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Demand for plasma-derived medicinal products in Italy. 2023

F. Candura, M.S. Massari, S. Profili, L. De Fulvio,
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EPIDEMIOLOGIA
E SANITÀ PUBBLICA

ISTITUTO SUPERIORE DI SANITÀ

Demand for plasma-derived medicinal products in Italy. 2023

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2025, vii, 149 p. Rapporti ISTISAN 25/7 EN

The Italian National Blood Centre in compliance with the national regulations about the coordination and provision of technical support to the regional and national planning of self-sufficiency in blood components and plasma-derived medicinal products, has led this 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 includes 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,that is the 2023 update published in the volume *Rapporto ISTISAN* 23/31, stems from a comparative analysis of the available data sources, thus representing an invaluable tool for planning self-sufficiency at national level.
Key words: Plasma-derived medicinal products; Demand; Self-sufficiency; Expenditure

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Analisi della domanda di medicinali plasmaderivati in Italia. 2023.
Fabio Candura, Maria Simona Massari, Samantha Profili, Lucia De Fulvio, Cristiana Chelucci, Chiara Brutti, Vincenzo De Angelis
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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 2023 dei dati sull'argomento pubblicati nel *Rapporto ISTISAN* 23/31 e che si configura come uno strumento fondamentale per la programmazione dell'autosufficienza nazionale.
Parole chiave: Medicinali plasmaderivati; Domanda; Autosufficienza; Spesa

Si ringraziano per il contributo al presente documento: Pierluigi Russo, Francesco Trotta (Area Strategia e Politiche del Farmaco, Agenzia Italiana del Farmaco), Odile Tchangmena Befeuka, Concettina Oliva, Domenico Di Giorgio (Ufficio Qualità dei Prodotti e Contrasto al Crimine Farmaceutico, Agenzia Italiana del Farmaco); Livia Cannata, Giacomo Silvioli, Ilaria Gentilini, Valentina Zambito (Centro Nazionale Sangue, Istituto Superiore di Sanità); le Aziende: Baxalta SpA, Bayer SpA, Biotest Italia srl, CSL Behring SpA, Grifols Italia SpA, Kedrion SpA, Novo Nordisk A/S, Octapharma Italy SpA, Pfizer Italia, Roche SpA, Takeda Italia SpA.

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La responsabilità dei dati scientifici e tecnici è dei singoli autori, che dichiarano di non avere conflitti di interesse.

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ACRONYMNS AND ABBREVIATIONS

3F-PCCs	3-Factor Prothrombin Complex Concentrates
4F-PCCs	4-Factor Prothrombin Complex Concentrates
AIC	Autorizzazione di Immissione in Commercio (Marketing Authorisation)
AIFA	*Agenzia Italiana del FArmaco* (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
CHO	Chinese Hamster Ovary cells
CMV	CytoMegaloVirus
DL	*Decreto Legge* (Decree Law)
DL.vo	*Decreto Legislativo* (Legislative Decree)
DM	*Decreto Ministeriale* (Ministerial Decree of the Ministry of Health)
ELC	Essential Levels of Care
E.-Romagna	Emilia-Romagna
F	Factor
pdFVII	Plasma-derived Factor VII
pdFVIII	Plasma-derived Factor VIII
pdFIX	Plasma-derived Factor IX
FVG or Friuli V. Giulia	Friuli Venezia Giulia
FU/s	FEIBA Unit/s
IG	ImmunoGlobulin
ISTAT	*Istituto Italiano di STATistica* (Italian National Statistics Institute)
IU	International Unit
IVIG	IntraVenous ImmunoGlobulin
LHC	Local Health Centre
LPS	Lombardy-Piedmont-Sardinia agreement
Min	Ministry
Min. of Def.	Ministry of Defence
MoH	Ministry of Health
NAIP	*Nuovo Accordo Interregionale per la Plasmaderivazione* (New Interregional Agreement for plasma-derived medicinal products)
NHS	National Health Service
NSIS	*Nuovo Sistema Informativo Sanitario* (New Health Information System)
PDMP	Plasma-Derived Medicinal Product
rFVIIa	Recombinant activated Factor VII
rFVIII	Recombinant Factor VIII
rFIX	Recombinant Factor IX
RTI	*Raggruppamento Temporaneo d'Impresa* (Temporary Business Grouping)
S/D	Solvent / Detergent (plasma)
SC/IM	SubCutaneous/IntraMuscular
ST	Transfusion Service
VAT	Value Added Tax
vWF	von Willebrand Factor
WHO	World Health Organisation

FOREWORD

The Italian National Blood Centre (Centro Nazionale Sangue, CNS) is a technical branch of the Italian Ministry of Health (MoH) and operates under the Istituto Superiore di Sanità (the National Institute of Health in Italy).

In compliance with the current laws, it supervises and coordinates the technical andscientific support to all aspectsconcerning the production of Plasma and Plasma-Derived Medicinal Products (PDMPs).

CNS primarly provides guidelines regarding the strategic objectives of the transfusion system, which include achieving and maintaining self-sufficiency at regional and national level in labile blood components and PDMPs.

This report concerning the calendar year 2023, also contains the PDMP demand included in the new industrial toll fractionation calls for tender at regional level. In actual fact, the management of toll fractionation services contracts is one of the well-established activities that contributes towards both the planning of plasma and PDMP production, in addition to the monitoring of their consumption and the pharmaceutical expenditure. The main aim of this annual Report, as well as the previous ones published from 2007 to 2022, is to provide some indications and the strategic instruments necessary to achieve and maintain self-sufficiency at regional and national level in plasma and PDMPs in accordance with the national planning objectives drafted in the national plasma and plasma-derived medicinal products programme 2016-2020, established by the Ministerial Decree (*Decreto Ministeriale*, DM) of the Ministry of Health of 2 December 2016 along with the National self-sufficiency in blood and blood products programme 2023, issued by the DM of August 1, 2023.

Dr Vincenzo De Angelis
Director General
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 the whole blood by centrifugation. PDMPs play a key, sometimes irreplaceable, role in the treatment of many acute and chronic clinical conditions (1).

Due to their biological nature, the quality and safety of PDMPs derive from quality checks carried out on the raw material – "plasma" – and on its origin, as well as on the industrial manufacturing processes, including removal and viral inactivation procedures (2).

National self-sufficiency of PDMPs is one of the objectives of the Transfusion System, achieved through the collection of plasma from voluntary, anonymous, unpaid donations, mostly coming from periodic donors, and the plasma sent to pharmaceutical companies authorized to sign agreements with the Regions and Autonomous Provinces (hereinafter Regions) for the purpose of producing PDMPs by toll fractionation system.

Regions, individually or in consortia, supply with the plasma collected by the Blood Establishments (BEs), the companies holder of the agreements for its industrial transformation aimed at the production of PDMPs. The contract with these companies, acting as service providers, is considered a "third party processing" method, which the Regions implement by means of tender procedures in compliance with the current legislation (3-4).

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, under a contract providing for the production of the following PDMPs: albumin, normal human immunoglobulins for intravenous use (IntraVenous ImmunoGlobulin, IVIG), Subcutaneous (SC)/IntraMuscular (IM) immunoglobulins (IG), plasma-derived Factor VIII concentrates (pdFVIII), pdFVIII and von Willebrand Factor (vWF) concentrates in combination (pdFVIII/vWF), and fibrinogen. These products were distributed for the first time to the Regions adhering to the NAIP in 2018 and since then togheter with FVIII, they too have been the subject of this Report.

In the second half of 2020, the Regions part of the Plasma Network agreement (PlaNet), led by the Tuscany Region, and to the Plasma/Plasma-Derived Interregional Grouping (Raggruppamento Interregionale Plasma e Plasmaderivati, RIPP), led by Emilia-Romagna Region, have begun to send plasma to companies awarded in the latest tenders, Takeda Italia SpA on one hand and, on the other, Kedrion SpA and Grifols Italia SpA grouped in a temporary business association (RTI). The launch of new agreements has significantly impacted the quantity and type of PDMPs by toll-fractionation available for the national System, starting from 2022 as per records available.

In actual fact the agreement with the company Takeda envisages an expansion of the basket of ancillary products returned by toll fractionation, such as FVII, 4-factor prothrombin complex (4F-PCCs), activated prothrombin complex concentrates (aPCCs) and Protein C, as well as the supply of mandatory products, and the production of SCIG, 3-factor prothrombin complex (3F-PCCs), plasma-derived Factor IX concentrates (pdFIX) and FVIII/vWF. With regard to the RIPP agreement, on the other hand, the agreement with Grifols and Kedrion also provides for the return of Anti-Thrombin (AT), FVIII/vWF, SCIG, pdFIX, 3F-PCCs, alpha 1-antitrypsin and local haemostatics.

While waiting for the awards of the tender within the fourth interregional agreement for toll fractionation, involving Lombardy, Piedmont and Sardinia, the following PDMPs albumin, IVIG, SCIG, AT, pdFVIII, pdFIX, 3F-PCCs and solvent/detergent virus-inactivated plasma,produced by toll fractionation by Kedrion SpA (hereafter Kedrion) under the contract prior to the enlargement to other possible commercial partners, also contributed to the 2023 national self-sufficiency.

Inasmuch as the clinical interest and its impact on the pharmaceutical expenditure, the Report also 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.

Hence, for each of the PDMPs whose supply is provisioned for in the contracts between the different Regions and the relevant contracted fractionator, the level of regional and national self-sufficiencies is estimated on a case-by-case basis.

Finally, it is outlined the pharmaceutical expenditure incurred by the NHS for drugs procurement on the market, in both cases when it is a portion of the NHS demand not covered by toll fractionation agreements, and otherwise.

The report, after stating the 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 the pharmaceutical expenditure. It is divided in four analytical sections:

– *Part A*
  PDMPs currently provisioned for in toll fractionation agreements.

– *Part B*
  Other PDMPs.

– *Part C*
  National and Regional PDMPs self-sufficiency in regard with the PDMPs provisioned for in toll fractionation agreements.

– *Part D*
  Pharmaceutical expenditure for plasma-derived and alternative recombinant medicinal products.

SOURCES AND METHODOLOGY

Data sources

Drug traceability flow

Since January 2005, the medicinal products traceability database (5) is being daily updated with data gathered from the delivery notes of medicinal products acquired regardless their being part of different reimbursement categories or dispensation regime. Every actor involved in the production and distribution – production sites, warehouses and wholesalers, pharmacies, hospitals etc. – is assigned a unique identifying code and each single package is tracked by a marketing authorisation code (*Autorizzazione all'Immissione in Commercio*, AIC code) at every step throughtout the entire supply chain process (Figure 1).

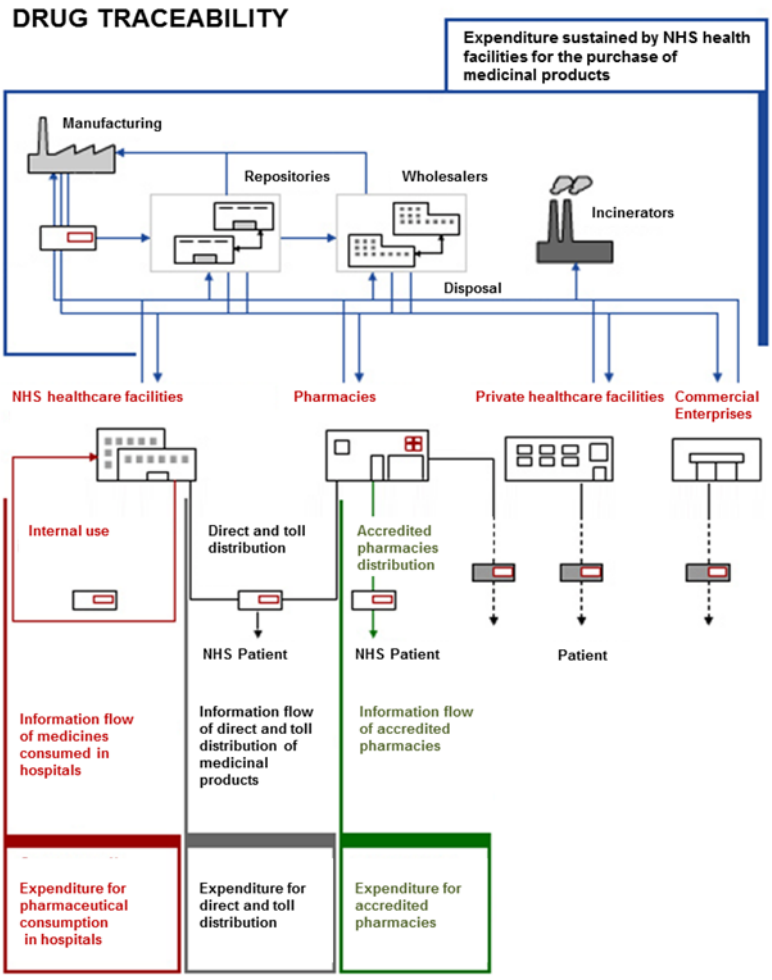

Figure 1. The drug traceability system in Italy (adapted by the CNS on data from www.salute.gov.it)

Pursuant to Italian law, if the final receiver is a public entity (e.g. hospital pharmacies, public healthcare facilities, etc.), the payment due is detected together with the quantity of the product, in order to monitor the pharmaceutical expenditure, in compliance with the law. Thus, the drug traceability system keeps track of the handling from one logistics site to another of all medicinal products identified by the AIC code and quantified by the number of packages, (cfr. all details below the dotted horizontal line in Figure 1) without considering the final users.

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 regarding the 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 as included in the Essential Levels of Care (ELC).

This information flow on nominal basis appears to be the most suitable for calculating the demand for PDMPs supplied through the public pharmacies network and managed by the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) (Figure 2).

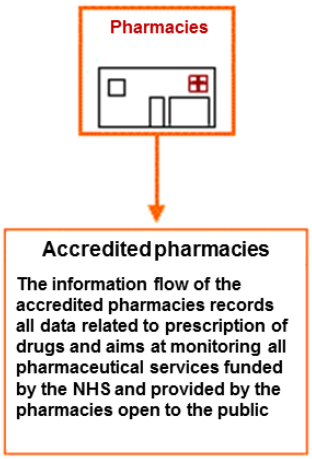

Figure 2. Scope of the information flow of accredited pharmacies (adapted by the CNS on data from www.salute.gov.it)

Information flow of the direct supply of medicinal products

The institutional information flow of the direct supply of medicinal products keeps record of the home use of medicinal products distributed by public healthcare facilities; direct supply can also occur through specific agreements with public pharmacies (toll distribution). This information flow, established by the DM of 31 July 2007 (7), is to detect:

- medicinal products given to patients for home consumption;
- 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 their class of reimbursement (A-C-H), including magistral formulations, officinal formulas and foreign pharmaceuticals not authorised to be sold in Italy and yet used pursuant to the DM of 11 February 1997 (8). In the latter cases, the pharmaceutical features is identified through the Anatomical Therapeutic Chemical (ATC) classification system (see dedicated paragraph).

This information flow consists of the following details, which are monthly submitted by the Regions to the MoH: accounting for the following: 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 supply of medicinal products, shown in Figure 3, records their delivery on a nominal basis.

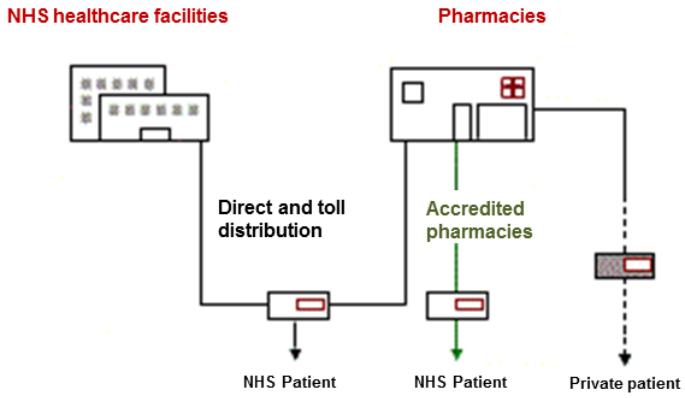

Figure 3. Medicinal products information flow (adapted by theCNS on data from www.salute.gov.it)

This information flow is the most suitable for quantifying the NHS demand for PDMPs, supplied through the direct distribution channel. The information recorded in this flow helps assessing the appropriateness of the prescriptions with regard to the facility in charge of the patients' care, as well as the suitability of the total number of medicinal products consumed by patients, while comparing the drug acquisition costs incurred by the single health facility, allows an indirect evaluation of the purchase tenders.

Information flow of medicines consumed in hospitals

The information flow regarding the monitoring of the consumption of medicinal products in hospitals, takes into consideration the medicinal products used by public healthcare facilities in their typical functions such as hospitalization, specialist day-surgery activities and diagnostic ones.

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 yet used in accordance with the DM of 11 February 1997 (8). In the latter cases, pharmaceutical performance is identified by the ATC code.

The information flow provides for the following details – which are monthly submitted to the MoH: providing facility, receiving operating unit, recipient activity regimen, drug code, disbursement date, quantity delivered and related expenditure (the average weighted cost per unit sustained by the health facility for the medicinal products purchase).

The transfer of toll-manufactured PDMPs is not associated with a purchase cost; however, an estimate of the aforementioned costs can be reckoned through the exchange fees as defined in the 17th of June 2021 State-Regions Agreement (9).

Therefore, the information flow monitoring the consumption of medicinal products in hospitals, 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 the 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.

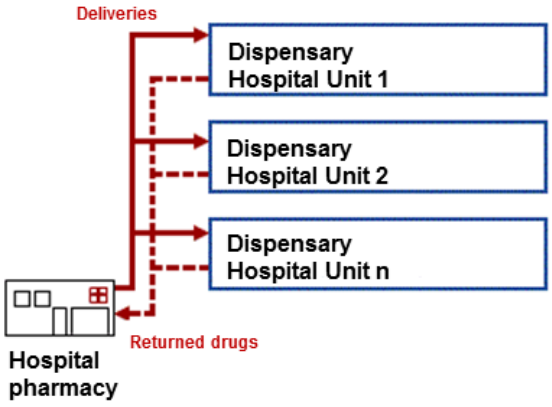

Figure 4. Information flow of medicines consumed in hospitals (adapted by the CNS on data from www.salute.gov.it)

Data on plasma-derived medicinal products produced from Italian plasma

CNS receives the data regarding the PDMPs distributed by Kedrion, CSL Behring, Grifols and Takeda on behalf of the Regions from the aforesaid companies, as part of their toll-manufacturing contracts. These figures add to 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 the DM of 11 February 1997 (8), and the DM of 11 May 2001 (10), are provided by the AIFA Product Quality Office.

Data processing and the ATC drug classification system

For the purpose of this report, different data sources have been accessed to detect the number of packages – by the reference year and their unique AIC codes – to identify the quantities of active ingredients in distributed PDMPs. Each AIC code was traced back to its relevant active ingredient and to its corresponding 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.whocc.no).

Under the ATC system, drugs are classified in different groups according to the target organ, their mechanism of action, as well as their 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 haemopoietic 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 every pharmaceutical product (AIC code). Medicinal products are thus 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, through the ATC classification, it is possible to perform a progressively more detailed identification of all drugs and substances for therapeutic use. Moreover indirectly, through the analysis of the active ingredients or of the prescribed therapeutic groups, it is possible

to formulate hypotheses on the incidence or prevalence of specified pathologies in the general population (11).

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

In order to make aggregate data comparable at regional level, the absolute quantities of each active ingredient of PDMPs are standardised for the resident population as of the 1st of 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, 2022-2023 (adapted by the CNS on data from ISTAT, 04/01/2024)

Region	2022	2023
Abruzzo	1,273,660	1,272,627
Aosta Valley	123,337	123,130
AP Bolzano	535,774	534,147
AP Trento	542,158	542,996
Apulia	3,912,166	3,907,683
Basilicata	539,999	537,577
Calabria	1,844,586	1,846,610
Campania	5,590,681	5,609,536
Emilia-Romagna	4,431,816	4,437,578
Friuli V. Giulia	1,197,295	1,194,248
Latium	5,715,190	5,720,536
Liguria	1,507,438	1,507,636
Lombardy	9,965,046	9,976,509
Marche	1,489,789	1,484,298
Molise	290,769	290,636
Piedmont	4,252,279	4,251,351
Sardinia	1,579,181	1,578,146
Sicily	4,801,468	4,814,016
Tuscany	3,676,285	3,661,981
Umbria	859,572	856,407
Veneto	4,854,633	4,849,553
Italy	58,983,122	58,997,201

Active ingredients and measurement units

For the purpose of quantifying the demand for PDMPs, Table 4 shows measurement units used for each active ingredient. As regards local haemostatics and combinations (ATC B02BC and B02BC30), the diverse commercial products are composed of a mixture of different active ingredients, whose relevant data are expressed in millilitres, with the exception of formulations where the number of sponges utilised are provided yearly.

Table 4. Active ingredients, ATC codes and measurement units

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

Self-sufficiency and pharmaceutical expenditure

For every PDMPs considered in the agreements between the different Regions and their affiliated companies (Kedrion, CSL Behring, Grifols and Takeda), the degree of self-sufficiency achieved has been assessed by comparing the actual supply with the NHS demand, except for polyvalent immunoglobulins. In consideration of the different models of health care organization recorded in the Italian regions, the actual supply was related to the total demand. In this Report, by productive capacity (or potential supply) is meant the theoretical quantity of PDMPs obtainable from the plasma sent by each Region for fractionation from July 2022 to June 2023. By contrast, by effective supply (or toll fractionation) is meant the quantity of PDMPs *de facto* distributed by companies to each Region during the 2023 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, the industrial yields and the planning.

By total demand is meant the regional PDMP consumption through all distribution channels (public and private healthcare facilities, pharmacies, etc.). While by NHS demand is meant the share of the total demand funded by the NHS.

Potential self-sufficiency is the percent ratio between the productive capacity and the NHS demand (unlike polyvalent immunoglobulins, whose potential supply is compared with total demand). While effective self-sufficiency is the percent ratio between the effective supply and the NHS demand (except for polyvalent immunoglobulins as explained above).

In the dedicated chapter, pharmaceutical expenditure is defined as the expenditure for the supply of PDMPs covered by the NHS in public health facilities and accredited pharmacies. As far as the first channel is concerned, the aggregate purchase cost of PDMPs incurred by public facilities has been 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 relevant on 31/12/2023, and applying any possible discounts provided for by Law 662/1996 (13), amended by Law 122/2010 (14).

As far as albumin, IVIG and pdFVIII, are concerned, as identified by the 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 in 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.

In regard with toll-fractionated medicinal products, it is not possible to provide an estimate of the relevant expenditure. Only the total amount paid by the Regions for plasma processing services, not including the costs sustained for the production of plasma as “raw material”, can be accounted for.

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 medicinal products 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, 31/12/2023)

AIC code	Brand name	g	Manufacturer	NHS class
049507041	ALBUMINA GRIFOLS*1FL 10mL 200 g/L	2	INSTITUTO GRIFOLS S.A	A
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
049507015	ALBUMINA GRIFOLS*1FL 100mL 50 g/L	5	INSTITUTO GRIFOLS S.A	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	LBF	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)
049507054	ALBUMINA GRIFOLS*1FL 50mL 200 g/L	10	INSTITUTO GRIFOLS S.A	A
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/100mL	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	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

AIC code	Brand name	g	Manufacturer	NHS class
049507027	ALBUMINA GRIFOLS*1FL 250mL 50 g/L	12,5	INSTITUTO GRIFOLS S.A	C
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
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)
049507066	ALBUMINA GRIFOLS*1FL100mL 200g/L	20	INSTITUTO GRIFOLS S.A	A
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
049507039	ALBUMINA GRIFOLS*1FL 500mL 50 g/L	25	INSTITUTO GRIFOLS S.A	C
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 50mL20%, 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*24SACCHE50mL 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 albumin[1] for the two-year period 2022-2023 with the variations in percentage, both at national and regional levels. In 2023, the national demand for this principle was about 34,553 kilograms (Table 6), equal to about 586 grams per 1,000 population, with a decrease of 3.6% from the previous year. The three Regions with the highest

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

standardised demand were Sardinia, E.-Romagna and Campania, with values equal to 939, 811 and 769 grams per 1,000 population, respectively. The Regions with the lowest demand were the AP of Bolzano, Piedmont and Molise, where it is between 346 and 409 grams grams per 1,000 population (Figure 5).

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,127,258	885.1	873,298	686.2	-22.5
Aosta Valley	64,300	521.3	73,760	599.0	14.9
AP Bolzano	214,828	401.0	184,640	345.7	-13.8
AP Trento	229,050	422.5	265,170	488.3	15.6
Apulia	2,121,725	542.3	1,891,590	484.1	-10.7
Basilicata	450,118	833.6	346,753	645.0	-22.6
Calabria	1,062,360	575.9	961,380	520.6	-9.6
Campania	4,159,853	744.1	4,316,193	769.4	3.4
E.-Romagna	3,245,633	732.3	3,599,790	811.2	10.8
Friuli V. Giulia	602,840	503.5	491,350	411.4	-18.3
Latium	2,681,010	469.1	2,763,275	483.0	3.0
Liguria	983,718	652.6	941,915	624.8	-4.3
Lombardy	6,743,008	676.7	6,395,853	641.1	-5.3
Marche	932,330	625.8	900,445	606.6	-3.1
Molise	152,378	524.1	108,795	374.3	-28.6
Piedmont	1,723,830	405.4	1,739,503	409.2	0.9
Sardinia	1,316,068	833.4	1,481,753	938.9	12.7
Sicily	3,295,173	686.3	2,982,878	619.6	-9.7
Tuscany	1,487,703	404.7	1,547,768	422.7	4.4
Umbria	587,700	683.7	564,450	659.1	-3.6
Veneto	2,665,713	549.1	2,122,453	437.7	-20.3
ITALY	35,846,590	607.7	34,553,008	585.7	-3.6

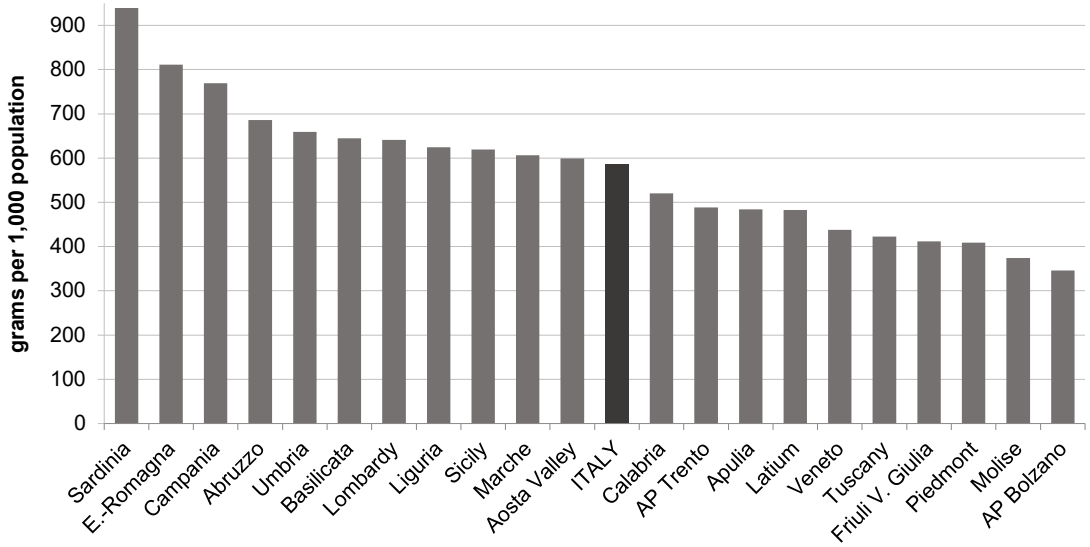

Figure 5. Total and regional demand (public and private) for albumin, expressed in grams per 1,000 population, 2023 (adapted by the CNS on data from the Traceability information flow)

In this two-year period, the total standardised demand for albumin showed a moderate decrease compared to the previous years (-3.6% compared to 2022) (17). The regions where there was a lesser use most evidently are Molise (-28%) and Basilicata and Abruzzo (-23%).While the AP of Trento (+16%) and Aosta Valley (+15%) are the Regions where demand shows the greatest growth.

Figure 6 highlights the eleven Regions with a higher demand compared to national demand, with a value higher than 30% for three of them. Figure 7 shows the standardised regional demand for albumin recorded in 2023 per distribution channel (public pharmacies compared to other facilities), as shown by the drug Traceability system (18).

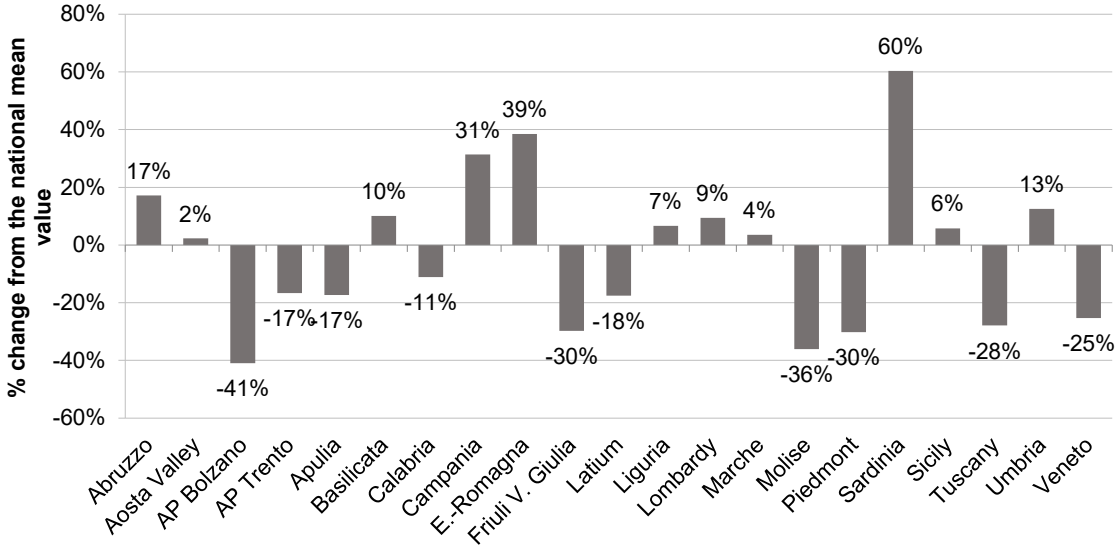

Figure 6. Percentage change from the national mean value of standardised regional demand for human albumin in 2023 (adapted by the CNS on data from the Traceability information flow)

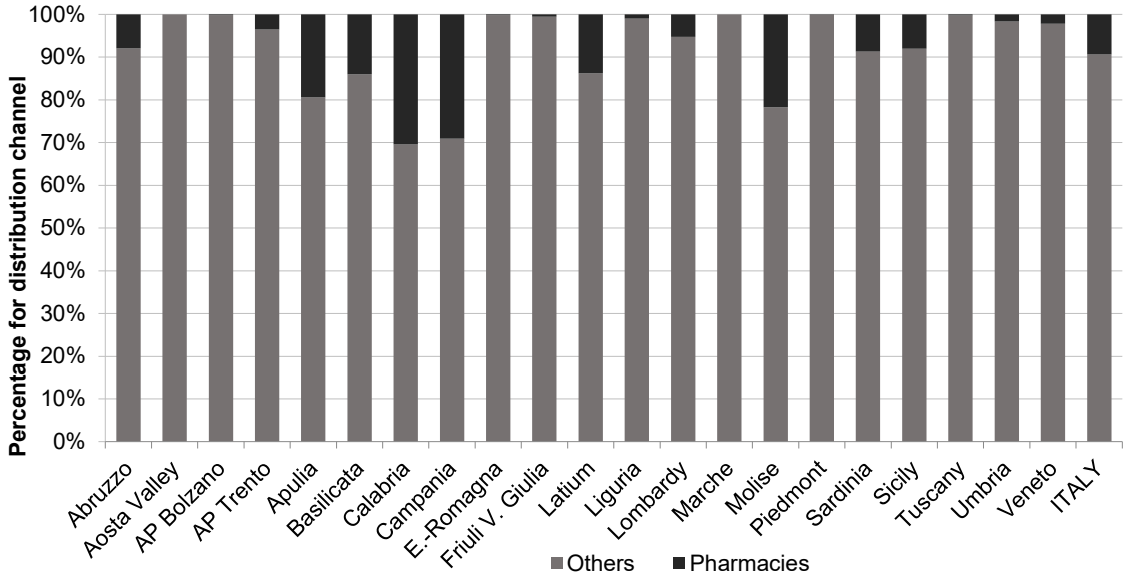

Figure 7. Standardised regional demand for albumin recorded per distribution channel, 2023 (adapted by the CNS on data from the Traceability information flow)

In 2023, about 9% of the national demand - approximately 3,232 kilograms - was distributed through public pharmacies.

The distribution channel of pharmacies was mostly used in Campania and Calabria, where they accounted for 29% and 30% respectively of the regional demand; still used to a lesser extent in Latium, Molise, Basilicata and Apulia (with percentages of between 14 and 22% of the total regional demand, while in the other Regions they were rarely used (<10%).

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 even though their use is not always fully justified by the available evidence in the scientific literature. Since 2007, both soluble IG preparations for subcutaneous/intramuscular infusion (SC/IM) and those for intravenous use (IntraVenous, IV) (19) have been available in Italy. IGs, like all other PDMPs, are prepared from human plasma pools, which guarantees the recipient a higher antibody coverage thanks to a significant idiotypical diversity. The preparations contain structurally and functionally intact IGs, with normal half-life and subclass proportions: 95% of monomeric IGG, small amounts of dimers, and variable amounts of IGA and IGM. Table 7 shows the names of the medicinal products containing IG that are currently marketed in Italy and the amount of the 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, 31/12/2023)

AIC code	Brand name	g	Manufacturer	NHS class
Normal human immunoglobulin for subcutaneous/intramuscular use				
036 800011	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				
045996016	CUTAQUIG*SC 1 FL 6 mL 165 mg/mL	0.9	OCTAPHARMA ITALY SpA	C
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	H
044244010	CUVITRU*SC 1FL 5mL 200mg/mL	1	BAXALTA ITALY Srl	H
049488012	XENBIFY*1FL 5mL 200 mg/mL	1	INSTITUTO GRIFOLS S.A	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
045996028	CUTAQUIG*SC 1 FL 10 mL 165 mg/mL	1.65	OCTAPHARMA ITALY SpA	C
040652101	OCTANORM*FL 12mL 165mg/mL	1.98	OCTAPHARMA ITALY SpA	H
045996030	CUTAQUIG*SC 1 FL 12 mL 165 mg/mL	1.98	OCTAPHARMA ITALY SpA	C
041157049	HIZENTRA*SC 1FL 10mL 200mg/mL	2	CSL BEHRING SpA	H
041157177	HIZENTRA*SC 1SIR 10mL 200mg/mL	2	CSL BEHRING SpA	H
044244022	CUVITRU*SC 1FL 10mL 200mg/mL	2	BAXALTA ITALY Srl	H
049488024	XENBIFY*1FL 10mL 200 mg/mL	2	INSTITUTO GRIFOLS S.A	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
045996042	CUTAQUIG*SC 1 FL 20 mL 165 mg/mL	3.3	OCTAPHARMA ITALY SpA	C
040652137	OCTANORM*FL 24mL 165mg/mL	3.96	OCTAPHARMA ITALY SpA	H
045996055	CUTAQUIG*SC 1 FL 24 mL 165 mg/mL	3.96	OCTAPHARMA ITALY SpA	C
041157102	HIZENTRA*SC 1FL 20mL 200mg/mL	4	CSL BEHRING SpA	H
041157191	HIZENTRA*SC 1FL 20mL 200mg/mL	4	CSL BEHRING SpA	H
043396023	NAXIGLO*SC FL 25mL 160mg/mL	4	KEDRION SpA	H

AIC code	Brand name	g	Manufacturer	NHS class
043398027	KEYCUTE*SC FL 25mL 160mg/mL	4	KEDRION SpA	H
044244034	CUVITRU*SC 1FL 20mL 200mg/mL	4	BAXALTA ITALY Srl	H
049488036	XENBIFY*1FL 20mL 200 mg/mL	4	INSTITUTO GRIFOLS S.A	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
045996067	CUTAQUIG*SC 1 FL 48 mL 165 mg/mL	7.92	OCTAPHARMA ITALY SpA	C
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
045996079	CUTAQUIG*SC 10 FL 6 mL 165 mg/mL	9.9	OCTAPHARMA ITALY SpA	C
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	H
042804031	HYQVIA*SC 1FL 100mL+1FL 5mL	10	BAXALTA ITALY Srl	H
044244059	CUVITRU*SC 1 FL 50mL 200 mg/mL	10	BAXALTA INN. GMBH	C(nn)
044244061	CUVITRU*SC 10FL 5mL 200 mg/mL	10	BAXALTA INN. GMBH	C(nn)
049488048	XENBIFY*1FL 50mL 200 MG/ML	10	INSTITUTO GRIFOLS S.A	H
040652024	OCTANORM*10FL 10mL 165mg/mL	16.5	OCTAPHARMA ITALY SpA	H
045996081	CUTAQUIG*SC 10 FL 10 mL 165 mg/mL	16.5	OCTAPHARMA ITALY SpA	C
040652099	OCTANORM*20FL 6mL 165mg/mL	19.8	OCTAPHARMA ITALY SpA	H
040652113	OCTANORM*10FL 12mL 165mg/mL	19.8	OCTAPHARMA ITALY SpA	H
045996093	CUTAQUIG*SC 10 FL 12 mL 165 mg/mL	19.8	OCTAPHARMA ITALY SpA	C
045996131	CUTAQUIG*SC 20 FL 6 mL 165 mg/mL	19.8	OCTAPHARMA ITALY SpA	C
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	H
042804043	HYQVIA*SC 1FL 200mL+1FL 10mL	20	BAXALTA ITALY Srl	H
044244073	CUVITRU*SC 20FL 5mL 200 mg/mL	20	BAXALTA INN. GMBH	C(nn)
044244085	CUVITRU*SC 10FL 10mL 200 mg/mL	20	BAXALTA INN. GMBH	C(nn)
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
045996105	CUTAQUIG*SC 10 FL 20 mL 165 mg/mL	33	OCTAPHARMA ITALY SpA	C
045996143	CUTAQUIG*SC 20 FL 10 mL 165 mg/mL	33	OCTAPHARMA ITALY SpA	C
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
045996117	CUTAQUIG*SC 10 FL 24 mL 165 mg/mL	39.6	OCTAPHARMA ITALY SpA	C
045996156	CUTAQUIG*SC 20 FL 12 mL 165 mg/mL	39.6	OCTAPHARMA ITALY SpA	C
041157064	HIZENTRA*20FL 10mL 200mg/mL	40	CSL BEHRING SpA	H
041157114	HIZENTRA*10FL 20mL 200mg/mL	40	CSL BEHRING SpA	H
041157203	HIZENTRA*10FL 20mL 200mg/mL	40	CSL BEHRING SpA	H
044244109	CUVITRU*SC 10FL 20mL 200 mg/mL	40	BAXALTA INN. GMBH	C(nn)
044244123	CUVITRU*SC 5FL 40mL 200 mg/mL	40	BAXALTA INN. GMBH	C(nn)
044244147	CUVITRU*SC 20FL 10mL 200 mg/mL	40	BAXALTA GMBH	C(nn)
041157090	HIZENTRA*20FL 15mL 200mg/mL	60	CSL BEHRING SpA	H
044244097	CUVITRU*SC 30FL 10mL 200 mg/mL	60	BAXALTA INN. GMBH	C(nn)
040652063	OCTANORM*20FL 20mL 165mg/mL	66	OCTAPHARMA ITALY SpA	H
045996168	CUTAQUIG*SC 20 FL 20 mL 165 mg/mL	66	OCTAPHARMA ITALY SpA	C
040652152	OCTANORM* 20FL 24mL 165mg/mL	79.2	OCTAPHARMA ITALY SpA	H
040652176	OCTANORM*10FL 48mL 165mg/mL	79.2	OCTAPHARMA ITALY SpA	H
045996129	CUTAQUIG*SC 10 FL 48 mL 165 mg/mL	79.2	OCTAPHARMA ITALY SpA	C
045996170	CUTAQUIG*SC 20 FL 24 mL 165 mg/mL	79.2	OCTAPHARMA ITALY SpA	C
041157126	HIZENTRA*20FL 20mL 200mg/mL	80	CSL BEHRING SpA	H
044244150	CUVITRU*SC 20FL 20ML 200 mg/mL	80	BAXALTA GMBH	C(nn)
044244162	CUVITRU*SC 10FL 40ML 200 mg/mL	80	BAXALTA GMBH	C(nn)
041157140	HIZENTRA*10FL 50mL 200mg/mL	100	CSL BEHRING SpA	C(nn)
044244111	CUVITRU*SC 30FL 20mL 200 mg/mL	120	BAXALTA INN. GMBH	C(nn)
040652188	OCTANORM* 20FL 48mL 165mg/mL	158.4	OCTAPHARMA ITALY SpA	H
045996182	CUTAQUIG*SC 20 FL 48 mL 165 mg/mL	158.4	OCTAPHARMA ITALY SpA	C

AIC code	Brand name	g	Manufacturer	NHS class
044244135	CUVITRU*SC 20FL 40mL 200 mg/mL	160	BAXALTA INN. GMBH	C(nn)
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	INSTITUTO 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	C
045410014	GAMUNEX *INF 1FL 10 mL 100mg/mL	1	Grifols Deutschland GmbH	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	H
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	C
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
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	H
044187033	GLOBIGA*INF 1FL 5g 100mg/mL	5	OCTAPHARMA ITALY SpA	C
045410026	GAMUNEX *INF 1FL 50 mL 100mg/mL	5	Grifols Deutschland GmbH	H
045410038	GAMUNEX *INF1FL 50mL 100mg/mL C.o	5	Grifols Deutschland GmbH	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	C
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

AIC code	Brand name	g	Manufacturer	NHS class
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	H
044187058	GLOBIGA*INF 1FL 10g 100mg/mL	10	OCTAPHARMA ITALY SpA	C
045410040	GAMUNEX *INF 1FL 100 mL 100mg/mL	10	Grifols Deutschland GmbH	H
045410053	GAMUNEX *INF 1FL100mL 100mg/mL C.o	10	Grifols Deutschland GmbH	H
025266192	IGVENA*EV 2FL 200ML 50G/L+SET	20	KEDRION SpA	C(nn)
029249087	PLITAGAMMA*INF 1 FL 400mL 50mg/mL	20	INSTITUTO 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	H
044187072	GLOBIGA*INF 1FL 20g 100mg/mL	20	OCTAPHARMA ITALY SpA	C
045410065	GAMUNEX *INF 1FL 200 mL 100mg/mL	20	Grifols Deutschland GmbH	H
045410077	GAMUNEX *INF1FL200mL 100mg/mL C.o	20	Grifols Deutschland GmbH	H
035143041	OCTAGAM*IV FL 500mL 5%	25	OCTAPHARMA ITALY SpA	H
025266204	IGVENA*EV 3FL 200ML 50G/L+SET	30	KEDRION SpA	C(nn)
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	C
039457080	GAMTEN*INF 1FL 300mL 100mg/mL	30	OCTAPHARMA ITALY SpA	C(nn)
039712070	PRIVIGEN*EV 1FL 400mL 100mg/mL	40	CSL BEHRING GMBH	C(nn)
045410089	GAMUNEX *INF 1FL 400 mL 100mg/mL	40	Grifols Deutschland GmbH	H
045410091	GAMUNEX *INF1FL400 mL 100mg/mL C.o	40	Grifols Deutschland GmbH	H
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 2022-2023 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 2023, the total national demand for IGs was 6,471,964 grams, equal to 109.7 grams per 1,000 population (Table 8). The three Regions with the highest standardised demand per 1,000 population were E.-Romagna with around 161 grams, and Marche and Aosta Valley with around 154 grams. The demand was lower in Calabria, Molise and Campania, where it ranged between 62 and 75 grams per 1,000 population. The demand for these PDMPs shows a slight increase in the two-year period 2022-2023 (+3.6%), featuring notable differences from one Region to another. The greatest increase is recorded in Molise (+25%) and in Friuli V. Giulia (+17%). The most marked decrease is instead observed in Basilicata (-21%).

