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Demand for plasma-derived medicinal products in Italy. 2021

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.
2021**

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2023, vii, 143 p. Rapporti ISTISAN 23/6 EN

With the aim of fulfilling the task assigned it pursuant to national regulations regarding coordinating and providing technical support to the planning of self-sufficiency in blood components and plasma-derived medicinal products at regional and national level, the Italian National Blood Centre has conducted an analysis in collaboration with the Information and Statistics Department of the Italian Health Ministry. The analysis of the demand for plasma-derived medicinal products and recombinant therapies included the assessment of self-sufficiency levels achieved and the costs sustained by the Italian National Health Service for the provision of these products. The content of this document, an update of the data for the year 2021 published in the *Rapporto ISTISAN 22/7*, stems from a comparative analysis of the available data sources. The document is also an invaluable tool for planning self-sufficiency at national level.

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

Istituto Superiore di Sanità

Analisi della domanda di medicinali plasmaderivati in Italia. 2021.

Fabio Candura, Maria Simona Massari, Samantha Profili, Lucia De Fulvio, Cristiana Chelucci, Chiara Brutti, Claudia Biffoli, Vincenzo De Angelis
2023, vii, 143 p. Rapporti ISTISAN 23/6 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 2021 dei dati sull'argomento pubblicati nel *Rapporto ISTISAN 22/7* e che si configura come uno strumento fondamentale per la programmazione dell'autosufficienza nazionale.

Parole chiave: Medicinali plasmaderivati; Domanda; Autosufficienza; Spesa

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ACRONYMS AND ABBREVIATIONS

3F-PCCs	3-Factor Prothrombin Complex Concentrates
4F-PCCs	4-Factor Prothrombin Complex Concentrates
AIC	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	Istituto Italiano di STATistica (Italian National Statistics Institute)
IU/s	International Unit/s
IVIG	IntraVenous ImmunoGlobulin
L	Law
LHC	Local Health Centre
LPS	Lombardy-Piedmont-Sardinia Agreement
Min	Ministry
Min. of Def.	Ministry of Defence
MoH	Ministry of Health
NAIP	Nuovo Accordo Interregionale per la Plasmaderivazione (New Interregional Agreement for plasma-derived medicinal products)
NHS	National Health Service
NSIS	Nuovo Sistema Informativo Sanitario (New Health Information System)
PDMP/s	Plasma-Derived Medicinal Product/s
rFVIIa	Recombinant activated Factor VII
rFVIII	Recombinant Factor VIII
rFIX	Recombinant Factor IX
RTI	Raggruppamento Temporaneo d'Impresa (Temporary Business Grouping)
S/D	Solvent / Detergent (plasma)
SC/IM	SubCutaneous/IntraMuscular
ST/s	Transfusion Service/s
UdR	Collection Units run by Donor Associations
VAT	Value Added Tax
vWF	von Willebrand Factor

FOREWORD

The Italian National Blood Centre (Centro Nazionale Sangue, CNS) is a technical body of the Italian Ministry of Health (MoH) which operates under the Istituto Superiore di Sanità (the National Institute of Health in Italy). In compliance with the current laws, it supervises the coordination and technical-scientific support to all matters concerning the production of Plasma and Plasma-Derived Medicinal Products (PDMPs).

The 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 relating to the calendar year 2021, also contains the PDMP demand included in the new industrial toll fractionation calls for tender at regional level. In point of 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 report, as well as the previous ones annually published from 2007 to 2020, is to provide 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 Ministerial Decree of the Ministry of Health (*Decreto Ministeriale*, DM) of 2 December 2016 along with the National self-sufficiency in blood and blood products programme 2021, issued by DM of 27 July 2021.

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 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 stipulate 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 the plasma collected by Blood Establishments (BEs), to the companies holder of the agreements for the industrial transformation of plasma aimed at the production of PDMPs. The contract with these companies, which operate as service providers, is considered a “third party processing” method, which the Regions implement by means of a tender procedure in accordance 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 that provides 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 NAIP in 2018 and, since FVIII, they are also the subject of this Report.

More recently, in the second half of 2020, the Regions adhering to the Plasma Network agreement (PLA.NET), led by the Tuscany Region, and to the Plasma/Plasma-Derived Interregional Grouping (*Raggruppamento Interregionale Plasma e Plasmaderivati*, RIPP), led by the Emilia-Romagna Region, have begun to send plasma to companies awarded the new tenders, Takeda Italia SpA on one hand and, on the other, Kedrion SpA and Grifols Italia SpA formed 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, that can be recorded starting from 2021.

Indeed, the agreement with Takeda company 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.

Pending the completion of the tender by the fourth interregional agreement for toll fractionation, made up of Lombardy, Piedmont and Sardinia, the following PDMPs from toll fractionation produced by the company Kedrion SpA (hereafter Kedrion) under the contract prior to the enlargement of the possible commercial partners, also contributed to national self-sufficiency in 2021: albumin, IVIG, SCIG, AT, pdFVIII, pdFIX, 3F-PCCs and solvent/detergent virus-inactivated plasma.

Inasmuch as the clinical interest and its impact on the pharmaceutical expenditure, the Report describes also 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 provided for the contracts between the Regions and the contracted fractionators, the level of regional and national self-sufficiencies is estimated on a case-by-case bases.

Finally, it is outlined the pharmaceutical expenditure incurred by the National Health Service (NHS) for procurement on the market, regardless of whether it is the portion of the NHS demand not covered by toll fractionation agreements, or 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 pharmaceutical expenditure. It is divided into four analytical sections:

- *Part A*
PDMPs currently provided by toll fractionation agreements.
- *Part B*
Other PDMPs.
- *Part C*
National and Regional PDMPs self-sufficiency in regard with the PDMPs provided by 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) has been updated daily 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 through a marketing authorisation code (*Autorizzazione all’Immissione in Commercio*, AIC code) at every step throughout the entire supply chain process (Figure 1).

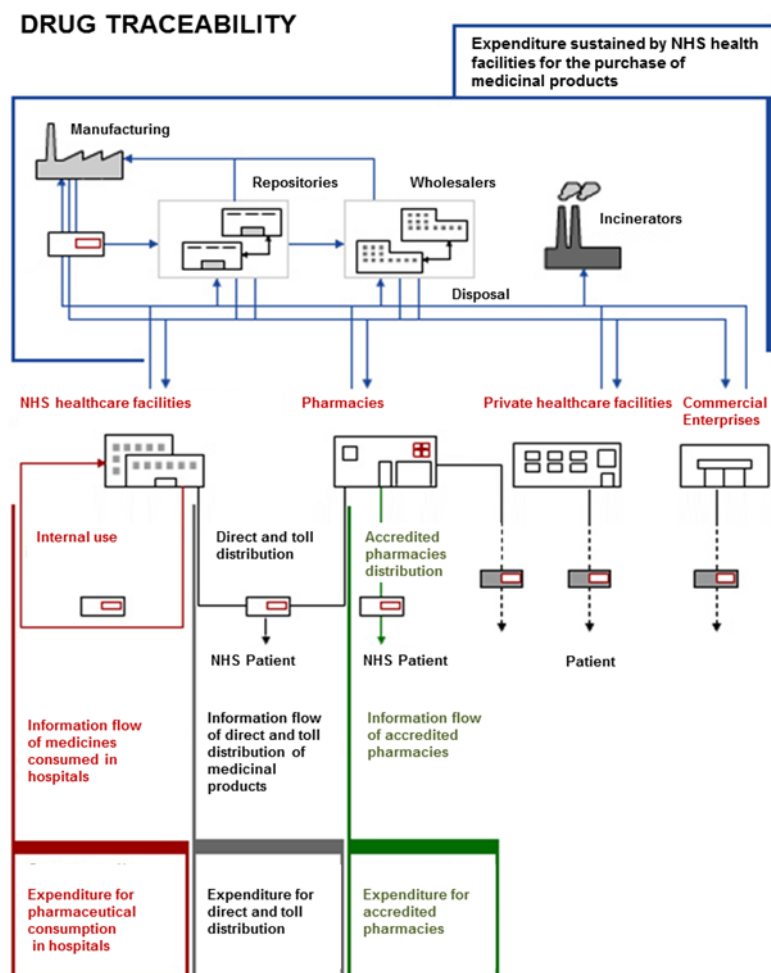


Figure 1. The drug traceability system in Italy (adapted by the CNS on data from www.salute.gov.it)

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 along with the quantity of the product too, so as to monitor the pharmaceutical expenditure. 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 any final user.

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

Information flow of accredited pharmacies

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

This dispensation regime concerns the medicinal products 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).

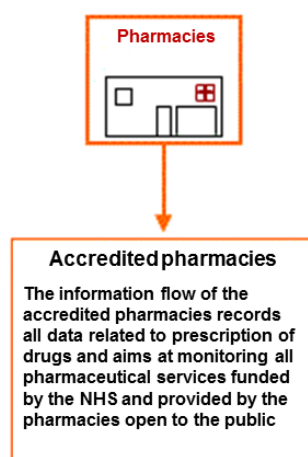


Figure 2. Scope of the information flow of accredited pharmacies
(adapted by the CNS on data from www.salute.gov.it)

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 DM of 31 July 2007 (7), is to detect:

- medicinal products given to the patient 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), the magistral formulations, officinal formulas and the foreign pharmaceuticals not authorised to be sold in Italy and yet used pursuant to 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: providing facility, prescription barcode (which through the prescription pad database can be traced to the prescriber), patient, medicinal product code, date of delivery, quantity delivered and related expenditure. Until 2009, only the costs, and not the related quantities, were recorded.

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

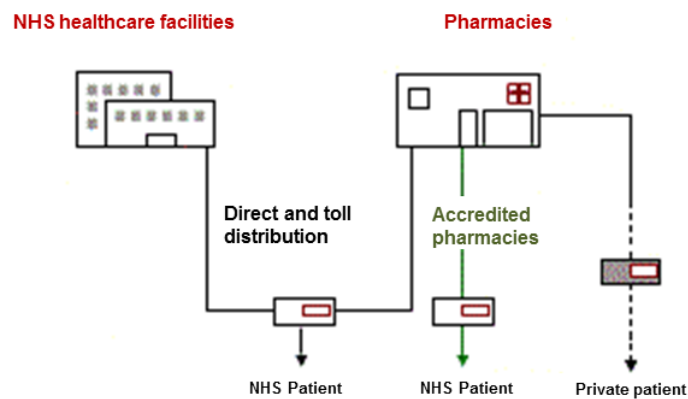


Figure 3. Medicinal products information flow
(adapted by theCNS on data from www.salute.gov.it)

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

Information flow of medicines consumed in hospitals

In order to monitor the consumption of medicinal products in hospitals, the information flow takes into consideration the medicinal products used by public healthcare facilities in their typical functions such as hospitalization, specialist day-surgery activities and diagnostic instrumental 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 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 regime, 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 State-Regions Agreement of 20 October 2015 (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.

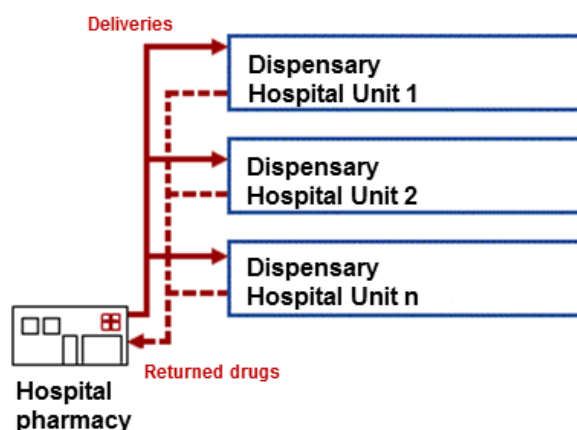


Figure 4. Information flow of medicines consumed in hospitals (adapted by the CNS on data from www.salute.gov.it)

Data on plasma-derived medicinal products produced from Italian plasma

The CNS receives the data regarding the PDMPs distributed by Kedrion, CSL Behring, Grifols and Takeda on behalf of the Regions from the aforesaid companies themselves 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 DM of 11 February 1997 (8), and 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 reference year and by unique AIC codes – and to identify quantities of active ingredients in distributed PDMPs.

Each AIC code was traced back to its relevant active ingredient and to the respective 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 and chemical and therapeutic properties.

The main groups of the ATC system are further divided into 5 hierarchical levels, shown in Table 1.

Table 1. ATC classification system

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

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

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

Level	Description
B	Blood and Blood 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 therefore classified according to their main therapeutic use. A medicinal product, however, can be used for two or more therapeutic indications of equal importance with different classification possibilities. When a drug is available in two or more dosages or pharmaceutical forms for different therapeutic uses, the classification is determined on the basis of the actual therapeutic use. Finally, preparations that cannot be uniquely classified in a particular group are coded in the fourth level with the letter X.

Therefore, 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 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, the 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 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 1 January of each year in question taken from the Italian National Statistics Institute (*Istituto Italiano di STATistica*, ISTAT) figures (12) (Table 3).

Table 3. Resident population by Region and Autonomous Province, 2020-2021
(adapted by the CNS on data from ISTAT, 31/5/2022)

Region	2020	2021
Abruzzo	1,293,941	1,281,012
Aosta Valley	125,034	124,089
AP Bolzano	532,644	534,912
AP Trento	545,425	542,166
Apulia	3,953,305	3,933,777
Basilicata	553,254	545,130
Calabria	1,894,110	1,860,601
Campania	5,712,143	5,624,260
Emilia-Romagna	4,464,119	4,438,937
Friuli V. Giulia	1,206,216	1,201,510
Latium	5,755,700	5,730,399
Liguria	1,524,826	1,518,495
Lombardy	10,027,602	9,981,554
Marche	1,512,672	1,498,236
Molise	300,516	294,294
Piedmont	4,311,217	4,274,945
Sardinia	1,611,621	1,590,044
Sicily	4,875,290	4,833,705
Tuscany	3,692,555	3,692,865
Umbria	870,165	865,452
Veneto	4,879,133	4,869,830
Italy	59,641,488	59,236,213

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 their relevant data are expressed in millilitres, with the exception of formulations where the number of sponges utilised will be provided per year.

Table 4. Active ingredients, ATC codes and measurement units

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

Self-sufficiency and pharmaceutical expenditure

For every PDMPs considered in the agreements between the Regions and their affiliated companies (Kedrion, CSL Behring, Grifols and Takeda), the degree of self-sufficiency achieved was assessed by comparing the actual supply with the NHS demand. In this report, by productive capacity (or potential supply) is meant the theoretical quantity of PDMPs derivable from the plasma sent by each Region for fractionation from July 2020 to June 2021. By contrast, by effective supply (or toll fractionation) is meant the quantity of PDMPs *de facto* distributed by companies to each Region during the 2021 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 referred to 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.

By potential self-sufficiency is meant the percent ratio between the productive capacity and the NHS demand. While effective self-sufficiency is referred to means the percent ratio between the effective supply and NHS demand.

In the dedicated chapter, pharmaceutical expenditure is defined as the expenditure for the supply of PDMPs covered by the NHS through public health facilities and 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 in force on 31/12/2021, and applying any eventual discounts provided for by L 662/1996 (13), amended by L 122/2010 (14).

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

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, 31/12/2021)

AIC code	Brand name	g	Manufacturer	NHS class
049507041	ALBUMINA GRIFOLS*1FL 10mL 200 g/L	2	ISTITUTO GRIFOLS S.A	C (nn)
034611032	ALBUMINA GRIFOLS*1FL 100mL 5%	5	GRIFOLS ITALIA SpA	C
036504025	ALBUREX* INFUS 1FL 100mL 5%	5	CSL BEHRING GmbH	C
039187012	ALBUNORM*1FL 100mL 5% 50g/L	5	OCTAPHARMA ITALY SPA	C
049507015	ALBUMINA GRIFOLS*1FL 100mL 50 g/L	5	ISTITUTO GRIFOLS S.A	C (nn)
010317028	ALBUMINA UM.IMMUNO*50mL 20%+S.	10	BAXTER SpA	A
011544020	ALBUMINA BEHRING*IV 50mL20%	10	CSL BEHRING SpA	A
021111024	UMANALBUMIN*INF FL 50mL 200g/L	10	KEDRION SpA	A
022515163	ALBITAL*1FL 50mL SOLUZ 20%+SET	10	KEDRION SpA	A
028989046	PLASBUMIN*EV 1FL 50mL 200g/L	10	GRIFOLS ITALIA SpA	A
029251030	ALBUTEIN*IV FL 50mL 200g/L	10	GRIFOLS ITALIA SpA	A
034611018	ALBUMINA GRIFOLS*1FL 50mL 20%	10	GRIFOLS ITALIA SpA	A
036176016	ALBUMINA LFB*FL 50mL 200mg/mL	10	LBF	A
036504052	ALBUREX*INFUS 1FL 50mL 20%	10	CSL BEHRING GmbH	A
037566054	ALBUMINA BAXTER*FL 50mL 200g/L	10	BAXALTA ITALY Srl	A
038109056	FLEXBUMIN*SAC INF 50mL 200g/L	10	BAXALTA ITALY Srl	A
038747034	OCTALBIN*IV 50mL 200mg/mL	10	OCTAPHARMA ITALY SPA	A
039073022	ALBIOMIN*FL 50mL 200g/L 20%	10	BIOTEST ITALIA Srl	A
039187063	ALBUNORM*1FL 50mL 20% 200g/L	10	OCTAPHARMA ITALY SPA	A
042029013	KALBI*FL 50mL 200g/L	10	KEDRION SpA	A
043358011	ALBUMEON*FL 50mL 200g/L 20%	10	CSL BEHRING SpA	A
044549018	PROBUMIN*FL 50 mL 200 g/L	10	GRIFOLS ITALIA SPA	C (nn)
049507054	ALBUMINA GRIFOLS*1FL 50mL 200 g/L	10	ISTITUTO GRIFOLS S.A	C (nn)
010317042	ALBUMINA UM.IMMUNO*50mL 25%+S.	12.5	BAXTER SpA	A
021111051	UMANALBUMIN*FL 250mL 5%	12.5	KEDRION SpA	C
021111087	UMANALBUMIN*INF FL 50mL 250g/L	12.5	KEDRION SpA	A
022515136	ALBITAL*1FL 50mL 25g/100mL+SET	12.5	KEDRION SpA	A
028989097	PLASBUMIN*EV 1FL 50mL 250g/L	12.5	GRIFOLS ITALIA SpA	A
029251016	ALBUTEIN*IV FL 250mL 50g/L	12.5	GRIFOLS ITALIA SpA	C
029251042	ALBUTEIN*IV FL 50mL 25%	12.5	GRIFOLS ITALIA SpA	A
034611044	ALBUMINA GRIFOLS*1FL 250mL 5%	12.5	GRIFOLS ITALIA SpA	C
034611069	ALBUMINA GRIFOLS*50mL 25g/100mL	12.5	GRIFOLS ITALIA SpA	A
036504037	ALBUREX* INFUS 1 FL 250mL 5%	12.5	CSL BEHRING GmbH	C
036504076	ALBUREX*INFUS 1FL 50mL 25%	12.5	CSL BEHRING GmbH	A
037566015	ALBUMINA BAXTER*1FL 250mL 50g	12.5	BAXALTA ITALY Srl	C
037566092	ALBUMINA BAXTER*FL 50mL 250g/L	12.5	BAXALTA ITALY Srl	A
038109070	FLEXBUMIN*SAC INF 50mL 250g/L	12.5	BAXALTA ITALY Srl	A
039073010	ALBIOMIN*INF 250mL 50g/L 5%	12.5	BIOTEST ITALIA Srl	C
039187036	ALBUNORM*1FL 250mL 5% 50g/L	12.5	OCTAPHARMA ITALY SPA	C
039187101	ALBUNORM*1FL 50mL 25% 250g/L	12.5	OCTAPHARMA ITALY SPA	A
042029025	KALBI*FL 50mL 250g/L+SET	12.5	KEDRION SpA	A

AIC code	Brand name	g	Manufacturer	NHS class
049507027	ALBUMINA GRIFOLS*1FL 250mL 50 g/L	12,5	ISTITUTO GRIFOLS S.A	C (nn)
021111101	UMANALBUMIN*EV FL 100mL 200g/L	20	KEDRION SpA	A
028989059	PLASBUMIN*EV 1FL 100mL 200g/L	20	GRIFOLS ITALIA SpA	A
034611020	ALBUMINA GRIFOLS*1FL 100mL 20%	20	GRIFOLS ITALIA SpA	A
036176028	ALBUMINA LFB* FL 100mL 200 mg/mL	20	LFB	C
036504064	ALBUREX*INFUS 1FL 100mL 20%	20	CSL BEHRING GmbH	A
037566078	ALBUMINA BAXTER*1FL 100mL 200g	20	BAXALTA ITALY Srl	A
038109068	FLEXBUMIN*SAC INF 100mL 200g/L	20	BAXALTA ITALY Srl	A
038747046	OCTALBIN*IV 100mL 200mg/mL	20	OCTAPHARMA ITALY SPA	A
039073034	ALBIOMIN*INF 100mL 200g/L 20%	20	BIOTEST ITALIA Srl	A
039187087	ALBUNORM*1FL 100mL 20% 200g/L	20	OCTAPHARMA ITALY SPA	A
043358023	ALBUMEON*FL 100mL 200g/L 20%	20	CSL BEHRING SpA	A
044549020	PROBUMIN*FL 100mL 200 g/L	20	GRIFOLS ITALIA SPA	C (nn)
049507066	ALBUMINA GRIFOLS*1FL100mL 200g/L	20	ISTITUTO GRIFOLS S.A	C (nn)
029251028	ALBUTEIN*IV FL 500mL 50g/L	25	GRIFOLS ITALIA SpA	C
034611057	ALBUMINA GRIFOLS*1FL 500mL 5%	25	GRIFOLS ITALIA SpA	C
034611071	ALBUMINA GRIFOLS25g/100mL	25	GRIFOLS ITALIA SpA	H
036504049	ALBUREX* INFUS 1FL 500mL 5%	25	CSL BEHRING GmbH	C
036504088	ALBUREX* INFUS 1FL 100mL 25%	25	CSL BEHRING GmbH	H
037566039	ALBUMINA BAXTER*1FL 500mL 50 g/L	25	BAXALTA ITALY Srl	C
037566116	ALBUMINA BAXTER*1FL100mL 250g/L	25	BAXALTA ITALY Srl	H
038109082	FLEXBUMIN*1SACCA 100mL 250g/L	25	BAXALTA ITALY Srl	H
039187051	ALBUNORM* 1 FL 500mL 5%, 50 g/L	25	OCTAPHARMA ITALY SPA	C
039187113	ALBUNORM* 1 FL 100mL 25%, 250 g/L	25	OCTAPHARMA ITALY SPA	H
049507039	ALBUMINA GRIFOLS*1FL 500mL 50 g/L	25	ISTITUTO GRIFOLS S.A	C (nn)
039187024	ALBUNORM*10FL 100mL 5% 50g/L	50	OCTAPHARMA ITALY SPA	C
036176030	ALBUMINA 200 mg/mL INF 6*50mL	60	LFB	C
039187075	ALBUNORM* 10FL 50mL20%, 200 g/L	100	OCTAPHARMA ITALY SPA	H
036176042	ALBUMINA 200 mg/mL INF 6*100mL	120	LFB	C
039187048	ALBUNORM* 10FL 250mL 5%, 50 g/L	125	OCTAPHARMA ITALY SPA	C
039187099	ALBUNORM*10FL 100mL 20%, 200 g/L	200	OCTAPHARMA ITALY SPA	H
038109017	FLEXBUMIN*24SACCHE 50mL 200g/L	240	BAXALTA ITALY Srl	H
038109031	FLEXBUMIN*12SACCHE 100mL200g/L	240	BAXALTA ITALY Srl	H
037566041	ALBUMINA BAXTER*10FL 500mL 50 g/L	250	BAXALTA ITALY Srl	C
037566027	ALBUMINA BAXTER* 24FL 250mL 50 g/L	300	BAXALTA ITALY Srl	C
038109029	FLEXBUMIN*12SACCHE 100mL 250 g/L	300	BAXALTA ITALY Srl	H
038109043	FLEXBUMIN*24SACCHE50mL 250g/L	300	BAXALTA ITALY Srl	H
037566066	ALBUMINA BAXTER*70FL 50mL 200 g/L	700	BAXALTA ITALY Srl	H
037566104	ALBUMINA BAXTER*70FL 50mL 250 g/L	875	BAXALTA ITALY Srl	H
037566080	ALBUMINA BAXTER*56FL 100mL 200 g/L	1120	BAXALTA ITALY Srl	H
037566128	ALBUMINA BAXTER*56FL 100mL 250 g/L	1400	BAXALTA ITALY Srl	H

Quantification and characterisation of the demand

Table 6 shows the total demand (expressed in grams) and the total standardised demand (expressed in grams per 1,000 population) of albumin¹ for the two-year period 2020-2021 with the variations in percentage, both at national and regional levels.

In 2021, the national demand for this principle was about 38,534 kilograms (Table 6), equal to 651 grams per 1,000 population. The two Regions with the highest standardised demand were Sardinia and Campania, with values equal to 874 and 823 grams per 1,000 population,

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.

respectively. The Regions with the lowest demand were the AP of Bolzano and Aosta Valley, with about 372 and 438 grams per 1,000 population, respectively (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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	864,860	668.4	1,033,150	806.5	20.7
Aosta Valley	63,070	504.4	54,360	438.1	-13.2
AP Bolzano	193,950	364.1	198,745	371.5	2.0
AP Trento	180,108	330.2	242,050	446.4	35.2
Apulia	2,157,803	545.8	2,605,545	662.4	21.3
Basilicata	413,815	748.0	370,983	680.5	-9.0
Calabria	1,187,863	627.1	1,135,108	610.1	-2.7
Campania	4,275,738	748.5	4,626,590	822.6	9.9
E.-Romagna	2,629,565	589.0	2,967,408	668.5	13.5
Friuli V. Giulia	383,435	317.9	584,430	486.4	53.0
Latium	3,433,058	596.5	3,396,963	592.8	-0.6
Liguria	868,725	569.7	1,116,945	735.6	29.1
Lombardy	7,196,825	717.7	6,728,863	674.1	-6.1
Marche	853,210	564.0	929,415	620.3	10.0
Molise	139,678	464.8	166,450	565.6	21.7
Piedmont	1,804,635	418.6	1,951,825	456.6	9.1
Sardinia	1,390,663	862.9	1,389,770	874.0	1.3
Sicily	3,535,708	725.2	3,938,353	814.8	12.3
Tuscany	1,515,105	410.3	1,739,573	471.1	14.8
Umbria	554,660	637.4	589,640	681.3	6.9
Veneto	2,570,970	526.9	2,767,985	568.4	7.9
Italy	36,213,440	607.2	38,534,148	650.5	7.1

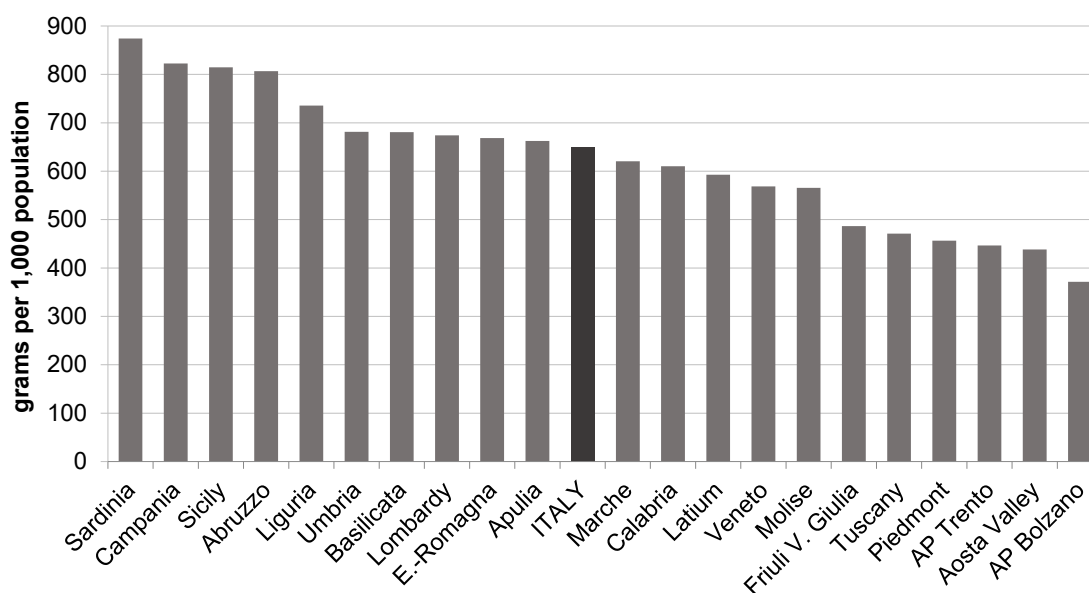


Figure 5. Total and regional demand (public and private) for albumin, expressed in grams per 1,000 population, 2021 (adapted by the CNS on data from the Traceability information flow)

In this two-year period, the total standardised demand for albumin showed a constant trend with respect to previous years (+7% compared to 2020) (17). The regions where the containment of use was most evident are Aosta Valley (-13%) and Basilicata (-9%). Friuli V. Giulia (+53%), AP Trento (+35%) and Liguria (+29%) are the Regions where demand shows the greatest growth.

Figure 6 highlights the eight Regions with a higher demand compared to national demand, with value greater than 20% for four of them. Figure 7 shows the standardised regional demand for albumin recorded in 2021 per distribution system (public pharmacies compared to other facilities), as shown by the drug Traceability system (18).

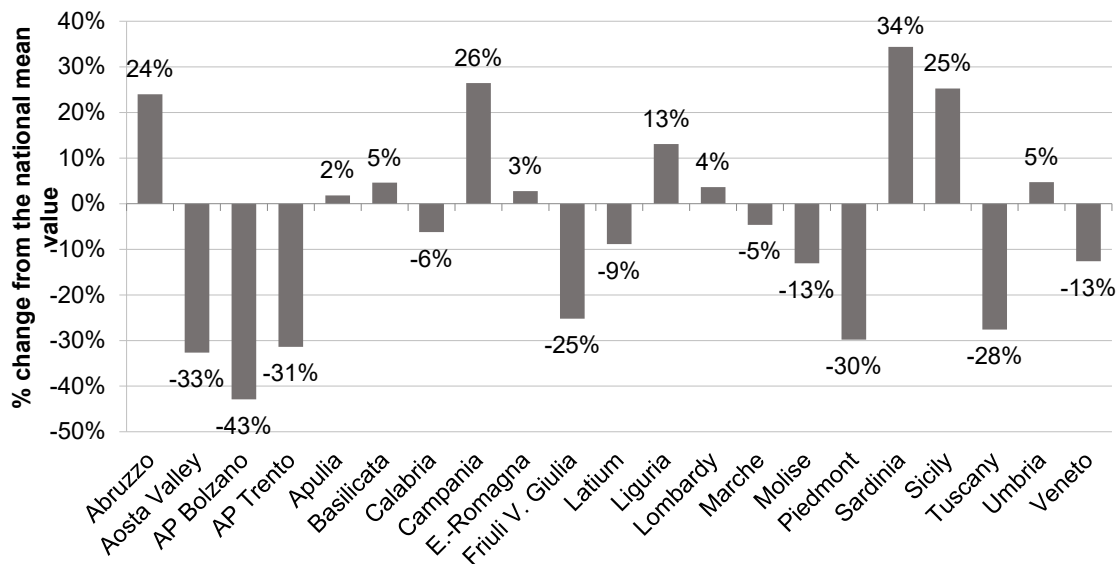


Figure 6. Percentage change from the national mean value of standardised regional demand for human albumin in 2021 (adapted by the CNS on data from the Traceability information flow)

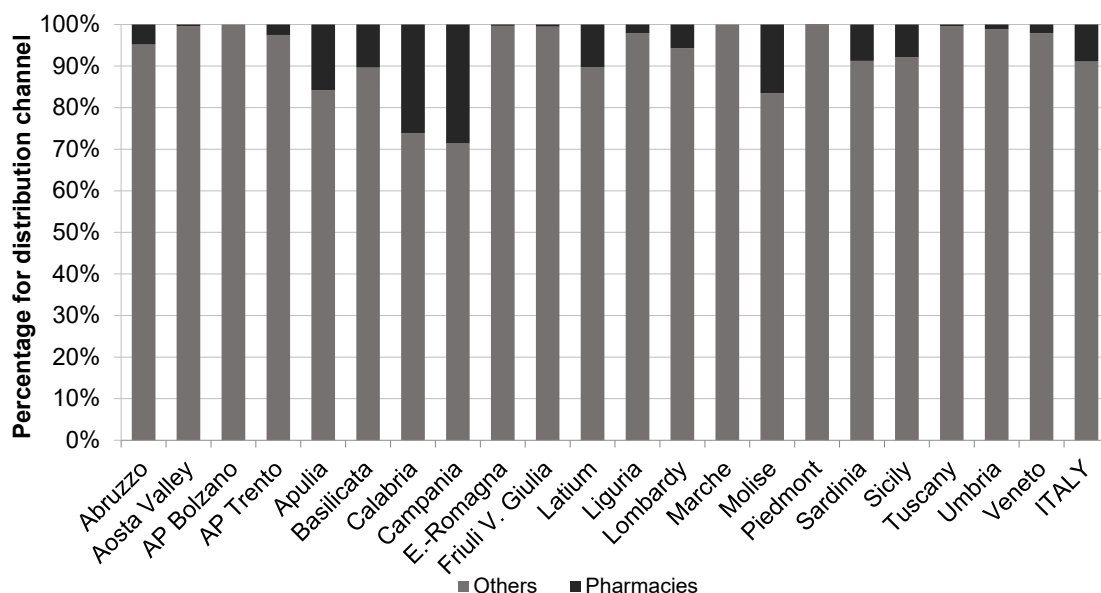


Figure 7. Standardised regional demand for albumin recorded per distribution channel, 2021 (adapted by the CNS on data from the Traceability information flow)

In 2021, about 9% of the national demand – approximately 3,438 kilograms – was distributed through public pharmacies.

Pharmacies as a distribution channel were particularly used in Campania and Calabria, where they accounted for 29% and 26% respectively of regional demand; they were still used to a lesser extent in Latium, Molise, Basilicata and Apulia (with percentages of between 10 and 16% 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 and their use is not always fully justified by the available evidence in scientific literature. Since 2007, both soluble IG preparations for subcutaneous/intramuscular infusion (SC/IM) and those for intravenous use (IntraVenous, IV) (19) have been available in Italy. IGs, like all other PDMPs, are prepared by using human plasma pools, which guarantees the recipient a higher antibody coverage thanks to a significant idiotypical diversity. The preparations contain structurally and functionally intact 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 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, 31/12/2021)

AIC code	Brand name	g	Manufacturer	NHS class
Normal human immunoglobulin for subcutaneous/intramuscular use				
036800011	SUBCUVIA*SC IM FL 5mL 160mg/mL	0.8	BAXALTA ITALY Srl	H
036800047	SUBCUVIA*SC IM FL10mL 160mg/mL	1.6	BAXALTA ITALY Srl	H
036800023	SUBCUVIA*SC IM 20FL5mL 160mg/mL	16	BAXALTA ITALY Srl	H
036800035	SUBCUVIA*SC IM 20FL10mL 160mg/mL	32	BAXALTA ITALY Srl	H
Normal human immunoglobulin for subcutaneous use				
045996016	CUTAQUIG*SC 1 FL 6 mL 165 mg/mL	0.9	OCTAPHARMA ITALY SPA	C
040652075	OCTANORM*1FL 6mL 165mg/mL	0.99	OCTAPHARMA ITALY SPA	H
041157013	HIZENTRA*SC 1FL 5mL 200mg/mL	1	CSL BEHRING SpA	H
041157153	HIZENTRA*SC 1SIR 5mL 200mg/mL	1	CSL BEHRING SpA	C(nn)
044244010	CUVITRU*SC 1FL 5mL 200mg/mL	1	BAXALTA ITALY Srl	H
049488012	XENBIFY*1FL 5mL 200 mg/mL	1	ISTITUTO GRIFOLS S.A	C(nn)
043396011	NAXIGLO*SC FL 10mL 160mg/mL	1.6	KEDRION SpA	H
043398015	KEYCUTE*SC FL 10mL 160mg/mL	1.6	KEDRION SpA	H
040652012	OCTANORM*1FL10mL 165mg/mL	1.65	OCTAPHARMA ITALY SPA	H
045996028	CUTAQUIG*SC 1 FL 10 mL 165 mg/mL	1.65	OCTAPHARMA ITALY SPA	C
040652101	OCTANORM*FL 12mL 165mg/mL	1.98	OCTAPHARMA ITALY SPA	H
045996030	CUTAQUIG*SC 1 FL 12 mL 165 mg/mL	1.98	OCTAPHARMA ITALY SPA	C
041157049	HIZENTRA*SC 1FL 10mL 200mg/mL	2	CSL BEHRING SpA	H
041157177	HIZENTRA*SC 1SIR 10mL 200mg/mL	2	CSL BEHRING SpA	C(nn)
044244022	CUVITRU*SC 1FL 10mL 200mg/mL	2	BAXALTA ITALY Srl	H
049488024	XENBIFY*1FL 10mL 200 mg/mL	2	ISTITUTO GRIFOLS S.A	C(nn)
042804017	HYQVIA*SC 1FL 25mL+1FL 1,25mL	2.5	BAXALTA ITALY Srl	H
041157076	HIZENTRA*1FL 15mL 200 mg/mL	3	CSL BEHRING SpA	H
040652048	OCTANORM*1FL 20mL 165mg/mL	3.3	OCTAPHARMA ITALY SPA	H
045996042	CUTAQUIG*SC 1 FL 20 mL 165 mg/mL	3.3	OCTAPHARMA ITALY SPA	C
040652137	OCTANORM*FL 24mL 165mg/mL	3.96	OCTAPHARMA ITALY SPA	H
045996055	CUTAQUIG*SC 1 FL 24 mL 165 mg/mL	3.96	OCTAPHARMA ITALY SPA	C
041157102	HIZENTRA*SC 1FL 20mL 200mg/mL	4	CSL BEHRING SpA	H

