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Demand for plasma-derived medicinal products in Italy. 2022

F. Candura, M.S. Massari, S. Profili, L. De Fulvio,
C. Chelucci, C. Brutti, C. Biffoli, V. De Angelis



EPIDEMIOLOGIA
E SANITÀ PUBBLICA

ISTITUTO SUPERIORE DI SANITÀ

**Demand for plasma-derived
medicinal products in Italy.
2022**

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2023, vii, 145 p. Rapporti ISTISAN 23/31/ 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 is the 2022 update published in the report *Rapporti ISTISAN 23/6* and 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

Istituto Superiore di Sanità

Analisi della domanda di medicinali plasmaderivati in Italia. 2022.

Fabio Candura, Maria Simona Massari, Samantha Profili, Lucia De Fulvio, Cristiana Chelucci, Chiara Brutti, Claudia Biffoli, Vincenzo De Angelis
2023, vii, 145 p. Rapporti ISTISAN 23/31 EN (in inglese)

Al fine di adempiere ai compiti ad esso assegnati dalla normativa vigente in materia di coordinamento e supporto tecnico alla programmazione dell'autosufficienza regionale e nazionale di emocomponenti e medicinali plasmaderivati, il Centro Nazionale Sangue ha effettuato, in collaborazione con l'Ufficio IV della Direzione Generale del Sistema Informativo e Statistico Sanitario del Ministero della Salute, l'analisi della domanda dei prodotti medicinali plasmaderivati e delle alternative terapeutiche di natura ricombinante, le valutazioni dei livelli di autosufficienza regionale e nazionale e la stima della spesa farmaceutica a carico del Servizio Sanitario Nazionale. Il confronto delle diverse fonti dati disponibili ha consentito l'elaborazione del presente documento che riporta l'aggiornamento relativo all'anno 2022 dei dati sull'argomento pubblicati nel *Rapporto ISTISAN 23/6* e che si configura come uno strumento fondamentale per la programmazione dell'autosufficienza nazionale.

Parole chiave: Medicinali plasmaderivati; Domanda; Autosufficienza; Spesa

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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
BZ	Bolzano
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	<i>Istituto Italiano di STATistica</i> (Italian National Statistics Institute)
IU/s	International Unit/s
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	<i>Nuovo Accordo Interregionale per la Plasmaderivazione</i> (New Interregional Agreement for plasma-derived medicinal products)
NHS	National Health Service
NSIS	<i>Nuovo Sistema Informativo Sanitario</i> (New Health Information System)
PDMP/s	Plasma-Derived Medicinal Product/s
rFVIIa	Recombinant activated Factor VII
rFVIII	Recombinant Factor VIII
rFIX	Recombinant Factor IX
RTI	<i>Raggruppamento Temporaneo d'Impresa</i> (Temporary Business Grouping)
S/D	Solvent / Detergent (plasma)
SC/IM	SubCutaneous/IntraMuscular
ST/s	Transfusion Service/s
UdR	Collection Units run by Donor Associations
VAT	Value Added Tax
vWF	von Willebrand Factor
WHO	World Health Organisation

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 National Institute of Health in Rome. In compliance with the current laws, it supervises and coordinates the technical and scientific support to all aspects concerning the production of Plasma and Plasma-Derived Medicinal Products (PDMPs).

CNS primarily 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 2022, 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 2021, 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 2022, issued by the DM of 26 May 2022.

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 together with FVIII, they too have been the subject of this Report.

More recently, 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 2022 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 throughout the entire supply chain process (Figure 1).

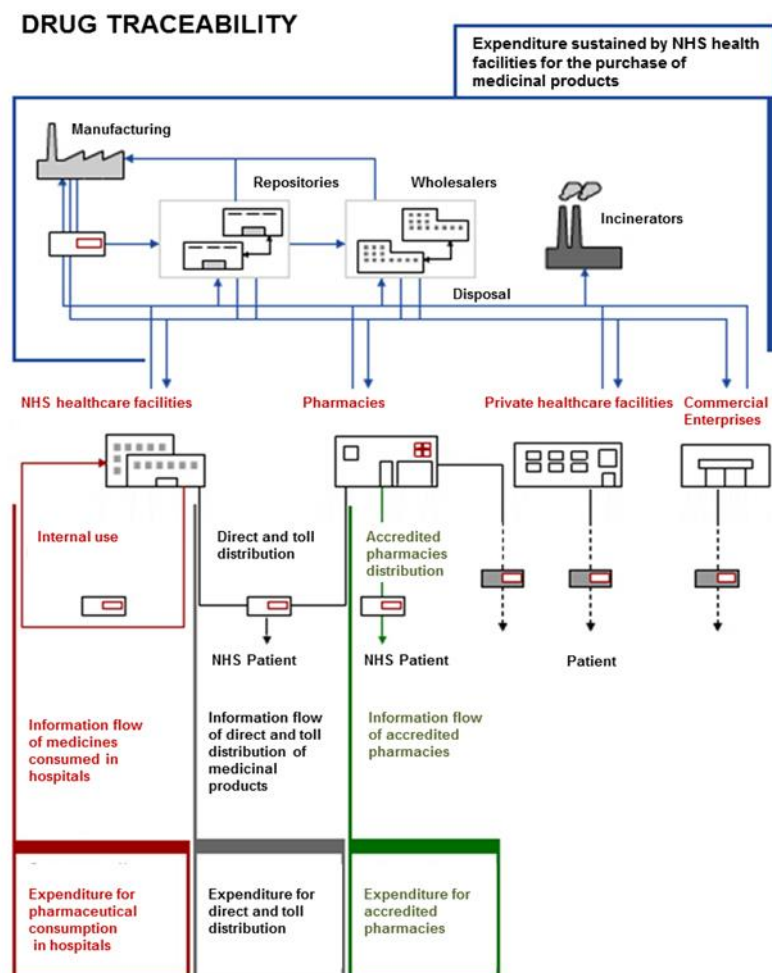


Figure 1. The drug traceability system in Italy
(adapted by the CNS on data from www.salute.gov.it)

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 (326/2003 Law) (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).

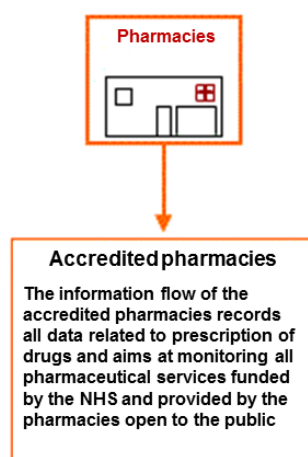


Figure 2. Scope of the information flow of accredited pharmacies (adapted by the CNS on data from www.salute.gov.it)

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, official 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.

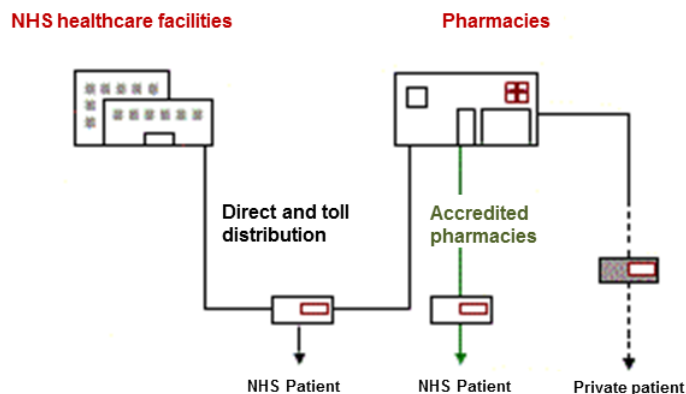


Figure 3. Medicinal products information flow
(adapted by theCNS on data from www.salute.gov.it)

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 20th of October 2015 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.

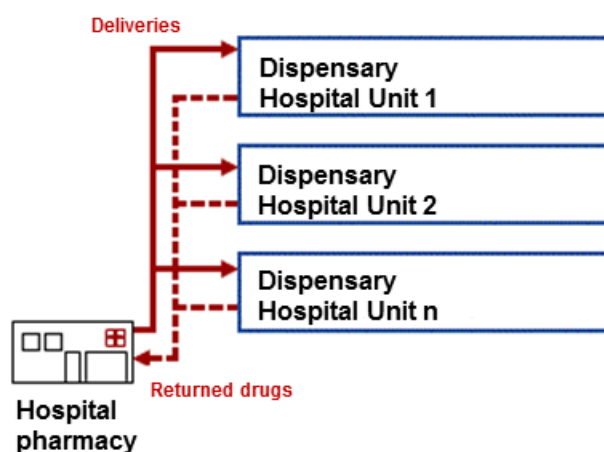


Figure 4. Information flow of medicines consumed in hospitals (adapted by the CNS on data from www.salute.gov.it)

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, 2021-2022
(adapted by the CNS on data from ISTAT, 07/08/2023)

Region	2021	2022
Abruzzo	1,281,012	1,273,660
Aosta Valley	124,089	123,337
AP Bolzano	534,912	535,774
AP Trento	542,166	542,158
Apulia	3,933,777	3,912,166
Basilicata	545,130	539,999
Calabria	1,860,601	1,844,586
Campania	5,624,260	5,590,681
Emilia-Romagna	4,438,937	4,431,816
Friuli V. Giulia	1,201,510	1,197,295
Latium	5,730,399	5,715,190
Liguria	1,518,495	1,507,438
Lombardy	9,981,554	9,965,046
Marche	1,498,236	1,489,789
Molise	294,294	290,769
Piedmont	4,274,945	4,252,279
Sardinia	1,590,044	1,579,181
Sicily	4,833,705	4,801,468
Tuscany	3,692,865	3,676,285
Umbria	865,452	859,572
Veneto	4,869,830	4,854,633
Italy	59,236,213	58,983,122

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

Self-sufficiency and pharmaceutical expenditure

For every 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 2021 to June 2022. By contrast, by effective supply (or toll fractionation) is meant the quantity of PDMPs *de facto* distributed by companies to each Region during the 2022 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 31/12/2022, 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, 31/12/2022)

AIC code	Brand name	g	Manufacturer	NHS class
049507041	ALBUMINA GRIFOLS*1FL 10 mL 200 g/L	2	ISTITUTO GRIFOLS S.A	C (nn)
034611032	ALBUMINA GRIFOLS*1FL 100 mL 5%	5	GRIFOLS ITALIA SpA	C
036504025	ALBUREX* INFUS 1FL 100 mL 5%	5	CSL BEHRING GmbH	C
039187012	ALBUNORM*1FL 100 mL 5% 50g/L	5	OCTAPHARMA Italy SpA	C
049507015	ALBUMINA GRIFOLS*1FL 100 mL 50 g/L	5	ISTITUTO GRIFOLS S.A	C (nn)
010317028	ALBUMINA UM.IMMUNO*50 mL 20%+S.	10	BAXTER SpA	A
011544020	ALBUMINA BEHRING*IV 50 mL20%	10	CSL BEHRING SpA	A
021111024	UMANALBUMIN*INF FL 50 mL 200g/L	10	KEDRION SpA	A
022515163	ALBITAL*1FL 50 mL SOLUZ 20%+SET	10	KEDRION SpA	A
028989046	PLASBUMIN*EV 1FL 50 mL 200g/L	10	GRIFOLS ITALIA SpA	A
029251030	ALBUTEIN*IV FL 50 mL 200g/L	10	GRIFOLS ITALIA SpA	A
034611018	ALBUMINA GRIFOLS*1FL 50 mL 20%	10	GRIFOLS ITALIA SpA	A
036176016	ALBUMINA LFB*FL 50 mL 200mg/mL	10	LBF	A
036504052	ALBUREX*INFUS 1FL 50 mL 20%	10	CSL BEHRING GmbH	A
037566054	ALBUMINA BAXTER*FL 50 mL 200g/L	10	BAXALTA Italy Srl	A
038109056	FLEXBUMIN*SAC INF 50 mL 200g/L	10	BAXALTA Italy Srl	A
038747034	OCTALBIN*IV 50 mL 200mg/mL	10	OCTAPHARMA Italy SpA	A
039073022	ALBIOMIN*FL 50 mL 200g/L 20%	10	BIOTEST ITALIA Srl	A
039187063	ALBUNORM*1FL 50 mL 20% 200g/L	10	OCTAPHARMA Italy SpA	A
042029013	KALBI*FL 50 mL 200g/L	10	KEDRION SpA	A
043358011	ALBUMEON*FL 50 mL 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 50 mL 200 g/L	10	ISTITUTO GRIFOLS S.A	C (nn)
010317042	ALBUMINA UM.IMMUNO*50 mL 25%+S.	12.5	BAXTER SpA	A
021111051	UMANALBUMIN*FL 250 mL 5%	12.5	KEDRION SpA	C
021111087	UMANALBUMIN*INF FL 50 mL 250g/L	12.5	KEDRION SpA	A
022515136	ALBITAL*1FL 50 mL 25g/100 mL+SET	12.5	KEDRION SpA	A
028989097	PLASBUMIN*EV 1FL 50 mL 250g/L	12.5	GRIFOLS ITALIA SpA	A
029251016	ALBUTEIN*IV FL 250 mL 50g/L	12.5	GRIFOLS ITALIA SpA	C
029251042	ALBUTEIN*IV FL 50 mL 25%	12.5	GRIFOLS ITALIA SpA	A
034611044	ALBUMINA GRIFOLS*1FL 250 mL 5%	12.5	GRIFOLS ITALIA SpA	C
034611069	ALBUMINA GRIFOLS*50 mL 25g/100 mL	12.5	GRIFOLS ITALIA SpA	A
036504037	ALBUREX* INFUS 1 FL 250 mL 5%	12.5	CSL BEHRING GmbH	C
036504076	ALBUREX*INFUS 1FL 50 mL 25%	12.5	CSL BEHRING GmbH	A
037566015	ALBUMINA BAXTER*1FL 250 mL 50g	12.5	BAXALTA Italy Srl	C
037566092	ALBUMINA BAXTER*FL 50 mL 250g/L	12.5	BAXALTA Italy Srl	A
038109070	FLEXBUMIN*SAC INF 50 mL 250g/L	12.5	BAXALTA Italy Srl	A
039073010	ALBIOMIN*INF 250 mL 50g/L 5%	12.5	BIOTEST ITALIA Srl	C
039187036	ALBUNORM*1FL 250 mL 5% 50g/L	12.5	OCTAPHARMA Italy SpA	C
039187101	ALBUNORM*1FL 50 mL 25% 250g/L	12.5	OCTAPHARMA Italy SpA	A
042029025	KALBI*FL 50 mL 250g/L+SET	12.5	KEDRION SpA	A

AIC code	Brand name	g	Manufacturer	NHS class
049507027	ALBUMINA GRIFOLS*1FL 250 mL 50 g/L	12,5	ISTITUTO GRIFOLS S.A	C (nn)
021111101	UMANALBUMIN*EV FL 100 mL 200g/L	20	KEDRION SpA	A
028989059	PLASBUMIN*EV 1FL 100 mL 200g/L	20	GRIFOLS ITALIA SpA	A
034611020	ALBUMINA GRIFOLS*1FL 100 mL 20%	20	GRIFOLS ITALIA SpA	A
036176028	ALBUMINA LFB* FL 100 mL 200 mg/mL	20	LFB	C
036504064	ALBUREX*INFUS 1FL 100 mL 20%	20	CSL BEHRING GmbH	A
037566078	ALBUMINA BAXTER*1FL 100 mL 200g	20	BAXALTA Italy Srl	A
038109068	FLEXBUMIN*SAC INF 100 mL 200g/L	20	BAXALTA Italy Srl	A
038747046	OCTALBIN*IV 100 mL 200mg/mL	20	OCTAPHARMA Italy SpA	A
039073034	ALBIOMIN*INF 100 mL 200g/L 20%	20	BIOTEST ITALIA Srl	A
039187087	ALBUNORM*1FL 100 mL 20% 200g/L	20	OCTAPHARMA Italy SpA	A
043358023	ALBUMEON*FL 100 mL 200g/L 20%	20	CSL BEHRING SpA	A
044549020	PROBUMIN*FL 100 mL 200 g/L	20	GRIFOLS ITALIA SpA	C (nn)
049507066	ALBUMINA GRIFOLS*1FL100 mL 200g/L	20	ISTITUTO GRIFOLS S.A	C (nn)
029251028	ALBUTEIN*IV FL 500 mL 50g/L	25	GRIFOLS ITALIA SpA	C
034611057	ALBUMINA GRIFOLS*1FL 500 mL 5%	25	GRIFOLS ITALIA SpA	C
034611071	ALBUMINA GRIFOLS25g/100 mL	25	GRIFOLS ITALIA SpA	H
036504049	ALBUREX* INFUS 1FL 500 mL 5%	25	CSL BEHRING GmbH	C
036504088	ALBUREX* INFUS 1FL 100 mL 25%	25	CSL BEHRING GmbH	H
037566039	ALBUMINA BAXTER*1FL 500 mL 50 g/L	25	BAXALTA Italy Srl	C
037566116	ALBUMINA BAXTER*1FL100 mL 250g/L	25	BAXALTA Italy Srl	H
038109082	FLEXBUMIN*1SACCA 100 mL 250g/L	25	BAXALTA Italy Srl	H
039187051	ALBUNORM* 1 FL 500 mL 5%, 50 g/L	25	OCTAPHARMA Italy SpA	C
039187113	ALBUNORM* 1 FL 100 mL 25%, 250 g/L	25	OCTAPHARMA Italy SpA	H
049507039	ALBUMINA GRIFOLS*1FL 500 mL 50 g/L	25	ISTITUTO GRIFOLS S.A	C (nn)
039187024	ALBUNORM*10FL 100 mL 5% 50g/L	50	OCTAPHARMA Italy SpA	C
036176030	ALBUMINA 200 mg/mL INF 6*50 mL	60	LFB	C
039187075	ALBUNORM* 10FL 50 mL20%, 200 g/L	100	OCTAPHARMA Italy SpA	H
036176042	ALBUMINA 200 mg/mL INF 6*100 mL	120	LFB	C
039187048	ALBUNORM* 10FL 250 mL 5%, 50 g/L	125	OCTAPHARMA Italy SpA	C
039187099	ALBUNORM*10FL 100 mL 20%, 200 g/L	200	OCTAPHARMA Italy SpA	H
038109017	FLEXBUMIN*24SACCHE 50 mL 200g/L	240	BAXALTA Italy Srl	H
038109031	FLEXBUMIN*12SACCHE 100 mL200g/L	240	BAXALTA Italy Srl	H
037566041	ALBUMINA BAXTER*10FL 500 mL 50 g/L	250	BAXALTA Italy Srl	C
037566027	ALBUMINA BAXTER* 24FL 250 mL 50 g/L	300	BAXALTA Italy Srl	C
038109029	FLEXBUMIN*12SACCHE 100 mL 250 g/L	300	BAXALTA Italy Srl	H
038109043	FLEXBUMIN*24SACCHE50 mL 250g/L	300	BAXALTA Italy Srl	H
037566066	ALBUMINA BAXTER*70FL 50 mL 200 g/L	700	BAXALTA Italy Srl	H
037566104	ALBUMINA BAXTER*70FL 50 mL 250 g/L	875	BAXALTA Italy Srl	H
037566080	ALBUMINA BAXTER*56FL 100 mL 200 g/L	1120	BAXALTA Italy Srl	H
037566128	ALBUMINA BAXTER*56FL 100 mL 250 g/L	1400	BAXALTA Italy Srl	H

Quantification and characterisation of the demand

Table 6 shows the total demand (expressed in grams) and the total standardised demand (expressed in grams per 1,000 population) of albumin¹ for the two-year period 2021-2022 with the variations in percentage, both at national and regional levels.

In 2022, the national demand for this principle was about 35,847 kilograms (Table 6), equal to 608 grams per 1,000 population, with a decrease of 7% from the previous year. The three

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

Regions with the highest standardised demand were Abruzzo, Basilicata and Sardinia, with values equal to 885, 834 and 833 grams per 1,000 population, respectively. The Regions with the lowest demand were the AP of Bolzano, Tuscany and Piedmont, where it is between 401 and 405 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,033,150	806.5	1,127,258	885.1	9.7
Aosta Valley	54,360	438.1	64,300	521.3	19.0
AP Bolzano	198,745	371.5	214,828	401.0	7.9
AP Trento	242,050	446.4	229,050	422.5	-5.4
Apulia	2,605,545	662.4	2,121,725	542.3	-18.1
Basilicata	370,983	680.5	450,118	833.6	22.5
Calabria	1,135,108	610.1	1,062,360	575.9	-5.6
Campania	4,626,590	822.6	4,159,853	744.1	-9.5
E.-Romagna	2,967,408	668.5	3,245,633	732.3	9.6
Friuli V. Giulia	584,430	486.4	602,840	503.5	3.5
Latium	3,396,963	592.8	2,681,010	469.1	-20.9
Liguria	1,116,945	735.6	983,718	652.6	-11.3
Lombardy	6,728,863	674.1	6,743,008	676.7	0.4
Marche	929,415	620.3	932,330	625.8	0.9
Molise	166,450	565.6	152,378	524.1	-7.3
Piedmont	1,951,825	456.6	1,723,830	405.4	-11.2
Sardinia	1,389,770	874.0	1,316,068	833.4	-4.7
Sicily	3,938,353	814.8	3,295,173	686.3	-15.8
Tuscany	1,739,573	471.1	1,487,703	404.7	-14.1
Umbria	589,640	681.3	587,700	683.7	0.4
Veneto	2,767,985	568.4	2,665,713	549.1	-3.4
Italy	38,534,148	650.5	35,846,590	607.7	-6.6

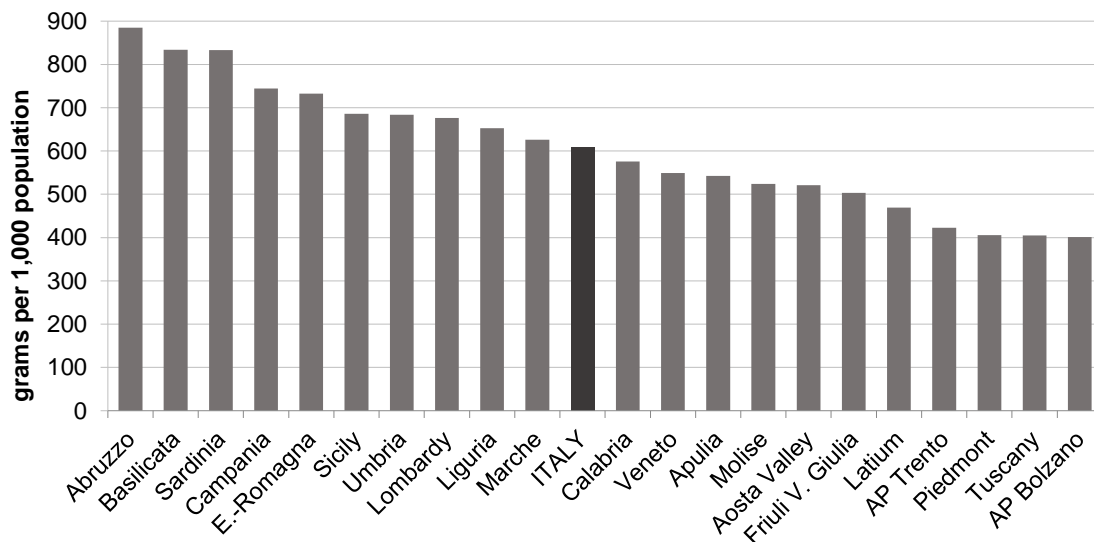


Figure 5. Total and regional demand (public and private) for albumin, expressed in grams per 1,000 population, 2022 (adapted by the CNS on data from the Traceability information flow)

In this two-year period, the total standardised demand for albumin showed a moderate decrease compared to the previous years (-7% compared to 2021) (17). The regions where there was a lesser use most evidently are Latium (-21%) and Apulia (-18%). While Basilicata (+23%) and Aosta Valley (+19%) are the Regions where demand shows the greatest growth.

Figure 6 highlights the eight Regions with a higher demand compared to national demand, with a value higher than 20% for five of them. Figure 7 shows the standardised regional demand for albumin recorded in 2022 per distribution system (public pharmacies compared to other facilities), as shown by the drug Traceability system (18).

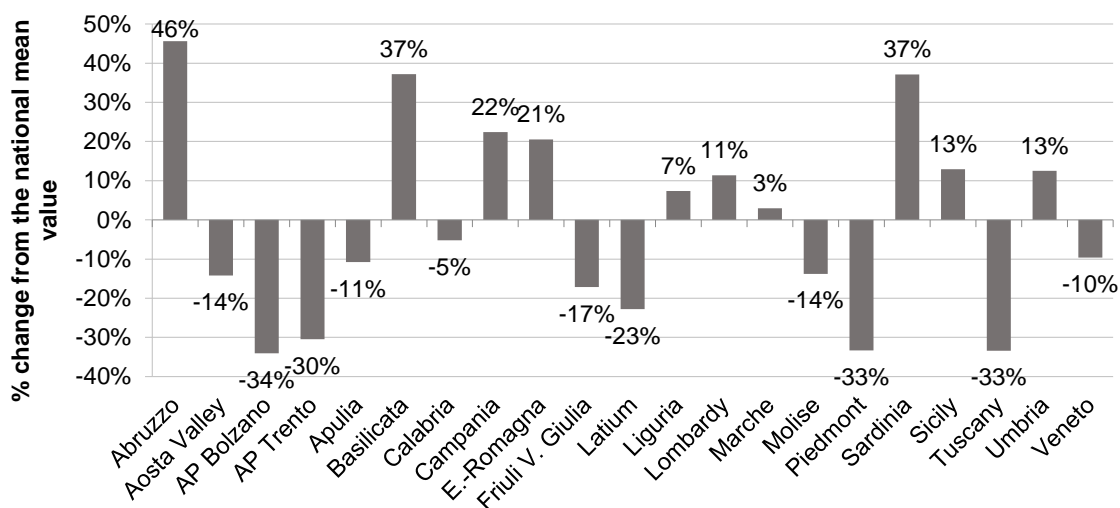


Figure 6. Percentage change from the national mean value of standardised regional demand for human albumin in 2022 (adapted by the CNS on data from the Traceability information flow)

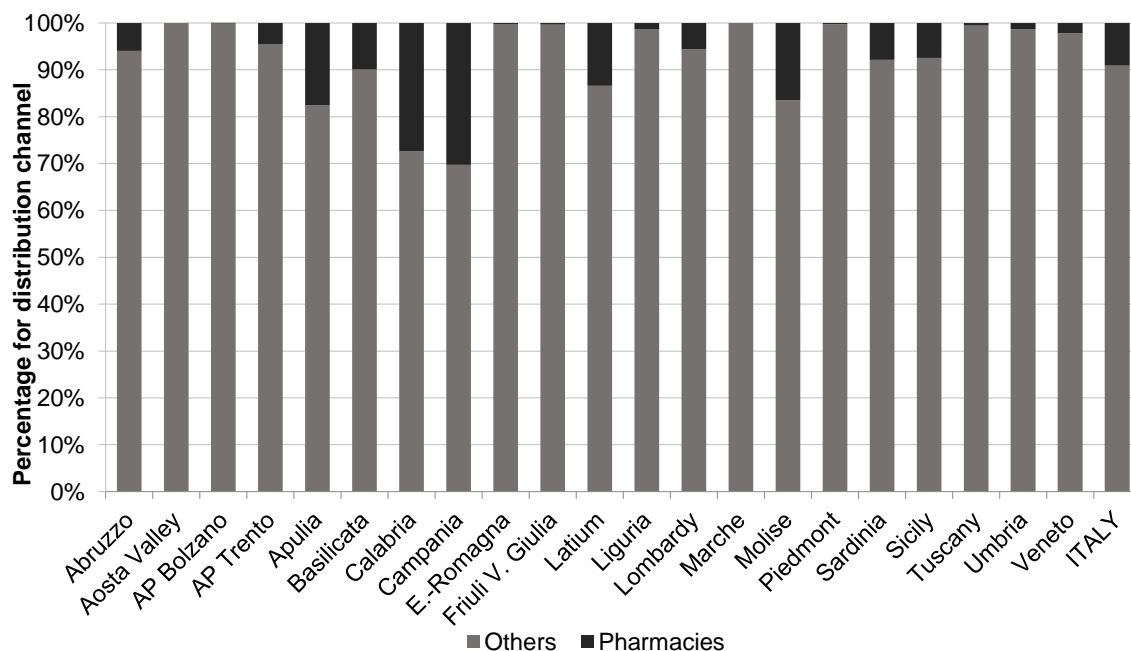


Figure 7. Standardised regional demand for albumin recorded per distribution channel, 2022 (adapted by the CNS on data from the Traceability information flow)

In 2022, about 9% of the national demand – approximately 3,257 kilograms – was distributed through public pharmacies. The distribution channel of pharmacies was mostly used in Campania and Calabria, where they accounted for 30% and 27% respectively of the regional demand; still used to a lesser extent in Latium, Molise, Basilicata and Apulia (with percentages of between 10 and 18% 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, 31/12/2022)

AIC code	Brand name	g	Manufacturer	NHS class
Normal human immunoglobulin for subcutaneous/intramuscular use				
036800011	SUBCUVIA*SC IM FL 5 mL 160mg/mL	0.8	BAXALTA Italy Srl	H
036800047	SUBCUVIA*SC IM FL10 mL 160mg/mL	1.6	BAXALTA Italy Srl	H
036800023	SUBCUVIA*SC IM 20FL5 mL 160mg/mL	16	BAXALTA Italy Srl	H
036800035	SUBCUVIA*SC IM 20FL10 mL 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 165 mg/mL	0.99	OCTAPHARMA Italy SpA	H
041157013	HIZENTRA*SC 1FL 5 mL 200mg/mL	1	CSL BEHRING SpA	H
041157153	HIZENTRA*SC 1SIR 5 mL 200mg/mL	1	CSL BEHRING SpA	C(nn)
044244010	CUVITRU*SC 1FL 5 mL 200mg/mL	1	BAXALTA Italy Srl	H
049488012	XENBIFY*1FL 5 mL 200 mg/mL	1	ISTITUTO GRIFOLS S.A	C(nn)
043396011	NAXIGLO*SC FL 10 mL 160mg/mL	1.6	KEDRION SpA	H
043398015	KEYCUTE*SC FL 10 mL 160mg/mL	1.6	KEDRION SpA	H
040652012	OCTANORM*1FL10 mL 165 mg/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 12 mL 165 mg/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 10 mL 200mg/mL	2	CSL BEHRING SpA	H
041157177	HIZENTRA*SC 1SIR 10 mL 200mg/mL	2	CSL BEHRING SpA	C(nn)
044244022	CUVITRU*SC 1FL 10 mL 200mg/mL	2	BAXALTA Italy Srl	H
049488024	XENBIFY*1FL 10 mL 200 mg/mL	2	ISTITUTO GRIFOLS S.A	C(nn)
042804017	HYQVIA*SC 1FL 25 mL+1FL 1,25 mL	2.5	BAXALTA Italy Srl	H
041157076	HIZENTRA*1FL 15 mL 200 mg/mL	3	CSL BEHRING SpA	H
040652048	OCTANORM*1FL 20 mL 165 mg/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 165 mg/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 20 mL 200mg/mL	4	CSL BEHRING SpA	H
041157191	HIZENTRA*SC 1FL 20 mL 200mg/mL	4	CSL BEHRING SpA	C(nn)

AIC code	Brand name	g	Manufacturer	NHS class
043396023	NAXIGLO*SC FL 25 mL 160mg/mL	4	KEDRION SpA	H
043398027	KEYCUTE*SC FL 25 mL 160mg/mL	4	KEDRION SpA	H
044244034	CUVITRU*SC 1FL 20 mL 200mg/mL	4	BAXALTA Italy Srl	H
049488036	XENBIFY*1FL 20 mL 200 mg/mL	4	ISTITUTO GRIFOLS S.A	C(nn)
042804029	HYQVIA*SC 1FL 50 mL+1FL 2,5 mL	5	BAXALTA Italy Srl	H
040652164	OCTANORM*FL 48mL 165 mg/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 40 mL 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 5 mL 200mg/mL	10	CSL BEHRING SpA	H
041157138	HIZENTRA*SC 1FL 50 mL 200mg/mL	10	CSL BEHRING SpA	C
041157165	HIZENTRA*SC 10SIR 5 mL 200mg/mL	10	CSL BEHRING SpA	C(nn)
042804031	HYQVIA*SC 1FL 100 mL+1FL 5 mL	10	BAXALTA Italy Srl	H
044244059	CUVITRU*SC 1 FL 50 mL 200 mg/mL	10	BAXALTA INN. GMBH	C(nn)
044244061	CUVITRU*SC 10FL 5 mL 200 mg/mL	10	BAXALTA INN. GMBH	C(nn)
049488048	XENBIFY*1FL 50 mL 200 MG/ML	10	ISTITUTO GRIFOLS S.A	C(nn)
040652024	OCTANORM*10FL 10 mL 165 mg/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 165 mg/mL	19.8	OCTAPHARMA Italy SpA	H
040652113	OCTANORM*10FL 12 mL 165 mg/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 5 mL 200mg/mL	20	CSL BEHRING SpA	H
041157052	HIZENTRA*10FL 10 mL 200mg/mL	20	CSL BEHRING SpA	H
041157189	HIZENTRA*SC 10SIR 10 mL 200mg/mL	20	CSL BEHRING SpA	C(nn)
042804043	HYQVIA*SC 1FL 200 mL+1FL 10 mL	20	BAXALTA Italy Srl	H
044244073	CUVITRU*SC 20FL 5 mL 200 mg/mL	20	BAXALTA INN. GMBH	C(nn)
044244085	CUVITRU*SC 10FL 10 mL 200 mg/mL	20	BAXALTA INN. GMBH	C(nn)
041157088	HIZENTRA*10FL 15 mL 200mg/mL	30	CSL BEHRING SpA	H
042804056	HYQVIA*SC 1FL 300 mL+1FL 15 mL	30	BAXALTA Italy Srl	H
040652036	OCTANORM*20FL 10 mL 165 mg/mL	33	OCTAPHARMA Italy SpA	H
040652051	OCTANORM*10FL 20 mL 165 mg/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 12 mL 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 10 mL 200mg/mL	40	CSL BEHRING SpA	H
041157114	HIZENTRA*10FL 20 mL 200mg/mL	40	CSL BEHRING SpA	H
041157203	HIZENTRA*10FL 20 mL 200mg/mL	40	CSL BEHRING SpA	C(nn)
044244109	CUVITRU*SC 10FL 20 mL 200 mg/mL	40	BAXALTA INN. GMBH	C(nn)
044244123	CUVITRU*SC 5FL 40 mL 200 mg/mL	40	BAXALTA INN. GMBH	C(nn)
044244147	CUVITRU*SC 20FL 10 mL 200 mg/mL	40	BAXALTA GMBH	C(nn)
041157090	HIZENTRA*20FL 15 mL 200mg/mL	60	CSL BEHRING SpA	H
044244097	CUVITRU*SC 30FL 10 mL 200 mg/mL	60	BAXALTA INN. GMBH	C(nn)
040652063	OCTANORM*20FL 20 mL 165 mg/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 165 mg/mL	79.2	OCTAPHARMA Italy SpA	H
040652176	OCTANORM*10FL 48mL 165 mg/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 20 mL 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 50 mL 200mg/mL	100	CSL BEHRING SpA	H
044244111	CUVITRU*SC 30FL 20 mL 200 mg/mL	120	BAXALTA INN. GMBH	C(nn)

AIC code	Brand name	g	Manufacturer	NHS class
040652188	OCTANORM* 20FL 48mL 165 mg/mL	158.4	OCTAPHARMA Italy SpA	H
045996182	CUTAQUIG*SC 20 FL 48 mL 165 mg/mL	158.4	OCTAPHARMA Italy SpA	C
044244135	CUVITRU*SC 20FL 40 mL 200 mg/mL	160	BAXALTA INN. GMBH	C(nn)
Normal human immunoglobulin for intravenous use				
029021019*	PENTAGLOBIN*EV FL 50mg/mL 10 mL	0.5	BIOTEST ITALIA Srl	C
029249075	PLITAGAMMA *INF 1 FL 10 mL 50mg/mL	0.5	ISTITUTO GRIFOLS SA	H
040267015	FLEBOGAMMA*INF 1FL 10 mL 50 mg/mL	0.5	GRIFOLS ITALIA SpA	H
025266141	IGVENA*EV 1FL 20 mL 50g/L	1	KEDRION SpA	H
035143054	OCTAGAM*IV 1FL 20 mL 50mg/mL	1	OCTAPHARMA Italy SpA	H
037107012	KIOVIG*EV FL 10 mL 100mg/mL	1	BAXTER SpA	H
037240052	INTRATECT*INF FL 50g/L 20 mL	1	BIOTEST ITALIA Srl	H
037240090	INTRATECT*INF FL 100g/L 10 mL	1	BIOTEST ITALIA Srl	H
037254012	VENITAL*EV FL 20 mL 50g/L	1	KEDRION SpA	H
044187019	GLOBIGA*INF 1FL 1g 100mg/mL	1	OCTAPHARMA Italy SpA	H
045410014	GAMUNEX *INF 1FL 10 mL 100mg/mL	1	Grifols Deutschland GmbH	H
037240126	INTRATECT*INF FL100g/L 200 mL	2	BIOTEST ITALIA Srl	H
039457015	GAMTEN*INF 1FL 20 mL 100mg/mL	2	OCTAPHARMA Italy SpA	H
043736014	IQYMUNE*FL INF 20 mL 100mg/mL	2	LFB	C(nn)
025266154	IGVENA*EV 1FL 50 mL 50g/L+SET	2.5	KEDRION SpA	H
029021033*	PENTAGLOBIN*EV 1FL 50mg/mL50 mL	2.5	BIOTEST ITALIA Srl	C
029249048	PLITAGAMMA*50 mL(2,5g)5%+SET	2.5	GRIFOLS ITALIA SpA	H
035143015	OCTAGAM*IV FL 50 mL 5%	2.5	OCTAPHARMA Italy SpA	H
037107024	KIOVIG*EV FL 25 mL 100mg/mL	2.5	BAXTER SpA	H
037240064	INTRATECT*INF FL 50g/L 50 mL	2.5	BIOTEST ITALIA Srl	H
037240138	INTRATECT*INF FL100 g/L 25 mL	2.5	BIOTEST ITALIA Srl	H
037254024	VENITAL*EV FL 50 mL 50g/L+SET	2.5	KEDRION SpA	H
039712043	PRIVIGEN*EV 1FL 25 mL 100mg/mL	2.5	CSL BEHRING SpA	H
040267027	FLEBOGAMMA DIF*FL 50 mL 50mg/mL	2.5	GRIFOLS ITALIA SpA	H
044187021	GLOBIGA*INF 1FL 2,5g 100mg/mL	2.5	OCTAPHARMA Italy SpA	H
033240033	GAMMAGARD*EV 1FL 50mg/mL 96mL	4.8	BAXTER SpA	H
025266166	IGVENA*EV 1FL 100 mL 50g/L+SET	5	KEDRION SpA	H
029021045*	PENTAGLOBIN*EV 1FL 50mg/mL100 mL	5	BIOTEST ITALIA Srl	C
029249051	PLITAGAMMA*100 mL(5g)5%+SET	5	GRIFOLS ITALIA SpA	H
035143027	OCTAGAM*IV FL 100 mL 5%	5	OCTAPHARMA Italy SpA	H
037107036	KIOVIG*EV FL 50 mL 100mg/mL	5	BAXTER SpA	H
037240076	INTRATECT*INF FL 50g/L 100 mL	5	BIOTEST ITALIA Srl	H
037240102	INTRATECT*INF FL 100g/L 50 mL	5	BIOTEST ITALIA Srl	H
037253034	KEYVEN*EV FL 100 mL 50g/L+SET	5	KEDRION SpA	H
037254036	VENITAL*EV FL 100 mL 50g/L+SET	5	KEDRION SpA	H
039457027	GAMTEN*INF 1FL 50 mL 100mg/mL	5	OCTAPHARMA Italy SpA	H
039712017	PRIVIGEN*EV 1FL 50 mL 100mg/mL	5	CSL BEHRING SpA	H
040267039	FLEBOGAMMA DIF*FL 100 mL 5g	5	GRIFOLS ITALIA SpA	H
040267066	FLEBOGAMMA DIF*EV 50 mL 5g	5	GRIFOLS ITALIA SpA	H
043736026	IQYMUNE*FL INF 50 mL 100mg/mL	5	LFB	C(nn)
044187033	GLOBIGA*INF 1FL 5g 100mg/mL	5	OCTAPHARMA Italy SpA	H
045410026	GAMUNEX *INF 1FL 50 mL 100mg/mL	5	Grifols Deutschland GmbH	H
045410038	GAMUNEX *INF1FL 50 mL 100mg/mL C.o	5	Grifols Deutschland GmbH	H
039457054	GAMTEN*INFUS 1FL 60 mL 100mg/mL	6	OCTAPHARMA Italy SpA	C(nn)
044187045	GLOBIGA*INF 1FL 6g 100mg/mL	6	OCTAPHARMA Italy SpA	H
033240045	GAMMAGARD*EV 1FL 50mg/mL 192 mL	9.6	BAXTER SpA	H
025266178	IGVENA*EV 1FL 200 mL 50g/L+SET	10	KEDRION SpA	H
029249063	PLITAGAMMA*200 mL(10g)5%+SET	10	GRIFOLS ITALIA SpA	H
035143039	OCTAGAM*IV FL 200 mL 5%	10	OCTAPHARMA Italy SpA	H
037107048	KIOVIG*EV FL 100 mL 100mg/mL	10	BAXTER SpA	H
037240088	INTRATECT*INF FL 50g/L 200 mL	10	BIOTEST ITALIA Srl	H
037240114	INTRATECT*INF FL100g/L 100 mL	10	BIOTEST ITALIA Srl	H
037253046	KEYVEN*EV FL 200 mL 50g/L+SET	10	KEDRION SpA	H
037254048	VENITAL*EV FL 200 mL 50g/L+SET	10	KEDRION SpA	H