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 (38.2%), Calabria (36.1%) and Latium (35.8%) while fewer were used in Sardinia, in the AP Bolzano, Aosta Valley and Friuli V. Giulia (≤7%). At national level, the demand for SC/IM IGs stood at 22% of the total demand for IGs.

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	154,193	121.1	124,736	98.0	-19.0
Aosta Valley	22,658	183.7	18,951	153.9	-16.2
AP Bolzano	52,290	97.6	54,312	101.7	4.2
AP Trento	52,250	96.4	55,751	102.7	6.5
Apulia	389,194	99.5	420,250	107.5	8.1
Basilicata	72,663	134.6	56,955	105.9	-21.3
Calabria	114,884	62.3	114,445	62.0	-0.5
Campania	408,832	73.1	420,967	75.0	2.6
E.-Romagna	615,557	138.9	714,645	161.0	15.9
Friuli V. Giulia	136,927	114.4	160,326	134.2	17.4
Latium	572,200	100.1	559,537	97.8	-2.3
Liguria	240,711	159.7	213,963	141.9	-11.1
Lombardy	988,409	99.2	1,038,612	104.1	5.0
Marche	196,973	132.2	228,817	154.2	16.6
Molise	17,264	59.4	21,511	74.0	24.7
Piedmont	523,382	123.1	528,166	124.2	0.9
Sardinia	117,034	74.1	128,954	81.7	10.3
Sicily	351,416	73.2	390,307	81.1	10.8
Tuscany	519,631	141.3	531,837	145.2	2.7
Umbria	122,398	142.4	125,773	146.9	3.1
Veneto	574,832	118.4	563,151	116.1	-1.9
ITALY	6,243,697	105.9	6,471,964	109.7	3.6

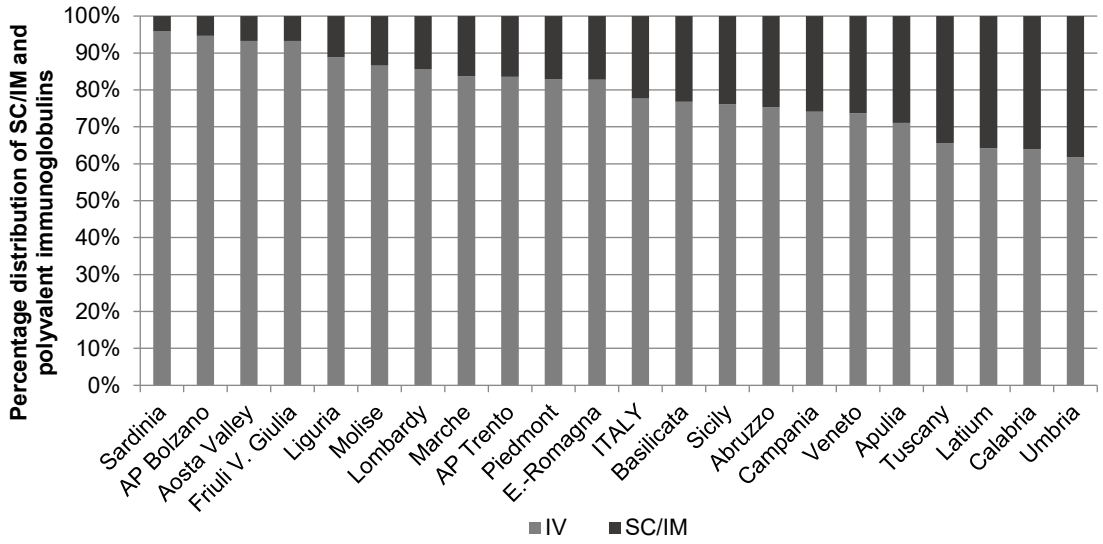

Figure 8. Total standardised demand (public and private) per administration of immunoglobulins (percentage on total), by Region, 2023 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for subcutaneous use

In 2023, the total demand for SC/IM IGs reached about 1,445,792 grams (24.5 grams per 1,000 population), with an increase of 3% compared to 2022 (Table 9).

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	28,488	22.4	30,760	24.2	8.1
Aosta Valley	1,883	15.3	1,278	10.4	-32.0
AP Bolzano	2,746	5.1	2,926	5.5	6.9
AP Trento	8,520	15.7	9,161	16.9	7.4
Apulia	102,276	26.1	121,439	31.1	18.9
Basilicata	15,231	28.2	13,237	24.6	-12.7
Calabria	39,208	21.3	41,259	22.3	5.1
Campania	111,446	19.9	109,022	19.4	-2.5
E.-Romagna	121,882	27.5	123,385	27.8	1.1
Friuli V. Giulia	8,972	7.5	10,821	9.1	20.9
Latium	199,237	34.9	200,270	35.0	0.4
Liguria	34,251	22.7	23,923	15.9	-30.2
Lombardy	135,763	13.6	149,874	15.0	10.3
Marche	35,725	24.0	37,238	25.1	4.6
Molise	2,944	10.1	2,886	9.9	-1.9
Piedmont	88,857	20.9	90,656	21.3	2.0
Sardinia	6,359	4.0	5,199	3.3	-18.2
Sicily	90,996	19.0	93,345	19.4	2.3
Tuscany	179,914	48.9	183,036	50.0	2.1
Umbria	42,118	49.0	48,025	56.1	14.4
Veneto	148,223	30.5	148,053	30.5	0.0
ITALY	1,405,036	23.8	1,445,792	24.5	2.9

The regional demands proved diversified with the highest value recorded of 56 grams per 1,000 population in Umbria followed by Tuscany and Latium with 50 and 35 grams per 1,000 population respectively.

However, the lowest values were recorded in Sardinia, AP of Bolzano and in Friuli V. Giulia, where they fluctuated between 3.3 and 9.1 grams per 1,000 population (Figure 9).

In Umbria, Tuscany, Latium, Apulia, Veneto, Emilia-Romagna, Marche and Basilicata a higher total demand compared to national demand was recorded (range: 0.5-129%) (Figure 10).

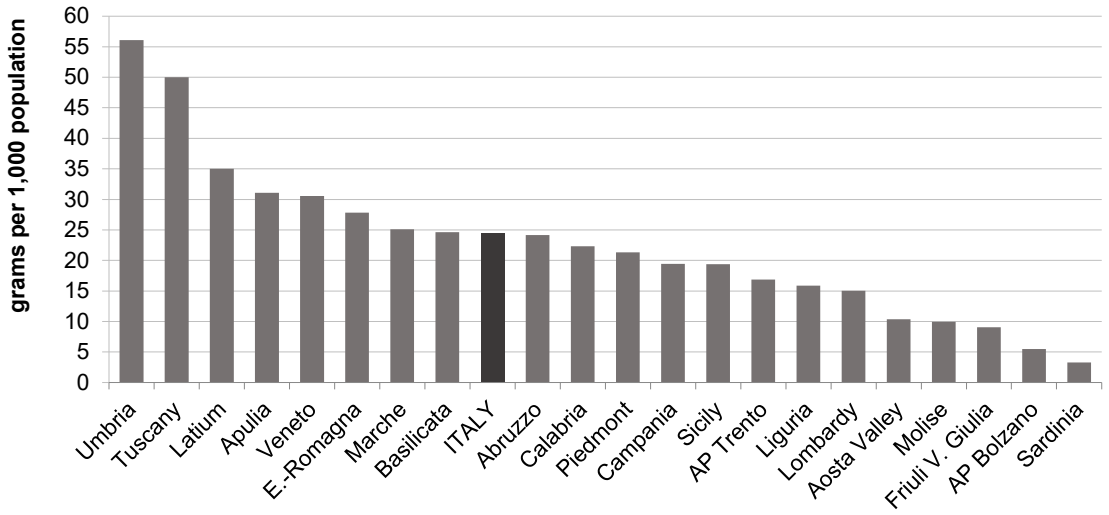

Figure 9.Total and regional demand (public and private) for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams per 1,000 population, 2023 (adapted by the CNS on data from the Traceability information flow)

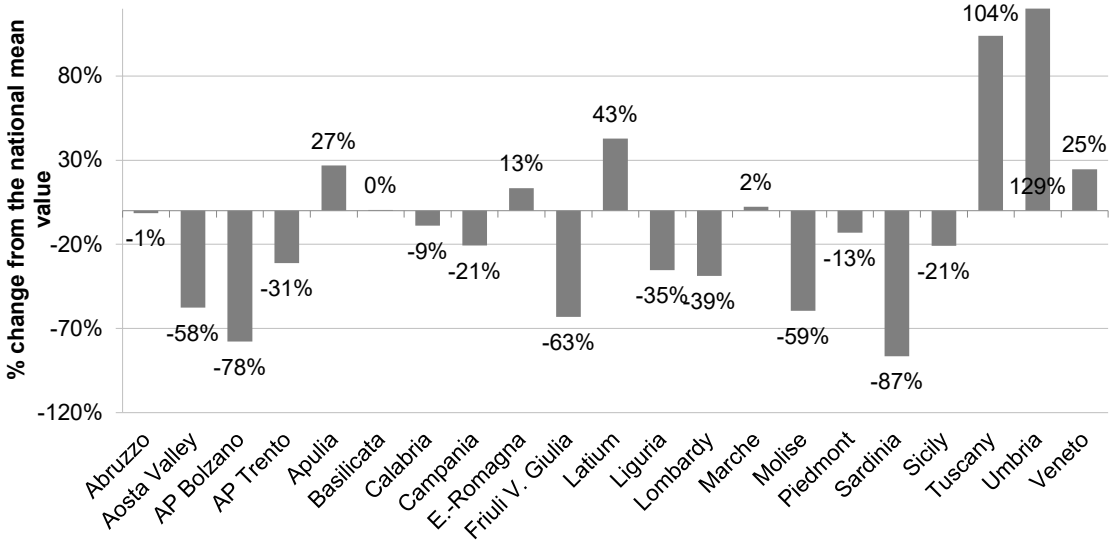

Figure 10. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for subcutaneous/ intramuscular use in 2023 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for intravenous use

Finally, Table 10 reports on the total and standardised demands for IG for intravenous use in 2022-2023.

Even, in this case, a general increase (about +3.9%) was observed, while it was not confirmed in Abruzzo, Basilicata, Calabria, Latium, Liguria, Umbria, Aosta Valley and Veneto.

Figure 11 shows the standardised regional demand for IVIGs in 2023 as recorded by the drug Traceability system.

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	125,705	98.7	93,976	73.8	-25.2
Aosta Valley	20,776	168.4	17,673	143.5	-14.8
AP Bolzano	49,544	92.5	51,386	96.2	4.0
AP Trento	43,730	80.7	46,590	85.8	6.4
Apulia	286,918	73.3	298,811	76.5	4.3
Basilicata	57,432	106.4	43,718	81.3	-23.5
Calabria	75,676	41.0	73,186	39.6	-3.4
Campania	297,387	53.2	311,946	55.6	4.5
E.-Romagna	493,675	111.4	591,260	133.2	19.6
Friuli V. Giulia	127,955	106.9	149,505	125.2	17.1
Latium	372,964	65.3	359,267	62.8	-3.8
Liguria	206,460	137.0	190,040	126.1	-8.0
Lombardy	852,646	85.6	888,738	89.1	4.1
Marche	161,248	108.2	191,580	129.1	19.3
Molise	14,320	49.2	18,625	64.1	30.1
Piedmont	434,525	102.2	437,510	102.9	0.7
Sardinia	110,675	70.1	123,755	78.4	11.9
Sicily	260,420	54.2	296,963	61.7	13.7
Tuscany	339,717	92.4	348,801	95.2	3.1
Umbria	80,280	93.4	77,748	90.8	-2.8
Veneto	426,609	87.9	415,098	85.6	-2.6
ITALY	4,838,661	82.0	5,026,172	85.2	3.9

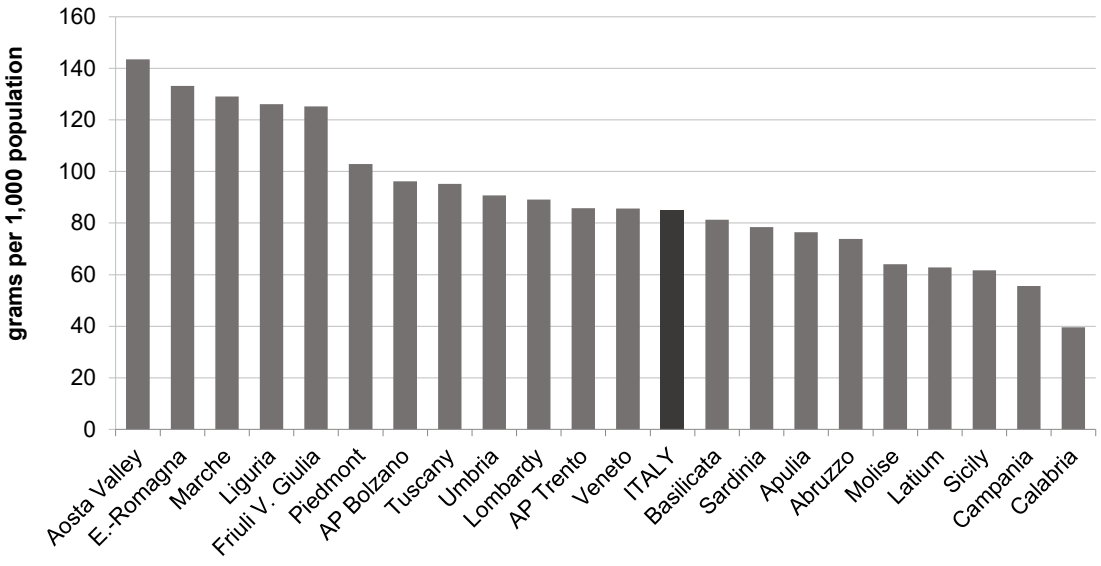

Figure 11. Total and regional demand (public and private) for normal human immunoglobulins for intravenous use, expressed in grams per 1,000 population, 2023 (adapted by the CNS on data from the Traceability information flow)

The highest demand for IVIGs was recorded in Aosta Valley, E.-Romagna and Marche, with volumes ranging between 143.5 and 129.1 grams per 1,000 population (+68%, +56% and +52% respectively, compared to the national mean value – Figure 12). The Regions where the standardized demand was lower were Calabria and Campania with recorded volumes between 40 and 56 grams per 1,000 population.

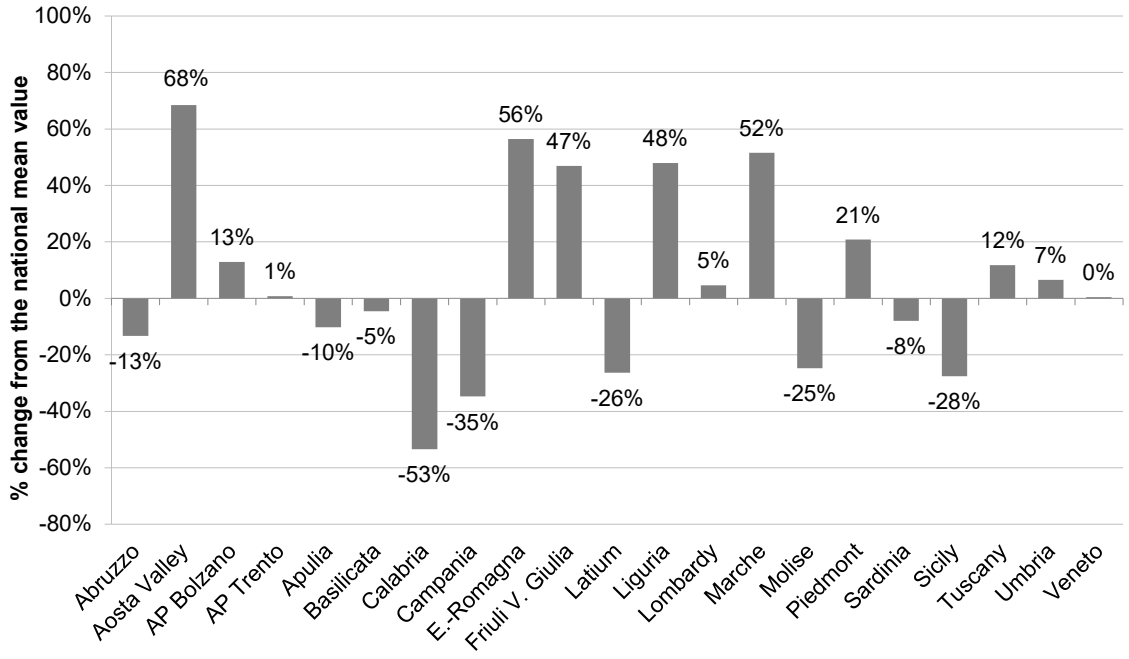

Figure 12. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for intravenous use in 2023 (adapted by the CNS on data from the Traceability information flow)

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 that 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 available on the Italian market and the relative quantity of the active ingredients 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
025766039	KYBERNIN P*IV FL 500IU+10mL+SET	500	CSL BEHRING SpA	H
027113012	ANTITROMBINA III IMMUNO*FL10mL	500	BAXALTA ITALY Srl	H
029378015	AT III KED*500IU+FL 10mL+SET	500	KEDRION SpA	H
031118019	ATENATIV*IV FL 500IU+FL 10mL	500	OCTAPHARMA ITALY SpA	H
034330035	ANBINEX*FL 500IU+SIR 10mL+SET	500	GRIFOLS ITALIA SpA	H
041800018	ATKED*FL 500IU+FL 20mL+SET	500	KEDRION SpA	H
044565012	ATTERTIUM FL 500IU+SIR 10mL	500	GRIFOLS ITALIA SpA	C(nn)
025766027	KYBERNIN P*IV FL 1000IU+F 20mL	1000	CSL BEHRING SpA	H
027113024	ANTITROMBINA III IMMUNO*FL20mL	1000	BAXALTA ITALY Srl	H
029378027	AT III KED*1000IU+FL 20mL+SET	1000	KEDRION SpA	H
031118021	ATENATIV*IV FL 1000IU+FL 20mL	1000	OCTAPHARMA ITALY SpA	H
034330047	ANBINEX*FL 1000IU+SIR 20mL+SET	1000	GRIFOLS ITALIA SpA	H
041800020	ATKED*FL 1000IU+FL 20mL+SET	1000	KEDRION SpA	H
044565024	ATTERTIUM FL 1000IU+SIR 20mL	1000	GRIFOLS ITALIA SpA	C(nn)
029378039	AT III KED*2000IU+FL 20mL+SET	2000	KEDRION SpA	H
041800032	ATKED*FL 2000IU+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*) for AT in the two-year period 2022-2023 with the relative percentage changes at national and regional levels.

In 2023, total AT demand was 117,992,500 IUs, equal to 2.0 IUs *per capita*, showing a slight decrease from the consumption recorded in the previous year (-12% compared to 2022). The Region where there was the most evident usage restraint was the AP of Bolzano (-59%).
Conversely, in two Regions there was a significant upward trend (>60%) in its use [range: Aosta Valley (+ 66%) – E.-Romagna (+ 87%)].

Figure 13 shows the regional and national standardised demand for AT in 2023. The Regions with the highest *per capita* demand were Calabria, Sicily and Aosta Valley, with a demand of 4.0 IUs for the first one and 3.5 and 3.4 IUs respectively for the other two Regions. The lowest demand, less than 1 IUs *per capita*, was recorded in the AP of Trento (0.9 IU) and AP of Bolzano (0.4 IU).

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,304,500	1.8	3,304,500	2.6	43.5
Aosta Valley	250,000	2.0	414,000	3.4	65.9
AP Bolzano	487,000	0.9	200,000	0.4	-58.8
AP Trento	444,000	0.8	502,000	0.9	12.9
Apulia	9,761,000	2.5	6,818,500	1.7	-30.1
Basilicata	1,703,000	3.2	1,470,000	2.7	-13.3
Calabria	7,603,500	4.1	7,467,000	4.0	-1.9
Campania	12,650,500	2.3	13,163,500	2.3	3.7
E.-Romagna	4,461,500	1.0	8,334,500	1.9	86.6
Friuli V. Giulia	4,120,000	3.4	2,980,000	2.5	-27.5
Latium	18,215,500	3.2	14,021,000	2.5	-23.1
Liguria	4,875,500	3.2	3,266,500	2.2	-33.0
Lombardy	12,872,000	1.3	11,187,500	1.1	-13.2
Marche	3,635,000	2.4	2,898,000	2.0	-20.0
Molise	744,000	2.6	708,000	2.4	-4.8
Piedmont	8,276,500	1.9	6,791,500	1.6	-17.9
Sardinia	1,934,500	1.2	2,262,500	1.4	17.0
Sicily	20,453,000	4.3	16,677,500	3.5	-18.7
Tuscany	7,860,000	2.1	7,931,500	2.2	1.3
Umbria	896,000	1.0	1,003,000	1.2	12.4
Veneto	10,577,500	2.2	6,591,500	1.4	-37.6
ITALY	134,124,500	2.3	117,992,500	2.0	-12.0

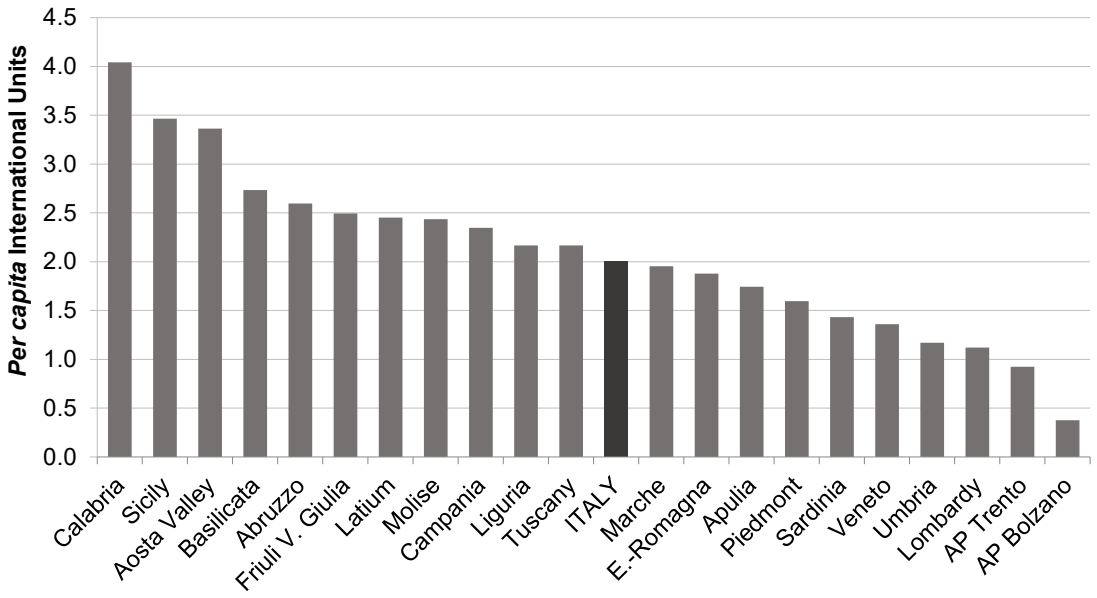

Figure 13. Total and regional demand (public and private) for antithrombin, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

Figure 14 shows the difference between the regional *per capita* percentage and the national mean value for the year 2023.

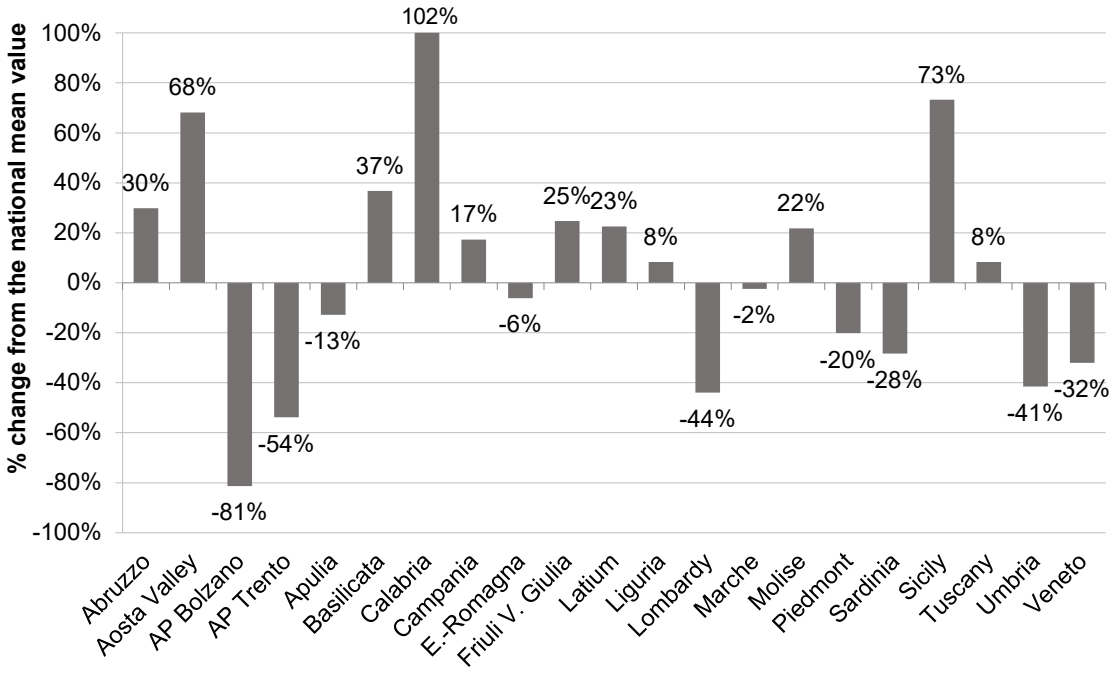

Figure 14. Percentage change from the national mean value of standardised regional demand for antithrombin in 2023 (adapted by the CNS on data from the Traceability information flow)

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 divided in plasma-derived concentrates (pdFVIII) and products obtained with genetic recombination techniques (rFVIII) (23). PdFVIII concentrates are obtained from plasma pools from 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 ± 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
033657014	BERIATE*F 250IU+SOLV+SET	250	CSL BEHRING SpA	A
038541013	HAEMOCTIN*FL 250IU+FL 5mL+SIR	250	BIOTEST PHARMA GMBH	A
023564216	EMOCLOT*FL 500IU+FL 10mL+SET	500	KEDRION SpA	A
033657026	BERIATE*F 500IU+SOLV+SET	500	CSL BEHRING SpA	A
038541025	HAEMOCTIN*FL 500IU+FL 10mL+SIR	500	BIOTEST PHARMA GMBH	A
041649017	KLOTT*FL 500IU+FL 10mL+SET	500	KEDRION SpA	A
023564228	EMOCLOT*FL 1000IU+FL 10mL+SET	1000	KEDRION SpA	A
033657038	BERIATE*F 1000IU+SOLV+S	1000	CSL BEHRING SpA	A
038541037	HAEMOCTIN*FL 1000IU+FL 10mL+SIR	1000	BIOTEST PHARMA GMBH	A
041649029	KLOTT*FL 1000IU+FL 10mL+SET	1000	KEDRION SpA	A
033657040	BERIATE*FL 2000IU+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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
Factor VIII and von Willebrand Factor in combination				
033077088	ALPHANATE*INF 1F 250IU+SIR+AD	250	GRIFOLS ITALIA SpA	A
033866043	FANHDI*INF FL 250IU+SIR SOLV+S	250	GRIFOLS ITALIA SpA	A
037148018	TALATE*250IU/190IU+FL5mL+SIR	250	BAXALTA INN.Gmbh	A
040112017	OCTANATE*INIET FL 250IU+FL 5mL	250	OCTAPHARMA ITALY SpA	A
042939013	VONCENTO*250IU/600IU+FL 5mL	250	CSL BEHRING SpA	C(nn)
044564019	PLITATE*INF FL 250IU+SIR SOLV+SET	250	GRIFOLS ITALIA SpA	C(nn)
023308152	EMOWIL*1F 500IU+F 10mL	500	KEDRION SpA	A
026600080	HAEMATEP*FL 500IU+FL 10mL+SET	500	CSL BEHRING SpA	A
033077090	ALPHANATE*INF 1F 500IU+SIR+AD	500	GRIFOLS ITALIA SpA	A
033866056	FANHDI*INF FL 500IU+SIR SOLV+S	500	GRIFOLS ITALIA SpA	A
037148020	TALATE*500IU/375IU+FL10mL+SIR	500	BAXALTA INN. Gmbh	A
039385036	WILATE*FL 500+500IU+FL 5mL+SIR	500	OCTAPHARMA ITALY SpA	A
040112029	OCTANATE*INIET FL 500IU+FL 10mL	500	OCTAPHARMA ITALY SpA	A
040112056	OCTANATE*INIET FL 5mL100IU/mL	500	OCTAPHARMA ITALY SpA	A
042939025	VONCENTO*500IU/1200IU+FL 10mL	500	CSL BEHRING SpA	C(nn)
042939037	VONCENTO*500IU/1200IU+FL 5mL	500	CSL BEHRING SpA	C(nn)
044564021	PLITATE*INF FL 500IU+SIR SOLV+SET	500	GRIFOLS ITALIA SpA	C(nn)
023308188	EMOWIL*1F 1000IU+F 10mL	1000	KEDRION SpA	A
026600078	HAEMATEP*FL 1000IU+FL 15mL+SET	1000	CSL BEHRING SpA	A
033077102	ALPHANATE*INF 1F 1000IU+SIR+AD	1000	GRIFOLS ITALIA SpA	A
033866068	FANHDI*INF FL 1000IU+SIR SOLV+S	1000	GRIFOLS ITALIA SpA	A
037148032	TALATE*1000IU/750IU+FL10mL+SIR	1000	BAXALTA ITALY Srl	A
039385024	WILATE*FL 900+800IU+FL 10mL+SIR	1000	OCTAPHARMA ITALY SpA	A
039385048	WILATE*FL 1000+1000IU+FL 10mL+SI	1000	OCTAPHARMA ITALY SpA	A
040112031	OCTANATE*INIET FL 1000IU+FL 10mL	1000	OCTAPHARMA ITALY SpA	A
040112068	OCTANATE*INIET FL 5mL 200IU/mL	1000	OCTAPHARMA ITALY SpA	A
042939049	VONCENTO*1000IU/2400IU+FL 10mL	1000	CSL BEHRING SpA	C(nn)
044564033	PLITATE*INF FL1000IU+SIR SOLV+SET	1000	GRIFOLS ITALIA SpA	C(nn)
033077114	ALPHANATE*INF 1F 1500IU+SIR+AD	1500	GRIFOLS ITALIA SpA	A
033866070	FANHDI*INF FL1500IU+SIR SOLV+S	1500	GRIFOLS ITALIASpA	A
044564045	PLITATE*INF FL1500IU+SIRSOLV+SET	1500	GRIFOLS ITALIA SpA	C(nn)
033077126	ALPHANATE *INF 1F 2000 IU+SIR+SET	2000	GRIFOLS ITALIA SpA	C
von Willebrand Factor				
037392026	WILFACTIN* 500IU+FL 5mL	500	LFB	C
037392014	WILFACTIN*1000IU+FL 10mL	1000	LFB	C
037392038	WILFACTIN*2000IU+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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
028687010	RECOMBINATE*FL 250IU+FL 10mL	250	BAXALTA ITALY Srl	A
028687046	RECOMBINATE*FL 250IU+FL 5mL	250	BAXALTA ITALY Srl	A
028687073	RECOMBINATE*FL 250IU+FL 5mL	250	BAXALTA ITALY Srl	A
028687109	RECOMBINATE*FL 250IU+FL 10mL	250	BAXALTA ITALY Srl	A
034421014	REFACTOAF*IV 1FL 250IU+SIR 4mL	250	PFIZER ITALIA Srl	A
034421091	REFACTOAF*IV 1SIR PRER 250IU	250	PFIZER ITALIA Srl	A
034955017	KOGENATE BAYER*250IU+1FL+1KI	250	BAYER SpA	A
034955043	KOGENATE BAYER*FL 250IU+SIR+1KI	250	BAYER SpA	A
034955070	KOGENATE BAYER*EV 250IU+SIR	250	BAYER SpA	A

AIC code	Brand name	IU	Manufacturer	NHS class
034956019	HELIXATE NEXGEN*250IU+1FL+1KIT	250	CSL BEHRING SpA	A
036160012	ADVATE*FL 250IU+FL SOLV 5mL	250	BAXTER SpA	A
036160075	ADVATE*FL 250IU+FL SOLV 2mL	250	BAXALTA ITALY Srl	A
036160113	ADVATE*FL 250IU+FL SOLV 5mL	250	BAXALTA ITALY Srl	A
036160176	ADVATE*FL 250IU+FL SOLV 2mL	250	BAXALTA ITALY Srl	A
043153016	NOVOEIGHT*EV FL 250IU+SIR 4mL	250	NOVO NORDISK SpA	A
043534015	NUWIQ*EV FL 250IU+SIR 2,5mL	250	KEDRION SpA	A
044725012	IBLIAS*FL POLV EV 250IU+FL 2,5mL	250	BAYER SpA	A
044726014	KOVALTRY*1FL POLV EV 250IU+SOLV	250	BAYER SpA	A
044726026	KOVALTRY*1FL POLV EV 250IU+SOLV	250	BAYER SpA	A
044726115	KOVALTRY* 1FL POLV EV 250 IU	250	BAYER AG	C(nn)
044726127	KOVALTRY* 1FL POLV EV 250 IU	250	BAYER AG	A
045255015	AFSTYLA 250IU+FL SOLV 2,5mL+SIR	250	CSL BEHRING GmbH	A
045273012	VIHUMA*EV 250IU+FL SOLV 2,5mL	250	OCTAPHARMA AB	C(nn)
028687022	RECOMBINATE*FL 500IU+FL 10mL	500	BAXALTA ITALY Srl	A
028687059	RECOMBINATE*FL 500IU+FL 5mL	500	BAXALTA ITALY Srl	A
028687085	RECOMBINATE*FL 500IU+FL 5mL	500	BAXALTA ITALY Srl	A
028687111	RECOMBINATE*FL 500IU+FL 10mL	500	BAXALTA ITALY Srl	A
034421026	REFACTOAF*IV 1FL 500IU+SIR 4mL	500	PFIZER ITALIA Srl	A
034421065	REFACTOAF*IV 1SIR PRER 500IU	500	PFIZER ITALIA Srl	A
034955029	KOGENATE BAYER*500IU+1FL+1KIT	500	BAYER SpA	A
034955056	KOGENATE BAYER*FL 500IU+SIR	500	BAYER SpA	A
034955082	KOGENATE BAYER*EV 500IU+SIR	500	BAYER SpA	A
034956021	HELIXATE NEXGEN*500IU+1FL+1KIT	500	CSL BEHRING SpA	A
036160024	ADVATE*FL 500IU+FL SOLV 5mL	500	BAXTER SpA	A
036160087	ADVATE*FL 500IU+FL SOLV 2mL	500	BAXALTA ITALY Srl	A
036160125	ADVATE*FL 500IU+FL SOLV 5mL	500	BAXALTA ITALY Srl	A
036160188	ADVATE*FL 500IU+FL SOLV 2mL	500	BAXALTA ITALY Srl	A
043153028	NOVOEIGHT*EV FL 500IU+SIR 4mL	500	NOVO NORDISK SpA	A
043534027	NUWIQ*EV FL 500IU+SIR 2,5mL	500	KEDRION SpA	A
044725024	IBLIAS*FL POLV EV 500IU+FL 2,5mL	500	BAYER SpA	A
044726038	KOVALTRY*1FL POLV EV 500IU+SOLV	500	BAYER SpA	A
044726040	KOVALTRY*1FL POLV EV 500IU+SOLV	500	BAYER SpA	A
044726139	KOVALTRY*1FL POLV EV 500IU	500	BAYER AG	C(nn)
044726141	KOVALTRY*1FL POLV EV 500IU	500	BAYER AG	A
045255027	AFSTYLA 500IU+FL SOLV 2,5mL+SIR	500	CSL BEHRING GmbH	A
045273024	VIHUMA*EV500IU+FL SOLV 2,5mL	500	OCTAPHARMA AB	C(nn)
028687034	RECOMBINATE*FL 1000IU+FL 10mL	1000	BAXALTA ITALY Srl	A
028687061	RECOMBINATE*FL 1000IU+FL 5mL	1000	BAXALTA ITALY Srl	A
028687097	RECOMBINATE*FL 1000IU+FL 5mL	1000	BAXALTA ITALY Srl	A
028687123	RECOMBINATE*FL 1000IU+FL 10mL	1000	BAXALTA ITALY Srl	A
034421038	REFACTO AF*IV 1FL 1000IU+SIR 4mL	1000	PFIZER ITALIA Srl	A
034421077	REFACTO AF*IV 1SIR PRER 1000IU	1000	PFIZER ITALIA Srl	A
034955031	KOGENATE BAYER*1000IU+1FL+1KIT	1000	BAYER SpA	A
034955068	KOGENATE BAYER*FL 1000IU+SIR	1000	BAYER SpA	A
034955094	KOGENATE BAYER*EV 1000IU+SIR	1000	BAYER SpA	A
034956033	HELIXATE NEXGEN*1000IU+1FL+KIT	1000	CSL BEHRING SpA	A
036160036	ADVATE*FL 1000IU+FL SOLV 5mL	1000	BAXTER SpA	A
036160099	ADVATE*FL 1000IU+FL SOLV 2mL	1000	BAXALTA ITALY Srl	A
036160137	ADVATE*FL 1000IU+FL SOLV 5mL	1000	BAXALTA ITALY Srl	A
036160190	ADVATE*FL 1000IU+FL SOLV 2mL	1000	BAXALTA ITALY Srl	A
043153030	NOVOEIGHT*EV FL 1000IU+SIR 4mL	1000	NOVO NORDISK SpA	A
043534039	NUWIQ*EV FL 1000IU+SIR 2,5mL	1000	KEDRION SpA	A
044725036	IBLIAS*FL POLV EV 1000IU+2,5 mL	1000	BAYER SpA	A
044726053	KOVALTRY*FL POLV EV 1000IU+SOLV	1000	BAYER SpA	A
044726065	KOVALTRY*FL POLV EV 1000IU+SOLV	1000	BAYER SpA	A
044726154	KOVALTRY* 1FL POLV EV 1000 IU	1000	BAYER AG	C(nn)
044726166	KOVALTRY* 1FL POLV EV 1000 IU	1000	BAYER AG	A

AIC code	Brand name	IU	Manufacturer	NHS class
045255039	AFSTYLA 1000IU+FL SOLV 2,5mL+SIR	1000	CSL BEHRING GmbH	A
045273036	VIHUMA*EV 1000IU+FL SOLV 2,5mL	1000	OCTAPHARMA AB	C(nn)
036160048	ADVATE*FL 1500IU+FL SOLV 5mL	1500	BAXTER SpA	A
036160101	ADVATE*FL 1500IU+FL SOLV 2mL	1500	BAXALTA ITALY Srl	A
036160149	ADVATE*FL 1500IU+FL SOLV 5mL	1500	BAXALTA ITALY Srl	A
036160202	ADVATE*FL 1500IU+FL SOLV 2mL	1500	BAXALTA ITALY Srl	A
043153042	NOVOEIGHT*EV FL 1500IU+SIR 4mL	1500	NOVO NORDISK SpA	A
043534080	NUWIQ*EV FL 1500UI+SIR 2,5ML	1500	OCTAPHARMA AB	A
045255041	AFSTYLA 1500IU+FL SOLV 2,5mL+SIR	1500	CSL BEHRING GmbH	A
034421040	REFACTOAF*IV 1FL 2000IU+SIR 4mL	2000	PFIZER ITALIA Srl	A
034421089	REFACTOAF*IV 1SIR PRER 2000IU	2000	PFIZER ITALIA Srl	A
034955106	KOGENATE BAYER*EV 2000IU+SIR	2000	BAYER SpA	A
034955118	KOGENATE BAYER*EV 2000IU+SIR	2000	BAYER SpA	A
036160051	ADVATE*FL 2000IU+FL SOLV 5mL	2000	BAXTER SpA	A
036160152	ADVATE*FL 2000IU+FL SOLV 5mL	2000	BAXALTA ITALY Srl	A
043153055	NOVOEIGHT*EV FL 2000IU+SIR 4mL	2000	NOVO NORDISK SpA	A
043534041	NUWIQ*EV FL 2000IU+SIR 2,5mL	2000	KEDRION SpA	A
044725048	IBLIAS*FL POLV EV 2000IU+FL 5mL	2000	BAYER SpA	A
044726077	KOVALTRY*FL POLV EV 2000IU+SOLV	2000	BAYER SpA	A
044726089	KOVALTRY*FL POLV EV 2000IU+SOLV	2000	BAYER SpA	A
045255054	AFSTYLA 2000IU+FL SOLV 2,5mL+SIR	2000	CSL BEHRING GmbH	A
045273048	VIHUMA*EV 2000IU+FL SOLV 2,5mL	2000	OCTAPHARMA AB	C(nn)
043534054	NUWIQ*EV FL 2500IU+SIR 2,5mL	2500	OCTAPHARMA AB	A
045255066	AFSTYLA 2500IU+FL SOLV 2,5mL+SIR	2500	CSL BEHRING GmbH	A
045273051	VIHUMA*EV 2500IU+FL SOLV 2,5mL	2500	OCTAPHARMA AB	C(nn)
034421053	REFACTO AF*IV 1SIR PRER 3000IU	3000	PFIZER ITALIA Srl	A
034955120	KOGENATE BAYER*EV 3000IU+SIR	3000	BAYER SpA	A
034955132	KOGENATE BAYER*EV 3000IU+SIR	3000	BAYER SpA	A
034956058	HELIXATE NEXGEN*3000IU+1FL+KIT	3000	CSL BEHRING SpA	A
036160063	ADVATE*FL 3000IU+FL SOLV 5mL	3000	BAXTER SpA	A
036160164	ADVATE*FL 3000IU+FL SOLV 5mL	3000	BAXALTA ITALY Srl	A
043153067	NOVOEIGHT*EV FL 3000IU+SIR 4mL	3000	NOVO NORDISK SpA	A
043534066	NUWIQ*EV FL 3000IU+SIR 2,5mL	3000	OCTAPHARMA AB	A
044725051	IBLIAS*FL POLV EV 3000IU+FL 5mL	3000	BAYER SpA	A
044726091	KOVALTRY*FL POLV EV 3000IU+SOLV	3000	BAYER SpA	A
044726103	KOVALTRY*FL POLV EV 3000IU+SOLV	3000	BAYER SpA	A
045255078	AFSTYLA 3000IU+FL SOLV 2,5mL+SIR	3000	CSL BEHRING GmbH	A
045273063	VIHUMA*EV 3000IU+FL SOLV 2,5mL	3000	OCTAPHARMA AB	C(nn)
043534078	NUWIQ*EV FL 4000IU+SIR 2,5mL	4000	OCTAPHARMA AB	C
045273075	VIHUMA*EV 4000IU+FL SOLV 2,5mL	4000	OCTAPHARMA AB	C(nn)
044726178	KOVALTRY*30FL 250UI+ SIR 3mL	7500	BAYER AG	C(nn)
044726180	KOVALTRY*30FL 250UI+ SIR 5mL	7500	BAYER AG	C(nn)
044726192	KOVALTRY*30FL 500UI+ SIR 3mL	15000	BAYER AG	C(nn)
044726204	KOVALTRY*30FL 500UI+SIR 5mL	15000	BAYER AG	C(nn)
044726216	KOVALTRY*30FL 1000UI+SIR 3mL	30000	BAYER AG	C(nn)
044726228	KOVALTRY*30FL 1000UI+SIR 5mL	30000	BAYER AG	C(nn)
044726230	KOVALTRY*30FL 2000UI+SIR 5mL	60000	BAYER AG	C(nn)
044726242	KOVALTRY*30FL 3000UI+SIR 5mL	90000	BAYER AG	C(nn)
Extended half-life Recombinant Factor VIII				
044563017	ELOCTA*IV 1FL 250IU+SIR PRERI	250	SOBI Srl	A
045936010	ADYNOVI*EV 250 IU+FL 2 mL+DISP	250	BAXALTA INN. Gmbh.	A
045936022	ADYNOVI*EV 250 IU + FL 2 mL + DISP	250	BAXALTA INN. Gmbh.	A
045936034	ADYNOVI*EV 250 IU + FL 5 mL + DISP	250	BAXALTA INN. Gmbh.	A
045936046	ADYNOVI*EV 250 IU + FL 5 mL + DISP	250	BAXALTA INN. Gmbh	A
047418013	JIVI* EV 250 IU + FL SOLV 2,5 mL + SIR	250	BAYER AG	A
044563029	ELOCTA*IV 1FL 500IU+SIR PRERI	500	SOBI Srl	A
045936059	ADYNOVI*EV 500IU + FL 2 mL + DISP	500	BAXALTA INN. Gmbh.	A

