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Demand for plasma-derived medicinal products in Italy. 2020

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

ISTITUTO SUPERIORE DI SANITÀ

Demand for plasma-derived medicinal products in Italy. 2020

Fabio Candura (a), Maria Simona Massari (a), Samantha Profili (a), Lucia De Fulvio (a), Cristiana Chelucci (b), Chiara Brutti (c), Claudia Biffoli (c), Vincenzo De Angelis (a)

(a) Centro Nazionale Sangue, Istituto Superiore di Sanità, Roma
(b) Centro nazionale per il controllo e la valutazione dei farmaci, Istituto Superiore di Sanità, Roma
(c) Direzione Generale del Sistema Informativo, Ministero della Salute, Roma

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The Italian National Blood Centre in compliance with the national regulations about the coordination and provision of technical support to the regional and national planning of self-sufficiency in blood components and plasma-derived medicinal products, has conducted this analysis in collaboration with the Information and Statistics Department of the Italian Health Ministry. The analysis of the demand for plasma-derived medicinal products and recombinant therapies includes the assessment of self-sufficiency levels achieved and the costs sustained by the Italian National Health Service for the provision of these products. The content of this document, an update of the data for the year 2020 published in the ISTISAN 21/13 Report, stems from a comparative analysis of the available data sources, thus representing an invaluable tool for planning self-sufficiency at national level.
Key words: Plasma-derived medicinal products; Demand; Self-sufficiency; Expenditure

Istituto Superiore di Sanità
Analisi della domanda di medicinali plasmaderivati in Italia. 2020
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Al fine di adempiere ai compiti ad esso assegnati dalla normativa vigente in materia di coordinamento e supporto tecnico alla programmazione dell'autosufficienza regionale e nazionale di emocomponenti e medicinali plasmaderivati, il Centro Nazionale Sangue ha effettuato, in collaborazione con l'Ufficio IV della Direzione Generale del Sistema Informativo e Statistico Sanitario del Ministero della Salute, l'analisi della domanda dei prodotti medicinali plasmaderivati e delle alternative terapeutiche di natura ricombinante, le valutazioni dei livelli di autosufficienza regionale e nazionale e la stima della spesa farmaceutica a carico del Servizio Sanitario Nazionale. Il confronto delle diverse fonti dati disponibili ha consentito l'elaborazione del presente documento che riporta l'aggiornamento relativo all'anno 2020 dei dati sull'argomento pubblicati nel Rapporto ISTISAN 21/13 e che si configura come uno strumento fondamentale per la programmazione dell'autosufficienza nazionale.
Parole chiave: Medicinali plasmaderivati; Domanda; Autosufficienza; Spesa

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

viale Regina Elena, 299 – 00161 Roma

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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
Friuli V. Giulia	Friuli Venezia Giulia
FU/s	FEIBA Unit/s
FVG	Friuli Venezia Giulia
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. 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
S/D	Solvent / Detergent (plasma)
SC/IM	SubCutaneous/IntraMuscular
ST/s	Transfusion Service/s
UdR	Collection Units run by Donor Associations
VAT	Value Added Tax
vWF	von Willebrand Factor
WHO	World Health Organisation

FOREWORD

The Italian National Blood Centre (Centro Nazionale Sangue, CNS) is a technical body of the Italian Ministry of Health (MoH) which operates under the National Institute of Health in Rome. 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 primarly provides guidelines regarding the strategic objectives of the transfusion system, which include achieving and maintaining self-sufficiency at regional and national level in labile blood components and PDMPs.

This report relating to the calendar year 2020, 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 2019, 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 2020, issued by DM of 24 July 2020.

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 2019, 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. 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.

Pending the full implementation of the new agreements and the completion of the tender by the fourth interregional agreement for toll-fractionation, consisting of Lombardy, Piedmont and Sardinia, in addition to the products supplied by CSL Behring, in 2020 they contributed to national self-sufficiency the following PDMPs by toll-fractionation, produced by the company Kedrion SpA (hereinafter Kedrion) under the contract prior to the expansion of possible business partners: albumin, IVIG, SCIG, Anti-Thrombin (AT), pdFVIII, plasma-derived Factor IX concentrates (pdFIX), 3-Factor Prothrombin Complex Concentrates (3-PCCs) and plasma virus-inactivated by solvent / detergent.

Inasmuch as the clinical interest and its impact on the pharmaceutical expenditure, the Report describes the demand for other PDMPs and for the recombinant medicinal products used for the

treatment of congenital and acquired bleeding disorders distributed through commercial channels, with a particular concern to long-acting and innovative haemostatic products.

Hence, for each of the PDMPs whose supply is provided for the contracts between the Regions and the fractionators (Kedrion and CSL Behring), 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 Helth System (NHS) for procurement on the market, regardeless 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 throughtout the entire supply chain process (Figure 1).

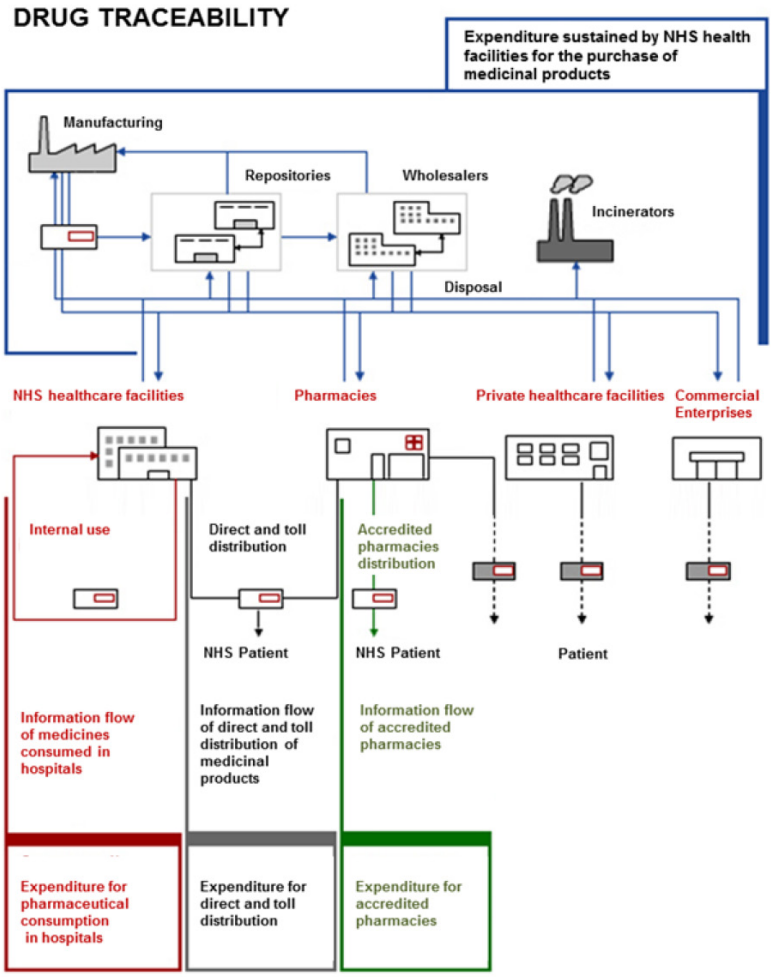

Figure 1. The drug traceability system in Italy (adapted by the CNS on data from www.salute.gov.it)

Pursuant to Italian law, if the final receiver is a public entity (e.g., hospital pharmacies, public healthcare facilities, etc.), the payment due is detected 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 (Law 326/2003) (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).

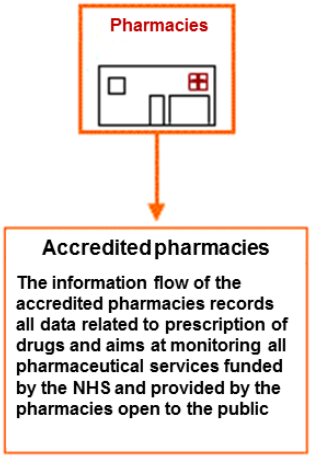

Figure 2. Scope of the information flow of accredited pharmacies (adapted by the CNS on data from www.salute.gov.it)

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.

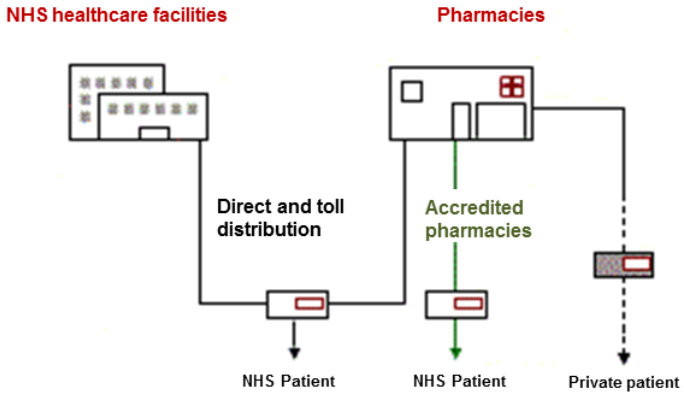

Figure 3. Medicinal products information flow (adapted by theCNS on data from www.salute.gov.it)

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 there 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.

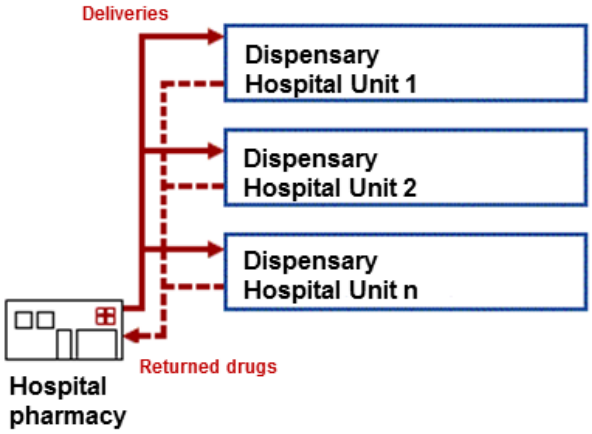

Figure 4. Information flow of medicines consumed in hospitals (adapted by the CNS on data from www.salute.gov.it)

Data on plasma-derived medicinal products produced from Italian plasma

The CNS receives the data regarding the PDMPs distributed by Kedrion and CSL Behring 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 11February 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, 2019-2020 (adapted by the CNS on data from ISTAT, 31/8/2021)

Region	2019	2020
Abruzzo	1,311,580	1,293,941
Aosta Valley	125,666	125,034
AP Bolzano	531,178	532,644
AP Trento	541,098	545,425
Apulia	4,029,053	3,953,305
Basilicata	562,869	553,254
Calabria	1,947,131	1,894,110
Campania	5,801,692	5,712,143
Emilia-Romagna	4,459,477	4,464,119
Friuli V. Giulia	1,215,220	1,206,216
Latium	5,879,082	5,755,700
Liguria	1,550,640	1,524,826
Lombardy	10,060,574	10,027,602
Marche	1,525,271	1,512,672
Molise	305,617	300,516
Piedmont	4,356,406	4,311,217
Sardinia	1,639,591	1,611,621
Sicily	4,999,891	4,875,290
Tuscany	3,729,641	3,692,555
Umbria	882,015	870,165
Veneto	4,905,854	4,879,133
Italy	60,359,546	59,641,488

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 PDMP considered in the agreements between the Regions and their affiliated Companies (Kedrion and CSL Behring), the degree of self-sufficiency achieved was assessed by comparing the actual supply with 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 2019 to June 2020. By contrast, by effective supply (or toll fractionation) is meant the quantity of PDMPs *de facto* distributed by Kedrion and CSL Behring to each Region during the 2020 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 reffered 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 31/12/2020, 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, 31/12/2020)

AIC code	Brand name	g	Manufacturer	NHS class
034611032	ALBUMINA GRIFOLS*1FL 100mL 5%	5	GRIFOLS ITALIA SpA	C
036504025	ALBUREX* INFUS 1FL 100mL 5%	5	CSL BEHRING GmbH	C
039187012	ALBUNORM*1FL 100mL 5% 50g/L	5	OCTAPHARMA Italy SPA	C
010317028	ALBUMINA UM.IMMUNO*50mL 20%+S.	10	BAXTER SpA	A
011544020	ALBUMINA BEHRING*IV 50mL20%	10	CSL BEHRING SpA	A
021111024	UMANALBUMIN*INF FL 50mL 200g/L	10	KEDRION SpA	A
022515163	ALBITAL*1FL 50mL SOLUZ 20%+SET	10	KEDRION SpA	A
028989046	PLASBUMIN*EV 1FL 50mL 200g/L	10	GRIFOLS ITALIA SpA	A
029251030	ALBUTEIN*IV FL 50mL 200g/L	10	GRIFOLS ITALIA SpA	A
034611018	ALBUMINA GRIFOLS*1FL 50mL 20%	10	GRIFOLS ITALIA SpA	A
036176016	ALBUMINA LFB*FL 50mL 200mg/mL	10	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)
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
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

AIC code	Brand name	g	Manufacturer	NHS class
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)
029251028	ALBUTEIN*IV FL 500mL 50g/L	25	GRIFOLS ITALIA SpA	C
034611057	ALBUMINA GRIFOLS*1FL 500mL 5%	25	GRIFOLS ITALIA SpA	C
034611071	ALBUMINA GRIFOLS25g/100mL	25	GRIFOLS ITALIA SpA	H
036504049	ALBUREX* INFUS 1FL 500mL 5%	25	CSL BEHRING GmbH	C
036504088	ALBUREX* INFUS 1FL 100mL 25%	25	CSL BEHRING GmbH	H
037566039	ALBUMINA BAXTER*1FL 500mL 50 g/L	25	BAXALTA Italy Srl	C
037566116	ALBUMINA BAXTER*1FL100mL 250g/L	25	BAXALTA Italy Srl	H
038109082	FLEXBUMIN*1SACCA 100mL 250g/L	25	BAXALTA Italy Srl	H
039187051	ALBUNORM" 1 FL 500mL 5%, 50 g/L	25	OCTAPHARMA Italy SPA	C
039187113	ALBUNORM* 1 FL 100mL 25%, 250 g/L	25	OCTAPHARMA Italy SPA	H
039187024	ALBUNORM*10FL 100mL 5% 50g/L	50	OCTAPHARMA Italy SPA	C
036176030	ALBUMINA 200 mg/mL INF 6*50mL	60	LFB	C
039187075	ALBUNORM* 10FL 50mL20%, 200 g/L	100	OCTAPHARMA Italy SPA	H
036176042	ALBUMINA 200 mg/mL INF 6*100mL	120	LFB	C
039187048	ALBUNORM* 10FL 250mL 5%, 50 g/L	125	OCTAPHARMA Italy SPA	C
039187099	ALBUNORM*10FL 100mL 20%, 200 g/L	200	OCTAPHARMA Italy SPA	H
038109017	FLEXBUMIN*24SACCHE 50mL 200g/L	240	BAXALTA Italy Srl	H
038109031	FLEXBUMIN*12SACCHE 100mL200g/L	240	BAXALTA Italy Srl	H
037566041	ALBUMINA BAXTER*10FL 500mL 50 g/L	250	BAXALTA Italy Srl	C
037566027	ALBUMINA BAXTER* 24FL 250mL 50 g/L	300	BAXALTA Italy Srl	C
038109029	FLEXBUMIN*12SACCHE 100mL 250 g/L	300	BAXALTA Italy Srl	H
038109043	FLEXBUMIN*24SACCHE50mL 250g/L	300	BAXALTA Italy Srl	H
037566066	ALBUMINA BAXTER*70FL 50mL 200 g/L	700	BAXALTA Italy Srl	H
037566104	ALBUMINA BAXTER*70FL 50mL 250 g/L	875	BAXALTA Italy Srl	H
037566080	ALBUMINA BAXTER*56FL 100mL 200 g/L	1120	BAXALTA Italy Srl	H
037566128	ALBUMINA BAXTER*56FL 100mL 250 g/L	1400	BAXALTA Italy Srl	H

Quantification and characterisation of the demand

Table 6 shows the total demand (expressed in grams) and the total standardised demand (expressed in grams per 1,000 population) of albumin[1] for the two-year period 2019-2020 with the variations in percentage, both at national and regional levels.

In 2020, the national demand for this ingredient was about 36,213 kilograms (Table 6), equal to 607 grams per 1,000 population. The two Regions with the highest standardised demand were Sardinia and Campania with values equal to 863 and 748 grams per 1,000 population, respectively. The Regions with the lowest demand were the AP of Trento and Friuli V.Giulia, with about 330 and 318 grams per 1,000 population, respectively (Figure 5).

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

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	788,006	600.8	864,860	668.4	11.2
Aosta Valley	54,740	435.6	63,070	504.4	15.8
APBolzano	170,735	321.4	193,950	364.1	13.3
APTrento	169,975	314.1	180,108	330.2	5.1
Apulia	2,149,115	533.4	2,157,803	545.8	2.3
Basilicata	374,618	665.6	413,815	748.0	12.4
Calabria	1,177,356	604.7	1,187,863	627.1	3.7
Campania	4,868,173	839.1	4,275,738	748.5	-10.8
E.-Romagna	2,719,348	609.8	2,629,565	589.0	-3.4
Friuli V. Giulia	485,748	399.7	383,435	317.9	-20.5
Latium	3,640,838	619.3	3,433,058	596.5	-3.7
Liguria	681,253	439.3	868,725	569.7	29.7
Lombardy	6,558,565	651.9	7,196,825	717.7	10.1
Marche	677,360	444.1	853,210	564.0	27.0
Molise	215,810	706.1	139,678	464.8	-34.2
Piedmont	1,524,778	350.0	1,804,635	418.6	19.6
Sardinia	1,406,075	857.6	1,390,663	862.9	0.6
Sicily	3,593,925	718.8	3,535,708	725.2	0.9
Tuscany	1,418,978	380.5	1,515,105	410.3	7.8
Umbria	487,178	552.3	554,660	637.4	15.4
Veneto	2,331,200	475.2	2,570,970	526.9	10.9
Italy	35,493,769	588.0	36,213,440	607.2	3.3

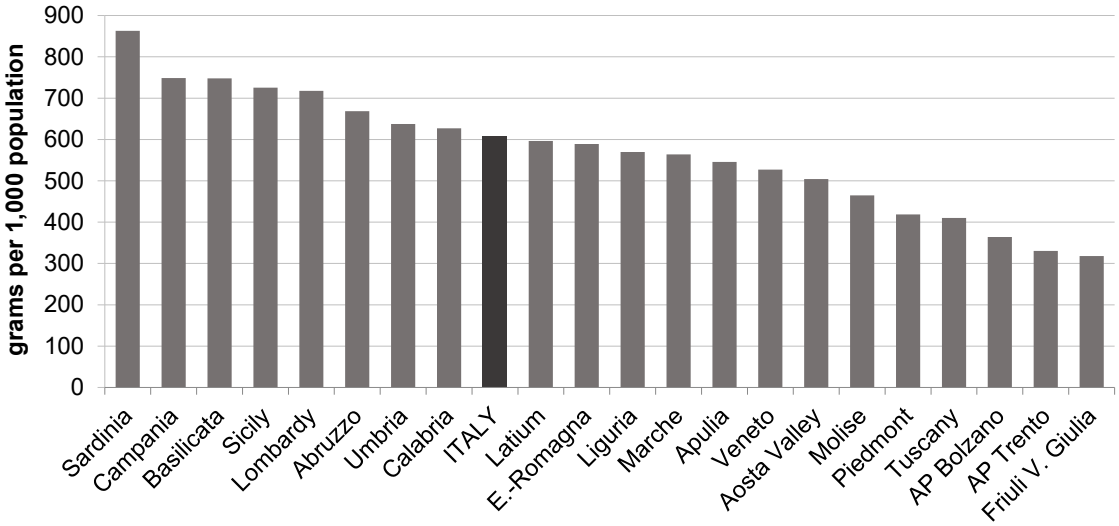

Figure 5. Total and regional demand (public and private) for albumin, expressed in grams per 1,000 population, 2020 (adapted by the CNS on data from the Traceability information flow)

In this two-year period, the total standardised demand for albumin showed a constant trend with respect to previous years (+3.3% compared to 2019) (17). The regions where the containment of use was most evident are Molise (-34%) and Friuli V.Giulia (-21%). Liguria (+30%), Marche (+27%) and Piedmont (+20%) 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 40% for one of them. Figure 7 shows the standardised regional demand for albumin recorded in 2020 per distribution channel (public pharmacies compared to other facilities), as shown by the drug Traceability system (18).

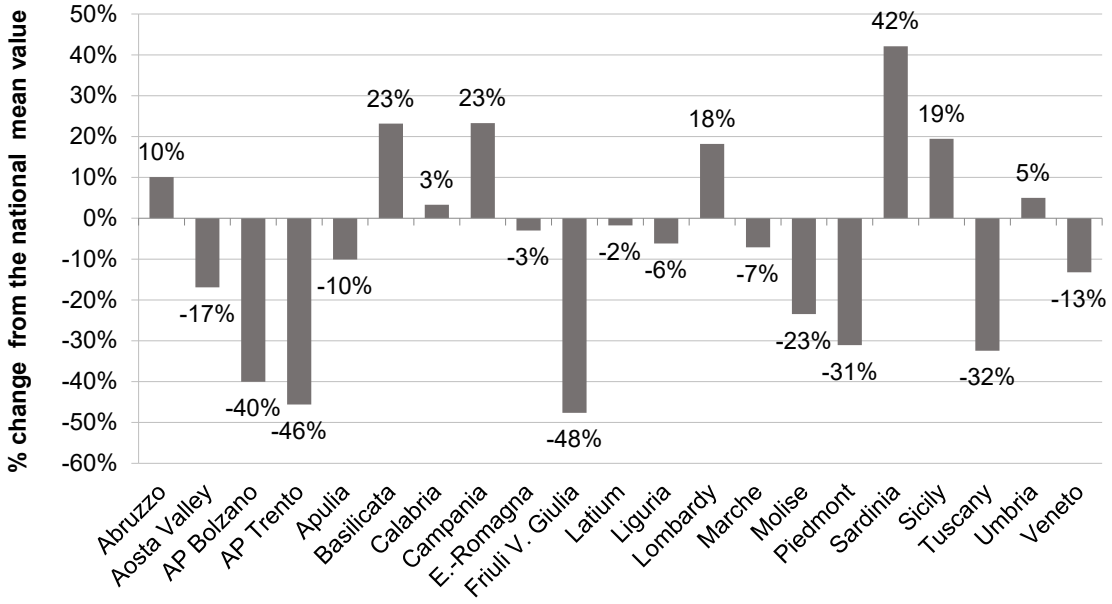

Figure 6. Percentage change from the national mean value of standardised regional demand for human albumin in 2020 (adapted by the CNS on data from the Traceability information flow)

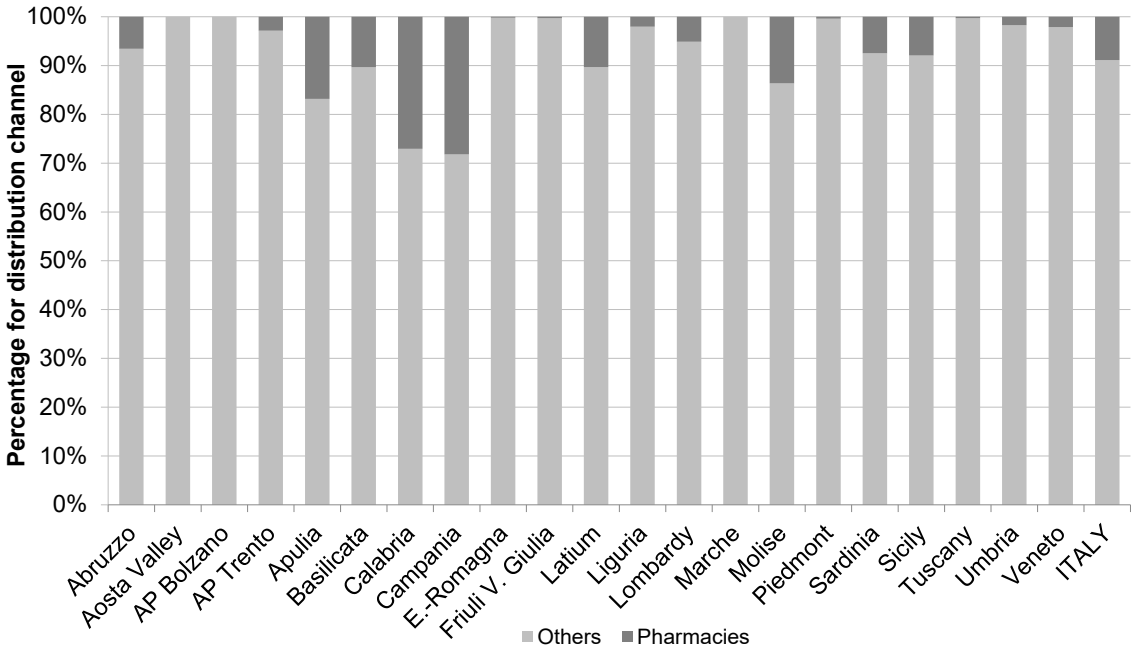

Figure 7. Standardised regional demand for albumin recorded per distribution channel, 2020 (adapted by the CNS on data from the Traceability information flow)

In 2020, about 9% of the national demand - approximately 3,221 kilograms - was distributed through public pharmacies.

Pharmacies as a distribution channel were particularly used in Campania and Calabria, where they accounted for 28% and 27% respectively of regional demand; they were still used to a lesser extent in Latium, Molise, Basilicata and Apulia (with percentages of between 10 and 17% 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, 31/12/2020)

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(nn)
040652075	OCTANORM*1FL 6mL 165mg/mL	0.99	OCTAPHARMA Italy SPA	H
041157013	HIZENTRA*SC 1FL 5mL 200mg/mL	1	CSL BEHRING SpA	H
041157153	HIZENTRA*SC 1SIR 5mL 200mg/mL	1	CSL BEHRING SpA	C(nn)
044244010	CUVITRU*SC 1FL 5mL 200mg/mL	1	BAXALTA Italy Srl	H
043396011	NAXIGLO*SC FL 10mL 160mg/mL	1.6	KEDRION SpA	H
043398015	KEYCUTE*SC FL 10mL 160mg/mL	1.6	KEDRION SpA	H
040652012	OCTANORM*1FL10mL 165mg/mL	1.65	OCTAPHARMA Italy SPA	H
045996028	CUTAQUIG*SC 1 FL 10 mL 165 mg/mL	1.65	OCTAPHARMA Italy SPA	C(nn)
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(nn)
041157049	HIZENTRA*SC 1FL 10mL 200mg/mL	2	CSL BEHRING SpA	H
041157177	HIZENTRA*SC 1SIR 10mL 200mg/mL	2	CSL BEHRING SpA	C(nn)
044244022	CUVITRU*SC 1FL 10mL 200mg/mL	2	BAXALTA Italy Srl	H
042804017	HYQVIA*SC 1FL 25mL+1FL 1,25mL	2.5	BAXALTA Italy Srl	H
041157076	HIZENTRA*1FL 15mL 200 mg/mL	3	CSL BEHRING SpA	H
040652048	OCTANORM*1FL 20mL 165mg/mL	3.3	OCTAPHARMA Italy SPA	H
045996042	CUTAQUIG*SC 1 FL 20 mL 165 mg/mL	3.3	OCTAPHARMA Italy SPA	C(nn)
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(nn)
041157102	HIZENTRA*SC 1FL 20mL 200mg/mL	4	CSL BEHRING SpA	H
043396023	NAXIGLO*SC FL 25mL 160mg/mL	4	KEDRION SpA	H
043398027	KEYCUTE*SC FL 25mL 160mg/mL	4	KEDRION SpA	H
044244034	CUVITRU*SC 1FL 20mL 200mg/mL	4	BAXALTA Italy Srl	H
042804029	HYQVIA*SC 1FL 50mL+1FL 2,5mL	5	BAXALTA Italy Srl	H

AIC code	Brand name	g	Manufacturer	NHS class
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(nn)
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(nn)
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)
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(nn)
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(nn)
045996131	CUTAQUIG*SC 20 FL 6 mL 165 mg/mL	19.8	OCTAPHARMA Italy SPA	C(nn)
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(nn)
045996143	CUTAQUIG*SC 20 FL 10 mL 165 mg/mL	33	OCTAPHARMA Italy SPA	C(nn)
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(nn)
045996156	CUTAQUIG*SC 20 FL 12 mL 165 mg/mL	39.6	OCTAPHARMA Italy SPA	C(nn)
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(nn)
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(nn)
045996170	CUTAQUIG*SC 20 FL 24 mL 165 mg/mL	79.2	OCTAPHARMA Italy SPA	C(nn)
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
045996182	CUTAQUIG*SC 20 FL 48 mL 165 mg/mL	158.4	OCTAPHARMA Italy SPA	C(nn)
044244135	CUVITRU*SC 20FL 40mL 200 mg/mL	160	BAXALTA INN. GMBH	C(nn)
Normal human immunoglobulin for intravenous use				
029021019*	PENTAGLOBIN*EV FL 50mg/mL 10mL	0.5	BIOTEST ITALIA Srl	C
029249075	PLITAGAMMA *INF 1 FL 10mL 50mg/mL	0.5	INSTITUTO GRIFOLS SA	H
040267015	FLEBOGAMMA*INF 1FL 10mL 50 mg/mL	0.5	GRIFOLS ITALIA SpA	H

AIC code	Brand name	g	Manufacturer	NHS class
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
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

AIC code	Brand name	g	Manufacturer	NHS class
045410053	GAMUNEX *INF 1FL100mL 100mg/mL C.o	10	Grifols Deutschland GmbH	H
029249087	PLITAGAMMA*INF 1 FL 400mL 50mg/mL	20	INSTITUTO GRIFOLS SA	H
035143066	OCTAGAM*IV 2FL 200mL 50mg/mL	20	OCTAPHARMA Italy SPA	H
037107051	KIOVIG*EV FL 200mL 100mg/mL	20	BAXTER SpA	H
039457041	GAMTEN*INF 1 FL 200mL 100mg/mL	20	OCTAPHARMA Italy SPA	H
039712031	PRIVIGEN*EV 1FL 200mL 100mg/mL	20	CSL BEHRING SpA	H
040267054	FLEBOGAMMA DIF*FL 400mL 20g	20	GRIFOLS ITALIA SpA	H
040267080	FLEBOGAMMA DIF*EV 200mL 20g	20	GRIFOLS ITALIA SpA	H
043736040	IQYMUNE*FL INF 200mL 100mg/mL	20	LFB	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
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 2019-2020 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 2020, the total national demand for IGs was 6,763,471 grams, equal to 113.4 grams per 1,000 population (Table 8). The three Regions with the highest standardised demand per 1,000 population were Aosta Valley with around 228 grams and Tuscany and Molise, both with around 205 grams per 1,000 population. The demand was lower in Sardinia, Calabria, Sicily and Basilicata, where it was between 62 and 77 grams per 1,000 population. The demand for these PDMPs rose sharply in the two-year period 2019-2020 (+7%), especially for the SC/IM formulations (+25%), featuring notable differences from one Region to another. However, a noteworthy decrease occurred in Latium Region (-6%).

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 (37.9%), Umbria (37.3%), Basilicata (37%) and Calabria (33.3%) while fewer were used in Friuli V. Giulia, Aosta Valley and Molise (<6.5%). At national level, the demand for SC/IM IGs stood at 24% of the total demand for IGs (21% in 2019).

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	123,896	94.5	142,883	110.4	16.9
Aosta Valley	24,098	191.8	28,545	228.3	19.1
AP Bolzano	46,847	88.2	50,274	94.4	7.0
AP Trento	51,816	95.8	54,273	99.5	3.9
Apulia	464,367	115.3	475,033	120.2	4.3
Basilicata	35,573	63.2	42,666	77.1	22.0
Calabria	118,200	60.7	122,730	64.8	6.7
Campania	448,300	77.3	476,261	83.4	7.9
E.-Romagna	506,953	113.7	557,477	124.9	9.9
Friuli V. Giulia	117,266	96.5	144,953	120.2	24.5
Latium	671,547	114.2	620,464	107.8	-5.6
Liguria	238,587	153.9	264,090	173.2	12.6
Lombardy	953,728	94.8	965,518	96.3	1.6
Marche	217,951	142.9	213,808	141.3	-1.1
Molise	45,059	147.4	61,537	204.8	38.9
Piedmont	526,250	120.8	560,389	130.0	7.6
Sardinia	99,427	60.6	99,037	61.5	1.3
Sicily	348,393	69.7	376,267	77.2	10.8
Tuscany	682,203	182.9	756,288	204.8	12.0
Umbria	101,526	115.1	117,566	135.1	17.4
Veneto	586,903	119.6	633,411	129.8	8.5
Italy	6,408,888	106.2	6,763,471	113.4	6.8

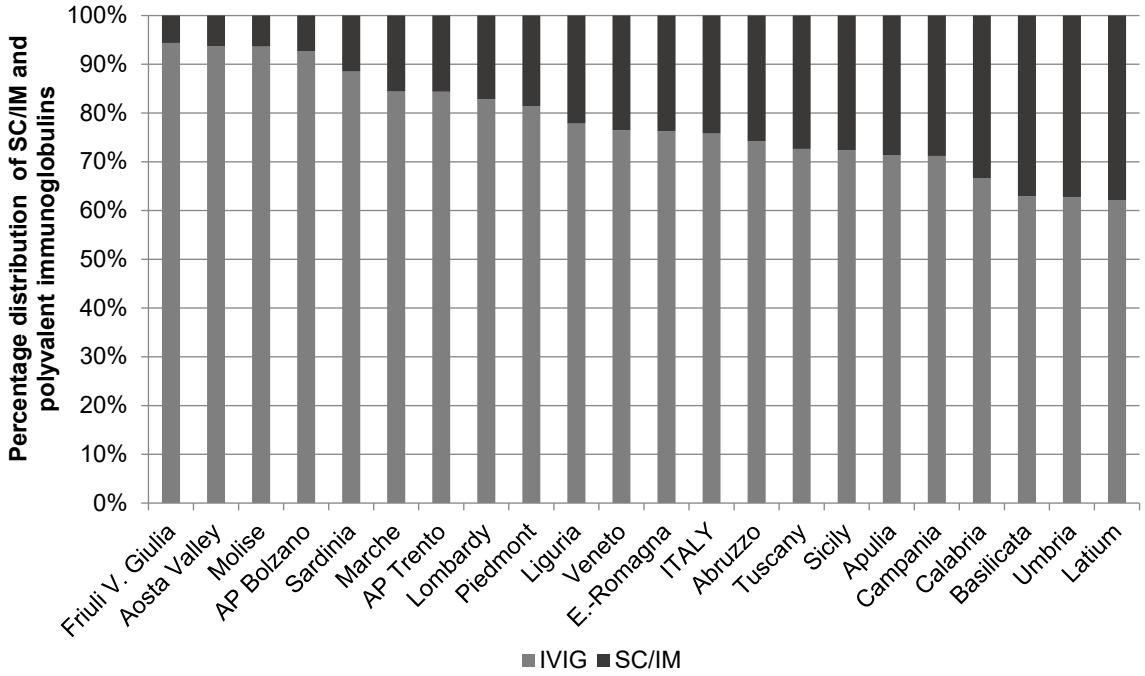

Figure 8. Total standardised demand (public and private) per administration of immunoglobulins (percentage on total), by Region, 2020 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for subcutaneous use

In 2020, the total demand for SC/IM IGs reached about 1,637,296 grams (27.5 grams per 1,000 population), with an increase of 25% compared to 2019 (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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	32,252	24.6	36,783	28.4	15.6
Aosta Valley	2,163	17.2	1,806	14.4	-16.1
AP Bolzano	4,151	7.8	3,700	6.9	-11.1
AP Trento	5,386	10.0	8,488	15.6	56.3
Apulia	119,373	29.6	136,342	34.5	16.4
Basilicata	11,480	20.4	15,807	28.6	40.1
Calabria	34,748	17.8	40,895	21.6	21.0
Campania	113,749	19.6	137,149	24.0	22.5
E.-Romagna	109,782	24.6	132,224	29.6	20.3
Friuli V. Giulia	5,008	4.1	8,138	6.7	63.7
Latium	186,314	31.7	235,300	40.9	29.0
Liguria	45,487	29.3	58,545	38.4	30.9
Lombardy	107,879	10.7	165,844	16.5	54.2
Marche	26,846	17.6	33,333	22.0	25.2
Molise	3,459	11.3	3,927	13.1	15.5
Piedmont	97,821	22.5	104,048	24.1	7.5
Sardinia	7,397	4.5	11,375	7.1	56.5
Sicily	88,861	17.8	104,059	21.3	20.1
Tuscany	170,137	45.6	206,787	56.0	22.8
Umbria	32,231	36.5	43,816	50.4	37.8
Veneto	118,001	24.1	148,931	30.5	26.9
Italy	1,322,527	21.9	1,637,296	27.5	25.3

The regional demands proved diversified where the highest values, between 56 and 38 grams per 1,000 population, were recorded in Tuscany, Umbria, Latium and Liguria, while the lowest values were recorded in Friuli V. Giulia, AP of Bolzano and Sardinia and were equal to 7 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: 4-104%) (Figure 10).