AIC code	Brand name	g	Manufacturer	NHS class
043396023	NAXIGLO*SC FL 25mL 160mg/mL	4	KEDRION SpA	H
043398027	KEYCUTE*SC FL 25mL 160mg/mL	4	KEDRION SpA	H
044244034	CUVITRU*SC 1FL 20mL 200mg/mL	4	BAXALTA ITALY Srl	H
049488036	XENBIFY*1FL 20mL 200 mg/mL	4	ISTITUTO GRIFOLS S.A	C(nn)
042804029	HYQVIA*SC 1FL 50mL+1FL 2,5mL	5	BAXALTA ITALY Srl	H
040652164	OCTANORM*FL 48mL 165mg/mL	7.92	OCTAPHARMA ITALY SPA	H
045996067	CUTAQUIG*SC 1 FL 48 mL 165 mg/mL	7.92	OCTAPHARMA ITALY SPA	C
044244046	CUVITRU*SC 1FL 40mL 200mg/mL	8	BAXALTA ITALY Srl	H
040652087	OCTANORM*10FL 6mL 165 mg/mL	9.9	OCTAPHARMA ITALY SPA	H
045996079	CUTAQUIG*SC 10 FL 6 mL 165 mg/mL	9.9	OCTAPHARMA ITALY SPA	C
041157025	HIZENTRA*10FL 5mL 200mg/mL	10	CSL BEHRING SpA	H
041157138	HIZENTRA*SC 1FL 50mL 200mg/mL	10	CSL BEHRING SpA	H
041157165	HIZENTRA*SC 10SIR 5mL 200mg/mL	10	CSL BEHRING SpA	C(nn)
042804031	HYQVIA*SC 1FL 100mL+1FL 5mL	10	BAXALTA ITALY Srl	H
044244059	CUVITRU*SC 1 FL 50mL 200 mg/mL	10	BAXALTA INN. GMBH	C(nn)
044244061	CUVITRU*SC 10FL 5mL 200 mg/mL	10	BAXALTA INN. GMBH	C(nn)
049488048	XENBIFY*1FL 50mL 200 MG/ML	10	ISTITUTO GRIFOLS S.A	C(nn)
040652024	OCTANORM*10FL 10mL 165mg/mL	16.5	OCTAPHARMA ITALY SPA	H
045996081	CUTAQUIG*SC 10 FL 10 mL 165 mg/mL	16.5	OCTAPHARMA ITALY SPA	C
040652099	OCTANORM*20FL 6mL 165mg/mL	19.8	OCTAPHARMA ITALY SPA	H
040652113	OCTANORM*10FL 12mL 165mg/mL	19.8	OCTAPHARMA ITALY SPA	H
045996093	CUTAQUIG*SC 10 FL 12 mL 165 mg/mL	19.8	OCTAPHARMA ITALY SPA	C
045996131	CUTAQUIG*SC 20 FL 6 mL 165 mg/mL	19.8	OCTAPHARMA ITALY SPA	C
041157037	HIZENTRA*20FL 5mL 200mg/mL	20	CSL BEHRING SpA	H
041157052	HIZENTRA*10FL 10mL 200mg/mL	20	CSL BEHRING SpA	H
041157189	HIZENTRA*SC 10SIR 10mL 200mg/mL	20	CSL BEHRING SpA	C(nn)
042804043	HYQVIA*SC 1FL 200mL+1FL 10mL	20	BAXALTA ITALY Srl	H
044244073	CUVITRU*SC 20FL 5mL 200 mg/mL	20	BAXALTA INN. GMBH	C(nn)
044244085	CUVITRU*SC 10FL 10mL 200 mg/mL	20	BAXALTA INN. GMBH	C(nn)
041157088	HIZENTRA*10FL 15mL 200mg/mL	30	CSL BEHRING SpA	H
042804056	HYQVIA*SC 1FL 300mL+1FL 15mL	30	BAXALTA ITALY Srl	H
040652036	OCTANORM*20FL 10mL 165mg/mL	33	OCTAPHARMA ITALY SPA	H
040652051	OCTANORM*10FL 20mL 165mg/mL	33	OCTAPHARMA ITALY SPA	H
045996105	CUTAQUIG*SC 10 FL 20 mL 165 mg/mL	33	OCTAPHARMA ITALY SPA	C
045996143	CUTAQUIG*SC 20 FL 10 mL 165 mg/mL	33	OCTAPHARMA ITALY SPA	C
040652125	OCTANORM*20FL 12mL 165 mg/mL	39.6	OCTAPHARMA ITALY SPA	H
040652149	OCTANORM*10FL 24mL 165 mg/mL	39.6	OCTAPHARMA ITALY SPA	H
045996117	CUTAQUIG*SC 10 FL 24 mL 165 mg/mL	39.6	OCTAPHARMA ITALY SPA	C
045996156	CUTAQUIG*SC 20 FL 12 mL 165 mg/mL	39.6	OCTAPHARMA ITALY SPA	C
041157064	HIZENTRA*20FL 10mL 200mg/mL	40	CSL BEHRING SpA	H
041157114	HIZENTRA*10FL 20mL 200mg/mL	40	CSL BEHRING SpA	H
044244109	CUVITRU*SC 10FL 20mL 200 mg/mL	40	BAXALTA INN. GMBH	C(nn)
044244123	CUVITRU*SC 5FL 40mL 200 mg/mL	40	BAXALTA INN. GMBH	C(nn)
044244147	CUVITRU*SC 20FL 10mL 200 mg/mL	40	BAXALTA GMBH	C(nn)
041157090	HIZENTRA*20FL 15mL 200mg/mL	60	CSL BEHRING SpA	H
044244097	CUVITRU*SC 30FL 10mL 200 mg/mL	60	BAXALTA INN. GMBH	C(nn)
040652063	OCTANORM*20FL 20mL 165mg/mL	66	OCTAPHARMA ITALY SPA	H
045996168	CUTAQUIG*SC 20 FL 20 mL 165 mg/mL	66	OCTAPHARMA ITALY SPA	C
040652152	OCTANORM* 20FL 24mL 165mg/mL	79.2	OCTAPHARMA ITALY SPA	H
040652176	OCTANORM*10FL 48mL 165mg/mL	79.2	OCTAPHARMA ITALY SPA	H
045996129	CUTAQUIG*SC 10 FL 48 mL 165 mg/mL	79.2	OCTAPHARMA ITALY SPA	C
045996170	CUTAQUIG*SC 20 FL 24 mL 165 mg/mL	79.2	OCTAPHARMA ITALY SPA	C
041157126	HIZENTRA*20FL 20mL 200mg/mL	80	CSL BEHRING SpA	H
044244150	CUVITRU*SC 20FL 20ML 200 mg/mL	80	BAXALTA GMBH	C(nn)
044244162	CUVITRU*SC 10FL 40ML 200 mg/mL	80	BAXALTA GMBH	C(nn)
041157140	HIZENTRA*10FL 50mL 200mg/mL	100	CSL BEHRING SpA	H
044244111	CUVITRU*SC 30FL 20mL 200 mg/mL	120	BAXALTA INN. GMBH	C(nn)
040652188	OCTANORM* 20FL 48mL 165mg/mL	158.4	OCTAPHARMA ITALY SPA	H

AIC code	Brand name	g	Manufacturer	NHS class
045996182	CUTAQUIG*SC 20 FL 48 mL 165 mg/mL	158.4	OCTAPHARMA ITALY SPA	C
044244135	CUVITRU*SC 20FL 40mL 200 mg/mL	160	BAXALTA INN. GMBH	C(nn)
Normal human immunoglobulin for intravenous use				
029021019*	PENTAGLOBIN*EV FL 50mg/mL 10mL	0.5	BIOTEST ITALIA Srl	C
029249075	PLITAGAMMA *INF 1 FL 10mL 50mg/mL	0.5	ISTITUTO GRIFOLS SA	H
040267015	FLEBOGAMMA*INF 1FL 10mL 50 mg/mL	0.5	GRIFOLS ITALIA SpA	H
025266141	IGVENA*EV 1FL 20mL 50g/L	1	KEDRION SpA	H
035143054	OCTAGAM*IV 1FL 20mL 50mg/mL	1	OCTAPHARMA ITALY SPA	H
037107012	KIOVIG*EV FL 10mL 100mg/mL	1	BAXTER SpA	H
037240052	INTRATECT*INF FL 50g/L 20mL	1	BIOTEST ITALIA Srl	H
037240090	INTRATECT*INF FL 100g/L 10mL	1	BIOTEST ITALIA Srl	H
037254012	VENITAL*EV FL 20mL 50g/L	1	KEDRION SpA	H
044187019	GLOBIGA*INF 1FL 1g 100mg/mL	1	OCTAPHARMA ITALY SPA	H
045410014	GAMUNEX *INF 1FL 10 mL 100mg/mL	1	Grifols Deutschland GmbH	H
037240126	INTRATECT*INF FL100g/L 200mL	2	BIOTEST ITALIA Srl	H
039457015	GAMTEN*INF 1FL 20mL 100mg/mL	2	OCTAPHARMA ITALY SPA	H
043736014	IQYMUNE*FL INF 20mL 100mg/mL	2	LFB	C(nn)
025266154	IGVENA*EV 1FL 50mL 50g/L+SET	2.5	KEDRION SpA	H
029021033*	PENTAGLOBIN*EV 1FL 50mg/mL50mL	2.5	BIOTEST ITALIA Srl	C
029249048	PLITAGAMMA*50mL(2,5g)5%+SET	2.5	GRIFOLS ITALIA SpA	H
035143015	OCTAGAM*IV FL 50mL 5%	2.5	OCTAPHARMA ITALY SPA	H
037107024	KIOVIG*EV FL 25mL 100mg/mL	2.5	BAXTER SpA	H
037240064	INTRATECT*INF FL 50g/L 50mL	2.5	BIOTEST ITALIA Srl	H
037240138	INTRATECT*INF FL100 g/L 25mL	2.5	BIOTEST ITALIA Srl	H
037254024	VENITAL*EV FL 50mL 50g/L+SET	2.5	KEDRION SpA	H
039712043	PRIVIGEN*EV 1FL 25mL 100mg/mL	2.5	CSL BEHRING SpA	H
040267027	FLEBOGAMMA DIF*FL 50mL 50mg/mL	2.5	GRIFOLS ITALIA SpA	H
044187021	GLOBIGA*INF 1FL 2,5g 100mg/mL	2.5	OCTAPHARMA ITALY SPA	H
033240033	GAMMAGARD*EV 1FL 50mg/mL 96mL	4.8	BAXTER SpA	H
025266166	IGVENA*EV 1FL 100mL 50g/L+SET	5	KEDRION SpA	H
029021045*	PENTAGLOBIN*EV 1FL 50mg/mL100mL	5	BIOTEST ITALIA Srl	C
029249051	PLITAGAMMA*100mL(5g)5%+SET	5	GRIFOLS ITALIA SpA	H
035143027	OCTAGAM*IV FL 100mL 5%	5	OCTAPHARMA ITALY SPA	H
037107036	KIOVIG*EV FL 50mL 100mg/mL	5	BAXTER SpA	H
037240076	INTRATECT*INF FL 50g/L 100mL	5	BIOTEST ITALIA Srl	H
037240102	INTRATECT*INF FL 100g/L 50mL	5	BIOTEST ITALIA Srl	H
037253034	KEYVEN*EV FL 100mL 50g/L+SET	5	KEDRION SpA	H
037254036	VENITAL*EV FL 100mL 50g/L+SET	5	KEDRION SpA	H
039457027	GAMTEN*INF 1FL 50mL 100mg/mL	5	OCTAPHARMA ITALY SPA	H
039712017	PRIVIGEN*EV 1FL 50mL 100mg/mL	5	CSL BEHRING SpA	H
040267039	FLEBOGAMMA DIF*FL 100mL 5g	5	GRIFOLS ITALIA SpA	H
040267066	FLEBOGAMMA DIF*EV 50mL 5g	5	GRIFOLS ITALIA SpA	H
043736026	IQYMUNE*FL INF 50mL 100mg/mL	5	LFB	C(nn)
044187033	GLOBIGA*INF 1FL 5g 100mg/mL	5	OCTAPHARMA ITALY SPA	H
045410026	GAMUNEX *INF 1FL 50 mL 100mg/mL	5	Grifols Deutschland GmbH	H
045410038	GAMUNEX *INF1FL 50mL 100mg/mL C.o	5	Grifols Deutschland GmbH	H
039457054	GAMTEN*INFUS 1FL 60mL 100mg/mL	6	OCTAPHARMA ITALY SPA	C(nn)
044187045	GLOBIGA*INF 1FL 6g 100mg/mL	6	OCTAPHARMA ITALY SPA	H
033240045	GAMMAGARD*EV 1FL 50mg/mL 192mL	9.6	BAXTER SpA	H
025266178	IGVENA*EV 1FL 200mL 50g/L+SET	10	KEDRION SpA	H
029249063	PLITAGAMMA*200mL(10g)5%+SET	10	GRIFOLS ITALIA SpA	H
035143039	OCTAGAM*IV FL 200mL 5%	10	OCTAPHARMA ITALY SPA	H
037107048	KIOVIG*EV FL 100mL 100mg/mL	10	BAXTER SpA	H
037240088	INTRATECT*INF FL 50g/L 200mL	10	BIOTEST ITALIA Srl	H
037240114	INTRATECT*INF FL100g/L 100mL	10	BIOTEST ITALIA Srl	H
037253046	KEYVEN*EV FL 200mL 50g/L+SET	10	KEDRION SpA	H
037254048	VENITAL*EV FL 200mL 50g/L+SET	10	KEDRION SpA	H
039457039	GAMTEN*INF 1FL100mL 100mg/mL	10	OCTAPHARMA ITALY SPA	H

AIC code	Brand name	g	Manufacturer	NHS class
039712029	PRIVIGEN*EV 1FL 100mL 100mg/mL	10	CSL BEHRING SpA	H
040267041	FLEBOGAMMA DIF*FL 200mL 10g	10	GRIFOLS ITALIA SpA	H
040267078	FLEBOGAMMA DIF*EV 100mL 10g	10	GRIFOLS ITALIA SpA	H
043736038	IQYMUNE*FL INF100mL 100mg/mL	10	LFB	C(nn)
044187058	GLOBIGA*INF 1FL 10g 100mg/mL	10	OCTAPHARMA ITALY SPA	H
045410040	GAMUNEX *INF 1FL 100 mL 100mg/mL	10	Grifols Deutschland GmbH	H
045410053	GAMUNEX *INF 1FL100mL 100mg/mL C.o	10	Grifols Deutschland GmbH	H
025266192	IGVENA*EV 2FL 200ML 50G/L+SET	20	KEDRION SpA	C(nn)
029249087	PLITAGAMMA*INF 1 FL 400mL 50mg/mL	20	ISTITUTO GRIFOLS SA	H
035143066	OCTAGAM*IV 2FL 200mL 50mg/mL	20	OCTAPHARMA ITALY SPA	H
037107051	KIOVIG*EV FL 200mL 100mg/mL	20	BAXTER SpA	H
039457041	GAMTEN*INF 1 FL 200mL 100mg/mL	20	OCTAPHARMA ITALY SPA	H
039712031	PRIVIGEN*EV 1FL 200mL 100mg/mL	20	CSL BEHRING SpA	H
040267054	FLEBOGAMMA DIF*FL 400mL 20g	20	GRIFOLS ITALIA SpA	H
040267080	FLEBOGAMMA DIF*EV 200mL 20g	20	GRIFOLS ITALIA SpA	H
043736040	IQYMUNE*FL INF 200mL 100mg/mL	20	LFB	C(nn)
044187072	GLOBIGA*INF 1FL 20g 100mg/mL	20	OCTAPHARMA ITALY SPA	H
045410065	GAMUNEX *INF 1FL 200 mL 100mg/mL	20	Grifols Deutschland GmbH	H
045410077	GAMUNEX *INF1FL200mL 100mg/mL C.o	20	Grifols Deutschland GmbH	H
035143041	OCTAGAM*IV FL 500mL 5%	25	OCTAPHARMA ITALY SPA	H
025266204	IGVENA*EV 3FL 200ML 50G/L+SET	30	KEDRION SpA	C(nn)
035143078	OCTAGAM*IV 3 FL 200mL 50mg/mL	30	OCTAPHARMA ITALY SPA	H
037107063	KIOVIG*EV FL 300mL 100mg/mL	30	BAXTER SpA	H
037240140	INTRATECT* INF 3FL 200mL 50g/L	30	BIOTEST ITALIA Srl	C
037240153	INTRATECT*INF 3FL 100mL 100g/L	30	BIOTEST ITALIA Srl	C
039457066	GAMTEN*INF 3FL 100mL 100mg/mL	30	OCTAPHARMA ITALY SPA	C(nn)
039712056	PRIVIGEN*EV 3FL 100mL 100mg/mL	30	CSL BEHRING GMBH	C
044187060	GLOBIGA*INF 3FL 10g 100mg/mL	30	OCTAPHARMA ITALY SPA	C(nn)
044187096	GLOBIGA*INF 1FL 30g 100mg/mL	30	OCTAPHARMA ITALY SPA	H
039457080	GAMTEN*INF 1FL 300mL 100mg/mL	30	OCTAPHARMA ITALY SPA	C(nn)
039712070	PRIVIGEN*EV 1FL 400mL 100mg/mL	40	CSL BEHRING GMBH	C(nn)
045410089	GAMUNEX *INF 1FL 400 mL 100mg/mL	40	Grifols Deutschland GmbH	H
045410091	GAMUNEX *INF1FL400 mL 100mg/mL C.o	40	Grifols Deutschland GmbH	H
037240165	INTRATECT* INF 3FL 200mL 100 g/L	60	BIOTEST ITALIA Srl	C
039457078	GAMTEN*INF 3FL 200mL 100mg/mL	60	OCTAPHARMA ITALY SPA	C(nn)
039712068	PRIVIGEN*EV 3FL 200mL 100mg/mL	60	CSL BEHRING GMBH	C
044187084	GLOBIGA*INF 3FL 20g 100mg/mL	60	OCTAPHARMA ITALY SPA	C(nn)

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

Quantification and characterisation of the demand

Table 8 shows the total demand (expressed in grams) and the total standardised demand (in grams per 1,000 population) for IGs for the period 2020-2021 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 2021, the total national demand for IGs was 6,482,066 grams, equal to 109.4 grams per 1,000 population (Table 8). The three Regions with the highest standardised demand per 1,000 population were Tuscany with around 190 grams, Aosta Valley with around 169 grams and Liguria with around 160 grams.

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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	142,883	110.4	135,984	106.2	-3.9
Aosta Valley	28,545	228.3	20,933	168.7	-26.1
AP Bolzano	50,274	94.4	54,536	102.0	8.0
AP Trento	54,273	99.5	53,108	98.0	-1.6
Apulia	475,033	120.2	442,736	112.5	-6.3
Basilicata	42,666	77.1	49,149	90.2	16.9
Calabria	122,730	64.8	118,288	63.6	-1.9
Campania	476,261	83.4	413,242	73.5	-11.9
E.-Romagna	557,477	124.9	577,184	130.0	4.1
Friuli V. Giulia	144,953	120.2	140,672	117.1	-2.6
Latium	620,464	107.8	613,751	107.1	-0.6
Liguria	264,090	173.2	242,618	159.8	-7.7
Lombardy	965,518	96.3	969,941	97.2	0.9
Marche	213,808	141.3	212,652	141.9	0.4
Molise	61,537	204.8	24,214	82.3	-59.8
Piedmont	560,389	130.0	534,047	124.9	-3.9
Sardinia	99,037	61.5	103,093	64.8	5.5
Sicily	376,267	77.2	356,730	73.8	-4.4
Tuscany	756,288	204.8	702,428	190.2	-7.1
Umbria	117,566	135.1	115,520	133.5	-1.2
Veneto	633,411	129.8	601,241	123.5	-4.9
Italy	6,763,471	113.4	6,482,066	109.4	-3.5

The demand was lower in Calabria, Sardinia, Campania and Sicily, where it was between 64 and 74 grams per 1,000 population.

The demand for these PDMPs shows a slight decrease in the two-year period 2020-2021 (-3.5%), featuring notable differences from one Region to another.

The greatest decrease is recorded in Molise (-60%), Aosta Valley and Campania, with -26% and -12% respectively. The most marked increase is instead observed in Basilicata (+17%).

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 (37.6%), Umbria (36.3%), Basilicata (31.5%) and Calabria (32%) while fewer were used in Friuli V. Giulia, Aosta Valley and in the AP Bolzano (<6.5%).

At national level, the demand for SC/IM IGs stood at 24% of the total demand for IGs, as in 2020.

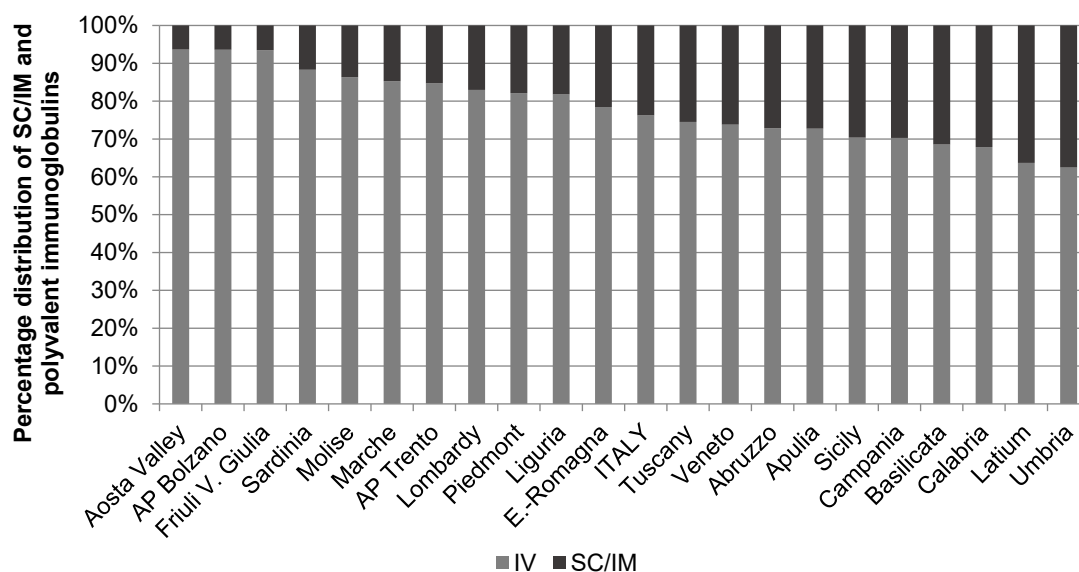


Figure 8. Total standardised demand (public and private) per administration of immunoglobulins (percentage on total), by Region, 2021 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for subcutaneous use

In 2021, the total demand for SC/IM IGs reached about 1,540,405 grams (26 grams per 1,000 population), with a decrease of -5% compared to 2020 (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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	36,783	28.4	36,909	28.8	1.4
Aosta Valley	1,806	14.4	1,333	10.7	-25.6
AP Bolzano	3,700	6.9	3,489	6.5	-6.1
AP Trento	8,488	15.6	8,118	15.0	-3.8
Apulia	136,342	34.5	120,680	30.7	-11.0
Basilicata	15,807	28.6	15,463	28.4	-0.7
Calabria	40,895	21.6	37,988	20.4	-5.4
Campania	137,149	24.0	122,799	21.8	-9.1
E.-Romagna	132,224	29.6	124,431	28.0	-5.4
Friuli V. Giulia	8,138	6.7	9,172	7.6	13.2
Latium	235,300	40.9	222,844	38.9	-4.9
Liguria	58,545	38.4	44,181	29.1	-24.2
Lombardy	165,844	16.5	165,098	16.5	0.0
Marche	33,333	22.0	31,367	20.9	-5.0
Molise	3,927	13.1	3,314	11.3	-13.8
Piedmont	104,048	24.1	95,458	22.3	-7.5
Sardinia	11,375	7.1	12,048	7.6	7.4
Sicily	104,059	21.3	105,701	21.9	2.5
Tuscany	206,787	56.0	179,090	48.5	-13.4
Umbria	43,816	50.4	43,395	50.1	-0.4
Veneto	148,931	30.5	157,527	32.3	6.0
Italy	1,637,296	27.5	1,540,405	26.0	-5.3

The regional demands proved diversified where the highest values, between 50 and 39 grams per 1,000 population, were recorded in Umbria, Tuscany and Latium, while the lowest values were recorded in AP of Bolzano, Sardinia and in Friuli V. Giulia and were between 6.5 and 7.5 grams per 1,000 population (Figure 9).

In Abruzzo, Basilicata, Emilia-Romagna, Latium, Liguria, Apulia, Tuscany, Umbria and Veneto, a higher total demand compared to national demand was recorded (range: 8-93%) (Figure 10).

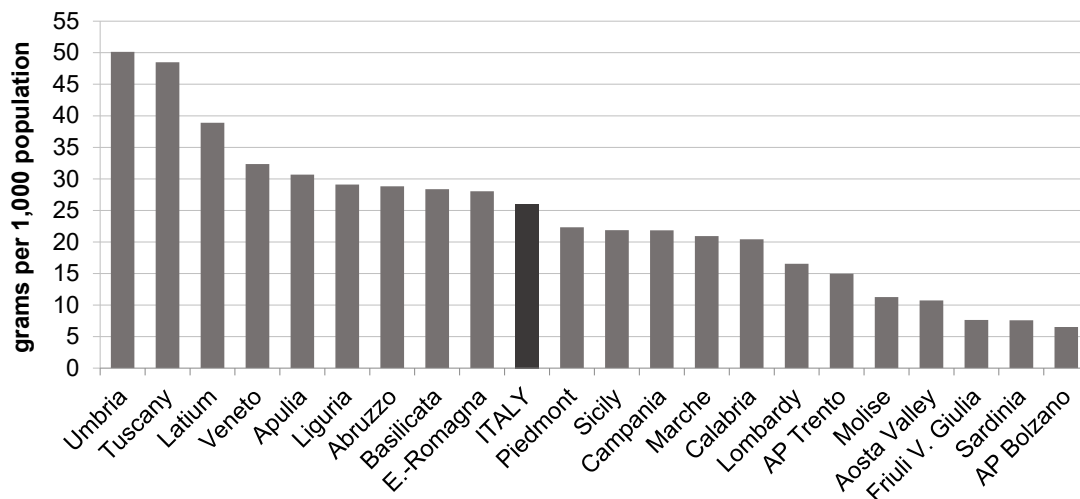


Figure 9. Total and regional demand (public and private) for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams per 1,000 population, 2021 (adapted by the CNS on data from the Traceability information flow)

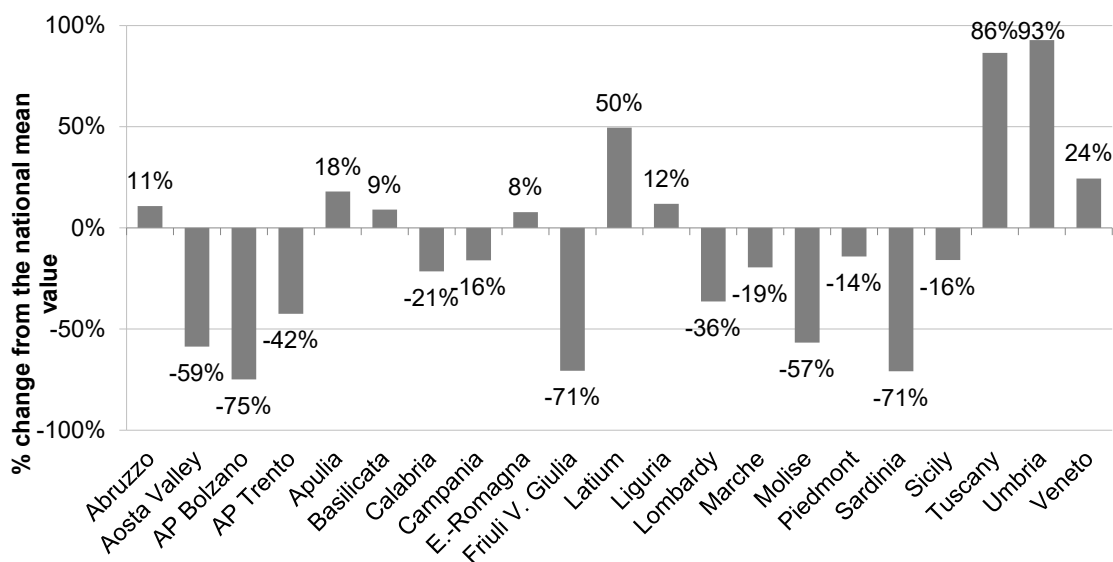


Figure 10. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for subcutaneous/ intramuscular use in 2021 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for intravenous use

Finally, Table 10 reports on the total and standardised demands for IG for intravenous use in 2020-2021.

Even, in this case, a general downward trend (about -3%) was observed, while it was not confirmed in Basilicata, Emilia-Romagna, Latium, Lombardy, Marche, AP Bolzano and Sardinia.

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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	106,100	82.0	99,075	77.3	-5.7
Aosta Valley	26,739	213.9	19,600	157.9	-26.1
AP Bolzano	46,574	87.4	51,047	95.4	9.1
AP Trento	45,785	83.9	44,990	83.0	-1.1
Apulia	338,691	85.7	322,056	81.9	-4.4
Basilicata	26,859	48.5	33,686	61.8	27.3
Calabria	81,835	43.2	80,300	43.2	-0.1
Campania	339,112	59.4	290,443	51.6	-13.0
E.-Romagna	425,254	95.3	452,752	102.0	7.1
Friuli V. Giulia	136,815	113.4	131,500	109.4	-3.5
Latium	385,164	66.9	390,907	68.2	1.9
Liguria	205,545	134.8	198,438	130.7	-3.1
Lombardy	799,674	79.7	804,843	80.6	1.1
Marche	180,475	119.3	181,285	121.0	1.4
Molise	57,610	191.7	20,900	71.0	-63.0
Piedmont	456,341	105.8	438,590	102.6	-3.1
Sardinia	87,663	54.4	91,045	57.3	5.3
Sicily	272,208	55.8	251,028	51.9	-7.0
Tuscany	549,501	148.8	523,337	141.7	-4.8
Umbria	73,750	84.8	72,125	83.3	-1.7
Veneto	484,480	99.3	443,714	91.1	-8.2
Italy	5,126,175	85.9	4,941,661	83.4	-2.9

Figure 11 shows the standardised regional demand for IVIGs in 2021 as recorded by the drug Traceability system.

The highest demand for IVIGs was recorded in Aosta Valley, Tuscany and Liguria, with volumes ranging between 158 and 131 grams per 1,000 population (+89%, +70% and +57% respectively, compared to the national mean value) (Figure 12). The Regions where the standardized demand is lower were Calabria and Campania with recorded volumes between 43 and 52 grams per 1,000 population.

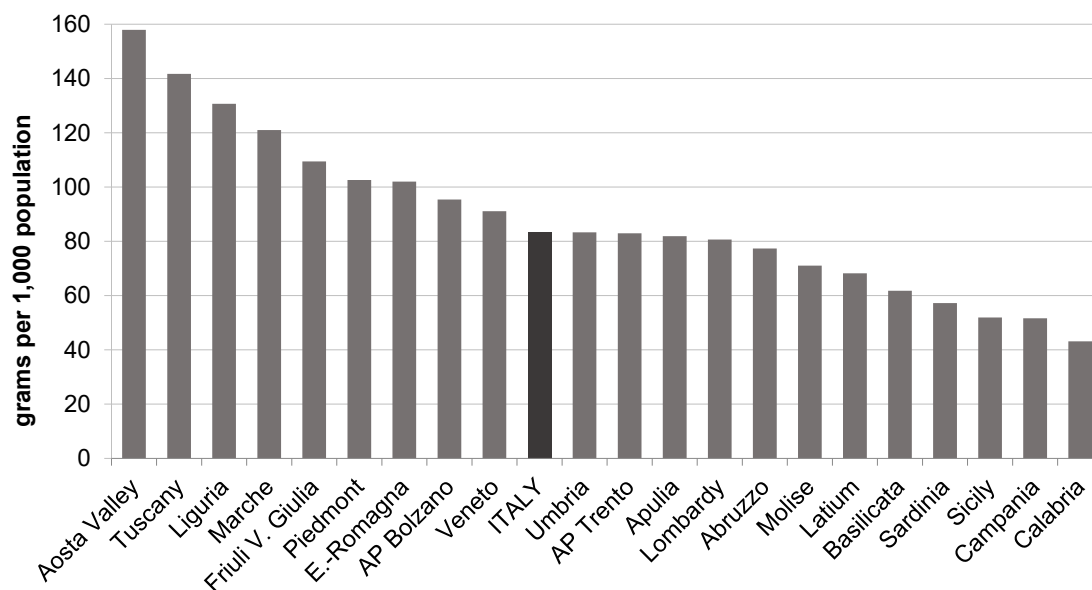


Figure 11. Total and regional demand (public and private) for normal human immunoglobulins for intravenous use, expressed in grams per 1,000 population, 2021 (adapted by the CNS on data from the Traceability information flow)

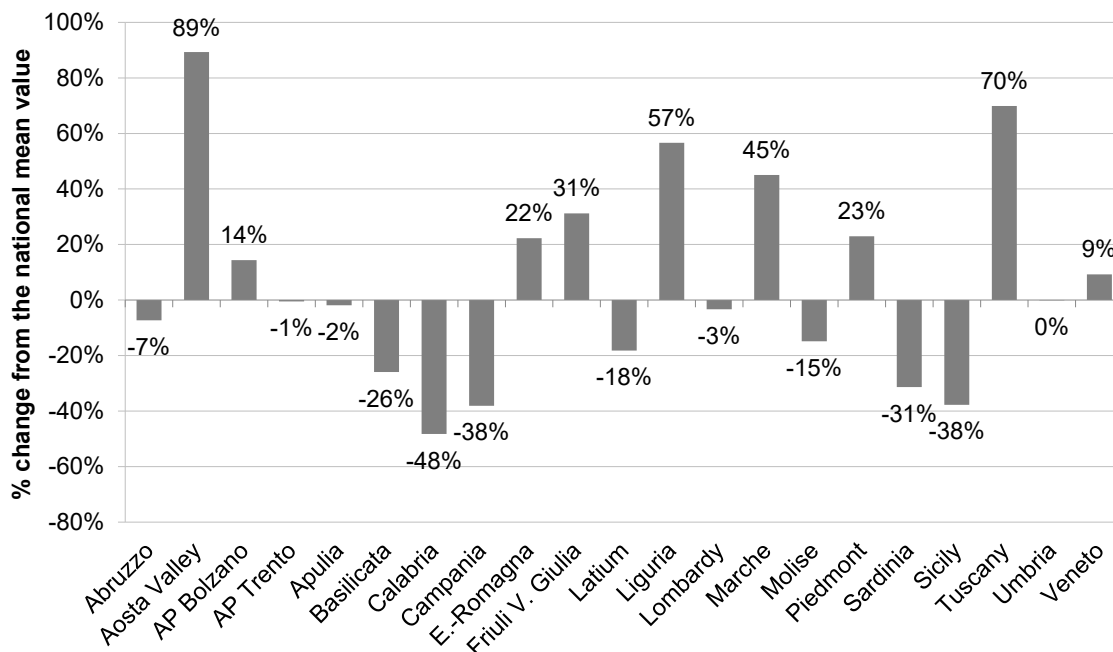


Figure 12. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for intravenous use in 2021 (adapted by the CNS on data from the Traceability information flow)

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 on the market in Italy and the relative quantity of active ingredient they contain measured in International Units (IUs).

Table 11. Products containing antithrombin currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AICcode	Brand name	IU	Manufacturer	NHS class
025766039	KYBERNIN P*IV FL 500IU+10mL+SET	500	CSL BEHRING SpA	H
027113012	ANTITROMBINA III IMMUNO*FL10mL	500	BAXALTA ITALY Srl	H
029378015	AT III KED*500IU+FL 10mL+SET	500	KEDRION SpA	H
031118019	ATENATIV*IV FL 500IU+FL 10mL	500	OCTAPHARMA ITALY SPA	H
034330035	ANBINEX*FL 500IU+SIR 10mL+SET	500	GRIFOLS ITALIA SpA	H
041800018	ATKED*FL 500IU+FL 20mL+SET	500	KEDRION SpA	H
044565012	ATTERTIUM FL 500IU+SIR 10mL	500	GRIFOLS ITALIA SpA	C(nn)
025766027	KYBERNIN P*IV FL 1000IU+F 20mL	1000	CSL BEHRING SpA	H
027113024	ANTITROMBINA III IMMUNO*FL20mL	1000	BAXALTA ITALY Srl	H
029378027	AT III KED*1000IU+FL 20mL+SET	1000	KEDRION SpA	H
031118021	ATENATIV*IV FL 1000IU+FL 20mL	1000	OCTAPHARMA ITALY SPA	H
034330047	ANBINEX*FL 1000IU+SIR 20mL+SET	1000	GRIFOLS ITALIA SpA	H
041800020	ATKED*FL 1000IU+FL 20mL+SET	1000	KEDRION SpA	H
044565024	ATTERTIUM FL 1000IU+SIR 20mL	1000	GRIFOLS ITALIA SpA	C(nn)
029378039	AT III KED*2000IU+FL 20mL+SET	2000	KEDRION SpA	H
041800032	ATKED*FL 2000IU+FL 20mL+SET	2000	KEDRION SpA	H

Quantification and characterisation of the demand

Table 12 shows the total demand (expressed in IUs) and the total standardised demand (expressed in IUs *per capita*) for AT in the two-year period 2020-2021 with the relative percentage changes at national and regional levels.

In 2021, total AT demand was 140,192,500 IUs, equal to 2.4 IUs *per capita*, highlighting an increase compared to the consumption recorded in previous years (+13% compared to 2020). Conversely, in five Regions there was a significant upward trend (>40%) in its use [range: Marche (+ 42%) – Molise (+ 117%)]. The Region in which the containment of use was most evident is Aosta Valley (-44%).

Figure 13 shows the regional and national standardised demand for AT in 2021. The Regions with the highest *per capita* demand were Sicily, Calabria, Latium and Tuscany, with a demand of 4.8 IUs for the first one and 4, 3.8 and 3.2 IUs respectively for the others Regions. The lowest demand, less than 1 IUs *per capita*, was recorded in the AP of Trento, Umbria, AP of Bolzano and Emilia-Romagna.

Table 12. Total demand (public and private) and total standardised demand for antithrombin, expressed in International Units and International Units *per capita*, and variations in percentage between 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	1,943,500	1.5	2,358,000	1.8	22.6
Aosta Valley	439,000	3.5	244,000	2.0	-44.0
AP Bolzano	347,000	0.7	436,000	0.8	25.1
APTrento	147,000	0.3	288,000	0.5	97.1
Apulia	6,444,000	1.6	9,589,500	2.4	49.6
Basilicata	1,218,000	2.2	1,128,000	2.1	-6.0
Calabria	7,376,500	3.9	7,380,500	4.0	1.9
Campania	14,392,000	2.5	15,100,500	2.7	6.6
E.-Romagna	3,305,000	0.7	3,992,000	0.9	21.5
Friuli V. Giulia	2,876,000	2.4	2,944,000	2.5	2.8
Latium	19,215,500	3.3	21,535,000	3.8	12.6
Liguria	3,973,500	2.6	4,759,000	3.1	20.3
Lombardy	15,020,000	1.5	11,935,000	1.2	-20.2
Marche	3,253,000	2.2	4,582,000	3.1	42.2
Molise	360,000	1.2	766,000	2.6	117.3
Piedmont	8,500,500	2.0	8,684,500	2.0	3.0
Sardinia	2,069,000	1.3	2,248,500	1.4	10.2
Sicily	18,372,500	3.8	23,005,500	4.8	26.3
Tuscany	7,633,000	2.1	11,656,500	3.2	52.7
Umbria	546,000	0.6	586,000	0.7	7.9
Veneto	7,047,500	1.4	6,974,000	1.4	-0.9
Italy	124,478,500	2.1	140,192,500	2.4	13.4

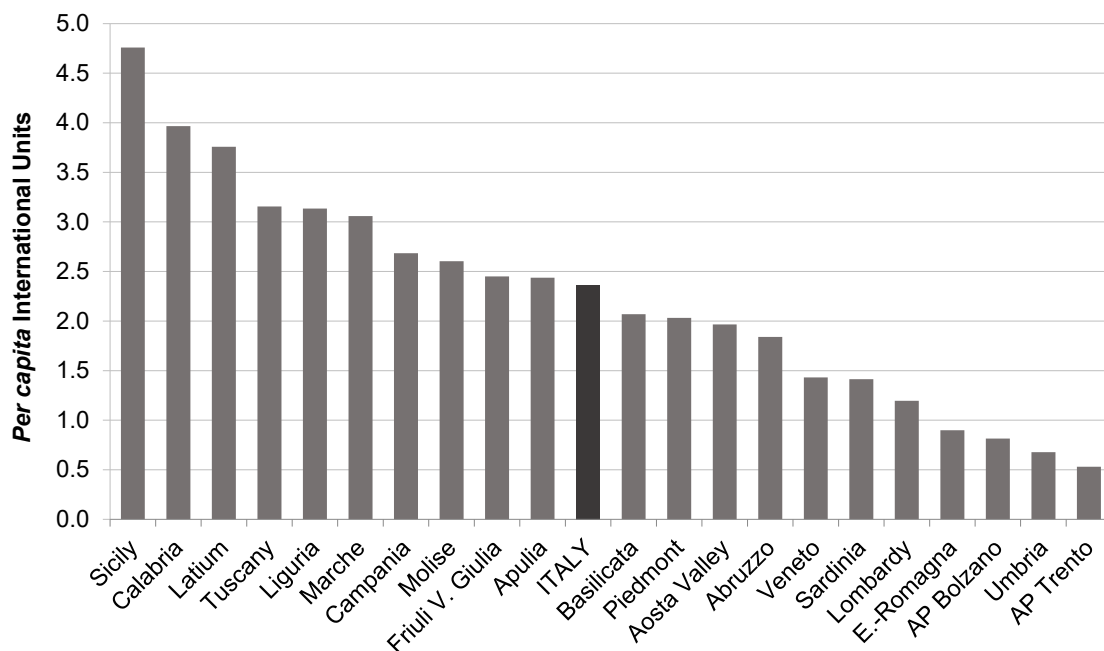


Figure 13. Total and regional demand (public and private) for antithrombin, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

Figure 14 shows the difference between the regional *per capita* percentage and the national mean value for the year 2021.