AIC code	Brand name	IU	Manufacturer	NHS class
045936061	ADYNOVI*EV 500IU + FL 2 mL + DISP	500	BAXALTA INN. Gmbh	A
045936073	ADYNOVI*EV 500IU + FL 5 mL + DISP	500	BAXALTA INN. Gmbh.	C(nn)
045936085	ADYNOVI*EV 500IU + FL 5 mL + DISP	500	BAXALTA INN. Gmbh	A
047418025	JIVI* EV 500 IU + FL SOLV 2,5 mL + SIR	500	BAYER AG	A
048083012	ESPEROCT* EV 500 IU + FL 4 mL + SIR	500	NOVO NORDISK A/S	A
044563031	ELOCTA*IV 1FL 750IU+SIR PRERI	750	SOBI Srl	A
044563043	ELOCTA*IV 1FL 750UI+SIR PRERI	750	SOBI Srl	A
044563056	ELOCTA*IV 1FL 1000IU+SIR PRERI	1000	SOBI Srl	A
045936097	ADYNOVI*EV 1000 IU + FL 2 mL + DISP	1000	BAXALTA INN. Gmbh	C(nn)
045936109	ADYNOVI*EV 1000 IU + FL 2 mL + DISP	1000	BAXALTA INN. Gmbh	A
045936111	ADYNOVI*EV 1000 IU + FL 5 mL + DISP	1000	BAXALTA INN. Gmbh	C(nn)
045936123	ADYNOVI*EV 1000 IU + FL 5 mL + DISP	1000	BAXALTA INN. Gmbh	A
047418037	JIVI* EV 1000 IU + FL 2,5 mL + SIR	1000	BAYER AG	A
048083024	ESPEROCT* EV 1000 IU+ FL 4 mL+ SIR	1000	NOVO NORDISK A/S	A
044563068	ELOCTA*IV 1FL 1500IU+SIR PRERI	1500	SOBI Srl	A
048083036	ESPEROCT* EV 1500 IU+ FL 4 mL+ SIR	1500	NOVO NORDISK A/S	A
044563070	ELOCTA*IV 1FL 2000IU+SIR PRERI	2000	SOBI Srl	A
045936135	ADYNOVI*EV 2000 IU + FL 5 mL + DISP	2000	BAXALTA INN. Gmbh	C(nn)
045936147	ADYNOVI*EV 2000 IU + FL 5 mL + DISP	2000	BAXALTA INN. Gmbh	A
047418049	JIVI* EV 2000 IU + FL 2,5 mL + SIR	2000	BAYER AG	A
048083048	ESPEROCT* EV 2000 IU+ FL 4 mL+ SIR	2000	NOVO NORDISK A/S	A
044563082	ELOCTA*IV 1FL 3000IU+SIR PRERI	3000	SOBI Srl	A
045936150	ADYNOVI*EV3000UI+FL5mL+DISP	3000	BAXALTA INN. Gmbh	C(nn)
045936162	ADYNOVI*EV3000UI+FL5mL+DISPPRE	3000	BAXALTA INN. Gmbh	C(nn)
047418052	JIVI* EV 3000 IU + FL 2,5 mL + SIR	3000	BAYER AG	A
048083051	ESPEROCT* EV 3000 IU+ FL 4 mL+ SIR	3000	NOVO NORDISK A/S	A
044563094	ELOCTA*IV 1FL 4000IU+SIR PRERI	4000	SOBI Srl	C(nn)
048083063	ESPEROCT* EV 4000 UI+ FL4 mL+SIR	4000	NOVO NORDISK A/S	C(nn)
044563106	ELOCTA*IV 1FL 5000IU+SIR PRERI	5000	SOBI Srl	C(nn)
048083075	ESPEROCT* EV 5000 UI+ FL4 mL+SIR	5000	NOVO NORDISK A/S	C(nn)
044563118	ELOCTA*IV 1FL 6000IU+SIR PRERI	6000	SOBI Srl	C(nn)
047418064	JIVI* 30FL 250 UI + SOLV 2,5 mL+SIR	7500	BAYER AG	C(nn)
047418076	JIVI* 30FL 500 UI + SOLV 2,5 mL+SIR	15000	BAYER AG	C(nn)
047418088	JIVI* 30FL 1000 UI + SOLV 2,5 mL+SIR	30000	BAYER AG	C(nn)
047418090	JIVI* 30FL 2000 UI + SOLV 2,5 mL+SIR	60000	BAYER AG	C(nn)
047418102	JIVI* 30FL 3000 UI + SOLV 2,5 mL+SIR	90000	BAYER AG	C(nn)

Quantification and characterisation of demand

In Italy, the total demand for both plasma-derived and recombinant formulations FVIII, was equal to 535,813,250 IUs in 2023 (Table 16); of these, about a sixth (16.5% of the total, 88,450,500 IUs) were human plasma-derived (Figure 15). The tendency to use pdFVIII varied significantly from one Region to another ranging from 3% in Basilicata and in the AP of Trento to 34.5% in Friuli V. Giulia. In 2023, the total FVIII demand *per capita* (plasma-derived and recombinant) was 9 IUs with a decrease of -3.6% compared to 2022.

The regional *per capita* demand shows significant fluctuations ranging from about 4 IUs in Friuli V. Giulia to about 14 IUs in Latium (Figure 16).

The most significant decreases in standardised regional demand were observed in Calabria, Aosta Valley and in the AP of Bolzano, where use decreased by -20% for the first, and -19%, for the other two. It is important to underline that for FVIII, strong fluctuations can occur due to the contingent needs of a few patients (immunotolerance treatments, surgeries, severe traumas, etc.). Seven Regions had a greater demand compared to the national average (Figure 17).

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	16,495,250	13.0	16,462,750	12.9	-0.1
Aosta Valley	746,000	6.0	603,000	4.9	-19.0
AP Bolzano	3,961,000	7.4	3,210,500	6.0	-18.7
AP Trento	3,341,500	6.2	3,805,500	7.0	13.7
Apulia	45,419,500	11.6	46,253,000	11.8	2.0
Basilicata	2,694,500	5.0	3,019,000	5.6	12.5
Calabria	20,314,500	11.0	16,235,250	8.8	-20.2
Campania	59,542,750	10.7	59,102,500	10.5	-1.1
E.-Romagna	47,262,500	10.7	45,408,750	10.2	-4.0
Friuli V. Giulia	4,961,000	4.1	4,772,000	4.0	-3.6
Latium	92,146,500	16.1	80,397,250	14.1	-12.8
Liguria	10,643,000	7.1	9,332,000	6.2	-12.3
Lombardy	77,466,000	7.8	76,526,750	7.7	-1.3
Marche	11,196,500	7.5	10,671,500	7.2	-4.3
Molise	2,021,000	7.0	3,322,000	11.4	64.4
Piedmont	31,253,000	7.3	31,435,750	7.4	0.6
Sardinia	12,823,000	8.1	13,189,000	8.4	2.9
Sicily	43,129,500	9.0	44,459,500	9.2	2.8
Tuscany	23,809,500	6.5	26,410,250	7.2	11.4
Umbria	5,979,000	7.0	6,679,000	7.8	12.1
Veneto	40,380,250	8.3	34,518,000	7.1	-14.4
ITALY	555,585,750	9.4	535,813,250	9.1	-3.6

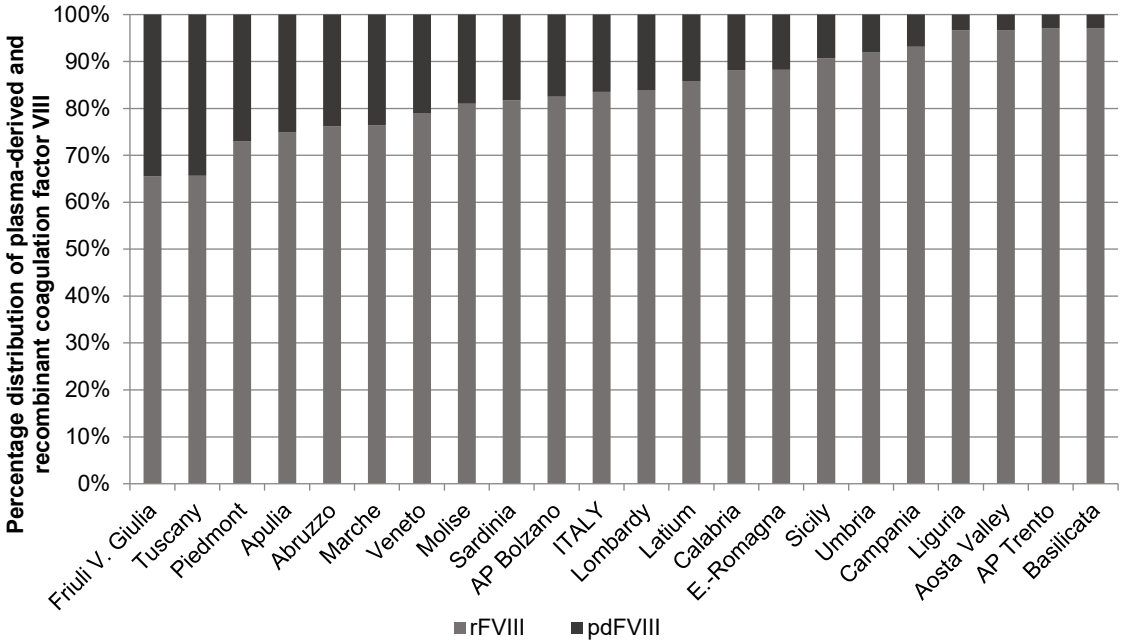

Figure 15. Percentage distribution of plasma-derived and recombinant coagulation Factor VIII, by Region, 2023 (adapted by the CNS on data from the Traceability information flow)

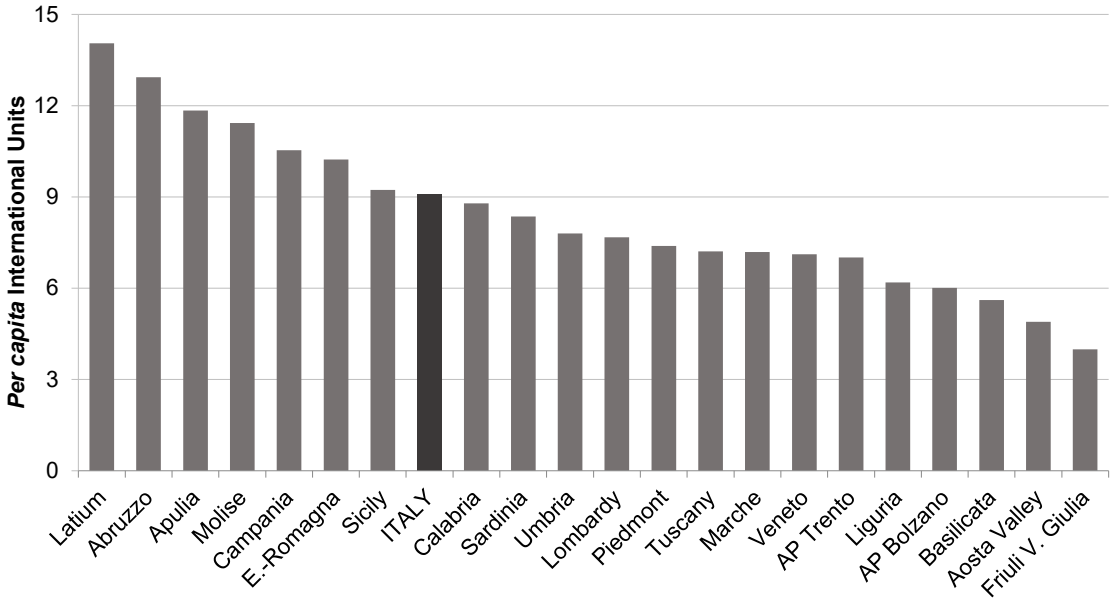

Figure 16. Total and regional demand (public and private) for coagulation Factor VIII, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

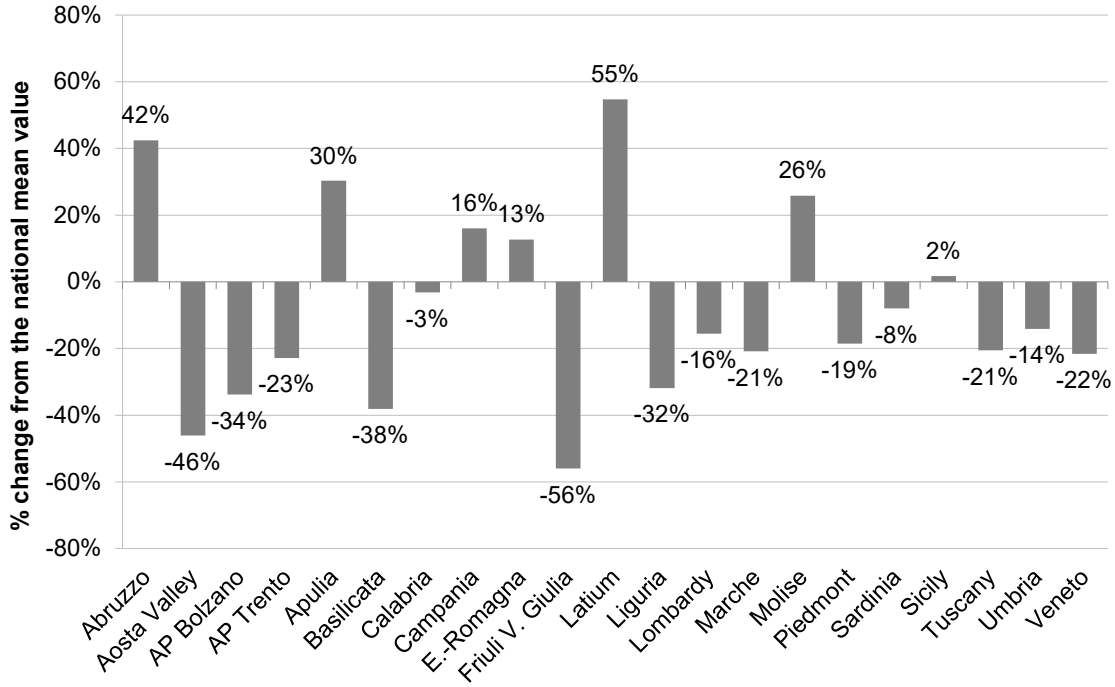

Figure 17. Percentage variation from the national mean value of standardised regional demand for coagulation Factor VIII in 2023 (adapted by the CNS on data from the Traceability information flow)

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

In 2023, the national demand for pdFVIII was about 16.5% - equivalent to 88,450,500 IUs - of the total demand. There is a downward trend of -4.6% compared to the 2022 value and a standardized total demand of 1.5 IU *per capita* (Table 17).

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	3,681,000	2.9	3,927,500	3.1	6.8
Aosta Valley	17,000	0.1	20,000	0.2	17.8
AP Bolzano	701,000	1.3	563,000	1.1	-19.4
AP Trento	20,000	0.0	114,000	0.2	469.1
Apulia	11,322,000	2.9	11,622,000	3.0	2.8
Basilicata	38,000	0.1	90,000	0.2	137.9
Calabria	1,873,500	1.0	1,919,000	1.0	2.3
Campania	4,949,000	0.9	4,072,000	0.7	-18.0
E.-Romagna	6,456,000	1.5	5,351,750	1.2	-17.2
Friuli V. Giulia	1,257,000	1.0	1,647,000	1.4	31.4
Latium	11,678,500	2.0	11,402,500	2.0	-2.5
Liguria	874,000	0.6	313,000	0.2	-64.2
Lombardy	14,367,500	1.4	12,380,250	1.2	-13.9
Marche	2,017,000	1.4	2,516,000	1.7	25.2
Molise	284,000	1.0	632,000	2.2	122.6
Piedmont	8,577,000	2.0	8,499,000	2.0	-0.9
Sardinia	2,250,000	1.4	2,407,000	1.5	7.0
Sicily	4,644,000	1.0	4,129,000	0.9	-11.3
Tuscany	7,332,000	2.0	9,066,000	2.5	24.1
Umbria	740,500	0.9	539,500	0.6	-26.9
Veneto	9,601,500	2.0	7,240,000	1.5	-24.5
ITALY	92,680,500	1.6	88,450,500	1.5	-4.6

Per capita demand varied significantly with the highest volumes in Apulia and Abruzzo (3 IUs *per capita*), Tuscany (2.5 IU *per capita*), Molise (2.2 IU *per capita*), Latium and Piedmont (2.0 IUs *per capita*); the corresponding percentage variation between the aforementioned values and the Italian mean value were of +106, +98%, +65%, +45% respectively for Apulia, Abruzzo, Tuscany and Molise and +33% in the case of the last two Regions. The lowest volumes (below 1 IU *per capita*) were recorded in Aosta Valley, Basilicata, Liguria, AP of Trento, Umbria, Campania and Sicily (Figures 18 and 19).

The decrease recorded at a national level is due to ten Italian regions showing declining demand (range: -0.9%; -64.2%); in contrast, Abruzzo, Basilicata, Calabria, Friuli V. Giulia, Marche, Molise, AP of Trento, Apulia, Sardinia, Tuscany and Aosta Valley show increases ranging from 2% to 469%.

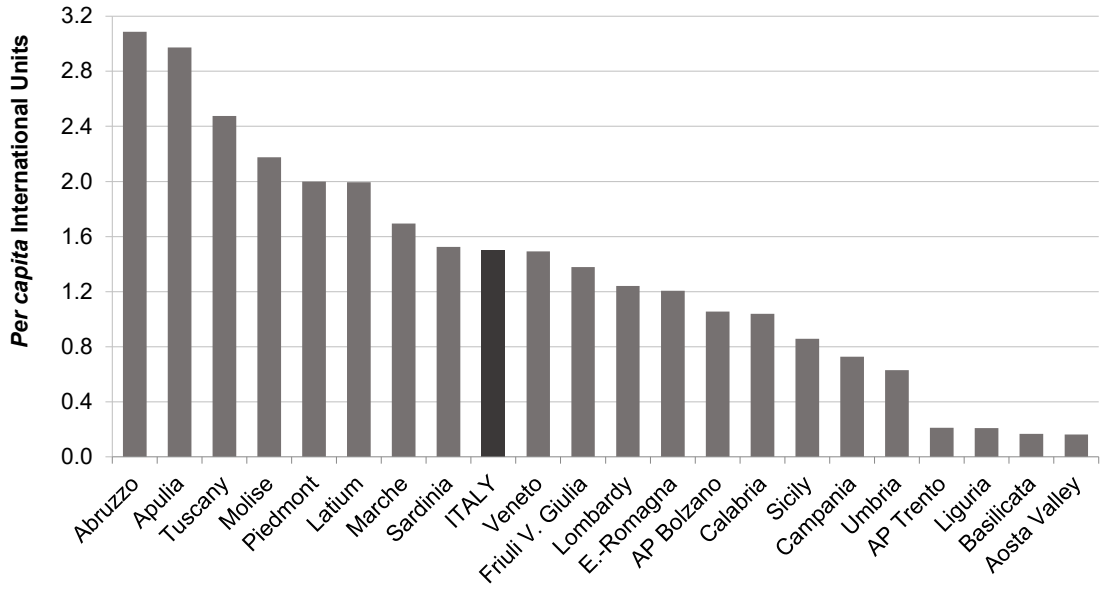

Figure 18. Total and regional demand (public and private) for plasma-derived coagulation Factor VIII, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

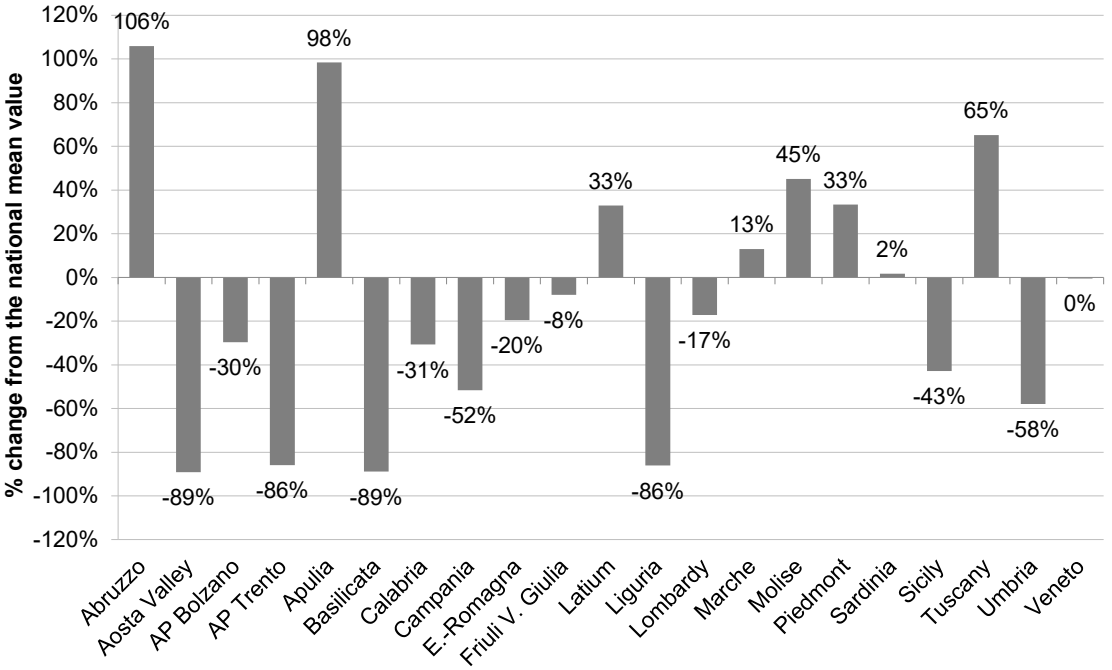

Figure 19. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor VIII in 2023 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor VIII (B02BD02)

In 2023, the total demand for plasma-derived FVIII was 41,024,000 IUs. The mean national demand *per capita* was about 0.7 IUs, with a range amongst Regions of 0.02 IUs and 1.5 IUs (Table 18).

Table 10. 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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	130,000	0.1	290,000	0.2	123.3
Aosta Valley	-	-	-	-	NA
AP Bolzano	400,000	0.7	430,000	0.8	7.8
AP Trento	-	-	-	-	NA
Apulia	5,687,000	1.5	5,207,000	1.3	-8.3
Basilicata	20,000	0.0	10,000	0.0	-49.8
Calabria	300,000	0.2	203,000	0.1	-32.4
Campania	261,000	0.0	-	-	-100.0
E.-Romagna	2,330,000	0.5	1,327,000	0.3	-43.1
Friuli V. Giulia	680,000	0.6	1,400,000	1.2	106.4
Latium	5,167,000	0.9	4,821,000	0.8	-6.8
Liguria	390,000	0.3	90,000	0.1	-76.9
Lombardy	9,449,000	0.9	8,208,000	0.8	-13.2
Marche	1,352,000	0.9	1,514,000	1.0	12.4
Molise	100,000	0.3	218,000	0.8	118.1
Piedmont	5,962,000	1.4	5,622,000	1.3	-5.7
Sardinia	633,000	0.4	318,000	0.2	-49.7
Sicily	881,000	0.2	1,327,000	0.3	50.2
Tuscany	4,358,000	1.2	5,409,000	1.5	24.6
Umbria	125,000	0.1	50,000	0.1	-59.9
Veneto	6,803,000	1.4	4,580,000	0.9	-32.6
ITALY	45,028,000	0.8	41,024,000	0.7	-8.9

The Regions with the highest *per capita* consumption of pdFVIII were Tuscany (1.5 IUs), Piedmont and Apulia (1.3 IUs).

The lowest utilisation was observed in Basilicata (0.02 IUs *per capita*). No consumption was recorded in Aosta Valley, in the AP of Trento and in Campania.

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

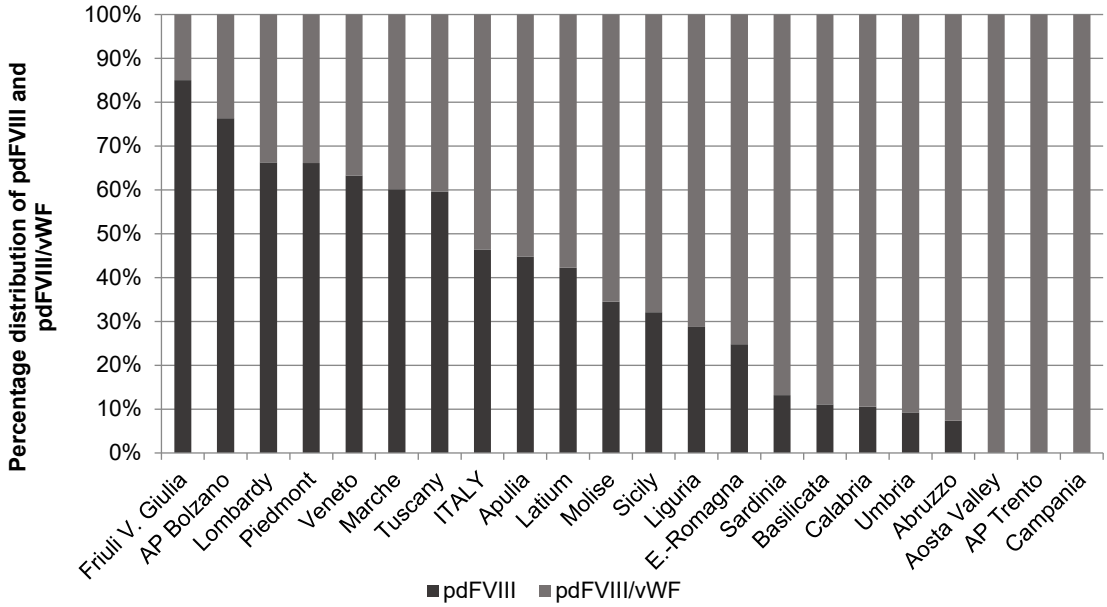

Figure 20. Percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination, by Region, 2023 (adapted by the CNS on data from the Traceability information flow)

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

In 2023, the national demand for FVIII and von Willebrand Factor in combination was 47,426,500 IUs, about 54% of the total demand for pdFVIII. The mean national demand *per capita* was 0.8 IUs, with a range between Regions of 0.1 IUs (Basilicata and Liguria) and 2.9 IUs (Abruzzo) (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 capita,* and variations in percentage between 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	3,551,000	2.8	3,637,500	2.9	2.5
Aosta Valley	17,000	0.1	20,000	0.2	17.8
AP Bolzano	301,000	0.6	133,000	0.2	-55.7
AP Trento	20,000	0.0	114,000	0.2	469.1
Apulia	5,635,000	1.4	6,415,000	1.6	14.0
Basilicata	18,000	0.0	80,000	0.1	346.4
Calabria	1,573,500	0.9	1,716,000	0.9	8.9
Campania	4,688,000	0.8	4,072,000	0.7	-13.4
E.-Romagna	4,126,000	0.9	4,024,750	0.9	-2.6
Friuli V. Giulia	577,000	0.5	247,000	0.2	-57.1
Latium	6,511,500	1.1	6,581,500	1.2	1.0
Liguria	484,000	0.3	223,000	0.1	-53.9
Lombardy	4,918,500	0.5	4,172,250	0.4	-15.3

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Marche	665,000	0.4	1,002,000	0.7	51.2
Molise	184,000	0.6	414,000	1.4	125.1
Piedmont	2,615,000	0.6	2,877,000	0.7	10.0
Sardinia	1,617,000	1.0	2,089,000	1.3	29.3
Sicily	3,763,000	0.8	2,802,000	0.6	-25.7
Tuscany	2,974,000	0.8	3,657,000	1.0	23.4
Umbria	615,500	0.7	489,500	0.6	-20.2
Veneto	2,798,500	0.6	2,660,000	0.5	-4.8
ITALY	47,652,500	0.8	47,426,500	0.8	-0.5

* 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 Regions with the highest *per capita* demand of FVIII and von Willebrand Factor in combination were Abruzzo (2.9 IUs), Apulia (1.6 IUs) and Molise (1.4 IUs). The lowest utilization equal to 0.1 IUs *per capita* was observed in Basilicata and Liguria (Figure 21).

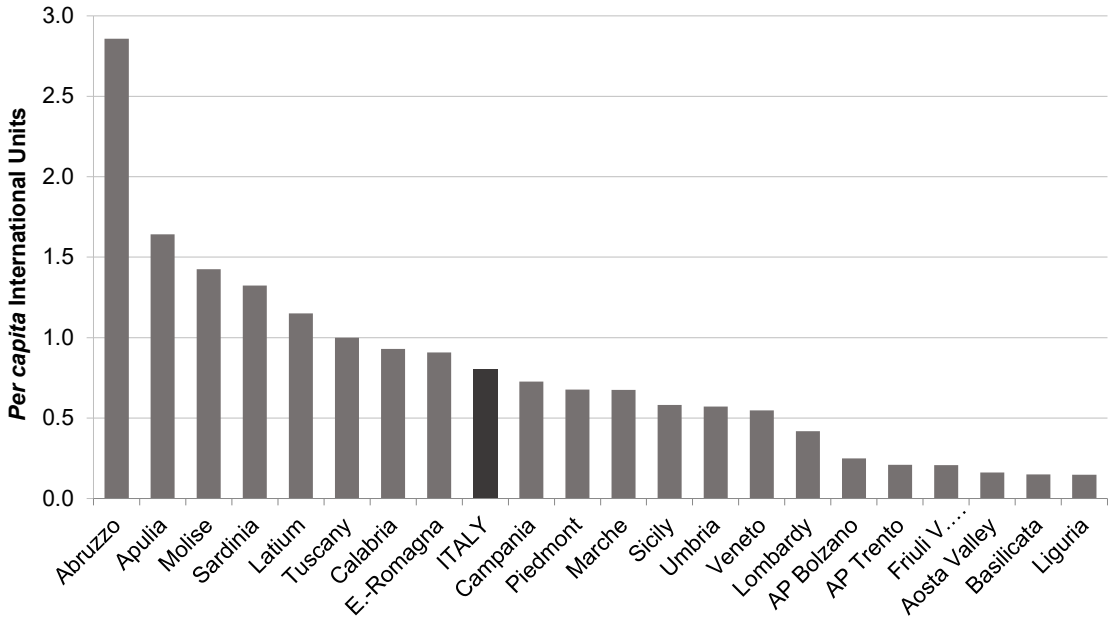

Figure 21. Total and regional demand (public and private) for pdFVIII and von Willebrand Factor in combination, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor VIII

In 2023, the total demand for rFVIII was 447,362,750 IUs, with a decrease of approximately -3.4% compared to 2022. The mean national demand *per capita* was about 8 IUs, with a range among different Regions of 2.6 IUs and 12.1 IUs (Table 20). The Regions in which the highest *per capita* utilisation of rFVIII was observed were Latium (12.1 IUs), Abruzzo and Campania (10 IUs) (Figure 22), with a percentage variation compared to the Italian mean value of +59%, +30% and +29%, respectively (Figure 23). The lowest utilisation - between 2.6 and 5.0 IUs *per capita* - was observed in Friuli V. Giulia, Aosta Valley, Tuscany and in the AP of Bolzano.

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	12,814,250	10.1	12,535,250	9.8	-2.1
Aosta Valley	729,000	5.9	583,000	4.7	-19.9
AP Bolzano	3,260,000	6.1	2,647,500	5.0	-18.5
AP Trento	3,321,500	6.1	3,691,500	6.8	11.0
Apulia	34,097,500	8.7	34,631,000	8.9	1.7
Basilicata	2,656,500	4.9	2,929,000	5.4	10.8
Calabria	18,441,000	10.0	14,316,250	7.8	-22.5
Campania	54,593,750	9.8	55,030,500	9.8	0.5
E.-Romagna	40,806,500	9.2	40,057,000	9.0	-2.0
Friuli V. Giulia	3,704,000	3.1	3,125,000	2.6	-15.4
Latium	80,468,000	14.1	68,994,750	12.1	-14.3
Liguria	9,769,000	6.5	9,019,000	6.0	-7.7
Lombardy	63,098,500	6.3	64,146,500	6.4	1.5
Marche	9,179,500	6.2	8,155,500	5.5	-10.8
Molise	1,737,000	6.0	2,690,000	9.3	54.9
Piedmont	22,676,000	5.3	22,936,750	5.4	1.2
Sardinia	10,573,000	6.7	10,782,000	6.8	2.0
Sicily	38,485,500	8.0	40,330,500	8.4	4.5
Tuscany	16,477,500	4.5	17,344,250	4.7	5.7
Umbria	5,238,500	6.1	6,139,500	7.2	17.6
Veneto	30,778,750	6.3	27,278,000	5.6	-11.3
ITALY	462,905,250	7.8	447,362,750	7.6	-3.4

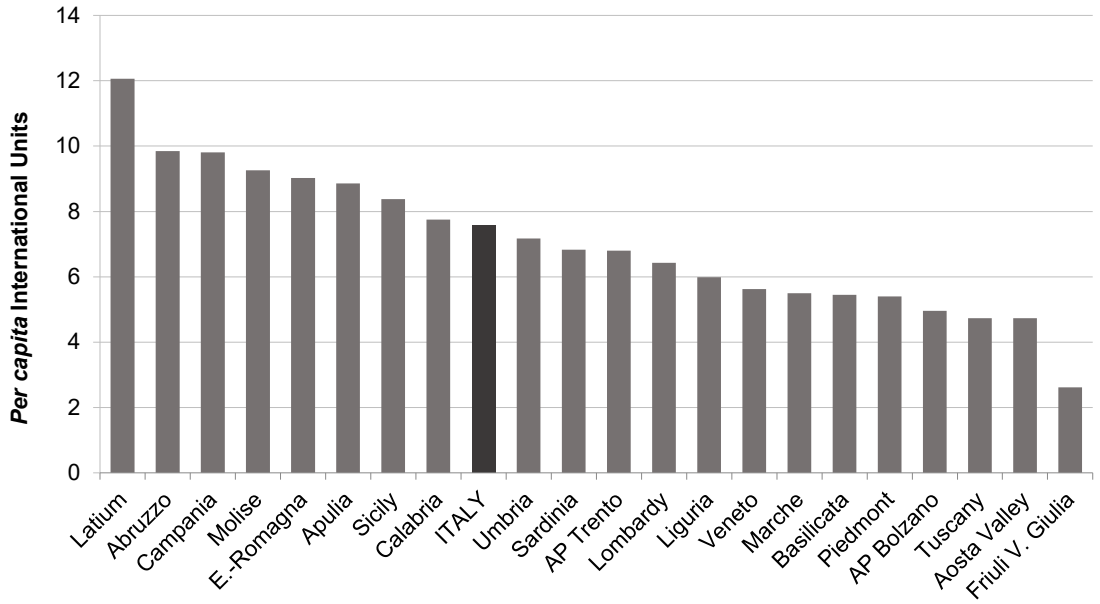

Figure 22. Total and regional demand (public and private) for recombinant coagulation Factor VIII, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

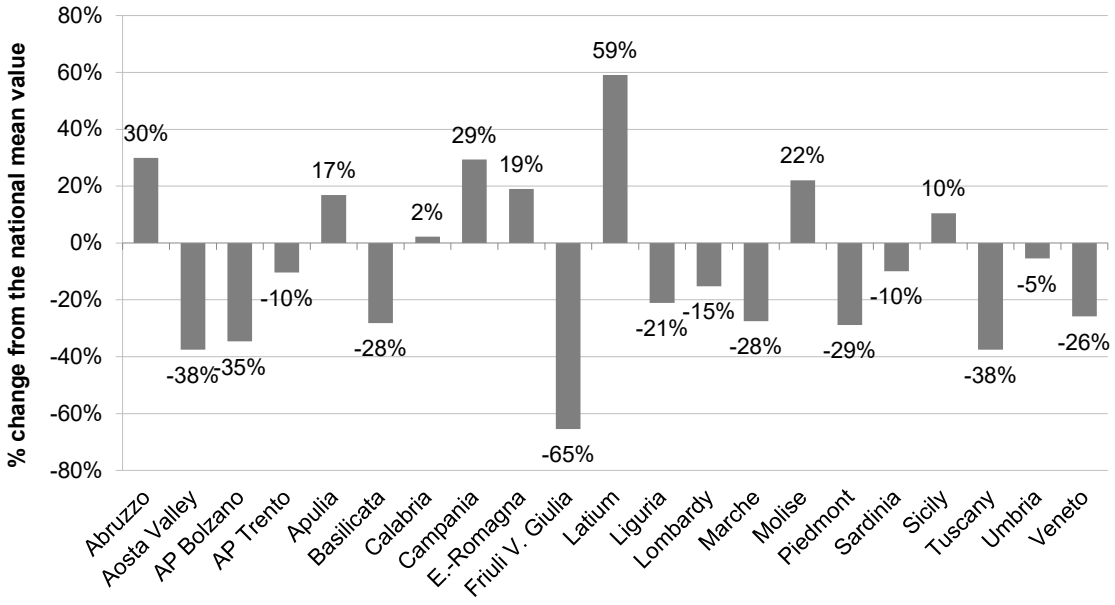

Figure 23. Percentage variation from the national mean value of standardised regional demand for recombinant coagulation Factor VIII in 2023 (adapted by the CNS on data from the Traceability information flow)

Extended half-life Recombinant Factor VIII

Part of the total demand for rFVIII is represented by drugs containing extended half-life molecules. In 2023, the demand for these products was equal to 266,998,250 IUs, about 60% of the total demand for rFVIII (Table 21) and recorded an increase of +12% compared to the previous year. The national demand *per capita* was about 4.5 IUs, with a range among Regions of 1.5 IUs in Basilicata and 7.3 IUs in Latium (+62% as compared to national mean value), (Figures 24 and 25).

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* and variations in percentage between 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	7,535,250	5.9	9,073,250	7.1	20.5
Aosta Valley	462000	3.7	546000	4.4	18.4
AP Bolzano	1,105,000	2.1	1,173,000	2.2	6.5
AP Trento	708000	1.3	824500	1.5	16.3
Apulia	15,406,250	3.9	20,004,500	5.1	30.0
Basilicata	616,000	1.1	794,500	1.5	29.6
Calabria	7,487,000	4.1	6,764,000	3.7	-9.8
Campania	25,776,250	4.6	31,356,500	5.6	21.2
E.-Romagna	24,667,500	5.6	27,412,000	6.2	11.0
Friuli V. Giulia	3,006,000	2.5	2,573,000	2.2	-14.2
Latium	40,323,000	7.1	42,007,000	7.3	4.1
Liguria	7,529,000	5.0	7,316,000	4.9	-2.8
Lombardy	29,428,750	3.0	35,009,250	3.5	18.8

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Marche	5,502,000	3.7	6,260,500	4.2	14.2
Molise	1,668,000,0	5.7	1,808,000,0	6.2	8.4
Piedmont	13,342,000	3.1	14,908,500	3.5	11.8
Sardinia	2827000	1.8	5157000	3.3	82.5
Sicily	16,683,500	3.5	19,256,000	4.0	15.1
Tuscany	10,667,000	2.9	10,979,750	3.0	3.3
Umbria	2,219,000	2.6	3,122,500	3.6	41.2
Veneto	20,811,000	4.3	20,652,500	4.3	-0.7
ITALY	237,769,500	4.0	266,998,250	4.5	12.3

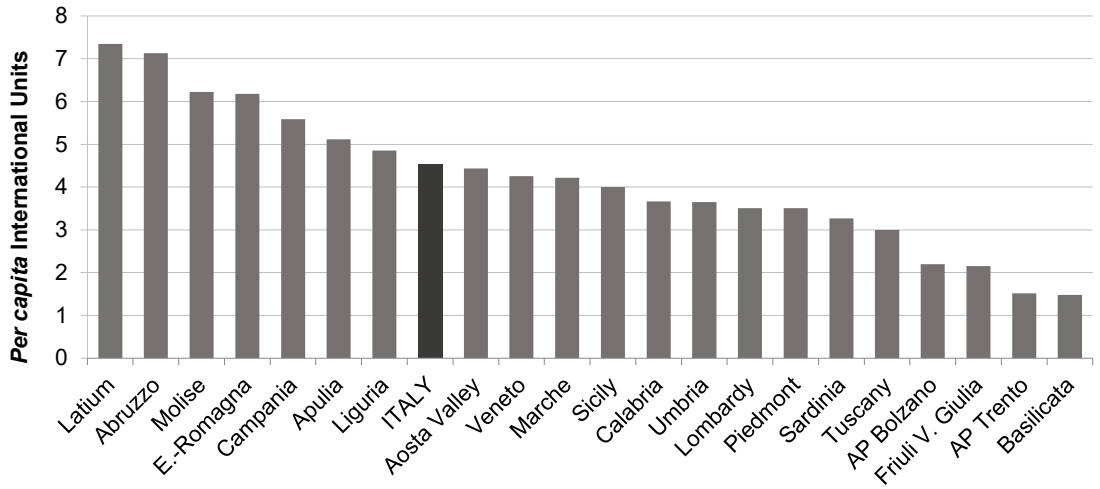

Figure 24. Total and regional demand (public and private) for extended half-life recombinant Factor VIII, expressed in International Units per capita, 2023 (adapted by the CNS on data from the Traceability information flow)

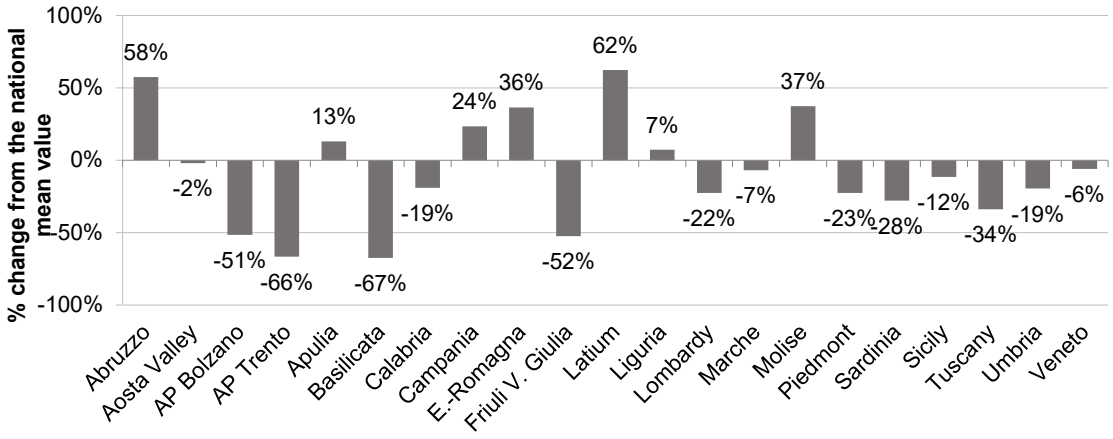

Figure 25. Percentage change from the national mean value of standardised regional demand for extended half-life recombinant Factor VIII in 2023 (adapted by the CNS on data from the Traceability information flow)

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 severe hemophilia A (congenital FVIII deficiency<1%) who have not developed factor VIII inhibitors with:

- severe disease (blood factor VIII level less than 1%)
- moderate disease (blood factor VIII level between 1% and 5%) with severe hemorrhagic phenotype.

