHRING GmbH	H

Quantification of the demand

In 2018, the total demand for alpha-1-antitrypsin was 28,705 g (0.5 g per 1,000 population) showing a significant downward trend compared to the previous year (-11%) (Table 60). The drop in demand was particularly significant in the Friuli V. Giulia, Tuscany and Molise Regions (-77%, -70%, -66% respectively). Instead, two Regions showed a marked increase compared to 2017: Campania (+118%) and Liguria (+74%). The Regions with the highest standardised regional demand were Aosta Valley and the AP of Bolzano (8.3 and 3.6 grams per 1,000 population, respectively).

Table 60. Total demand (public and private) and total standardised demand for alpha-1-proteinase inhibitor, expressed in grams and grams per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	777	0.6	889	0.7	15.0
Aosta Valley	1,001	7.9	1,042	8.3	4.7
AP Bolzano	3,096	5.9	1,883	3.6	-39.6
AP Trento	640	1.2	474	0.9	-26.1
Apulia	965	0.2	1,014	0.3	5.5
Basilicata	-	-	-	0.0	NA
Calabria	220	0.1	282	0.1	28.7
Campania	1,602	0.3	3,484	0.6	117.9
E.-Romagna	2,169	0.5	1,701	0.4	-21.6
Friuli-V.Giulia	2,157	1.8	490	0.4	-77.2
Latium	1,182	0.2	1,266	0.2	7.1

Region	2017		2018		% Var 2017-2018
	g	g per 1,000 pop	g	g per 1,000 pop	
Liguria	739	0.5	1,279	0.8	74.0
Lombardy	7,256	0.7	6,078	0.6	-16.4
Marche	251	0.2	295	0.2	18.0
Molise	108	0.3	36	0.1	-66.5
Piedmont	2,642	0.6	2,182	0.5	-17.1
Sardinia	1,466	0.9	1,182	0.7	-19.1
Sicily	1,318	0.3	957	0.2	-27.0
Tuscany	1,404	0.4	422	0.1	-69.9
Umbria	207	0.2	168	0.2	-18.4
Veneto	3,117	0.6	3,581	0.7	14.9
ITALY	32,317	0.5	28,705	0.5	-11.0

PLASMA-DERIVED C1-INHIBITOR (ATC B06AC01)

Human C1 esterase inhibitor is a heat-labile plasma protein that inhibits the uncontrolled activation of the classical complement pathway (in particular that of C1 esterase) the deficiency of which is responsible for hereditary angio-oedema. The mean concentration of the C1 inhibitor in plasma is approximately 0.2 g/L (40).

Table 61 shows the brand names of medicinal products containing human C1 esterase inhibitor currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 61. Products containing human C1 esterase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
039056015	BERINERT*IV FL 500UI+FL 10ML	500	CSL BEHRING SpA	A
039056027	BERINERT*IV FL 1500UI+FL 10ML	1500	CSL BEHRING SpA	A
042017018	CINRYZE*EV 2FL 500UI+2FL	1000	SHIRE ITALIA SpA	A
039056039	BERINERT*IV FL 2000UI + FL 4ML+ SET	2000	CSL BEHRING GMBH	C
039056041	BERINERT*IV FL 3000UI + FL 6ML+ SET	3000	CSL BEHRING GMBH	C

Quantification of the demand

In 2018, the total demand for C1 esterase inhibitor was 11,831,500 IUs (196 IUs per 1,000 population), a decrease of -2.4% (Table 62) compared to 2017. A marked variability in standardised regional demands was observed, with maximum volumes in Aosta Valley, Sardinia, Umbria and Sicily (1,303, 394, 351 and 340 IUs per 1,000 population, respectively) and minimum volumes in Friuli-V. Giulia, AP of Trento and Molise (range: 5-11 IUs per 1,000 population). Half of the Italian Regions showed a reduction in demand, while the others recorded an increase in some cases very significant (AP of Bolzano +1,986%).

Table 62. Total demand (public and private) and total standardised demand for C1 esterase inhibitor, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	316,500	239.4	288,000	219.0	-8.5
Aosta Valley	68,000	535.9	164,500	1303.5	143.2
AP Bolzano	2,000	3.8	42,000	79.6	1986.1
AP Trento	13,000	24.1	6,000	11.1	-54.0
Apulia	1,113,500	274.0	1,049,000	259.1	-5.4
Basilicata	45,000	78.9	48,000	84.6	7.3
Calabria	339,000	172.5	462,000	236.1	36.9
Campania	1,637,500	280.4	1,688,000	289.7	3.3
E.-Romagna	460,000	103.4	439,000	98.6	-4.6
Friuli-V. Giulia	7,500	6.2	6,500	5.3	-13.2
Latium	1,306,000	221.4	910,000	154.3	-30.3
Liguria	168,500	107.6	134,500	86.4	-19.8
Lombardy	1,789,500	178.6	1,613,000	160.7	-10.0

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Marche	280,500	182.4	301,000	196.5	7.7
Molise	5,500	17.7	3,500	11.3	-36.0
Piedmont	585,000	133.2	646,500	147.7	10.9
Sardinia	626,000	378.7	650,000	394.4	4.1
Sicily	1,698,500	335.9	1,708,000	339.8	1.2
Tuscany	367,000	98.1	124,500	33.3	-66.0
Umbria	231,000	259.9	310,500	351.0	35.1
Veneto	1,084,000	220.9	1,237,000	252.2	14.2
ITALY	12,143,500	200.4	11,831,500	195.6	-2.4

COAGULATION FACTOR X (ATC B02BD13)

Congenital Factor X deficiency (or Stuart-Prower factor deficiency) is an inherited haemorrhagic disorder characterised by the decreased activity of the Factor X (FX) antigen, which causes severe or moderate bleeding. The prevalence of homozygous forms is estimated at 1/1,000,000. No gender differences were reported. Haemorrhagic episodes are usually treated with 3F-PCCs or fresh frozen plasma (41).

Table 63 shows the brand names of drugs containing FXpd currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 63. Products containing coagulation Factor X currently available on the Italian market (adapted by the CNS on data from Farmadati and the Product Quality and Pharmacrime Office- AIFA, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
*	FACTOR X P BEHRING 1FL	600-1200§	CSL BEHRING SpA	-
044840015	COAGADEX 100UI/ML- IV 2,5 mL	250	BIO PROD. LAB. LTD	C
044840027	COAGADEX 100UI/ML- IV 5 mL	500	BIO PROD. LAB. LTD	C(nn)

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

§ The average quantity of active ingredient contained was used in the definition of the demand.

Quantification of the demand

Products containing FX concentrates are used exclusively in Lombardy, where in 2018 the demand was for 78,000 IUs (7.8 IUs per 1,000 population) (Table 64).

Table 64. Total demand (public and private) and total standardised demand for coagulation Factor X expressed in International Units and International Units per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from Product Quality and Pharmacrime Office-AIFA)

Region	2017		2018		Var % 2017-2018
	IU	IU per 1,000 pop	UI	IU per 1,000 pop	
Lombardy	48,000	4.8	78,000	7.8	62.2
ITALY	48,000	0.8	78,000	1.3	62.8

COAGULATION FACTOR XI (ATC B02BD)

Factor XI (FXI), also known as plasma thromboplastin antecedent (PTA) or Rosenthal factor, is a plasma glycoprotein responsible for activating FIX (42). Congenital FXI deficiency causes an inherited recessive autosomal haemorrhagic disorder characterised by reduced FXI levels and activity, which causes moderate bleeding generally following trauma or surgery. The prevalence of homozygous forms is estimated at 1/1,000,000; in specific ethnic groups there is a significantly higher prevalence of severe forms (43). Table 65 shows the brand names of drugs containing FXI currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 65. Products containing recombinant coagulation factor XI currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Name of medicinal product	IU	Manufacturer	NHS class
-*	HEMOLEVEN 100UI/mL 10mL	1000	LFB	-

* Medicinal product registered abroad and imported under the provisions of DM 11/02/1997 (8) and DM 11/05/2001 (10).

Quantification of the demand

In 2018, the demand for FXI was 33,000 IUs (0.5 IU per 1,000 population) (Table 66) mainly in the Friuli-Venezia Giulia Region (17,000 IUs and 14 IUs *per capita*). No demand was observed in the majority of Italian Regions.

Table 66. Total demand (public and private) and total standardised demand for coagulation factor XI expressed in International Units and International Units per 1,000 population, 2018 (adapted by the CNS on data from the Product Quality and Pharmacrime Office-AIFA)

Region	2018	
	IU	IU per 1,000 pop
Abruzzo	-	-
Aosta Valley	-	-
AP Bolzano	-	-
AP Trento	-	-
Apulia	5,000	1.2
Basilicata	-	-
Calabria	-	-
Campania	-	-
Emilia-Romagna	-	-
Friuli-Venezia Giulia	17,000	14.0
Latium	-	-
Liguria	-	-
Lombardy	10,000	1.0
Marche	-	-
Molise	-	-
Piedmont	1,000	0.2
Sardinia	-	-
Sicily	-	-
Tuscany	-	-
Umbria	-	-
Veneto	-	-
ITALY	33,000	0.5

COAGULATION FACTOR XIII (ATC B02BD07)

Plasma-derived coagulation Factor XIII (FXIIIpd), also called fibrin stabilising factor, plasma protransglutaminase or Laki-Lorand factor, plays a fundamental role in coagulation processes and is used in the replacement therapy for congenital FXIII deficiency, an autosomal-recessive disorder, whose prevalence is estimated at around 1/2,000,000 (44).

Depending on the level of FXIII activity, severe forms (FXIII<1%), moderate (between 1 and 4%) and mild (FXIII>5%) are distinguished. Where products containing FXIIIpd are not available, fresh frozen plasma is used as an alternative (44).

Since 2014, products obtained with recombinant genetic techniques (rFXIII) have been available (45,46). However, only since 2016 has their utilization been recorded and then only in certain Regions.

Table 67 and Table 68 show the brand names of drugs containing FXIIIpd and rFXIII, respectively, currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 67. Products containing plasma-derived coagulation factor XIII distributed in ITALY (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
024644015*	FIBROGAMMIN 1FL 250UI	250	CSL BEHRING GmbH	H
042605016	CLUVIAT FL 250UI	250	CSL BEHRING GmbH	H
024644027*	FIBROGAMMIN 1FL 1250UI	1250	CSL BEHRING GmbH	H
042605028	CLUVIAT FL 1250UI	1250	CSL BEHRING GmbH	H

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Table 68. Products containing recombinant coagulation factor XIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
043034014	NOVOTHIRTEEN*EV FL 2500UI	2500	NOVO NORDISK SpA	H

Quantification of the demand

In 2018, the total demand for FXIII was 727,000 IUs (12 IUs per 1,000 population) and less than half, equal to 307,000 IUs (5.1 IUs per 1,000 population), was for pdFXIII. The latter recorded an increase of 7.3% compared to 2017 (Table 69).

In 2018, there was no utilisation of FXIII in some Regions. In Abruzzo, Basilicata and Calabria, only rFXIII was used (Table 70).

Table 69. Total demand (public and private) and total standardised demand for plasma-derived coagulation factor XIII expressed in International Units and International Units per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow and the Product Quality and Pharmacrime Office-AIFA)

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	9,000	16.7	9,000	16.7	-0.2
Apulia	-	-	9,750	2.4	NA
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	97,250	21.9	106,750	24.0	9.7
Friuli-V. Giulia	-	-	-	-	NA
Latium	51,750	8.8	46,250	7.8	-10.6
Liguria	750	0.5	2,000	1.3	168.1
Lombardy	37,500	3.7	48,750	4.9	29.8
Marche	5,250	3.4	15,250	10.0	191.7
Molise	-	-	-	-	NA
Piedmont	18,750	4.3	15,750	3.6	-15.7
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	18,500	4.9	-	-	-100.0
Umbria	-	-	-	-	NA
Veneto	47,750	9.7	53,500	10.9	12.1
ITALY	286,500	4.7	307,000	5.1	7.3

Table 70. Total demand (public and private) and total standardised demand for recombinant coagulation factor XIII expressed in International Units and International Units per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow and the Product Quality and Pharmacrime office, AIFA)

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	65,000	49.2	65,000	49.4	0.5
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	37,500	65.7	40,000	70.5	7.3
Calabria	107,500	54.7	122,500	62.6	14.4
Campania	-	-	-	-	NA
E.-Romagna	-	-	-	-	NA
Friuli-V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	45,000	28.7	40,000	25.7	-10.6
Lombardy	62,500	6.2	65,000	6.5	3.8
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	45,000	10.2	70,000	16.0	56.1
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	15,000	3.1	17,500	3.6	16.7
ITALY	377,500	6.2	420,000	6.9	11.5

PROTEIN C (ATC B01AD12)

Protein C is one of the most important factors of the anticoagulant system along with AT and protein S. It is a vitamin K-dependent serine-protease produced by the liver, which is indicated in purpura fulminans and in patients with severe congenital deficiencies. The mean concentration of protein C in plasma is approximately 3-5 µg / mL (47). Table 71 shows the brand names of drugs containing protein C currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 71. Products containing protein C currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	IU	Manufacturer	NHS class
035389016	CEPROTIN*IV 500UI	500	BAXTER SpA	H
035389028	CEPROTIN*IV 1000UI	1000	BAXTER SpA	H

Quantification of the demand

In 2018, the national demand for protein C stood at a volume of 848,500 IUs (14 IUs per 1,000 population) with a slight increase compared to 2017 (+6%) (Table 72).

Table 72. Total demand (public and private) and total standardised demand for protein C, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	16,500	12.5	-	-	-100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	3,000	5.7	-	-	-100.0
AP Trento	-	-	-	-	NA
Apulia	36,000	8.9	35,000	8.6	-2.4
Basilicata	-	-	-	-	NA
Calabria	22,000	11.2	62,500	31.9	185.3
Campania	250,000	42.8	163,500	28.1	-34.5
E.-Romagna	14,000	3.1	-	-	-100.0
Friuli-V. Giulia	-	-	-	-	NA
Latium	70,000	11.9	161,000	27.3	130.1
Liguria	24,000	15.3	39,500	25.4	65.5
Lombardy	149,000	14.9	240,000	23.9	60.8
Marche	-	-	28,000	18.3	NA
Molise	-	-	-	-	NA
Piedmont	66,000	15.0	2,500	0.6	-96.2
Sardinia	-	-	14,500	8.8	NA
Sicily	87,500	17.3	64,000	12.7	-26.4
Tuscany	5,000	1.3	-	-	-100.0
Umbria	4,000	4.5	30,000	33.9	653.6
Veneto	53,000	10.8	8,000	1.6	-84.9
ITALY	800,000	13.2	848,500	14.0	6.2

The maximum regional demand was in Umbria, Calabria and Campania, with 34, 32 and 28 IUs per 1,000 population respectively. The minimum regional demand was in Piedimont, Veneto, Apulia and Sardinia, with volumes between 0.6 and 8.8 IUs per 1,000 population.