AIC code	Brand name	g	Manufacturer	NHS class
039457039	GAMTEN*INF 1FL100 mL 100mg/mL	10	OCTAPHARMA Italy SpA	H
039712029	PRIVIGEN*EV 1FL 100 mL 100mg/mL	10	CSL BEHRING SpA	H
040267041	FLEBOGAMMA DIF*FL 200 mL 10g	10	GRIFOLS ITALIA SpA	H
040267078	FLEBOGAMMA DIF*EV 100 mL 10g	10	GRIFOLS ITALIA SpA	H
043736038	IQYMUNE*FL INF100 mL 100mg/mL	10	LFB	C(nn)
044187058	GLOBIGA*INF 1FL 10g 100mg/mL	10	OCTAPHARMA Italy SpA	H
045410040	GAMUNEX *INF 1FL 100 mL 100mg/mL	10	Grifols Deutschland GmbH	H
045410053	GAMUNEX *INF 1FL100 mL 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 400 mL 50mg/mL	20	ISTITUTO GRIFOLS SA	H
035143066	OCTAGAM*IV 2FL 200 mL 50mg/mL	20	OCTAPHARMA Italy SpA	H
037107051	KIOVIG*EV FL 200 mL 100mg/mL	20	BAXTER SpA	H
039457041	GAMTEN*INF 1 FL 200 mL 100mg/mL	20	OCTAPHARMA Italy SpA	H
039712031	PRIVIGEN*EV 1FL 200 mL 100mg/mL	20	CSL BEHRING SpA	H
040267054	FLEBOGAMMA DIF*FL 400 mL 20g	20	GRIFOLS ITALIA SpA	H
040267080	FLEBOGAMMA DIF*EV 200 mL 20g	20	GRIFOLS ITALIA SpA	H
043736040	IQYMUNE*FL INF 200 mL 100mg/mL	20	LFB	C(nn)
044187072	GLOBIGA*INF 1FL 20g 100mg/mL	20	OCTAPHARMA Italy SpA	H
045410065	GAMUNEX *INF 1FL 200 mL 100mg/mL	20	Grifols Deutschland GmbH	H
045410077	GAMUNEX *INF1FL200 mL 100mg/mL C.o	20	Grifols Deutschland GmbH	H
035143041	OCTAGAM*IV FL 500 mL 5%	25	OCTAPHARMA Italy SpA	H
025266204	IGVENA*EV 3FL 200ML 50G/L+SET	30	KEDRION SpA	C(nn)
035143078	OCTAGAM*IV 3 FL 200 mL 50mg/mL	30	OCTAPHARMA Italy SpA	H
037107063	KIOVIG*EV FL 300 mL 100mg/mL	30	BAXTER SpA	H
037240140	INTRATECT* INF 3FL 200 mL 50g/L	30	BIOTEST ITALIA Srl	C
037240153	INTRATECT*INF 3FL 100 mL 100g/L	30	BIOTEST ITALIA Srl	C
039457066	GAMTEN*INF 3FL 100 mL 100mg/mL	30	OCTAPHARMA Italy SpA	C(nn)
039712056	PRIVIGEN*EV 3FL 100 mL 100mg/mL	30	CSL BEHRING GMBH	C
044187060	GLOBIGA*INF 3FL 10g 100mg/mL	30	OCTAPHARMA Italy SpA	C(nn)
044187096	GLOBIGA*INF 1FL 30g 100mg/mL	30	OCTAPHARMA Italy SpA	H
039457080	GAMTEN*INF 1FL 300 mL 100mg/mL	30	OCTAPHARMA Italy SpA	C(nn)
039712070	PRIVIGEN*EV 1FL 400 mL 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 200 mL 100 g/L	60	BIOTEST ITALIA Srl	C
039457078	GAMTEN*INF 3FL 200 mL 100mg/mL	60	OCTAPHARMA Italy SpA	C(nn)
039712068	PRIVIGEN*EV 3FL 200 mL 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 2021-2022 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 2022, the total national demand for IGs was 6,243,697 grams, equal to 105.9 grams per 1,000 population (Table 8). The three Regions with the highest standardised demand per 1,000 population were Aosta Valley with around 184 grams and Liguria with around 160 grams. The demand was lower in Molise, Calabria, Campania and Sicily, where it ranged between 59 and 73 grams per 1,000 population. The demand for these PDMPs shows a slight decrease in the two-year period 2021-2022 (-3.3%), featuring notable differences from one Region to another. The greatest decrease is recorded in Molise (-28%) and

in Tuscany (-26%). The most marked increase is instead observed in Basilicata (+49%). Figure 8 shows which Regions tended to use more SC/IM formulations and which preferred IV ones. More SC/IM formulations were used in Latium (34.8%), Tuscany (34.6%), Umbria (34.4%) and Calabria (34.1%) while fewer were used in Friuli V. Giulia, Sardinia and in the AP Bolzano (<7%). At national level, the demand for SC/IM IGs stood at 23% 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	135,984	106.2	154,193	121.1	14.0
Aosta Valley	20,933	168.7	22,658	183.7	8.9
AP Bolzano	54,536	102.0	52,290	97.6	-4.3
AP Trento	53,108	98.0	52,250	96.4	-1.6
Apulia	442,736	112.5	389,194	99.5	-11.6
Basilicata	49,149	90.2	72,663	134.6	49.2
Calabria	118,288	63.6	114,884	62.3	-2.0
Campania	413,242	73.5	408,832	73.1	-0.5
E.-Romagna	577,184	130.0	615,557	138.9	6.8
Friuli V. Giulia	140,672	117.1	136,927	114.4	-2.3
Latium	613,751	107.1	572,200	100.1	-6.5
Liguria	242,618	159.8	240,711	159.7	-0.1
Lombardy	969,941	97.2	988,409	99.2	2.1
Marche	212,652	141.9	196,973	132.2	-6.8
Molise	24,214	82.3	17,264	59.4	-27.8
Piedmont	534,047	124.9	523,382	123.1	-1.5
Sardinia	103,093	64.8	117,034	74.1	14.3
Sicily	356,730	73.8	351,416	73.2	-0.8
Tuscany	702,428	190.2	519,631	141.3	-25.7
Umbria	115,520	133.5	122,398	142.4	6.7
Veneto	601,241	123.5	574,832	118.4	-4.1
Italy	6,482,066	109.4	6,243,697	105.9	-3.3

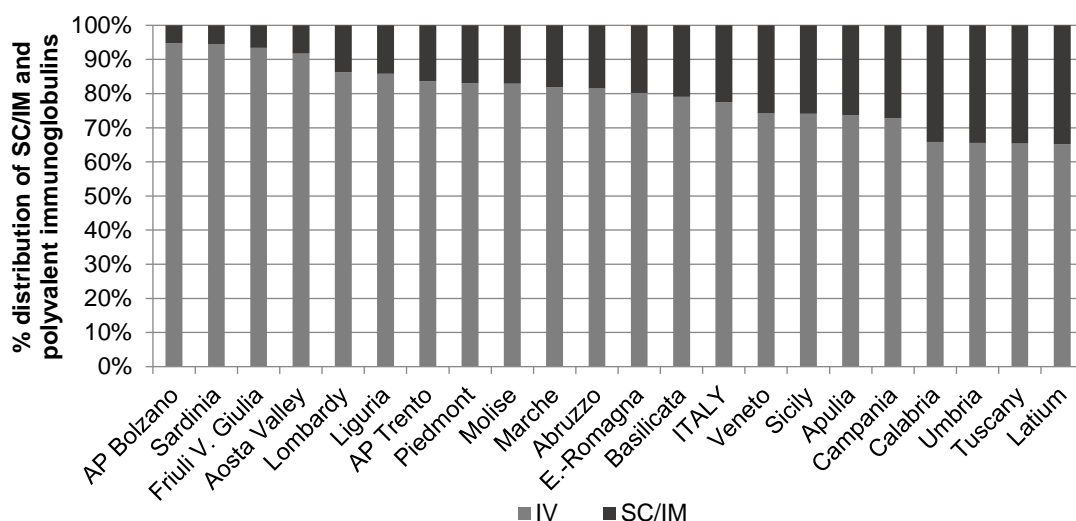


Figure 8. Total standardised demand (public and private) per administration of immunoglobulins (percentage on total), by Region, 2022 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for subcutaneous use

In 2022, the total demand for SC/IM IGs reached about 1,405,036 grams (24 grams per 1,000 population), with a decrease of 8% compared to 2021 (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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	36,909	28.8	28,488	22.4	-22.4
Aosta Valley	1,333	10.7	1,883	15.3	42.1
AP Bolzano	3,489	6.5	2,746	5.1	-21.4
AP Trento	8,118	15.0	8,520	15.7	5.0
Apulia	120,680	30.7	102,276	26.1	-14.8
Basilicata	15,463	28.4	15,231	28.2	-0.6
Calabria	37,988	20.4	39,208	21.3	4.1
Campania	122,799	21.8	111,446	19.9	-8.7
E.-Romagna	124,431	28.0	121,882	27.5	-1.9
Friuli V. Giulia	9,172	7.6	8,972	7.5	-1.8
Latium	222,844	38.9	199,237	34.9	-10.4
Liguria	44,181	29.1	34,251	22.7	-21.9
Lombardy	165,098	16.5	135,763	13.6	-17.6
Marche	31,367	20.9	35,725	24.0	14.5
Molise	3,314	11.3	2,944	10.1	-10.1
Piedmont	95,458	22.3	88,857	20.9	-6.4
Sardinia	12,048	7.6	6,359	4.0	-46.9
Sicily	105,701	21.9	90,996	19.0	-13.3
Tuscany	179,090	48.5	179,914	48.9	0.9
Umbria	43,395	50.1	42,118	49.0	-2.3
Veneto	157,527	32.3	148,223	30.5	-5.6
Italy	1,540,405	26.0	1,405,036	23.8	-8.4

The regional demands proved diversified with the highest value recorded of 49 grams per 1,000 population in Umbria and Tuscany followed by Latium with 35 grams per 1,000 population.

However, the lowest values were recorded in Sardinia, AP of Bolzano and in Friuli V. Giulia, where they fluctuated between 4 and 7.5 grams per 1,000 population (Figure 9).

In Umbria, Tuscany, Latium, Veneto, Basilicata, Emilia-Romagna, Apulia and Marche, a higher total demand compared to national demand was recorded (range: 1-106%) (Figure 10).

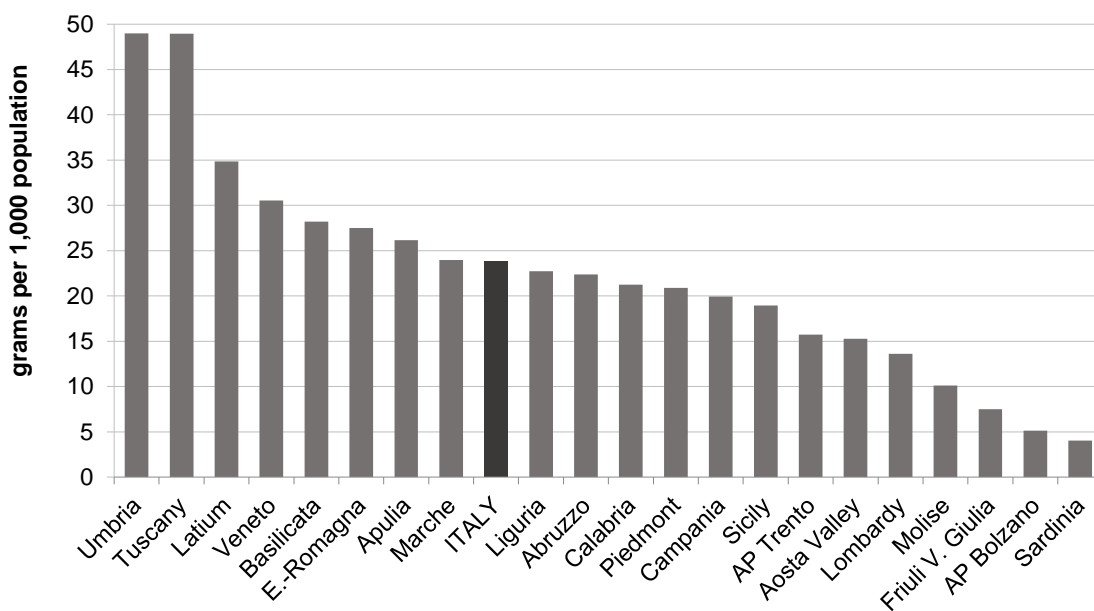


Figure 9. Total and regional demand (public and private) for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams per 1,000 population, 2022 (adapted by the CNS on data from the Traceability information flow)

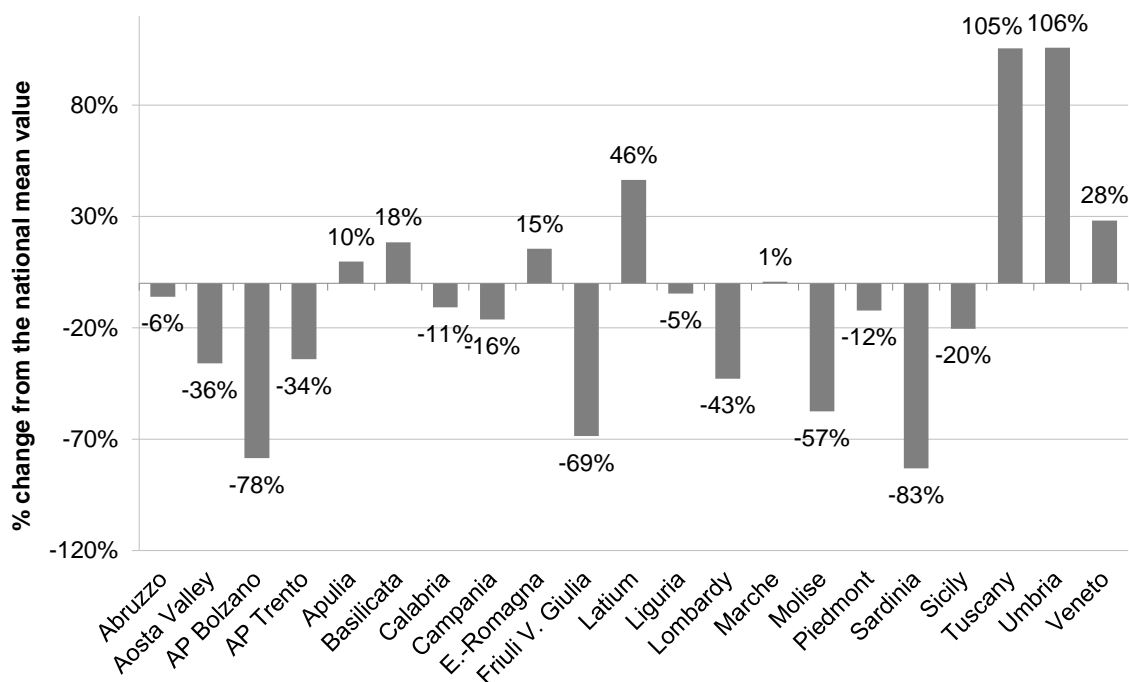


Figure 10. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for subcutaneous/ intramuscular use in 2022 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for intravenous use

Finally, Table 10 reports on the total and standardised demands for IG for intravenous use in 2021-2022.

Even, in this case, a general downward trend (about -1.7%) was observed, while it was not confirmed in Abruzzo, Basilicata, Campania, E.-Romagna, Liguria, Lombardy, Sardinia, Sicily, Umbria and Aosta Valley.

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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021- 2022
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	99,075	77.3	125,705	98.7	27.6
Aosta Valley	19,600	157.9	20,776	168.4	6.6
AP Bolzano	51,047	95.4	49,544	92.5	-3.1
AP Trento	44,990	83.0	43,730	80.7	-2.8
Apulia	322,056	81.9	286,918	73.3	-10.4
Basilicata	33,686	61.8	57,432	106.4	72.1
Calabria	80,300	43.2	75,676	41.0	-4.9
Campania	290,443	51.6	297,387	53.2	3.0
E.-Romagna	452,752	102.0	493,675	111.4	9.2
Friuli V. Giulia	131,500	109.4	127,955	106.9	-2.4
Latium	390,907	68.2	372,964	65.3	-4.3
Liguria	198,438	130.7	206,460	137.0	4.8
Lombardy	804,843	80.6	852,646	85.6	6.1
Marche	181,285	121.0	161,248	108.2	-10.5
Molise	20,900	71.0	14,320	49.2	-30.7
Piedmont	438,590	102.6	434,525	102.2	-0.4
Sardinia	91,045	57.3	110,675	70.1	22.4
Sicily	251,028	51.9	260,420	54.2	4.4
Tuscany	523,337	141.7	339,717	92.4	-34.8
Umbria	72,125	83.3	80,280	93.4	12.1
Veneto	443,714	91.1	426,609	87.9	-3.6
Italy	4,941,661	83.4	4,838,661	82.0	-1.7

Figure 11 shows the standardised regional demand for IVIGs in 2022 as recorded by the drug Traceability system.

The highest demand for IVIGs was recorded in Aosta Valley, Liguria and E.-Romagna, with volumes ranging between 168 and 111 grams per 1,000 population (+105%, +67% and +36% respectively, compared to the national mean value – Figure 12). The Regions where the standardized demand was lower were Calabria and Molise with recorded volumes between 41 and 49 grams per 1,000 population.

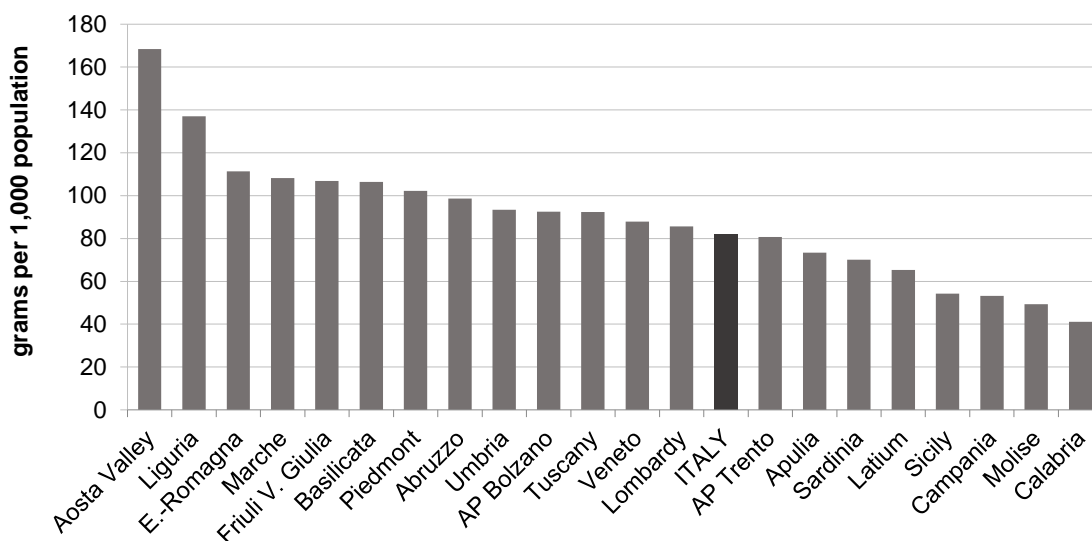


Figure 11. Total and regional demand (public and private) for normal human immunoglobulins for intravenous use, expressed in grams per 1,000 population, 2022 (adapted by the CNS on data from the Traceability information flow)

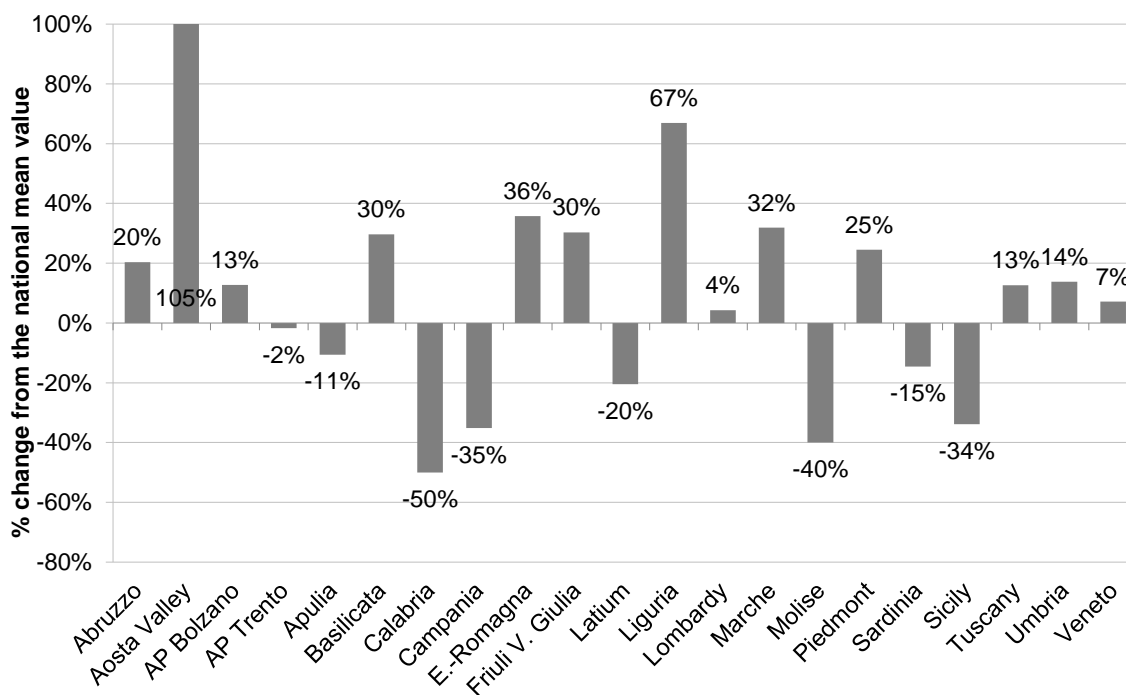


Figure 12. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for intravenous use in 2022 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2022)

AICcode	Brand name	IU	Manufacturer	NHS class
025766039	KYBERNIN P*IV FL 500 IU+10 mL+SET	500	CSL BEHRING SpA	H
027113012	ANTITROMBINA III IMMUNO*FL10 mL	500	BAXALTA Italy Srl	H
029378015	AT III KED*500 IU+FL 10 mL+SET	500	KEDRION SpA	H
031118019	ATENATIV*IV FL 500 IU+FL 10 mL	500	OCTAPHARMA Italy SpA	H
034330035	ANBINEX*FL 500 IU+SIR 10 mL+SET	500	GRIFOLS ITALIA SpA	H
041800018	ATKED*FL 500 IU+FL 20 mL+SET	500	KEDRION SpA	H
044565012	ATTERTIUM FL 500 IU+SIR 10 mL	500	GRIFOLS ITALIA SpA	C(nn)
025766027	KYBERNIN P*IV FL 1000 IU+F 20 mL	1000	CSL BEHRING SpA	H
027113024	ANTITROMBINA III IMMUNO*FL20 mL	1000	BAXALTA Italy Srl	H
029378027	AT III KED*1000 IU+FL 20 mL+SET	1000	KEDRION SpA	H
031118021	ATENATIV*IV FL 1000 IU+FL 20 mL	1000	OCTAPHARMA Italy SpA	H
034330047	ANBINEX*FL 1000 IU+SIR 20 mL+SET	1000	GRIFOLS ITALIA SpA	H
041800020	ATKED*FL 1000 IU+FL 20 mL+SET	1000	KEDRION SpA	H
044565024	ATTERTIUM FL 1000 IU+SIR 20 mL	1000	GRIFOLS ITALIA SpA	C(nn)
029378039	AT III KED*2000 IU+FL 20 mL+SET	2000	KEDRION SpA	H
041800032	ATKED*FL 2000 IU+FL 20 mL+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 2021-2022 with the relative percentage changes at national and regional levels.

In 2022, total AT demand was 134,124,500 IUs, equal to 2.3 IUs *per capita*, showing a slight decrease from the consumption recorded in the previous year (-4% compared to 2021). The region where there was the most evident usage restraint was Tuscany (-32%)

Conversely, in four Regions there was a significant upward trend (>50%) in its use [range: Veneto (+ 52%) – AP of Trento (+ 54%)].

Figure 13 shows the regional and national standardised demand for AT in 2022. The Regions with the highest *per capita* demand were Sicily, Calabria, Friuli V. Giulia and Liguria, with a demand of 4.3 IUs for the first one and 4.1, 3.4 and 3.2 IUs respectively for the other Regions. The lowest demand, less than 1 IUs *per capita*, was recorded in the AP of Trento (0.8 IU) and AP of Bolzano (0.9 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,358,000	1.8	2,304,500	1.8	-1.7
Aosta Valley	244,000	2.0	250,000	2.0	3.1
AP Bolzano	436,000	0.8	487,000	0.9	11.5
APTrento	288,000	0.5	444,000	0.8	54.2
Apulia	9,589,500	2.4	9,761,000	2.5	2.4
Basilicata	1,128,000	2.1	1,703,000	3.2	52.4
Calabria	7,380,500	4.0	7,603,500	4.1	3.9
Campania	15,100,500	2.7	12,650,500	2.3	-15.7
E.-Romagna	3,992,000	0.9	4,461,500	1.0	11.9
Friuli V. Giulia	2,944,000	2.5	4,120,000	3.4	40.4
Latium	21,535,000	3.8	18,215,500	3.2	-15.2
Liguria	4,759,000	3.1	4,875,500	3.2	3.2
Lombardy	11,935,000	1.2	12,872,000	1.3	8.0
Marche	4,582,000	3.1	3,635,000	2.4	-20.2
Molise	766,000	2.6	744,000	2.6	-1.7
Piedmont	8,684,500	2.0	8,276,500	1.9	-4.2
Sardinia	2,248,500	1.4	1,934,500	1.2	-13.4
Sicily	23,005,500	4.8	20,453,000	4.3	-10.5
Tuscany	11,656,500	3.2	7,860,000	2.1	-32.3
Umbria	586,000	0.7	896,000	1.0	53.9
Veneto	6,974,000	1.4	10,577,500	2.2	52.1
Italy	140,192,500	2.4	134,124,500	2.3	-3.9

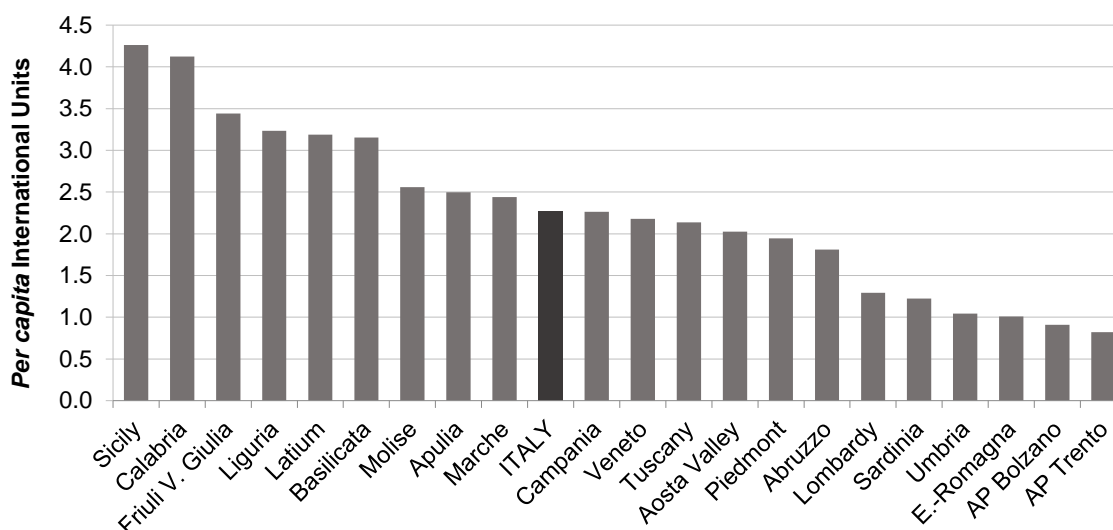


Figure 13. Total and regional demand (public and private) for antithrombin, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

Figure 14 shows the difference between the regional *per capita* percentage and the national mean value for the year 2022.

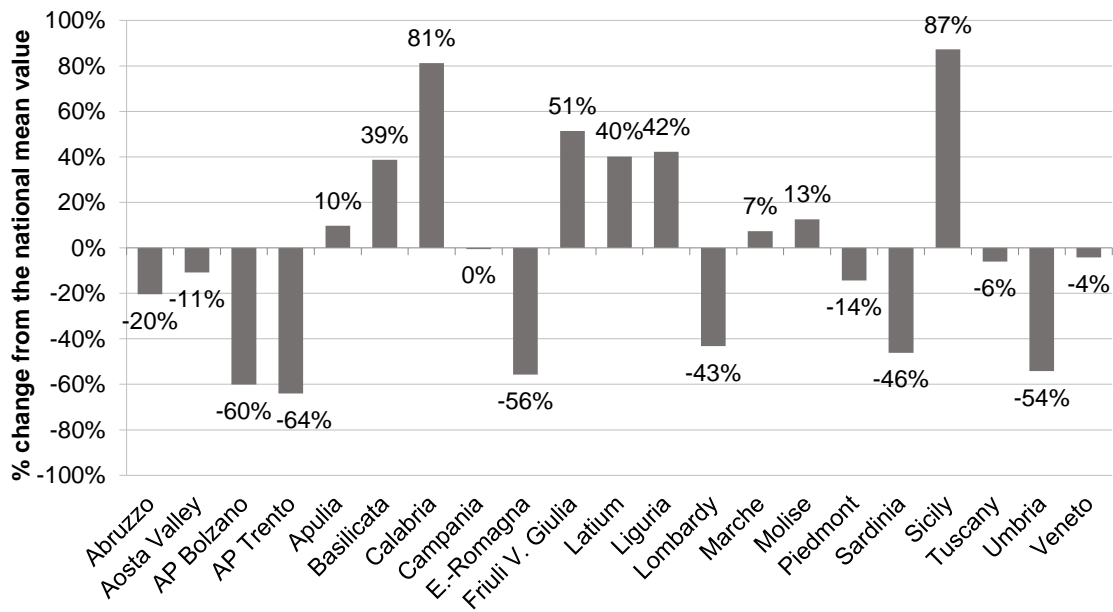


Figure 14. Percentage change from the national mean value of standardised regional demand for antithrombin in 2022 (adapted by the CNS on data from the Traceability information flow)

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 $2.1 \pm 0.4\%$ of normal activity.