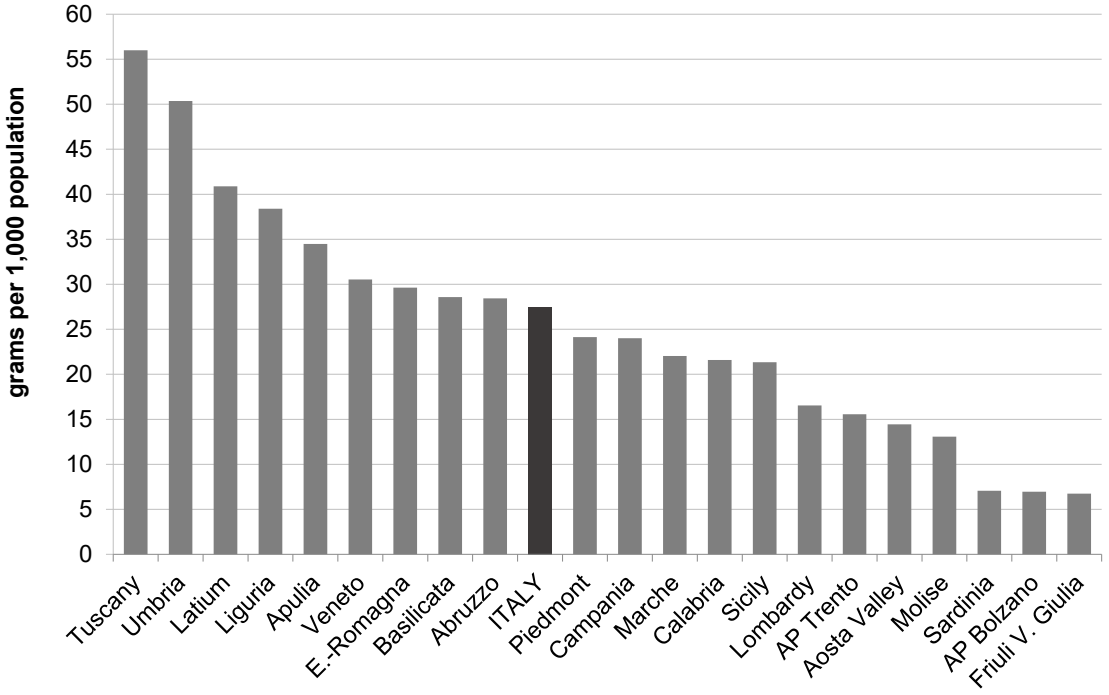

Figure 9.Total and regional demand (public and private) for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams per 1,000 population, 2020 (adapted by the CNS on data from the Traceability information flow)

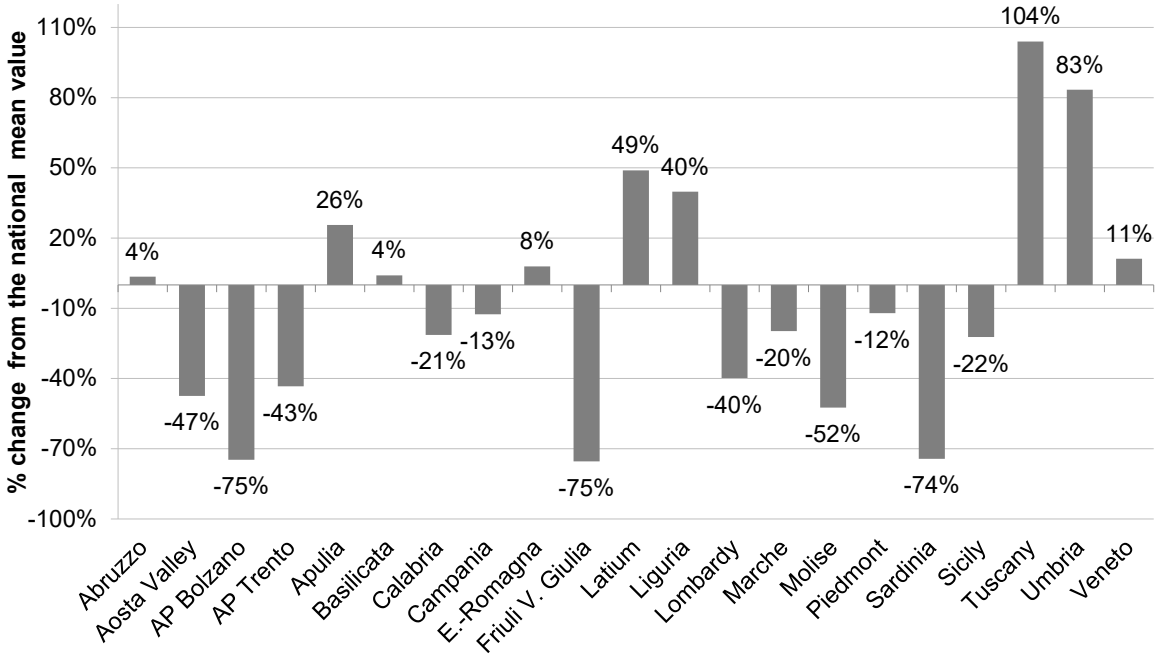

Figure 10. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for subcutaneous/ intramuscular use in 2020 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for intravenous use

Finally, Table 10 reports on the total and standardised demands for IG for intravenous use in 2019-2020. Even, in this case, a general upward trend (about +2%) was observed, while it was not confirmed in Latium, Lombardy, Marche and Sardinia.

However, for these Regions, a substitution of the use of preparations for IV administration with those for SC / IM administration appears likely.

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	91,644	69.9	106,100	82.0	17.4
Aosta Valley	21,935	174.5	26,739	213.9	22.5
AP Bolzano	42,696	80.4	46,574	87.4	8.8
AP Trento	46,430	85.8	45,785	83.9	-2.2
Apulia	344,993	85.6	338,691	85.7	0.1
Basilicata	24,093	42.8	26,859	48.5	13.4
Calabria	83,452	42.9	81,835	43.2	0.8
Campania	334,551	57.7	339,112	59.4	3.0
E.-Romagna	397,171	89.1	425,254	95.3	7.0
Friuli V. Giulia	112,258	92.4	136,815	113.4	22.8
Latium	485,232	82.5	385,164	66.9	-18.9
Liguria	193,100	124.5	205,545	134.8	8.2
Lombardy	845,848	84.1	799,674	79.7	-5.1
Marche	191,105	125.3	180,475	119.3	-4.8
Molise	41,600	136.1	57,610	191.7	40.8
Piedmont	428,430	98.3	456,341	105.8	7.6
Sardinia	92,030	56.1	87,663	54.4	-3.1
Sicily	259,532	51.9	272,208	55.8	7.6
Tuscany	512,067	137.3	549,501	148.8	8.4
Umbria	69,295	78.6	73,750	84.8	7.9
Veneto	468,902	95.6	484,480	99.3	3.9
Italy	5,086,361	84.3	5,126,175	85.9	2.0

Figure 11 shows the standardised regional demand for IVIGs in 2020 as recorded by the drug Traceability system. The highest demand for IVIGs was recorded in Aosta Valley, Molise and Tuscany, with volumes ranging between 149 and 214 grams per 1,000 population (+149%, +123% and +73% respectively, compared to the national mean value – Figure 12). The Regions where the standardized demand is lower were Basilicata and Calabria with recorded volumes between 43 and 49 grams per 1,000 population.

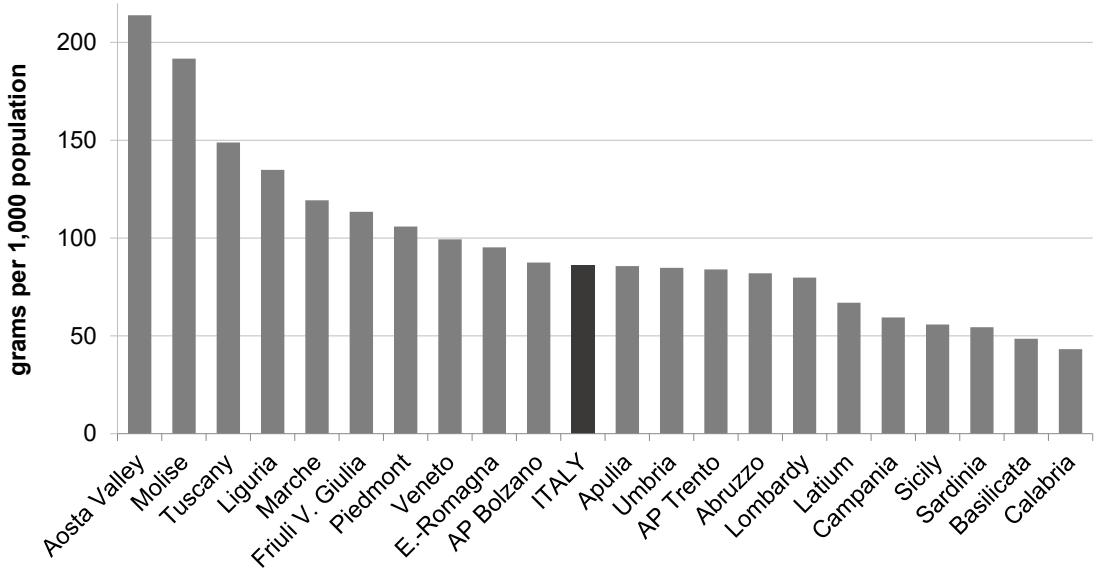

Figure 11. Total and regional demand (public and private) for normal human immunoglobulins for intravenous use, expressed in grams per 1,000 population, 2020 (adapted by the CNS on data from the Traceability information flow)

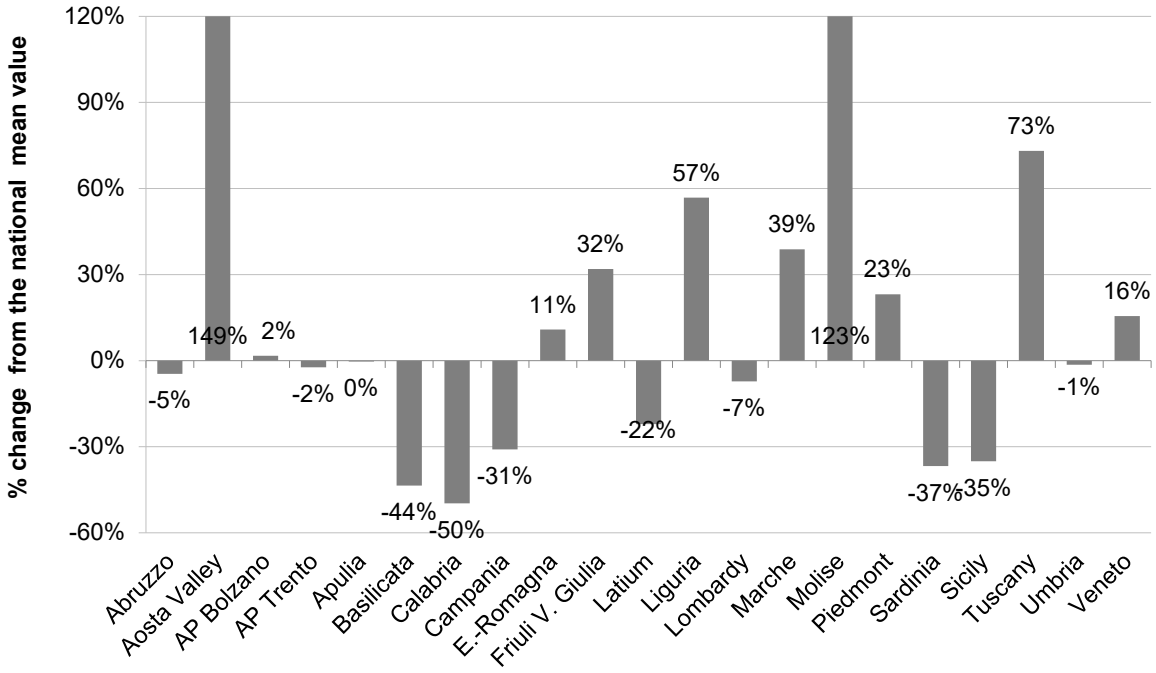

Figure 12. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for intravenous use in 2020 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2020)

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 2019-2020 with the relative percentage changes at national and regional levels.

In 2020, total AT demand was 124,478,500 IUs, equal to 2.1 IUs *per capita*, highlighting an increase compared to the consumption recorded in previous years (+7% compared to 2019).
Conversely, in three Regions there was a significant upword trend in its use [range: Liguria (+ 61%) – Aosta Valley (+ 130%)]. The Region in which the containment of use was most evident is Molise (-62%).
Figure 13 shows the regional and national standardised demand for AT in 2020. The Regions with the highest *per capita* demand were Calabria, Sicily, Aosta Valley and Latium, with a demand of 3.9 IUs for the first one and 3.8, 3.5 and 3.3 IUs respectively for the others Regions. The lowest demand, between 0.3 and 0.7 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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,408,500	1.1	1,943,500	1.5	39.9
Aosta Valley	192,000	1.5	439,000	3.5	129.8
AP Bolzano	202,000	0.4	347,000	0.7	71.3
APTrento	200,000	0.4	147,000	0.3	-27.1
Apulia	8,360,500	2.1	6,444,000	1.6	-21.4
Basilicata	1,170,000	2.1	1,218,000	2.2	5.9
Calabria	10,402,500	5.3	7,376,500	3.9	-27.1
Campania	16,209,000	2.8	14,392,000	2.5	-9.8
E.-Romagna	2,732,000	0.6	3,305,000	0.7	20.8
Friuli V. Giulia	2,634,000	2.2	2,876,000	2.4	10.0
Latium	20,023,500	3.4	19,215,500	3.3	-2.0
Liguria	2,508,500	1.6	3,973,500	2.6	61.1
Lombardy	8,671,500	0.9	15,020,000	1.5	73.8
Marche	2,917,000	1.9	3,253,000	2.2	12.4
Molise	972,000	3.2	360,000	1.2	-62.3
Piedmont	6,898,000	1.6	8,500,500	2.0	24.5
Sardinia	1,984,000	1.2	2,069,000	1.3	6.1
Sicily	17,292,500	3.5	18,372,500	3.8	9.0
Tuscany	6,400,500	1.7	7,633,000	2.1	20.5
Umbria	786,000	0.9	546,000	0.6	-29.6
Veneto	6,002,500	1.2	7,047,500	1.4	18.1
Italy	117,966,500	2.0	124,478,500	2.1	6.8

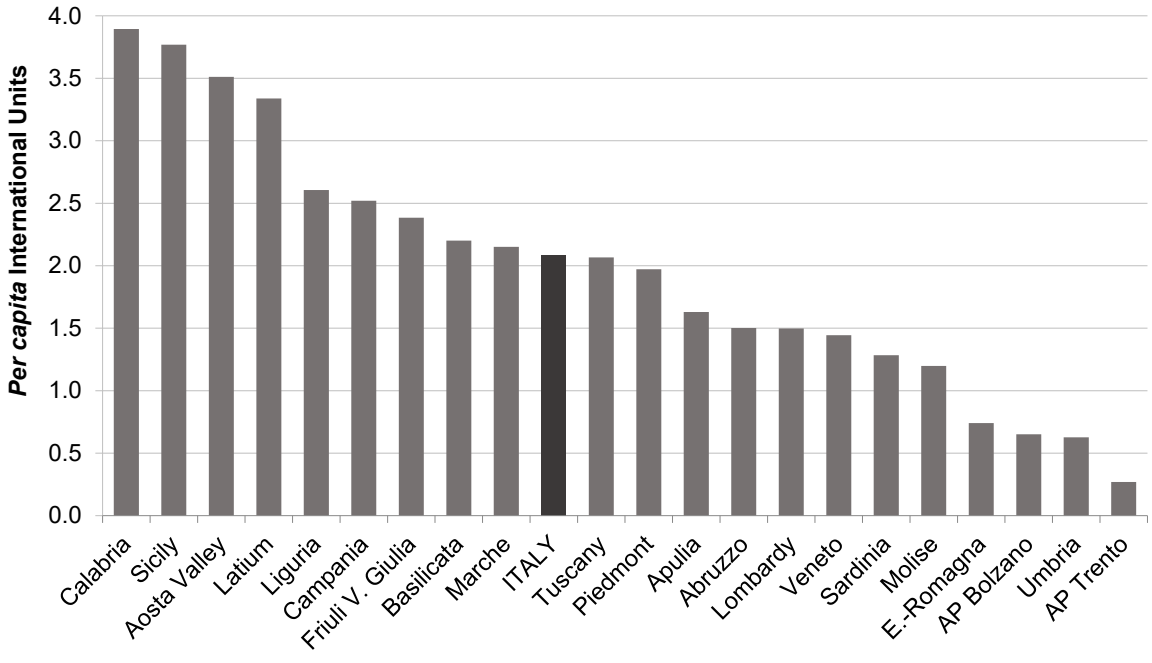

Figure 13. Total and regional demand (public and private) for antithrombin, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

Figure 14 shows the difference between the regional *per capita* percentage and the national mean value for the year 2020.

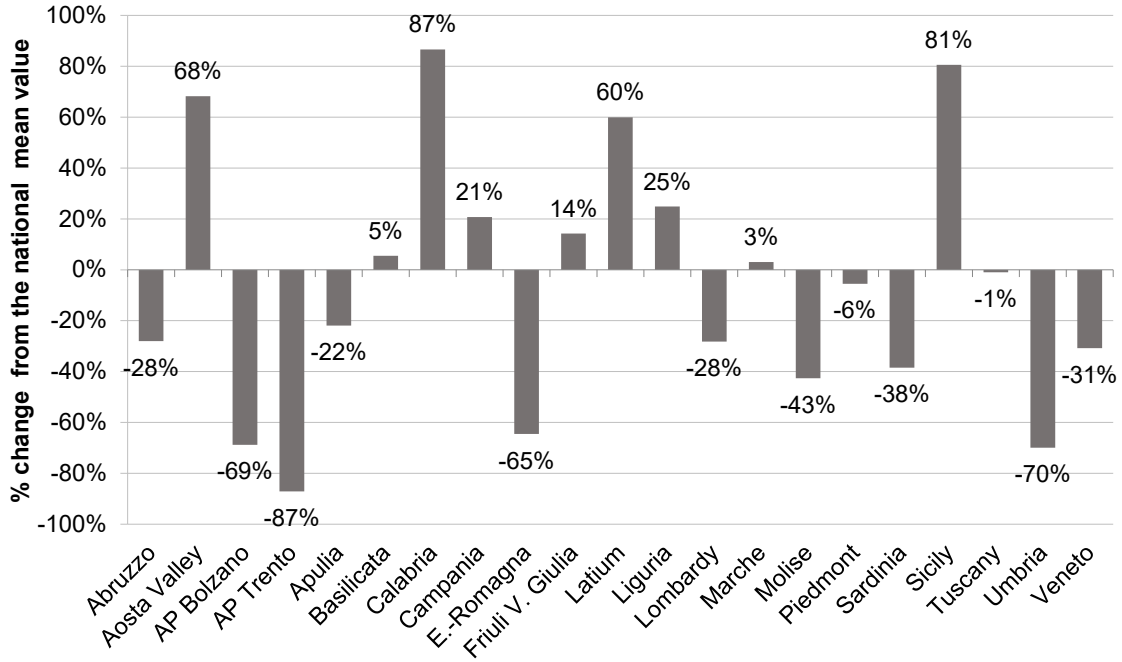

Figure 14. Percentage change from the national mean value of standardised regional demand for antithrombin in 2020 (adapted by the CNS on data from the Traceability information flow)

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 ± 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, 31/12/2020)

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, 31/12/2020)

AIC code	Brand name	IU	Manufacturer	NHS class
Factor VIII and von Willebrand Factor in combination				
033077088	ALPHANATE*INF 1F 250IU+SIR+AD	250	GRIFOLS ITALIA SpA	A
033866043	FANHDI*INF FL 250IU+SIR SOLV+S	250	GRIFOLS ITALIA SpA	A
037148018	TALATE*250IU/190IU+FL5mL+SIR	250	BAXALTA INN.Gmbh	A
040112017	OCTANATE*INIET FL 250IU+FL 5mL	250	OCTAPHARMA Italy SpA	A
042939013	VONCENTO*250IU/600IU+FL 5mL	250	CSL BEHRING SpA	C(nn)
044564019	PLITATE*INF FL 250IU+SIR SOLV+SET	250	GRIFOLS ITALIA SpA	C(nn)
023308152	EMOWIL*1F 500IU+F 10mL	500	KEDRION SpA	A
026600080	HAEMATEP*FL 500IU+FL 10mL+SET	500	CSL BEHRING SpA	A
033077090	ALPHANATE*INF 1F 500IU+SIR+AD	500	GRIFOLS ITALIA SpA	A
033866056	FANHDI*INF FL 500IU+SIR SOLV+S	500	GRIFOLS ITALIA SpA	A
037148020	TALATE*500IU/375IU+FL10mL+SIR	500	BAXALTA INN. Gmbh	A
039385036	WILATE*FL 500+500IU+FL 5mL+SIR	500	OCTAPHARMA Italy SpA	A
040112029	OCTANATE*INIET FL 500IU+FL 10mL	500	OCTAPHARMA Italy SpA	A
040112056	OCTANATE*INIET FL 5mL100IU/mL	500	OCTAPHARMA Italy SpA	A
042939025	VONCENTO*500IU/1200IU+FL 10mL	500	CSL BEHRING SpA	C(nn)
042939037	VONCENTO*500IU/1200IU+FL 5mL	500	CSL BEHRING SpA	C(nn)
044564021	PLITATE*INF FL 500IU+SIR SOLV+SET	500	GRIFOLS ITALIA SpA	C(nn)
023308188	EMOWIL*1F 1000IU+F 10mL	1000	KEDRION SpA	A
026600078	HAEMATEP*FL 1000IU+FL 15mL+SET	1000	CSL BEHRING SpA	A
033077102	ALPHANATE*INF 1F 1000IU+SIR+AD	1000	GRIFOLS ITALIA SpA	A
033866068	FANHDI*INF FL 1000IU+SIR SOLV+S	1000	GRIFOLS ITALIA SpA	A
037148032	TALATE*1000IU/750IU+FL10mL+SIR	1000	BAXALTA Italy Srl	A
039385024	WILATE*FL 900+800IU+FL 10mL+SIR	1000	OCTAPHARMA Italy SpA	A
039385048	WILATE*FL 1000+1000IU+FL 10mL+SI	1000	OCTAPHARMA Italy SpA	A
040112031	OCTANATE*INIET FL 1000IU+FL 10mL	1000	OCTAPHARMA Italy SpA	A
040112068	OCTANATE*INIET FL 5mL 200IU/mL	1000	OCTAPHARMA Italy SpA	A
042939049	VONCENTO*1000IU/2400IU+FL 10mL	1000	CSL BEHRING SpA	C(nn)
044564033	PLITATE*INF FL1000IU+SIR SOLV+SET	1000	GRIFOLS ITALIA SpA	C(nn)
033077114	ALPHANATE*INF 1F 1500IU+SIR+AD	1500	GRIFOLS ITALIA SpA	A
033866070	FANHDI*INF FL1500IU+SIR SOLV+S	1500	GRIFOLS ITALIASpA	A
044564045	PLITATE*INF FL1500IU+SIRSOLV+SET	1500	GRIFOLS ITALIA SpA	C(nn)
033077126	ALPHANATE *INF 1F 2000 IU+SIR+SET	2000	GRIFOLS ITALIA SpA	C
von Willebrand Factor				
037392026	WILFACTIN* 500IU+FL 5mL	500	LFB	C
037392014	WILFACTIN*1000IU+FL 10mL	1000	LFB	C
037392038	WILFACTIN*2000IU+FL 20mL	2000	LFB	C

Table 15. Products containing recombinant coagulation Factor VIII and long-acting recombinant Factor VIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2020)

AIC code	Brand name	IU	Manufacturer	NHS class
028687010	RECOMBINATE*FL 250IU+FL 10mL	250	BAXALTA Italy Srl	A
028687046	RECOMBINATE*FL 250IU+FL 5mL	250	BAXALTA Italy Srl	A
028687073	RECOMBINATE*FL 250IU+FL 5mL	250	BAXALTA Italy Srl	A
028687109	RECOMBINATE*FL 250IU+FL 10mL	250	BAXALTA Italy Srl	A
034421014	REFACTOAF*IV 1FL 250IU+SIR 4mL	250	PFIZER ITALIA Srl	A
034421091	REFACTOAF*IV 1SIR PRER 250IU	250	PFIZER ITALIA Srl	A
034955017	KOGENATE BAYER*250IU+1FL+1KI	250	BAYER SpA	A
034955043	KOGENATE BAYER*FL 250IU+SIR+1KI	250	BAYER SpA	A
034955070	KOGENATE BAYER*EV 250IU+SIR	250	BAYER SpA	A
034956019	HELIXATE NEXGEN*250IU+1FL+1KIT	250	CSL BEHRING SpA	A

AIC code	Brand name	IU	Manufacturer	NHS class
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)
045255039	AFSTYLA 1000IU+FL SOLV 2,5mL+SIR	1000	CSL BEHRING GmbH	A

AIC code	Brand name	IU	Manufacturer	NHS class
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
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
044563031	ELOCTA*IV 1FL 750IU+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

AIC code	Brand name	IU	Manufacturer	NHS class
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)

Quantification and characterisation of demand

In Italy, the total demand for both plasma-derived and recombinant formulations FVIII, was equal to 583,759,200 IUs in 2020 (Table 16); of these, about a fifth (17% of the total, 99,035,950 IUs) were human plasma-derived (Figure 15). The tendency to use pdFVIII varied significantly from one Region to another ranging from 1.4% in AP of Trento to 32% in AP of Bolzano. In 2020, the total FVIII demand *per capita* (plasma-derived and recombinant) was 10 IUs with a decrease of -3.4% compared to 2019.

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	14,686,500	11.2	14,014,500	10.8	-3.3
Aosta Valley	858,000	6.8	764,000	6.1	-10.5
AP Bolzano	3,553,750	6.7	3,290,000	6.2	-7.7
AP Trento	3,715,500	6.9	2,899,500	5.3	-22.6
Apulia	49,264,750	12.2	50,628,250	12.8	4.7
Basilicata	6,830,500	12.1	5,002,000	9.0	-25.5
Calabria	30,021,500	15.4	22,808,750	12.0	-21.9
Campania	74,252,750	12.8	69,249,700	12.1	-5.3
E.-Romagna	39,877,750	8.9	37,765,750	8.5	-5.4
Friuli V. Giulia	4,550,500	3.7	3,995,000	3.3	-11.6
Latium	97,726,750	16.6	92,996,850	16.2	-2.8
Liguria	13,287,000	8.6	12,915,250	8.5	-1.2
Lombardy	79,028,750	7.9	80,485,750	8.0	2.2
Marche	10,446,000	6.8	10,028,500	6.6	-3.2
Molise	2,812,500	9.2	2,182,000	7.3	-21.1
Piedmont	43,113,250	9.9	39,325,000	9.1	-7.8
Sardinia	13,258,500	8.1	13,478,700	8.4	3.4
Sicily	49,252,250	9.9	48,952,500	10.0	1.9
Tuscany	26,442,000	7.1	28,206,950	7.6	7.7
Umbria	6,840,500	7.8	7,146,500	8.2	5.9
Veneto	41,981,250	8.6	37,623,750	7.7	-9.9
Italy	611,800,250	10.1	583,759,200	9.8	-3.4

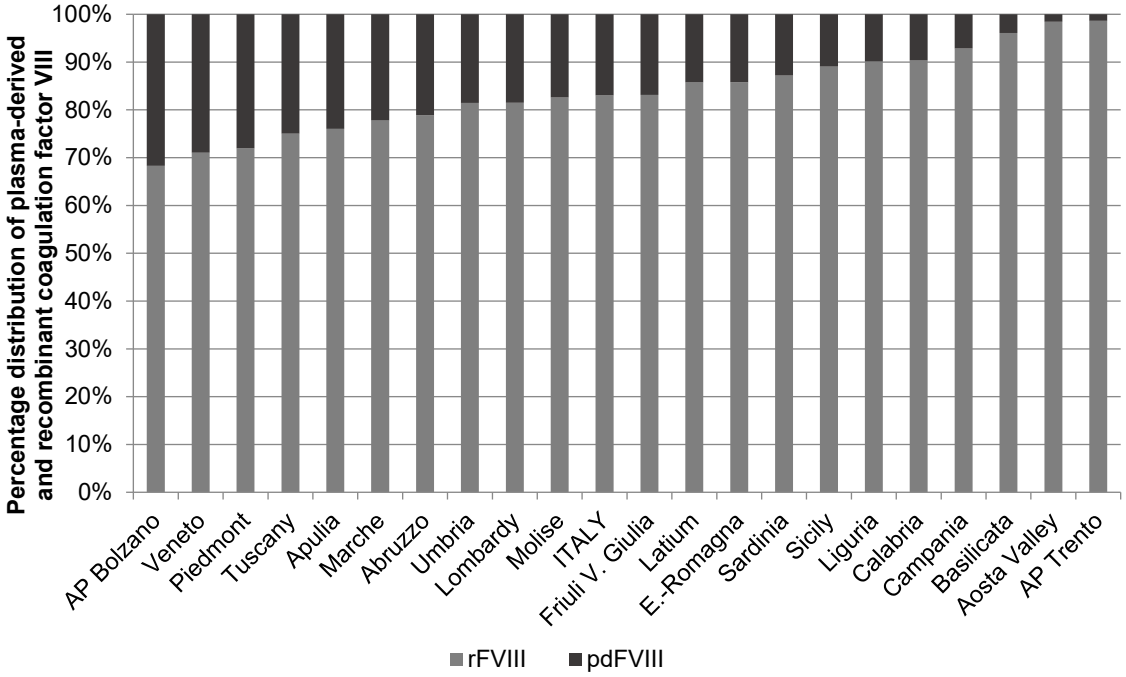

Figure 15. Percentage distribution of plasma-derived and recombinant coagulation Factor VIII, by Region, 2020 (adapted by the CNS on data from the Traceability information flow)

The regional *per capita* demand shows significant fluctuations ranging from about 3.3 IUs in Friuli V. Giulia to about 16 IUs in Lazio (Figure 16).

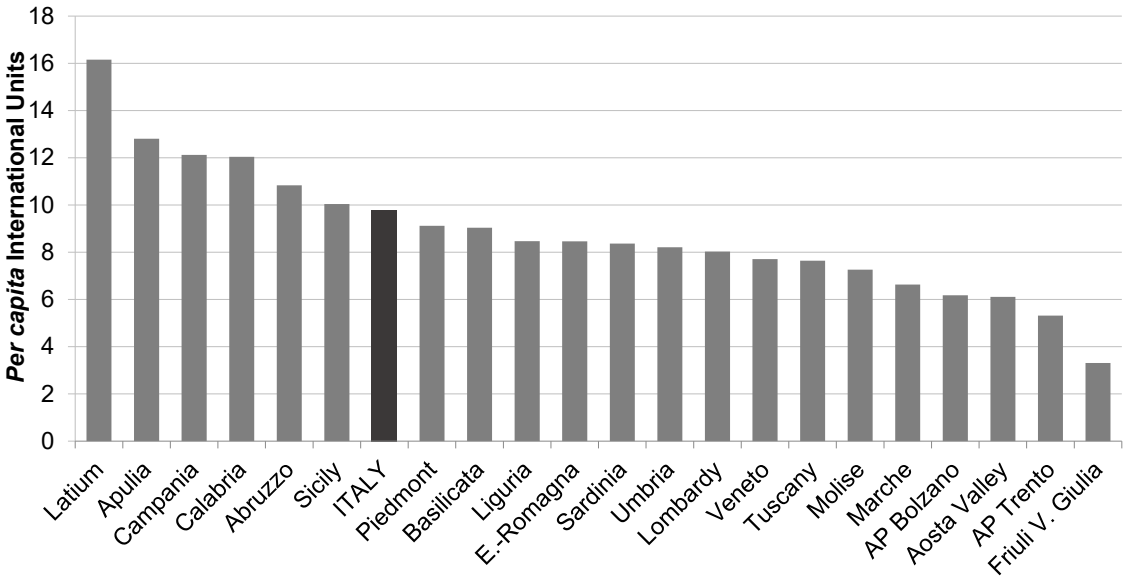

Figure 16. Total and regional demand (public and private) for coagulation Factor VIII, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

The most significant decreases in standardised regional demand were observed in Basilicata and in the AP of Trento, where use decreased by -26% and -23%, 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).