OTHER PLASMA PROTEIN FRACTIONS (ATC B05AA02)

Other plasma protein fractions include products with different compositions and therapeutic indications and include solvent/detergent-treated plasma (*Plasmasafe*TM, *Plasmagrade*TM and *Octaplas*TM) and products with an albumin content of between 85 and 90% (*Umanserum*TM).

Solvent/detergent-treated plasma is a product obtained from a pool of hundreds of donors of the same blood group and has the following characteristics:

- high lot-to-lot standardisation;
- declaration of the concentration/activity of biologically active proteins;
- reduction of immunological risks due to the presence of antibodies, cells (or their fragments);
- inactivation of potentially transmissible pathogens.

Solvent/detergent-treated plasma has the same therapeutic indications as fresh frozen plasma.

Table 73 shows the brand names of the drugs containing other plasma protein fractions currently available on the Italian market and the amount of active ingredient they contain expressed in millilitres (mL).

Table 73. Products containing other plasma protein fractions currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2018)

AIC code	Brand name	mL	Manufacturer	NHS class
033369012	PLASMASAFE*INFUS SACCA 200ML	200	KEDRION SpA	H
034540017	OCTAPLAS*INFUS SACCA 200ML	200	OCTAPHARMA PHARM.	H
041868011	PLASMAGRADE*INFUS SACCA 200ML	200	KEDRION SpA	H
021112040	UMANSERUM*INFUS 250ML 5%	250	KEDRION SpA	C

Quantification of the demand

As regards the different composition and different clinical use, the demands of these two sub-groups of medicinal products have been quantified distinctly.

Table 74 shows the utilisation of *Plasmasafe*TM and *Octaplas*TM, while Table 75 shows the data related to *Umanserum*TM, the demand for which, in 2018, recorded an increase of 11% compared to 2017, and a total volume of 7,060,250 mL.

The national demand for solvent/detergent-treated plasma in 2018 increased by 3.9% compared to 2017, with a regional upward trend in Apulia (8%), Campania (28.2%), E.-Romagna (121%), Liguria (3.1%), Molise (1.8%), Piedmont (8%) and Tuscany (25.7%).

Table 74. Total demand (public and private) and total standardised demand for solvent/detergent-treated plasma (excluding Umanserum™), expressed in millilitres and millilitres per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	172,000	130.1	16,000	12.2	-90.6
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	10,000	18.5	NA
Apulia	3,250,000	799.7	3,495,000	863.3	8.0
Basilicata	754,000	1,322.0	630,000	1110.9	-16.0
Calabria	1,004,000	510.9	894,000	456.9	-10.6
Campania	4,389,200	751.7	5,616,000	963.8	28.2
E.-Romagna	280,000	62.9	619,400	139.1	121.0
Friuli-V. Giulia	-	-	12,000	9.9	NA
Latium	4,488,000	760.9	4,507,800	735.6	-3.3
Liguria	650,000	415.3	666,800	428.3	3.1
Lombardy	608,000	60.7	504,000	50.2	-17.2
Marche	1,913,000	1,243.8	1,592,000	1039.3	-16.4
Molise	384,000	1,236.9	388,400	1259.0	1.8
Piedmont	4,152,000	945.2	4,468,000	1021.1	8.0
Sardinia	14,000	8.5	8,000	4.9	-42.7
Sicily	4,401,800	870.5	4,325,800	860.5	-1.1
Tuscany	1,724,000	460.7	2,164,400	579.2	25.7
Umbria	-	-	4,000	4.5	NA
Veneto	3,952,000	805.3	3,571,800	728.2	-9.6
ITALY	32,136,000	530.4	33,493,400	550.9	3.9

Table 75. Total demand (public and private) and total standardised demand for Umanserum™ expressed in millilitres and millilitres per 1,000 population, and variations in percentage between 2017 and 2018 (adapted by the CNS on data from the traceability information flow)

Region	2017		2018		% Var 2017-2018
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	3,136,250	771.7	3,953,750	976.7	26.6
Basilicata	-	-	86,250	152.1	NA
Calabria	293,750	149.5	222,500	113.7	-23.9
Campania	-	-	-	-	NA
E.-Romagna	-	-	-	-	NA
Friuli-V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	-	-	-	-	NA
Lombardy	-	-	-	-	NA
Marche	-	-	-	-	NA
Molise	2,500	8.1	-	-	-100.0
Piedmont	-	-	87,500	20.0	NA
Sardinia	-	-	-	-	NA
Sicily	2,936,250	580.7	2,705,250	538.1	-7.3
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	-	-	5,000	1.0	NA
ITALY	6,368,750	105.1	7,060,250	116.7	11.1

PART C
**National self-sufficiency in toll-fractionated plasma
derived medicinal products**

SELF-SUFFICIENCY

According to Italian legislation, the term PDMP self-sufficiency refers to the capacity of regional health systems (through agreements signed by several or by single Regions) to satisfy their needs for PDMPs. This is achieved by utilising products obtained from the processing of plasma collected by BEs and sent to companies to be toll fractionated, which also reduces the quantity of PDMPs supplied via the pharmaceutical market. However, PDMP self-sufficiency must take into account the levels of appropriateness of clinical use and the management of available resources.

Self-sufficiency in PDMPs and blood components was one of the objectives of Law 219/2005:

- aimed at guaranteeing the same quality and safety as regards transfusion therapy to all citizens. It is a supra-regional supra-industrial non-divisible national interest for which the Regions and the Health Authorities have to compete through public tenders;
- to this end, the law establishes some principles of regional health planning (Art. 11) and entrusts all coordination activities to the CNS (Art. 12). It also recognizes the annual programme of national self-sufficiency (Art. 14);
- as the instrument to determine every aspect of national self-sufficiency, such as historical consumption, real needs, production levels required, resources, the criteria for financing the system, the methods of compensation between the Regions and the levels of import and export if necessary.

Furthermore, Article 26 of the Legislative Decree of 20 December 2007, n. 261 (48) provides for the definition of a programme by the MoH through a special decree. The objective of said decree is to develop the collection of plasma in BEs and BCUs, and promote the rational and appropriate use of PDMPs while, with the DM of 2 December 2016, the first national plasma and PDMP programme for the five-year period 2016-2020 was published (49).

Toll fractionation system

The plasma collected in Italy comes from voluntary, periodic, responsible, anonymous and non-remunerated donations. The Regions, individually or in association, send the plasma collected by the BEs, belonging to their territory, to the authorised and affiliated company for it to be industrially transformed into PDMPs. The contract with companies, which operate as service providers, is considered a “toll fractionation process” and constitutes a contract agreement for the production of PDMPs. The acquisition of toll fractionation processes is carried out through a tender procedure in compliance with current legislation. For this purpose, during 2015 and 2016, in addition to the Lombardy-Piedmont-Sardinia Agreement (LPS) which had already been implemented, three new inter-regional agreements were signed:

- the New Interregional Agreement for Plasma-Derived Medicinal Products (Nuovo Accordo Interregionale per la Plasmaderivazione, NAIP), which includes Abruzzo, Basilicata, Friuli-Venezia Giulia, Liguria, the AP of Bolzano, the AP of Trento, Umbria, Veneto (Leading Region), and Aosta Valley;
- the Plasma/Plasma-Derived Interregional Grouping (Raggruppamento Interregionale Plasma e Plasmaderivati, RIPP) to which Calabria, Emilia-Romagna (Leading Region), Apulia and Sicily belong;

- the Plasma Network (PlaNet) which includes Campania, Latium (including the General Inspectorate of Military Health), Marche, Molise and Tuscany (Leading Region).

Under the terms of this type of agreement, as set down in the DM of 12 April 2012 (50), the production of PDMPs is defined by a quali-quantitative production plan. The company in question agrees to produce the quantity and to guarantee the quality of the PDMPs requested by the Regions respecting both the scheduled times and specified procedures; the contracting Regions, in turn, undertake to make the necessary plasma available according to agreed quantities and quality specifications. The Regions have the right to full ownership of the plasma sent for industrial processing, of all the pharmaceutical specialties derived from it, as well as of the residual material. Consequently, the supplier of the industrial processing service cannot use the plasma, the intermediate fractions or the finished products nor the residual raw material for purposes other than those provided for under the agreement, without a prior agreement with the Regions. For the purposes of the tender notice, the abovementioned DM affirms that the production of at least human albumin, FVIII and IV IGs has to be considered. In other words, these three PDMPs must be included in the company's offer while all the other PDMPs are to be considered as optional.

Pursuant to the DM of 5 December 2014, the only companies authorized to fractionate national plasma are Baxter Manufacturing, Csl Behring SpA, Grifols Italia, Kedrion, Octapharma Italy (51).

In 2016, the tender for the supply of toll fractionation services for the NAIP Regions was won by CSL Behring S.p.A. The contract provided for the supply of albumin, IV IGs, SC/IM IGs, pdFVIII, FVIII / vWF in combination and fibrinogen. Even if the plasma started to be sent to CSL for fractionation in May 2017, no products were returned to NAIP Regions before 2018.

The agreements with the toll fractionation company Kedrion remained in place for all the other Regions. The contracts were for the production of albumin, IV IGs, pdFVIII, pdFIX, 3F-PCCs, AT and solvent detergent virus-inactivated plasma.

Plasma for fractionation

From 2000 to 2018, the quantity of plasma collected on a national scale (Figure 37) steadily increased, from a total of 462,805 kilograms sent to the fractionation industry in 2000 to 844,498 kilograms in 2018, with an increase of 82% in the period under examination.

The mean annual rate of change over the period considered was 3.4% with two peak growth periods - between 2004-2006 and 2008-2010. From the year 2008 there was a steady decline in the annual rate of change (Figure 38) which, in 2014, reached the lowest value for the entire period considered (-1.1%). The variation in percentage between 2017 and 2018 was 1.1%.

The amount of plasma sent for industrial fractionation by the individual Regions, however, varied greatly in both quantitative and qualitative terms. In 2018, the Regions participating in the LPS agreement collected about one third of the plasma sent for fractionation for a total of 245,898 kilograms (21.1 %). The NAIP Regions sent 196,231 (23.2%) kilograms of plasma to CSL Behring for fractionation, while 215,212 (25.5%) and 187,157 (22.2%) kilograms were respectively sent by RIPP and Planet Regions to Kedrion, pending the launch of the new tenders for the assignment of the plasma toll-fractionation service (Figure 38). As regards the amount of plasma sent for fractionation in 2018, for the resident population, the NAIP Regions sent 16.9 kilograms per 1,000 population (almost comparable to the 2017 volume for the same Regions), the LPS Regions 15.3 kilograms, the RIPP Regions 13.9 kilograms and the Planet Regions 10.8 kilograms per 1,000 population (Figure 40).

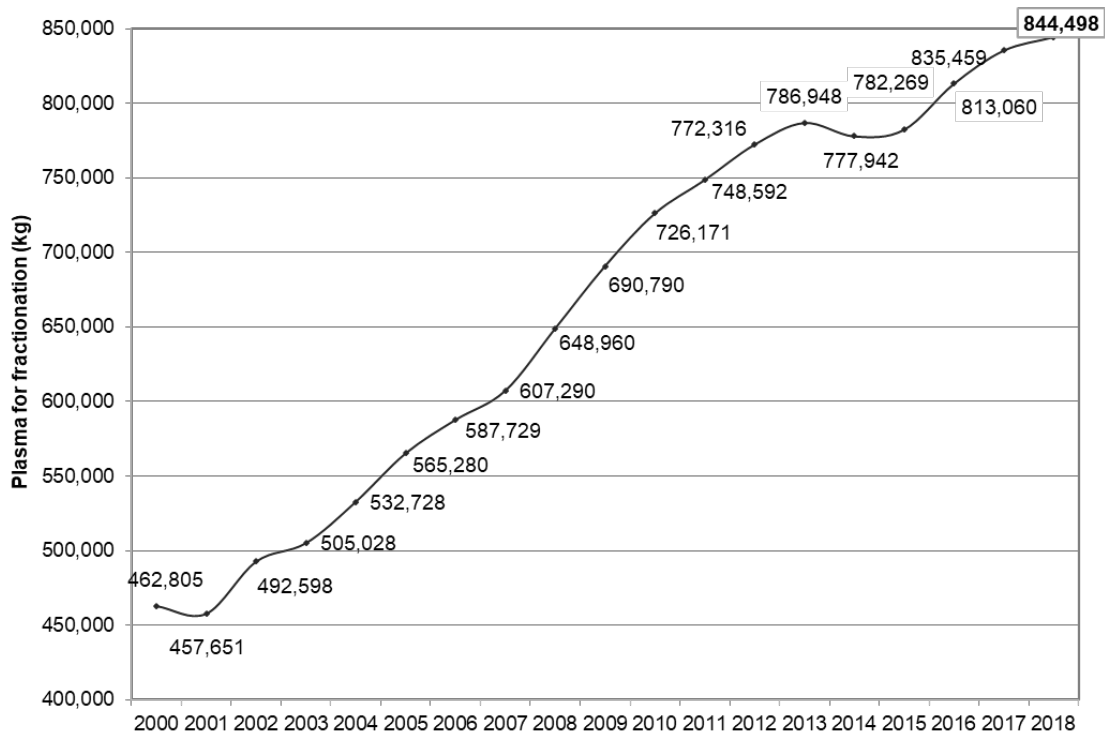


Figure 37. Plasma sent for fractionation 2000-2018
(adapted by the CNS on Kedrion and CSL Behring data, December 2019)

