RAPPORTI ISTISAN 21|13 EN

ISSN: 1123-3117 (cartaceo) • 2384-8936 (online)

Demand for plasma-derived medicinal products in Italy. 2019

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EPIDEMIOLOGIA
E SANITÀ PUBBLICA

ISTITUTO SUPERIORE DI SANITÀ

Demand for plasma-derived medicinal products in Italy. 2019

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)

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2021, vii, 138 p. Rapporti ISTISAN 21/13 EN

The Italian National Blood Centre in compliance with the national regulations about the coordination and provision of technical support to the regional and national planning of self-sufficiency in blood components and plasma-derived medicinal products, has 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 2019 published in the Rapporto ISTISAN 20/23, 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. 2019.
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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 2019 dei dati sull'argomento pubblicati nel Rapporto ISTISAN 20/23 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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Citare questo documento come segue:
Candura F, Massari MS, Profili S, De Fulvio L, Chelucci C, Brutti C, Biffoli C, De Angelis V. *Demand for plasma-derived medicinal products in Italy. 2019.* Roma: Istituto Superiore di Sanità; 2021. (Rapporti ISTISAN 21/13 EN).

Legale rappresentante dell'Istituto Superiore di Sanità: *Silvio Brusaferro*
Registro della Stampa - Tribunale di Roma n. 114 (cartaceo) e n. 115 (online) del 16 maggio 2014

Direttore responsabile della serie: *Paola De Castro*
Redazione*: Sandra Salinetti*
La responsabilità dei dati scientifici e tecnici è dei singoli autori, che dichiarano di non avere conflitti di interesse.

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ACRONYMNS AND ABBREVIATIONS

3F-PCCs	3-Factor Prothrombin Complex Concentrates
4F-PCCs	4-Factor Prothrombin Complex Concentrates
AIC	*Autorizzazione di Immissione in Commerci*o (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
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 Nazionale di Statistica* (Italian National Statistics Institute)
IU/s	International Unit/s
IVIG	IntraVenous ImmunoGlobulin
LHC	Local Health Centre
LPS	Lombardy-Piedmont-Sardinia Agreement
Min	Ministry
Min. of Def.	Ministry of Defence
MoH	Ministry of Health
NAIP	*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 (Istituto Superiore di Sanità) 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 2019, 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 2018, 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 2019, issued by DM of 31 July 2019.

Dr Vincenzo De Angelis
Director
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).

In Italy plasma comes exclusively from voluntary, anonymous and unremunerated donations of mostly periodic donors. Regions and Autonomous Provinces (APs) (hereinafter Regions), whether 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).

In June 2017, the New Interregional Agreement for Plasma-Derived Medicinal Products (*Nuovo Accordo Interregionale per la Plasmaderivazione*, NAIP), led by the Veneto Region, started to send plasma for fractionation to CSL Behring, the company that won the tender launched in 2015 pursuant to Law no. 219 of 21 October 2005, (Law 219/2005) (4), and signed a contract providing for the production of the following PDMPs: albumin, normal human immunoglobulins for intravenous use (IntraVenous ImmunoGlobulin, IVIG), subcutaneous (SC)/ intramuscular (IM) immunoglobulins (IG), Factor VIII concentrates of plasma origin (pdFVIII), pdFVIII and von Willebrand Factor (vWF) in combination concentrates (pdFVIII/vWF), and fibrinogen.

In 2018, the distribution of PDMPs manufactured by CSL Behring and returned to NAIP Regions was recorded for the first time. Pending the launching of other tenders for the assignment of the plasma toll-fractionation service, the other Regions were still affiliated exclusively with the company Kedrion SpA (hereinafter Kedrion), whose contract provided for the production of the following PDMPs: albumin, IVIG, Anti-Thrombin (AT), pdFVIII, plasma-derived Factor IX concentrates (pdFIX), and 3-factor Prothrombin Complex Concentrates (3F-PCCs).

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 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).

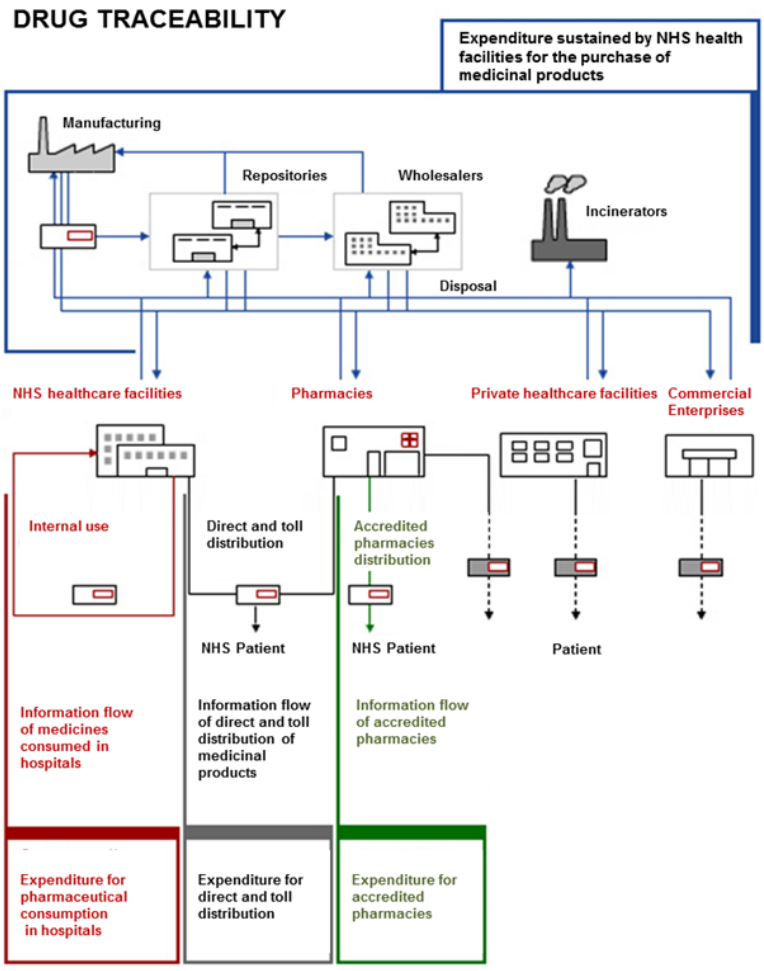

Figure 1. The drug traceability system in Italy (adapted by the CNS on data from www.salute.gov.it)

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).

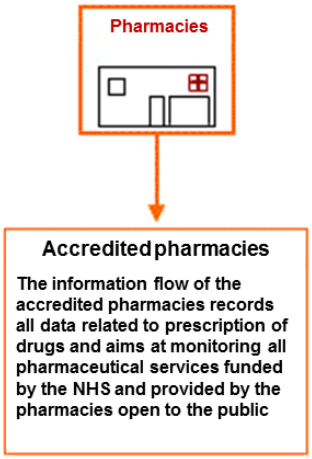

Figure 2. Scope of the information flow of accredited pharmacies (adapted by the CNS on data from www.salute.gov.it)

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.

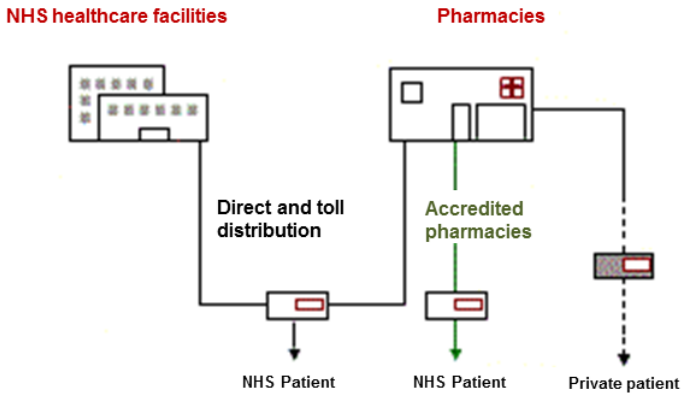

Figure 3. Medicinal products information flow (adapted by theCNS on data from www.salute.gov.it)

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.

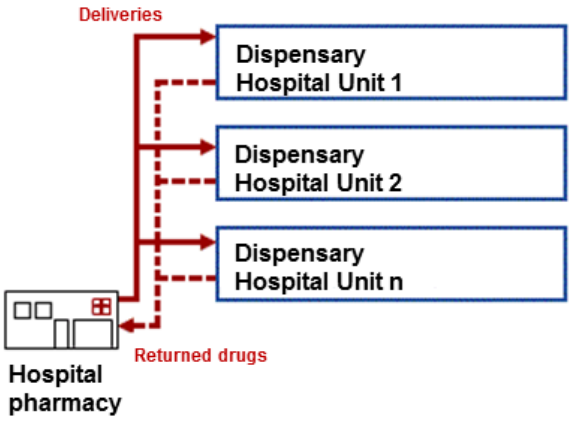

Figure 4. Information flow of medicines consumed in hospitals (adapted by the CNS on data from www.salute.gov.it)

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, 2018-2019 (adapted by the CNS on data from ISTAT, 31/8/2020)

Region	2018	2019
Abruzzo	1,315,196	1,311,580
Aosta Valley	126,202	125,666
AP Bolzano	527,750	531,178
AP Trento	539,898	541,098
Apulia	4,048,242	4,029,053
Basilicata	567,118	562,869
Calabria	1,956,687	1,947,131
Campania	5,826,860	5,801,692
Emilia-Romagna	4,452,629	4,459,477
Friuli V. Giulia	1,215,538	1,215,220
Latium	5,896,693	5,879,082
Liguria	1,556,981	1,550,640
Lombardy	10,036,258	10,060,574
Marche	1,531,753	1,525,271
Molise	308,493	305,617
Piedmont	4,375,865	4,356,406
Sardinia	1,648,176	1,639,591
Sicily	5,026,989	4,999,891
Tuscany	3,736,968	3,729,641
Umbria	884,640	882,015
Veneto	4,905,037	4,905,854
Italy	60,483,973	60,359,546

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 2018 to June 2019. 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 2019 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 31/12/2018, and applying any eventual discounts provided for by Law 662/1996 (13), amended by Law 122/2010 (14).

As far as albumin, IVIG and pdFVIII, are concerned, as identified by 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, 31/12/2019)

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 2018-2019 with the variations in percentage, both at national and regional levels.

In 2019, the national demand for this ingredient was about 35,493 kilograms (Table 6), equal to 588 grams per 1,000 population. The two Regions with the highest standardised demand were Sardinia and Campania with values exceeding eight hundred grams (857.6 and 839.1 grams, respectively). The Regions with the lowest demand were the AP of Trento and the AP of Bolzano, with about 314 and 321 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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	830,828	631.7	788,006	600.8	-4.9
Aosta Valley	81,970	649.5	54,740	435.6	-32.9
APBolzano	179,885	340.9	170,735	321.4	-5.7
APTrento	181,903	336.9	169,975	314.1	-6.8
Apulia	2,117,368	523.0	2,149,115	533.4	2.0
Basilicata	356,763	629.1	374,618	665.6	5.8
Calabria	1,088,155	556.1	1,177,356	604.7	8.7
Campania	5,084,775	872.6	4,868,173	839.1	-3.8
E.-Romagna	2,546,528	571.9	2,719,348	609.8	6.6
Friuli V. Giulia	465,298	382.8	485,748	399.7	4.4
Latium	3,227,708	547.4	3,640,838	619.3	13.1
Liguria	667,428	428.7	681,253	439.3	2.5
Lombardy	6,363,728	634.1	6,558,565	651.9	2.8
Marche	743,548	485.4	677,360	444.1	-8.5
Molise	225,550	731.1	215,810	706.1	-3.4
Piedmont	1,502,955	343.5	1,524,778	350.0	1.9
Sardinia	1,428,023	866.4	1,406,075	857.6	-1.0
Sicily	3,340,583	664.5	3,593,925	718.8	8.2
Tuscany	1,710,363	457.7	1,418,978	380.5	-16.9
Umbria	485,428	548.7	487,178	552.3	0.7
Veneto	2,314,323	471.8	2,331,200	475.2	0.7
Italy	34,943,103	577.7	35,493,769	588.0	1.8

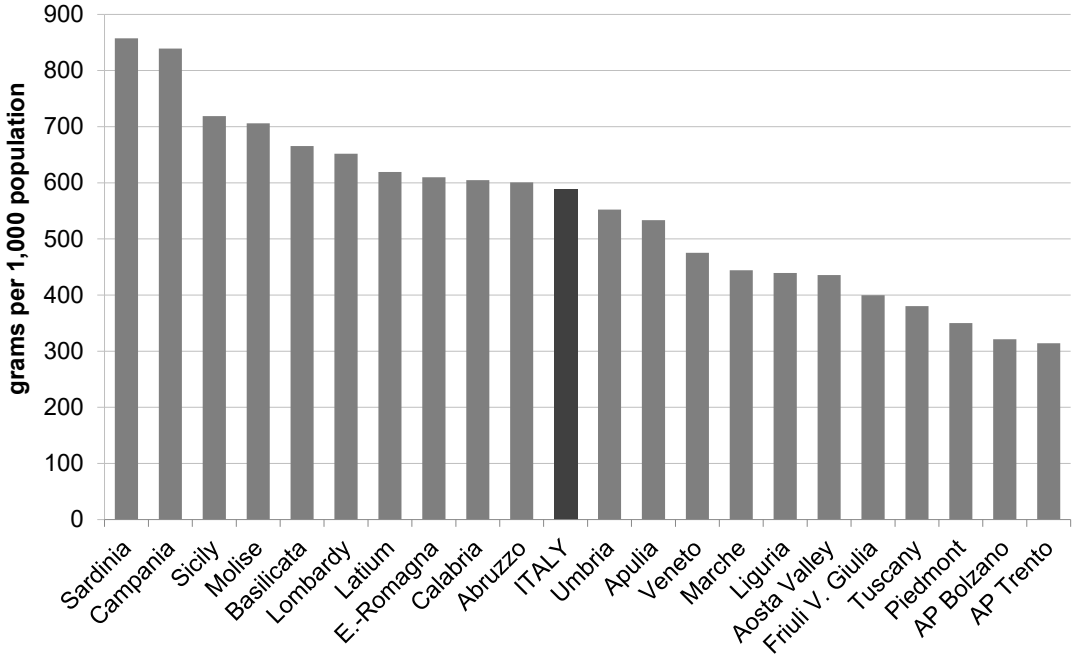

Figure 5. Total and regional demand (public and private) for albumin, expressed in grams per 1,000 population, 2019 (adapted by the CNS on data from the Traceability information flow)

In this two-year period, the total standardised demand for albumin showed a constant trend with respect to previous years (+1.8% compared to 2018) (17). The regions where the containment of use was most evident are Aosta Valley (-33%), Tuscany (-17%). Latium (+13%), Emilia-Romagna (+7%) and Calabria (+9%) are the Regions where demand shows the greatest growth.

Figure 6 highlights the eight Regions with a higher demand compared to national demand, with values equal to or greater than 40% for two of them.