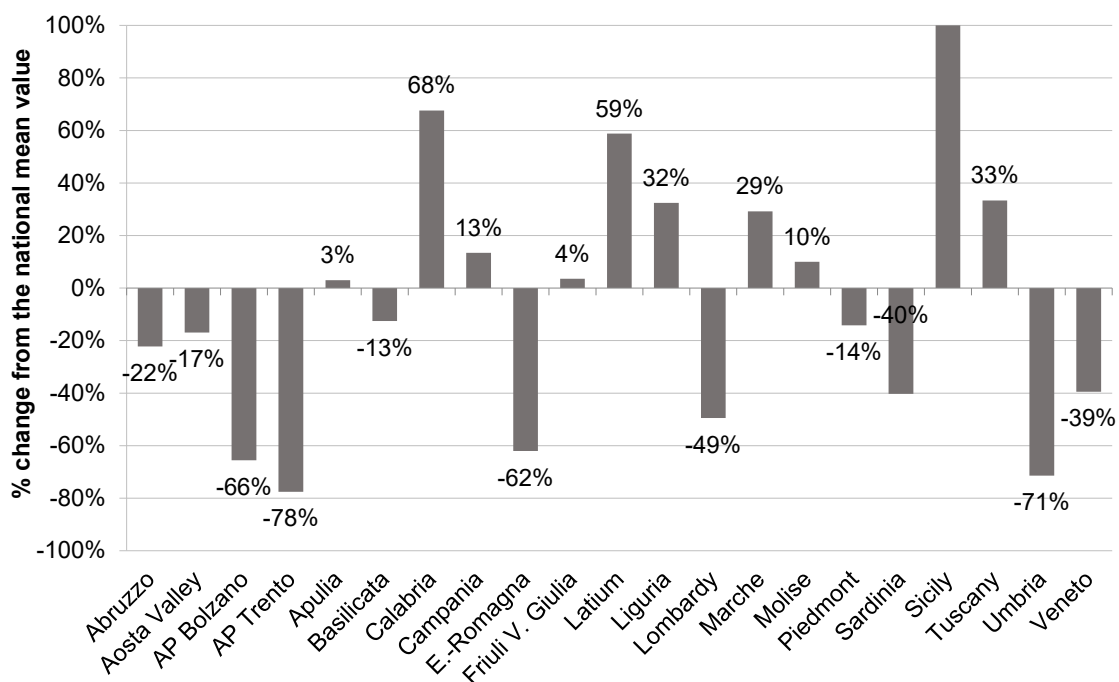


Figure 14. Percentage change from the national mean value of standardised regional demand for antithrombin in 2021 (adapted by the CNS on data from the Traceability information flow)

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

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

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

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

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

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

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

Table 13. Products containing plasma-derived coagulation Factor VIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Table 14. Products containing plasma-derived coagulation Factor VIII and von Willebrand Factor in combination, and Von Willebrand Factor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AIC code	Brand name	IU	Manufacturer	NHS class
Factor VIII and von Willebrand Factor in combination				
033077088	ALPHANATE*INF 1F 250IU+SIR+AD	250	GRIFOLS ITALIA SpA	A
033866043	FANHDI*INF FL 250IU+SIR SOLV+S	250	GRIFOLS ITALIA SpA	A
037148018	TALATE*250IU/190IU+FL5mL+SIR	250	BAXALTA INN.Gmbh	A
040112017	OCTANATE*INIET FL 250IU+FL 5mL	250	OCTAPHARMA ITALY SpA	A
042939013	VONCENTO*250IU/600IU+FL 5mL	250	CSL BEHRING SpA	C(nn)
044564019	PLITATE*INF FL 250IU+SIR SOLV+SET	250	GRIFOLS ITALIA SpA	C(nn)
023308152	EMOWIL*1F 500IU+F 10mL	500	KEDRION SpA	A
026600080	HAEMATEP*FL 500IU+FL 10mL+SET	500	CSL BEHRING SpA	A
033077090	ALPHANATE*INF 1F 500IU+SIR+AD	500	GRIFOLS ITALIA SpA	A
033866056	FANHDI*INF FL 500IU+SIR SOLV+S	500	GRIFOLS ITALIA SpA	A
037148020	TALATE*500IU/375IU+FL10mL+SIR	500	BAXALTA INN. Gmbh	A
039385036	WILATE*FL 500+500IU+FL 5mL+SIR	500	OCTAPHARMA ITALY SpA	A
040112029	OCTANATE*INIET FL 500IU+FL 10mL	500	OCTAPHARMA ITALY SpA	A
040112056	OCTANATE*INIET FL 5mL100IU/mL	500	OCTAPHARMA ITALY SpA	A
042939025	VONCENTO*500IU/1200IU+FL 10mL	500	CSL BEHRING SpA	C(nn)
042939037	VONCENTO*500IU/1200IU+FL 5mL	500	CSL BEHRING SpA	C(nn)
044564021	PLITATE*INF FL 500IU+SIR SOLV+SET	500	GRIFOLS ITALIA SpA	C(nn)
023308188	EMOWIL*1F 1000IU+F 10mL	1000	KEDRION SpA	A
026600078	HAEMATEP*FL 1000IU+FL 15mL+SET	1000	CSL BEHRING SpA	A
033077102	ALPHANATE*INF 1F 1000IU+SIR+AD	1000	GRIFOLS ITALIA SpA	A
033866068	FANHDI*INF FL 1000IU+SIR SOLV+S	1000	GRIFOLS ITALIA SpA	A
037148032	TALATE*1000IU/750IU+FL10mL+SIR	1000	BAXALTA ITALY Srl	A
039385024	WILATE*FL 900+800IU+FL 10mL+SIR	1000	OCTAPHARMA ITALY SpA	A
039385048	WILATE*FL 1000+1000IU+FL 10mL+SI	1000	OCTAPHARMA ITALY SpA	A
040112031	OCTANATE*INIET FL 1000IU+FL 10mL	1000	OCTAPHARMA ITALY SpA	A
040112068	OCTANATE*INIET FL 5mL 200IU/mL	1000	OCTAPHARMA ITALY SpA	A
042939049	VONCENTO*1000IU/2400IU+FL 10mL	1000	CSL BEHRING SpA	C(nn)
044564033	PLITATE*INF FL1000IU+SIR SOLV+SET	1000	GRIFOLS ITALIA SpA	C(nn)
033077114	ALPHANATE*INF 1F 1500IU+SIR+AD	1500	GRIFOLS ITALIA SpA	A
033866070	FANHDI*INF FL1500IU+SIR SOLV+S	1500	GRIFOLS ITALIA SpA	A
044564045	PLITATE*INF FL1500IU+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* 500IU+FL 5mL	500	LFB	C
037392014	WILFACTIN*1000IU+FL 10mL	1000	LFB	C
037392038	WILFACTIN*2000IU+FL 20mL	2000	LFB	C

Table 15. Products containing recombinant coagulation Factor VIII and long-acting recombinant Factor VIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

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

AIC code	Brand name	IU	Manufacturer	NHS class
045255039	AFSTYLA 1000IU+FL SOLV 2,5mL+SIR	1000	CSL BEHRING GmbH	A
045273036	VIHUMA*EV 1000IU+FL SOLV 2,5mL	1000	OCTAPHARMA AB	C(nn)
036160048	ADVATE*FL 1500IU+FL SOLV 5mL	1500	BAXTER SpA	A
036160101	ADVATE*FL 1500IU+FL SOLV 2mL	1500	BAXALTA ITALY Srl	A
036160149	ADVATE*FL 1500IU+FL SOLV 5mL	1500	BAXALTA ITALY Srl	A
036160202	ADVATE*FL 1500IU+FL SOLV 2mL	1500	BAXALTA ITALY Srl	A
043153042	NOVOEIGHT*EV FL 1500IU+SIR 4mL	1500	NOVO NORDISK SpA	A
045255041	AFSTYLA 1500IU+FL SOLV 2,5mL+SIR	1500	CSL BEHRING GmbH	A
034421040	REFACTOAF*IV 1FL 2000IU+SIR 4mL	2000	PFIZER ITALIA Srl	A
034421089	REFACTOAF*IV 1SIR PRER 2000IU	2000	PFIZER ITALIA Srl	A
034955106	KOGENATE BAYER*EV 2000IU+SIR	2000	BAYER SpA	A
034955118	KOGENATE BAYER*EV 2000IU+SIR	2000	BAYER SpA	A
036160051	ADVATE*FL 2000IU+FL SOLV 5mL	2000	BAXTER SpA	A
036160152	ADVATE*FL 2000IU+FL SOLV 5mL	2000	BAXALTA ITALY Srl	A
043153055	NOVOEIGHT*EV FL 2000IU+SIR 4mL	2000	NOVO NORDISK SpA	A
043534041	NUWIQ*EV FL 2000IU+SIR 2,5mL	2000	KEDRION SpA	A
044725048	IBLIAS*FL POLV EV 2000IU+FL 5mL	2000	BAYER SpA	A
044726077	KOVALTRY*FL POLV EV 2000IU+SOLV	2000	BAYER SpA	A
044726089	KOVALTRY*FL POLV EV 2000IU+SOLV	2000	BAYER SpA	A
045255054	AFSTYLA 2000IU+FL SOLV 2,5mL+SIR	2000	CSL BEHRING GmbH	A
045273048	VIHUMA*EV 2000IU+FL SOLV 2,5mL	2000	OCTAPHARMA AB	C(nn)
043534054	NUWIQ*EV FL 2500IU+SIR 2,5mL	2500	OCTAPHARMA AB	A
045255066	AFSTYLA 2500IU+FL SOLV 2,5mL+SIR	2500	CSL BEHRING GmbH	A
034421053	REFACTO AF*IV 1SIR PRER 3000IU	3000	PFIZER ITALIA Srl	A
034955120	KOGENATE BAYER*EV 3000IU+SIR	3000	BAYER SpA	A
034955132	KOGENATE BAYER*EV 3000IU+SIR	3000	BAYER SpA	A
034956058	HELIXATE NEXGEN*3000IU+1FL+KIT	3000	CSL BEHRING SpA	A
036160063	ADVATE*FL 3000IU+FL SOLV 5mL	3000	BAXTER SpA	A
036160164	ADVATE*FL 3000IU+FL SOLV 5mL	3000	BAXALTA ITALY Srl	A
043153067	NOVOEIGHT*EV FL 3000IU+SIR 4mL	3000	NOVO NORDISK SpA	A
043534066	NUWIQ*EV FL 3000IU+SIR 2,5mL	3000	OCTAPHARMA AB	A
044725051	IBLIAS*FL POLV EV 3000IU+FL 5mL	3000	BAYER SpA	A
044726091	KOVALTRY*FL POLV EV 3000IU+SOLV	3000	BAYER SpA	A
044726103	KOVALTRY*FL POLV EV 3000IU+SOLV	3000	BAYER SpA	A
045255078	AFSTYLA 3000IU+FL SOLV 2,5mL+SIR	3000	CSL BEHRING GmbH	A
043534078	NUWIQ*EV FL 4000IU+SIR 2,5mL	4000	OCTAPHARMA AB	C
044726178	KOVALTRY*30FL 250UI+ SIR 3mL	7500	BAYER AG	C(nn)
044726180	KOVALTRY*30FL 250UI+ SIR 5mL	7500	BAYER AG	C(nn)
044726192	KOVALTRY*30FL 500UI+ SIR 3mL	15000	BAYER AG	C(nn)
044726204	KOVALTRY*30FL 500UI+SIR 5mL	15000	BAYER AG	C(nn)
044726216	KOVALTRY*30FL 1000UI+SIR 3mL	30000	BAYER AG	C(nn)
044726228	KOVALTRY*30FL 1000UI+SIR 5mL	30000	BAYER AG	C(nn)
044726230	KOVALTRY*30FL 2000UI+SIR 5mL	60000	BAYER AG	C(nn)
044726242	KOVALTRY*30FL 3000UI+SIR 5mL	90000	BAYER AG	C(nn)
Extended half-life Recombinant Factor VIII				
044563017	ELOCTA*IV 1FL 250IU+SIR PRERI	250	SOBI Srl	A
045936010	ADYNOVI*EV 250 IU+FL 2 mL+DISP	250	BAXALTA INN. GmbH.	A
045936022	ADYNOVI*EV 250 IU + FL 2 mL + DISP	250	BAXALTA INN. GmbH.	A
045936034	ADYNOVI*EV 250 IU + FL 5 mL + DISP	250	BAXALTA INN. GmbH.	A
045936046	ADYNOVI*EV 250 IU + FL 5 mL + DISP	250	BAXALTA INN. GmbH	A
047418013	JIVI* EV 250 IU + FL SOLV 2,5 mL + SIR	250	BAYER AG	A
044563029	ELOCTA*IV 1FL 500IU+SIR PRERI	500	SOBI Srl	A
045936059	ADYNOVI*EV 500IU + FL 2 mL + DISP	500	BAXALTA INN. GmbH.	A
045936061	ADYNOVI*EV 500IU + FL 2 mL + DISP	500	BAXALTA INN. GmbH	A
045936073	ADYNOVI*EV 500IU + FL 5 mL + DISP	500	BAXALTA INN. GmbH.	C(nn)
045936085	ADYNOVI*EV 500IU + FL 5 mL + DISP	500	BAXALTA INN. GmbH	A
047418025	JIVI* EV 500 IU + FL SOLV 2,5 mL + SIR	500	BAYER AG	A
048083012	ESPEROCT* EV 500 IU + FL 4 mL + SIR	500	NOVO NORDISK A/S	A

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

Quantification and characterisation of demand

In Italy, the total demand for both plasma-derived and recombinant formulations FVIII, was equal to 567,778,700 IUs in 2021 (Table 16); of these, about a sixth (16% of the total, 92,059,700 IUs) were human plasma-derived (Figure 15).

The tendency to use pdFVIII varied significantly from one Region to another ranging from 1.1% in Aosta Valley to 27% in Apulia. In 2021, the total FVIII demand *per capita* (plasma-derived and recombinant) was 10 IUs with a decrease of -2.1% compared to 2020.

The regional *per capita* demand shows significant fluctuations ranging from about 4 IUs in Friuli V. Giulia to about 17 IUs in Latium (Figure 16).

The most significant decreases in standardised regional demand were observed in Basilicata and in Liguria, where use decreased by -39% and -25%, 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.). However, 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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	14,014,500	10.8	14,304,750	11.2	3.1
Aosta Valley	764,000	6.1	940,000	7.6	24.0
AP Bolzano	3,290,000	6.2	2,634,000	4.9	-20.3
AP Trento	2,899,500	5.3	3,271,500	6.0	13.5
Apulia	50,628,250	12.8	48,099,250	12.2	-4.5
Basilicata	5,002,000	9.0	2,996,500	5.5	-39.2
Calabria	22,808,750	12.0	23,102,000	12.4	3.1
Campania	69,249,700	12.1	66,754,500	11.9	-2.1
E.-Romagna	37,765,750	8.5	44,246,750	10.0	17.8
Friuli V. Giulia	3,995,000	3.3	4,826,250	4.0	21.3
Latium	92,996,850	16.2	97,587,750	17.0	5.4
Liguria	12,915,250	8.5	9,646,500	6.4	-25.0
Lombardy	80,485,750	8.0	75,966,500	7.6	-5.2
Marche	10,028,500	6.6	9,342,000	6.2	-5.9
Molise	2,182,000	7.3	2,734,000	9.3	27.9
Piedmont	39,325,000	9.1	33,886,250	7.9	-13.1
Sardinia	13,478,700	8.4	13,526,200	8.5	1.7
Sicily	48,952,500	10.0	45,406,250	9.4	-6.4
Tuscany	28,206,950	7.6	25,224,750	6.8	-10.6
Umbria	7,146,500	8.2	6,438,500	7.4	-9.4
Veneto	37,623,750	7.7	36,844,500	7.6	-1.9
Italy	583,759,200	9.8	567,778,700	9.6	-2.1

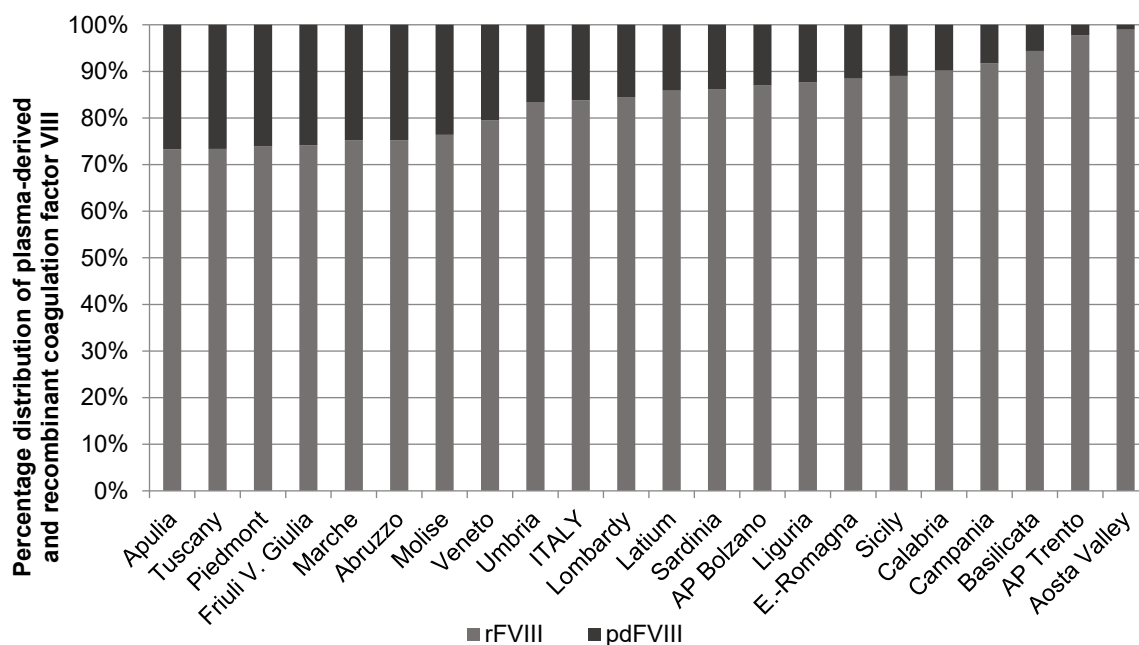


Figure 15. Percentage distribution of plasma-derived and recombinant coagulation Factor VIII, by Region, 2021 (adapted by the CNS on data from the Traceability information flow)

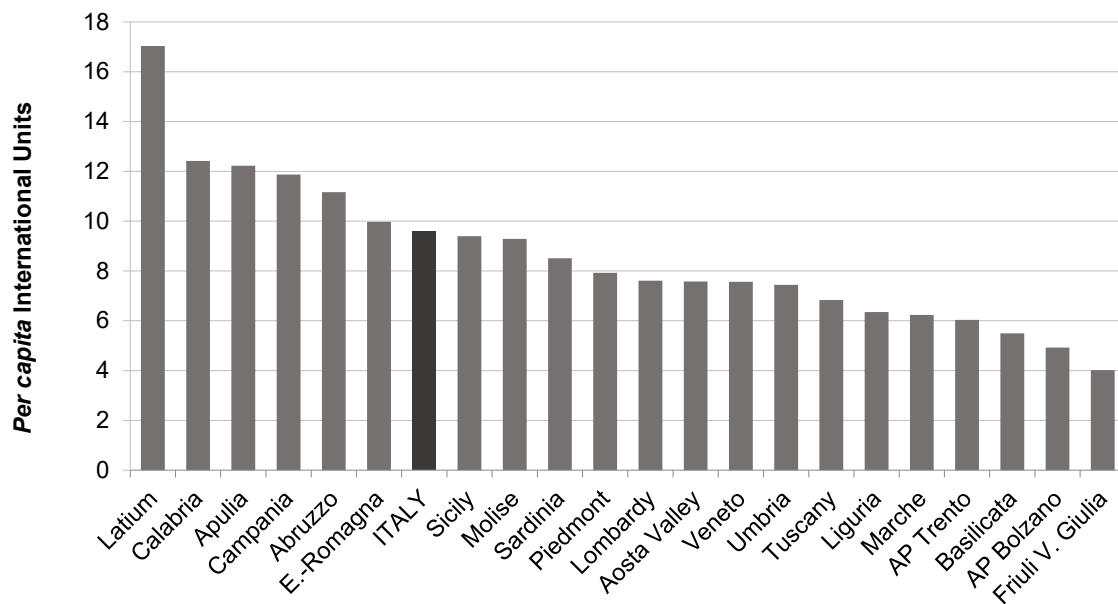


Figure 16. Total and regional demand (public and private) for coagulation Factor VIII, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

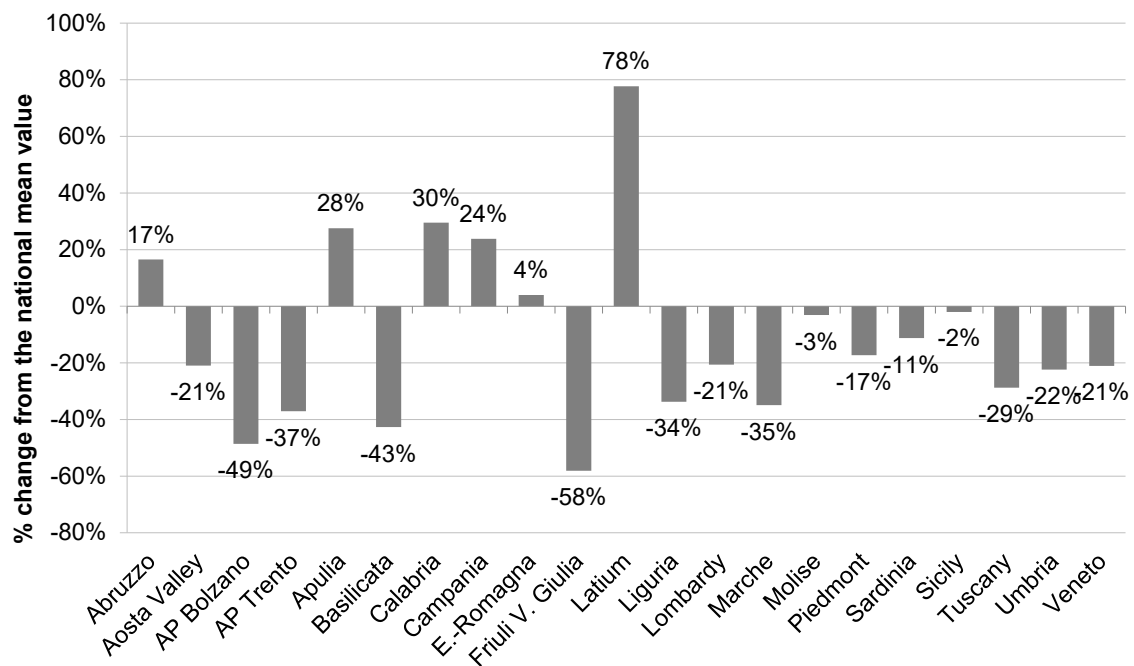


Figure 17. Percentage change from the national mean value of standardised regional demand for coagulation Factor VIII in 2021 (adapted by the CNS on data from the Traceability information flow)

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

In 2021, the national demand for pdFVIII was about 16% - equivalent to 92,059,700 IUs - of the total demand.

There is a downward trend of 6.5% compared to the 2020 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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,958,000	2.3	3,543,500	2.8	21.0
Aosta Valley	12,000	0.1	10,000	0.1	-16.0
AP Bolzano	1,043,000	2.0	343,000	0.6	-67.3
AP Trento	39,500	0.1	73,000	0.1	85.9
Apulia	12,134,500	3.1	12,855,500	3.3	6.5
Basilicata	195,000	0.4	168,000	0.3	-12.6
Calabria	2,203,250	1.2	2,276,500	1.2	5.2
Campania	4,967,700	0.9	5,532,500	1.0	13.1
E.-Romagna	5,371,000	1.2	5,110,000	1.2	-4.3
Friuli V. Giulia	674,000	0.6	1,249,000	1.0	86.0
Latium	13,269,100	2.3	13,782,000	2.4	4.3
Liguria	1,273,500	0.8	1,199,000	0.8	-5.8
Lombardy	14,902,500	1.5	11,851,500	1.2	-20.1
Marche	2,229,000	1.5	2,317,000	1.5	4.9
Molise	380,000	1.3	646,000	2.2	73.6
Piedmont	11,032,000	2.6	8,846,500	2.1	-19.1
Sardinia	1,727,200	1.1	1,877,200	1.2	10.2
Sicily	5,362,000	1.1	5,028,000	1.0	-6.3
Tuscany	7,048,200	1.9	6,719,000	1.8	-4.7
Umbria	1,325,000	1.5	1,068,000	1.2	-19.0
Veneto	10,889,500	2.2	7,564,500	1.6	-30.4
Italy	99,035,950	1.7	92,059,700	1.6	-6.5

Per capita demand varied significantly with the highest volumes in Apulia (3.3 IUs *per capita*), Abruzzo (2.8 IUs *per capita*) and Latium (2.4 IUs *per capita*); the corresponding percentage change between the aforementioned values and the Italian mean value were of +110%, +78% and +55%, respectively.

The lowest volumes (below 1 IU *per capita*) were recorded in Aosta Valley, the AP of Trento, the AP of Bolzano, Basilicata and Liguria (Figures 18 and 19).

The national trend decreased in many Italian Regions (range: -67%; -4.3%) with the exception of Abruzzo, Calabria, Campania, Friuli V. Giulia, Latium, Marche, Molise, AP of Trento, Apulia and Sardinia where there were increases between 4% and 86%.

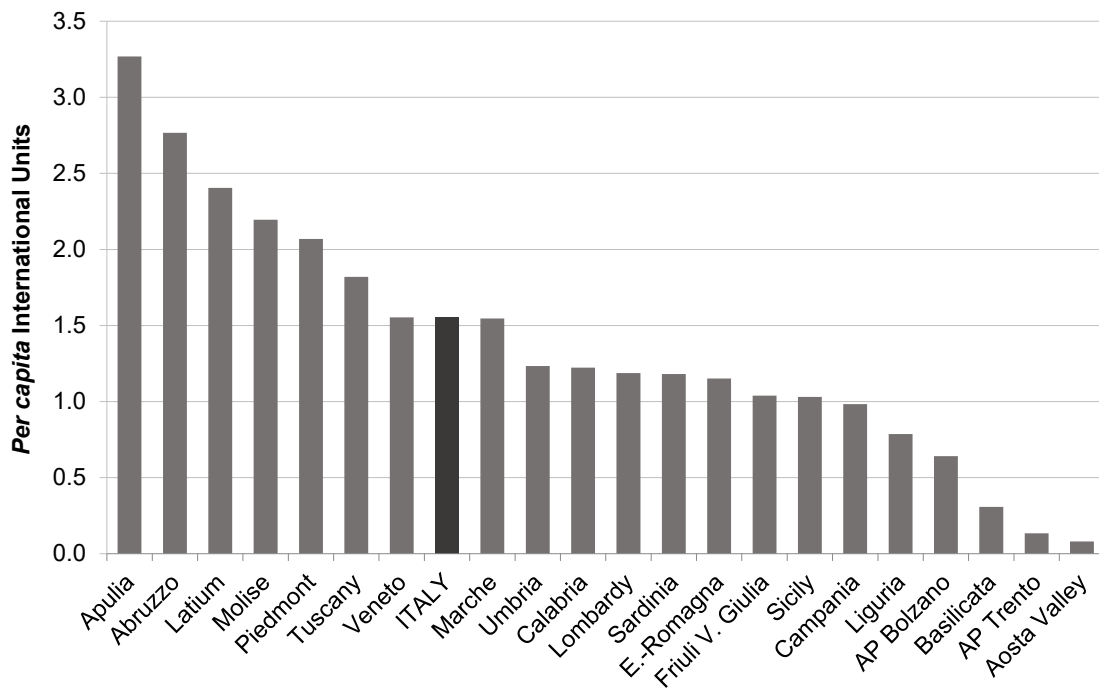


Figure 18. Total and regional demand (public and private) for plasma-derived coagulation Factor VIII, expressed in International Units per capita, 2021 (adapted by the CNS on data from the Traceability information flow)

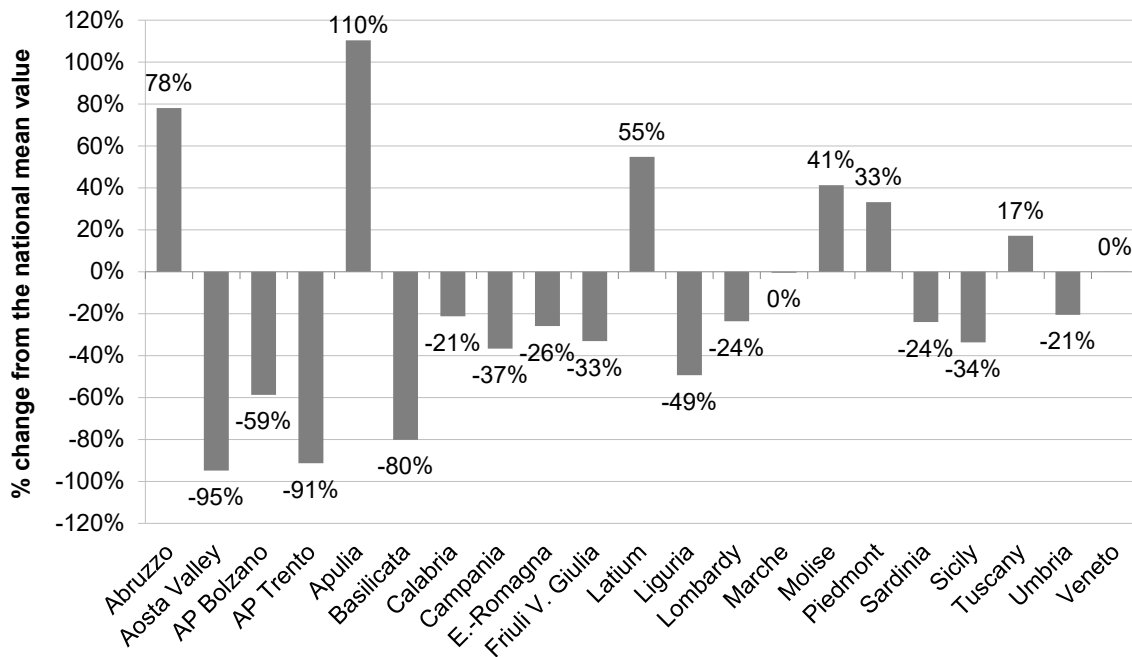


Figure 19. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor VIII in 2021 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor VIII (B02BD02)

In 2021, the total demand for plasma-derived FVIII was 42,606,000 IUs. The mean national demand *per capita* was about 0.7 IUs, with a range amongst Regions of 0.004 IUs and 1.5 IUs (Table 18).

The Regions with the highest *per capita* consumption of pdFVIII were Apulia (1.5 IUs) and Piedmont (1.4 IUs).

The lowest utilisation was observed in Campania and in Abruzzo (0.004 IUs and 0.1 IUs *per capita*, respectively). No consumption was recorded in Aosta Valley.

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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	120,000	0.1	94,000	0.1	-20.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	288,000	0.5	300,000	0.6	3.7
AP Trento	3,000	0.0	-	-	-100.0
Apulia	5,314,000	1.3	5,860,000	1.5	10.8
Basilicata	36,000	0.1	87,000	0.2	145.3
Calabria	643,000	0.3	565,000	0.3	-10.5
Campania	150,000	0.0	20,000	0.0	-86.5
E.-Romagna	3,192,000	0.7	1,725,000	0.4	-45.7
Friuli V. Giulia	256,000	0.2	868,000	0.7	240.4
Latium	5,234,000	0.9	5,890,000	1.0	13.0
Liguria	704,000	0.5	835,000	0.5	19.1
Lombardy	9,647,000	1.0	7,456,000	0.7	-22.4
Marche	1,805,000	1.2	1,880,000	1.3	5.2
Molise	180,000	0.6	344,000	1.2	95.2
Piedmont	8,749,000	2.0	6,097,000	1.4	-29.7
Sardinia	285,000	0.2	427,000	0.3	51.9
Sicily	763,000	0.2	785,000	0.2	3.8
Tuscany	4,361,000	1.2	4,165,000	1.1	-4.5
Umbria	396,000	0.5	226,000	0.3	-42.6
Veneto	8,269,000	1.7	4,982,000	1.0	-39.6
Italy	50,395,000	0.8	42,606,000	0.7	-14.9

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

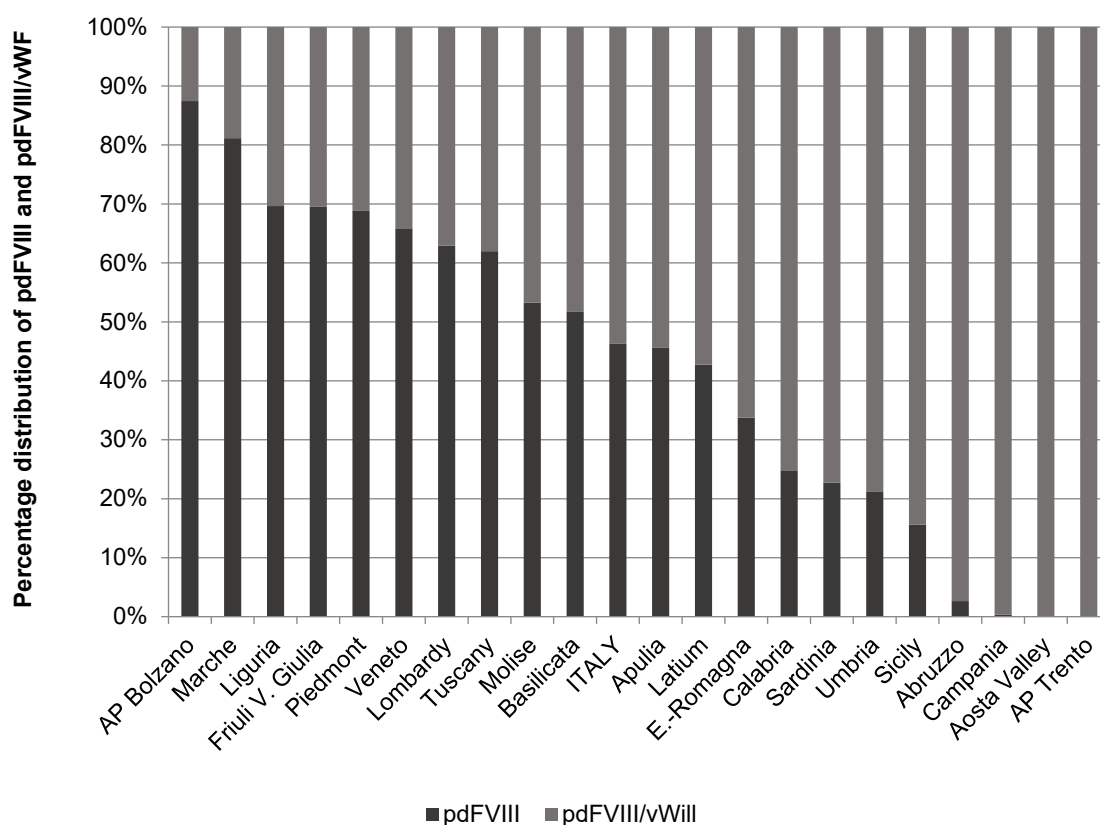


Figure 20. Percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination, by Region, 2021 (adapted by the CNS on data from the Traceability information flow)

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

In 2021, the national demand for FVIII and von Willebrand Factor in combination was 49,453,700 IUs, about 54% of the total demand for pdFVIII.

The mean national demand *per capita* was 0.8 IUs, with a range between Regions of 0.1 IUs (Aosta Valley, AP of Bolzano, AP of Trento and Basilicata) and 2.7 IUs (Abruzzo) (Table 19).

The Regions with the highest *per capita* demand of FVIII and von Willebrand Factor in combination were Abruzzo (2.7 IUs), Apulia (1.8 IUs) and Latium (1.4 IUs). The lowest utilization equal to 0.1 IUs *per capita* was observed in the Aosta Valley, AP of Bolzano, AP of Trento and Basilicata (Figure 21).

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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,838,000	2.2	3,449,500	2.7	22.8
Aosta Valley	12,000	0.1	10,000	0.1	-16.0
AP Bolzano	755,000	1.4	43,000	0.1	-94.3
AP Trento	36,500	0.1	73,000	0.1	101.2
Apulia	6,820,500	1.7	6,995,500	1.8	3.1
Basilicata	159,000	0.3	81,000	0.1	-48.3
Calabria	1,560,250	0.8	1,711,500	0.9	11.7
Campania	4,817,700	0.8	5,512,500	1.0	16.2
E.-Romagna	2,179,000	0.5	3,385,000	0.8	56.2
Friuli V. Giulia	418,000	0.3	381,000	0.3	-8.5
Latium	8,035,100	1.4	7,892,000	1.4	-1.3
Liguria	569,500	0.4	364,000	0.2	-35.8
Lombardy	5,255,500	0.5	4,395,500	0.4	-16.0
Marche	424,000	0.3	437,000	0.3	4.1
Molise	200,000	0.7	302,000	1.0	54.2
Piedmont	2,283,000	0.5	2,749,500	0.6	21.5
Sardinia	1,442,200	0.9	1,450,200	0.9	1.9
Sicily	4,599,000	0.9	4,243,000	0.9	-6.9
Tuscany	2,687,200	0.7	2,554,000	0.7	-5.0
Umbria	929,000	1.1	842,000	1.0	-8.9
Veneto	2,620,500	0.5	2,582,500	0.5	-1.3
Italy	48,640,950	0.8	49,453,700	0.8	2.4

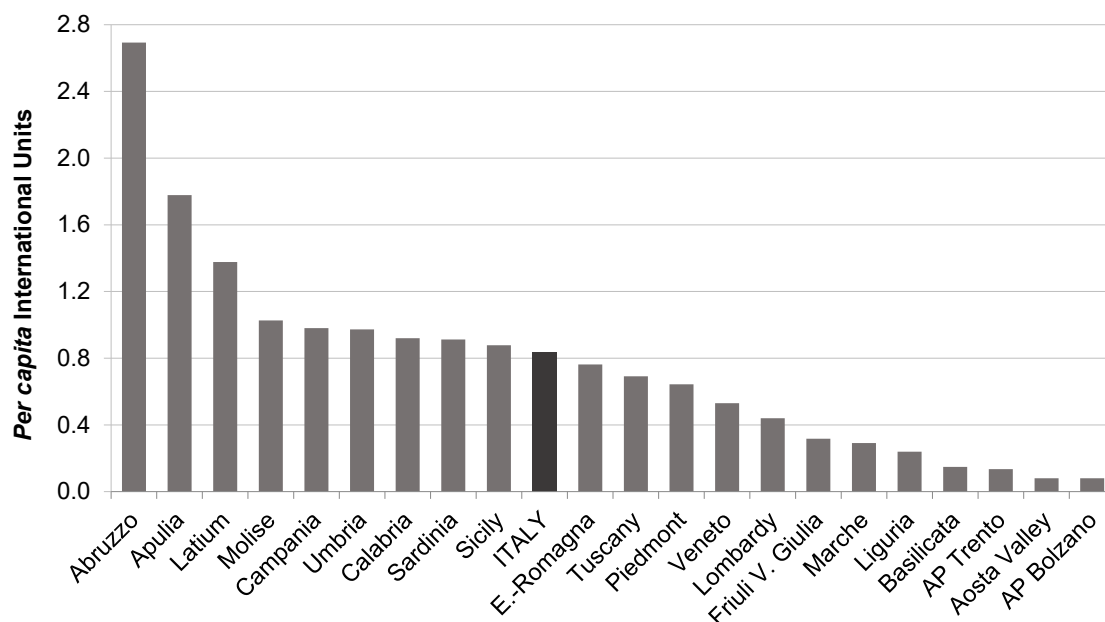


Figure 21. Total and regional demand (public and private) for pdFVIII and von Willebrand Factor in combination, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor VIII

In 2021, the total demand for rFVIII was 475,719,000 IUs, with a decrease of approximately -1.2% compared to 2020. The mean national demand *per capita* was about 8 IUs, with a range between Regions of 3 IUs and 14.6 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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	11,056,500	8.5	10,761,250	8.4	-1.7
Aosta Valley	752,000	6.0	930,000	7.5	24.6
AP Bolzano	2,247,000	4.2	2,291,000	4.3	1.5
AP Trento	2,860,000	5.2	3,198,500	5.9	12.5
Apulia	38,493,750	9.7	35,243,750	9.0	-8.0
Basilicata	4,807,000	8.7	2,828,500	5.2	-40.3
Calabria	20,605,500	10.9	20,825,500	11.2	2.9
Campania	64,282,000	11.3	61,222,000	10.9	-3.3
E.-Romagna	32,394,750	7.3	39,136,750	8.8	21.5
Friuli V. Giulia	3,321,000	2.8	3,577,250	3.0	8.1
Latium	79,727,750	13.9	83,805,750	14.6	5.6
Liguria	11,641,750	7.6	8,447,500	5.6	-27.1
Lombardy	65,583,250	6.5	64,115,000	6.4	-1.8
Marche	7,799,500	5.2	7,025,000	4.7	-9.1
Molise	1,802,000	6.0	2,088,000	7.1	18.3
Piedmont	28,293,000	6.6	25,039,750	5.9	-10.7
Sardinia	11,751,500	7.3	11,649,000	7.3	0.5
Sicily	43,590,500	8.9	40,378,250	8.4	-6.6
Tuscany	21,158,750	5.7	18,505,750	5.0	-12.5
Umbria	5,821,500	6.7	5,370,500	6.2	-7.2
Veneto	26,734,250	5.5	29,280,000	6.0	9.7
Italy	484,723,250	8.1	475,719,000	8.0	-1.2

The Regions in which the highest *per capita* utilisation of rFVIII was observed were Latium (14.6 IUs), Calabria and Campania (11 IUs) (Figure 22), with a percentage change compared to the Italian mean value of +82%, +39% and +36%, respectively (Figure 23).