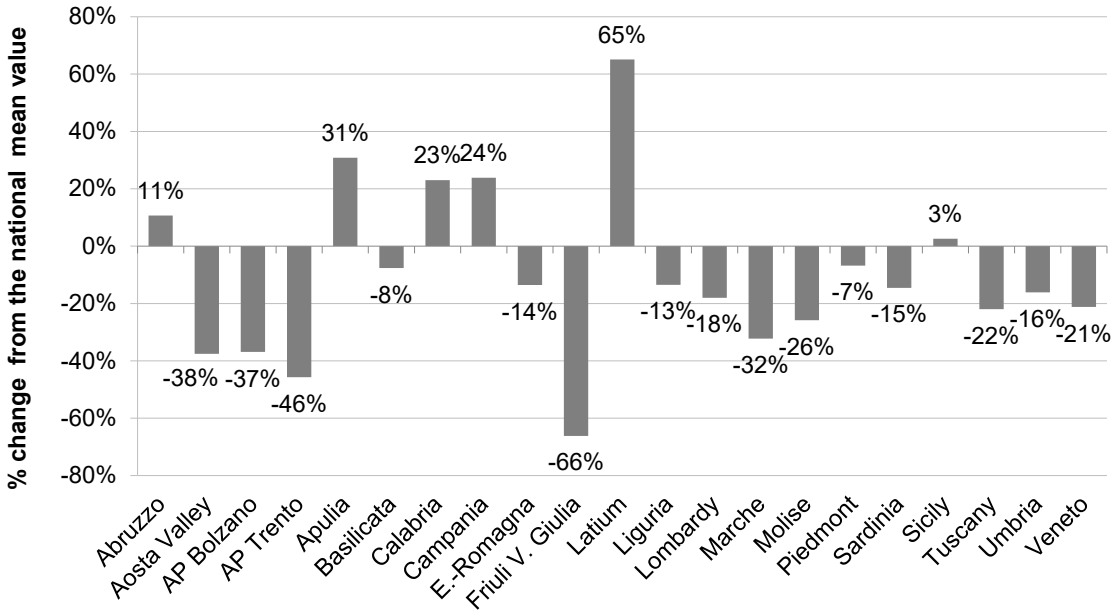

Figure 17. **Percentage change from the national mean value of standardised regional demand for coagulation Factor VIII in 2020 (adapted by the CNS on data from the Traceability information flow)**

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

In 2020, the national demand for pdFVIII was about 17% – equivalent to 99,035,950 IUs – of the total demand. There is a downward trend of 9.8% compared to the 2019 value and a standardized total demand of 1.7 IU *per capita* (Table 17). *Per capita* demand varied significantly with the highest volumes in Apulia (3.1 IUs *per capita*), Piedmont (2.6 IUs *per capita*) and in Abruzzo and Latium (2.3 IUs *per capita*); the corresponding percentage change between the aforementioned values and the Italian mean value were of +85%, +54%, +38% and +39%, respectively. The lowest volumes (below 1 IU *per capita*) were recorded in Aosta Valley, the AP of Trento, Basilicata, Campania, Liguria and Friuli V. Giulia (Figures 18 and 19).

The national trend decreased in many Italian Regions (range: -69%; -1.6%) with the exception of Abruzzo, Basilicata, Calabria, Apulia, Sicily, Tuscany and Aosta Valley, where there were increases of between 3% e il 116%.

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,577,000	2.0	2,958,000	2.3	16.3
Aosta Valley	10,000	0.1	12,000	0.1	20.6
AP Bolzano	1,226,000	2.3	1,043,000	2.0	-15.2
AP Trento	128,000	0.2	39,500	0.1	-69.4
Apulia	11,284,500	2.8	12,134,500	3.1	9.6
Basilicata	92,000	0.2	195,000	0.4	115.6
Calabria	1,614,500	0.8	2,203,250	1.2	40.3
Campania	8,072,500	1.4	4,967,700	0.9	-37.5
E.-Romagna	5,900,250	1.3	5,371,000	1.2	-9.1
Friuli V. Giulia	759,000	0.6	674,000	0.6	-10.5
Latium	13,778,500	2.3	13,269,100	2.3	-1.6
Liguria	1,401,000	0.9	1,273,500	0.8	-7.6
Lombardy	18,924,000	1.9	14,902,500	1.5	-21.0
Marche	2,331,000	1.5	2,229,000	1.5	-3.6
Molise	605,000	2.0	380,000	1.3	-36.1
Piedmont	13,798,000	3.2	11,032,000	2.6	-19.2
Sardinia	2,395,000	1.5	1,727,200	1.1	-26.6
Sicily	5,324,000	1.1	5,362,000	1.1	3.3
Tuscany	5,857,000	1.6	7,048,200	1.9	21.5
Umbria	1,441,000	1.6	1,325,000	1.5	-6.8
Veneto	13,541,500	2.8	10,889,500	2.2	-19.1
Italy	111,059,750	1.8	99,035,950	1.7	-9.8

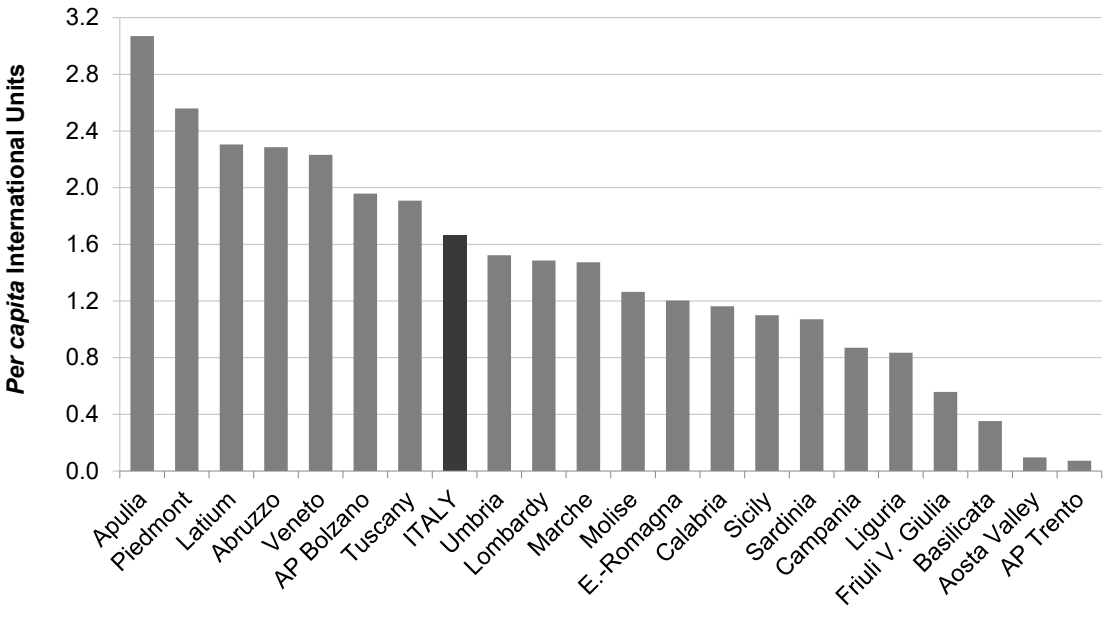

Figure 18. Total and regional demand (public and private) for plasma-derived coagulation Factor VIII, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

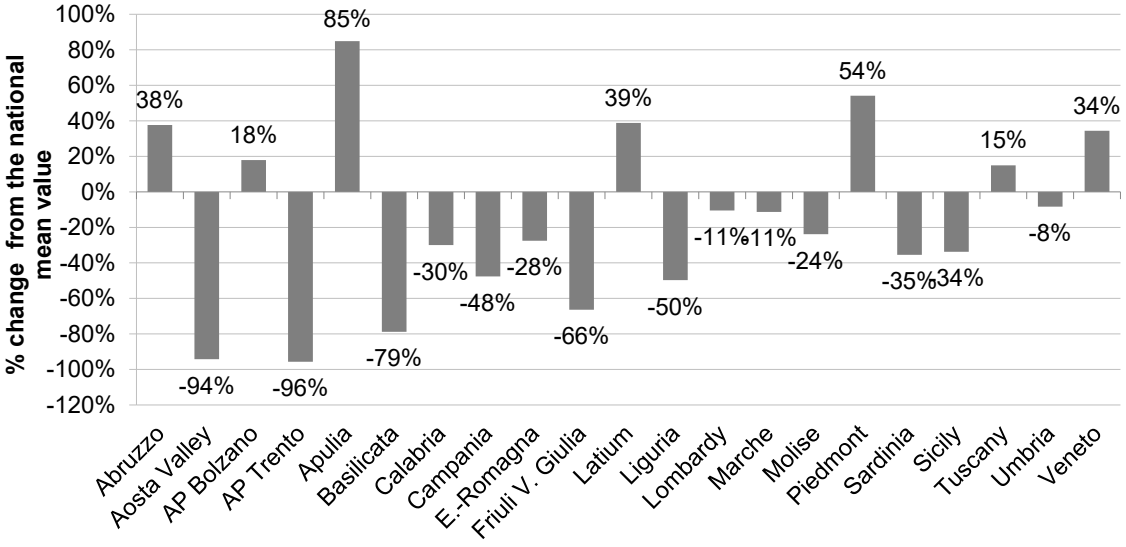

Figure 19. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor VIII in 2020 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor VIII (B02BD02)

In 2020, the total demand for plasma-derived FVIII was 50,395,000 IUs (Table 18).

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	60,000	0.0	120,000	0.1	102.7
Aosta Valley	-	-	-	-	NA
AP Bolzano	352,000	0.7	288,000	0.5	-18.4
AP Trento	17,000	0.0	3,000	0.0	-82.5
Apulia	4,543,000	1.1	5,314,000	1.3	19.2
Basilicata	52,000	0.1	36,000	0.1	-29.6
Calabria	507,000	0.3	643,000	0.3	30.4
Campania	3,846,000	0.7	150,000	0.0	-96.0
E.-Romagna	2,881,000	0.6	3,192,000	0.7	10.7
Friuli V. Giulia	576,000	0.5	256,000	0.2	-55.2
Latium	4,713,000	0.8	5,234,000	0.9	13.4
Liguria	992,000	0.6	704,000	0.5	-27.8
Lombardy	12,987,000	1.3	9,647,000	1.0	-25.5
Marche	1,792,000	1.2	1,805,000	1.2	1.6
Molise	200,000	0.7	180,000	0.6	-8.5
Piedmont	10,127,000	2.3	8,749,000	2.0	-12.7
Sardinia	869,000	0.5	285,000	0.2	-66.6
Sicily	1,017,000	0.2	763,000	0.2	-23.1
Tuscany	3,582,000	1.0	4,361,000	1.2	23.0
Umbria	496,000	0.6	396,000	0.5	-19.1
Veneto	10,962,000	2.2	8,269,000	1.7	-24.2
Italy	60,571,000	1.0	50,395,000	0.8	-15.8

The mean national demand *per capita* was about 0.8 IUs, with a range amongst Regions of 0.005 IUs and 2 IUs.

The Regions with the highest *per capita* consumption of pdFVIII were Piedmont (2 IUs) and Veneto (1.7 IUs). The lowest utilisation was observed in AP of Trento and in Campania (0.005 IUs and 0.03 IUs *per capita*, respectively). No consumption was recorded in Aosta Valley. Figure 20 shows the percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination by Region.

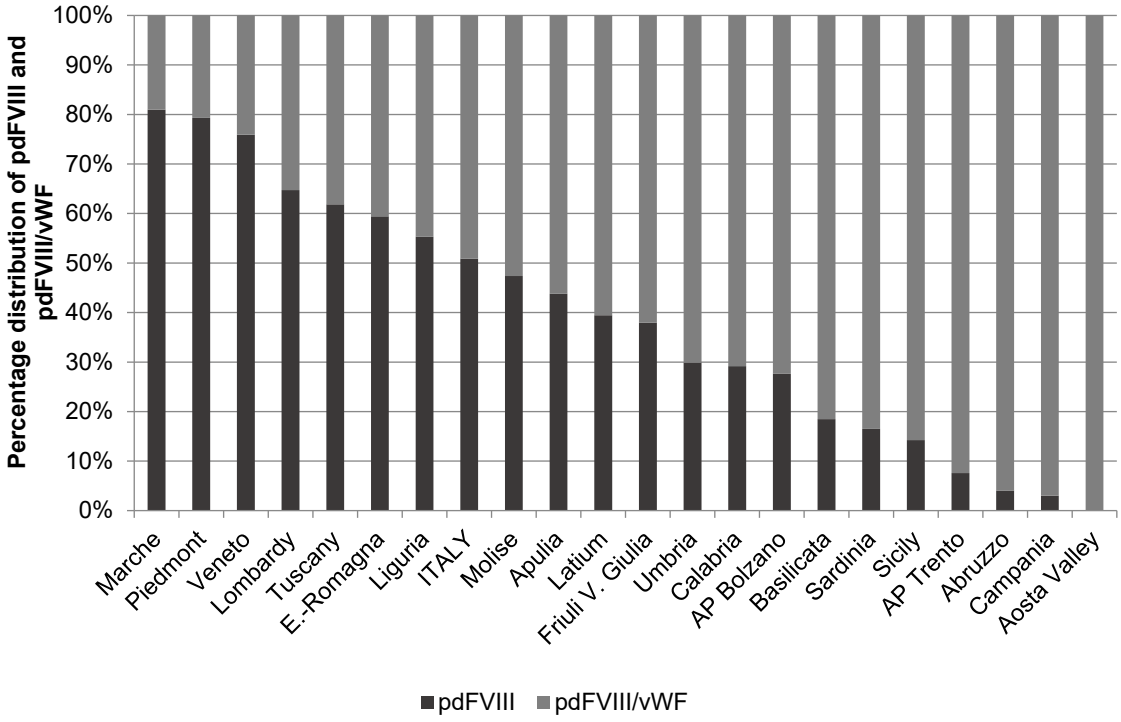

Figure 20. Percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination, by Region, 2020 (adapted by the CNS on data from the Traceability information flow)

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

In 2020, the national demand for FVIII and von Willebrand Factor in combination was 48,640,950 IUs, about 49% 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 and AP of Trento) and 2.2 IUs (Abruzzo) (Table 19). The Regions with the highest *per capita* demand of FVIII and von Willebrand Factor in combination were Abruzzo (2.2 IUs), Apulia (1.7 IUs) and AP of Bolzano and Latium (1.4 IUs). The lowest utilization equal to 0.1 IUs *per capita* was observed in the Aosta Valley and AP of Trento (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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,517,000	1.9	2,838,000	2.2	14.3
Aosta Valley	10,000	0.1	12,000	0.1	20.6
AP Bolzano	874,000	1.6	755,000	1.4	-13.9
AP Trento	111,000	0.2	36,500	0.1	-67.4
Apulia	6,741,500	1.7	6,820,500	1.7	3.1
Basilicata	40,000	0.1	159,000	0.3	304.4
Calabria	1,107,500	0.6	1,560,250	0.8	44.8
Campania	4,226,500	0.7	4,817,700	0.8	15.8
E.-Romagna	3,019,250	0.7	2,179,000	0.5	-27.9
Friuli V. Giulia	183,000	0.2	418,000	0.3	130.1
Latium	9,065,500	1.5	8,035,100	1.4	-9.5
Liguria	409,000	0.3	569,500	0.4	41.6
Lombardy	5,937,000	0.6	5,255,500	0.5	-11.2
Marche	539,000	0.4	424,000	0.3	-20.7
Molise	405,000	1.3	200,000	0.7	-49.8
Piedmont	3,671,000	0.8	2,283,000	0.5	-37.2
Sardinia	1,526,000	0.9	1,442,200	0.9	-3.9
Sicily	4,307,000	0.9	4,599,000	0.9	9.5
Tuscany	2,275,000	0.6	2,687,200	0.7	19.3
Umbria	945,000	1.1	929,000	1.1	-0.4
Veneto	2,579,500	0.5	2,620,500	0.5	2.1
Italy	50,488,750	0.8	48,640,950	0.8	-2.5

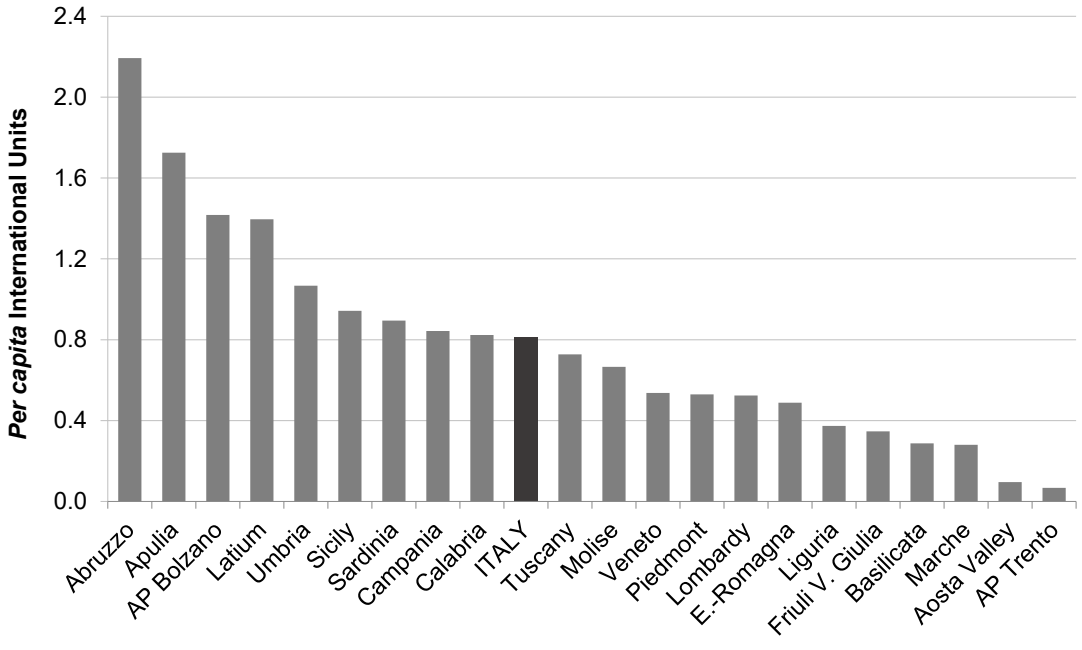

Figure 21. Total and regional demand (public and private) for pdFVIII and von Willebrand Factor in combination, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor VIII

In 2020, the total demand for rFVIII was 484,723,250 IUs, with a decrease of approximately -2% compared to 2019. The mean national demand *per capita* was about 8.1 IUs, with a range between Regions of 2.8 IUs and 13.9 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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	12,109,500	9.2	11,056,500	8.5	-7.5
Aosta Valley	848,000	6.7	752,000	6.0	-10.9
AP Bolzano	2,327,750	4.4	2,247,000	4.2	-3.7
AP Trento	3,587,500	6.6	2,860,000	5.2	-20.9
Apulia	37,980,250	9.4	38,493,750	9.7	3.3
Basilicata	6,738,500	12.0	4,807,000	8.7	-27.4
Calabria	28,407,000	14.6	20,605,500	10.9	-25.4
Campania	66,180,250	11.4	64,282,000	11.3	-1.3
E.-Romagna	33,977,500	7.6	32,394,750	7.3	-4.8
Friuli V. Giulia	3,791,500	3.1	3,321,000	2.8	-11.8
Latium	83,948,250	14.3	79,727,750	13.9	-3.0
Liguria	11,886,000	7.7	11,641,750	7.6	-0.4
Lombardy	60,104,750	6.0	65,583,250	6.5	9.5
Marche	8,115,000	5.3	7,799,500	5.2	-3.1
Molise	2,207,500	7.2	1,802,000	6.0	-17.0
Piedmont	29,315,250	6.7	28,293,000	6.6	-2.5
Sardinia	10,863,500	6.6	11,751,500	7.3	10.1
Sicily	43,928,250	8.8	43,590,500	8.9	1.8
Tuscany	20,585,000	5.5	21,158,750	5.7	3.8
Umbria	5,399,500	6.1	5,821,500	6.7	9.3
Veneto	28,439,750	5.8	26,734,250	5.5	-5.5
Italy	500,740,500	8.3	484,723,250	8.1	-2.0

The Regions in which the highest *per capita* utilisation of rFVIII was observed were Latium (13.9 IUs), Campania and Calabria (11 IUs) (Figure 22), with a percentage change compared to the Italian mean value of +70%, +38% and +34%, respectively (Figure 23).

The lowest utilisation – between 2.8 and 5.7 IUs *per capita* – was observed in Friuli V. Giulia, Marche, AP of Bolzano, AP of Trento, Tuscany and Veneto.

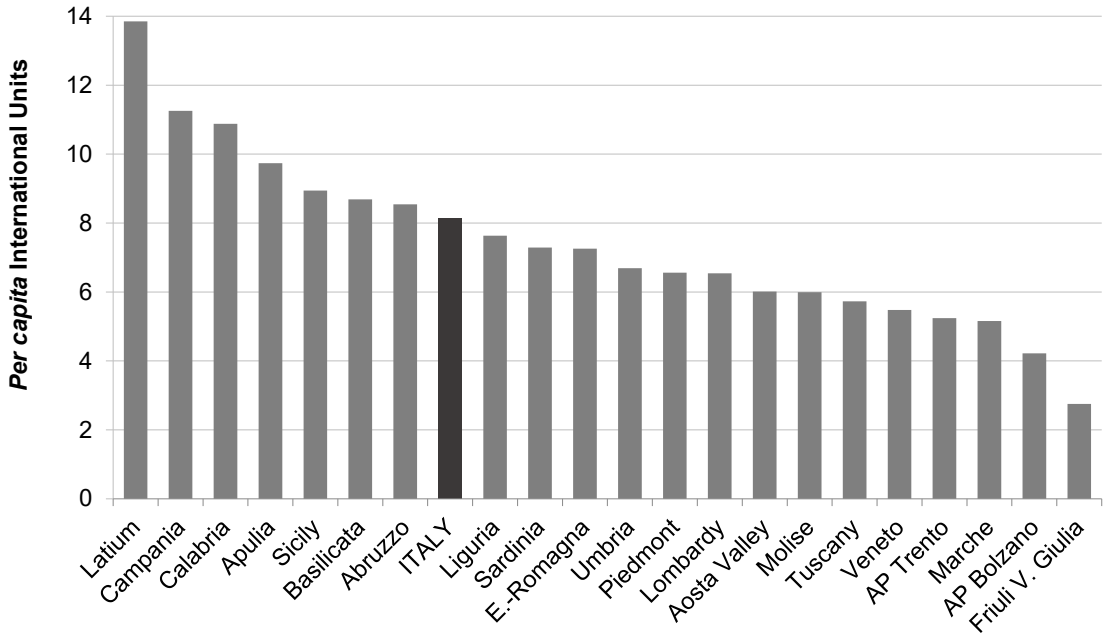

Figure 22. Total and regional demand (public and private) for recombinant coagulation Factor VIII, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

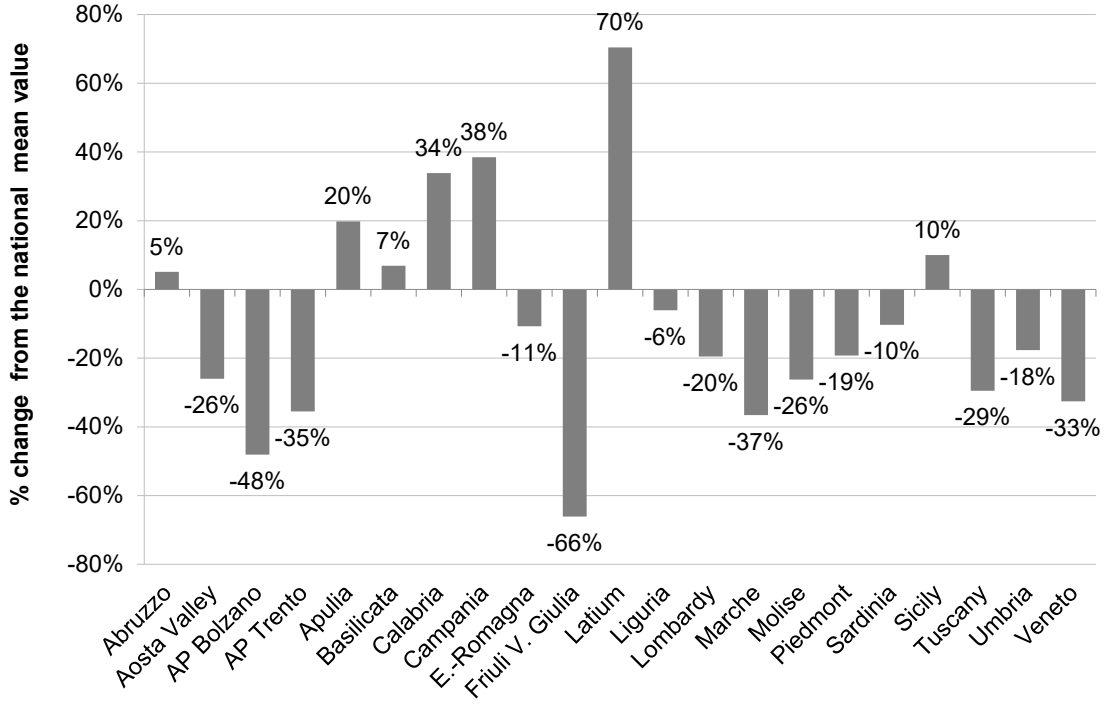

Figure 23. Percentage change from the national mean value of standardised regional demand for recombinant coagulation Factor VIII in 2020 (adapted by the CNS on data from the Traceability information flow)

Extended half-life Recombinant Factor VIII

Part of the total demand for rFVIII is represented by drugs containing extended half-life molecules. In 2020, the demand for these products was equal to 103,274,250 IUs, about 21% of the total demand for rFVIII (Table 21).

Table 21. Total demand (public and private) and total standardised demand for long-acting recombinant coagulation Factor VIII, expressed in International Units and International Units *per capita* and variations in percentage between 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,189,000	0.9	1,127,500	0.9	-3.9
Aosta Valley	-	-	84,000	0.7	100.0
AP Bolzano	-	-	170,000	0.3	100.0
AP Trento	-	-	672000	1.2	100.0
Apulia	2,768,250	0.7	4,305,000	1.1	58.5
Basilicata	-	-	2,000	0.0	100.0
Calabria	3,407,500	1.8	3,153,500	1.7	-4.9
Campania	7,436,750	1.3	8,168,500	1.4	11.6
E.-Romagna	10,023,750	2.2	11,757,250	2.6	17.2
Friuli V. Giulia	430,000	0.4	670,000	0.6	57.0
Latium	13,924,500	2.4	15,820,500	2.7	16.1
Liguria	4,360,000	2.8	5,299,500	3.5	23.6
Lombardy	13,838,500	1.4	18,246,250	1.8	32.3
Marche	853,500	0.6	1,359,000	0.9	60.6
Molise	-	-	-	-	NA
Piedmont	10,402,250	2.4	11,356,250	2.6	10.3
Sardinia	812,000	0.5	1237000	0.8	55.0
Sicily	4,188,500	0.8	4,616,250	0.9	13.0
Tuscany	4,887,500	1.3	5,842,500	1.6	20.7
Umbria	1454000	1.6	1,670,000	1.9	16.4
Veneto	4,596,000	0.9	7,717,250	1.6	68.8
Italy	84,572,000	1.4	103,274,250	1.7	23.6

The national demand *per capita* was about 1.7 IUs, with a range among Regions of 0.004 IUs in Basilicata and 3.5 IUs in Liguria. In Molise no demand was recorded (Figures 24 and Figure 25).

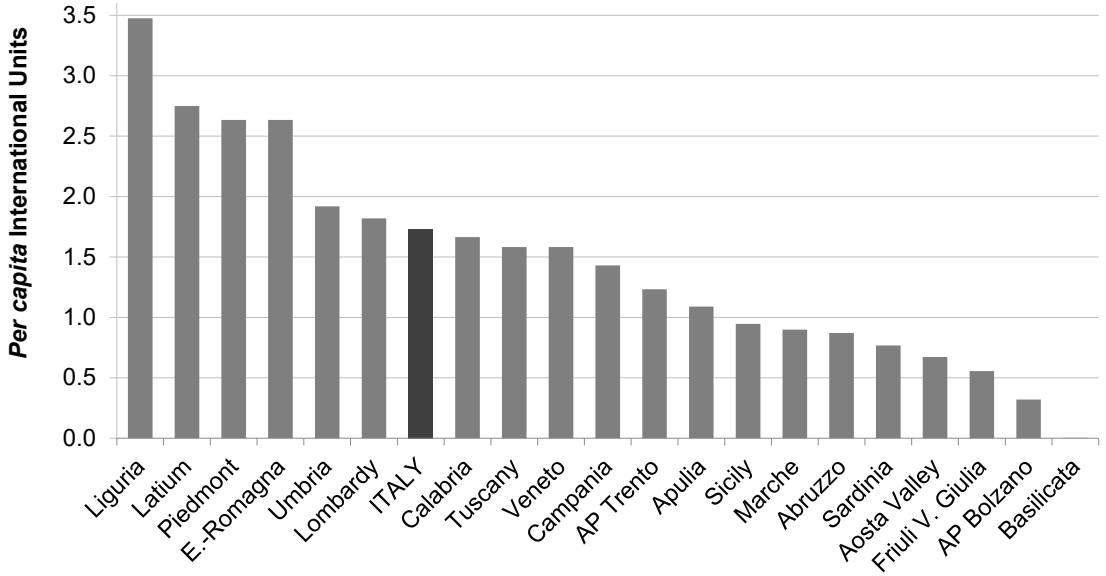

Figure 24. Total and regional demand (public and private) for extended half-life recombinant Factor VIII, expressed in International Units per capita, 2020 (adapted by the CNS on data from the Traceability information flow)

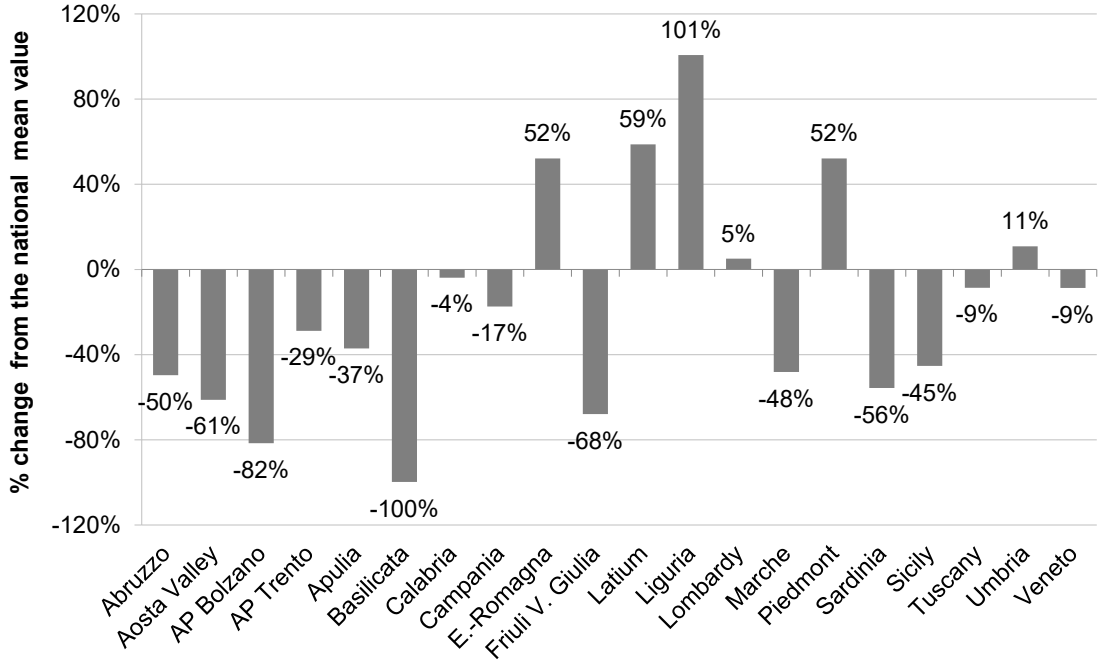

Figure 25. Percentage change from the national mean value of standardised regional demand for extended half-life recombinant Factor VIII in 2020 (adapted by the CNS on data from the Traceability information flow)

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. Inhbitors 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 emicizuma currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2020)

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

Quantification and characterisation of the demand

Table 23 shows the total and per 1,000 population demand for drugs containing Emicizumab for the year 2020, at national and regional levels and the percentage change from the previous year.

The total national demand for Emicizumab formulation for the year 2020 was 865,755 mg.

The national demand (mg per 1,000 population) was about 14.5 mg, but not all Regions recorded Emicizumab consumption (Table 23). The standardised demand for Emicizumab ranged from a minimum of 4.7 mg in Latium to a maximum of 26.6 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 2020 and variations in percentage between 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	mg	mg per 1,000 population	mg	mg per 1,000 population	
Abruzzo	6,660	5.1	21,180	16.4	222
Aosta Valley	-	-	-	-	NA
AP Bolzano	3,120	5.9	8,670	16.3	177
AP Trento	-	-	-	-	NA
Apulia	7,740	1.9	35,640	9.0	369
Basilicata	-	-	5,310	9.6	100
Calabria	14,520	7.5	38,745	20.5	174
Campania	28,770	5.0	74,670	13.1	164
E.-Romagna	10,020	2.2	54,450	12.2	443
Friuli V. Giulia	420	0.3	13,200	10.9	3,066
Latium	5,070	0.9	27,135	4.7	447
Liguria	840	0.5	20,955	13.7	2,437
Lombardy	49,830	5.0	205,590	20.5	314
Marche	6,300	4.1	11,010	7.3	76
Molise	-	-	-	-	NA
Piedmont	39,870	9.2	114,885	26.6	191
Sardinia	-	-	-	-	NA
Sicily	16,980	3.4	55,575	11.4	236
Tuscany	21,480	5.8	92,895	25.2	337
Umbria	4,440	5.0	14,400	16.5	229
Veneto	21,825	4.4	71,445	14.6	229
Italy	237,885	3.9	865,755	14.5	268

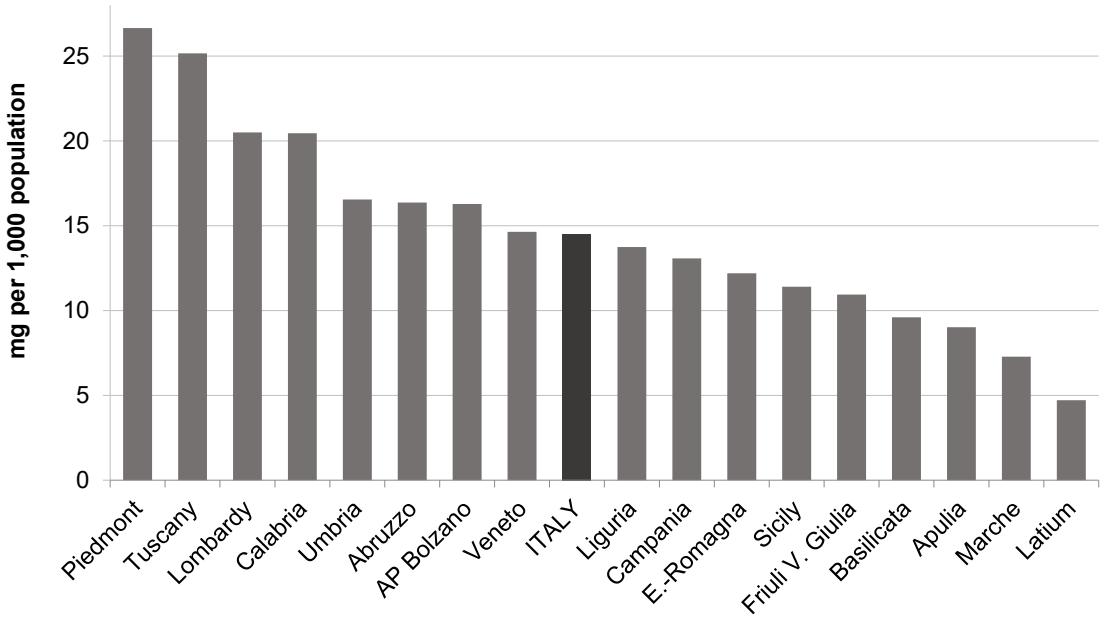

Figure 26. Total and regional demand (public and private) for Emicizumab expressed in mg per 1,000 population 2020 (adapted by the CNS on data from the Traceability information flow)

Figure 27 shows the variations in percentage of each Region compared to the national average. The Regions where the highest value was recorded, compared to the national average, are Piedmont (+ 84%) and Tuscany (+ 73%).