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

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

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

Table 13. Products containing plasma-derived coagulation Factor VIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
033657014	BERIATE*F 250 IU+SOLV+SET	250	CSL BEHRING SpA	A
038541013	HAEMOCTIN*FL 250 IU+FL 5 mL+SIR	250	BIOTEST PHARMA GMBH	A
023564216	EMOCLOT*FL 500 IU+FL 10 mL+SET	500	KEDRION SpA	A
033657026	BERIATE*F 500 IU+SOLV+SET	500	CSL BEHRING SpA	A
038541025	HAEMOCTIN*FL 500 IU+FL 10 mL+SIR	500	BIOTEST PHARMA GMBH	A
041649017	KLOTT*FL 500 IU+FL 10 mL+SET	500	KEDRION SpA	A
023564228	EMOCLOT*FL 1000 IU+FL 10 mL+SET	1000	KEDRION SpA	A
033657038	BERIATE*F 1000 IU+SOLV+S	1000	CSL BEHRING SpA	A
038541037	HAEMOCTIN*FL 1000 IU+FL 10 mL+SIR	1000	BIOTEST PHARMA GMBH	A
041649029	KLOTT*FL 1000 IU+FL 10 mL+SET	1000	KEDRION SpA	A
033657040	BERIATE*FL 2000 IU+FL 10 mL	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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
Factor VIII and von Willebrand Factor in combination				
033077088	ALPHANATE*INF 1F 250 IU+SIR+AD	250	GRIFOLS ITALIA SpA	A
033866043	FANHDI*INF FL 250 IU+SIR SOLV+S	250	GRIFOLS ITALIA SpA	A
037148018	TALATE*250 IU/190 IU+FL5 mL+SIR	250	BAXALTA INN.Gmbh	A
040112017	OCTANATE*INIET FL 250 IU+FL 5 mL	250	OCTAPHARMA Italy SpA	A
042939013	VONCENTO*250 IU/600 IU+FL 5 mL	250	CSL BEHRING SpA	C(nn)
044564019	PLITATE*INF FL 250 IU+SIR SOLV+SET	250	GRIFOLS ITALIA SpA	C(nn)
023308152	EMOWIL*1F 500 IU+F 10 mL	500	KEDRION SpA	A
026600080	HAEMATEP*FL 500 IU+FL 10 mL+SET	500	CSL BEHRING SpA	A
033077090	ALPHANATE*INF 1F 500 IU+SIR+AD	500	GRIFOLS ITALIA SpA	A
033866056	FANHDI*INF FL 500 IU+SIR SOLV+S	500	GRIFOLS ITALIA SpA	A
037148020	TALATE*500 IU/375IU+FL10 mL+SIR	500	BAXALTA INN. Gmbh	A
039385036	WILATE*FL 500+500 IU+FL 5 mL+SIR	500	OCTAPHARMA Italy SpA	A
040112029	OCTANATE*INIET FL 500 IU+FL 10 mL	500	OCTAPHARMA Italy SpA	A
040112056	OCTANATE*INIET FL 5 mL100 IU/mL	500	OCTAPHARMA Italy SpA	A
042939025	VONCENTO*500 IU/1200 IU+FL 10 mL	500	CSL BEHRING SpA	C(nn)
042939037	VONCENTO*500 IU/1200 IU+FL 5 mL	500	CSL BEHRING SpA	C(nn)
044564021	PLITATE*INF FL 500 IU+SIR SOLV+SET	500	GRIFOLS ITALIA SpA	C(nn)
023308188	EMOWIL*1F 1000 IU+F 10 mL	1000	KEDRION SpA	A
026600078	HAEMATEP*FL 1000 IU+FL 15 mL+SET	1000	CSL BEHRING SpA	A
033077102	ALPHANATE*INF 1F 1000 IU+SIR+AD	1000	GRIFOLS ITALIA SpA	A
033866068	FANHDI*INF FL 1000 IU+SIR SOLV+S	1000	GRIFOLS ITALIA SpA	A
037148032	TALATE*1000 IU/750 IU+FL10 mL+SIR	1000	BAXALTA Italy Srl	A
039385024	WILATE*FL 900+800 IU+FL 10 mL+SIR	1000	OCTAPHARMA Italy SpA	A
039385048	WILATE*FL 1000+1000 IU+FL 10 mL+SI	1000	OCTAPHARMA Italy SpA	A
040112031	OCTANATE*INIET FL 1000 IU+FL 10 mL	1000	OCTAPHARMA Italy SpA	A
040112068	OCTANATE*INIET FL 5 mL 200 IU/mL	1000	OCTAPHARMA Italy SpA	A
042939049	VONCENTO*1000 IU/2400 IU+FL 10 mL	1000	CSL BEHRING SpA	C(nn)
044564033	PLITATE*INF FL1000 IU+SIR SOLV+SET	1000	GRIFOLS ITALIA SpA	C(nn)
033077114	ALPHANATE*INF 1F 1500 IU+SIR+AD	1500	GRIFOLS ITALIA SpA	A
033866070	FANHDI*INF FL1500 IU+SIR SOLV+S	1500	GRIFOLS ITALIA SpA	A
044564045	PLITATE*INF FL1500 IU+SIR SOLV+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* 500 IU+FL 5 mL	500	LFB	C
037392014	WILFACTIN*1000 IU+FL 10 mL	1000	LFB	C
037392038	WILFACTIN*2000 IU+FL 20 mL	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, 31/12/2022)

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

AIC code	Brand name	IU	Manufacturer	NHS class
034955070	KOGENATE BAYER*EV 250 IU+SIR	250	BAYER SpA	A
034956019	HELIXATE NEXGEN*250 IU+1FL+1KIT	250	CSL BEHRING SpA	A
036160012	ADVATE*FL 250 IU+FL SOLV 5 mL	250	BAXTER SpA	A
036160075	ADVATE*FL 250 IU+FL SOLV 2 mL	250	BAXALTA Italy Srl	A
036160113	ADVATE*FL 250 IU+FL SOLV 5 mL	250	BAXALTA Italy Srl	A
036160176	ADVATE*FL 250 IU+FL SOLV 2 mL	250	BAXALTA Italy Srl	A
043153016	NOVOEIGHT*EV FL 250 IU+SIR 4mL	250	NOVO NORDISK SpA	A
043534015	NUWIQ*EV FL 250 IU+SIR 2,5 mL	250	KEDRION SpA	A
044725012	IBLIAS*FL POLV EV 250 IU+FL 2,5 mL	250	BAYER SpA	A
044726014	KOVALTRY*1FL POLV EV 250 IU+SOLV	250	BAYER SpA	A
044726026	KOVALTRY*1FL POLV EV 250 IU+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	C(nn)
045255015	AFSTYLA 250 IU+FL SOLV 2,5 mL+SIR	250	CSL BEHRING GmbH	A
045273012	VIHUMA*EV 250 IU+FL SOLV 2,5 mL	250	OCTAPHARMA AB	C(nn)
028687022	RECOMBIMATE*FL 500 IU+FL 10 mL	500	BAXALTA Italy Srl	A
028687059	RECOMBIMATE*FL 500 IU+FL 5 mL	500	BAXALTA Italy Srl	A
028687085	RECOMBIMATE*FL 500 IU+FL 5 mL	500	BAXALTA Italy Srl	A
028687111	RECOMBIMATE*FL 500 IU+FL 10 mL	500	BAXALTA Italy Srl	A
034421026	REFACTOAF*IV 1FL 500 IU+SIR 4mL	500	PFIZER ITALIA Srl	A
034421065	REFACTOAF*IV 1SIR PRER 500 IU	500	PFIZER ITALIA Srl	A
034955029	KOGENATE BAYER*500 IU+1FL+1KIT	500	BAYER SpA	A
034955056	KOGENATE BAYER*FL 500 IU+SIR	500	BAYER SpA	A
034955082	KOGENATE BAYER*EV 500 IU+SIR	500	BAYER SpA	A
034956021	HELIXATE NEXGEN*500 IU+1FL+1KIT	500	CSL BEHRING SpA	A
036160024	ADVATE*FL 500 IU+FL SOLV 5 mL	500	BAXTER SpA	A
036160087	ADVATE*FL 500 IU+FL SOLV 2 mL	500	BAXALTA Italy Srl	A
036160125	ADVATE*FL 500 IU+FL SOLV 5 mL	500	BAXALTA Italy Srl	A
036160188	ADVATE*FL 500 IU+FL SOLV 2 mL	500	BAXALTA Italy Srl	A
043153028	NOVOEIGHT*EV FL 500 IU+SIR 4mL	500	NOVO NORDISK SpA	A
043534027	NUWIQ*EV FL 500 IU+SIR 2,5 mL	500	KEDRION SpA	A
044725024	IBLIAS*FL POLV EV 500 IU+FL 2,5 mL	500	BAYER SpA	A
044726038	KOVALTRY*1FL POLV EV 500 IU+SOLV	500	BAYER SpA	A
044726040	KOVALTRY*1FL POLV EV 500 IU+SOLV	500	BAYER SpA	A
044726139	KOVALTRY*1FL POLV EV 500 IU	500	BAYER AG	C(nn)
044726141	KOVALTRY*1FL POLV EV 500 IU	500	BAYER AG	C(nn)
045255027	AFSTYLA 500 IU+FL SOLV 2,5 mL+SIR	500	CSL BEHRING GmbH	A
045273024	VIHUMA*EV500 IU+FL SOLV 2,5 mL	500	OCTAPHARMA AB	C(nn)
028687034	RECOMBIMATE*FL 1000 IU+FL 10 mL	1000	BAXALTA Italy Srl	A
028687061	RECOMBIMATE*FL 1000 IU+FL 5 mL	1000	BAXALTA Italy Srl	A
028687097	RECOMBIMATE*FL 1000 IU+FL 5 mL	1000	BAXALTA Italy Srl	A
028687123	RECOMBIMATE*FL 1000 IU+FL 10 mL	1000	BAXALTA Italy Srl	A
034421038	REFACTO AF*IV 1FL 1000 IU+SIR 4mL	1000	PFIZER ITALIA Srl	A
034421077	REFACTO AF*IV 1SIR PRER 1000 IU	1000	PFIZER ITALIA Srl	A
034955031	KOGENATE BAYER*1000 IU+1FL+1KIT	1000	BAYER SpA	A
034955068	KOGENATE BAYER*FL 1000 IU+SIR	1000	BAYER SpA	A
034955094	KOGENATE BAYER*EV 1000 IU+SIR	1000	BAYER SpA	A
034956033	HELIXATE NEXGEN*1000 IU+1FL+KIT	1000	CSL BEHRING SpA	A
036160036	ADVATE*FL 1000 IU+FL SOLV 5 mL	1000	BAXTER SpA	A
036160099	ADVATE*FL 1000 IU+FL SOLV 2 mL	1000	BAXALTA Italy Srl	A
036160137	ADVATE*FL 1000 IU+FL SOLV 5 mL	1000	BAXALTA Italy Srl	A
036160190	ADVATE*FL 1000 IU+FL SOLV 2 mL	1000	BAXALTA Italy Srl	A
043153030	NOVOEIGHT*EV FL 1000 IU+SIR 4mL	1000	NOVO NORDISK SpA	A
043534039	NUWIQ*EV FL 1000 IU+SIR 2,5 mL	1000	KEDRION SpA	A
044725036	IBLIAS*FL POLV EV 1000 IU+2,5 mL	1000	BAYER SpA	A
044726053	KOVALTRY*FL POLV EV 1000 IU+SOLV	1000	BAYER SpA	A
044726065	KOVALTRY*FL POLV EV 1000 IU+SOLV	1000	BAYER SpA	A
044726154	KOVALTRY* 1FL POLV EV 1000 IU	1000	BAYER AG	C(nn)

AIC code	Brand name	IU	Manufacturer	NHS class
044726166	KOVALTRY* 1FL POLV EV 1000 IU	1000	BAYER AG	C(nn)
045255039	AFSTYLA 1000 IU+FL SOLV 2,5 mL+SIR	1000	CSL BEHRING GmbH	A
045273036	VIHUMA*EV 1000 IU+FL SOLV 2,5 mL	1000	OCTAPHARMA AB	C(nn)
036160048	ADVATE*FL 1500 IU+FL SOLV 5 mL	1500	BAXTER SpA	A
036160101	ADVATE*FL 1500 IU+FL SOLV 2 mL	1500	BAXALTA Italy Srl	A
036160149	ADVATE*FL 1500 IU+FL SOLV 5 mL	1500	BAXALTA Italy Srl	A
036160202	ADVATE*FL 1500 IU+FL SOLV 2 mL	1500	BAXALTA Italy Srl	A
043153042	NOVOEIGHT*EV FL 1500 IU+SIR 4mL	1500	NOVO NORDISK SpA	A
045255041	AFSTYLA 1500 IU+FL SOLV 2,5 mL+SIR	1500	CSL BEHRING GmbH	A
034421040	REFACTOAF*IV 1FL 2000 IU+SIR 4mL	2000	PFIZER ITALIA Srl	A
034421089	REFACTOAF*IV 1SIR PRER 2000 IU	2000	PFIZER ITALIA Srl	A
034955106	KOGENATE BAYER*EV 2000 IU+SIR	2000	BAYER SpA	A
034955118	KOGENATE BAYER*EV 2000 IU+SIR	2000	BAYER SpA	A
036160051	ADVATE*FL 2000 IU+FL SOLV 5 mL	2000	BAXTER SpA	A
036160152	ADVATE*FL 2000 IU+FL SOLV 5 mL	2000	BAXALTA Italy Srl	A
043153055	NOVOEIGHT*EV FL 2000 IU+SIR 4mL	2000	NOVO NORDISK SpA	A
043534041	NUWIQ*EV FL 2000 IU+SIR 2,5 mL	2000	KEDRION SpA	A
044725048	IBLIAS*FL POLV EV 2000 IU+FL 5 mL	2000	BAYER SpA	A
044726077	KOVALTRY*FL POLV EV 2000 IU+SOLV	2000	BAYER SpA	A
044726089	KOVALTRY*FL POLV EV 2000 IU+SOLV	2000	BAYER SpA	A
045255054	AFSTYLA 2000 IU+FL SOLV 2,5 mL+SIR	2000	CSL BEHRING GmbH	A
045273048	VIHUMA*EV 2000 IU+FL SOLV 2,5 mL	2000	OCTAPHARMA AB	C(nn)
043534054	NUWIQ*EV FL 2500 IU+SIR 2,5 mL	2500	OCTAPHARMA AB	A
045255066	AFSTYLA 2500 IU+FL SOLV 2,5 mL+SIR	2500	CSL BEHRING GmbH	A
034421053	REFACTO AF*IV 1SIR PRER 3000 IU	3000	PFIZER ITALIA Srl	A
034955120	KOGENATE BAYER*EV 3000 IU+SIR	3000	BAYER SpA	A
034955132	KOGENATE BAYER*EV 3000 IU+SIR	3000	BAYER SpA	A
034956058	HELIXATE NEXGEN*3000 IU+1FL+KIT	3000	CSL BEHRING SpA	A
036160063	ADVATE*FL 3000 IU+FL SOLV 5 mL	3000	BAXTER SpA	A
036160164	ADVATE*FL 3000 IU+FL SOLV 5 mL	3000	BAXALTA Italy Srl	A
043153067	NOVOEIGHT*EV FL 3000 IU+SIR 4mL	3000	NOVO NORDISK SpA	A
043534066	NUWIQ*EV FL 3000 IU+SIR 2,5 mL	3000	OCTAPHARMA AB	A
044725051	IBLIAS*FL POLV EV 3000 IU+FL 5 mL	3000	BAYER SpA	A
044726091	KOVALTRY*FL POLV EV 3000 IU+SOLV	3000	BAYER SpA	A
044726103	KOVALTRY*FL POLV EV 3000 IU+SOLV	3000	BAYER SpA	A
045255078	AFSTYLA 3000 IU+FL SOLV 2,5 mL+SIR	3000	CSL BEHRING GmbH	A
043534078	NUWIQ*EV FL 4000 IU+SIR 2,5 mL	4000	OCTAPHARMA AB	C
044726178	KOVALTRY*30FL 250UI+ SIR 3mL	7500	BAYER AG	C(nn)
044726180	KOVALTRY*30FL 250UI+ SIR 5 mL	7500	BAYER AG	C(nn)
044726192	KOVALTRY*30FL 500UI+ SIR 3mL	15000	BAYER AG	C(nn)
044726204	KOVALTRY*30FL 500UI+SIR 5 mL	15000	BAYER AG	C(nn)
044726216	KOVALTRY*30FL 1000UI+SIR 3mL	30000	BAYER AG	C(nn)
044726228	KOVALTRY*30FL 1000UI+SIR 5 mL	30000	BAYER AG	C(nn)
044726230	KOVALTRY*30FL 2000UI+SIR 5 mL	60000	BAYER AG	C(nn)
044726242	KOVALTRY*30FL 3000UI+SIR 5 mL	90000	BAYER AG	C(nn)
Extended half-life Recombinant Factor VIII				
044563017	ELOCTA*IV 1FL 250 IU+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 500 IU+SIR PRERI	500	SOBI Srl	A
045936059	ADYNOVI*EV 500 IU + FL 2 mL + DISP	500	BAXALTA INN. GmbH.	A
045936061	ADYNOVI*EV 500 IU + FL 2 mL + DISP	500	BAXALTA INN. GmbH.	A
045936073	ADYNOVI*EV 500 IU + FL 5 mL + DISP	500	BAXALTA INN. GmbH.	C(nn)
045936085	ADYNOVI*EV 500 IU + FL 5 mL + DISP	500	BAXALTA INN. GmbH.	A
047418025	JIVI* EV 500 IU + FL SOLV 2,5 mL + SIR	500	BAYER AG	A

AIC code	Brand name	IU	Manufacturer	NHS class
048083012	ESPEROCT* EV 500 IU + FL 4 mL + SIR	500	NOVO NORDISK A/S	A
044563031	ELOCTA*IV 1FL 750 IU+SIR PRERI	750	SOBI Srl	A
044563043	ELOCTA*IV 1FL 750UI+SIR PRERI	750	SOBI Srl	A
044563056	ELOCTA*IV 1FL 1000 IU+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 1500 IU+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 2000 IU+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 3000 IU+SIR PRERI	3000	SOBI Srl	A
045936150	ADYNOVI*EV3000UI+FL5 mL+DISP	3000	BAXALTA INN. Gmbh	C(nn)
045936162	ADYNOVI*EV3000UI+FL5 mL+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 4000 IU+SIR PRERI	4000	SOBI Srl	C(nn)
044563106	ELOCTA*IV 1FL 5000 IU+SIR PRERI	5000	SOBI Srl	C(nn)
044563118	ELOCTA*IV 1FL 6000 IU+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 555,585,750 IUs in 2022 (Table 16); of these, about a sixth (17% of the total, 92,680,500 IUs) were human plasma-derived (Figure 15). The tendency to use pdFVIII varied significantly from one Region to another ranging from 0.6% in AP of Trento to 31% in Tuscany. In 2022, the total FVIII demand *per capita* (plasma-derived and recombinant) was 9 IUs with a decrease of -1.7% compared to 2021.

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

The most significant decreases in standardised regional demand were observed in Molise and in Aosta Valley, where use decreased by -25% and -20%, respectively.

It is important to underline that for FVIII, strong fluctuations can occur due to the contingent needs of a few patients (immunotolerance treatments, surgeries, severe traumas, etc.). Six 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	14,304,750	11.2	16,495,250	13.0	16.0
Aosta Valley	940,000	7.6	746,000	6.0	-20.2
AP Bolzano	2,634,000	4.9	3,961,000	7.4	50.1
AP Trento	3,271,500	6.0	3,341,500	6.2	2.1
Apulia	48,099,250	12.2	45,419,500	11.6	-5.0
Basilicata	2,996,500	5.5	2,694,500	5.0	-9.2
Calabria	23,102,000	12.4	20,314,500	11.0	-11.3
Campania	66,754,500	11.9	59,542,750	10.7	-10.3
E.-Romagna	44,246,750	10.0	47,262,500	10.7	7.0
Friuli V. Giulia	4,826,250	4.0	4,961,000	4.1	3.2
Lazio	97,587,750	17.0	92,146,500	16.1	-5.3
Liguria	9,646,500	6.4	10,643,000	7.1	11.1
Lombardy	75,966,500	7.6	77,466,000	7.8	2.1
Marche	9,342,000	6.2	11,196,500	7.5	20.5
Molise	2,734,000	9.3	2,021,000	7.0	-25.2
Piedmont	33,886,250	7.9	31,253,000	7.3	-7.3
Sardinia	13,526,200	8.5	12,823,000	8.1	-4.5
Sicily	45,406,250	9.4	43,129,500	9.0	-4.4
Tuscany	25,224,750	6.8	23,809,500	6.5	-5.2
Umbria	6,438,500	7.4	5,979,000	7.0	-6.5
Veneto	36,844,500	7.6	40,380,250	8.3	9.9
Italy	567,778,700	9.6	555,585,750	9.4	-1.7

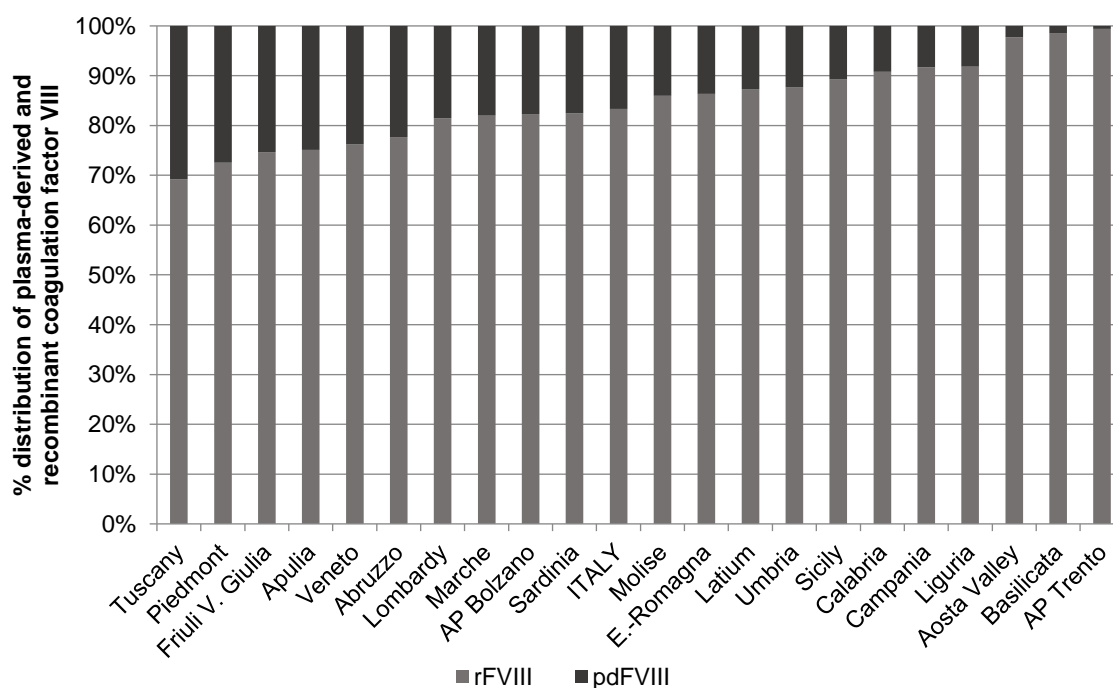


Figure 15. Percentage distribution of plasma-derived and recombinant coagulation Factor VIII, by Region, 2022 (adapted by the CNS on data from the Traceability information flow)

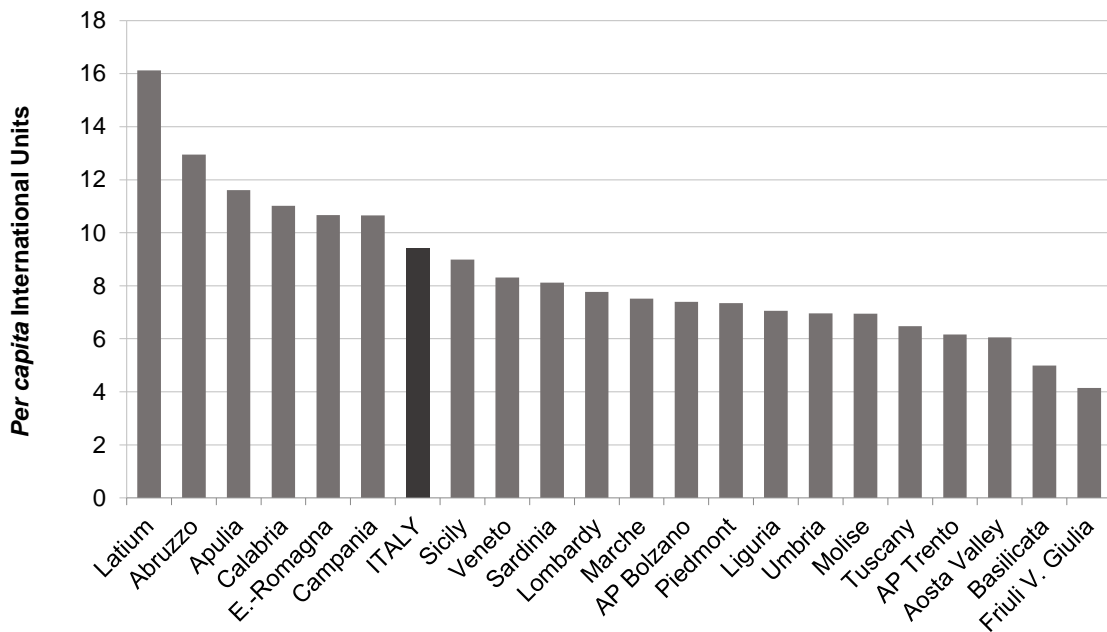


Figure 16. Total and regional demand (public and private) for coagulation Factor VIII, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

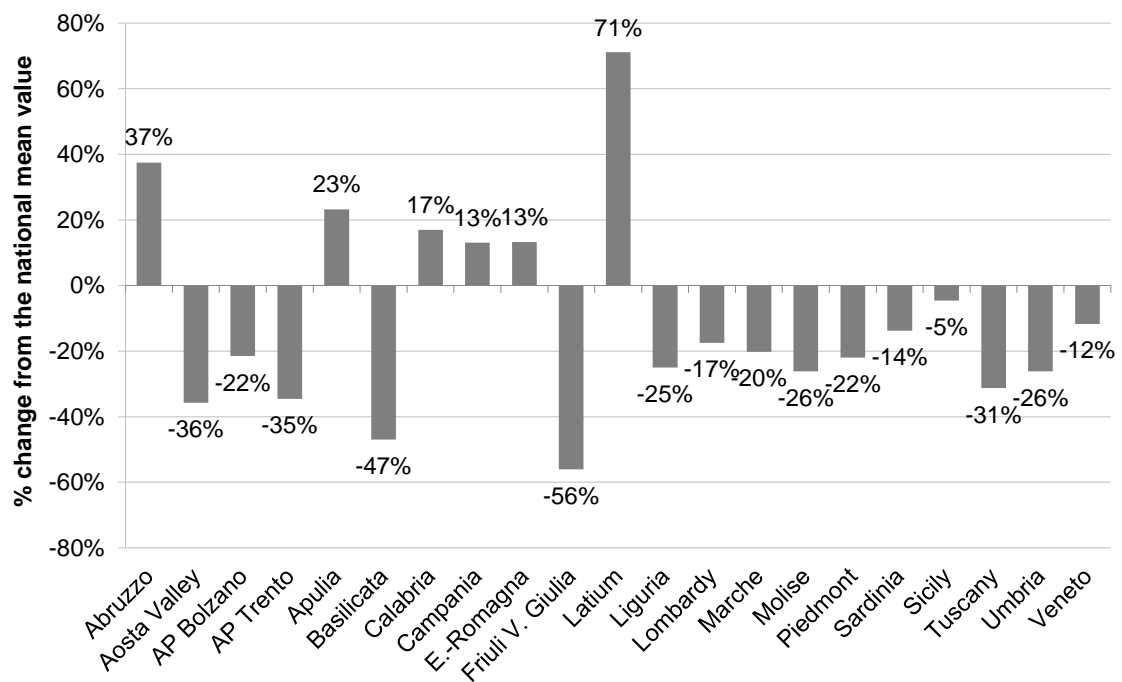


Figure 17. Percentage variation from the national mean value of standardized regional demand for coagulation Factor VIII in 2022 (adapted by the CNS on data from the Traceability information flow)

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

In 2022, the national demand for pdFVIII was about 17% - equivalent to 92,680,500 IUs - of the total demand. There is an upward trend of 1.2% compared to the 2021 value and a standardized total demand of 1.6 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	3,543,500	2.8	3,681,000	2.9	4.5
Aosta Valley	10,000	0.1	17,000	0.1	71.0
AP Bolzano	343,000	0.6	701,000	1.3	104.0
AP Trento	73,000	0.1	20,000	0.0	-72.6
Apulia	12,855,500	3.3	11,322,000	2.9	-11.4
Basilicata	168,000	0.3	38,000	0.1	-77.2
Calabria	2,276,500	1.2	1,873,500	1.0	-17.0
Campania	5,532,500	1.0	4,949,000	0.9	-10.0
E.-Romagna	5,110,000	1.2	6,456,000	1.5	26.5
Friuli V. Giulia	1,249,000	1.0	1,257,000	1.0	1.0
Lazio	13,782,000	2.4	11,678,500	2.0	-15.0
Liguria	1,199,000	0.8	874,000	0.6	-26.3
Lombardy	11,851,500	1.2	14,367,500	1.4	21.4
Marche	2,317,000	1.5	2,017,000	1.4	-12.5
Molise	646,000	2.2	284,000	1.0	-55.5
Piedmont	8,846,500	2.1	8,577,000	2.0	-2.5
Sardinia	1,877,200	1.2	2,250,000	1.4	20.7
Sicily	5,028,000	1.0	4,644,000	1.0	-6.2
Tuscany	6,719,000	1.8	7,332,000	2.0	9.6
Umbria	1,068,000	1.2	740,500	0.9	-30.2
Veneto	7,564,500	1.6	9,601,500	2.0	27.3
Italy	92,059,700	1.6	92,680,500	1.6	1.2

Per capita demand varied significantly with the highest volumes in Apulia and Abruzzo (2.9 IUs *per capita*), Lazio, Piedmont, Tuscany and Veneto (2.0 IUs *per capita*); the corresponding percentage variation between the aforementioned values and the Italian mean value were of +84% in the case of the first two regions, +30%, +28%, +27% and +26%, respectively for the remaining four. The lowest volumes (below 1 IU *per capita*) were recorded in Basilicata, Campania, Liguria, AP of Trento, Umbria and Aosta Valley (Figures 18 and 19).

Despite the slight increase recorded at the national level, twelve Italian regions show declining demand (range: -77%; -2.5%); in contrast, Abruzzo, Emilia-Romagna, Friuli V. Giulia, Lombardy, PA of Bolzano, Sardinia, Tuscany, Aosta Valley and Veneto show increases ranging from 1% to 104%.

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

Table 18. Total demand (public and private) and total standardised demand for plasma-derived coagulation FVIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	94,000	0.1	130,000	0.1	39.1
Aosta Valley	-	-	-	-	NA
AP Bolzano	300,000	0.6	400,000	0.7	33.1
AP Trento	-	-	-	-	NA
Apulia	5,860,000	1.5	5,687,000	1.5	-2.4
Basilicata	87,000	0.2	20,000	0.0	-76.8
Calabria	565,000	0.3	300,000	0.2	-46.4
Campania	20,000	0.0	261,000	0.0	1212.8
E.-Romagna	1,725,000	0.4	2,330,000	0.5	35.3
Friuli V. Giulia	868,000	0.7	680,000	0.6	-21.4
Latium	5,890,000	1.0	5,167,000	0.9	-12.0
Liguria	835,000	0.5	390,000	0.3	-53.0
Lombardy	7,456,000	0.7	9,449,000	0.9	26.9
Marche	1,880,000	1.3	1,352,000	0.9	-27.7
Molise	344,000	1.2	100,000	0.3	-70.6
Piedmont	6,097,000	1.4	5,962,000	1.4	-1.7
Sardinia	427,000	0.3	633,000	0.4	49.3
Sicily	785,000	0.2	881,000	0.2	13.0
Tuscany	4,165,000	1.1	4,358,000	1.2	5.1
Umbria	226,000	0.3	125,000	0.1	-44.3
Veneto	4,982,000	1.0	6,803,000	1.4	37.0
Italy	42,606,000	0.7	45,028,000	0.8	6.1

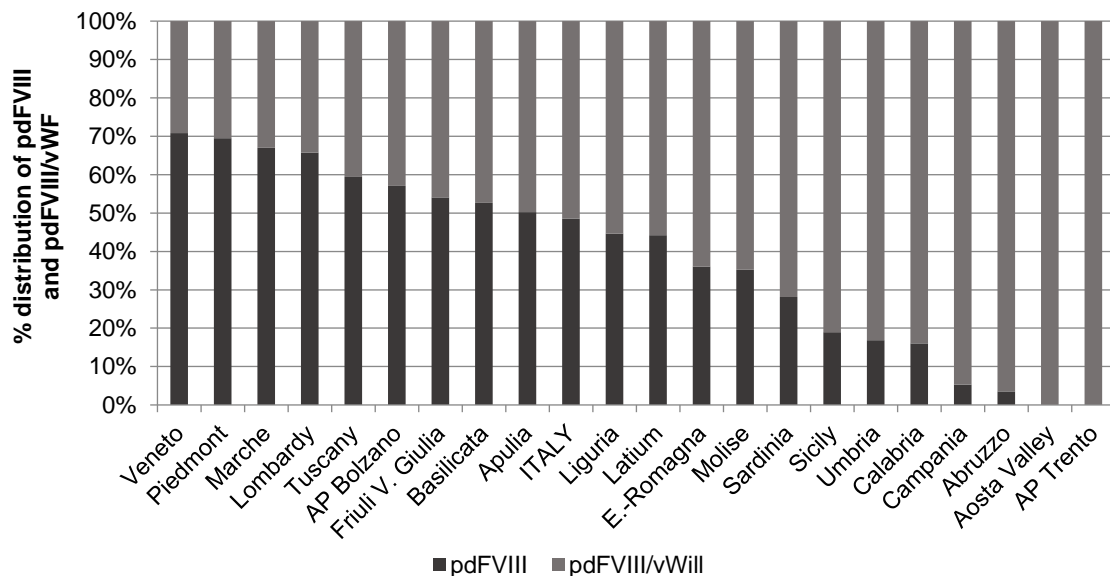


Figure 20. Percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination, by Region, 2022 (adapted by the CNS on data from the Traceability information flow)

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

In 2022, the national demand for FVIII and von Willebrand Factor in combination was 47,652,500 IUs, about 51% of the total demand for pdFVIII. The mean national demand *per capita* was 0.8 IUs, with a range between Regions of 0.03 IUs (Basilicata) and 2.8 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	3,449,500	2.7	3,551,000	2.8	3.5
Aosta Valley	10,000	0.1	17,000	0.1	71.0
AP Bolzano	43,000	0.1	301,000	0.6	598.9
AP Trento	73,000	0.1	20,000	0.0	-72.6
Apulia	6,995,500	1.8	5,635,000	1.4	-19.0
Basilicata	81,000	0.1	18,000	0.0	-77.6
Calabria	1,711,500	0.9	1,573,500	0.9	-7.3
Campania	5,512,500	1.0	4,688,000	0.8	-14.4
E.-Romagna	3,385,000	0.8	4,126,000	0.9	22.1
Friuli V. Giulia	381,000	0.3	577,000	0.5	52.0
Latium	7,892,000	1.4	6,511,500	1.1	-17.3
Liguria	364,000	0.2	484,000	0.3	33.9
Lombardy	4,395,500	0.4	4,918,500	0.5	12.1
Marche	437,000	0.3	665,000	0.4	53.0
Molise	302,000	1.0	184,000	0.6	-38.3
Piedmont	2,749,500	0.6	2,615,000	0.6	-4.4
Sardinia	1,450,200	0.9	1,617,000	1.0	12.3
Sicily	4,243,000	0.9	3,763,000	0.8	-10.7
Tuscany	2,554,000	0.7	2,974,000	0.8	17.0
Umbria	842,000	1.0	615,500	0.7	-26.4
Veneto	2,582,500	0.5	2,798,500	0.6	8.7
Italy	49,453,700	0.8	47,652,500	0.8	-3.2

The Regions with the highest *per capita* demand of FVIII and von Willebrand Factor in combination were Abruzzo (2.8 IUs), Apulia (1.4 IUs) and Latium (1.1 IUs). The lowest utilization equal to 0.03 IUs *per capita* was observed in Basilicata (Figure 21).

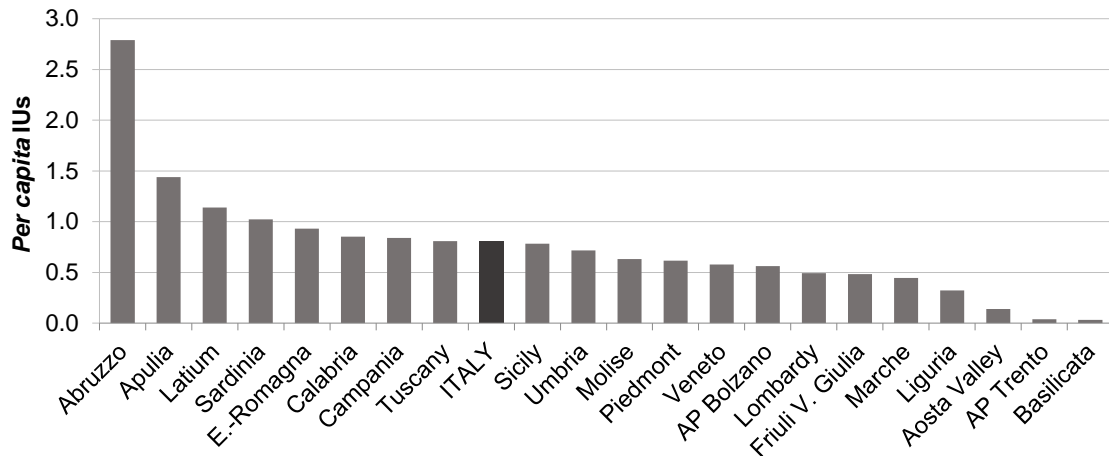


Figure 21. Total and regional demand (public and private) for pdFVIII and von Willebrand Factor in combination, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor VIII

In 2022, the total demand for rFVIII was 462,905,250 IUs, with a decrease of approximately -2.3% compared to 2021. The mean national demand *per capita* was about 8 IUs, with a range among different Regions of 3 IUs and 14 IUs (Table 20).

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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	10,761,250	8.4	12,814,250	10.1	19.8
Aosta Valley	930,000	7.5	729,000	5.9	-21.1
AP Bolzano	2,291,000	4.3	3,260,000	6.1	42.1
AP Trento	3,198,500	5.9	3,321,500	6.1	3.8
Apulia	35,243,750	9.0	34,097,500	8.7	-2.7
Basilicata	2,828,500	5.2	2,656,500	4.9	-5.2
Calabria	20,825,500	11.2	18,441,000	10.0	-10.7
Campania	61,222,000	10.9	54,593,750	9.8	-10.3
E.-Romagna	39,136,750	8.8	40,806,500	9.2	4.4
Friuli V. Giulia	3,577,250	3.0	3,704,000	3.1	3.9
Latium	83,805,750	14.6	80,468,000	14.1	-3.7
Liguria	8,447,500	5.6	9,769,000	6.5	16.5
Lombardy	64,115,000	6.4	63,098,500	6.3	-1.4
Marche	7,025,000	4.7	9,179,500	6.2	31.4
Molise	2,088,000	7.1	1,737,000	6.0	-15.8
Piedmont	25,039,750	5.9	22,676,000	5.3	-9.0
Sardinia	11,649,000	7.3	10,573,000	6.7	-8.6
Sicily	40,378,250	8.4	38,485,500	8.0	-4.0
Tuscany	18,505,750	5.0	16,477,500	4.5	-10.6
Umbria	5,370,500	6.2	5,238,500	6.1	-1.8
Veneto	29,280,000	6.0	30,778,750	6.3	5.4
Italy	475,719,000	8.0	462,905,250	7.8	-2.3

The Regions in which the highest *per capita* utilisation of rFVIII was observed were Latium (14.1 IUs), Abruzzo and Calabria (10 IUs) (Figure 22), with a percentage variation compared to the Italian mean value of +79%, +28% and +27%, respectively (Figure 23). The lowest utilisation – between 3.1 and 5.9 IUs *per capita* – was observed in Friuli V. Giulia, Tuscany, Basilicata, Piedmont and Aosta Valley.

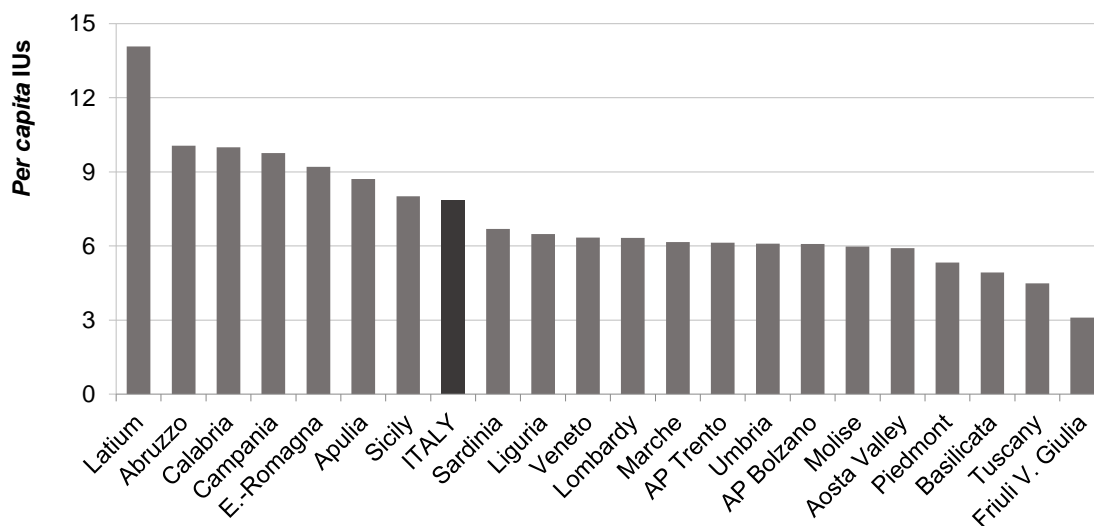


Figure 22. Total and regional demand (public and private) for recombinant coagulation Factor VIII, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

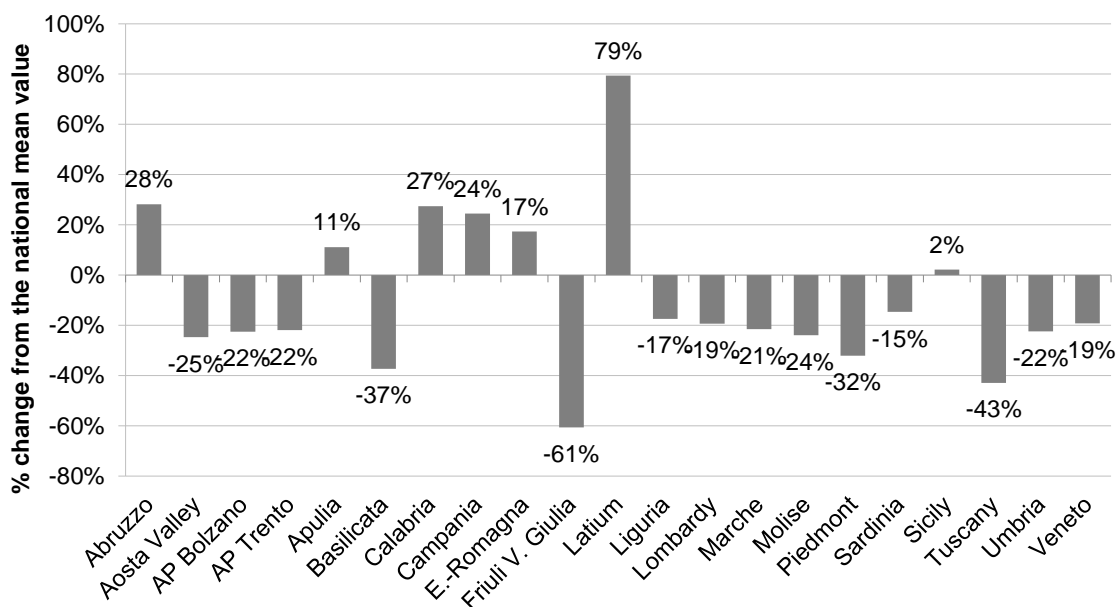


Figure 23. Percentage variation from the national mean value of standardised regional demand for recombinant coagulation Factor VIII in 2022 (adapted by the CNS on data from the Traceability information flow)

Extended half-life Recombinant Factor VIII

Part of the total demand for rFVIII is represented by drugs containing extended half-life molecules. In 2022, the demand for these products was equal to 237,769,500 IUs, about 51% of the total demand for rFVIII (Table 21).