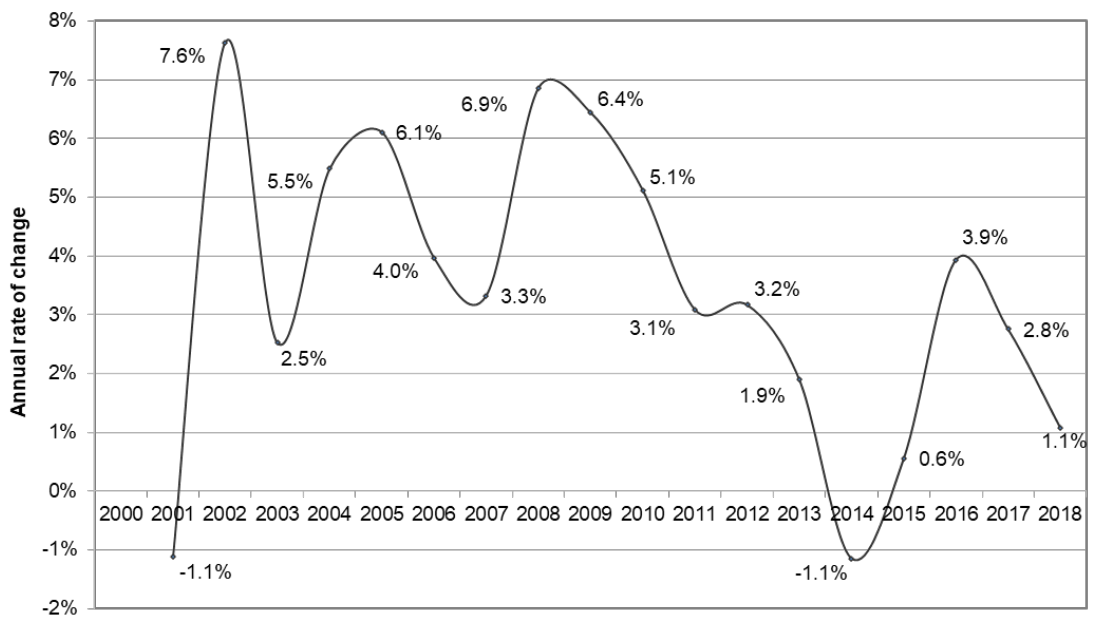


Figure 38. Annual rate of change in the amount of plasma for fractionation, from 2001 to 2018
(adapted by the CNS on Kedrion and CSL Behring data, December 2019)

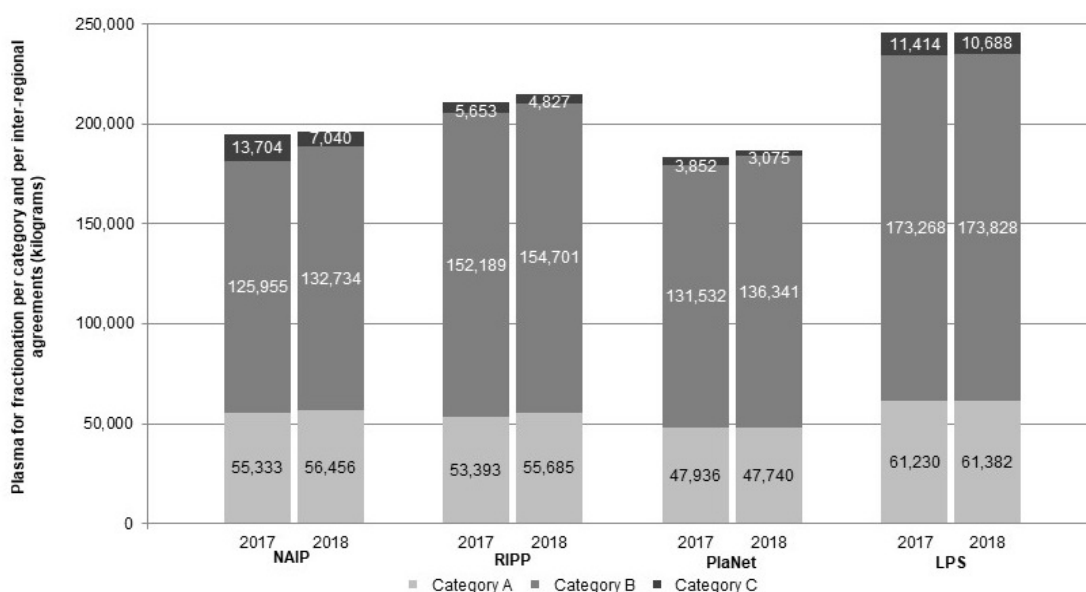


Figure 39. Total amount of plasma for fractionation by category under interregional agreements (kilograms), 2017-2018 (adapted by the CNS on data provided by Kedrion and CSL Behring, December 2019)

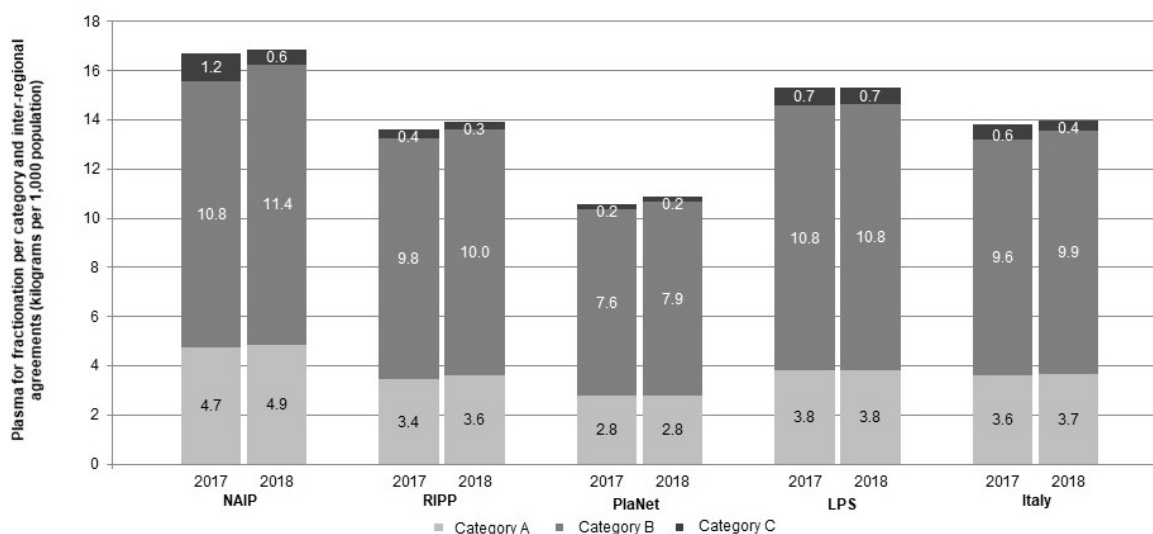


Figure 40. Total amount of plasma for fractionation by category under interregional agreements (kilograms per 1,000 population), 2017-2018 (adapted by the CNS on data provided by Kedrion and CSL Behring, December 2019)

In 2018, although the national volume stood at 14 kilograms per thousand population, the volumes of each single Region differed greatly. In fact, the best performance was achieved by Marche with 23.2 kilograms per 1,000 population, Friuli-Venezia Giulia with 22.2 and Emilia-Romagna with 19.9, while the lowest volumes were recorded in Calabria, Latium and Campania with 8.8, 7.5 and 5.5 kilograms per thousand population, respectively (Figure 41).

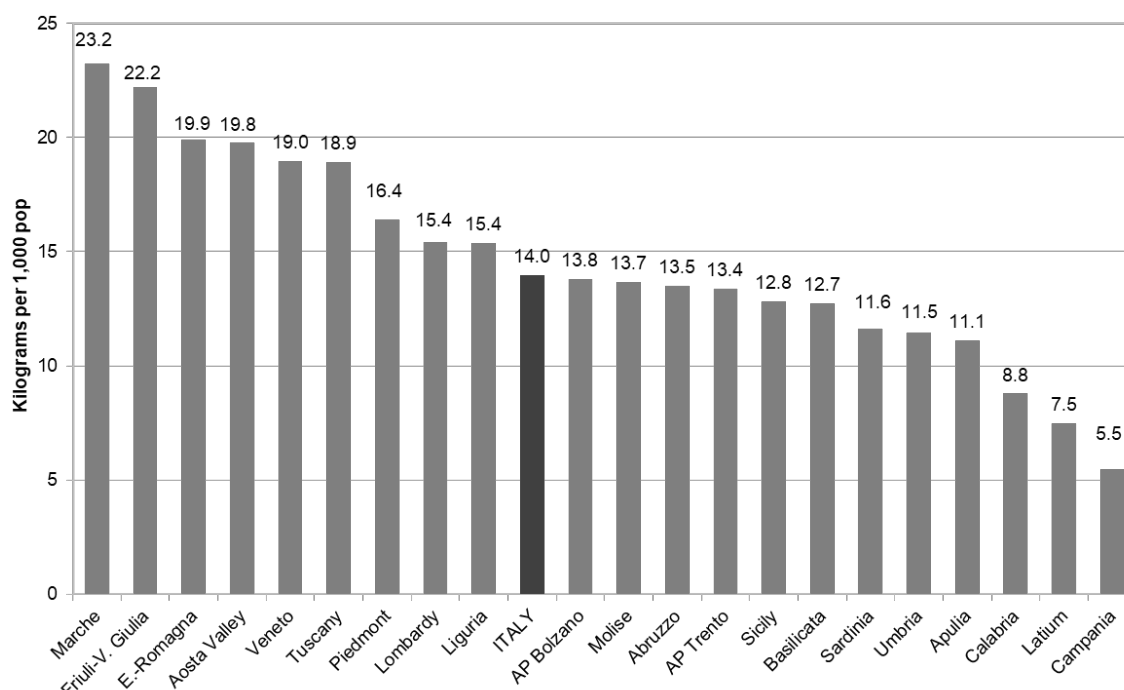


Figure 41. Total amount of plasma (kilograms per 1,000 population) for fractionation by Region, year 2018
(adapted by the CNS on data provided by Kedrion and CSL Behring, December 2019)

Supply of PDMPs from toll fractionation

In 2018, the total quantity of plasma sent for fractionation by the Italian Regions was 844,498 kilograms (Table 76); of these, 26.2% (221,263 kilograms) was apheresis plasma (category A), 70.1 % (597,604 kilograms) recovered plasma (category B) and the remaining 3% (25,631 kilograms) plasma intended solely for the recovery of non-labile proteins (category C). The percentages of all three categories of plasma sent for fractionation varied from one regional area to another and from one consortium to another. In particular, the percentages of apheresis plasma (category A) for fractionation varied from 25.0% sent by the LPS consortium to 28.8 sent by NAIP, while the percentage of plasma intended solely for the recovery of non-labile proteins (category C) varied from 1.6% sent by PlaNet to 4.3% sent by the LPS consortium. Table 77 shows the amount of PDMPs potentially obtainable from the industrial manufacturing of the total amount of plasma sent for fractionation in 2018 (from July 2017 to June 2018). These figures show the quantities, expressed in grams and IUs, of medicinal products the fractionators potentially guaranteed the consortia (potential supply or production capacity) determined from the industrial yields and contractual agreements.

Additional quantities of plasma, around 18,000 kilograms, as shown in Table 78, were sent to Kedrion for the production of plasma solvent/detergent-treated plasma, outside the scope of the previous mentioned regional agreements.

Table 79 provides the quantities of PDMPs distributed to the individual Regions in 2018 in accordance with the specified production and distribution programmes (effective supply or toll fractionation).

Table 76. Total quantity, expressed in kilograms, quantity per 1,000 population and variation in percentage for the years 2017-2018 classified by Region and plasma category (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	A	%	B	%	C	%	Tot. Fract.	Total per 1,000 pop
Abruzzo	5,087	5.6	12,520	-0.3	173	33.3	17,780	13.5
Aosta Valley	965	13.8	1,534	0.8	0	0.0	2,498	19.8
AP Bolzano	1,242	4.1	6,046	3.0	0	0.0	7,288	13.8
AP Trento	607	-12.1	6,623	0.0	0	0.0	7,229	13.4
Basilicata	1,682	6.7	4,746	6.0	798	-6.7	7,227	12.7
Friuli-V. Giulia	12,029	6.0	14,878	-2.4	69	-82.3	26,976	22.2
Liguria	5,874	12.4	18,070	2.9	24	-43.2	23,967	15.4
Umbria	1,328	38.9	8,817	-0.9	0	0.0	10,145	11.5
Veneto	27,642	-3.6	59,500	11.8	5,977	-51.4	93,120	19.0
NAIP	56,456	2.0	132,734	5.4	7,040	-48.6	196,231	16.9
Apulia	5,816	12.8	37,121	4.2	2,117	-18.8	45,054	11.1
Calabria	829	17.4	16,353	-4.7	15	-50.7	17,197	8.8
Emilia-Romagna	33,929	1.0	52,075	-1.4	2,586	-12.1	88,590	19.9
Sicily	15,110	8.3	49,152	5.5	109	48.1	64,371	12.8
RIPP	55,685	4.3	154,701	1.7	4,827	-14.6	215,212	13.9
Campania	364	141.8	30,273	2.5	1,317	-37.0	31,955	5.5
Latium	4,318	2.8	38,298	9.7	1,599	7.0	44,214	7.5
Marche	13,917	5.3	21,686	5.7	-	-	35,603	23.2
Molise	749	-38.7	3,468	-16.3	-	-	4,217	13.7
Tuscany	28,393	-2.6	42,385	0.2	-	-	70,778	18.9
Ministry of Defence	-	-	230	73.1	159	-39.8	390	-
PlaNet	47,740	-0.4	136,341	3.7	3,075	-20.2	187,157	10.8
Lombardy	41,598	1.1	108,033	0.4	5,283	-2.9	154,914	15.4
Piedmont	18,993	-1.6	50,218	-0.3	2,646	-12.1	71,857	16.5
Sardinia	791	-0.2	15,576	1.9	2,759	-6.9	19,127	11.5
LPS	61,382	0.2	173,828	0.3	10,688	-6.4	245,898	15.3
ITALY	221,263	1.5	597,604	2.5	25,631	-26.0	844,498	14.0