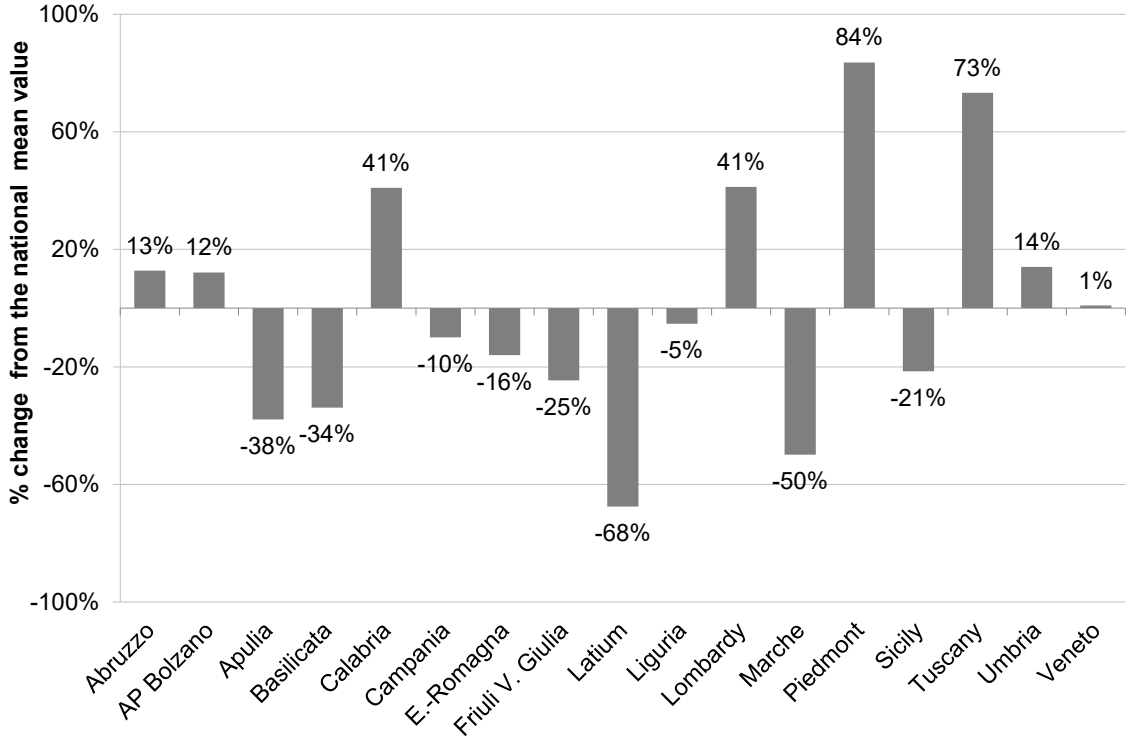

Figure 27. Percentage change from the national mean value of standardised regional demand for Emicizumab in 2020 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2020)

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, 31/12/2020)

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

AIC code	Brand name	IU	Manufacturer	NHS class
Extended half- recombinant Factor IX life				
044888016	ALPROLIX*1FL 250IU+1SIR 5mL	250	SOBI Srl	A
044891012	IDELVION*EV FL 250IU+FL 2,5mL	250	CSL BEHRING SpA	A
044888028	ALPROLIX*1FL 500IU+1SIR 5mL	500	SOBI Srl	A
044891024	IDELVION*EV FL 500IU+FL 2,5mL	500	CSL BEHRING SpA	A
045488018	REFIXIA*EV FL 500 IU+ FL 4 mL+SIR	500	NOVO NORDISK A/S	C
044888030	ALPROLIX*1FL 1000IU+1SIR 5mL	1000	SOBI Srl	A
044891036	IDELVION*EV FL 1000IU+FL 2,5mL	1000	CSL BEHRING SpA	A
045488020	REFIXIA*EV FL 1000IU+ FL 4mL+SIR	1000	NOVO NORDISK A/S	C
045488032	REFIXIA*EV FL 2000 IU+FL 4mL+SIR	1500	NOVO NORDISK A/S	C
044888042	ALPROLIX*1FL 2000IU+1SIR 5mL	2000	SOBI Srl	A
044891048	IDELVION*EV FL 2000IU+FL 2,5mL	2000	CSL BEHRING SpA	A
044888055	ALPROLIX*1FL 3000IU+1SIR 5mL	3000	SOBISrl	A
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 2019-2020, at national and regional levels. The total demand for FIX formulations recorded in 2020 was 57,876,850 IUs (Table 26); about 9% of the aforementioned amount (5,377,100 IUs) was plasma-derived. There was a decreasing demand for both pdFIX (-28%) and rFIX (-0.6%).

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,000,000	1.5	1,906,000	1.5	-3.4
Aosta Valley	-	-	-	-	NA
APBolzano	30,000	0.1	38,000	0.1	26.3
APTrento	438,500	0.8	475,000	0.9	7.5
Apulia	5,926,000	1.5	5,973,500	1.5	2.7
Basilicata	264,750	0.5	327,750	0.6	25.9
Calabria	2,180,250	1.1	1,042,750	0.6	-50.8
Campania	5,906,000	1.0	6,632,000	1.2	14.1
E.-Romagna	3,952,500	0.9	3,396,500	0.8	-14.2
Friuli V. Giulia	804,000	0.7	752,000	0.6	-5.8
Latium	6,330,750	1.1	5,534,100	1.0	-10.7
Liguria	2,322,000	1.5	2,372,000	1.6	3.9
Lombardy	7,988,000	0.8	8,958,500	0.9	12.5
Marche	1,688,000	1.1	1,852,000	1.2	10.6
Molise	-	-	10,000	0.0	100.0
Piedmont	4,301,000	1.0	4,231,750	1.0	-0.6
Sardinia	89,000	0.1	46,750	0.0	-46.6
Sicily	4,562,000	0.9	4,259,500	0.9	-4.2
Tuscany	8,267,000	2.2	6,054,750	1.6	-26.0
Umbria	440,500	0.5	435,000	0.5	0.1
Veneto	3,478,500	0.7	3,579,000	0.7	3.5
Italy	60,968,750	1.0	57,876,850	1.0	-3.9

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

In 2020, the standardised demand for plasma-derived and recombinant FIX was 1 IUs *per capita*, with significantly different regional trends: these ranged from a minimum – close to zero – in Sardinia and Molise (-97% compared to the Italian mean value), to a maximum in Tuscany and Liguria (1.6 IUs), Abruzzo and Apulia with 1.5 IUs *per capita* (+69%, +60%, 52% and +56% percentage change compared to the national mean value, respectively) (Figures 28 and 29).

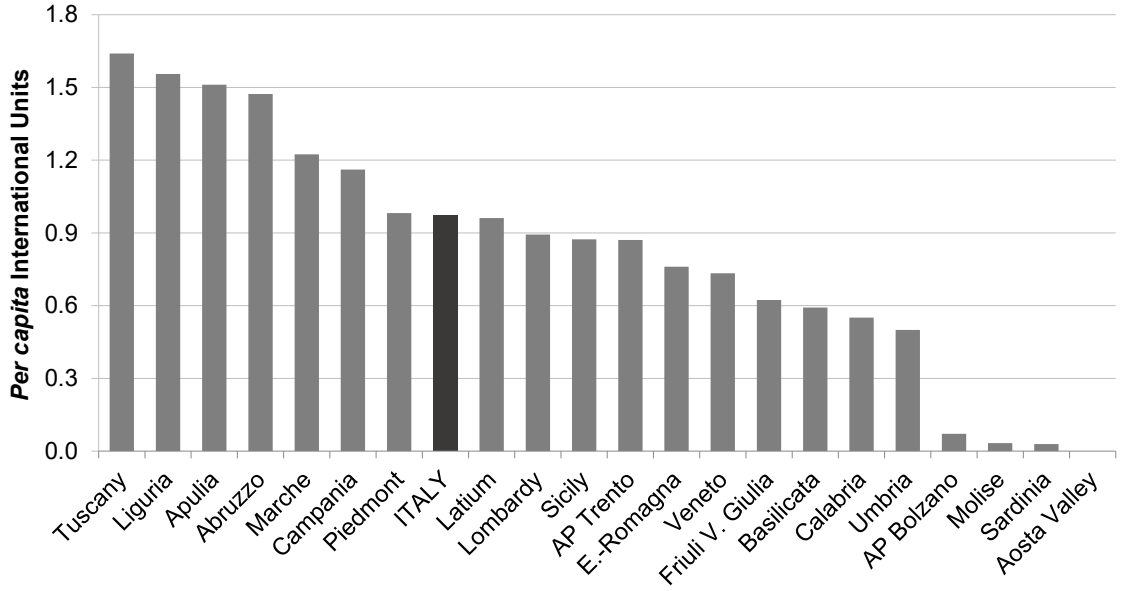

Figure 28. Total and regional demand (public and private) for coagulation Factor IX, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

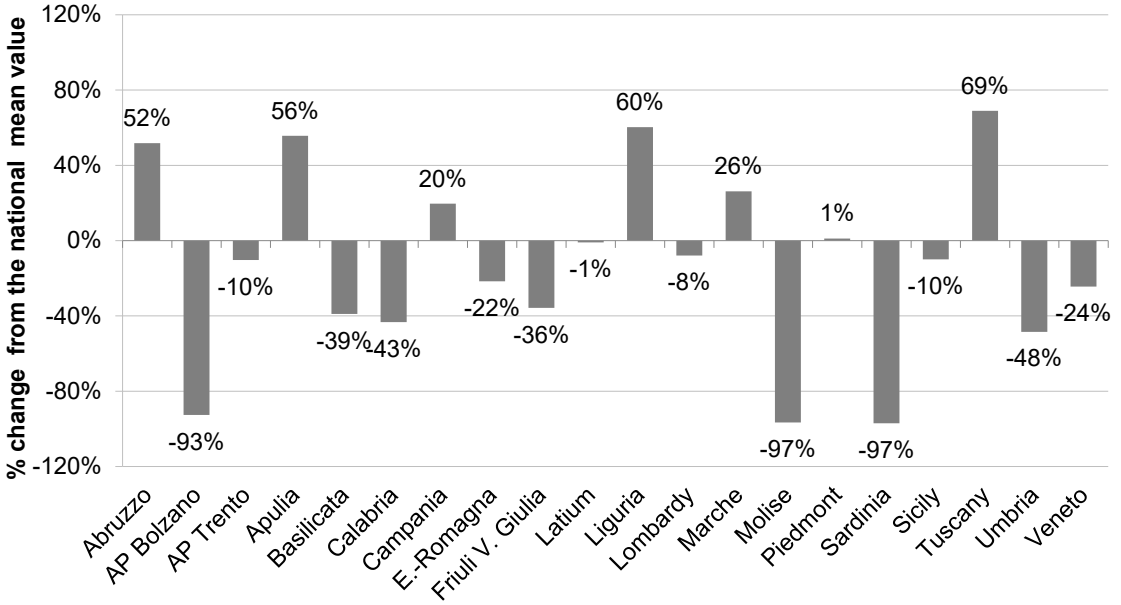

Figure 29. Percentage change from the national mean value of standardised regional demand for coagulation Factor IX (International Units *per capita*) in 2020 (adapted by the CNS on data from the Traceability information flow)

In eleven Regions there were percentage increases in demand (range: 0.1-100%) which is instead decreasing in nine Regions (range: -0.6; -51%) (*see* Table 26).

In Sardinia, AP of Trento and Friuli V.Giulia rFIX was used almost exclusively while in Liguria, Latium, Basilicata, Piedmont, Calabria, Tuscany, Apulia, Sicily and Campania the rFIX demand reached volumes of above 90% (Figure 30).

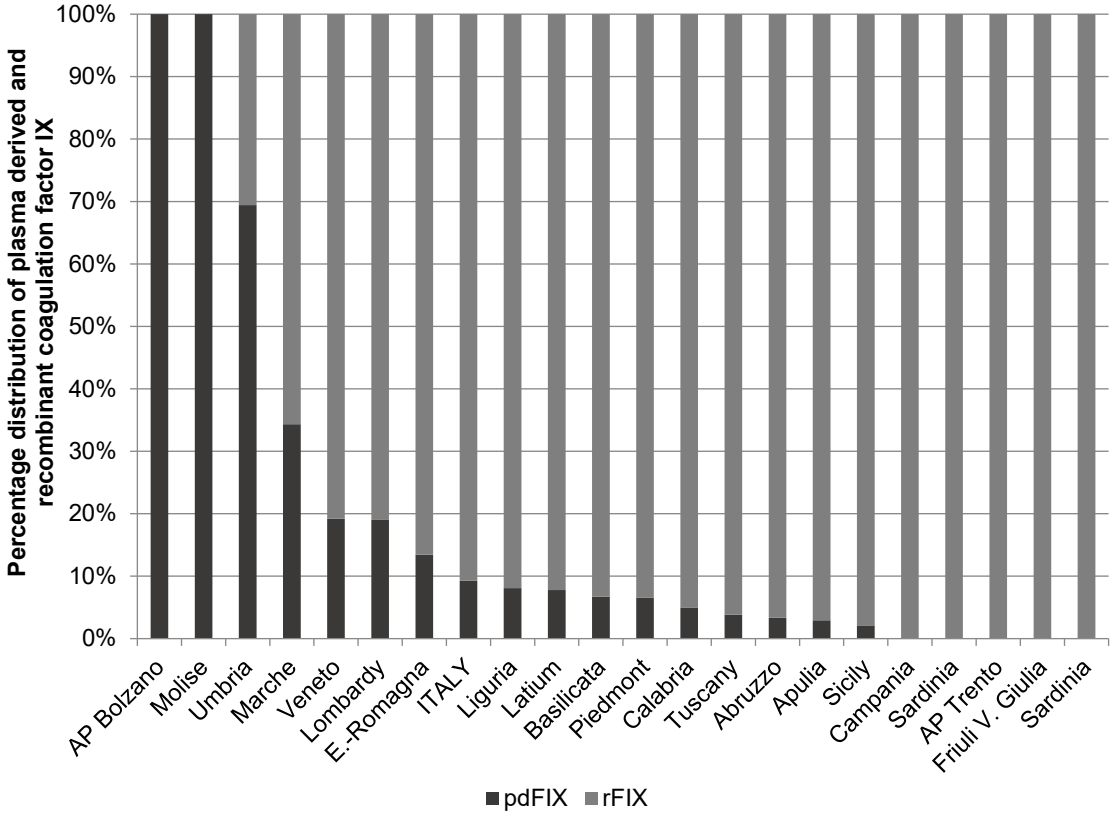

Figure 30. Distribution expressed in % of Factor IX per type, by Region, 2020 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor IX

In 2020, the total demand for pdFIX (expressed in absolute values and *per capita* volumes), showed a decrease of 28% compared to 2019, for an absolute value of 5,377,100 IUs, equal to 0.1 IUs *per capita* (Table 27).

The Regions with the highest *per capita* demand for pdFIX were Marche and Umbria with 0.4 IUs and 0.3 IUs respectively; in 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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	30,000	0.0	64,000	0.0	116.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	26,000	0.0	38,000	0.1	45.8
AP Trento	-	-	-	-	NA
Apulia	83,000	0.0	176,000	0.0	116.1
Basilicata	10,000	0.0	22,000	0.0	123.8
Calabria	58,000	0.0	52,000	0.0	-7.8
Campania	-	-	5,000	0.0	100.0
E.-Romagna	290,500	0.1	457,000	0.1	57.2
Friuli V.Giulia	32,000	0.0	-	-	-100.0
Latium	1,441,500	0.2	431,100	0.1	-69.5
Liguria	64,000	0.0	192,000	0.1	205.1
Lombardy	1,388,000	0.1	1,704,000	0.2	23.2
Marche	778,000	0.5	636,000	0.4	-17.6
Molise	-	-	10,000	0.0	100.0
Piedmont	218,000	0.1	278,000	0.1	28.9
Sardinia	-	-	-	-	NA
Sicily	172,000	0.0	90,000	0.0	-46.3
Tuscany	2,026,000	0.5	232,000	0.1	-88.4
Umbria	153,500	0.2	302,000	0.3	99.4
Veneto	749,000	0.2	688,000	0.1	-7.6
Italy	7,519,500	0.1	5,377,100	0.1	-27.6

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

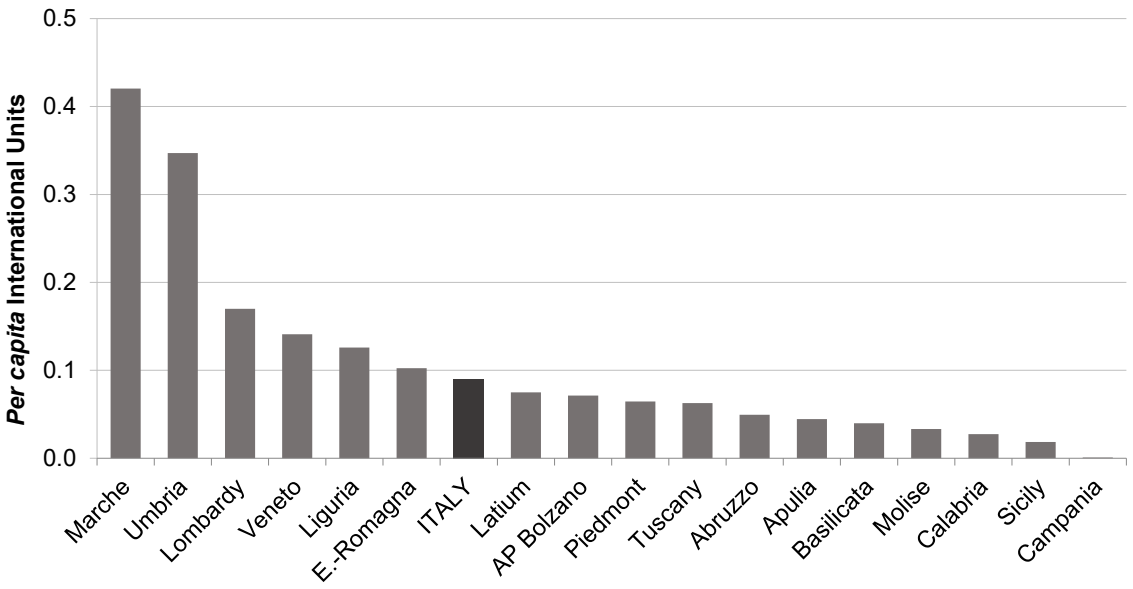

Figure 31. Total and regional demand (public and private) for plasma-derived coagulation Factor IX, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

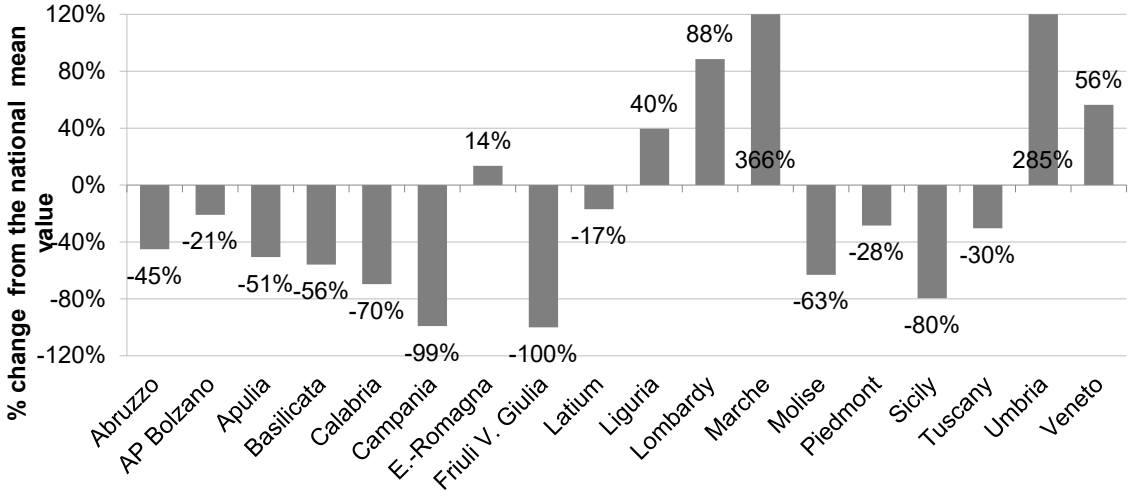

Figure 32. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor IX in 2020 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor IX

The total demand for rFIX showed, in the period 2019-2020, a decrease of -0.6%, registering a value of 52,449,750 IUs in 2020, 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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,970,000	1.5	1,842,000	1.4	-5.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	4000	0.0	-	-	-100.0
AP Trento	438500	0.8	475,000	0.9	7.5
Apulia	5,843,000	1.5	5,797,500	1.5	1.1
Basilicata	254,750	0.5	305,750	0.6	22.1
Calabria	2,122,250	1.1	990,750	0.5	-52.0
Campania	5,906,000	1.0	6,627,000	1.2	14.0
E.-Romagna	3,662,000	0.8	2,939,500	0.7	-19.8
Friuli V. Giulia	772,000	0.6	752,000	0.6	-1.9
Latium	4,889,250	0.8	5,103,000	0.9	6.6
Liguria	2,258,000	1.5	2,180,000	1.4	-1.8
Lombardy	6,600,000	0.7	7,254,500	0.7	10.3
Marche	910,000	0.6	1,216,000	0.8	34.7
Molise	-	-	-	-	NA
Piedmont	4,083,000	0.9	3,953,750	0.9	-2.2
Sardinia	89000	0.1	46,750	0.0	-46.6
Sicily	4,390,000	0.9	4,169,500	0.9	-2.6
Tuscany	6,241,000	1.7	5,822,750	1.6	-5.8
Umbria	287,000	0.3	133,000	0.2	-53.0
Veneto	2,729,500	0.6	2,891,000	0.6	6.5
Italy	53,449,250	0.9	52,499,750	0.9	-0.6

The Regions with the highest *per capita* demand of rFIX (Figure 33) were Tuscany, Apulia, Liguria and Abruzzo with 1.6 IU for the first one and 1.5 IU for the second one and 1.4 IU for the other two Regions (+79%, + 67% +62% and + 62% compared to the national average) (Figure 34).

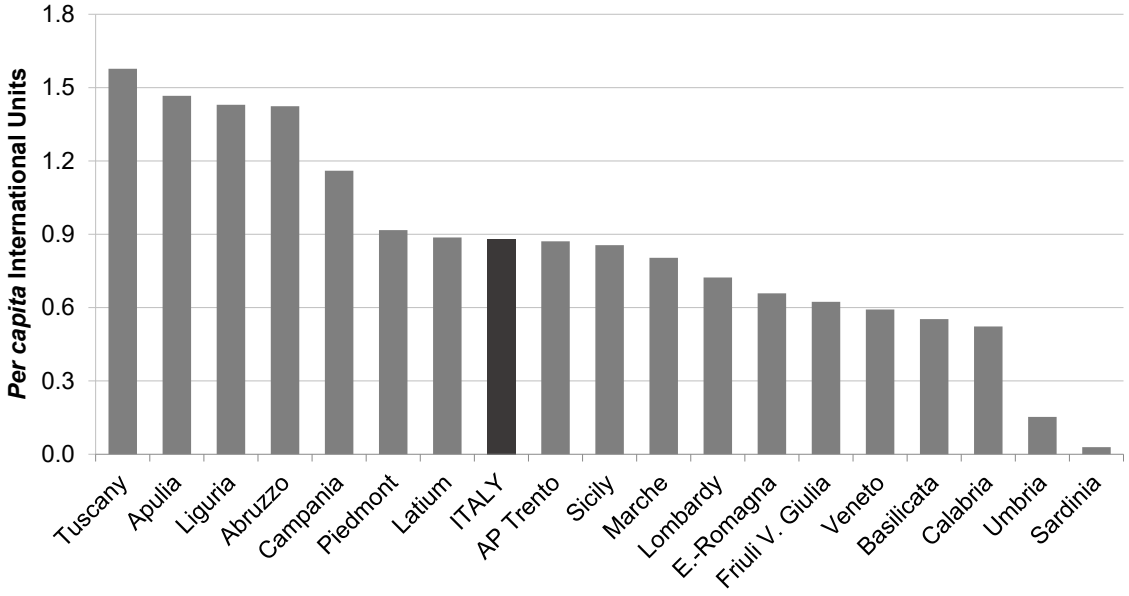

Figure 33. Total and regional demand (public and private) for recombinant coagulation Factor IX, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

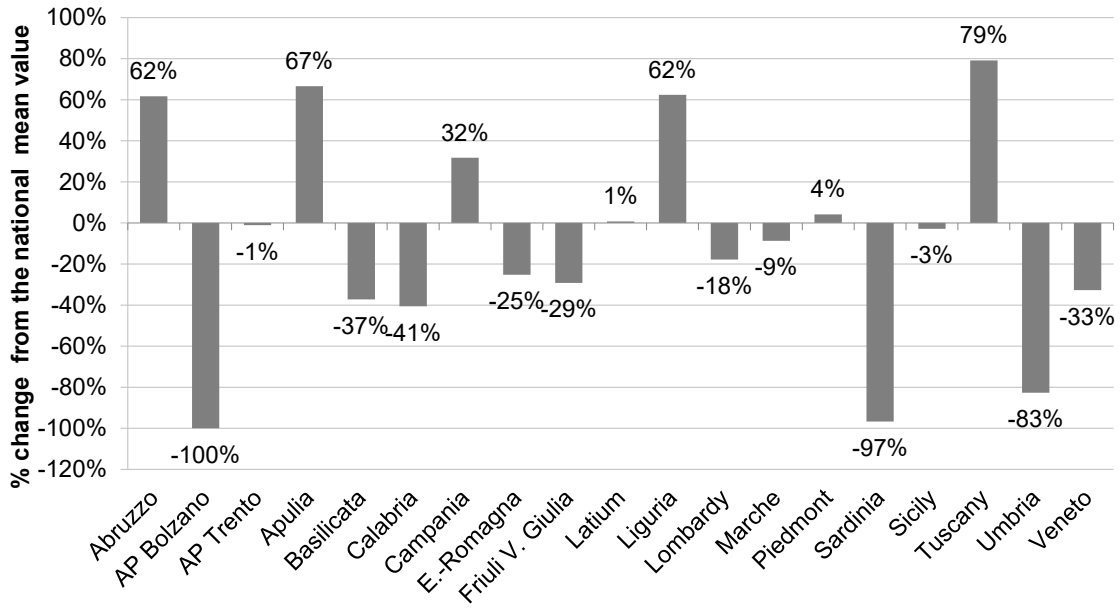

Figure 34. Percentage change from the national mean value of standardised regional demand for recombinant coagulation Factor IX in 2020 (adapted by the CNS on data from the Traceability information flow)

In Aosta Valley, AP of Bolzano and Molise there was no reported consumption of rFIX in 2020.

In 2020 there was a decrease in *per capita* demand, compared to 2019, in almost all Regions. The most evident decreases occurred in AP of Bolzano (-100%), Umbria (-53%), Calabria (-52%) and Sardinia (-47%).

Extended half- recombinant Factor IX life

Out of 52.5 million IUs of rFIX demand, extended half-life recombinant Factor IX molecules recorded a total demand of 32,952,750 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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,317,000	1.0	1,197,000	0.9	-7.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	3,681,500	0.9	4,530,500	1.1	25.4
Basilicata	68,750	0.1	98,750	0.2	46.1
Calabria	1,198,250	0.6	484,750	0.3	-58.4
Campania	2,534,750	0.4	2,642,000	0.5	5.9
E.-Romagna	2,822,000	0.6	2,502,000	0.6	-11.4
Friuli V. Giulia	686,000	0.6	704,000	0.6	3.4
Latium	2,253,000	0.4	2,400,500	0.4	8.8
Liguria	1,836,000	1.2	1,871,000	1.2	3.6
Lombardy	5,261,750	0.5	6,173,500	0.6	17.7
Marche	484,000	0.3	699,000	0.5	45.6
Molise	-	-	-	-	NA
Piedmont	2,576,500	0.6	2,817,750	0.7	10.5
Sardinia	40000	0.0	46750	0.0	18.9
Sicily	1,504,000	0.3	2,027,500	0.4	38.3
Tuscany	2,050,000	0.5	2,541,750	0.7	25.2
Umbria	245,000	0.3	107,000	0.1	-55.7
Veneto	1,802,000	0.4	2,109,000	0.4	17.7
Italy	30,360,500	0.5	32,952,750	0.6	9.8

The mean national demand *per capita* was about 0.6 IU, with a range among Regions of 0.03 IU and 1.2 IU. In Molise, in the APs of Trento and Bolzano and in the Aosta Valley there was no consumption for these drugs in 2020 (Figure 35 and 36).

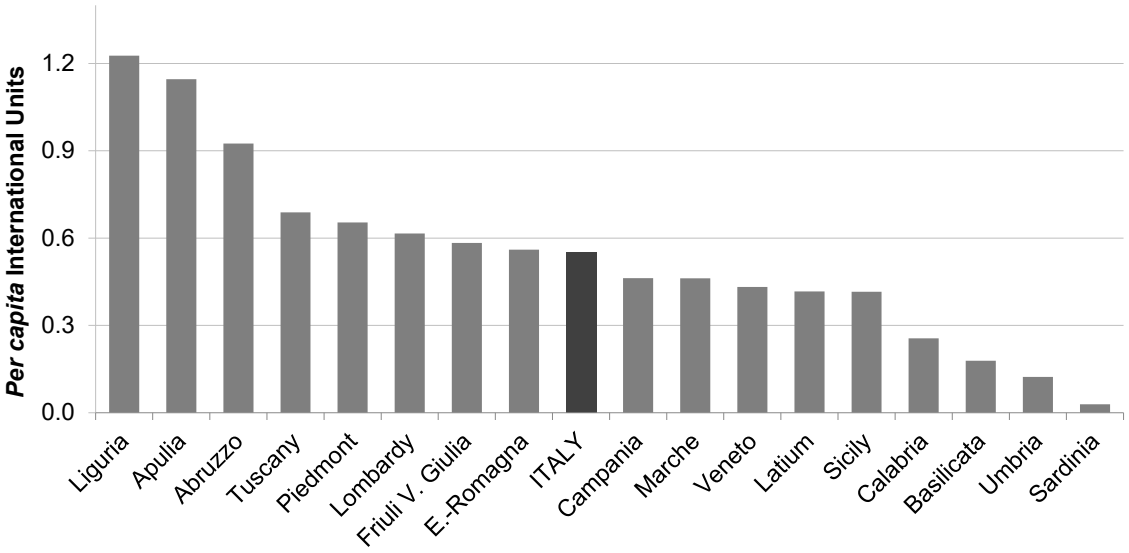

Figure 35. Total and regional demand (public and private) for extended half-life recombinant Factor IX, expressed in International Units per capita, 2020 (adapted by the CNS on data from the Traceability information flow)

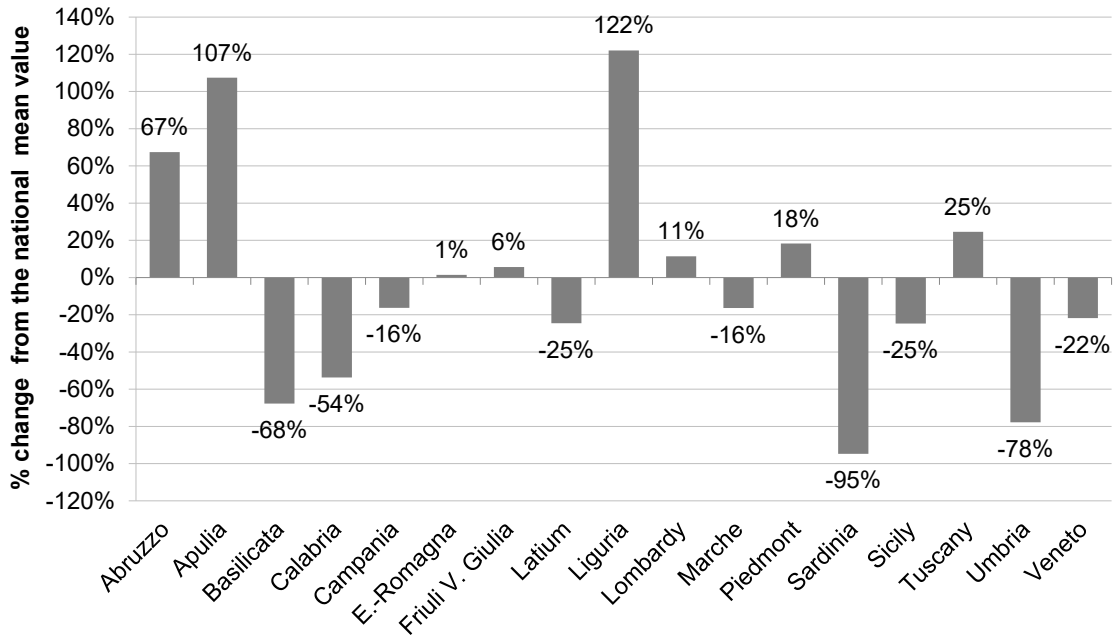

Figure 36. Percentage change from the national mean value of standardised regional demand for extended half-life recombinant Factor IX in 2020 (adapted by the CNS on data from the Traceability information flow)

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 31show 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, 31/12/2020)

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, 31/12/2020)

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 2019-2020, at both national and regional level.