The use of Emicizumab is also indicated in patients who have developed factor VIII inhibitors, which are antibodies in the blood that act against factor VIII drugs and prevent them from functioning properly. Emicizumab can be used in all age groups and is administered via subcutaneous way 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 function as 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 amount of the contained active ingredients expressed in milligrams (mg).

Table 22. Products containing emicizuma currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2023)

AIC code	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 2023, at national and regional levels and the percentage change from the previous year.

The total national demand for Emicizumab formulation shows a strong increase for the year 2023 and its was 2,472,975 mg, with an increase of +20% compared to the year 2022. The national demand (mg per 1,000 population) was about 42 mg, and only in the AP of Trento there is no consumption of Emicizumab (Table 23). The standardised demand for Emicizumab ranged from a minimum of 1.6 mg in Sardinia to a maximum of 87 mg in Aosta Valley (Figure 26).

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 2023 and variations in percentage between 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	mg	mg per 1,000 population	mg	mg per 1,000 population	
Abruzzo	47,745	37.5	56,130	44.1	17.7
Aosta Valley	7,350,0	59.6	10,710,0	87.0	46.0
AP Bolzano	13,620	25.4	24,615	46.1	81.3
AP Trento	-	-	-	-	NA
Apulia	74,055	18.9	83,040	21.3	12.3
Basilicata	17,760	32.9	14,340	26.7	-18.9
Calabria	75,165	40.7	106,575	57.7	41.6
Campania	193,755	34.7	223,500	39.8	15.0
E.-Romagna	114,480	25.8	132,180	29.8	15.3
Friuli V. Giulia	33,390	27.9	41,280	34.6	23.9
Latium	81,105	14.2	142,845	25.0	76.0
Liguria	50,520	33.5	46,485	30.8	-8.0
Lombardy	409,215	41.1	519,495	52.1	26.8
Marche	52,590	35.3	66,000	44.5	26.0
Molise	18,240,0	62.7	16,350,0	56.3	-10.3
Piedmont	289,125	68.0	309,240	72.7	7.0
Sardinia	1,320,0	0.8	2,475,0	1.6	87.6
Sicily	127,620	26.6	165,210	34.3	29.1
Tuscany	219,240	59.6	247,905	67.7	13.5
Umbria	36,780	42.8	48,465	56.6	32.3
Veneto	196,200	40.4	216,135	44.6	10.3
ITALY	2,059,275	34.9	2,472,975	41.9	20.1

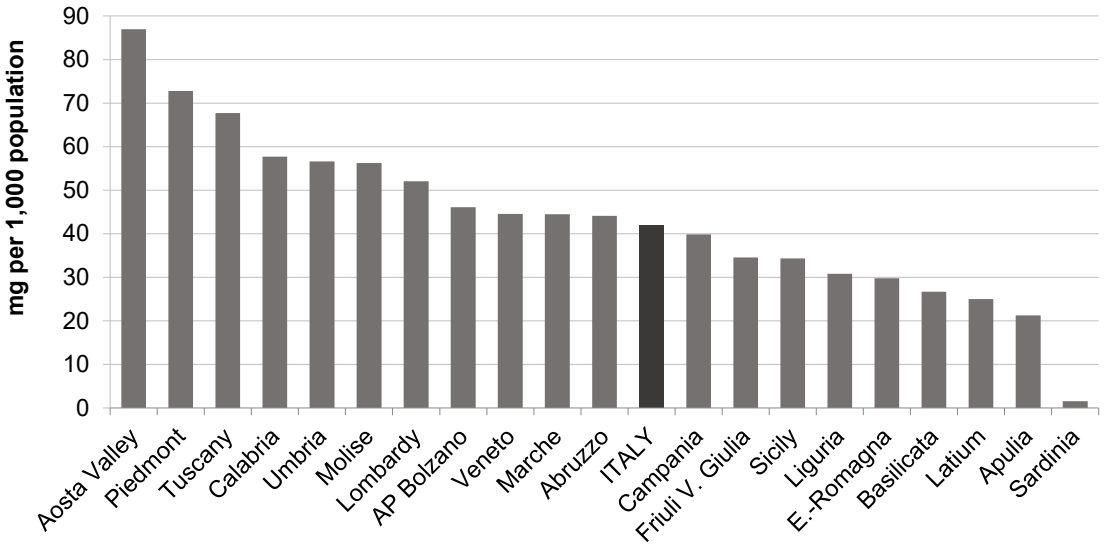

Figure 26. Total and regional demand (public and private) for Emicizumab expressed in mg per 1,000 population 2023 (adapted by the CNS on data from the Traceability information flow)

Figure 27 shows the variations in percentage of each Region compared to the national average. The Regions where the highest value was recorded are Aosta Valley (+ 108%) and Piedmont (+ 74%).

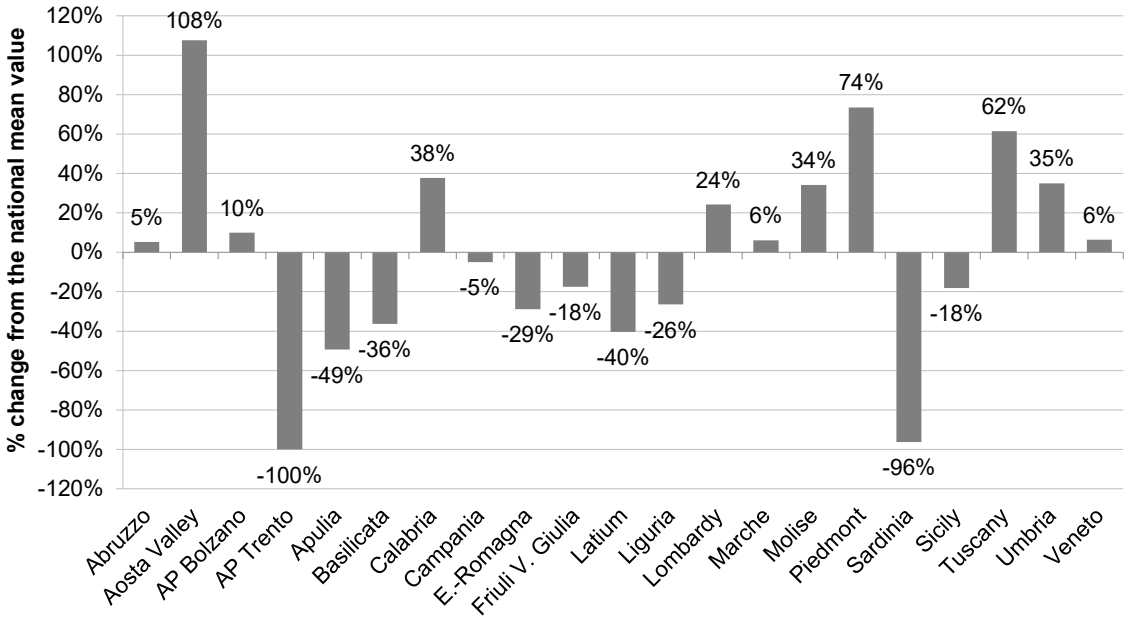

Figure 27. Percentage change from the national mean value of standardised regional demand for Emicizumab in 2023 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
025841089	AIMAFIX*FL 500IU+FL 10mL+SET	500	KEDRION SpA	A
028142026	MONONINE*EV F 500IU+F 5mL+KIT	500	CSL BEHRING SpA	A
029250065	ALPHANINE*EV 500IU+SIR 10mL+A	500	GRIFOLS ITALIA SpA	A
039072020	HAEMOBIONINE*1FL 500IU	500	BIOTEST ITALIA Srl	A
040092013	OCTANINE*FL 500IU+FL 5mL	500	OCTAPHARMA ITALY SpA	A
041799026	IXED*FL 500IU+FL 10mL+SET	500	KEDRION SpA	A
038324024	FIXNOVE*FL 600IU+FL 10mL	600	BAXALTA ITALY Srl	A
025841103	AIMAFIX*FL 1000IU+FL 10mL+SET	1000	KEDRION SpA	A
028142038	MONONINE*EV F 1000IU	1000	CSL BEHRING SpA	A
029250077	ALPHANINE “1000 IU/10 mL	1000	GRIFOLS ITALIA SpA	A
039072032	HAEMOBIONINE*1FL 1000IU	1000	BIOTEST ITALIA Srl	A
040092025	OCTANINE*FL 1000IU+FL	1000	OCTAPHARMA ITALY SpA	A
041799038	IXED*FL 1000IU+FL 10mL+SET	1000	KEDRION SpA	A
038324036	FIXNOVE*FL 1200IU+FL 10mL	1200	BAXALTA ITALY Srl	A
029250089	ALPHANINE “1500 IU/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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
033535016	BENEFIX*IV 1FL 250IU	250	PFIZER ITALIA Srl	A
033535042	BENEFIX*IV 1FL 250IU+SIR 5mL+SE	250	PFIZER ITALIA Srl	A
043796010	RIXUBIS*IV 1FL 250IU 5mL	250	BAXTER SpA	A
033535028	BENEFIX*IV 1FL 500IU	500	PFIZER ITALIA Srl	A
033535055	BENEFIX*IV 1FL 500IU+SIR 5mL+SE	500	PFIZER ITALIA Srl	A
043796022	RIXUBIS*IV 1FL 500IU 5mL	500	BAXTER SpA	A
033535030	BENEFIX*IV 1FL 1000IU	1000	PFIZER ITALIA Srl	A
033535067	BENEFIX*IV 1FL 1000IU+SIR 5mL+S	1000	PFIZER ITALIA Srl	A
043796034	RIXUBIS*IV 1FL 1000IU 5mL	1000	BAXTER SpA	A
033535093	BENEFIX*IV 1FL 1500IU+SIR5mL+S	1500	PFIZER EUROPE MA EEIG	A
033535079	BENEFIX*IV 1FL 2000IU+SIR 5mL+S	2000	PFIZER ITALIA Srl	A
043796046	RIXUBIS*IV 1FL 2000IU 5mL	2000	BAXTER SpA	A
033535081	BENEFIX*IV 1FL 3000IU+SIR 5mL+S	3000	PFIZER ITALIA Srl	A
043796059	RIXUBIS*IV 1FL 3000IU 5mL	3000	BAXTER SpA	A

AIC code	Brand name	IU	Manufacturer	NHS class
Extended half- recombinant Factor IX life				
044888016	ALPROLIX*1FL 250IU+1SIR 5mL	250	SOBI Srl	A
044891012	IDELVION*EV FL 250IU+FL 2,5mL	250	CSL BEHRING SpA	A
044888028	ALPROLIX*1FL 500IU+1SIR 5mL	500	SOBI Srl	A
044891024	IDELVION*EV FL 500IU+FL 2,5mL	500	CSL BEHRING SpA	A
045488018	REFIXIA*EV FL 500 IU+ FL 4 mL+SIR	500	NOVO NORDISK A/S	C
044888030	ALPROLIX*1FL 1000IU+1SIR 5mL	1000	SOBI Srl	A
044891036	IDELVION*EV FL 1000IU+FL 2,5mL	1000	CSL BEHRING SpA	A
045488020	REFIXIA*EV FL 1000IU+ FL 4mL+SIR	1000	NOVO NORDISK A/S	C
045488032	REFIXIA*EV FL 2000 IU+FL 4mL+SIR	1500	NOVO NORDISK A/S	C
044888042	ALPROLIX*1FL 2000IU+1SIR 5mL	2000	SOBI Srl	A
044891048	IDELVION*EV FL 2000IU+FL 2,5mL	2000	CSL BEHRING SpA	A
044888055	ALPROLIX*1FL 3000IU+1SIR 5mL	3000	SOBISrl	A
045488044	REFIXIA*EV FL 3000UI+FL 4mL+SIR	3000	NOVO NORDISK A/S	C(nn)
044891051	IDELVION*EV FL 3500IU+FL 5 ML	3500	CSL BEHRING SpA	C(nn)

Quantification and characterisation of the demand

Table 26 illustrates the total and *per capita* demand for plasma-derived and recombinant FIX for the two-year period 2022-2023, 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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,511,500	2.0	2,174,000	1.7	-13.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	49,500	0.1	236,000	0.4	378.2
AP Trento	570,500	1.1	744,000	1.4	30.2
Apulia	5,769,000	1.5	5,447,500	1.4	-5.5
Basilicata	309,500	0.6	250,500	0.5	-18.7
Calabria	1,591,500	0.9	1,705,500	0.9	7.0
Campania	6,933,500	1.2	7,512,000	1.3	8.0
E.-Romagna	4,681,500	1.1	4,749,500	1.1	1.3
Friuli V. Giulia	1,075,500	0.9	946,000	0.8	-11.8
Latium	4,999,200	0.9	5,862,700	1.0	17.2
Liguria	2,063,000	1.4	2,194,000	1.5	6.3
Lombardy	10,750,600	1.1	11,117,150	1.1	3.3
Marche	2,147,600	1.4	1,788,800	1.2	-16.4
Molise	76,000	0.3	136,800	0.5	80.1
Piedmont	4,851,000	1.1	4,374,750	1.0	-9.8
Sardinia	6,000	0.0	6,000	0.0	0.1
Sicily	4,025,500	0.8	4,542,500	0.9	12.5
Tuscany	7,930,950	2.2	6,853,900	1.9	-13.2
Umbria	629,000	0.7	632,500	0.7	0.9
Veneto	3,393,000	0.7	3,709,000	0.8	9.4
ITALY	64,363,850	1.1	64,983,100	1.1	0.9

* 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 2023 was 64,983,100 IUs (Table 26); about 5.7% of the aforementioned amount (3,699,600 IUs) was plasma-derived. There was a sharp decrease in demand for FIXpd (-46%) and an increase for FIXr (+6.6%), especially due to the long half-life formulations for which an increase of +18.6% was recorded in the two-year period considered.

In 2023, the standardised demand for plasma-derived and recombinant FIX was 1.1 IUs *per capita*, with significantly different regional trends: these ranged from a minimum – close to zero – in Sardinia (-99.7% compared to the Italian mean value), to a maximum in Tuscany (1.9 IUs), Abruzzo (1.7 IUs), Liguria (1.5 IUs), AP of Trento and Apulia with 1.4 IUs *per capita* (+70%, +55%, +32%, +27% and +24% compared to the national mean value, respectively) (Figures 28 and 29). No consumption in Aosta Valley was registered.

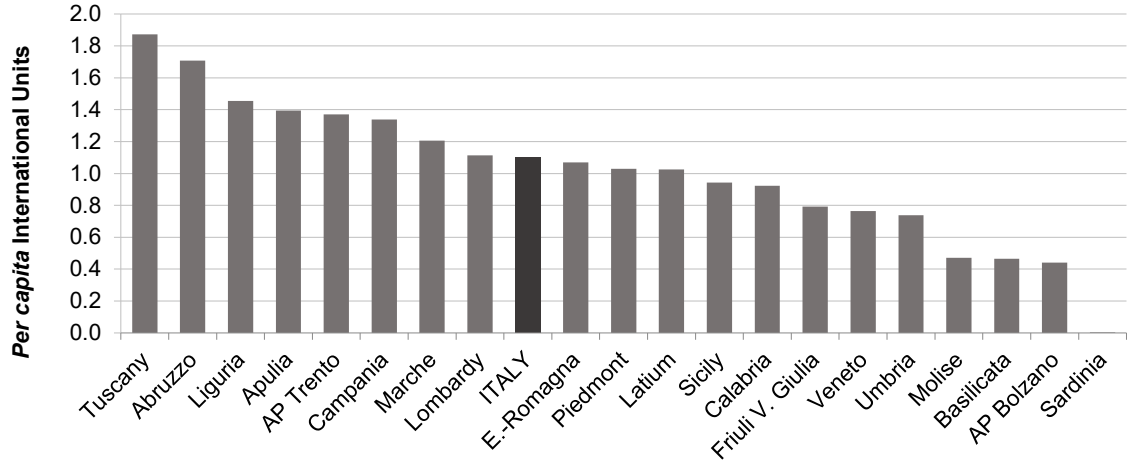

Figure 28. Total and regional demand (public and private) for coagulation Factor IX, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

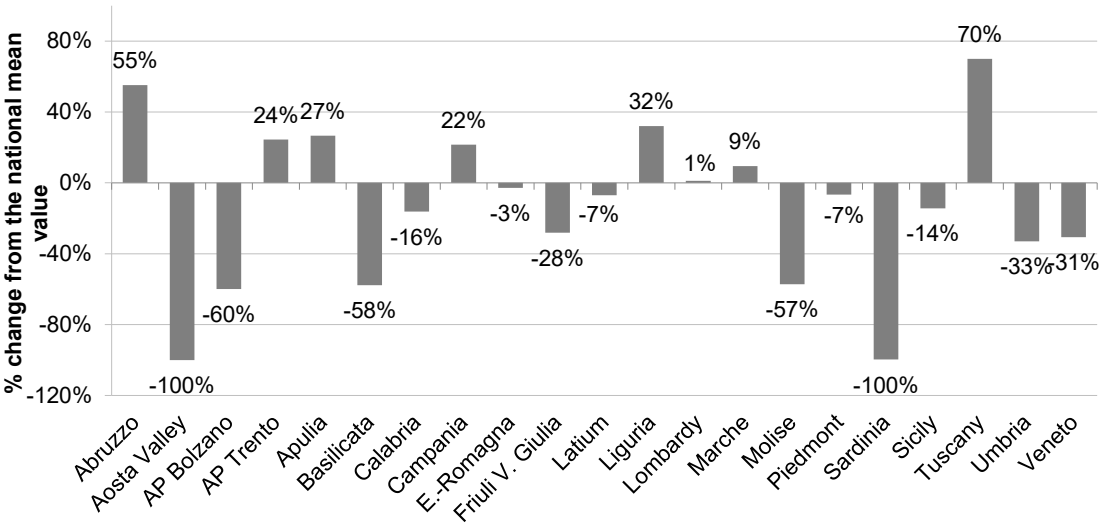

Figure 29. Percentage variation from the national mean value of standardised regional demand for coagulation Factor IX (International Units *per capita*) in 2023 (adapted by the CNS on data from the Traceability information flow)

In thirteen Regions there were percentage increases in demand (range: 0.1-378%) which is instead decreasing in seven Regions (range: -5.5; -18.7%) (Table 26). In Sardinia, Apulia, AP of Trento, Friuli V.Giulia, Basilicata and Abruzzo rFIX was used exclusively, while in Calabria, Sicily, AP of Bolzano, Piedmont, Tuscany, E.-Romagna,Veneto, Campania and Liguria the rFIX demand reached volumes of above 95% (Figure 30).

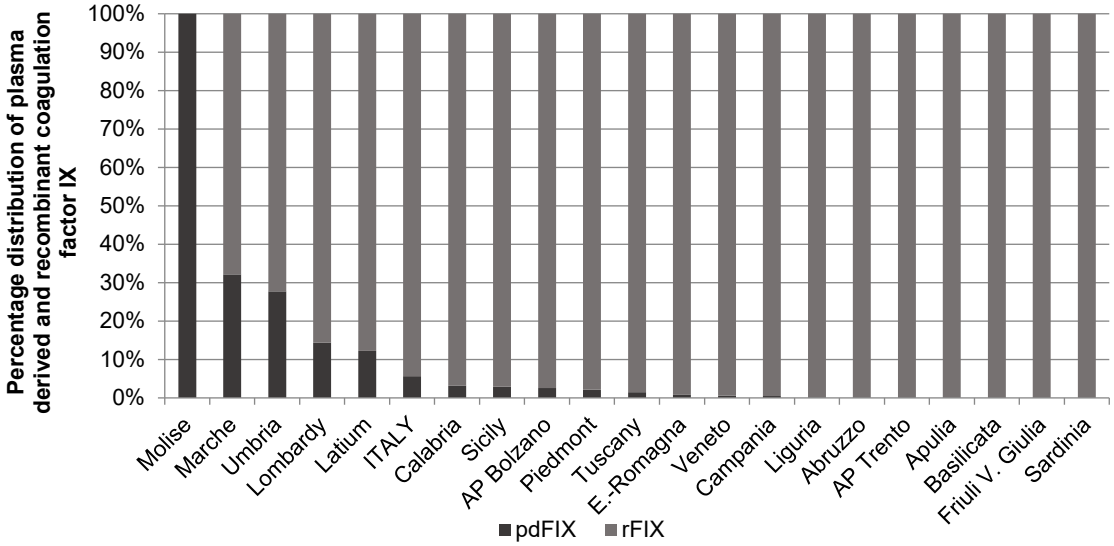

Figure 30. Distribution expressed in % of Factor IX per type, by Region, 2023 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor IX

In 2023, the total demand for pdFIX (expressed in absolute values and *per capita* volumes), showed a decrease of 46% compared to 2022, for an absolute value of 3,699,600 IUs, equal to 0.1 IUs *per capita* (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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	6,000	0.0	100.0
AP Trento	-	-	-	-	NA
Apulia	387,000	0.1	-	-	-100.0
Basilicata	7,000	0.0	-	-	-100.0
Calabria	31,000	0.0	54,000	0.0	74.0
Campania	54,000	0.0	36,000	0.0	-33.6
E.-Romagna	59,000	0.0	43,000	0.0	-27.2
Friuli V. Giulia	-	-	-	-	NA
Latium	298,200	0.1	715,200	0.1	139.6
Liguria	4,000	0.0	4,000	0.0	0.0
Lombardy	2,372,100	0.2	1,603,400	0.2	-32.5
Marche	1,053,600	0.7	574,800	0.4	-45.2

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Molise	76,000	0.3	136,800	0.5	80.1
Piedmont	423,000	0.1	94,000	0.0	-77.8
Sardinia	-	-	-	-	NA
Sicily	118,000	0.0	130,000	0.0	9.9
Tuscany	1,625,200	0.4	104,400	0.0	-93.6
Umbria	289,500	0.3	175,500	0.2	-39.2
Veneto	72,500	0.0	22,500	0.0	-68.9
ITALY	6,870,100	0.1	3,699,600	0.1	-46.2

* The amounts of pdFIX contained in Factor X P Behring® are not included.

The Regions with the highest *per capita* demand were Molise and Marche with 0.5 IUs and 0.4 IUs respectively; in Abruzzo, Basilicata, Friuli V.Giulia, AP of Trento, Apulia, Sardinia and Aosta Valley there was no reported consumption of pdFIX (Figures 31 and 32).

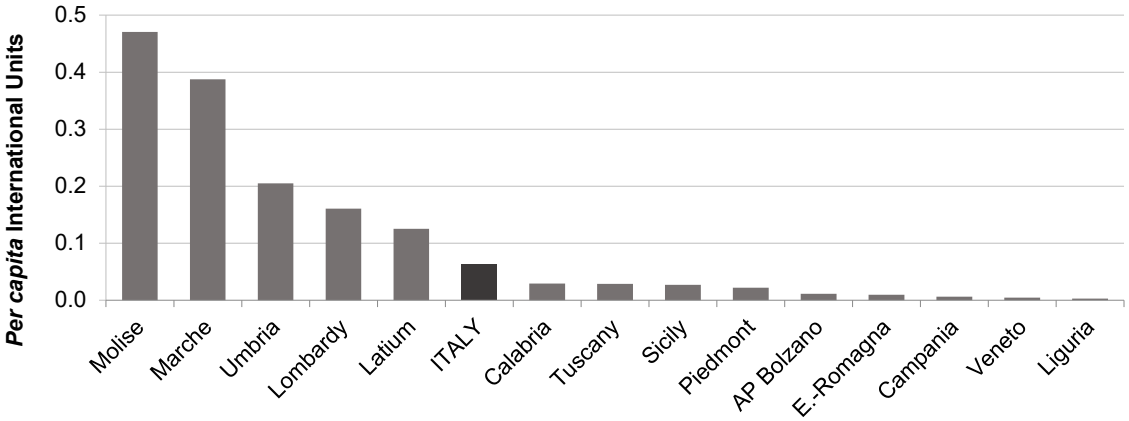

Figure 31. Total and regional demand (public and private) for plasma-derived coagulation Factor IX, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

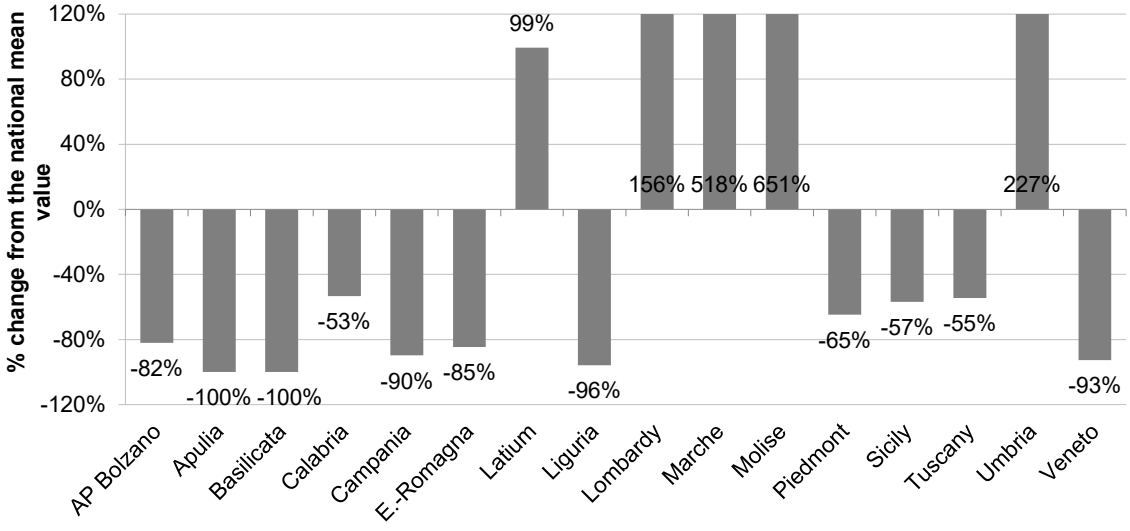

Figure 32. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor IX in 2023 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor IX

The total demand for rFIX showed, in the period 2022-2023, an increase of +6.6%, registering a value of 61,283,500 IUs in 2023, equal to 1.0 IU *per capita* (Table 28).

The Regions with the highest *per capita* demand (Figure 33) were Tuscany, Abruzzo, Apulia, Liguria and the AP of Trento with 1.8 IU for the first one, 1.7 IU for the second one, 1.5 IU for the third and 1.4 IU for the last two.

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,511,500	2.0	2,174,000	1.7	-13.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	49,500	0.1	230,000	0.4	366.1
AP Trento	570,500	1.1	744,000	1.4	30.2
Apulia	5,382,000	1.4	5,447,500	1.4	1.3
Basilicata	302,500	0.6	250,500	0.5	-16.8
Calabria	1,560,500	0.8	1,651,500	0.9	5.7
Campania	6,879,500	1.2	7,476,000	1.3	8.3
E.-Romagna	4,622,500	1.0	4,706,500	1.1	1.7
Friuli V. Giulia	1,075,500	0.9	946,000	0.8	-11.8
Latium	4,701,000	0.8	5,147,500	0.9	9.4
Liguria	2,059,000	1.4	2,190,000	1.5	6.3
Lombardy	8,378,500	0.8	9,513,750	1.0	13.4
Marche	1,094,000	0.7	1,214,000	0.8	11.4
Molise	-	-	-	-	NA
Piedmont	4,428,000	1.0	4,280,750	1.0	-3.3
Sardinia	6,000	0.0	6,000	0.0	0.1
Sicily	3,907,500	0.8	4,412,500	0.9	12.6
Tuscany	6,305,750	1.7	6,749,500	1.8	7.5
Umbria	339,500	0.4	457,000	0.5	35.1
Veneto	3,320,500	0.7	3,686,500	0.8	11.1
ITALY	57,493,750	1.0	61,283,500	1.0	6.6

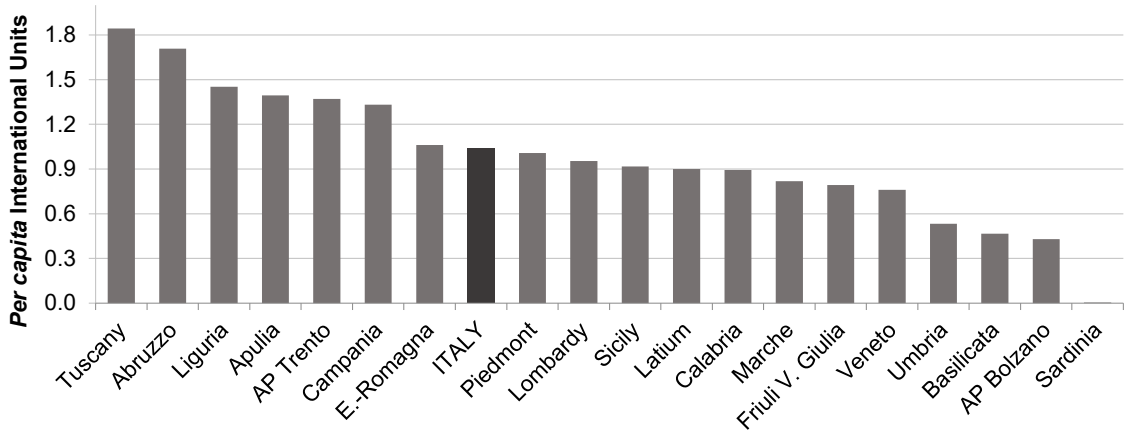

Figure 33. Total and regional demand (public and private) for recombinant coagulation Factor IX, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

Figure 34 shows the percentage difference from the Italian average of the demand for recombinant origin Factor IX, by Region. In Aosta Valley and Molise there was no reported consumption of rFIX in 2023, while, in the same year, there was an increase in *per capita* demand, compared to 2022, which is particularly evident in the AP of Bolzano (+366%) and in Umbria (+35%); instead a significant decrease occurred in Basilicata (-17%).

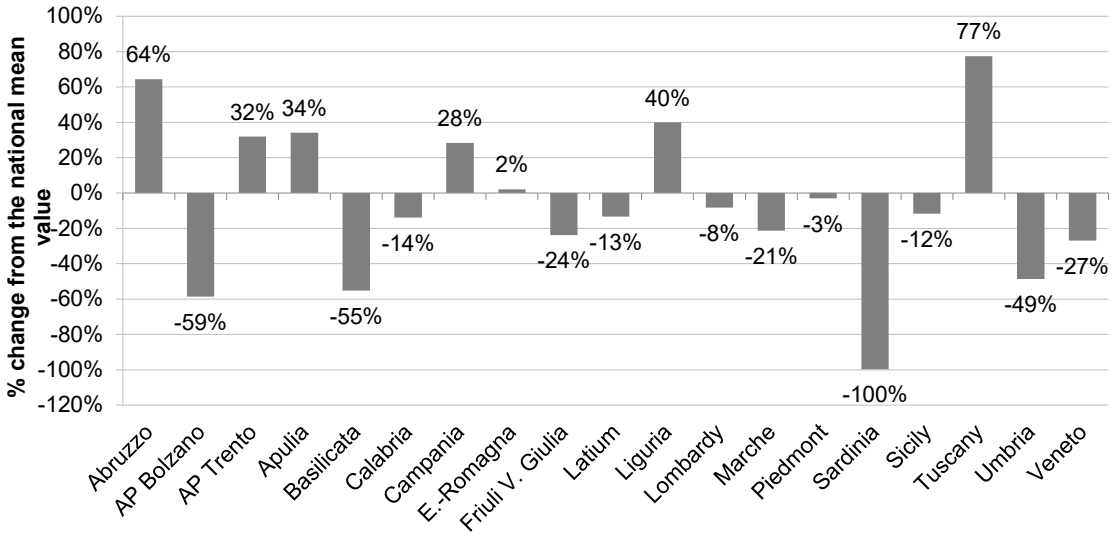

Figure 34. Percentage variation from the national mean value of standardised regional demand for recombinant coagulation Factor IX in 2023 (adapted by the CNS on data from the Traceability information flow)

Extended half- recombinant Factor IX life

Out of 61.3 million IUs of rFIX demand, extended half-life recombinant Factor IX molecules recorded a total demand of 45,889,750 IUs, about 75% of the total (Table 29). The mean national demand *per capita* was about 0.8 IU, with a range among Regions of 0.1 IU and 1.5 IU. In Molise, Sardinia and in the Aosta Valley there was no consumption for these drugs in 2023 (Figure 35 and 36).

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* and variations in percentage between 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,995,500	1.6	1,914,500	1.5	-4.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	48,000,0	0.1	230,000,0	0.4	380.6
AP Trento	24,500,0	0.0	53,000,0	0.1	116.0
Apulia	4,211,000	1.1	4,628,500	1.2	10.0
Basilicata	125,500	0.2	139,500	0.3	11.7
Calabria	1,066,500	0.6	1,194,500	0.6	11.9
Campania	3,417,500	0.6	4,727,500	0.8	37.9
E.-Romagna	3,945,000	0.9	4,088,000	0.9	3.5
Friuli V. Giulia	1,067,500	0.9	944,000	0.8	-11.3

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Latium	2,714,500	0.5	3,173,500	0.6	16.8
Liguria	1,865,000	1.2	2,090,000	1.4	12.0
Lombardy	6,544,500	0.7	8,037,000	0.8	22.7
Marche	966,000	0.6	1,125,000	0.8	16.9
Molise	-	-	-	-	NA
Piedmont	2,765,500	0.7	3,594,750	0.8	30.0
Sardinia	-	-	-	-	NA
Sicily	2,230,500	0.5	3,131,500	0.7	40.0
Tuscany	2,756,750	0.7	3,230,000	0.9	17.6
Umbria	327,500	0.4	442,000	0.5	35.5
Veneto	2,601,500	0.5	3,146,500	0.6	21.1
ITALY	38,672,750	0.7	45,889,750	0.8	18.6

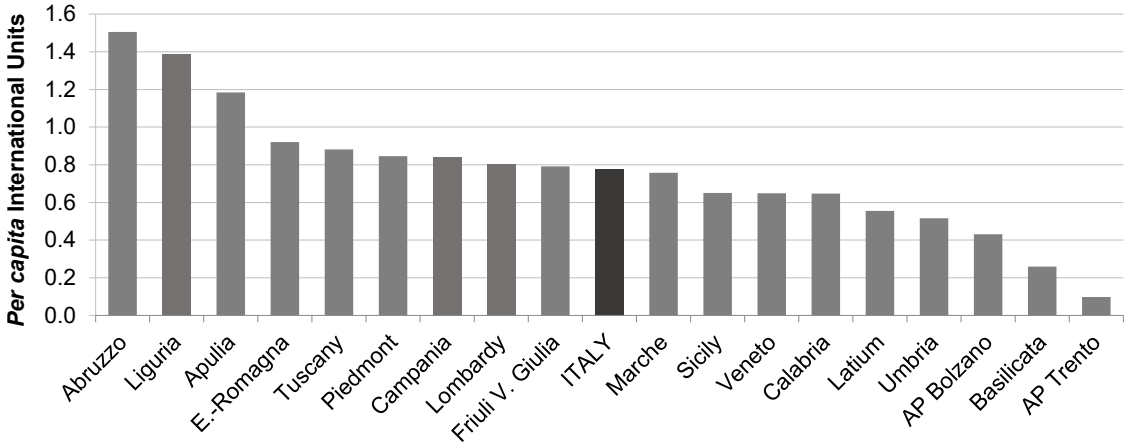

Figure 35. Total and regional demand (public and private) for extended half-life recombinant Factor IX, expressed in International Units per capita, 2023 (adapted by the CNS on data from the Traceability information flow)

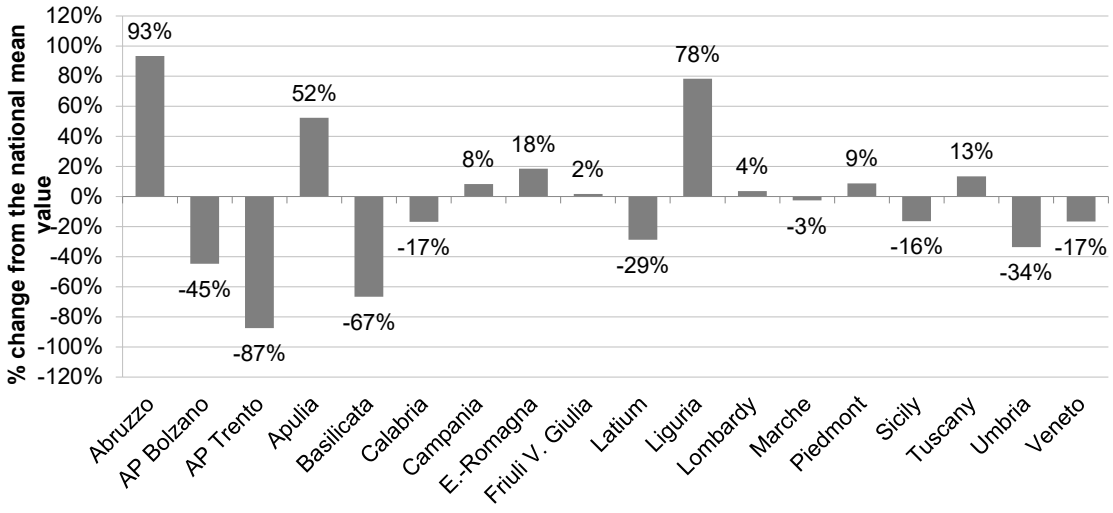

Figure 36. Percentage variation from the national mean value of standardised regional demand for extended half-life recombinant Factor IX in 2023 (adapted by the CNS on data from the Traceability information flow)

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

Prothrombin Complex Concentrates (PCCs) are plasma-derived therapeutic medicinal products 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), or 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 the active ingredients 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
023309103	UMANCOMPLEX D.I.*FL 500IU+F20mL	500	KEDRION SpA	A
041850013	KEDCOM*FL 500IU+FL 20mL+SET	500	KEDRION SpA	H
023288032	PROTROMPLEX TIM3*F 600IU+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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
049861014	COFACT*FL 250 UI + FL SOLV 10mL	250	Prothya Biosolutions Netherlands B.V.	H
038844015	CONFIDEX*500IU+1FL SOLV 20mL	500	CSL BEHRING GMBH	H
039240015	PRONATIV*500IU+FL SOLV 20mL	500	OCTAPHARMA ITALY	H
049861026	COFACT*FL 500 UI + FL SOLV 20mL	500	Prothya Biosolutions Netherlands B.V.	H
043304029	PROPLEX*FL 500UI+FL SOLV 17mL	500	BAXALTA ITALY Srl	C(nn)
043304017	PROPLEX*FL 600IU/20mL+FL SOLV	600	BAXALTA ITALY Srl	H
038844027	CONFIDEX 1000*FL POLV+FL 40mL	1000	CSL BEHRING SpA	H
039240027	PRONATIV*1000IU+FL SOLV 20mL	1000	OCTAPHARMA ITALY	H

Quantification and characterisation of the demand

Table 32 shows the total demand and the standardised one (expressed in IUs *per capita*) for 3F-PCCs in the two-year period 2022-2023, at both national and regional level.