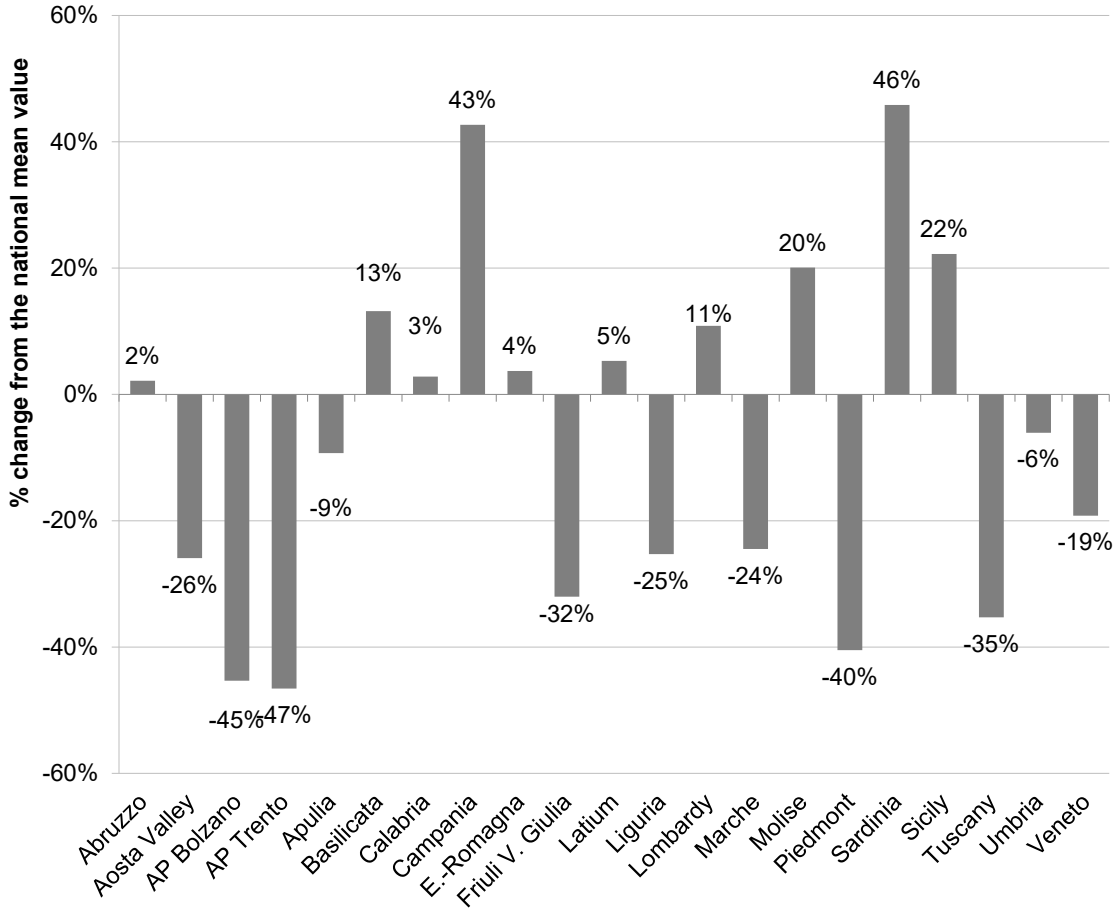

Figure 6. Percentage change from the national mean value of standardised regional demand for human albumin in 2019 (adapted by the CNS on data from the Traceability information flow)

Figure 7 shows the standardised regional demand for albumin recorded in 2019 per distribution channel (public pharmacies compared to other facilities), as shown by the drug Traceability system (18). In 2019, about 9% of the national demand – approximately 3,139 kilograms – was distributed through public pharmacies.

Pharmacies as a distribution channel were particularly used in Campania and Calabria, where they accounted for 24% 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 16% of the total regional demand. While in the other Regionsthey were rarely used (<10%).

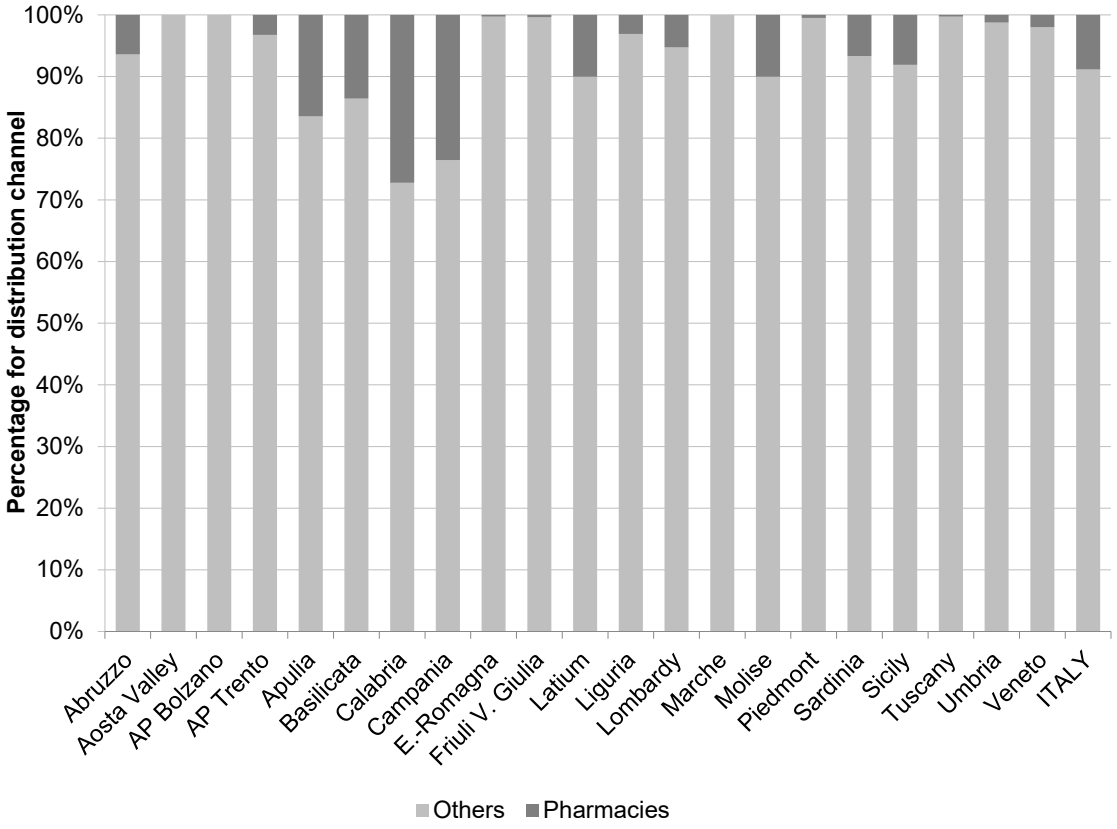

Figure 7. Standardised regional demand for albumin recorded per distribution channel, 2019 (adapted by the CNS on data from the Traceability information flow)

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

Immunoglobulins (IGs) are used in substitutive immunodeficiency therapy and in the treatment of autoimmune diseases or systemic inflammatory processes. However, in clinical practice they are used much more extensively and their use is not always fully justified by the available evidence in scientific literature. Since 2007, both soluble IG preparations for subcutaneous/intramuscular infusion (SC/IM) and those for intravenous use (IntraVenous, IV) (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, 31/12/2019)

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)
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
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
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

AIC code	Brand name	g	Manufacturer	NHS class
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
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

AIC code	Brand name	g	Manufacturer	NHS class
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
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 2018-2019 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 2019, the total national demand for IGs was 6,408,888 grams, equal to 106.2 grams per 1,000 population (Table 8). The three Regions with the highest standardised demand per 1,000 population were Aosta Valley, Tuscany and Liguria, with around 192, 183 and 154 grams, respectively. The demand was lower in Sardinia, Calabria and Basilicata, where it was between 60 and 63 grams per 1,000 population. The demand for these PDMPs rose sharply in the two-year period 2018-2019 (+8%), especially for the SC/IM formulations (+17%), featuring notable differences from one Region to another. This trend was not observed in Calabria, Basilicata and Molise where demand remained substantially stable. However, a noteworthy decrease occurred in Friuli Venezia Giulia Region (-14%).

Figure 8 shows which Regions tended to use more SC/IM formulations and which preferred IV ones. More SC/IM formulations were used in Umbria (31.7%), Calabria (29.4%) and Basilicata (32.3%) while fewer were used in Friuli Venezia Giulia, Sardinia and Molise (<8%). At national level, the demand for SC/IM IGs stood at 21% of the total demand for IGs (19% in 2018).

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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	119,245	90.7	123,896	94.5	4.2
Aosta Valley	20,623	163.4	24,098	191.8	17.3
AP Bolzano	44,385	84.1	46,847	88.2	4.9
AP Trento	42,183	78.1	51,816	95.8	22.6
Apulia	451,209	111.5	464,367	115.3	3.4
Basilicata	35,668	62.9	35,573	63.2	0.5
Calabria	118,232	60.4	118,200	60.7	0.5
Campania	408,658	70.1	448,300	77.3	10.2
E.-Romagna	466,126	104.7	506,953	113.7	8.6
Friuli V. Giulia	137,063	112.8	117,266	96.5	-14.4
Latium	597,037	101.2	671,547	114.2	12.8
Liguria	203,291	130.6	238,587	153.9	17.8
Lombardy	865,107	86.2	953,728	94.8	10.0
Marche	209,528	136.8	217,951	142.9	4.5
Molise	45,757	148.3	45,059	147.4	-0.6
Piedmont	497,587	113.7	526,250	120.8	6.2
Sardinia	95,110	57.7	99,427	60.6	5.1
Sicily	335,524	66.7	348,393	69.7	4.4
Tuscany	638,183	170.8	682,203	182.9	7.1
Umbria	94,805	107.2	101,526	115.1	7.4
Veneto	508,498	103.7	586,903	119.6	15.4
Italy	5,933,819	98.1	6,408,888	106.2	8.2

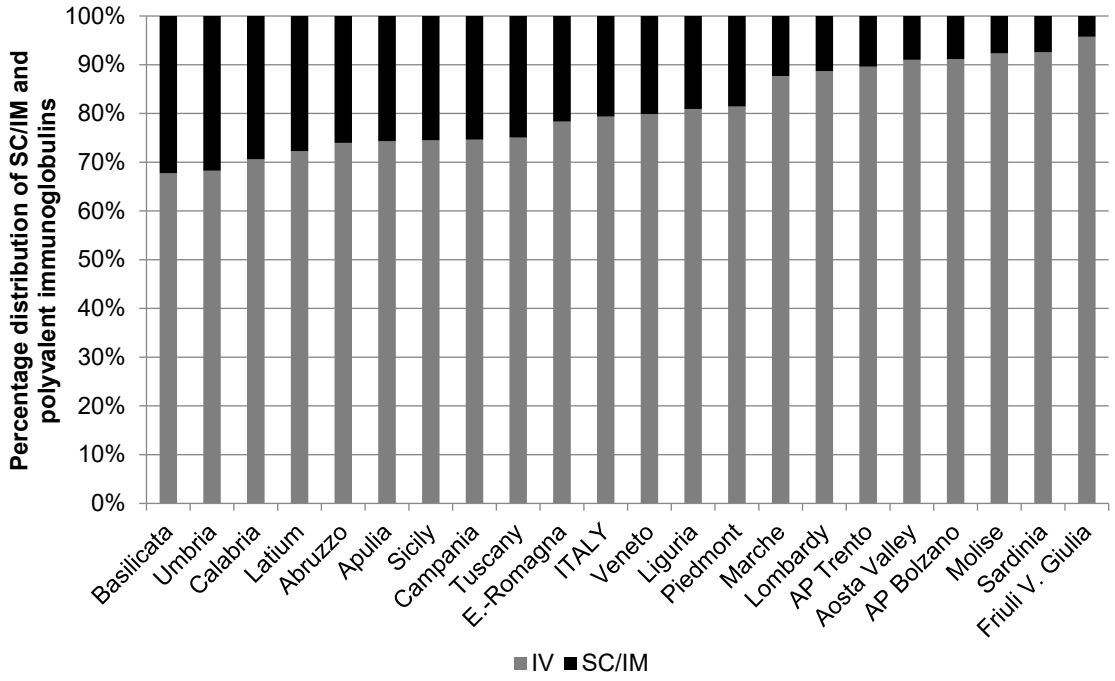

Figure 8. Total standardised demand (public and private) per administration of immunoglobulins (percentage on total), by Region, 2019 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for subcutaneous use

In 2019, the total demand for SC/IM IGs reached about 1,322,527 grams (21.9 grams per 1,000 population), with an increase of 17% compared to 2018 (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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	29,696	22.6	32,252	24.6	8.9
Aosta Valley	1,944	15.4	2,163	17.2	11.7
AP Bolzano	2,740	5.2	4,151	7.8	50.5
AP Trento	3,293	6.1	5,386	10.0	63.2
Apulia	111,664	27.6	119,373	29.6	7.4
Basilicata	9,683	17.1	11,480	20.4	19.5
Calabria	32,970	16.8	34,748	17.8	5.9
Campania	89,513	15.4	113,749	19.6	27.6
E.-Romagna	94,088	21.1	109,782	24.6	16.5
Friuli V. Giulia	9,231	7.6	5,008	4.1	-45.7
Latium	161,603	27.4	186,314	31.7	15.6
Liguria	39,621	25.4	45,487	29.3	15.3
Lombardy	104,276	10.4	107,879	10.7	3.2
Marche	23,693	15.5	26,846	17.6	13.8
Molise	4,697	15.2	3,459	11.3	-25.7
Piedmont	81,344	18.6	97,821	22.5	20.8
Sardinia	6,220	3.8	7,397	4.5	19.5
Sicily	70,441	14.0	88,861	17.8	26.8
Tuscany	131,107	35.1	170,137	45.6	30.0
Umbria	30,445	34.4	32,231	36.5	6.2
Veneto	94,006	19.2	118,001	24.1	25.5
Italy	1,132,275	18.7	1,322,527	21.9	17.0

The regional demands proved diversified where the highest values, between 46 and 29 grams per 1,000 population, were recorded in Tuscany, Umbria, Apulia and Liguria. While the lowest values were recorded in Friuli Venezia Giulia, Sardinia and in AP of Bolzano and were equal to 4, 5 and 8 grams per 1,000 population respectively (Figure 9).

In Abruzzo, Emilia-Romagna, Latium, Liguria, Piedmont, Apulia, Tuscany, Umbria and Veneto, a higher total demand compared to national demand was recorded (range: 2-108%) (Figure 10).