In 2020 there was a slight decrease in the total demand (-5.3%) compared to 2019; it stood at 35,032,700 IUs, equal to 0.6 IU *per capita*. There were considerable differences in the use of 3F-PCCs from one Region to another with standardised values ranging from 0.3 IUs (Abruzzo, Basilicata, Calabria and Latium) to 1.2 IU (Sardinia), with a percentage change compared to the Italian mean value of over 50% in Sardinia (+98%) (Figures 37 and 38). In 2020, the national demand for 4F-PCCs was 11,411,500 IUs, equal to 25% of the overall demand for PCCs, with a standardised demand of 0.2 IU *per capita* and with an increase of 20% 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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	715,000	0.5	377,500	0.3	-46.5
AostaValley	80,000	0.6	98,500	0.8	23.7
APBolzano	432,000	0.8	368,000	0.7	-15.0
APTrento	379,000	0.7	346,500	0.6	-9.3
Apulia	2,238,000	0.6	2,123,000	0.5	-3.3
Basilicata	340,000	0.6	161,000	0.3	-51.8
Calabria	404,500	0.2	563,500	0.3	43.2
Campania	2,210,500	0.4	2,139,000	0.4	-1.7
E.-Romagna	3,761,500	0.8	3,498,000	0.8	-7.1
Friuli V. Giulia	832,000	0.7	704,000	0.6	-14.8
Latium	1,837,500	0.3	1,634,700	0.3	-9.1
Liguria	1,053,000	0.7	1,007,000	0.7	-2.7
Lombardy	6,343,300	0.6	6,297,800	0.6	-0.4
Marche	1,286,000	0.8	802,000	0.5	-37.1
Molise	260,500	0.9	110,000	0.4	-57.1
Piedmont	3,276,500	0.8	3,302,500	0.8	1.9
Sardinia	1,697,000	1.0	1,875,000	1.2	12.4
Sicily	3,173,000	0.6	3,323,000	0.7	7.4
Tuscany	2,519,500	0.7	1,976,000	0.5	-20.8
Umbria	586,000	0.7	475,000	0.5	-17.8
Veneto	4,018,500	0.8	3,850,700	0.8	-3.7
Italy	37,443,300	0.6	35,032,700	0.6	-5.3

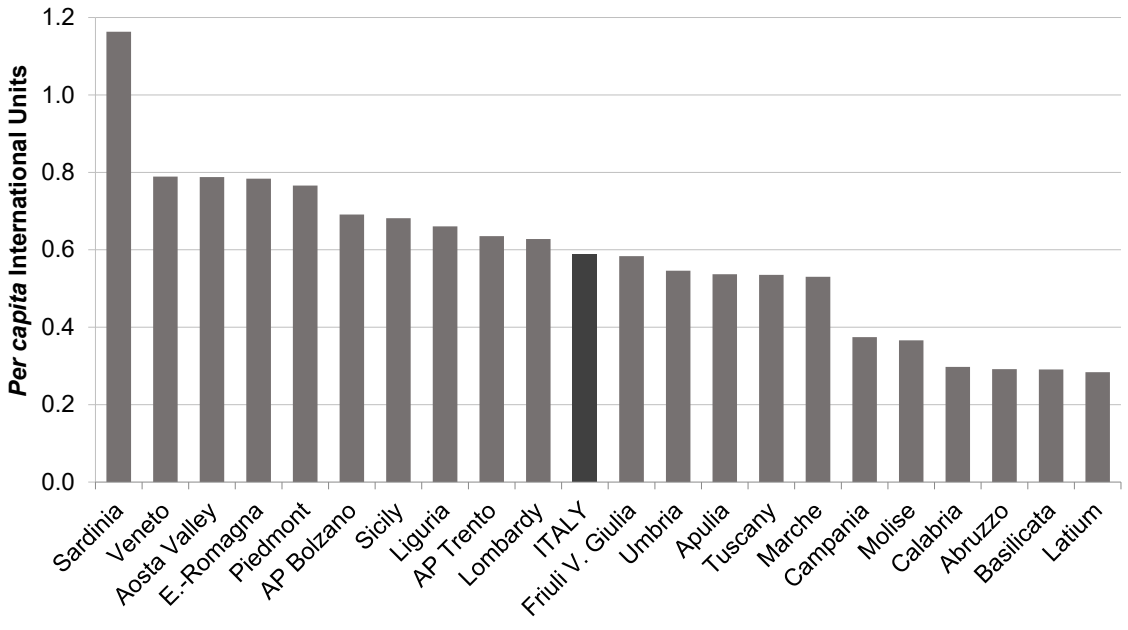

Figure 37. Total and regional demand (public and private) for 3-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

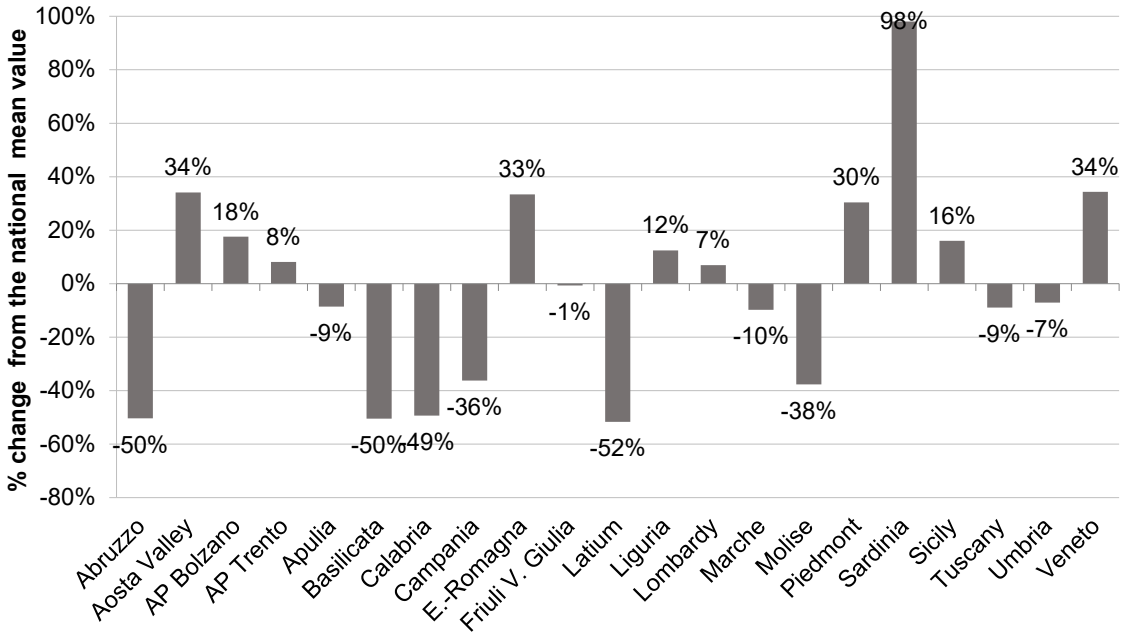

Figure 38. Percentage change from the national mean value of standardised regional demand for 3-factor prothrombin complex concentrates in 2020 (adapted by the CNS on data from the Traceability information flow)

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 2019-2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	571,000	0.4	575,500	0.4	2.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	521,000	1.0	562,500	1.1	7.7
AP Trento	49,500	0.1	52,000	0.1	4.2
Apulia	196,500	0.0	150,500	0.0	-21.9
Basilicata	238,000	0.4	180,000	0.3	-23.1
Calabria	411,000	0.2	391,000	0.2	-2.2
Campania	1,221,000	0.2	1,227,000	0.2	2.1
E.-Romagna	1,055,500	0.2	1,093,500	0.2	3.5
Friuli V. Giulia	4,000	0.0	-	0.0	-100.0
Latium	847,500	0.1	2,181,000	0.4	162.9
Liguria	149,500	0.1	283,000	0.2	92.5
Lombardy	801,500	0.1	980,000	0.1	22.7
Marche	177,000	0.1	143,000	0.1	-18.5
Molise	62,000	0.2	-	0.0	-100.0
Piedmont	767,500	0.2	773,500	0.2	1.8
Sardinia	666,500	0.4	735,500	0.5	12.3
Sicily	519,000	0.1	584,000	0.1	15.4
Tuscany	1,167,000	0.3	1,320,500	0.4	14.3
Umbria	61,000	0.1	49,000	0.1	-18.6
Veneto	105,500	0.0	130,000	0.0	23.9
Italy	9,591,500	0.2	11,411,500	0.2	20.4

Also for this PDMP, there were considerable differences regarding utilisation from one Region to another. With the exception of Basilicata, Calabria, Friuli V. Giulia, Marche, Molise, Apulia and Umbria, all the Regions recorded significant increases in the demand.

The Region with the highest demand in 2020 was the AP of Bolzano with 1.1 IU *per capita*, followed by Sardinia with 0.5 IU and Abruzzo, Latium 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 2020.

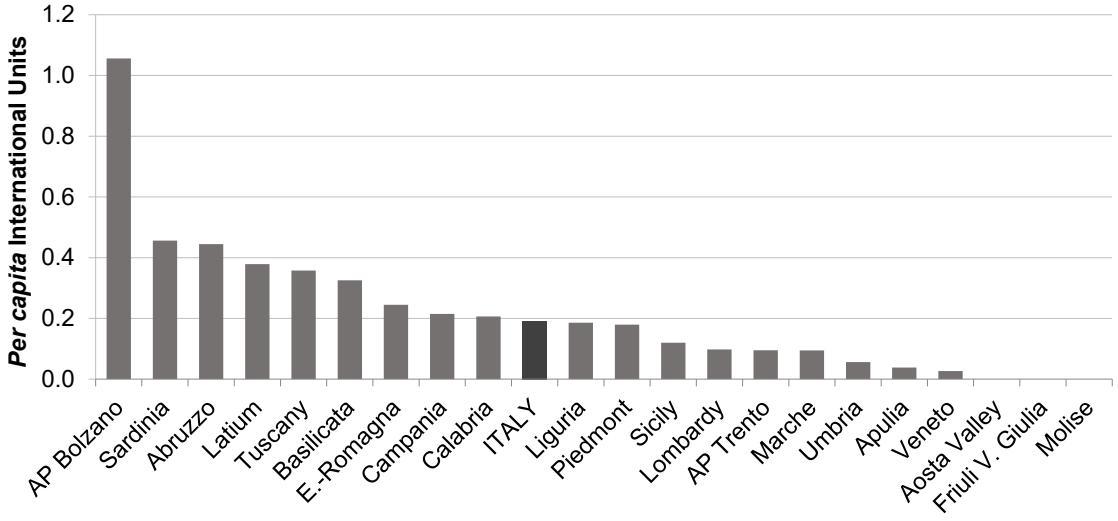

Figure 39. Total and regional demand (public and private) for 4-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2020 (adapted by the CNS on data from the Traceability information flow)

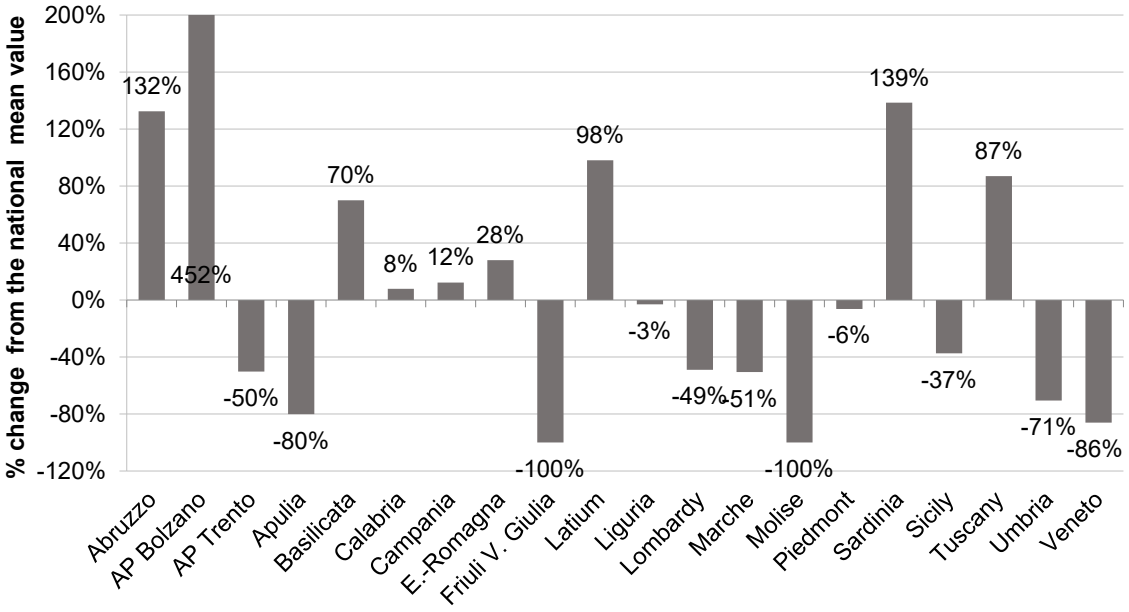

Figure 40. Percentage change from the national mean value of standardised regional demand for 4-factor prothrombin complex concentrates in 2020 (adapted by the CNS on data from the Traceability information flow)

FIBRINOGEN (ATC B02BB01)

Fibrinogen is one of the most abundant coagulation factors in plasma, with a mean concentration of about 2-4 g/L. It is converted into fibrin by thrombin and is the maincomponent of the coagulation phase. Fibrin, therefore, can be considered both a structural protein and a coagulation factor. In order to provide adequate structural support, the plasma concentration of fibrinogen must be relatively high. A deficiency of fibrinogen thus implies a lower capacity of the blood to coagulate, with a consequent increase in the tendency to bleeding (32).

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

Table 34 shows the brand names of medicinal products containing fibrinogen currently available on the Italian market and the amount of 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, 31/12/2020)

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(nn)
048798019	FIBRYGA*FLPOLV 1g 100Mm+F50mL	1	OCTAPHARMA Italy SPA	C(nn)
044380018	FIBRICLOTTE*FL POLV 1,5g 100mL	1.5	LFB	C(nn)

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

Quantification of the demand

Table 35 shows the total demand and the total standardised demand (g per 1,000 population) for fibrinogen over the two-year period 2019-2020 at regional and national level.

In 2020, total fibrinogen demand showed a significant increase (+10%) compared to the previous year. Its volume of 47,719 g, with a standardised demand of 0.8 g per 1,000 population, confirmed the rapid upward trend. The increase was mainly linked to the imported product. All Regions, with the exception of Basilicata, Emilia-Romagna, Friuli V.Giulia, Molise, Apulia, Sardinia and Umbria, contributed to this growth to different extents.

Figure 41 shows the regional and national standardised demand for fibrinogen in 2020. The Regions with the highest demand per 1,000 population were AP of Bolzano (2.1 g) then Calabria (1.5 g) and Abruzzo and Veneto with 1.3 g. The lowest demand, between 0.2 g and 0.5 g per 1,000 population, was recorded in Molise, Basilicata, Liguria, Lombardy and Apulia.

Table 35. Total demand (public and private) and total standardised demand for fibrinogen, expressed in grams and grams per 1,000 population, and variations in percentage between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2019		2020		% Var 2019-2020
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,523	1.2	1,666	1.3	10.9
Aosta Valley	59	0.5	70	0.6	19.2
AP Bolzano	788	1.5	1,118	2.1	41.5
AP Trento	291	0.5	581	1.1	97.8
Apulia	2,498	0.6	2,138	0.5	-12.8
Basilicata	480	0.9	240	0.4	-49.1
Calabria	2,182	1.1	2,792	1.5	31.5
Campania	4,319	0.7	4,471	0.8	5.1
E.-Romagna	3,645	0.8	3,491	0.8	-4.3
Friuli V. Giulia	1,103	0.9	983	0.8	-10.2
Latium	5,148	0.9	5,334	0.9	5.8
Liguria	502	0.3	642	0.4	30.1
Lombardy	4,587	0.5	5,001	0.5	9.4
Marche	1,030	0.7	1,078	0.7	5.5
Molise	73	0.2	62	0.2	-13.6
Piedmont	1,893	0.4	2,462	0.6	31.4
Sardinia	1,936	1.2	1,839	1.1	-3.4
Sicily	2,627	0.5	3,126	0.6	22.0
Tuscany	2,650	0.7	3,283	0.9	25.1
Umbria	1,047	1.2	860	1.0	-16.7
Veneto	5,600	1.1	6,482	1.3	16.4
Italy	43,981	0.7	47,719	0.8	9.8

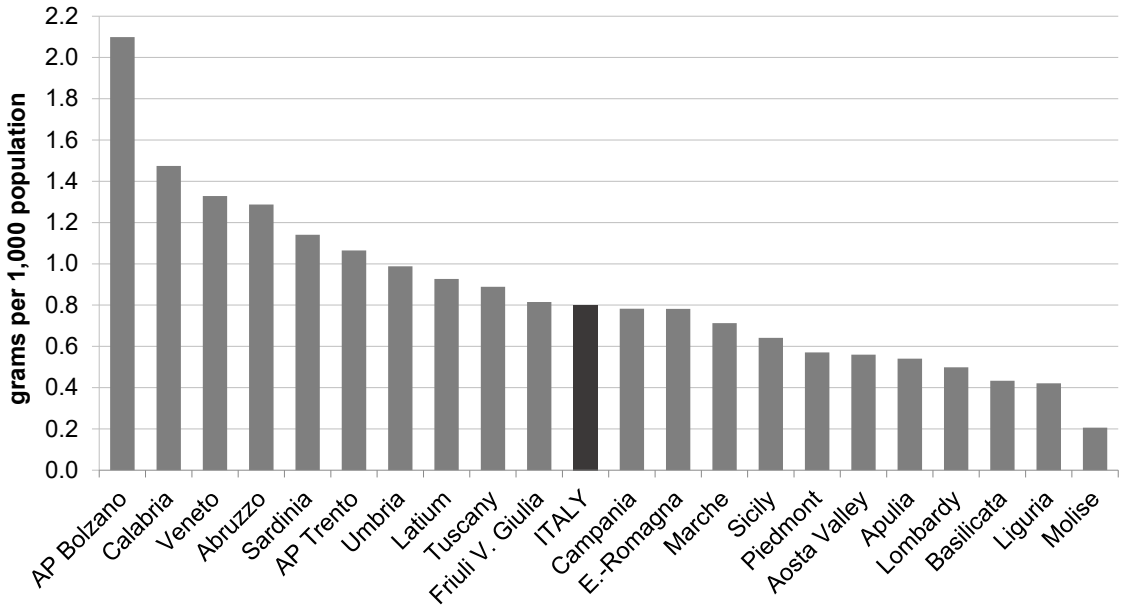

Figure 41. Total and regional demand (public and private) for fibrinogen, expressed in grams per 1,000 population, 2020 (adapted by the CNS on data from the Traceability information flow)

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 principle 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, 31/12/2020)

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

Table 37. Products containing hepatitis B immunoglobulins for subcutaneous/intramuscular use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2020)

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

Quantification of the demand

Tables 38 and 39 show respectively the total demand and the total standardised demand (expressed in IUs *per capita*) of hepatitis B IG formulations for IV and for SC/IM use for the two-year period 2019-2020, at national and at regional level.

The national demand for hepatitis B IGs for IV use, showed a downward trend (-8.2%) already observed in previous years (34). The total demand in 2020 was almost 14,7 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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow).

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	21,000	0.0	28,000	0.0	35.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	1,704,500	0.4	1,806,000	0.5	8.0
Basilicata	1,000	0.0	2,000	0.0	103.5
Calabria	211,500	0.1	181,500	0.1	-11.8
Campania	4,370,500	0.8	3,136,500	0.5	-27.1
E.-Romagna	2,194,000	0.5	1,406,000	0.3	-36.0
Friuli V. Giulia	375,000	0.3	280,000	0.2	-24.8
Latium	465,500	0.1	790,000	0.1	73.3
Liguria	32,000	0.0	2,500	0.0	-92.1
Lombardy	1,681,500	0.2	1,589,500	0.2	-5.2
Marche	155,500	0.1	537,500	0.4	248.5
Molise	22,000	0.1	6,000	0.0	-72.3
Piedmont	657,500	0.2	737,500	0.2	13.3
Sardinia	466,000	0.3	517,000	0.3	12.9
Sicily	297,500	0.1	186,500	0.0	-35.7
Tuscany	991,500	0.3	1,070,000	0.3	9.0
Umbria	-	-	-	-	NA
Veneto	2,503,500	0.5	2,379,000	0.5	-4.5
Italy	16,150,000	0.3	14,655,500	0.2	-8.2

Campania, despite a significant decrease in its regional demand, continued to be the Region with the highest demand, together with Veneto and Apulia (0.5 IU *per capita*), which represent 50% of the national demand.

On the other hand, the national demand for antihepatitis B SC/IM IG, shows a decrease, equal to -6% of the demand recorded in 2019; the total consumption for 2020 is approximately 70 million IUs (1.2 IUs *per capita*) (Table 39) and accounted 83% 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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow).

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	565,020	0.4	643,240	0.5	15.4
Aosta Valley	223,960	1.8	250,500	2.0	12.4
AP Bolzano	112,160	0.2	126,480	0.2	12.5
AP Trento	172,000	0.3	206,620	0.4	19.2
Apulia	6,067,860	1.5	5,942,960	1.5	-0.2
Basilicata	294,960	0.5	302,580	0.5	4.4
Calabria	1,577,300	0.8	1,772,060	0.9	15.5
Campania	31,401,800	5.4	22,464,420	3.9	-27.3
E.-Romagna	3,446,080	0.8	3,868,000	0.9	12.1
Friuli V. Giulia	256,640	0.2	365,220	0.3	43.4
Latium	2,162,600	0.4	2,760,600	0.5	30.4
Liguria	634,000	0.4	576,960	0.4	-7.5
Lombardy	10,168,380	1.0	11,264,060	1.1	11.1
Marche	714,120	0.5	681,040	0.5	-3.8
Molise	138,460	0.5	157,560	0.5	15.7
Piedmont	4,936,840	1.1	5,236,060	1.2	7.2
Sardinia	3,397,540	2.1	3,506,440	2.2	5.0
Sicily	3,132,700	0.6	3,049,260	0.6	-0.2
Tuscany	3,375,320	0.9	3,939,900	1.1	17.9
Umbria	314,820	0.4	338,180	0.4	8.9
Veneto	2,395,600	0.5	2,621,000	0.5	10.0
Italy	75,488,160	1.3	70,073,140	1.2	-6.1

TETANUS IMMUNOGLOBULINS (ATC J06BB02)

Table 40 shows drugs containing tetanus IGs currently available on the Italian market and the amount of active principle 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, 31/12/2020).

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 2020 the total demand for tetanus IGs was 124,246,683 IUs (2.1 IUs *per capita*), showing a decrease of 14.5% compared to 2019 (Table 41).

The Regions with the highest demand, expressed as standardised volume for the resident population, were Campania (4.2 IUs *per capita*), and Abruzzo and Calabria (3.5 and 3.8 IUs *per capita,* respectively).

In 2020, the demand decreased – in some cases very significantly - in almost all Regions, with the exception of Friuli V. Giulia (+23%).

A significant amount of tetanus IGs was imported under the provisions of DM of 11 February 1997 and DM of 11 May 2001, however no detailed information about the regional distribution was available. Therefore they were inserted under the heading “Not Specified Region” and accounted for 888,183 IUs.

Table 41. Total demand (public and private) and total standardised demand, expressed in International Units and International Units *per capita*, for tetanus immunoglobulins and variations in percentage between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	5,867,750	4.5	4,551,000	3.5	-21.4
Aosta Valley	382,750	3.0	366,250	2.9	-3.8
AP Bolzano	742,500	1.4	527,500	1.0	-29.2
AP Trento	518,500	1.0	432,000	0.8	-17.3
Apulia	8,131,250	2.0	7,534,000	1.9	-5.6
Basilicata	2,064,750	3.7	1,386,250	2.5	-31.7
Calabria	7,551,500	3.9	7,133,250	3.8	-2.9
Campania	29,078,750	5.0	24,272,750	4.2	-15.2
E.-Romagna	7,702,250	1.7	5,711,500	1.3	-25.9
Friuli V. Giulia	341,500	0.3	418,500	0.3	23.5
Latium	12,572,250	2.1	10,904,000	1.9	-11.4
Liguria	4,498,500	2.9	3,672,250	2.4	-17.0
Lombardy	18,100,250	1.8	13,497,750	1.3	-25.2
Marche	5,245,250	3.4	4,116,000	2.7	-20.9
Molise	868,250	2.8	741,750	2.5	-13.1
Piedmont	5,921,250	1.4	4,539,750	1.1	-22.5
Sardinia	4,966,750	3.0	4,459,750	2.8	-8.6
Sicily	12,792,500	2.6	12,214,000	2.5	-2.1
Tuscany	13,360,500	3.6	11,929,000	3.2	-9.8
Umbria	2,258,500	2.6	1,646,500	1.9	-26.1
Veneto	3,659,000	0.7	3,304,750	0.7	-9.2
Not specified Region	417,500	NA	888,183	NA	NA
Italy	147,042,000	2.4	124,246,683	2.1	-14.5

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 principle 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, 31/12/2020)

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 2019 and 2020 remained broadly stable and stood at 111,419,375 IUs in 2020 (1.9 IUs *per capita*), with the highest peak in the AP of Bolzano and the lowest level in Friuli V. Giulia (3.7 and 0.1 IUs *per capita*, respectively) (Table 43).

Table 43. Total demand (public and private) and total standardised demand for anti-D (Rh) immunoglobulins, expressed in International Units and in International Units *per capita* and variations in percentage between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,599,500	2.0	2,574,000	2.0	0.4
Aosta Valley	262,500	2.1	295,500	2.4	13.1
AP Bolzano	2,303,750	4.3	1,961,000	3.7	-15.1
AP Trento	1,534,250	2.8	1,336,750	2.5	-13.6
Apulia	5,779,500	1.4	5,895,000	1.5	4.0
Basilicata	1,266,875	2.3	1,004,500	1.8	-19.3
Calabria	2,548,000	1.3	2,395,250	1.3	-3.4
Campania	9,308,875	1.6	9,901,000	1.7	8.0
E.-Romagna	10,829,250	2.4	11,124,875	2.5	2.6
Friuli V. Giulia	1,520,250	1.3	162,000	0.1	-89.3
Latium	10,749,000	1.8	8,421,000	1.5	-20.0
Liguria	2,751,000	1.8	2,752,000	1.8	1.7
Lombardy	21,195,625	2.1	22,167,000	2.2	4.9

Region	2019		2020		% Var 2019-2020
	IU	IU *per capita*	IU	IU *per capita*	
Marche	3,225,000	2.1	2,980,500	2.0	-6.8
Molise	443,500	1.5	295,000	1.0	-32.4
Piedmont	9,797,750	2.2	8,081,375	1.9	-16.7
Sardinia	1,403,000	0.9	1,347,000	0.8	-2.3
Sicily	7,498,500	1.5	8,497,500	1.7	16.2
Tuscany	7,510,750	2.0	8,109,875	2.2	9.1
Umbria	1,396,500	1.6	1,702,500	2.0	23.6
Veneto	12,944,375	2.6	10,415,750	2.1	-19.1
Italy	116,867,750	1.9	111,419,375	1.9	-3.5

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 principle 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, 31/12/2020)

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

Quantification of the demand

Table 45 shows the total demand and the total standardised demand (U *per capita*) for CMV IGs for the two-year period 2019-2020, 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 (U) and U *per capita*, and variations in percentages between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	U	U *per capita*	U	U *per capita*	
Abruzzo	210,000	0.2	521,000	0.4	151.5
Aosta Valley	17,000	0.1	9,000	0.1	-46.8
AP Bolzano	18,000	0.0	87,000	0.2	382.0
AP Trento	-	-	-	-	NA
Apulia	646,000	0.2	280,000	0.1	-55.8
Basilicata	165,000	0.3	100,000	0.2	-38.3
Calabria	255,000	0.1	80,000	0.0	-67.7
Campania	334,000	0.1	251,000	0.0	-23.7
E.-Romagna	2,682,000	0.6	866,000	0.2	-67.7
Friuli V. Giulia	1,266,000	1.0	1,092,000	0.9	-13.1
Latium	956,000	0.2	690,000	0.1	-26.3
Liguria	2,000	0.0	61,000	0.0	3,001.6
Lombardy	2,046,000	0.2	1,148,000	0.1	-43.7
Marche	480,000	0.3	258,000	0.2	-45.8
Molise	-	-	-	-	NA
Piedmont	2,158,000	0.5	2,582,000	0.6	20.9
Sardinia	-	-	25,000	0.0	100.0
Sicily	937,000	0.2	422,000	0.1	-53.8
Tuscany	132,000	0.0	329,000	0.1	151.7
Umbria	40,000	0.0	8,000	0.0	-79.7
Veneto	3,146,000	0.6	3,881,000	0.8	24.0
Italy	15,490,000	0.3	12,690,000	0.2	-17.1

During the period under examination, the CMV IGs national demand decreased by 17% compared to the previous year and stood at 12,690,000 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 (0.9 U *per capita*), followed by Veneto (0.8 U *per capita*) and Piedmont (0.6 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 (35,36,37).

Table 46 shows the brand names of medicinal products containing Var IGs currently available on the Italian market and the amount of active principle 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, 31/12/2020)

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 2019-2020, at national and regional levels. The national demand for IG anti-Var showed a sharp decline (-19%). Total demand in 2020 was 69,500 IUs (1.2 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 2019 and 2020 (adapted by the CNS on data from the Product Quality and Pharmacrime Office - AIFA)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	1,500	1.1	5,000	3.9	237.9
Aosta Valley	1,750	13.9	-	0.0	-100.0
AP Bolzano	625	1.2	2,500	4.7	298.9
AP Trento	1,000	1.8	2,625	4.8	160.4
Apulia	2,125	0.5	15,000	3.8	619.4
Basilicata	-	0.0	-	0.0	NA
Calabria	375	0.2	-	0.0	-100.0
Campania	2,625	0.5	1,500	0.3	-42.0
Emilia-Romagna	11,625	2.6	8,750	2.0	-24.8
Friuli V. Giulia	3,625	3.0	-	0.0	-100.0
Latium	3,750	0.6	2,875	0.5	-21.7
Liguria	4,000	2.6	500	0.3	-87.3

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Lombardy	35,375	3.5	10,625	1.1	-69.9
Marche	5,500	3.6	4,625	3.1	-15.2
Molise	-	0.0	-	0.0	NA
Piedmont	1,750	0.4	7,125	1.7	311.4
Sardinia	125	0.1	250	0.2	103.5
Sicily	-	0.0	-	0.0	NA
Tuscany	1,375	0.4	3,125	0.8	129.6
Umbria	3,125	3.5	-	0.0	-100.0
Veneto	6,375	1.3	5,000	1.0	-21.1
Italy	86,625	1.4	69,500	1.2	-18.8

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 principle 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, 31/12/2020)

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 2020, the total demand for rabies IGs, recorded in eight Regions, showed a remarkable decrease compared to 2019 (-26%). The total demand amounted to 134,850 IUs (2.3 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 2019 and 2020 (adapted by the CNS on data from theProduct Quality and Pharmacrime Office – AIFA)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop.	IU	IU per 1,000 pop.	
Abruzzo	-	0.0	-	0.0	NA
Aosta Valley	4,500	35.8	6,000	48.0	34.0
AP Bolzano	5,550	10.4	2,100	3.9	-62.3
AP Trento	3,000	5.5	-	0.0	-100.0
Apulia	3,150	0.8	600	0.2	-80.6
Basilicata	-	0.0	-	0.0	NA
Calabria	-	0.0	-	0.0	NA
Campania	-	0.0	-	0.0	NA
E.-Romagna	16,650	3.7	28,350	6.4	70.1
Friuli V. Giulia	-	0.0	46,650	38.7	100.0
Latium	1,500	0.3	-	0.0	-100.0
Liguria	-	0.0	-	0.0	NA
Lombardy	14,850	1.5	40,350	4.0	172.6
Marche	1,500	1.0	750	0.5	-49.6
Molise	-	0.0	-	0.0	NA
Piedmont	-	0.0	-	0.0	NA
Sardinia	-	0.0	-	0.0	NA
Sicily	-	0.0	-	0.0	NA
Tuscany	5,700	1.5	-	0.0	-100.0
Umbria	-	0.0	-	0.0	NA
Veneto	129,150	26.3	10,050	2.1	-92.2
Italy	185,550	3.1	134,850	2.3	-26.4

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

Table 50 shows the brand names of drugs containing local haemostatics - combinations currently on the market in Italy and the amount of active principle 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, 31/12/2020)

AIC code	Brand name	mL	Manufacturer	NHS class
035941018	BERIPLAST P*FL POLV 0,5mL+FL	0.5	CSL BEHRING GmbH	C
035941020	BERIPLAST P*FL POLV 1mL+FL+SET	1	CSL BEHRING GmbH	C
035941032	BERIPLAST P*FL POLV 3mL+FL+SET	3	CSL BEHRING GmbH	C
039546015	ARTISS SOL. ADESIVO TISSUTALE	1	BAXTER SpA	H
025243179	TISSEEL 2ml ADESIVO TISSUTALE	2	BAXTER SpA	H
039546027	ARTISS SOL. ADESIaVO TISSUTALE	2	BAXTER SpA	H
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
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 principle 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 2020, the total demand for local haemostatics-combinations reached a volume of about 249,989 mL (4.2 mL per 1,000 population), recording a notable decrease (-4%) compared to the volume of 2019 (Table 51). In 2020, the total demand for local haemostatics–combinations, expressed in number of gelatin sponges, amounted to 36,088 sponges, recording a decrease compared to 2019 (-2%) (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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	7,602	5.8	7,632	5.9	1.8
Aosta Valley	708	5.6	404	3.2	-42.6
AP Bolzano	2,282	4.3	2,073	3.9	-9.4
AP Trento	2,936	5.4	2,472	4.5	-16.5
Apulia	16,950	4.2	17,688	4.5	6.4
Basilicata	3,112	5.5	3,190	5.8	4.3
Calabria	4,996	2.6	5,232	2.8	7.7
Campania	38,774	6.7	36,177	6.3	-5.2
Emilia-Romagna	12,382	2.8	12,056	2.7	-2.7
Friuli V. Giulia	4,264	3.5	3,150	2.6	-25.6
Latium	22,768	3.9	27,688	4.8	24.2
Liguria	4,556	2.9	4,814	3.2	7.5
Lombardy	52,497	5.2	44,909	4.5	-14.2
Marche	4,826	3.2	4,278	2.8	-10.6
Molise	876	2.9	510	1.7	-40.8
Piedmont	16,001	3.7	14,030	3.3	-11.4
Sardinia	5,906	3.6	5,422	3.4	-6.6
Sicily	16,886	3.4	16,784	3.4	1.9
Tuscany	16,019	4.3	15,337	4.2	-3.3
Umbria	4,384	5.0	3,674	4.2	-15.1
Veneto	24,987	5.1	22,469	4.6	-9.6
Italy	263,712	4.4	249,989	4.2	-4.1

Table 52. Total demand (public and private) for local haemostatics-combinations, expressed in number of gelatin sponges, and variations in percentage between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019	2020	% Var 2019-2020
Abruzzo	1,395	1,394	-0.1
Aosta Valley	259	105	-59.5
AP Bolzano	398	514	29.1
AP Trento	178	190	6.7
Apulia	1,959	1,978	1.0
Basilicata	931	715	-23.2
Calabria	2,170	2,123	-2.2
Campania	4,953	4,472	-9.7
Emilia-Romagna	1,531	1,331	-13.1
Friuli V. Giulia	743	1,035	39.3
Latium	2,146	2,523	17.6
Liguria	481	475	-1.2
Lombardy	5,309	5,711	7.6
Marche	1,697	1,315	-22.5
Molise	36	6	-83.3
Piedmont	2,799	2,830	1.1
Sardinia	601	510	-15.1
Sicily	2,523	2,719	7.8
Tuscany	3,122	2,856	-8.5
Umbria	947	800	-15.5
Veneto	2,646	2,486	-6.0
Italy	36,824	36,088	-2.0

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 principle 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, 31/12/2020)

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

Quantification of the demand

In 2020, the total demand and the total standardised national demand for FVII was approximately 5 million IUs showing a decrease of -14.5% compared to 2019 (Table 54).

Despite this, a substantial increases were recorded in Liguria (+891%) and in Molise (+104%). In 2020, 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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	113,400	86.5	108,000	83.5	-3.5
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	253,200	62.8	378,600	95.8	52.4
Basilicata	136,200	242.0	45,600	82.4	-65.9
Calabria	90,000	46.2	53,400	28.2	-39.0
Campania	403,800	69.6	270,000	47.3	-32.1
E.-Romagna	573,600	128.6	120,600	27.0	-79.0
Friuli V. Giulia	-	-	-	-	NA
Latium	1,798,200	305.9	1,594,200	277.0	-9.4
Liguria	4,800	3.1	46,800	30.7	891.5
Lombardy	1,728,600	171.8	1,352,400	134.9	-21.5
Marche	1,200	0.8	1,200	0.8	0.8
Molise	270,000	883.5	541,800	1802.9	104.1
Piedmont	238,800	54.8	231,000	53.6	-2.3
Sardinia	-	-	-	-	NA
Sicily	285,600	57.1	285,600	58.6	2.6
Tuscany	28,800	7.7	18,600	5.0	-34.8
Umbria	4,800	5.4	3,600	4.1	-24.0
Veneto	62,400	12.7	14,400	3.0	-76.8
Italy	5,993,400	99.3	5,065,800	84.9	-14.5

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 principle 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, 31/12/2020)

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 2019-2020, at national and regional level. The total demand for rFVIIa recorded in 2020 was 77,961 mg (1.3 mg per 1,000 population) substantially stable compared to 2019.