The lowest utilisation – between 3 and 5.9 IUs *per capita* – was observed in Friuli V. Giulia, AP of Bolzano, Marche, Tuscany, Basilicata, Liguria, Piedmont and in AP of Trento.

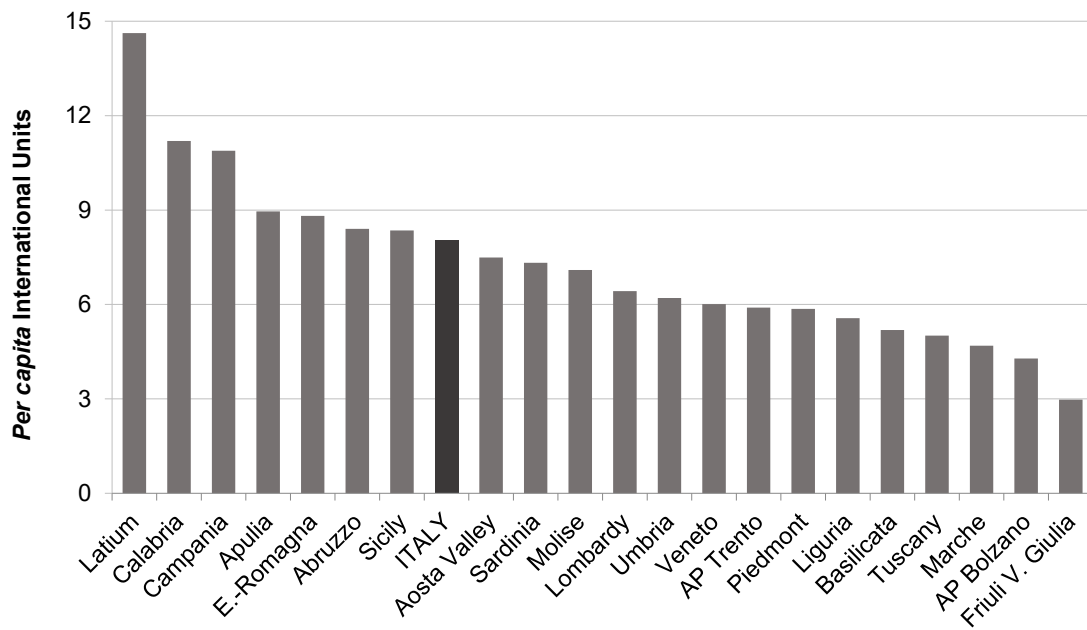


Figure 22. Total and regional demand (public and private) for recombinant coagulation Factor VIII, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

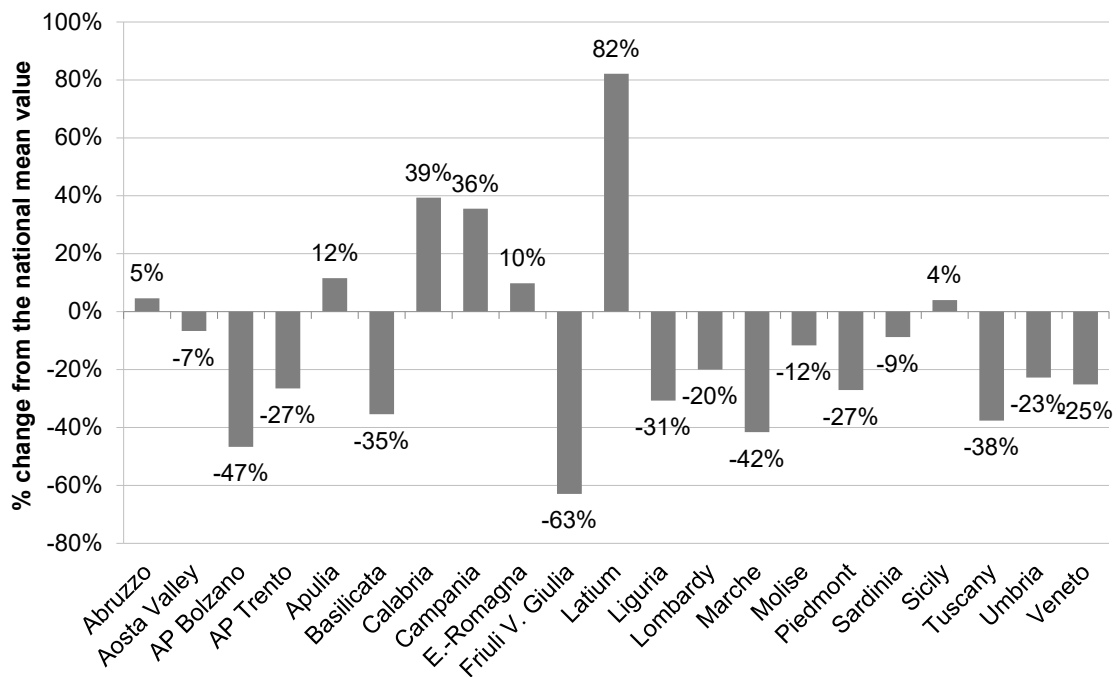


Figure 23. Percentage change from the national mean value of standardised regional demand for recombinant coagulation Factor VIII in 2021 (adapted by the CNS on data from the Traceability information flow)

Extended half-life Recombinant Factor VIII

Part of the total demand for rFVIII is represented by drugs containing extended half-life molecules. In 2021, the demand for these products was equal to 177,193,750 IUs, about 37% of the total demand for rFVIII (Table 21).

The national demand *per capita* was about 3 IUs, with a range among Regions of 0.7 IUs in the AP of Bolzano and 5.5 IUs in Latium (+85% as compared to national mean value), (Figures 24 and 25).

Table 21. Total demand (public and private) and total standardised demand for long-acting recombinant coagulation Factor VIII, expressed in International Units and International Units *per capita* and variations in percentage between 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	1,127,500	0.9	5,491,000	4.3	391.9
Aosta Valley	84,000	0.7	546,000	4.4	555.0
AP Bolzano	170,000	0.3	362,000	0.7	112.0
AP Trento	672,000	1.2	518,000	1.0	-22.5
Apulia	4,305,000	1.1	8,892,000	2.3	107.6
Basilicata	2,000	0.0	444,000	0.8	22,430.8
Calabria	3,153,500	1.7	4,745,000	2.6	53.2
Campania	8,168,500	1.4	16,462,000	2.9	104.7
E.-Romagna	11,757,250	2.6	19,501,000	4.4	66.8
Friuli V. Giulia	670,000	0.6	2,857,250	2.4	328.1
Latium	15,820,500	2.7	31,711,750	5.5	101.3
Liguria	5,299,500	3.5	5,913,000	3.9	12.0
Lombardy	18,246,250	1.8	22,807,250	2.3	25.6
Marche	1,359,000	0.9	3,599,000	2.4	167.4
Molise	-	0.0	949,000	3.2	NA
Piedmont	11,356,250	2.6	12,378,000	2.9	9.9
Sardinia	1,237,000	0.8	1,464,000	0.9	20.0
Sicily	4,616,250	0.9	12,790,000	2.6	179.4
Tuscany	5,842,500	1.6	7,279,500	2.0	24.6
Umbria	1,670,000	1.9	2,026,000	2.3	22.0
Veneto	7,717,250	1.6	16,458,000	3.4	113.7
Italy	103,274,250	1.7	177,193,750	3.0	72.7

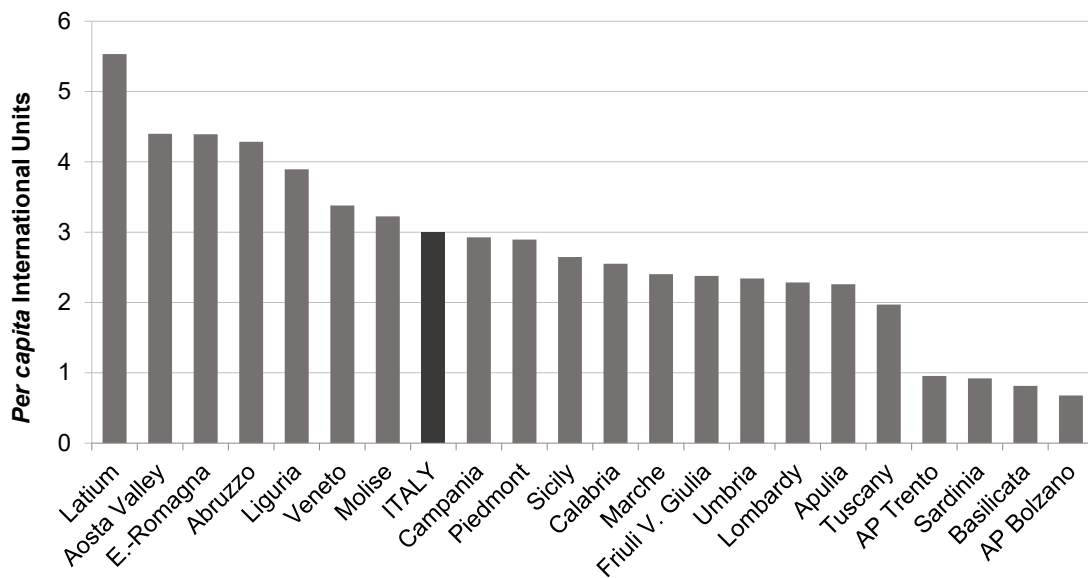


Figure 24. Total and regional demand (public and private) for extended half-life recombinant Factor VIII, expressed in International Units per capita, 2021 (adapted by the CNS on data from the Traceability information flow)

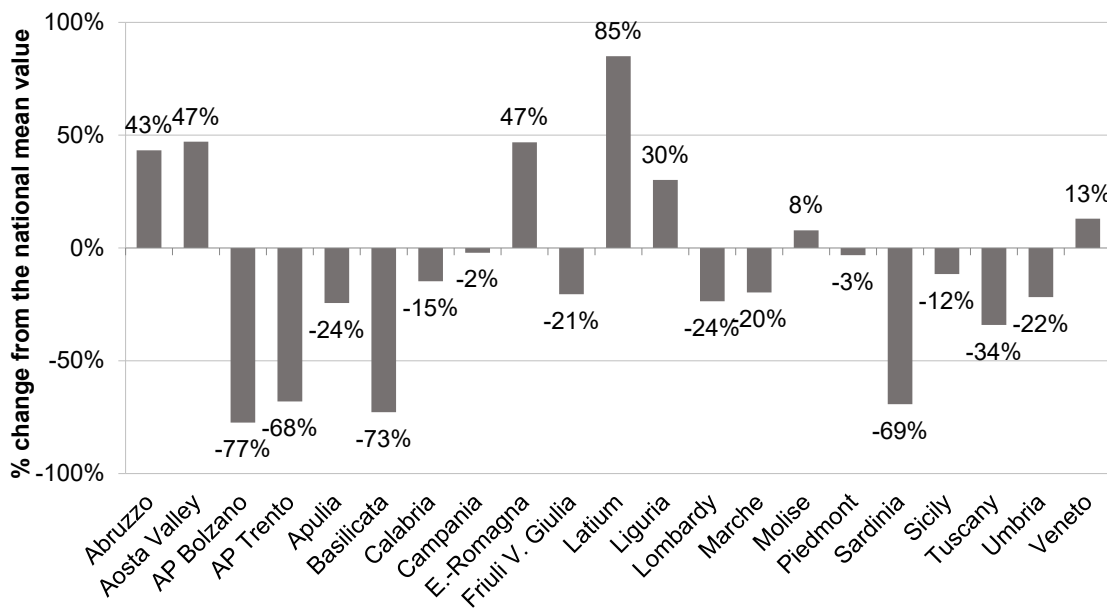


Figure 25. Percentage change from the national mean value of standardized regional demand for extended half-life recombinant Factor VIII in 2021 (adapted by the CNS on data from the Traceability information flow)

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

Besides the well-known bypassing agents, activated Prothrombin Complex Concentrates (aPCCs) and recombinant activated Factor VII (rFVIIa), used to treat or prevent bleeding in haemophilia patients with inhibitors, Emicizumab is a monoclonal antibody which has been designed to 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 related amount of active ingredient contained expressed in milligrams (mg).

Table 22. Products containing Emicizumab currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification and characterisation of the demand

Table 23 shows the total and per 1,000 population demand for drugs containing Emicizumab for the year 2021, 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 2021 and its was 1,499,490 mg.

The national demand (mg per 1,000 population) was about 25.3 mg, but not all Regions recorded Emicizumab consumption (Table 23).

The standardised demand for Emicizumab ranged from a minimum of 11.5 mg in Latium to a maximum of 43.2 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 2021 and variations in percentage between 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	mg	mg per 1,000 population	mg	mg per 1,000 population	
Abruzzo	21,180	16.4	31,305	24.4	49.3
Aosta Valley	-	-	-	-	NA
AP Bolzano	8,670	16.3	10,635	19.9	22.1
AP Trento	-	-	-	-	NA
Apulia	35,640	9.0	50,805	12.9	43.3
Basilicata	5,310	9.6	13,500	24.8	158.0
Calabria	38,745	20.5	56,010	30.1	47.2
Campania	74,670	13.1	138,270	24.6	88.1
E.-Romagna	54,450	12.2	98,685	22.2	82.3
Friuli V. Giulia	13,200	10.9	22,560	18.8	71.6
Latium	27,135	4.7	65,655	11.5	143.0
Liguria	20,955	13.7	44,340	29.2	112.5
Lombardy	205,590	20.5	310,380	31.1	51.7
Marche	11,010	7.3	37,365	24.9	242.6
Molise	-	-	9,330,0	31.7	100
Piedmont	114,885	26.6	184,875	43.2	62.3
Sardinia	-	-	-	-	NA
Sicily	55,575	11.4	113,655	23.5	106.3
Tuscany	92,895	25.2	151,800	41.1	63.4
Umbria	14,400	16.5	25,665	29.7	79.2
Veneto	71,445	14.6	134,655	27.7	88.8
Italy	865,755	14.5	1,499,490	25.3	74.4

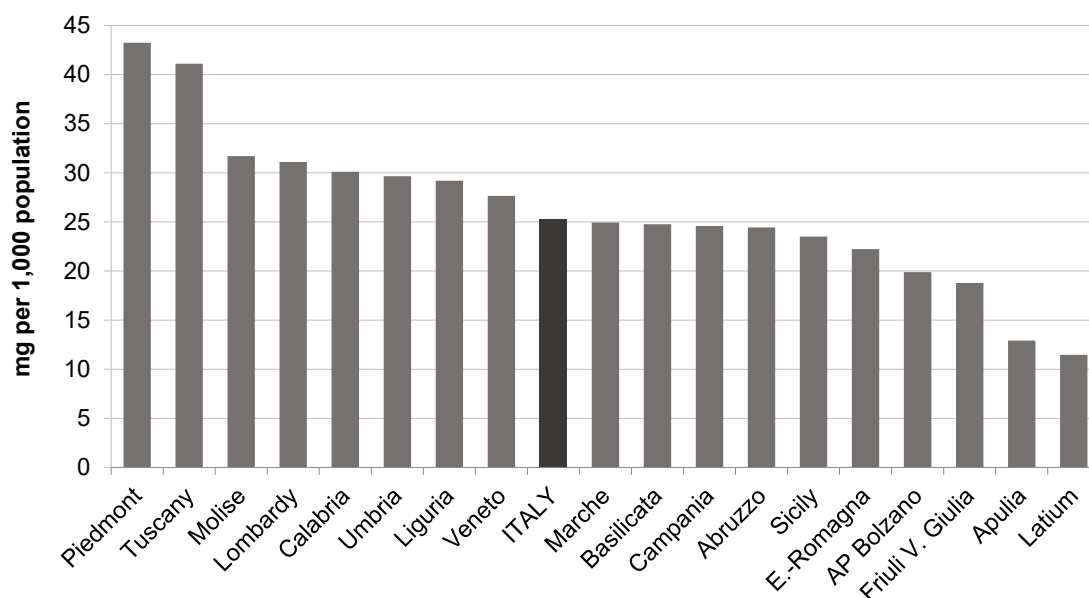


Figure 26. Total and regional demand (public and private) for Emicizumab expressed in mg per 1,000 population 2021 (adapted by the CNS on data from the Traceability information flow)

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 (+ 71%) and Tuscany (+ 62%).

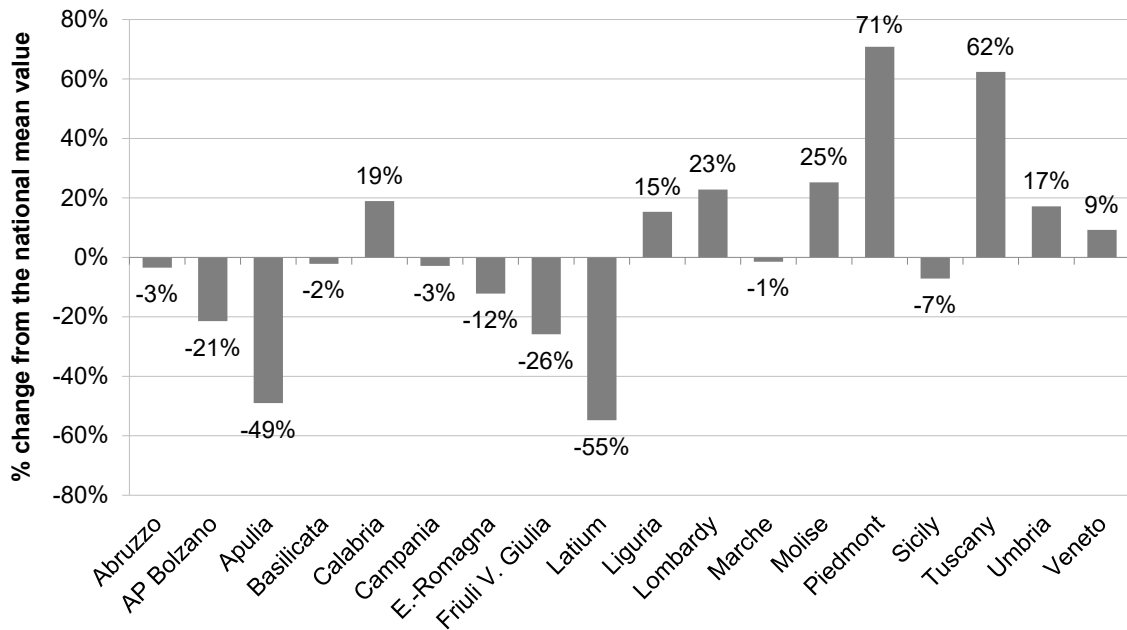


Figure 27. Percentage change from the national mean value of standardised regional demand for Emicizumab in 2021 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2021)

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

Table 25. Products containing recombinant coagulation Factor IX and long-acting recombinant Factor IX currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

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

Quantification and characterisation of the demand

Table 26 illustrates the total and *per capita* demand for plasma-derived and recombinant FIX for the two-year period 2020-2021, at national and regional levels.

The total demand for FIX formulations recorded in 2021 was 61,155,700 IUs (Table 26); about 9% of the aforementioned amount (5,512,700 IUs) was plasma-derived. There was an increasing demand for both pdFIX (+3%) and rFIX (-6.7%).

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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	1,906,000	1.5	2,191,250	1.7	16.1
Aosta Valley	-	-	-	-	NA
APBolzano	38,000	0.1	61,250	0.1	60.5
APTrento	475,000	0.9	202,000	0.4	-57.2
Apulia	5,973,500	1.5	6,072,500	1.5	2.2
Basilicata	327,750	0.6	310,250	0.6	-3.9
Calabria	1,042,750	0.6	1,993,000	1.1	94.6
Campania	6,632,000	1.2	6,710,750	1.2	2.8
E.-Romagna	3,396,500	0.8	3,729,750	0.8	10.4
Friuli V. Giulia	752,000	0.6	727,000	0.6	-2.9
Latium	5,534,100	1.0	6,077,250	1.1	10.3
Liguria	2,372,000	1.6	1,881,000	1.2	-20.4
Lombardy	8,958,500	0.9	9,947,500	1.0	11.6
Marche	1,852,000	1.2	2,085,200	1.4	13.7
Molise	10,000	0.0	20,000	0.1	104.2
Piedmont	4,231,750	1.0	4,934,000	1.2	17.6
Sardinia	46,750	0.0	38,000	0.0	-17.6
Sicily	4,259,500	0.9	4,239,000	0.9	0.4
Tuscany	6,054,750	1.6	6,142,000	1.7	1.4
Umbria	435,000	0.5	545,000	0.6	26.0
Veneto	3,579,000	0.7	3,249,000	0.7	-9.0
Italy	57,876,850	1.0	61,155,700	1.0	6.4

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

In 2021, the standardised demand for plasma-derived and recombinant FIX was 1 IU *per capita*, with significantly different regional trends: these ranged from a minimum - close to zero - in Sardinia (-98% compared to the Italian mean value), to a maximum in Abruzzo and Tuscany (1.7 IUs), Apulia and Marche with respectively 1.5 IUs and 1.4 IUs *per capita* (+66%, +61%, 50% and +35% percentage change compared to the national mean value, respectively) (Figures 28 and 29). No consumption in Aosta Valley was registered.

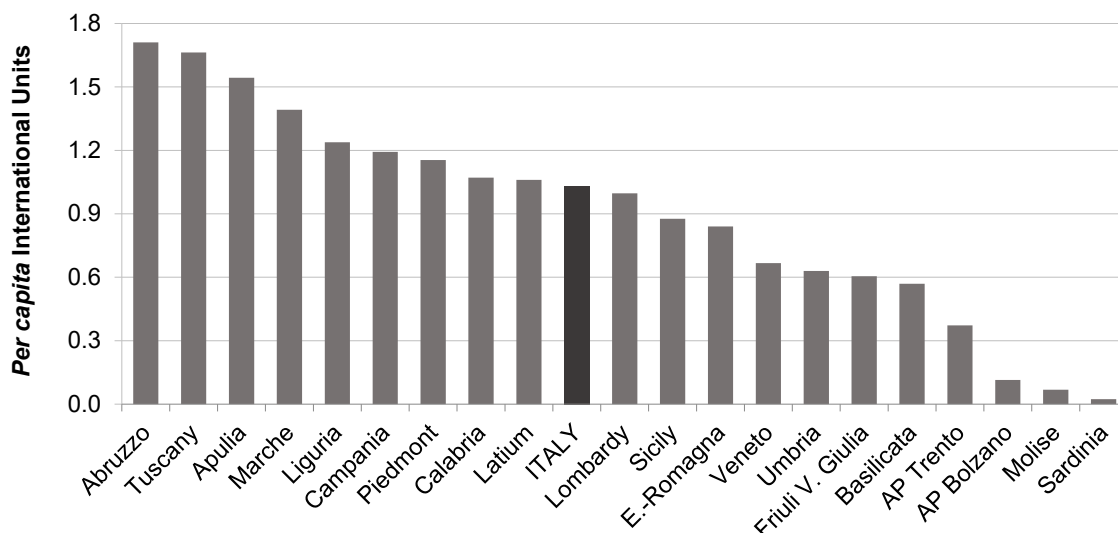


Figure 28. Total and regional demand (public and private) for coagulation Factor IX, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

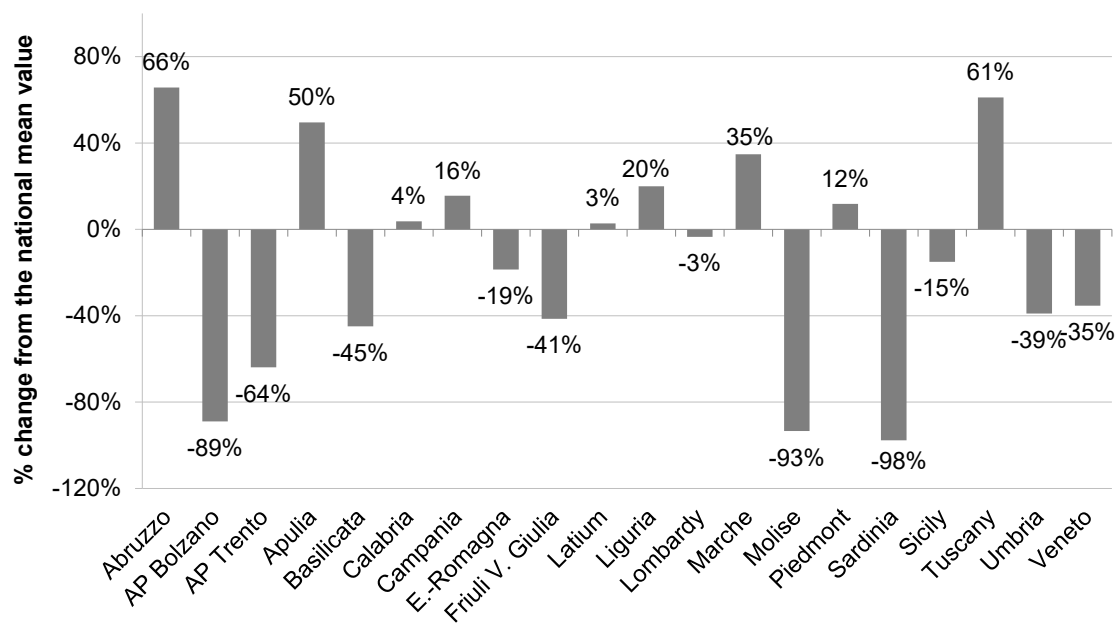


Figure 29. Percentage change from the national mean value of standardized regional demand for coagulation Factor IX (International Units *per capita*) in 2021 (adapted by the CNS on data from the Traceability information flow)

In fourteen Regions there were percentage increases in demand (range: 0.4-104%) which is instead decreasing in six Regions (range: -3; -57%) (Table 26). In Sardinia, AP of Trento, Friuli V.Giulia, Basilicata and Abruzzo rFIX was used exclusively, while in Apulia, Tuscany, Sicily, Emilia-Romagna, Calabria, Liguria and Campania the rFIX demand reached volumes of above 95% (Figure 30).

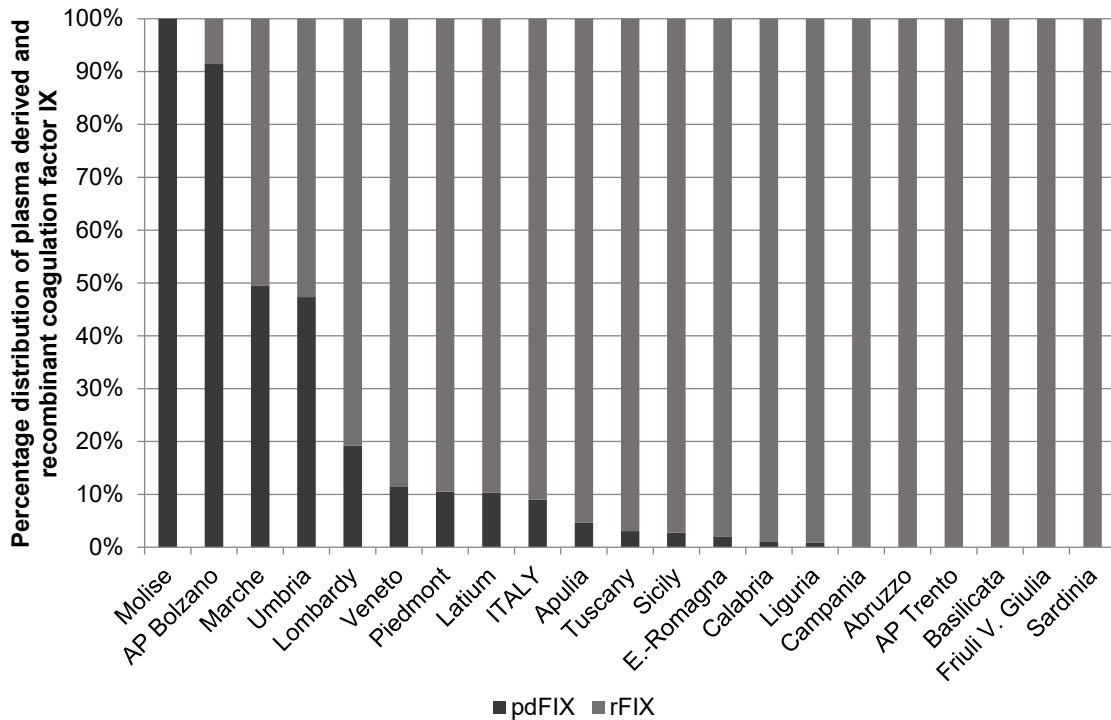


Figure 30. Distribution expressed in % of Factor IX per type, by Region, 2021 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor IX

In 2021, the total demand for pdFIX (expressed in absolute values and *per capita* volumes), showed an increase of 3% compared to 2020, for an absolute value of 5,512,700 IUs, equal to 0.1 IUs *per capita* (Table 27).

The Regions with the highest *per capita* demand were Marche and Umbria with 0.7 IUs and 0.3 IUs respectively; in Abruzzo, Basilicata, Friuli V.Giulia, AP of Trento, Sardinia and Aosta Valley there was no reported consumption of pdFIX (Figures 31 and 32).

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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	64,000	0.0	-	-	-100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	38,000	0.1	56,000	0.1	46.7
AP Trento	-	-	-	-	NA
Apulia	176,000	0.0	282,000	0.1	61.0
Basilicata	22,000	0.0	-	0.0	-100.0
Calabria	52,000	0.0	20,000	0.0	-60.8
Campania	5,000	0.0	12,000	0.0	143.8
E.-Romagna	457,000	0.1	77,000	0.0	-83.1
Friuli V.Giulia	-	-	-	-	NA
Latium	431,100	0.1	625,000	0.1	45.6
Liguria	192,000	0.1	16,000	0.0	-91.6
Lombardy	1,704,000	0.2	1,917,000	0.2	13.0
Marche	636,000	0.4	1,033,200	0.7	64.0
Molise	10,000	0.0	20,000	0.1	104.2
Piedmont	278,000	0.1	518,000	0.1	87.9
Sardinia	-	-	-	-	NA
Sicily	90,000	0.0	116,000	0.0	30.0
Tuscany	232,000	0.1	188,000	0.1	-19.0
Umbria	302,000	0.3	258,000	0.3	-14.1
Veneto	688,000	0.1	374,500	0.1	-45.5
Italy	5,377,100	0.1	5,512,700	0.1	3.2

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

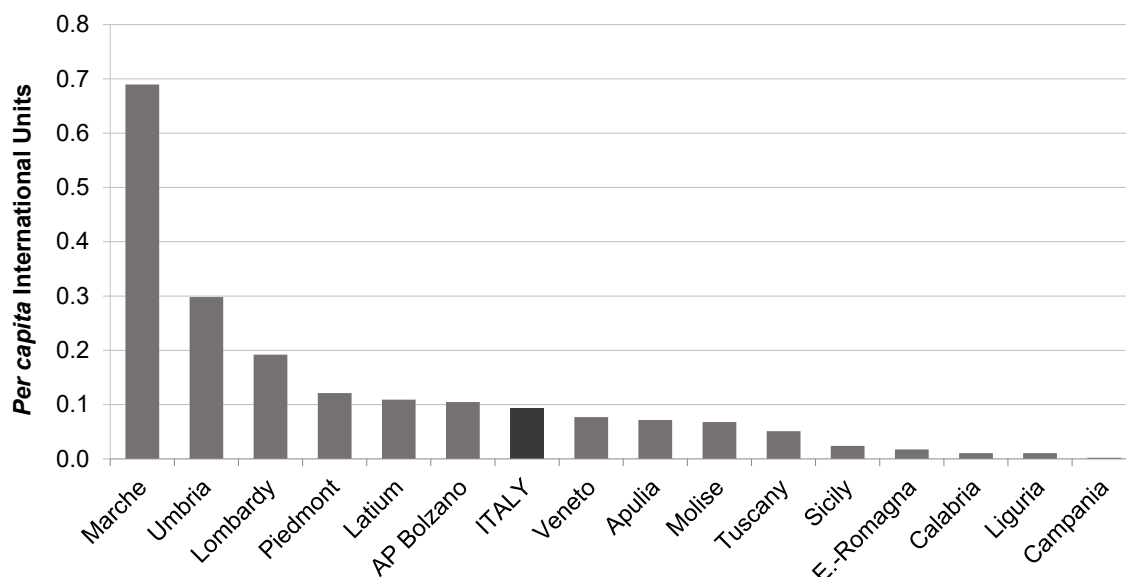


Figure 31. Total and regional demand (public and private) for plasma-derived coagulation Factor IX, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

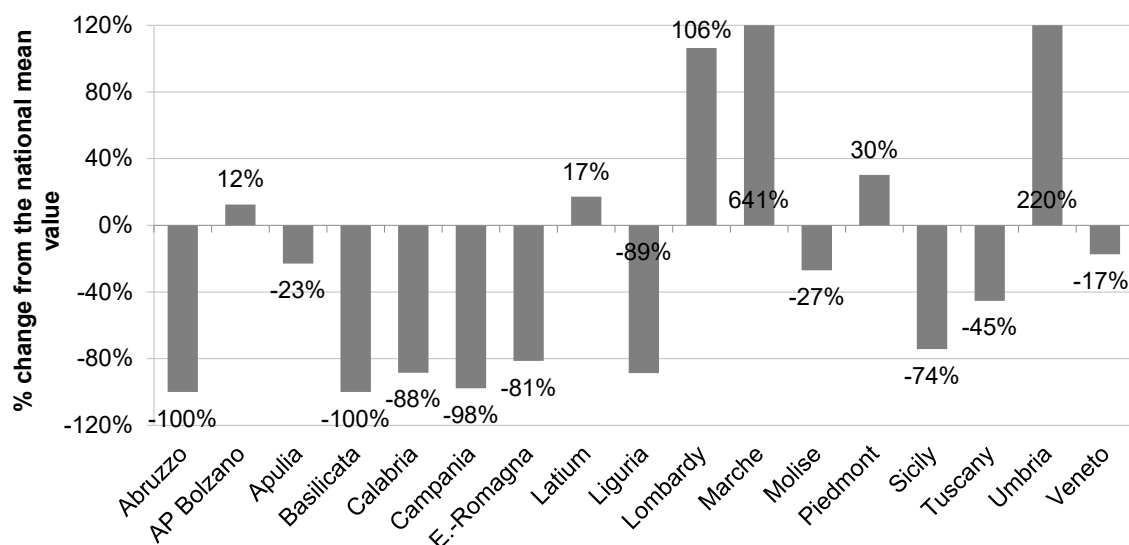


Figure 32. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor IX in 2021
(adapted by the CNS on data from the Traceability information flow)

Recombinant Factor IX

The total demand for rFIX showed, in the period 2020-2021, an increase of +6.7%, registering a value of 55,643,000 IUs in 2021, equal to 0.9 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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	1,842,000	1.4	2,191,250	1.7	20.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	5,250,0	0.0	100.0
AP Trento	475,000	0.9	202,000	0.4	-57.2
Apulia	5,797,500	1.5	5,790,500	1.5	0.4
Basilicata	305,750	0.6	310,250	0.6	3.0
Calabria	990,750	0.5	1,973,000	1.1	102.7
Campania	6,627,000	1.2	6,698,750	1.2	2.7
E.-Romagna	2,939,500	0.7	3,652,750	0.8	25.0
Friuli V. Giulia	752,000	0.6	727,000	0.6	-2.9
Latium	5,103,000	0.9	5,452,250	1.0	7.3
Liguria	2,180,000	1.4	1,865,000	1.2	-14.1
Lombardy	7,254,500	0.7	8,030,500	0.8	11.2
Marche	1,216,000	0.8	1,052,000	0.7	-12.7
Molise	-	-	-	-	NA
Piedmont	3,953,750	0.9	4,416,000	1.0	12.6
Sardinia	46,750	0.0	38,000	0.0	-17.6
Sicily	4,169,500	0.9	4,123,000	0.9	-0.3
Tuscany	5,822,750	1.6	5,954,000	1.6	2.2
Umbria	133,000	0.2	287,000	0.3	117.0
Veneto	2,891,000	0.6	2,874,500	0.6	-0.4
Italy	52,499,750	0.9	55,643,000	0.9	6.7

The Regions with the highest *per capita* demand (Figure 33) were Abruzzo, Tuscany, Apulia, Liguria and Campania with 1.7 IU for the first one and 1.6 IU for the second one and 1.5 IU and 1,2 IU for the other two Regions (+82%, + 72% +57% ,+31%and + 27% compared to the national average) (Figure 34).

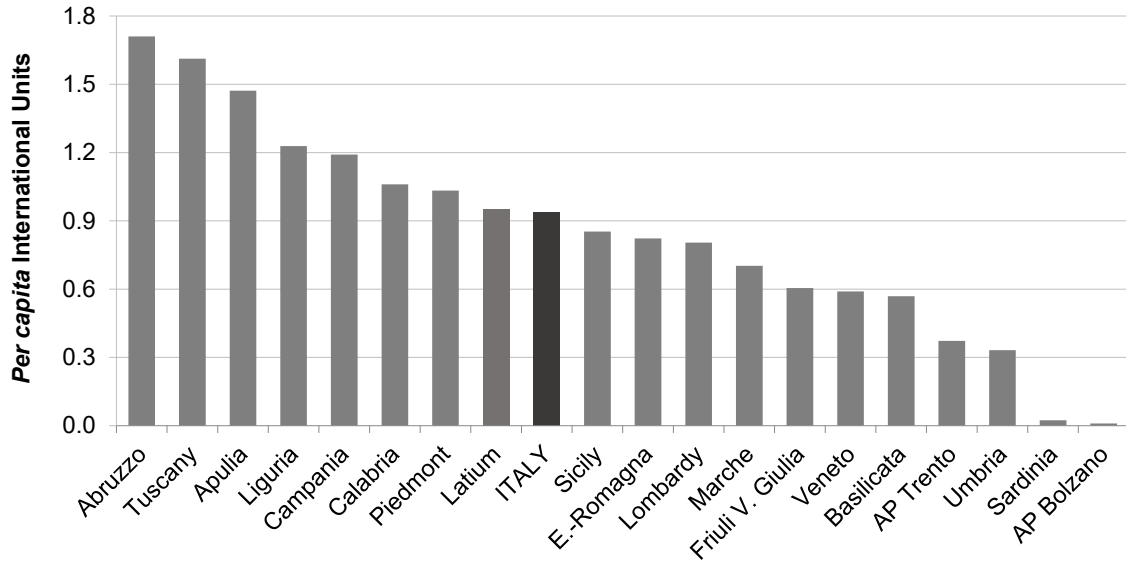


Figure 33. Total and regional demand (public and private) for recombinant coagulation Factor IX, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

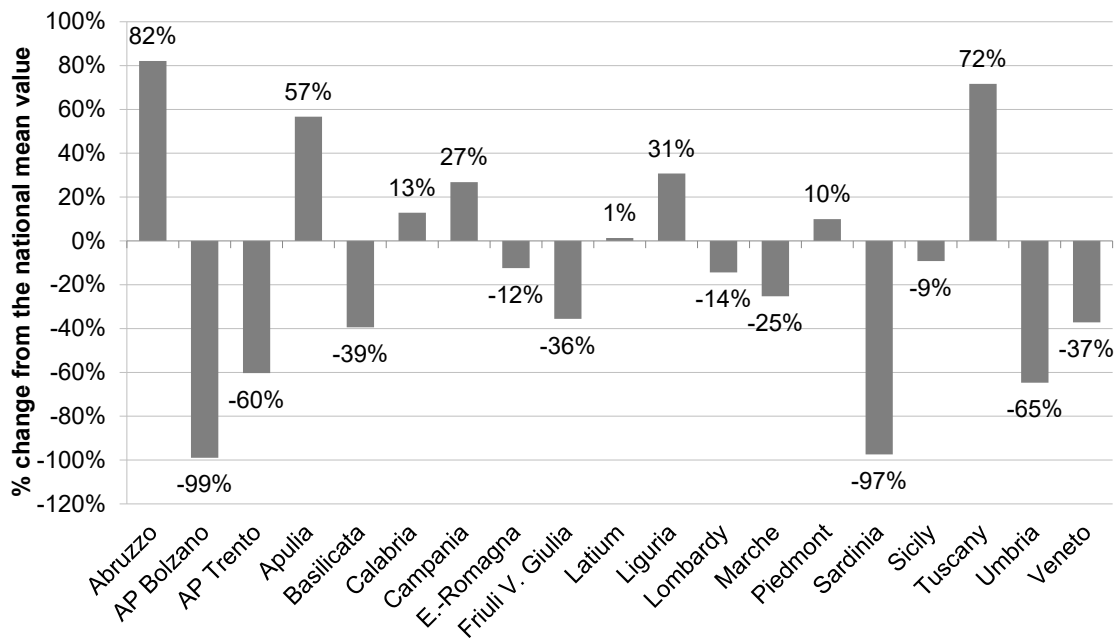


Figure 34. Percentage change from the national mean value of standardised regional demand for recombinant coagulation Factor IX in 2021 (adapted by the CNS on data from the Traceability information flow)

In Aosta Valley and Molise there was no reported consumption of rFIX in 2021. In 2021 there was an increase in *per capita* demand, compared to 2020, which is particularly evident in Umbria (+117%) and Calabria (+103%); instead a significant decrease was in the AP of Trento (-57%).