In 2023 there was a decrease in the total demand (-8.5%) compared to 2022; it stood at 33,536,400 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 0.1 IUs (Aosta Valley) to 1.0 IU (Veneto), with a percentage change compared to the Italian mean value of over 67% for the latter (Figures 37 and 38). In 2023, the national demand for 4F-PCCs was 23,607,700 IUs, equal to

41% of the overall demand for PCCs, with a standardised demand of 0.4 IU *per capita* and with an increase of 25% compared to the previous year (Table 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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	156,000	0.1	361,000	0.3	131.6
Aosta Valley	45,000	0.4	10,000	0.1	-77.7
AP Bolzano	290,500	0.5	251,000	0.5	-13.3
AP Trento	431,500	0.8	250,000	0.5	-42.2
Apulia	2,611,500	0.7	1,775,500	0.5	-31.9
Basilicata	316,000	0.6	419,500	0.8	33.4
Calabria	678,000	0.4	742,000	0.4	9.3
Campania	2,017,500	0.4	1,558,500	0.3	-23.0
E.-Romagna	3,386,000	0.8	3,367,500	0.8	-0.7
Friuli V. Giulia	560,500	0.5	261,000	0.2	-53.3
Latium	1,781,500	0.3	1,751,700	0.3	-1.8
Liguria	876,500	0.6	998,500	0.7	13.9
Lombardy	6,671,000	0.7	7,209,500	0.7	7.9
Marche	1,057,300	0.7	614,200	0.4	-41.7
Molise	239,500	0.8	155,000	0.5	-35.3
Piedmont	3,456,000	0.8	3,213,500	0.8	-7.0
Sardinia	930,000	0.6	692,000	0.4	-25.5
Sicily	3,174,000	0.7	2,813,500	0.6	-11.6
Tuscany	3,068,400	0.8	2,094,000	0.6	-31.5
Umbria	258,500	0.3	397,500	0.5	54.3
Veneto	4,647,000	1.0	4,601,000	0.9	-0.9
ITALY	36,652,200	0.6	33,536,400	0.6	-8.5

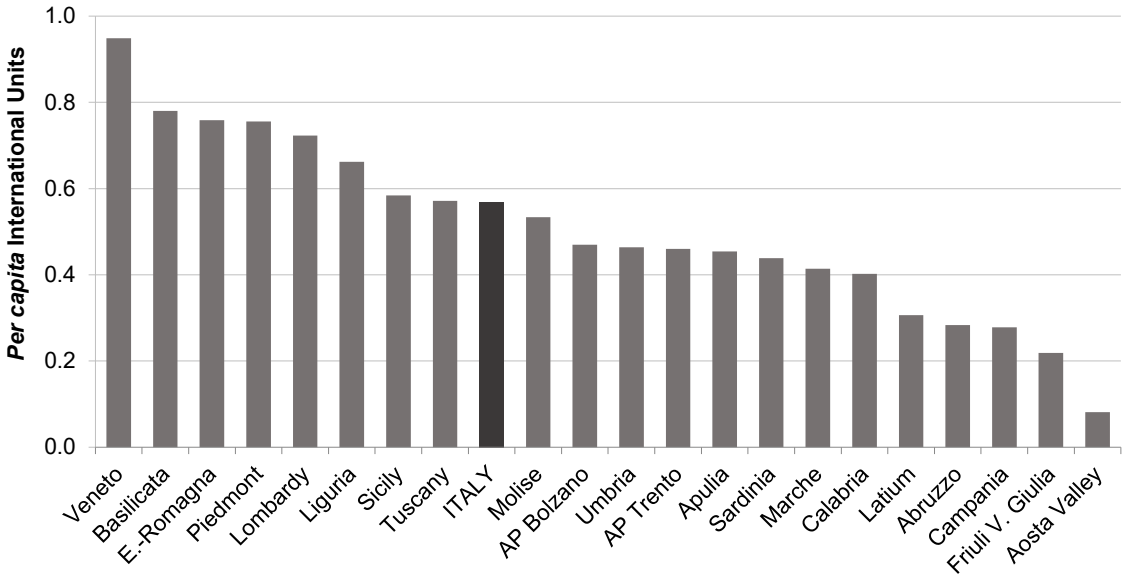

Figure 37. Total and regional demand (public and private) for 3-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

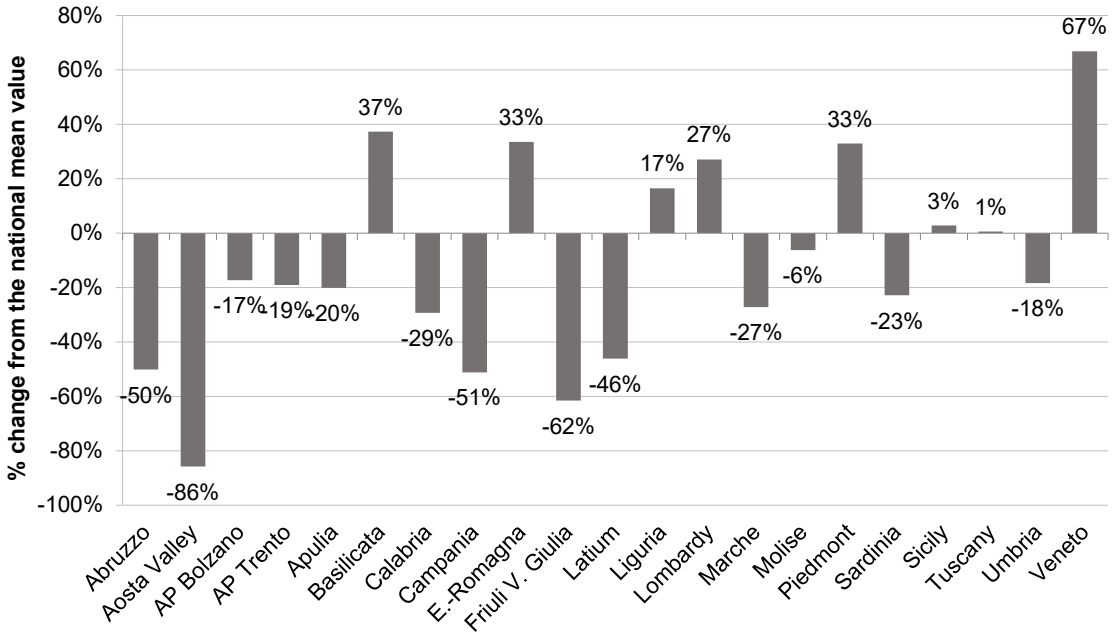

Figure 38. Percentage variation from the national mean value of standardised regional demand for 3-factor prothrombin complex concentrates in 2023 (adapted by the CNS on data from the Traceability information flow)

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 2022-2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,024,500	0.8	978,500	0.8	-4.4
Aosta Valley	-	-	100,500	0.8	100.0
AP Bolzano	530,000	1.0	1,099,000	2.1	108.0
AP Trento	87,500	0.2	135,000	0.2	54.0
Apulia	231,300	0.1	370,100	0.1	60.2
Basilicata	194,500	0.4	293,000	0.5	51.3
Calabria	354,000	0.2	414,500	0.2	17.0
Campania	1,641,500	0.3	2,820,300	0.5	71.2
E.-Romagna	1,943,000	0.4	2,391,800	0.5	22.9
Friuli V. Giulia	-	-	-	-	NA
Latium	3,743,100	0.7	2,978,300	0.5	-20.5
Liguria	968,000	0.6	1,260,000	0.8	30.1
Lombardy	1,687,500	0.2	2,196,000	0.2	30.0
Marche	201,500	0.1	799,700	0.5	298.3
Molise	-	-	-	-	NA
Piedmont	1,343,000	0.3	1,774,300	0.4	32.1
Sardinia	1,433,000	0.9	1,296,500	0.8	-9.5
Sicily	691,500	0.1	619,300	0.1	-10.7
Tuscany	1,622,000	0.4	2,097,400	0.6	29.8
Umbria	353,500	0.4	635,500	0.7	80.4
Veneto	880,500	0.2	1,348,000	0.3	53.3
ITALY	18,929,900	0.3	23,607,700	0.4	24.7

Also for 4F-PCCs, there were considerable differences regarding its utilisation from one Region to another. With the exception of Abruzzo, Latium, Sardinia ans Sicily, all the Regions recorded significant increases in the demand.

The Region with the highest demand in 2023 was the AP of Bolzano with 2.1 IU *per capita*, followed by Sardinia, Abruzzo, Aosta Valley and Liguria all with 0.8 UI *per capita* (Figure 39).

Figure 40 shows percentage variations compared to the Italian mean values of the standardised regional demand for 4F-PCCs as recorded by the drug Traceability system in 2023.

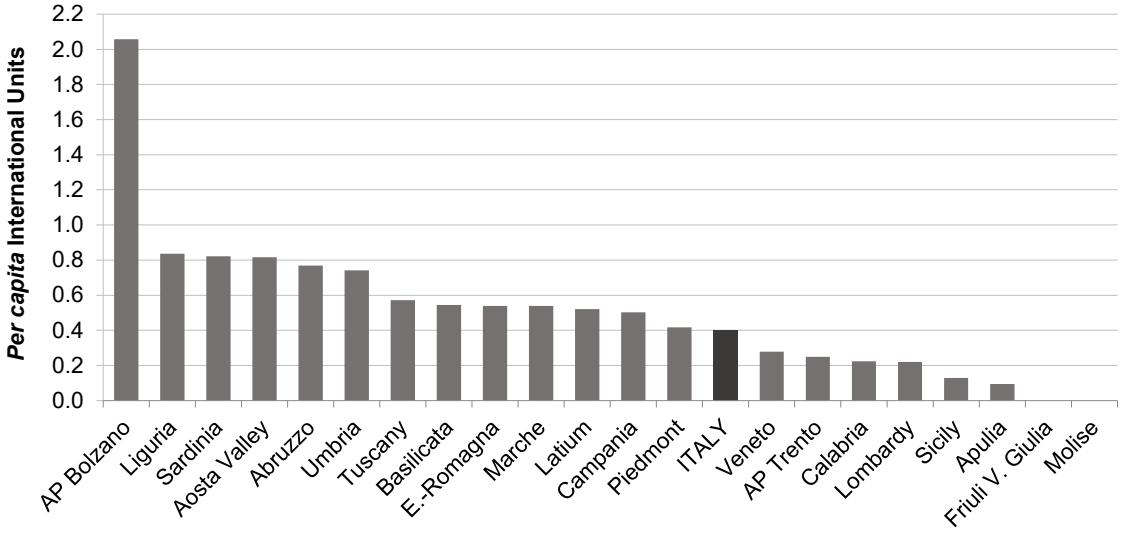

Figure 39. Total and regional demand (public and private) for 4-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2023 (adapted by the CNS on data from the Traceability information flow)

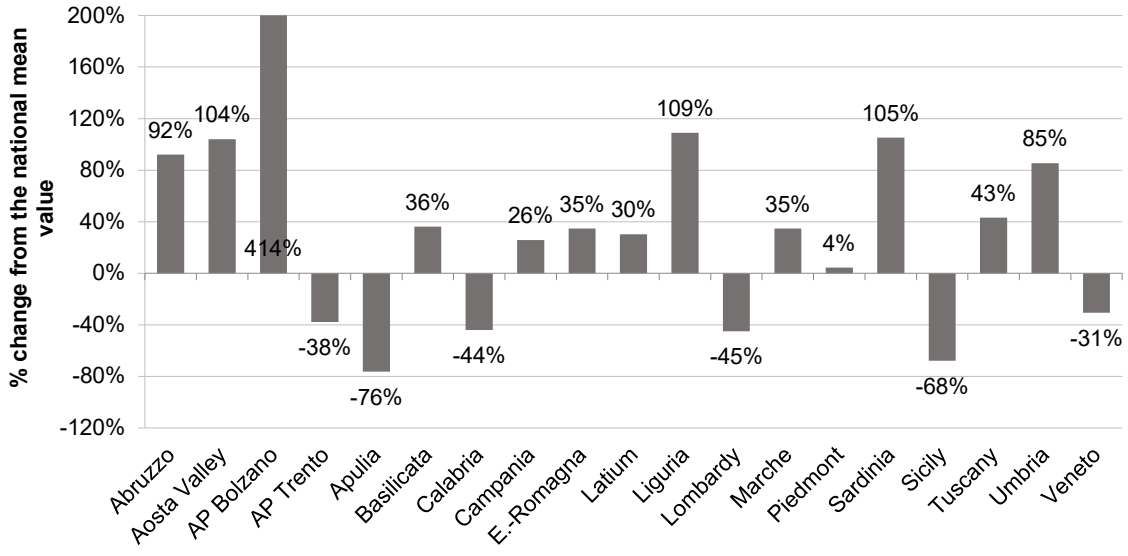

Figure 40. Percentage variation from the national mean value of standardised regional demand for 4-factor prothrombin complex concentrates in 2023 (adapted by the CNS on data from the Traceability information flow)

FIBRINOGEN (ATC B02BB01)

Fibrinogen is one of the most present coagulation factors in plasma, with an average concentration of about 2-4 g/L. It is converted into fibrin by thrombin and is the maincomponent 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 thus 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 the active ingredients 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, 31/12/2023)

AIC code	Brand name	g	Manufacturer	NHS class
*E00178010	HAEMOCOMPLETTAN P 1F 1g	1	CSL BEHRING SpA	H
040170019	RIASTAP FL POLV 1g 20mg/mL	1	CSL BEHRING SpA	C
040170021	RIASTAP*F POLV 1g20mg/mL+DISP	1	CSL BEHRING SpA	C
048798019	FIBRYGA*FLPOLV 1g 100Mm+F50mL	1	OCTAPHARMA ITALY SpA	A
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 2022-2023 at regional and national level.

In 2023, total fibrinogen demand showed a significant increase (+11.7%) compared to the previous year. Its volume of 66,899 g, with a standardised demand of 1.1 g per 1,000 population, confirmed the rapid upward trend. All Regions, with the exception of Basilicata, Latium, Molise and Sardinia contributed to this growth to different extents.

Figure 41 shows the regional and national standardised demand for fibrinogen in 2023. The Regions with the highest demand per 1,000 population were the AP of Bolzano (2.7 g), then Veneto (2.3 g), Umbria (1.9 g), Abruzzo (1.5 g) and Friuli V. Giulia with 1.4 g. The lowest demand, between 0.02 g and 0.8 g per 1,000 population, was recorded in Molise, Aosta Valley, Piedmont and Sicily.

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,491	1.2	1,959	1.5	31.5
Aosta Valley	30	0.2	63	0.5	110.4
AP Bolzano	862	1.6	1,450	2.7	68.7
AP Trento	360	0.7	690	1.3	91.4
Apulia	2,849	0.7	3,941	1.0	38.5
Basilicata	635	1.2	494	0.9	-21.9
Calabria	1,514	0.8	1,849	1.0	22.0
Campania	4,955	0.9	5,233	0.9	5.3
E.-Romagna	4,473	1.0	5,122	1.2	14.4
Friuli V. Giulia	1,465	1.2	1,680	1.4	15.0
Latium	6,873	1.2	4,999	0.9	-27.3
Liguria	1,226	0.8	1,727	1.1	40.8
Lombardy	9,082	0.9	9,389	0.9	3.3
Marche	1,418	1.0	1,808	1.2	28.0
Molise	150	0.5	6	0.0	-96.0
Piedmont	2,837	0.7	3,469	0.8	22.3
Sardinia	2,060	1.3	2,041	1.3	-0.9
Sicily	3,744	0.8	3,955	0.8	5.4
Tuscany	3,353	0.9	4,433	1.2	32.7
Umbria	1,420	1.7	1,660	1.9	17.3
Veneto	9,078	1.9	10,933	2.3	20.6
ITALY	59,872	1.0	66,899	1.1	11.7

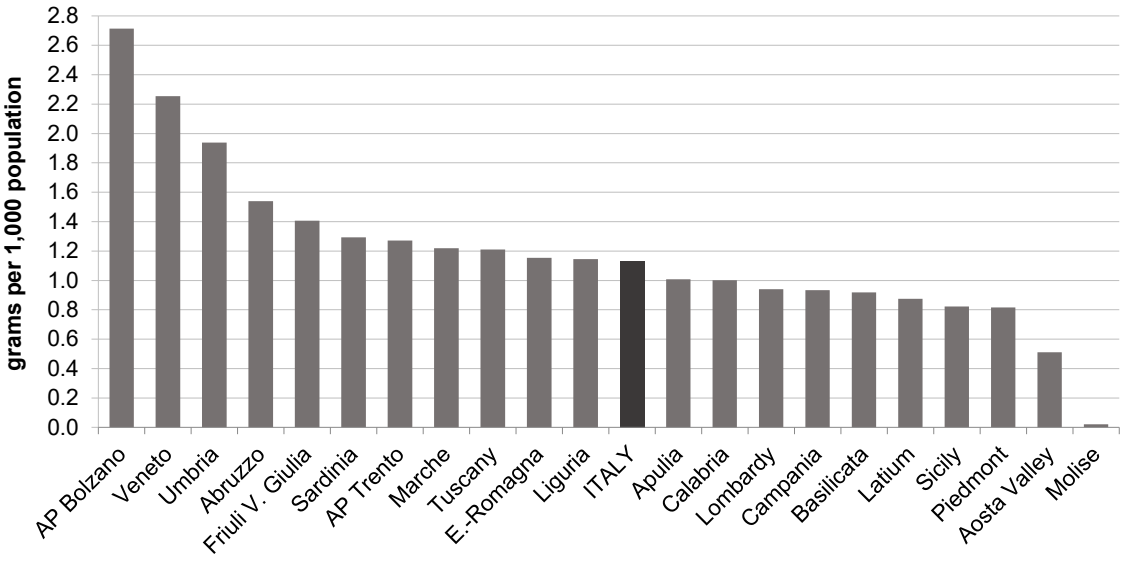

Figure 41. Total and regional demand (public and private) for fibrinogen, expressed in grams per 1,000 population, 2023 (adapted by the CNS on data from the Traceability information flow)

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 the 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
035561012	NEOHEPATECT*IV 1F 100IU 2mL	100	BIOTEST PHARMA GMBH	H
026415048	VENBIG*1F 500IU+F 10mL+SET	500	KEDRION SpA	H
035561024	NEOHEPATECT*IV 1F 500IU 10mL	500	BIOTEST PHARMA GMBH	H
038059010	KEYVENB"500IU/10mL+SET	500	KEDRION SpA	H
038059034	KEYVENB"50IU/mL" F. CON 500IU	500	KEDRION SpA	H
041985019	VEBIKED"50IU/mL"FL CON 500IU	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	INSTITUTO GRIFOLS S.A.	H
035561036	NEOHEPATECT*IV FL 2000IU 40mL	2000	BIOTEST PHARMA GMBH	H
026415051	VENBIG*F 2500IU/50mL+F 45mL+SET	2500	KEDRION SpA	H
038059022	KEYVENB"2500IU/45mL+SET	2500	KEDRION SpA	H
038059046	KEYVENB"50IU/mL" F 2500IU	2500	KEDRION SpA	H
041985021	VEBIKED"50IU/mL" FL 2500IU+SET	2500	KEDRION SpA	C(nn)
035561048	NEOHEPATECT*IV FL 5000IU 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	INSTITUTO 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
023782028	UMAN BIG "180 IU/1mL SOLUZ. INIET"	180	KEDRION SpA	A
025653015	IMMUNOHBS*IM 1F 1mL 180IU	180	KEDRION SpA	A
042002016	KEDHBS 180 IU/1mL - 1FL 1mL	180	KEDRION SpA	A
023782016	UMANBIG*IM 1FL 3mL 540IU	540	KEDRION SpA	A
025653027	IMMUNOHBS*IM 1F 3mL 540IU	540	KEDRION SpA	A
042002028	KEDHBS 540 IU/3mL - 1FL 3mL	540	KEDRION SpA	A
035320011	IGANTIBE*IM 1F 3mL 600IU/3mL	600	INSTITUTO GRIFOLS S.A.	A
025653054	IMMUNOHBS*IM 1SIR 1000IU 3mL	1000	KEDRION SpA	A
035320023	IGANTIBE*IM 1F 5mL 1000IU/5mL	1000	INSTITUTO GRIFOLS S.A.	A
042002030	KEDHBS 1000 IU/3mL 1SIR 3mL	1000	KEDRION SpA	A
039644012	ZUTECTRA*SC 5SIR 1mL 500IU	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 2022-2023, at national and at regional level. The national demand for hepatitis B IGs for IV use, showed a downward trend (-5.1%) already observed in previous years (34).

The total demand in 2023 was almost 12,8 million IUs (0.2 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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	24,000	0.0	18,000	0.0	-24.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	1,139,500	0.3	1,546,500	0.4	35.9
Basilicata	1,000	0.0	2,000	0.0	100.9
Calabria	105,000	0.1	115,500	0.1	9.9
Campania	2,855,000	0.5	2,479,000	0.4	-13.5
E.-Romagna	2,352,500	0.5	1,497,500	0.3	-36.4
Friuli V. Giulia	-	-	-	-	NA
Latium	720,000	0.1	1,065,000	0.2	47.8
Liguria	92,500	0.1	180,000	0.1	94.6
Lombardy	1,009,500	0.1	1,195,500	0.1	18.3
Marche	225,500	0.2	121,000	0.1	-46.1
Molise	-	-	-	-	NA
Piedmont	267,500	0.1	547,500	0.1	104.7
Sardinia	601,000	0.4	629,000	0.4	4.7
Sicily	495,000	0.1	490,000	0.1	-1.3
Tuscany	860,000	0.2	901,000	0.2	5.2
Umbria	-	-	-	-	NA
Veneto	2,703,000	0.6	1,977,000	0.4	-26.8
ITALY	13,451,000	0.2	12,764,500	0.2	-5.1

Veneto, Apulia, Campania and Sardinia are the regions with the highest demand (0.4 IU per capita) together accounting for more than 50 percent of national demand.

On the other hand, the national demand for antihepatitis B SC/IM IG, shows a slight decrease, equal to -2% of the demand recorded in 2022; the total consumption for 2023 is approximately 59.9 million IUs (1.0 IUs *per capita*) (Table 39) and accounted 82% of the total demand for antihepatitis 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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	544,180	0.4	560,000	0.4	3.0
Aosta Valley	202,200	1.6	207,800	1.7	2.9
AP Bolzano	132,040	0.2	90,620	0.2	-31.2
AP Trento	178,160	0.3	177,320	0.3	-0.6
Apulia	5,938,860	1.5	6,376,640	1.6	7.5
Basilicata	254,360	0.5	248,300	0.5	-1.9
Calabria	1,296,400	0.7	1,347,240	0.7	3.8
Campania	18,737,560	3.4	18,322,120	3.3	-2.5
E.-Romagna	3,664,360	0.8	4,113,820	0.9	12.1
Friuli V. Giulia	218,400	0.2	288,200	0.2	32.3
Latium	2,313,740	0.4	2,343,740	0.4	1.2
Liguria	538,700	0.4	526,020	0.3	-2.4
Lombardy	9,055,200	0.9	8,353,780	0.8	-7.9
Marche	659,980	0.4	695,740	0.5	5.8
Molise	184,780	0.6	202,480	0.7	9.6
Piedmont	4,627,540	1.1	4,480,820	1.1	-3.1
Sardinia	3,733,300	2.4	2,994,300	1.9	-19.7
Sicily	2,877,280	0.6	2,956,000	0.6	2.5
Tuscany	3,134,400	0.9	2,628,320	0.7	-15.8
Umbria	358,480	0.4	319,720	0.4	-10.5
Veneto	2,538,500	0.5	2,634,340	0.5	3.9
ITALY	61,188,420	1.0	59,867,320	1.0	-2.2

TETANUS IMMUNOGLOBULINS (ATC J06BB02)

Table 40 shows drugs containing tetanus IGs currently available on the Italian market and the amount of the 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
022488047	TETANUSGAMMA*IM 1SIR 250IU 2mL	250	KEDRION SpA	A
022488062	TETANUSGAMMA*IM SIR 250IU 1mL	250	KEDRION SpA	A
022601088	TETABULIN*IM 1SIR 250IU 1mL	250	BAXTER SpA	A
022635041	GAMMATET P*IM 1F 250IU 1mL	250	CSL BEHRING SpA	A
022635066	GAMMATET P*IM 1SIR 250IU 1mL	250	CSL BEHRING SpA	A
033863010	IGANTET*IM 1SIR 1mL 250IU	250	GRIFOLS ITALIA SpA	A
022488050	TETANUSGAMMA*IM 1SIR 500IU 2mL	500	KEDRION SpA	A
022601090	TETABULIN*IM 1SIR 500IU 2mL	500	BAXTER SpA	A
022635054	GAMMATET P*IM 1F 500IU 2mL	500	CSL BEHRING SpA	A
022635078	GAMMATET P*IM 1SIR 500IU 2mL	500	CSL BEHRING SpA	A
033863022	IGANTET*IM 1SIR 2mL 500IU	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 2023 the total demand for tetanus IGs was 122,583,250 IUs (2.1 IUs *per capita*), showing an increase of +3% compared to 2022 (Table 41).

The Regions with the highest demand, expressed as standardised volume for the resident population, were Campania (4.1 IUs *per capita*), Abruzzo (3.9 IUs *per capita*), Calabria (3.3 IUs *per capita*), Basilicata and Molise (3.1 IUs *per capita*). In 2023, the demand increased – in some cases very significantly - in almost all Regions, with the exception of Friuli V. Giulia (-89%), Liguria (-3.9%), Lombardy (-2.7%), AP of Trento (-1.8%), Sicily (-3.7%) and Veneto (-15.5%).

For the year 2023, there were no imports of anti-tetanus IGs under the provisions of the DM of 11 February 1997 and the DM of 11 May 2001, as it had happened in the previous years, when they were listed under the heading “Not Specified Region”.

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	4,388,250	3.4	4,994,250	3.9	13.9
Aosta Valley	293,250	2.4	326,750	2.7	11.6
AP Bolzano	550,750	1.0	631,500	1.2	15.0
AP Trento	466,000	0.9	458,250	0.8	-1.8
Apulia	6,149,750	1.6	6,604,750	1.7	7.5
Basilicata	1,668,750	3.1	1,673,500	3.1	0.7
Calabria	5,304,750	2.9	6,043,500	3.3	13.8
Campania	21,985,000	3.9	22,826,000	4.1	3.5
E.-Romagna	5,921,500	1.3	6,366,250	1.4	7.4
Friuli V. Giulia	235,000	0.2	26,250	0.0	-88.8
Latium	10,150,250	1.8	10,833,000	1.9	6.6
Liguria	3,855,250	2.6	3,704,000	2.5	-3.9
Lombardy	16,312,000	1.6	15,884,250	1.6	-2.7
Marche	3,991,250	2.7	4,114,250	2.8	3.5
Molise	736,750	2.5	886,500	3.1	20.4
Piedmont	4,353,500	1.0	4,754,250	1.1	9.2
Sardinia	3,365,750	2.1	4,012,000	2.5	19.3
Sicily	13,294,250	2.8	12,831,000	2.7	-3.7
Tuscany	10,639,000	2.9	10,876,000	3.0	2.6
Umbria	1,960,250	2.3	2,166,500	2.5	10.9
Veneto	3,043,500	0.6	2,570,500	0.5	-15.5
ITALY	118,664,750	2.0	122,583,250	2.1	3.3

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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
039596010	RHESONATIV*1F 1mL 625IU/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 625IU/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 1500IU/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 625IU/mL	12500	OCTAPHARMA ITALY SpA	A

Quantification of the demand

The national demand for anti-D IGs between 2022 and 2023 showed an increase and stood at 106,128,750 IUs in 2023 (1.8 IUs *per capita*), with the highest peak in the AP of Bolzano and the lowest level in Friuli V. Giulia (3.7 and 0.1 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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,590,500	2.0	2,298,000	1.8	-11.2
Aosta Valley	298,500	2.4	268,500	2.2	-9.9
AP Bolzano	1,913,125	3.6	1,996,250	3.7	4.7
AP Trento	1,475,000	2.7	1,504,500	2.8	1.8
Apulia	5,184,000	1.3	6,315,000	1.6	22.0
Basilicata	1,132,500	2.1	948,000	1.8	-15.9
Calabria	2,706,000	1.5	2,644,500	1.4	-2.4
Campania	5,240,000	0.9	6,862,000	1.2	30.5
E.-Romagna	9,858,625	2.2	10,093,750	2.3	2.3
Friuli V. Giulia	225,000	0.2	135,000	0.1	-39.8
Latium	7,974,750	1.4	8,739,000	1.5	9.5
Liguria	2,498,500	1.7	2,577,000	1.7	3.1
Lombardy	20,979,625	2.1	21,551,125	2.2	2.6

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Marche	2,794,500	1.9	2,656,500	1.8	-4.6
Molise	317,125	1.1	298,500	1.0	-5.8
Piedmont	7,967,750	1.9	8,139,375	1.9	2.2
Sardinia	1,194,000	0.8	1,287,000	0.8	7.9
Sicily	7,582,500	1.6	7,559,500	1.6	-0.6
Tuscany	8,230,500	2.2	8,309,250	2.3	1.4
Umbria	1,333,500	1.6	1,668,000	1.9	25.5
Veneto	9,937,500	2.0	10,278,000	2.1	3.5
ITALY	101,433,500	1.7	106,128,750	1.8	4.6

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 the active ingredients they contain expressed in U (Unit of the Paul-Erlich Institute and in References preparation).

Table 44. Products containing cytomegalovirus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2023)

AIC Code	Brand name	IU	Manufacturer	NHS class
26167015	CYTOTECT BIOTEST*EV 10mL 500U	500	BIOTEST PHARMA GmbH	H
26167027	CYTOTECT BIOTEST*EV 20mL 1000U	1000	BIOTEST PHARMA GmbH	H
26167041	CYTOTECT BIOTEST*EV 10mL1000U	1000	BIOTEST PHARMA GmbH	H
46731016	CYTOMEGATECT*EV10mL100U	1000	BIOTESTPHARMAGmbH	H
26167039	CYTOTECT BIOTEST*EV 50mL 2500U	2500	BIOTEST PHARMA GmbH	H
26167054	CYTOTECTBIOTEST*EV50mL 5000U	5000	BIOTESTPHARMAGmbH	H
46731028	CYTOMEGATECT*EV50mL 100U	5000	BIOTESTPHARMAGmbH	H

Quantification of the demand

Table 45 shows the total demand and the total standardised demand (U *per capita*) for CMV IGs for the two-year period 2022-2023, at national and regional levels.

Table 45. Total demand (public and private) and total standardised demand for cytomegalovirus immunoglobulins products, expressed in References preparation Unit of the Paul-Erlich Institute and in References preparation Unit of the Paul-Erlich Institute *per capita*, and variations in percentages between 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	255,000	0.2	73,000	0.1	-71.3
Aosta Valley	21,000	0.2	15,000	0.1	-28.5
AP Bolzano	183,000	0.3	-	-	-100.0
AP Trento	-	-	-	-	NA
Apulia	347,000	0.1	799,000	0.2	130.5
Basilicata	100,000	0.2	95,000	0.2	-4.6
Calabria	410,000	0.2	670,000	0.4	63.2
Campania	517,000	0.1	1,204,000	0.2	132.1
E.-Romagna	2,007,000	0.5	1,056,000	0.2	-47.5
Friuli V. Giulia	1,150,000	1.0	510,000	0.4	-55.5
Latium	729,000	0.1	627,000	0.1	-14.1
Liguria	20,000	0.0	55,000	0.0	175.0
Lombardy	2,586,000	0.3	860,000	0.1	-66.8
Marche	256,000	0.2	127,000	0.1	-50.2
Molise	-	-	-	-	NA

Region	2022		2023		% Var 2022-2023
	IU	IU *per capita*	IU	IU *per capita*	
Piedmont	3,055,000	0.7	3,598,000	0.8	17.8
Sardinia	-	-	48,000,0	0.0	100.0
Sicily	1,269,000	0.3	1,355,000	0.3	6.5
Tuscany	1,045,000	0.3	986,000	0.3	-5.3
Umbria	-	-	219,000	0.3	100.0
Veneto	2,627,000	0.5	2,469,000	0.5	-5.9
ITALY	16,577,000	0.3	14,766,000	0.3	-10.9

During the period under examination, the CMV IGs national demand decreased by 11% compared to the previous year and stood at 14,766,000 U. However, the national average showed strong fluctuations, trends varied from one Region to another; Piedmont was the Region with the highest standardized demand (0.8 U *per capita*), followed by Veneto (0.5 U *per capita*) and Friuli V. Giulia and Calabria (0.4 U *per capita*).

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 the active ingredients 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
026978027*	VARITECT 25 IU/mL 1F 5mL	125	BIOTEST PHARMA GmbH	H
026978015*	VARITECT 25 IU/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 specific IG anti-Var zoster (IV) in the two-year period 2022-2023, at national and regional levels. The national demand for IG anti-Var over the time interval examined, showed a strong decrease (-10%). Total demand in 2023 was 99,375 IUs (1.7 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 2022 and 2023 (adapted by the CNS on data from the Product Quality and Pharmacrime Office - AIFA)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	1,000	0.8	100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	6,375	11.9	2,750	5.1	-56.7
AP Trento	-	-	500	0.9	100.0
Apulia	750	0.2	3,375	0.9	350.5
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	1,125	0.2	100.0
E.-Romagna	27,875	6.3	9,875	2.2	-64.6
Friuli V. Giulia	15,125	12.6	18,500	15.5	22.6
Latium	3,375	0.6	5,875	1.0	73.9

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Liguria	-	-	625	0.4	100.0
Lombardy	30,375	3.0	10,375	1.0	-65.9
Marche	11,625	7.8	29,125	19.6	151.5
Molise	-	-	-	-	NA
Piedmont	4,500	1.1	4,000	0.9	-11.1
Sardinia	125	0.1	-	-	-100.0
Sicily	125	0.0	-	-	-100.0
Tuscany	5,625	1.5	2,125	0.6	-62.1
Umbria	2,500	2.9	4,000	4.7	60.6
Veneto	2,000	0.4	6,125	1.3	206.6
ITALY	110,375	1.9	99,375	1.7	-10.0

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, 31/12/2023)

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

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

Quantification of the demand

In 2023, the total demand for anti-rabies IG, recorded in only thirteen regions, showed a significant increase compared to 2022 (+6%) and, therefore, the total demand amounted to 250,800 IUs (4.3 IUs per thousand population units) (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 2022 and 2023 (adapted by the CNS on data from theProduct Quality and Pharmacrime Office – AIFA)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	750	0.6	900	0.7	20.1
Aosta Valley	3,000	24.3	1,500	12.2	-49.9
AP Bolzano	13,050	24.4	5,250	9.8	-59.6
AP Trento	-	-	-	-	NA
Apulia	8,100	2.1	5,400	1.4	-33.3
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	1,050	0.2	-	-	-100
E.-Romagna	18,000	4.1	24,000	5.4	33.2
Friuli V. Giulia	88,350	73.8	61,800	51.7	-29.9
Latium	-	-	3,000	0.5	100.0
Liguria	-	-	-	-	NA
Lombardy	40,350	4.0	63,150	6.3	56.3
Marche	3,000	2.0	7,500	5.1	150.9
Molise	-	-	-	-	NA
Piedmont	14,850	3.5	17,700	4.2	19.2
Sardinia	-	-	-	-	NA

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Sicily	-	-	1,800	0.4	100.0
Tuscany	13,650	3.7	29,850	8.2	119.5
Umbria	-	-	-	-	NA
Veneto	31,500	6.5	28,950	6.0	-8.0
ITALY	235,650	4.0	250,800	4.3	6.4

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 the active ingredients 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, 31/12/2023)

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
039546078	ARTISS*1SIR 1mL+1mL	1	BAXTER SpA	C
025243179	TISSEEL 2ml ADESIVO TISSUTALE	2	BAXTER SpA	H
039546027	ARTISS SOL. ADESIaVO TISSUTALE	2	BAXTER SpA	C
039546080	ARTISS*1SIR 2mL+2mL	2	BAXTER SpA	C
039591019	EVICEL*2FL 1ml 90mg/ml+1200IU	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
025243181	TISSEEL 4mL ADESIVO TISSUTALE	4	BAXTER SpA	H
039591021	EVICEL*2FL 2mL 90mg/mL+1200IU	4	OMRIX BIOPHARMA	H
039546039	ARTISS SOL. ADESIVO TISSUTALE	5	BAXTER SpA	C
039546092	ARTISS*1SIR 5mL+5mL	5	BAXTER SpA	C
042046021	SILKETAL 5ml ADESIVO TISSUTALE	5	KEDRION SpA	C
044152027	KOLFIB*FL POLV SOLV 5mL	5	KEDRION SpA	C
025243193	TISSEEL 10ml ADESIVO TISSUTALE	10	BAXTER SpA	H
039591033	EVICEL*2FL 5ml 90mg/mL+1200IU	10	OMRIX BIOPHARMA	H
042046033	SILKETAL 10ml ADESIVO TISSUTALE	10	KEDRION SpA	C
044152039	KOLFIB*FL POLV SOLV 10mL	10	KEDRION SpA	C
		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+40IU/cm^2	1	OMRIX BIOPHARMA	C
036557027	TACHOSIL*2SPUGNE 4,8cmx4,8cm	2	TAKEDA ITALY SpA	C
043011028	EVARREST*2BUST 8,1mg+40IU/cm^2	2	OMRIX BIOPHARMA	C
036557041	TACHOSIL*5MATRICI 3 cm X 2,5 cm	5	TAKEDA Gmbh	C

Quantification of demand

The various products with an ATC code related to local haemostatics–combinations despite not always having the same composition, they can still be considered equivalent, their active ingredient is expressed in mL and mL per 1,000 population (Table 51). However, in the case of those 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).

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	12,504	9.8	13,066	10.3	4.6
Aosta Valley	196	1.6	334	2.7	70.7
AP Bolzano	2,915	5.4	3,095	5.8	6.5
AP Trento	3,134	5.8	3,334	6.1	6.2
Apulia	32,006	8.2	35,558	9.1	11.2
Basilicata	3,136	5.8	3,673	6.8	17.7
Calabria	5,380	2.9	4,444	2.4	-17.5
Campania	55,993	10.0	68,443	12.2	21.8
E.-Romagna	29,382	6.6	39,312	8.9	33.6
Friuli V. Giulia	4,746	4.0	4,996	4.2	5.5
Latium	45,915	8.0	42,899	7.5	-6.7
Liguria	7,848	5.2	7,518	5.0	-4.2
Lombardy	73,912	7.4	74,526	7.5	0.7
Marche	5,052	3.4	4,580	3.1	-9.0
Molise	3,820	13.1	8,060	27.7	111.1
Piedmont	19,600	4.6	22,226	5.2	13.4
Sardinia	11,182	7.1	13,822	8.8	23.7
Sicily	25,628	5.3	29,992	6.2	16.7
Tuscany	27,276	7.4	28,316	7.7	4.2
Umbria	3,406	4.0	4,694	5.5	38.3
Veneto	30,429	6.3	29,940	6.2	-1.5
ITALY	403,460	6.8	442,828	7.5	9.7

Table 52. Total demand (public and private) for local haemostatics-combinations, expressed in number of gelatin sponges, and variations in percentage between 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022	2023	% Var 2022-2023
Abruzzo	1,538	1,357	-11.8
Aosta Valley	263	210	-20.2
AP Bolzano	555	481	-13.3
AP Trento	328	262	-20.1
Apulia	1,978	1,688	-14.7
Basilicata	729	825	13.2
Calabria	2,035	1,960	-3.7
Campania	4,629	5,846	26.3
Emilia-Romagna	1,828	2,383	30.4
Friuli V. Giulia	705	1,137	61.3
Latium	3,264	2,861	-12.3
Liguria	535	505	-5.6
Lombardy	7,668	7,934	3.5
Marche	1,347	1,530	13.6
Molise	4	-	-100.0
Piedmont	3,743	3,996	6.8
Sardinia	243	521	114.4
Sicily	2,266	2,944	29.9
Tuscany	3,028	2,936	-3.0
Umbria	1,033	982	-4.9
Veneto	2,970	2,819	-5.1
ITALY	40,689	43,177	6.1

In 2023, the total demand for local haemostatics-combinations reached a volume of about 442,828 mL (7.5 mL per 1,000 population), recording a noticeble increase (+10%) compared to their volume in 2022 (Table 51).

In 2023, the total demand for local haemostatics–combinations, expressed in number of gelatin sponges, also appeared to increase slightly compared to the previous year (+6%), it amounted to 43,177 sponges (Table 52).

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 the active ingredients 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, 31/12/2023)

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

Quantification of the demand

In 2023, the total demand and the total standardised national demand for FVII was approximately 6.5 million IUs, showing a slightly decrease over 2022 (-2.6%) (Table 54).

The largest decreases were recorded in Marche (-100%), Liguria (-67%) and Lombardy (-23%). An increase in the consumption of FVII was recorded in particular in Tuscany (+177%), in Abruzzo (127%) and in Veneto (+100%). In 2023, 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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	368,400	289.2	837,000	657.7	127.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	477,000	121.9	462,000	118.2	-3.0
Basilicata	61,200	113.3	52,200	97.1	-14.3
Calabria	40,200	21.8	35,400	19.2	-12.0
Campania	473,400	84.7	442,800	78.9	-6.8
E.-Romagna	183,600	41.4	282,000	63.5	53.4
Friuli V. Giulia	-	-	-	-	NA
Latium	2,252,400	394.1	1,936,200	338.5	-14.1
Liguria	79,200	52.5	26,400	17.5	-66.7
Lombardy	1,846,200	185.3	1,418,400	142.2	-23.3
Marche	32,400	21.7	-	-	-100.0
Molise	307,200	1056.5	339,600	1168.5	10.6
Piedmont	306,600	72.1	239,400	56.3	-21.9
Sardinia	-	-	-	-	NA
Sicily	239,400	49.9	397,200	82.5	65.5
Tuscany	12,600	3.4	34,800	9.5	177.3
Umbria	1,200	1.4	1,200	1.4	0.4
Veneto	-	-	2,400	0.5	100.0
ITALY	6,681,000	113.3	6,507,000	110.3	-2.6

RECOMBINANT ACTIVATED FACTOR VII (EPTACOG ALFA ACTIVATED) (ATC B02BD08)

Table 55 shows the brand names of medicinal products containing rFVIIa currently available on the Italian market and the amount of the active ingredients 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, 31/12/2023)

AIC code	Brand name	mg	Manufacturer	NHS class
029447048	NOVOSEVEN*IV 1mg(50KIU)+1,1mL	1	NOVO NORDISK SpA	H
029447087	NOVOSEVEN*IV 1mg(50KIU)+1mL	1	NOVO NORDISK SpA	H
050298013	CEVENFACTA*EV 1 mg +Sol 1,1 mL	1	LFB	A
029447012	NOVOSEVEN*IV 1,2mg(60KIU)+2,2mL	1.2	NOVO NORDISK SpA	H
029447051	NOVOSEVEN*IV 2mg(100KIU)+2,1mL	2	NOVO NORDISK SpA	H
029447099	NOVOSEVEN*IV 2mg(100KIU)+2mL	2	NOVO NORDISK SpA	H
050298025	CEVENFACTA*EV 2 mg +Sol 2,2 mL	2	LFB	A
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(250KIU)+5,2mL	5	NOVO NORDISK SpA	H
029447101	NOVOSEVEN*IV 5mg(250KIU)+5mL	5	NOVO NORDISK SpA	H
050298037	CEVENFACTA*EV 5 mg +Sol 5,2 mL	5	LFB	A
029447075	NOVOSEVEN*IV8mg (400KIU)+8,1mL	8	NOVO NORDISK SpA	H
029447113	NOVOSEVEN*IV 8mg(400KIU)+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 2022-2023, at national and regional level. The total demand for rFVIIa recorded in 2023 was 31,770 mg (0.5 mg per 1,000 population) with a marked decrease compared to 2022 (-26%).