Table 77. Potential supply of toll fractionated PDMPs based on the amount of plasma sent for fractionation from July 2017 to June 2018 and the yields provided by the fractionation industry – Year 2018 (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	2 nd semester 2017		1 st semester 2018		TOTAL	Albumin	Human Immunoglobulin	Factor VIII		Factor VIII / vW Factor		FIX / 3F-PCC		Antithrombin		Fibrinogen
	kg	kg	kg	kg				g	g	IU	IU	IU	IU	IU	IU	
Abruzzo	8,628	8,929	17,557	438,920	86,028	1,745,523	548,593	-	-	-	-	-	-	-	-	768
Aosta Valley	1,207	1,284	2,492	62,292	12,209	247,727	77,857	-	-	-	-	-	-	-	-	109
AP Bolzano	3,535	3,465	6,999	174,983	34,297	695,883	218,706	-	-	-	-	-	-	-	-	306
AP Trento	3,659	3,406	7,065	176,613	34,616	702,364	220,743	-	-	-	-	-	-	-	-	309
Basilicata	3,458	3,743	7,200	180,007	35,281	715,863	224,986	-	-	-	-	-	-	-	-	315
Friuli-V. Giulia	13,502	12,935	26,438	660,938	129,544	2,628,462	826,088	-	-	-	-	-	-	-	-	1,157
Liguria	11,461	11,972	23,433	585,830	114,823	2,329,765	732,212	-	-	-	-	-	-	-	-	1,025
Umbria	4,637	4,988	9,626	240,641	47,166	956,995	300,770	-	-	-	-	-	-	-	-	421
Veneto	46,591	45,188	91,779	2,294,481	449,718	9,124,837	2,867,806	-	-	-	-	-	-	-	-	4,015
NAIP	96,678	95,911	192,588	4,814,703	943,682	19,147,419	6,017,761	-	-	-	-	-	-	-	-	8,425
Apulia	22,558	22,667	45,225	1,166,803	171,855	5,584,018	-	-	-	6,602,837	-	-	6,195,813	-	-	-
Calabria	9,069	8,532	17,601	454,097	66,882	2,282,300	-	-	-	2,569,694	-	-	2,411,288	-	-	-
Emilia-Romagna	43,832	44,438	88,270	2,277,372	335,427	11,137,381	-	-	-	12,887,454	-	-	12,093,022	-	-	-
Sicily	31,093	31,181	62,274	1,606,668	236,641	8,082,194	-	-	-	9,091,998	-	-	8,531,532	-	-	-
RIPP	106,553	106,817	213,370	5,504,940	810,805	27,085,893	-	-	-	31,151,983	-	-	29,231,656	-	-	-
Campania	15,998	15,276	31,274	806,857	118,839	3,775,844	-	-	-	4,565,934	-	-	4,284,472	-	-	-
Lazio	20,157	22,141	42,298	1,091,289	160,732	5,319,567	-	-	-	6,175,511	-	-	5,794,828	-	-	-
Marche	16,929	18,289	35,219	908,641	133,831	4,578,423	-	-	-	5,141,922	-	-	4,824,954	-	-	-
Molise	2,800	2,212	5,012	129,312	19,046	651,572	-	-	-	731,766	-	-	686,657	-	-	-
Tuscany	34,827	35,780	70,608	1,821,684	268,310	9,179,026	-	-	-	10,308,752	-	-	9,673,281	-	-	-
Ministry of Defence	204	204	407	10,512	1,548	28,799	-	-	-	59,487	-	-	55,820	-	-	-
PlaNet	90,915	93,902	184,818	4,768,294	702,307	23,533,231	-	-	-	26,983,371	-	-	25,320,013	-	-	-
Lombardy	74,289	78,410	152,699	3,939,630	580,256	19,174,835	-	-	-	22,294,032	-	-	20,919,742	-	-	-
Piedmont	35,315	36,455	71,770	1,851,662	272,725	8,964,467	-	-	-	10,478,399	-	-	9,832,471	-	-	-
Sardinia	9,810	9,350	19,160	494,322	72,807	2,096,620	-	-	-	2,797,328	-	-	2,624,890	-	-	-
LPS	119,414	124,215	243,628	6,285,615	925,788	30,235,922	-	-	-	35,569,760	-	-	33,377,103	-	-	-
ITALY	413,559	420,845	834,404	21,373,552	3,382,582	100,002,464	6,017,761	93,705,114	87,928,771	8,425						

Table 78. Potential supply of solvent/detergent-treated plasma based on the amount of plasma sent for fractionation from July 2017 to June 2018 and the yields provided by the industry – Year 2018 (adapted by the CNS on data provided by Kedrion)

Region	2nd semester 2016		1st semester 2017		TOTAL	Solvent/detergent-treated plasma mL
	kg	kg	kg	kg		
Abruzzo	-	-	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Apulia	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-
Calabria	-	-	-	-	-	-
Campania	3,263.2	-	3,247.4	-	6,511	5,996,241
E.-Romagna	-	-	-	-	-	-
Friuli-V. Giulia	1,414.5	-	1,353.4	-	2,768	2,549,207
Lazio	-	-	-	-	-	-
Liguria	-	-	-	-	-	-
Lombardy	-	-	-	-	-	-
Marche	1,188.0	-	1,167.0	-	2,355	2,168,885
Molise	-	-	101.9	-	102	93,886
Piedmont	2,004.5	-	2,449.2	-	4,454	4,101,911
Sardinia	-	-	-	-	-	-
Sicily	665.7	-	1,011.3	-	1,677	1,544,590
Tuscany	-	-	-	-	-	-
Umbria	-	-	-	-	-	-
Veneto	-	-	-	-	-	-
Ministry of Defence	-	-	-	-	-	-
ITALY	8,535.9	-	9,330.2	-	17,867	16,454,720

Table 79. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs classified by region for the year 2018)
(adapted by theCNS on data provided by Kedrion)

Region	Albumin g	IVIg g	SC/Ig g	Factor VIII IU	Factor VIII / vW Factor IU	Factor IX IU	3-factor prothrombin complex IU	Antithrombin IU	Fibrinogen g	Solvent/detergent- treated plasma mL
Abruzzo	430,030	62,515	3,040	43,000	50,000	35,000	431,500	2,433,000	450	-
Aosta Valley	80,000	16,900	1,020	-	3,000	-	96,000	363,000	-	-
AP Bolzano	130,000	27,740	800	330,000	610,000	-	592,000	250,000	-	-
AP Trento	165,000	30,615	1,000	13,000	40,000	-	451,500	200,000	180	-
Basilicata	240,000	21,825	640	55,000	10,000	30,000	190,000	1,376,000	140	-
Friuli-V. Giulia	458,500	122,003	4,000	911,000	100,000	316,000	1,097,500	3,253,000	430	-
Liguria	600,000	91,300	2,720	864,000	410,000	-	1,371,000	2,272,000	210	82,000
Umbria	478,170	57,380	5,840	534,000	110,000	-	555,000	534,000	470	-
Veneto	2,101,800	397,800	14,620	9,151,000	1,040,000	1,175,000	4,085,500	6,021,000	558	3,507,800
NAIP	4,683,500	828,078	33,680	11,901,000	2,373,000	1,556,000	8,870,000	16,702,000	2,438	3,589,800
Apulia	1,228,500	134,440	-	4,706,000	-	489,000	1,409,000	5,919,000	-	2,209,000
Calabria	585,300	61,285	480	777,000	-	78,000	467,000	6,532,000	-	-
E.-Romagna	2,115,290	320,100	-	2,053,000	-	757,000	4,157,500	2,427,000	-	-
Sicily	2,234,000	238,820	-	811,000	-	114,000	3,177,000	15,900,000	-	1,585,800
RIPP	6,163,090	754,645	480	8,347,000	0	1,438,000	9,210,500	30,778,000	0	3,794,800
Campania	1,119,160	111,050	3,104	5,128,000	-	-	1,762,500	4,584,000	-	4,880,000
Lazio	982,820	151,625	-	8,765,000	-	34,000	1,575,000	6,956,000	-	2,968,600
Marche	626,400	173,670	-	1,835,000	-	640,000	739,500	2,653,000	-	1,592,000
Molise	93,000	9,770	-	608,000	-	-	244,000	1,163,000	-	388,400
Tuscany	1,353,160	259,948	-	4,317,000	-	869,000	3,302,000	6,374,000	-	-
PlaNet	4,174,540	706,063	3,104	20,653,000	0	1,543,000	7,623,000	21,730,000	0	9,829,000
Lombardy	3,867,200	547,500	480	13,672,000	-	359,000	5,059,000	4,099,000	-	504,000
Piedmont	1,197,000	337,780	-	11,613,000	-	845,000	2,673,500	6,110,000	-	4,468,000
Sardinia	998,850	76,625	-	2,738,000	-	-	1,100,000	1,486,000	-	-
LPS	6,063,050	961,905	480	28,023,000	0	1,204,000	8,832,500	11,695,000	0	4,972,000
ITALY	21,084,180	3,250,690	37,744	68,924,000	2,373,000	5,741,000	34,536,000	80,905,000	2,438	22,185,600

ANALYSIS OF SELF-SUFFICIENCY

Albumin

In 2018, the Italian NHS demand for albumin accounted for 83% of the total. The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, was 73% (- 1% compared to 2017) while the effective self-sufficiency, considered as the ratio of the actual supply of toll fractionation to NHS demand, was 72% (+ 2% compared to 2017) (Table 80).

Table 80. Estimates of regional and national self-sufficiency in albumin, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	830,828	746,098	438,920	430,030	59	58
Aosta Valley	81,970	81,740	62,292	80,000	76	98
AP Bolzano	179,885	178,775	174,983	130,000	98	73
AP Trento	181,903	171,948	176,613	165,000	103	96
Basilicata	356,763	352,973	180,007	240,000	51	68
Friuli-V. Giulia	465,298	463,730	660,938	458,500	143	99
Liguria	667,428	644,195	585,830	600,000	91	93
Umbria	485,428	483,903	240,641	478,170	50	99
Veneto	2,314,323	2,152,895	2,294,481	2,101,800	107	98
NAIP	5,563,823	5,276,255	4,814,703	4,683,500	91	89
Apulia	2,117,368	1,742,120	1,166,803	1,228,500	67	71
Calabria	1,088,155	985,720	454,097	585,300	46	59
E.-Romagna	2,546,528	2,297,078	2,277,372	2,115,290	99	92
Sicily	3,340,583	2,797,470	1,606,668	2,234,000	57	80
RIPP	9,092,633	7,822,388	5,504,940	6,163,090	70	79
Campania	5,084,775	4,673,925	806,857	1,119,160	17	24
Latium	3,227,708	1,821,063	1,091,289	982,820	60	54
Marche	743,548	635,935	908,641	626,400	143	99
Molise	225,550	112,090	129,312	93,000	115	83
Tuscany	1,710,363	1,573,465	1,821,684	1,353,160	116	86
Min. of Def.	-	-	10,512	-	NA	NA
PlaNet	10,991,943	8,816,478	4,768,294	4,174,540	54	47
Lombardy	6,363,728	4,480,508	3,939,630	3,867,200	88	86
Piedmont	1,502,955	1,305,310	1,851,662	1,197,000	142	92
Sardinia	1,428,023	1,390,153	494,322	998,850	36	72
LPS	9,294,705	7,175,970	6,285,615	6,063,050	88	84
ITALY	34,943,103	29,091,090	21,373,552	21,084,180	73	72

The Regions that in 2018 achieved effective self-sufficiency – more than 90% – were Aosta Valley, AP of Trento, Friuli-Venezia Giulia, Liguria, Umbria, Veneto, Emilia-Romagna, Marche, and Piedmont.

The Regions that mainly derived benefits from interregional compensation in 2018 were the NAIP Regions Umbria (99% effective self-sufficiency compared to the potential 50%) and Basilicata (68% compared to 51%), the LPS Region Sardinia (72% compared to 36%), and the RIPP Regions Calabria (effective self-sufficiency 59% compared to the potential 46%) and Sicily (effective self-sufficiency 80% compared to the potential 57%).

The Regions farthest from the objective of effective self-sufficiency were Campania, Latium and Abruzzo, with percentages ranging between 24 and 58% of the NHS demand satisfied by the toll fractionation supply.

Normal human immunoglobulins

In 2018, the NHS demand for normal IGs accounted for 93% of the total demand (Table 81).

Table 81. Estimates of regional and national self-sufficiency in human immunoglobulins, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	119,245	116,325	86,028	65,555	74	56
Aosta Valley	20,623	20,623	12,209	17,920	59	87
AP Bolzano	44,385	44,385	34,297	28,540	77	64
AP Trento	42,183	42,183	34,616	31,615	82	75
Basilicata	35,668	35,668	35,281	22,465	99	63
Friuli-V. Giulia	137,063	137,063	129,544	126,003	95	92
Liguria	203,291	202,531	114,823	94,020	57	46
Umbria	94,805	92,805	47,166	63,220	51	68
Veneto	508,498	502,900	449,718	412,420	89	82
NAIP	1,205,761	1,194,484	943,682	861,758	79	72
Apulia	451,209	417,764	171,855	134,440	41	32
Calabria	118,232	116,927	66,882	61,765	57	53
E.-Romagna	466,126	465,056	335,427	320,100	72	69
Sicily	335,524	327,154	236,641	238,820	72	73
RIPP	1,371,091	1,326,901	810,805	755,125	61	57
Campania	408,658	392,397	118,839	114,154	30	29
Latium	597,037	441,511	160,732	151,625	36	34
Marche	209,528	207,609	133,831	173,670	64	84
Molise	45,757	14,467	19,046	9,770	132	68
Tuscany	638,183	632,534	268,310	259,948	42	41
Min. of Def.	-	-	1,548	-	NA	NA
PlaNet	1,899,163	1,688,517	702,307	709,167	42	42
Lombardy	865,107	695,056	580,256	547,980	83	79
Piedmont	497,587	496,777	272,725	337,780	55	68
Sardinia	95,110	95,110	72,807	76,625	77	81
LPS	1,457,804	1,286,943	925,788	962,385	72	75
ITALY	5,933,819	5,496,845	3,382,582	3,288,434	62	60

The national potential self-sufficiency, expressed by the ratio of the potential supply to the NHS demand, in 2018 was 62%, where effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to NHS demand, was 60%.

The only Region to achieve effective self-sufficiency in IGs in 2018 – more than 90% – was Friuli-Venezia Giulia, while the Regions that achieved the lowest effective self-sufficiency were Apulia (32%), Latium (34%) and Calabria (53%). For the sake of clarity, it is worth underlining that the 2018 contract arrangements between RIPP, Planet and LPS Regions and Kedrion did not include the provision of SC/IM IGs although an experimental production of a few vials was distributed. Conversely, NAIP Regions, taking advantage of the supply of both SC/IM and IV IGs according to their contract with CSL Behring, could partially switch from the production of one IG formulation to another depending on their specific needs or strategies.

Normal human immunoglobulins for intravenous use

In 2018, the NHS demand for IV IGs accounted for 81% of the total demand (Table 82).