Extended half- recombinant Factor IX life

Out of 55.6 million IUs of rFIX demand, extended half-life recombinant Factor IX molecules recorded a total demand of 34,837,250 IUs, about 63% 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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	1,197,000	0.9	1,609,500	1.3	35.8
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	250	0.0	100
AP Trento	-	-	-	-	NA
Apulia	4,530,500	1.1	4,788,500	1.2	6.2
Basilicata	98,750	0.2	94,250	0.2	-3.1
Calabria	484,750	0.3	777,000	0.4	63.2
Campania	2,642,000	0.5	2,870,750	0.5	10.4
E.-Romagna	2,502,000	0.6	3,090,250	0.7	24.2
Friuli V. Giulia	704,000	0.6	701,000	0.6	0.0
Latium	2,400,500	0.4	2,546,250	0.4	6.5
Liguria	1,871,000	1.2	1,690,000	1.1	-9.3
Lombardy	6,173,500	0.6	6,427,500	0.6	4.6
Marche	699,000	0.5	774,000	0.5	11.8
Molise	-	-	-	-	NA
Piedmont	2,817,750	0.7	2,630,500	0.6	-5.9
Sardinia	46750	0.0	-	-	-100.0
Sicily	2,027,500	0.4	1,959,000	0.4	-2.5
Tuscany	2,541,750	0.7	2,488,000	0.7	-2.1
Umbria	107,000	0.1	221,000	0.3	107.7
Veneto	2,109,000	0.4	2,169,500	0.4	3.1
Italy	32,952,750	0.6	34,837,250	0.6	6.4

The mean national demand *per capita* was about 0.6 IU, with a range among Regions of 0.0005 IU and 1.3 IU. In Molise, in the AP of Trento, Sardinia and in the Aosta Valley there was no consumption for these drugs in 2021 (Figure 35 and 36).

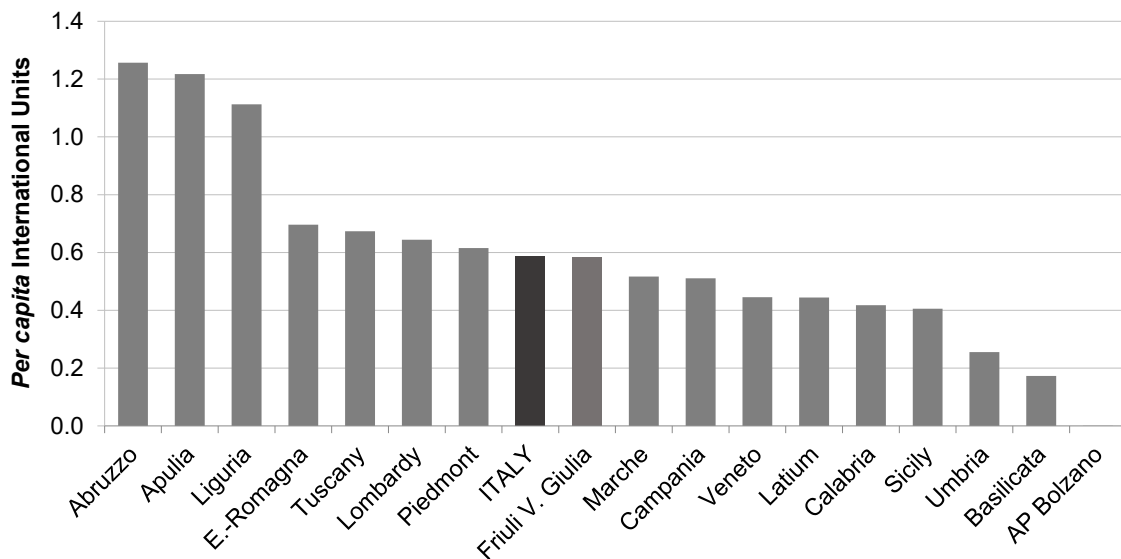


Figure 35. Total and regional demand (public and private) for extended half-life recombinant Factor IX, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

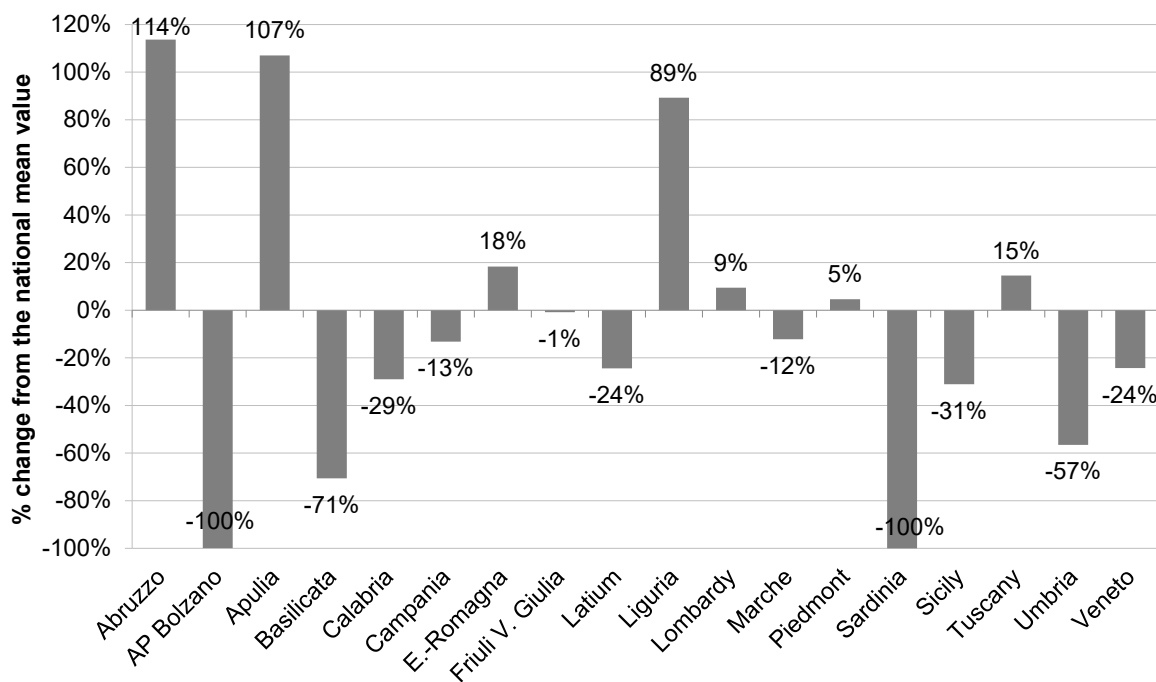


Figure 36. Percentage change from the national mean value of standardized regional demand for extended half-life recombinant Factor IX in 2021 (adapted by the CNS on data from the Traceability information flow)

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 active ingredient contained expressed in IUs.

Table 30. Products containing 3-factor prothrombin complex concentrates currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AICcode	Brand name	IU	Manufacturer	NHS class
023309103	UMANCOMPLEX D.I.*FL 500IU+F20mL	500	KEDRION SpA	A
041850013	KEDCOM*FL 500IU+FL 20mL+SET	500	KEDRION SpA	H
023288032	PROTROMPLEX TIM3*F 600IU+20mL	600	BAXTER AG	A

Table 31. Products containing 4-factor prothrombin complex concentrates currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification and characterisation of the demand

Table 32 shows the total demand and standardised one (expressed in IUs *per capita*) for 3F-PCCs in the two-year period 2020-2021, at both national and regional level.

In 2021 there was a slight increase in the total demand (+4%) compared to 2020; it stood at 36,099,800 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 (Friuli V. Giulia) to 0.9 IU (Emilia-Romagna, Piedmont, Sardinia and Aosta Valley), with a percentage change compared to the Italian mean value of over 50% only for Aosta Valley (+52%) (Figures 37 and 38). In 2021, the national demand for 4F-PCCs was 15,411,400 IUs, equal to 30% of the overall demand for PCCs, with a standardised demand of 0.3 IU *per capita* and with an increase of 36% 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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	377,500	0.3	371,000	0.3	-0.7
AostaValley	98,500	0.8	115,000	0.9	17.6
APBolzano	368,000	0.7	265,500	0.5	-28.2
APTrento	346,500	0.6	332,500	0.6	-3.5
Apulia	2,123,000	0.5	2,289,000	0.6	8.4
Basilicata	161,000	0.3	163,000	0.3	2.8
Calabria	563,500	0.3	705,500	0.4	27.5
Campania	2,139,000	0.4	2,507,000	0.4	19.0
E.-Romagna	3,498,000	0.8	3,774,500	0.9	8.5
Friuli V. Giulia*	704,000	0.6	150,000	0.1	-78.6
Latium	1,634,700	0.3	1,797,500	0.3	10.4
Liguria	1,007,000	0.7	1,272,500	0.8	26.9
Lombardy	6,297,800	0.6	5,901,000	0.6	-5.9
Marche	802,000	0.5	872,000	0.6	9.8
Molise	110,000	0.4	164,000	0.6	52.2
Piedmont	3,302,500	0.8	3,834,500	0.9	17.1
Sardinia	1,875,000	1.2	1,452,500	0.9	-21.5
Sicily	3,323,000	0.7	3,148,000	0.7	-4.5
Tuscany	1,976,000	0.5	2,776,300	0.8	40.5
Umbria	475,000	0.5	332,500	0.4	-29.6
Veneto	3,850,700	0.8	3,876,000	0.8	0.8
Italy	35,032,700	0.6	36,099,800	0.6	3.8

*Data to be confirmed

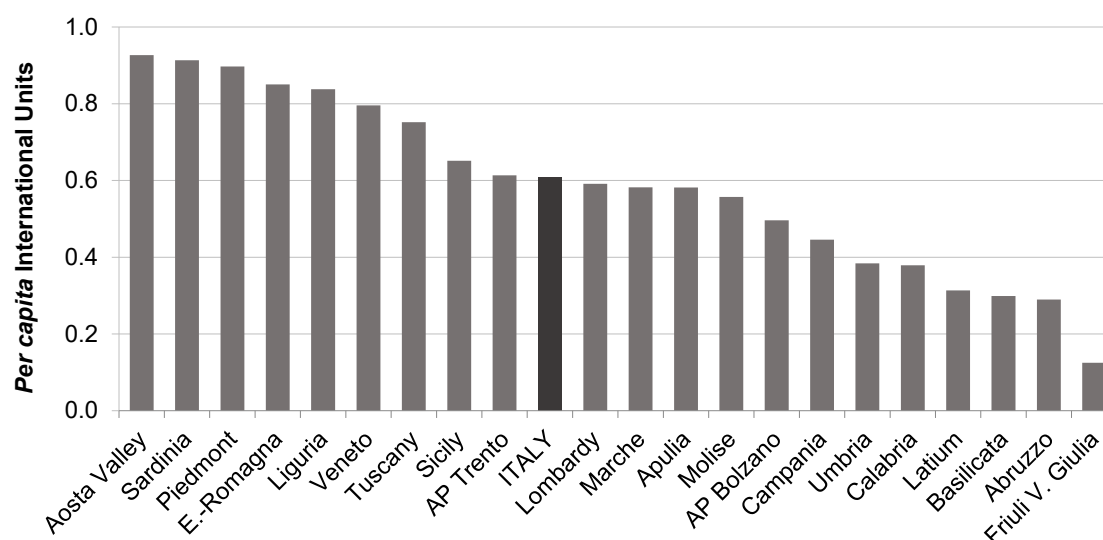


Figure 37. Total and regional demand (public and private) for 3-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

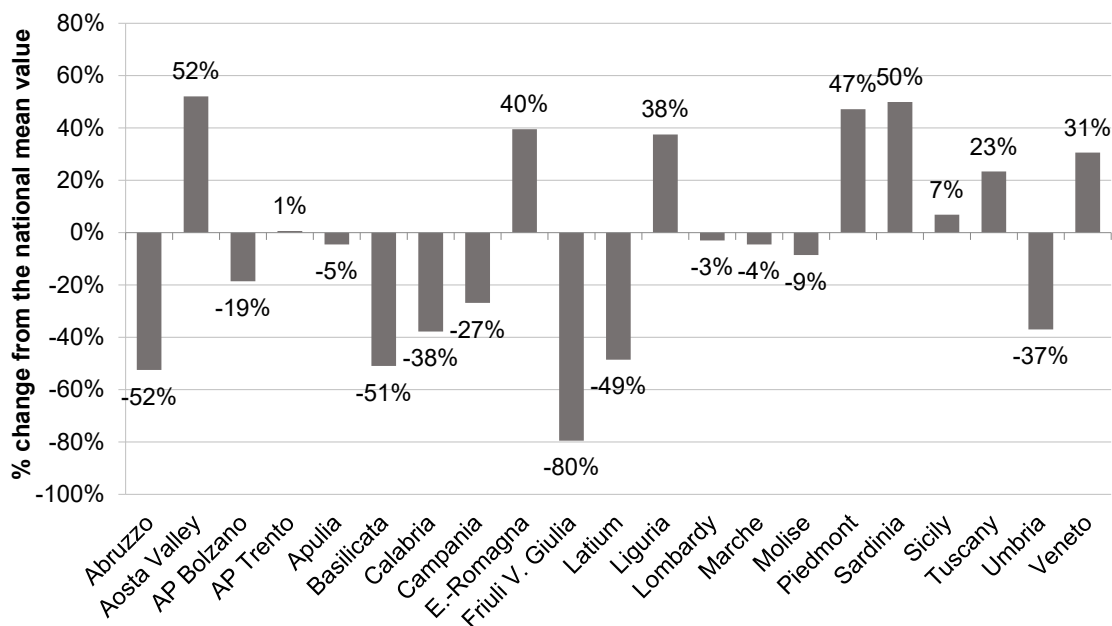


Figure 38. Percentage change from the national mean value of standardised regional demand for 3-factor prothrombin complex concentrates in 2021 (adapted by the CNS on data from the Traceability information flow)

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 2020-2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	575,500	0.4	935,100	0.7	64.1
Aosta Valley	-	0.0	-	0.0	NA
AP Bolzano	562,500	1.1	730,000	1.4	29.2
AP Trento	52,000	0.1	41,000	0.1	-20.7
Apulia	150,500	0.0	205,000	0.1	36.9
Basilicata	180,000	0.3	185,000	0.3	4.3
Calabria	391,000	0.2	267,500	0.1	-30.4
Campania	1,227,000	0.2	1,715,000	0.3	42.0
E.-Romagna	1,093,500	0.2	1,422,000	0.3	30.8
Friuli V. Giulia*	-	0.0	-	0.0	NA
Latium	2,181,000	0.4	3,225,800	0.6	48.6
Liguria	283,000	0.2	649,000	0.4	130.3
Lombardy	980,000	0.1	1,105,000	0.1	13.3
Marche	143,000	0.1	169,500	0.1	19.7
Molise	-	0.0	-	0.0	NA
Piedmont	773,500	0.2	1,032,500	0.2	34.6
Sardinia	735,500	0.5	1,121,000	0.7	54.5
Sicily	584,000	0.1	627,000	0.1	8.3
Tuscany	1,320,500	0.4	1,462,000	0.4	10.7
Umbria	49,000	0.1	282,500	0.3	479.7
Veneto	130,000	0.0	236,500	0.0	82.3
Italy	11,411,500	0.2	15,411,400	0.3	36.0

*Data to be confirmed

Also for 4F-PCCs, there were considerable differences regarding utilisation from one Region to another. With the exception of Calabria and AP of Trento, all the Regions recorded significant increases in the demand. The Region with the highest demand in 2021 was the AP of Bolzano with 1.4 IU *per capita*, followed by Abruzzo and Sardinia with 0.7 IU, Latium with 0.6 UI, Liguria and Tuscany with 0.4 IU *per capita* (Figure 39). Figure 40 shows percentage changes compared to the Italian mean values of the standardised regional demand for 4F-PCCs as recorded by the drug Traceability system in 2021.

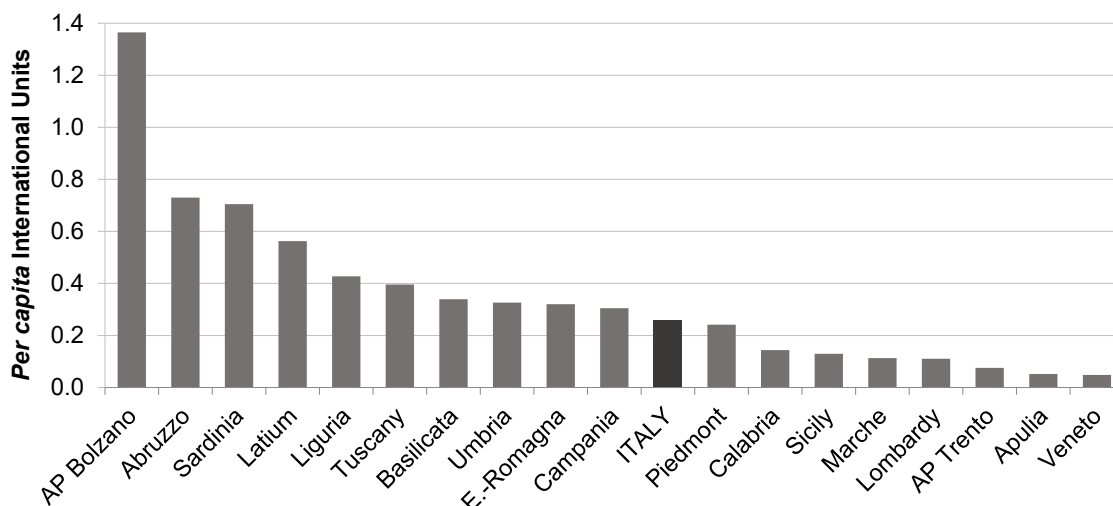


Figure 39. Total and regional demand (public and private) for 4-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2021 (adapted by the CNS on data from the Traceability information flow)

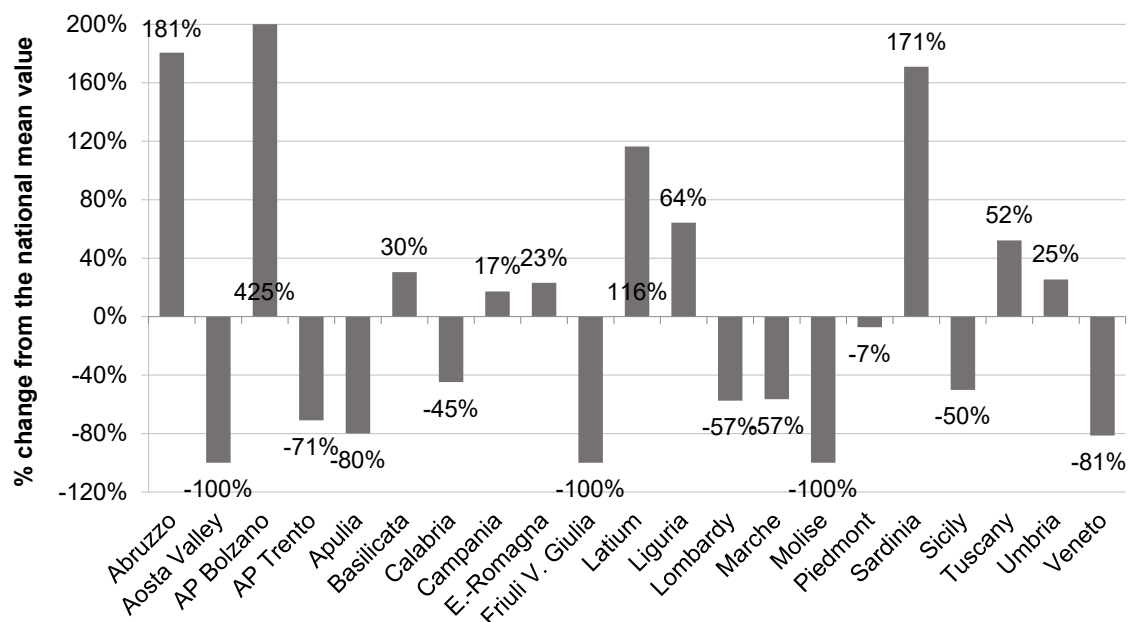


Figure 40. Percentage change from the national mean value of standardised regional demand for 4-factor prothrombin complex concentrates in 2021 (adapted by the CNS on data from the Traceability information flow)

FIBRINOGEN (ATC B02BB01)

Fibrinogen is one of the most present coagulation factors in plasma, with a mean concentration of about 2-4 g/L. It is converted into fibrin by thrombin and is the main component of the coagulation phase. Fibrin, therefore, can be considered both a structural protein and a coagulation factor.

In order to provide adequate structural support, the plasma concentration of fibrinogen must be relatively high. A deficiency of fibrinogen 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 active ingredient they contain expressed in grams (g).

Table 34. Products containing fibrinogen currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AIC code	Brand name	g	Manufacturer	NHS class
*E00178010	HAEMOCOMPLETTAN P 1F 1g	1	CSL BEHRING SpA	H
040170019	RIASTAP FL POLV 1g 20mg/mL	1	CSL BEHRING SpA	C
040170021	RIASTAP*F POLV 1g20mg/mL+DISP	1	CSL BEHRING SpA	C
048798019	FIBRYGA*FLPOLV 1g 100Mm+F50mL	1	OCTAPHARMA ITALY SPA	A
044380018	FIBRICLOTTE*FL POLV 1,5g 100mL	1.5	LFB	C(nn)

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

Quantification of the demand

Table 35 shows the total demand and the total standardised demand (g per 1,000 population) for fibrinogen over the two-year period 2020-2021 at regional and national level.

In 2021, total fibrinogen demand showed a significant increase (+13.4%) compared to the previous year. Its volume of 53,759 g, with a standardised demand of 0.9 g per 1,000 population, confirmed the rapid upward trend. All Regions, with the exception of Abruzzo, Calabria, Campania, Molise, the APs of Bolzano and Trento, Tuscany and Aosta Valley contributed to this growth to different extents.

Figure 41 shows the regional and national standardised demand for fibrinogen in 2021. The Regions with the highest demand per 1,000 population were Veneto (1.6 g) then AP of Bolzano (1.5 g), Umbria (1.4 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 Molise, Aosta Valley, Liguria, Sicily, Piedmont and Lombardy.

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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2020		2021		% Var 2020-2021
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,666	1.3	1,266	1.0	-23.2
Aosta Valley	70	0.6	50	0.4	-28.0
AP Bolzano	1,118	2.1	810	1.5	-27.9
AP Trento	581	1.1	410	0.8	-29.0
Apulia	2,138	0.5	3,069	0.8	44.3
Basilicata	240	0.4	430	0.8	81.8
Calabria	2,792	1.5	1,710	0.9	-37.7
Campania	4,471	0.8	4,356	0.8	-1.1
E.-Romagna	3,491	0.8	4,484	1.0	29.2
Friuli V. Giulia	983	0.8	1,100	0.9	12.3
Latium	5,334	0.9	6,037	1.1	13.7
Liguria	642	0.4	882	0.6	38.0
Lombardy	5,001	0.5	7,101	0.7	42.6
Marche	1,078	0.7	1,125	0.8	5.4
Molise	62	0.2	50	0.2	-17.6
Piedmont	2,462	0.6	3,041	0.7	24.6
Sardinia	1,839	1.1	2,038	1.3	12.3
Sicily	3,126	0.6	3,423	0.7	10.4
Tuscany	3,283	0.9	3,201	0.9	-2.5
Umbria	860	1.0	1,215	1.4	42.0
Veneto	6,482	1.3	7,961	1.6	23.1
Italy	47,719	0.8	53,759	0.9	13.4

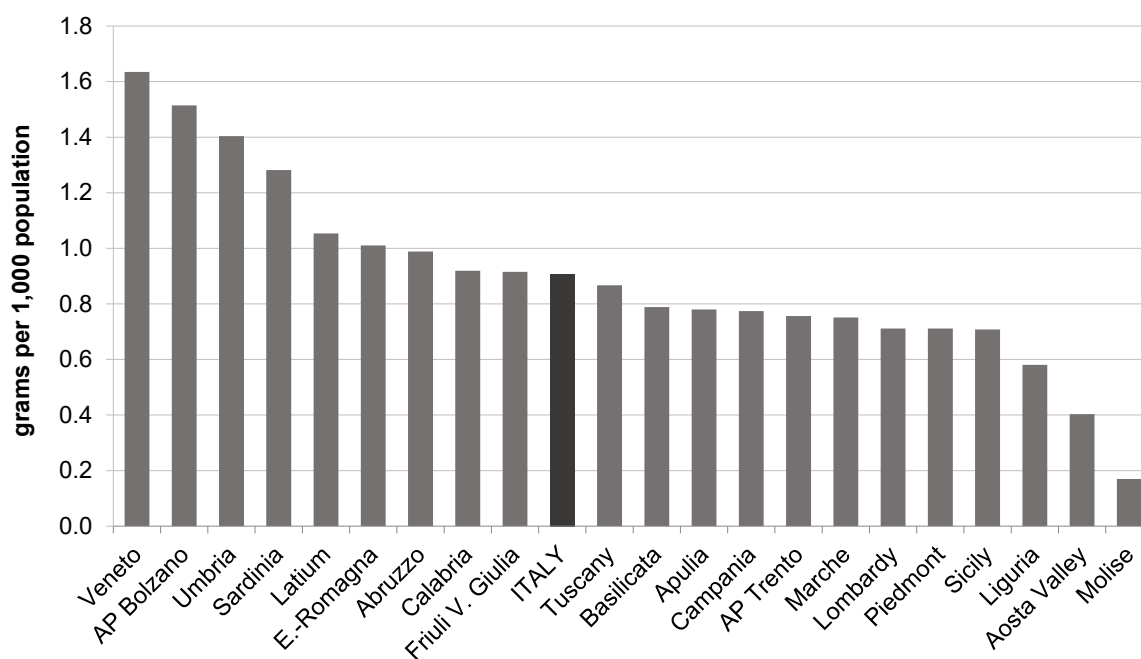


Figure 41. Total and regional demand (public and private) for fibrinogen, expressed in grams per 1,000 population, 2021 (adapted by the CNS on data from the Traceability information flow)

PART B
Other plasma-derived medicinal products

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

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

Table 36. Products containing hepatitis B immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AIC code	Brand name	IU	Manufacturer	NHS class
035561012	NEOHEPATECT*IV 1F 100IU 2mL	100	BIOTEST PHARMA GMBH	H
026415048	VENBIG*1F 500IU+F 10mL+SET	500	KEDRION SpA	H
035561024	NEOHEPATECT*IV 1F 500IU 10mL	500	BIOTEST PHARMA GMBH	H
038059010	KEYVENB*500IU/10mL+SET	500	KEDRION SpA	H
038059034	KEYVENB*50IU/mL" F. CON 500IU	500	KEDRION SpA	H
041985019	VEBIKED*50IU/mL"FL CON 500IU	500	KEDRION SpA	C(nn)
038445019	NIULIVA*250 IU/mL 1SIR 2.4 mL	600	GRIFOLS ITALIA SpA	H
038445021	NIULIVA*INF 1SIR 4mL"250IU/mL	1000	ISTITUTO GRIFOLS S.A.	H
035561036	NEOHEPATECT*IV FL 2000IU 40mL	2000	BIOTEST PHARMA GMBH	H
026415051	VENBIG*F 2500IU/50mL+F 45mL+SET	2500	KEDRION SpA	H
038059022	KEYVENB*2500IU/45mL+SET	2500	KEDRION SpA	H
038059046	KEYVENB*50IU/mL" F 2500IU	2500	KEDRION SpA	H
041985021	VEBIKED*50IU/mL" FL 2500IU+SET	2500	KEDRION SpA	C(nn)
035561048	NEOHEPATECT*IV FL 5000IU 100mL	5000	BIOTEST ITALIA Srl	H
038445033	NIULIVA*INF 1FL 20mL 250IU/mL	5000	GRIFOLS ITALIA SpA	H
038445045	NIULIVA*250IU/mL" 1F. 40mL	10000	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, 31/12/2021)

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

Quantification of the demand

Tables 38 and 39 show respectively the total demand and the total standardised demand (expressed in IUs *per capita*) of hepatitis B IG formulations for IV and for SC/IM use for the two-year period 2020-2021, at national and at regional level. The national demand for hepatitis B IGs for IV use, showed a downward trend (-1.3%) already observed in previous years (34).

The total demand in 2021 was almost 14,4 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	28,000	0.0	22,000	0.0	-20.6
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	1,806,000	0.5	2,021,500	0.5	12.5
Basilicata	2,000	0.0	1,000	0.0	-49.3
Calabria	181,500	0.1	160,000	0.1	-10.3
Campania	3,136,500	0.5	3,133,000	0.6	1.4
E.-Romagna	1,406,000	0.3	1,970,000	0.4	40.9
Friuli V. Giulia	280,000	0.2	245,000	0.2	-12.2
Latium	790,000	0.1	775,000	0.1	-1.5
Liguria	2,500	0.0	98,500	0.1	3,856.4
Lombardy	1,589,500	0.2	1,419,000	0.1	-10.3
Marche	537,500	0.4	362,500	0.2	-31.9
Molise	6,000	0.0	-	-	-100.0
Piedmont	737,500	0.2	532,500	0.1	-27.2
Sardinia	517,000	0.3	665,000	0.4	30.4
Sicily	186,500	0.0	457,500	0.1	147.4
Tuscany	1,070,000	0.3	1,290,000	0.3	20.6
Umbria	-	-	-	-	NA
Veneto	2,379,000	0.5	1,210,000	0.2	-49.0
Italy	14,655,500	0.2	14,362,500	0.2	-1.3

Campania continued to be the Region with the highest demand (0.6 IU *per capita*), followed by Apulia (0.5 IU *per capita*), Emilia-Romagna and Sardinia (0.4 IU *per capita*), which together represent more than 50% of the national demand.

On the other hand, the national demand for antihepatitis B SC/IM IG, shows a strong decrease, equal to -10% of the demand recorded in 2020; the total consumption for 2021 is approximately 63 million IUs (1.1 IUs *per capita*) (Table 39) and accounted 81,4% 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020- 2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	643,240	0.5	591,720	0.5	-7.1
Aosta Valley	250,500	2.0	245,360	2.0	-1.3
AP Bolzano	126,480	0.2	160,760	0.3	26.6
AP Trento	206,620	0.4	223,020	0.4	8.6
Apulia	5,942,960	1.5	5,822,360	1.5	-1.5
Basilicata	302,580	0.5	240,280	0.4	-19.4
Calabria	1,772,060	0.9	1,377,640	0.7	-20.9
Campania	22,464,420	3.9	18,457,980	3.3	-16.6
E.-Romagna	3,868,000	0.9	3,819,340	0.9	-0.7
Friuli V. Giulia	365,220	0.3	297,440	0.2	-18.2
Latium	2,760,600	0.5	2,398,360	0.4	-12.7
Liguria	576,960	0.4	680,840	0.4	18.5
Lombardy	11,264,060	1.1	9,971,940	1.0	-11.1
Marche	681,040	0.5	660,320	0.4	-2.1
Molise	157,560	0.5	181,100	0.6	17.4
Piedmont	5,236,060	1.2	5,138,000	1.2	-1.0
Sardinia	3,506,440	2.2	3,485,820	2.2	0.8
Sicily	3,049,260	0.6	2,976,140	0.6	-1.6
Tuscany	3,939,900	1.1	3,325,880	0.9	-15.6
Umbria	338,180	0.4	399,200	0.5	18.7
Veneto	2,621,000	0.5	2,426,140	0.5	-7.3
Italy	70,073,140	1.2	62,879,640	1.1	-9.7

TETANUS IMMUNOGLOBULINS (ATC J06BB02)

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

Table 40. Products containing tetanus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

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

Quantification of the demand

In 2021 the total demand for tetanus IGs was 117,126,250 IUs (2 IUs *per capita*), showing a decrease of -5% compared to 2020 (Table 41).

The Regions with the highest demand, expressed as standardised volume for the resident population, were Campania (4.1 IUs *per capita*), Abruzzo and Calabria (3.2 IUs *per capita*) and Tuscany (3 IU *per capita*).

In 2021, the demand decreased – in some cases very significantly – in almost all Regions, with the exception of the AP of Trento (+29%), Friuli V. Giulia (+11%), Basilicata (+9%), Emilia-Romagna and Lombardy (+6%), the AP of Bolzano and Molise (+4%) and Piedmont (+2%).

For the year 2021, there were no imports of anti-tetanus IGs under the provisions of DM of 11 February 1997 and DM of 11 May 2001, as it happened in previous years, when were inserted 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacovigilance Office - AIFA)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	4,551,000	3.5	4,157,500	3.2	-7.7
Aosta Valley	366,250	2.9	262,500	2.1	-27.8
AP Bolzano	527,500	1.0	550,250	1.0	3.9
AP Trento	432,000	0.8	552,250	1.0	28.6
Apulia	7,534,000	1.9	6,735,000	1.7	-10.2
Basilicata	1,386,250	2.5	1,492,500	2.7	9.3
Calabria	7,133,250	3.8	5,919,750	3.2	-15.5
Campania	24,272,750	4.2	23,069,750	4.1	-3.5
E.-Romagna	5,711,500	1.3	6,032,500	1.4	6.2
Friuli V. Giulia	418,500	0.3	461,500	0.4	10.7
Latium	10,904,000	1.9	10,239,250	1.8	-5.7
Liguria	3,672,250	2.4	3,537,500	2.3	-3.3
Lombardy	13,497,750	1.3	14,278,250	1.4	6.3
Marche	4,116,000	2.7	3,788,750	2.5	-7.1
Molise	741,750	2.5	751,750	2.6	3.5
Piedmont	4,539,750	1.1	4,584,000	1.1	1.8
Sardinia	4,459,750	2.8	3,570,000	2.2	-18.9
Sicily	12,214,000	2.5	11,362,750	2.4	-6.2
Tuscany	11,929,000	3.2	11,034,500	3.0	-7.5
Umbria	1,646,500	1.9	1,576,500	1.8	-3.7
Veneto	3,304,750	0.7	3,169,500	0.7	-3.9
Not specified Region	888,183	NA	-	-	NA
Italy	124,246,683	2.1	117,126,250	2.0	-5.1

ANTI-D (RH) IMMUNOGLOBULINS (ATC J06BB01)

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

Table 42. Products containing anti-D (Rh) immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification of the demand

The national demand for anti-D GIs between 2020 and 2021 remained broadly stable and stood at 106,277,375 IUs in 2021 (1.8 IUs *per capita*), with the highest peak in the AP of Bolzano and the lowest level in Friuli V. Giulia (3.9 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU <i>per capita</i>	IU	IU <i>per capita</i>	
Abruzzo	2,574,000	2.0	2,374,500	1.9	-6.8
Aosta Valley	295,500	2.4	256,500	2.1	-12.5
AP Bolzano	1,961,000	3.7	2,061,875	3.9	4.7
AP Trento	1,336,750	2.5	1,510,625	2.8	13.7
Apulia	5,895,000	1.5	6,033,000	1.5	2.8
Basilicata	1,004,500	1.8	910,500	1.7	-8.0
Calabria	2,395,250	1.3	2,257,500	1.2	-4.1
Campania	9,901,000	1.7	6,282,000	1.1	-35.6
E.-Romagna	11,124,875	2.5	9,282,250	2.1	-16.1
Friuli V. Giulia	162,000	0.1	195,000	0.2	20.8
Latium	8,421,000	1.5	10,243,500	1.8	22.2
Liguria	2,752,000	1.8	2,748,500	1.8	0.3
Lombardy	22,167,000	2.2	20,886,375	2.1	-5.3

Region	2020		2021		% Var 2020-2021
	IU	IU per capita	IU	IU per capita	
Marche	2,980,500	2.0	2,695,500	1.8	-8.7
Molise	295,000	1.0	273,375	0.9	-5.4
Piedmont	8,081,375	1.9	8,762,625	2.0	9.3
Sardinia	1,347,000	0.8	1,285,500	0.8	-3.3
Sicily	8,497,500	1.7	7,489,500	1.5	-11.1
Tuscany	8,109,875	2.2	8,420,250	2.3	3.8
Umbria	1,702,500	2.0	1,567,500	1.8	-7.4
Veneto	10,415,750	2.1	10,741,000	2.2	3.3
Italy	111,419,375	1.9	106,277,375	1.8	-4.0

CYTOMEGALOVIRUS IMMUNOGLOBULINS (ATC J06BB09)

Table 44 shows the brand names of medicinal products containing cytomegalovirus immunoglobulins (anti-CMV IGs) currently available on the Italian market and the amount of active ingredient they contain expressed in 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, 31/12/2021)

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

Quantification of the demand

Table 45 shows the total demand and the total standardised demand (*U per capita*) for CMV IGs for the two-year period 2020-2021, 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	U	U per capita	U	U per capita	
Abruzzo	521,000	0.4	22,000	0.0	-95.7
Aosta Valley	9,000	0.1	-	-	-100.0
AP Bolzano	87,000	0.2	9,000	0.0	-89.7
AP Trento	-	-	-	-	NA
Apulia	280,000	0.1	894,000	0.2	220.9
Basilicata	100,000	0.2	62,000	0.1	-37.1
Calabria	80,000	0.0	525,000	0.3	568.1
Campania	251,000	0.0	767,000	0.1	210.4
E.-Romagna	866,000	0.2	1,770,000	0.4	105.5
Friuli V. Giulia	1,092,000	0.9	1,825,000	1.5	67.8
Latium	690,000	0.1	351,000	0.1	-48.9
Liguria	61,000	0.0	35,000	0.0	-42.4
Lombardy	1,148,000	0.1	1,971,000	0.2	72.5
Marche	258,000	0.2	300,000	0.2	17.4

Region	2020		2021		% Var 2020-2021
	U	U per capita	U	U per capita	
Molise	-	-	-	-	NA
Piedmont	2,582,000	0.6	1,607,000	0.4	-37.2
Sardinia	25,000	0.0	-	-	-100.0
Sicily	422,000	0.1	656,000	0.1	56.8
Tuscany	329,000	0.1	557,000	0.2	69.3
Umbria	8,000	0.0	24,000	0.0	201.6
Veneto	3,881,000	0.8	3,080,000	0.6	-20.5
Italy	12,690,000	0.2	14,455,000	0.2	14.7

During the period under examination, the CMV IGs national demand increased by 15% compared to the previous year and stood at 14,455,000 U. However, the national average showed strong fluctuations and trends varied from one Region to another; Friuli V. Giulia was the Region with the highest standardized demand (1.5 U per capita), followed by Veneto (0.6 U per capita), Piedmont and Emilia-Romagna (0.4 U per capita).