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Abruzzo	905	0.7	495	0.4	-45.3
Aosta Valley	190,0	1.5	26,0	0.2	-86.3
AP Bolzano	244	0.5	73	0.1	-70.0
AP Trento	302	0.6	9	0.0	-97.0
Apulia	2,548	0.7	2,213	0.6	-13.0
Basilicata	57	0.1	22	0.0	-61.2
Calabria	2,185	1.2	923	0.5	-57.8
Campania	3,155	0.6	2,371	0.4	-25.1
E.-Romagna	6,465	1.5	2,753	0.6	-57.5
Friuli V. Giulia	1,648	1.4	1,406	1.2	-14.5

Region	2022		2023		% Var 2022-2023
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Latium	2,297	0.4	2,037	0.4	-11.4
Liguria	374	0.2	331	0.2	-11.5
Lombardy	4,357	0.4	3,654	0.4	-16.2
Marche	553	0.4	529	0.4	-4.0
Molise	24	0.1	80	0.3	233.5
Piedmont	1,913	0.4	1,416	0.3	-26.0
Sardinia	496	0.3	1,975	1.3	298.4
Sicily	3,011	0.6	1,862	0.4	-38.3
Tuscany	7,401	2.0	4,755	1.3	-35.5
Umbria	201	0.2	253	0.3	26.3
Veneto	4,519	0.9	4,587	0.9	1.6
ITALY	42,845	0.7	31,770	0.5	-25.9

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 the active ingredients 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, 31/12/2023)

AIC code	Brand name	FU	Manufacturer	NHS class
024744043	FEIBA*IV FL 500IU+F 20mL	500	BAXALTA ITALY Srl	A
024744068	FEIBA*FL 500FU+BAXJECT II HF	500	BAXALTA ITALY Srl	A
024744056	FEIBA TIM3*IV FL 1000IU+F 20mL	1000	BAXTER AG	A
024744070	FEIBA*FL 1000FU+BAXJECT II HF	1000	BAXTER AG	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 2022-2023 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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	FU	FU per 1,000 pop	FU	FU per 1,000 pop	
Abruzzo	1,767,000	1.4	1,618,000	1.3	-8.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	40,000	0.0	364,000	0.1	811.0
Basilicata	-	-	-	-	NA
Calabria	-	-	847,000,0	0.5	100.0
Campania	793,000	0.1	656,000	0.1	-17.6
E.-Romagna	406,000	0.1	334,000	0.1	-17.8
Friuli V. Giulia	12,000	0.0	348,000	0.3	2807.4
Latium	351,000	0.1	400,000	0.1	13.9
Liguria	257,000	0.2	130,000	0.1	-49.4
Lombardy	847,000	0.1	2,917,000	0.3	244.0
Marche	211,000,0	0.1	87,000,0	0.1	-58.6
Molise	-	-	-	-	NA
Piedmont	267,000	0.1	98,000	0.0	-63.3
Sardinia	427,000	0.3	646,000	0.4	51.4
Sicily	351,000	0.1	36,000	0.0	-89.8
Tuscany	-	-	12,000,0	0.0	100.0
Umbria	-	-	-	-	NA
Veneto	800,000	0.2	292,000	0.1	-63.5
ITALY	6,529,000	0.1	8,785,000	0.1	34.5

In 2023, national demand for CCPa was clearly growing compared to that found in the previous year (+34.5%), with some regional variability. Its total volume was 8,785,000 FUs (0.1 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 fulfills 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, 31/12/2023)

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
046292013	PLITALFA*EV 1F 1000MG/40ML	1000	GRIFOLS Italia SpA	C(nn)
037709021	PROLASTIN*EV 4F 1g/40mL+F40mL	4000	INST. GRIFOLS S.A.	C(nn)
044479020	RESPREEZA*EV 1FL 76mL + 4g+SET	4000	CSL BEHRING GmbH	C(nn)
044479032	RESPREEZA*EV 1FL 95mL+ 5g+ SET	5000	CSL BEHRING GmbH	H

Quantification of the demand

In 2023, the total demand for alpha-1-antitrypsin was 82,930 g (1.4 g per 1,000 population) recording a significant upward trend compared to the previous year (+17%) (Table 55). In particular in E.-Romagna and Umbria the demand exceeded the value recorded in the previous year (+62% and +56%, respectively). The highest regional standardized demand is in Sardinia and in the AP of Bolzano (4 and 7 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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	2,230	1.8	2,477	1.9	11.2
Aosta Valley	984	8.0	450	3.7	-54.2
AP Bolzano	3,109	5.8	3,833	7.2	23.7
AP Trento	821	1.5	666	1.2	-19.0
Apulia	3,790	1.0	2,887	0.7	-23.7
Basilicata	-	0.0	-	0.0	NA
Calabria	1,726	0.9	1,627	0.9	-5.8
Campania	7,790	1.4	9,911	1.8	26.8
E.-Romagna	4,824	1.1	7,842	1.8	62.4
Friuli V. Giulia	2,240	1.9	2,490	2.1	11.4
Latium	5,069	0.9	5,580	1.0	10.0

Region	2022		2023		% Var 2022-2023
	g	g per 1,000 pop	g	g per 1,000 pop	
Liguria	2,689	1.8	3,255	2.2	21.0
Lombardy	10,213	1.0	11,574	1.2	13.2
Marche	612	0.4	787	0.5	29.1
Molise	63	0.2	70	0.2	11.2
Piedmont	5,988	1.4	7,508	1.8	25.4
Sardinia	5,840	3.7	6,853	4.3	17.4
Sicily	4,753	1.0	5,528	1.1	16.0
Tuscany	3,743	1.0	3,795	1.0	1.8
Umbria	1,017	1.2	1,580	1.8	55.9
Veneto	3,448	0.7	4,217	0.9	22.4
ITALY	70,949	1.2	82,930	1.4	16.9

PLASMA-DERIVED C1-ESTERASE 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 Italian market and the amount of the active ingredients 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, 31/12/2023)

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

Quantification of the demand

In 2023, the total demand for C1 esterase inhibitor was 20,386,000 IUs (346 IUs per 1,000 population), and showed a clear increase compared to the previous year (+55%) (Table 62).

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	196,000	153.9	480,000	377.2	145.1
Aosta Valley	1,500	12.2	10,500	85.3	601.2
AP Bolzano	22,000	41.1	61,000	114.2	178.1
AP Trento	5,000	9.2	105,500	194.3	2006.7
Apulia	1,057,500	270.3	1,307,500	334.6	23.8
Basilicata	80,000	148.1	20,000	37.2	-74.9
Calabria	615,000	333.4	475,500	257.5	-22.8
Campania	1,977,500	353.7	1,851,500	330.1	-6.7
E.-Romagna	232,500	52.5	782,000	176.2	235.9
Friuli V. Giulia	20,000	16.7	25,500	21.4	27.8
Latium	2,425,500	424.4	3,870,500	676.6	59.4
Liguria	19,000	12.6	55,500	36.8	192.1
Lombardy	1,488,500	149.4	3,267,500	327.5	119.3
Marche	241,000	161.8	524,000	353.0	118.2
Molise	8,000	27.5	8,000	27.5	0.0
Piedmont	1,241,000	291.8	1,373,000	323.0	10.7
Sardinia	546,000	345.7	671,500	425.5	23.1
Sicily	1,348,000	280.7	3,099,500	643.8	129.3

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Tuscany	420,500	114.4	684,500	186.9	63.4
Umbria	73,000	84.9	304,500	355.6	318.7
Veneto	1,112,000	229.1	1,408,500	290.4	26.8
ITALY	13,129,500	222.6	20,386,000	345.5	55.2

An exceptional variability in standardised regional demands was observed, with maximum volumes in Latium, Sicily, Sardinia and Abruzzo (677, 644, 426 and 377 IUs per 1,000 population, respectively) and minimum volumes in Liguria, Friuli Venezia Giulia, Molise, Basilicata and in Aosta Valley (range: 21 – 85 IUs per 1,000 population). Most regions showed an increase from the previous year, in some cases even a particularly marked one, as in the case of the AP of Trento (+2006.7%); exceptions were Basilicata, Calabria and Campania, where, on the other hand, decreases in demand were recorded in the two-year period under consideration. Demand remained almost stable in Molise (+0.0%).

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 have been reported. Haemorrhagic episodes are usually treated with 3F-PCCs or fresh frozen plasma (41).

Table 63 shows the brand names of medicinal products containing pdFX currently on the Italian market and the amount of the active ingredients 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, 31/12/2023)

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

* Medicinal products imported under the provisions of the DM of 11 February 1997 (8) and of the 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 Calabria and Lombardy; in 2023 the national demand was 78,000 IUs (1.3 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 2022 and 2023 (adapted by the CNS on data from Product Quality and Pharmacrime Office-AIFA)

Region	2022		2023		Var % 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Calabria	-	-	42,000	22.7	100.0
Lombardy	15,600	1.6	36,000	3.6	130.5
ITALY	15,600	0.3	78,000	1.3	399.9

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 medicinal products containing FXI currently on the Italian market 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
-*	HEMOLEVEN 100IU/mL 10mL	1000	LFB	-

* Medicinal product registered abroad and imported under the provisions of Ministerial Decree 11 February 1997 (8) and Ministerial Decree 11 May 2001 (10).

Quantification of the demand

In 2023, the demand for FXI was 12,000 IUs (0.2 IU per 1,000 population), showing a decrease compared to 2022 (-20%) (Table 66). Demand was detected only in four Italian Regions: E.-Romagna, Friuli Venezia Giulia, Liguria and Piedmont.

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, and variations in percentage between 2022 and 2023 (adapted by the CNS on data from theProduct Quality and Pharmacrime Office-AIFA)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	-	-	2,000	0.5	100.0
Friuli V. Giulia	8,000	6.7	6,000	5.0	-24.8
Latium	-	-	-	-	NA
Liguria	-	-	2,000	1.3	100.0
Lombardy	-	-	-	-	NA
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	7,000	1.6	2,000	0.5	-71.4

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	-	-	-	-	NA
ITALY	15,000	0.3	12,000	0.2	-20.0

COAGULATION FACTOR XIII (ATC B02BD07)

Plasma-derived coagulation Factor XIII (pdFXIII), 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 (FXIII<1%), moderate (between 1 and 4%) and mild (FXIII>5%) forms are distinguished. Should products containing pdFXIII be 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 utilisation been recorded and then only in certain Regions.

Table 67 and Table 68 show the brand names of medicinal products containing pdFXIII and rFXIII, respectively, currently available on the Italian market and the amount of the active ingredients 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, 31/12/2023)

AIC code	Brand name	IU	Manufacturer	NHS class
024644015*	FIBROGAMMIN 1FL 250IU	250	CSL BEHRING GmbH	H
042605016	CLUVIAT FL 250IU	250	CSL BEHRING GmbH	H
024644027*	FIBROGAMMIN 1FL 1250IU	1250	CSL BEHRING GmbH	H
042605028	CLUVIAT FL 1250IU	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, 31/12/2023)

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

Quantification of the demand

In 2023, the total demand for FXIII was 1,008,750 IUs (17.1 IUs per 1,000 population) and less than half, equal to 486,250 IUs (8.2 IUs per 1,000 population), was for pdFXIII. The latter recorded an increase of +20% compared to 2022 (Table 69). The highest demand for Factor XIII of plasma origin was maximum in the AP of Trento and Emilia-Romagna (71 IUs and 31 IUs per 1,000 population respectively).

In 2023, there was no utilisation of FXIII in some Regions (Molise, Sardinia and Aosta Valley).

In Abruzzo, Basilicata, Calabria, Campania and Friuli V. Giulia rFXIII was used exclusively (Table 70). In Latium, Marche, the AP of Bolzano, the AP of Trento, Apulia, Sicily, Tuscany and Umbria instead pdFXIII was used exclusively.

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow and theProduct Quality and Pharmacrime Office-AIFA)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	3,750	7.0	8,750	16.4	134.0
AP Trento	20,000	36.9	38,500	70.9	92.2
Apulia	7,500	1.9	12,500	3.2	66.9
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	137,500	31.0	138,500	31.2	0.6
Friuli V. Giulia	-	-	-	-	NA
Latium	54,250	9.5	40,500	7.1	-25.4
Liguria	27,500	18.2	41,750	27.7	51.8
Lombardy	13,500	1.4	30,000	3.0	122.0
Marche	29,000	19.5	39,750	26.8	37.6
Molise	-	-	-	-	NA
Piedmont	14,500	3.4	25,000	5.9	72.5
Sardinia	-	-	-	-	NA
Sicily	-	-	2,500	0.5	100.0
Tuscany	19,500	5.3	32,500	8.9	67.3
Umbria	-	-	2,500,0	2.9	100.0
Veneto	79,000	16.3	73,500	15.2	-6.9
ITALY	406,000	6.9	486,250	8.2	19.7

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow and the Product Quality and Pharmacrime office, AIFA)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	40,000	31.4	52,500	41.3	31.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	30,000	55.6	30,000	55.8	0.5
Calabria	132,500	71.8	170,000	92.1	28.2
Campania	15,000,0	2.7	37,500,0	6.7	149.2
E.-Romagna	17,500,0	3.9	15,000,0	3.4	-14.4
Friuli V. Giulia	-	-	15,000,0	12.6	100.0
Latium	-	-	-	-	NA
Liguria	70,000	46.4	65,000	43.1	-7.2
Lombardy	92,500	9.3	87,500	8.8	-5.5
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	40,000	9.4	30,000	7.1	-25.0
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	12,500	2.6	20,000	4.1	60.2
ITALY	450,000	7.6	522,500	8.9	16.1

PROTEIN C (ATC B01AD12)

Protein C is one of the most important factors of the anticoagulant system togheter 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 medicinal products containing protein C currently available on the Italian market and the amount of the active ingredients 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, 31/12/2023)

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

Quantification of the demand

In 2023, the national demand for protein C stood at a volume of 718,500 IUs (12.2 IUs per 1,000 population) with an increase of 9% compared to 2022 (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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	11,000	8.6	5,000	3.9	-54.5
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	13,000	3.3	8,000	2.0	-38.4
Basilicata	-	-	1,000	1.9	100.0
Calabria	178,500	96.8	181,000	98.0	1.3
Campania	193,000	34.5	211,500	37.7	9.2
E.-Romagna	4,000	0.9	5,000	1.1	24.8
Friuli V. Giulia	-	-	-	-	NA
Latium	97,500	17.1	135,500	23.7	38.8
Liguria	24,000	15.9	45,000	29.8	87.5
Lombardy	54,500	5.5	80,000	8.0	46.6
Marche	24,000	16.1	12,000	8.1	-49.8
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	20,000	12.7	-	0.0	-100.0
Sicily	10,000	2.1	6,500	1.4	-35.2
Tuscany	5,000	1.4	13,000	3.5	161.0
Umbria	8,000	9.3	-	0.0	-100.0
Veneto	15,500	3.2	15,000	3.1	-3.1
ITALY	658,000	11.2	718,500	12.2	9.2

The highest regional demand was recorded in Calabria and Campania, with 98 and 38 IUs per 1,000 population respectively.

The lowest regional demand was in Emilia-Romagna, Sicily, Basilicata and Apulia with volumes between 1.1 and 2.0 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*™, *Plasmagrade*™ and *Octaplas*™) and products with an albumin content between 85 and 90% (*Umanserum*™).

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

– high batch-to-batch standardisation;
– declaration of the concentration/activity of biologically active proteins;
– reduction of the 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 the active ingredients 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, 31/12/2023)

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 subgroups of medicinal products have been quantified distinctly. Table 74 shows the utilisation of *Plasmasafe*™ and *Octaplas*™, while Table 75 illustrates the data related to *Umanserum*™, the demand for which, in 2023, recorded a decrease of -12%, and a total volume of 6,540,000 mL.

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	2,840,000	725.9	3,104,000	794.3	9.4
Basilicata	680,000	1259.3	448,000	833.4	-33.8
Calabria	1,056,000	572.5	1,038,000	562.1	-1.8
Campania	3,954,800	707.4	4,056,200	723.1	2.2

Region	2022		2023		% Var 2022-2023
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
E.-Romagna	318,000	71.8	346,000	78.0	8.7
Friuli V. Giulia	20,000	16.7	-	-	-100.0
Latium	3,317,600	580.5	3,104,200	542.6	-6.5
Liguria	360,000	238.8	126,000	83.6	-65.0
Lombardy	420,000	42.1	476,000	47.7	13.2
Marche	1,449,000	972.6	1,774,000	1195.2	22.9
Molise	408,000	1403.2	228,000	784.5	-44.1
Piedmont	4,178,000	982.5	3,782,000	889.6	-9.5
Sardinia	36,000	22.8	6,400	4.1	-82.2
Sicily	3,026,800	630.4	3,235,200	672.0	6.6
Tuscany	1,438,200	391.2	1,156,000	315.7	-19.3
Umbria	72,000	83.8	146,000	170.5	103.5
Veneto	1,016,200	209.3	984,000	202.9	-3.1
ITALY	24,590,600	416.9	24,010,000	407.0	-2.4

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 2022 and 2023 (adapted by the CNS on data from the Traceability information flow)

Region	2022		2023		% Var 2022-2023
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	4,200,000	1073.6	2,990,000	765.2	-28.7
Basilicata	45,000	83	3,750	7.0	-91.6
Calabria	416,250	226	300,000	162	-28.0
Campania	-	-	250	0.0	100.0
E.-Romagna	-	-	-	-	NA
Friuli V. Giulia	-	-	-	-	NA
Latium	37,500	7	550,000	96	1,365.3
Liguria	-	-	-	-	NA
Lombardy	87,250	8.8	500	0.1	-99.4
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	-	-	-	-	NA
Sicily	2,415,250	503.0	2,617,750	543.8	8.1
Tuscany	-	-	-	-	NA
Umbria	202,000	235.0	77,750	90.8	-61.4
Veneto	-	-	-	-	NA
ITALY	7,403,250	125.5	6,540,000	110.9	-11.7

The national demand for solvent/detergent-treated plasma in 2023 decreased by -2.4% compared to 2022, with large regional differences; the most noticeable decrease was recorded in Liguria (-65%) and in Sardinia (-82%), as well as in Friuli V. Giulia, which recorded no demand for the year. In contrast, a significant increase in demand was recorded in Umbria (+103.5%).

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

SELF-SUFFICIENCY

According to the 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 meet their needs for PDMPs. This is achieved by using products obtained from the processing of the plasma collected by BEs and dispatched 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 is one of the objectives of the 219/2005 Law, which aimes at guaranteeing the same standards of quality and safety in the transfusion therapy to all citizens. It is a non-divisible national and supraregional interest, for which the Regions and the Health Authorities have to contribute to its final accomplishment.

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 acknowledges the annual programme of national self-sufficiency (Art. 14) as the instrument to determine every aspect of national self-sufficiency, such as historical consumptions, real needs, production levels required, resources, prospective financing criteria, compensation methods among the Regions and import/export levels whenever necessary.

Furthermore, Article 26 of the 20th of December 2007 Legislative Decree, n. 261 (48) provides for the definition of a programme by the MoH focusing on developing the collection of plasma in BEs and BCUs, promoting 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, from their local territory, to the authorised and affiliated company for it to be industrially transformed into PDMPs. The contract with the 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 the toll fractionation processes is carried out through a tender procedure in compliance with the current legislation. For this purpose, during 2015 and 2016, in addition to the Lombardy-Piedmont-Sardinia Agreement (LPS) by then already 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 V. 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) of which Calabria, Emilia-Romagna (Leading Region), Apulia and Sicily are part;
- 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 forth in the DM of 12 April 2012 (50), and later in the DM of 19 December 2022 (51), 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 complying with the schedules and the established procedures. The contracting Regions, in turn, undertake to make available the necessary plasma 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, nor 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 purpose of the call for tender, DM of 12 April 2012 ruled d that at least human albumin, FVIII and IG-IV had to be guaranteed to be produced, while the subsequent DM of 19 December 2022 considers only albumin and immunoglobulins, both intravenous and subcutaneous administration, as production driver products. All 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 (52).

In 2016, the tender for the supply of toll fractionation services for the NAIP Regions was won by CSL Behring SpA The contract provided for the supply of albumin, IV IGs, SC/IM IGs, pdFVIII, FVIII / vWF in combination and fibrinogen.

In December 2016, the call for tenders was published for the provision of contract fractionation services for the RIPP Regions, and won by the companies Kedrion and Grifols, with the first plasma collection taking place in November 2020. On the other hand, regarding the PlaNet Agreement Regions, Takeda company, winner of the tender launched in November 2017, started plasma collection in September 2020. Until then, therefore, for all Regions, excluding those of the NAIP, the agreements with the contract fractionation company Kedrion, whose contracts covered the production of albumin, IVIG, pdFVIII, pdFIX, 3F-PCCs, AT and solvent/detergent virus-inactivated plasma, remained in force.

Plasma for fractionation

Since the year 2000, the amount of plasma collected nationwide (Figure 42) has steadily increased, going from a total of 462,805 kilograms sent for fractionation in the year 2000 to 880,193 kilograms in 2023, with a percentage increase over the entire period considered, by 90%.

The mean annual rate of variation over the period considered was 2.9%. In the year 2020 there was, for the first time in the last twenty years, a decrease of -1.7% compared to the previous year (Figure 43), probably due to the consequences that the pandemic event has triggered in terms of plasma collection.

In 2023, a sharp increase was observed compared to the previous year (+4.4%). However, the delivery of plasma to industrial fractionation by individual regions shows extreme variability in terms of quantity and quality.

In 2023, the Regions participating in the LPS agreement collected about one third of the plasma sent for fractionation for a share equal to 254,480 kilograms (29%), those adhering to the RIPP 240,824 kilograms (27%), those of the NAIP 201,277 kilograms (23%) and those of the PlaNet 183,612 kilograms (21%) (Figure 44).

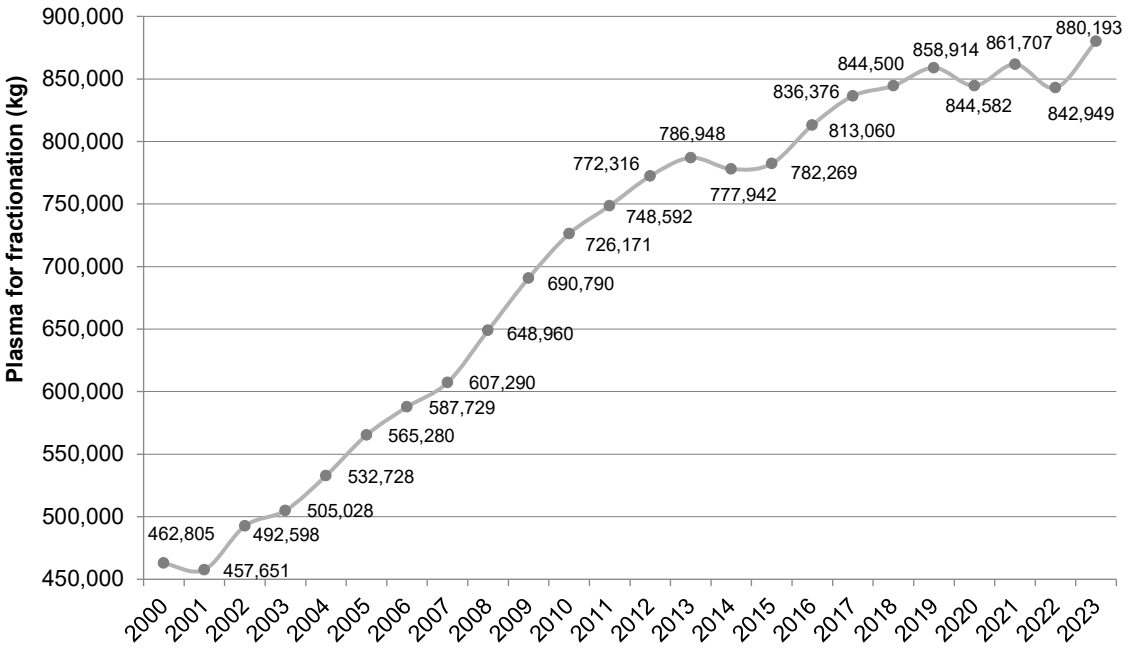

Figure 42. Plasma sent for fractionation 2000-2023
(adapted by the CNS on fractionation companies data, January 2024)

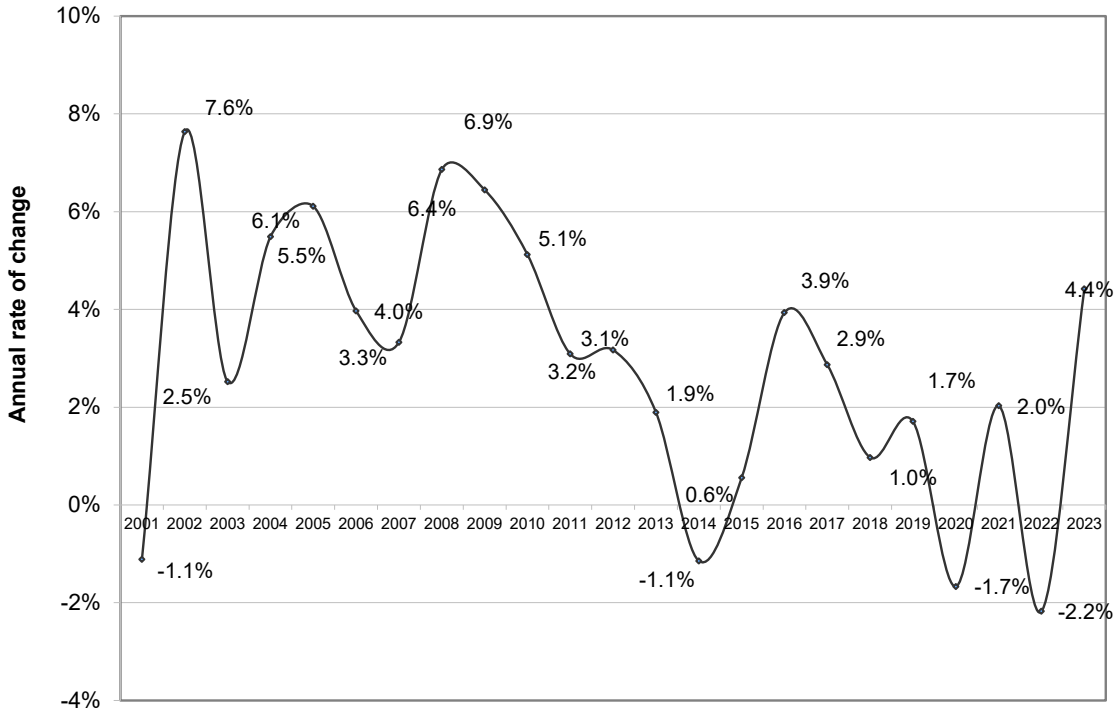

Figure 43. Annual rate of variation in the amount of plasma for fractionation, from 2001 to 2023
(adapted by the CNS on fractionation companies data, January 2024)

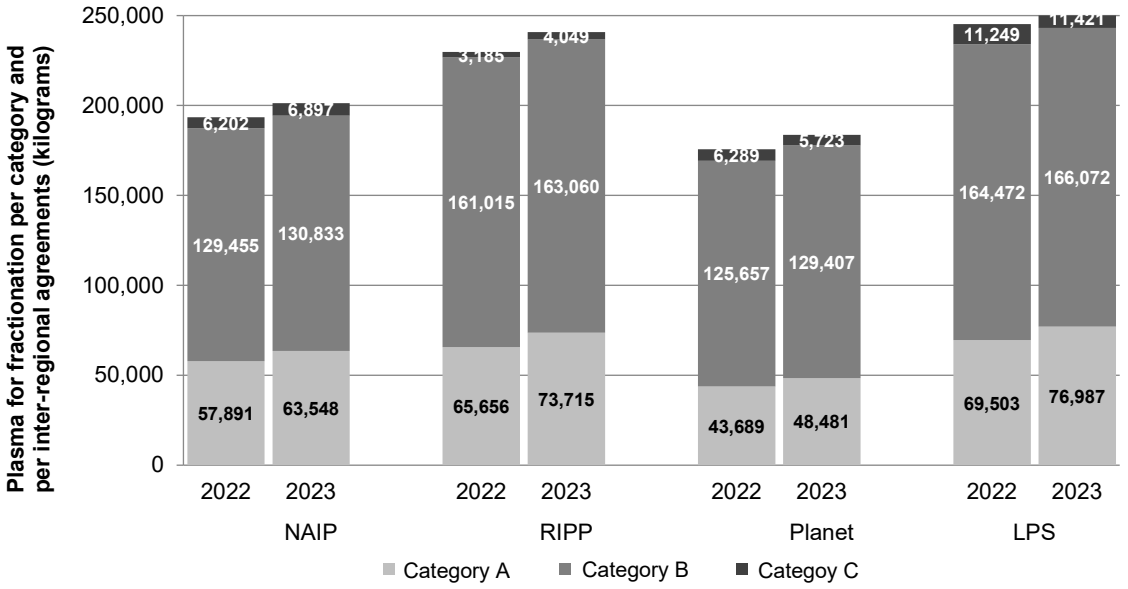

Figure 44. Total amount of plasma for fractionation by category under interregional agreements (kilograms), 2022-2023 (adapted by the CNS on fractionation companies data, January 2024)

As regards the amount of plasma sent for fractionation in 2023, for the resident population, the NAIP Regions sent 17.6 kilograms of plasma per thousand population units for processing (16.9 in 2022, with the same number of regions and PPAAs participating), LPS 16,1 kilograms (15.5 kilograms of plasma per thousand population units in 2022), RIPP 16.0 (15.3 kilograms of plasma per thousand population units in 2022), and finally PlaNet contributed 11.0 kilograms of plasma per thousand population units (10.5 kilograms of plasma per thousand population units the previous year) (Figure 45).

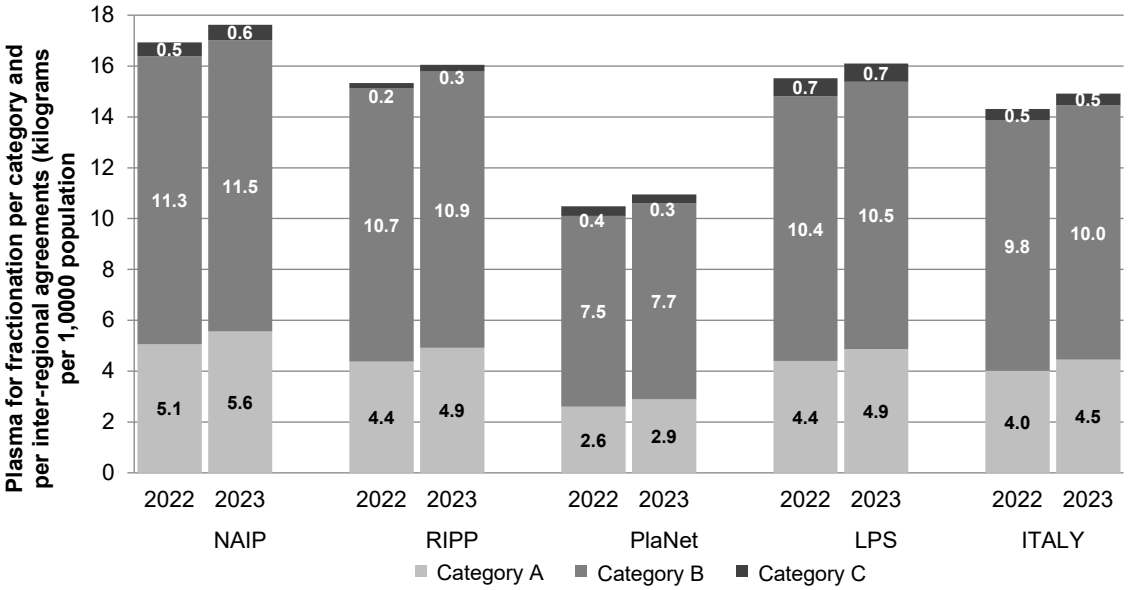

Figure 45. Total amount of plasma for fractionation by category under interregional agreements (kilograms per 1,000 population), 2022-2023 (adapted by the CNS on fractionation companies data, January 2024)

In 2023, although the national volume of plasma for fractionation stood at 14.9 kilograms per 1,000 population (14.3 in 2022), with regional contributions in volumes differing greatly one from another. In point of fact, the best performance was achieded by Friuli V. Giulia with 24.2 kilograms per 1,000 population, followed by Marche with 23.9 and Emilia-Romagna with 22.5, while the lowest volumes were recorded in Campania, Latium and Calabria with 5.6, 8.3 and 10.7 kilograms per 1,000 population, respectively (Figure 46).

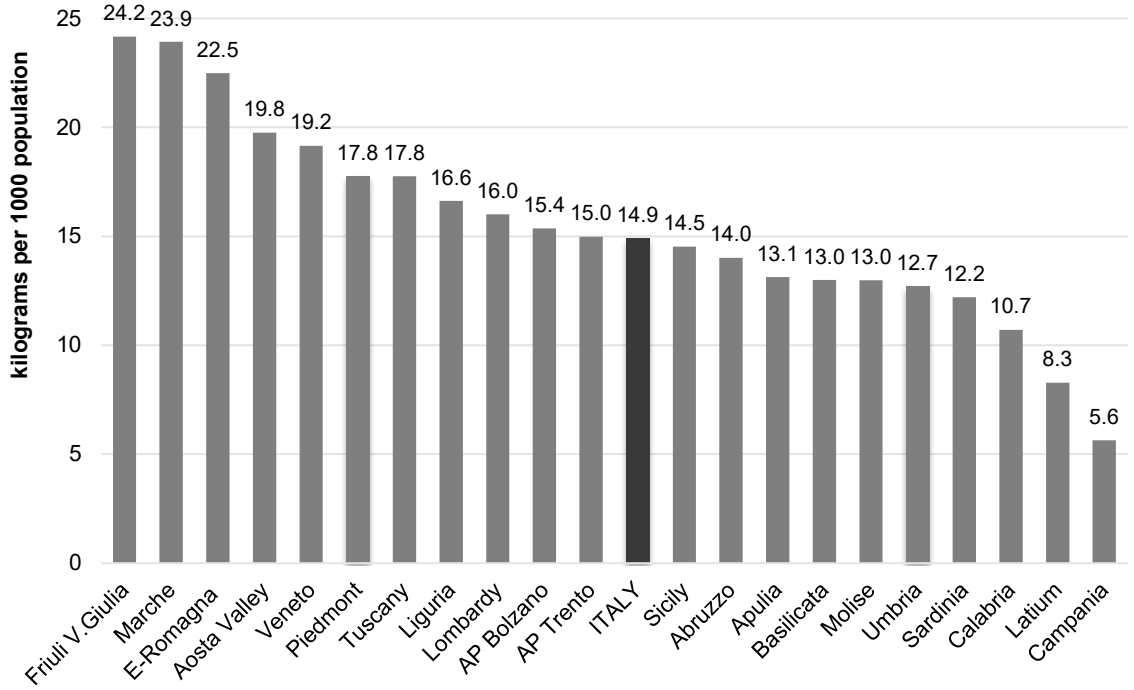

Figure 46.Total amount of plasma (kilograms per 1,000 population) for fractionation by Region, year 2023 (adapted by the CNS on fractionation companies data, January 2024)

Supply of PDMPs from toll fractionation

In 2023, the total quantity of plasma sent for fractionation by the Italian Regions was 880,193 kilograms (Table 76); of these, 30% (262,732 kilograms) was apheresis plasma (category A), 67% (589,372 kilograms) recovered plasma (category B) and the remaining 3% (28,090 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 26.4% sent by PlaNet to 31.6% sent by NAIP, while the percentage of plasma intended solely for the recovery of non-labile proteins (category C) varied from 1.7% sent by RIPP to 4.5% sent by the LPS consortium.

Table 76. Total quantity, expressed in kilograms, quantity per 1,000 population and variation in percentage for the years 2022-2023 classified by Region and plasma category (adapted by the CNS on fractionation companies data, January 2024)

Region	A	%	B	%	C	%	Tot. Fract.	Total per 1,000 pop
Abruzzo	4,857	1.5	12,865	-4.1	117	-23.2	17,839	14.0
Aosta Valley	1,102	2.8	1,330	-8.5	-	NA	2,432	19.8
AP Bolzano	2,556	25.4	5,652	-4.3	-	NA	8,208	15.4
AP Trento	1,342	97.4	6,796	3.0	-	NA	8,138	15.0
Basilicata	1,940	33.1	3,335	-16.9	1,712	32.5	6,987	13.0
Friuli V. Giulia	13,976	0.0	14,761	1.2	119	347.8	28,855	24.2
Liguria	6,783	14.3	18,278	1.5	-	NA	25,061	16.6
Umbria	1,916	19.0	8,947	5.4	-	NA	10,862	12.7
Veneto	29,076	10.4	58,870	3.3	4,949	4.6	92,896	19.2
NAIP	**63,548**	**9.8**	**130,833**	**1.1**	**6,897**	**11.2**	**201,277**	**17.6**
Apulia	8,474	23.3	41,823	4.5	1,021	8.5	51,318	13.1
Calabria	2,421	77.9	17,344	0.5	5	-46.1	19,770	10.7
Emilia-Romagna	43,693	8.2	53,077	-1.1	3,007	35.2	99,777	22.5
Sicily	19,128	12.2	50,816	1.5	15	55.2	69,960	14.5
RIPP	**73,715**	**12.3**	**163,060**	**1.3**	**4,049**	**27.1**	**240,824**	**16.0**
Campania	622	-6.5	30,179	9.9	849	-11.4	31,650	5.6
Latium	5,423	25.0	37,200	6.8	4,751	-8.2	47,374	8.3
Marche	16,496	8.6	19,010	-2.3	-	NA	35,506	23.9
Molise	875	202.2	2,899	-2.7	-	NA	3,774	13.0
Tuscany	25,065	8.0	39,980	-1.9	-	NA	65,045	17.8
Ministry of Defence	-	NA	140	-12.3	123	-21.5	262	NA
PlaNet	**48,481**	**11.0**	**129,407**	**3.0**	**5,723**	**-9.0**	**183,612**	**11.0**
Lombardy	51,390	11.1	99,208	-0.4	9,073	-0.4	159,671	16.0
Piedmont	25,080	10.6	48,410	3.6	2,059	3.5	75,549	17.8
Sardinia	517	-9.0	18,454	1.7	289	88.6	19,260	12.2
LPS	**76,987**	**10.8**	**166,072**	**1.0**	**11,421**	**1.5**	**254,480**	**16.1**
ITALY	**262,732**	**11.0**	**589,372**	**1.5**	**28,090**	**4.3**	**880,193**	**14.9**

Tables 77 and 78 shows the amount of PDMPs potentially obtainable from the industrial manufacturing of the total amount of plasma sent for fractionation in 2023 (from July 2022 to June 2023). These figures show the quantities, expressend in grams and IUs, of medicinal products that the fractionators have potentially guaranteed the consortia (potential supply or production capacity) estimated from the industrial yields and contractual agreements. Further quantities of plasma, around 19,000 kilograms, as shown in Table 79, were sent to Kedrion for the production of plasma solvent/detergent-treated, beyond the provisions of the aforementioned regional agreements. Tables 80 and 81 provide the quantities of PDMPs distributed to the individual Regions in 2023 in accordance with the specified production and distribution programmes (effective supply or toll fractionation).