Table 21. Total demand (public and private) and total standardised demand for long-acting recombinant coagulation Factor VIII, expressed in International Units and International Units *per capita* and variations in percentage between 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	5,491,000	4.3	7,535,250	5.9	38.0
Aosta Valley	546000	4.4	462000	3.7	-14.9
AP Bolzano	362,000	0.7	1,105,000	2.1	204.8
AP Trento	518000	1.0	708000	1.3	36.7
Apulia	8,892,000	2.3	15,406,250	3.9	74.2
Basilicata	444,000	0.8	616,000	1.1	40.1
Calabria	4,745,000	2.6	7,487,000	4.1	59.2
Campania	16,462,000	2.9	25,776,250	4.6	57.5
E.-Romagna	19,501,000	4.4	24,667,500	5.6	26.7
Friuli V. Giulia	2,857,250	2.4	3,006,000	2.5	5.6
Latium	31,711,750	5.5	40,323,000	7.1	27.5
Liguria	5,913,000	3.9	7,529,000	5.0	28.3
Lombardy	22,807,250	2.3	29,428,750	3.0	29.2
Marche	3,599,000	2.4	5,502,000	3.7	53.7
Molise	949,000	3.2	1,668,000	5.7	77.9
Piedmont	12,378,000	2.9	13,342,000	3.1	8.4
Sardinia	1464000	0.9	2827000	1.8	94.4
Sicily	12,790,000	2.6	16,683,500	3.5	31.3
Tuscany	7,279,500	2.0	10,667,000	2.9	47.2
Umbria	2,026,000	2.3	2,219,000	2.6	10.3
Veneto	16,458,000	3.4	20,811,000	4.3	26.8
Italy	177,193,750	3.0	237,769,500	4.0	34.8

The national demand *per capita* was about 4 IUs, with a range among Regions of 1.1 IUs in Basilicata and 7.1 IUs in Latium (+75% as compared to national mean value) (Figures 24 and 25).

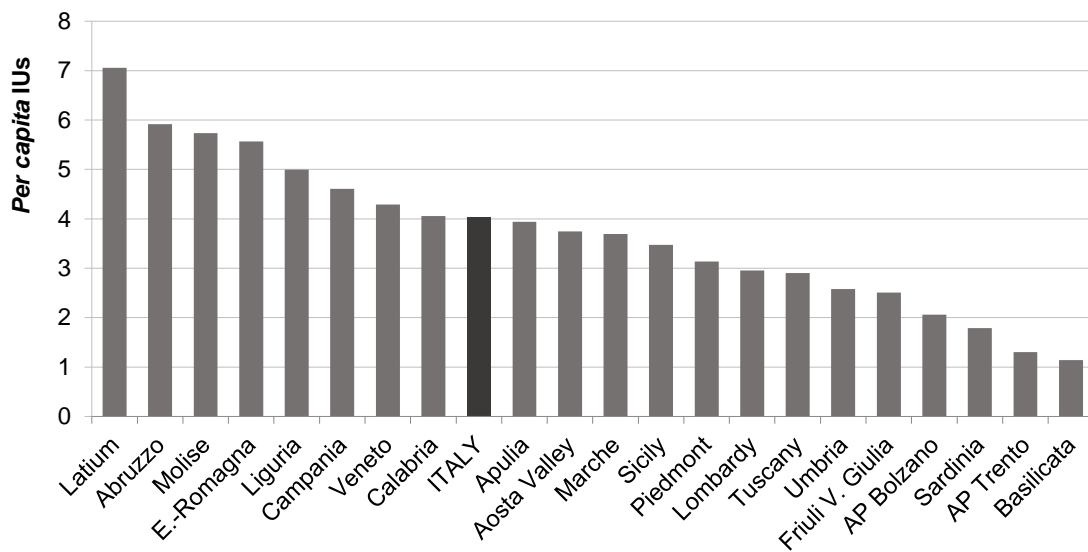


Figure 24. Total and regional demand (public and private) for extended half-life recombinant Factor VIII, expressed in International Units per capita, 2022 (adapted by the CNS on data from the Traceability information flow)

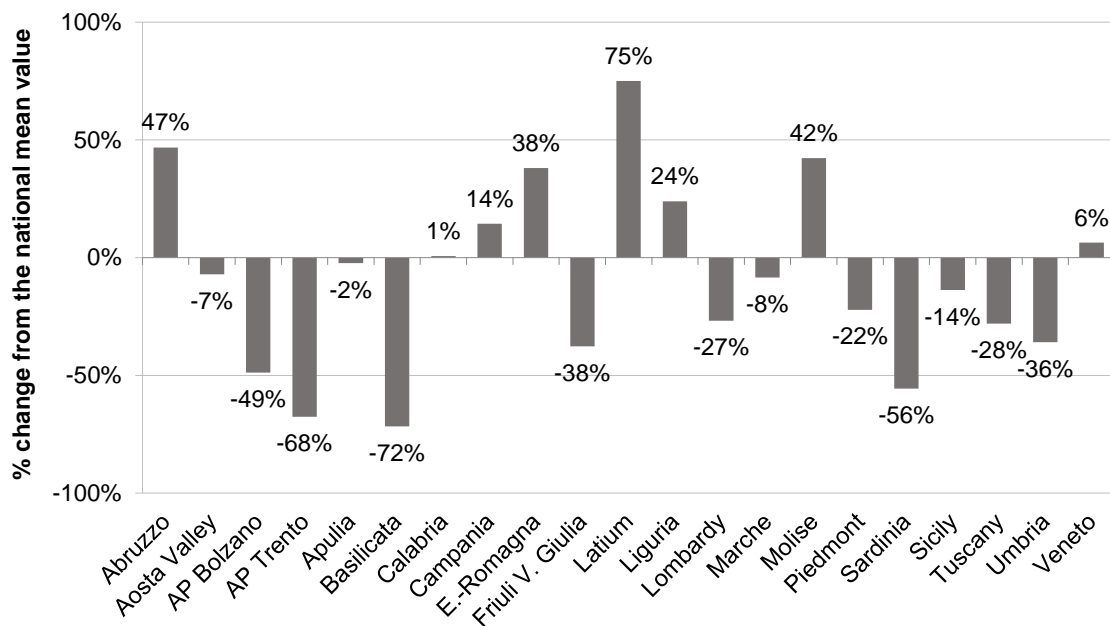


Figure 25. Percentage change from the national mean value of standardised regional demand for extended half-life recombinant Factor VIII in 2022 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2022)

AICcode	Brand name	mg	Manufacturer	NHS class
046130011	HEMLIBRA*SC1 FL 1 mL 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 1 mL 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 2022, 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 2022 and its was 2,059,275 mg, with an increase of +38% compared to the year 2021. The national demand (mg per 1,000 population) was about 35 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 0.8 mg in Sardinia to a maximum of 68 mg in Piedmont (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 2022 and variations in percentage between 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	mg	mg per 1,000 population	mg	mg per 1,000 population	
Abruzzo	31,305	24.4	47,745	37.5	53.4
Aosta Valley	-	-	7,350	59.6	100.0
AP Bolzano	10,635	19.9	13,620	25.4	27.9
AP Trento	-	-	-	-	NA
Apulia	50,805	12.9	74,055	18.9	46.6
Basilicata	13,500	24.8	17,760	32.9	32.8
Calabria	56,010	30.1	75,165	40.7	35.4
Campania	138,270	24.6	193,755	34.7	41.0
E.-Romagna	98,685	22.2	114,480	25.8	16.2
Friuli V. Giulia	22,560	18.8	33,390	27.9	48.5
Latium	65,655	11.5	81,105	14.2	23.9
Liguria	44,340	29.2	50,520	33.5	14.8
Lombardy	310,380	31.1	409,215	41.1	32.1
Marche	37,365	24.9	52,590	35.3	41.5
Molise	9,330	31.7	18,240	62.7	100.0
Piedmont	184,875	43.2	289,125	68.0	57.2
Sardinia	-	-	1,320	0.8	100.0
Sicily	113,655	23.5	127,620	26.6	13.0
Tuscany	151,800	41.1	219,240	59.6	45.1
Umbria	25,665	29.7	36,780	42.8	44.3
Veneto	134,655	27.7	196,200	40.4	46.2
Italy	1,499,490	25.3	2,059,275	34.9	37.9

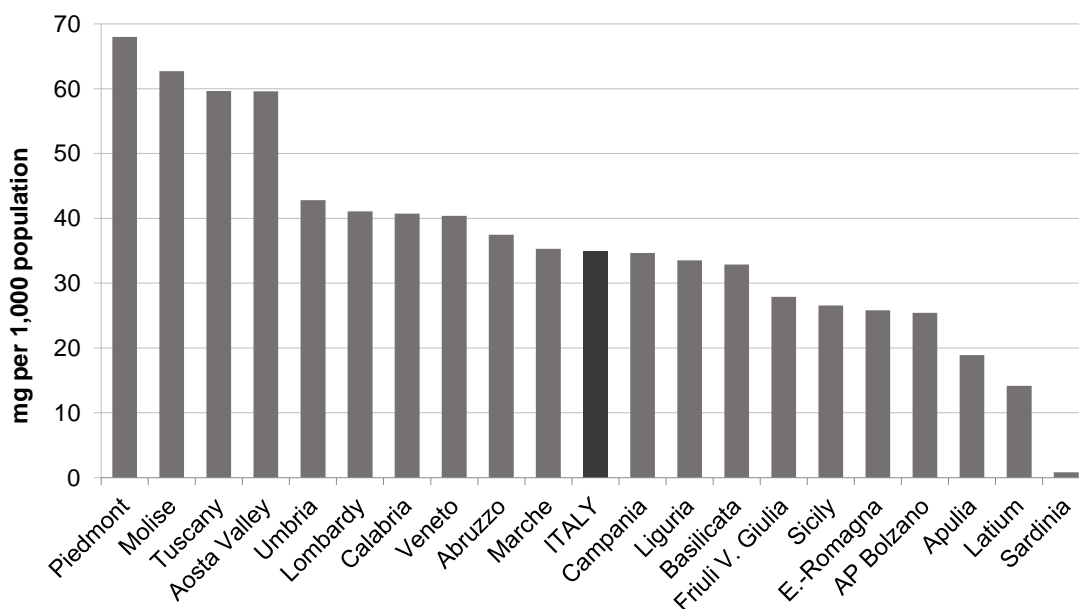


Figure 26. Total and regional demand (public and private) for Emicizumab expressed in mg per 1,000 population 2022 (adapted by the CNS on data from the Traceability information flow)

Figure 27 shows the variations in percentage of each Region compared to the national average. The Regions where the highest value was recorded are Piedmont (+ 95%) and Molise (+ 80%).

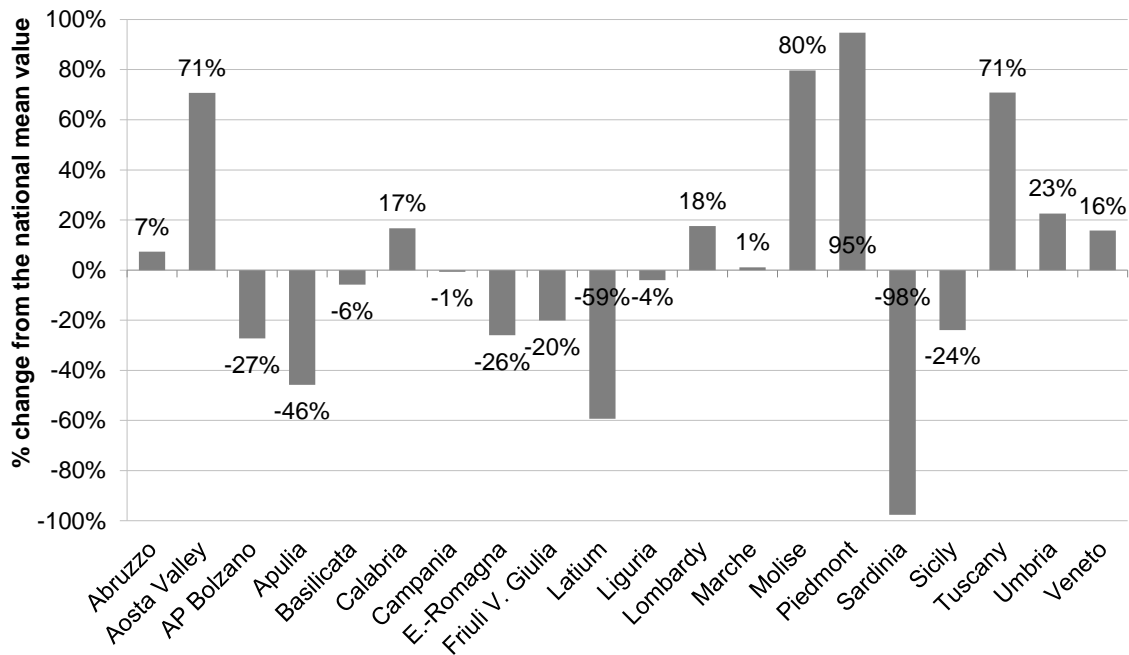


Figure 27. Percentage change from the national mean value of standardised regional demand for Emicizumab in 2022 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
025841089	AIMAFIX*FL 500 IU+FL 10 mL+SET	500	KEDRION SpA	A
028142026	MONONINE*EV F 500 IU+F 5 mL+KIT	500	CSL BEHRING SpA	A
029250065	ALPHANINE*EV 500 IU+SIR 10 mL+A	500	GRIFOLS ITALIA SpA	A
039072020	HAEMOBIONINE*1FL 500 IU	500	BIOTEST ITALIA Srl	A
040092013	OCTANINE*FL 500 IU+FL 5 mL	500	OCTAPHARMA Italy SpA	A
041799026	IXED*FL 500 IU+FL 10 mL+SET	500	KEDRION SpA	A
038324024	FIXNOVE*FL 600 IU+FL 10 mL	600	BAXALTA Italy Srl	A
025841103	AIMAFIX*FL 1000 IU+FL 10 mL+SET	1000	KEDRION SpA	A
028142038	MONONINE*EV F 1000 IU	1000	CSL BEHRING SpA	A
029250077	ALPHANINE "1000 IU/10 mL	1000	GRIFOLS ITALIA SpA	A
039072032	HAEMOBIONINE*1FL 1000 IU	1000	BIOTEST ITALIA Srl	A
040092025	OCTANINE*FL 1000 IU+FL	1000	OCTAPHARMA Italy SpA	A
041799038	IXED*FL 1000 IU+FL 10 mL+SET	1000	KEDRION SpA	A
038324036	FIXNOVE*FL 1200 IU+FL 10 mL	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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
033535016	BENEFIX*IV 1FL 250 IU	250	PFIZER ITALIA Srl	A
033535042	BENEFIX*IV 1FL 250 IU+SIR 5 mL+SE	250	PFIZER ITALIA Srl	A
043796010	RIXUBIS*IV 1FL 250 IU 5 mL	250	BAXTER SpA	A
033535028	BENEFIX*IV 1FL 500 IU	500	PFIZER ITALIA Srl	A
033535055	BENEFIX*IV 1FL 500 IU+SIR 5 mL+SE	500	PFIZER ITALIA Srl	A
043796022	RIXUBIS*IV 1FL 500 IU 5 mL	500	BAXTER SpA	A
033535030	BENEFIX*IV 1FL 1000 IU	1000	PFIZER ITALIA Srl	A
033535067	BENEFIX*IV 1FL 1000 IU+SIR 5 mL+S	1000	PFIZER ITALIA Srl	A
043796034	RIXUBIS*IV 1FL 1000 IU 5 mL	1000	BAXTER SpA	A
033535093	BENEFIX*IV 1FL 1500 IU+SIR5 mL+S	1500	PFIZER EUROPE MA EEIG	A
033535079	BENEFIX*IV 1FL 2000 IU+SIR 5 mL+S	2000	PFIZER ITALIA Srl	A
043796046	RIXUBIS*IV 1FL 2000 IU 5 mL	2000	BAXTER SpA	A
033535081	BENEFIX*IV 1FL 3000 IU+SIR 5 mL+S	3000	PFIZER ITALIA Srl	A
043796059	RIXUBIS*IV 1FL 3000 IU 5 mL	3000	BAXTER SpA	A

AIC code	Brand name	IU	Manufacturer	NHS class
Extended half- recombinant Factor IX life				
044888016	ALPROLIX*1FL 250 IU+1SIR 5 mL	250	SOBI Srl	A
044891012	IDELVION*EV FL 250 IU+FL 2,5 mL	250	CSL BEHRING SpA	A
044888028	ALPROLIX*1FL 500 IU+1SIR 5 mL	500	SOBI Srl	A
044891024	IDELVION*EV FL 500 IU+FL 2,5 mL	500	CSL BEHRING SpA	A
045488018	REFIXIA*EV FL 500 IU+ FL 4 mL+SIR	500	NOVO NORDISK A/S	C
044888030	ALPROLIX*1FL 1000 IU+1SIR 5 mL	1000	SOBI Srl	A
044891036	IDELVION*EV FL 1000 IU+FL 2,5 mL	1000	CSL BEHRING SpA	A
045488020	REFIXIA*EV FL 1000 IU+ 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 2000 IU+1SIR 5 mL	2000	SOBI Srl	A
044891048	IDELVION*EV FL 2000 IU+FL 2,5 mL	2000	CSL BEHRING SpA	A
044888055	ALPROLIX*1FL 3000 IU+1SIR 5 mL	3000	SOBI Srl	A
044891051	IDELVION*EV FL 3500 IU+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 2021-2022, at national and regional levels. The total demand for FIX formulations recorded in 2022 was 64,363,850 IUs (Table 26); about 11% of the aforementioned amount (6,870,100 IUs) was plasma-derived. There was an increasing demand for both pdFIX (+25%) and rFIX (+4%).

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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,191,250	1.7	2,511,500	2.0	15.3
Aosta Valley	-	-	-	-	NA
APBolzano	61,250	0.1	49,500	0.1	-19.3
APTrento	202,000	0.4	570,500	1.1	182.4
Apulia	6,072,500	1.5	5,769,000	1.5	-4.5
Basilicata	310,250	0.6	309,500	0.6	0.7
Calabria	1,993,000	1.1	1,591,500	0.9	-19.5
Campania	6,710,750	1.2	6,933,500	1.2	3.9
E.-Romagna	3,729,750	0.8	4,681,500	1.1	25.7
Friuli V. Giulia	727,000	0.6	1,075,500	0.9	48.5
Latium	6,077,250	1.1	4,999,200	0.9	-17.5
Liguria	1,881,000	1.2	2,063,000	1.4	10.5
Lombardy	9,947,500	1.0	10,750,600	1.1	8.3
Marche	2,085,200	1.4	2,147,600	1.4	3.6
Molise	20,000	0.1	76,000	0.3	284.6
Piedmont	4,934,000	1.2	4,851,000	1.1	-1.2
Sardinia	38,000	0.0	6,000	0.0	-84.1
Sicily	4,239,000	0.9	4,025,500	0.8	-4.4
Tuscany	6,142,000	1.7	7,930,950	2.2	29.7
Umbria	545,000	0.6	629,000	0.7	16.2
Veneto	3,249,000	0.7	3,393,000	0.7	4.8
Italy	61,155,700	1.0	64,363,850	1.1	5.7

* 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.

In 2022, the standardised demand for plasma-derived and recombinant FIX was 1.1 IU *per capita*, with significantly different regional trends: these ranged from a minimum – close to zero – in Sardinia (-99.6% compared to the Italian mean value), to a maximum in Tuscany (2.2 UI), Abruzzo and Apulia with respectively 2.0 IU and 1.5 IU *per capita* (+98%, +81%, +35% percentage change compared to the national mean value, respectively) (Figures 28 and 29). No consumption in Aosta Valley was registered.

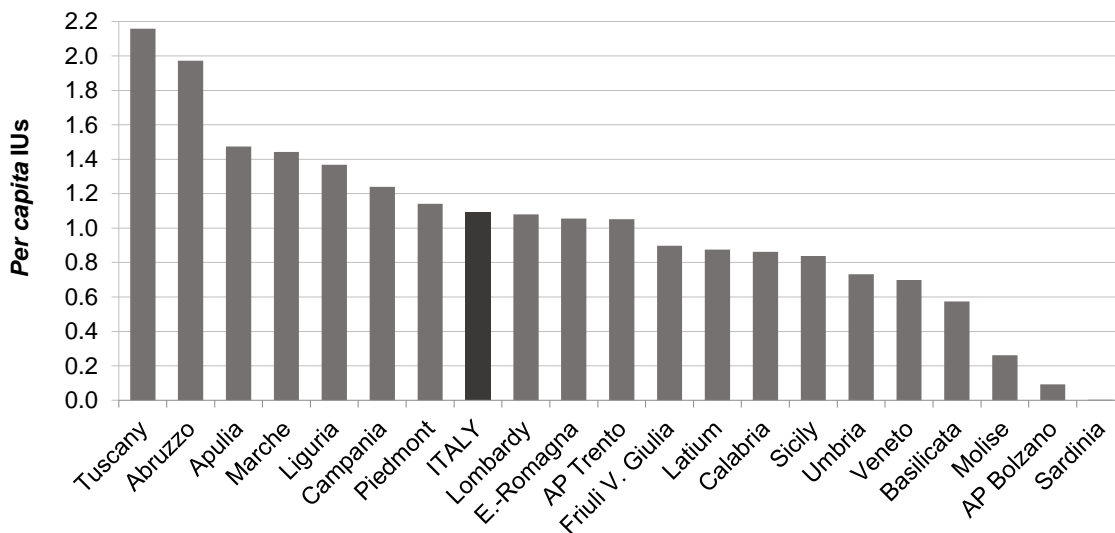


Figure 28. Total and regional demand (public and private) for coagulation Factor IX, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

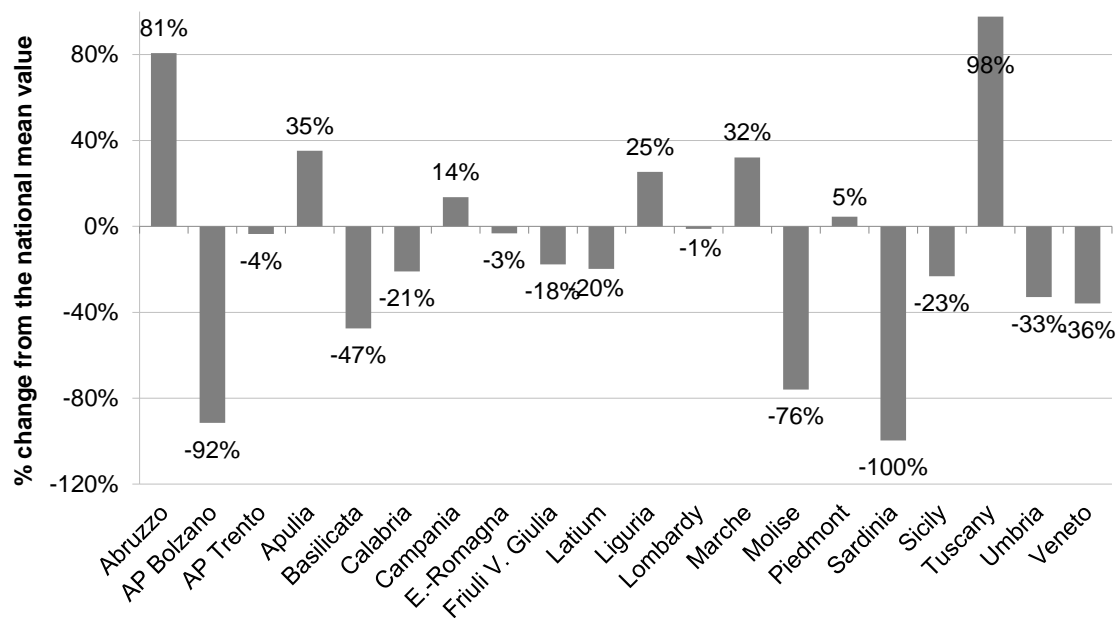


Figure 29. Percentage variation from the national mean value of standardized regional demand for coagulation Factor IX (International Units *per capita*) in 2022 (adapted by the CNS on data from the Traceability information flow)

In thirteen Regions there were percentage increases in demand (range: 0.7-285%) which is instead decreasing in seven Regions (range: -1.2; -84%) (Table 26). In Sardinia, AP of Trento, AP of Bolzano, Friuli V.Giulia and Abruzzo rFIX was used exclusively, while in Liguria, Campania, E.-Romagna, Calabria, Veneto, Basilicata and Sicily the rFIX demand reached volumes of above 95% (Figure 30).

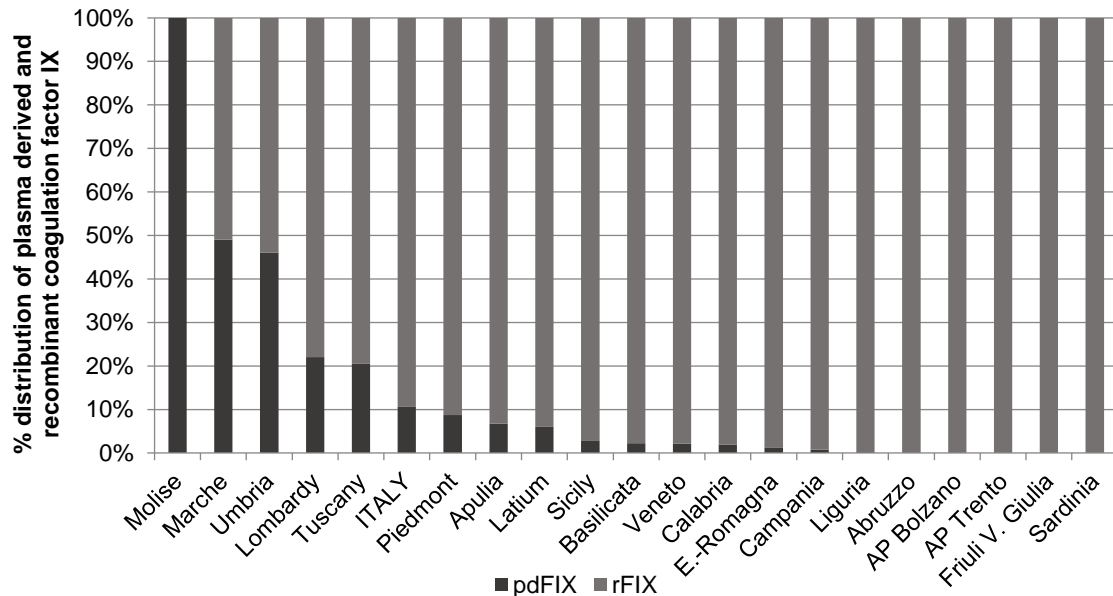


Figure 30. Distribution expressed in % of Factor IX per type, by Region, 2022 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor IX

In 2022, the total demand for pdFIX (expressed in absolute values and *per capita* volumes), showed an increase of 25% compared to 2021, for an absolute value of 6,870,100 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	56,000	0.1	-	-	-100.0
AP Trento	-	-	-	-	NA
Apulia	282,000	0.1	387,000	0.1	38.0
Basilicata	-	0.0	7,000	0.0	100.0
Calabria	20,000	0.0	31,000	0.0	56.3
Campania	12,000	0.0	54,000	0.0	352.7
E.-Romagna	77,000	0.0	59,000	0.0	-23.3
Friuli V. Giulia	-	-	-	-	NA
Latium	625,000	0.1	298,200	0.1	-52.2
Liguria	16,000	0.0	4,000	0.0	-74.8

Region	2021		2022		% Var 2021-2022
	IU	IU per capita	IU	IU per capita	
Lombardy	1,917,000	0.2	2,372,100	0.2	23.9
Marche	1,033,200	0.7	1,053,600	0.7	2.6
Molise	20,000	0.1	76,000	0.3	284.6
Piedmont	518,000	0.1	423,000	0.1	-17.9
Sardinia	-	-	-	-	NA
Sicily	116,000	0.0	118,000	0.0	2.4
Tuscany	188,000	0.1	1,625,200	0.4	768.4
Umbria	258,000	0.3	289,500	0.3	13.0
Veneto	374,500	0.1	72,500	0.0	-80.6
Italy	5,512,700	0.1	6,870,100	0.1	25.2

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

The Regions with the highest *per capita* demand were Marche and Tuscany with 0.7 IUs and 0.4 IUs respectively; in Abruzzo, Friuli V.Giulia, AP of Bolzano, AP of Trento, Sardinia and Aosta Valley there was no reported consumption of pdFIX (Figures 31 and 32).

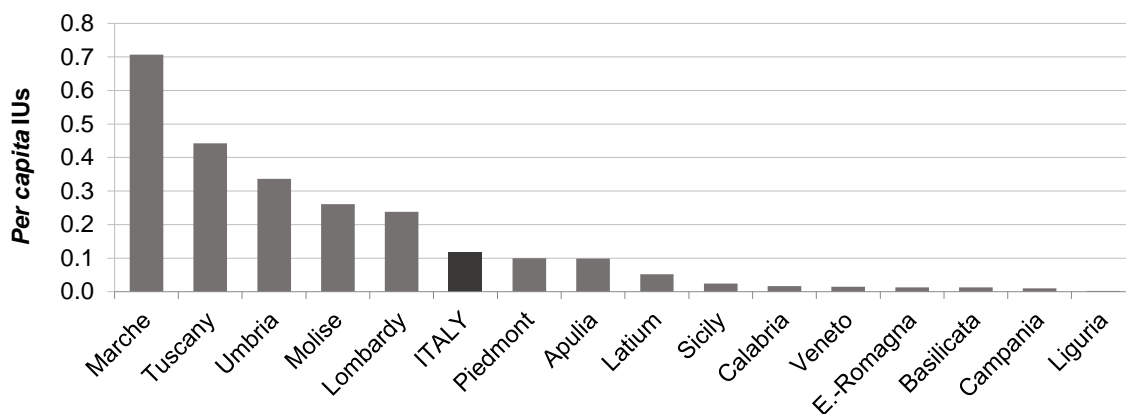


Figure 31. Total and regional demand (public and private) for plasma-derived coagulation Factor IX, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

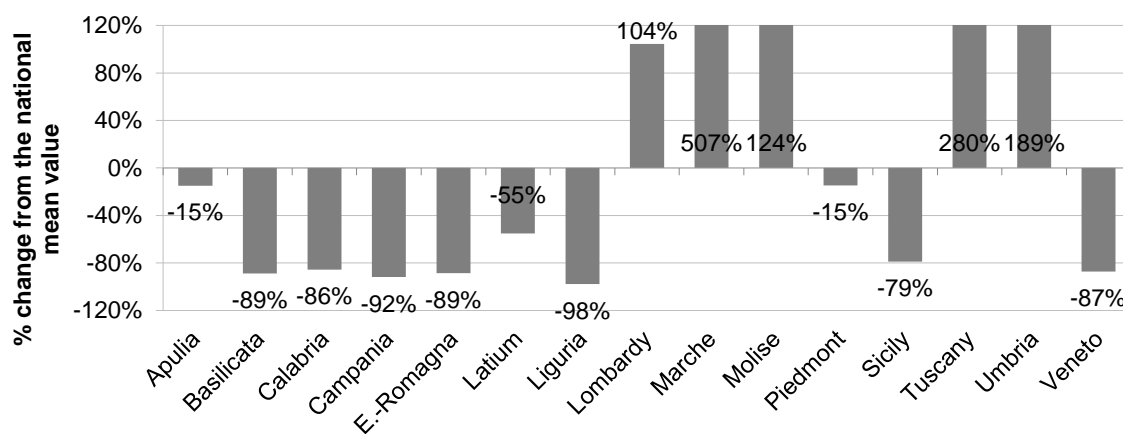


Figure 32. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor IX in 2022 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor IX

The total demand for rFIX showed, in the period 2021-2022, an increase of +3.8%, registering a value of 57,493,750 IUs in 2022, equal to 1.0 IU *per capita* (Table 28).

Table 28. Total demand (public and private) and total standardised demand for recombinant coagulation Factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,191,250	1.7	2,511,500	2.0	15.3
Aosta Valley	-	-	-	-	NA
AP Bolzano	5,250	0.0	49,500	0.1	841.3
AP Trento	202,000	0.4	570,500	1.1	182.4
Apulia	5,790,500	1.5	5,382,000	1.4	-6.5
Basilicata	310,250	0.6	302,500	0.6	-1.6
Calabria	1,973,000	1.1	1,560,500	0.8	-20.2
Campania	6,698,750	1.2	6,879,500	1.2	3.3
E.-Romagna	3,652,750	0.8	4,622,500	1.0	26.8
Friuli V. Giulia	727,000	0.6	1,075,500	0.9	48.5
Latium	5,452,250	1.0	4,701,000	0.8	-13.5
Liguria	1,865,000	1.2	2,059,000	1.4	11.2
Lombardy	8,030,500	0.8	8,378,500	0.8	4.5
Marche	1,052,000	0.7	1,094,000	0.7	4.6
Molise	-	-	-	-	NA
Piedmont	4,416,000	1.0	4,428,000	1.0	0.8
Sardinia	38,000	0.0	6,000	0.0	-84.1
Sicily	4,123,000	0.9	3,907,500	0.8	-4.6
Tuscany	5,954,000	1.6	6,305,750	1.7	6.4
Umbria	287,000	0.3	339,500	0.4	19.1
Veneto	2,874,500	0.6	3,320,500	0.7	15.9
Italy	55,643,000	0.9	57,493,750	1.0	3.8

The Regions with the highest *per capita* demand (Figure 33) were Abruzzo, Tuscany, Apulia, Liguria and Campania with 2.0 IU for the first one, 1.7 IU for the second one, 1.4 IU for the third and fourth and 1.2 IU for the last (+102%, +76%, +41%, +40% and +26% compared to the national average) (Figure 34).

In Aosta Valley and Molise there was no reported consumption of rFIX in 2022.

In 2022 there was an increase in *per capita* demand, compared to 2021, which is particularly evident in the AP of Trento (+182%) and in the AP of Bolzano (+841%); instead a significant decrease occurred in Sardinia (-84%).

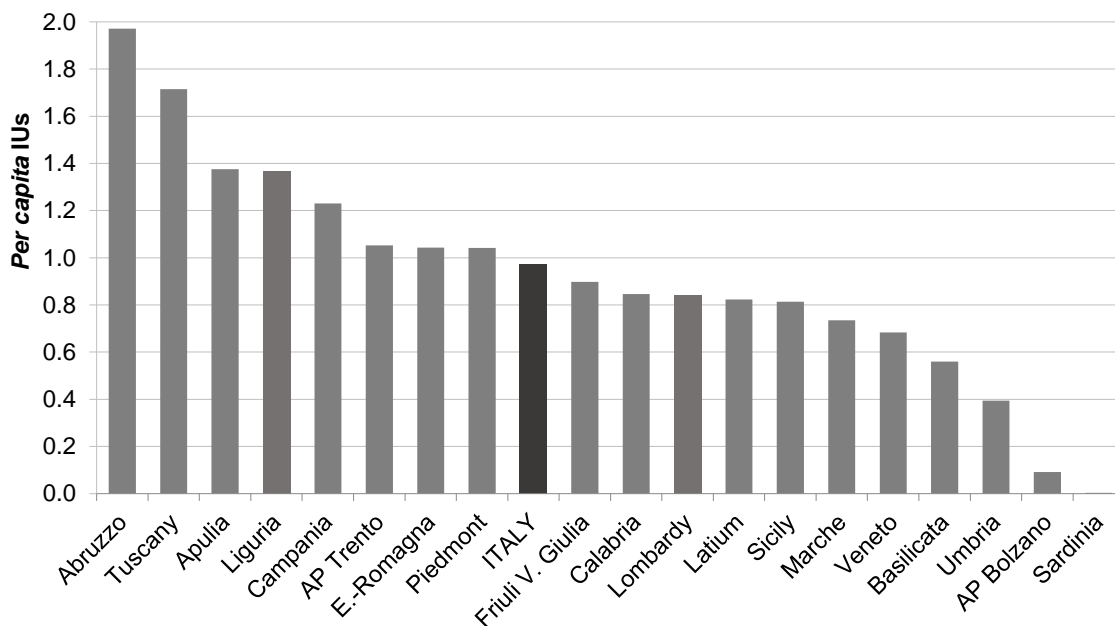


Figure 33. Total and regional demand (public and private) for recombinant coagulation Factor IX, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

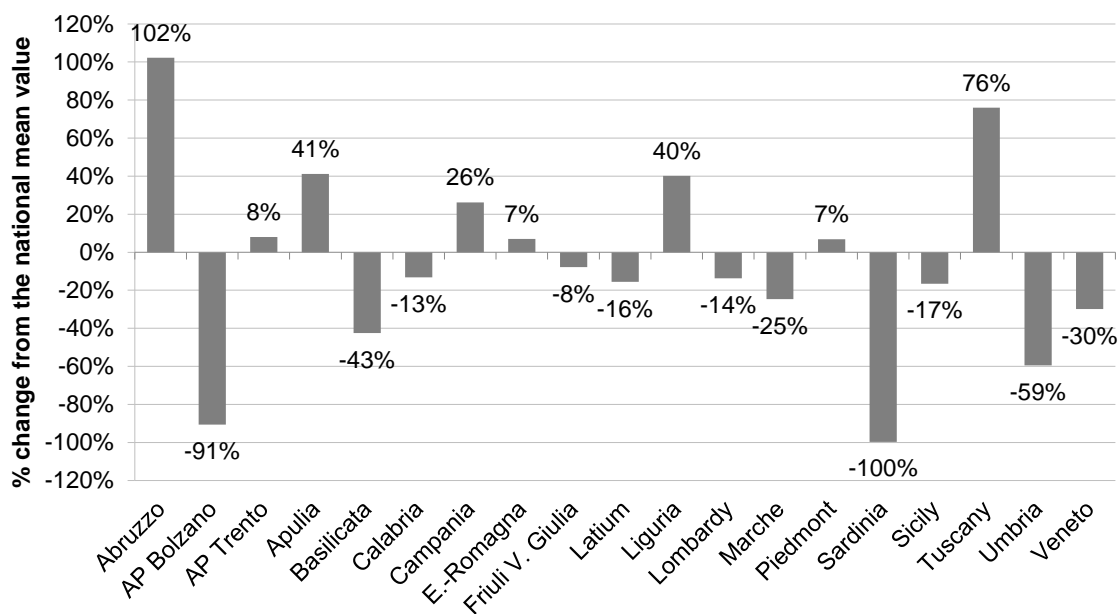


Figure 34. Percentage variation from the national mean value of standardised regional demand for recombinant coagulation Factor IX in 2022 (adapted by the CNS on data from the Traceability information flow)

Extended half- recombinant Factor IX life

Out of 57.5 million IUs of rFIX demand, extended half-life recombinant Factor IX molecules recorded a total demand of 38,672,750 IUs, about 67% of the total (Table 29).