Table 82. Estimates of regional and national self-sufficiency in human immunoglobulin for intravenous use, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	89,549	86,629	86,028	62,515	99	72
Aosta Valley	18,679	18,679	12,209	16,900	65	90
AP Bolzano	41,645	41,645	34,297	27,740	82	67
AP Trento	38,890	38,890	34,616	30,615	89	79
Basilicata	25,985	25,985	35,281	21,825	136	84
Friuli-V. Giulia	127,833	127,833	129,544	122,003	101	95
Liguria	163,670	163,350	114,823	91,300	70	56
Umbria	64,360	62,360	47,166	57,380	76	92
Veneto	414,492	408,894	449,718	397,800	110	97
NAIP	985,103	974,265	943,682	828,078	97	85
Apulia	339,545	306,180	171,855	134,440	56	44
Calabria	85,262	84,617	66,882	61,285	79	72
E.-Romagna	372,038	371,108	335,427	320,100	90	86
Sicily	265,083	256,593	236,641	238,820	92	93
RIPP	1,061,929	1,018,499	810,805	754,645	80	74
Campania	319,145	306,020	118,839	111,050	39	36
Latium	435,434	281,514	160,732	151,625	57	54
Marche	185,835	183,940	133,831	173,670	73	94
Molise	41,060	9,770	19,046	9,770	195	100
Tuscany	507,076	501,426	268,310	259,948	54	52
Min. of Def.	-	-	1,548	-	NA	NA
PlaNet	1,488,549	1,282,670	702,307	706,063	55	55
Lombardy	760,831	621,032	580,256	547,500	93	88
Piedmont	416,243	415,513	272,725	337,780	66	81
Sardinia	88,890	88,890	72,807	76,625	82	86
LPS	1,265,964	1,125,435	925,788	961,905	82	85
ITALY	4,801,544	4,400,869	3,382,582	3,250,690	77	74

The national potential self-sufficiency, expressed by the ratio of the potential supply to NHS demand, in 2018 was 77%, the same as in 2017. Effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to NHS demand, was 74%, against 73% in 2017. The Regions that in 2018 achieved effective self-sufficiency (more than 90%) were Friuli-Venezia Giulia, Umbria, Veneto, Sicily, Marche and Molise. The effective self-sufficiency achieved by Campania, Apulia and Tuscany was less than 52%.

Antithrombin

NHS demand for AT compared to national total demand dropped from 94% in 2011 to 90% in 2018. Effective self-sufficiency recorded a value of 78% in 2018, significantly lower than the potential self-sufficiency (85%) (Table 83).

Table 83. Estimates of regional and national self-sufficiency in antithrombin, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	2,458,000	2,433,000	-	2,433,000	-	100
Aosta Valley	363,000	363,000	-	363,000	-	100
AP Bolzano	250,000	250,000	-	250,000	-	100
AP Trento	200,000	200,000	-	200,000	-	100
Basilicata	1,556,000	1,556,000	-	1,376,000	-	88
Friuli-V. G.	3,253,000	3,253,000	-	3,253,000	-	100
Liguria	2,374,000	2,347,000	-	2,272,000	-	97
Umbria	534,000	534,000	-	534,000	-	100
Veneto	6,046,500	6,021,000	-	6,021,000	-	100
NAIP	17,034,500	16,957,000	0	16,702,000	-	98
Apulia	6,907,000	6,152,500	6,195,813	5,919,000	101	96
Calabria	7,806,000	7,032,000	2,411,288	6,532,000	34	93
E.-Romagna	2,826,500	2,493,500	12,093,022	2,427,000	485	97
Sicily	17,713,000	16,590,000	8,531,532	15,900,000	51	96
RIPP	35,252,500	32,268,000	29,231,656	30,778,000	91	95
Campania	17,832,000	16,661,500	4,284,472	4,584,000	26	28
Latium	19,004,500	14,510,500	5,794,828	6,956,000	40	48
Marche	2,665,000	2,653,000	4,824,954	2,653,000	182	100
Molise	1,225,500	1,163,000	686,657	1,163,000	59	100
Tuscany	6,434,000	6,430,000	9,673,281	6,374,000	150	99
Min. of Def.	-	-	55,820	-	NA	NA
PlaNet	47,161,000	41,418,000	25,320,013	21,730,000	61	52
Lombardy	8,020,500	5,113,500	20,919,742	4,099,000	409	80
Piedmont	6,410,500	6,110,000	9,832,471	6,110,000	161	100
Sardinia	1,507,000	1,505,000	2,624,890	1,486,000	174	99
LPS	15,938,000	12,728,500	33,377,103	11,695,000	262	92
ITALY	115,386,000	103,371,500	87,928,771	80,905,000	85	78

Since AT is not included among the PDMPs provided under the CSL Behring toll fractionation contract, the potential supply for NAIP Regions was equal to zero. However, their NHS demand could be met by the existing stock of products provided within the scope of the previous agreement with Kedrion and by interregional compensation.

All the Regions achieved effective self-sufficiency of more than 90% of the total NHS demand in 2018, except for Basilicata, Campania, Latium and Lombardy. The Regions that mainly took advantage from interregional compensation in 2018 were Calabria (93% effective vs. 34% potential self-sufficiency), Sicily (96% effective vs. potential 51%), and Latium (48% effective vs. 40% potential self-sufficiency). The Regions farthest from the objective of effective self-sufficiency were Campania (28%) and Latium (48%).

Coagulation factor VIII

In 2018, under the contract arrangements in force, NAIP Regions could benefit from:

- the still existing stock of plasma-derived coagulation factor VIII provided within the scope of the previous agreement with Kedrion (Klott™);
- the potential supply of plasma-derived coagulation factor VIII produced by CSL Behring (Beriate™);
- the supply of plasma-derived coagulation factor VIII and von Willebrand factor in combination (Haemate P™);
- Interregional compensation.

All other Regions, within the framework of the contract with Kedrion, could have taken advantage of the supply and huge stock of plasma-derived coagulation factor VIII, Klott®.

In the analysis of demand and supply for pdFVIII, it should be taken into account that the choice of the pharmaceutical specialty for the treatment of haemophilia A is based on considerations matured within the therapeutic alliance between doctor and patient, which have to be safeguarded and may not even allow the prescribed medicine to be replaced with a medicine from the same class or ATC group. Therefore, in this report self-sufficiency is described by distinguishing pdFVIII from pdFVIII in combination with vWF.

Plasma-derived coagulation factor VIII

In 2018, all the Regions largely achieved effective self-sufficiency in pdFVIII (Table 84).

Table 84. Estimates of regional and national self-sufficiency in plasma-derived factor VIII, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	43,000	43,000	1,745,523	43,000	4,059	100
Aosta Valley	-	-	247,727	-	NA	NA
AP Bolzano	330,000	330,000	695,883	330,000	211	100
AP Trento	13,000	13,000	702,364	13,000	5,403	100
Basilicata	55,000	55,000	715,863	55,000	1,302	100
Friuli-V. G.	911,000	911,000	2,628,462	911,000	289	100
Liguria	864,000	864,000	2,329,765	864,000	270	100
Umbria	534,000	534,000	956,995	534,000	179	100
Veneto	9,151,000	9,151,000	9,124,837	9,151,000	100	100
NAIP	11,901,000	11,901,000	19,147,419	11,901,000	160	100

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Apulia	5,046,000	5,046,000	5,584,018	4,706,000	111	93
Calabria	777,000	777,000	2,282,300	777,000	294	100
E.-Romagna	2,053,000	2,053,000	11,137,381	2,053,000	542	100
Sicily	811,000	811,000	8,082,194	811,000	997	100
RIPP	8,687,000	8,687,000	27,085,893	8,347,000	312	96
Campania	5,130,000	5,130,000	3,775,844	5,128,000	74	100
Latium	8,765,000	8,765,000	5,319,567	8,765,000	61	100
Marche	1,835,000	1,835,000	4,578,423	1,835,000	250	100
Molise	608,000	608,000	651,572	608,000	107	100
Tuscany	4,317,000	4,317,000	9,179,026	4,317,000	213	100
Min. of Def.	-	-	28,799	-	NA	NA
PlaNet	20,655,000	20,655,000	23,533,231	20,653,000	114	100
Lombardy	14,212,000	14,212,000	19,174,835	13,672,000	135	96
Piedmont	11,613,000	11,613,000	8,964,467	11,613,000	77	100
Sardinia	2,738,000	2,738,000	2,096,620	2,738,000	77	100
LPS	28,563,000	28,563,000	30,235,922	28,023,000	106	98
ITALY	69,836,000	69,836,000	100,002,464	68,924,000	143	99

Plasma-derived coagulation factor VIII and von Willebrand factor in combination

Table 85 shows the regional and national self-sufficiency in plasma-derived factor VIII and von Willebrand factor in combination.

Table 85. Estimates of regional and national self-sufficiency in plasma-derived factor VIII and von Willebrand factor in combination, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,517,000	1,517,000	548,593	50,000	36	3
Aosta Valley	3,000	3,000	77,857	3,000	2,595	100
AP Bolzano	850,000	850,000	218,706	610,000	26	72
AP Trento	54,000	54,000	220,743	40,000	409	74
Basilicata	317,000	317,000	224,986	10,000	71	3
Friuli-V. G.	396,500	402,500	826,088	100,000	205	25
Liguria	830,000	829,000	732,212	410,000	88	49
Umbria	1,033,000	1,033,000	300,770	110,000	29	11
Veneto	2,355,500	2,355,500	2,867,806	1,040,000	122	44
NAIP	7,356,000	7,361,000	6,017,761	2,373,000	82	32
Apulia	6,685,500	6,685,500	-	-	-	-
Calabria	754,000	658,500	-	-	-	-
E.-Romagna	4,335,750	4,336,750	-	-	-	-
Sicily	4,073,000	4,238,000	-	-	-	-
RIPP	15,848,250	15,918,750	0	0	-	-

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Campania	4,112,000	4,112,000	-	-	-	-
Latium	8,455,000	8,130,000	-	-	-	-
Marche	730,000	730,000	-	-	-	-
Molise	211,000	206,000	-	-	-	-
Tuscany	2,355,000	2,355,000	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	15,863,000	15,533,000	0	0	-	-
Lombardy	5,411,000	5,382,500	-	-	-	-
Piedmont	5,655,500	5,637,500	-	-	-	-
Sardinia	1,475,000	1,475,000	-	-	-	-
LPS	12,541,500	12,495,000	0	0	-	-
ITALY	51,578,750	51,277,750	6,017,761	2,373,000	12	5

Coagulation factor IX and 3-factor Prothrombin Complex Concentrates

The industrial production of pdFIX and 3F-PCCs is strictly alternative and therefore self-sufficiency in these two PDMPs were analysed together.

National self-sufficiency in pdFIX and 3F-PCCs was substantially reached (96% of the NHS demand), as in previous years. The regional self-sufficiency still showed differences but the range, varying from 67 to 100% – a lower level compared to 2017 – confirmed the need for improvement in the inter-regional exchange and compensation mechanisms (Table 86).

Table 86. Estimates of regional and national self-sufficiency in plasma-derived factor IX and 3-factor prothrombin complex concentrates, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	662,500	662,500	-	466,500	-	70
Aosta Valley	96,000	96,000	-	96,000	-	100
AP Bolzano	592,000	592,000	-	592,000	-	100
AP Trento	451,500	451,500	-	451,500	-	100
Basilicata	220,000	220,000	-	220,000	-	100
Friuli-V. G.	1,413,500	1,413,500	-	1,413,500	-	100
Liguria	1,491,000	1,371,000	-	1,371,000	-	100
Umbria	669,000	669,000	-	555,000	-	83
Veneto	5,405,500	5,380,500	-	5,260,500	-	98
NAIP	11,001,000	10,856,000	0	10,426,000	-	96
Apulia	2,522,500	1,898,000	6,602,837	1,898,000	348	100
Calabria	569,500	545,000	2,569,694	545,000	472	100
E.-Romagna	5,235,500	4,997,000	12,887,454	4,914,500	258	98
Sicily	3,573,500	3,347,000	9,091,998	3,291,000	272	98
RIPP	11,901,000	10,787,000	31,151,983	10,648,500	289	99

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Campania	2,962,000	2,632,000	4,565,934	1,762,500	173	67
Latium	1,907,500	1,745,350	6,175,511	1,609,000	354	92
Marche	1,382,000	1,382,000	5,141,922	1,379,500	372	100
Molise	250,000	244,000	731,766	244,000	300	100
Tuscany	4,515,500	4,180,000	10,308,752	4,171,000	247	100
Min. of Def.	-	-	59,487	-	NA	NA
PlaNet	11,017,000	10,183,350	26,983,371	9,166,000	265	90
Lombardy	6,254,800	5,794,000	22,294,032	5,418,000	385	94
Piedmont	3,683,000	3,578,500	10,478,399	3,518,500	293	98
Sardinia	1,110,800	1,110,800	2,797,328	1,100,000	252	99
LPS	11,048,600	10,483,300	35,569,760	10,036,500	339	96
ITALY	44,967,600	41,994,900	93,705,114	40,277,000	223	96

Fibrinogen

RiaSTAP™ is a product containing fibrinogen concentrate currently made available by CSL Behring under the toll fractionation contract with NAIP Regions. RiaSTAP is indicated for the treatment of congenital fibrinogen deficiency, which comprises congenital afibrinogenemia and hypofibrinogenemia. Other indications are met by other products available on the Italian market.

In 2018, the potential self-sufficiency in RiaSTAP was almost two times the NHS demand for this PDMP (Table 87). However, only effective self-sufficiency of 57% was achieved, showing possible room for improvement in the interregional compensation policies. All NAIP Regions, except for Liguria and Veneto, achieved effective self-sufficiency (more than 90%).