VARICELLA/ZOSTER IMMUNOGLOBULINS FOR INTRAVENOUS USE (ATC J06BB03)

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

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

Table 46. Products containing specific varicella/zoster immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

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

Quantification of the demand

Table 47 shows the total demand and the total standardised demand (IUs per 1,000 population) of specific IG anti-Var zoster (IV) in the two-year period 2020-2021, at national and regional levels. The national demand for IG anti-Var showed a sharp increase (+61%). Total demand in 2021 was 111,000 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 2020 and 2021 (adapted by the CNS on data from the Product Quality and Pharmacrime Office - AIFA)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	5,000	3.9	6,250	4.9	26.3
Aosta Valley	-	-	-	-	NA
AP Bolzano	2,500	4.7	3,750	7.0	49.4
AP Trento	2,625	4.8	-	0.0	-100.0
Apulia	15,000	3.8	8,500	2.2	-43.1
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	1,500	0.3	125	0.0	-91.5
Emilia-Romagna	8,750	2.0	10,125	2.3	16.4
Friuli V. Giulia	-	0.0	18,625	15.5	100.0
Latium	2,875	0.5	9,125	1.6	218.8
Liguria	500	0.3	2,250	1.5	351.9

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Lombardy	10,625	1.1	22,875	2.3	116.3
Marche	4,625	3.1	21,000	14.0	358.4
Molise	-	-	-	-	NA
Piedmont	7,125	1.7	625	0.1	-91.2
Sardinia	250	0.2	125	0.1	-49.3
Sicily	-	-	-	-	NA
Tuscany	3,125	0.8	2,750	0.7	-12.0
Umbria	-	-	2,625	3.0	100.0
Veneto	5,000	1.0	2,250	0.5	-54.9
Italy	69,500	1.2	111,000	1.9	60.8

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, 31/12/2021)

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

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

Quantification of the demand

In 2021, the total demand for rabies IGs, recorded in eleven Regions, showed a remarkable decrease compared to 2020 (-19%). The total demand amounted to 108,150 IUs (1.8 IUs per 1,000 population) (Table 49).

Table 49. Total demand (public and private) and total standardised demand for rabies immunoglobulin, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2020 and 2021 (adapted by the CNS on data from the Product Quality and Pharmacrime Office – AIFA)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop.	IU	IU per 1,000 pop.	
Abruzzo	-	-	-	-	NA
Aosta Valley	6,000	48.0	3,000	24.2	-49.6
AP Bolzano	2,100	3.9	8,250	15.4	291.2
AP Trento	-	-	-	-	NA
Apulia	600	0.2	2,850	0.7	377.4
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	28,350	6.4	11,100	2.5	-60.6
Friuli V. Giulia	46,650	38.7	49,800	41.4	7.2
Latium	-	-	2,400	0.4	100.0
Liguria	-	-	-	-	NA
Lombardy	40,350	4.0	1,500	0.2	-96.3
Marche	750	0.5	2,250	1.5	202.9
Molise	-	-	-	-	NA
Piedmont	-	-	5,100	1.2	100.0
Sardinia	-	-	-	-	NA

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop.	IU	IU per 1,000 pop.	
Sicily	-	-	-	-	NA
Tuscany	-	-	2,400	0.6	100.0
Umbria	-	-	-	-	NA
Veneto	10,050	2.1	19,500	4.0	94.4
Italy	134,850	2.3	108,150	1.8	-19.3

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

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

Table 50. Products containing local haemostatics-combinations currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AIC code	Brand name	mL	Manufacturer	NHS class
035941018	BERIPLAST P*FL POLV 0,5mL+FL	0.5	CSL BEHRING GmbH	C
035941020	BERIPLAST P*FL POLV 1mL+FL+SET	1	CSL BEHRING GmbH	C
035941032	BERIPLAST P*FL POLV 3mL+FL+SET	3	CSL BEHRING GmbH	C
039546015	ARTISS SOL. ADESIVO TISSUTALE	1	BAXTER SpA	H
039546078	ARTISS*1SIR 1mL+1mL	1	BAXTER SpA	C
025243179	TISSEEL 2ml ADESIVO TISSUTALE	2	BAXTER SpA	H
039546027	ARTISS SOL. ADESIVO TISSUTALE	2	BAXTER SpA	H
039546080	ARTISS*1SIR 2mL+2mL	2	BAXTER SpA	C
039591019	EVICEL*2FL 1ml 90mg/ml+1200IU	2	OMRIX BIOPHARMA	H
042046019	SILKETAL 2,5ml ADESIVO TISSUTALE	2.5	KEDRION SpA	C
044152015	KOLFIB*FL POLV SOLV 2,5mL	2.5	KEDRION SpA	C
025243181	TISSEEL 4mL ADESIVO TISSUTALE	4	BAXTER SpA	H
039591021	EVICEL*2FL 2mL 90mg/mL+1200IU	4	OMRIX BIOPHARMA	H
039546039	ARTISS SOL. ADESIVO TISSUTALE	5	BAXTER SpA	H
039546092	ARTISS*1SIR 5mL+5mL	5	BAXTER SpA	C
042046021	SILKETAL 5ml ADESIVO TISSUTALE	5	KEDRION SpA	C
044152027	KOLFIB*FL POLV SOLV 5mL	5	KEDRION SpA	C
025243193	TISSEEL 10ml ADESIVO TISSUTALE	10	BAXTER SpA	H
039591033	EVICEL*2FL 5ml 90mg/mL+1200IU	10	OMRIX BIOPHARMA	H
042046033	SILKETAL 10ml ADESIVO TISSUTALE	10	KEDRION SpA	C
044152039	KOLFIB*FL POLV SOLV 10mL	10	KEDRION SpA	C
sponges				
036557015	TACHOSIL*1SPUGNA 9,5cmx4,8cm	1	TAKEDA ITALY SpA	C
036557039	TACHOSIL*1MATRICE 3 cmx2,5 cm	1	TAKEDA GmbH	C
036557054	TACHOSIL*1MATRICE 4,8cmx4,8cm	1	TAKEDA ITALY SpA	C
043011016	EVARREST*1BUST 8,1mg+40IU/cm ²	1	OMRIX BIOPHARMA	C
036557027	TACHOSIL*2SPUGNE 4,8cmx4,8cm	2	TAKEDA ITALY SpA	C
043011028	EVARREST*2BUST 8,1mg+40IU/cm ²	2	OMRIX BIOPHARMA	C
036557041	TACHOSIL*5MATRICI 3 cm X 2,5 cm	5	TAKEDA GmbH	C

Quantification of demand

The various products with an ATC code related to local haemostatics–combinations despite not always having the same composition, they can still be considered equivalent, their active ingredient is expressed in mL and mL per 1,000 population (Table 51). 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). In 2021, the total demand for local haemostatics-combinations reached a volume of about 284,635 mL (4.8 mL per 1,000 population), recording a notable increase (+15%) compared to the volume of 2020 (Table 51). In 2021, the total demand for local haemostatics–combinations, expressed in number of gelatin

sponges, also appeared to increase significantly compared to the previous year (+16%) and amounted to 41,768 sponges (Table 52).

Table 51. Total demand (public and private) and total standardised demand for local haemostatics-combinations, expressed in millilitres and in millilitres per 1,000 population, and variations in percentage between 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	7,632	5.9	8,925	7.0	18.1
Aosta Valley	404	3.2	324	2.6	-19.2
AP Bolzano	2,073	3.9	2,180	4.1	4.7
AP Trento	2,472	4.5	3,054	5.6	24.3
Apulia	17,688	4.5	17,518	4.5	-0.5
Basilicata	3,190	5.8	3,078	5.6	-2.1
Calabria	5,232	2.8	4,928	2.6	-4.1
Campania	36,177	6.3	45,785	8.1	28.5
Emilia-Romagna	12,056	2.7	13,492	3.0	12.5
Friuli V. Giulia	3,150	2.6	2,972	2.5	-5.3
Latium	27,688	4.8	27,654	4.8	0.3
Liguria	4,814	3.2	5,652	3.7	17.9
Lombardy	44,909	4.5	52,570	5.3	17.6
Marche	4,278	2.8	5,362	3.6	26.5
Molise	510	1.7	1,020	3.5	104.2
Piedmont	14,030	3.3	15,834	3.7	13.8
Sardinia	5,422	3.4	6,564	4.1	22.7
Sicily	16,784	3.4	19,390	4.0	16.5
Tuscany	15,337	4.2	20,366	5.5	32.8
Umbria	3,674	4.2	3,500	4.0	-4.2
Veneto	22,469	4.6	24,467	5.0	9.1
Italy	249,989	4.2	284,635	4.8	14.6

Table 52. Total demand (public and private) for local haemostatics-combinations, expressed in number of gelatin sponges, and variations in percentage between 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020	2021	% Var 2020-2021
Abruzzo	1,394	1,449	3.9
Aosta Valley	105	222	111.4
AP Bolzano	514	495	-3.7
AP Trento	190	182	-4.2
Apulia	1,978	2,311	16.8
Basilicata	715	852	19.2
Calabria	2,123	2,302	8.4
Campania	4,472	5,030	12.5
Emilia-Romagna	1,331	1,533	15.2
Friuli V. Giulia	1,035	980	-5.3
Latium	2,523	3,037	20.4
Liguria	475	662	39.4
Lombardy	5,711	7,423	30.0
Marche	1,315	1,436	9.2
Molise	6	4	-33.3
Piedmont	2,830	3,646	28.8
Sardinia	510	383	-24.9
Sicily	2,719	2,722	0.1
Tuscany	2,856	3,667	28.4
Umbria	800	868	8.5
Veneto	2,486	2,564	3.1
Italy	36,088	41,768	15.7

COAGULATION FACTOR VII (ATC B02BD05)

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

Table 53. Products containing Factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification of the demand

In 2021, the total demand and the total standardised national demand for FVII was approximately 5 million IUs, substantially stable compared to 2020 (+1%) (Table 54).

Despite this, a substantial increases were recorded in Abruzzo (+195%) and in Campania (+40%). In 2021, 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	108,000	83.5	315,000	245.9	194.6
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	378,600	95.8	252,000	64.1	-33.1
Basilicata	45,600	82.4	42,000	77.0	-6.5
Calabria	53,400	28.2	27,000	14.5	-48.5
Campania	270,000	47.3	373,200	66.4	40.4
E.-Romagna	120,600	27.0	133,800	30.1	11.6
Friuli V. Giulia	-	-	-	-	NA
Latium	1,594,200	277.0	1,552,200	270.9	-2.2
Liguria	46,800	30.7	36,600	24.1	-21.5
Lombardy	1,352,400	134.9	1,590,600	159.4	18.2
Marche	1,200	0.8	1,200	0.8	1.0
Molise	541,800	1802.9	309,600	1052.0	-41.6
Piedmont	231,000	53.6	260,400	60.9	13.7
Sardinia	-	-	-	-	NA
Sicily	285,600	58.6	174,000	36.0	-38.6
Tuscany	18,600	5.0	15,600	4.2	-16.1
Umbria	3,600	4.1	4,200	4.9	17.3
Veneto	14,400	3.0	-	-	-100.0
Italy	5,065,800	84.9	5,087,400	85.9	1.1

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 active ingredient they contain, expressed in milligrams (mg).

Table 55. Products containing recombinant activated Factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AIC code	Brand name	mg	Manufacturer	NHS class
029447048	NOVOSEVEN*IV 1mg(50KIU)+1,1mL	1	NOVO NORDISK SpA	H
029447087	NOVOSEVEN*IV 1mg(50KIU)+1mL	1	NOVO NORDISK SpA	H
029447012	NOVOSEVEN*IV 1,2mg(60KIU)+2,2mL	1.2	NOVO NORDISK SpA	H
029447051	NOVOSEVEN*IV 2mg(100KIU)+2,1mL	2	NOVO NORDISK SpA	H
029447099	NOVOSEVEN*IV 2mg(100KIU)+2mL	2	NOVO NORDISK SpA	H
029447024	NOVOSEVEN*IV 2,4mg(120 KIU)	2.4	NOVO NORDISK SpA	H
029447036	NOVOSEVEN*IV 4,8 mg(240 KIU)	4.8	NOVO NORDISK SpA	H
029447063	NOVOSEVEN*IV 5mg(250KIU)+5,2mL	5	NOVO NORDISK SpA	H
029447101	NOVOSEVEN*IV 5mg(250KIU)+5mL	5	NOVO NORDISK SpA	H
029447075	NOVOSEVEN*IV8mg (400KIU)+8,1mL	8	NOVO NORDISK SpA	H
029447113	NOVOSEVEN*IV 8mg(400KIU)+8mL	8	NOVO NORDISK SpA	H

Quantification of the demand

Table 56 shows the total demand (mg) and the total standardised demand (mg per 1,000 population) of rFVIIa over the two-year period 2020-2021, at national and regional level. The total demand for rFVIIa recorded in 2021 was 55,895 mg (0.9 mg per 1,000 population) with a marked decrease compared to 2020 (-28%).

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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Abruzzo	501	0.4	164	0.1	-66.9
Aosta Valley	-	-	4,0	0.0	100.0
AP Bolzano	1,135	2.1	-	0.0	-100.0
AP Trento	62	0.1	412	0.8	568.5
Apulia	8,277	2.1	12,782	3.2	55.2
Basilicata	9	0.0	13	0.0	46.6
Calabria	4,643	2.5	3,490	1.9	-23.5
Campania	18,217	3.2	3,607	0.6	-79.9
E.-Romagna	2,862	0.6	4,404	1.0	54.8
Friuli V. Giulia	8,064	6.7	781	0.7	-90.3
Latium	5,236	0.9	1,407	0.2	-73.0

Region	2020		2021		% Var 2020-2021
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Liguria	123	0.1	1,988	1.3	1,523.0
Lombardy	3,846	0.4	5,935	0.6	55.0
Marche	1,338	0.9	622	0.4	-53.1
Molise	258	0.9	76	0.3	-69.9
Piedmont	2,154	0.5	3,737	0.9	75.0
Sardinia	83	0.1	327	0.2	299.3
Sicily	3,986	0.8	1,898	0.4	-52.0
Tuscany	9,731	2.6	10,628	2.9	9.2
Umbria	25	0.0	229	0.3	821.0
Veneto	7,411	1.5	3,391	0.7	-54.2
Italy	77,961	1.3	55,895	0.9	-27.8

FACTOR VIII INHIBITOR BYPASSING ACTIVITY (ATC B02BD03)

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

Table 57. Products containing Factor VIII inhibitor bypassing activity currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AIC code	Brand name	FU	Manufacturer	NHS class
024744043	FEIBA*IV FL 500IU+F 20mL	500	BAXALTA ITALY Srl	A
024744068	FEIBA*FL 500FU+BAXJECT II HF	500	BAXALTA ITALY Srl	A
024744056	FEIBA TIM3*IV FL 1000IU+F 20mL	1000	BAXTER AG	A
024744070	FEIBA*FL 1000FU+BAXJECT II HF	1000	BAXTER AG	A

Quantification of the demand

Table 58 shows the total demand and the total standardised demand (FUs *per capita*) of Factor VIII inhibitor bypassing activity, or aPCCs, over the two-year period 2020-2021 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	FU	FU <i>per capita</i>	FU	FU <i>per capita</i>	
Abruzzo	1,084,000	0.8	1,252,000	1.0	16.7
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	2,000	0.0	194,000	0.0	9,648.2
Basilicata	-	-	-	-	NA
Calabria	-	-	136,000	0.1	100.0
Campania	993,000	0.2	1,302,000	0.2	33.2
E.-Romagna	523,000	0.1	66,000	0.0	-87.3
Friuli V. Giulia	858,000	0.7	175,000	0.1	-79.5
Latium	793,000	0.1	103,000	0.0	-87.0
Liguria	15,000	0.0	128,000	0.1	756.9
Lombardy	1,895,000	0.2	1,534,000	0.2	-18.7
Marche	-	-	243,000	0.2	100.0
Molise	-	-	-	-	NA
Piedmont	290,000	0.1	195,000	0.0	-32.2
Sardinia	285,000	0.2	316,000	0.2	12.4
Sicily	2,047,000	0.4	463,000	0.1	-77.2
Tuscany	867,000	0.2	118,000	0.0	-86.4
Umbria	-	-	-	-	NA
Veneto	242,000	0.0	350,000	0.1	44.9
Italy	9,894,000	0.2	6,575,000	0.1	-33.1

In 2021, the national demand for aPCCs was in sharp decline compared to the previous year (-33%), with some regional variability. Its total volume was 6,575,000 FUs (0.1 FUs *per capita*).

ALPHA-1-PROTEINASE INHIBITOR (ATC B02AB02)

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

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

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

Table 59. Products containing alpha-1-proteinase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

AIC code	Brand name	mg	Manufacturer	NHS class
037709019	PROLASTIN*EV 1F 1g/40mL+F40mL	1000	GRIFOLS ITALIA SpA	H
044479018	RESPREEZA*EV 1FL 20mL+SOL 1g	1000	CSL BEHRING GmbH	H
046292013	PLITALFA*EV 1F 1000MG/40ML	1000	GRIFOLS Italia SpA	C(nn)
037709021	PROLASTIN*EV 4F 1g/40mL+F40mL	4000	INST. GRIFOLS S.A.	C(nn)
044479020	RESPREEZA*EV 1FL 76mL + 4g+SET	4000	CSL BEHRING GmbH	C(nn)
044479032	RESPREEZA*EV 1FL 95mL+ 5g+ SET	5000	CSL BEHRING GmbH	H

Quantification of the demand

In 2021, the total demand for alpha-1-antitrypsin was 58,492 g (1.0 g per 1,000 population) recording a significant upward trend compared to the previous year (+ 13.4%) (Table 55). In particular in Marche, Umbria and Molise the demand exceeded the value recorded in the previous year (+90%, +78% and +63%, 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).

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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,557	1.2	1,819	1.4	18.0
Aosta Valley	997	8.0	957	7.7	-3.3
AP Bolzano	2,650	5.0	3,249	6.1	22.1
AP Trento	636	1.2	578	1.1	-8.6
Apulia	1,768	0.4	2,254	0.6	28.1
Basilicata	-	-	-	-	NA
Calabria	1,028	0.5	1,420	0.8	40.6
Campania	6,679	1.2	6,866	1.2	4.4

Region	2020		2021		% Var 2020-2021
	g	g per 1,000 pop	g	g per 1,000 pop	
E.-Romagna	3,024	0.7	3,376	0.8	12.3
Friuli V. Giulia	2,000	1.7	2,035	1.7	2.1
Lazio	3,084	0.5	3,860	0.7	25.7
Liguria	1,803	1.2	2,099	1.4	16.9
Lombardy	9,152	0.9	8,834	0.9	-3.0
Marche	223	0.1	420	0.3	90.2
Molise	30	0.1	48	0.2	63.4
Piedmont	3,153	0.7	3,984	0.9	27.4
Sardinia	4,322	2.7	4,918	3.1	15.3
Sicily	3,072	0.6	4,251	0.9	39.6
Tuscany	2,822	0.8	3,381	0.9	19.8
Umbria	320	0.4	565	0.7	77.5
Veneto	3,592	0.7	3,578	0.7	-0.2
Italy	51,912	0.9	58,492	1.0	13.4

PLASMA-DERIVED C1-ESTERASE INHIBITOR (ATC B06AC01)

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

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

Table 61. Products containing human C1 esterase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification of the demand

In 2021, the total demand for C1 esterase inhibitor was 13,198,500 IUs (223 IUs per 1,000 population), and was substantially stable compared to the previous year (+0.2%) (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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	170,000	131.4	309,000	241.2	83.6
Aosta Valley	128,500	1,027.7	57,500	463.4	-54.9
AP Bolzano	22,000	41.3	90,000	168.3	307.4
AP Trento	29,500	54.1	10,500	19.4	-64.2
Apulia	734,500	185.8	668,500	169.9	-8.5
Basilicata	77,500	140.1	55,000	100.9	-28.0
Calabria	888,000	468.8	685,000	368.2	-21.5
Campania	2,311,000	404.6	1,880,500	334.4	-17.4
E.-Romagna	431,500	96.7	388,000	87.4	-9.6
Friuli V. Giulia	36,500	30.3	24,500	20.4	-32.6
Latium	2,145,000	372.7	2,372,500	414.0	11.1
Liguria	21,000	13.8	23,500	15.5	12.4
Lombardy	1,993,000	198.8	1,609,000	161.2	-18.9
Marche	333,500	220.5	187,500	125.1	-43.2
Molise	1,000	3.3	11,500	39.1	1,074.3

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Piedmont	613,500	142.3	1,001,000	234.2	64.5
Sardinia	582,000	361.1	612,000	384.9	6.6
Sicily	1,232,500	252.8	1,350,500	279.4	10.5
Tuscany	463,000	125.4	564,000	152.7	21.8
Umbria	235,000	270.1	265,500	306.8	13.6
Veneto	814,500	166.9	1,033,000	212.1	27.1
Italy	13,263,000	222.4	13,198,500	222.8	0.2

An exceptional variability in standardised regional demands was observed, with maximum volumes in the Aosta Valley, Latium, Sardinia and Calabria (463, 414, 385 and 368 IUs per 1,000 population, respectively) and minimum volumes in Liguria, in the AP of Trento, Friuli V. Giulia and Molise (range: 15 – 39 IUs per 1,000 population). In Basilicata, Calabria, Campania, Emilia-Romagna, Friuli V. Giulia, Lombardy, Marche, AP of Trento and Apulia the demand was decreasing. In the remaining Regions there is an increase in the demand for C1 inhibitor, particularly evident in Molise (+ 1.074%).

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 active ingredient they contain, expressed in IUs.

Table 63. Products containing coagulation Factor X currently available on the Italian market (adapted by the CNS on data from Farmadati and the Product Quality and Pharmacrime Office- AIFA, 31/12/2021)

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

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

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

Quantification of the demand

Products containing FX concentrates are used exclusively in Lombardy, where in 2021 the demand was for 48,000 IUs (5 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 2020 and 2021 (adapted by the CNS on data from Product Quality and Pharmacrime Office-AIFA)

Region	2020		2021		Var % 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Lombardy	60,000	6.0	48,000	4.8	-19,6
ITALY	60,000	1.0	48,000	0.8	-19,5

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, 31/12/2021)

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

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

Quantification of the demand

In 2021, the demand for FXI was 14,000 IUs (0.2 IU per 1,000 population) significantly lower than 2020 (Table 66). Demand was observed only in two Italian Regions: Veneto 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 2020 and 2021 (adapted by the CNS on data from the Product Quality and Pharmacrime Office-AIFA)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	2,000*	0.5	-	-	-100.0
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	2,000*	0.4	-	-	-100.0
Friuli V. Giulia	19,333*	16.0	10,000	8.3	-48.1
Latium	2,667*	0.5	-	-	-100.0
Liguria	-	-	-	-	NA
Lombardy	-	-	-	-	NA
Marche	-	-	-	-	NA

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Molise	-	-	-	-	NA
Piedmont	3,333*	0.8	-	-	-100.0
Sardinia	-	-	-	-	NA
Sicily	2,667*	0.5	-	-	-100.0
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	2,667*	0.5	4,000	0.8	50.3
Italy	34,667	0.6	14,000	0.2	-59.3

*estimated values

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 active ingredient they contain, expressed in IUs.

Table 67. Products containing plasma-derived coagulation Factor XIII distributed in Italy (adapted by the CNS on data from Farmadati, 31/12/2021)

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

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

Table 68. Products containing recombinant coagulation Factor XIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification of the demand

In 2021, the total demand for FXIII was 807,250 IUs (13.6 IUs per 1,000 population) and less than half, equal to 329,750 IUs (5.6 IUs per 1,000 population), was for pdFXIII. The latter recorded a decrease of -3% compared to 2020 (Table 69). In 2021, there was no utilisation of FXIII in some Regions. The highest demand for Factor XIII of plasma origin was in Emilia-Romagna, AP of Trento and AP of Bolzano (22 IUs, 21 IUs and 16 IUs per 1,000 population respectively). While in Abruzzo, Basilicata and Calabria rFXIII was used exclusively (Table 70).

In Latium, Marche, AP of Bolzano, AP of Trento 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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow and the Product Quality and Pharmacrime Office-AIFA)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	1,000	0.8	-	-	-100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	8,750	16.4	100.0
AP Trento	9,750	17.9	11,250	20.8	16.1
Apulia	-	-	-	-	NA
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	125,000	28.0	99,250	22.4	-20.1
Friuli V. Giulia	-	-	-	-	NA
Latium	52,500	9.1	41,250	7.2	-21.1
Liguria	-	-	20,000	13.2	100.0
Lombardy	40,000	4.0	26,250	2.6	-34.1
Marche	6,500	4.3	10,750	7.2	67.0
Molise	-	-	-	-	NA
Piedmont	14,250	3.3	11,250	2.6	-20.4
Sardinia	-	-	-	-	NA
Sicily	4,500	0.9	-	-	-100.0
Tuscany	23,500	6.4	24,500	6.6	4.2
Umbria	-	-	-	-	NA
Veneto	65,500	13.4	76,500	15.7	17.0
Italy	342,500	5.7	329,750	5.6	-3.1

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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow and the Product Quality and Pharmacrime Office, AIFA)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	45,000	34.8	67,500	52.7	51.5
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	30,000	54.2	32,500	59.6	9.9
Calabria	150,000	79.2	170,000	91.4	15.4
Campania	-	-	-	-	NA
E.-Romagna	-	-	20,000	4.5	100.0
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	65,000	42.6	67,500	44.5	4.3
Lombardy	52,500	5.2	90,000	9.0	72.2
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	22,500	5.2	10,000	2.3	-55.2
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	17,500	3.6	20,000	4.1	14.5
Italy	382,500	6.4	477,500	8.1	25.7

PROTEIN C (ATC B01AD12)

Protein C is one of the most important factors of the anticoagulant system along with AT and protein S. It is a vitamin K-dependent serine-protease produced by the liver, which is indicated in purpura fulminans and in patients with severe congenital deficiencies. The mean concentration of protein C in plasma is approximately 3-5 µg / mL (47).

Table 71 shows the brand names of medicinal products containing protein C currently available on the Italian market and the amount of active ingredient they contain, expressed in IUs.

Table 71. Products containing protein C currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification of the demand

In 2021, the national demand for protein C stood at a volume of 379,500 IUs (6.4 IUs per 1,000 population) with a decrease of 41% compared to 2020 (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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	4,000	3.1	5,500	4.3	38.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	11,000	2.8	-	-	-100.0
Basilicata	-	-	-	-	NA
Calabria	197,000	104.0	179,500	96.5	-7.2
Campania	151,000	26.4	70,500	12.5	-52.6
E.-Romagna	4,000	0.9	2,000	0.5	-49.7
Friuli V. Giulia	-	-	-	-	NA
Latium	48,500	8.4	22,000	3.8	-54.4
Liguria	59,000	38.7	-	-	-100.0
Lombardy	71,500	7.1	52,000	5.2	-26.9
Marche	12,000	7.9	5,000	3.3	-57.9
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	29,000	18.0	-	-	-100.0
Sicily	31,500	6.5	29,000	6.0	-7.1
Tuscany	3,000	0.8	500	0.1	-83.3
Umbria	8,000	9.2	6,000	6.9	-24.6
Veneto	16,500	3.4	7,500	1.5	-54.5
Italy	646,000	10.8	379,500	6.4	-40.9

The highest regional demand was recorded in Calabria and Campania, with 96.5 and 12.5 IUs per 1,000 population respectively.

The lowest regional demand was in Tuscany, Emilia-Romagna and Veneto with volumes between 0.1 and 1.5 IUs per 1,000 population.

OTHER PLASMA PROTEIN FRACTIONS (ATC B05AA02)

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

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

- high 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 active ingredient they contain, expressed in millilitres (mL).

Table 73. Products containing other plasma protein fractions currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2021)

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

Quantification of the demand

As regards the different composition and different clinical use, the demands of these two sub-groups of medicinal products have been quantified distinctly. Table 74 shows the utilisation of Plasmasafe™ and Octaplas™, while Table 75 illustrates the data related to Umanserum™, the demand for which, in 2021, recorded an increase of +28%, and a total volume of 8,301,000 mL.

The national demand for solvent/detergent-treated plasma in 2021 increased by +9% compared to 2020, with remarkable increases at regional level in Umbria (+217%) and in Piedmont (+50%). High decreases in demand were instead recorded in Friuli V. Giulia (-100%) and in Sardinia (-88%).

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 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	10,000	18.3	10,000	18.4	0.6
Apulia	2,814,000	711.8	3,193,000	811.7	14.0
Basilicata	462,000	835.1	510,000	935.6	12.0
Calabria	895,000	472.5	889,600	478.1	1.2
Campania	4,546,600	796.0	4,213,000	749.1	-5.9
E.-Romagna	592,000	132.6	674,000	151.8	14.5
Friuli V. Giulia	20,000	16.6	-	-	-100.0
Latium	4,097,400	711.9	4,060,200	708.5	-0.5
Liguria	545,200	357.5	544,400	358.5	0.3
Lombardy	448,000	44.7	474,000	47.5	6.3
Marche	1,560,000	1,031.3	1,648,000	1,100.0	6.7
Molise	341,200	1,135.4	436,000	1,481.5	30.5
Piedmont	3,562,000	826.2	5,282,000	1,235.6	49.5
Sardinia	106,000	65.8	12,800	8.1	-87.8
Sicily	3,756,200	770.5	3,945,400	816.2	5.9
Tuscany	1,338,000	362.4	1,430,000	387.2	6.9
Umbria	26,000	29.9	82,000	94.7	217.1
Veneto	1,468,000	300.9	1,476,000	303.1	0.7
Italy	26,587,600	445.8	28,880,400	487.5	9.4

Table 75. Total demand (public and private) and total standardised demand for Umanserum™ expressed in millilitres and millilitres per 1,000 population, and variations in percentage between 2020 and 2021 (adapted by the CNS on data from the Traceability information flow)

Region	2020		2021		% Var 2020-2021
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	3,892,500	984.6	5,325,500	1,353.8	37.5
Basilicata	141,250	255.3	105,000	192.6	-24.6
Calabria	268,750	141.9	300,000	161.2	13.6
Campania	-	-	-	-	NA
E.-Romagna	-	-	-	-	NA
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	-	-	-	-	NA
Lombardy	175,000	17.5	138,250	13.9	-20.6
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	-	-	-	-	NA
Sicily	1,952,750	400.5	2,292,250	474.2	18.4
Tuscany	-	-	-	-	NA
Umbria	111,500	128.1	140,000	161.8	26.2
Veneto	-	-	-	-	NA
Italy	6,541,750	109.7	8,301,000	140.1	27.8

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

SELF-SUFFICIENCY

According to Italian legislation, the term PDMP self-sufficiency refers to the capacity of regional health systems (through agreements signed by several or by single Regions) to 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 Law 219/2005.

It 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 Legislative Decree of 20 December 2007, 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 companies, which operate as service providers, is considered a “toll fractionation process” and constitutes a contract agreement for the production of PDMPs.

The acquisition of toll fractionation processes is carried out through a tender procedure in compliance with current legislation. For this purpose, during 2015 and 2016, in addition to the Lombardy-Piedmont-Sardinia Agreement (LPS) 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), the production of PDMPs is defined by a quali-quantitative production plan. The company in question agrees to produce the quantity and to guarantee the quality of the PDMPs requested by the Regions complying with the schedules and the established procedures.

The contracting Regions, in turn, undertake to make available the necessary plasma according to agreed quantities and quality specifications. The Regions have the right to full ownership of the plasma sent for industrial processing, of all the pharmaceutical specialties derived from it, as well as of the residual material. Consequently, the supplier of the industrial processing service cannot use the plasma, the intermediate fractions or the finished products nor the residual raw material for purposes other than those provided for under the agreement, without a prior agreement with the Regions. For the purposes of the tender notice, the abovementioned DM states that the production of at least human albumin, FVIII and IV IGs has to be taken into consideration. In other words, these three PDMPs must be included in the company's offer while all the other PDMPs are to be considered as optional.

Pursuant to the DM of 5 December 2014, the only companies authorized to fractionate national plasma are Baxter Manufacturing, Csl Behring SpA, Grifols Italia, Kedrion, Octapharma Italy (51). In 2016, the tender for the supply of toll fractionation services for the NAIP Regions was won by CSL Behring 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, won by the companies Kedrion and Grifols, with the first plasma collection taking place in November 2020. On the other hand, regarding the Pla.Net 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 861,707 kilograms in 2021, with a percentage increase over the entire period considered, by 86.2%.

The mean annual rate of change over the period considered was 3%, with two peak growth periods between the years 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 2021, plasma for fractionation recorded an increase of 2% compared to the previous year.

The amount of plasma sent for industrial fractionation by the individual Regions, however, varied greatly in both quantitative and qualitative terms.

In 2021, the Regions participating in the LPS agreement collected about one third of the plasma sent for fractionation for a share equal to 246,753 kilograms (29%), those adhering to the RIPP 234,662 kilograms (27%), those of the NAIP 195,807 kilograms (23%) and those of the PlaNet 184,485 kilograms (21%) (Figure 44).

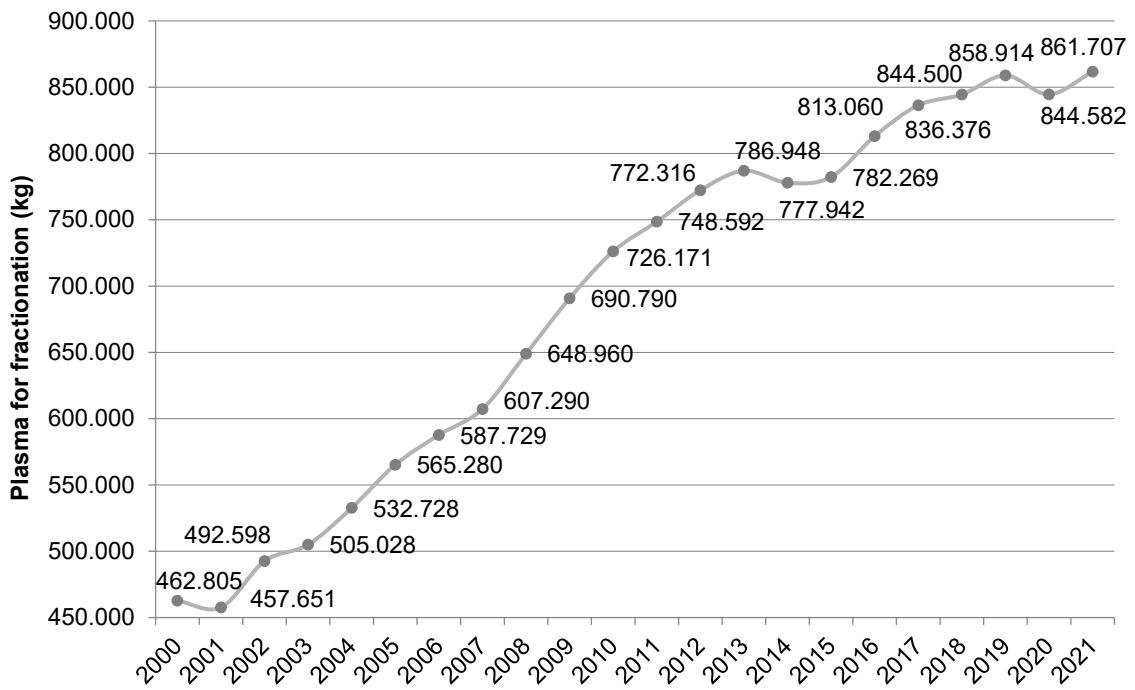


Figure 42. Plasma sent for fractionation 2000-2021
(adapted by the CNS on fractionation companies data, January 2022)

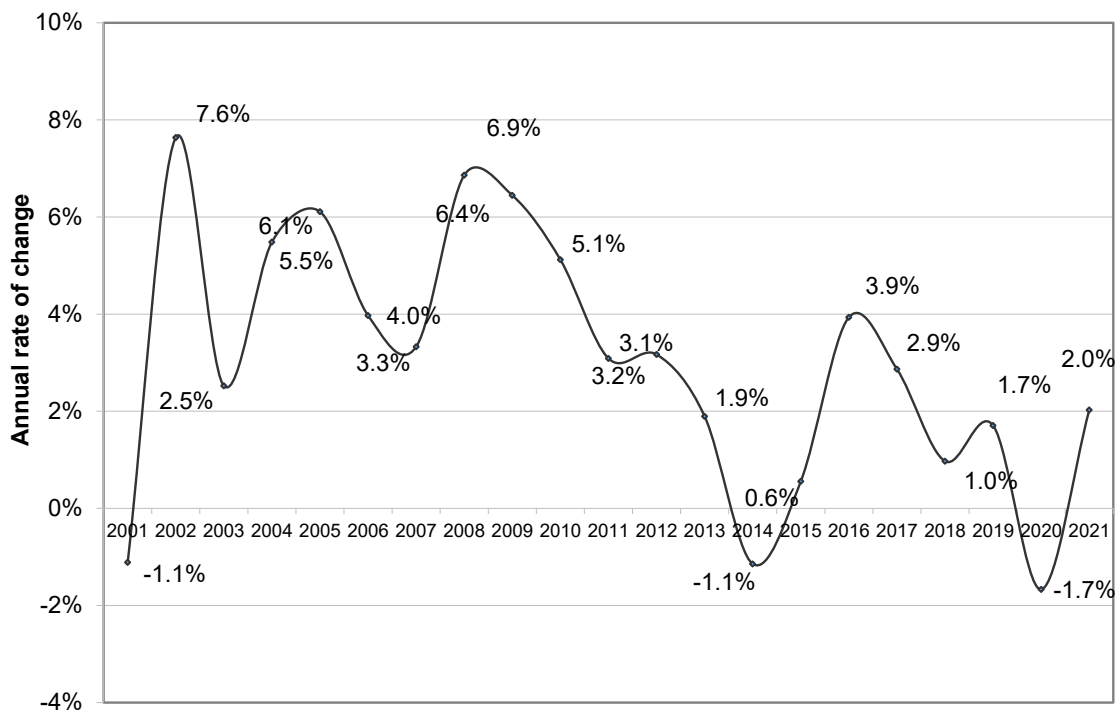


Figure 43. Annual rate of change in the amount of plasma for fractionation, from 2001 to 2021
(adapted by the CNS on fractionation companies data, January 2022)

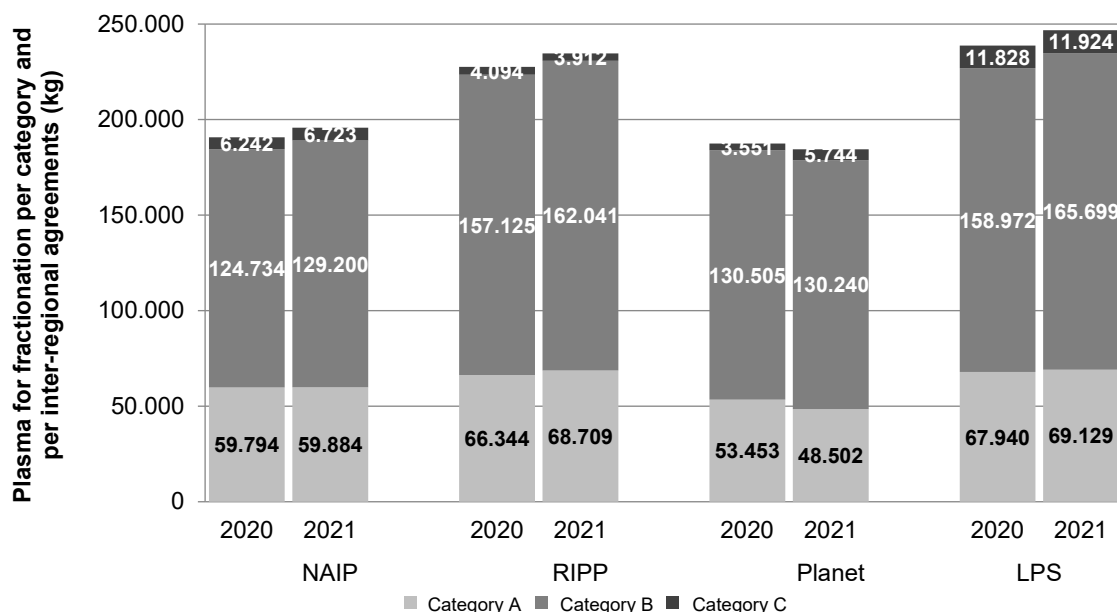


Figure 44. Total amount of plasma for fractionation by category under interregional agreements (kilograms), 2020-2021 (adapted by the CNS on fractionation companies data, January 2022)

As regards the amount of plasma sent for fractionation in 2021, for the resident population, the NAIP Regions sent 17.1 kilograms of plasma per 1,000 population (16.5 in 2020, with the same Regions and participating autonomous provinces), the LPS Regions 15.6 kilograms, as well as RIPP Regions (15.0 kilograms for both in 2020) and the PlaNet Regions 11.0 kilograms per 1,000 population, like the previous year (Figure 45).