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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	1,609,500	1.3	1,995,500	1.6	24.7
Aosta Valley	-	-	-	-	NA
AP Bolzano	250	0.0	48,000	0.1	19069.1
AP Trento	-	-	24,500	0.0	100.0
Apulia	4,788,500	1.2	4,211,000	1.1	-11.6
Basilicata	94,250	0.2	125,500	0.2	34.4
Calabria	777,000	0.4	1,066,500	0.6	38.5
Campania	2,870,750	0.5	3,417,500	0.6	19.8
E.-Romagna	3,090,250	0.7	3,945,000	0.9	27.9
Friuli V. Giulia	701,000	0.6	1,067,500	0.9	52.8
Latium	2,546,250	0.4	2,714,500	0.5	6.9
Liguria	1,690,000	1.1	1,865,000	1.2	11.2
Lombardy	6,427,500	0.6	6,544,500	0.7	2.0
Marche	774,000	0.5	966,000	0.6	25.5
Molise	-	-	-	-	NA
Piedmont	2,630,500	0.6	2,765,500	0.7	5.7
Sardinia	-	-	-	-	NA
Sicily	1,959,000	0.4	2,230,500	0.5	14.6
Tuscany	2,488,000	0.7	2,756,750	0.7	11.3
Umbria	221,000	0.3	327,500	0.4	49.2
Veneto	2,169,500	0.4	2,601,500	0.5	20.3
Italy	34,837,250	0.6	38,672,750	0.7	11.5

The mean national demand *per capita* was about 0.7 IU, with a range among Regions of 0.05 IU and 1.6 IU. In Molise, Sardinia and in the Aosta Valley there was no consumption for these drugs in 2022 (Figure 35 and 36).

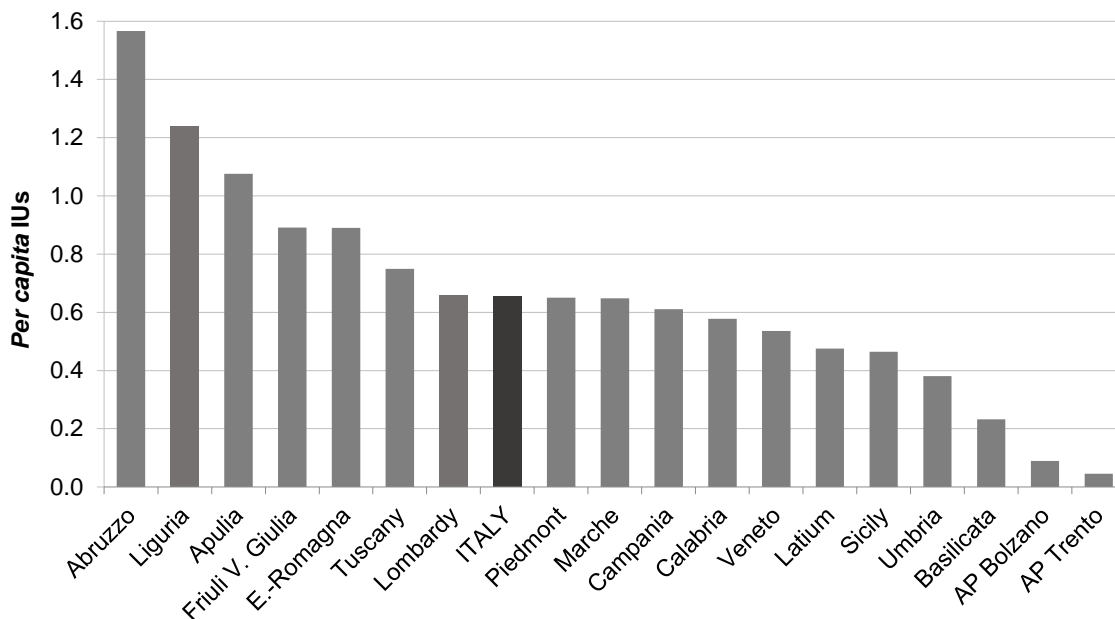


Figure 35. Total and regional demand (public and private) for extended half-life recombinant Factor IX, expressed in International Units per capita, 2022 (adapted by the CNS on data from the Traceability information flow)

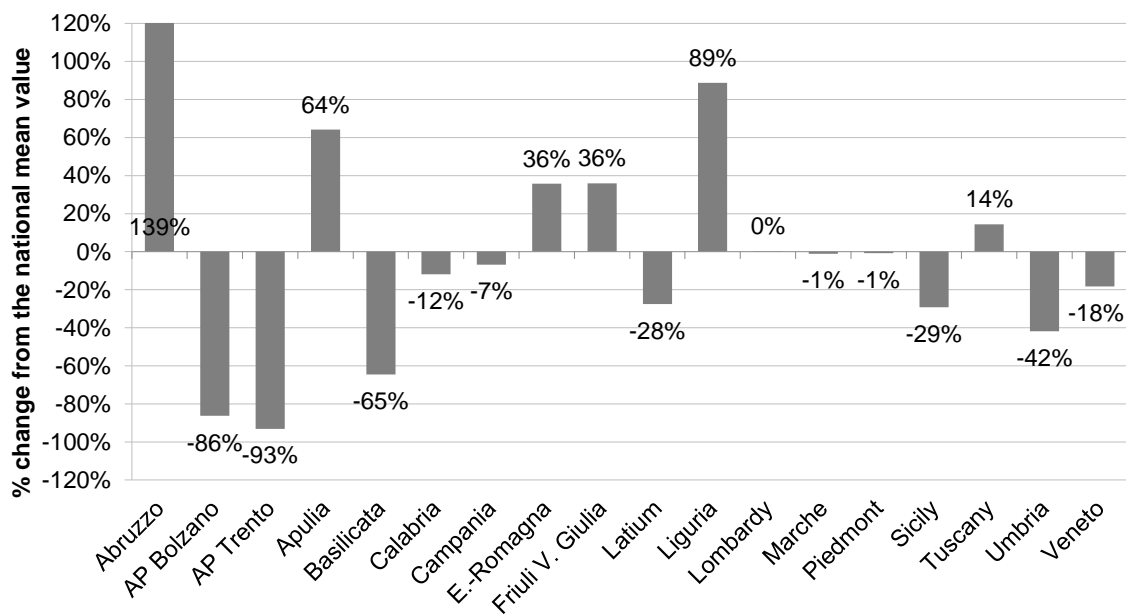


Figure 36. Percentage variation from the national mean value of standardised regional demand for extended half-life recombinant Factor IX in 2022 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2022)

AICcode	Brand name	IU	Manufacturer	NHS class
023309103	UMANCOMPLEX D.I.*FL 500 IU+F20 mL	500	KEDRION SpA	A
041850013	KEDCOM*FL 500 IU+FL 20 mL+SET	500	KEDRION SpA	H
023288032	PROTROMPLEX TIM3*F 600 IU+20 mL	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, 31/12/2022)

AICcode	Brand name	IU	Manufacturer	NHS class
049861014	COFACT*FL 250 UI + FL SOLV 10 mL	250	Prothya Biosolutions Netherlands B.V.	C(nn)
038844015	CONFIDEX*500 IU+1FL SOLV 20 mL	500	CSL BEHRING GMBH	H
039240015	PRONATIV*500 IU+FL SOLV 20 mL	500	OCTAPHARMA Italy	H
049861026	COFACT*FL 500 UI + FL SOLV 20 mL	500	Prothya Biosolutions Netherlands B.V.	C(nn)
043304017	PROPLEX*FL 600 IU/20 mL+FL SOLV	600	BAXALTA Italy Srl	H
038844027	CONFIDEX 1000*FL POLV+FL 40 mL	1000	CSL BEHRING SpA	H
039240027	PRONATIV*1000 IU+FL SOLV 20 mL	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 2021-2022, at both national and regional level.

In 2022 there was a slight increase in the total demand (+2%) compared to 2021; it stood at 36,652,200 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 (Abruzzo) to 1.0 IU (Veneto), with a percentage change compared to the Italian mean value of over 50% for the latter (Figures 37 and 38). In 2022, the national demand for 4F-PCCs was 18,929,900 IUs, equal to 34% of the overall demand for PCCs, with a standardised demand of 0.3 IU *per capita* and with an increase of 23% 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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	371,000	0.3	156,000	0.1	-57.7
AostaValley	115,000	0.9	45,000	0.4	-60.6
APBolzano	265,500	0.5	290,500	0.5	9.2
APTrento	332,500	0.6	431,500	0.8	29.8
Apulia	2,289,000	0.6	2,611,500	0.7	14.7
Basilicata	163,000	0.3	316,000	0.6	95.7
Calabria	705,500	0.4	678,000	0.4	-3.1
Campania	2,507,000	0.4	2,017,500	0.4	-19.0
E.-Romagna	3,774,500	0.9	3,386,000	0.8	-10.1
Friuli V. Giulia	150,000	0.1	560,500	0.5	275.0
Latium	1,797,500	0.3	1,781,500	0.3	-0.6
Liguria	1,272,500	0.8	876,500	0.6	-30.6
Lombardy	5,901,000	0.6	6,671,000	0.7	13.2
Marche	872,000	0.6	1,057,300	0.7	21.9
Molise	164,000	0.6	239,500	0.8	47.8
Piedmont	3,834,500	0.9	3,456,000	0.8	-9.4
Sardinia	1,452,500	0.9	930,000	0.6	-35.5
Sicily	3,148,000	0.7	3,174,000	0.7	1.5
Tuscany	2,776,300	0.8	3,068,400	0.8	11.0
Umbria	332,500	0.4	258,500	0.3	-21.7
Veneto	3,876,000	0.8	4,647,000	1.0	20.3
Italy	36,099,800	0.6	36,652,200	0.6	2.0

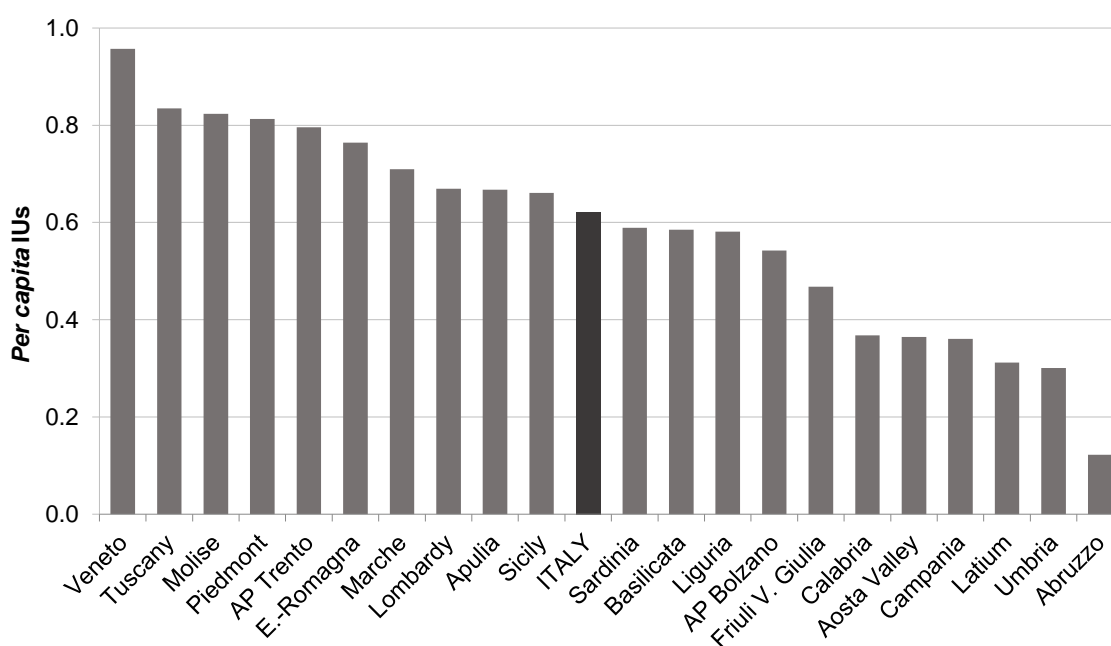


Figure 37. Total and regional demand (public and private) for 3-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

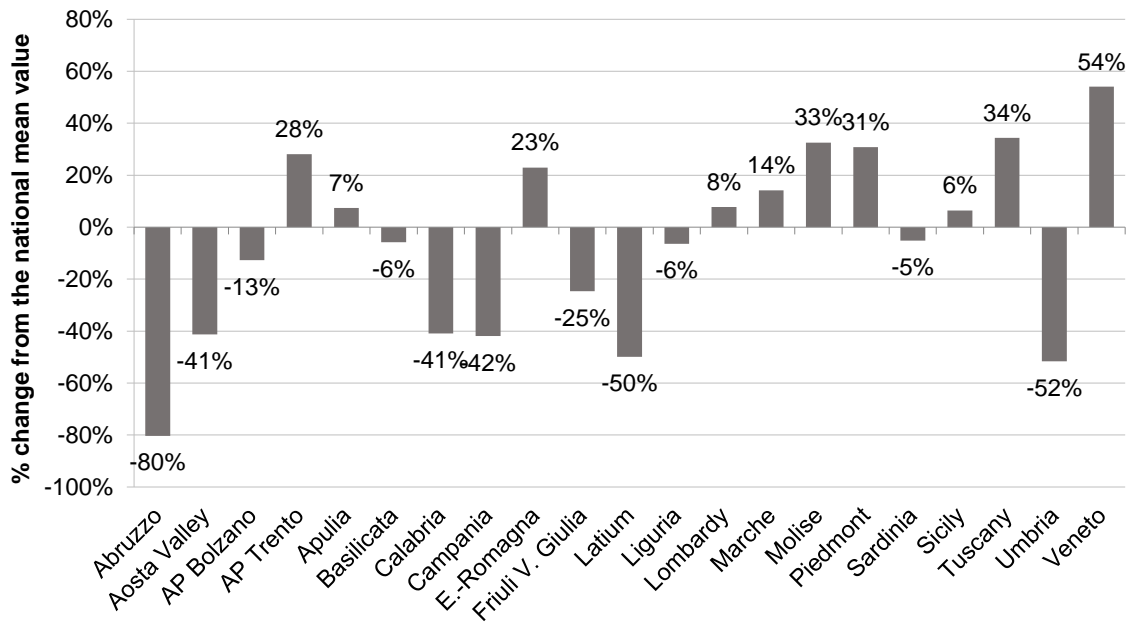


Figure 38. Percentage variation from the national mean value of standardised regional demand for 3-factor prothrombin complex concentrates in 2022 (adapted by the CNS on data from the Traceability information flow)

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 2021-2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	935,100	0.7	1,024,500	0.8	10.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	730,000	1.4	530,000	1.0	-27.5
AP Trento	41,000	0.1	87,500	0.2	113.4
Apulia	205,000	0.1	231,300	0.1	13.5
Basilicata	185,000	0.3	194,500	0.4	6.1
Calabria	267,500	0.1	354,000	0.2	33.5
Campania	1,715,000	0.3	1,641,500	0.3	-3.7
E.-Romagna	1,422,000	0.3	1,943,000	0.4	36.9
Friuli V. Giulia	-	-	-	-	NA
Latium	3,225,800	0.6	3,743,100	0.7	16.3
Liguria	649,000	0.4	968,000	0.6	50.2
Lombardy	1,105,000	0.1	1,687,500	0.2	53.0
Marche	169,500	0.1	201,500	0.1	19.6
Molise	-	-	-	-	NA
Piedmont	1,032,500	0.2	1,343,000	0.3	30.8
Sardinia	1,121,000	0.7	1,433,000	0.9	28.7
Sicily	627,000	0.1	691,500	0.1	11.0
Tuscany	1,462,000	0.4	1,622,000	0.4	11.4
Umbria	282,500	0.3	353,500	0.4	26.0
Veneto	236,500	0.0	880,500	0.2	273.5
Italy	15,411,400	0.3	18,929,900	0.3	23.4

Also for 4F-PCCs, there were considerable differences regarding its utilisation from one Region to another. With the exception of Campania and AP Bolzano, all the Regions recorded significant increases in the demand. The Region with the highest demand in 2022 was the AP of Bolzano with 1.0 IU *per capita*, followed by Sardinia, Abruzzo and Latium with 0.9 IU, 0.8 UI and 0.7 IU *per capita* respectively (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 2022.

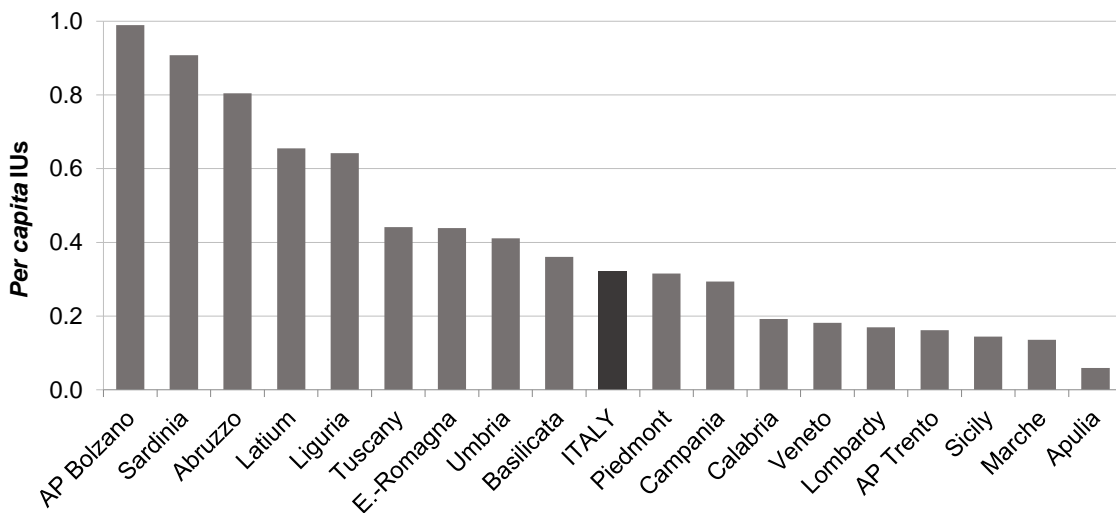


Figure 39. Total and regional demand (public and private) for 4-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2022 (adapted by the CNS on data from the Traceability information flow)

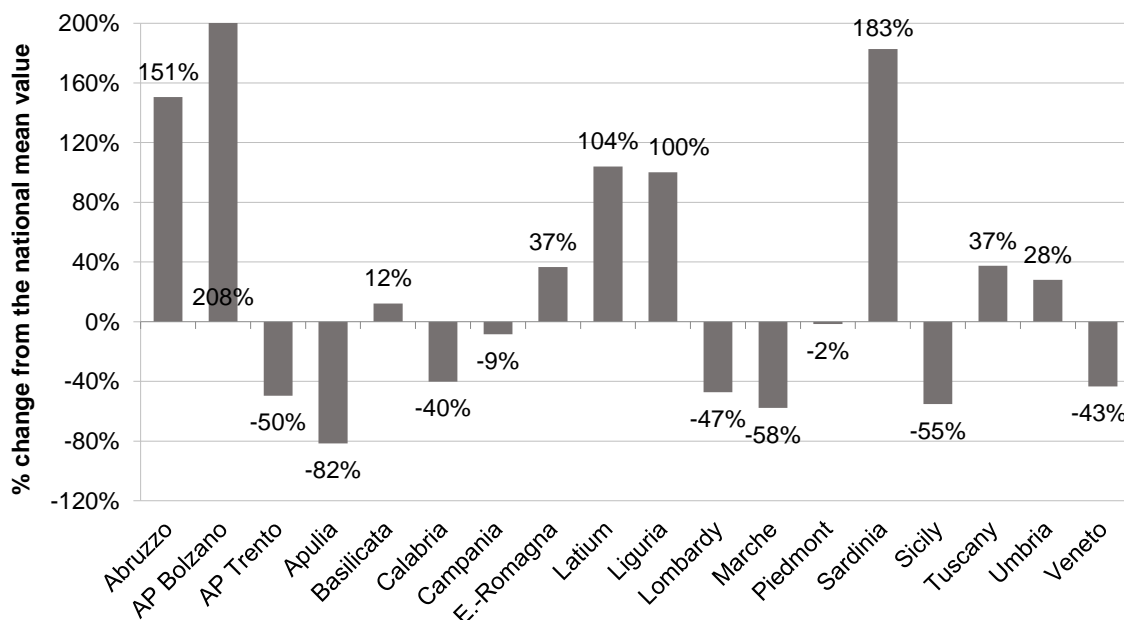


Figure 40. Percentage variation from the national mean value of standardised regional demand for 4-factor prothrombin complex concentrates in 2022 (adapted by the CNS on data from the Traceability information flow)

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 main component of the coagulation phase. Fibrin, therefore, can be considered both a structural protein and a coagulation factor.

In order to provide adequate structural support, the plasma concentration of fibrinogen must be relatively high. A deficiency of fibrinogen 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, 31/12/2022)

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+F50 mL	1	OCTAPHARMA Italy SpA	A
044380018	FIBRICLOTTE*FL POLV 1,5g 100 mL	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 2021-2022 at regional and national level.

In 2022, total fibrinogen demand showed a significant increase (+11.9%) compared to the previous year. Its volume of 59,872 g, with a standardised demand of 1.0 g per 1,000 population, confirmed the rapid upward trend. All Regions, with the exception of Calabria, E.-Romagna, Piedmont, AP of Trento, Apulia and Aosta Valley contributed to this growth to different extents.

Figure 41 shows the regional and national standardised demand for fibrinogen in 2022. The Regions with the highest demand per 1,000 population were Veneto (1.9 g), then Umbria (1.7 g), the AP of Bolzano (1.6 g) and Sardinia with 1.3 g. The lowest demand, between 0.2 g and 0.7 g per 1,000 population, was recorded in Aosta Valley, Molise, in the AP of Trento, Piedmont and Apulia.

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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2021		2022		% Var 2021-2022
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,266	1.0	1,491	1.2	18.5
Aosta Valley	50	0.4	30	0.2	-39.6
AP Bolzano	810	1.5	862	1.6	6.2
AP Trento	410	0.8	360	0.7	-12.2
Apulia	3,069	0.8	2,849	0.7	-6.7
Basilicata	430	0.8	635	1.2	49.0
Calabria	1,710	0.9	1,514	0.8	-10.7
Campania	4,356	0.8	4,955	0.9	14.4
E.-Romagna	4,484	1.0	4,473	1.0	-0.1
Friuli V. Giulia	1,100	0.9	1,465	1.2	33.7
Latium	6,037	1.1	6,873	1.2	14.2
Liguria	882	0.6	1,226	0.8	40.0
Lombardy	7,101	0.7	9,082	0.9	28.1
Marche	1,125	0.8	1,418	1.0	26.8
Molise	50	0.2	150	0.5	203.6
Piedmont	3,041	0.7	2,837	0.7	-6.2
Sardinia	2,038	1.3	2,060	1.3	1.8
Sicily	3,423	0.7	3,744	0.8	10.1
Tuscany	3,201	0.9	3,353	0.9	5.2
Umbria	1,215	1.4	1,420	1.7	17.7
Veneto	7,961	1.6	9,078	1.9	14.4
Italy	53,759	0.9	59,872	1.0	11.9

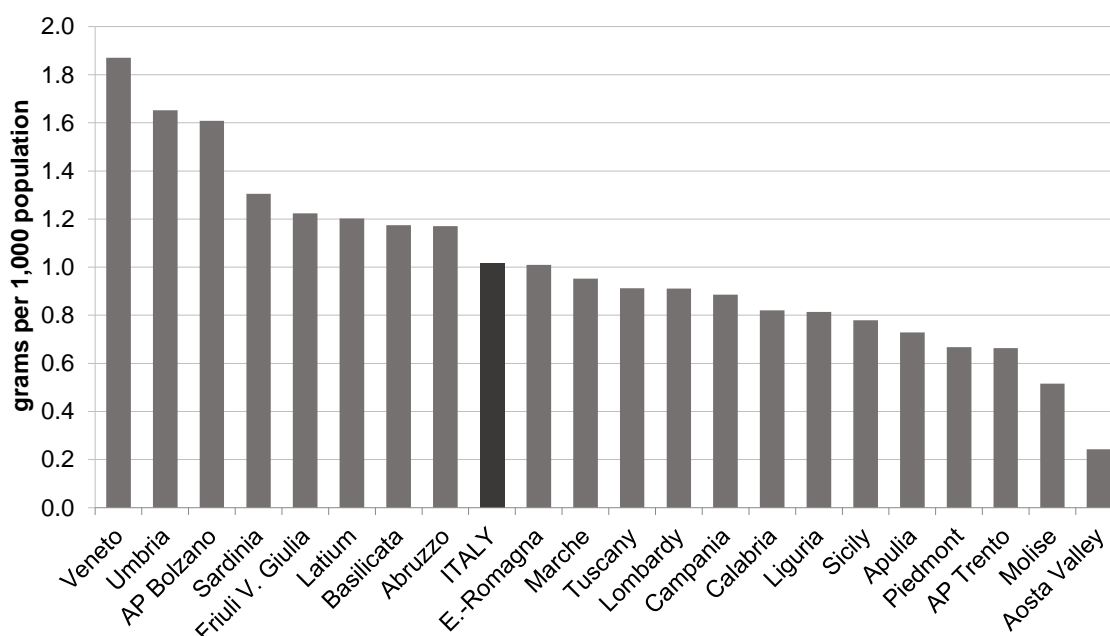


Figure 41. Total and regional demand (public and private) for fibrinogen, expressed in grams per 1,000 population, 2022 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2022)

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

Table 37. Products containing hepatitis B immunoglobulins for subcutaneous/intramuscular use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
023782028	UMAN BIG "180 IU/1 mL SOLUZ. INIET"	180	KEDRION SpA	A
025653015	IMMUNOHBS*IM 1F 1 mL 180 IU	180	KEDRION SpA	A
042002016	KEDHBS 180 IU/1 mL - 1FL 1 mL	180	KEDRION SpA	A
023782016	UMANBIG*IM 1FL 3mL 540 IU	540	KEDRION SpA	A
025653027	IMMUNOHBS*IM 1F 3mL 540 IU	540	KEDRION SpA	A
042002028	KEDHBS 540 IU/3mL - 1FL 3mL	540	KEDRION SpA	A
035320011	IGANTIBE*IM 1F 3mL 600 IU/3mL	600	ISTITUTO GRIFOLS S.A.	A
025653054	IMMUNOHBS*IM 1SIR 1000 IU 3mL	1000	KEDRION SpA	A
035320023	IGANTIBE*IM 1F 5 mL 1000 IU/5 mL	1000	ISTITUTO GRIFOLS S.A.	A
042002030	KEDHBS 1000 IU/3mL 1SIR 3mL	1000	KEDRION SpA	A
039644012	ZUTECTRA*SC 5SIR 1 mL 500 IU	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 2021-2022, at national and at regional level.

The national demand for hepatitis B IGs for IV use, showed a downward trend (-5.9%) already observed in previous years (34). The total demand in 2022 was almost 13,5 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow).

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	22,000	0.0	24,000	0.0	9.7
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	2,021,500	0.5	1,139,500	0.3	-43.3
Basilicata	1,000	0.0	1,000	0.0	1.0
Calabria	160,000	0.1	105,000	0.1	-33.8
Campania	3,133,000	0.6	2,855,000	0.5	-8.3
E.-Romagna	1,970,000	0.4	2,352,500	0.5	19.6
Friuli V. Giulia	245,000	0.2	-	-	-100.0
Latium	775,000	0.1	720,000	0.1	-6.8
Liguria	98,500	0.1	92,500	0.1	-5.4
Lombardy	1,419,000	0.1	1,009,500	0.1	-28.7
Marche	362,500	0.2	225,500	0.2	-37.4
Molise	-	-	-	-	NA
Piedmont	532,500	0.1	267,500	0.1	-49.5
Sardinia	665,000	0.4	601,000	0.4	-9.0
Sicily	457,500	0.1	495,000	0.1	8.9
Tuscany	1,290,000	0.3	860,000	0.2	-33.0
Umbria	-	-	-	-	NA
Veneto	1,210,000	0.2	2,703,000	0.6	124.1
Italy	14,362,500	0.2	13,451,000	0.2	-5.9

Veneto is the region with the highest demand (0.6 IU per capita), followed by Campania and Emilia-Romagna (both with 0.5 IU *per capita*) and Sardinia (with 0.4 IU *per capita*), together accounting for more than 60 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 2021; the total consumption for 2022 is approximately 61.2 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow).

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	591,720	0.5	544,180	0.4	-7.5
Aosta Valley	245,360	2.0	202,200	1.6	-17.1
AP Bolzano	160,760	0.3	132,040	0.2	-18.0
AP Trento	223,020	0.4	178,160	0.3	-20.1
Apulia	5,822,360	1.5	5,938,860	1.5	2.6
Basilicata	240,280	0.4	254,360	0.5	6.9
Calabria	1,377,640	0.7	1,296,400	0.7	-5.1
Campania	18,457,980	3.3	18,737,560	3.4	2.1
E.-Romagna	3,819,340	0.9	3,664,360	0.8	-3.9
Friuli V. Giulia	297,440	0.2	218,400	0.2	-26.3
Latium	2,398,360	0.4	2,313,740	0.4	-3.3
Liguria	680,840	0.4	538,700	0.4	-20.3
Lombardy	9,971,940	1.0	9,055,200	0.9	-9.0
Marche	660,320	0.4	659,980	0.4	0.5
Molise	181,100	0.6	184,780	0.6	3.3
Piedmont	5,138,000	1.2	4,627,540	1.1	-9.5
Sardinia	3,485,820	2.2	3,733,300	2.4	7.8
Sicily	2,976,140	0.6	2,877,280	0.6	-2.7
Tuscany	3,325,880	0.9	3,134,400	0.9	-5.3
Umbria	399,200	0.5	358,480	0.4	-9.6
Veneto	2,426,140	0.5	2,538,500	0.5	5.0
Italy	62,879,640	1.1	61,188,420	1.0	-2.3

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, 31/12/2022).

AIC code	Brand name	IU	Manufacturer	NHS class
022488047	TETANUSGAMMA*IM 1SIR 250 IU 2 mL	250	KEDRION SpA	A
022488062	TETANUSGAMMA*IM SIR 250 IU 1 mL	250	KEDRION SpA	A
022601088	TETABULIN*IM 1SIR 250 IU 1 mL	250	BAXTER SpA	A
022635041	GAMMATET P*IM 1F 250 IU 1 mL	250	CSL BEHRING SpA	A
022635066	GAMMATET P*IM 1SIR 250 IU 1 mL	250	CSL BEHRING SpA	A
033863010	IGANTET*IM 1SIR 1 mL 250 IU	250	GRIFOLS ITALIA SpA	A
022488050	TETANUSGAMMA*IM 1SIR 500 IU 2 mL	500	KEDRION SpA	A
022601090	TETABULIN*IM 1SIR 500 IU 2 mL	500	BAXTER SpA	A
022635054	GAMMATET P*IM 1F 500 IU 2 mL	500	CSL BEHRING SpA	A
022635078	GAMMATET P*IM 1SIR 500 IU 2 mL	500	CSL BEHRING SpA	A
033863022	IGANTET*IM 1SIR 2 mL 500 IU	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 2022 the total demand for tetanus IGs was 118,664,750 IUs (2 IUs *per capita*), showing an increase of +2% compared to 2021 (Table 41).

The Regions with the highest demand, expressed as standardised volume for the resident population, were Campania (3.9 IUs *per capita*), Abruzzo (3.4 IUs *per capita*), Basilicata (3.1 IUs *per capita*), Tuscany and Calabria (2.9 IUs *per capita*).

In 2022, the demand decreased – in some cases very significantly - in almost all Regions, with the exception of Sicily (+18%), Abruzzo (+6%), Basilicata (+13%), Liguria (+10%), Lombardy (+14%), Marche (+6%), Umbria (+25%) and Aosta Valley (+12%).

For the year 2022, 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	4,157,500	3.2	4,388,250	3.4	6.2
Aosta Valley	262,500	2.1	293,250	2.4	12.4
AP Bolzano	550,250	1.0	550,750	1.0	-0.1
AP Trento	552,250	1.0	466,000	0.9	-15.6
Apulia	6,735,000	1.7	6,149,750	1.6	-8.2
Basilicata	1,492,500	2.7	1,668,750	3.1	12.9
Calabria	5,919,750	3.2	5,304,750	2.9	-9.6
Campania	23,069,750	4.1	21,985,000	3.9	-4.1
E.-Romagna	6,032,500	1.4	5,921,500	1.3	-1.7
Friuli V. Giulia	461,500	0.4	235,000	0.2	-48.9
Latium	10,239,250	1.8	10,150,250	1.8	-0.6
Liguria	3,537,500	2.3	3,855,250	2.6	9.8
Lombardy	14,278,250	1.4	16,312,000	1.6	14.4
Marche	3,788,750	2.5	3,991,250	2.7	5.9
Molise	751,750	2.6	736,750	2.5	-0.8
Piedmont	4,584,000	1.1	4,353,500	1.0	-4.5
Sardinia	3,570,000	2.2	3,365,750	2.1	-5.1
Sicily	11,362,750	2.4	13,294,250	2.8	17.8
Tuscany	11,034,500	3.0	10,639,000	2.9	-3.1
Umbria	1,576,500	1.8	1,960,250	2.3	25.2
Veneto	3,169,500	0.7	3,043,500	0.6	-3.7
Italy	117,126,250	2.0	118,664,750	2.0	1.7

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, 31/12/2022)

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

Quantification of the demand

The national demand for anti-D GIs between 2021 and 2022 remained broadly stable and stood at 101,433,500 IUs in 2022 (1.7 IUs *per capita*), with the highest peak in the AP of Bolzano and the lowest level in Friuli V. Giulia (3.6 and 0.2 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,374,500	1.9	2,590,500	2.0	9.7
Aosta Valley	256,500	2.1	298,500	2.4	17.1
AP Bolzano	2,061,875	3.9	1,913,125	3.6	-7.4
AP Trento	1,510,625	2.8	1,475,000	2.7	-2.4
Apulia	6,033,000	1.5	5,184,000	1.3	-13.6
Basilicata	910,500	1.7	1,132,500	2.1	25.6
Calabria	2,257,500	1.2	2,706,000	1.5	20.9
Campania	6,282,000	1.1	5,240,000	0.9	-16.1
E.-Romagna	9,282,250	2.1	9,858,625	2.2	6.4
Friuli V. Giulia	195,000	0.2	225,000	0.2	15.8
Latium	10,243,500	1.8	7,974,750	1.4	-21.9
Liguria	2,748,500	1.8	2,498,500	1.7	-8.4
Lombardy	20,886,375	2.1	20,979,625	2.1	0.6

Region	2021		2022		% Var 2021-2022
	IU	IU per capita	IU	IU per capita	
Marche	2,695,500	1.8	2,794,500	1.9	4.3
Molise	273,375	0.9	317,125	1.1	17.4
Piedmont	8,762,625	2.0	7,967,750	1.9	-8.6
Sardinia	1,285,500	0.8	1,194,000	0.8	-6.5
Sicily	7,489,500	1.5	7,582,500	1.6	1.9
Tuscany	8,420,250	2.3	8,230,500	2.2	-1.8
Umbria	1,567,500	1.8	1,333,500	1.6	-14.3
Veneto	10,741,000	2.2	9,937,500	2.0	-7.2
Italy	106,277,375	1.8	101,433,500	1.7	-4.1

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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
26167015	CYTOTECT BIOTEST*EV 10 mL 500U	500	BIOTEST PHARMA GmbH	H
26167027	CYTOTECT BIOTEST*EV 20 mL 1000U	1000	BIOTEST PHARMA GmbH	H
26167041	CYTOTECT BIOTEST*EV 10 mL1000U	1000	BIOTEST PHARMA GmbH	H
46731016	CYTOMEGATECT*EV10 mL100U	1000	BIOTESTPHARMAGmbH	H
26167039	CYTOTECT BIOTEST*EV 50 mL 2500U	2500	BIOTEST PHARMA GmbH	H
26167054	CYTOTECTBIOTEST*EV 50 mL 5000U	5000	BIOTESTPHARMAGmbH	H
46731028	CYTOMEGATECT*EV 50 mL 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 2021-2022, 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	U	U <i>per capita</i>	U	U <i>per capita</i>	
Abruzzo	22,000	0.0	255,000	0.2	1065.8
Aosta Valley	-	-	21,000	0.2	100.0
AP Bolzano	9,000	0.0	183,000	0.3	1930.1
AP Trento	-	-	-	-	NA
Apulia	894,000	0.2	347,000	0.1	-61.0
Basilicata	62,000	0.1	100,000	0.2	62.8
Calabria	525,000	0.3	410,000	0.2	-21.2
Campania	767,000	0.1	517,000	0.1	-32.2
E.-Romagna	1,770,000	0.4	2,007,000	0.5	13.6
Friuli V. Giulia	1,825,000	1.5	1,150,000	1.0	-36.8
Latium	351,000	0.1	729,000	0.1	108.2
Liguria	35,000	0.0	20,000	0.0	-42.4
Lombardy	1,971,000	0.2	2,586,000	0.3	31.4
Marche	300,000	0.2	256,000	0.2	-14.2

Region	2021		2022		% Var 2021-2022
	U	U per capita	U	U per capita	
Molise	-	-	-	-	NA
Piedmont	1,607,000	0.4	3,055,000	0.7	91.1
Sardinia	-	-	-	-	NA
Sicily	656,000	0.1	1,269,000	0.3	94.7
Tuscany	557,000	0.2	1,045,000	0.3	88.5
Umbria	24,000	0.0	-	-	-100.0
Veneto	3,080,000	0.6	2,627,000	0.5	-14.4
Italy	14,455,000	0.2	16,577,000	0.3	15.2

During the period under examination, the CMV IGs national demand increased by 15% compared to the previous year and stood at 16,577,000 U. However, the national average showed strong fluctuations, trends varied from one Region to another; Friuli V. Giulia was the Region with the highest standardized demand (1.0 U *per capita*), followed by Piedmont (0.7 U *per capita*) and Veneto and E.-Romagna (0.5 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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
026978027*	VARITECT 25 IU/mL 1F 5 mL	125	BIOTEST PHARMA GmbH	H
026978015*	VARITECT 25 IU/mL 1F 20 mL	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 2021-2022, at national and regional levels. The national demand for IG anti-Var over the time interval examined, remained almost stable (-0.1%). Total demand in 2022 was 110,375 IUs (1.9 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 2021 and 2022 (adapted by the CNS on data from the Product Quality and Pharmacrime Office - AIFA)

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	6,250	4.9	-	-	-100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	3,750	7.0	6,375	11.9	69.7
AP Trento	-	-	-	-	NA
Apulia	8,500	2.2	750	0.2	-91.1
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	125	0.0	-	-	-100.0
Emilia-Romagna	10,125	2.3	27,875	6.3	175.8
Friuli V. Giulia	18,625	15.5	15,125	12.6	-18.5

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Latium	9,125	1.6	3,375	0.6	-62.9
Liguria	2,250	1.5	-	-	-100.0
Lombardy	22,875	2.3	30,375	3.0	33.0
Marche	21,000	14.0	11,625	7.8	-44.3
Molise	-	-	-	-	NA
Piedmont	625	0.1	4,500	1.1	623.8
Sardinia	125	0.1	125	0.1	0.7
Sicily	-	-	125	-	100.0
Tuscany	2,750	0.7	5,625	1.5	105.5
Umbria	2,625	3.0	2,500	2.9	-4.1
Veneto	2,250	0.5	2,000	0.4	-10.8
Italy	111,000	1.9	110,375	1.9	-0.1

RABIES IMMUNOGLOBULINS (ATC J06BB05)

Human immunoglobulins with rabies-specific antibodies (rabies IGs) are used for post-exposure prophylaxis in cases of scratches, bites or other injuries caused by rabid or potentially rabid animals. They are obtained from selected plasma donors with high titers of anti-rabies antibodies (38).