Table 87. Estimates of regional and national self- sufficiency in fibrinogen, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	450	450	768	450	171	100
Aosta Valley	-	-	109	-	NA	NA
AP Bolzano	-	-	306	-	NA	NA
AP Trento	180	180	309	180	172	100
Basilicata	140	140	315	140	225	100
Friuli-V. G.	430	430	1,157	430	269	100
Liguria	296	296	1,025	210	346	71
Umbria	470	470	421	470	90	100
Veneto	688	683	4,015	558	588	82
NAIP	2,654	2,649	8,425	2,438	318	92
Apulia	45	45	-	-	-	-
Calabria	-	-	-	-	NA	NA
E.-Romagna	52	52	-	-	-	-
Sicily	55	55	-	-	-	-
RIPP	152	152	-	-	-	-

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Campania	272	272	-	-	-	-
Latium	8	-	-	-	-	-
Marche	-	-	-	-	-	-
Molise	-	-	-	-	-	-
Tuscany	-	-	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	280	272	-	-	-	-
Lombardy	237	192	-	-	-	-
Piedmont	463	463	-	-	-	-
Sardinia	584	584	-	-	-	-
LPS	1,284	1,239	-	-	-	-
ITALY	4,370	4,312	8,425	2,438	195	57

Solvent/detergent virus-inactivated plasma

Differently from the main PDMPs that were included in the agreements between the Regions and the fractionation company regarding the toll fractionation process, the production of solvent/detergent virus-inactivated plasma (S/D plasma) from national plasma was determined by the production planning of the individual Regions (and in some cases of Local Health Centers). Therefore, not all the Regions contributed to the achievement of national self-sufficiency. For S/D plasma, the therapeutic indications are the same as those for fresh-frozen plasma. There is not sufficient evidence to justify the priority or preferential use of S/D plasma rather than fresh frozen plasma (52).

In 2018, the NHS demand for S/D plasma was almost equal to the total demand. For the same year, effective national self-sufficiency was 67% vs. 66% recorded in 2017 (Table 88).

Table 88. Estimates of regional and national self-sufficiency in solvent/detergent virus-inactivated plasma, 2018

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	mL	mL	mL	mLab	%	%
Abruzzo	16,000	16,000	-	-	-	-
Aosta Valley	-	-	-	-	NA	NA
AP Bolzano	-	-	-	-	NA	NA
AP Trento	10,000	10,000	-	-	-	-
Basilicata	630,000	630,000	-	-	-	-
Friuli-V. G.	12,000	8,000	-	-	-	-
Liguria	666,800	666,800	-	82,000	-	12
Umbria	4,000	4,000	-	-	-	-
Veneto	3,571,800	3,507,800	-	3,507,800	-	100
NAIP	4,910,600	4,842,600	0	3,589,800	-	74
Apulia	3,495,000	3,425,000	-	2,209,000	-	64
Calabria	894,000	894,000	-	-	-	-
E.-Romagna	619,400	583,400	-	-	-	-
Sicily	4,325,800	4,325,800	1,544,590	1,585,800	36	37
RIPP	9,334,200	9,228,200	1,544,590	3,794,800	17	41

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	mL	mL	mL	mLab	%	%
Campania	5,616,000	5,570,000	5,996,241	4,880,000	108	88
Latium	4,507,800	4,507,800	2,549,207	2,968,600	57	66
Marche	1,592,000	1,592,000	2,168,885	1,592,000	136	100
Molise	388,400	388,400	93,886	388,400	24	100
Tuscany	2,164,400	2,164,400	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	14,268,600	14,222,600	10,808,219	9,829,000	76	69
Lombardy	504,000	504,000	-	504,000	-	100
Piedmont	4,468,000	4,468,000	4,101,911	4,468,000	92	100
Sardinia	8,000	8,000	-	-	-	-
LPS	4,980,000	4,980,000	4,101,911	4,972,000	82	100
ITALY	33,493,400	33,273,400	16,454,720	22,185,600	49	67

For the Regions that used S/D plasma produced by toll fractionation, effective regional self-sufficiency varied from 12% in Liguria to 100% in Veneto, Marche, Molise, Lombardy and Piedmont.

PART D
**Expenditure for the purchase of plasma-derived
and recombinant medicinal products**

EXPENDITURE FOR PLASMA-DERIVED AND RECOMBINANT MEDICINAL PRODUCTS

This chapter describes the pharmaceutical expenditure incurred by the NHS for the purchase of the following medicinal products on the commercial market:

1. PDMPs included in the agreements between the Regions and the toll fractionation companies purchased in 2018 for the quota of the demand not covered by toll fractionation (albumin, IV IGs, SC/IM IGs, pdFVIII, pdFVIII/vWF, pdFIX, 3F-PCC, AT and fibrinogen);
2. Recombinant medicinal products, including extended half-life products, used in the treatment of coagulation disorders (rFVIIa, rFVIII, rFIX and rFXIII)²;
3. Specific immunoglobulins and all the other PDMPs, including solvent/detergent-treated plasma.

With regard to the medicinal products distributed through public health facilities, the aggregate purchase cost was quantified based on information taken from the drug traceability system. For the distribution through accredited pharmacies, on the other hand, the quantities of PDMPs provided by AIFA were valued based on the price in force on 31/12/2018, applying the discounts envisaged by law for pharmaceutical expenditure.

Tables 89 and 90 show the NHS total expenditure and the NHS total *per capita* expenditure incurred by the Regions for the purchase of the medicinal products specified in point one. In 2018, expenditure for the purchase of the aforementioned PDMPs was approximately 171.1 million euros (2.83 euro *per capita*). The analysis of trends in the total *per capita* expenditure classified by active ingredient showed, except IV IGs (+5%), a general decreasing tendency: 3F-PCCs (-17%), Albumin (-7%) and pdFVIII (-20%), pdFIX (-53%) and AT (-24%).

In 2018, the total expenditure for recombinant coagulation factors was around 410.8 million euros (6.79 euros *per capita*). Table 91 shows also the total and the total *per capita* expenditure for the purchase of recombinant medicinal products (rFVIIa, rFVIII, rFIX and rFXIII), including extended half-life products. The Regions with the highest *per capita* expenditure were Calabria, Latium, and Campania, with 11.75, 9.06 and 8.80 euros respectively. Overall, the expenditure for recombinant factors between 2017 and 2018 slightly decreased (-2%). In particular, the expenditure increased for rFVIII (+1%), rFIX (+21%), while it significantly decreased for rFVIIa (-37%).

In 2018, as regards all the other PDMPs (Tables 92-95), the total expenditure was approximately 100.8 million euros, equivalent to around 1.67 euros *per capita*. With regard to all specific IGs, a slight decrease in *per capita* expenditure was observed (Table 93). The remaining PDMPs (Table 95) recorded a significant decrease in the *per capita* expenditure (-19%) particularly for the purchase of aPCCs (-42%), C1-inhibitor (-15%), solvent/detergent-treated plasma (-10%), alpha-1 proteinase inhibitor (-7%), and local haemostatics agents (-4%). An increase of *per capita* expenditure was recorded for FVII (+17%), PCCs4 (+16%) and products containing protein C (+2%).

² In 2018, Emicizumab was provided by Roche without any cost for the Regions.

Table 89. Estimate of total expenditure and total *per capita* expenditure incurred by the National Health Service for the purchase on the market of main plasma-derived medicinal products included in toll fractionation contracts in 2018

Region	Albumin		Human immunoglobulin intravenous use		Factor VIII		Total	
	€	€ per capita	€	€ per capita	€	€ per capita	€	€ per capita
Abruzzo	781,870	0.59	1,026,746	0.78	-	-	1,808,616	1.38
Aosta Valley	4,286	0.03	77,064	0.61	-	-	81,350	0.64
AP Bolzano	92,695	0.18	547,520	1.04	-	-	640,214	1.21
AP Trento	26,994	0.05	366,234	0.68	-	-	393,228	0.73
Basilicata	321,694	0.57	246,643	0.43	-	-	568,337	1.00
Friuli-V. G.	16,630	0.01	355,945	0.29	-	-	372,574	0.31
Liguria	144,695	0.09	2,918,363	1.87	-	-	3,063,057	1.97
Umbria	18,421	0.02	226,081	0.26	-	-	244,502	0.28
Veneto	194,521	0.04	804,400	0.16	-	-	998,921	0.20
NAIP	1,601,805	0.14	6,568,995	0.56	-	-	8,170,800	0.70
Apulia	1,761,371	0.44	7,786,979	1.92	149,600	0.04	9,697,950	2.40
Calabria	1,427,193	0.73	1,004,286	0.51	-	-	2,431,479	1.24
E.-Romagna	475,133	0.11	2,522,391	0.57	-	-	2,997,524	0.67
Sicily	1,602,857	0.32	1,246,513	0.25	-	-	2,849,369	0.57
RIPP	5,266,554	0.34	12,560,168	0.81	149,600	0.01	17,976,322	1.16
Campania	9,054,685	1.55	8,217,222	1.41	682	0.00	17,272,589	2.96
Latium	2,344,258	0.40	4,767,599	0.81	-	-	7,111,857	1.21
Marche	22,515	0.01	571,767	0.37	-	-	594,282	0.39
Molise	75,386	0.24	-	NA	-	-	75,386	0.24
Tuscany	456,730	0.12	8,967,719	2.40	-	-	9,424,449	2.52
Min. of Def.	-	-	-	-	-	-	-	NA
PlaNet	11,953,573	0.69	22,524,307	1.30	682	0.00	34,478,562	1.99
Lombardy	1,851,049	0.18	3,191,884	0.32	219,780	0.02	5,262,714	0.52
Piedmont	229,122	0.05	2,941,575	0.67	-	-	3,170,697	0.72
Sardinia	973,412	0.59	525,975	0.32	-	-	1,499,387	0.91
LPS	3,053,583	0.19	6,659,434	0.41	219,780	0.01	9,932,798	0.62
ITALY	21,875,515	0.36	48,312,904	0.80	370,062	0.01	70,558,481	1.17

Table 90. Estimate of total expenditure and total *per capita* expenditure incurred by the National Health Service for the purchase on the market of ancillary plasma-derived medicinal products included in toll fractionation contracts in 2018

Region	SC/Ig		FVIII/vWF		FIX		3F-PCC		AT		Fibrinogen		Total	
	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc
Abruzzo	1,412,887	1.07	821,919	0.62	84,768	0.06	4,114	0.00	-	-	444,840	0.34	2,768,528	2.11
Aosta Valley	48,156	0.38	-	0.00	-	-	-	-	-	-	20,240	0.16	68,396	0.54
AP Bolzano	106,054	0.20	133,056	0.25	-	-	-	-	-	-	282,040	0.53	521,150	0.99
AP Trento	124,714	0.23	7,854	0.01	-	-	-	-	-	-	55,880	0.10	188,448	0.35
Basilicata	485,406	0.86	166,797	0.29	-	-	-	-	23,562	0.04	48,400	0.09	724,165	1.28
Friuli-V. G.	280,959	0.23	179,906	0.15	-	-	-	-	-	-	169,400	0.14	630,265	0.52
Liguria	1,753,012	1.13	229,955	0.15	-	-	-	-	8,855	0.01	166,760	0.11	2,158,582	1.39
Umbria	1,236,677	1.40	500,874	0.57	51,018	0.06	-	-	-	-	263,560	0.30	2,052,129	2.32
Veneto	4,176,555	0.85	718,444	0.15	59,400	0.01	-	-	-	-	1,611,720	0.33	6,566,119	1.34
NAIP	9,624,420	0.83	2,758,805	0.24	195,186	0.02	4,114	0.00	32,417	0.00	3,062,840	0.26	15,677,781	1.35
Apulia	5,803,563	1.43	3,375,017	0.83	-	-	-	-	38,484	0.01	942,040	0.23	10,159,105	2.51
Calabria	1,750,455	0.89	361,602	0.18	-	-	-	-	61,551	0.03	636,240	0.33	2,809,847	1.44
E.-Romagna	4,907,174	1.10	2,294,850	0.52	14,850	0.00	13,860	0.00	18,032	0.00	1,492,040	0.34	8,740,806	1.96
Sicily	3,590,366	0.71	2,383,668	0.47	-	-	14,476	0.00	82,610	0.02	872,960	0.17	6,944,079	1.38
RIPP	16,051,558	1.04	8,415,137	0.54	14,850	0.00	28,336	0.00	200,676	0.01	3,943,280	0.25	28,653,837	1.85
Campania	4,536,134	0.78	2,032,589	0.35	-	-	200,855	0.03	1,301,955	0.22	2,105,400	0.36	10,176,933	1.75
Lazio	8,243,768	1.40	4,235,778	0.72	26,222	0.00	23,786	0.00	809,204	0.14	1,720,840	0.29	15,059,598	2.55
Marche	1,267,999	0.83	384,402	0.25	-	-	21,328	0.01	-	-	420,640	0.27	2,094,368	1.37
Molise	259,543	0.84	113,762	0.37	-	-	-	-	-	-	20,680	0.07	393,985	1.28
Tuscany	6,759,354	1.81	1,177,385	0.32	-	-	2,079	0.00	6,727	0.00	1,100,880	0.29	9,046,425	2.42
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	NA	-	NA
PlaNet	21,066,798	1.22	7,943,916	0.46	26,222	0.00	248,047	0.01	2,117,885	0.12	5,368,440	0.31	36,771,308	2.13
Lombardy	3,927,453	0.39	3,936,957	0.39	196,032	0.02	-	-	156,233	0.02	1,702,800	0.17	9,919,475	0.99
Piedmont	4,305,721	0.98	2,819,381	0.64	30,690	0.01	-	-	-	-	546,480	0.12	7,702,273	1.76
Sardinia	291,883	0.18	749,451	0.45	-	-	2,257	0.00	2,113	0.00	727,760	0.44	1,773,464	1.08
LPS	8,525,057	0.53	7,505,789	0.47	226,722	0.01	2,257	0.00	158,346	0.01	2,977,040	0.19	19,395,212	1.21
ITALY	55,267,833	0.91	26,623,647	0.44	460,010	0.01	262,095	0.00	2,509,324	0.04	15,351,600	0.25	100,498,138	1.66

Table 91. Estimate of the total expenditure and the total *per capita* expenditure for recombinant factors VII, VIII, IX and XIII in 2018