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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Abruzzo	381	0.3	501	0.4	33.3
Aosta Valley	23	0.2	-	-	-100.0
AP Bolzano	101	0.2	1,135	2.1	1,020.7
AP Trento	20	0.0	62	0.1	207.5
Apulia	9,422	2.3	8,277	2.1	-10.5
Basilicata	43	0.1	9	0.0	-78.7
Calabria	7,267	3.7	4,643	2.5	-34.3
Campania	10,021	1.7	18,217	3.2	84.6
E.-Romagna	2,569	0.6	2,862	0.6	11.3
Friuli V. Giulia	10,900	9.0	8,064	6.7	-25.5
Latium	3,560	0.6	5,236	0.9	50.2
Liguria	337	0.2	123	0.1	-62.9
Lombardy	10,626	1.1	3,846	0.4	-63.7

Region	2019		2020		% Var 2019-2020
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Marche	1,775	1.2	1,338	0.9	-24.0
Molise	383	1.3	258	0.9	-31.5
Piedmont	2,171	0.5	2,154	0.5	0.3
Sardinia	21	0.0	83	0.1	302.1
Sicily	4,648	0.9	3,986	0.8	-12.1
Tuscany	4,539	1.2	9,731	2.6	116.5
Umbria	436	0.5	25	0.0	-94.2
Veneto	8,467	1.7	7,411	1.5	-12.0
Italy	77,710	1.3	77,961	1.3	1.5

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 principle 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, 31/12/2020)

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 2019-2020 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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	FU	FU *per capita*	FU	FU *per capita*	
Abruzzo	1,497,000	1.1	1,084,000	0.8	-26.6
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	164,000	0.0	2,000	0.0	-98.8
Basilicata	-	-	-	-	NA
Calabria	527,000	0.3	-	-	-100.0
Campania	2,000,000	0.3	993,000	0.2	-49.6
E.-Romagna	671,000	0.2	523,000	0.1	-22.1
Friuli V. Giulia	616,000	0.5	858,000	0.7	40.3
Latium	687,000	0.1	793,000	0.1	17.9
Liguria	7,000	0.0	15,000	0.0	117.9
Lombardy	1,037,000	0.1	1,895,000	0.2	83.3
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	285,000	0.1	290,000	0.1	2.8
Sardinia	86,000	0.1	285,000	0.2	237.1
Sicily	1,480,000	0.3	2,047,000	0.4	41.8
Tuscany	854,000,0	0.2	867,000,0	0.2	2.5
Umbria	-	-	-	-	NA
Veneto	85,000	0.0	242,000	0.0	186.3
Italy	9,996,000	0.2	9,894,000	0.2	0.2

In 2020, the national demand for aPCCs was almost stable compared to the previous year (+0.2%), with some regional variations. Its total volume was 9,894,000 FUs (0.2 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 principle 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, 31/12/2020)

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)
044479020	RESPREEZA*EV 1FL 76mL + 4g+SET	4000	CSL BEHRING GmbH	C(nn)
044479032	RESPREEZA*EV 1FL 95mL+ 5g+ SET	5000	CSL BEHRING GmbH	C(nn)

Quantification of the demand

In 2020, the total demand for alpha-1-antitrypsin was 51,912 g (0.9 g per 1,000 population) recording a significant upward trend compared to the previous year (+ 12.5%) (Table 55). In particular in Umbria, Sardinia and Tuscany the demand exceeded the value recorded in the previous year (+72%, +49% and +41%, respectively). The highest regional standardized demand is in the Aosta Valley and in the AP of Bolzano (8 and 5 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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,647	1.3	1,557	1.2	-4.2
Aosta Valley	972	7.7	997	8.0	3.1
AP Bolzano	2,677	5.0	2,650	5.0	-1.3
AP Trento	626	1.2	636	1.2	0.8
Apulia	1,328	0.3	1,768	0.4	35.7
Basilicata	3	0.0	-	-	-100.0
Calabria	832	0.4	1,028	0.5	27.0
Campania	5,729	1.0	6,679	1.2	18.4
E.-Romagna	2,338	0.5	3,024	0.7	29.2
Friuli V.Giulia	2,200	1.8	2,000	1.7	-8.4
Latium	2,621	0.4	3,084	0.5	20.2
Liguria	1,356	0.9	1,803	1.2	35.2

Region	2019		2020		% Var 2019-2020
	g	g per 1,000 pop	g	g per 1,000 pop	
Lombardy	9,290	0.9	9,152	0.9	-1.2
Marche	276	0.2	223	0.1	-18.5
Molise	78	0.3	30	0.1	-60.9
Piedmont	3,340	0.8	3,153	0.7	-4.6
Sardinia	2,953	1.8	4,322	2.7	48.9
Sicily	2,339	0.5	3,072	0.6	34.7
Tuscany	2,017	0.5	2,822	0.8	41.3
Umbria	189	0.2	320	0.4	71.6
Veneto	3,883	0.8	3,592	0.7	-7.0
Italy	46,694	0.8	51,912	0.9	12.5

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 principle 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, 31/12/2020)

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 2020, the total demand for C1 esterase inhibitor was 13,263,000 IUs (222 IUs per 1,000 population), recording an increase of 2.7% (Table 62) compared to 2019.

Table 62. Total demand (public and private) and total stdardised demand for C1 esterase inhibitor, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	224,500	171.2	170,000	131.4	-23.2
Aosta Valley	129,500	1030.5	128,500	1,027.7	-0.3
AP Bolzano	50,000	94.1	22,000	41.3	-56.1
AP Trento	18,500	34.2	29,500	54.1	58.2
Apulia	858,000	213.0	734,500	185.8	-12.8
Basilicata	56,000	99.5	77,500	140.1	40.8
Calabria	871,500	447.6	888,000	468.8	4.7
Campania	1,856,500	320.0	2,311,000	404.6	26.4
E.-Romagna	554,500	124.3	431,500	96.7	-22.3
Friuli V. Giulia	18,000	14.8	36,500	30.3	104.3
Latium	2,085,000	354.6	2,145,000	372.7	5.1
Liguria	29,000	18.7	21,000	13.8	-26.4
Lombardy	1,800,000	178.9	1,993,000	198.8	11.1
Marche	236,000	154.7	333,500	220.5	42.5
Molise	10,500	34.4	1,000	3.3	-90.3
Piedmont	639,500	146.8	613,500	142.3	-3.1
Sardinia	576,000	351.3	582,000	361.1	2.8

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Sicily	1,219,000	243.8	1,232,500	252.8	3.7
Tuscany	592,500	158.9	463,000	125.4	-21.1
Umbria	276,000	312.9	235,000	270.1	-13.7
Veneto	964,000	196.5	814,500	166.9	-15.0
Italy	13,064,500	216.4	13,263,000	222.4	2.7

An exceptional variability in standardised regional demands was observed, with maximum volumes in the Aosta Valley, Calabria and Campania (1,028, 469 e 405 IUs per 1,000 population, respectively) and minimum volumes in Molise, Liguria and Friuli V.Giulia (range: 3-30 IUs per 1,000 population). In Aosta Valley the demand can be considered as stable, while in Abruzzo, Emilia-Romagna, Liguria, Molise, Piedmont, AP of Bolzano, Apulia, Tuscany, Umbria and Veneto the demand was decreasing. In the remaining Regions there is an increase in the demand for C1 inhibitor.

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 principle 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, 31/12/2020)

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 2020 the demand was for 60,000 IUs (6 IUs per 1,000 population) (Table 64).

Table 64. Total demand (public and private) and total standardised demand for coagulation Factor X expressed in International Units and International Units per 1,000 population, and variations in percentage between 2019 and 2020 (adapted by the CNS on data from Product Quality and Pharmacrime Office-AIFA)

Region	2019		2020		Var % 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Lombardy	36,000	3.6	60,000	6.0	67.2
Italy	36,000	0.6	60,000	1.0	68.7

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 principle 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, 31/12/2020)

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 DM 11 February 1997 (8) and DM 11 May 2001 (10).

Quantification of the demand

In 2020, the demand for FXI was 34,667 IUs (0.6 IU per 1,000 population) significantly higher than 2019 (Table 66). Demand was observed only in few Italian Regions.

Table 66. Total demand (public and private) and total standardised demand for coagulation Factor XI expressed in International Units and International Units per 1,000 population, and variations in percentage between 2019 and 2020 (adapted by the CNS on data from theProduct Quality and Pharmacrime Office-AIFA)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	3,450	0.9	2,000*	0.5	-40.9
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	2,606	0.6	2,000*	0.4	-23.3
Friuli V. Giulia	11,730	9.7	19,333*	16.0	66.0
Latium	2,608	0.4	2,667 *	0.5	4.4
Liguria	-	-	-	-	NA
Lombardy	-	-	-	-	NA
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	-	-	3,333*	0.8	NA
Sardinia	-	-	-	-	NA

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Sicily	2,606	0.5	2,667*	0.5	4.9
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	-	-	2,667*	0.5	NA
Italy	23,000	0.4	34,667*	0.6	52.5

*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 principle 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, 31/12/2020)

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, 31/12/2020)

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

Quantification of the demand

In 2020, the total demand for FXIII was 725,000 IUs (12 IUs per 1,000 population) and less than half, equal to 342,500 IUs (5.7 IUs per 1,000 population), was for pdFXIII. The latter recorded an increase of 5% compared to 2019 (Table 69).

In 2020, 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 Veneto (28 IUs, 18 IUs and 13 IUs per 1,000 population respectively).

While in Basilicata, Calabria, Liguria rFXIII was used exclusively (Table 70).

Table 69. Total demand (public and private) and total standardised demand for plasma-derived coagulation Factor XIII expressed in International Units and International Units per 1,000 population, and variations in percentage between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow and theProduct Quality and Pharmacrime Office-AIFA)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	1,000,0	0.8	100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	9,750	18.0	9,750	17.9	-0.8
Apulia	-	-	-	-	NA
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	107,250	24.0	125,000	28.0	16.4
Friuli V. Giulia	-	-	-	-	NA
Latium	44,750	7.6	52,500	9.1	19.8
Liguria	-	-	-	-	NA
Lombardy	42,500	4.2	40,000	4.0	-5.6
Marche	12,750	8.4	6,500	4.3	-48.6
Molise	-	-	-	-	NA
Piedmont	11,250	2.6	14,250	3.3	28.0
Sardinia	4,000	2.4	-	-	-100.0
Sicily	-	-	4,500	0.9	100.0
Tuscany	11,000	2.9	23,500	6.4	115.8
Umbria	-	-	-	-	NA
Veneto	87,500	17.8	65,500	13.4	-24.7
Italy	330,750	5.5	342,500	5.7	4.8

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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow and the Product Quality and Pharmacrime office, AIFA)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	75,000	57.2	45,000	34.8	-39.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	30,000	53.3	30,000	54.2	1.7
Calabria	135,000	69.3	150,000	79.2	14.2
Campania	-	-	-	-	NA
E.-Romagna	10,000	2.2	-	-	-100.0
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	55,000	35.5	65,000	42.6	20.2
Lombardy	52,500	5.2	52,500	5.2	0.3
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	30,000	6.9	22,500	5.2	-24.2
Sardinia	-	-	-	-	NA
Sicily	2,500	0.5	-	-	-100.0
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	25,000	5.1	17,500	3.6	-29.6
Italy	415,000	6.9	382,500	6.4	-6.7

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 principle 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, 31/12/2020)

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 2020, the national demand for protein C stood at a volume of 646,000 IUs (10.8 IUs per 1,000 population) with a decrease of 7% compared to 2019 (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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	7,000	5.3	4,000,0	3.1	-42.1
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	3,000	0.7	11,000	2.8	273.7
Basilicata	-	-	-	-	NA
Calabria	132,500	68.0	197,000	104.0	52.8
Campania	127,500	22.0	151,000	26.4	20.3
E.-Romagna	8,000	1.8	4,000,0	0.9	-50.1
Friuli V. Giulia	-	-	-	-	NA
Latium	139,500	23.7	48,500	8.4	-64.5
Liguria	25,000	16.1	59,000	38.7	140.0
Lombardy	78,000	7.8	71,500	7.1	-8.0
Marche	15,000	9.8	12,000	7.9	-19.3
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	34,000	20.7	29,000	18.0	-13.2
Sicily	62,000	12.4	31,500	6.5	-47.9
Tuscany	40,000	10.7	3,000,0	0.8	-92.4
Umbria	-	-	8,000	9.2	100.0
Veneto	31,000	6.3	16,500	3.4	-46.5
Italy	702,500	11.6	646,000	10.8	-6.9

The highest regional demand was recorded in Calabria, Liguria and Campania, with 104, 39 e 26 IUs per 1,000 population respectively. The lowest regional demand was in Tuscany, Emilia-Romagna, Apulia Abruzzo and Veneto with volumes between 0.8 and 3.4 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 principle 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, 31/12/2020)

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 2020, recorded a decrease of -14%, and a total volume of 6,541,750 mL.

The national demand for solvent/detergent-treated plasma in 2020 decreased by -11% compared to 2019, with remarkable decreases at regional level in Veneto (-46%) and in Friuli V.Giulia (-37%). High increases in demand were instead recorded in Emilia-Romagna (+ 47%).

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 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano		-	-	-	NA
AP Trento	10,000	18.5	10,000	18.3	-0.8
Apulia	3,050,400	757.1	2,814,000	711.8	-6.0
Basilicata	496,000	881.2	462,000	835.1	-5.2
Calabria	957,000	491.5	895,000	472.5	-3.9
Campania	4,730,000	815.3	4,546,600	796.0	-2.4
E.-Romagna	401,200	90.0	592,000	132.6	47.4
Friuli V. Giulia	32,000	26.3	20,000	16.6	-37.0
Latium	4,925,200	837.7	4,097,400	711.9	-15.0
Liguria	776,000	500.4	545,200	357.5	-28.6
Lombardy	406,000	40.4	448,000	44.7	10.7
Marche	1,804,000	1182.7	1,560,000	1031.3	-12.8
Molise	468,200	1532.0	341,200	1135.4	-25.9
Piedmont	3,508,000	805.3	3,562,000	826.2	2.6
Sardinia	100,000	61.0	106,000	65.8	7.8
Sicily	4,391,800	878.4	3,756,200	770.5	-12.3
Tuscany	1,263,600	338.8	1,338,000	362.4	7.0
Umbria	30,000	34.0	26,000	29.9	-12.2
Veneto	2,726,000	555.7	1,468,000	300.9	-45.9
Italy	30,075,400	498.3	26,587,600	445.8	-10.5

Table 75. Total demand (public and private) and total standardised demand for Umanserum™ expressed in millilitres and millilitres per 1,000 population, and variations in percentage between 2019 and 2020 (adapted by the CNS on data from the Traceability information flow)

Region	2019		2020		% Var 2019-2020
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	3,992,500	990.9	3,892,500	984.6	-0.6
Basilicata	110,000	195.4	141,250	255.3	30.6
Calabria	215,000	110.4	268,750	141.9	28.5
Campania	-	-	-	-	NA
E.-Romagna	-	-	-	-	NA
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	-	-	-	-	NA
Lombardy	25,000	2.5	175,000	17.5	602.3
Marche	-	-	-	-	NA
Molise	2,500	8.2	-	-	-100.0
Piedmont	-	-	-	-	NA
Sardinia	-	-	-	-	NA
Sicily	3,010,000	602.0	1,952,750	400.5	-33.5
Tuscany	300,000	80.4	-	-	-100.0
Umbria	25,000	28.3	111,500	128.1	352.1
Veneto	-	-	-	-	NA
Italy	7,680,000	127.2	6,541,750	109.7	-13.8

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 aimes at guaranteeing the same standards of quality and safety in the transfusion therapy to all citizens. It is a non-divisible national and supraregional interest, for which the Regions and the Health Authorities have to contribute to its final accomplishment.

To this end, the law establishes some principles of regional health planning (Art. 11) and entrusts all coordination activities to the CNS (Art. 12). It also acknowledges the annual programme of national self-sufficiency (Art. 14) as the instrument to determine every aspect of national self-sufficiency, such as historical consumptions, real needs, production levels required, resources, prospective financing criteria, compensation methods among the Regions and import/export levels whenever necessary.

Furthermore, Article 26 of the 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. Even if the plasma started to be sent to CSL for fractionation in May 2017, no products were returned to the NAIP Regions before 2018.

The agreements with the toll fractionation company Kedrion remained in force for all the other Regions. The contracts provide for the production of albumin, IV IGs, pdFVIII, pdFIX, 3F-PCCs, AT and solvent detergent virus-inactivated plasma. In the last months of 2020, the companies Takeda Italia SpA and Grifols Italia SpA also began collecting plasma for fractionation, with the start of product distribution scheduled for 2021.

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 844,582 kilograms in 2020, with a percentage increase over the entire period considered, by 82.5%.

The mean annual rate of change over the period considered was 3.1%, 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.

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

In 2020, the Regions participating in the LPS agreement collected about one third of the plasma sent for fractionation for a share equal to 238,741 kilograms, those adhering to the RIPP 227,562 kilograms, those of the NAIP 190,770 kilograms and those of the PlaNet 187,509 kilograms, equal respectively to 28%, 27%, 23% and 22% of the national total (Figure 44). As regards the amount of plasma sent for fractionation in 2020, for the resident population, the NAIP Regions sent 16.5 kilograms of plasma per 1,000 population (17.0 in 2019, with the same Regions and participating autonomous provinces), the LPS Regions 15.0 kilograms, as well as RIPP Regions that are the only ones to show an increase compared to the previous year and the PlaNet Regions 11.0 kilograms per 1,000 population (Figure 45).

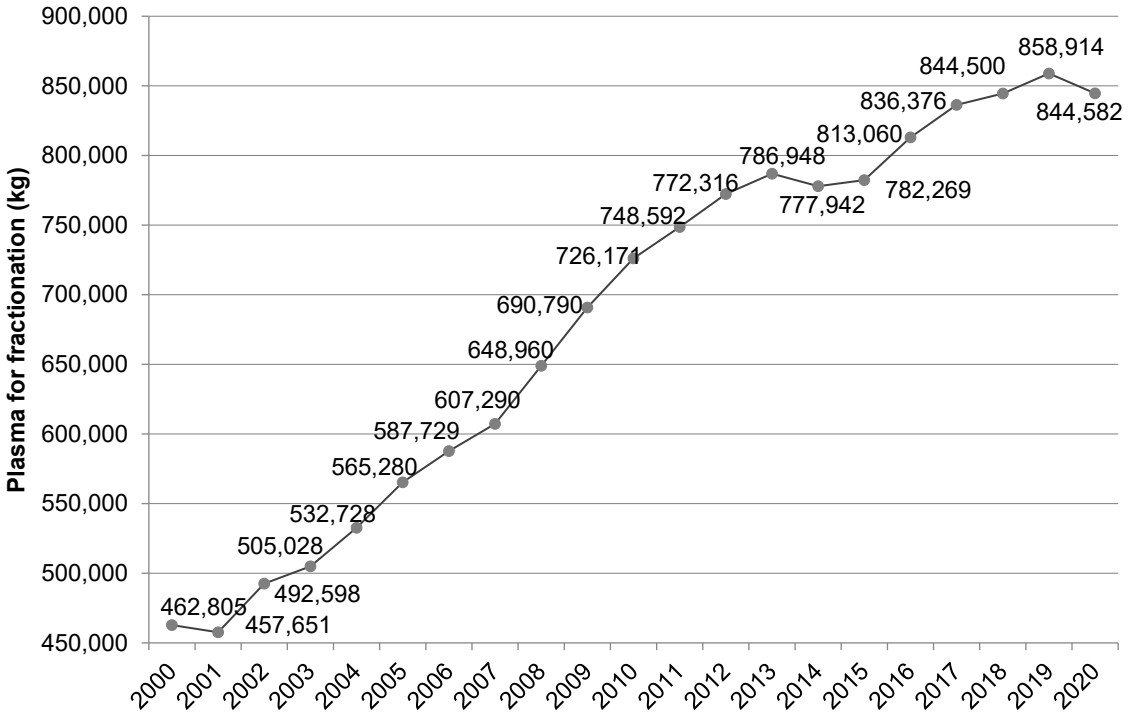

Figure 42. Plasma sent for fractionation 2000-2020
(adapted by the CNS on Kedrion and CSL Behring data, October 2021)

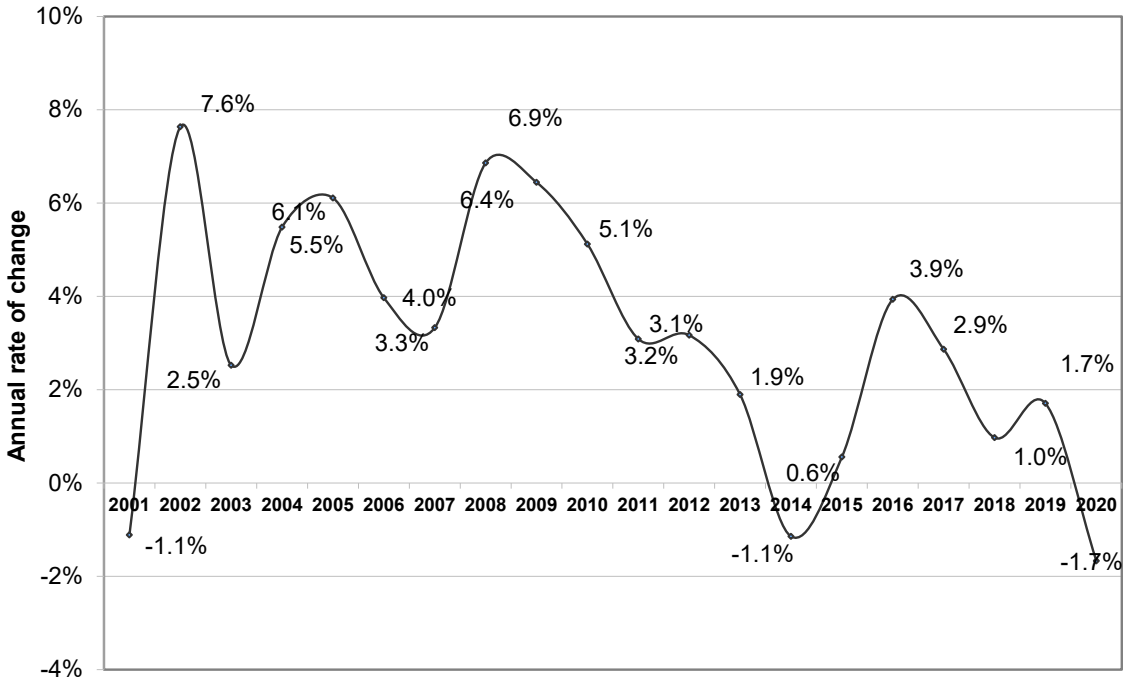

Figure 43. Annual rate of change in the amount of plasma for fractionation, from 2001 to 2020
(adapted by the CNS on Kedrion and CSL Behring data, October 2021)

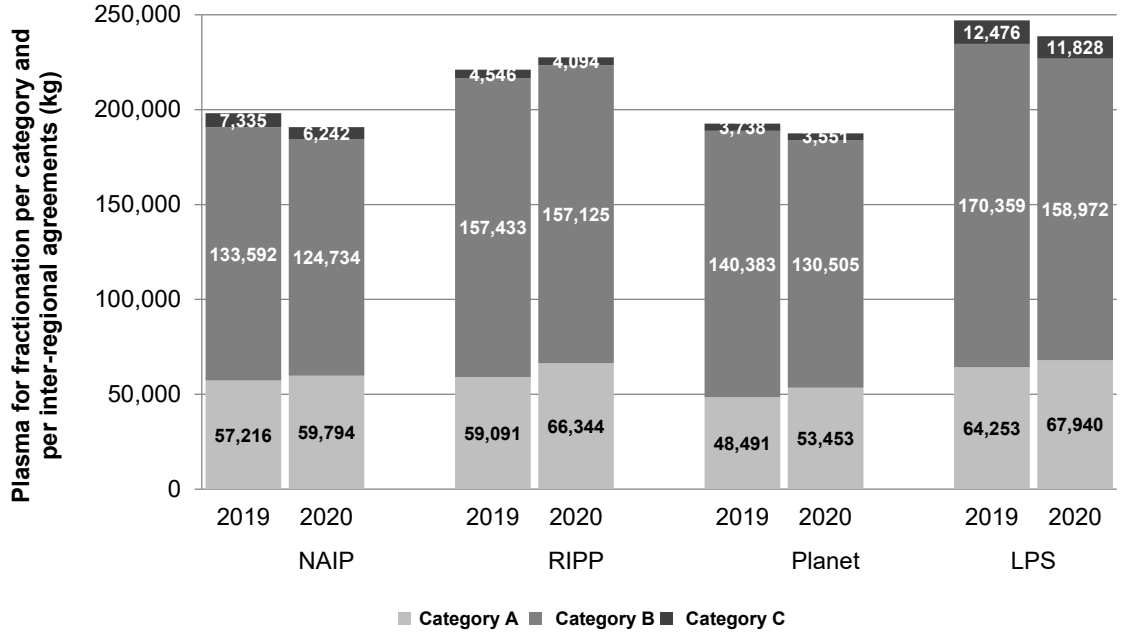

Figure 44. Total amount of plasma for fractionation by category under interregional agreements (kilograms), 2019-2020 (adapted by the CNS on data provided by Kedrion and CSL Behring, October 2021)

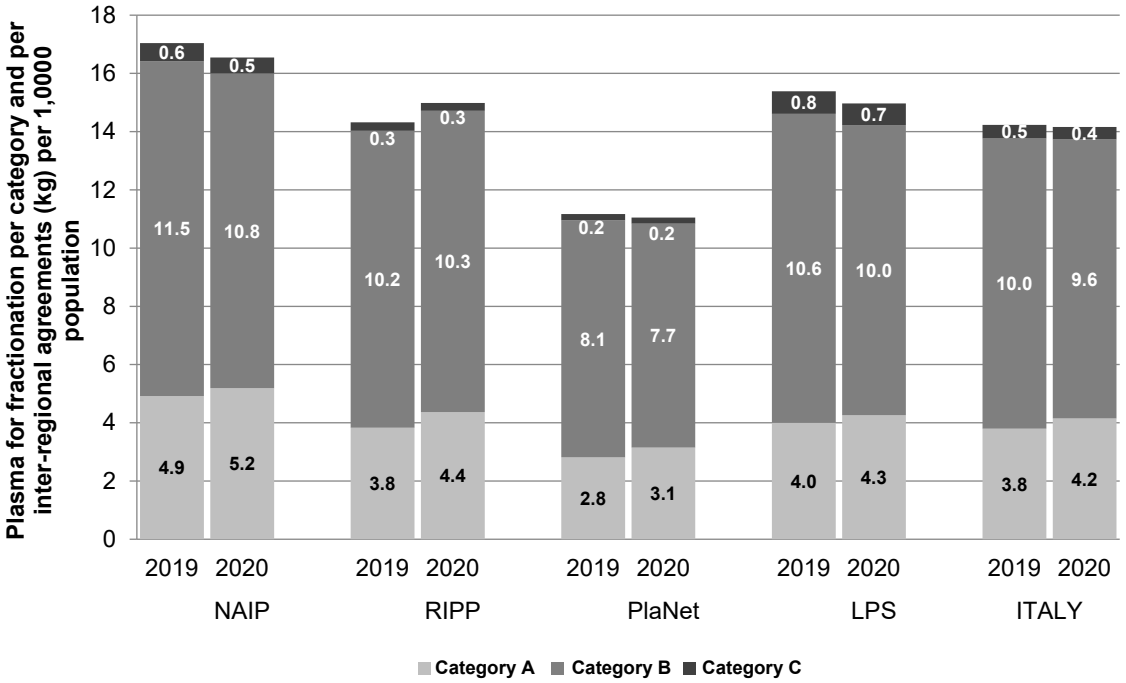

Figure 45. Total amount of plasma for fractionation by category under interregional agreements (kilograms per 1,000 population), 2019-2020 (adapted by the CNS on data provided by Kedrion and CSL Behring, October 2021)

In 2020, although the national volume stood at 14.2 kilograms per 1,000 population (as in 2019), with regional contributions in volumes differing greatly one from another. In point of fact, the best performance was achieded by Friuli V. Giulia with 23.8 kilograms per 1,000 population, followed by Marche with 23.3 and Emilia-Romagna with 21.9, while the lowest volumes were recorded in Calabria, Latium and Campania with 10.1, 7.5 and 5.9 kilograms per 1,000 population, respectively (Figure 46).

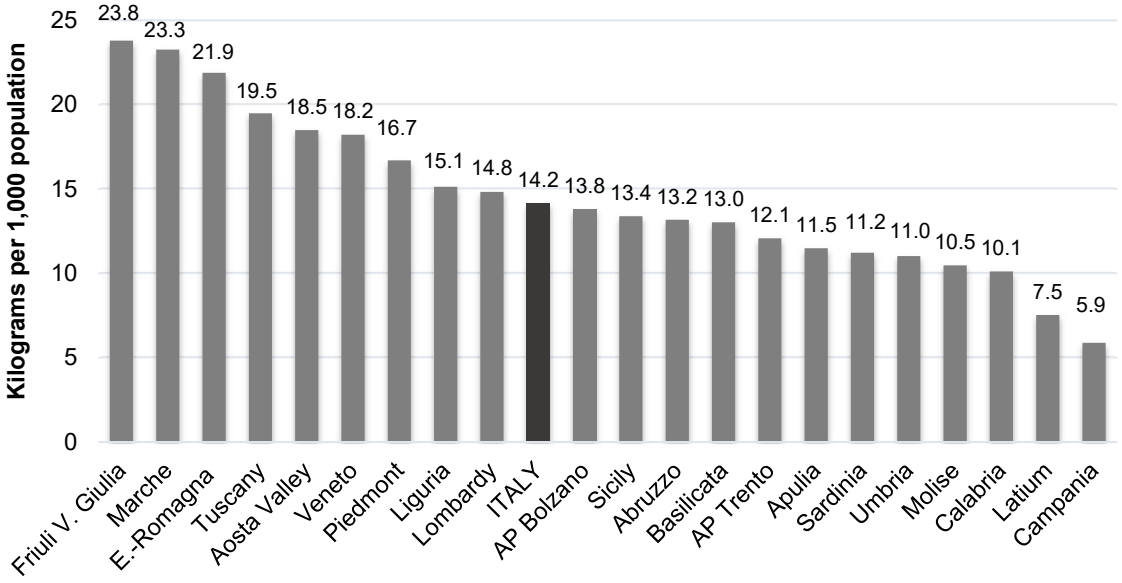

Figure 46.Total amount of plasma (kilograms per 1,000 population) for fractionation by Region, year 2020 (adapted by the CNS on data provided by Kedrion and CSL Behring, October 2021)

Supply of PDMPs from toll fractionation

In 2020, the total quantity of plasma sent for fractionation by the Italian Regions was 844,582 kilograms (Table 76); of these, 29% (247,531 kilograms) was apheresis plasma (category A), 68% (571,337 kilograms) recovered plasma (category B) and the remaining 3% (25,714 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 28.5% sent by PlaNet and LPS consortium to 31.3% sent by NAIP, while the percentage of plasma intended solely for the recovery of non-labile proteins (category C) varied from 1.8% sent by RIPP to 5.0% sent by the LPS consortium. Table 77 shows the amount of PDMPs potentially obtainable from the industrial manufacturing of the total amount of plasma sent for fractionation in 2020 (from July 2019 to June 2020). These figures show the quantities, expressend in grams and IUs, of medicinal products that the fractionators have potentially guaranteed the consortia (potential supply or production capacity) estimated from the industrial yields and contractual agreements. Further quantities of plasma, around 13,700 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 2020 in accordance with the specified production and distribution programmes (effective supply or toll fractionation).