Table 48 shows the brand names of drugs containing rabies IGs currently on the market in Italy and the amount of active ingredient they contain, expressed in IUs.

Table 48. Products containing rabies immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
- *	BERIRAB P 150 IU/mL 2 mL	300	CSL BEHRING GmbH	-
- *	BERIRAB P 150 IU/mL 5 mL	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 2022, the total demand for anti-rabies GI, recorded in only twelve regions, showed a significant increase compared to 2021 (+118%) and, therefore, the total demand amounted to 235,650 IUs (4 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 2021 and 2022 (adapted by the CNS on data from the Product Quality and Pharmacrime Office – AIFA)

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop.	IU	IU per 1,000 pop.	
Abruzzo	-	-	750	0.6	100.0
Aosta Valley	3,000	24.2	3,000	24.3	0.6
AP Bolzano	8,250	15.4	13,050	24.4	57.9
AP Trento	-	-	-	-	NA
Apulia	2,850	0.7	8,100	2.1	185.8
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	1,050	0.2	100.0
E.-Romagna	11,100	2.5	18,000	4.1	62.4
Friuli V. Giulia	49,800	41.4	88,350	73.8	78.0
Latium	2,400	0.4	-	-	-100.0
Liguria	-	-	-	-	NA
Lombardy	1,500	0.2	40,350	4.0	2594.5
Marche	2,250	1.5	3,000	2.0	34.1
Molise	-	-	-	-	NA
Piedmont	5,100	1.2	14,850	3.5	192.7

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop.	IU	IU per 1,000 pop.	
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	2,400	0.6	13,650	3.7	471.3
Umbria	-	-	-	-	NA
Veneto	19,500	4.0	31,500	6.5	62.0
Italy	108,150	1.8	235,650	4.0	118.8

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, 31/12/2022)

AIC code	Brand name	mL	Manufacturer	NHS class
035941018	BERIPLAST P*FL POLV 0,5 mL+FL	0.5	CSL BEHRING GmbH	C
035941020	BERIPLAST P*FL POLV 1 mL+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 1 mL+1 mL	1	BAXTER SpA	C
025243179	TISSEEL 2 mL ADESIVO TISSUTALE	2	BAXTER SpA	H
039546027	ARTISS SOL. ADESIVO TISSUTALE	2	BAXTER SpA	H
039546080	ARTISS*1SIR 2 mL+2 mL	2	BAXTER SpA	C
039591019	EVICEL*2FL 1 mL 90 mg/mL+1200 IU	2	OMRIX BIOPHARMA	H
042046019	SILKETAL 2,5 mL ADESIVO TISSUTALE	2.5	KEDRION SpA	C
044152015	KOLFIB*FL POLV SOLV 2,5 mL	2.5	KEDRION SpA	C
025243181	TISSEEL 4mL ADESIVO TISSUTALE	4	BAXTER SpA	H
039591021	EVICEL*2FL 2 mL 90 mg/mL+1200 IU	4	OMRIX BIOPHARMA	H
039546039	ARTISS SOL. ADESIVO TISSUTALE	5	BAXTER SpA	H
039546092	ARTISS*1SIR 5 mL+5 mL	5	BAXTER SpA	C
042046021	SILKETAL 5 mL ADESIVO TISSUTALE	5	KEDRION SpA	C
044152027	KOLFIB*FL POLV SOLV 5 mL	5	KEDRION SpA	C
025243193	TISSEEL 10 mL ADESIVO TISSUTALE	10	BAXTER SpA	H
039591033	EVICEL*2FL 5 mL 90 mg/mL+1200 IU	10	OMRIX BIOPHARMA	H
042046033	SILKETAL 10 mL ADESIVO TISSUTALE	10	KEDRION SpA	C
044152039	KOLFIB*FL POLV SOLV 10 mL	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 4,8 cmx4,8cm	1	TAKEDA Italy SpA	C
043011016	EVARREST*1BUST 8,1 mg+40 IU/cm ²	1	OMRIX BIOPHARMA	C
036557027	TACHOSIL*2SPUGNE 4,8 cmx4,8cm	2	TAKEDA Italy SpA	C
043011028	EVARREST*2BUST 8,1 mg+40 IU/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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	8,925	7.0	12,504	9.8	40.9
Aosta Valley	324	2.6	196	1.6	-39.1
AP Bolzano	2,180	4.1	2,915	5.4	33.5
AP Trento	3,054	5.6	3,134	5.8	2.6
Apulia	17,518	4.5	32,006	8.2	83.7
Basilicata	3,078	5.6	3,136	5.8	2.9
Calabria	4,928	2.6	5,380	2.9	10.1
Campania	45,785	8.1	55,993	10.0	23.0
Emilia-Romagna	13,492	3.0	29,382	6.6	118.1
Friuli V. Giulia	2,972	2.5	4,746	4.0	60.3
Latium	27,654	4.8	45,915	8.0	66.5
Liguria	5,652	3.7	7,848	5.2	39.9
Lombardy	52,570	5.3	73,912	7.4	40.8
Marche	5,362	3.6	5,052	3.4	-5.2
Molise	1,020	3.5	3,820	13.1	279.0
Piedmont	15,834	3.7	19,600	4.6	24.4
Sardinia	6,564	4.1	11,182	7.1	71.5
Sicily	19,390	4.0	25,628	5.3	33.1
Tuscany	20,366	5.5	27,276	7.4	34.5
Umbria	3,500	4.0	3,406	4.0	-2.0
Veneto	24,467	5.0	30,429	6.3	24.8
Italy	284,635	4.8	403,460	6.8	42.4

Table 52. Total demand (public and private) for local haemostatics-combinations, expressed in number of gelatin sponges, and variations in percentage between 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021	2022	% Var 2021-2022
Abruzzo	1,449	1,538	6.1
Aosta Valley	222	263	18.5
AP Bolzano	495	555	12.1
AP Trento	182	328	80.2
Apulia	2,311	1,978	-14.4
Basilicata	852	729	-14.4
Calabria	2,302	2,035	-11.6
Campania	5,030	4,629	-8.0
Emilia-Romagna	1,533	1,828	19.2
Friuli V. Giulia	980	705	-28.1
Latium	3,037	3,264	7.5
Liguria	662	535	-19.2
Lombardy	7,423	7,668	3.3
Marche	1,436	1,347	-6.2
Molise	4	4	0.0
Piedmont	3,646	3,743	2.7
Sardinia	383	243	-36.6
Sicily	2,722	2,266	-16.8
Tuscany	3,667	3,028	-17.4
Umbria	868	1,033	19.0
Veneto	2,564	2,970	15.8
Italy	41,768	40,689	-2.6

In 2022, the total demand for local haemostatics-combinations reached a volume of about 403,460 mL (6.8 mL per 1,000 population), recording a noticeable increase (+42%) compared to their volume in 2021 (Table 51).

In 2022, the total demand for local haemostatics-combinations, expressed in number of gelatin sponges, also appeared to decrease slightly compared to the previous year (-3%), it amounted to 40,689 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, 31/12/2022)

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

Quantification of the demand

In 2022, the total demand and the total standardised national demand for FVII was approximately 6.7 million IUs, showing a marked increase over 2021 (+32%) (Table 54).

The largest increases were recorded in Marche (+2,615%), Liguria (+118%) and Apulia (+90%). In 2022, 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	315,000	245.9	368,400	289.2	17.6
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	252,000	64.1	477,000	121.9	90.3
Basilicata	42,000	77.0	61,200	113.3	47.1
Calabria	27,000	14.5	40,200	21.8	50.2
Campania	373,200	66.4	473,400	84.7	27.6
E.-Romagna	133,800	30.1	183,600	41.4	37.4
Friuli V. Giulia	-	-	-	-	NA
Latium	1,552,200	270.9	2,252,400	394.1	45.5
Liguria	36,600	24.1	79,200	52.5	118.0
Lombardy	1,590,600	159.4	1,846,200	185.3	16.3
Marche	1,200	0.8	32,400	21.7	2,615.3
Molise	309,600	1052.0	307,200	1056.5	0.4
Piedmont	260,400	60.9	306,600	72.1	18.4
Sardinia	-	-	-	-	NA
Sicily	174,000	36.0	239,400	49.9	38.5
Tuscany	15,600	4.2	12,600	3.4	-18.9
Umbria	4,200	4.9	1,200	1.4	-71.2
Veneto	-	-	-	-	NA
Italy	5,087,400	85.9	6,681,000	113.3	31.9

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, 31/12/2022)

AIC code	Brand name	mg	Manufacturer	NHS class
029447048	NOVOSEVEN*IV 1 mg (50KIU)+1,1 mL	1	NOVO NORDISK SpA	H
029447087	NOVOSEVEN*IV 1 mg (50KIU)+1 mL	1	NOVO NORDISK SpA	H
029447012	NOVOSEVEN*IV 1,2 mg (60KIU)+2,2 mL	1.2	NOVO NORDISK SpA	H
029447051	NOVOSEVEN*IV 2 mg (100KIU)+2,1 mL	2	NOVO NORDISK SpA	H
029447099	NOVOSEVEN*IV 2 mg (100KIU)+2 mL	2	NOVO NORDISK SpA	H
029447024	NOVOSEVEN*IV 2,4mg (120 KIU)	2.4	NOVO NORDISK SpA	H
029447036	NOVOSEVEN*IV 4,8 mg (240 KIU)	4.8	NOVO NORDISK SpA	H
029447063	NOVOSEVEN*IV 5 mg (250KIU)+5,2 mL	5	NOVO NORDISK SpA	H
029447101	NOVOSEVEN*IV 5 mg (250KIU)+5 mL	5	NOVO NORDISK SpA	H
029447075	NOVOSEVEN*IV8 mg (400KIU)+8,1 mL	8	NOVO NORDISK SpA	H
029447113	NOVOSEVEN*IV 8 mg (400KIU)+8 mL	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 2021-2022, at national and regional level. The total demand for rFVIIa recorded in 2022 was 42,845 mg (0.7 mg per 1,000 population) with a marked decrease compared to 2021 (-23%).

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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Abruzzo	164	0.1	905	0.7	455.0
Aosta Valley	4	0.0	190	1.5	4679.0
AP Bolzano	-	-	244	0.5	100.0
AP Trento	412	0.8	302	0.6	-26.7
Apulia	12,782	3.2	2,548	0.7	-80.0
Basilicata	13	0.0	57	0.1	342.6
Calabria	3,490	1.9	2,185	1.2	-36.8
Campania	3,607	0.6	3,155	0.6	-12.0
E.-Romagna	4,404	1.0	6,465	1.5	47.0
Friuli V. Giulia	781	0.7	1,648	1.4	111.8
Latium	1,407	0.2	2,297	0.4	63.7
Liguria	1,988	1.3	374	0.2	-81.0

Region	2021		2022		% Var 2021-2022
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Lombardy	5,935	0.6	4,357	0.4	-26.5
Marche	622	0.4	553	0.4	-10.6
Molise	76	0.3	24	0.1	-68.0
Piedmont	3,737	0.9	1,913	0.4	-48.5
Sardinia	327	0.2	496	0.3	52.7
Sicily	1,898	0.4	3,011	0.6	59.7
Tuscany	10,628	2.9	7,401	2.0	-30.0
Umbria	229	0.3	201	0.2	-11.6
Veneto	3,391	0.7	4,519	0.9	33.7
Italy	55,895	0.9	42,845	0.7	-23.0

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, 31/12/2022)

AIC code	Brand name	FU	Manufacturer	NHS class
024744043	FEIBA*IV FL 500 IU+F 20 mL	500	BAXALTA Italy Srl	A
024744068	FEIBA*FL 500FU+BAXJECT II HF	500	BAXALTA Italy Srl	A
024744056	FEIBA TIM3*IV FL 1000 IU+F 20 mL	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 2021-2022 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	FU	FU <i>per capita</i>	FU	FU <i>per capita</i>	
Abruzzo	1,252,000	1.0	1,767,000	1.4	41.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	194,000	0.0	40,000	0.0	-79.3
Basilicata	-	-	-	-	NA
Calabria	136,000	0.1	-	-	-100.0
Campania	1,302,000	0.2	793,000	0.1	-38.7
E.-Romagna	66,000	0.0	406,000	0.1	516.1
Friuli V. Giulia	175,000	0.1	12,000	0.0	-93.1
Latium	103,000	0.0	351,000	0.1	241.7
Liguria	128,000	0.1	257,000	0.2	102.3
Lombardy	1,534,000	0.2	847,000	0.1	-44.7
Marche	243,000	0.2	211,000	0.1	100.0
Molise	-	-	-	-	NA
Piedmont	195,000	0.0	267,000	0.1	37.7
Sardinia	316,000	0.2	427,000	0.3	36.1
Sicily	463,000	0.1	351,000	0.1	-23.7
Tuscany	118,000	0.0	-	-	-100.0
Umbria	-	-	-	-	NA
Veneto	350,000	0.1	800,000	0.2	129.3
Italy	6,575,000	0.1	6,529,000	0.1	-0.3

In 2022, national demand for CCPa was in line with that found in the previous year (-0.3%), with some regional variability.

Its total volume was 6,529,000 UF (0.1 UF *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 gg/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, 31/12/2022)

AIC code	Brand name	mg	Manufacturer	NHS class
037709019	PROLASTIN*EV 1F 1g/40 mL+F40 mL	1000	GRIFOLS ITALIA SpA	H
044479018	RESPREEZA*EV 1FL 20 mL+SOL 1g	1000	CSL BEHRING GmbH	H
046292013	PLITALFA*EV 1F 1000MG/40ML	1000	GRIFOLS Italia SpA	C(nn)
037709021	PROLASTIN*EV 4F 1g/40 mL+F40 mL	4000	INST. GRIFOLS S.A.	C(nn)
044479020	RESPREEZA*EV 1FL 76mL + 4g+SET	4000	CSL BEHRING GmbH	C(nn)
044479032	RESPREEZA*EV 1FL 95 mL+ 5g+ SET	5000	CSL BEHRING GmbH	H

Quantification of the demand

In 2022, the total demand for alpha-1-antitrypsin was 70,949 g (1.2 g per 1,000 population) recording a significant upward trend compared to the previous year (+22%) (Table 60). In particular in Umbria and Apulia the demand exceeded the value recorded in the previous year (+81% and +69%, respectively). The highest regional standardized demand is in the Aosta Valley and in the AP of Bolzano (8 and 6 grams per 1,000 population, respectively), as in the previous year.

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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,819	1.4	2,230	1.8	23.3
Aosta Valley	957	7.7	984	8.0	3.4
AP Bolzano	3,249	6.1	3,109	5.8	-4.5
AP Trento	578	1.1	821	1.5	42.0
Apulia	2,254	0.6	3,790	1.0	69.1
Basilicata	-	-	-	-	NA
Calabria	1,420	0.8	1,726	0.9	22.6

Region	2021		2022		% Var 2021-2022
	g	g per 1,000 pop	g	g per 1,000 pop	
Campania	6,866	1.2	7,790	1.4	14.1
E.-Romagna	3,376	0.8	4,824	1.1	43.1
Friuli V. Giulia	2,035	1.7	2,240	1.9	10.5
Latium	3,860	0.7	5,069	0.9	31.7
Liguria	2,099	1.4	2,689	1.8	29.0
Lombardy	8,834	0.9	10,213	1.0	15.8
Marche	420	0.3	612	0.4	46.5
Molise	48	0.2	63	0.2	32.8
Piedmont	3,984	0.9	5,988	1.4	51.1
Sardinia	4,918	3.1	5,840	3.7	19.6
Sicily	4,251	0.9	4,753	1.0	12.6
Tuscany	3,381	0.9	3,743	1.0	11.2
Umbria	565	0.7	1,017	1.2	81.2
Veneto	3,578	0.7	3,448	0.7	-3.3
Italy	58,492	1.0	70,949	1.2	21.8

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 gg/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, 31/12/2022)

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

Quantification of the demand

In 2022, the total demand for C1 esterase inhibitor was 13,129,500 IUs (223 IUs per 1,000 population), and was substantially stable compared to the previous year (-0.1%) (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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	309,000	241.2	196,000	153.9	-36.2
Aosta Valley	57,500	463.4	1,500	12.2	-97.4
AP Bolzano	90,000	168.3	22,000	41.1	-75.6
AP Trento	10,500	19.4	5,000	9.2	-52.4
Apulia	668,500	169.9	1,057,500	270.3	59.1
Basilicata	55,000	100.9	80,000	148.1	46.8
Calabria	685,000	368.2	615,000	333.4	-9.4
Campania	1,880,500	334.4	1,977,500	353.7	5.8
E.-Romagna	388,000	87.4	232,500	52.5	-40.0
Friuli V. Giulia	24,500	20.4	20,000	16.7	-18.1
Latium	2,372,500	414.0	2,425,500	424.4	2.5
Liguria	23,500	15.5	19,000	12.6	-18.6
Lombardy	1,609,000	161.2	1,488,500	149.4	-7.3

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Marche	187,500	125.1	241,000	161.8	29.3
Molise	11,500	39.1	8,000	27.5	-29.6
Piedmont	1,001,000	234.2	1,241,000	291.8	24.6
Sardinia	612,000	384.9	546,000	345.7	-10.2
Sicily	1,350,500	279.4	1,348,000	280.7	0.5
Tuscany	564,000	152.7	420,500	114.4	-25.1
Umbria	265,500	306.8	73,000	84.9	-72.3
Veneto	1,033,000	212.1	1,112,000	229.1	8.0
Italy	13,198,500	222.8	13,129,500	222.6	-0.1

An exceptional variability in standardised regional demands was observed, with maximum volumes in Latium, Campania, Sardinia and Calabria (424, 354, 346 and 333 IUs per 1,000 population, respectively) and minimum volumes in the AP of Trento, Aosta Valley, Liguria, Friuli V. Giulia, Molise, AP of Bolzano and E.-Romagna (range: 9-53 IUs per 1,000 population). Most regions showed a decrease from the previous year, in some cases even a particularly marked one; exceptions were Basilicata, Campania, Latium, Marche, Piedmont, Apulia and Veneto, where, on the other hand, increases in demand were recorded in the two-year period under consideration. Demand remained almost stable in Sicily (+0.5%).

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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
*	FACTOR X P BEHRING 1FL	600-1200§	CSL BEHRING SpA	-
044840015	COAGADEX 100 IU/mL- IV 2,5 mL	250	BIO PROD. LAB. LTD	C
044840027	COAGADEX 100 IU/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 Lombardy, where in 2022 the demand was for 15,600 IUs (1.6 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 2021 and 2022 (adapted by the CNS on data from Product Quality and Pharmacrime Office-AIFA)

Region	2021		2022		Var % 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Lombardy	48,000	4.8	15,600	1.6	-67.4
Italy	48,000	0.8	15,600	0.3	-67.4

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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
-*	HEMOLEVEN 100 IU/mL 10 mL	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 2022, the demand for FXI was 15,000 IUs (0.3 IU per 1,000 population), showing a slight increase compared to 2021 (Table 66). Demand was detected only in two Italian Regions: Piedmont and Friuli V. Giulia.

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 2021 and 2022 (adapted by the CNS on data from the Product Quality and Pharmacovigilance Office-AIFA)

Region	2021		2022		% Var 2021-2022
	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	-	-	-	-	NA
Friuli V. Giulia	10,000	8.3	8,000	6.7	-19.7
Latium	-	-	-	-	NA
Liguria	-	-	-	-	NA
Lombardy	-	-	-	-	NA
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Piedmont	-	-	7,000	1.6	100.0
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	4,000	0.8	-	-	-100.0
Italy	14,000	0.2	15,000	0.3	7.6

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, 31/12/2022)

AIC code	Brand name	IU	Manufacturer	NHS class
024644015*	FIBROGAMMIN 1FL 250 IU	250	CSL BEHRING GmbH	H
042605016	CLUVIAT FL 250 IU	250	CSL BEHRING GmbH	H
024644027*	FIBROGAMMIN 1FL 1250 IU	1250	CSL BEHRING GmbH	H
042605028	CLUVIAT FL 1250 IU	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, 31/12/2022)

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

Quantification of the demand

In 2022, the total demand for FXIII was 856,000 IUs (14.5 IUs per 1,000 population) and less than half, equal to 406,000 IUs (6.9 IUs per 1,000 population), was for pdFXIII. The latter recorded an increase of +24% compared to 2021 (Table 69).

In 2022, there was no utilisation of FXIII in some Regions. The highest demand for Factor XIII of plasma origin was in the AP of Trento and Emilia-Romagna (37 IUs and 31 IUs per 1,000 population respectively). In Abruzzo, Basilicata, Calabria and Campania rFXIII was used exclusively (Table 70).

In Latium, Marche, the AP of Bolzano, the AP of Trento, Apulia and Tuscany 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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow and the Product Quality and Pharmacovigilance Office-AIFA)

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	8,750	16.4	3,750	7.0	-57.2
AP Trento	11,250	20.8	20,000	36.9	77.8
Apulia	-	-	7,500	1.9	100.0
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	99,250	22.4	137,500	31.0	38.8
Friuli V. Giulia	-	-	-	-	NA
Latium	41,250	7.2	54,250	9.5	31.9
Liguria	20,000	13.2	27,500	18.2	38.5
Lombardy	26,250	2.6	13,500	1.4	-48.5
Marche	10,750	7.2	29,000	19.5	171.3
Molise	-	-	-	-	NA
Piedmont	11,250	2.6	14,500	3.4	29.6
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	24,500	6.6	19,500	5.3	-20.0
Umbria	-	-	-	-	NA
Veneto	76,500	15.7	79,000	16.3	3.6
Italy	329,750	5.6	406,000	6.9	23.7

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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow and the Product Quality and Pharmacovigilance office, AIFA)

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	67,500	52.7	40,000	31.4	-40.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	32,500	59.6	30,000	55.6	-6.8
Calabria	170,000	91.4	132,500	71.8	-21.4
Campania	-	-	15,000	2.7	100.0
E.-Romagna	20,000	4.5	17,500	3.9	-12.4
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	67,500	44.5	70,000	46.4	4.5
Lombardy	90,000	9.0	92,500	9.3	2.9
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	10,000	2.3	40,000	9.4	302.1
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	20,000	4.1	12,500	2.6	-37.3
Italy	477,500	8.1	450,000	7.6	-5.4

PROTEIN C (ATC B01AD12)

Protein C is one of the most important factors of the anticoagulant system together 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, 31/12/2022)

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

Quantification of the demand

In 2022, the national demand for protein C stood at a volume of 658,000 IUs (11.2 IUs per 1,000 population) with an increase of 74% compared to 2021 (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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	5,500	4.3	11,000	8.6	101.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	13,000	3.3	100.0
Basilicata	-	-	-	-	NA
Calabria	179,500	96.5	178,500	96.8	0.3
Campania	70,500	12.5	193,000	34.5	175.4
E.-Romagna	2,000	0.5	4,000	0.9	100.3
Friuli V. Giulia	-	-	-	-	NA
Latium	22,000	3.8	97,500	17.1	344.4
Liguria	-	-	24,000	15.9	100.0
Lombardy	52,000	5.2	54,500	5.5	5.0
Marche	5,000	3.3	24,000	16.1	382.7
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	-	-	20,000	12.7	100.0
Sicily	29,000	6.0	10,000	2.1	-65.3
Tuscany	500	0.1	5,000	1.4	904.5
Umbria	6,000	6.9	8,000	9.3	34.2
Veneto	7,500	1.5	15,500	3.2	107.3
Italy	379,500	6.4	658,000	11.2	74.1

The highest regional demand was recorded in Calabria and Campania, with 96.8 and 34.5 IUs per 1,000 population respectively. The lowest regional demand was in Emilia-Romagna, Tuscany, and Sicily with volumes between 0.9 and 2.1 IUs per 1,000 population.

OTHER PLASMA PROTEIN FRACTIONS (ATC B05AA02)

Other plasma protein fractions include products with different compositions and therapeutic indications and include solvent/detergent-treated plasma (*Plasmasafe*TM, *Plasmagrade*TM and *Octaplas*TM)² and products with an albumin content between 85 and 90% (*Umanserum*TM).

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, 31/12/2022)

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

Quantification of the demand

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

Table 74 shows the utilisation of *Plasmasafe*TM and *Octaplas*TM, while Table 75 illustrates the data related to *Umanserum*TM, the demand for which, in 2022, recorded a decrease of -10%, and a total volume of 7,403,250 mL.

The national demand for solvent/detergent-treated plasma in 2022 decreased by -14.5% compared to 2021, with large regional differences; the most noticeable decrease was recorded in Emilia-Romagna (-53%) and Liguria (-33%), as well as in the PA of Trento, which recorded no demand for the year. In contrast, a significant increase in demand was recorded in Sardinia (+183%).

² *Plasmagrade*® constitutes an AIC copy of *Plasmasafe*® dedicated to national plasma.

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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	10,000	18.4	-	-	-100.0
Apulia	3,193,000	811.7	2,840,000	725.9	-10.6
Basilicata	510,000	935.6	680,000	1259.3	34.6
Calabria	889,600	478.1	1,056,000	572.5	19.7
Campania	4,213,000	749.1	3,954,800	707.4	-5.6
E.-Romagna	674,000	151.8	318,000	71.8	-52.7
Friuli V. Giulia	-	-	20,000	16.7	100.0
Latium	4,060,200	708.5	3,317,600	580.5	-18.1
Liguria	544,400	358.5	360,000	238.8	-33.4
Lombardy	474,000	47.5	420,000	42.1	-11.2
Marche	1,648,000	1100.0	1,449,000	972.6	-11.6
Molise	436,000	1481.5	408,000	1403.2	-5.3
Piedmont	5,282,000	1235.6	4,178,000	982.5	-20.5
Sardinia	12,800	8.1	36,000	22.8	183.2
Sicily	3,945,400	816.2	3,026,800	630.4	-22.8
Tuscany	1,430,000	387.2	1,438,200	391.2	1.0
Umbria	82,000	94.7	72,000	83.8	-11.6
Veneto	1,476,000	303.1	1,016,200	209.3	-30.9
Italy	28,880,400	487.5	24,590,600	416.9	-14.5

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 2021 and 2022 (adapted by the CNS on data from the Traceability information flow)

Region	2021		2022		% Var 2021-2022
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	5,325,500	1353.8	4,200,000	1073.6	-20.7
Basilicata	105,000	192.6	45,000	83	-56.7
Calabria	300,000	161.2	416,250	226	40.0
Campania	-	-	-	-	NA
E.-Romagna	-	-	-	-	NA
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	37,500	7	100.0
Liguria	-	-	-	-	NA
Lombardy	138,250	13.9	87,250	8.8	-36.8
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	-	-	-	-	NA
Sicily	2,292,250	474.2	2,415,250	503.0	6.1
Tuscany	-	-	-	-	NA
Umbria	140,000	161.8	202,000	235.0	45.3
Veneto	-	-	-	-	NA
Italy	8,301,000	140.1	7,403,250	125.5	-10.4

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 aims 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 qualitative and 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 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 842,949 kilograms in 2022, with a percentage increase over the entire period considered, by 82.1%.

The mean annual rate of variation over the period considered was 2.8%, with two peaks in over the periods between 2004-2006 and 2008-2010. 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 2022, a value similar to that recorded in 2020 was observed, and plasma collection for fractionation recorded a decrease of 2% from the previous year. However, the delivery of plasma to industrial fractionation by individual regions shows extreme variability in terms of quantity and quality.

In 2022, the Regions participating in the LPS agreement collected about one third of the plasma sent for fractionation for a share equal to 244,997 kilograms (29%), those adhering to the RIPP 229,151 kilograms (27%), those of the NAIP 193,548 kilograms (23%) and those of the PlaNet 175,253 kilograms (21%) (Figure 44).

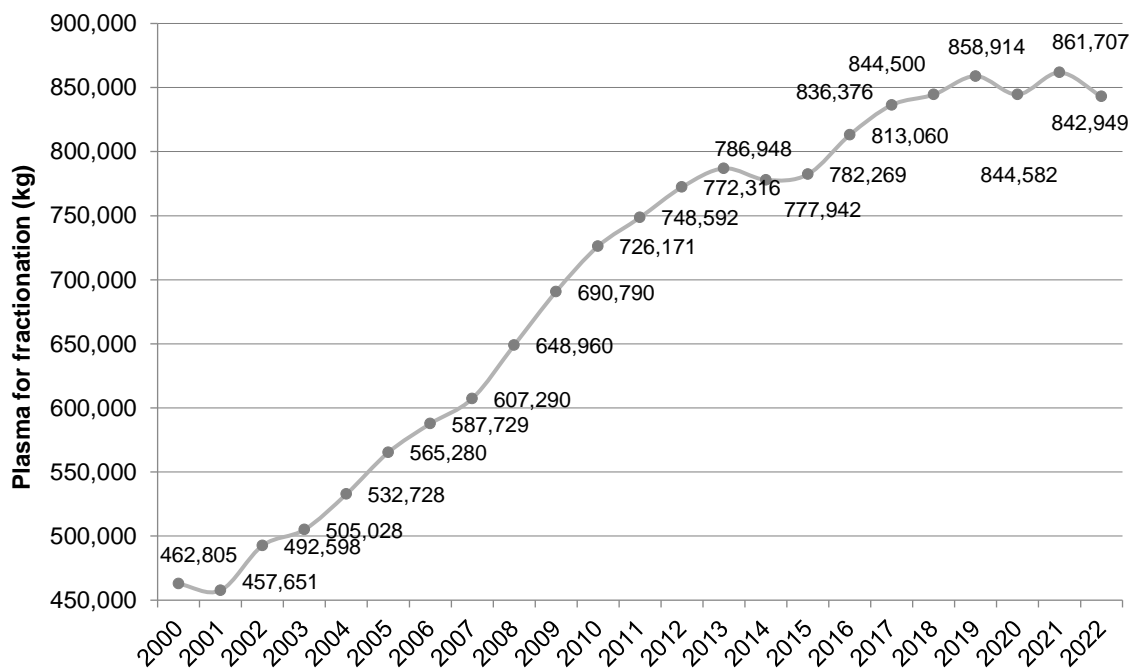


Figure 42. Plasma sent for fractionation 2000-2022
(adapted by the CNS on fractionation companies data, January 2023)

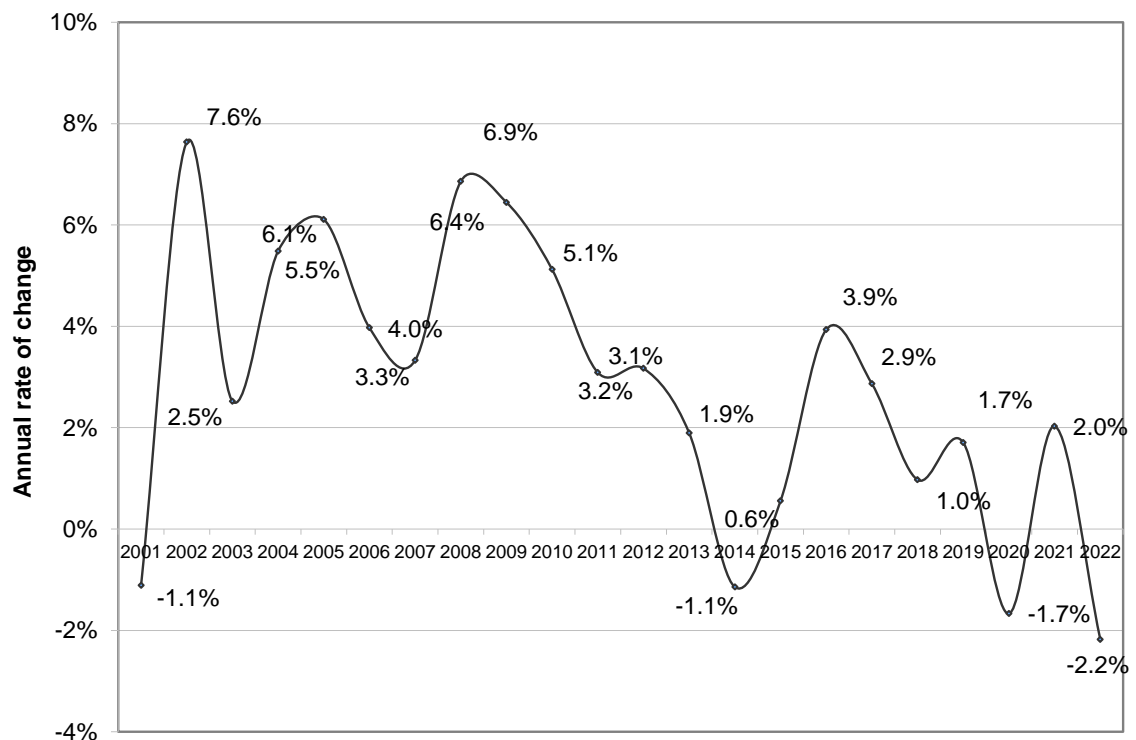


Figure 43. Annual rate of variation in the amount of plasma for fractionation, from 2001 to 2022
(adapted by the CNS on fractionation companies data, January 2023)

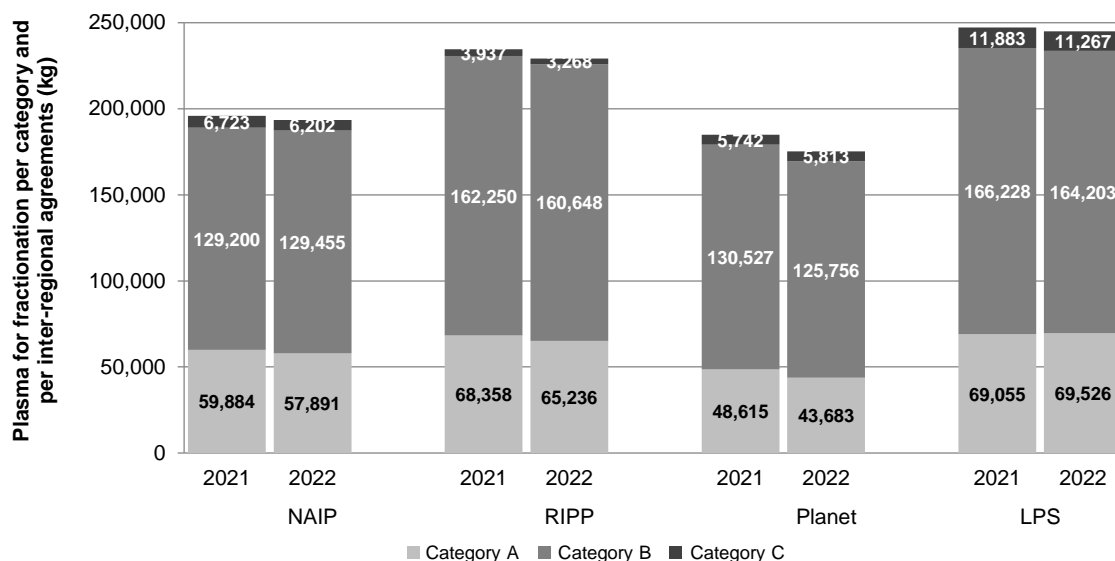


Figure 44. Total amount of plasma for fractionation by category under interregional agreements (kilograms), 2021-2022 (adapted by the CNS on fractionation companies data, January 2023)

As regards the amount of plasma sent for fractionation in 2022, for the resident population, the NAIP Regions sent 16.9 kilograms of plasma per thousand population units for processing (17.1 in 2021, with the same number of regions and PPAAs participating), LPS 15, 5 kilograms, RIPP 15.3 (15.6 kilograms of plasma per thousand population units for both in 2021), and finally PlaNet contributed 10.5 kilograms of plasma per thousand population units (11 kilograms of plasma per thousand population units the previous year) (Figure 45).