Region	rFVIIa		rFVIII		rFIX		rFXIII		Total	
	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc
Abruzzo	203,253	0.15	6,287,472	4.78	2,354,504	1.79	403,629	0.31	9,248,858	7.03
Aosta Valley	-	-	595,573	4.72	-	-	-	-	595,573	4.72
AP Bolzano	31,071	0.06	1,467,420	2.78	30,123	0.06	-	-	1,528,613	2.90
AP Trento	3,884	0.01	1,894,188	3.51	349,634	0.65	-	-	2,247,705	4.16
Basilicata	78,971	0.14	3,489,209	6.15	247,746	0.44	248,387	0.44	4,064,313	7.17
Friuli-V. G.	3,158,832	2.60	4,160,994	3.42	1,167,384	0.96	-	-	8,487,210	6.98
Liguria	683,552	0.44	4,985,279	3.20	2,943,883	1.89	248,387	0.16	8,861,101	5.69
Umbria	434,339	0.49	3,833,305	4.33	301,166	0.34	-	-	4,568,810	5.16
Veneto	1,912,130	0.39	17,696,061	3.61	2,858,148	0.58	108,669	0.02	22,575,009	4.60
NAIP	6,506,031	0.56	44,409,500	3.82	10,252,588	0.88	1,009,073	0.09	62,177,192	5.34
Apulia	3,980,909	0.98	25,804,795	6.37	8,072,570	1.99	-	-	37,858,274	9.35
Calabria	3,900,639	1.99	16,997,402	8.69	1,324,743	0.68	760,686	0.39	22,983,470	11.75
E.-Romagna	418,805	0.09	18,590,504	4.18	4,874,572	1.09	-	-	23,883,881	5.36
Sicily	4,336,276	0.86	31,274,125	6.22	3,838,409	0.76	-	-	39,448,810	7.85
RIPP	12,636,628	0.82	92,666,825	5.98	18,110,295	1.17	760,686	0.05	124,174,435	8.02
Campania	4,213,286	0.72	39,948,598	6.86	7,125,352	1.22	-	-	51,287,235	8.80
Lazio	2,369,774	0.40	46,317,921	7.85	4,755,046	0.81	-	-	53,442,740	9.06
Marche	800,717	0.52	5,481,567	3.58	1,629,758	1.06	-	-	7,912,042	5.17
Molise	45,311	0.15	1,846,065	5.98	-	-	-	-	1,891,376	6.13
Tuscany	2,790,520	0.75	12,640,294	3.38	5,520,071	1.48	-	-	20,950,886	5.61
Min. of Def.									135,484,279	NA
PlaNet	10,219,608	0.59	106,234,445	6.14	19,030,227	1.10	-	-	135,484,279	7.83
Lombardy	5,014,644	0.50	39,149,960	3.90	9,724,762	0.97	403,629	0.04	54,292,995	5.41
Piedmont	3,681,858	0.84	19,034,115	4.35	4,920,518	1.12	434,678	0.10	28,071,169	6.41
Sardinia	267,335	0.16	6,283,668	3.81	33,370	0.02	-	-	6,584,373	3.99
LPS	8,963,837	0.56	64,467,744	4.01	14,678,649	0.91	838,307	0.05	88,948,537	5.54
ITALY	38,326,105	0.63	307,778,515	5.09	62,071,759	1.03	2,608,066	0.04	410,784,443	6.79

Table 92. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of specific immunoglobulins in 2018

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs	Rabies IGs	TOTAL
Abruzzo	283,270	6,692	177,704	48,000	59,736	755	-	576,158
A.Valley	50,160	-	15,744	6,583	-	3,160	-	75,647
APBZ	33,353	-	15,160	-	-	-	2,479	50,992
APTn	71,829	-	28,631	32,421	-	3,868	2,156	138,904
Basilicata	119,503	855	43,311	17,329	24,973	-	-	205,971
Friuli-V.G.	116,705	7,714	52,252	85,937	72,613	4,483	21,776	361,479
Liguria	242,620	6,776	163,881	-	1,951	3,766	-	418,995
Umbria	121,226	2,200	62,014	-	9,320	5,205	-	199,965
Veneto	1,052,753	293,430	94,240	195,497	677,875	5,503	20,913	2,340,212
NAIP	2,091,419	317,667	652,938	385,766	846,468	26,741	47,324	4,368,323
Apulia	2,603,453	592,437	272,902	-	67,421	2,429	431	3,539,074
Calabria	566,021	73,867	212,532	48,448	7,633	87	-	908,587
ER	889,824	253,517	269,007	187,448	492,847	17,987	7,438	2,118,068
Sicily	1,713,070	1,100	378,743	124,064	95,770	-	-	2,312,747
RIPP	5,772,368	920,921	1,133,184	359,960	663,671	20,503	7,869	8,878,477
Campania	9,958,894	664,328	827,228	91,963	72,937	3,954	-	11,619,305
Latium	1,039,100	177,171	123,888	178,629	76,948	9,402	1,078	1,606,215
Marche	224,702	48,586	153,152	-	95,338	8,553	1,078	531,409
Molise	76,958	5,742	19,541	9,261	-	-	-	111,502
Tuscany	728,826	116,290	466,915	145,639	62,209	3,698	6,468	1,530,045
MofDef.	-	-	-	-	-	-	-	-
PlaNet	12,028,481	1,012,117	1,590,723	425,493	307,432	25,608	8,624	15,398,477
Lombardy	5,136,598	283,066	380,058	422,144	229,615	43,144	16,062	6,510,688
Piedmont	2,099,052	173,695	135,341	185,889	486,701	824	-	3,081,501
Sardinia	1,659,381	58,644	119,402	27,975	-	173	-	1,865,575
LPS	8,895,030	515,405	634,801	636,008	716,316	44,141	16,062	11,457,763
Not specified region	-	-	147,033	-	-	-	-	-
ITALY	28,787,298	2,766,110	4,158,679	1,807,227	2,533,887	116,992	79,880	40,103,040

Table 93. Estimate of standardised expenditure (euro per capita and euro per 1,000 population) incurred by the National Health Service for the purchase on the market of specific immunoglobulins in 2018

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs*	Rabies IGs*	TOTAL
Abruzzo	0.22	0.01	0.14	0.04	0.05	0.57	-	0.44
A. Valley	0.40	-	0.12	0.05	-	25.04	-	0.60
AP BZ	0.06	-	0.03	-	-	-	4.70	0.10
AP TN	0.13	-	0.05	0.06	-	7.16	3.99	0.26
Basilicata	0.21	0.00	0.08	0.03	0.04	-	-	0.36
Friuli-V. G.	0.10	0.01	0.04	0.07	0.06	3.69	17.91	0.30
Liguria	0.16	0.00	0.11	-	0.00	2.42	-	0.27
Umbria	0.14	0.00	0.07	-	0.01	5.88	-	0.23
Veneto	0.21	0.06	0.02	0.04	0.14	1.12	4.26	0.48
NAIP ⁴	0.18	0.03	0.06	0.03	0.07	2.30	4.07	0.38
Apulia	0.64	0.15	0.07	-	0.02	0.60	0.11	0.87
Calabria	0.29	0.04	0.11	0.02	0.00	0.04	-	0.46
ER	0.20	0.06	0.06	0.04	0.11	4.04	1.67	0.48
Sicily	0.34	0.00	0.08	0.02	0.02	-	-	0.46
RIPP	0.37	0.06	0.07	0.02	0.04	1.32	0.51	0.57
Campania	1.71	0.11	0.14	0.02	0.01	0.68	-	1.99
Latiium	0.18	0.03	0.02	0.03	0.01	1.59	0.18	0.27
Marche	0.15	0.03	0.10	-	0.06	5.58	0.70	0.35
Molise	0.25	0.02	0.06	0.03	-	-	-	0.36
Tuscany	0.20	0.03	0.12	0.04	0.02	0.99	1.73	0.41
M of Def.	-	-	-	-	-	-	-	-
PlaNet	0.70	0.06	0.09	0.02	0.02	1.48	0.50	0.89
Lombardy	0.51	0.03	0.04	0.04	0.02	4.30	1.60	0.65
Piedmont	0.48	0.04	0.03	0.04	0.11	0.19	-	0.70
Sardinia	1.01	0.04	0.07	0.02	-	0.11	-	1.13
LPS	0.55	0.03	0.04	0.04	0.04	2.75	1.00	0.71
ITALY	0.48	0.05	0.07	0.03	0.04	1.93	1.32	0.66

*values per 1,000 population

Table 94. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of all other PDMPs in 2018

Region	FVII	FVIII inhibitor activity	Local Haemostatic agents-combinations	Other plasma proteins fractions	4-factor PCa	Alpha-1-proteinase inhibitor	Human C1 esterase inhibitor	Factor X*	Factor XI	Factor XIII	Protein C	TOTAL
Abruzzo	250,161	2,065,394	439,858	6,072	138,243	234,696	350,240	-	-	-	-	3,484,665
A. Valley	-	-	67,980	-	-	252,930	192,531	-	-	-	-	513,441
AP BZ	-	19,589	196,702	-	172,373	456,576	55,290	-	-	-	-	900,530
AP TN	-	160,383	54,402	3,570	11,220	125,136	8,193	-	-	14,066	-	376,970
Basilicata	44,805	-	414,938	243,165	48,187	-	56,179	-	-	-	-	807,273
Friuli-V. G.	-	17,140	400,445	3,146	38,012	279,673	32,186	-	43,010	2,465	63,360	813,612
Liguria	-	430,954	198,082	229,249	39,644	319,454	-	-	-	-	65,670	1,283,208
Umbria	-	-	263,101	1,572	17,266	44,167	363,409	-	-	-	12,320	755,185
Veneto	29,870	348,926	847,666	-	38,144	879,774	1,558,647	-	-	83,223	-	3,798,570
NAIP	324,836	3,042,386	2,883,174	486,774	503,088	2,592,406	2,616,676	-	43,010	99,754	141,350	12,733,452
Apulia	249,685	575,424	784,647	472,315	13,021	267,696	1,259,521	-	12,650	15,238	76,318	3,726,515
Calabria	11,107	1,886,172	744,092	357,287	21,481	74,402	543,988	-	-	-	132,369	3,770,896
ER	199,756	2,032,352	445,755	227,635	333,406	449,064	524,184	-	-	151,599	-	4,363,751
Sicily	143,651	1,074,413	888,969	1,085,963	64,987	252,648	2,055,798	-	-	-	105,600	5,672,029
RIPP	604,199	5,568,362	2,863,462	2,143,198	432,895	1,043,810	4,383,492	-	12,650	166,837	314,287	17,533,191
Campania	296,386	-	1,587,961	265,291	241,054	899,977	-	-	-	-	268,125	3,558,794
Latium	1,091,880	731,743	851,070	613,867	153,390	322,944	1,345,384	-	-	72,283	63,360	5,245,921
Marche	933	-	365,193	-	54,934	77,740	-	-	-	23,834	53,900	576,534
Molise	242,694	-	10,664	-	-	9,504	4,682	-	-	-	-	267,544
Tuscany	12,601	571,748	1,123,921	829,971	229,223	478,128	-	-	-	33,602	5,225	3,284,420
M of Def.	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	1,644,494	1,303,491	3,938,810	1,709,129	678,602	1,788,293	1,350,066	-	-	129,719	390,610	12,933,213
Lombardy	1,286,061	3,325,080	1,645,381	-	88,534	1,596,392	2,243,517	26,483	25,300	76,190	369,072	10,682,010
Piedmont	159,618	1,876,852	1,090,048	-	213,382	531,946	812,614	-	2,530	24,615	3,988	4,715,593
Sardinia	-	497,068	277,462	3,047	185,030	289,553	841,566	-	-	-	30,250	2,123,976
LPS	1,445,679	5,699,000	3,012,892	3,047	486,945	2,417,891	3,897,697	26,483	27,830	100,806	403,310	17,521,579
ITALY	4,019,208	15,613,238	12,698,337	4,342,148	2,101,529	7,842,400	12,247,930	26,483	83,490	497,116	1,249,556	60,721,435

Table 95. Estimate of standardised per capita expenditure incurred by the National Health Service for the purchase of all other PDMPs in 2018

Region	FVII	FVIII inhibitor activity	Local Haemostatic agents-combinations	Other plasma Proteins fractions	4-factor prothrombin complex concentrates	Alpha-1-proteinase inhibitor	Human C1 esterase inhibitor	Factor X*	Factor XI*	Factor XIII *	Protein C	TOTAL
Abruzzo	0.19	1.57	0.33	0.00	0.11	0.18	0.27	-	-	-	-	2.65
A. Valley	-	-	0.54	-	-	2.00	1.53	-	-	-	-	4.07
AP BZ	-	0.04	0.37	-	0.33	0.87	0.10	-	-	-	-	1.71
AP TN	-	0.30	0.10	0.01	0.02	0.23	0.02	-	-	26.05	-	0.70
Basilicata	0.08	-	0.73	0.43	0.08	-	0.10	-	-	-	-	1.42
Friuli-V. G.	-	0.01	0.33	0.00	0.03	0.23	0.03	-	35.38	-	-	0.67
Liguria	-	0.28	0.13	0.15	0.03	0.21	-	-	-	1.58	0.04	0.82
Umbria	-	-	0.30	0.00	0.02	0.05	0.41	-	-	-	0.07	0.85
Veneto	0.01	0.07	0.17	-	0.01	0.18	0.32	-	-	16.97	0.00	0.77
NAIP	0.03	0.26	0.25	0.04	0.04	0.22	0.22	-	3.70	8.57	0.01	1.09
Apulia	0.06	0.14	0.19	0.12	0.00	0.07	0.31	-	3.12	3.76	0.02	0.92
Calabria	0.01	0.96	0.38	0.18	0.01	0.04	0.28	-	-	-	0.07	1.93
ER	0.04	0.46	0.10	0.05	0.07	0.10	0.12	-	-	34.05	-	0.98
Sicily	0.03	0.21	0.18	0.22	0.01	0.05	0.41	-	-	-	0.02	1.13
RIPP	0.04	0.36	0.18	0.14	0.03	0.07	0.28	-	0.82	10.77	0.02	1.13
Campania	0.05	-	0.27	0.05	0.04	0.15	-	-	-	-	0.05	0.61
Latiium	0.19	0.12	0.14	0.10	0.03	0.05	0.23	-	-	12.26	0.01	0.89
Marche	0.00	-	0.24	-	0.04	0.05	-	-	-	15.56	0.04	0.38
Molise	0.79	-	0.03	-	-	0.03	0.02	-	-	-	-	0.87
Tuscany	0.00	0.15	0.30	0.22	0.06	0.13	-	-	-	8.99	0.00	0.88
M of Def.	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	0.10	0.08	0.23	0.10	0.04	0.10	0.08	-	-	7.50	0.02	0.75
Lombardy	0.13	0.33	0.16	-	0.01	0.16	0.22	2.64	2.52	7.59	0.04	1.06
Piedmont	0.04	0.43	0.25	-	0.05	0.12	0.19	-	0.58	5.63	0.00	1.08
Sardinia	-	0.30	0.17	0.00	0.11	0.18	0.51	-	-	-	0.02	1.29
LPS	0.09	0.35	0.19	0.00	0.03	0.15	0.24	1.65	1.73	6.28	0.03	1.09
ITALY	0.07	0.26	0.21	0.07	0.03	0.13	0.20	0.44	1.38	8.22	0.02	1.00

*values per 1,000 population

National and Regional mean price per gram or International Unit

Tables 96-98 show the mean price per unit paid by the Regions to buy albumin, IVIGs and pdFVIII/vWF in combination (ATC B02BD06).