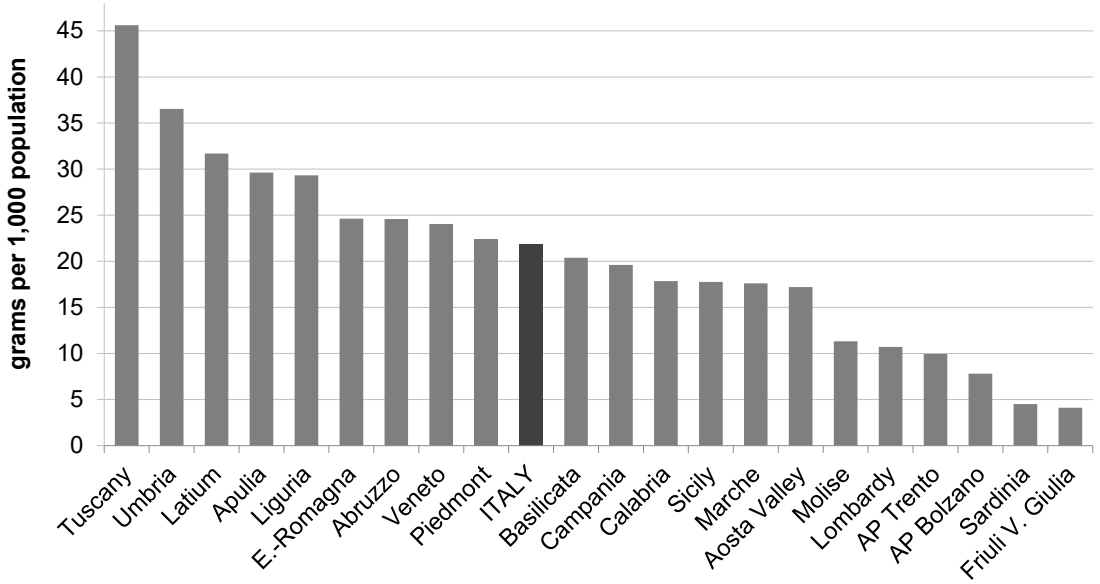

Figure 9.Total and regional demand (public and private) for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams per 1,000 population, 2019 (adapted by the CNS on data from the Traceability information flow)

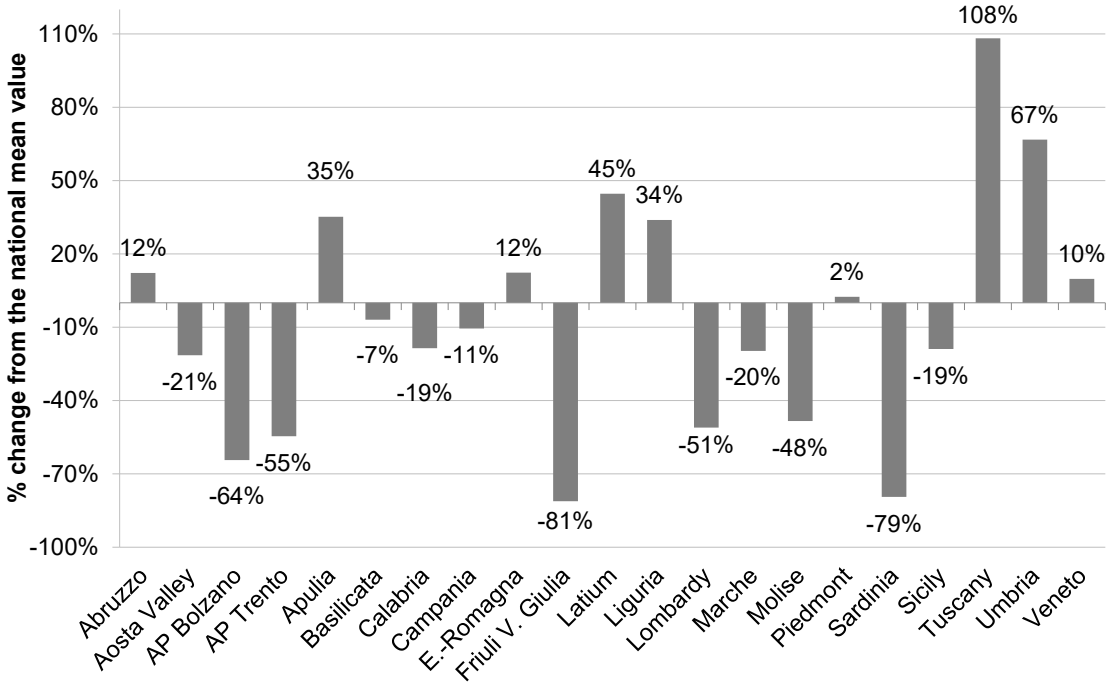

Figure 10. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for subcutaneous/ intramuscular use in 2019 (adapted by the CNS on data from the Traceability information flow)

Normal human immunoglobulins for intravenous use

Finally, Table 10 reports on the total and standardised demands for IG for intravenous use in 2018-2019.

Even, in this case, a general upward trend (about +6%) was observed, while it was not confirmed in Friuli Venezia Giulia, Basilicata, Sicily and Calabria. However, in some of these Regions (Basilicata, Sicily and Calabria), 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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	89,549	68.1	91,644	69.9	2.6
Aosta Valley	18,679	148.0	21,935	174.5	17.9
AP Bolzano	41,645	78.9	42,696	80.4	1.9
AP Trento	38,890	72.0	46,430	85.8	19.1
Apulia	339,545	83.9	344,993	85.6	2.1
Basilicata	25,985	45.8	24,093	42.8	-6.6
Calabria	85,262	43.6	83,452	42.9	-1.6
Campania	319,145	54.8	334,551	57.7	5.3
E.-Romagna	372,038	83.6	397,171	89.1	6.6
Friuli V. Giulia	127,833	105.2	112,258	92.4	-12.2
Latium	435,434	73.8	485,232	82.5	11.8
Liguria	163,670	105.1	193,100	124.5	18.5
Lombardy	760,831	75.8	845,848	84.1	10.9
Marche	185,835	121.3	191,105	125.3	3.3
Molise	41,060	133.1	41,600	136.1	2.3
Piedmont	416,243	95.1	428,430	98.3	3.4
Sardinia	88,890	53.9	92,030	56.1	4.1
Sicily	265,083	52.7	259,532	51.9	-1.6
Tuscany	507,076	135.7	512,067	137.3	1.2
Umbria	64,360	72.8	69,295	78.6	8.0
Veneto	414,492	84.5	468,902	95.6	13.1
Italy	4,801,544	79.4	5,086,361	84.3	6.2

Figure 11 shows the standardised regional demand for IVIGs in 2019 as recorded by the drug Traceability system. The highest demand for IVIGs was recorded in Aosta Valley,Tuscany and Molise with volumes ranging between 136 and 174 grams per 1,000 population (+107%, +63% and +62% respectively, compared to the national mean value – Figure 12). The Regions where the standardized demand is lower were Basilicata and Calabria with recorded volumes of 43 grams per 1,000 population.

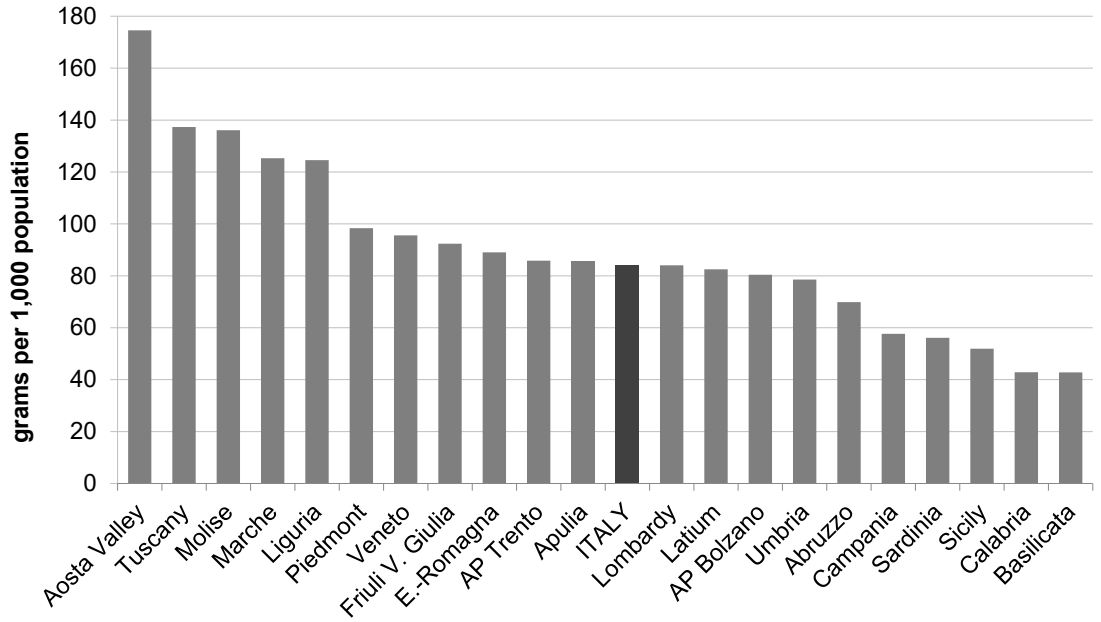

Figure 11.Total and regional demand (public and private) for normal human immunoglobulins for intravenous use, expressed in grams per 1,000 population, 2019 (adapted by the CNS on data from the Traceability information flow)

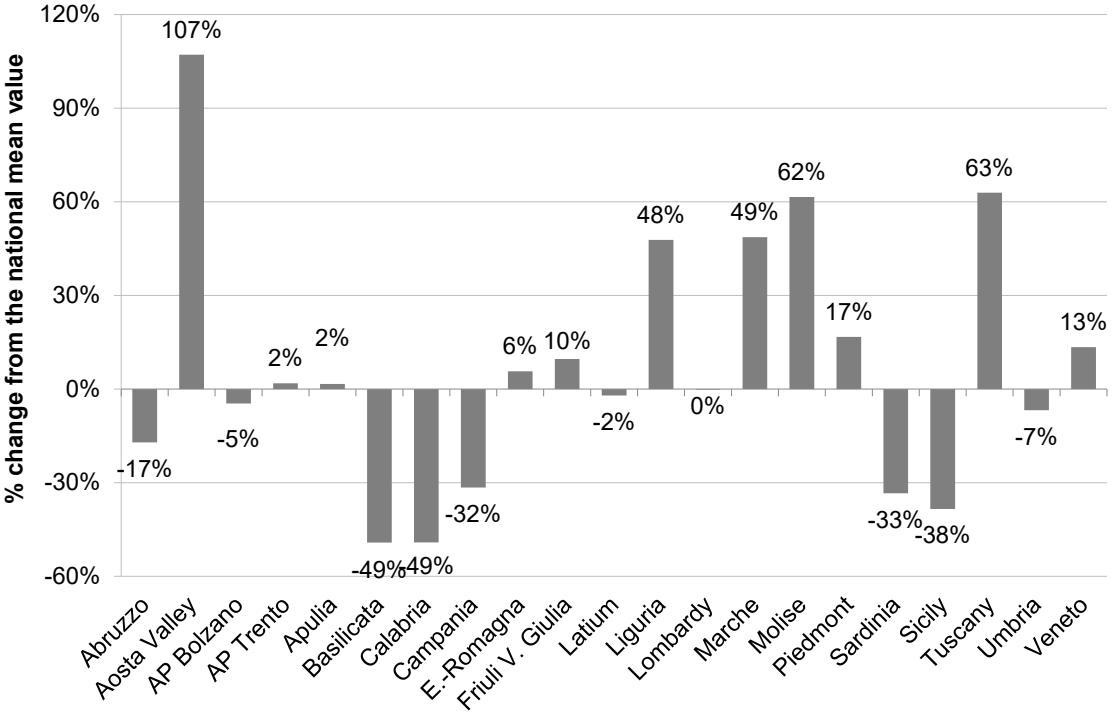

Figure 12. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for intravenous use in 2019 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2019)

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 2018-2019 with the relative percentage changes at national and regional levels.

In 2019, total AT demand was 117,966,500 IUs, equal to 2.0 IUs *per capita*, highlighting an increase compared to the consumption recorded in previous years (+2.4% compared to 2018). Conversely, in three Regions there was a significant upword trend in its use [range: Umbria (+47.6%) – Sardinia (+32.3%)]. The Region in which the containment of use was most evident is the Aosta Valley (-47%).

Figure 13 shows the regional and national standardised demand for AT in 2019. The Regions with the highest *per capita* demand were Calabria, Sicily, Latium and Molise, with a demand of 5.3 IUs for the first one and 3.5, 3.4 and 3.2 IUs respectively for the others Regions. The lowest demand, between 0.4 and 0.6 IUs *per capita*, was recorded in the AP of Trento, the 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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,458,000	1.9	1,408,500	1.1	-42.5
Aosta Valley	363,000	2.9	192,000	1.5	-46.9
AP Bolzano	250,000	0.5	202,000	0.4	-19.7
APTrento	200,000	0.4	200,000	0.4	-0.2
Apulia	6,907,000	1.7	8,360,500	2.1	21.6
Basilicata	1,556,000	2.7	1,170,000	2.1	-24.2
Calabria	7,806,000	4.0	10,402,500	5.3	33.9
Campania	17,832,000	3.1	16,209,000	2.8	-8.7
E.-Romagna	2,826,500	0.6	2,732,000	0.6	-3.5
Friuli V. Giulia	3,253,000	2.7	2,634,000	2.2	-19.0
Latium	19,004,500	3.2	20,023,500	3.4	5.7
Liguria	2,374,000	1.5	2,508,500	1.6	6.1
Lombardy	8,020,500	0.8	8,671,500	0.9	7.9
Marche	2,665,000	1.7	2,917,000	1.9	9.9
Molise	1,225,500	4.0	972,000	3.2	-19.9
Piedmont	6,410,500	1.5	6,898,000	1.6	8.1
Sardinia	1,507,000	0.9	1,984,000	1.2	32.3
Sicily	17,713,000	3.5	17,292,500	3.5	-1.8
Tuscany	6,434,000	1.7	6,400,500	1.7	-0.3
Umbria	534,000	0.6	786,000	0.9	47.6
Veneto	6,046,500	1.2	6,002,500	1.2	-0.7
Italy	115,386,000	1.9	117,966,500	2.0	2.4

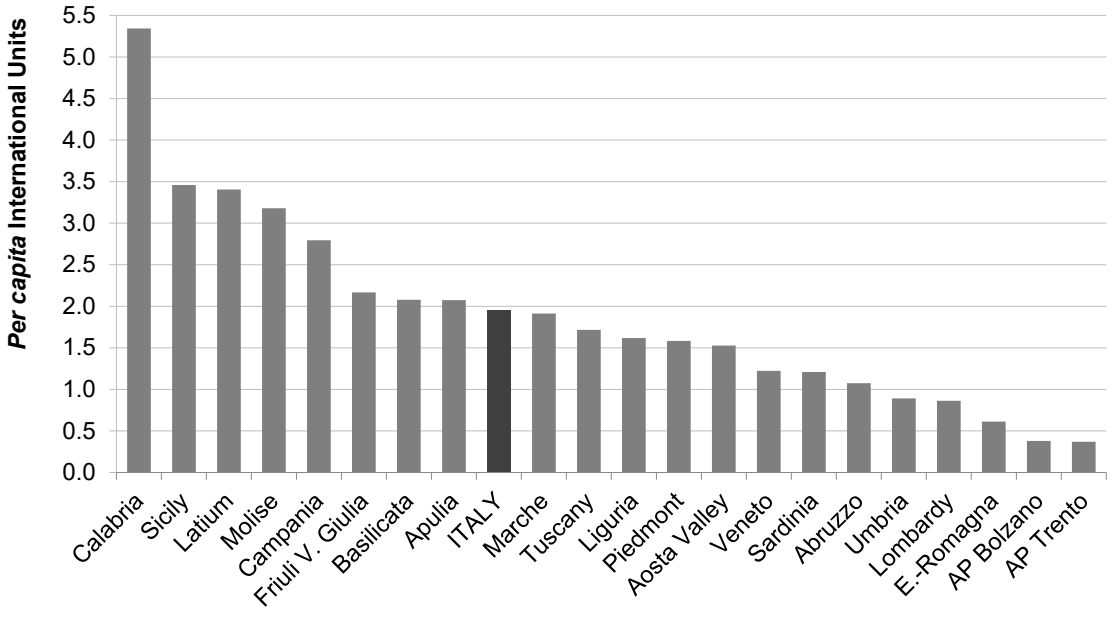

Figure 13. Total and regional demand (public and private) for antithrombin, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

Figure 14 shows the difference between the regional *per capita* percentage and the national mean value for the year 2019.