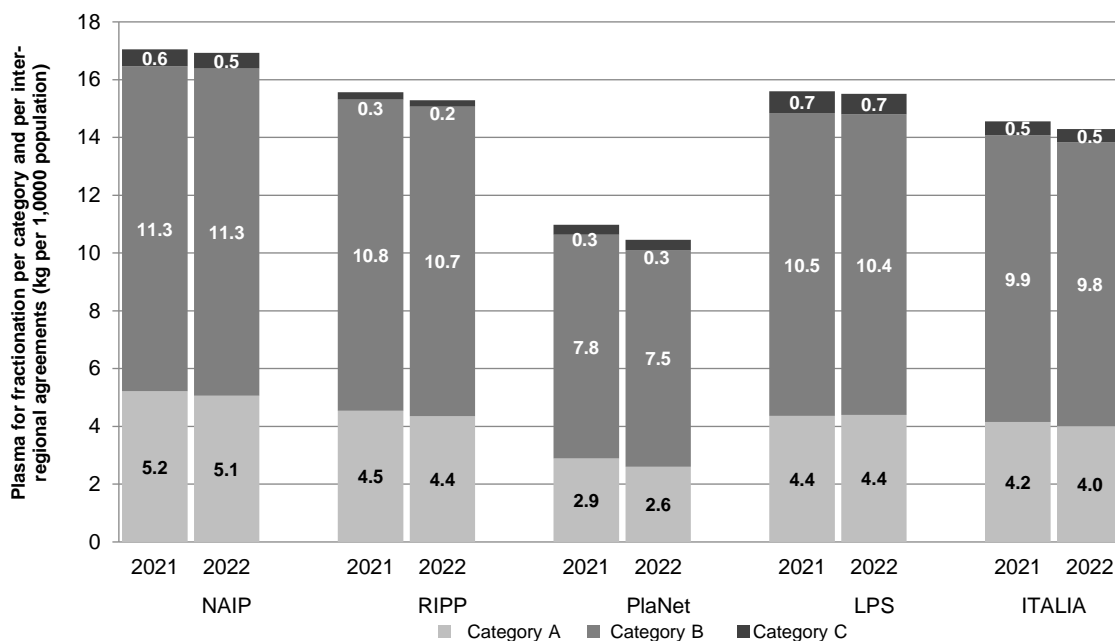


Figure 45. Total amount of plasma for fractionation by category under interregional agreements (kilograms per 1,000 population), 2021-2022 (adapted by the CNS on fractionation companies data, January 2023)

In 2022, although the national volume of plasma for fractionation stood at 14.3 kilograms per 1,000 population (14.5 in 2021), with regional contributions in volumes differing greatly one from another. In point of fact, the best performance was achieved by Friuli V. Giulia with 23.9 kilograms per 1,000 population, followed by Marche with 23.3 and Emilia-Romagna with 21.7, while the lowest volumes were recorded in Calabria, Latium and Campania with 10.1, 7.8 and 5.1 kilograms per 1,000 population, respectively (Figure 46).

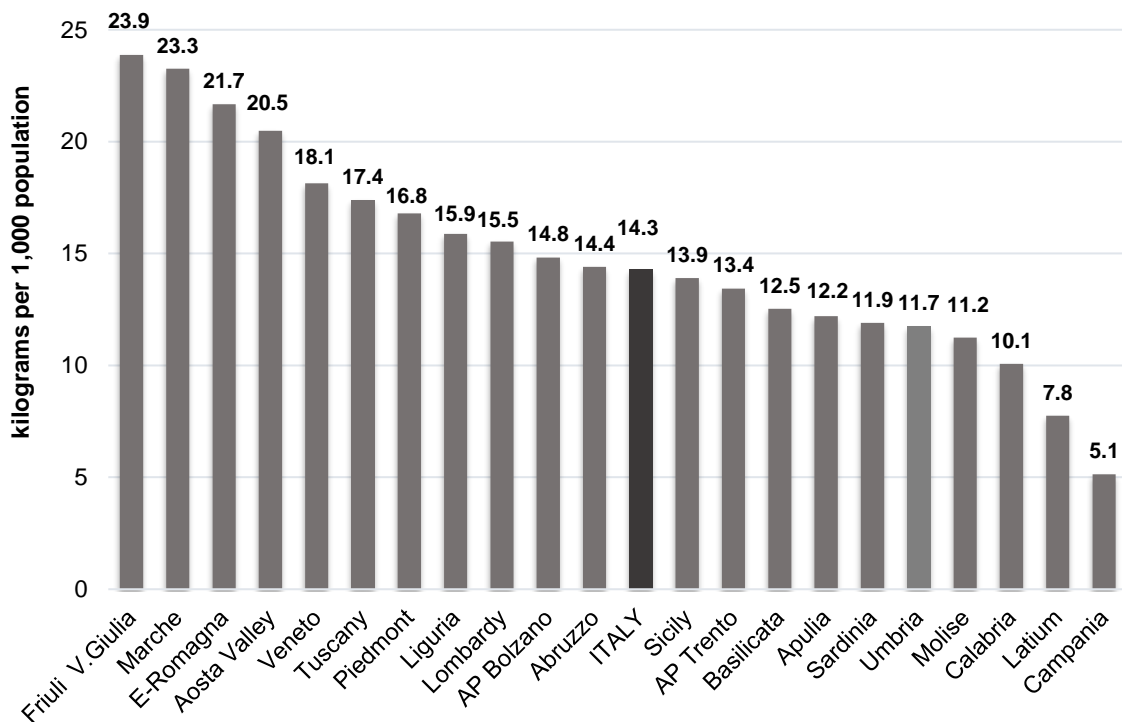


Figure 46. Total amount of plasma (kilograms per 1,000 population) for fractionation by Region, year 2022 (adapted by the CNS on fractionation companies data, January 2023)

Supply of PDMPs from toll fractionation

In 2022, the total quantity of plasma sent for fractionation by the Italian Regions was 842,949 kilograms (Table 76); of these, 28% (236,336 kilograms) was apheresis plasma (category A), 69% (580,063 kilograms) recovered plasma (category B) and the remaining 3% (26,551 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 24.9% sent by PlaNet to 29.9% sent by NAIP, while the percentage of plasma intended solely for the recovery of non-labile proteins (category C) varied from 1.4% sent by RIPP to 4.6% sent by the LPS consortium.

Table 76. Total quantity, expressed in kilograms, quantity per 1,000 population and variation in percentage for the years 2021-2022 classified by Region and plasma category (adapted by the CNS on fractionation companies data, January 2023)

Region	A	%	B	%	C	%	Tot. Fract.	Total per 1,000 pop
Abruzzo	4,786	-5.9	13,411	5.0	152	81.5	18,349	14.4
Aosta Valley	1,073	-10.6	1,454	6.0	-	-	2,527	20.5
AP Bolzano	2,038	7.2	5,906	-2.1	-	-	7,944	14.8
AP Trento	680	22.0	6,599	-0.9	-	-	7,279	13.4
Basilicata	1,458	-9.8	4,015	-9.9	1,293	-15.1	6,765	12.5
Friuli V. Giulia	13,975	-4.7	14,579	0.7	26	-65.6	28,581	23.9
Liguria	5,934	-2.8	18,009	3.2	-	-	23,943	15.9
Umbria	1,609	-14.4	8,490	-2.5	-	-	10,099	11.7
Veneto	26,339	-2.0	56,992	-0.5	4,731	-6.1	88,061	18.1
NAIP	57,891	-3.3	129,455	0.2	6,202	-7.7	193,548	16.9
Apulia	6,859	3.8	39,952	3.3	931	-45.0	47,741	12.2
Calabria	1,365	22.6	17,201	-1.6	9	-100.0	18,575	10.1
Emilia-Romagna	40,104	-6.9	53,652	-1.6	2,318	3.5	96,074	21.7
Sicily	16,908	-3.6	49,843	-3.3	10	227.6	66,761	13.9
RIPP	65,236	-4.6	160,648	-1.0	3,268	-17.0	229,151	15.3
Campania	659	-1.7	27,148	-8.7	904	-42.3	28,710	5.1
Latium	4,338	-1.6	35,225	1.0	4,773	22.1	44,336	7.8
Marche	15,193	-4.1	19,452	-3.0	-	-100.0	34,645	23.3
Molise	290	166.4	2,981	10.0	-	-	3,270	11.2
Tuscany	23,204	-15.9	40,772	-5.1	-	-	63,976	17.4
Ministry of Defence	-	-	180	0.0	136	-48.3	316	NA
PlaNet	43,683	-10.1	125,756	-3.7	5,813	1.2	175,253	10.5
Lombardy	46,267	0.5	99,420	-0.9	9,127	-4.0	154,815	15.5
Piedmont	22,708	1.7	46,697	-3.0	1,989	-6.3	71,394	16.8
Sardinia	551	-21.3	18,086	1.8	151	-40.2	18,788	11.9
LPS	69,526	0.7	164,203	-1.2	11,267	-5.2	244,997	15.5
Italy	236,336	-3.9	580,063	-1.4	26,551	-6.1	842,949	14.3

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 2022 (from July 2021 to June 2022). These figures show the quantities, expressed 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 22,000 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 2022 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 2021 to June 2022 and the yields provided by the fractionation industry – year 2022 (adapted by the CNS on fractionation companies data, March 2023)

Region	2nd semester 2021 kg	1st semester 2022 kg	Total kg	Albumin g	SCIG* g	IVIG** g
Abruzzo	9,453	8,496	17,949	455,910	89,746	89,746
Aosta Valley	1,139	1,393	2,532	64,307	12,659	12,659
AP Bolzano	4,084	3,934	8,018	203,658	40,090	40,090
AP Trento	3,458	3,491	6,950	176,528	34,750	34,750
Basilicata	3,862	3,019	6,881	174,785	34,406	34,406
FVG	14,135	14,069	28,204	716,379	141,019	141,019
Liguria	11,973	11,646	23,618	599,900	118,091	118,091
Umbria	5,719	4,614	10,332	262,442	51,662	51,662
Veneto	43,717	43,618	87,335	2,218,319	436,677	436,677
NAIP	97,540	94,280	191,820	4,872,228	959,100	959,100
Apulia	23,042	23,619	46,660	1,203,365	168,910	190,840
Calabria	9,262	8,801	18,063	465,853	65,389	73,879
E.-Romagna	49,202	48,104	97,306	2,508,832	102,395	397,982
Sicily	35,147	32,986	68,133	1,757,140	246,640	278,662
RIPP	116,653	113,509	230,162	5,935,190	583,334	941,363
Campania	16,338	14,921	31,259	790,862	140,667	156,297
Lazio	21,391	21,740	43,131	1,091,220	194,090	215,656
Marche	18,246	17,202	35,448	896,845	159,518	177,242
Molise	1,507	1,448	2,954	74,746	13,295	14,772
Tuscany	33,476	31,809	65,285	1,651,708	293,782	326,425
Ministry of Def.	175	164	340	8,595	1,529	1,699
PlaNet	91,133	87,285	178,418	4,513,975	802,881	892,090
Lombardy	77,923	78,142	156,065	4,024,910	564,954	638,305
Piedmont	35,608	35,474	71,082	1,833,203	257,317	290,725
Sardinia	9,535	9,161	18,696	482,178	67,681	76,468
LPS	123,066	122,777	245,843	6,340,290	889,952	1,005,498
Italy	428,392	417,851	846,243	21,661,683	3,235,266	3,798,051

* 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 79. Potential supply of solvent/detergent-treated plasma based on the amount of plasma sent for fractionation from July 2021 to June 2022 and the yields provided by the fractionation industry – year 2022 (adapted by the CNS on data provided by Kedrion)

Region	2nd semester 2021		1st semester 2022		Total	Solvent/detergent- treated plasma	
	kg	kg	kg	kg		kg	mL
Abruzzo	-	-	-	-	-	-	-
Aosta Valley	-	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-	-
Apulia	-	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-	-
Calabria	-	-	-	-	-	-	-
Campania	2,638	-	2,372	-	5,010	-	4,634,250
E.-Romagna	-	-	-	-	-	-	-
Friuli V. Giulia	-	-	-	-	-	-	-
Lazio	1,898	-	1,816	-	3,714	-	3,435,450
Liguria	-	-	-	-	-	-	-
Lombardy	-	-	-	-	-	-	-
Marche	-	-	109	-	109	-	100,825
Molise	448	-	302	-	750	-	693,750
Piedmont	2,829	-	3,081	-	5,910	-	5,466,750
Sardinia	-	-	-	-	-	-	-
Sicily	714	-	1,225	-	1,939	-	1,793,575
Tuscany	836	-	1,947	-	2,783	-	2,574,275
Umbria	-	-	-	-	-	-	-
Veneto	966	-	891	-	1,857	-	1,717,725
Ministry of Defence	-	-	-	-	-	-	-
Italy	10,329	-	11,743	-	22,072	-	20,416,600

Table 80. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs (driver) classified by Region for the year 2022 (adapted by the CNS on fractionation companies data, March 2023)

Region	Albumin		IVIG		SCIG	
	g	g	g	g	g	g
Abruzzo	915,000		124,000		10,980	
Aosta Valley	64,200		19,650		600	
AP Bolzano	209,400		47,200		1,320	
AP Trento	207,600		41,000		2,600	
Basilicata	339,600		50,450		3,440	
Friuli V. Giulia	594,600		124,800		3,300	
Liguria	810,600		186,200		2,700	
Umbria	577,200		74,300		9,040	
Veneto	2,417,840		405,645		25,520	
NAIP	6,136,040		1,073,245		59,500	
Apulia	1,207,020		185,610		18,624	
Calabria	524,220		72,190		-	
E.-Romagna	2,672,250		461,255		3,616	
Sicily	1,827,080		231,835		140	
RIPP	6,230,570		950,890		22,380	
Campania	931,850		199,705		3,760	
Latium	814,505		137,300		670	
Marche	833,880		117,045		20,752	
Molise	91,000		12,400		96	
Tuscany	1,397,115		328,200		58,748	
Ministry of Defence	2,000		440		-	
PiaNet	4,070,350		795,090		84,026	
Lombardy	4,161,330		516,113		4,672	
Piedmont	1,445,810		364,003		-	
Sardinia	884,930		68,940		-	
LPS	6,492,070		949,055		4,672	
Italy	22,929,030		3,768,280		170,578	

Table 81. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs classified by Region for the year 2022 (adapted by the CNS on fractionation companies data, March 2023)

Region	Factor VIII	Factor VIII / vW Factor	Factor IX	3F-PCCs	AT	Fibrinogen	S/D-treated plasma	Protein C	Alpha-1	aPCCs
	UI	UI	UI	UI	UI	g	mL	UI	g	UF
Abruzzo	130,000	2,030,000	-	156,000	-	1,220	-	-	-	-
Aosta Valley	-	-	-	30,000	-	30	-	-	-	-
AP Bolzano	400,000	300,000	-	170,500	288,000	690	-	-	-	-
AP Trento	-	20,000	-	306,500	224,000	360	-	-	-	-
Basilicata	20,000	10,000	-	68,000	704,000	370	-	-	-	-
Friuli V. Giulia	680,000	530,000	-	560,500	2,016,000	1,050	-	-	-	-
Liguria	390,000	480,000	-	221,000	1,760,000	450	-	-	-	-
Umbria	105,000	360,000	-	174,500	490,000	1,060	-	-	-	-
Veneto	6,480,000	1,850,000	-	1,185,500	4,800,000	4,250	886,200	-	-	-
NAIP	8,205,000	5,580,000	-	2,872,500	10,282,000	9,480	886,200	-	-	-
Apulia	5,687,000	110,000	387,000	1,976,000	8,560,000	-	-	-	1,132	-
Calabria	300,000	-	31,000	678,000	7,365,000	-	-	-	-	-
E.-Romagna	2,330,000	30,000	59,000	3,056,000	4,073,000	-	-	-	2,280	-
Sicily	881,000	40,000	118,000	3,009,500	18,222,000	-	1,131,400	-	280	-
RIPP	9,198,000	180,000	595,000	8,719,500	38,220,000	-	1,131,400	-	3,692	-
Campania	261,000	609,000	54,000	1,265,000	4,991,000	-	3,810,800	189,000	-	382,000
Lazio	5,121,000	104,000	289,200	1,626,500	8,192,000	-	2,386,600	81,000	-	238,000
Marche	1,352,000	-	1,053,600	1,057,300	3,625,000	-	1,449,000	-	-	66,000
Molise	100,000	-	76,000	235,500	742,000	-	408,000	-	-	-
Tuscany	4,358,000	773,000	1,625,200	3,062,900	7,858,000	-	654,000	5,000	-	-
Min.of Defence	-	-	-	6,000	-	-	-	-	-	-
PlaNet	11,192,000	1,486,000	3,098,000	7,253,200	25,408,000	-	8,708,400	275,000	-	686,000
Lombardy	8,824,000	-	1,268,000	6,206,000	8,759,500	-	420,000	-	-	-
Piedmont	5,962,000	-	183,000	3,006,500	7,778,500	-	4,178,000	-	-	-
Sardinia	628,000	-	-	930,000	1,905,000	-	20,000	-	-	-
LPS	15,414,000	-	1,451,000	10,142,500	18,443,000	-	4,618,000	-	-	-
Italy	44,009,000	7,246,000	5,144,000	28,987,700	92,353,000	9,480	15,344,000	275,000	3,692	686,000

ANALYSIS OF SELF-SUFFICIENCY

Albumin

In 2022, the Italian NHS demand for albumin accounted for 88% of the total. The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, was 68% (+2% compared to 2021) while the effective self-sufficiency, considered as the ratio between the actual supply of toll fractionation and the NHS demand, was 72% (71% in 2021). The Regions that in 2022 achieved effective self-sufficiency – more than 90% – were Friuli V. Giulia, the AP of Bolzano, the AP of Trento, Umbria, Aosta Valley, Veneto, Tuscany and Marche (Table 82).

Table 77. Estimates of regional and national self-sufficiency in albumin, 2022

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,127,258	1,067,233	455,910	915,000	43	86
Aosta Valley	64,300	64,200	64,307	64,200	100	100
AP Bolzano	214,828	214,273	203,658	209,400	95	98
AP Trento	229,050	226,050	176,528	207,600	78	92
Basilicata	450,118	446,655	174,785	339,600	39	76
Friuli V. Giulia	602,840	596,620	716,379	594,600	120	100
Liguria	983,718	971,463	599,900	810,600	62	83
Umbria	587,700	585,113	262,442	577,200	45	99
Veneto	2,665,713	2,484,940	2,218,319	2,417,840	89	97
NAIP	6,925,523	6,656,545	4,872,228	6,136,040	73	92
Apulia	2,121,725	1,849,758	1,203,365	1,207,020	65	65
Calabria	1,062,360	962,828	465,853	524,220	48	54
E.-Romagna	3,245,633	3,068,663	2,508,832	2,672,250	82	87
Sicily	3,295,173	2,685,750	1,757,140	1,827,080	65	68
RIPP	9,724,890	8,566,998	5,935,190	6,230,570	69	73
Campania	4,159,853	3,953,280	790,862	931,850	20	24
Latium	2,681,010	1,904,365	1,091,220	814,505	57	43
Marche	932,330	855,110	896,845	833,880	105	98
Molise	152,378	116,078	74,746	91,000	64	78
Tuscany	1,487,703	1,423,463	1,651,708	1,397,115	116	98
Min. of Def.	-	-	8,595	2,000	-	-
PlaNet	9,413,273	8,252,295	4,513,975	4,070,350	55	49
Lombardy	6,743,008	5,242,513	4,024,910	4,161,330	77	79
Piedmont	1,723,830	1,664,033	1,833,203	1,445,810	110	87
Sardinia	1,316,068	1,288,193	482,178	884,930	37	69
LPS	9,782,905	8,194,738	6,340,290	6,492,070	77	79
Italy	35,846,590	31,670,575	21,661,683	22,929,030	68	72

The Regions that mostly benefitted from interregional compensation in 2022 were: Umbria (99% effective self-sufficiency compared to the potential 45%) and Abruzzo (86% compared to 43%) for NAIP; Sardinia (69% compared to 37%) for LPS; Calabria (effective self-sufficiency 54% compared to the potential 48%) for the RIPP consortium; and Molise for the PlaNet consortium (effective self-sufficiency 78% compared to the potential 64%).

The Regions that remained farthest from the goal of effective self-sufficiency were Campania, Latium, Calabria, Apulia, Sicily and Sardinia, with percentages ranging between 24% and 69% of the NHS demand met by the toll fractionation supply.

Normal human immunoglobulins

In 2022, the NHS demand for normal IGs accounted for 94% of the total demand (Table 83).

Table 78. Estimates of regional and national self-sufficiency in human immunoglobulins, 2022

Region	Total demand*	NHS demand*	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	153,568	153,568	89,746	134,980	58	88
Aosta Valley	22,658	22,658	12,659	20,250	56	89
AP Bolzano	52,196	52,196	40,090	48,520	77	93
AP Trento	52,195	52,195	34,750	43,600	67	84
Basilicata	68,263	68,263	34,406	53,890	50	79
Friuli V. Giulia	134,997	134,897	141,019	128,100	104	95
Liguria	237,626	237,451	118,091	188,900	50	79
Umbria	122,368	122,368	51,662	83,340	42	68
Veneto	564,838	559,303	436,677	431,165	77	76
NAIP	1,408,708	1,402,898	959,100	1,132,745	68	80
Apulia	381,024	366,709	184,953	204,234	49	54
Calabria	114,484	114,484	70,971	72,190	62	63
E.-Romagna	610,635	610,635	338,983	464,871	56	76
Sicily	337,017	328,887	270,016	231,975	80	69
RIPP	1,443,160	1,420,715	864,924	973,270	60	67
Campania	386,745	385,270	151,793	203,465	39	53
Latium	566,755	433,241	208,075	137,970	37	24
Marche	192,955	192,535	173,961	137,797	90	71
Molise	17,264	15,344	14,520	12,496	84	72
Tuscany	515,856	515,576	315,040	386,948	61	75
Min. of Def.	-	-	-	440	-	-
PlaNet	1,679,575	1,541,966	863,388	879,116	51	52
Lombardy	985,410	801,606	628,199	520,785	64	53
Piedmont	518,639	517,630	285,001	364,003	55	70
Sardinia	117,034	116,214	75,990	68,940	65	59
LPS	1,621,083	1,435,450	989,191	953,727	61	59
Italy	6,152,526	5,801,029	3,676,603	3,938,858	60	64

* The value does not include *Pentaglobin*TM.

The national potential self-sufficiency, expressed by the ratio of the potential supply to the total demand, in 2022 was 60%, where effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to total demand, was 64%.

The only Region to achieve effective self-sufficiency in IGs in 2022 – more than 90% – was Friuli V. Giulia and AP of Bolzano, while the Regions that achieved the lowest effective self-sufficiency were Latium (24%), Campania (53%), Apulia (54%) and Sardinia (59%).

Normal human immunoglobulins for subcutaneous use

In 2022, the NHS demand for immunoglobulins for subcutaneous/intramuscular use represented approximately 97% of the total demand (Table 84).

Table 79. Estimates of regional and national self-sufficiency in human immunoglobulin for subcutaneous use, 2022

Region	Total demand	NHS demand	Potential supply*	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	28,488	28,488	89,746	10,980	315	39
Aosta Valley	1,883	1,883	12,659	600	672	32
AP Bolzano	2,746	2,746	40,090	1,320	1460	48
AP Trento	8,520	8,520	34,750	2,600	408	31
Basilicata	15,231	15,231	34,406	3,440	226	23
Friuli V. Giulia	8,972	8,972	141,019	3,300	1572	37
Liguria	34,251	34,251	118,091	2,700	345	8
Umbria	42,118	42,118	51,662	9,040	123	21
Veneto	148,223	148,223	436,677	25,520	295	17
NAIP	290,431	290,431	959,100	59,500	330	20
Apulia	102,276	102,276	168,910	18,624	165	18
Calabria	39,208	39,208	65,389	-	167	0
E.-Romagna	121,882	121,882	102,395	3,616	84	3
Sicily	90,996	90,996	246,640	140	271	0
RIPP	354,361	354,361	583,334	22,380	165	6
Campania	111,446	111,446	140,667	3,760	126	3
Latium	199,237	199,110	194,090	670	97	0
Marche	35,725	35,725	159,518	20,752	447	58
Molise	2,944	2,944	13,295	96	452	3
Tuscany	179,914	179,914	293,782	58,748	163	33
Min. of Def.	-	-	1,529	-	-	-
PlaNet	529,265	529,139	802,881	84,026	152	16
Lombardy	135,763	100,171	564,954	4,672	416	3
Piedmont	88,857	88,738	257,317	-	290	0
Sardinia	6,359	6,359	67,681	-	1064	0
LPS	230,978	195,267	889,952	4,672	385	2
Italy	1,405,036	1,369,199	3,235,266	170,578	230	12

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

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

No Region in 2022 achieved effective self-sufficiency > 90%; the highest values of self-sufficiency were recorded in Marche and in the AP of Bolzano with self-sufficiency rates of 58% and 48% respectively.

Normal human immunoglobulins for intravenous use

In 2022, the NHS demand for IV IGs accounted for 93% of the total demand (Table 85).

Table 80. Estimates of regional and national self-sufficiency in human immunoglobulin for intravenous use, 2022

Region	Total demand**	NHS demand**	Potential supply*	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	125,080	125,080	89,746	124,000	72	99
Aosta Valley	20,776	20,776	12,659	19,650	61	95
AP Bolzano	49,450	49,450	40,090	47,200	81	95
AP Trento	43,675	43,675	34,750	41,000	80	94
Basilicata	53,032	53,032	34,406	50,450	65	95
Friuli V. Giulia	126,025	125,925	141,019	124,800	112	99
Liguria	203,375	203,200	118,091	186,200	58	92
Umbria	80,250	80,250	51,662	74,300	64	93
Veneto	416,615	411,080	436,677	405,645	105	97
NAIP	1,118,277	1,112,467	959,100	1,073,245	86	96
Apulia	278,748	264,433	190,840	185,610	68	67
Calabria	75,276	75,276	73,879	72,190	98	96
E.-Romagna	488,753	488,753	397,982	461,255	81	94
Sicily	246,021	237,891	278,662	231,835	113	94
RIPP	1,088,799	1,066,354	941,363	950,890	86	87
Campania	275,299	273,824	156,297	199,705	57	73
Latium	367,518	234,131	215,656	137,300	59	37
Marche	157,230	156,810	177,242	117,045	113	74
Molise	14,320	12,400	14,772	12,400	103	87
Tuscany	335,942	335,662	326,425	328,200	97	98
Min. of Def.	-	-	1,699	440	-	-
PlaNet	1,150,310	1,012,827	892,090	795,090	78	69
Lombardy	849,647	701,436	638,305	516,113	75	61
Piedmont	429,783	428,893	290,725	364,003	68	85
Sardinia	110,675	109,855	76,468	68,940	69	62
LPS	1,390,105	1,240,183	1,005,498	949,055	72	68
Italy	4,747,490	4,431,831	3,798,051	3,768,280	80	79

*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 national potential self-sufficiency, expressed by the ratio of the potential supply to total demand, in 2022 was 80%. Effective self-sufficiency, assumed as the ratio of the actual supply of toll fractionation to total demand, was 79%.

The Regions that in 2022 achieved effective self-sufficiency (more than 90%) were all regions of the NAIP along with Calabria, E.-Romagna, Sicily and Tuscany.

Latium is the Region with the lowest effective self-sufficiency value, equal to 37%.

Antithrombin

In 2022 NHS demand for AT accounted for about 92 percent of total demand. Effective self-sufficiency recorded a value of 75% in 2022 (73% in 2021), slightly higher than the potential self-sufficiency (72%) (Table 86).

Table 81. Estimates of regional and national self-sufficiency in antithrombin, 2022

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	2,304,500	2,254,000	-	-	-	-
Aosta Valley	250,000	250,000	-	-	-	-
AP Bolzano	487,000	487,000	-	288,000	-	59
AP Trento	444,000	444,000	-	224,000	-	50
Basilicata	1,703,000	1,703,000	-	704,000	-	41
FVG	4,120,000	4,120,000	-	2,016,000	-	49
Liguria	4,875,500	4,718,500	-	1,760,000	-	37
Umbria	896,000	896,000	-	490,000	-	55
Veneto	10,577,500	10,557,000	-	4,800,000	-	45
NAIP	25,657,500	25,429,500	-	10,282,000	-	40
Apulia	9,761,000	8,959,000	9,069,600	8,560,000	101	96
Calabria	7,603,500	7,470,000	3,611,200	7,365,000	48	99
E.-Romagna	4,461,500	4,073,000	15,227,015	4,073,000	374	100
Sicily	20,453,000	19,119,000	13,626,000	18,222,000	71	95
RIPP	42,279,000	39,621,000	41,533,815	38,220,000	105	96
Campania	12,650,500	11,971,000	-	4,991,000	-	42
Latium	18,215,500	14,345,000	-	8,192,000	-	57
Marche	3,635,000	3,625,000	-	3,625,000	-	100
Molise	744,000	742,000	-	742,000	-	100
Tuscany	7,860,000	7,858,000	-	7,858,000	-	100
Min. of Def.	-	-	-	-	-	-
PlaNet	43,105,000	38,541,000	-	25,408,000	-	66
Lombardy	12,872,000	9,704,500	29,357,000	8,759,500	303	90
Piedmont	8,276,500	7,778,500	13,873,400	7,778,500	178	100
Sardinia	1,934,500	1,934,500	3,701,600	1,905,000	191	98
LPS	23,083,000	19,417,500	46,932,000	18,443,000	242	95
Italy	134,124,500	123,009,000	88,465,815	92,353,000	72	75

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. Nevertheless, 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 2022, with the exception of NAIP regions and Campania and Latium. The regions that benefited most from interregional compensation or product stocks related to the previous convention in 2022 were Marche, 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 2022, 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 2022, all the Regions largely achieved effective self-sufficiency in pdFVIII (Table 87).

Table 82. Estimates of regional and national self-sufficiency in plasma-derived Factor VIII, 2022

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	130,000	130,000	683,865	130,000	526	100
AostaValley	-	-	96,460	-	NA	NA
APBolzano	400,000	400,000	305,486	400,000	76	100
APTrento	-	-	264,792	-	NA	NA
Basilicata	20,000	20,000	262,177	20,000	1311	100
FVG	680,000	680,000	1,074,568	680,000	158	100
Liguria	390,000	390,000	899,850	390,000	231	100
Umbria	125,000	125,000	393,663	105,000	315	84
Veneto	6,803,000	6,803,000	3,327,479	6,480,000	49	95
NAIP	8,548,000	8,548,000	7,308,342	8,205,000	85	96
Apulia	5,687,000	5,687,000	6,348,720	5,687,000	112	100
Calabria	300,000	300,000	2,527,840	300,000	843	100
E.-Romagna	2,330,000	2,330,000	3,894,940	2,330,000	167	100
Sicily	881,000	881,000	9,538,200	881,000	1083	100
RIPP	9,198,000	9,198,000	22,309,700	9,198,000	243	100
Campania	261,000	261,000	-	261,000	0	100
Latium	5,167,000	5,121,000	-	5,121,000	0	100
Marche	1,352,000	1,352,000	-	1,352,000	0	100
Molise	100,000	100,000	-	100,000	0	100
Tuscany	4,358,000	4,358,000	-	4,358,000	0	100
Min.ofDef.	-	-	-	-	NA	NA
PlaNet	11,238,000	11,192,000	-	11,192,000	0	100

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Lombardy	9,449,000	9,354,000	20,549,900	8,824,000	220	94
Piedmont	5,962,000	5,962,000	9,711,380	5,962,000	163	100
Sardinia	633,000	633,000	2,591,120	628,000	409	99
LPS	16,044,000	15,949,000	32,852,400	15,414,000	206	97
Italy	45,028,000	44,887,000	62,470,442	44,009,000	139	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 2022 was 16%.

Table 83. Estimates of regional and national self-sufficiency in plasma-derived Factor VIII and von Willebrand Factor in combination, 2022

Region	Total demand*	NHS demand*	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	3,379,000	3,379,000	215,219	2,030,000	6	60
Aosta Valley	17,000	17,000	30,357		179	0
AP Bolzano	301,000	301,000	96,139	300,000	32	100
AP Trento	20,000	20,000	83,332	20,000	417	100
Basilicata	18,000	18,000	82,509	10,000	458	56
FVG	577,000	576,000	338,176	530,000	59	92
Liguria	484,000	484,000	283,191	480,000	59	99
Umbria	615,500	615,500	123,889	360,000	20	58
Veneto	2,249,500	2,239,500	1,047,187	1,850,000	47	83
NAIP	7,661,000	7,650,000	2,300,000	5,580,000	30	73
Apulia	5,635,000	5,635,000	-	110,000	-	2
Calabria	1,529,500	1,523,500	-	-	-	-
E.-Romagna	4,126,000	4,103,000	8,619,921	30,000	210	1
Sicily	3,124,000	3,092,000	-	40,000	-	1
RIPP	14,414,500	14,353,500	8,619,921	180,000	60	1
Campania	4,508,000	4,506,000	4,376,310	609,000	97	14
Latium	6,511,500	6,274,000	6,038,369	104,000	96	2
Marche	585,000	585,000	4,962,779	-	848	-
Molise	184,000	178,000	413,613	-	232	-
Tuscany	2,905,000	2,904,000	9,139,889	773,000	315	27
Min. of Def.	-	-	47,559	-	-	-
PlaNet	14,693,500	14,447,000	24,978,520	1,486,000	173	10
Lombardy	4,240,500	4,208,000	-	-	-	-
Piedmont	2,434,000	2,396,000	-	-	-	-
Sardinia	1,614,000	1,614,000	-	-	-	-
LPS	8,288,500	8,218,000	-	-	-	-
Italy	45,057,500	44,668,500	35,898,441	7,246,000	80	16

* 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 (about 90% of the NHS demand), the regional self-sufficiency still bore significant differences with a range, varying from 32 to 100% confirming the need of improvement in the inter-regional exchange and compensation mechanisms (Table 89).

Table 84. Estimates of regional and national self-sufficiency in plasma-derived Factor IX and 3-factor prothrombin complex concentrates, 2022

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	156,000	156,000	-	156,000	-	100
Aosta Valley	45,000	45,000	-	30,000	-	67
AP Bolzano	290,500	170,500	-	170,500	-	100
AP Trento	431,500	431,500	-	306,500	-	71
Basilicata	323,000	215,000	-	68,000	-	32
FVG	560,500	560,500	-	560,500	-	100
Liguria	880,500	369,500	-	221,000	-	60
Umbria	548,000	464,000	-	174,500	-	38
Veneto	4,719,500	3,020,500	-	1,185,500	-	39
NAIP	7,954,500	5,432,500	-	2,872,500	-	53
Apulia	2,998,500	2,363,000	11,953,860	2,363,000	506	100
Calabria	709,000	709,000	4,627,645	709,000	653	100
E.-Romagna	3,445,000	3,115,000	7,246,562	3,115,000	233	100
Sicily	3,292,000	3,154,500	17,454,893	3,127,500	553	99
RIPP	10,444,500	9,341,500	41,282,960	9,314,500	442	100
Campania	2,071,500	1,841,000	17,974,132	1,319,000	976	72
Latium	2,079,700	1,925,200	24,800,446	1,915,700	1,288	100
Marche	2,110,900	2,110,900	20,382,842	2,110,900	966	100
Molise	315,500	311,500	1,698,769	311,500	545	100
Tuscany	4,693,600	4,691,600	37,538,829	4,688,100	800	100
Min. of Def.	-	-	195,333	6,000	NA	-
PlaNet	11,271,200	10,880,200	102,590,350	10,351,200	943	95
Lombardy	9,043,100	8,546,000	39,982,225	7,474,000	468	87
Piedmont	3,879,000	3,429,500	18,210,477	3,189,500	531	93
Sardinia	930,000	930,000	4,789,806	930,000	515	100
LPS	13,852,100	12,905,500	62,982,508	11,593,500	488	90
Italy	43,522,300	38,559,700	206,855,818	34,131,700	536	89

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 2022, the potential self-sufficiency in RiaSTAP was equal to 55% (28% in 2021) (Table 90).

However, effective self-sufficiency of 23% was achieved (25% in 2021), also given the marked increase of demand in 2022 (+12%). Most of NAIP Regions, except for Liguria and Veneto, achieved effective self-sufficiency higher than 80%.

Table 85. Estimates of regional and national self-sufficiency in fibrinogen by toll manufacturing system, 2022

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,440	1,440	2,132	1,220	148	85
Aosta Valley	30	30	301	30	1,003	100
AP Bolzano	862	862	953	690	111	80
AP Trento	360	360	826	360	229	100
Basilicata	420	420	817	370	195	88
Friuli V. G.	1,050	1,050	3,351	1,050	319	100
Liguria	1,226	1,226	2,806	450	229	37
Umbria	1,100	1,100	1,227	1,060	112	96
Veneto	9,072	9,048	10,375	4,250	115	47
NAIP	15,560	15,536	22,788	9,480	147	61
Apulia	411	385	-	-	-	-
Calabria	651	633	-	-	-	-
E.-Romagna	4,192	3,869	-	-	-	-
Sicily	3,571	3,448	-	-	-	-
RIPP	8,825	8,335	-	-	-	-
Campania	4,628	4,228	-	-	-	-
Latium	4,560	3,097	-	-	-	-
Marche	1,386	1,386	-	-	-	-
Molise	-	-	-	-	-	-
Tuscany	-	-	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	10,574	8,711	-	-	-	-
Lombardy	6,672	3,852	-	-	-	-
Piedmont	2,653	2,626	-	-	-	-
Sardinia	2,060	2,060	-	-	-	-
LPS	11,385	8,538	-	-	-	-
Italy	46,344	41,120	22,788	9,480	55	23

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 2022, the NHS demand for S/D plasma was almost equal to the total demand. For the same year, effective national self-sufficiency was 64% (53% in 2021) (Table 91).

Table 86. Estimates of regional and national self-sufficiency in solvent/detergent virus-inactivated plasma, 2022

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	680,000	680,000	-	-	-	-
Friuli V. G.	20,000	20,000	-	-	-	-
Liguria	360,000	360,000	-	-	-	-
Umbria	72,000	72,000	-	-	-	-
Veneto	1,016,200	886,200	1,717,725	886,200	194	100
NAIP	2,148,200	2,018,200	1,717,725	886,200	85	44
Apulia	2,840,000	2,650,000	-	-	-	-
Calabria	1,056,000	1,056,000	-	-	-	-
E.-Romagna	318,000	318,000	-	-	-	-
Sicily	3,026,800	3,026,800	1,793,575	1,131,400	59	37
RIPP	7,240,800	7,050,800	1,793,575	1,131,400	25	16
Campania	3,954,800	3,912,800	4,634,250	3,810,800	118	97
Latium	3,317,600	3,218,600	3,435,450	2,386,600	107	74
Marche	1,449,000	1,449,000	100,825	1,449,000	7	100
Molise	408,000	408,000	693,750	408,000	170	100
Tuscany	1,438,200	1,438,200	2,574,275	654,000	179	45
Min. of Def.	-	-	-	-	-	-
PlaNet	10,567,600	10,426,600	11,438,550	8,708,400	110	84
Lombardy	420,000	420,000	-	420,000	-	100
Piedmont	4,178,000	4,178,000	5,466,750	4,178,000	131	100
Sardinia	36,000	36,000	-	20,000	-	56
LPS	4,634,000	4,634,000	5,466,750	4,618,000	118	100
Italy	24,590,600	24,129,600	20,416,600	15,344,000	85	64

Protein C

In 2021, for the first time, 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 2022 275,000 IU of protein C were distributed among Campania, Latium and Tuscany, enabling these Regions to reach a self-sufficiency percentage of 98% for the first and 100% for the other two. At the national level, the self-sufficiency percentage stood at 43% (Table 92).