Table 76. Total quantity, expressed in kilograms, quantity per 1,000 population and variation in percentage for the years 2019-2020 classified by Region and plasma category (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	A	%	B	%	C	%	Tot. Fract.	Total per 1,000 pop
Abruzzo	4,839	-5.9	12,159	-6.1	49	-63.3	17,047	13.2
Aosta Valley	1,080	32.4	1,233	-18.4	-	-	2,312	18.5
AP Bolzano	1,524	10.8	5,824	-1.6	-	-	7,348	13.8
AP Trento	469	-12.4	6,118	-9.7	-	-	6,587	12.1
Basilicata	1,552	6.1	4,900	-7.7	757	32.0	7,209	13.0
Friuli V. Giulia	14,907	11.7	13,548	-7.0	252	-66.2	28,707	23.8
Liguria	6,222	-0.7	16,853	-5.0	-	-	23,075	15.1
Umbria	1,904	11.3	7,687	-13.1	-	-	9,591	11.0
Veneto	27,298	2.8	56,412	-5.9	5,183	-11.9	88,893	18.2
NAIP	**59,794**	**4.5**	**124,734**	**-6.6**	**6,242**	**-14.9**	**190,770**	**16.5**
Apulia	6,189	0.3	37,599	-0.5	1,642	3.3	45,431	11.5
Calabria	1,210	9.6	17,942	5.4	5	-84.0	19,158	10.1
Emilia-Romagna	43,432	16.0	51,862	-1.7	2,408	-16.8	97,702	21.9
Sicily	15,512	7.9	49,721	-0.2	38	35.8	65,272	13.4
RIPP	**66,344**	**12.3**	**157,125**	**-0.2**	**4,094**	**-10.0**	**227,562**	**15.0**
Campania	702	-7.9	31,294	-4.1	1,612	-3.4	33,609	5.9
Latium	5,551	20.6	35,998	-8.2	1,778	2.9	43,327	7.5
Marche	15,539	12.4	19,655	-7.0	-	-	35,194	23.3
Molise	197	-77.9	2,950	-20.2	-	-	3,147	10.5
Tuscany	31,463	10.8	40,483	-7.1	-	-	71,947	19.5
Ministry of Defence	-	-	124	-15.2	160	-53.0	285	0.0
PlaNet	**53,453**	**10.2**	**130,505**	**-7.0**	**3,551**	**-5.0**	**187,509**	**11.0**
Lombardy	44,353	3.9	95,068	-6.7	9,250	-0.2	148,671	14.8
Piedmont	22,808	10.0	46,797	-6.7	2,380	-9.6	71,984	16.7
Sardinia	779	-5.7	17,107	-6.7	199	-65.6	18,085	11.2
LPS	**67,940**	**5.7**	**158,972**	**-6.7**	**11,828**	**-5.2**	**238,741**	**15.0**
Italy	**247,531**	**8.1**	**571,337**	**-5.1**	**25,714**	**-8.5**	**844,582**	**14.2**

Table 77. Potential supply of toll fractionated PDMPs based on the amount of plasma sent for fractionation from July 2019 to June 2020 and the yields provided by the fractionation industry – year 2020 (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	2nd semester 2019	1st semester 2020	TOTAL	Albumin	SCIG*	IVIG**	Factor VIII	Factor VIII / vW Factor	FIX / 3F-PCC	Antithrombin	Fibrinogen
	kg	kg	kg	g	g	g	UI	UI	UI	UI	g
Abruzzo	9,417	7,642	17,059	426,473	83,589	83,589	1,552,362	511,768	-	-	660
Aosta Valley	1,045	1,280	2,325	58,126	11,393	11,393	211,578	69,751	-	-	90
AP Bolzano	3,668	3,407	7,075	176,881	34,669	34,669	643,845	212,257	-	-	274
AP Trento	3,668	3,104	6,772	169,297	33,182	33,182	616,242	203,157	-	-	262
Basilicata	3,829	3,448	7,277	181,915	35,655	35,655	662,171	218,298	-	-	281
Friuli V. Giulia	14,824	14,514	29,338	733,460	143,758	143,758	2,669,793	880,152	-	-	1,135
Liguria	12,038	11,399	23,437	585,928	114,842	114,842	2,132,780	703,114	-	-	907
Umbria	5,556	4,399	9,955	248,880	48,781	48,781	905,925	298,656	-	-	385
Veneto	46,536	44,475	91,011	2,275,270	445,953	445,953	8,281,983	2,730,324	-	-	3,521
NAIP	**100,581**	**93,669**	**194,249**	**4,856,231**	**951,821**	**951,821**	**17,676,679**	**5,827,477**	**-**	**-**	**7,514**
Apulia	23,256	23,415	46,670	1,213,431	158,679	193,682	6,773,741	-	6,813,880	6,393,846	-
Calabria	8,686	9,169	17,855	464,235	60,708	74,099	2,684,498	-	2,606,856	2,446,160	-
Emilia-Romagna	46,561	46,414	92,975	2,417,359	316,116	385,848	13,579,356	-	13,574,398	12,737,620	-
Sicily	31,532	32,454	63,986	1,663,647	217,554	265,544	9,623,029	-	9,342,016	8,766,139	-
RIPP	**110,036**	**111,452**	**221,487**	**5,758,671**	**753,057**	**919,172**	**32,660,625**	**-**	**32,337,150**	**30,343,764**	**-**
Campania	18,409	17,112	35,521	923,548	120,772	147,412	5,345,921	-	5,186,077	4,866,387	-
Latium	23,083	21,114	44,197	1,149,127	150,270	183,418	6,651,675	-	6,452,788	6,055,013	-
Marche	16,666	17,177	33,843	879,919	115,066	140,449	5,093,378	-	4,941,084	4,636,497	-
Molise	2,241	1,526	3,767	97,931	12,806	15,631	566,872	-	549,923	516,023	-
Tuscany	36,570	36,090	72,660	1,889,164	247,045	301,540	10,935,353	-	10,608,383	9,954,441	-
Min. of Defence	253	133	386	10,034	1,312	1,602	58,083	-	56,346	52,873	-
PlaNet	**97,222**	**93,152**	**190,374**	**4,949,723**	**647,272**	**790,052**	**28,651,283**	**-**	**27,794,600**	**26,081,234**	**-**
Lombardy	76,002	73,661	149,663	3,891,244	508,855	621,102	21,113,954	-	21,850,832	20,503,863	-
Piedmont	36,983	36,260	73,243	1,904,312	249,025	303,958	10,640,295	-	10,693,445	10,034,260	-
Sardinia	10,572	9,467	20,039	521,016	68,133	83,162	2,969,401	-	2,925,703	2,745,351	-
LPS	**123,557**	**119,388**	**242,945**	**6,316,572**	**826,013**	**1,008,222**	**34,723,650**	**-**	**35,469,980**	**33,283,474**	**-**
Italy	**431,395**	**417,660**	**849,056**	**21,881,196**	**3,178,163**	**3,669,268**	**113,712,237**	**5,827,477**	**95,601,729**	**89,708,472**	**7,514**

* 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 sentfor fractionation from July 2019 to June 2020 and the yields provided by the fractionation industry – year 2020 (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	-	-	-	-
Campania	959	1,216	2,176	2,003,880
E.-Romagna	-	-	-	-
Friuli V. Giulia	-	-	-	-
Latium	1,450	1,276	2,726	2,510,656
Liguria	-	-	-	-
Lombardy	-	-	-	-
Marche	1,175	435	1,610	1,482,624
Molise	15	438	453	417,055
Piedmont	2,143	2,379	4,522	4,165,067
Sardinia	-	-	-	-
Sicily	1,140	1,088	2,228	2,051,538
Tuscany	-	-	-	-
Umbria	-	-	-	-
Veneto	-	-	-	-
Ministry of Defence	-	-	-	-
Italy	**6,882**	**6,832**	**13,714**	**12,630,819**

Table 79. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs classified by Region for the year 2020 (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	Albumin	IVIg	SC/Ig	Factor VIII	Factor VIII / vW Factor	Factor IX	3-factor prothrombin complex	Antithrombin	Fibrinogen	Solvent/detergent-treated plasma
	g	g	g	UI	UI	UI	UI	UI	g	mL
Abruzzo	480,000	89,100	4,640	120,000	60,000	64,000	370,000	1,278,000	1,170	-
Aosta Valley	63,000	26,600	1,320	-	12,000	-	98,500	259,000	70	-
AP Bolzano	180,000	41,418	1,840	288,000	720,000	38,000	368,000	287,000	800	-
AP Trento	166,800	44,755	2,580	3,000	10,000	-	346,500	147,000	280	-
Basilicata	277,200	19,800	1,360	36,000	50,000	22,000	161,000	948,000	240	-
Friuli V. Giulia	375,600	127,450	3,040	256,000	380,000	-	704,000	2,876,000	980	-
Liguria	619,800	172,683	4,840	704,000	480,000	192,000	800,000	1,846,000	500	47,200
Umbria	543,000	62,675	18,140	396,000	300,000	20,000	475,000	546,000	810	-
Veneto	2,323,250	440,573	53,920	8,269,000	1,690,000	688,000	3,336,000	5,922,000	1,580	1,358,000
NAIP	**5,028,650**	**1,025,053**	**91,680**	**10,072,000**	**3,702,000**	**1,024,000**	**6,659,000**	**14,109,000**	**6,430**	**1,405,200**
Apulia	1,316,150	182,870	4,568	4,970,000	-	176,000	1,339,000	5,754,000	-	36,000
Calabria	671,010	80,305	-	643,000	-	52,000	561,000	5,638,000	-	-
E.-Romagna	2,277,850	398,615	1,248	3,192,000	-	457,000	3,044,500	2,769,000	-	-
Sicily	2,456,500	244,110	-	763,000	-	90,000	3,146,000	16,138,000	-	1,734,200
RIPP	**6,721,510**	**905,900**	**5,816**	**9,568,000**	**-**	**775,000**	**8,090,500**	**30,299,000**	**-**	**1,770,200**
Campania	1,105,800	159,330	12,628	150,000	-	-	1,641,500	8,511,000	-	4,498,600
Latium	1,141,710	182,060	3,168	4,637,000	-	337,000	1,498,500	8,450,000	-	2,679,800
Marche	731,600	170,525	120	1,805,000	-	636,000	802,000	3,253,000	-	1,560,000
Molise	79,500	12,940	660	180,000	-	-	102,000	356,000	-	341,200
Tuscany	1,230,100	287,400	6,704	4,361,000	-	232,000	1,973,000	7,309,000	-	-
Ministry of Defence	-	-	-	-	-	-	-	-	-	-
PlaNet	**4,288,710**	**812,255**	**23,280**	**11,133,000**	**-**	**1,205,000**	**6,017,000**	**27,879,000**	**-**	**9,079,600**
Lombardy	4,368,340	494,195	4,940	9,067,000	-	818,000	6,084,000	9,034,000	-	440,000
Piedmont	1,541,000	337,030	480	8,749,000	-	263,000	3,076,500	7,922,000	-	3,562,000
Sardinia	963,450	66,388	920	285,000	-	-	1,860,000	1,877,000	-	106,000
LPS	**6,872,790**	**897,613**	**6,340**	**18,101,000**	**-**	**1,081,000**	**11,020,500**	**18,833,000**	**-**	**4,108,000**
Italy	**22,911,660**	**3,640,820**	**127,116**	**48,874,000**	**3,702,000**	**4,085,000**	**31,787,000**	**91,120,000**	**6,430**	**16,363,000**

ANALYSIS OF SELF-SUFFICIENCY

Albumin

In 2020, the Italian NHS demand for albumin accounted for 83% of the total. The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, was 73% (-3% compared to 2019) while the effective self-sufficiency, considered as the ratio between the actual supply of toll fractionation and the NHS demand, was 76% as in 2019 (Table 80).

The Regions that in 2020 achieved effective self-sufficiency – more than 90% – were Friuli V. Giulia, AP of Bolzano, AP of Trento, Umbria, Aosta Valley, Veneto, Emilia-Romagna, Marche and Piedmont.

Table 80. Estimates of regional and national self-sufficiency in albumin, 2020

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	864,860	792,180	426,473	480,000	54	61
Aosta Valley	63,070	63,000	58,126	63,000	92	100
AP Bolzano	193,950	193,500	176,881	180,000	91	93
AP Trento	180,108	171,980	169,297	166,800	98	97
Basilicata	413,815	408,540	181,915	277,200	45	68
Friuli V. Giulia	383,435	376,750	733,460	375,600	195	100
Liguria	868,725	843,745	585,928	619,800	69	73
Umbria	554,660	552,630	248,880	543,000	45	98
Veneto	2,570,970	2,383,138	2,275,270	2,323,250	95	97
NAIP	**6,093,593**	**5,785,463**	**4,856,231**	**5,028,650**	**84**	**87**
Apulia	2,157,803	1,746,578	1,213,431	1,316,150	69	75
Calabria	1,187,863	1,068,823	464,235	671,010	43	63
E.-Romagna	2,629,565	2,402,773	2,417,359	2,277,850	101	95
Sicily	3,535,708	2,887,955	1,663,647	2,456,500	58	85
RIPP	**9,510,938**	**8,106,128**	**5,758,671**	**6,721,510**	**71**	**83**
Campania	4,275,738	3,701,933	923,548	1,105,800	25	30
Latium	3,433,058	1,988,078	1,149,127	1,141,710	58	57
Marche	853,210	742,950	879,919	731,600	118	98
Molise	139,678	98,545	97,931	79,500	99	81
Tuscany	1,515,105	1,447,948	1,889,164	1,230,100	130	85
Min. of Def.	-	-	10,034	-	-	-
PlaNet	**10,216,788**	**7,979,453**	**4,949,723**	**4,288,710**	**62**	**54**
Lombardy	7,196,825	5,209,975	3,891,244	4,368,340	75	84
Piedmont	1,804,635	1,674,648	1,904,312	1,541,000	114	92
Sardinia	1,390,663	1,331,765	521,016	963,450	39	72
LPS	**10,392,123**	**8,216,388**	**6,316,572**	**6,872,790**	**77**	**84**
Italy	**36,213,440**	**30,087,430**	**21,881,196**	**22,911,660**	**73**	**76**

The Regions that mostly benefitted from interregional compensation in 2020 were: Umbria (98% effective self-sufficiency compared to the potential 45%) and Basilicata (68% compared to 45%) for NAIP, Sardinia (72% compared to 39%) for LPS, Calabria (effective self-sufficiency 63% compared to the potential 43%) and Sicily (effective self-sufficiency 85% compared to the potential 58%) for the RIPP consortium.

The Regions that remained farthest from the goal of effective self-sufficiency were Campania, Latium, Abruzzo, Calabria and Basilicata, with percentages ranging between 30 and 68% of the NHS demand met by the toll fractionation supply.

Normal human immunoglobulins

In 2020, the NHS demand for normal IGs accounted for 92% of the total demand (Table 81).

Table 81. Estimates of regional and national self-sufficiencyin human immunoglobulins, 2020

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	142,883	142,733	83,589	93,740	59	66
Aosta Valley	28,545	28,545	11,393	27,920	40	98
AP Bolzano	50,274	50,274	34,669	43,258	69	86
AP Trento	54,273	54,273	33,182	47,335	61	87
Basilicata	42,666	42,666	35,655	21,160	84	50
Friuli V. Giulia	144,953	144,953	143,758	130,490	99	90
Liguria	264,090	261,515	114,842	177,523	44	68
Umbria	117,566	108,866	48,781	80,815	45	74
Veneto	633,411	603,976	445,953	494,493	74	82
NAIP	**1,478,661**	**1,437,801**	**951,821**	**1,116,733**	**66**	**78**
Apulia	475,033	448,908	183,636	187,438	41	42
Calabria	122,730	122,730	69,637	80,305	57	65
E.-Romagna	557,477	556,817	369,309	399,863	66	72
Sicily	376,267	367,397	252,272	244,110	69	66
RIPP	**1.531.507**	**1.495.852**	**874.853**	**911.716**	**58**	**61**
Campania	476,261	453,173	139,741	171,958	31	38
Latium	620,464	508,271	170,848	185,228	34	36
Marche	213,808	213,158	136,491	170,645	64	80
Molise	61,537	16,942	15,451	13,600	91	80
Tuscany	756,288	692,933	286,639	294,104	41	42
Min. of Def.	-	-	-	-	NA	NA
PlaNet	**2,128,358**	**1,884,477**	**749,170**	**835,535**	**40**	**44**
Lombardy	965,518	772,586	601,822	499,135	78	65
Piedmont	560,389	545,854	293,758	337,510	54	62
Sardinia	99,037	98,337	81,436	67,308	83	68
LPS	**1,624,944**	**1,416,778**	**977,016**	**903,953**	**69**	**64**
Italy	**6,763,471**	**6,234,908**	**3,552,860**	**3,767,936**	**57**	**60**

The national potential self-sufficiency, espressed by the ratio of the potential supply to the NHS demand, in 2020 was 57%, where effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to NHS demand, was 60%.

The only Region to achieve effective self-sufficiency in IGs in 2020 - more than 90% - was Friuli V. Giulia and Aosta Valley while the Regions that achieved the lowest effective self-sufficiency were Campania (38%), Latium (36%) and Tuscany and Apulia (42%).

Normal human immunoglobulins for subcutaneous use

In 2020, the NHS demand for immunoglobulins for subcutaneous/intramuscular use represented approximately 97.5% of the total demand (Table 82).

Table 82. Estimates of regional and national self-sufficiency in human immunoglobulin for subcutaneous use, 2020

Region	Total demand	NHS demand	Potential supply*	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	36,783	36,783	83,589	4,640	227	13
Aosta Valley	1,806	1,806	11,393	1,320	631	73
AP Bolzano	3,700	3,700	34,669	1,840	937	50
AP Trento	8,488	8,488	33,182	2,580	391	30
Basilicata	15,807	15,807	35,655	1,360	226	9
Friuli V. Giulia	8,138	8,138	143,758	3,040	1,767	37
Liguria	58,545	58,545	114,842	4,840	196	8
Umbria	43,816	43,656	48,781	18,140	112	42
Veneto	148,931	148,931	445,953	53,920	299	36
NAIP	**326,014**	**325,854**	**951,821**	**91,680**	**292**	**28**
Apulia	136,342	136,342	158,679	4,568	116	3
Calabria	40,895	40,895	60,708	-	148	0
E.-Romagna	132,224	132,224	316,116	1,248	239	1
Sicily	104,059	104,059	217,554	-	209	0
RIPP	**413,520**	**413,520**	**753,057**	**5,816**	**182**	**1**
Campania	137,149	137,419	120,772	12,628	88	9
Latium	235,300	233,294	150,270	3,168	64	1
Marche	33,333	33,333	115,066	120	345	0
Molise	3,927	3,927	12,806	660	326	17
Tuscany	206,787	206,517	247,045	6,704	120	3
Min. of Def.	-	-	1,312		NA	NA
PlaNet	**616,496**	**614,490**	**647,272**	**23,280**	**105**	**4**
Lombardy	165,844	126,840	508,855	4,940	401	4
Piedmont	104,048	103,808	249,025	480	240	0
Sardinia	11,375	11,375	68,133	920	599	8
LPS	**281,267**	**242,022**	**826,013**	**6,340**	**341**	**3**
Italy	**1,637,296**	**1,595,886**	**3,178,163**	**127,116**	**199**	**8**

*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 8%.

No Region in 2020 achieved effective self-sufficiency > 90%; the highest values of self-sufficiency were recorded in the Aosta Valley and in the AP of Bolzano with self-sufficiency rates above 50%.

Normal human immunoglobulins for intravenous use

In 2020, the NHS demand for IV IGs accounted for 90.5% of the total demand (Table 83).

Table 83. Estimates of regional and national self-sufficiency in human immunoglobulin for for intravenous use, 2020

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	106,100	105,950	83,589	89,100	79	84
Aosta Valley	26,739	26,739	11,393	26,600	43	99
AP Bolzano	46,574	46,574	34,669	41,418	74	89
AP Trento	45,785	45,785	33,182	44,755	72	98
Basilicata	26,859	26,859	35,655	19,800	133	74
Friuli V. Giulia	136,815	136,815	143,758	127,450	105	93
Liguria	205,545	202,970	114,842	172,683	57	85
Umbria	73,750	65,210	48,781	62,675	75	96
Veneto	484,480	455,045	445,953	440,573	98	97
NAIP	**1,152,647**	**1,111,947**	**951,821**	**1,025,053**	**86**	**92**
Apulia	338,691	312,566	193,682	182,870	62	59
Calabria	81,835	81,835	74,099	80,305	91	98
E.-Romagna	425,254	424,594	385,848	398,615	91	94
Sicily	272,208	263,338	265,544	244,110	101	93
RIPP	**1,117,988**	**1,082,333**	**919,172**	**905,900**	**85**	**84**
Campania	339,112	315,755	147,412	159,330	47	50
Latium	385,164	274,977	183,418	182,060	67	66
Marche	180,475	179,825	140,449	170,525	78	95
Molise	57,610	13,015	15,631	12,940	120	99
Tuscany	549,501	486,416	301,540	287,400	62	59
Min. of Def.			1,602		-	NA
PlaNet	**1,511,862**	**1,269,987**	**790,052**	**812,255**	**62**	**64**
Lombardy	799,674	645,747	621,102	494,195	96	77
Piedmont	456,341	442,046	303,958	337,030	69	76
Sardinia	87,663	86,963	83,162	66,388	96	76
LPS	**1,343,678**	**1,174,755**	**1,008,222**	**897,613**	**86**	**76**
Italy	**5,126,175**	**4,639,022**	**3,669,268**	**3,640,820**	**79**	**78**

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

The national potential self-sufficiency, espressed by the ratio of the potential supply to NHS demand, in 2020 was 79% (78% in 2019). Effective self-sufficiency, assumed as the ratio of the actual supply of toll fractionation to NHS demand, was 78%, against 79% in 2019.

The Regions that in 2020 achieved effective self-sufficiency (more than 90%) were Friuli V. Giulia, AP of Trento, Umbria, Aosta Valley, Veneto, Calabria, Emilia-Romagna, Sicily, Marche and Molise.

Campania is the only Region with an effective self-sufficiency lower than 50%.

Antithrombin

NHS demand for AT compared to national total demand dropped from 94% in 2011 to 88% in 2020. Effective self-sufficiency recorded a value of 83% in 2020, slightly higher than the potential self-sufficiency (82%) (Table 84).

Table 84. Estimates of regional and national self-sufficiency in antithrombin, 2020

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,943,500	1,893,000	-	1,278,000	-	68
Aosta Valley	439,000	439,000	-	259,000	-	59
AP Bolzano	347,000	347,000	-	287,000	-	83
AP Trento	147,000	147,000	-	147,000	-	100
Basilicata	1,218,000	1,218,000	-	948,000	-	78
FVG	2,876,000	2,876,000	-	2,876,000	-	100
Liguria	3,973,500	3,949,500	-	1,846,000	-	47
Umbria	546,000	546,000	-	546,000	-	100
Veneto	7,047,500	6,983,000	-	5,922,000	-	85
NAIP	**18,537,500**	**18,398,500**	**-**	**14,109,000**	**-**	**77**
Apulia	6,444,000	5,888,000	6,393,846	5,754,000	109	98
Calabria	7,376,500	6,013,000	2,446,160	5,638,000	41	94
E.-Romagna	3,305,000	2,854,000	12,737,620	2,769,000	446	97
Sicily	18,372,500	16,678,000	8,766,139	16,138,000	53	97
RIPP	**35,498,000**	**31,433,000**	**30,343,764**	**30,299,000**	**97**	**96**
Campania	14,392,000	13,299,000	4,866,387	8,511,000	37	64
Latium	19,215,500	14,713,000	6,055,013	8,450,000	41	57
Marche	3,253,000	3,253,000	4,636,497	3,253,000	143	100
Molise	360,000	356,000	516,023	356,000	145	100
Tuscany	7,633,000	7,326,500	9,954,441	7,309,000	136	100
Min. of Def.	-	-	52,873		NA	NA
PlaNet	**44,853,500**	**38,947,500**	**26,081,234**	**27,879,000**	**67**	**72**
Lombardy	15,020,000	10,706,500	20,503,863	9,034,000	192	84
Piedmont	8,500,500	7,922,000	10,034,260	7,922,000	127	100
Sardinia	2,069,000	2,063,000	2,745,351	1,877,000	133	91
LPS	**25,589,500**	**20,691,500**	**33,283,474**	**18,833,000**	**161**	**91**
Italy	**124,478,500**	**109,470,500**	**89,708,472**	**91,120,000**	**82**	**83**

Since AT is not included among the PDMPs provided under the CSL Behring toll fractionation contract, its potential supply for NAIP Regions was equal to zero.

Neverthless, their NHS demand could be met by the existing stock of products provided within the scope of the previous agreement with Kedrion and by interregional compensation.

All the Regions achieved effective self-sufficiency of more than 90% of the total NHS demand in 2020, except for Abruzzo, Basilicata, Liguria, AP of Bolzano, Aosta Valley, Veneto, Campania, Latium and Lombardy.

The Regions that mostly benefitted from interregional compensation in 2020 were Calabria (94% effective vs. 41% potential self-sufficiency), Sicily (97% effective vs. 53% potential), and Campania (64% effective vs. 37% potential self-sufficiency). The farthest Regions from the objective of effective self-sufficiency were Liguria (47%) and Latium (57%).

Coagulation Factor VIII

In 2020, 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.

All other Regions, within the scope of the contract with Kedrion, could have benefitted from the supply and the huge stock of plasma-derived coagulation Factor VIII, Klott®.

In the analysis of demand and supply for pdFVIII, it should be taken into account that the choice of the pharmaceutical specialty for the treatment of haemophilia A is based on considerations 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.

Plasma-derived coagulation Factor VIII

In 2020, all the Regions largely achieved effective self-sufficiency in pdFVIII (Table 85).

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.

Table 85. Estimates of regional and national self-sufficiency in plasma-derived Factor VIII, 2020

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	120,000	120,000	1,552,362	120,000	1,294	100
Aosta Valley	-	-	211,578	-	NA	NA
AP Bolzano	288,000	288,000	643,845	288,000	224	100
AP Trento	3,000	3,000	616,242	3,000	20,541	100
Basilicata	36,000	36,000	662,171	36,000	1,839	100
FVG	256,000	256,000	2,669,793	256,000	1,043	100
Liguria	704,000	704,000	2,132,780	704,000	303	100
Umbria	396,000	396,000	905,925	396,000	229	100
Veneto	8,269,000	8,269,000	8,281,983	8,269,000	100	100
NAIP	**10,072,000**	**10,072,000**	**17,676,679**	**10,072,000**	**176**	**100**
Apulia	5,314,000	5,314,000	6,773,741	4,970,000	127	94
Calabria	643,000	643,000	2,684,498	643,000	417	100
E.-Romagna	3,192,000	3,192,000	13,579,356	3,192,000	425	100
Sicily	763,000	763,000	9,623,029	763,000	1,261	100
RIPP	**9,912,000**	**9,912,000**	**32,660,625**	**9,568,000**	**330**	**97**
Campania	150,000	150,000	5,345,921	150,000	3,564	100
Latium	5,234,000	4,637,000	6,651,675	4,637,000	143	100
Marche	1,805,000	1,805,000	5,093,378	1,805,000	282	100
Molise	180,000	180,000	566,872	180,000	315	100
Tuscany	4,361,000	4,361,000	10,935,353	4,361,000	251	100
Min. of Def.	-	-	58,083	-	NA	NA
PlaNet	**11,730,000**	**11,133,000**	**28,651,283**	**11,133,000**	**257**	**100**
Lombardy	9,647,000	9,637,000	21,113,954	9,067,000	219	94
Piedmont	8,749,000	8,749,000	10,640,295	8,749,000	122	100
Sardinia	285,000	285,000	2,969,401	285,000	1,042	100
LPS	**18,681,000**	**18,671,000**	**34,723,650**	**18,101,000**	**186**	**97**
Italy	**50,395,000**	**49,788,000**	**113,712,237**	**48,874,000**	**228**	**98**

Table 86. Estimates of regional and national self-sufficiencyin plasma-derived Factor VIII and von Willebrand Factor in combination, 2020

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	2,838,000	2,838,000	511,768	60,000	18	2
Aosta Valley	12,000	12,000	69,751	12,000	581	100
AP Bolzano	755,000	755,000	212,257	720,000	28	95
AP Trento	36,500	36,500	203,157	10,000	557	27
Basilicata	159,000	155,000	218,298	50,000	141	32
FVG	418,000	418,000	880,152	380,000	211	91
Liguria	569,500	569,500	703,114	480,000	123	84
Umbria	929,000	929,000	298,656	300,000	32	32
Veneto	2,620,500	2,605,000	2,730,324	1,690,000	105	65
NAIP	**8,337,500**	**8,318,000**	**5,827,477**	**3,702,000**	**70**	**45**
Apulia	6,820,500	6,815,500	-	-	-	-
Calabria	1,560,250	1,280,000	-	-	-	-
E.-Romagna	2,179,000	2,179,000	-	-	-	-
Sicily	4,599,000	4,577,000	-	-	-	-
RIPP	**15,158,750**	**14,851,500**	**-**	**-**	**-**	**-**

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Campania	4,817,700	4,817,500	-	-	-	-
Latium	8,035,100	6,349,500	-	-	-	-
Marche	424,000	424,000	-	-	-	-
Molise	200,000	200,000	-	-	-	-
Tuscany	2,687,200	2,686,000	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	**16,164,000**	**14,477,000**	**-**	**-**	**-**	**-**
Lombardy	5,255,500	5,124,000	-	-	-	-
Piedmont	2,283,000	2,279,000	-	-	-	-
Sardinia	1,442,200	1,442,200	-	-	-	-
LPS	**8,980,700**	**8,845,200**	**-**	**-**	**-**	**-**
Italy	**48,640,950**	**46,491,700**	**5,827,477**	**3,702,000**	**13**	**8**

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 (95% of the NHS demand), the regional self-sufficiency still bore significant differences with a range, varying from 64 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, 2020

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	441,500	434,000	-	434,000	-	100
Aosta Valley	98,500	98,500	-	98,500	-	100
AP Bolzano	406,000	406,000	-	406,000	-	100
AP Trento	346,500	346,500	-	346,500	-	100
Basilicata	183,000	183,000	-	183,000	-	100
FVG	704,000	704,000	-	704,000	-	100
Liguria	1,199,000	992,000	-	992,000	-	100
Umbria	777,000	777,000	-	495,000	-	64
Veneto	4,538,700	4,476,000	-	4,024,000	-	90
NAIP	**8,694,200**	**8,417,000**	**-**	**7,683,000**	**-**	**91**
Apulia	2,299,000	1,515,000	6,813,880	1,515,000	450	100
Calabria	615,500	613,000	2,606,856	613,000	425	100
E.-Romagna	3,955,000	3,655,500	13,574,398	3,501,500	371	96
Sicily	3,413,000	3,271,000	9,342,016	3,236,000	286	99
RIPP	**10,282,500**	**9,054,500**	**32,337,150**	**8,865,500**	**357**	**98**

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Campania	2,144,000	1,862,000	5,186,077	1,641,500	279	88
Latium	2,065,800	1,873,200	6,452,788	1,835,500	344	98
Marche	1,438,000	1,438,000	4,941,084	1,438,000	344	100
Molise	120,000	112,000	549,923	102,000	491	91
Tuscany	2,208,000	2,205,000	10,608,383	2,205,000	481	100
Min. of Def.	-	-	56,346	-	NA	NA
PlaNet	**7,975,800**	**7,490,200**	**27,794,600**	**7,222,000**	**371**	**96**
Lombardy	8,001,800	7,745,000	21,850,832	6,902,000	282	89
Piedmont	3,580,500	3,364,500	10,693,445	3,339,500	318	99
Sardinia	1,875,000	1,875,000	2,925,703	1,860,000	156	99
LPS	**13,457,300**	**12,984,500**	**35,469,980**	**12,101,500**	**273**	**93**
Italy	**40,409,800**	**37,946,200**	**95,601,729**	**35,872,000**	**252**	**95**

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 2020, the potential self-sufficiency in RiaSTAP was equal to 62% (Table 88).

However, effective self-sufficiency of 53% was achieved, showing possible room for improvement in the interregional compensation policies. All NAIP Regions, except for Liguria, Umbria and Veneto, achieved effective self-sufficiency equal to 100%.

Table 88. Estimates of regional and national self- sufficiency in fibrinogen, 2020

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	1,170	1,170	660	1,170	56	100
Aosta Valley	70	70	90	70	128	100
AP Bolzano	800	800	274	800	34	100
AP Trento	280	280	262	280	94	100
Basilicata	240	240	281	240	117	100
FVG	983	980	1,135	980	116	100
Liguria	530	530	907	500	171	94
Umbria	860	860	385	810	45	94
Veneto	4,000	3,990	3,521	1,580	88	40
NAIP	**8,933**	**8,920**	**7,514**	**6,430**	**84**	**72**
Apulia	54	34	-	-	-	0
Calabria	-	-	-	-	-	0
E.-Romagna	107	71	-	-	-	0
Sicily	10	10	-	-	-	0
RIPP	**171**	**115**	**-**	**-**	**-**	**0**

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Campania	348	328	-	-	-	0
Latium	652	5	-	-	-	0
Marche	-	-	-	-	-	0
Molise	-	-	-	-	-	0
Tuscany	-	-	-	-	-	0
Min. of Def.	-	-	-	-	-	0
PlaNet	**1,000**	**333**	**-**	**-**	**-**	**0**
Lombardy	789	340	-	-	-	0
Piedmont	1,900	1,867	-	-	-	0
Sardinia	483	483	-	-	-	0
LPS	**3,172**	**2,690**	**-**	**-**	**-**	**-**
Italy	**13,276**	**12,058**	**7,514**	**6,430**	**62**	**53**

Solvent/detergent virus-inactivated plasma

Differently from the main PDMPs that were included in the agreements between the Regions and the fractionation company regarding the toll fractionation process, the production of solvent/detergent virus-inactivated plasma (S/D plasma) from national plasma was determined by the production planning of the individual Regions (and in some cases of Local Health Centers). Therefore, not all the Regions contributed to the achievement of national self-sufficiency.

For S/D plasma, the therapeutic indications are the same as those for fresh-frozen plasma. There is not sufficient evidence to justify the priority or preferential use of S/D plasma rather than fresh frozen plasma (52).

In 2020, the NHS demand for S/D plasma was almost equal to the total demand. For the same year, effective national self-sufficiency was 62%, as in 2019 (Table 89).

Table 89. Estimates of regional and national self-sufficiency in solvent/detergent virus-inactivated plasma, 2020

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	462,000	462,000	-	-	-	-
FVG	20,000	20,000	-	-	-	-
Liguria	545,200	545,200	-	47,200	-	9
Umbria	26,000	26,000	-	-	-	-
Veneto	1,468,000	1,358,000	-	1,358,000	-	100
NAIP	**2,531,200**	**2,421,200**	**-**	**1,405,200**	**-**	**58**

Region	Total demand	NHS demand	Potential supply**	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	mL	mL	mL	mL	%	%
Apulia	2,814,000	2,814,000	-	36,000	-	1
Calabria	895,000	895,000	-	-	-	-
E.-Romagna	592,000	592,000	-	-	-	-
Sicily	3,756,200	3,756,200	2,051,538	1,734,200	55	46
RIPP	**8,057,200**	**8,057,200**	**2,051,538**	**1,770,200**	**25**	**22**
Campania	4,546,600	4,512,600	2,003,880	4,498,600	44	100
Latium	4,097,400	4,063,400	2,510,656	2,679,800	62	66
Marche	1,560,000	1,560,000	1,482,624	1,560,000	95	100
Molise	341,200	341,200	417,055	341,200	122	100
Tuscany	1,338,000	1,338,000	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	**11,883,200**	**11,815,200**	**6,414,214**	**9,079,600**	**54**	**77**
Lombardy	448,000	442,000	-	440,000	-	100
Piedmont	3,562,000	3,562,000	4,165,067	3,562,000	117	100
Sardinia	106,000	106,000	-	106,000	-	100
LPS	**4,116,000**	**4,110,000**	**4,165,067**	**4,108,000**	**101**	**100**
Italy	**26,587,600**	**26,403,600**	**12,630,819**	**16,363,000**	**48**	**62**

For the Regions that used S/D plasma produced by toll fractionation, effective regional self-sufficiency ranged from 1% in Apulia to 100% in Veneto, Campania, Marche, Molise, Lombardy, Piedmont and Sardinia.

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 purchased in 2018 for the quota of the demand not covered by toll fractionation (albumin, IV IGs, SC/IM IGs, pdFVIII, pdFVIII/vWF, pdFIX, 3F-PCC, AT and fibrinogen);
2. Recombinant medicinal products, including extended half-life products, used in the treatment of coagulation disorders (rFVIIa, rFVIII, rFIX and rFXIII)[i];
3. Emicizumab
4. polyvalent immunoglubulins for sc / im administration, specific immunoglobulins and all other MPDs, 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 2020, applying the discounts envisaged by law for pharmaceutical expenditure.

Tables 90 and 91 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 2020, expenditure for the purchase of the aforementioned PDMPs was approximately 189,6 million euros (3.1 euro *per capita*) recording an increase, compared to 2019, of approximately 19.5 million euros (+11.5%).

Table 92 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 447,2 million euros (7.5 euros *per capita*). The Regions with the highest *per capita* expenditure were Campania with 11.1 euros *per capita* spent and Latium with 10.1 euros *per capita*.

The expenditure for recombinant factors decreased compared to 2019 (-2%). Table 93 shows the expenditure incurred in 2020 for the purchase of Emicizumab which has undergone an increase of + 173%, from 0.27 to 0.75 euros *per capita*, reflecting how much the use of this drug is progressively increasing.

In 2020, as regards all the other PDMPs (Tables 94-97), the total expenditure was approximately 108,3 million euros, equal to around 1.82 euros *per capita* of which approximately 39 million for the purchase of specific immunoglobulins, a cost comparable to that of 2019 (Table 94), in regard to the *per capita* expenditure (0.65) (Table 95).

The other MPDs (Tables 96-97), recorded a marked decrease in expenditure compared to the previous year (-4.3%), in particular as regards FVII (-14%), local haemostatics (-12%), the other plasma protein fractions (-10%) and activated prothrombin complex concentrates (-7%). On the other hand, an increase in expenditure was recorded for FX (+232%), FXI (+51%), alpha-1 proteinase (+10%) and for protein C (+6%).