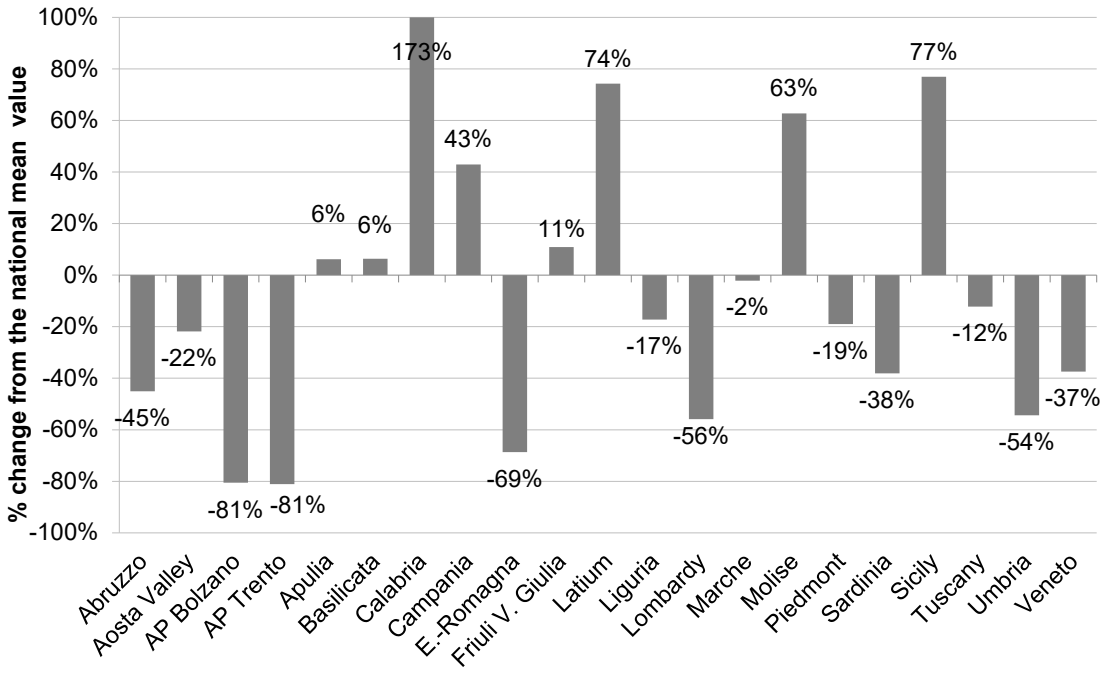

Figure 14. Percentage change from the national mean value of standardised regional demand for antithrombin in 2019 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2019)

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, 31/12/2019)

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, 31/12/2019)

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	C(nn)
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	C(nn)
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	C(nn)
047418025	JIVI* EV 500 IU + FL SOLV 2,5 mL + SIR	500	BAYER AG	C(nn)
048083012	ESPEROCT* EV 500 IU + FL 4 mL + SIR	500	NOVO NORDISK A/S	C(nn)
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	C(nn)
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	C(nn)
047418037	JIVI* EV 1000 IU + FL 2,5 mL + SIR	1000	BAYER AG	C(nn)
048083024	ESPEROCT* EV 1000 IU+ FL 4 mL + SIR	1000	NOVO NORDISK A/S	C(nn)
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	C(nn)
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	C(nn)
047418049	JIVI* EV 2000 IU + FL 2,5 mL + SIR	2000	BAYER AG	C(nn)
048083048	ESPEROCT* EV 2000 IU+ FL 4 mL + SIR	2000	NOVO NORDISK A/S	C(nn)
044563082	ELOCTA*IV 1FL 3000IU+SIR PRERI	3000	SOBI Srl	A
047418052	JIVI* EV 3000 IU + FL 2,5 mL + SIR	3000	BAYER AG	C(nn)
048083051	ESPEROCT* EV 3000 IU+ FL 4 mL + SIR	3000	NOVO NORDISK A/S	C(nn)
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 611,800,250 IUs in 2019 (Table 16); of these, about a fifth (18% of the total - 111,059,750 IUs) were human plasma-derived (Figure 15). The tendency to use pdFVIII varied significantly from one Region to another ranging from 1% in Aosta Valley to 34% in AP of Bolzano. In 2019, the total FVIII demand *per capita* (plasma-derived and recombinant) was 10 IUs with an increase of 5.5% compared to 2018.

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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	10,392,750	7.9	14,686,500	11.2	41.7
Aosta Valley	844,000	6.7	858,000	6.8	2.1
AP Bolzano	3,219,500	6.1	3,553,750	6.7	9.7
AP Trento	3,066,500	5.7	3,715,500	6.9	20.9
Apulia	49,464,250	12.2	49,264,750	12.2	0.1
Basilicata	5,501,000	9.6	6,830,500	12.1	25.8
Calabria	25,121,750	12.8	30,021,500	15.4	20.1
Campania	72,703,250	12.5	74,252,750	12.8	2.6
E.-Romagna	34,100,000	7.7	39,877,750	8.9	16.8
Friuli V. Giulia	7,825,000	6.4	4,550,500	3.7	-41.8
Latium	84,913,500	14.4	97,726,750	16.6	15.4
Liguria	12,154,500	7.8	13,287,000	8.6	9.8
Lombardy	75,610,250	7.5	79,028,750	7.9	4.3
Marche	10,459,000	6.8	10,446,000	6.8	0.3
Molise	3,488,000	11.3	2,812,500	9.2	-18.6
Piedmont	45,210,250	10.3	43,113,250	9.9	-4.2
Sardinia	13,950,000	8.5	13,258,500	8.1	-4.5
Sicily	49,959,500	9.9	49,252,250	9.9	-0.6
Tuscany	27,082,000	7.2	26,442,000	7.1	-2.2
Umbria	7,543,500	8.5	6,840,500	7.8	-9.0
Veneto	38,850,500	7.9	41,981,250	8.6	8.0
Italy	581,459,000	9.6	611,800,250	10.1	5.5

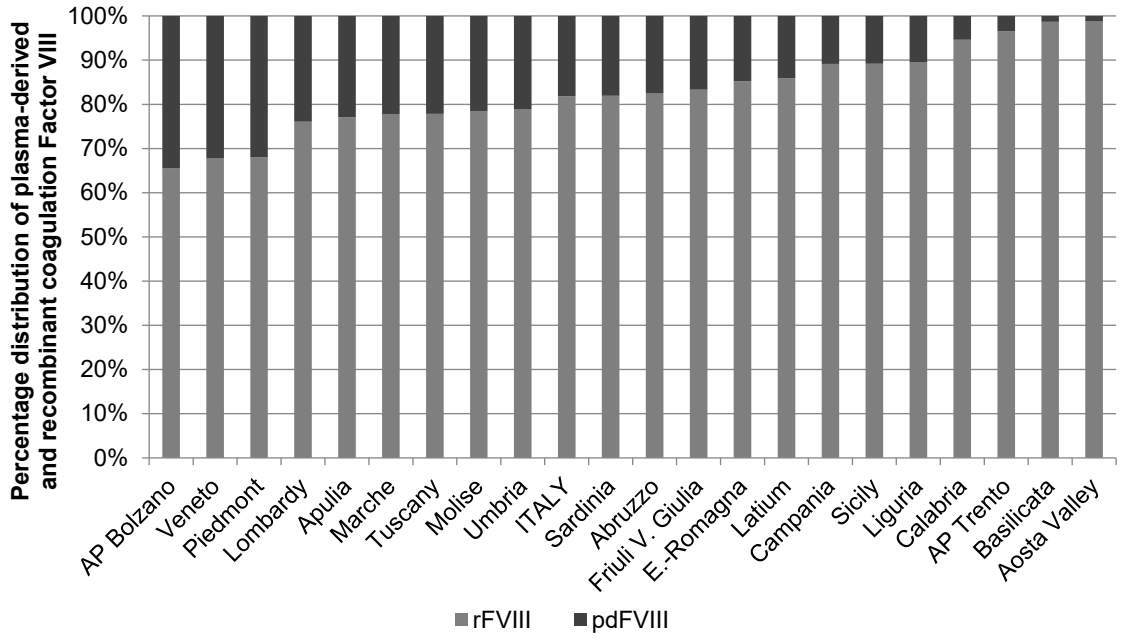

Figure 15. Percentage distribution of plasma-derived and recombinant coagulation Factor VIII, by Region, 2019 (adapted by the CNS on data from the Traceability information flow)

The regional *per capita* demand shows significant fluctuations ranging from about 3.7 IU in Friuli Venezia Giulia to about 17 IU in Lazio (Figure 16).

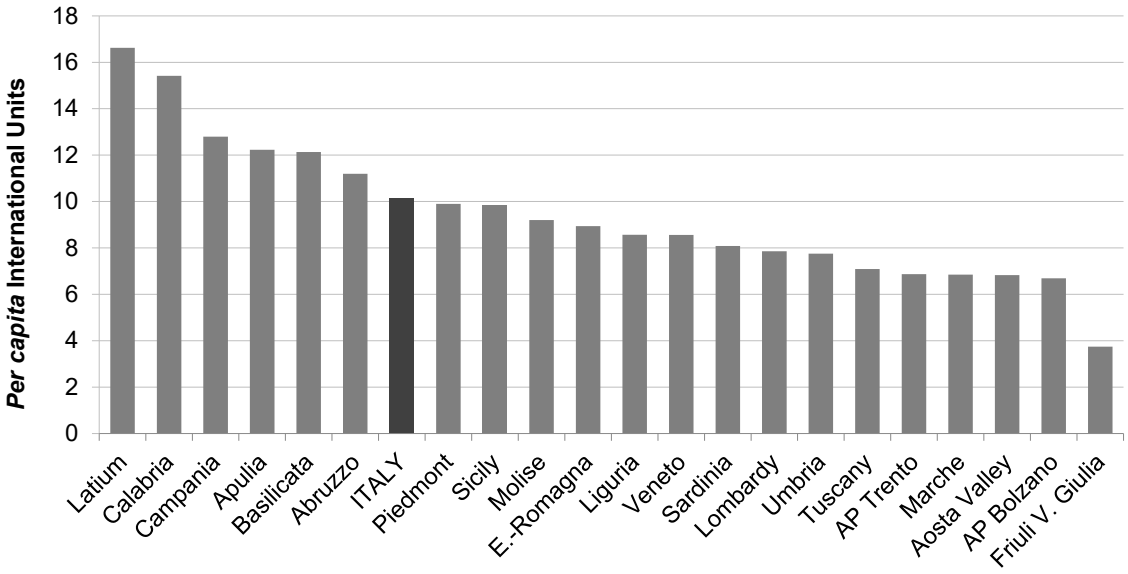

Figure 16. Total and regional demand (public and private) for coagulation Factor VIII, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

The most significant increases in standardised regional demand were observed in Abruzzo and Basilicata, where use increased by 42% and 26%, 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).

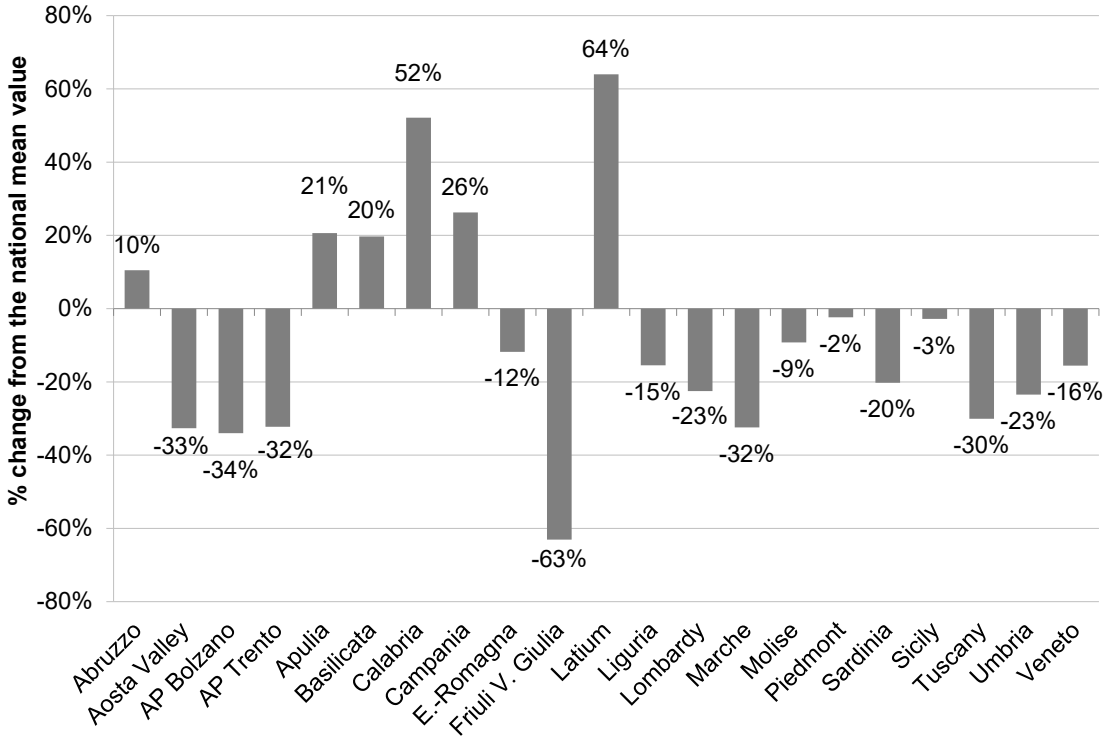

Figure 17. Percentage change from the national mean value of standardised regional demand for coagulation Factor VIII in 2019 (adapted by the CNS on data from the Traceability information flow)

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

In 2019, the national demand for pdFVIII was about 18% – equivalent to 111,059,750 IUs – of the total demand. There is a downward trend of 8.3% compared to the 2018 value and a standardized total demand of 1.8 IU *per capita* (Table 17). *Per capita* demand varied significantly with the highest volumes in Piedmont (3.2 IUs *per capita*), Apulia and Veneto (2.8 IUs *per capita*) and Latium (2.3 IUs *per capita*); the corresponding percentage changes between the aforementioned regional values and the Italian mean value were of +72%, +52%, +50% e +27%, respectively. The lowest volumes (below 1 IU *per capita*) were recorded in Aosta Valley, the AP of Trento, Basilicata, Liguria and Friuli Venezia Giulia (Figures 18 and 19).

The national trend decreased in many Italian Regions (range: -75%; -3.4%) with the exception of Abruzzo, Calabria, AP of Bolzano, AP of Trento, Sicily, Aosta Valley and Veneto, where there were increases of between 3% e il 235%.