Table 87. Estimates of regional and national self-sufficiency in Protein C, 2022

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	11,000	11,000	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-
Friuli V. G.	-	-	-	-	-	-
Liguria	24,000	24,000	-	-	-	-
Umbria	8,000	8,000	-	-	-	-
Veneto	15,500	15,500	-	-	-	-
NAIP	58,500	58,500	-	-	-	-
Apulia	13,000	13,000	-	-	-	-
Calabria	178,500	178,500	-	-	-	-
E.-Romagna	4,000	4,000	-	-	-	-
Sicily	10,000	10,000	-	-	-	-
RIPP	205,500	205,500	-	-	-	-
Campania	193,000	193,000	3,813,642	189,000	1,976	98
Latium	97,500	81,000	5,262,008	81,000	6,496	100
Marche	24,000	24,000	4,324,707	-	18,020	-
Molise	-	-	360,434	-	NA	-
Tuscany	5,000	5,000	7,964,760	5,000	159,295	100
Min. of Def.	-	-	41,445	-	NA	NA
PlaNet	319,500	303,000	21,766,996	275,000	7,184	91
Lombardy	54,500	54,500	-	-	-	-
Piedmont	-	-	-	-	-	-
Sardinia	20,000	20,000	-	-	-	-
LPS	74,500	74,500	-	-	-	-
Italy	658,000	641,500	21,766,996	275,000	3,393	43

Activated prothrombin complex concentrates

In 2022, for the first time, 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 2022, 686,000 UF of aPCCs were distributed among Campania, Latium and Marche, enabling these three regions to reach a self-sufficiency percentage of 48%, 73% and 31%, respectively. At the national level, the percentage of self-sufficiency stood at 11% (Table 93).

Table 88. Estimates of regional and national self-sufficiency in Activated Prothrombin Complex Concentrates, 2022

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	FU	FU	FU	FU	%	%
Abruzzo	1,767,000	1,767,000	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-
Friuli V. G.	12,000	12,000	-	-	-	-
Liguria	257,000	257,000	-	-	-	-
Umbria	-	-	-	-	-	-
Veneto	800,000	797,000	-	-	-	-
NAIP	2,836,000	2,833,000	-	-	-	-
Apulia	40,000	40,000	-	-	-	-
Calabria	-	-	-	-	-	-
E.-Romagna	406,000	406,000	-	-	-	-
Sicily	351,000	351,000	-	-	-	-
RIPP	797,000	797,000	-	-	-	-
Campania	793,000	793,000	18,755,616	382,000	2,365	48
Latium	351,000	328,000	25,878,726	238,000	7,890	73
Marche	211,000	211,000	21,269,052	66,000	10,080	31
Molise	-	-	1,772,628	-	NA	-
Tuscany	-	-	39,170,952	-	NA	-
Min. of Def.	-	-	203,826	-	NA	-
PlaNet	1,355,000	1,332,000	107,050,800	686,000	8,037	52
Lombardy	847,000	824,000	-	-	-	-
Piedmont	267,000	267,000	-	-	-	-
Sardinia	427,000	427,000	-	-	-	-
LPS	1,541,000	1,518,000	-	-	-	-
Italy	6,529,000	6,480,000	107,050,800	686,000	1,652	11

Alpha-1-proteinase inhibitor

Plitalfa is a product containing the human alpha 1-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 2022, potential self-sufficiency in *Plitalfa* was 91% (Table 94). Actual self-sufficiency recorded only within the same RIPP regions was 83% of NHS demand.

Table 89. Estimates of regional and national self-sufficiency in Alpha-1 by toll manufacturing system, 2022

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	-	-	-	-	-	-
Friuli V. G.	-	-	-	-	-	-
Liguria	-	-	-	-	-	-
Umbria	-	-	-	-	-	-
Veneto	-	-	-	-	-	-
NAIP	-	-	-	-	-	-
Apulia	2,360	1,276	-	1,132	-	89
Calabria	-	-	-	-	-	-
E.-Romagna	2,900	2,900	4,052	2,280	140	79
Sicily	280	280	-	280	-	100
RIPP	5,540	4,456	4,052	3,692	91	83
Campania	-	-	-	-	-	-
Latium	-	-	-	-	-	-
Marche	-	-	-	-	-	-
Molise	-	-	-	-	-	-
Tuscany	-	-	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	-	-	-	-	-	-
Lombardy	-	-	-	-	-	-
Piedmont	-	-	-	-	-	-
Sardinia	-	-	-	-	-	-
LPS	-	-	-	-	-	-
Italy	5,540	4,456	4,052	3,692	91	83

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);
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 2022, applying the discounts envisaged by law for pharmaceutical expenditure.

Tables 95 and 96 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 2022, the expenditure for purchasing the aforementioned PDMPs was approximately 205,6 million euros (3.5 euro *per capita*). Table 97 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 406 million euros (6.9 euros *per capita*). The Regions with the highest *per capita* expenditure were Abruzzo with 10.0 euros *per capita* spent and Latium with 9.3 euros *per capita*.

The expenditure for recombinant factors decreased compared to 2021 (-3.6%). Table 98 shows the expenditure incurred in 2022 for the purchase of Emicizumab which has experienced an increase of +24%, from 1.27 to 1.58 euros *per capita*, reflecting how much the use of this drug is progressively increasing.

In 2022, as regards all the other PDMPs (Tables 99-102), the total expenditure was approximately 90 million euros, equal to around 1.52 euros *per capita* of which approximately 35.5 million for the purchase of specific immunoglobulins, a slightly lower cost compared to year 2021 (-2%) (Table 99), also in regard to the *per capita* expenditure equal to 0.60 (0.61 in 2021) (Table 100).

The other PDMPs (Tables 101-102), recorded a slightly increase in expenditure compared to the previous year (+6%), in particular as regards FVII (+31%), 4F-PCCs (+21%), local haemostatics (+14%), FXI (+7%), FXIII (+21%). On the other hand, a decrease in expenditure was recorded for the other plasma protein fractions (-19%), C1-inhibitor (-4%) and FX (-68%).

Table 95. 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 2022

Region	Albumin		Human Immunoglobulin intravenous use*		Human Immunoglobulin subcutaneous use**		Total	
	€	€ per capita	€	€ per capita	€	€ per capita	€	€ per capita
Abruzzo	431,000	0.34	115,383	0.09	1,113,140	0.00	1,659,522	1.30
Aosta Valley	0	0.00	67,178	0.54	72,877	0.00	140,056	1.14
AP Bolzano	10,691	0.02	133,769	0.25	87,635	0.00	232,095	0.43
AP Trento	57,681	0.11	160,980	0.30	364,422	0.00	583,083	1.08
Basilicata	307,162	0.57	535,488	0.99	680,537	0.00	1,523,187	2.82
Friuli V. G.	7,876	0.01	240,026	0.20	326,942	0.00	574,843	0.48
Liguria	387,345	0.26	1,282,809	0.85	1,789,182	0.00	3,459,336	2.29
Umbria	30,443	0.04	331,040	0.39	1,844,229	0.00	2,205,712	2.57
Veneto	246,303	0.05	1,218,985	0.25	7,336,496	0.00	8,801,784	1.81
NAIP	1,478,501	0.13	4,085,657	0.36	13,615,459	0.00	19,179,618	1.68
Apulia	2,052,503	0.52	4,547,488	1.16	5,069,007	1.30	11,668,998	2.98
Calabria	1,469,952	0.80	74,702	0.04	2,339,032	0.00	3,883,686	2.11
E.-Romagna	283,416	0.06	1,156,883	0.26	7,141,522	0.00	8,581,821	1.94
Sicily	2,270,568	0.47	1,408,794	0.29	5,482,105	0.00	9,161,467	1.91
RIPP	6,076,438	0.41	7,187,866	0.48	20,031,667	1.34	33,295,972	2.22
Campania	8,243,105	1.47	6,355,159	1.14	6,581,238	0.00	21,179,503	3.79
Lazio	2,841,375	0.50	5,847,580	1.02	11,461,890	0.00	20,150,845	3.53
Marche	47,999	0.03	2,789,435	1.87	863,231	0.00	3,700,665	2.48
Molise	99,198	0.34	0	0.00	160,469	0.00	259,666	0.89
Tuscany	66,357	0.02	782,858	0.21	7,274,033	0.00	8,123,248	2.21
Min. of Def.	-	-	-	-	-	0.00	0	NA
PlaNet	11,298,034	0.67	15,775,031	0.94	26,340,861	0.00	53,413,927	3.19
Lombardy	3,003,992	0.30	10,875,702	1.09	5,738,739	0.58	19,618,434	1.97
Piedmont	466,602	0.11	3,475,132	0.82	5,036,037	0.00	8,977,771	2.11
Sardinia	979,722	0.62	2,359,549	1.49	377,984	0.00	3,717,255	2.35
LPS	4,450,316	0.28	16,710,384	1.06	11,152,760	0.71	32,313,460	2.05
Italy	23,303,289	0.40	43,758,939	0.74	71,140,748	1.21	138,202,976	2.34

* Includes high-titre IG and imported products

** Includes imported products

Table 96. 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 2022

Region	FVIII		FVIII/VWF		FIX		3F-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.
Abruzzo	-	-	900,341	0.71	-	-	-	-	242,187	0.19	132,440	0.10	20,691	0.02	2,163,356	1.70	555,114	0.44	4,014,129	3.2
Aosta Valley	-	-	4,114	0.03	-	-	3,795	0.03	25,430	0.21	-	-	-	-	-	-	227,137	1.84	260,475	2.1
AP Bolzano	-	-	550	0.001	-	-	-	-	21,233	0.04	75,680	0.14	-	-	-	-	740,732	1.38	838,196	1.6
AP Trento	-	-	-	-	-	-	34,375	0.06	22,748	0.04	-	-	-	-	-	-	192,722	0.36	249,845	0.5
Basilicata	-	-	2,464	0.00	2,310	0.00	40,040	0.07	102,177	0.19	116,380	0.22	-	-	-	-	-	263,371	0.5	
Friuli-V. G.	-	-	25,300	0.02	-	-	-	-	202,727	0.17	171,644	0.14	-	-	-	-	-	-	-	
Liguria	-	-	2,200	0.001	1,188	0.00	42,287	0.03	317,463	0.21	341,440	0.23	52,536	0.03	14,692	0.01	533,702	0.45	948,065	0.8
Umbria	7,148	0.01	128,753	0.15	127,380	0.15	-	-	47,340	0.06	153,164	0.18	17,512	0.02	314,648	0.21	631,216	0.42	1,702,978	1.1
Veneto	128,282	0.03	869,665	0.18	28,141	0.01	493,571	0.10	607,588	0.13	2,113,756	0.44	18,563	0.00	975,767	0.20	268,488	0.31	749,784	0.9
NAIP	135,430	0.01	1,933,387	0.17	159,019	0.01	614,067	0.05	1,588,893	0.14	3,104,504	0.27	109,302	0.01	3,468,462	0.30	3,981,644	0.35	15,094,707	1.3
Apulia	-	-	2,791,581	0.71	-	-	-	-	41,983	0.01	1,005,871	0.26	28,457	0.01	48,400	0.01	347,215	0.09	4,263,507	1.1
Calabria	-	-	887,451	0.48	-	-	-	-	11,204	0.01	612,762	0.33	378,460	0.21	-	-	455,664	0.25	2,345,540	1.3
E-Romagna	-	-	2,226,760	0.50	-	-	-	-	-116	0.00	1,702,360	0.38	-	-	497,070	0.11	454,391	0.10	4,880,466	1.1
Sicily	-	-	2,386,604	0.50	-	-	7,395	0.00	96,468	0.02	1,408,261	0.29	17,050	0.00	378,146	0.08	1,180,872	0.25	5,474,796	1.1
RIPP	-	-	8,292,396	0.55	-	-	7,395	0.00	149,538	0.01	4,729,254	0.32	423,967	0.03	923,617	0.06	2,438,142	0.16	16,964,310	1.1
Campania	-	-	2,110,098	0.38	-	-	114,840	0.02	689,856	0.12	1,926,815	0.34	8,756	0.00	401,917	0.07	1,961,444	0.35	7,213,726	1.3
Lazio	-	-	2,760,707	0.48	934	0.00	2,120	0.00	650,741	0.11	1,299,981	0.23	-	0.00	110,187	0.02	1,195,153	0.21	6,019,822	1.1
Marche	-	-	411,609	0.28	-	-	-	-	-	-	623,286	0.42	38,500	0.03	177,525	0.12	156,293	0.10	1,407,213	0.9
Molise	-	-	79,882	0.27	-	-	-	-	-	-	-	-	-	-	-	-	14,414	0.05	94,296	0.3
Tuscany	-	-	1,102,964	0.30	-	-	909	0.00	-	-	1,382,559	0.38	-297	-	-66,113	-	925,798	0.25	3,345,820	0.9
Min. Def.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	-	-	6,465,260	0.39	934	0.00	117,869	0.01	1,340,597	0.08	5,232,641	0.31	46,959	0.00	623,517	0.04	4,253,102	0.25	18,080,878	1.1
Lombardy	213,318	0.02	3,099,689	0.31	568,039	0.06	-	-	95,253	0.01	2,030,380	0.20	83,810	0.01	1,008,832	0.10	2,603,582	0.26	9,702,903	1.0
Piedmont	-	-	1,044,639	0.25	96,888	0.02	-	-	-	-	1,025,102	0.24	-	-	326,888	0.08	1,378,577	0.32	3,872,094	0.9
Sardinia	1,980	0.00	716,358	0.45	-	-	-	-	3,050	0.00	906,400	0.57	30,646	0.02	522,781	0.33	1,477,810	0.94	3,659,026	2.3
LPS	215,298	0.01	4,860,686	0.31	664,927	0.04	-	-	98,304	0.01	3,961,882	0.25	114,456	0.01	1,858,501	0.12	5,459,969	0.35	17,234,022	1.1
ITALY	350,727	0.01	21,551,729	0.37	824,880	0.01	739,331	0.01	3,177,331	0.05	17,028,281	0.29	694,684	0.01	6,874,097	0.12	16,132,857	0.27	67,373,917	1.1

Table 97. Estimate of the total expenditure and the total per capita expenditure for recombinant Factors VII, VIII, IX and XIII in 2022

Region	rFVIIa		FVIIIr		FIXr		FXIIIr		Totale	
	€	€ pc	€	€ pc	€ pc	€ pc	€	€ pc	€	€ pc
Abruzzo	585,810	0.46	8,168,214	6.41	3,723,371	2.92	248,387	0.20	12,725,782	10.0
Aosta Valley	122,988	1.00	433,974	3.52	-	-	-	-	556,962	4.5
AP Bolzano	157,942	0.29	1,943,257	3.63	107,442	0.20	-	-	2,208,641	4.1
AP Trento	195,485	0.36	2,250,656	4.15	465,718	0.86	-	-	2,911,859	5.4
Basilicata	36,896	0.07	1,812,512	3.36	301,890	0.56	186,290	0.34	2,337,588	4.3
FVG	1,066,753	0.89	2,239,848	1.87	1,948,047	1.63	-	-	5,254,649	4.4
Liguria	242,091	0.16	6,496,527	4.31	3,708,071	2.46	434,678	0.29	10,881,367	7.2
Umbria	130,108	0.15	3,357,522	3.91	701,818	0.82	-	-	4,189,448	4.9
Veneto	2,813,176	0.58	19,178,958	3.95	5,633,103	1.16	77,621	0.02	27,702,858	5.7
NAIP	5,351,249	0.47	45,881,467	4.01	16,589,460	1.45	946,976	0.08	68,769,153	6.0
Apulia	1,645,438	0.42	20,831,512	5.32	8,664,018	2.21	-	-	31,140,968	8.0
Calabria	1,405,292	0.76	11,875,745	6.44	2,003,242	1.09	822,783	0.45	16,107,062	8.7
E.-Romagna	4,089,655	0.92	26,319,231	5.94	8,495,372	1.92	108,669	0.02	39,012,927	8.8
Sicily	1,944,496	0.40	25,792,031	5.37	5,081,060	1.06	-	-	32,817,587	6.8
RIPP	9,084,881	0.61	84,818,519	5.66	24,243,692	1.62	931,452	0.06	119,078,544	7.9
Campania	2,019,956	0.36	36,015,346	6.44	8,955,827	1.60	93,145	0.02	47,084,274	8.4
Lazio	1,437,656	0.25	45,203,922	7.91	6,292,083	1.10	-	-	52,933,661	9.3
Marche	357,960	0.24	6,085,948	4.09	1,840,780	1.24	-	-	8,284,688	5.6
Molise	12,946	0.04	872,573	3.00	-	-	-	-	885,519	3.0
Tuscany	4,784,207	1.30	10,164,940	2.77	7,820,503	2.13	-	-	22,769,650	6.2
Min. of Def.	-	-	-	-	-	-	-	-	-	-
PlaNet	8,612,725	0.51	98,342,728	5.87	24,909,193	1.49	93,145	0.01	131,957,792	7.9
Lombardy	2,335,466	0.23	41,079,441	4.12	13,416,356	1.35	574,395	0.06	57,405,659	5.8
Piedmont	1,231,404	0.29	14,261,947	3.35	5,758,392	1.35	248,387	0.06	21,500,130	5.1
Sardinia	313,941	0.20	6,889,546	4.36	4,551	0.00	-	-	7,208,038	4.6
LPS	3,880,811	0.25	62,230,935	3.94	19,179,298	1.21	822,783	0.05	86,113,827	5.5
Italy	26,929,667	0.46	291,273,649	4.94	84,921,643	1.44	2,794,356	0.05	405,919,315	6.9

Table 98. Estimate of the total expenditure and the total per capita expenditure for Emicizumab in 2022

Region	€	€ pc
Abruzzo	2,175,246	1.71
Aosta Valley	334,863	2.72
AP Bolzano	620,522	1.16
AP Trento	-	-
Basilicata	809,140	1.50
Friuli V. Giulia.	1,521,236	1.27
Liguria	2,301,672	1.53
Umbria	1,675,682	1.95
Veneto	8,936,065	1.84
NAIP	18,374,426	1.61
Apulia	3,369,819	0.86
Calabria	3,424,489	1.86
E.-Romagna	5,215,667	1.18
Sicily	5,811,917	1.21
RIPP	17,821,892	1.19
Campania	8,827,408	1.58
Lazio	3,378,020	0.59
Marche	2,395,980	1.61
Molise	831,007	2.86
Tuscany	9,985,538	2.72
Min. of Def.	-	-
PlaNet	25,417,953	1.52
Lombardy	18,602,580	1.87
Piedmont	13,172,428	3.10
Sardinia	60,139	0.04
LPS	31,835,146	2.02
Italy	93,449,418	1.58

Table 99. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of specific immunoglobulins in 2022

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs	Rabies IGs	Total
Abruzzo	242,389	4,462	232,092	55,531	52,510	-	539	587,522
Aosta Valley	53,772	-	14,181	7,035	3,955	-	2,156	81,099
AP Bolzano	30,705	-	23,483	40,919	37,683	4,540	9,379	146,709
AP Trento	80,641	-	25,495	35,224	-	-	-	141,359
Basilicata	120,407	176	83,470	23,806	20,592	-	-	248,452
Friuli V. Giulia	107,837	-	7,213	63	226,210	10,758	63,494	415,575
Liguria	188,357	10,256	178,879	57,844	4,118	-	-	439,455
Umbria	100,067	-	95,648	30,178	-	1,799	-	227,692
Veneto	1,041,821	333,902	183,500	275,832	487,469	1,418	22,638	2,346,580
NAIP	1,965,997	348,796	843,960	526,431	832,537	18,515	98,206	4,634,442
Apulia	2,465,386	135,518	357,994	107,873	65,292	571	5,821	3,138,455
Catabria	621,466	33,872	332,170	69,300	74,322	-	-	1,131,129
E.-Romagna	832,873	232,203	332,186	235,545	394,095	19,812	12,936	2,059,651
Sicily	1,237,090	1,375	696,158	167,627	253,461	95	-	2,355,806
RIPP	5,156,815	402,968	1,718,508	580,345	787,170	20,478	18,757	8,685,041
Campania	5,355,323	238,364	1,353,577	118,219	100,176	-	755	7,166,413
Lazio	907,834	58,421	529,177	142,794	78,867	2,571	-	1,719,664
Marche	292,581	31,157	209,363	61,808	51,730	8,250	2,156	657,044
Molise	83,614	-	36,397	8,081	-	-	-	128,092
Tuscany	713,670	80,240	518,707	149,751	215,186	4,179	9,810	1,691,544
Min. of Def.	-	-	-	-	-	-	-	-
PiaNet	7,353,021	408,182	2,647,221	480,653	445,959	15,000	12,720	11,362,757
Lombardy	4,345,219	160,151	564,369	385,007	341,953	21,611	28,998	5,847,307
Piedmont	2,104,418	23,843	208,484	190,751	575,671	3,191	10,672	3,117,029
Sardinia	1,532,382	60,821	191,006	27,292	-	95	-	1,811,597
LPS	7,982,019	244,814	963,859	603,050	917,624	24,897	39,670	10,775,933
Italy	22,457,852	1,404,760	6,173,548	2,190,480	2,983,290	78,890	169,354	35,458,173

Table 100. 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 2022

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs*	Rabies IGs*	Total
Abruzzo	0.19	0.00	0.18	0.04	0.04	-	0.42	0.46
Aosta Valley	0.44	-	0.11	0.06	0.03	-	17.48	0.66
AP Bolzano	0.06	-	0.04	0.08	0.07	8.47	17.50	0.27
AP Trento	0.15	-	0.05	0.06	-	-	-	0.26
Basilicata	0.22	0.00	0.15	0.04	0.04	-	-	0.46
Friuli V. Giulia	0.09	-	0.01	0.00	0.19	8.99	53.03	0.35
Liguria	0.12	0.01	0.12	0.04	0.003	-	-	0.29
Umbria	0.12	-	0.11	0.04	0.00	2.09	-	0.26
Veneto	0.21	0.07	0.04	0.06	0.10	0.29	4.66	0.48
NAIP	0.17	0.03	0.07	0.05	0.07	1.62	8.59	0.41
Apulia	0.63	0.03	0.09	0.03	0.02	0.15	1.49	0.80
Calabria	0.34	0.02	0.18	0.04	0.04	-	-	0.61
E.-Romagna	0.19	0.05	0.07	0.05	0.09	4.47	2.92	0.46
Sicily	0.26	0.00	0.14	0.03	0.05	0.02	-	0.49
RIPP	0.34	0.03	0.11	0.04	0.05	1.37	1.25	0.58
Campania	0.96	0.04	0.24	0.02	0.02	-	0.13	1.28
Lazio	0.16	0.01	0.09	0.02	0.01	0.45	-	0.30
Marche	0.20	0.02	0.14	0.04	0.03	5.54	1.45	0.44
Molise	0.29	-	0.13	0.03	-	-	-	0.44
Tuscany	0.19	0.02	0.14	0.04	0.06	1.14	2.67	0.46
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	0.44	0.02	0.16	0.03	0.03	0.89	0.76	0.68
Lombardy	0.44	0.02	0.06	0.04	0.03	2.17	2.91	0.59
Piedmont	0.49	0.01	0.05	0.04	0.14	0.75	2.51	0.73
Sardinia	0.97	0.04	0.12	0.02	-	0.06	-	1.15
LPS	0.51	0.02	0.06	0.04	0.06	1.58	2.51	0.68
Italy	0.38	0.02	0.10	0.04	0.05	1.34	2.87	0.60

* values per 1,000 population

Table 101. Estimate of standardised expenditure incurred by the National Health Service for the purchase of all other PDMPs in 2022

Region	FVII	Local Haemostatic agents- combinations	Other plasma Proteins fractions	4-factor prothrombin complex concentrates	Human C1 esterase inhibitor	Factor X	Factor XI	Factor XIII	Total
Abruzzo	286,565	979,901	-	280,188	232,989	-	-	-	1,779,643
Aosta Valley	-	79,349	-	-	1,755	-	-	-	81,104
AP Bolzano	-	343,166	-	152,746	25,749	-	-	5,861	527,522
AP Trento	-	223,779	-	25,168	1,170	-	-	31,258	281,375
Basilicata	47,605	420,354	273,097	60,740	93,632	-	-	-	895,428
Friuli V. Giulia	-	452,298	7,832	-	23,544	-	80,960	-	564,634
Liguria	61,607	465,051	142,956	274,589	22,238	-	-	42,979	1,009,420
Umbria	933	454,367	52,070	110,433	58,001	-	-	-	675,804
Veneto	-	2,050,804	-	249,163	1,249,289	-	-	123,468	3,672,724
NAIP	396,711	5,469,068	475,955	1,153,028	1,708,367	-	80,960	203,565	9,487,653
Apulia	264,163	1,629,416	1,565,691	25,165	860,088	-	-	11,667	4,356,190
Calabria	31,270	956,528	486,870	108,723	573,745	-	-	-	2,157,136
E.-Romagna	142,816	1,515,074	125,054	500,522	279,897	-	-	214,896	2,778,258
Sicily	183,885	1,742,862	1,048,579	130,878	1,517,660	-	-	-	4,623,864
RIPP	622,134	5,843,880	3,226,193	765,287	3,231,391	-	-	226,563	13,915,448
Campania	334,526	3,968,381	39,214	386,552	2,361,436	-	-	-	7,090,110
Lazio	1,311,101	1,898,611	340,050	235,451	2,726,598	-	-	75,018	6,586,828
Marche	25,203	591,384	-	71,439	281,875	-	-	45,324	1,015,224
Molise	238,960	19,392	-	-	9,361	-	-	-	267,713
Tuscany	9,800	2,168,351	299,739	430,367	492,135	-	-	30,476	3,430,867
Min. of Def.	-	-	-	-	-	-	-	-	-
PlaNet	1,919,590	8,646,118	679,002	1,123,809	5,871,406	-	-	150,818	18,390,743
Lombardy	1,343,619	3,748,939	7,797	145,110	1,717,173	17,160	-	14,847	6,994,645
Piedmont	237,093	1,798,990	-	328,038	1,576,673	-	70,840	22,662	4,034,296
Sardinia	-	574,025	6,292	394,361	639,038	-	-	-	1,613,716
LPS	1,580,712	6,121,953	14,089	867,509	3,932,884	17,160	70,840	37,509	12,642,657
Italy	4,519,147	26,081,019	4,395,240	3,909,633	14,744,047	17,160	151,800	618,455	54,436,501

Table 102. 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 2022

Region	FVII	Local Haemostatic agents-combinations	Other plasma Proteins fractions	4-factor prothrombin complex concentrates	Human C1 esterase inhibitor	Factor X *	Factor XI*	Factor XIII *	Total
Abruzzo	0.22	0.77	-	0.22	0.18	-	-	-	1.40
Aosta Valley	-	0.64	-	-	0.01	-	-	-	0.66
AP Bolzano	-	0.64	-	0.29	0.05	-	-	10.94	0.98
AP Trento	-	0.41	-	0.05	0.00	-	-	57.65	0.52
Basilicata	0.09	0.78	0.51	0.11	0.17	-	-	-	1.66
Friuli V. Giulia	-	0.38	0.01	-	0.02	-	67.62	-	0.47
Liguria	0.04	0.31	0.09	0.18	0.01	-	-	28.51	0.67
Umbria	0.001	0.53	0.06	0.13	0.07	-	-	-	0.79
Veneto	-	0.42	-	0.05	0.26	-	-	25.43	0.76
NAIP	0.03	0.48	0.04	0.10	0.15	-	7.08	17.80	0.83
Apulia	0.07	0.42	0.40	0.01	0.22	-	-	2.98	1.11
Calabria	0.02	0.52	0.26	0.06	0.31	-	-	-	1.17
E.-Romagna	0.03	0.34	0.03	0.11	0.06	-	-	48.49	0.63
Sicily	0.04	0.36	0.22	0.03	0.32	-	-	-	0.96
RIPP	0.04	0.39	0.22	0.05	0.22	-	-	15.11	0.93
Campania	0.06	0.71	0.01	0.07	0.42	-	-	-	1.27
Lazio	0.23	0.33	0.06	0.04	0.48	-	-	13.13	1.15
Marche	0.02	0.40	-	0.05	0.19	-	-	30.42	0.68
Molise	0.82	0.07	-	-	0.03	-	-	-	0.92
Tuscany	0.00	0.59	0.08	0.12	0.13	-	-	8.29	0.93
Min. of Def.	-	-	-	-	-	-	-	-	-
PlaNet	0.11	0.52	0.04	0.07	0.35	-	-	9.00	1.10
Lombardy	0.13	0.38	0.001	0.01	0.17	1.7	-	1.49	0.70
Piedmont	0.06	0.42	-	0.08	0.37	-	16.66	5.33	0.95
Sardinia	-	0.36	0.004	0.25	0.40	-	-	-	1.02
LPS	0.10	0.39	0.001	0.05	0.25	1.1	4.48	2.37	0.80
Italy	0.08	0.44	0.07	0.07	0.25	0.3	2.57	10.49	0.92

* values per 1,000 population

National and Regional mean price per gram or International Unit

Tables 103-105 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 103), the national mean price per gram was 2.76 euros (2.67 in the year 2021). The variability observed among Regions (range: 2.14-3.96 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, 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 18,474,261 euros (0.49 euros per IU), and almost entirely accounted for the distribution through NHS facilities (96% like in 2021) (Table 104).

The market demand for IV IGs (excluding the specific demand for products containing IVIGs with high titers of IGM - *see* Table 7) recorded an expenditure equal to 35,670,618 million euros with a decrease of -2% compared to 2021. The mean unit price per gram at national level was 56.63 euros (range: 48.18-61.60 euros) (Table 105).

Table 103. 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 2022

Region	Mean price		Demand		Total expenditure	
	NHS facilities €/g	Pharmacies €/g	NHS facilities g	Pharmacies g	Total €	NHS facilities €
			%	%	%	%
Abruzzo	1.95	3.95	85,000	67,233	165,636	265,364
Aosta Valley	-	-	-	-	-	-
AP Bolzano	2.17	3.97	4,813	60	10,453	238
AP Trento	2.09	3.92	8,000	10,450	16,731	40,950
Basilicata	2.10	3.94	62,420	44,635	131,198	175,964
Friuli V. Giulia	-	3.90	-	2,020	-	7,876
Liguria	2.27	3.93	147,125	13,738	333,422	53,923
Umbria	2.09	3.93	375	7,538	784	29,660
Veneto	2.42	3.94	6,240	58,620	15,129	231,174
NAIP	2.14	3.94	313,973	204,293	673,352	805,149
Apulia	2.16	3.94	270,145	372,593	584,738	1,467,764
Calabria	2.24	3.92	147,925	290,683	331,060	1,138,891
E.-Romagna	2.60	3.90	98,875	6,688	257,313	26,104
Sicily	2.14	3.91	612,895	245,775	1,309,504	961,063
RIPP	2.20	3.92	1,129,840	915,738	2,482,616	3,593,822
Campania	1.89	3.90	1,762,725	1,258,705	3,338,516	4,904,589
Lazio	1.95	3.94	731,050	358,810	1,429,101	1,412,273
Marche	2.26	-	21,230	-	47,999	-
Molise	-	3.96	-	25,078	-	99,198
Tuscany	1.89	3.93	18,200	8,148	34,356	32,001
Min. of Def.	-	-	-	-	-	-
PlaNet	1.91	3.91	2,533,205	1,650,740	4,849,973	6,448,061
Lombardy	2.16	3.94	702,810	378,373	1,514,805	1,489,187
Piedmont	2.10	3.94	213,663	4,560	448,658	17,944
Sardinia	1.90	3.95	299,870	103,393	570,851	408,871
LPS	2.08	3.94	1,216,343	486,325	2,534,315	1,916,001
Italy	2.03	3.92	5,193,360	3,257,095	10,540,257	12,763,033
			61	39	45	55

Table 104. 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 2022

Region	Mean price *			Demand*			Total expenditure*			
	NHS facilities €/UI	Pharmacies €/UI	Total €/UI	NHS facilities UI	Pharmacies UI	%	Total €	%	NHS facilities €	%
Abruzzo	0.51	-	0.51	1,349,000	-	100	694,163	100	-	0
Aosta Valley	0.24	-	0.24	17,000	-	100	4,114	100	-	0
AP Bolzano	0.55	-	0.55	1,000	-	100	550	100	-	0
AP Trento	-	-	-	-	-	-	-	-	-	-
Basilicata	0.31	-	0.31	8,000	-	100	2,464	100	-	0
Friuli V. Giulia	0.55	-	0.55	46,000	-	100	25,300	100	-	0
Liguria	0.55	-	0.55	4,000	-	100	2,200	100	-	0
Umbria	0.50	-	0.50	255,500	-	100	128,753	100	-	0
Veneto	0.54	-	0.54	389,500	-	100	211,571	100	-	0
NAIP	0.52	-	0.52	2,070,000	-	100	1,069,114	100	-	0
Apulia	0.51	-	0.51	5,525,000	-	100	2,791,581	100	-	0
Calabria	0.55	0.60	0.55	1,521,500	2,000	99.9	833,498	99.9	1,210	0.1
E.-Romagna	0.55	-	0.55	4,073,000	-	100	2,226,760	100	-	0
Sicily	0.53	0.54	0.53	2,824,000	228,000	93	1,498,613	92	122,013	8
RIPP	0.53	0.54	0.53	13,943,500	230,000	98	7,350,452	98	123,223	2
Campania	0.49	-	0.49	3,897,000	-	100	1,894,330	100	-	0
Lazio	0.44	0.59	0.45	6,006,500	163,500	97	2,663,465	96	97,241	4
Marche	0.54	-	0.54	585,000	-	100	315,712	100	-	0
Molise	0.45	-	0.45	178,000	-	100	79,882	100	-	0
Tuscany	0.48	-	0.48	2,131,000	-	100	1,020,252	100	-	0
Min. of Def.	-	-	-	-	-	-	-	-	-	-
PlaNet	0.47	0.59	0.47	12,797,500	163,500	99	5,973,642	98	97,241	2
Lombardy	0.54	0.60	0.55	3,225,000	983,000	77	1,728,557	75	591,598	25
Piedmont	0.35	-	0.35	2,396,000	-	100	827,672	100	-	0
Sardinia	0.44	-	0.44	1,614,000	-	100	712,762	100	-	0
LPS	0.45	0.60	0.47	7,235,000	983,000	88	3,268,991	85	591,598	15
Italy	0.49	0.59	0.49	36,046,000	1,376,500	96	17,662,199	96	812,062	4

* The value does not include Wilfactin (vWF)

Table 105. National and Regional mean price per gram for the purchase of intravenous immunoglobulins by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2022

Region	Mean price per gram (€)	Total demand	Total expenditure
	NHS facilities* (€/g)	NHS facilities* (g)	NHS facilities* (€)
Abruzzo	59.98	1,080	64,783
Aosta Valley	59.68	1,126	67,178
AP Bolzano	55.79	2,250	125,497
AP Trento	58.37	2,675	156,140
Basilicata	57.44	2,582	148,288
Friuli V. Giulia	60.50	1,125	68,063
Liguria	59.75	17,000	1,015,729
Umbria	55.20	5,950	328,466
Veneto	59.17	5,435	321,585
NAIP	58.53	39,222	2,295,728
Apulia	54.62	64,998	3,550,030
Calabria	50.38	836	42,114
E.-Romagna	54.11	13,538	732,547
Sicily	58.77	2,141	125,843
RIPP	54.60	81,514	4,450,534
Campania	60.64	74,119	4,494,684
Latium	55.68	96,631	5,380,718
Marche	61.60	39,765	2,449,612
Molise	-	-	-
Tuscany	60.39	7,462	450,658
Min. of Def.	-	-	-
PlaNet	58.61	217,977	12,775,672
Lombardy	57.53	185,323	10,662,520
Piedmont	48.18	64,890	3,126,614
Sardinia	57.67	40,915	2,359,549
LPS	55.47	291,128	16,148,684
Italy	56.63	629,841	35,670,618

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

FINAL CONSIDERATIONS

The national demand for albumin, although slightly lower than that recorded in 2021, was still quite high at about 608 grams per 1,000 population.

An increased demand was observed in Basilicata (+23%), in Aosta Valley (+19%), Abruzzo and E.-Romagna (+10%). The Regions with the highest standardised demand per 1,000 population were Abruzzo, Basilicata and Sardinia, with standardised volumes of 885, 834 and 833 grams, respectively.

About 9% of the national demand was distributed through public pharmacies, reaching a quantity of approximately 3,257 kilograms. The pharmacy channel was particularly used in Calabria and Campania where it accounts respectively for 27% and 30% of the regional demands.

In the two-year period 2021-2022 the total demand of IG registered a -3.3%; there was a -8% in the demand for SC/IM-IG, and a -2% in the 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 Aosta Valley, Liguria and Umbria, with around 184, 160 and 142 grams.

The demand for AT recorded a slight decrease (-4%) in 2022, in contrast to demand for 3F-PCCs (+2%) and demand for 4F-PCCs (+23%), which continued to rise.

As regards the haemophilia A treatment, on one hand, the demand for pdFVIII (alone and in combination with vWF) has remained roughly constant (+1.2%); there was a slight decrease in the demand for rFVIII (-2%), despite the increased use of medicinal products with extended half-life FVIII (+35%).

The consumption of Emicizumab also increased significantly (+38%) while the demand for the activated prothrombin complex remained unchanged (-0.3%).

Concerning the haemophilia B treatment, the clinical use of recombinant FIX (+4% compared to 2021), especially that with extended half-life (+12%), progressively replaced the demand for pdFIX.

The total volume of plasma sent by Regions for fractionation decreased by 2.2% compared to the previous year. There were still great differences in the volumes from one Region to another, ranging from 5.1 kilograms per 1,000 population sent by Campania to 23.9 sent by Friuli V. Giulia, with an average volume of 14.3 kilograms per 1,000 population.

The level of albumin self-sufficiency fell to 72% of the NHS demand (71% in 2021). As regards IGs, on the other hand, self-sufficiency in human immunoglobulin for intravenous and subcutaneous/intramuscular use (excluding high titre Ig) achieved at national level was 64% of the total demand, while self-sufficiency in IV IG reached 79% (excluding high titre Ig); self-sufficiency for SC / IM IG was 12%.

The self-sufficiency of AT was equal to 75% of the NHS demand, higher than in the 2021 when it was 73%.

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 96.7 million euros, in line with the costs estimated by the contracts in force in 2022, while approximately 3.6 million

euros had to be taken into account for the treatment of plasma virus-inactivated by solvent / detergent, for a total of approximately 100 million euros.

The estimated expenditure incurred by the NHS in 2022 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 205.6 million euros. An additional 89.9 million euros were used for the purchase of all the other PDMPs. The cost of purchasing Emicizumab was 93.5 million euros. The expenditure associated to recombinant products was about 406 million euros. The total expenditure for medicinal products described in this report was around 3.4% of the total NHS pharmaceutical expenditure recorded in 2022 (55).

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