Table 90. 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 2020

Region	Albumin		Human Immunoglobulin intravenous use		Factor VIII		Total	
	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*
Abruzzo	751,483	0.58	905,811	0.70	-	-	1,657,294	1.28
Aosta Valley	-	0.00	7,147	0.06	-	-	7,147	0.06
AP Bolzano	31,841	0.06	196,961	0.37	-	-	228,802	0.43
AP Trento	20,089	0.04	54,362	0.10	-	-	74,451	0.14
Basilicata	359,878	0.65	555,707	1.00	-	-	915,585	1.65
Friuli V. G.	4,472	0.00	732,234	0.61	-	-	736,705	0.61
Liguria	474,744	0.31	1,584,351	1.04	-	-	2,059,095	1.35
Umbria	37,936	0.04	138,997	0.16	-	-	176,933	0.20
Veneto	226,347	0.05	1,018,497	0.21	-	-	1,244,844	0.26
NAIP	**1,906,791**	**0.17**	**5,194,066**	**0.45**	**-**	**-**	**7,100,857**	**0.62**
Apulia	1,573,755	0.40	6,708,513	1.70	151,360	0.04	8,433,628	2.13
Calabria	1,425,104	0.75	87,329	0.05	-	-	1,512,433	0.80
E.-Romagna	326,103	0.07	1,504,890	0.34	-	-	1,830,993	0.41
Sicily	1,389,559	0.29	1,469,642	0.30	-	-	2,859,202	0.59
RIPP	**4,714,521**	**0.31**	**9,770,375**	**0.64**	**151,360**	**0.01**	**14,636,255**	**0.96**
Campania	7,292,384	1.28	7,516,605	1.32	-	-	14,808,989	2.59
Latium	2,318,691	0.40	3,426,197	0.60	-	-	5,744,889	1.00
Marche	25,237	0.02	603,513	0.40	-	-	628,751	0.42
Molise	75,149	0.25	6,600	0.02	-	-	81,749	0.27
Tuscany	508,869	0.14	9,984,111	2.70	-	-	10,492,980	2.84
Min. of Def.	-	-	-	-	-	-	NA	NA
PlaNet	**10,220,330**	**0.60**	**21,537,027**	**1.27**	**-**	**-**	**31,757,357**	**1.87**
Lombardy	2,414,161	0.24	7,580,127	0.76	231,990	0.02	10,226,278	1.02
Piedmont	349,016	0.08	4,998,593	1.16	-	-	5,347,609	1.24
Sardinia	878,534	0.55	880,629	0.55	-	-	1,759,163	1.09
LPS	**3,641,711**	**0.23**	**13,459,349**	**0.84**	**231,990**	**0.01**	**17,333,050**	**1.09**
Italy	**20,483,353**	**0.34**	**49,960,817**	**0.84**	**383,350**	**0.01**	**70,827,520**	**1.19**

Table 91. 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 2020

Region	SC/Ig		FVIII/vWF		FIX		3F-PCC		AT		Fibrinogen		Total	
	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*
Abruzzo	1,693,865	1.31	1,475,797	1.14	-	-	-	-	63,792	0.05	218,240	0.17	3,451,694	2.7
Aosta Valley	24,755	0.20	0	0.00	-	-	-	-	18,612	0.15	-	-	43,367	0.3
AP Bolzano	97,760	0.18	19,404	0.04	-	-	-	-	6,316	0.01	139,920	0.26	263,400	0.5
AP Trento	311,516	0.57	14,867	0.03	-	-	-	-	-	-	132,440	0.24	458,822	0.8
Basilicata	761,064	1.38	57,858	0.10	-	-	-	-	35,343	0.06	-	-	854,265	1.5
FVG	263,710	0.22	20,900	0.02	-	-	-	-	-	-	-	-	284,610	0.2
Liguria	2,637,556	1.73	62,183	0.04	-	-	-	-	234,596	0.15	62,480	0.04	2,996,815	2.0
Umbria	1,332,451	1.53	325,010	0.37	124,080	0.14	-	-	-	-	22,000	0.03	1,803,541	2.1
Veneto	5,577,128	1.14	613,125	0.13	-	-	129,418	0.03	113,721	0.02	2,152,480	0.44	8,585,872	1.8
NAIP	**12,699,804**	**1.10**	**2,589,144**	**0.22**	**124,080**	**0.01**	**129,418**	**0.01**	**472,380**	**0.04**	**2,727,560**	**0.24**	**18,742,387**	**1.6**
Apulia	6,870,356	1.74	3,452,802	0.87	-	-	-	-	14,150	0.00	926,640	0.23	11,263,949	2.8
Calabria	2,148,924	1.13	701,170	0.37	-	-	-	-	40,013	0.02	1,180,080	0.62	4,070,186	2.1
E.-Romagna	6,817,419	1.53	1,192,891	0.27	-	-	40,487	0.01	22,066	0.00	1,520,200	0.34	9,593,063	2.1
Sicily	5,354,465	1.10	2,429,000	0.50	-	-	9,048	0.00	64,651	0.01	1,373,240	0.28	9,230,404	1.9
RIPP	**21,191,165**	**1.40**	**7,775,863**	**0.51**	**-**	**-**	**49,534**	**0.00**	**140,880**	**0.01**	**5,000,160**	**0.33**	**34,157,602**	**2.2**
Campania	6,353,800	1.11	2,368,643	0.41	-	-	50,936	0.01	516,146	0.09	1,955,800	0.34	11,245,325	2.0
Latium	11,821,780	2.05	3,045,409	0.53	3,988	0.00	10,349	0.00	637,679	0.11	2,062,280	0.36	17,581,485	3.1
Marche	1,749,797	1.16	229,649	0.15	-	-	-	-	-	-	474,320	0.31	2,453,766	1.6
Molise	170,684	0.57	110,502	0.37	4,840	0.02	-	-	-	-	27,280	0.09	313,307	1.0
Tuscany	10,048,802	2.72	1,397,286	0.38	-	-	-	-	2,102	0.00	1,444,520	0.39	12,892,710	3.5
Min. of Def.		-		-	-	-	-	-	-	-	-	-	-	NA
PlaNet	**30,144,864**	**1.78**	**7,151,490**	**0.42**	**8,828**	**0.00**	**61,285**	**0.00**	**1,155,927**	**0.07**	**5,964,200**	**0.35**	**44,486,593**	**2.6**
Lombardy	6,411,073	0.64	2,859,977	0.29	445,484	0.04	-	-	217,735	0.02	2,002,880	0.20	11,937,148	1.2
Piedmont	5,375,005	1.25	925,341	0.21	5,310	0.00	2,541	0.00	570	0.00	1,068,760	0.25	7,377,526	1.7
Sardinia	499,808	0.31	717,720	0.45	-	-	2,850	0.00	20,847	0.01	849,640	0.53	2,090,865	1.3
LPS	**12,285,886**	**0.77**	**4,503,037**	**0.28**	**450,793**	**0.03**	**5,391**	**0.00**	**239,152**	**0.01**	**3,921,280**	**0.25**	**21,405,539**	**1.3**
Italy	**76,321,719**	**1.28**	**22,019,534**	**0.37**	**583,701**	**0.01**	**245,628**	**0.00**	**2,008,340**	**0.03**	**17,613,200**	**0.30**	**118,792,121**	**2.0**

Table 92. Estimate of the total expenditure and the total *per capita* expenditure for recombinant Factors VII, VIII, IX and XIII in 2020

Region	rFVIIa		rFVIII		rFIX		rFXIII		Total	
	€	€ *pc*	€	€ *pc*	€ *pc*	€ *pc*	€	€ *pc*	€	€ *pc*
Abruzzo	324,300	0.25	7,616,057	5.89	2,530,313	1.96	279,436	0.22	10,750,105	8.3
Aosta Valley	-	-	479,828	3.84	-	-	-	-	479,828	3.8
AP Bolzano	734,691	1.38	1,375,747	2.58	-	-	-	-	2,110,438	4.0
AP Trento	40,133	0.07	1,985,256	3.64	360,252	0.66	-	-	2,385,641	4.4
Basilicata	5,826	0.01	3,363,866	6.08	288,909	0.52	186,290	0.34	3,844,891	6.9
FVG	5,219,842	4.33	1,949,454	1.62	1,486,440	1.23	-	-	8,655,736	7.2
Liguria	79,618	0.05	8,057,736	5.28	3,491,745	2.29	403,629	0.26	12,032,729	7.9
Umbria	16,183	0.02	4,094,637	4.71	248,554	0.29	-	-	4,359,374	5.0
Veneto	4,794,565	0.98	17,496,488	3.59	4,738,457	0.97	108,669	0.02	27,138,180	5.6
NAIP	**11,215,157**	**0.97**	**46,419,070**	**4.03**	**13,144,670**	**1.14**	**978,025**	**0.08**	**71,756,921**	**6.2**
Apulia	4,935,658	1.25	24,654,621	6.24	9,443,570	2.39	-	-	39,033,849	9.9
Calabria	3,005,422	1.59	12,623,816	6.66	1,103,718	0.58	931,452	0.49	17,664,407	9.3
E.-Romagna	1,852,576	0.41	21,176,641	4.74	5,429,561	1.22	-	-	28,458,778	6.4
Sicily	2,569,144	0.53	30,453,175	6.25	4,866,562	1.00	-	-	37,888,881	7.8
RIPP	**12,362,800**	**0.81**	**88,908,252**	**5.85**	**20,843,412**	**1.37**	**931,452**	**0.06**	**123,045,916**	**8.1**
Campania	11,779,454	2.06	43,875,153	7.68	7,840,594	1.37	-	-	63,495,201	11.1
Latium	2,852,660	0.50	49,487,201	8.60	5,657,437	0.98	-	-	57,997,298	10.1
Marche	866,095	0.57	5,427,433	3.59	1,788,200	1.18	-	-	8,081,728	5.3
Molise	159,237	0.53	1,169,738	3.89	0	0.00	-	-	1,328,975	4.4
Tuscany	6,298,894	1.71	13,818,840	3.74	6,985,709	1.89	-	-	27,103,443	7.3
Min. of Def.	-	-	-	-	-	-	-	-	-	-
PlaNet	**21,956,339**	**1.29**	**113,778,366**	**6.70**	**22,271,940**	**1.31**	**-**	**-**	**158,006,645**	**9.3**
Lombardy	2,402,783	0.24	45,633,886	4.55	12,372,163	1.23	326,008	0.03	60,734,841	6.1
Piedmont	1,376,814	0.32	18,766,386	4.35	5,233,512	1.21	139,718	0.03	25,516,430	5.9
Sardinia	53,726	0.03	7,989,427	4.96	95,288	0.06	-	-	8,138,440	5.0
LPS	**3,833,323**	**0.24**	**72,389,699**	**4.54**	**17,700,963**	**1.11**	**465,726**	**0.03**	**94,389,711**	**5.9**
Italy	**49,367,620**	**0.83**	**321,495,387**	**5.39**	**73,960,984**	**1.24**	**2,375,203**	**0.04**	**447,199,193**	**7.5**

Table 93. Estimate of the total expenditure and the total *per capita* expenditure for Emicizumab in 2020

Region	Emicizumab	
	€	€ *per capita*
Abruzzo	1,015,978	0.79
Aosta Valley	-	-
AP Bolzano	463,637	0.87
AP Trento	-	-
Basilicata	268,057	0.48
Friuli V. Giulia.	679,338	0.56
Liguria	951,830	0.62
Umbria	792,273	0.91
Veneto	3,700,552	0.76
NAIP	**7,871,665**	**0.68**
Apulia	1,601,853	0.41
Calabria	2,115,575	1.12
E.-Romagna	2,914,879	0.65
Sicily	2,998,174	0.61
RIPP	**9,630,481**	**0.63**
Campania	4,034,272	0.71
Latium	1,276,103	0.22
Marche	583,928	0.39
Molise	-	-
Tuscany	4,966,631	1.35
Min. of Def.	-	-
PlaNet	**10,860,934**	**0.64**
Lombardy	10,638,345	1.06
Piedmont	6,026,095	1.40
Sardinia	-	-
LPS	**16,664,440**	**1.04**
Italy	**45,027,520**	**0.75**

Table 94. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of specific immunoglobulins in 2020

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs	Rabies IGs	Total
Abruzzo	296,318	5,205	241,702	54,770	107,458	3,247	-	708,700
Aosta Valley	76,737	-	20,984	6,282	1,858	-	4,312	110,173
AP Bolzano	35,434	-	25,285	41,736	17,948	1,612	1,509	123,523
AP Trento	92,118	-	22,626	28,795	0	1,698	-	145,238
Basilicata	126,136	570	72,951	16,168	20,634	-	-	236,460
Friuli V. Giulia	148,366	39,732	23,069	-	215,328	-	33525,8	460,021
Liguria	213,599	277	177,750	51,972	11,584	322	-	455,504
Umbria	93,500	-	83,761	32,468	1,647	-	-	211,377
Veneto	998,078	293,635	168,234	250,203	711,801	3,223	7,223	2,432,397
NAIP	**2,080,285**	**339,419**	**836,363**	**482,396**	**1,088,258**	**10,102**	**46,570**	**4,883,393**
Apulia	2,573,186	251,717	433,515	103,442	47,958	9,669	431	3,419,919
Calabria	653,497	58,298	406,671	51,444	14,502	-	-	1,184,412
E.-Romagna	890,884	165,499	306,940	217,156	173,496	5,652	20,374	1,780,001
Sicily	1,608,232	1,788	838,895	116,952	87,039	-	-	2,652,905
RIPP	**5,725,800**	**477,302**	**1,986,021**	**488,994**	**322,994**	**15,322**	**20,805**	**9,037,238**
Campania	6,234,982	368,821	1,480,478	87,134	47,687	967	-	8,220,068
Latium	1,050,016	136,963	563,876	156,293	41,029	1,895	-	1,950,072
Marche	277,164	72,504	239,311	58,801	51,826	2,987	539	703,132
Molise	76,760	1,914	41,265	6,802	-	-	-	126,740
Tuscany	837,757	124,291	592,996	142,109	67,837	2,164	-	1,767,155
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	**8,476,679**	**704,493**	**2,917,925**	**451,140**	**208,379**	**8,013**	**539**	**12,767,167**
Lombardy	5,378,210	333,490	493,647	389,426	149,887	6,903	28,998	6,780,562
Piedmont	2,314,637	82,129	232,267	174,871	488,127	4,592	-	3,296,623
Sardinia	1,599,544	85,646	253,534	27,361	4,532	173	-	1,970,790
LPS	**9,292,392**	**501,265**	**979,448**	**591,658**	**642,545**	**11,668**	**28,998**	**12,047,975**
Not specified region	-	-	46,125*	-	-	-	-	46,125
Italy	**25,575,155**	**2,022,478**	**6,765,882**	**2,014,188**	**2,262,176**	**45,106**	**96,912**	**38,781,898**

*estimated value

Table 95. 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 2020

Regione	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs*	Rabies IGs*	Total
Abruzzo	0.23	0.00	0.19	0.04	0.08	2.51	-	0.55
Aosta Valley	0.61	-	0.17	0.05	0.01	-	34.49	0.88
AP Bolzano	0.07	-	0.05	0.08	0.03	3.03	2.83	0.23
AP Trento	0.17	-	0.04	0.05	0.00	3.11	-	0.27
Basilicata	0.23	0.00	0.13	0.03	0.04	-	-	0.43
Friuli V. Giulia	0.12	0.03	0.02	-	0.18	-	27.79	0.38
Liguria	0.14	0.00	0.12	0.03	0.0076	0.21	-	0.30
Umbria	0.11	-	0.10	0.04	0.00	-	-	0.24
Veneto	0.20	0.06	0.03	0.05	0.15	0.66	1.48	0.50
NAIP	**0.18**	**0.03**	**0.07**	**0.04**	**0.09**	**0.88**	**4.04**	**0.42**
Apulia	0.65	0.06	0.11	0.03	0.01	2.45	0.11	0.87
Calabria	0.35	0.03	0.21	0.03	0.01	-	-	0.63
E.-Romagna	0.20	0.04	0.07	0.05	0.04	1.27	4.56	0.40
Sicily	0.33	0.00	0.17	0.02	0.02	-	-	0.54
RIPP	**0.38**	**0.03**	**0.13**	**0.03**	**0.02**	**1.01**	**1.37**	**0.60**
Campania	1.09	0.06	0.26	0.02	0.01	0.17	-	1.44
Latium	0.18	0.02	0.10	0.03	0.01	0.33	-	0.34
Marche	0.18	0.05	0.16	0.04	0.03	1.97	0.36	0.46
Molise	0.26	0.01	0.14	0.02	-	-	-	0.42
Tuscany	0.23	0.03	0.16	0.04	0.02	0.59	-	0.48
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	**0.50**	**0.04**	**0.17**	**0.03**	**0.01**	**0.47**	**0.03**	**0.75**
Lombardy	0.54	0.03	0.05	0.04	0.01	0.69	2.89	0.68
Piedmont	0.54	0.02	0.05	0.04	0.11	1.07	-	0.76
Sardinia	0.99	0.05	0.16	0.02	0.00	0.11	-	1.22
LPS	**0.58**	**0.03**	**0.06**	**0.04**	**0.04**	**0.73**	**1.82**	**0.76**
Italy	**0.43**	**0.03**	**0.11**	**0.03**	**0.04**	**0.76**	**1.62**	**0.65**

* values per 1,000 population

Table 96. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of all other PDMPs in 2020

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	Protein C	Total
Abruzzo	84,009	1,251,012	808,055	-	163,092	391,502	199,205	-		1562,88	6,000	2,904,438
Aosta Valley	-	-	49,110	-	-	229,900	153,388	-		-	-	432,398
AP Bolzano	-	-	283,209	-	167,146	624,707	26,640	-		-	-	1,101,702
AP Trento	-	-	154,793	3,927	15,138	155,282	34,527	-		15,238	-	378,905
Basilicata	35,471	-	384,858	200,639	58,911	-	90,706	-		-	-	770,585
Friuli V. Giulia	-	267,120	484,174	7,865	-	471,460	37,418	-	63,800	-	-	1,331,837
Liguria	33,095	34,726	337,910	199,462	84,376	433,986	24,578	-		-	149,490	1,297,621
Umbria	2,800	-	376,512	23,341	15,308	84,480	275,702	-		-	16715,96	794,859
Veneto	11,201	272,129	1,576,429	-	37,301	866,321	960,736	-	8,800	102,369	23,099	3,858,385
NAIP	**166,576**	**1,824,986**	**4,455,051**	**435,234**	**541,271**	**3,257,637**	**1,802,900**	**-**	**72,600**	**119,170**	**195,304**	**12,870,729**
Apulia	215,614	2,200	1,104,736	1,572,367	19,222	432,718	716,534	-	6,600	-	21,890	4,091,881
Calabria	38,248	-	901,978	399,796	57,729	271,392	652,554	-		-	388,927	2,710,623
E.-Romagna	93,811	569,416	693,664	232,804	315,984	730,097	514,696	-	6,600	202,393	7,960	3,367,425
Sicily	224,429	2,316,264	1,422,197	1,069,935	112,137	811,008	1,428,814	-	8,800	-	47,740	7,441,325
RIPP	**572,101**	**2,887,880**	**4,122,576**	**3,274,902**	**505,073**	**2,245,215**	**3,312,598**	**-**	**22,000**	**202,393**	**466,516**	**17,611,254**
Campania	186,133	999,602	3,043,986	5,482	325,542	1,682,623	2,719,560	-		-	231,750	9,194,678
Latium	1,006,263	769,950	1,366,687	561,724	121,146	777,955	2,196,152	-	8,800	73,455	30,610	6,912,742
Marche	933	-	528,586	-	69,212	57,000	390,328	-		10,159	23,100	1,079,319
Molise	225,707	-	26,949	-	-	7,920	1,170	-		-	-	261,747
Tuscany	14,468	997,142	1,629,051	514,395	358,362	716,132	525,510	-		36,728	5,970	4,797,758
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	0
PlaNet	**1,433,506**	**2,766,694**	**6,595,258**	**1,081,602**	**874,261**	**3,241,631**	**5,832,721**	**-**	**8,800**	**120,342**	**291,430**	**22,246,244**
Lombardy	1,299,433	1,964,270	2,288,620	22,458	76,481	2,399,947	2,374,723	66,000		62,515	104,081	10,658,528
Piedmont	161,654	319,654	1,288,087	-	212,539	726,859	737,336	-	11,000	22,271	-	3,479,401
Sardinia	-	329,448	383,739	-	212,291	1,099,190	619,631	-		-	55,860	2,700,159
LPS	**1,461,087**	**2,613,372**	**3,960,447**	**22,458**	**501,311**	**4,225,997**	**3,731,690**	**66,000**	**11,000**	**84,786**	**159,941**	**16,838,087**
Italy	**3,633,270**	**10,092,931**	**19,133,331**	**4,814,195**	**2,421,916**	**12,970,479**	**14,679,909**	**66,000**	**114,400**	**526,690**	**1,113,192**	**69,566,314**

*estimated value

Table 97. Estimate of standardised expenditure (*per capita* and euro per 1,000 population) incurred by the National Health Service for the purchase on the market of all other PDMPs in 2020

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*	Protein C	Total
Abruzzo	0.06	0.97	0.62	-	0.13	0.30	0.15	-	-	-	0.00	2.24
Aosta Valley	-	-	0.39	-	-	1.84	1.23	-	-	-	-	3.46
AP Bolzano	-	-	0.53	0.00	0.31	1.17	0.05	-	-	-	-	2.07
AP Trento	-	-	0.28	0.01	0.03	0.28	0.06	-	-	27.94	-	0.69
Basilicata	0.06	-	0.70	0.36	0.11	0.00	0.16	-	-	-	-	1.39
Friuli V. Giulia	-	0.22	0.40	0.01	0.00	0.39	0.03	-	52.89	-	-	1.10
Liguria	0.02	0.02	0.22	0.13	0.06	0.28	0.02	-	-	-	0.10	0.85
Umbria	0.00	-	0.43	0.03	0.02	0.10	0.32	-	-	-	-	0.91
Veneto	0.00	0.06	0.32	-	0.01	0.18	0.20	-	-	20.98	0.00	0.79
NAIP	**0.01**	**0.16**	**0.39**	**0.04**	**0.05**	**0.28**	**0.16**	**-**	**6.30**	**10.34**	**0.02**	**1.12**
Apulia	0.05	0.00	0.28	0.40	0.00	0.11	0.18	-	1.67	-	0.0055	1.04
Calabria	0.02	-	0.48	0.21	0.03	0.14	0.34	-	-	-	0.21	1.43
E.-Romagna	0.02	0.13	0.16	0.05	0.07	0.16	0.12	-	1.48	45.34	0.0018	0.75
Sicily	0.05	0.48	0.29	0.22	0.02	0.17	0.29	-	1.81	-	0.01	1.53
RIPP	**0.04**	**0.19**	**0.27**	**0.22**	**0.03**	**0.15**	**0.22**	**-**	**1.45**	**13.33**	**0.03**	**1.16**
Campania	0.03	0.17	0.53	0.00	0.06	0.29	0.48	-	-	-	0.04	1.61
Latium	0.17	0.13	0.24	0.10	0.02	0.14	0.38	-	1.53	12.76	0.01	1.20
Marche	0.00	-	0.35	-	0.05	0.04	0.26	-	-	6.72	0.02	0.71
Molise	0.75	-	0.09	-	-	0.03	0.00	-	-	-	-	0.87
Tuscany	0.00	0.27	0.44	0.14	0.10	0.19	0.14	-	-	9.95	0.00	1.30
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**0.08**	**0.16**	**0.39**	**0.06**	**0.05**	**0.19**	**0.34**	**-**	**0.52**	**7.09**	**0.02**	**1.31**
Lombardy	0.13	0.20	0.23	0.00	0.01	0.24	0.24	6.6	-	6.23	0.01	1.06
Piedmont	0.04	0.07	0.30	0.00	0.05	0.17	0.17	-	-	5.17	0.00	0.81
Sardinia	-	0.20	0.24	0.00	0.13	0.68	0.38	-	-	0.00	0.03	1.68
LPS	**0.09**	**0.16**	**0.25**	**0.00**	**0.03**	**0.26**	**0.23**	**4.1**	**-**	**5.32**	**0.01**	**1.06**
ITALY	**0.06**	**0.17**	**0.32**	**0.08**	**0.04**	**0.22**	**0.25**	**1.1**	**1.92**	**8.83**	**0.02**	**1.17**

* values per 1,000 population

National and Regional mean price per gram or International Unit

Tables 98-100 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 exceed 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 98), the national mean price per gram was 2.85 euros. The variability observed between Regions (range: 2.12-3.95 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, Emilia-Romagna, 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 Friuli V.Giulia, AP of Trento, Umbria, Molise and Veneto, the commercial demand (although not significant) was mainly dispensed through the accredited pharmacies channel, showing significantly higher mean prices per gram.

The overall expenditure of pdFVIII/vWF on the market was 21,677,119 euros (0.51 euros per IU), and almost entirely accounted for the distribution through NHS facilities (96%) (95% in 2019) (Table 99).

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 38,807,169 million euros with an increase of 10% compared to 2019. The mean unit price per gram at national level was 44.89 euros (range: 34.84-51.89 euros) (Table 100).

Table 98. 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 2020

Region	Mean price			Demand				Total expenditure			
	NHS facilities	Pharmacies	Total	NHS facilities		Pharmacies		NHS facilities		Pharmacies	
	€/g	€/g	€/g	g	%	g	%	€	%	€	%
Abruzzo	2.07	3.94	2.41	255,415	82%	56,765	18%	527,858	70%	223,625	30%
Aosta Valley	-	-	-	-	-	-	-	-	-	-	-
AP Bolzano	2.36	-	2.36	13,500	100%	-	0%	31,841	100%	-	0%
AP Trento	-	3.88	3.88	-	0%	5,180	100%	-	0%	20,089	100%
Basilicata	2.16	3.93	2.74	88,585	67%	42,755	33%	191,650	53%	168,228	47%
Friuli V. Giulia	-	3.89	3.89	-	0%	1,150	100%	-	0%	4,472	100%
Liguria	1.96	3.94	2.12	206,175	92%	17,770	8%	404,786	85%	69,958	15%
Umbria	-	3.94	3.94	-	0%	9,630	100%	-	0%	37,936	100%
Veneto	2.35	3.93	3.78	5,890	10%	53,998	90%	13,870	6%	212,477	94%
NAIP	**2.05**	**3.93**	**2.52**	**569,565**	**75%**	**187,248**	**25%**	**1,170,006**	**61%**	**736,785**	**39%**
Apulia	2.19	3.93	3.66	67,145	16%	363,283	84%	147,037	9%	1,426,718	91%
Calabria	2.19	3.91	3.58	76,300	19%	321,513	81%	166,940	12%	1,258,163	88%
E.-Romagna	2.55	3.93	2.61	119,575	96%	5,348	4%	305,089	94%	21,013	6%
Sicily	1.98	3.88	3.22	150,450	35%	281,005	65%	298,016	21%	1,091,543	79%
RIPP	**2.22**	**3.91**	**3.40**	**413,470**	**30%**	**971,148**	**70%**	**917,084**	**19%**	**3,797,437**	**81%**
Campania	1.88	3.88	2.81	1,390,090	54%	1,206,043	46%	2,608,578	36%	4,683,806	64%
Latium	1.89	3.93	2.74	492,973	58%	353,395	42%	930,126	40%	1,388,565	60%
Marche	2.22	-	2.22	11,350	100%	-	0%	25,237	100%	-	0%
Molise	-	3.95	3.95	-	0%	19,045	100%	-	0%	75,149	100%
Tuscany	2.30	3.92	2.34	213,208	98%	4,640	2%	490,690	96%	18,179	4%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**1.92**	**3.89**	**2.77**	**2,107,620**	**57%**	**1,583,123**	**43%**	**4,054,632**	**40%**	**6,165,698**	**60%**
Lombardy	2.05	3.92	2.87	473,150	56%	368,485	44%	968,150	40%	1,446,012	60%
Piedmont	2.54	3.94	2.61	126,488	95%	7,160	5%	320,772	92%	28,244	8%
Sardinia	1.77	3.95	2.39	264,350	72%	103,965	28%	468,174	53%	410,360	47%
LPS	**2.03**	**3.93**	**2.71**	**863,988**	**64%**	**479,610**	**36%**	**1,757,096**	**48%**	**1,884,615**	**52%**
Italy	**2.00**	**3.91**	**2.85**	**3,954,643**	**55%**	**3,221,128**	**45%**	**7,898,817**	**39%**	**12,584,536**	**61%**

Table 99. 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 2020

Region	Mean price*			Demand*				Total expenditure*			
	NHS facilities	Pharmacies	Total	NHS facilities		Pharmacies		NHS facilities		Pharmacies	
	€/IU	€/IU	€/IU	IU	%	IU	%	€	%	€	%
Abruzzo	0.53	0.00	0.53	2,778,000	100%	-	0%	1,475,797	100%	-	0%
Aosta Valley	-	-	-	-	-	-	-	-	-	-	-
AP Bolzano	0.55	0.00	0.55	35,000	100%	-	0%	19,404	100%	-	0%
AP Trento	0.56	0.00	0.56	26,500	100%	-	0%	14,867	100%	-	0%
Basilicata	0.55	0.00	0.55	105,000	100%	-	0%	57,858	100%	-	0%
Friuli V. Giulia	0.55	0.00	0.55	38,000	100%	-	0%	20,900	100%	-	0%
Liguria	0.55	0.00	0.55	69,500	100%	-	0%	38,225	100%	-	0%
Umbria	0.52	0.00	0.52	629,000	100%	-	0%	325,010	100%	-	0%
Veneto	0.53	0.00	0.53	719,000	100%	-	0%	378,177	100%	-	0%
NAIP	**0.53**	**-**	**0.53**	**4,400,000**	**100%**	**-**	**0%**	**2,330,238**	**100%**	**-**	**0%**
Apulia	0.51	-	0.51	6,815,500	100%	-	0%	3,452,802	100%	-	0%
Calabria	0.55	0.60	0.55	1,277,000	100%	3,000	0%	699,369	100%	1,801	0%
E.-Romagna	0.55	-	0.55	2,179,000	100%	-	0%	1,192,891	100%	-	0%
Sicily	0.53	0.53	0.53	4,279,000	93%	298,000	7%	2,269,959	93%	159,041	7%
RIPP	**0.52**	**0.53**	**0.52**	**14,550,500**	**98%**	**301,000**	**2%**	**7,615,022**	**98%**	**160,842**	**2%**
Campania	0.48	0.00	0.48	4,763,500	100%	-	0%	2,303,912	100%	-	0%
Latium	0.48	0.60	0.48	6,204,500	98%	145,000	2%	2,958,227	97%	87,182	3%
Marche	0.54	0.00	0.54	424,000	100%	-	0%	229,649	100%	-	0%
Molise	0.55	0.00	0.55	190,000	95%	10,000	5%	104,500	95%	6,002	5%
Tuscany	0.52	0.00	0.52	2,686,000	100%	-	0%	1,397,286	100%	-	0%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**0.49**	**0.60**	**0.49**	**14,268,000**	**99%**	**155,000**	**1%**	**6,993,575**	**99%**	**93,185**	**1%**
Lombardy	0.54	0.60	0.56	4,010,000	79%	1,098,000	21%	2,180,539	77%	660,659	23%
Piedmont	0.41	0.00	0.41	2,279,000	100%	-	0%	925,341	100%	-	0%
Sardinia	0.50	0.00	0.50	1,442,200	100%	-	0%	717,720	100%	-	0%
LPS	**0.49**	**0.60**	**0.51**	**7,731,200**	**88%**	**1,098,000**	**12%**	**3,823,599**	**85%**	**660,659**	**15%**
Italy	**0.51**	**0.59**	**0.51**	**40,949,700**	**96%**	**1,554,000**	**4%**	**20,762,434**	**96%**	**914,685**	**4%**

* The value does not include Wilfactin (vWF)

Table 100. 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 2020

Region	Mean price per gram (€) NHS facilities	Total demand (g) NHS facilities	Total expenditure NHS facilities*
Abruzzo	48.99	14,532	711,903
Aosta Valley	51.34	139	7,147
AP Bolzano	37.73	5,109	192,781
AP Trento	40.48	750	30,360
Basilicata	49.05	2,164	106,159
Friuli V. Giulia	49.47	1,485	73,466
Liguria	45.13	24,880	1,122,747
Umbria	51.89	2,315	120,121
Veneto	49.23	6,105	300,565
NAIP	**46.37**	**57,480**	**2,665,249**
Apulia	48.09	117,236	5,637,317
Calabria	46.51	1,130	52,569
E.-Romagna	47.52	19,298	916,962
Sicily	46.26	3,690	170,707
RIPP	**47.95**	**141,354**	**6,777,555**
Campania	34.84	110,910	3,864,255
Latium	36.18	91,617	3,314,657
Marche	48.35	4,935	238,599
Molise	-	-	-
Tuscany	48.20	187,951	9,059,077
Min. of Def.	-	-	-
PlaNet	**41.67**	**395,412**	**16,476,589**
Lombardy	49.47	149,141	7,378,567
Piedmont	46.01	100,590	4,628,579
Sardinia	42.80	20,575	880,629
LPS	**47.68**	**270,306**	**12,887,776**
Italy	**44.89**	**864,552**	**38,807,169**

* 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 (607 grams per 1,000 population).

An increased demand was observed in particular in Liguria (+30%), Marche (+27%) and Piedmont (+20%). The Regions with the highest standardised demand per 1,000 population were Sardinia, Campania and Basilicata with standardised volumes of 863, 749 and 748 grams, respectively.

About 9% of the national demand was distributed through public pharmacies, reaching a quantity of approximately 3,221 kilograms, The pharmacy channel was particularly used in Calabria and Campania where it accounts respectively for 27 and 28% of the regional demands.

The growth trend of the demand for IG was confirmed in the two-year period 2019-2020: +7% of the demand for IG; + 25% of the demand for SC/IM IG.

There were notable differences from one region to another, The three regions with the highest standardised demand per 1,000 population were the Aosta Valley, Tuscany and Molise, with around 228 for the first and 205 for the other two Regions.

The demand for AT has increased slightly (+7%) in 2020 like the demand of 4F-PCCs (+ 20%), while the demand for 3F-PCCs is decreased (-5%).

As regards the haemophilia A treatment, on one hand, the demand for pdFVIII (alone and in combination with vWF) significantly decreased (-10%); on the other, there was an evident decrease in the demand for rFVIII (-2%), despite the increased use of medicinal products with extended half-life FVIII (+ 24%).

The consumption of Emicizumab also increased significantly (+ 268%) while remains stable, after the decrease recordered in 2019, the demand for the activated prothrombin complex (+0.2%).

Concerning the haemophilia B treatment, the clinical use of extended half-life FIX (+10% compared to 2019) progressively replaced the demand for pdFIX.

The total volume of plasma sent by Regions for fractionation decreased by -1.7%, 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 23.8 sent by Friuli V. Giulia, with an average volume of 14.2 kilograms per 1,000 population.

The level of albumin self-sufficiency stood at around 76% of the NHS demand. As regards IGs, on the other hand, self-sufficiency in human immunoglobulin for intravenous and subcutaneous/intramuscolar use achieved at national level was 60%, while self-sufficiency in IV IG reached 81% (excluding high titre Ig); self-sufficiency for SC / IM IG was only 8%.

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

Generally, the system could benefit from better coordination and improveed 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 113 million euros, in line with the costs estimated by the contracts in force in 2020 and approximately 3,5 million euros had to be taken into account for the treatment of plasma virus-inactivated by solvent / detergent, for a total of approximately 116,5 million euros.

The estimate of the expenditure incurred by the NHS in 2020 for the procurement on the market of PDMPs included in the toll fractionation agreements between the Regions and

companies for the quantity not covered by self-sufficiency amounted to 190 million euros. An additional 108.3 million euros were used for the purchase of all the other PDMPs.

The cost of purchasing Emicizumab was 45 million euros.

The expenditure associated to recombinant products was about 447,2 million euros. The total expenditure for medicinal products described in this report was around 3.4% of the total NHS pharmaceutical expenditure recorded in 2020 (54).

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