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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,560,000	1.2	2,577,000	2.0	65.6
Aosta Valley	3,000	0.0	10,000	0.1	234.8
AP Bolzano	1,180,000	2.2	1,226,000	2.3	3.2
AP Trento	67,000	0.1	128,000	0.2	90.6
Apulia	11,731,500	2.9	11,284,500	2.8	-3.4
Basilicata	402,000	0.7	92,000	0.2	-75.1
Calabria	1,531,000	0.8	1,614,500	0.8	6.0
Campania	9,242,000	1.6	8,072,500	1.4	-12.3
E.-Romagna	6,389,750	1.4	5,900,250	1.3	-7.8
Friuli V. Giulia	1,313,500	1.1	759,000	0.6	-41.9
Latium	17,220,000	2.9	13,778,500	2.3	-19.7
Liguria	1,694,000	1.1	1,401,000	0.9	-17.0
Lombardy	19,623,000	2.0	18,924,000	1.9	-3.8
Marche	2,565,000	1.7	2,331,000	1.5	-8.7
Molise	819,000	2.7	605,000	2.0	-25.4
Piedmont	17,268,500	3.9	13,798,000	3.2	-19.7
Sardinia	4,213,000	2.6	2,395,000	1.5	-42.9
Sicily	5,049,000	1.0	5,324,000	1.1	9.6
Tuscany	6,672,000	1.8	5,857,000	1.6	-12.0
Umbria	1,567,000	1.8	1,441,000	1.6	-7.8
Veneto	11,506,500	2.3	13,541,500	2.8	17.7
Italy	121,616,750	2.0	111,059,750	1.8	-8.3

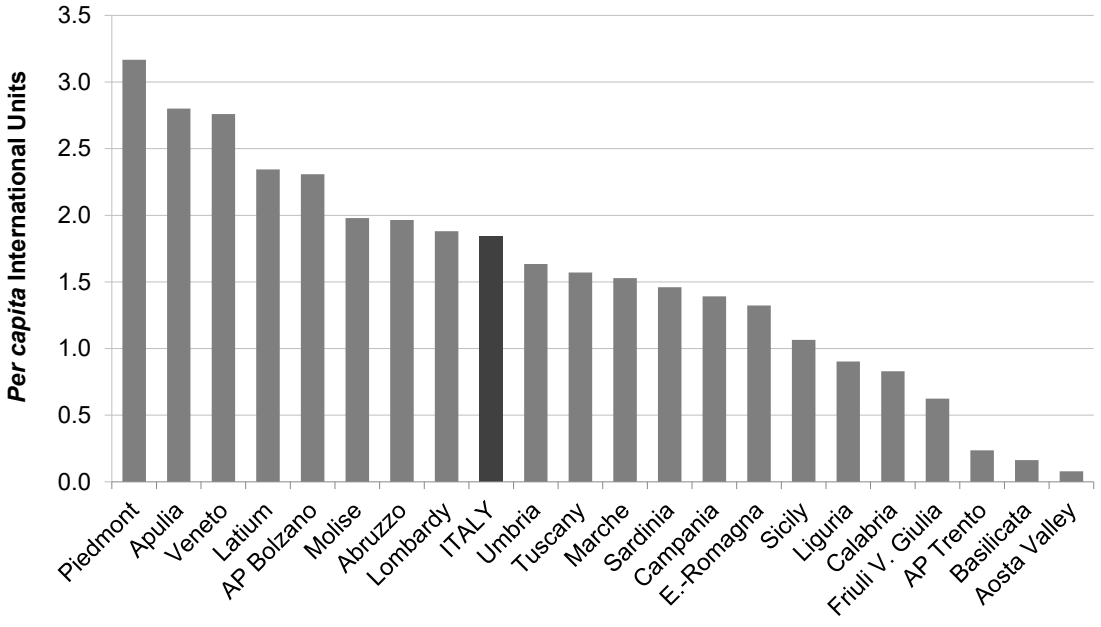

Figure 18. Total and regional demand (public and private) for plasma-derived coagulation Factor VIII, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

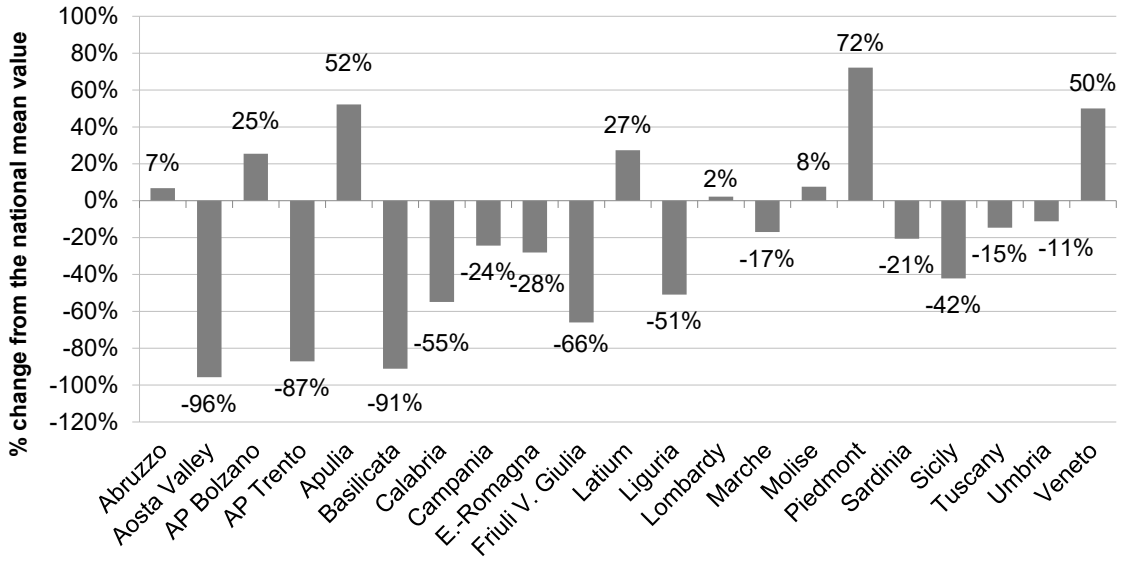

Figure 19. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor VIII in 2019 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor VIII (B02BD02)

In 2019, the total demand for plasma-derived FVIII was 60,571,000 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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	43,000	0.0	60,000	0.0	39.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	330,000	0.6	352,000	0.7	6.0
AP Trento	13,000	0.0	17,000	0.0	30.5
Apulia	5,046,000	1.2	4,543,000	1.1	-9.5
Basilicata	85,000	0.1	52,000	0.1	-38.4
Calabria	777,000	0.4	507,000	0.3	-34.4
Campania	5,130,000	0.9	3,846,000	0.7	-24.7
E.-Romagna	2,053,000	0.5	2,881,000	0.6	40.1
Friuli V. Giulia	911,000	0.7	576,000	0.5	-36.8
Latium	8,765,000	1.5	4,713,000	0.8	-46.1
Liguria	864,000	0.6	992,000	0.6	15.3
Lombardy	14,212,000	1.4	12,987,000	1.3	-8.8
Marche	1,835,000	1.2	1,792,000	1.2	-1.9
Molise	608,000	2.0	200,000	0.7	-66.8
Piedmont	11,613,000	2.7	10,127,000	2.3	-12.4
Sardinia	2,738,000	1.7	869,000	0.5	-68.1
Sicily	811,000	0.2	1,017,000	0.2	26.1
Tuscany	4,317,000	1.2	3,582,000	1.0	-16.9
Umbria	534,000	0.6	496,000	0.6	-6.8
Veneto	9,151,000	1.9	10,962,000	2.2	19.8
Italy	69,836,000	1.2	60,571,000	1.0	-13.1

The mean national demand *per capita* was about 1.0 IUs, with a range amongst Regions of 0.03 IUs and 2.3 IUs.

The Regions with the highest *per capita* consumption of pdFVIII were Piedmont (2.3 IUs) and Veneto (2.2 IUs). The lowest utilisation was observed in AP of Trento and in Abruzzo (0.03 IUs and 0.04 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.

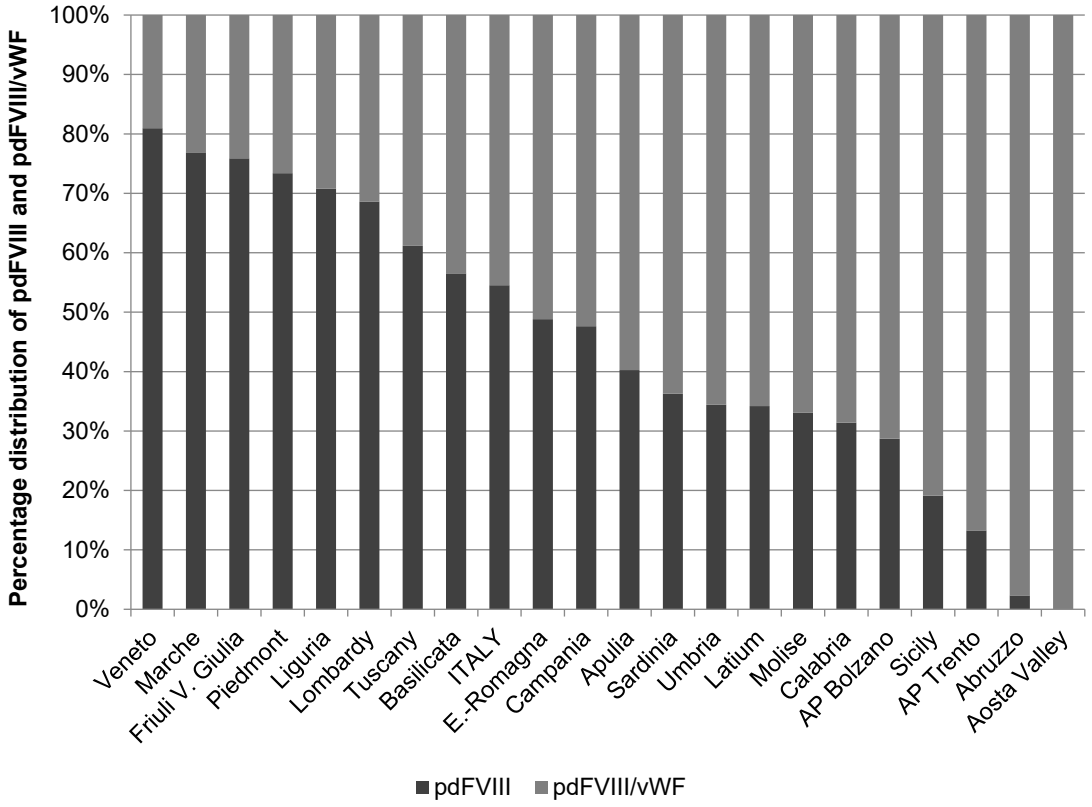

Figure 20. Percentage distribution of plasma-derived FVIII and plasma-derived FVIII/von Willebrand in combination, by Region, 2019 (adapted by the CNS on data from the Traceability information flow)

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

In 2019, the national demand for FVIII and von Willebrand Factor in combination was 50,488,750 IUs, about 43% of the total demand for pdFVIII. The mean national demand *per capita* was 0.8 IUs, with a range between Regions of 0.1 IUs (Basilicata) and 1.9 IUs (Abruzzo) (Table 19).

The Regions with the highest *per capita* demand of FVIII and von Willebrand Factor in combination were Abruzzo (1.9 IUs), Apulia (1.7 IUs) and AP of Bolzano (1.6 IUs). The lowest utilization equal to 0.1 IU *per capita* was observed in the Aosta Valley and Basilicata (Figure 21).

Table 19. Total demand (public and private) and total standardised demand for FVIII and Von Willebrand Factor in combination, expressed in International Units and International Units *per capita,* and variations in percentage between 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,517,000	1.2	2,517,000	1.9	66.4
Aosta Valley	3,000	0.0	10,000	0.1	234.8
AP Bolzano	850,000	1.6	874,000	1.6	2.2
AP Trento	54,000	0.1	111,000	0.2	105.1
Apulia	6,685,500	1.7	6,741,500	1.7	1.3
Basilicata	317,000	0.5	40,000	0.1	-86.0
Calabria	754,000	0.4	1,107,500	0.6	47.6
Campania	4,112,000	0.7	4,226,500	0.7	3.2
E.-Romagna	4,336,750	1.0	3,019,250	0.7	-30.5
Friuli V. Giulia	402,500	0.3	183,000	0.2	-53.8
Latium	8,455,000	1.4	9,065,500	1.5	7.5
Liguria	830,000	0.5	409,000	0.3	-50.5
Lombardy	5,411,000	0.5	5,937,000	0.6	9.5
Marche	730,000	0.5	539,000	0.4	-25.9
Molise	211,000	0.7	405,000	1.3	93.7
Piedmont	5,655,500	1.3	3,671,000	0.8	-34.8
Sardinia	1,475,000	0.9	1,526,000	0.9	4.0
Sicily	4,238,000	0.8	4,307,000	0.9	6.3
Tuscany	2,355,000	0.6	2,275,000	0.6	-3.2
Umbria	1,033,000	1.2	945,000	1.1	-8.2
Veneto	2,355,500	0.5	2,579,500	0.5	9.5
Italy	51,780,750	0.9	50,488,750	0.8	-1.9

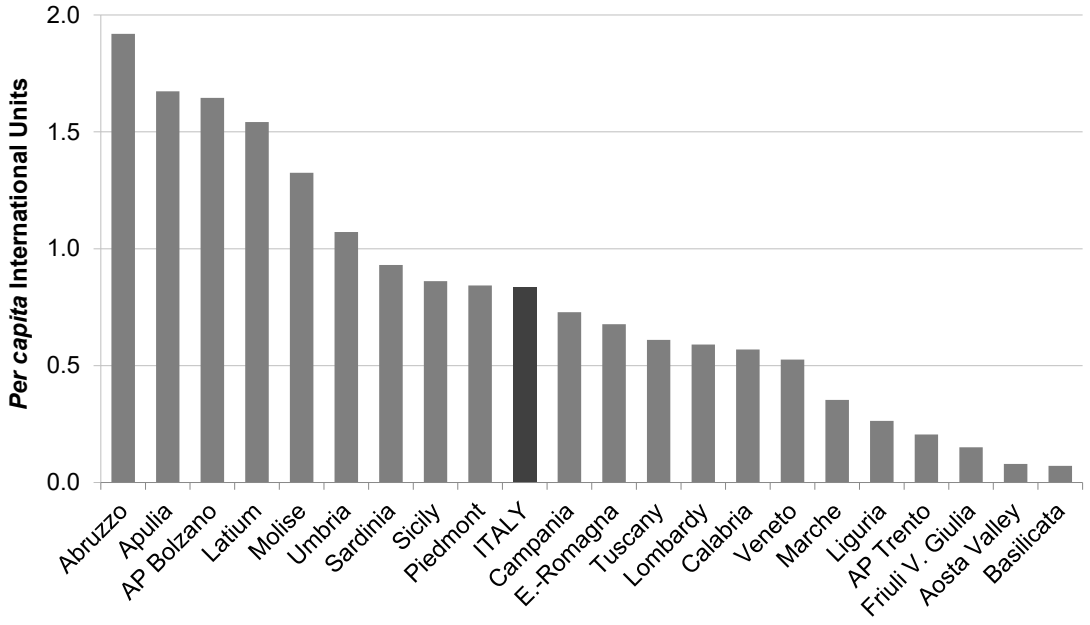

Figure 21. Total and regional demand (public and private) for pdFVIII and von Willebrand Factor in combination, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor VIII

In 2019, the total demand for rFVIII was 500,740,500 IUs, with an increase of approximately 9% compared to 2018.