Table 77. Potential supply of toll fractionated PDMPs (driver) based on the amount of plasma sent for fractionation from July 2022 to June 2023 and the yields provided by the fractionation industry – year 2023 (adapted by the CNS on fractionation companies data, March 2024)

Region	2nd semester 2022	1st semester 2023	TOTAL	Albumin	SCIG*	IVIG**
	kg	kg	kg	g	g	g
Abruzzo	9,853	8,977	18,830	478,272	94,148	94,148
Aosta Valley	1,133	1,391	2,525	64,128	12,624	12,624
AP Bolzano	4,010	3,832	7,842	199,178	39,208	39,208
AP Trento	3,787	4,033	7,820	198,633	39,101	39,101
Basilicata	3,746	3,547	7,293	185,253	36,467	36,467
FVG	14,512	14,503	29,015	736,982	145,075	145,075
Liguria	12,297	12,437	24,734	628,233	123,668	123,668
Umbria	5,486	5,500	10,986	279,042	54,930	54,930
Veneto	44,443	46,076	90,519	2,299,192	452,597	452,597
NAIP	**99,267**	**100,296**	**199,563**	**5,068,912**	**997,817**	**997,817**
Apulia	24,204	24,990	49,194	1,268,221	178,082	201,203
Calabria	9,819	9,680	19,499	502,684	70,586	79,751
E.-Romagna	47,632	49,794	97,426	2,511,645	97,776	398,473
Sicily	34,154	34,377	68,531	1,766,729	248,082	280,292
RIPP	**115,809**	**118,841**	**234,650**	**6,049,280**	**594,527**	**959,719**
Campania	14,172	14,110	28,282	715,533	127,269	141,410
Latium	22,597	24,040	46,636	1,179,903	209,864	233,182
Marche	17,442	17,924	35,366	894,766	159,148	176,831
Molise	1,822	1,803	3,626	91,734	16,316	18,129
Tuscany	32,167	32,758	64,924	1,642,590	292,160	324,622
Ministry of Defence	151	123	275	6,946	1,236	1,373
PlaNet	**88,351**	**90,758**	**179,110**	**4,531,472**	**805,993**	**895,548**
Lombardy	76,840	83,168	160,008	4,125,006	579,229	654,433
Piedmont	35,907	37,750	73,657	1,898,877	266,638	301,257
Sardinia	9,699	11,006	20,705	533,775	74,952	84,683
LPS	**122,446**	**131,924**	**254,370**	**6,557,659**	**920,819**	**1,040,373**
ITALY	**425,873**	**441,820**	**867,693**	**22,207,322**	**3,319,157**	**3,893,458**

* potential supply deriving from the processing of 100% of the plasma delivered for the production of Immunoglobulins for subcutaneous administration
** potential supply deriving from the processing of 100% of the plasma delivered for the production of Immunoglobulins for intravenous administration

Table 78. Potential supply of toll fractionated PDMPs based on the amount of plasma sent for fractionation from July 2022 to June 2023 and the yields provided by the fractionation industry – year 2023 (adapted by the CNS on fractionation companies data, March 2024)

Region	2nd semester 2022	1st semester 2023	TOTAL	FVIII	FVIII/vWF	FIX/3F-PCCs	AT	Fibrinogen	Alpha-1	aPCCs	4F-PCCs	FVII	Protein C
	kg	kg	kg	UI	UI	UI	UI	g	g	UF	UI	UI	UI
Abruzzo	9,853	8,977	18,830	717,407	217,014	-	-	2,237	-	-	-	-	-
Aosta Valley	1,133	1,391	2,525	96,192	29,098	-	-	300	-	-	-	-	-
AP Bolzano	4,010	3,832	7,842	298,767	90,376	-	-	932	-	-	-	-	-
APTrento	3,787	4,033	7,820	297,949	90,129	-	-	929	-	-	-	-	-
Basilicata	3,746	3,547	7,293	277,880	84,058	-	-	866	-	-	-	-	-
FVG	14,512	14,503	29,015	1,105,472	334,403	-	-	3,447	-	-	-	-	-
Liguria	12,297	12,437	24,734	942,349	285,058	-	-	2,938	-	-	-	-	-
Umbria	5,486	5,500	10,986	418,563	126,614	-	-	1,305	-	-	-	-	-
Veneto	44,443	46,076	90,519	3,448,787	1,043,250	-	-	10,754	-	-	-	-	-
NAIP	**99,267**	**100,296**	**199,563**	**7,603,368**	**2,300,000**	**-**	**-**	**23,708**	**-**	**-**	**-**	**-**	**-**
Apulia	24,204	24,990	49,194	6,760,452	-	16,534,595	9,960,000	-	-	-	-	-	-
Calabria	9,819	9,680	19,499	2,728,778	-	6,553,809	3,320,000	-	-	-	-	-	-
E.-Romagna	47,632	49,794	97,426	3,713,826	8,794,266	9,078,331	30,361,481	-	4,000	-	-	-	-
Sicily	34,154	34,377	68,531	9,591,631	-	23,033,954	13,280,000	-	-	-	-	-	-
RIPP	**115,809**	**118,841**	**234,650**	**22,794,688**	**8,794,266**	**55,200,690**	**56,921,481**	**-**	**4,000**	**-**	**-**	**-**	**-**
Campania	14,172	14,110	28,282	-	3,959,473	16,262,121	-	-	-	16,969,170	14,621,768	5,656,390	3,450,398
Latium	22,597	24,040	46,636	-	6,529,109	26,815,982	-	-	-	27,981,894	24,111,065	9,327,298	5,689,652
Marche	17,442	17,924	35,366	-	4,951,274	20,335,588	-	-	-	21,219,744	18,284,346	7,073,248	4,314,681
Molise	1,822	1,803	3,626	-	507,618	2,084,858	-	-	-	2,175,504	1,874,559	725,168	442,352
Tuscany	32,167	32,758	64,924	-	9,089,429	37,331,582	-	-	-	38,954,694	33,565,961	12,984,898	7,920,788
Min.Def.	151	123	275	-	38,438	157,872	-	-	-	164,736	141,948	54,912	33,496
PlaNet	**88,351**	**90,758**	**179,110**	**-**	**25,075,340**	**102,988,003**	**-**	**-**	**-**	**107,465,742**	**92,599,648**	**35,821,914**	**21,851,368**
Lombardy	76,840	83,168	160,008	21,151,051	-	53,780,289	29,880,000	-	-	-	-	-	-
Piedmont	35,907	37,750	73,657	10,002,655	-	24,756,854	14,940,000	-	-	-	-	-	-
Sardinia	9,699	11,006	20,705	2,873,141	-	6,959,158	3,320,000	-	-	-	-	-	-
LPS	**122,446**	**131,924**	**254,370**	**34,026,846**	**-**	**85,496,301**	**48,140,000**	**-**	**-**	**-**	**-**	**-**	**-**
ITALY	**425,873**	**441,820**	**867,693**	**64,424,903**	**36,169,606**	**243,684,993**	**105,061,481**	**23,708**	**4,000**	**107,465,742**	**92,599,648**	**35,821,914**	**21,851,368**

Table 79. Potential supply of solvent/detergent-treated plasma based on the amount of plasma sent for fractionation from July 2022 to June 2023 and the yields provided by the fractionation industry – year 2023 (adapted by the CNS on data provided by Kedrion)

Region	2nd semester 2022	1st semester 2023	Total	Solvent/ detergent-treated plasma
	kg	kg	kg	mL
Abruzzo	-	-	-	-
Aosta Valley	-	-	-	-
AP Bolzano	-	-	-	-
AP Trento	-	-	-	-
Apulia	-	-	-	-
Basilicata	-	-	-	-
Calabria	-	-	-	-
Campania	3,023	2,426	5,449	5,040,247
E.-Romagna	-	-	-	-
Friuli V. Giulia	-	-	-	-
Latium	755	760	1,514	1,400,515
Liguria	-	-	-	-
Lombardy	-	-	-	-
Marche	90	589	679	627,918
Molise	286	120	406	375,222
Piedmont	2,408	2,719	5,127	4,742,456
Sardinia	-	-	-	-
Sicily	356	706	1,062	982,099
Tuscany	1,450	1,808	3,258	3,013,823
Umbria	-	-	-	-
Veneto	806	898	1,704	1,576,391
Ministry of Defence	-	-	-	-
ITALY	**9,173**	**10,025**	**19,199**	**17,758,670**

Table 80. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs (driver) classified by Region for the year 2023 (adapted by the CNS on fractionation companies data, March 2024)

Region	Albumin g	IVIG g	SCIG g
Abruzzo	640,200	89,750	7,120
AostaValley	64,800	17,500	440
APBolzano	159,000	47,450	700
APTrento	228,600	39,250	2,680
Basilicata	231,000	39,050	840
FriuliV.Giulia	482,400	144,200	2,340
Liguria	687,600	175,250	2,840
Umbria	528,000	76,100	7,720
Veneto	2,018,370	397,760	22,640
NAIP	**5,039,970**	**1,026,310**	**47,320**
Apulia	1,098,790	197,965	21,624
Calabria	465,000	72,000	104
E.-Romagna	2,407,510	397,520	4,536
Sicily	1,818,220	271,620	1,848
RIPP	**5,789,520**	**939,105**	**28,112**
Campania	941,888	136,980	2,000
Latium	1,058,975	205,365	53,328
Marche	865,740	149,940	19,736
Molise	79,150	15,645	704
Tuscany	2,317,790	326,210	99,820
Ministry of Defence	9,860	-	-
PlaNet	**5,273,403**	**834,140**	**175,588**
Lombardy	3,976,760	480,153	-
Piedmont	1,485,250	379,060	-
Sardinia	952,600	68,895	-
LPS	**6,414,610**	**928,108**	**-**
ITALY	**22,517,503**	**3,727,663**	**251,020**

Table 81. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs classified by Region for the year 2023 (adapted by the CNS on fractionation companies data, March 2024)

Region	Factor VIII	Factor VIII/ vW Factor	Factor IX	3F-PCCs	AT	Fibrinogen	S/D - treated plasma	Protein C	Alpha-1	aPCCs	4F-PCCs
	UI	UI	UI	UI	UI	g	mL	UI	g	UF	UI
Abruzzo	290,000	2,350,000	-	307,500	1,188,000	1,510	-	-	-	-	-
Aosta Valley	-	-	-	-	165,000	50	-	-	-	-	-
AP Bolzano	430,000	130,000	-	251,000	120,000	1,300	-	-	-	-	-
AP Trento	-	20,000	-	250,000	502,000	690	-	-	-	-	-
Basilicata	10,000	30,000	-	240,000	990,000	330	-	-	-	-	-
Friuli V. Giulia	1,400,000	190,000	-	261,000	2,170,000	1,660	-	-	-	-	-
Liguria	90,000	80,000	-	753,000	2,475,000	640	-	-	-	-	-
Umbria	50,000	160,000	-	381,500	815,000	1,660	-	-	-	-	-
Veneto	4,260,000	830,000	-	4,000,000	6,215,000	8,900	964,000	-	-	-	-
NAIP	**6,530,000**	**3,790,000**	**-**	**6,444,000**	**14,640,000**	**16,740**	**964,000**	**-**	**-**	**-**	**-**
Apulia	5,207,000	902,000	-	1,172,000	6,384,000	-	-	-	1,751	-	-
Calabria	203,000	120,000	54,000	739,500	7,309,000	-	-	-	20	-	-
E.-Romagna	1,327,000	568,000	43,000	2,946,500	2,807,000	-	-	-	2,594	-	-
Sicily	1,327,000	52,000	130,000	2,667,000	14,409,000	-	1,259,200	-	2,486	-	-
RIPP	**8,064,000**	**1,642,000**	**227,000**	**7,525,000**	**30,909,000**	**-**	**1,259,200**	**-**	**6,851**	**-**	**-**
Campania	-	221,000	36,000	159,000	695,000	-	3,542,200	178,000	-	648,000	571,800
Latium	4,811,000	561,000	715,200	1,724,200	6,860,000	-	1,749,600	118,000	-	370,000	294,600
Marche	1,514,000	517,000	574,800	508,200	2,268,000	-	1,774,000	12,000	-	72,000	622,200
Molise	218,000	32,000	136,800	149,000	702,000	-	228,000	-	-	-	-
Tuscany	5,407,000	6,986,000	3,704,400	2,086,500	7,924,000	2,286	910,000	13,000	-	2,010,000	1,845,000
Min.of Defence	-	-	-	15,000	210,000	-	-	-	-	-	-
PlaNet	**11,950,000**	**8,317,000**	**5,167,200**	**4,641,900**	**18,659,000**	**2,286**	**8,203,800**	**321,000**	**-**	**3,100,000**	**3,333,600**
Lombardy	7,498,000	-	974,000	6,883,000	7,831,500	-	476,000	-	-	-	-
Piedmont	5,622,000	-	94,000	2,927,500	6,404,500	-	3,782,000	-	-	-	-
Sardinia	298,000	-	-	692,000	2,061,000	-	-	-	-	-	-
LPS	**13,418,000**	**-**	**1,068,000**	**10,502,500**	**16,297,000**	**-**	**4,258,000**	**-**	**-**	**-**	**-**
ITALY	**39,962,000**	**13,749,000**	**6,462,200**	**29,113,400**	**80,505,000**	**19,026**	**14,685,000**	**321,000**	**6,851**	**3,100,000**	**3,333,600**

ANALYSIS OF SELF-SUFFICIENCY

Albumin

In 2023, the Italian NHS demand for albumin accounted for 85% of the total. The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, was 75% (+7% compared to 2022) while the effective self-sufficiency, considered as the ratio between the actual supply of toll fractionation and the NHS demand, was 73% (72% in 2022) (Table 82).

The Regions that in 2023 achieved effective self-sufficiency - more than 90% - were Friuli V. Giulia, the AP of Bolzano, the AP of Trento, Umbria, Aosta Valley, Veneto, E.-Romagna, Tuscany and Marche.

Table 82. Estimates of regional and national self-sufficiency in albumin, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	873,298	797,713	478,272	640,200	60	80
Aosta Valley	73,760	67,000	64,128	64,800	96	97
AP Bolzano	184,640	164,360	199,178	159,000	121	97
AP Trento	265,170	241,610	198,633	228,600	82	95
Basilicata	346,753	332,180	185,253	231,000	56	70
Friuli V. Giulia	491,350	485,230	736,982	482,400	152	99
Liguria	941,915	857,073	628,233	687,600	73	80
Umbria	564,450	537,205	279,042	528,000	52	98
Veneto	2,122,453	2,072,140	2,299,192	2,018,370	111	97
NAIP	**5,863,788**	**5,554,510**	**5,068,912**	**5,039,970**	**91**	**91**
Apulia	1,891,590	1,612,223	1,268,221	1,098,790	79	68
Calabria	961,380	856,483	502,684	465,000	59	54
E.-Romagna	3,599,790	2,567,435	2,511,645	2,407,510	98	94
Sicily	2,982,878	2,413,773	1,766,729	1,818,220	73	75
RIPP	**9,435,638**	**7,449,913**	**6,049,280**	**5,789,520**	**81**	**78**
Campania	4,316,193	4,007,103	715,533	941,888	18	24
Latium	2,763,275	1,886,398	1,179,903	1,058,975	63	56
Marche	900,445	829,515	894,766	808,720	108	97
Molise	108,795	102,833	91,734	79,150	89	77
Tuscany	1,547,768	1,499,753	1,642,590	1,483,135	110	99
Min. of Def.	-	-	6,946		-	-
PlaNet	**9,636,475**	**8,325,600**	**4,531,472**	**4,371,868**	**54**	**53**
Lombardy	6,395,853	4,987,073	4,125,006	3,976,760	83	80
Piedmont	1,739,503	1,684,370	1,898,877	1,485,250	113	88
Sardinia	1,481,753	1,453,558	533,775	952,600	37	66
LPS	**9,617,108**	**8,125,000**	**6,557,659**	**6,414,610**	**81**	**79**
ITALY	**34,553,008**	**29,455,023**	**22,207,322**	**21,615,968**	**75**	**73**

The Regions that mostly benefitted from interregional compensation in 2023 were: Umbria (98% effective self-sufficiency compared to the potential 52%) and Abruzzo (80% compared to 60%) for NAIP, Sardinia (66% compared to 37%) for LPS, Sicily (effective self-sufficiency 75% compared to the potential 73%) for the RIPP consortium and Campania for the PlaNet consortium (effective self-sufficiency 24% compared to the potential 18%).

The Regions that remained farthest from the goal of effective self-sufficiency were Campania, Latium, Calabria, Apulia and Sardinia, with percentages ranging between 24% and 68% of the NHS demand met by the toll fractionation supply.

Normal human immunoglobulins

In 2023, the NHS demand for normal IGs accounted for 93% of the total demand (Table 83).

The national potential self-sufficiency, espressed by the ratio of the potential supply to the total demand, in 2023 was 59%, where effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to total demand, was 62%.

Table 83. Estimates of regional and national self-sufficiency in human immunoglobulins, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	123,590	123,430	94,148	96,870	76	78
Aosta Valley	18,951	18,951	12,624	17,940	67	95
AP Bolzano	54,258	54,258	39,208	48,050	72	89
AP Trento	55,661	55,661	39,101	41,630	70	75
Basilicata	53,350	53,350	36,467	39,890	68	75
Friuli V. Giulia	156,501	156,221	145,075	146,540	93	94
Liguria	211,408	211,173	123,668	178,090	58	84
Umbria	125,740	125,740	54,930	84,220	44	67
Veneto	555,843	553,648	452,597	420,400	81	76
NAIP	**1,355,302**	**1,352,432**	**997,817**	**1,073,630**	**74**	**79**
Apulia	409,982	407,572	194,355	219,589	47	54
Calabria	113,845	113,845	76,430	72,104	67	63
E.-Romagna	709,006	553,276	346,144	402,056	49	57
Sicily	373,315	366,665	272,238	273,468	73	73
RIPP	**1,606,147**	**1,441,357**	**889,167**	**967,217**	**55**	**60**
Campania	397,022	394,322	137,527	138,980	35	35
Latium	557,990	497,541	224,813	258,693	40	46
Marche	225,708	222,598	173,914	169,676	77	75
Molise	21,511	18,531	17,886	16,349	83	76
Tuscany	528,899	528,774	313,388	426,030	59	81
Min. of Def.	-	-	-	-	-	-
PlaNet	**1,731,130**	**1,661,766**	**867,528**	**1,009,728**	**50**	**58**
Lombardy	1,034,052	850,782	643,533	480,153	62	46
Piedmont	524,006	522,396	295,268	379,060	56	72
Sardinia	128,954	128,884	84,291	68,895	65	53
LPS	**1,687,012**	**1,502,062**	**1,023,092**	**928,108**	**61**	**55**
ITALY	**6,379,591**	**5,957,617**	**3,777,604**	**3,978,683**	**59**	**62**

* The value does not include *Pentaglobin*™.

Some Regions managed to achieve actual self-sufficiency in IG in 2023 above 90%, such as Friuli V. Giulia and Aosta Valley, while the Regions that achieved the lowest actual self-sufficiency were Latium and Lombardy (46%) and Campania (35%).

Normal human immunoglobulins for subcutaneous use

In 2023, the NHS demand for immunoglobulins for subcutaneous/intramuscular use represented approximately 97% of the total demand (Table 84).

The effective self-sufficiency, regarded as the ratio between the actual supply of the processing account and the total demand, was 17% (12% in 2022).

No Region in 2023 achieved effective self-sufficiency > 90%; the highest values of self-sufficiency were recorded in Marche and in Tuscany with self-sufficiency rates of 53% and 55% respectively.

Table 84. Estimates of regional and national self-sufficiency in human immunoglobulin for subcutaneous use, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	30,760	30,600	94,148	7,120	306	23
Aosta Valley	1,278	1,278	12,624	440	988	34
AP Bolzano	2,926	2,926	39,208	600	1,340	21
AP Trento	9,161	9,161	39,101	2,380	427	26
Basilicata	13,237	13,237	36,467	840	276	6
Friuli V. Giulia	10,821	10,821	145,075	2,340	1,341	22
Liguria	23,923	23,923	123,668	2,840	517	12
Umbria	48,025	48,025	54,930	8,120	114	17
Veneto	148,053	148,053	452,597	22,640	306	15
NAIP	**288,185**	**288,025**	**997,817**	**47,320**	**346**	**16**
Apulia	121,439	121,439	178,082	21,624	147	18
Calabria	41,259	41,259	70,586	104	171	0
E.-Romagna	123,385	123,385	97,776	4,536	79	4
Sicily	93,345	93,345	248,082	1,848	266	2
RIPP	**379,427**	**379,427**	**594,527**	**28,112**	**157**	**7**
Campania	109,022	109,022	127,269	2,000	117	2
Latium	200,270	197,256	209,864	53,328	105	27
Marche	37,238	37,238	159,148	19,736	427	53
Molise	2,886	2,886	16,316	704	565	24
Tuscany	183,036	182,961	292,160	99,820	160	55
Min. of Def.	-	-	1,236	-	-	-
PlaNet	**532,451**	**529,361**	**805,993**	**175,588**	**151**	**33**
Lombardy	149,874	113,546	579,229	-	386	0
Piedmont	90,656	90,656	266,638	-	294	0
Sardinia	5,199	5,199	74,952	-	1,442	0
LPS	**245,730**	**209,401**	**920,819**	**-**	**375**	**0**
ITALY	**1,445,792**	**1,406,214**	**3,319,157**	**251,020**	**230**	**17**

*potential offer deriving from the processing of 100% of the plasma delivered for the production of Immunoglobulins for subcutaneous administration

Normal human immunoglobulins for intravenous use

In 2023, the NHS demand for IV IGs accounted for 92% of the total demand (Table 85).

The national potential self-sufficiency, espressed by the ratio of the potential supply to total demand, in 2023 was 79%. Effective self-sufficiency, assumed as the ratio of the actual supply of toll fractionation to total demand, was 76%.

Table 85. Estimates of regional and national self-sufficiency in human immunoglobulin for intravenous use, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	92,830	92,830	94,148	89,750	101	97
Aosta Valley	17,673	17,673	12,624	17,500	71	99
AP Bolzano	51,332	51,332	39,208	47,450	76	92
AP Trento	46,500	46,500	39,101	39,250	84	84
Basilicata	40,113	40,113	36,467	39,050	91	97
Friuli V. Giulia	145,680	145,400	145,075	144,200	100	99
Liguria	187,485	187,250	123,668	175,250	66	93
Umbria	77,715	77,715	54,930	76,100	71	98
Veneto	407,790	405,595	452,597	397,760	111	98
NAIP	**1,067,118**	**1,064,408**	**997,817**	**1,026,310**	**94**	**96**
Apulia	288,543	286,133	201,203	197,965	70	69
Calabria	72,586	72,586	79,751	72,000	110	99
E.-Romagna	585,621	429,891	398,473	397,520	68	68
Sicily	279,970	273,320	280,292	271,620	100	97
RIPP	**1,226,720**	**1,061,930**	**959,719**	**939,105**	**78**	**77**
Campania	288,001	285,301	141,410	136,980	49	48
Latium	357,720	300,285	233,182	205,365	65	57
Marche	188,470	185,360	176,831	149,940	94	80
Molise	18,625	15,645	18,129	15,645	97	84
Tuscany	345,864	345,814	324,622	326,210	94	94
Min. of Def.	-	-	1,373	-	-	-
PlaNet	**1,198,679**	**1,132,404**	**895,548**	**834,140**	**75**	**70**
Lombardy	884,177	737,236	654,433	480,153	74	54
Piedmont	433,350	431,740	301,257	379,060	70	87
Sardinia	123,755	123,685	84,683	68,895	68	56
LPS	**1,441,282**	**1,292,661**	**1,040,373**	**928,108**	**72**	**64**
ITALY	**4,933,799**	**4,551,403**	**3,893,458**	**3,727,663**	**79**	**76**

* potential offer deriving from the processing of 100% of the plasma delivered for the production of Immunoglobulins for intravenous administration

** The value does not include *Pentaglobin*™.

The Regions that in 2023 achieved effective self-sufficiency (more than 90%) were all regions of the NAIP, except of the AP of Trento, along with Calabria, Sicily and Tuscany.

Campania is the Region with the lowest effective self-sufficiency value, equal to 48%.

Antithrombin

In 2023 NHS demand for AT accounted for about 89% of total demand. Effective self-sufficiency recorded a value of 77% in 2023 (75% in 2022), less than the potential self-sufficiency (100%) (Table 86).

Table 86. Estimates of regional and national self-sufficiency in antithrombin, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	3,304,500	3,282,500	-	1,188,000	-	36
Aosta Valley	414,000	414,000	-	165,000	-	40
AP Bolzano	200,000	200,000	-	120,000	-	60
AP Trento	502,000	502,000	-	502,000	-	100
Basilicata	1,470,000	1,470,000	-	990,000	-	67
FVG	2,980,000	2,980,000	-	2,170,000	-	73
Liguria	3,266,500	3,162,500	-	2,475,000	-	78
Umbria	1,003,000	1,003,000	-	815,000	-	81
Veneto	6,591,500	6,590,000	-	6,215,000	-	94
NAIP	**19,731,500**	**19,604,000**	**-**	**14,640,000**	**-**	**75**
Apulia	6,818,500	6,415,500	9,960,000	6,384,000	155	100
Calabria	7,467,000	7,409,000	3,320,000	7,309,000	45	99
E.-Romagna	8,334,500	2,807,000	30,361,481	2,807,000	1,082	100
Sicily	16,677,500	15,110,000	13,280,000	14,409,000	88	95
RIPP	**39,297,500**	**31,741,500**	**56,921,481**	**30,909,000**	**179**	**97**
Campania	13,163,500	12,644,500	-	695,000	-	5
Latium	14,021,000	12,073,000	-	6,860,000	-	57
Marche	2,898,000	2,898,000	-	2,268,000	-	78
Molise	708,000	702,000	-	702,000	-	100
Tuscany	7,931,500	7,924,000	-	7,924,000	-	100
Min. of Def.	-	-	-	-	-	-
PlaNet	**38,722,000**	**36,241,500**	**-**	**18,449,000**	**-**	**51**
Lombardy	11,187,500	8,623,500	29,880,000	7,831,500	346	91
Piedmont	6,791,500	6,404,500	14,940,000	6,404,500	233	100
Sardinia	2,262,500	2,260,000	3,320,000	2,061,000	147	91
LPS	**20,241,500**	**17,288,000**	**48,140,000**	**16,297,000**	**278**	**94**
ITALY	**117,992,500**	**104,875,000**	**105,061,481**	**80,295,000**	**100**	**77**

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

Some regions have achieved actual self-sufficiency of more than 90% of NHS demand by 2023, with the exception of almost all NAIP regions (except the AP of Trento and Veneto), and Campania, Marche and Latium. The regions that benefited most from interregional compensation or product stocks related to the previous convention in 2023 were the AP of Trento, Molise and Tuscany (100% effective *vs.* 0% potential).

Coagulation Factor VIII

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 stemming from the therapeutic alliance between doctor and patient, which has to be safeguarded and may not even allow for 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. In 2023, under the contract arrangements in force, NAIP Regions could benefit from:

– the still existing stock of plasma-derived coagulation Factor VIII provided for in 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.

The PlaNet Regions, under the previous contract with Kedrion, were able to benefit from the supply and huge stock of pdFVIII, Klott®.

Plasma-derived coagulation Factor VIII

In 2023, all the Regions largely achieved effective self-sufficiency in pdFVIII (Table 87).

Table 87. Estimates of regional and national self-sufficiency in plasma-derived Factor VIII, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	290,000	290,000	717,407	290,000	247	100
Aosta Valley	-	-	96,192	-	NA	NA
AP Bolzano	430,000	430,000	298,767	430,000	69	100
AP Trento	-	-	297,949	-	NA	NA
Basilicata	10,000	10,000	277,880	10,000	2,779	100
FVG	1,400,000	1,400,000	1,105,472	1,400,000	79	100
Liguria	90,000	90,000	942,349	90,000	1,047	100
Umbria	50,000	50,000	418,563	50,000	837	100
Veneto	4,580,000	4,580,000	3,448,787	4,260,000	75	93
NAIP	**6,850,000**	**6,850,000**	**7,603,368**	**6,530,000**	**111**	**95**
Apulia	5,207,000	5,207,000	6,760,452	5,207,000	130	100
Calabria	203,000	203,000	2,728,778	203,000	1,344	100
E.-Romagna	1,327,000	1,327,000	3,713,826	1,327,000	280	100
Sicily	1,327,000	1,327,000	9,591,631	1,327,000	723	100
RIPP	**8,064,000**	**8,064,000**	**22,794,688**	**8,064,000**	**283**	**100**
Campania	-	-	-	-	-	-
Latium	4,821,000	4,811,000	-	4,811,000	-	100
Marche	1,514,000	1,514,000	-	1,514,000	-	100
Molise	218,000	218,000	-	218,000	-	100
Tuscany	5,409,000	5,407,000	-	5,407,000	-	100
Min. of Def.	-	-	-	-	-	-
PlaNet	**11,962,000**	**11,950,000**	**-**	**11,950,000**	**-**	**100**

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Lombardy	8,208,000	8,139,000	21,151,051	7,498,000	260	92
Piedmont	5,622,000	5,622,000	10,002,655	5,622,000	178	100
Sardinia	318,000	318,000	2,873,141	298,000	904	94
LPS	**14,148,000**	**14,079,000**	**34,026,846**	**13,418,000**	**242**	**95**
ITALY	**41,024,000**	**40,943,000**	**64,424,903**	**39,962,000**	**157**	**98**

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

Table 88 shows the regional and national self-sufficiency in plasma-derived Factor VIII and von Willebrand Factor in combination. For this active ingredient, the effective self-sufficiency recorded in 2023 was 18%.

Table 88. Estimates of regional and national self-sufficiencyin plasma-derived Factor VIII and von Willebrand Factor in combination, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	3,416,500	3,336,500	217,014	2,350,000	7	70
Aosta Valley	20,000	20,000	29,098	-	145	0
AP Bolzano	133,000	133,000	90,376	130,000	68	98
AP Trento	114,000	114,000	90,129	20,000	79	18
Basilicata	80,000	80,000	84,058	30,000	105	38
FVG	247,000	231,000	334,403	190,000	145	82
Liguria	223,000	223,000	285,058	80,000	128	36
Umbria	489,500	489,500	126,614	160,000	26	33
Veneto	2,058,000	2,054,000	1,043,250	830,000	51	40
NAIP	**6,781,000**	**6,681,000**	**2,300,000**	**3,790,000**	**34**	**57**
Apulia	6,409,000	6,406,500	-	846,000	-	13
Calabria	1,201,000	1,185,000	-	60,000	-	5
E.-Romagna	3,921,750	3,921,750	8,794,266	568,000	224	14
Sicily	2,142,000	2,142,000	-	52,000	-	2
RIPP	**13,673,750**	**13,655,250**	**8,794,266**	**1,526,000**	**64**	**11**
Campania	3,876,000	3,875,000	3,959,473	221,000	102	6
Latium	6,581,500	6,130,000	6,529,109	561,000	107	9
Marche	897,000	895,000	4,951,274	517,000	553	58
Molise	414,000	356,000	507,618	32,000	143	9
Tuscany	3,578,000	3,578,000	9,089,429	986,000	254	28
Min. of Def.	-	-	38,438	-	-	-
PlaNet	**15,346,500**	**14,834,000**	**25,075,340**	**2,317,000**	**169**	**16**
Lombardy	3,811,250	3,352,500	-	-	-	-
Piedmont	2,785,000	2,782,000	-	-	-	-
Sardinia	2,089,000	2,089,000	-	-	-	-
LPS	**8,685,250**	**8,223,500**	**-**	**-**	**-**	**-**
ITALY	**44,486,500**	**43,393,750**	**36,169,606**	**7,633,000**	**83**	**18**

* The value does not include *Wilfactin*.

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 have been analysed together.

While national self-sufficiency in pdFIX and 3F-PCCs was substantially reached (higher than 90% of the NHS demand), the regional self-sufficiency still bore significant differences with a range, varying from 0 to 100% confirming the need of improvement in the inter-regional exchange and compensation mechanisms (Table 89).

Table 89. Estimates of regional and national self- sufficiency in plasma-derived Factor IX and 3-factor prothrombin complex concentrates, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	361,000	361,000	-	307,500	-	85
Aosta Valley	10,000	10,000	-	-	-	0
AP Bolzano	257,000	257,000	-	251,000	-	98
AP Trento	250,000	250,000	-	250,000	-	100
Basilicata	419,500	419,500	-	240,000	-	57
FVG	261,000	261,000	-	261,000	-	100
Liguria	1,002,500	797,000	-	753,000	-	94
Umbria	573,000	573,000	-	381,500	-	67
Veneto	4,623,500	4,603,000	-	4,000,000	-	87
NAIP	**7,757,500**	**7,531,500**	**-**	**6,444,000**	**-**	**86**
Apulia	1,775,500	1,172,000	16,534,595	1,172,000	1,411	100
Calabria	796,000	793,500	6,553,809	793,500	826	100
E.-Romagna	3,410,500	2,989,500	9,078,331	2,989,500	304	100
Sicily	2,943,500	2,839,500	23,033,954	2,797,000	811	99
RIPP	**8,925,500**	**7,794,500**	**55,200,690**	**7,752,000**	**708**	**99**
Campania	1,594,500	1,444,500	16,262,121	195,000	1,126	13
Latium	2,466,900	2,439,400	26,815,982	2,439,400	1,099	100
Marche	1,189,000	1,189,000	20,335,588	1,083,000	1,710	91
Molise	291,800	285,800	2,084,858	285,800	729	100
Tuscany	2,198,400	2,192,400	37,331,582	2,190,900	1,703	100
Min. of Def.	-	-	157,872		NA	-
PlaNet	**7,740,600**	**7,551,100**	**102,988,003**	**6,194,100**	**1,364**	**82**
Lombardy	8,812,900	8,460,000	53,780,289	7,857,000	636	93
Piedmont	3,307,500	3,021,500	24,756,854	3,021,500	819	100
Sardinia	692,000	692,000	6,959,158	692,000	1,006	100
LPS	**12,812,400**	**12,173,500**	**85,496,301**	**11,570,500**	**702**	**95**
ITALY	**37,236,000**	**35,050,600**	**243,684,993**	**31,960,600**	**695**	**91**

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.

In 2023, the potential self-sufficiency in RiaSTAP was equal to 54% (55% in 2022) (Table 90).

However, effective self-sufficiency of 44% was achieved (23% in 2022), also given the marked increase of demand also in 2023 (+12%), demonstrating a continuing upward trend for this product. Most of NAIP Regions, except for Liguria, Abruzzo and Aosta Valley, achieved effective self-sufficiency higher than 80%.

Table 90. Estimates of regional and national self-sufficiency in fibrinogen by toll manufacturing system, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,920	1,920	2,237	1,510	117	79
Aosta Valley	63	63	300	50	476	79
AP Bolzano	1,450	1,450	932	1,300	64	90
AP Trento	690	690	929	690	135	100
Basilicata	330	330	866	330	263	100
FVG	1,660	1,660	3,447	1,660	208	100
Liguria	1,583	1,583	2,938	640	186	40
Umbria	1,660	1,660	1,305	1,660	79	100
Veneto	10,863	10,863	10,754	8,900	99	82
NAIP	**20,219**	**20,219**	**23,708**	**16,740**	**117**	**83**
Apulia	81	-	-	-	-	-
Calabria	65	56	-	-	-	-
E.-Romagna	590	509	-	-	-	-
Sicily	3,349	3,132	-	-	-	-
RIPP	**4,085**	**3,697**	**-**	**-**	**-**	**-**
Campania	4,544	4,177	-	-	-	-
Latium	3,628	2,224	-	-	-	-
Marche	1,791	1,791	-	-	-	-
Molise	6	6	-	-	-	-
Tuscany	2,287	2,286	-	2,286	-	100
Min. of Def.	-	-	-	-	-	-
PlaNet	**12,256**	**10,484**	**-**	**2,286**	**-**	**22**
Lombardy	6,775	4,031	-	-	-	-
Piedmont	3,264	3,238	-	-	-	-
Sardinia	2,039	2,039	-	-	-	-
LPS	**12,078**	**9,308**	**-**	**-**	**-**	**-**
ITALY	**48,638**	**43,708**	**23,708**	**19,026**	**54**	**44**

Solvent/detergent virus-inactivated plasma

Differently from the main PDMPs that were included in the agreements between the Regions and the fractionation company, 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 2023, the NHS demand for S/D plasma was almost equal to the total demand. For the same year, effective national self-sufficiency was 62% (64% in 2022) (Table 91).

Some of the Regions that used S/D plasma produced by toll fractionation, have achieved effective regional self-sufficiency of 100%, such as Veneto, Marche, Molise, Lombardy and Piedmont.

Table 91. Estimates of regional and national self-sufficiency in solvent/detergent virus-inactivated plasma, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	mL	mL	mL	mL	%	%
Abruzzo	-	-	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	448,000	448,000	-	-	-	-
FVG	-	-	-	-	-	-
Liguria	126,000	126,000	-	-	-	-
Umbria	146,000	146,000	-	-	-	-
Veneto	984,000	964,000	1,576,391	964,000	164	100
NAIP	**1,704,000**	**1,684,000**	**1,576,391**	**964,000**	**94**	**57**
Apulia	3,104,000	3,104,000	-	-	-	-
Calabria	1,038,000	1,038,000	-	-	-	-
E.-Romagna	346,000	346,000	-	-	-	-
Sicily	3,235,200	3,235,200	982,099	1,259,200	30	39
RIPP	**7,723,200**	**7,723,200**	**982,099**	**1,259,200**	**13**	**16**
Campania	4,056,200	4,030,200	5,040,247	3,542,200	125	88
Latium	3,104,200	2,846,200	1,400,515	1,749,600	49	61
Marche	1,774,000	1,774,000	627,918	1,774,000	35	100
Molise	228,000	228,000	375,222	228,000	165	100
Tuscany	1,156,000	1,156,000	3,013,823	910,000	261	79
Min. of Def.	-	-	-	-	-	-
PlaNet	**10,318,400**	**10,034,400**	**10,457,724**	**8,203,800**	**104**	**82**
Lombardy	476,000	476,000	-	476,000	-	100
Piedmont	3,782,000	3,782,000	4,742,456	3,782,000	125	100
Sardinia	6,400	6,400	-		-	-
LPS	**4,264,400**	**4,264,400**	**4,742,456**	**4,258,000**	**111**	**100**
ITALY	**24,010,000**	**23,706,000**	**17,758,670**	**14,685,000**	**75**	**62**

Protein C

In 2021, for the first time in Italy, the distribution by toll fractionation of protein C from Takeda company began, which includes this active ingredient as an ancillary product in its agreement with the Regions. In the 2023, 321,000 IU of protein C were distributed among Campania, Latium, Marche and Tuscany, enabling these Regions to reach a self-sufficiency percentage of 84% for the first and 100% for the other three. At the national level, the self-sufficiency percentage stood at 46% (Table 92).

Table 92. Estimates of regional and national self-sufficiency in Protein C, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	5,000	5,000	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	1,000	1,000	-	-	-	-
FVG	-	-	-	-	-	-
Liguria	45,000	45,000	-	-	-	-
Umbria	-	-	-	-	-	-
Veneto	15,000	15,000	-	-	-	-
NAIP	**66,000**	**66,000**	**-**	**-**	**-**	**-**
Apulia	8,000	8,000	-	-	-	-
Calabria	181,000	181,000	-	-	-	-
E.-Romagna	5,000	5,000	-	-	-	-
Sicily	6,500	6,500	-	-	-	-
RIPP	**200,500**	**200,500**	**-**	**-**	**-**	**-**
Campania	211,500	211,500	3,450,398	178,000	1,631	84
Latium	135,500	118,000	5,689,652	118,000	4,822	100
Marche	12,000	12,000	4,314,681	12,000	35,956	100
Molise	-	-	442,352	-	NA	NA
Tuscany	13,000	13,000	7,920,788	13,000	60,929	100
Min. of Def.	-	-	33,496	-	NA	NA
PlaNet	**372,000**	**354,500**	**21,851,368**	**321,000**	**6,164**	**91**
Lombardy	80,000	80,000	-	-	-	-
Piedmont	-	-	-	-	-	-
Sardinia	-	-	-	-	-	-
LPS	**80,000**	**80,000**	**-**	**-**	**-**	**-**
ITALY	**718,500**	**701,000**	**21,851,368**	**321,000**	**3,117**	**46**

Activated Prothrombin Complex Concentrates

In 2023, for the first time in Italy, the distribution of activated Prothrombin Complex Concentrates on consignment began by the Takeda Company, which included this active ingredient as an ancillary product in its agreement with the Regions. In 2023, 1.1 milion FU of

aPCCs were distributed among Campania, Latium, Marche and Tuscany enabling these Regions to reach a self-sufficiency percentage of 99%, 93%, 83% and 100%, respectively. At the national level, the percentage of self-sufficiency stood at 13% (Table 93).

Table 93. Estimates of regional and national self-sufficiency in activated Prothrombin Complex Concentrates, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	FU	FU	FU	FU	%	%
Abruzzo	1,618,000	1,618,000	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-
FVG	348,000	348,000	-	-	-	-
Liguria	130,000	130,000	-	-	-	-
Umbria	-	-	-	-	-	-
Veneto	292,000	292,000	-	-	-	-
NAIP	**2,388,000**	**2,388,000**	**-**	**-**	**-**	**-**
Apulia	364,000	364,000	-	-	-	-
Calabria	847,000	707,000	-	-	-	-
E.-Romagna	334,000	334,000	-	-	-	-
Sicily	36,000	36,000	-	-	-	-
RIPP	**1,581,000**	**1,441,000**	**-**	**-**	**-**	**-**
Campania	656,000	656,000	16,969,170	648,000	2,587	99
Latium	400,000	400,000	27,981,894	370,000	6,995	93
Marche	87,000	87,000	21,219,744	72,000	24,391	83
Molise	-	-	2,175,504	-	NA	NA
Tuscany	12,000	10,000	38,954,694	10,000	389,547	100
Min. of Def.	-	-	164,736	-	NA	NA
PlaNet	**1,155,000**	**1,153,000**	**107,465,742**	**1,100,000**	**9,321**	**95**
Lombardy	2,917,000	2,911,000	-	-	-	-
Piedmont	98,000	98,000	-	-	-	-
Sardinia	646,000	646,000	-	-	-	-
LPS	**3,661,000**	**3,655,000**	**-**	**-**	**-**	**-**
ITALY	**8,785,000**	**8,637,000**	**107,465,742**	**1,100,000**	**1,244**	**13**

Alpha-1-proteinase inhibitor

Plitalfa is a product containing the human alpha1-proteinase inhibitor currently made available by Grifols under the RIPP Agreement fractionation contract with Regions. *Plitalfa* is indicated for chronic replacement therapy in individuals with documented severe alpha1-proteinase inhibitor deficiency. Because it is the only drug containing this active ingredient to be returned by toll fractionation contracts, specific product self-sufficiency was considered. In 2023, actual self-sufficiency recorded only within the same RIPP regions was 100% of NHS demand (Table 94).

Table 94. Estimates of regional and national self-sufficiency in Alpha-1 by toll manufacturing system, 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	-	-	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-
FVG	-	-	-	-	-	-
Liguria	-	-	-	-	-	-
Umbria	-	-	-	-	-	-
Veneto	-	-	-	-	-	-
NAIP	**-**	**-**	**-**	**-**	**-**	**-**
Apulia	1,254	1,254	-	1,254	-	100
Calabria	20	20	-	20	-	100
E.-Romagna	5,784	2,594	4,000	2,594	154	100
Sicily	1,976	1,976	-	1,976	-	100
RIPP	**9,034**	**5,844**	**4,000**	**5,844**	**68**	**100**
Campania	-	-	-	-	-	-
Latium	-	-	-	-	-	-
Marche	-	-	-	-	-	-
Molise	-	-	-	-	-	-
Tuscany	-	-	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	**-**	**-**	**-**	**-**	**-**	**-**
Lombardy	-	-	-	-	-	-
Piedmont	-	-	-	-	-	-
Sardinia	-	-	-	-	-	-
LPS	**-**	**-**	**-**	**-**	**-**	**-**
ITALY	**9,034**	**5,844**	**4,000**	**5,844**	**68**	**100**

4-Factor Prothrombin Complex Concentrates

Proplex is a preparation obtained from human plasma containing blood coagulation factors II, VII, IX and X and also protein C, which play an important role in blood coagulation. *Proplex* is therefore used in cases of acquired or congenital deficiency of coagulation factors for the prevention and treatment of bleeding.

On subcontracting this product was made available by the Takeda Company for the first time in 2023, as part of the current agreement with the PlaNet Agreement. Being the only medicine containing this active ingredient to be returned on account, specific product self-sufficiency was considered. In 2023, potential self-sufficiency in Proplex was found to be 99% (Table 95). The actual self-sufficiency recorded only within the same PlaNet Regions was equal to 100% of the NHS demand.

Table 95. Estimates of regional and national self-sufficiency in 4-Factor Prothrombin Complex Concentrates by toll manufacturing system (Proplex), 2023

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	-	-	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-
FVG	-	-	-	-	-	-
Liguria	-	-	-	-	-	-
Umbria	30,000	30,000	-	-	-	-
Veneto	-	-	-	-	-	-
NAIP	**30,000**	**30,000**	**-**	**-**	**-**	**-**
Apulia	78,600	-	-	-	-	-
Calabria	-	-	-	-	-	-
E.-Romagna	10,800	-	-	-	-	-
Sicily	13,800	-	-	-	-	-
RIPP	**103,200**	**-**	**-**	**-**	**-**	**-**
Campania	571,800	571,800	14,621,768	571,800	2,557	100
Latium	550,800	294,600	24,111,065	294,600	8,184	100
Marche	622,200	622,200	18,284,346	622,200	2,939	100
Molise	-	-	1,874,559	-	-	-
Tuscany	1,847,400	1,845,000	33,565,961	1,845,000	1,819	100
Min. of Def.	-	-	141,948	-	-	-
PlaNet	**3,592,200**	**3,333,600**	**92,599,648**	**3,333,600**	**2,778**	**100**
Lombardy	81,000	-	-	-	-	-
Piedmont	40,800	-	-	-	-	-
Sardinia	-	-	-	-	-	-
LPS	**121,800**	**-**	**-**	**-**	**-**	**-**
ITALY	**3,847,200**	**3,363,600**	**92,599,648**	**3,333,600**	**2,753**	**99**

INTERREGIONAL AND INTER-AGREEMENT EXCHANGE OF PLASMA-DERIVATIVE MEDICINAL PRODUCTS

Exchanges of plasmaderived products are an important strategy for optimizing the use of available resources in the country's healthcare system, ensuring that patients receive the therapies they need, reducing the vulnerability associated with dependence on external providers, and equipping the System with greater autonomy. The exchange mechanism also offers a significant economic benefit to the Health System; thanks to what was established by the *State Regions Agreement* of June 17, 2021, it is possible to access plasmaderivatives produced by toll fractionation system at significantly reduced costs. This reduction in costs not only lightens the budgets of individual health facilities but also allows for more efficient use of public resources, enabling funds to be invested in the Blood Transfusion System itself, as well as other critical areas of public health.

In addition, the practice of exchanges makes it possible to optimize stock management by avoiding the accumulation of surplus products, while also preventing their expiration. Finally, careful planning efforts can help feed the system of product exchanges, while also increasing the self-sufficiency of the System. In the year 2023, exchanges or purchases at the *State Regions Agreement* rate of the products made available by the various agreement mainly involved four active ingredients: antithrombin (14.2 million IU exchanged), 3-Factor prothrombin complex concentrates (3.5 million IU), albumin (704 kg), Von Willebrand Factor and coagulation Factor VIII in combination (762,000 IU) and fibrinogen (2,300 g), with an economic valuation at average unit cost recorded in the market in the year 2023 of approximately 5.9 million (Table 96).

Table 96. Active ingredients subject to exchange or acquisition at ASR rate of June 17, 2021 - year 2023

From	To	Active ingredient	Unit of measure	g/IU	Economic valuation at average unit cost 2023 (euro)
RIPP	NAIP	Antithrombin	UI	10,846,000	1,084,600
Tuscany	Marche	Antithrombin	UI	2,348,000	234,800
RIPP	Marche	Antithrombin	UI	1,000,000	100,000
RIPP	NAIP	3-F PCCs	UI	2,968,500	742,125
RIPP	PlaNet	3-F PCCs	UI	410,500	102,625
Tuscany	Marche	3-F PCCs	UI	111,500	27,875
NAIP	PlaNet	Fibrinogen	g	2,286	919,865
Marche	Tuscany	FVIII/vWF	UI	762,000	379,574
Marche	Tuscany	IVIg	g	1,000	60,049
Marche	Tuscany	SCIg	g	3,500	235,265
PlaNet	NAIP	Albumin	g	500,080	1,437,083
PlaNet	RIPP	Albumin	g	50,000	143,685
Tuscany	Marche	Albumin	g	96,148	276,300
Marche	RIPP	Albumin	g	57,690	165,784
TOTAL					**5,909,630**

Over the past few years, the different regional levels of plasma collection for industrial processing, combined with the expansion and diversification of products available under the new

agreements, have generated situations of regional and interregional surpluses, encouraging the intensification of interregional and inter-agreement exchanges of MPDs and production intermediates and limiting the use, by hospital companies, of the market, with significant savings for the National Health Service. Figure 47 shows in economic terms the value of products exchanged from 2016 to 2023, with a total trade value of about 67 million euros over the period.