The price varied depending on the distribution channel (NHS facilities and pharmacies open to the public). For each PDMP, the percentage of product by distribution channel and the costs recorded in both distribution channels were reported.

The aforementioned prices include VAT. However, it should be noted that in some Regions (e.g. Marche for IVIGs) the mean price per unit exceeded the maximum price of transfer to public health facilities as defined by the AIFA resolution of 5 August 2006 (53).

Regarding albumin (Table 96), the national mean price per gram was 2.15 euros. The variability observed between Regions (range: 1.90-3.96 euro per gram) was affected by the different contribution of each distribution channel to the definition of costs, as well as volumes. In particular, the mean price paid by NHS facilities was subject to variability that could be linked to the different contracts awarded following a tender procedure, while the cost recorded through the public pharmacies was substantially similar for all Regions. In fact, the prices of the packages and the discounts applied are the same nationwide and the slight differences are probably due to the different composition of the “basket” compared to the dosages and relative prices.

The AP Bolzano, Emilia-Romagna, Marche, Tuscany and Piedmont were the Regions in which more than 90% of the commercial demand was dispensed by NHS facilities.

In other Regions, such as the AP Trento, Molise, Veneto and Calabria, the commercial demand (although not significant) was mainly dispensed through the accredited pharmacies channel, showing significantly higher mean prices per gram.

The overall expenditure of pdFVIII/vWF on the market was € 26,623,647 (€ 0.54 per IU), and almost entirely accounted for the distribution through NHS facilities (96%) (97% in 2017) (Table 97).

The market demand for IV IGs (excluding the specific demand for products containing IVIGs with high titers of IGM - see Table 7) recorded an expenditure of € 41.1 million euros with an increase of 3.5% compared to 2017, in line with the increasing availability of toll fractionation products. The mean unit price per gram at national level was 38.66 euros (range: 35.34-47.09 euros) (Table 98).

Table 96. National and Regional mean price per gram for the purchase of albumin by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2018

Region	Mean price per gram			Demand						Total expenditure						
	NHS facilities		Pharmacies	NHS facilities		Pharmacies		NHS facilities		Pharmacies		NHS facilities		Pharmacies		
	g	%	g	%	g	%	g	%	g	%	g	%	g	%		
Abruzzo	2.11	3.94	2.47	80%	253,810	80%	62,258	20%	536,736	69%	245,135	31%	3,366	79%	920	21%
Aosta Valley	2.24	3.83	2.46	86%	1,500	86%	240	14%	3,366	79%	920	21%	92,695	100%	-	0%
AP Bolzano	1.90	NA	1.90	100%	48,775	100%	-	0%	6,948	100%	26,994	100%	-	0%	26,994	100%
AP Trento	NA	3.89	3.89	0%	-	0%	6,948	100%	-	0%	26,994	100%	-	0%	26,994	100%
Basilicata	2.19	3.95	2.85	62%	70,570	62%	42,403	38%	154,301	48%	167,393	52%	3,951	24%	12,678	76%
Friuli-V. G.	1.98	3.93	3.18	38%	2,000	38%	3,230	62%	3,951	24%	12,678	76%	3,951	24%	12,678	76%
Liguria	2.08	3.92	3.27	35%	15,575	35%	28,620	65%	32,473	22%	112,222	78%	4,572	25%	13,849	75%
Umbria	2.09	3.91	3.21	38%	2,188	38%	3,545	62%	4,572	25%	13,849	75%	25,212	13%	169,309	87%
Veneto	3.12	3.94	3.81	16%	8,080	16%	43,015	84%	853,305	53%	748,500	47%	853,305	53%	748,500	47%
NAIP	2.12	3.93	2.70	68%	402,498	68%	190,258	32%	853,305	53%	748,500	47%	853,305	53%	748,500	47%
Apulia	2.32	3.93	3.43	31%	159,550	31%	354,070	69%	370,619	21%	1,390,752	79%	181,714	13%	1,245,479	87%
Calabria	2.23	3.91	3.56	20%	81,625	20%	318,795	80%	446,195	94%	28,938	6%	610,331	38%	992,526	62%
E.-Romagna	2.56	3.93	2.61	96%	174,425	96%	7,363	4%	1,608,858	31%	3,657,695	69%	610,331	38%	992,526	62%
Sicily	1.98	3.88	2.84	55%	307,668	55%	255,803	45%	1,608,858	31%	3,657,695	69%	610,331	38%	992,526	62%
RIPP	2.22	3.91	3.17	44%	723,268	44%	936,030	56%	1,608,858	31%	3,657,695	69%	1,608,858	31%	3,657,695	69%
Campania	1.92	3.88	2.55	68%	2,422,215	68%	1,132,550	32%	4,661,527	51%	4,393,157	49%	1,065,083	45%	1,279,175	55%
Latium	2.08	3.93	2.80	61%	512,395	61%	325,848	39%	1,065,083	45%	1,279,175	55%	21,405	95%	1,110	5%
Marche	2.31	3.96	2.36	97%	9,255	97%	280	3%	21,405	95%	1,110	5%	-	0%	75,386	100%
Molise	NA	3.95	3.95	0%	-	0%	19,090	100%	-	0%	75,386	100%	-	0%	75,386	100%
Tuscany	1.98	3.94	2.07	95%	209,628	95%	10,678	5%	414,696	91%	42,034	9%	414,696	91%	42,034	9%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	1.95	3.89	2.58	68%	3,153,493	68%	1,488,445	32%	6,162,711	52%	5,790,862	48%	6,162,711	52%	5,790,862	48%
Lombardy	1.95	3.92	3.02	46%	280,203	46%	333,105	54%	546,208	30%	1,304,841	70%	199,264	87%	29,858	13%
Piedmont	1.98	3.95	2.12	93%	100,750	93%	7,560	7%	199,264	87%	29,858	13%	529,484	54%	443,928	46%
Sardinia	1.90	3.95	2.49	71%	278,775	71%	112,528	29%	1,274,956	42%	1,778,628	58%	529,484	54%	443,928	46%
LPS	1.93	3.92	2.74	59%	659,728	59%	453,193	41%	1,274,956	42%	1,778,628	58%	1,274,956	42%	1,778,628	58%
ITALY	1.07	3.90	2.15	62%	9,218,243	62%	5,682,658	38%	9,899,831	31%	22,172,741	69%	9,899,831	31%	22,172,741	69%

Table 97. National and Regional mean price per gram for the purchase of factor VIII / von Willebrand factor in combination by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2018

Region	Mean price per gram				Demand				Total expenditure			
	NHS facilities		Pharmacies		NHS facilities		Pharmacies		NHS facilities		Pharmacies	
	€	€	g	%	g	%	g	%	g	%	g	%
Abruzzo	0.56	NA	1,467,000	100%	-	0%	821,919	100%	-	0%	-	0%
Aosta Valley	NA	NA	-	NA	-	NA	-	NA	-	NA	-	NA
AP Bolzano	0.55	NA	240,000	100%	-	0%	133,056	100%	-	0%	-	0%
AP Trento	0.56	NA	14,000	100%	-	0%	7,854	100%	-	0%	-	0%
Basilicata	0.54	NA	307,000	100%	-	0%	166,797	100%	-	0%	-	0%
Friuli-V. G.	0.61	0.60	260,500	88%	36,000	12%	158,192	88%	21,714	12%	21,714	12%
Liguria	0.55	NA	419,000	100%	-	0%	229,955	100%	-	0%	-	0%
Umbria	0.54	NA	923,000	100%	-	0%	500,874	100%	-	0%	-	0%
Veneto	0.55	NA	1,315,500	100%	-	0%	718,444	100%	-	0%	-	0%
NAIP	0.55	0.60	4,946,000	99%	36,000	1%	2,737,091	99%	21,714	1%	21,714	1%
Apulia	0.50	NA	6,685,500	100%	-	0%	3,375,017	100%	-	0%	-	0%
Calabria	0.55	NA	658,500	100%	-	0%	361,602	100%	-	0%	-	0%
E.-Romagna	0.53	1.20	4,334,750	100%	1,000	0%	2,293,650	100%	1,200	0%	1,200	0%
Sicily	0.56	0.53	4,073,000	96%	165,000	4%	2,295,608	96%	88,060	4%	88,060	4%
RIPP	0.53	0.54	15,751,750	99%	166,000	1%	8,325,877	99%	89,260	1%	89,260	1%
Campania	0.49	NA	4,112,000	100%	-	0%	2,032,589	100%	-	0%	-	0%
Latium	0.52	0.60	8,099,500	100%	30,500	0%	4,217,383	100%	18,395	0%	18,395	0%
Marche	0.53	NA	730,000	100%	-	0%	384,402	100%	-	0%	-	0%
Molise	0.55	NA	206,000	100%	-	0%	113,762	100%	-	0%	-	0%
Tuscany	0.50	NA	2,355,000	100%	-	0%	1,177,385	100%	-	0%	-	0%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	0.51	0.60	15,502,500	100%	30,500	0%	7,925,521	100%	18,395	0%	18,395	0%
Lombardy	0.78	0.60	3,895,500	72%	1,487,000	28%	3,042,571	77%	894,386	23%	894,386	23%
Piedmont	0.50	NA	5,637,500	100%	-	0%	2,819,381	100%	-	0%	-	0%
Sardinia	0.51	NA	1,475,000	100%	-	0%	749,451	100%	-	0%	-	0%
LPS	0.60	0.60	11,008,000	88%	1,487,000	12%	6,611,403	88%	894,386	12%	894,386	12%
ITALY	0.54	0.52	47,208,250	96%	1,952,000	4%	25,599,892	96%	1,023,755	4%	1,023,755	4%

Table 98. National and Regional mean price per gram for the purchase of intravenous immunoglobulins by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2018

Region	Mean price per gram NHS facilities	Total demand (g) NHS facilities	Total expenditure NHS facilities*
Abruzzo	42.29	23,951	1,012,789
Aosta Valley	43.31	1,779	77,064
AP Bolzano	39.03	13,803	538,725
AP Trento	40.48	7,550	305,624
Basilicata	42.68	2,598	110,862
Friuli-V. G.	44.94	3,400	152,797
Liguria	39.02	69,650	2,717,723
Umbria	42.68	4,655	198,696
Veneto	41.63	2,960	123,214
NAIP	40.18	130,346	5,237,493
Apulia	43.50	163,865	7,128,070
Calabria	41.92	22,747	953,450
E.-Romagna	44.78	44,871	2,009,379
Sicily	43.73	6,003	262,541
RIPP	43.60	237,486	10,353,439
Campania	35.34	164,705	5,821,103
Latium	35.79	127,503	4,562,881
Marche	47.09	7,855	369,873
Molise	NA	-	-
Tuscany	35.93	235,379	8,457,759
Min. of Def.			
PiaNet	35.88	535,442	19,211,615
Lombardy	42.59	72,065	3,069,047
Piedmont	35.73	74,330	2,656,171
Sardinia	42.88	12,265	525,975
LPS	39.40	158,660	6,251,193
ITALY	38.66	1,061,934	41,053,740

* The value does not include *Pentaglobin*TM.

FINAL CONSIDERATIONS

The national demand for albumin was still particularly high and confirmed the increase observed in 2017 (578 grams per 1,000 population), a countertendency to the trend observed in previous years.

An increased demand was observed in particular in Molise (+56%), Friuli-Venezia Giulia (+23%) and the AP of Bolzano (+20%), all small Regions with a low population density. The regions with the highest standardised demand per 1,000 population were Campania, Sardinia and Molise with standardised volumes of 873, 866 and 731 grams, respectively.

About 9% of the national demand was distributed through public pharmacies, reaching a quantity of approximately 3,068 kilograms. The pharmacy channel is particularly used in Calabria and Campania where it accounts respectively for 29 and 32% of regional demands.

The growth trend of the demand for IG was confirmed in the two-year period 2017-2018: +10% of the demand for IG; + 21.3% of the demand for SC/IM IG. There were notable differences from one region to another. The three regions with the highest standardised demand per 1,000 population were Tuscany, Aosta Valley and Molise, with around 171, 163 and 148 grams respectively.

The demand for AT slightly decreased (-3%) in 2018, while the demand for 3F-PCCs and 4F-PCCs slightly increased (respectively + 1% and 3%).

As regards the haemophilia A treatment, on one hand, the demand for pdFVIII (alone and in combination with vWF) significantly decreased (-8%), on the other, there was an almost stable consumption and demand for rFVIII (+1%) and for extended half-life FVIII (+1%). For the first time the consumption of Emicizumab was recorded, and this was associated with the decrease in the demand for aPPCs and rFVIIa.

Concerning the haemophilia B treatment, the clinical use of extended half-life FIX progressively replaced the demand for pdFIX and for rFIX (decreased respectively by -15 and -9%).

The total volume of plasma sent by Regions for fractionation increased by 1.1%. There were still great differences in the volumes from one Region to another, ranging from 5.5 kilograms per 1,000 population sent by Campania to 23.2 sent by Friuli-Venezia Giulia, with an average volume of 14.0 kilograms per 1,000 population.

The level of albumin self-sufficiency was stable, around 72%. As regards IVIGs, on the other hand, self-sufficiency in human immunoglobulin for intravenous and subcutaneous/intramuscular use achieved at national level was 60%, while self-sufficiency in IV IG reached 74%.

National self-sufficiency was substantially reached in pdFVIII, pdFIX and 3F-PCCs.

Generally, the system could benefit from better coordination and improved interregional compensation and planning, in order to enhance the opportunities offered by the toll fractionation system.

The expenditure sustained by the Regions for PDMPs produced by toll fractionation, excluding the expenditure associated with the production of plasma (collection, processing, biological qualification, storage and transport), was estimated to be about 115 million euros, in line with the costs foreseen by the contracts in force in 2018. An additional 4.9 million euros had to be taken into account for the processing of solvent/detergent virus-inactivated plasma, for a total of about 120 million euros.

The estimate of the expenditure incurred by the NHS in 2018 for the procurement on the market of PDMPs included in the toll fractionation agreements between the Regions and

companies for the quantity not covered by self-sufficiency amounted to 171.1 million euros. An additional 100.8 million euros were due to the purchase of all the other PDMPs.

The expenditure associated to recombinant products was about 410.8 million euros. The total expenditure for medicinal products described in this report was around 2.3% of the total NHS pharmaceutical expenditure recorded in 2018 (54).

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