The mean national demand *per capita* was about 8.3 IUs, with a range between Regions of 3.1 IUs and 14.6 IUs (Table 20).

Table 20. Total demand (public and private) and total standardised demand for recombinant coagulation Factor VIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	8,832,750	6.7	12,109,500	9.2	37.5
Aosta Valley	841,000	6.7	848,000	6.7	1.3
AP Bolzano	2,039,500	3.9	2,327,750	4.4	13.4
AP Trento	2,999,500	5.6	3,587,500	6.6	19.3
Apulia	37,732,750	9.3	37,980,250	9.4	1.1
Basilicata	5,099,000	9.0	6,738,500	12.0	33.2
Calabria	23,590,750	12.1	28,407,000	14.6	21.0
Campania	63,461,250	10.9	66,180,250	11.4	4.7
E.-Romagna	27,710,250	6.2	33,977,500	7.6	22.4
Friuli V. Giulia	6,511,500	5.4	3,791,500	3.1	-41.8
Latium	67,693,500	11.5	83,948,250	14.3	24.4
Liguria	10,460,500	6.7	11,886,000	7.7	14.1
Lombardy	55,987,250	5.6	60,104,750	6.0	7.1
Marche	7,894,000	5.2	8,115,000	5.3	3.2
Molise	2,669,000	8.7	2,207,500	7.2	-16.5
Piedmont	27,941,750	6.4	29,315,250	6.7	5.4
Sardinia	9,737,000	5.9	10,863,500	6.6	12.2
Sicily	44,910,500	8.9	43,928,250	8.8	-1.7
Tuscany	20,410,000	5.5	20,585,000	5.5	1.1
Umbria	5,976,500	6.8	5,399,500	6.1	-9.4
Veneto	27,344,000	5.6	28,439,750	5.8	4.0
Italy	459,842,250	7.6	500,740,500	8.3	9.1

The Regions in which the highest *per capita* utilisation of rFVIII was observed were Calabria (14.6 IUs), Latium (14.3 IUs) and Basilicata (12 IUs) (Figure 22), with a percentage change compared to the Italian mean value of +76%, +72% and +44%, respectively (Figure 23).

The lowest utilisation – between 3.1 and 5.8 IUs *per capita* – was observed in the Friuli Venezia Giulia, Marche, Tuscany and Veneto.

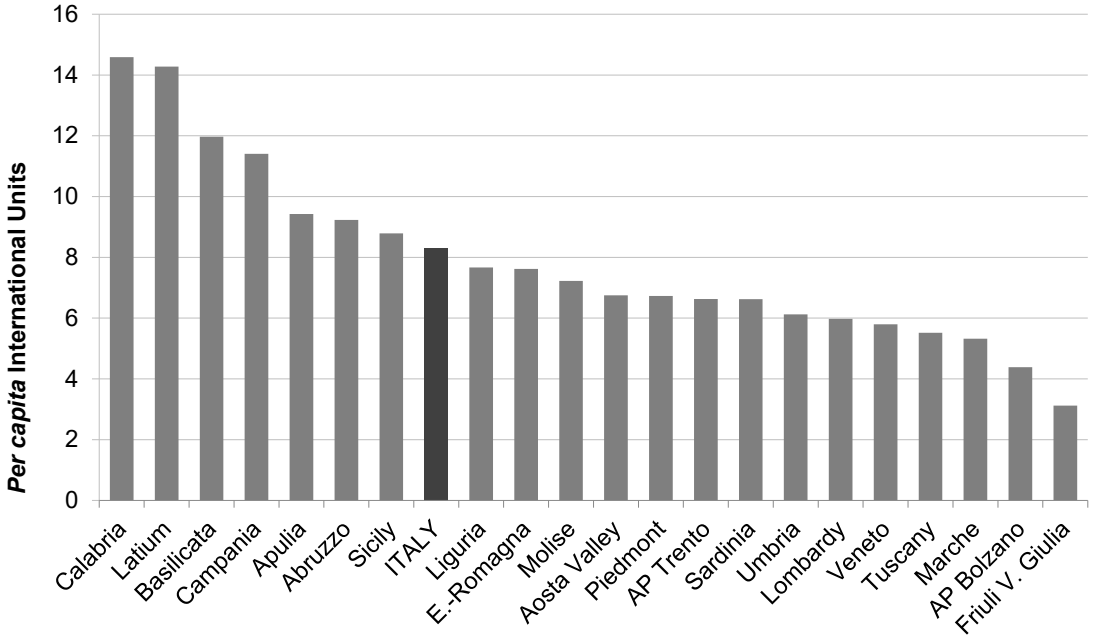

Figure 22. Total and regional demand (public and private) for recombinant coagulation Factor VIII, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

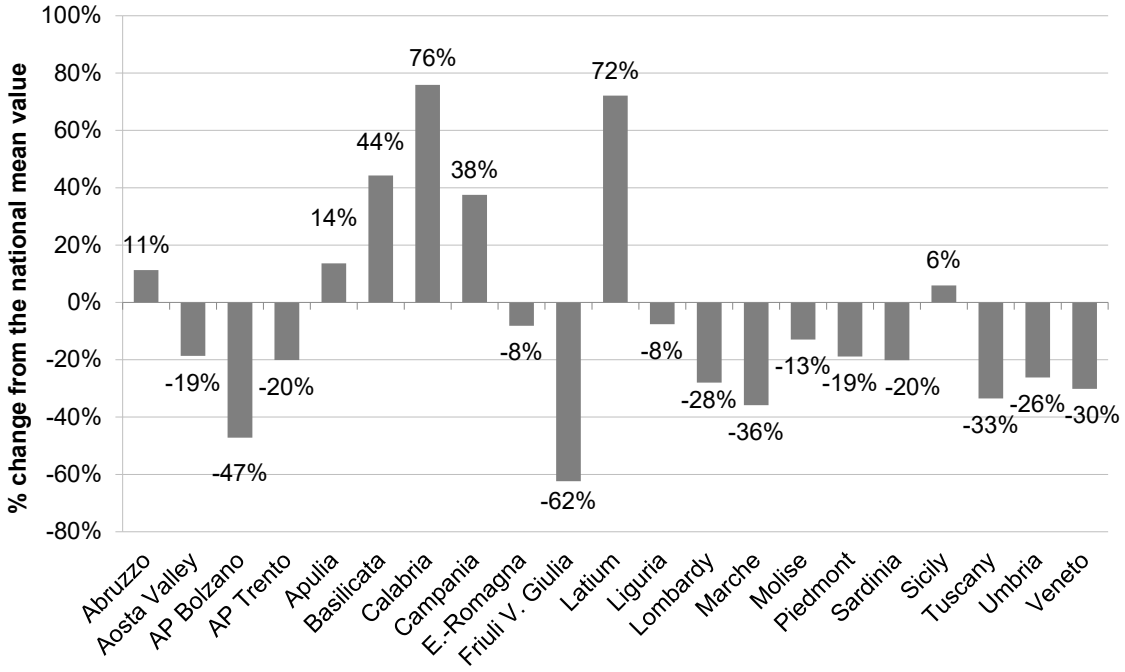

Figure 23. Percentage change from the national mean value of standardised regional demand for recombinant coagulation Factor VIII in 2019 (adapted by the CNS on data from the Traceability information flow)

Extended half-life recombinant Factor VIII

Part of the total demand for rFVIII is represented by drugs containing extended half-life molecules. In 2019, the demand for these products was equal to 84,572,000 IUs, about 7% of the total demand for rFVIII.

The national demand *per capita* was about 1.4 IUs, with a range among Regions of 0.4 IUs in Friuli Venezia Giulia and 2.8 IUs in Liguria. In Aosta Valley, Basilicata, Molise and in APs of Trento and Bolzano, no demand was recorded (Table 21).

Table 21. Total demand (public and private) and total standardised demand for long-acting recombinant coagulation Factor VIII, expressed in International Units and International Units per capita and variations in percentage between 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	908,250	0.7	1,189,000	0.9	30
Aosta Valley	-	-	-	-	NA
AP Bolzano	90000	0.2	-	-	-100
AP Trento	-	-	-	-	NA
Apulia	1,522,000	0.4	2,768,250	0.7	72
Basilicata	-	-	-	-	NA
Calabria	2,907,000	1.5	3,407,500	1.8	17
Campania	6,511,750	1.1	7,436,750	1.3	17
E.-Romagna	5,710,000	1.3	10,023,750	2.2	73
Friuli V. Giulia	462,500	0.4	430,000	0.4	-12
Latium	6,454,500	1.1	13,924,500	2.4	115
Liguria	3,248,000	2.1	4,360,000	2.8	34
Lombardy	9,063,500	0.9	13,838,500	1.4	53
Marche	456,000	0.3	853,500	0.6	87
Molise	-	-	-	-	NA
Piedmont	6,215,500	1.4	10,402,250	2.4	71
Sardinia	552,000	0.3	812000	0.5	65
Sicily	2,040,000	0.4	4,188,500	0.8	109
Tuscany	2,782,500	0.7	4,887,500	1.3	87
Umbria	438000	0.5	1,454,000	1.6	230
Veneto	2,994,000	0.6	4,596,000	0.9	56
Italy	52,355,500	0.9	84,572,000	1.4	56

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, 31/12/2019)

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

Quantification and characterisation of the demand

Table 23 shows the total and per 1,000 population demand for drugs containing Emicizumab for the year 2019, at national and regional levels and the percentage change from the previous year.

The total national demand for Emicizumab formulation for the year 2019 was 237,885 mg.

The national demand (mg per 1,000 population) was about 3.9 IUs, but not all Regions recorded Emicizumab consumption (Table 23). The standardised demand for Emicizumab ranged from a minimum of 0.3 mg in Friuli Venezia Giulia to a maximum of 9.2 mg in Piedmont (Figure 24).

Table 23. Total demand (public and private) and total standardised demand for Emicizumab expressed in mg and mg per 1,000 population for the year 2019 and variations in percentage between 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	mg	mg per 1,000 population	mg	mg per 1,000 population	
Abruzzo	-	-	6,660	5.1	100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	3,120	5.9	100.0
AP Trento	-	-	-	-	NA
Apulia	-	-	7,740	1.9	100.0
Basilicata	-	-	-	-	NA
Calabria	-	-	14,520	7.5	100.0
Campania	4,650	0.8	28,770	5.0	521.4
E.-Romagna	1,620	0.4	10,020	2.2	517.6
Friuli V. Giulia	-	-	420	0.3	100.0
Latium	-	-	5,070	0.9	100.0
Liguria	-	-	840	0.5	100.0
Lombardy	8,820	0.9	49,830	5.0	463.6
Marche	-	-	6,300	4.1	100.0
Molise	-	-	-	-	NA
Piedmont	1,470	0.3	39,870	9.2	2,624.4
Sardinia	-	-	-	-	NA
Sicily	-	-	16,980	3.4	100.0
Tuscany	960	0.3	21,480	5.8	2,141.9
Umbria	1,500	1.7	4,440	5.0	196.9
Veneto	7,215	1.5	21,825	4.4	202.4
Italy	26,235	0.4	237,885	3.9	808.6

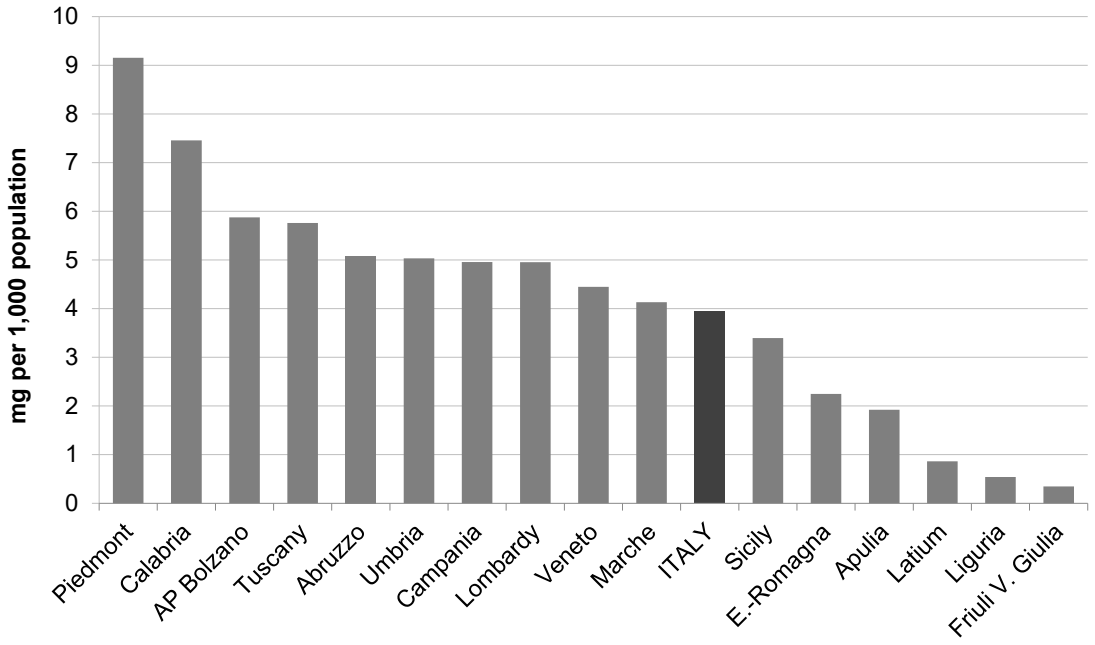

Figure 24. Total and regional demand (public and private) for Emicizumab expressed in mg per 1,000 population 2019 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2019)

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, 31/12/2019)

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

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 2018-2019, at national and regional levels. The total demand for FIX formulations recorded in 2019 was 60,968,750 IUs (Table 26); about 12% of the aforementioned amount (7,519,500 IUs) was plasma-derived. There was a growing demand for both pdFIX (+5%) and rFIX (+7%).

Table 26. Total demand (public and private) and total standardised demand for coagulation Factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,119,000	1.6	2,000,000	1.5	-5.4
Aosta Valley	-	-	-	-	NA
APBolzano	21,000	0.0	30,000	0.1	41.9
APTrento	461,000	0.9	438,500	0.8	-5.1
Apulia	6,351,000	1.6	5,926,000	1.5	-6.2
Basilicata	299,750	0.5	264,750	0.5	-11.0
Calabria	1,123,250	0.6	2,180,250	1.1	95.1
Campania	7,550,000	1.3	5,906,000	1.0	-21.4
E.-Romagna	3,962,250	0.9	3,952,500	0.9	-0.4
Friuli V. Giulia	1,052,000	0.9	804,000	0.7	-23.6
Latium	4,674,500	0.8	6,330,750	1.1	35.8
Liguria	1,957,000	1.3	2,322,000	1.5	19.1
Lombardy	6,944,250	0.7	7,988,000	0.8	14.8
Marche	1,878,000	1.2	1,688,000	1.1	-9.7
Molise	-	-	-	-	NA
Piedmont	4,165,250	1.0	4,301,000	1.0	3.7
Sardinia	44,000	0.0	89,000	0.1	103.3
Sicily	3,904,500	0.8	4,562,000	0.9	17.5
Tuscany	6,484,000	1.7	8,267,000	2.2	27.7
Umbria	278,000	0.3	440,500	0.5	58.9
Veneto	3,788,500	0.8	3,478,500	0.7	-8.2
Italy	57,057,250	0.9	60,968,750	1.0	7.1

* 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 2019, 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 the AP of Bolzano (-95% and -94% percentage change compared to the Italian mean value, respectively), to a maximum in Tuscany (2.2 IUs) and Abruzzo, Liguria and Apulia with 1.5 IUs *per capita* (+119%, +51%, 48% e +46% percentage change compared to the national mean value, respectively) (Figures 25 and 26).