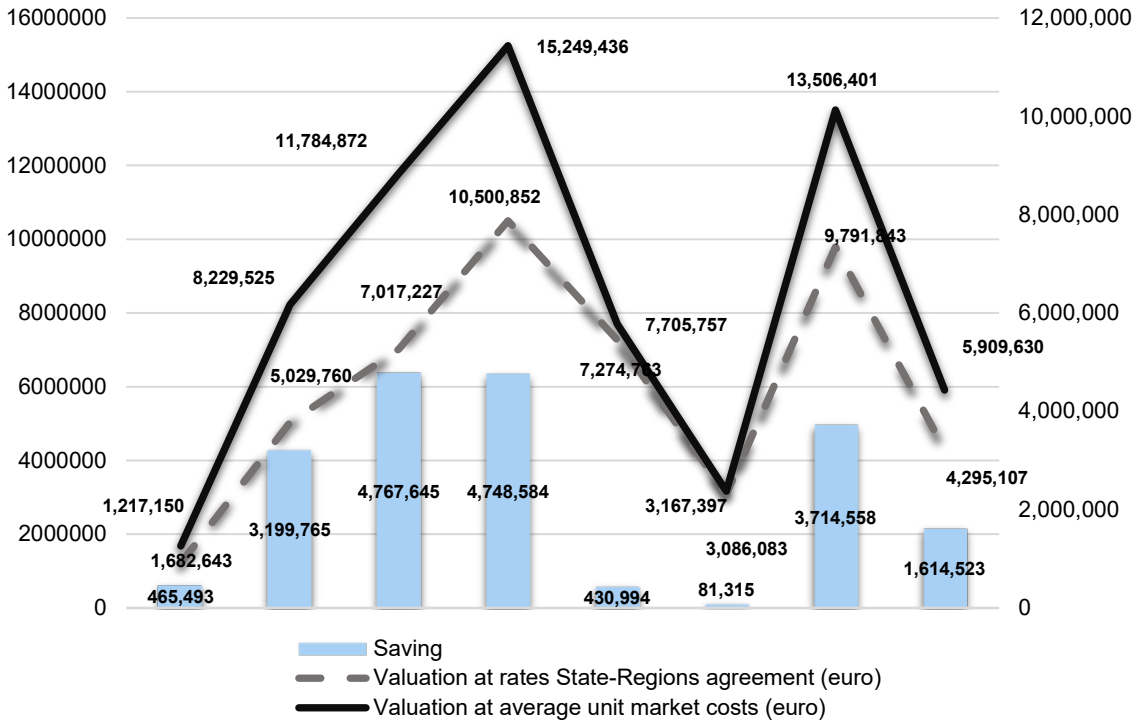

Figura 47. Economic valuation of active ingredients from toll manufacturing system exchanged in the years 2016-2023 (adapted by the CNS on data from the Traceability information flow)

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 market:

1. PDMPs included in the agreements between the Regions and the toll fractionation companies for the quota of the demand not covered by toll fractionation (albumin, IV IGs, SC/IM IGs, pdFVIII, pdFVIII/vWF, pdFIX, 3F-PCC, AT, Protein C, aPCCs, alpha-1 antitrypsin and fibrinogen);
2. recombinant medicinal products, including extended half-life products, used in the treatment of coagulation disorders (rFVIIa, rFVIII, rFIX and rFXIII)[i];
3. Emicizumab;
4. specific immunoglobulins and all other PDMPs, for which the distribution of the products by toll fractionation is not foreseen or in any case that has not taken place, including the production of solvent/detergent-treated plasma from national 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 the 31st of December 2023, applying the discounts envisaged by law for pharmaceutical expenditure.

Tables 97 and 98 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 2023, the expenditure for purchasing the aforementioned PDMPs was approximately 230,9 million euros (3.9 euro *per capita*). Table 99 shows the total and total *per capita* expenditure relative to supply of recombinant medicinal products (rFVIIa, rFVIII, rFIX and rFXIII), including extended-half life ones.

For these drugs, the total expenditure was 394 million euros (6.7 euros *per capita*). The Regions with the highest *per capita* expenditure were Abruzzo with 9.3 euros *per capita* spent and Latium and Campania with 8.6 and 8.5 euros *per capita* respectively.

The expenditure for recombinant factors decreased compared to 2022 (-2.8%). Table 100 shows the expenditure incurred in 2023 for the purchase of Emicizumab which has experienced an increase of +20%, from 1.58 to 1.90 euros *per capita*, reflecting how much the use of this drug is progressively increasing.

In 2023, as regards all the other PDMPs (Tables 101-104), the total expenditure was approximately 92 million euros, equal to around 1.55 euros *per capita* of which approximately 35.7 million for the purchase of specific immunoglobulins, a slightly higher cost compared to year 2022 (+0.7%) (Table 101), with a *per capita* expenditure of 0.60, as in the previous year (Table 102).

The other PDMPs (Tables 103-104), recorded a slightly increase in expenditure compared to the previous year (+3%), in particular as regards local haemostatics (+15%), C1-inhibitor (+9%) FX (+1,393%), FXIII (+22%). On the other hand, a decrease in expenditure was recorded for the other plasma protein fractions (-2%), and FXI (-20%). Substantially stable was the expenditure incurred on coagulation FVII (+0.05%).

Table 97. 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 2023

Region	Albumin		Human Immunoglobulin intravenous use*		Human Immunoglobulin subcutaneous use		Total	
	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita e*
Abruzzo	470,400	0.37	290,378	0.23	1,556,459	1.22	2,317,237	1.82
Aosta Valley	5,772	0.05	10,890	0.09	52,800	0.43	69,462	0.56
AP Bolzano	14,138	0.03	241,541	0.45	160,537	0.30	416,216	0.78
AP Trento	46,038	0.08	453,145	0.83	471,910	0.87	971,093	1.79
Basilicata	309,046	0.57	381,245	0.71	819,243	1.52	1,509,534	2.81
Friuli V. G.	11,190	0.01	416,928	0.35	552,548	0.46	980,666	0.82
Liguria	428,672	0.28	961,861	0.64	1,325,723	0.88	2,716,256	1.80
Umbria	36,261	0.04	95,304	0.11	2,532,159	2.96	2,663,724	3.11
Veneto	203,219	0.04	1,159,384	0.24	8,419,947	1.74	9,782,550	2.02
NAIP	**1,524,737**	**0.13**	**4,010,675**	**0.35**	**15,891,327**	**1.39**	**21,426,739**	**1.88**
Calabria	1,756,766	0.45	6,138,107	1.57	6,755,910	1.73	14,650,783	3.75
E.-Romagna	1,394,703	0.76	89,045	0.05	2,746,948	1.49	4,230,696	2.29
Puglia	412,335	0.09	2,341,474	0.53	8,244,173	1.86	10,997,981	2.48
Sicilia	1,837,115	0.38	1,627,348	0.34	6,173,164	1.28	9,637,626	2.00
RIPP	**5,400,919**	**0.36**	**10,195,974**	**0.68**	**23,920,194**	**1.59**	**39,517,087**	**2.63**
Campania	8,321,078	1.48	11,169,164	1.99	7,325,905	1.31	26,816,147	4.78
Lazio	2,439,288	0.43	5,578,092	0.98	9,494,344	1.66	17,511,723	3.06
Marche	51,027	0.03	2,540,013	1.71	1,139,372	0.77	3,730,412	2.51
Molise	93,673	0.32	0	0.00	138,897	0.48	232,570	0.80
Toscana	39,031	0.01	1,451,010	0.40	5,693,372	1.55	7,183,413	1.96
M. Difesa	-	-	-	-	-	-	-	NA
PlaNet	**10,944,096**	**0.65**	**20,738,278**	**1.24**	**23,791,890**	**1.42**	**55,474,264**	**3.31**
Lombardy	2,991,924	0.30	15,706,149	1.57	7,637,887	0.77	26,335,960	2.64
Piedmont	423,022	0.10	3,517,836	0.83	6,073,505	1.43	10,014,364	2.36
Sardinia	1,242,444	0.79	3,311,792	2.10	335,686	0.21	4,889,922	3.10
LPS	**4,657,391**	**0.29**	**22,535,777**	**1.43**	**14,047,078**	**0.89**	**41,240,246**	**2.61**
ITALY	**22,527,143**	**0.38**	**57,480,704**	**0.97**	**77,650,489**	**1.32**	**157,658,336**	**2.67**

* Includes high-title IG and imported products

Table 98. 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 2023

Region	FVIII		FVIII/vWF		FIX		3F-PCC		4F-PCC		AT		Fibrinogen		Protein C		aPCCs		Alpha-1 antitrypsin		Total	
	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.	€	€ p.c.
Abruzzo	-	-	772,562	0.6	-	-	15,598	0.0	262,414	0.2	229,225	0.2	197,560	0.2	10,945	0.0	1,980,935	1.6	616,600	0.5	4,085,839	3.2
A.Valley	-	-	5,183	0.0	-	-	2,530	0.0	26,632	0.2	24,980	0.2	4,882	0.0	-	-	-	-	105,146	0.9	169,352	1.4
APBolzano	-	-	1,650	0.0	1,907	0.0	-	-	316,732	0.6	8,536	0.0	66,000	0.1	-	-	-	-	890,573	1.7	1,285,398	2.4
APTrento	-	-	52,734	0.1	-	-	-	-	38,462	0.1	-	-	-	-	-	-	-	-	156,337	0.3	247,532	0.5
Basilicata	-	-	24,101	0.0	-	-	51,337	0.1	91,501	0.2	46,679	0.1	71,940	0.1	2,189	0.0	-	-	-	-	287,746	0.5
FVG	-	-	22,602	0.0	-	-	-	-	-	0.0	77,517	0.1	8,272	0.0	-	-	426,056	0.4	592,827	0.5	1,127,275	0.9
Liguria	-	-	75,535	0.1	1,188	0.0	11,083	0.0	356,847	0.2	73,508	0.0	475,398	0.3	98,505	0.1	159,080	0.1	764,079	0.5	2,015,221	1.3
Umbria	-	-	173,237	0.2	77,220	0.1	4,259	0.0	194,022	0.2	21,855	0.0	-	-	-	-	-	-	411,017	0.5	881,611	1.0
Veneto	98,560	0.0	1,383,618	0.3	8,848	0.0	163,034	0.0	377,671	0.1	45,509	0.0	892,849	0.2	23,925	0.0	351,374	0.1	988,883	0.2	4,334,271	0.9
NAIP	**98,560**	**0.0**	**2,511,222**	**0.2**	**89,164**	**0.0**	**247,840**	**0.0**	**1,664,280**	**0.1**	**527,807**	**0.0**	**1,716,901**	**0.2**	**135,564**	**0.0**	**2,917,446**	**0.3**	**4,525,462**	**0.4**	**14,434,245**	**1.3**
Apulia	-	-	2,865,200	0.7	-	-	-	-	35,593	0.0	3,119	0.0	1,153,656	0.3	17,512	0.0	441,201	0.1	393,929	0.1	4,910,209	1.3
Calabria	-	-	1,235,310	0.7	-	-	-	-	132,937	0.1	10,670	0.0	769,283	0.4	380,809	0.2	862,945	0.5	423,192	0.2	3,815,146	2.1
ER	-	-	1,966,115	0.4	-	-	-	-	600,213	0.1	-	-	1,696,595	0.4	10,945	0.0	408,845	0.1	487,977	0.1	5,170,690	1.2
Sicily	-	-	1,901,528	0.4	-	-	11,641	0.0	104,627	0.0	71,712	0.0	1,404,992	0.3	14,229	0.0	23,701	0.0	937,728	0.2	4,470,158	0.9
RIPP	**-**	**-**	**7,968,153**	**0.5**	**-**	**-**	**11,641**	**0.0**	**873,369**	**0.1**	**85,501**	**0.0**	**5,024,527**	**0.3**	**423,494**	**0.0**	**1,736,692**	**0.1**	**2,242,826**	**0.1**	**18,366,202**	**1.2**
Campania	-	-	1,997,512	0.4	-	-	271,290	0.0	519,161	0.1	1,181,012	0.2	1,661,259	0.3	73,332	0.0	9,794	0.0	2,493,846	0.4	8,207,205	1.5
Latium	-	-	2,912,784	0.5	-	-	-	-	187,975	0.0	550,493	0.1	1,143,885	0.2	-	-	36,729	0.0	1,309,669	0.2	6,141,535	1.1
Marche	-	-	331,225	0.2	-	-	28,334	0.0	50,125	0.0	97,020	0.1	795,183	0.5	-	-	-	-	199,012	0.1	1,500,899	1.0
Molise	-	-	175,648	0.6	-	-	-	-	-	0.0	-	-	2,382	0.0	-	-	-	-	16,447	0.1	194,477	0.7
Tuscany	-	-	1,259,180	0.3	-	-	389	0.0	66,654	0.0	-	-	884,871	0.2	-	-	2,449	0.0	940,120	0.3	3,153,663	0.9
Min.Def.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA
PlaNet	**-**	**-**	**6,676,349**	**0.4**	**0**	**0.0**	**300,013**	**0.0**	**823,915**	**0.0**	**1,828,525**	**0.1**	**4,487,580**	**0.3**	**73,332**	**0.0**	**48,972**	**0.0**	**4,959,093**	**0.3**	**19,197,780**	**1.1**
Lombardy	257,362	0.0	2,322,783	0.2	317,284	0.0	-	-	252,518	0.0	75,777	0.0	2,103,803	0.2	152,453	0.0	3,563,969	0.4	2,923,725	0.3	11,969,675	1.2
Piedmont	-	-	1,008,118	0.2	-	-	-	-	447,290	0.1	-	-	1,215,999	0.3	-	-	119,976	0.0	1,759,458	0.4	4,550,840	1.1
Sardinia	7,920	0.0	901,985	0.6	-	-	-	-	357,485	0.2	20,577	0.0	897,160	0.6	-	-	790,875	0.5	1,733,809	1.1	4,709,811	3.0
LPS	**265,282**	**0.0**	**4,232,887**	**0.3**	**317,284**	**0.0**	**-**	**-**	**1,057,292**	**0.1**	**96,354**	**0.0**	**4,216,962**	**0.3**	**152,453**	**0.0**	**4,474,820**	**0.3**	**6,416,992**	**0.4**	**21,230,326**	**1.3**
ITALY	**363,842**	**0.0**	**21,388,611**	**0.4**	**406,448**	**0.0**	**559,494**	**0.0**	**4,418,856**	**0.1**	**2,538,187**	**0.0**	**15,445,970**	**0.3**	**784,843**	**0.0**	**9,177,931**	**0.2**	**18,144,373**	**0.3**	**73.228.554**	**1.2**

Table 99. Estimate of the total expenditure and the total *per capita* expenditure for recombinant Factors VII, VIII, IX and XIII in 2023

Region	rFVIIa		FVIIIr		FIXr		FXIIIr		Total	
	€	€ *pc*	€	€ *pc*	€ *pc*	€ *pc*	€	€ *pc*	€	€ *pc*
Abruzzo	305,952	0.24	7,847,697	6.17	3,345,631	2.63	326,008	0.26	11,825,289	9.3
AostaValley	15,707	0.13	351,094	2.85	-	-	-	-	366,801	3.0
APBolzano	194,706	0.36	1,552,190	2.91	382,030	0.72	-	-	2,128,925	4.0
APTrento	5,437	0.01	2,493,589	4.59	627,961	1.16	-	-	3,126,988	5.8
Basilicata	13,291	0.02	1,980,025	3.68	270,535	0.50	186,290	0.35	2,450,141	4.6
FVG	909,072	0.76	1,837,211	1.54	1,546,309	1.29	93,145	0.08	4,385,737	3.7
Liguria	203,292	0.13	5,920,694	3.93	3,825,636	2.54	403,629	0.27	10,353,251	6.9
Umbria	155,954	0.18	4,010,341	4.68	830,184	0.97	-	-	4,996,479	5.8
Veneto	2,770,668	0.57	16,902,517	3.49	5,925,448	1.22	124,194	0.03	25,722,827	5.3
NAIP	**4,574,078**	**0.40**	**42,895,358**	**3.76**	**16,753,736**	**1.47**	**1,133,267**	**0.10**	**65,356,438**	**5.7**
Apulia	1,380,004	0.35	21,206,175	5.43	8,724,408	2.23	-	-	31,310,587	8.0
Calabria	588,480	0.32	9,052,931	4.90	2,539,632	1.38	1,055,646	0.57	13,236,689	7.2
E.-Romagna	1,715,589	0.39	25,391,617	5.72	8,275,737	1.86	93,145	0.02	35,476,088	8.0
Sicily	1,137,369	0.24	26,749,432	5.56	6,070,509	1.26	-	-	33,957,309	7.1
RIPP	**4,821,442**	**0.32**	**82,400,155**	**5.49**	**25,610,285**	**1.71**	**1,148,791**	**0.08**	**113,980,673**	**7.6**
Campania	1,452,543	0.26	35,656,095	6.36	10,236,794	1.82	232,863	0.04	47,578,295	8.5
Latium	608,791	0.11	41,603,716	7.27	6,833,747	1.19	-	-	49,046,253	8.6
Marche	325,025	0.22	5,327,861	3.59	1,996,762	1.35	-	-	7,649,648	5.2
Molise	51,784	0.18	1,394,280	4.80	-	-	-	-	1,446,064	5.0
Tuscany	2,907,432	0.79	10,494,319	2.87	8,178,580	2.23	-	-	21,580,331	5.9
Min.ofDef.	-	-	-	-	-	-	-	-	-	-
PlaNet	**5,345,576**	**0.32**	**94,476,270**	**5.63**	**27,245,883**	**1.62**	**232,863**	**0.01**	**127,300,592**	**7.6**
Lombardy	1,871,239	0.19	40,750,089	4.08	14,925,475	1.50	543,347	0.05	58,090,151	5.8
Piedmont	846,008	0.20	14,315,936	3.37	6,296,743	1.48	186,290	0.04	21,644,979	5.1
Sardinia	1,158,181	0.73	6,861,298	4.35	4,551	0.00	-	-	8,024,029	5.1
LPS	**3,875,429**	**0.25**	**61,927,324**	**3.92**	**21,226,769**	**1.34**	**729,637**	**0.05**	**87,759,159**	**5.6**
ITALY	**18,616,525**	**0.32**	**281,699,107**	**4.77**	**90,836,673**	**1.54**	**3,244,558**	**0.05**	**394,396,863**	**6.7**

Table 100. Estimate of the total expenditure and the total *per capita* expenditure for Emicizumab in 2023

Region	€	€ *pc*
Abruzzo	2,557,264	2.01
Aosta Valley	487,943	3.96
AP Bolzano	1,121,450	2.10
AP Trento	-	-
Basilicata	653,325	1.22
Friuli V. Giulia.	1,880,702	1.57
Liguria	2,117,839	1.40
Umbria	2,208,047	2.58
Veneto	9,844,546	2.03
NAIP	**20,871,115**	**1.83**
Apulia	3,783,271	0.97
Calabria	4,855,516	2.63
E.-Romagna	6,022,072	1.36
Sicily	7,526,906	1.56
RIPP	**22,187,764**	**1.48**
Campania	10,182,579	1.82
Latium	6,233,108	1.09
Marche	3,006,935	2.03
Molise	744,900	2.56
Tuscany	11,289,674	3.08
Min. of Def.	-	-
PlaNet	**31,457,196**	**1.88**
Lombardy	23,667,997	2.37
Piedmont	14,088,860	3.31
Sardinia	112,760	0.07
LPS	**37,869,617**	**2.40**
ITALY	**112,385,692**	**1.90**

Table 101. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of specific immunoglobulins in 2023

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs	Rabies IGs	Total
Abruzzo	250,946	3,346	257,413	52,125	15,032	709	647	580,218
Aosta Valley	54,470	-	15,140	6,836	2,719	0	1,078	80,244
AP Bolzano	20,592	-	25,552	42,475	-	1,963	3,773	94,356
AP Trento	80,274	-	21,876	32,702	-	355	-	135,206
Basilicata	129,138	352	82,646	24,756	19,562	-	-	256,455
Friuli V. Giulia	147,886	-	1,533	-	99,350	13,144	44,414	306,328
Liguria	168,110	19,958	171,826	59,301	11,326	450	-	430,971
Umbria	105,743	-	107,486	41,972	45,096	2,836	-	303,133
Veneto	1,072,300	236,226	142,990	273,461	459,000	4,376	20,805	2,209,158
NAIP	**2,029,459**	**259,882**	**826,463**	**533,629**	**652,086**	**23,833**	**70,717**	**4,396,070**
Apulia	2,539,948	160,876	383,823	146,757	121,352	2,492	3,881	3,359,129
Calabria	598,631	36,477	375,548	75,521	121,453	-	-	1,207,631
E.-Romagna	938,614	149,639	355,282	260,117	202,910	7,022	17,248	1,930,832
Sicily	1,328,467	-	784,222	182,633	247,104	-	1,294	2,543,719
RIPP	**5,405,660**	**346,993**	**1,898,875**	**665,028**	**692,819**	**9,514**	**22,422**	**9,041,311**
Campania	5,559,879	206,972	1,426,222	125,653	234,988	804	-	7,554,519
Latium	965,096	99,781	558,260	165,092	84,633	4,475	2,156	1,879,492
Marche	297,353	19,150	220,583	66,898	24,796	20,659	5,390	654,829
Molise	93,260	-	44,006	8,741	-	-	-	146,006
Tuscany	537,457	84,066	537,182	171,667	203,037	1,619	21,452	1,556,479
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	**7,453,045**	**409,969**	**2,786,252**	**538,050**	**547,455**	**27,557**	**28,998**	**11,791,326**
Lombardy	4,045,797	177,199	596,596	441,090	144,144	7,455	45,384	5,457,664
Piedmont	2,005,037	43,362	212,659	211,500	677,550	2,836	12,720	3,165,665
Sardinia	1,503,592	82,377	213,054	32,493	8,898	-	-	1,840,415
LPS	**7,554,426**	**302,938**	**1,022,309**	**685,084**	**830,593**	**10,292**	**58,104**	**10,463,744**
ITALY	**22,442,589**	**1,319,782**	**6,533,899**	**2,421,791**	**2,722,953**	**71,195**	**180,242**	**35,692,451**

Table 102. 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 2023

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs*	Rabies IGs*	Total
Abruzzo	0.20	0.00	0.20	0.04	0.01	0.56	0.51	0.46
Aosta Valley	0.44	-	0.12	0.06	0.02	-	8.75	0.65
AP Bolzano	0.04	-	0.05	0.08	-	3.68	7.06	0.18
AP Trento	0.15	-	0.04	0.06	-	0.65	-	0.25
Basilicata	0.24	0.00	0.15	0.05	0.04	-	-	0.48
Friuli V. Giulia	0.12	-	0.00	-	0.08	11.01	37.19	0.26
Liguria	0.11	0.01	0.11	0.04	0.008	0.30	-	0.29
Umbria	0.12	-	0.13	0.05	0.05	3.31	-	0.35
Veneto	0.22	0.05	0.03	0.06	0.09	0.90	4.29	0.46
NAIP	0.18	0.02	0.07	0.05	0.06	2.09	6.19	0.39
Apulia	0.65	0.04	0.10	0.04	0.03	0.64	0.99	0.86
Calabria	0.32	0.02	0.20	0.04	0.07	-	-	0.65
E.-Romagna	0.21	0.03	0.08	0.06	0.05	1.58	3.89	0.44
Sicily	0.28	-	0.16	0.04	0.05	-	0.27	0.53
RIPP	0.36	0.02	0.13	0.04	0.05	0.63	1.49	0.60
Campania	0.99	0.04	0.25	0.02	0.04	0.14	-	1.35
Latium	0.17	0.02	0.10	0.03	0.01	0.78	0.38	0.33
Marche	0.20	0.01	0.15	0.05	0.02	13.92	3.63	0.44
Molise	0.32	-	0.15	0.03	-	-	-	0.50
Tuscany	0.15	0.02	0.15	0.05	0.06	0.44	5.86	0.43
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	0.44	0.02	0.17	0.03	0.03	1.64	1.73	0.70
Lombardy	0.41	0.02	0.06	0.04	0.01	0.75	4.55	0.55
Piedmont	0.47	0.01	0.05	0.05	0.16	0.67	2.99	0.74
Sardinia	0.95	0.05	0.14	0.02	0.01	-	-	1.17
LPS	**0.48**	**0.02**	**0.06**	**0.04**	**0.05**	**0.65**	**3.68**	**0.66**
ITALY	**0.38**	**0.02**	**0.11**	**0.04**	**0.05**	**0.00**	**0.00**	**0.60**

*values per 1,000 population

Table 103. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of all other PDMPs in 2023

Region	FVII	Local Haemostatic agents-combinations	Other plasma Proteins fractions	Human C1 esterase inhibitor	Factor X	Factor XI	Factor XIII	Total
Abruzzo	651,073	976,087	-	358,980	-	-	-	1,986,140
Aosta Valley	-	76,401	-	12,135	-	-	-	88,536
AP Bolzano	-	335,555	-	44,370	-	-	13,675	393,601
AP Trento	-	224,699	-	90,434	-	-	60,171	375,303
Basilicata	40,605	484,102	176,318	23,408	-	-	-	724,433
Friuli V. Giulia	-	587,630	-	29,668	-	60,720	-	678,018
Liguria	20,536	451,593	50,074	63,470	-	20,240	65,250	671,162
Umbria	933	493,795	68,155	178,049	-	-	3,907	744,839
Veneto	1,867	2,068,328	-	1,088,512	-	-	114,872	3,273,579
NAIP	**715,014**	**5,698,189**	**294,548**	**1,889,026**	-	**80,960**	**257,875**	**8,935,611**
Apulia	308,035	1,840,935	1,586,095	769,613	-	-	19,426	4,524,104
Calabria	27,536	928,631	466,554	498,935	216,678	-	-	2,138,335
E.-Romagna	219,358	2,106,324	136,065	578,319	-	20,240	216,459	3,276,765
Sicily	303,834	2,209,985	1,096,281	2,070,513	-	-	-	5,680,613
RIPP	**858,763**	**7,085,876**	**3,284,995**	**3,917,381**	**216,678**	**20,240**	**235,885**	**15,619,817**
Campania	325,076	4,962,522	187,612	2,015,894	-	-	-	7,491,104
Latium	1,199,361	2,163,536	442,135	2,778,221	-	-	59,389	6,642,643
Marche	-	624,698	-	370,402	-	-	62,124	1,057,224
Molise	214,691	162,029	-	5,073	-	-	-	381,793
Tuscany	27,064	2,263,126	94,027	704,249	-	-	50,794	3,139,260
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	**1,766,192**	**10,175,912**	**723,774**	**5,873,839**	-	-	**172,307**	**18,712,023**
Lombardy	995,351	4,055,793	68	2,068,173	39,600	-	46,886	7,205,871
Piedmont	186,221	2,112,644	-	1,690,819	-	20,240	39,072	4,048,996
Sardinia	-	811,094	2,605	591,687	-	-	-	1,405,386
LPS	**1,181,572**	**6,979,531**	**2,673**	**4,350,679**	**39,600**	**20,240**	**85,958**	**12,660,253**
ITALY	**4,521,540**	**29,939,507**	**4,305,990**	**16,030,924**	**256,278**	**121,440**	**752,025**	**55,927,704**

Table 104. Estimate of standardised expenditure (*per capita* and euro per 1,000 population) incurred by the National Health Service for the purchase on the market of all other PDMPs in 2023

Region	FVII	Local Haemostatic agents-combinations	Other plasma Proteins fractions	Human C1 esterase inhibitor	Factor X *	Factor XI*	Factor XIII *	Total
Abruzzo	0.51	0.77	-	0.28	-	-	-	1.56
Aosta Valley	-	0.62	-	0.10	-	-	-	0.72
AP Bolzano	-	0.63	-	0.08	-	-	25.60	0.74
AP Trento	-	0.41	-	0.17	-	-	110.81	0.69
Basilicata	0.08	0.90	0.33	0.04	-	-	-	1.35
Friuli V. Giulia	-	0.49	-	0.02	-	50.84	-	0.57
Liguria	0.01	0.30	0.03	0.04	-	13.42	43.28	0.45
Umbria	0.001	0.58	0.08	0.21	-	-	4.56	0.87
Veneto	0.00	0.43	-	0.22	-	-	23.69	0.68
NAIP	**0.06**	**0.50**	**0.03**	**0.17**	**-**	**7.09**	**22.58**	**0.78**
Apulia	0.08	0.47	0.41	0.20	-	-	4.97	1.16
Calabria	0.01	0.50	0.25	0.27	117.34	-	-	1.16
E.-Romagna	0.05	0.47	0.03	0.13	-	4.56	48.78	0.74
Sicily	0.06	0.46	0.23	0.43	-	-	-	1.18
RIPP	**0.06**	**0.47**	**0.22**	**0.26**	**14.44**	**1.35**	**15.72**	**1.04**
Campania	0.06	0.88	0.03	0.36	-	-	-	1.34
Latium	0.21	0.38	0.08	0.49	-	-	10.38	1.16
Marche	-	0.42	-	0.25	-	-	41.85	0.71
Molise	0.74	0.56	-	0.02	-	-	-	1.31
Tuscany	0.01	0.62	0.03	0.19	-	-	13.87	0.86
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	**0.11**	**0.61**	**0.04**	**0.35**	**-**	**-**	**10.28**	**1.12**
Lombardy	0.10	0.41	0.000	0.21	4.0	-	4.70	0.72
Piedmont	0.04	0.50	-	0.40	-	4.76	9.19	0.95
Sardinia	-	0.51	0.002	0.37	-	-	-	0.89
LPS	**0.07**	**0.44**	**0.000**	**0.28**	**2.5**	**1.28**	**5.44**	**0.80**
ITALY	**0.08**	**0.51**	**0.07**	**0.27**	**4.3**	**2.06**	**12.75**	**0.95**

* values per 1,000 populatione

National and Regional mean price per gram or International Unit

Tables 105-107 show the mean price per unit paid by the Regions to purchase 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. All the aforementioned prices include VAT.

However, it should be noted that in some Regions the mean price per unit exceeded the maximum sale price to the NHS public structures as defined in the annex to the 5th of August 2006 AIFA resolution of (54).

Regarding albumin (Table 105), the national mean price per gram was 2.87 euros (2.76 in the year 2022). The variability observed among Regions (range: 2.12-3.96 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 in all Regions. In actual 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.

Liguria, the AP of Bolzano, Aosta Valley, E.-Romagna, Marche and Piedmont were the Regions where more than 90% of the commercial demand was dispensed by NHS facilities, and where the use of the pharmacy channel was modest.

In other Regions, such as Friuli V. Giulia, Molise and Umbria, 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 (without Wilfactin) on the market was 17,884,678 euros (0.50 euros per IU), and almost entirely accounted for the distribution through NHS facilities (95%) (Table 106).

The market demand for IVIGs (excluding the specific demand for products containing IVIGs with high titers of IGM - see Table 7) recorded an expenditure equal to 49,464,516 million euros with an increase of +28% compared to 2022. The mean unit price per gram at national level was 60.05 euros (range: 56.82-63.64 euros) (Table 107).

Table 105. 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 2023

Region	Mean price			Demand				Total expenditure			
	NHS facilities	Pharmacies	Total	NHS facilities		Pharmacies		NHS facilities		Pharmacies	
	€/g	€/g	€/g	g	%	g	%	€	%	€	%
Abruzzo	2.23	3.95	2.99	88,200	56%	69,313	44%	196,716	42%	273,684	58%
Aosta Valley	2.62	-	2.62	2,200,00	100%	-	0%	5,772	100%	-	0%
AP Bolzano	2.58	3.97	2.64	5,120	96%	240	4%	13,186	93%	952	7%
AP Trento	2.59	3.89	3.54	3,550	27%	9,460	73%	9,203	20%	36,835	80%
Basilicata	2.24	3.94	3.05	52,600	52%	48,580	48%	117,680	38%	191,366	62%
Friuli V. Giulia	-	3.95	3.95	-	0%	2,830	100%	-	0%	11,190	100%
Liguria	2.45	3.93	2.53	160,225	95%	9,248	5%	392,288	92%	36,384	8%
Umbria	-	3.94	3.94	-	0%	9,205	100%	-	0%	36,261	100%
Veneto	2.61	3.95	3.78	6,950	13%	46,820	87%	18,145	9%	185,074	91%
NAIP	**2.36**	**3.94**	**2.96**	**318,845**	**62%**	**195,695**	**38%**	**752,990**	**49%**	**771,747**	**51%**
Apulia	2.13	3.93	3.42	146,175	28%	367,258	72%	311,817	18%	1,444,949	82%
Calabria	2.52	3.91	3.56	98,525	25%	292,958	75%	248,693	18%	1,146,010	82%
E.-Romagna	2.53	3.90	2.58	154,375	97%	5,550	3%	390,715	95%	21,620	5%
Sicily	2.52	3.93	3.08	356,840	60%	238,713	40%	899,972	49%	937,143	51%
RIPP	**2.45**	**3.92**	**3.25**	**755,915**	**46%**	**904,478**	**54%**	**1,851,196**	**34%**	**3,549,723**	**66%**
Campania	1.89	3.90	2.71	1,808,190	59%	1,257,025	41%	3,415,858	41%	4,905,220	59%
Latium	2.11	3.93	2.95	446,900	54%	380,523	46%	942,864	39%	1,496,424	61%
Marche	2.45	-	2.45	20,795	100%	-	0%	51,027	100%	-	0%
Molise	-	3.96	3.96	-	0%	23,683	100%	-	0%	93,673	100%
Tuscany	1.94	3.90	2.35	13,150	79%	3,468	21%	25,520	65%	13,511	35%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**1.94**	**3.91**	**2.77**	**2,289,035**	**58%**	**1,664,698**	**42%**	**4,435,269**	**41%**	**6,508,828**	**59%**
Lombardy	2.47	3.94	2.96	673,445	67%	336,868	33%	1,665,908	56%	1,326,017	44%
Piedmont	2.11	3.93	2.12	197,625	99%	1,495	1%	417,147	99%	5,875	1%
Sardinia	1.98	3.94	2.48	372,460	74%	128,498	26%	735,949	59%	506,495	41%
LPS	**2.27**	**3.94**	**2.72**	**1,243,530**	**73%**	**466,860**	**27%**	**2,819,003**	**61%**	**1,838,387**	**39%**
ITALY	**2.14**	**3.92**	**2.87**	**4,607,325**	**59%**	**3,231,730**	**41%**	**9,858,458**	**44%**	**12,668,685**	**56%**

Table 106. National and Regional mean price per IU for the purchase of Factor VIII/ von Willebrand Factor in combination by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2023

Region	Mean price *			Demand*				Total expenditure*			
	NHS facilities	Pharmacies	Total	NHS facilities		Pharmacies		NHS facilities		Pharmacies	
	€/IU	€/IU	€/IU	IU	%	IU	%	€	%	€	%
Abruzzo	0.51	-	0.51	986,500	100%	-	0%	507,646	100%	-	0%
Aosta Valley	0.26	-	0.26	20,000	100%	-	0%	5,183	100%	-	0%
AP Bolzano	0.55	-	0.55	3,000	100%	-	0%	1,650	100%	-	0%
AP Trento	0.56	-	0.56	94,000	100%	-	0%	52,734	100%	-	0%
Basilicata	0.48	-	0.48	50,000	100%	-	0%	24,101	100%	-	0%
Friuli V. Giulia	0.55	0.60	0.55	40,000	98%	1,000	2%	22,000	97%	602	3%
Liguria	0.53	-	0.53	143,000	100%	-	0%	75,535	100%	-	0%
Umbria	0.53	-	0.53	329,500	100%	-	0%	173,237	100%	-	0%
Veneto	0.54	-	0.54	1,224,000	100%	-	0%	661,992	100%	-	0%
NAIP	**0.53**	**0.60**	**0.53**	**2,890,000**	**100%**	**1,000**	**0,03%**	**1,524,078**	**100%**	**602**	**0,04%**
Apulia	0.52	-	0.52	5,560,500	100%	-	0%	2,865,200	100%	-	0%
Calabria	0.55	-	0.55	1,125,000	100,0%	-	0%	617,972	100%	-	0%
E.-Romagna	0.55	-	0.55	3,353,750	100%	-	0%	1,842,664	100%	-	0%
Sicily	0.53	0.54	0.53	1,760,000	84%	330,000	16%	933,779	84%	176,598	16%
RIPP	**0.53**	**0.54**	**0.53**	**11,799,250**	**97%**	**330,000**	**3%**	**6,259,615**	**97%**	**176,598**	**3%**
Campania	0.49	-	0.49	3,654,000	100%	-	0%	1,775,641	100%	-	0%
Latium	0.52	0.60	0.52	5,506,000	99%	63,000	1%	2,874,726	99%	38,058	1%
Marche	0.54	-	0.54	378,000	100%	-	0%	205,361	100%	-	0%
Molise	0.54	-	0.54	324,000	100%	-	0%	175,648	100%	-	0%
Tuscany	0.45	-	0.45	2,592,000	100%	-	0%	1,164,481	100%	-	0%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**0.50**	**0.60**	**0.50**	**12,454,000**	**99%**	**63,000**	**1%**	**6,195,858**	**99%**	**38,058**	**1%**
Lombardy	0.55	0.60	0.56	2,305,500	69%	1,047,000	31%	1,260,229	67%	629,819	33%
Piedmont	0.32	-	0.32	2,782,000	100%	-	0%	897,837	100%	-	0%
Sardinia	0.43	-	0.43	2,089,000	100%	-	0%	901,985	100%	-	0%
LPS	**0.43**	**0.60**	**0.45**	**7,176,500**	**87%**	**1,047,000**	**13%**	**3,060,050**	**83%**	**629,819**	**17%**
ITALY	**0.50**	**0.59**	**0.50**	**34,319,750**	**96%**	**1,441,000**	**4%**	**17,039,601**	**95%**	**845,077**	**5%**

*The value does not include Wilfactin (vWF)

Table 107. National and Regional mean price per gram for the purchase of intravenous immunoglobulins by distribution channel

Region	Mean price per gram (€) NHS facilities* (€/g)	Total demand NHS facilities* (g)	Total expenditure NHS facilities* (€)
Abruzzo	61.54	3,080	189,530
Aosta Valley	63.02	173	10,890
AP Bolzano	60.78	3,882	235,950
AP Trento	61.41	7,250	445,225
Basilicata	60.21	1,063	64,005
Friuli V. Giulia	63.43	1,200	76,120
Liguria	62.15	12,000	745,821
Umbria	57.29	1,615	92,516
Veneto	59.52	7,835	466,318
NAIP	**61.06**	**38,098**	**2,326,374**
Apulia	59.61	88,168	5,255,687
Calabria	63.02	586	36,905
E.-Romagna	56.82	32,371	1,839,238
Sicily	60.10	1,700	102,178
RIPP	**58.90**	**122,825**	**7,234,009**
Campania	61.28	148,321	9,089,724
Latium	58.22	94,920	5,526,414
Marche	63.64	35,420	2,254,222
Molise	-	-	-
Tuscany	60.83	19,604	1,192,510
Min. of Def.	-	-	-
PlaNet	**60.56**	**298,264**	**18,062,869**
Lombardy	59.75	257,083	15,360,169
Piedmont	60.16	52,680	3,169,303
Sardinia	60.45	54,790	3,311,792
LPS	**59.91**	**364,553**	**21,841,264**
ITALY	**60.05**	**823,740**	**49,464,516**

* The value does not include *Pentaglobin*™and imported products.,

FINAL CONSIDERATIONS

The national demand for albumin, although slightly lower than that recorded in 2022, was still quite high at about 586 grams per 1,000 population.

An increased demand was observed in the AP of Trento (+16%), in Aosta Valley (+15%), Sardinia (+13%) and E.-Romagna (+11%). The Regions with the highest standardised demand per 1,000 population were Sardinia, E.-Romagna and Campania, with standardised volumes of 939, 811 and 769 grams, respectively.

About 9% of the national demand was distributed through public pharmacies, reaching a quantity of approximately 3,232 kilograms, The pharmacy channel was particularly used in Calabria and Campania where it accounts respectively for 30% and 29% of the regional demands.

In the two-year period 2022-2023 the total demand of IG registered a +3.6%; in particular, there was +3% in demand for SC/IM-IG and +4% in demand for IVIG.

There were noticeable differences from one region to another, The three Regions with the highest standardised demand per 1,000 population were E.-Romagna, Marche and Aosta Valley, respectively with about 161 grams/1000 pop. for the first, and 154 grams/1000 pop. for the other two Regions..

The demand for AT recorded a sharp decrease (-12%) in 2023, as well as the demand for 3F-PCCs (-8.5%); on the contrary, the demand for 4F-PCCs is confirmed to be continuously rising (+25%).

As regards the haemophilia A treatment, the demand for pdFVIII (alone and in combination with vWF) shows a slight decrease (-5%), as well as for demand for FVIIIr (-3.4%), despite increased use of medicinal products with extended half-life FVIII (+12%).

The consumption of Emicizumab also increased significantly (+20%) as well as for the activated prothrombin complex (+35%).

Concerning the haemophilia B treatment, the clinical use of recombinant FIX (+7% compared to 2022), especially that with extended half-life (+19%), progressively replaced the demand for pdFIX (-46% compared to the previous year).

The total volume of plasma sent by Regions for fractionation increased by 4.4% compared to the previous year. There were still great differences in the volumes from one Region to another, ranging from 5.6 kilograms per 1,000 population sent by Campania to 24.2 sent by Friuli V. Giulia, with an average volume of 14.9 kilograms per 1,000 population.

The level of albumin self-sufficiency fell to 73% of the NHS demand (72% in 2022). As regards IGs, on the other hand, self-sufficiency in human immunoglobulin for intravenous and subcutaneous/intramuscolar use (excluding high titre IG) achieved at national level was 62% of the total demand, while self-sufficiency in IVIG reached 76% (excluding high titre IG); self-sufficiency for SC / IM IG was 17%.

The self-sufficiency of AT was equal to 77% of the NHS demand, higher than in the 2022 when it was 75%.

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 101.1 million euros, in line with the costs estimated by the contracts in force in 2023, while approximately 3.2 million

euros had to be taken into account for the treatment of plasma virus-inactivated by solvent / detergent, for a total of approximately 104.3 million euros.

The estimated expenditure incurred by the NHS in 2023 for the market supply of the PDMPs included in the toll fractionation agreements between Regions and companies, for the quantity not produced under the agreements, was approximately 230.9 million euros. An additional 91.6 million euros were used for the purchase of all the other PDMPs. The cost of purchasing Emicizumab was 112.4 million euros. The expenditure associated to recombinant products was about 394.4 million euros. The total expenditure for medicinal products described in this Report was around 3.3% of the total NHS pharmaceutical expenditure recorded in 2023 (55).

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