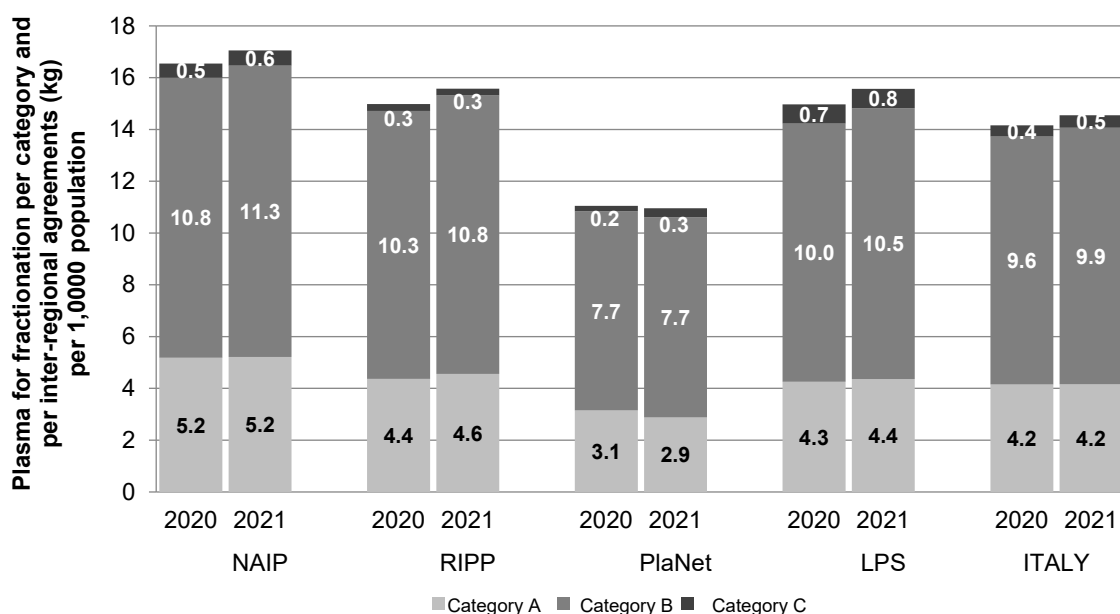


Figure 45. Total amount of plasma for fractionation by category under interregional agreements (kilograms per 1,000 population), 2020-2021 (adapted by the CNS on fractionation companies data, January 2022)

In 2021, although the national volume of plasma for fractionation stood at 14.5 kilograms per 1,000 population (14.2 in 2020), with regional contributions in volumes differing greatly one from another. In point of fact, the best performance was achieved by Friuli V. Giulia with 24.3 kilograms per 1,000 population, followed by Marche with 24.0 and Emilia-Romagna with 22.7, while the lowest volumes were recorded in Molise, Latium and Campania with 9.6, 7.5 and 5.7 kilograms per 1,000 population, respectively (Figure 46).

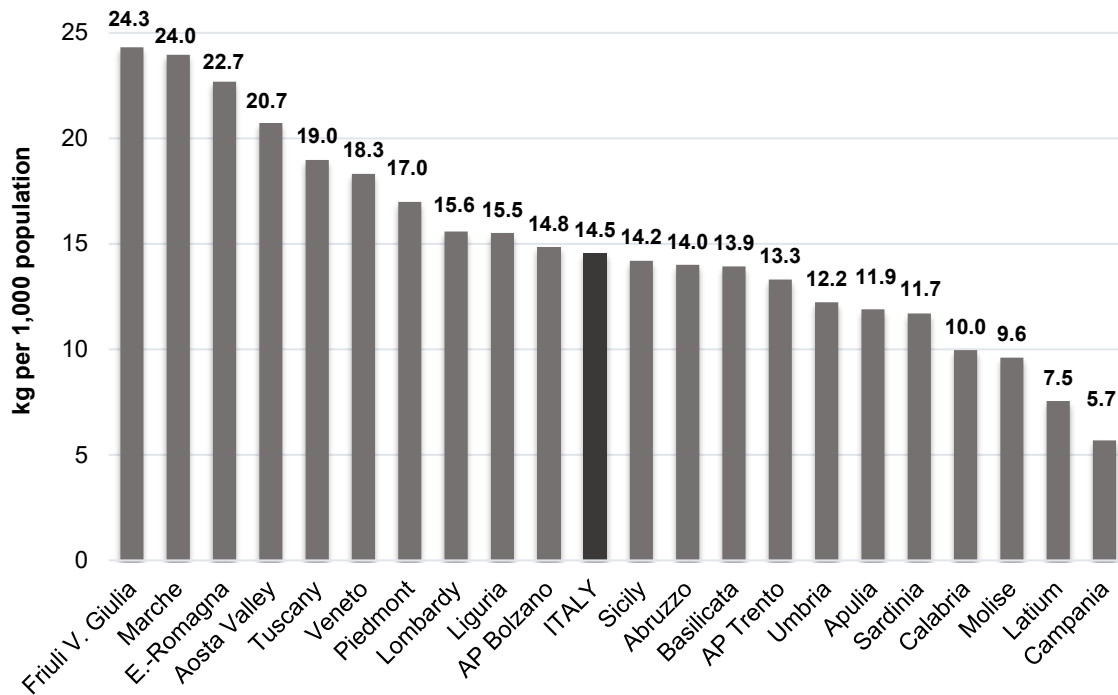


Figure 46. Total amount of plasma (kilograms per 1,000 population) for fractionation by Region, year 2021 (adapted by the CNS on fractionation companies data, January 2022)

Supply of PDMPs from toll fractionation

In 2021, the total quantity of plasma sent for fractionation by the Italian Regions was 861,707 kilograms (Table 76); of these, 29% (246,224 kilograms) was apheresis plasma (category A), 68% (587,180 kilograms) recovered plasma (category B) and the remaining 3% (28,303 kilograms) plasma intended solely for the recovery of non-labile proteins (category C).

The percentages of all three categories of plasma sent for fractionation varied from one regional area to another and from one consortium to another. In particular, the percentages of apheresis plasma (category A) for fractionation varied from 26.3% sent by PlaNet and LPS consortium to 30.6% sent by NAIP, while the percentage of plasma intended solely for the recovery of non-labile proteins (category C) varied from 1.7% sent by RIPP to 4.8% sent by the LPS consortium.

Table 76. Total quantity, expressed in kilograms, quantity per 1,000 population and variation in percentage for the years 2020-2021 classified by Region and plasma category (adapted by the CNS on fractionation companies data, January 2022)

Region	A	%	B	%	C	%	Tot. Fract.	Total per 1,000 pop
Abruzzo	5,087	5.1	12,770	5.0	84	70.9	17,941	14.0
Aosta Valley	1,200	11.2	1,372	11.3	-	-	2,572	20.7
AP Bolzano	1,900	24.7	6,032	3.6	-	-	7,932	14.8
AP Trento	557	18.7	6,659	8.8	-	-	7,216	13.3
Basilicata	1,616	4.1	4,455	-9.1	1,522	101.1	7,593	13.9
Friuli V. Giulia	14,661	-1.6	14,471	6.8	77	-69.4	29,209	24.3
Liguria	6,102	-1.9	17,453	3.6	-	-	23,554	15.5
Umbria	1,879	-1.3	8,707	13.3	-	-	10,586	12.2
Veneto	26,881	-1.5	57,283	1.5	5,040	-2.8	89,204	18.3
NAIP	59,884	0.1	129,200	3.6	6,723	7.7	195,807	17.1
Apulia	6,522	5.4	38,615	2.7	1,666	1.4	46,803	11.9
Calabria	1,105	-8.7	17,436	-2.8	0	-100.0	18,541	10.0
Emilia-Romagna	43,648	0.5	54,801	5.7	2,242	-6.9	100,692	22.7
Sicily	17,434	12.4	51,189	3.0	4	-90.5	68,626	14.2
RIPP	68,709	3.6	162,041	3.1	3,912	-4.4	234,662	15.6
Campania	681	-3.0	29,744	-5.0	1,567	-2.8	31,992	5.7
Latium	4,435	-20.1	34,887	-3.1	3,937	121.5	43,260	7.5
Marche	15,845	2.0	20,047	2.0	2	100	35,894	24.0
Molise	109	-44.9	2,719	-7.8	-	-	2,828	9.6
Tuscany	27,432	-12.8	42,637	5.3	-	-	70,069	19.0
Ministry of Defence	-	-	205	65.1	238	48.2	443	NA
PlaNet	48,502	-9.3	130,240	-0.2	5,744	61.8	184,485	11.0
Lombardy	46,096	3.9	99,893	5.1	9,550	3.2	155,539	15.6
Piedmont	22,343	-2.0	48,143	2.9	2,126	-10.7	72,612	17.0
Sardinia	690	-11.5	17,664	3.3	248	25.1	18,602	11.7
LPS	69,129	1.7	165,699	4.2	11,924	0.8	246,753	15.6
Italy	246,224	-0.5	587,180	2.8	28,303	10.1	861,707	14.5

Table 77 shows the amount of PDMPs potentially obtainable from the industrial manufacturing of the total amount of plasma sent for fractionation in 2021 (from July 2020 to June 2021).

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 15,900 kilograms, as shown in Table 78, were sent to Kedrion for the production of plasma solvent/detergent-treated, beyond the provisions of the aforementioned regional agreements.

Table 79 lays out the quantities of PDMPs distributed to the individual Regions in 2021 in accordance with the specified production and distribution programmes (effective supply or toll fractionation).

Table 77. Potential supply of toll fractionated PDMPs based on the amount of plasma sent for fractionation from July 2020 to June 2021 and the yields provided by the fractionation industry – year 2021 (adapted by the CNS on fractionation companies data, march 2022)

Region	2nd semester 2020		1st semester 2021		Total	Albumin	SCIG *	IGIV**	Factor VIII		FIX/CCP3	Anti-thrombin	Fibrinogen	aPCCs		FVII	Protein C
	kg	kg	kg	kg					g	g				UI	UI		
Abruzzo	9,405	8,488	17,893	447,336	87,678	1,590,729	520,700	-	-	-	-	-	966	-	-	-	-
Aosta Valley	1,032	1,433	2,465	61,626	12,079	219,144	71,733	-	-	-	-	-	133	-	-	-	-
AP Bolzano	3,941	3,848	7,788	194,711	38,163	692,392	226,644	-	-	-	-	-	421	-	-	-	-
AP Trento	3,483	3,757	7,241	181,015	35,479	643,688	210,701	-	-	-	-	-	391	-	-	-	-
Basilicata	3,761	3,731	7,492	187,304	36,712	666,053	218,022	-	-	-	-	-	405	-	-	-	-
FVG	14,193	15,074	29,267	731,680	143,409	2,601,853	851,675	-	-	-	-	-	1,580	-	-	-	-
Liguria	11,676	11,582	23,258	581,444	113,963	2,067,616	676,801	-	-	-	-	-	1,256	-	-	-	-
Umbria	5,192	4,867	10,059	251,478	49,290	894,255	292,720	-	-	-	-	-	543	-	-	-	-
Veneto	44,418	45,487	89,904	2,247,610	440,532	7,992,503	2,616,219	-	-	-	-	-	4,855	-	-	-	-
NAIP	97,101	98,267	195,368	4,884,205	957,304	17,368,231	5,685,214	-	-	-	-	-	10,550	-	-	-	-
Apulia	22,017	23,925	45,942	1,184,848	166,311	187,903	6,193,650	-	-	11,769,918	8,848,072	-	-	-	-	-	-
Calabria	9,984	9,333	19,317	498,198	69,929	79,008	2,704,447	-	-	4,948,945	3,863,496	-	-	-	-	-	-
E.-Romagna	51,312	51,081	102,393	2,640,273	212,820	418,786	8,084,255	-	-	15,061,394	27,265,562	-	-	-	-	-	-
Sicily	32,817	33,958	66,775	1,722,125	241,725	273,109	9,347,049	-	-	17,107,062	13,352,927	-	-	-	-	-	-
RIPP	116,130	118,297	234,427	6,045,443	690,785	958,807	26,329,402	5,445,552	48,887,319	53,330,058	-	-	-	-	-	-	-
Campania	15,883	15,969	31,852	809,933	136,016	151,693	1,104,943	3,295,019	15,663,650	1,578,490	-	-	-	14,121,510	12,168,034	4,707,170	2,871,374
Lazio	22,213	22,272	44,485	1,130,597	190,992	212,921	1,402,310	4,765,548	22,248,871	2,003,301	-	-	-	20,423,778	17,598,489	6,807,926	4,152,835
Marche	18,017	17,648	35,666	906,546	152,942	170,518	1,201,597	3,791,591	17,771,441	1,716,567	-	-	-	16,249,674	14,001,802	5,416,558	3,304,100
Molise	1,622	1,312	2,934	74,613	12,517	13,961	109,127	301,637	1,438,560	155,895	-	-	-	1,292,730	1,113,902	430,910	262,855
Tuscany	35,895	37,010	72,905	1,852,422	313,863	349,831	2,260,980	7,945,788	36,771,919	3,229,971	-	-	-	34,053,378	29,342,661	11,351,126	6,924,187
Ministry of Def.	151	267	418	10,626	1,786	1,992	7,344	43,429	205,965	-	-	-	-	186,126	160,379	62,042	37,846
PlaNet	93,782	94,478	188,260	4,784,737	808,116	900,915	6,086,301	20,143,012	94,100,406	8,684,224	-	-	-	86,327,196	74,385,267	28,775,732	17,553,197
Lombardy	75,010	77,900	152,910	3,943,544	563,534	625,401	20,046,994	-	39,173,969	28,638,562	-	-	-	-	-	-	-
Piedmont	35,728	37,015	72,743	1,876,034	263,329	297,518	9,833,765	-	18,635,948	14,048,236	-	-	-	-	-	-	-
Sardinia	8,615	9,186	17,801	459,089	64,440	72,806	2,452,731	-	4,560,452	3,503,901	-	-	-	-	-	-	-
LPS	119,353	124,100	243,454	6,278,667	881,302	995,725	32,333,489	-	62,370,369	46,190,699	-	-	-	-	-	-	-
Italy	426,367	435,143	861,509	21,993,052	3,337,507	3,812,752	82,117,424	31,273,779	205,358,094	108,204,981	10,550	86,327,196	74,385,267	28,775,732	17,553,197	-	-

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

Table 78. Potential supply of solvent/detergent-treated plasma based on the amount of plasma sent for fractionation from July 2020 to June 2021 and the yields provided by the fractionation industry – year 2021 (adapted by the CNS on data provided by Kedrion)

Region	2nd semester 2019 kg	1st semester 2020 kg	Total kg	Solvent/detergent-treated plasma mL
Abruzzo	-	-	-	-
Aosta Valley	-	-	-	-
AP Bolzano	-	-	-	-
AP Trento	-	-	-	-
Apulia	-	-	-	-
Basilicata	-	-	-	-
Calabria	-	15	15	14,135
Campania	1,330	2,252	3,582	3,312,983
E.-Romagna	-	-	-	-
Friuli V. Giulia	-	-	-	-
Lazio	1,329	1,862	3,191	2,951,948
Liguria	-	-	-	-
Lombardy	-	-	-	-
Marche	184	-	184	170,218
Molise	566	534	1,100	1,017,815
Piedmont	1,945	2,213	4,158	3,846,190
Sardinia	-	-	-	-
Sicily	1,198	779	1,977	1,828,834
Tuscany	-	-	-	-
Umbria	-	-	-	-
Veneto	786	932	1,718	1,589,202
Ministry of Defence	-	-	-	-
Italy	7,338	8,588	15,926	14,731,325

Table 79. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs classified by Region for the year 2021 (adapted by the CNS on fractionation companies data, march 2022)

Region	Albumin		IVIG		SCIG		Factor VIII		Factor VIII / vW Factor		Factor IX		3-factor prothrombin complex		Anti-thrombin		Fibrinogen		Solvent/detergent-treated plasma		Protein C	
	g	g	g	g	g	g	UI	UI	UI	UI	UI	UI	UI	UI	UI	UI	g	g	mL	mL	UI	UI
Abruzzo	782,400	92,900	15,260	94,000	1,620,000	-	366,000	317,000	1,120	-	-	-	-	-	-	-	-	-	-	-	-	-
Aosta Valley	54,000	18,600	480	-	10,000	-	70,500	84,000	50	-	-	-	-	-	-	-	-	-	-	-	-	-
AP Bolzano	190,200	46,423	1,620	300,000	40,000	-	265,500	105,000	660	48,000	-	-	-	-	-	-	-	-	-	-	-	-
AP Trento	201,600	43,090	2,660	-	30,000	-	192,500	57,000	410	-	-	-	-	-	-	-	-	-	-	-	-	-
Basilicata	245,400	25,400	3,580	87,000	80,000	-	161,000	271,000	170	-	-	-	-	-	-	-	-	-	-	-	-	-
Friuli V. Giulia	557,400	125,425	4,340	868,000	270,000	-	150,000	494,000	1,100	-	-	-	-	-	-	-	-	-	-	-	-	-
Liguria	758,400	171,088	2,620	821,000	330,000	-	518,500	367,000	340	-	-	-	-	-	-	-	-	-	-	-	-	40,400
Umbria	580,800	54,300	16,720	226,000	380,000	-	332,500	121,000	780	-	-	-	-	-	-	-	-	-	-	-	-	-
Veneto	2,562,600	406,875	42,680	4,907,000	1,850,000	-	2,139,000	909,000	4,950	47,000	-	-	-	-	-	-	-	-	-	-	-	1,076,000
NAIP	5,932,800	984,100	89,960	7,303,000	4,610,000	-	95,000	2,725,000	9,580	4,195,500	4,610,000	95,000	2,725,000	4,195,500	2,725,000	9,580	1,116,400	1,116,400	1,116,400	1,116,400	1,116,400	1,116,400
Apulia	1,570,370	232,180	8,468	5,458,000	-	-	282,000	8,267,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Calabria	554,300	79,515	-	554,000	-	-	20,000	6,816,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
E.-Romagna	2,651,900	430,795	1,488	1,725,000	-	-	77,000	3,389,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sicily	2,171,640	221,050	80	785,000	-	-	116,000	18,542,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RIPP	6,948,210	963,540	10,036	8,522,000	4,610,000	10,036	495,000	37,014,000	1,589,000	495,000	8,522,000	495,000	37,014,000	8,522,000	37,014,000	1,589,000	1,589,000	1,589,000	1,589,000	1,589,000	1,589,000	1,589,000
Campania	622,075	69,385	6,508	20,000	302,000	-	12,000	7,360,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Latium	1,133,400	170,015	3,292	5,042,000	22,000	-	610,000	8,811,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Marche	782,043	172,030	5,529	1,840,000	-	-	1,033,200	4,570,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Molise	90,480	13,800	516	344,000	-	-	20,000	762,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tuscany	1,442,475	357,140	33,411	4,165,000	441,000	-	188,000	11,630,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ministry of Defence	-	175	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	4,070,473	782,545	49,256	11,411,000	765,000	49,256	1,863,200	33,133,000	7,406,800	1,863,200	7,406,800	1,863,200	33,133,000	7,406,800	33,133,000	7,406,800	7,406,800	7,406,800	7,406,800	7,406,800	7,406,800	7,406,800
Lombardy	4,243,900	497,998	1,752	6,809,000	-	-	831,000	8,082,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Piedmont	1,573,460	338,895	256	6,077,000	-	-	177,000	8,088,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sardinia	963,700	75,800	60	427,000	-	-	-	2,230,000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LPS	6,781,060	912,693	2,068	13,313,000	1,008,000	2,068	1,008,000	18,400,000	10,347,500	1,008,000	10,347,500	1,008,000	18,400,000	10,347,500	18,400,000	4,868,000	4,868,000	4,868,000	4,868,000	4,868,000	4,868,000	4,868,000
Italy	23,732,543	3,642,878	151,320	40,549,000	5,375,000	40,549,000	3,461,200	91,272,000	30,533,800	3,461,200	30,533,800	3,461,200	91,272,000	30,533,800	91,272,000	9,580	14,976,600	14,976,600	14,976,600	14,976,600	14,976,600	14,976,600

ANALYSIS OF SELF-SUFFICIENCY

Albumin

In 2021, the Italian NHS demand for albumin accounted for 86% of the total. The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, was 66% (-7% compared to 2020) while the effective self-sufficiency, considered as the ratio between the actual supply of toll fractionation and the NHS demand, was 71% (76% in 2020). The Regions that in 2021 achieved effective self-sufficiency – more than 90% – were Friuli V. Giulia, AP of Bolzano, Umbria, Aosta Valley, Veneto, Emilia-Romagna and Marche (Table 80).

Table 80. Estimates of regional and national self-sufficiency in albumin, 2021

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,033,150	962,813	447,336	782,400	46	81
Aosta Valley	54,360	54,240	61,626	54,000	114	100
AP Bolzano	198,745	197,375	194,711	190,200	99	96
AP Trento	242,050	234,270	181,015	201,600	77	86
Basilicata	370,983	367,688	187,304	245,400	51	67
Friuli V. Giulia	584,430	577,300	731,680	557,400	127	97
Liguria	1,116,945	1,084,513	581,444	758,400	54	70
Umbria	589,640	589,110	251,478	580,800	43	99
Veneto	2,767,985	2,647,105	2,247,610	2,562,600	85	97
NAIP	6,958,288	6,714,413	4,884,205	5,932,800	73	88
Apulia	2,605,545	2,149,005	1,184,848	1,570,370	55	73
Calabria	1,135,108	1,030,408	498,198	554,300	48	54
E.-Romagna	2,967,408	2,738,255	2,640,273	2,651,900	96	97
Sicily	3,938,353	3,185,995	1,722,125	2,171,640	54	68
RIPP	10,646,413	9,103,663	6,045,443	6,948,210	66	76
Campania	4,626,590	4,067,063	809,933	622,075	20	15
Latium	3,396,963	2,118,958	1,130,597	1,133,400	53	53
Marche	929,415	804,605	906,546	782,043	113	97
Molise	166,450	117,928	74,613	90,480	63	77
Tuscany	1,739,573	1,651,343	1,852,422	1,442,475	112	87
Min. of Def.	-	-	10,626	-	-	-
PlaNet	10,858,990	8,759,895	4,784,737	4,070,473	55	46
Lombardy	6,728,863	5,469,030	3,943,544	4,243,900	72	78
Piedmont	1,951,825	1,815,290	1,876,034	1,573,460	103	87
Sardinia	1,389,770	1,347,355	459,089	963,700	34	72
LPS	10,070,458	8,631,675	6,278,667	6,781,060	73	79
Italy	38,534,148	33,209,645	21,993,052	23,732,543	66	71

The Regions that mostly benefitted from interregional compensation in 2021 were: Umbria (99% effective self-sufficiency compared to the potential 43%) and Abruzzo (81% compared to

46%) for NAIP, Sardinia (72% compared to 34%) for LPS, Apulia (effective self-sufficiency 73% compared to the potential 55%) and Sicily (effective self-sufficiency 68% compared to the potential 54%) for the RIPP consortium.

The Regions that remained farthest from the goal of effective self-sufficiency were Campania, Latium, Calabria, Basilicata and Sicily, with percentages ranging between 15 and 68% of the NHS demand met by the toll fractionation supply.

Normal human immunoglobulins

In 2021, the NHS demand for normal IGs accounted for 93% of the total demand (Table 81).

Table 81. Estimates of regional and national self-sufficiency in human immunoglobulins, 2021

Region	Total demand*	NHS demand*	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	135,734	134,584	87,678	108,160	65	80
Aosta Valley	20,933	20,933	12,079	19,080	58	91
AP Bolzano	54,508	54,508	38,163	48,043	70	88
AP Trento	53,108	53,108	35,479	45,750	67	86
Basilicata	44,839	44,839	36,712	28,980	82	65
Friuli V. Giulia	136,557	136,557	143,409	129,765	105	95
Liguria	238,273	237,744	113,963	173,708	48	73
Umbria	115,500	105,380	49,290	71,020	47	67
Veneto	589,825	573,965	440,532	449,555	77	78
NAIP	1,389,276	1,361,617	957,304	1,074,060	70	79
Apulia	430,420	397,900	181,849	240,648	46	60
Calabria	118,113	118,113	76,088	79,515	64	67
E.-Romagna	570,188	568,618	373,838	432,283	66	76
Sicily	338,205	329,260	263,301	221,130	80	67
RIPP	1,456,926	1,413,891	895,077	973,576	63	69
Campania	375,625	351,457	146,568	75,893	42	22
Latium	612,831	464,197	204,947	173,307	44	37
Marche	210,247	209,527	167,896	177,559	80	85
Molise	24,114	17,114	13,762	14,316	80	84
Tuscany	689,518	671,688	340,489	390,551	51	58
Min. of Def.	-	-	-	175	-	-
PlaNet	1,912,334	1,713,982	873,662	831,801	51	49
Lombardy	966,710	791,686	613,127	499,750	77	63
Piedmont	530,998	528,283	291,371	339,151	55	64
Sardinia	103,013	99,845	71,828	75,860	72	76
LPS	1,600,721	1,419,814	976,327	914,761	69	64
Italy	6,359,257	5,909,304	3,702,369	3,794,198	63	64

* The value does not include *Pentaglobin*TM.

The national potential self-sufficiency, expressed by the ratio of the potential supply to the NHS demand, in 2021 was 63%, where effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to NHS demand, was 64%.

The only Region to achieve effective self-sufficiency in IGs in 2021 – more than 90% – was Friuli V. Giulia and Aosta Valley while the Regions that achieved the lowest effective self-sufficiency were Campania (22%), Latium (37%), Tuscany (58%) and Apulia (60%).

Normal human immunoglobulins for subcutaneous use

In 2021, the NHS demand for immunoglobulins for subcutaneous / intramuscular use represented approximately 97% of the total demand (Table 82).

Table 82. Estimates of regional and national self-sufficiency in human immunoglobulin for subcutaneous use, 2021

Region	Total demand	NHS demand	Potential supply*	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	36,909	35,909	87,678	15,260	244	42
Aosta Valley	1,333	1,333	12,079	480	906	36
AP Bolzano	3,489	3,489	38,163	1,620	1094	46
AP Trento	8,118	8,118	35,479	2,660	437	33
Basilicata	15,463	15,463	36,712	3,580	237	23
Friuli V. Giulia	9,172	9,172	143,409	4,340	1564	47
Liguria	44,181	44,181	113,963	2,620	258	6
Umbria	43,395	43,395	49,290	16,720	114	39
Veneto	157,527	157,527	440,532	42,680	280	27
NAIP	319,587	318,587	957,304	89,960	300	28
Apulia	120,680	120,680	166,311	8,468	138	7
Calabria	37,988	37,988	69,929	-	184	0
E.-Romagna	124,431	124,431	212,820	1,488	171	1
Sicily	105,701	105,701	241,725	80	229	0
RIPP	388,800	388,800	690,785	10,036	178	3
Campania	122,799	122,799	136,016	6,508	111	5
Latium	222,844	221,350	190,992	3,292	86	1
Marche	31,367	31,367	152,942	5,529	488	18
Molise	3,314	3,314	12,517	516	378	16
Tuscany	179,090	177,090	313,863	33,411	177	19
Min. of Def.	-	-	1,786	-	-	-
PlaNet	559,413	555,919	808,116	49,256	145	9
Lombardy	165,098	121,642	553,534	1,752	455	1
Piedmont	95,458	95,378	263,329	256	276	0
Sardinia	12,048	9,360	64,440	60	688	1
LPS	272,604	226,380	881,302	2,068	389	1
Italy	1,540,405	1,489,687	3,337,507	151,320	224	10

*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 SSN demand, was 10%.

No Region in 2021 achieved effective self-sufficiency > 90%; the highest values of self-sufficiency were recorded in Friuli V. Giulia and in the AP of Bolzano with self-sufficiency rates above 50%.

Normal human immunoglobulins for intravenous use

In 2021, the NHS demand for IV IGs accounted for 92% of the total demand (Table 83).

Table 83. Estimates of regional and national self-sufficiency in human immunoglobulin for intravenous use, 2021

Region	Total demand**	NHS demand **	Potential supply*	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	98,825	98,675	87,678	92,900	89	94
Aosta Valley	19,600	19,600	12,079	18,600	62	95
AP Bolzano	51,019	51,019	38,163	46,423	75	91
AP Trento	44,990	44,990	35,479	43,090	79	96
Basilicata	29,376	29,376	36,712	25,400	125	86
Friuli V. Giulia	127,385	127,385	143,409	125,425	113	98
Liguria	194,093	193,563	113,963	171,088	59	88
Umbria	72,105	61,985	49,290	54,300	80	88
Veneto	432,298	416,438	440,532	406,875	106	98
NAIP	1,069,689	1,043,030	957,304	984,100	92	94
Apulia	309,741	277,221	187,903	232,180	68	84
Calabria	80,125	80,125	79,008	79,515	99	99
E.-Romagna	445,756	444,186	418,786	430,795	94	97
Sicily	232,503	223,558	273,109	221,050	122	99
RIPP	1,068,126	1,025,091	958,807	963,540	94	94
Campania	252,826	228,658	151,693	69,385	66	30
Latium	389,987	242,847	212,921	170,015	88	70
Marche	178,880	178,160	170,518	172,030	96	97
Molise	20,800	13,800	13,961	13,800	101	100
Tuscany	510,427	494,597	349,831	357,140	71	72
Min. of Def.	-	-	1,992	175	-	-
PlaNet	1,352,920	1,158,062	900,915	782,545	78	68
Lombardy	801,612	670,044	625,401	497,998	93	74
Piedmont	435,540	432,905	297,518	338,895	69	78
Sardinia	90,965	90,485	72,806	75,800	80	84
LPS	1,328,117	1,193,434	995,725	912,693	83	76
Italy	4,818,852	4,419,617	3,812,752	3,642,878	86	82

* 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*TM.

The national potential self-sufficiency, expressed by the ratio of the potential supply to NHS demand, in 2021 was 86%. Effective self-sufficiency, assumed as the ratio of the actual supply of toll fractionation to NHS demand, was 82%.

The Regions that in 2021 achieved effective self-sufficiency (more than 90%) were Friuli V. Giulia, Abruzzo, AP of Bolzano, AP of Trento, Aosta Valley, Veneto, Calabria, Emilia-Romagna, Sicily, Marche and Molise.

Campania is the Region with the lowest effective self-sufficiency value, equal to 30%.

Antithrombin

NHS demand for AT compared to national total demand dropped from 94% in 2011 to 89% in 2021. Effective self-sufficiency recorded a value of 73% in 2021 (83% in 2020), significantly lower than the potential self-sufficiency (86%) (Table 84).

Table 84. Estimates of regional and national self-sufficiency in antithrombin, 2021

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	2,358,000	2,322,000	-	317,000	-	14
Aosta Valley	244,000	244,000	-	84,000	-	34
AP Bolzano	436,000	436,000	-	105,000	-	24
AP Trento	288,000	287,000	-	57,000	-	20
Basilicata	1,128,000	1,128,000	-	271,000	-	24
FVG	2,944,000	2,944,000	-	494,000	-	17
Liguria	4,759,000	4,706,000	-	367,000	-	8
Umbria	586,000	586,000	-	121,000	-	21
Veneto	6,974,000	6,939,500	-	909,000	-	13
NAIP	19,717,000	19,592,500	-	2,725,000	-	14
Apulia	9,589,500	8,674,000	8,848,072	8,267,000	102	95
Calabria	7,380,500	7,276,000	3,863,496	6,816,000	53	94
E.-Romagna	3,992,000	3,398,000	27,265,562	3,389,000	802	100
Sicily	23,005,500	19,283,000	13,352,927	18,542,000	69	96
RIPP	43,967,500	38,631,000	53,330,058	37,014,000	138	96
Campania	15,100,500	14,233,000	1,578,490	7,360,000	11	52
Latium	21,535,000	16,603,000	2,003,301	8,811,000	12	53
Marche	4,582,000	4,570,000	1,716,567	4,570,000	38	100
Molise	766,000	762,000	155,895	762,000	20	100
Tuscany	11,656,500	11,650,000	3,229,971	11,630,000	28	100
Min. of Def.	-	-	-	-	-	-
PlaNet	53,640,000	47,818,000	8,684,224	33,133,000	18	69
Lombardy	11,935,000	8,726,500	28,638,562	8,082,000	328	93
Piedmont	8,684,500	8,090,000	14,048,236	8,088,000	174	100
Sardinia	2,248,500	2,245,000	3,503,901	2,230,000	156	99
LPS	22,868,000	19,061,500	46,190,699	18,400,000	242	97
Italy	140,192,500	125,103,000	108,204,981	91,272,000	86	73

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. Most Regions achieved effective self-sufficiency of more than 90% of the total NHS demand in 2021, except for Abruzzo, Basilicata, Friuli V. Giulia, Liguria, AP of Bolzano, AP of Trento, Umbria, Aosta Valley, Veneto, Campania and Latium. The Regions that mostly benefitted from interregional compensation in 2021 were Marche (100% effective vs. 38% potential self-sufficiency), Molise (100% effective vs. 20% potential), and Tuscany (100% effective vs. 28% potential self-sufficiency). The farthest Regions from the objective of effective self-sufficiency were Liguria (8%), Veneto (13%) and Abruzzo (14%).

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 2021, 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 Pla.Net 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 2021, all the Regions largely achieved effective self-sufficiency in pdFVIII (Table 85).

Table 85. Estimates of regional and national self-sufficiency in plasma-derived Factor VIII, 2021

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	94,000	94,000	1,590,729	94,000	1,692	100
Aosta Valley	-	-	219,144	-	NA	NA
AP Bolzano	300,000	300,000	692,392	300,000	231	100
AP Trento	-	-	643,688	-	NA	NA
Basilicata	87,000	87,000	666,053	87,000	766	100
FVG	868,000	868,000	2,601,853	868,000	300	100
Liguria	835,000	835,000	2,067,616	821,000	248	98
Umbria	226,000	226,000	894,255	226,000	396	100
Veneto	4,982,000	4,972,000	7,992,503	4,907,000	161	99
NAIP	7,392,000	7,382,000	17,368,231	7,303,000	235	99
Apulia	5,860,000	5,860,000	6,193,650	5,458,000	106	93
Calabria	565,000	554,000	2,704,447	554,000	488	100
E.-Romagna	1,725,000	1,725,000	8,084,255	1,725,000	469	100
Sicily	785,000	785,000	9,347,049	785,000	1,191	100
RIPP	8,935,000	8,924,000	26,329,402	8,522,000	295	95
Campania	20,000	20,000	1,104,943	20,000	5,525	100
Latium	5,890,000	5,042,000	1,402,310	5,042,000	28	100
Marche	1,880,000	1,840,000	1,201,597	1,840,000	65	100
Molise	344,000	344,000	109,127	344,000	32	100
Tuscany	4,165,000	4,165,000	2,260,980	4,165,000	54	100
Min. of Def.	-	-	7,344	-	NA	-
PlaNet	12,299,000	11,411,000	6,086,301	11,411,000	53	100

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Lombardy	7,456,000	7,444,000	20,046,994	6,809,000	269	91
Piedmont	6,097,000	6,097,000	9,833,765	6,077,000	161	100
Sardinia	427,000	427,000	2,452,731	427,000	574	100
LPS	13,980,000	13,968,000	32,333,489	13,313,000	231	95
Italy	42,606,000	41,685,000	82,117,424	40,549,000	197	97

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

Table 86 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 2021 was 12%.

Table 86. Estimates of regional and national self-sufficiency in plasma-derived Factor VIII and von Willebrand Factor in combination, 2021

Region	Total demand*	NHS demand*	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	3,449,500	3,449,500	520,700	1,620,000	15	47
AostaValley	10,000	10,000	71,733	10,000	717	100
APBolzano	43,000	43,000	226,644	40,000	527	93
APTrento	73,000	73,000	210,701	30,000	289	41
Basilicata	81,000	80,000	218,022	80,000	273	100
FVG	381,000	381,000	851,675	270,000	224	71
Liguria	336,000	336,000	676,801	330,000	201	98
Umbria	842,000	842,000	292,720	380,000	35	45
Veneto	2,127,500	2,125,500	2,616,219	1,850,000	123	87
NAIP	7,343,000	7,340,000	5,685,214	4,610,000	77	63
Apulia	6,969,500	6,894,500	-	-	-	-
Calabria	1,711,500	1,466,000	-	-	-	-
E.-Romagna	3,217,000	3,217,000	5,445,552	-	169	-
Sicily	4,172,000	4,165,500	-	-	-	-
RIPP	16,070,000	15,743,000	5,445,552	-	35	-
Campania	5,240,500	5,240,500	3,295,019	302,000	63	6
Latium	7,892,000	6,802,500	4,765,548	22,000	70	0
Marche	433,000	433,000	3,791,591	-	876	-
Molise	302,000	296,000	301,637	-	102	-
Tuscany	2,517,000	2,517,000	7,945,788	441,000	316	18
Min.ofDef.	-	-	43,429	-	-	-
PlaNet	16,384,500	15,289,000	20,143,012	765,000	132	5
Lombardy	4,367,500	4,073,500	-	-	-	-
Piedmont	2,712,500	2,679,500	-	-	-	-
Sardinia	1,446,200	1,446,200	-	-	-	-
LPS	8,526,200	8,199,200	-	-	-	-
Italy	48,323,700	46,571,200	31,273,779	5,375,000	67	12

* 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 52 to 100% confirming the need of improvement in the inter-regional exchange and compensation mechanisms (Table 87).

Table 87. Estimates of regional and national self-sufficiency in plasma-derived Factor IX and 3-factor prothrombin complex concentrates, 2021

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	371,000	366,000	-	366,000	-	100
Aosta Valley	115,000	115,000	-	70,500	-	61
AP Bolzano	321,500	321,500	-	313,500	-	98
AP Trento	332,500	332,500	-	192,500	-	58
Basilicata	163,000	163,000	-	161,000	-	99
FVG	150,000	150,000	-	150,000	-	100
Liguria	1,288,500	1,001,500	-	518,500	-	52
Umbria	590,500	590,500	-	332,500	-	56
Veneto	4,250,500	4,173,500	-	2,186,000	-	52
NAIP	7,582,500	7,213,500	-	4,290,500	-	59
Apulia	2,571,000	1,944,000	11,769,918	1,944,000	605	100
Calabria	725,500	692,000	4,948,945	692,000	715	100
E.-Romagna	3,851,500	3,373,000	15,061,394	3,370,500	447	100
Sicily	3,264,000	3,098,500	17,107,062	3,072,500	552	99
RIPP	10,412,000	9,107,500	48,887,319	9,079,000	537	100
Campania	2,519,000	2,236,500	15,663,650	1,897,000	700	85
Latium	2,422,500	2,353,000	22,248,871	2,331,500	946	99
Marche	1,905,200	1,903,200	17,771,441	1,903,200	934	100
Molise	184,000	180,000	1,438,560	180,000	799	100
Tuscany	2,964,300	2,963,800	36,771,919	2,958,300	1,241	100
Min. of Def.	-	-	205,965	-	NA	-
PlaNet	9,995,000	9,636,500	94,100,406	9,270,000	976	96
Lombardy	7,818,000	7,482,000	39,173,969	6,442,000	524	86
Piedmont	4,352,500	3,988,000	18,635,948	3,461,000	467	87
Sardinia	1,452,500	1,452,500	4,560,452	1,452,500	314	100
LPS	13,623,000	12,922,500	62,370,369	11,355,500	483	88
Italy	41,612,500	38,880,000	205,358,094	33,995,000	528	87

Fibrinogen

RiaSTAP™ is a product containing fibrinogen concentrate currently made available by CSL Behring under the toll fractionation contract with NAIP Regions. RiaSTAP is indicated for the

treatment of congenital fibrinogen deficiency, which comprises congenital afibrinogenemia and hypofibrinogenemia. Other indications are met by other products available on the Italian market.

In 2021, the potential self-sufficiency in RiaSTAP was equal to 28% (62% in 2020) (Table 88). However, effective self-sufficiency of 25% was achieved (53% in 2020), also given the marked increase of demand in 2021 (+13%). Most of NAIP Regions, except for Abruzzo, Basilicata, Liguria, AP of Bolzano and Veneto, achieved effective self-sufficiency equal to 100%.