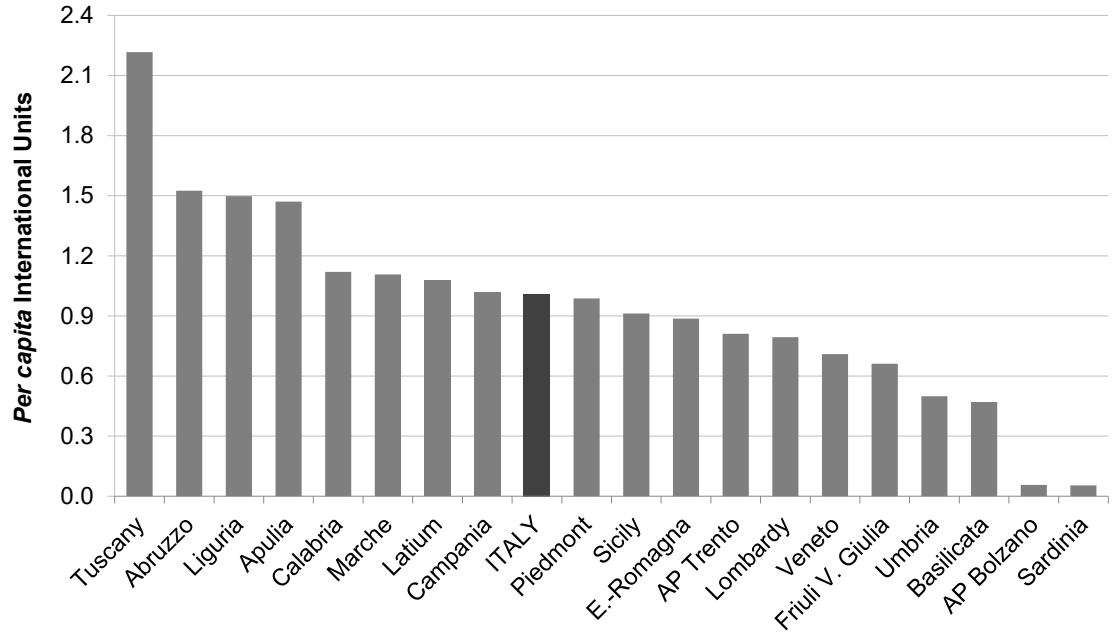

Figure 25. Total and regional demand (public and private) for coagulation Factor IX, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

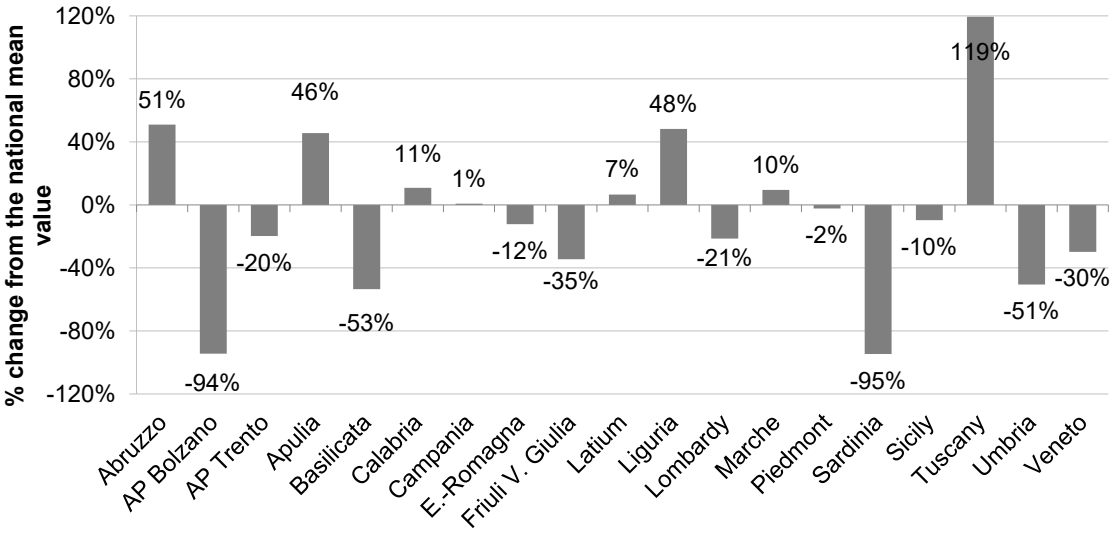

Figure 26. Percentage change from the national mean value of standardised regional demand for coagulation Factor IX (International Units *per capita*) in 2019 (adapted by the CNS on data from the Traceability information flow)

In ten Regions there were percentage increases in demand (range: 3-103%) which is instead decreasing in nine Regions (range: -0.4; -24%) (Table 26).

In Campania, AP of Trento and Sardinia rFIX was used almost exclusively, while in Apulia, Abruzzo, Calabria, Liguria, Sicily, Friuli Venezia Giulia, Piedmont and Emilia-Romagna, the rFIX demand reached volumes of above 90% (Figure 27).

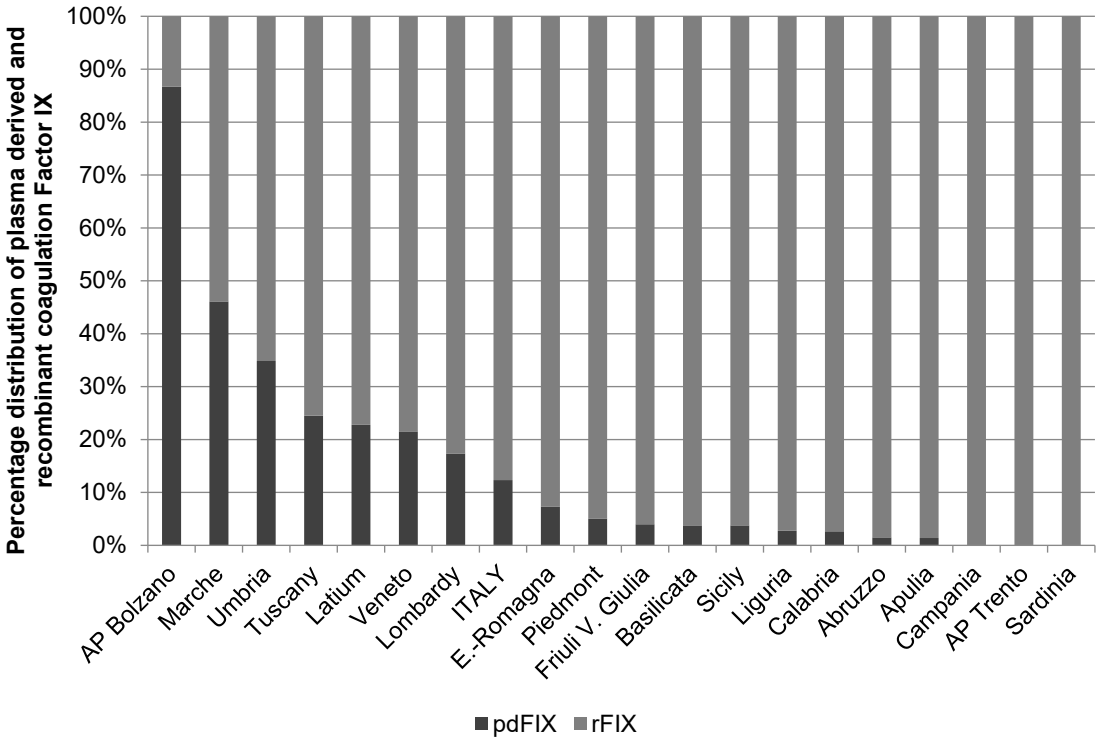

Figure 27. Distribution expressed in % of Factor IX per type, by Region, 2019 (adapted by the CNS on data from the Traceability information flow)

Plasma-derived Factor IX

In 2019, the total demand for pdFIX (expressed in absolute values and *per capita* volumes), showed an increase of 5% compared to 2018, for an absolute value of 7,519,500 IUs, equal to 0.1 IU *per capita* (Table 27).

The Regions with the highest *per capita* demand for pdFIX were Tuscany and Marche with 0.5 IUs; in Campania, Molise, AP of Trento, Sardinia and Aosta Valley there was no reported consumption of pdFIX (Figures 28 and 29).

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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	214,000	0.2	30,000	0.0	-85.9
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	26,000	0.0	100.0
AP Trento	-	-	-	-	NA
Apulia	489,000	0.1	83,000	0.0	-82.9
Basilicata	30,000	0.1	10,000	0.0	-66.4
Calabria	82,000	0.0	58,000	0.0	-28.9
Campania	-	-	-	-	NA
E.-Romagna	787,000	0.2	290,500	0.1	-63.1
Friuli V.Giulia	316,000	0.3	32,000	0.0	-89.9
Latium	205,500	0.0	1,441,500	0.2	603.6
Liguria	-	-	64,000	0.0	100.0
Lombardy	771,000	0.1	1,388,000	0.1	79.6
Marche	640,000	0.4	778,000	0.5	22.1
Molise	-	-	-	-	NA
Piedmont	905,000	0.2	218,000	0.1	-75.8
Sardinia	-	-	-	-	NA
Sicily	114,000	0.0	172,000	0.0	51.7
Tuscany	1,212,000	0.3	2,026,000	0.5	67.5
Umbria	114,000	0.1	153,500	0.2	35.0
Veneto	1,295,000	0.3	749,000	0.2	-42.2
Italy	7,174,500	0.1	7,519,500	0.1	5.0

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

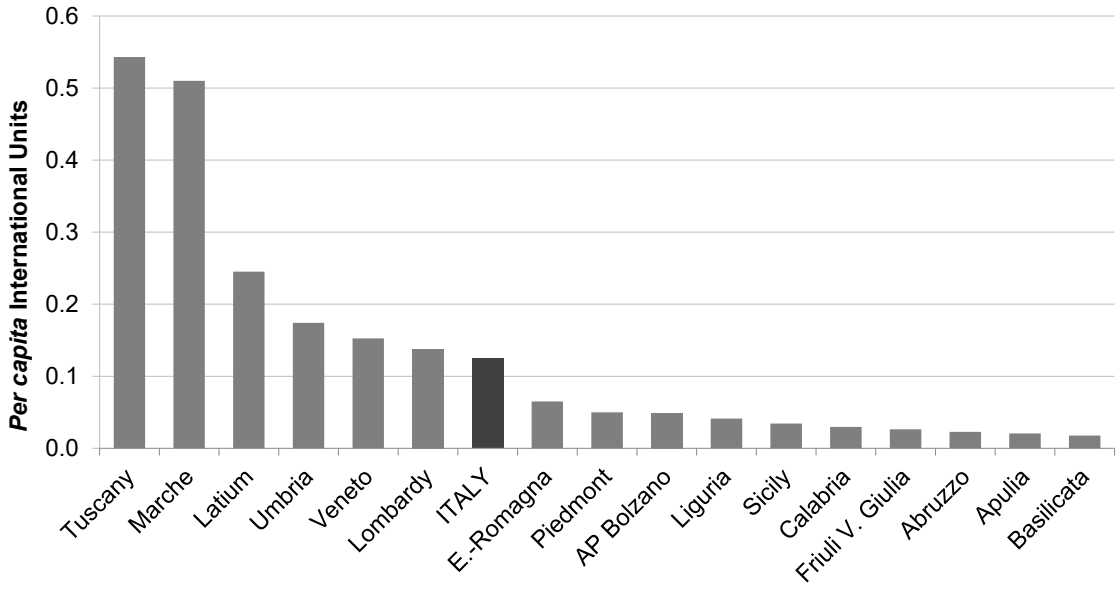

Figure 28. Total and regional demand (public and private) for plasma-derived coagulation Factor IX, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

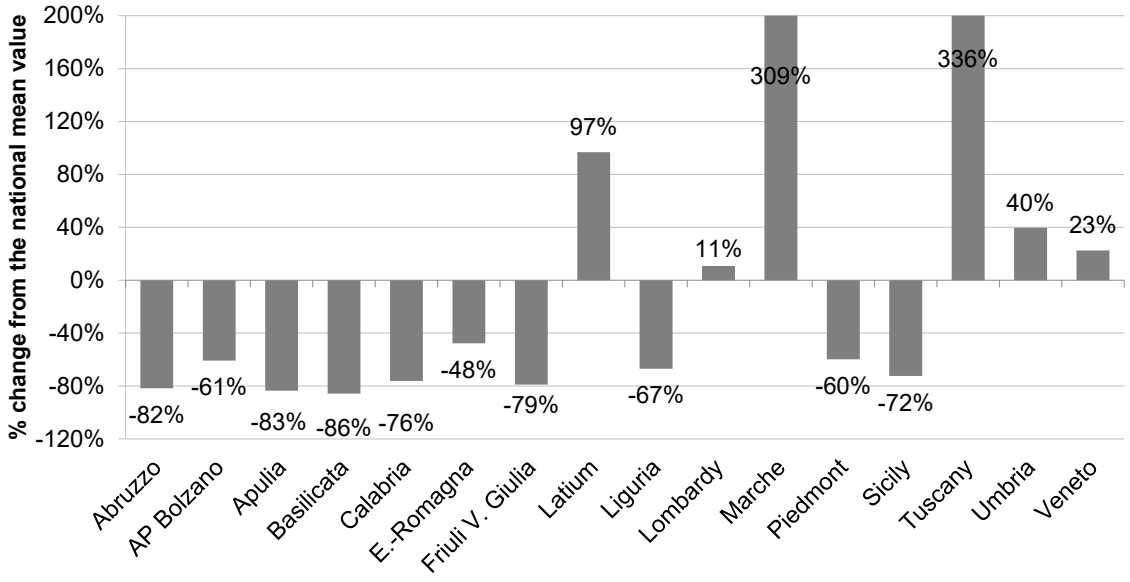

Figure 29. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation Factor IX in 2019 (adapted by the CNS on data from the Traceability information flow)

Recombinant Factor IX

The total demand for rFIX showed, in the period 2018-2019, an increase of 7%, registering a value of 53,449,250 IUs in 2019, 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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,905,000	1.4	1,970,000	1.5	3.7
Aosta Valley	-	-	-	-	NA
AP Bolzano	21,000	0.0	4,000	0.0	-81.1
AP Trento	461,000	0.9	438,500	0.8	-5.1
Apulia	5,862,000	1.4	5,843,000	1.5	0.2
Basilicata	269,750	0.5	254,750	0.5	-4.8
Calabria	1,041,250	0.5	2,122,250	1.1	104.8
Campania	7,550,000	1.3	5,906,000	1.0	-21.4
E.-Romagna	3,175,250	0.7	3,662,000	0.8	15.2
Friuli V. Giulia	736,000	0.6	772,000	0.6	4.9
Latium	4,469,000	0.8	4,889,250	0.8	9.7
Liguria	1,957,000	1.3	2,258,000	1.5	15.9
Lombardy	6,173,250	0.6	6,600,000	0.7	6.7
Marche	1,238,000	0.8	910,000	0.6	-26.2
Molise	-	-	-	-	NA
Piedmont	3,260,250	0.7	4,083,000	0.9	25.8
Sardinia	44,000	0.0	89,000	0.1	103.3
Sicily	3,790,500	0.8	4,390,000	0.9	16.4
Tuscany	5,272,000	1.4	6,241,000	1.7	18.6
Umbria	164,000	0.2	287,000	0.3	75.5
Veneto	2,493,500	0.5	2,729,500	0.6	9.4
Italy	49,882,750	0.8	53,449,250	0.9	7.4

The Regions with the highest *per capita* demand of rFIX (Figure 30) were Tuscany, Abruzzo, Liguria and Apulia with 1.7 IU for the first one and 1.5 IU for the other three Regions (+ 89%, +70%, + 64% and + 64% compared to the national average) (Figure 31).