Table 88. Estimates of regional and national self- sufficiency in fibrinogen, 2021

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,266	1,262	966	1,120	77	89
Aosta Valley	50	50	133	50	266	100
AP Bolzano	810	810	421	660	52	81
AP Trento	410	410	391	410	95	100
Basilicata	370	370	405	170	109	46
Friuli V. G.	1,100	1,100	1,580	1,100	144	100
Liguria	882	876	1,256	340	143	39
Umbria	780	780	543	780	70	100
Veneto	7,961	7,951	4,855	4,950	61	62
NAIP	13,629	13,609	10,550	9,580	78	70
Apulia	1,775	1,300	-	-	-	0
Calabria	1,570	1,554	-	-	-	0
E.-Romagna	4,228	3,931	-	-	-	0
Sicily	3,332	2,467	-	-	-	0
RIPP	10,905	9,252	-	-	-	0
Campania	3,988	3,381	-	-	-	0
Latium	4,315	1,499	-	-	-	0
Marche	1,125	1,125	-	-	-	0
Molise	5	-	-	-	-	0
Tuscany	722	722	-	-	-	0
Min. of Def.	-	-	-	-	-	0
PlaNet	10,155	6,727	-	-	-	0
Lombardy	6,622	3,640	-	-	-	0
Piedmont	2,917	2,898	-	-	-	0
Sardinia	2,038	2,038	-	-	-	0
LPS	11,577	8,576	-	-	-	-
Italy	46,266	38,164	10,550	9,580	28	25

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 2021, the NHS demand for S/D plasma was almost equal to the total demand. For the same year, effective national self-sufficiency was 53% (62% in 2020) (Table 89).

Table 89. Estimates of regional and national self-sufficiency in solvent/detergent virus-inactivated plasma, 2021

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	10,000	10,000	-	-	-	-
Basilicata	510,000	510,000	-	-	-	-
Friuli V. G.	-	-	-	-	-	-
Liguria	544,400	544,400	-	40,400	-	7
Umbria	82,000	82,000	-	-	-	-
Veneto	1,476,000	1,334,000	1,589,202	1,076,000	119	81
NAIP	2,622,400	2,480,400	1,589,202	1,116,400	64	45
Apulia	3,193,000	3,013,000	-	-	-	-
Calabria	889,600	889,600	14,135	13,600	1,6	2
E.-Romagna	674,000	674,000	-	-	-	-
Sicily	3,945,400	3,945,400	1,828,834	1,575,400	46	40
RIPP	8,702,000	8,522,000	1,842,969	1,589,000	22	19
Campania	4,213,000	4,157,000	3,312,983	3,132,000	80	75
Latium	4,060,200	3,968,200	2,951,948	2,503,200	74	63
Marche	1,648,000	1,648,000	170,218	1,396,000	10	85
Molise	436,000	436,000	1,017,815	372,000	233	85
Tuscany	1,430,000	1,430,000	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	11,787,200	11,639,200	7,452,965	7,403,200	64	64
Lombardy	474,000	474,000	-	374,000	-	79
Piedmont	5,282,000	5,282,000	3,846,190	4,494,000	73	85
Sardinia	12,800	12,800	-	-	-	-
LPS	5,768,800	5,768,800	3,846,190	4,868,000	67	84
Italy	28,880,400	28,410,400	14,731,325	14,976,600	52	53

For the Regions that used S/D plasma produced by toll fractionation, effective regional self-sufficiency ranged from 2% in Emilia-Romagna to 85% in Marche, Molise and Piedmont.

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.

27,000 IU of protein C were distributed between Marche and Campania, enabling these two Regions to reach a self-sufficiency percentage of 100% and 31% respectively. At national level, the self-sufficiency percentage stood at 7% (Table 90).

Table 90. Estimates of regional and national self-sufficiency in Protein C, 2021

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	5,500	5,500	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Basilicata	-	-	-	-	-	-
Friuli V. G.	-	-	-	-	-	-
Liguria	-	-	-	-	-	-
Umbria	6,000	6,000	-	-	-	-
Veneto	7,500	7,500	-	-	-	-
NAIP	19,000	19,000	-	-	-	-
Apulia	-	-	-	-	-	-
Calabria	179,500	179,500	-	-	-	-
E.-Romagna	2,000	2,000	-	-	-	-
Sicily	29,000	29,000	-	-	-	-
RIPP	210,500	210,500	-	-	-	-
Campania	70,500	70,500	2,871,374	22,000	4,073	31
Latium	22,000	9,000	4,152,835	-	46,143	-
Marche	5,000	5,000	3,304,100	5,000	66,082	100
Molise	-	-	262,855	-	NA	-
Tuscany	500	500	6,924,187	-	1,384,837	-
Min. of Def.	-	-	37,846	-	NA	-
PlaNet	98,000	85,000	17,553,197	27,000	20,651	32
Lombardy	52,000	52,000	-	-	-	-
Piedmont	-	-	-	-	-	-
Sardinia	-	-	-	-	-	-
LPS	52,000	52,000	-	-	-	-
Italy	379,500	366,500	17,553,197	27,000	4,789	7

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 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 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 2021, applying the discounts envisaged by law for pharmaceutical expenditure.

Tables 91 and 92 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 2021, expenditure for the purchase of the aforementioned PDMPs was approximately 186,9 million euros (3.2 euro *per capita*) recording a decrease, compared to 2020, of approximately 2.7 million euros (-1.4%). Table 93 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 421 million euros (7.1 euros *per capita*). The Regions with the highest *per capita* expenditure were Apulia with 10.2 euros *per capita* spent and Calabria with 9.7 euros *per capita*.

The expenditure for recombinant factors decreased compared to 2020 (-6%). Table 94 shows the expenditure incurred in 2021 for the purchase of Emicizumab which has undergone an increase of + 67%, from 0.75 to 1.27 euros *per capita*, reflecting how much the use of this drug is progressively increasing.

In 2021, as regards all the other PDMPs (Tables 95-98), the total expenditure was approximately 109,4 million euros, equal to around 1.85 euros *per capita* of which approximately 36 million for the purchase of specific immunoglobulins, a slightly lower cost compared year 2020 (-7%) (Table 95), also in regard to the *per capita* expenditure equal to 0.61 (0.65 in 2020) (Table 96).

The other MPDs (Tables 97-98), recorded a slightly increase in expenditure compared to the previous year (+5%), in particular as regards 4F-PCCs (+33%), local haemostatics (+20%), FXI (+24%), the other plasma protein fractions (+13%), alpha-1 proteinase (+11%) and C1-inhibitor (+5%). On the other hand, a decrease in expenditure was recorded for activated prothrombin complex concentrates (-25%), FX (-20%), FVII (-5%) and FXIII (-3%).

Table 91. 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 2021

Region	Albumin		Human Immunoglobulin intravenous use		Factor VIII		Total	
	€	€ per capita	€	€ per capita	€	€ per capita	€	€ per capita
Abruzzo	490,084	0.38	341,547	0.27	-	-	831,631	0.65
Aosta Valley	951	0.01	56,307	0.45	-	-	57,258	0.46
AP Bolzano	17,454	0.03	193,890	0.36	-	-	211,344	0.40
AP Trento	73,262	0.14	93,226	0.17	-	-	166,488	0.31
Basilicata	337,938	0.62	590,362	1.08	-	-	928,300	1.70
Friuli V. G.	44,881	0.04	437,996	0.36	-	-	482,877	0.40
Liguria	696,555	0.46	1,566,839	1.03	5,390	0.00	2,268,783	1.49
Umbria	30,555	0.04	396,608	0.46	-	-	427,162	0.49
Veneto	278,728	0.06	1,322,467	0.27	24,195	0.00	1,625,389	0.33
NAIP	1,970,407	0.17	4,999,241	0.44	29,585	0.00	6,999,233	0.61
Apulia	1,988,303	0.51	3,275,114	0.83	176,880	0.04	5,440,298	1.38
Calabria	1,556,923	0.84	47,066	0.03	-	-	1,603,989	0.86
E.-Romagna	171,015	0.04	1,276,781	0.29	-	-	1,447,797	0.33
Sicily	2,626,908	0.54	1,709,629	0.35	-	-	4,336,537	0.90
RIPP	6,343,149	0.42	6,308,591	0.42	176,880	0.01	12,828,621	0.85
Campania	9,150,505	1.63	9,268,721	1.65	-	-	18,419,226	3.27
Latium	2,574,930	0.45	3,324,150	0.58	-	-	5,899,080	1.03
Marche	50,161	0.03	544,218	0.36	-	-	594,379	0.40
Molise	108,440	0.37	-	-	-	-	108,440	0.37
Tuscany	474,246	0.13	7,692,713	2.08	-	-	8,166,960	2.21
Min. of Def.	-	-	-	-	-	-	-	NA
PlaNet	12,358,282	0.73	20,829,802	1.24	-	-	33,188,084	1.97
Lombardy	3,151,777	0.32	8,989,954	0.90	264,332	0.03	12,406,063	1.24
Piedmont	509,332	0.12	4,585,443	1.07	7,678	0.00	5,102,453	1.19
Sardinia	971,381	0.61	700,292	0.44	-	-	1,671,673	1.05
LPS	4,632,490	0.29	14,275,689	0.90	272,010	0.02	19,180,189	1.21
Italy	25,304,329	0.43	46,413,323	0.78	478,475	0.01	72,196,127	1.22

Table 92. 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 2021

Region	SCIG		FVIII/vWF		FIX		3F-PCC		AT		Fibrinogen		Protein C		Total	
	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc	€	€ pc
Abruzzo	1,189,760	0.93	944,301	0.74	-	-	-	-	209,597	0.16	62,480	0.05	10,692	0.01	2,406,137	1.9
Aosta Valley	43,722	0.35	-	-	-	-	11,307	0.09	16,544	0.13	-	-	-	-	71,573	0.6
AP Bolzano	101,760	0.19	618	0.001	3,168	0.01	-	-	35,318	0.07	66,000	0.12	-	-	206,864	0.4
AP Trento	288,207	0.53	24,123	0.04	-	-	38,500	0.07	24,541	0.05	-	-	-	-	375,371	0.7
Basilicata	628,173	1.15	-	-	-	-	572	0.00	89,336	0.16	114,400	0.21	-	-	832,482	1.5
FVG	255,160	0.21	61,050	0.05	-	-	-	-	260,526	0.22	-	-	-	-	576,735	0.5
Liguria	2,115,985	1.39	2,507	0.002	4,536	0.00	133,694	0.09	462,150	0.30	236,104	0.16	-	-	2,954,977	1.9
Umbria	1,440,683	1.66	236,392	0.27	113,520	0.13	-	-	53,084	0.06	189,486	0.22	13,134	0.02	2,033,165	2.3
Veneto	6,140,786	1.26	658,526	0.14	127,732	0.03	464,530	0.10	637,177	0.13	1,320,440	0.27	11,715	0.00	9,349,192	1.9
NAIP	12,204,235	1.06	1,927,517	0.17	248,956	0.02	648,603	0.06	1,788,273	0.16	1,988,910	0.17	35,541	0.00	18,842,036	1.6
Apulia	6,043,424	1.54	3,441,692	0.87	-	-	-	-	42,806	0.01	897,665	0.23	-	-	10,425,588	2.7
Calabria	2,060,208	1.11	802,740	0.43	-	-	-	-	47,724	0.03	682,867	0.37	377,569	0.20	3,593,539	1.9
E.-Romagna	6,496,548	1.46	1,956,361	0.44	-	-	657	0.00	1,485	0.00	1,729,640	0.39	4,378	0.00	10,184,691	2.3
Sicily	5,610,419	1.16	2,264,179	0.47	-	-	6,721	0.00	88,715	0.02	1,083,280	0.22	47,850	0.01	9,053,314	1.9
RIPP	20,210,600	1.34	8,464,972	0.56	-	-	7,378	0.00	180,731	0.01	4,393,452	0.29	429,797	0.03	33,686,930	2.2
Campania	6,046,321	1.08	3,407,886	0.61	-	-	74,894	0.01	683,113	0.12	1,547,040	0.28	80,025	0.01	11,759,254	2.1
Latium	11,753,720	2.05	2,810,383	0.49	4,716	0.00	1,895	0.00	823,551	0.14	1,171,776	0.20	17,545	0.00	16,566,040	2.9
Marche	1,370,278	0.91	237,266	0.16	-	-	-	-	-	-	495,000	0.33	-	-	2,102,544	1.4
Molise	147,930	0.50	163,438	0.56	-	-	-	-	-	-	-	-	-	-	311,367	1.1
Tuscany	7,763,754	2.10	1,064,547	0.29	-	-	1,285	0.00	2,356	0.00	1,339,858	0.36	798	0.00	10,171,800	2.8
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PiaNet	27,082,003	1.61	7,683,520	0.46	4,716	0.00	78,073	0.00	1,509,020	0.09	4,553,675	0.27	98,368	0.01	41,009,373	2.4
Lombardy	6,785,458	0.68	2,277,489	0.23	549,588	0.06	-	-	78,810	0.01	1,589,373	0.16	79,427	0.01	11,280,718	1.1
Piedmont	5,068,769	1.19	1,017,903	0.24	127,023	0.03	47,263	0.01	207	0.00	1,275,120	0.30	-	-	7,536,283	1.8
Sardinia	667,287	0.42	718,327	0.45	-	-	-	-	1,551	0.00	896,720	0.56	-	-	2,283,885	1.4
LPS	12,521,514	0.79	4,013,719	0.25	676,611	0.04	47,263	0.00	80,567	0.01	3,761,213	0.24	79,427	0.01	21,180,313	1.3
Italy	72,018,352	1.22	22,089,727	0.37	930,283	0.02	781,317	0.01	3,558,591	0.06	14,697,250	0.25	643,132	0.01	114,718,652	1.9

Table 93. Estimate of the total expenditure and the total per capita expenditure for recombinant Factors VII, VIII, IX and XIII in 2021

Region	rFVIIa		FVIIIr		FIXr		FXIIIr		Total	
	€	€ pc	€	€ pc	€ pc	€ pc	€	€ pc	€	€ pc
Abruzzo	106,158	0.08	7,017,695	5.48	3,073,903	2.40	419,153	0.33	10,616,909	8.3
Aosta Valley	2,589	0.02	551,006	4.44	-	-	-	-	553,596	4.5
AP Bolzano	-	-	1,383,942	2.59	4,337	0.01	-	-	1,388,279	2.6
AP Trento	266,688	0.49	2,173,136	4.01	153,202	0.28	-	-	2,593,027	4.8
Basilicata	8,415	0.02	1,957,036	3.59	289,723	0.53	201,815	0.37	2,456,989	4.5
FVG	505,544	0.42	2,100,931	1.75	1,393,851	1.16	-	-	4,000,326	3.3
Liguria	1,277,772	0.84	5,634,009	3.71	3,352,009	2.21	419,153	0.28	10,682,944	7.0
Umbria	148,232	0.17	3,716,534	4.29	529,525	0.61	-	-	4,394,291	5.1
Veneto	2,192,414	0.45	18,615,714	3.82	4,798,600	0.99	124,194	0.03	25,730,921	5.3
NAIP	4,507,812	0.39	43,150,003	3.76	13,595,150	1.18	1,164,315	0.10	62,417,280	5.4
Apulia	7,939,796	2.02	22,555,954	5.73	9,747,643	2.48	-	-	40,243,392	10.2
Calabria	2,257,788	1.21	12,980,317	6.98	1,761,124	0.95	1,055,646	0.57	18,054,875	9.7
E.-Romagna	2,850,068	0.64	25,342,920	5.71	6,881,162	1.55	124,194	0.03	35,198,343	7.9
Sicily	1,216,283	0.25	27,746,181	5.74	4,959,653	1.03	-	-	33,922,117	7.0
RIPP	14,263,935	0.95	88,625,371	5.88	23,349,582	1.55	1,179,839	0.08	127,418,728	8.5
Campania	2,291,292	0.41	41,384,913	7.36	8,177,832	1.45	-	-	51,854,037	9.2
Lazio	518,489	0.09	47,093,760	8.22	6,284,709	1.10	-	-	53,896,958	9.4
Marche	401,329	0.27	4,748,242	3.17	1,686,072	1.13	-	-	6,835,643	4.6
Molise	46,606	0.16	1,201,488	4.08	-	-	-	-	1,248,094	4.2
Tuscany	6,879,521	1.86	12,058,196	3.27	7,226,653	1.96	-	-	26,164,370	7.1
Min. of Def.	-	-	-	-	-	-	-	-	-	-
PlaNet	10,137,237	0.60	106,486,599	6.32	23,375,266	1.39	-	-	139,999,102	8.3
Lombardy	3,607,413	0.36	41,827,969	4.19	13,002,438	1.30	558,871	0.06	58,996,691	5.9
Piedmont	2,418,327	0.57	15,895,820	3.72	5,649,464	1.32	62,097	0.01	24,025,707	5.6
Sardinia	205,842	0.13	7,868,691	4.95	28,820	0.02	-	-	8,103,353	5.1
LPS	6,231,581	0.39	65,592,480	4.14	18,680,722	1.18	620,968	0.04	91,125,751	5.8
Italy	35,140,566	0.59	303,854,454	5.13	79,000,719	1.33	2,965,122	0.05	420,960,861	7.1

Table 94. Estimate of the total expenditure and the total per capita expenditure for Emicizumab in 2021

Region	€	€/pc
Abruzzo	1,572,015	1.23
Aosta Valley	-	-
AP Bolzano	534,805	1.00
AP Trento	-	-
Basilicata	677,662	1.24
Friuli V. Giulia.	1,131,777	0.94
Liguria	2,226,467	1.47
Umbria	1,291,993	1.49
Veneto	6,781,281	1.39
NAIP	14,216,000	1.24
Apulia	2,561,764	0.65
Calabria	2,820,239	1.52
E.-Romagna	4,944,344	1.11
Sicily	5,696,141	1.18
RIPP	16,022,487	1.06
Campania	6,938,965	1.23
Lazio	3,158,645	0.55
Marche	1,884,177	1.26
Molise	467,449	1.59
Tuscany	7,628,110	2.07
Min. of Def.	-	-
PlaNet	20,077,347	1.19
Lombardy	15,582,940	1.56
Piedmont	9,297,197	2.17
Sardinia	-	-
LPS	24,880,137	1.57
Italy	75,195,971	1.27

Table 95. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of specific immunoglobulins in 2021

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs	Rabies IGs	Total
Abruzzo	271,795	4,090	223,416	50,921	4,530	4,704	-	559,457
Aosta Valley	74,864	-	14,995	5,361	-	-	2,156	97,375
AP Bolzano	39,731	-	24,797	44,532	1,853	2,672	5,929	119,515
AP Trento	98,485	-	28,352	32,683	-	-	-	159,520
Basilicata	106,897	176	77,461	16,571	12,767	-	-	213,872
Friuli V. Giulia	104,117	-	26,846	102	348,693	13,319	35,790	528,866
Liguria	202,923	11,517	165,751	55,590	7,207	1,609	-	444,598
Umbria	103,748	-	78,053	29,411	4,942	1,868	-	218,022
Veneto	980,328	149,471	184,515	269,335	553,837	1,609	14,014	2,153,108
NAIP	1,982,888	165,254	824,187	504,506	933,829	25,780	57,889	4,494,334
Apulia	2,522,493	236,788	375,989	113,422	147,270	6,027	2,048	3,404,037
Calabria	633,194	51,260	357,026	51,063	95,169	-	-	1,187,711
E.-Romagna	836,700	205,668	334,619	189,701	343,282	7,212	7,977	1,925,160
Sicily	1,415,697	3,438	740,016	125,147	124,301	-	-	2,408,599
RIPP	5,408,084	497,154	1,807,650	479,333	710,022	13,240	10,025	8,925,507
Campania	5,452,466	324,182	1,355,178	84,598	149,807	95	-	7,366,326
Lazio	969,711	80,814	519,846	159,367	46,950	6,951	1,725	1,785,364
Marche	275,298	49,937	216,048	53,537	58,449	14,891	1,617	669,777
Molise	84,595	-	39,180	6,193	-	-	-	129,968
Tuscany	787,216	130,741	559,408	172,362	114,697	2,095	1,725	1,768,244
Min. of Def.	-	-	-	-	-	-	-	-
PiaNet	7,569,286	585,674	2,689,660	476,057	369,904	24,031	5,067	11,719,679
Lombardy	4,712,041	260,344	534,676	376,725	239,072	16,319	1,078	6,140,256
Piedmont	2,296,121	54,475	225,892	182,620	303,309	443	3,665	3,066,525
Sardinia	1,502,445	67,943	204,670	26,624	-	95	-	1,801,777
LPS	8,510,607	382,762	965,237	585,969	542,382	16,857	4,743	11,008,558
Italy	23,470,865	1,630,844	6,286,734	2,045,865	2,556,137	79,908	77,724	36,148,078

Table 96. 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 2021

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs*	Rabies IGs*	Total
Abruzzo	0.21	0.00	0.17	0.04	0.00	3.67	-	0.44
Aosta Valley	0.60	-	0.12	0.04	-	-	17.37	0.78
AP Bolzano	0.07	-	0.05	0.08	0.00	5.00	11.08	0.22
AP Trento	0.18	-	0.05	0.06	-	-	-	0.29
Basilicata	0.20	0.00	0.14	0.03	0.02	-	-	0.39
Friuli V. Giulia	0.09	-	0.02	0.00	0.29	11.08	29.79	0.44
Liguria	0.13	0.01	0.11	0.04	0.0047	1.06	-	0.29
Umbria	0.12	-	0.09	0.03	0.01	2.16	-	0.25
Veneto	0.20	0.03	0.04	0.06	0.11	0.33	2.88	0.44
NAIP	0.17	0.01	0.07	0.04	0.08	2.25	5.04	0.39
Apulia	0.64	0.06	0.10	0.03	0.04	1.53	0.52	0.87
Calabria	0.34	0.03	0.19	0.03	0.05	-	-	0.64
E.-Romagna	0.19	0.05	0.08	0.04	0.08	1.62	1.80	0.43
Sicily	0.29	0.00	0.15	0.03	0.03	-	-	0.50
RIPP	0.36	0.03	0.12	0.03	0.05	0.88	0.67	0.59
Campania	0.97	0.06	0.24	0.02	0.03	0.02	-	1.31
Lazio	0.17	0.01	0.09	0.03	0.01	1.21	0.30	0.31
Marche	0.18	0.03	0.14	0.04	0.04	9.94	1.08	0.45
Molise	0.29	-	0.13	0.02	-	-	-	0.44
Tuscany	0.21	0.04	0.15	0.05	0.03	0.57	0.47	0.48
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	0.45	0.03	0.16	0.03	0.02	1.43	0.30	0.70
Lombardy	0.47	0.03	0.05	0.04	0.02	1.63	0.11	0.62
Piedmont	0.54	0.01	0.05	0.04	0.07	0.10	0.86	0.72
Sardinia	0.94	0.04	0.13	0.02	-	0.06	-	1.13
LPS	0.54	0.02	0.06	0.04	0.03	1.06	0.30	0.69
Italy	0.40	0.03	0.11	0.03	0.04	1.35	1.31	0.61

*value per 1,000 population

Table 97. Estimate of total expenditure incurred by the National Health Service for the purchase of all other PDMPs in 2021

Region	FVII	FVIII inhibitor bypassing activity	Local Haemostatic agents-combinations	Other plasma Proteins fractions	4-factor prothrombin complex concentrates	Alpha-1-proteinase inhibitor	Human C1 esterase inhibitor	Factor X	Factor XI	Factor XIII	Total
Abruzzo	245,027	1,532,828	922,396	-	260,263	452,804	379,755	-	-	-	3,793,073
Aosta Valley	-	-	73,721	-	-	218,962	67,298	-	-	-	359,981
AP Bolzano	-	-	288,239	-	210,386	765,623	117,304	-	-	13,675	1,395,228
AP Trento	-	-	185,303	3,927	11,816	135,680	12,289	-	-	17,582	366,598
Basilicata	32,670	-	470,155	213,777	57,774	-	64,372	-	-	-	838,748
Friuli V. Giulia	-	192,215	478,737	-	-	483,784	21,652	-	101,200	-	1,277,588
Liguria	28,470	156,712	465,687	199,423	187,657	482,435	25,749	-	-	31,258	1,577,390
Umbria	3,267	-	402,804	48,702	88,253	149,160	311,190	-	-	-	1,003,376
Veneto	-	417,486	1,702,602	-	64,909	852,054	1,233,258	-	40,480	119,560	4,430,350
NAIP	309,435	2,299,241	4,989,645	465,829	881,057	3,540,501	2,232,868	-	141,680	182,076	15,042,331
Apulia	129,281	232,320	1,271,523	1,848,083	21,357	559,009	762,137	-	-	-	4,823,710
Calabria	21,002	149,262	1,010,998	395,736	85,792	374,880	483,010	-	-	-	2,520,681
E.-Romagna	104,078	80,805	834,544	265,051	376,029	797,310	458,982	-	-	155,116	3,071,913
Sicily	131,545	521,491	1,609,249	1,179,378	105,623	1,122,264	1,587,883	-	-	-	6,257,433
RIPP	385,907	983,878	4,726,314	3,688,248	588,800	2,853,463	3,292,011	-	-	155,116	16,673,737
Campania	258,185	1,272,163	3,678,743	245,872	427,811	1,723,754	2,226,750	-	-	-	9,833,279
Latium	923,032	117,184	1,617,940	483,420	158,041	923,746	2,614,424	-	-	62,124	6,899,910
Marche	933	297,507	618,353	-	78,674	103,270	219,450	-	-	16,801	1,334,989
Molise	233,360	-	39,949	-	-	10,982	8,467	-	-	-	292,758
Tuscany	13,068	144,469	2,160,873	547,884	396,076	849,414	661,591	-	-	38,291	4,811,665
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlaNet	1,428,578	1,831,322	8,115,859	1,277,175	1,060,602	3,611,167	5,730,681	-	-	117,216	23,172,600
Lombardy	1,130,827	1,865,170	3,038,801	17,169	114,633	2,264,541	2,060,158	52,800	-	41,026	10,585,125
Piedmont	202,556	238,739	1,665,333	-	276,042	911,539	1,290,502	-	-	17,582	4,602,294
Sardinia	-	386,882	425,288	4,734	302,469	1,251,404	763,341	-	-	-	3,134,118
LPS	1,333,383	2,490,790	5,129,422	21,903	693,144	4,427,485	4,114,001	52,800	-	-	18,321,536
Italy	3,457,303	7,605,232	22,961,239	5,453,155	3,223,603	14,432,616	15,369,561	52,800	141,680	513,015	73,210,205

Table 98. Stima della spesa standardizzata (euro per capita ed euro per mille unità di popolazione) per altri medicinali plasmaderivati, anno 2021

Region	FVII	FVIII inhibitor bypassing activity	Local Haemostatic agents-combinations	Other plasma Proteins fractions	4-factor prothrombin complex concentrates	Alpha-1-proteinase inhibitor	Human C1 esterase inhibitor	Factor X*	Factor XI*	Factor XIII*	Total
Abruzzo	0.19	1.20	0.72	-	0.20	0.35	0.30	-	-	-	2.96
Aosta Valley	-	-	0.59	-	-	1.76	0.54	-	-	-	2.90
AP Bolzano	-	-	0.54	-	0.39	1.43	0.22	-	-	25.57	2.61
AP Trento	-	-	0.34	0.01	0.02	0.25	0.02	-	-	32.43	0.68
Basilicata	0.06	-	0.86	0.39	0.11	-	0.12	-	-	-	1.54
Friuli V. Giulia	-	0.16	0.40	-	-	0.40	0.02	-	84.23	-	1.06
Liguria	0.02	0.10	0.31	0.13	0.12	0.32	0.02	-	-	20.58	1.04
Umbria	0.004	-	0.47	0.06	0.10	0.17	0.36	-	-	-	1.16
Veneto	-	0.09	0.35	-	0.01	0.17	0.25	-	8.31	24.55	0.91
NAIP	0.03	0.20	0.43	0.04	0.08	0.31	0.19	-	12.34	15.86	1.31
Apulia	0.03	0.06	0.32	0.47	0.01	0.14	0.19	-	-	-	1.23
Calabria	0.01	0.08	0.54	0.21	0.05	0.20	0.26	-	-	-	1.35
E.-Romagna	0.02	0.02	0.19	0.06	0.08	0.18	0.10	-	-	34.94	0.69
Sicily	0.03	0.11	0.33	0.24	0.02	0.23	0.33	-	-	-	1.29
RIPP	0.03	0.07	0.31	0.24	0.04	0.19	0.22	-	-	10.30	1.11
Campania	0.05	0.23	0.65	0.04	0.08	0.31	0.40	-	-	-	1.75
Lazio	0.16	0.02	0.28	0.08	0.03	0.16	0.46	-	-	10.84	1.20
Marche	0.00	0.20	0.41	-	0.05	0.07	0.15	-	-	11.21	0.89
Molise	0.79	-	0.14	-	-	0.04	0.03	-	-	-	0.99
Tuscany	0.00	0.04	0.59	0.15	0.11	0.23	0.18	-	-	10.37	1.30
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlanNet	0.08	0.11	0.48	0.08	0.06	0.21	0.34	-	-	6.96	1.38
Lombardy	0.11	0.19	0.30	0.002	0.01	0.23	0.21	5.3	-	4.11	1.06
Piedmont	0.05	0.06	0.39	-	0.06	0.21	0.30	-	-	4.11	1.08
Sardinia	-	0.24	0.27	0.003	0.19	0.79	0.48	-	-	-	1.97
LPS	0.08	0.16	0.32	0.001	0.04	0.28	0.26	3.3	-	3.70	1.16
Italy	0.06	0.13	0.39	0.09	0.05	0.24	0.26	0.9	2.39	8.66	1.24

*values per 1,000 population

National and Regional mean price per gram or International Unit

Tables 99-101 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. 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 public structures of the NHS as defined in the annex to the AIFA determination of 05 August 2006 (53).

Regarding albumin (Table 99), the national mean price per gram was 2.67 euros. The variability observed between Regions (range: 1.98-3.96 euro per gram) was affected by the different contribution of each distribution channel to the definition of costs, as well as volumes.

In particular, the mean price paid by NHS facilities was subject to variability that could be linked to the different contracts awarded following a tender procedure, while the cost recorded through the public pharmacies was substantially similar for all Regions.

In point of fact, the prices of the packages and the discounts applied are the same nationwide and the slight differences are probably due to the different composition of the “basket” compared to the dosages and relative prices.

The Liguria, AP of Bolzano, Marche, Tuscany 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 the Aosta Valley, Umbria and Molise, 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 20,790,722 euros (0.50 euros per IU), and almost entirely accounted for the distribution through NHS facilities (96% like in 2020) (Table 100).

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 36,216,211 million euros with a decrease of -7% compared to 2020.

The mean unit price per gram at national level was 46.62 euros (range: 37.04-56.33 euros) (Table 101).

Table 99. 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 2021

Region	Mean price			Demand				Total expenditure			
	NHS facilities €/g	Pharmacies €/g	Total €/g	NHS facilities g	%	Pharmacies g	%	NHS facilities €	%	Pharmacies €	%
Abruzzo	2.25	3.94	2.72	130,438	72%	49,975	28%	293,033	60%	197,051	40%
Aosta Valley	-	3.96	3.96	-	0%	240,00	100%	-	0%	951,39	100%
AP Bolzano	2.43	-	2.43	7,175	100%	-	0%	17,454	100%	-	0%
AP Trento	1.86	3.91	2.24	26,550	81%	6,120	19%	49,356	67%	23,906	33%
Basilicata	2.22	3.94	2.76	83,800	69%	38,488	31%	186,265	55%	151,674	45%
Friuli V. Giulia	1.98	3.90	2.26	17,000	85%	2,900	15%	33,585	75%	11,296	25%
Liguria	2.00	3.94	2.14	303,210	93%	22,903	7%	606,433	87%	90,122	13%
Umbria	2.27	3.95	3.68	1,350	16%	6,960	84%	3,058	10%	27,496	90%
Veneto	1.92	3.94	3.30	26,860	32%	57,645	68%	51,612	19%	227,115	81%
NAIP	2.08	3.94	2.52	596,383	76%	185,230	24%	1,240,796	63%	729,611	37%
Apulia	2.21	3.93	3.44	166,025	29%	412,610	71%	366,739	18%	1,621,564	82%
Calabria	2.21	3.91	3.27	179,675	38%	296,433	62%	397,231	26%	1,159,691	74%
E.-Romagna	1.73	3.91	1.98	76,325	88%	10,030	12%	131,775	77%	39,240	23%
Sicily	2.02	3.89	2.59	703,520	69%	310,835	31%	1,417,898	54%	1,209,010	46%
RIPP	2.06	3.91	2.94	1,125,545	52%	1,029,908	48%	2,313,643	36%	4,029,506	64%
Campania	1.89	3.89	2.66	2,121,435	62%	1,323,553	38%	4,008,408	44%	5,142,097	56%
Latium	1.88	3.93	2.61	634,143	64%	351,415	36%	1,194,382	46%	1,380,548	54%
Marche	2.22	-	2.22	22,563	100%	-	0%	50,161	100%	-	0%
Molise	-	3.95	3.95	-	0%	27,448	100%	-	0%	108,440	100%
Tuscany	2.21	3.89	2.27	201,143	96%	7,725	4%	444,199	94%	30,047	6%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PiaNet	1.91	3.90	2.64	2,979,283	64%	1,710,140	36%	5,697,150	46%	6,661,133	54%
Lombardy	1.95	3.93	2.57	838,853	68%	386,278	32%	1,634,368	52%	1,517,409	48%
Piedmont	2.07	3.94	2.11	237,575	98%	4,255	2%	492,582	97%	16,750	3%
Sardinia	1.87	3.95	2.53	261,800	68%	121,855	32%	489,868	50%	481,513	50%
LPS	1.96	3.93	2.50	1,338,228	72%	512,388	28%	2,616,818	56%	2,015,672	44%
Italy	1.97	3.91	2.67	6,039,438	64%	3,437,665	36%	11,866,407	47%	13,435,922	53%

Table 100. 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 2021

Region	Mean price *			Demand*						Total expenditure*		
	NHS facilities €/UI	Pharmacies €/UI	Total €/UI	NHS facilities UI	%	Pharmacies UI	%	NHS facilities €	%	Pharmacies €	%	
Abruzzo	0.52	-	0.52	1,829,500	100%	-	0%	944,301	100%	-	0%	
Aosta Valley	-	-	-	-	-	-	-	-	-	-	-	
AP Bolzano	0.21	-	0.21	3,000	100%	-	0%	618	100%	-	0%	
AP Trento	0.56	-	0.56	43,000	100%	-	0%	24,123	100%	-	0%	
Basilicata	-	-	-	-	-	-	-	-	-	-	-	
Friuli V. Giulia	0.55	-	0.55	111,000	100%	-	0%	61,050	100%	-	0%	
Liguria	0.42	-	0.42	6,000	100%	-	0%	2,507	100%	-	0%	
Umbria	0.51	-	0.51	462,000	100%	-	0%	236,392	100%	-	0%	
Veneto	0.41	-	0.41	275,500	100%	-	0%	113,111	100%	-	0%	
NAIP	0.51	-	0.51	2,730,000	100%	-	0%	1,382,102	100%	-	0%	
Apulia	0.50	-	0.50	6,894,500	100%	-	0%	3,417,718	100%	-	0%	
Calabria	0.55	0.60	0.55	1,442,000	98%	24,000	2%	788,265	98%	14,475	2%	
E.-Romagna	0.55	-	0.55	3,217,000	100%	-	0%	1,754,977	100%	-	0%	
Sicily	0.52	0.53	0.52	3,869,500	93%	296,000	7%	2,021,096	93%	157,974	7%	
RIPP	0.52	0.54	0.52	15,423,000	98%	320,000	2%	7,982,056	98%	172,449	2%	
Campania	0.62	-	0.62	4,938,500	100%	-	0%	3,081,836	100%	-	0%	
Latium	0.41	0.60	0.41	6,641,500	98%	139,000	2%	2,726,549	97%	83,834	3%	
Marche	0.54	-	0.54	433,000	100%	-	0%	232,471	100%	-	0%	
Molise	0.55	0.60	0.55	284,000	96%	12,000	4%	156,200	96%	7,238	4%	
Tuscany	0.49	-	0.49	2,076,000	100%	-	0%	1,020,195	100%	-	0%	
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	
PiaNet	0.50	0.60	0.50	14,373,000	99%	151,000	1%	7,217,251	99%	91,071	1%	
Lombardy	0.54	0.60	0.55	3,022,500	74%	1,051,000	26%	1,627,200	72%	631,510	28%	
Piedmont	0.36	-	0.36	2,679,500	100%	-	0%	973,550	100%	-	0%	
Sardinia	0.49	-	0.49	1,446,200	100%	-	0%	713,533	100%	-	0%	
LPS	0.46	0.60	0.48	7,148,200	87%	1,051,000	13%	3,314,283	84%	631,510	16%	
Italy	0.50	0.59	0.50	39,674,200	96%	1,522,000	4%	19,895,692	96%	895,030	4%	

* The value does not include Wilfactin (vWF)

Table 101. 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 2021

Region	Mean price per gram (€) NHS facilities* (€/g)	Total demand NHS facilities* (g)	Total expenditure NHS facilities* (€)
Abruzzo	56.21	5,775	324,607
Aosta Valley	56.33	1,000	56,307
AP Bolzano	41.64	4,596	191,382
AP Trento	49.07	1,900	93,226
Basilicata	53.09	3,976	211,082
Friuli V. Giulia	47.95	1,960	93,982
Liguria	52.70	22,475	1,184,479
Umbria	51.38	7,685	394,892
Veneto	37.04	9,563	354,190
NAIP	49.28	58,929	2,904,146
Apulia	49.35	45,041	2,222,550
Calabria	52.19	610	31,859
E.-Romagna	49.37	13,391	661,133
Sicily	43.97	2,508	110,284
RIPP	49.16	61,551	3,025,826
Campania	39.41	159,273	6,276,547
Lazio	44.93	72,832	3,272,274
Marche	55.98	6,130	343,160
Molise	-	-	-
Tuscany	47.96	137,457	6,592,119
Min. of Def.	-	-	-
PlaNet	43.88	375,692	16,484,100
Lombardy	50.88	172,046	8,753,742
Piedmont	46.33	94,010	4,355,585
Sardinia	47.18	14,685	692,812
LPS	49.16	280,741	13,802,139
ITALY	46.62	776,913	36,216,211

* The value does not include Pentaglobin™

FINAL CONSIDERATIONS

The national demand for albumin was still particularly high and confirmed the increase observed in previous years (651 grams per 1,000 population).

An increased demand was observed in particular in Friuli V. Giulia (+53%), in the AP of Trento (+35%), Liguria (+29%) and Molise (+22%). The Regions with the highest standardised demand per 1,000 population were Sardinia, Campania and Sicily with standardised volumes of 874, 823 and 815 grams, respectively.

About 9% of the national demand was distributed through public pharmacies, reaching a quantity of approximately 3,438 kilograms. The pharmacy channel was particularly used in Calabria and Campania where it accounts respectively for 26% and 29% of the regional demands.

In the two-year period 2020-2021 the total demand of IG registered -3.5%; there was a -5% in the demand for SC/IM-IG, and a -3% in the demand for IVIG.

There were notable differences from one region to another. The three Regions with the highest standardised demand per 1,000 population were Tuscany, Aosta Valley and Liguria, with around 190, 169 and 160 grams.

The demand for AT has increased (+13%) in 2021 like the demand of 4F-PCCs (+36%), and the demand for 3F-PCCs (+4%).

As regards the haemophilia A treatment, on one hand, the demand for pdFVIII (alone and in combination with vWF) decreased (-6.5%); on the other, there was a slightly decrease in the demand for rFVIII (-1.2%), despite the increased use of medicinal products with extended half-life FVIII (+73%).

The consumption of Emicizumab also increased significantly (+74%) while the demand for the activated prothrombin complex fell sharply (-33%).

Concerning the haemophilia B treatment, the clinical use of recombinant FIX (+7% compared to 2020) progressively replaced the demand for pdFIX.

The total volume of plasma sent by Regions for fractionation increased by +2% compared to previous year. There were still great differences in the volumes from one Region to another, ranging from 6 kilograms per 1,000 population sent by Campania to 24.3 sent by Friuli V. Giulia, with an average volume of 14.5 kilograms per 1,000 population.

The level of albumin self-sufficiency fell to 71% of the NHS demand (76% in 2020). 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%, while self-sufficiency in IV IG reached 82% (excluding high titre Ig); self-sufficiency for SC / IM IG was only 10%.

The self-sufficiency of AT was equal to 73% of the NHS demand, a sharp decline compared to the year 2020 in which it was equal to 83%.

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 99 million euros, in line with the costs estimated by the contracts in force in 2021 and approximately 3 million euros had to be taken into account for the treatment of plasma virus-inactivated by solvent / detergent, for a total of approximately 102 million euros.

The estimated expenditure incurred by the NHS in 2021 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 186.9 million euros. An additional 109.4 million euros were used for the purchase of all the other PDMPs. The cost of purchasing Emicizumab was 75 million euros. The expenditure associated to recombinant products was about 421 million euros. The total expenditure for medicinal products described in this report was around 3.6% of the total NHS pharmaceutical expenditure recorded in 2021 (54).

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