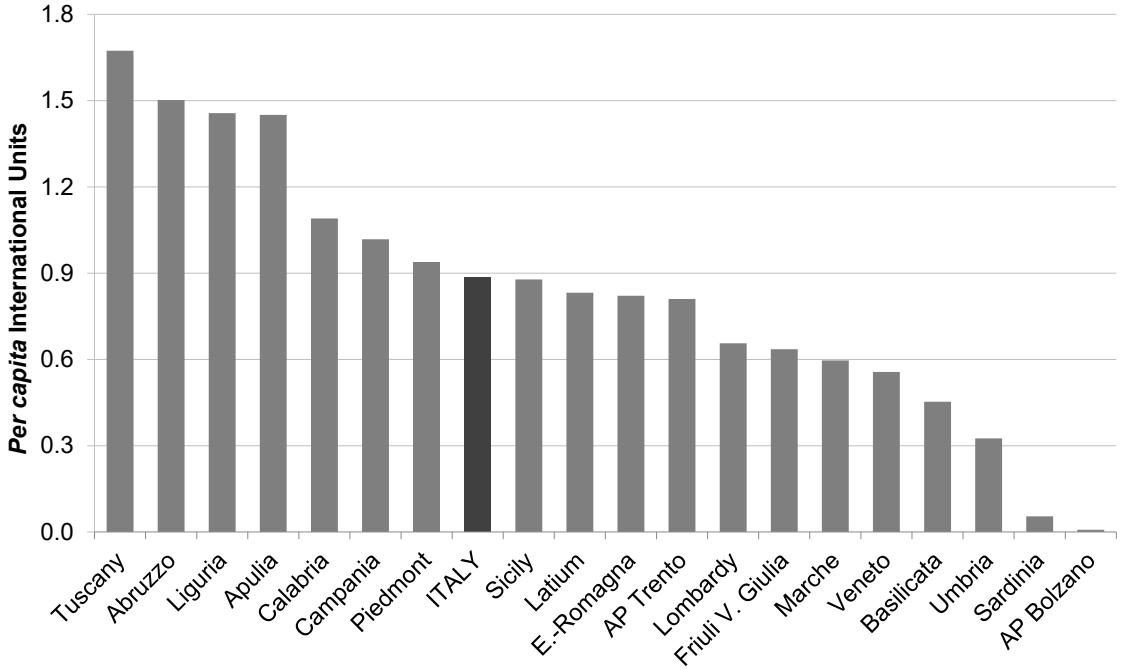

Figure 30. Total and regional demand (public and private) for recombinant coagulation Factor IX, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

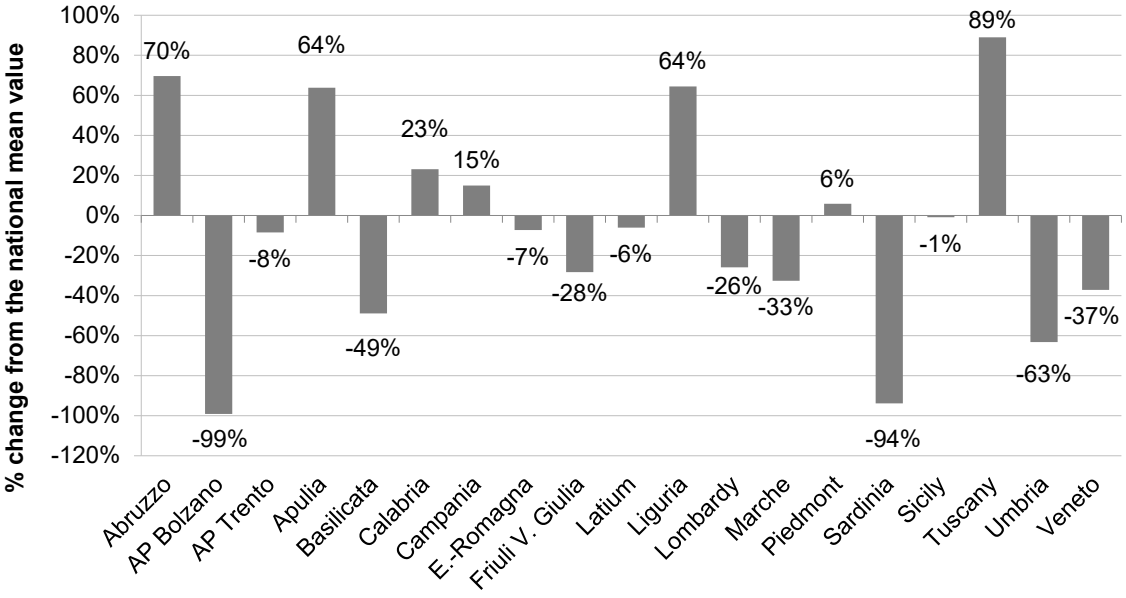

Figure 31. Percentage change from the national mean value of standardised regional demand for recombinant coagulation factor IX in 2019 (adapted by the CNS on data from the traceability information flow)

In Aosta Valley and Molise there was no reported consumption of rFIX in 2019. In 2019 there was an increase in *per capita* demand, compared to 2018, in almost all Regions. The greatest increases occurred in Calabria, Sardinia and Umbria.

Extended half-life recombinant Factor IX

Out of 53 million IUs of rFIX demand, extended half-life recombinant Factor IX molecules recorded a total demand of 30,360,500 IUs, about 57% 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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	969,500	0.7	1,317,000	1.0	43.4
Aosta Valley	-	-	-	-	NA
AP Bolzano	10,000	0.0	-	-	-100.0
AP Trento	-	-	-	-	NA
Apulia	2,969,500	0.7	3,681,500	0.9	30.5
Basilicata	74,750	0.1	68,750	0.1	22.1
Calabria	408,250	0.2	1,198,250	0.6	207.7
Campania	1,309,000	0.2	2,534,750	0.4	118.4
E.-Romagna	1,957,000	0.4	2,822,000	0.6	58.2
Friuli V. Giulia	448,000	0.4	686,000	0.6	41.1
Latium	1,626,500	0.3	2,253,000	0.4	27.7
Liguria	1,488,000	1	1,836,000	1.2	18.4
Lombardy	4,207,750	0.4	5,261,750	0.5	30.8
Marche	587,500	0.4	484,000	0.3	-20.7
Molise	-	-	-	-	NA
Piedmont	2,448,750	0.6	2,576,500	0.6	-1.4
Sardinia	-	-	40,000	0.0	100.0
Sicily	1,141,500	0.2	1,504,000	0.3	50.4
Tuscany	2,639,500	0.7	2,050,000	0.5	-21.5
Umbria	137,000	0.2	245,000	0.3	38.9
Veneto	764,500	0.2	1,802,000	0.4	83.7
Italy	23,187,000	0.4	30,360,500	0.5	25.7

The mean national demand *per capita* was about 0.5 IU, with a range among Regions of 0.1 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 2019.

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, 31/12/2019)

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, 31/12/2019)

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 2018-2019, at both national and regional level.

In 2019 there was a slight decrease in the total demand (-0.7%) compared to 2018; it stood at 37,443,300 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 0.2 IUs (Calabria) to 1 IU (Sardinia), with a percentage change compared to the Italian mean value of over 50% in Sardinia (+67%) (Figures 32 and 33). In 2019, the national demand for 4F-PCCs was 9,591,500 IUs, equal to 20% of the overall demand for PCCs, with a standardised demand of 0.2 IU *per capita* and with an increase of 6.5% 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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	448,500	0.3	715,000	0.5	59.9
AostaValley	96,000	0.8	80,000	0.6	-16.3
APBolzano	592,000	1.1	432,000	0.8	-27.5
APTrento	451,500	0.8	379,000	0.7	-16.2
Apulia	2,033,500	0.5	2,238,000	0.6	10.6
Basilicata	190,000	0.3	340,000	0.6	80.3
Calabria	487,500	0.2	404,500	0.2	-16.6
Campania	2,962,000	0.5	2,210,500	0.4	-25.0
E.-Romagna	4,448,500	1.0	3,761,500	0.8	-15.6
Friuli V. Giulia	1,097,500	0.9	832,000	0.7	-24.2
Latium	1,702,000	0.3	1,837,500	0.3	8.3
Liguria	1,491,000	1.0	1,053,000	0.7	-29.1
Lombardy	5,483,800	0.5	6,343,300	0.6	15.4
Marche	742,000	0.5	1,286,000	0.8	74.1
Molise	250,000	0.8	260,500	0.9	5.2
Piedmont	2,778,000	0.6	3,276,500	0.8	18.5
Sardinia	1,110,800	0.7	1,697,000	1.0	53.6
Sicily	3,459,500	0.7	3,173,000	0.6	-7.8
Tuscany	3,303,500	0.9	2,519,500	0.7	-23.6
Umbria	555,000	0.6	586,000	0.7	5.9
Veneto	4,110,500	0.8	4,018,500	0.8	-2.3
Italy	37,793,100	0.6	37,443,300	0.6	-0.7

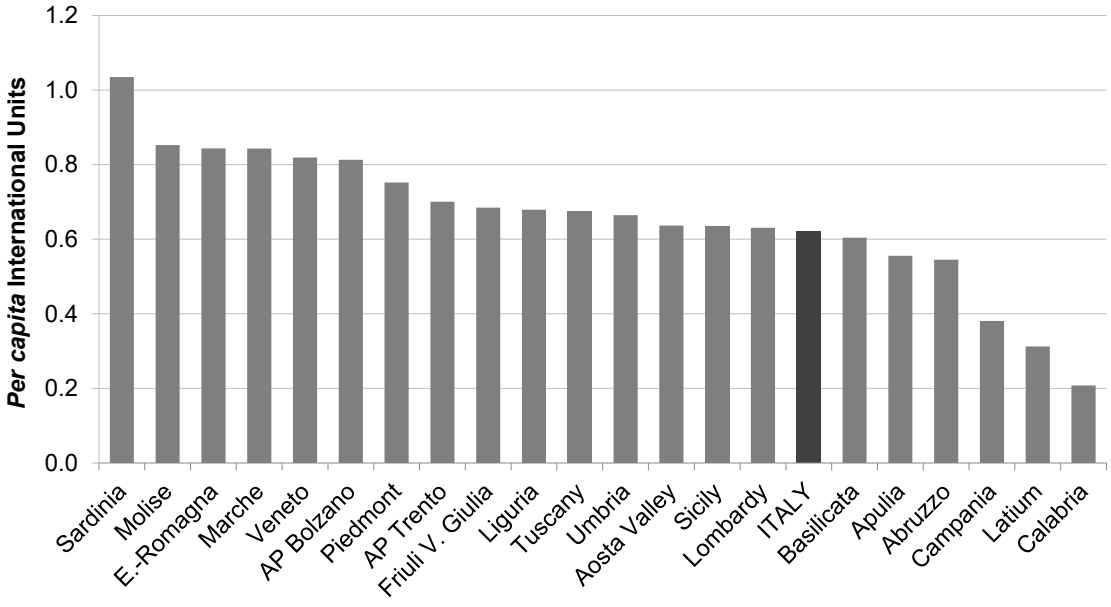

Figure 32. Total and regional demand (public and private) for 3-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

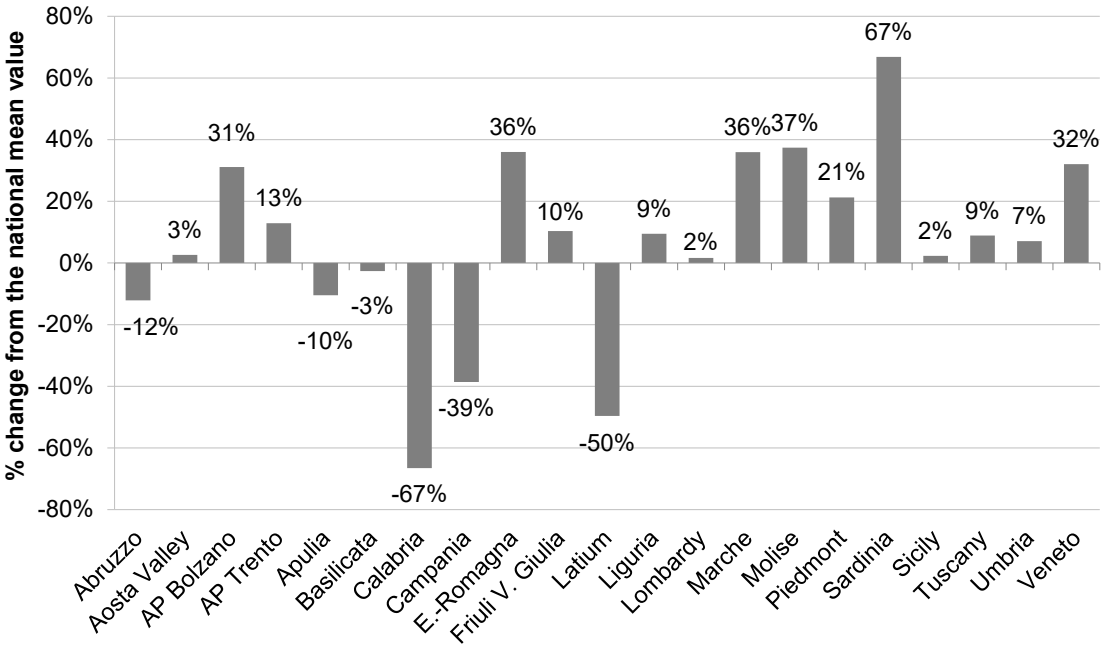

Figure 33. Percentage change from the national mean value of standardised regional demand for 3-factor prothrombin complex concentrates in 2019 (adapted by the CNS on data from the Traceability information flow)

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 2018-2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	385,500	0.3	571,000	0.4	48.5
Aosta Valley	-	-	-	-	NA
AP Bolzano	569,000	1.1	521,000	1.0	-9.0
AP Trento	25,500	0.0	49,500	0.1	93.7
Apulia	164,000	0.0	196,500	0.0	20.4
Basilicata	147,000	0.3	238,000	0.4	63.1
Calabria	316,500	0.2	411,000	0.2	30.5
Campania	1,211,000	0.2	1,221,000	0.2	1.3
E.-Romagna	1,134,000	0.3	1,055,500	0.2	-7.1
Friuli V. Giulia	122,000	0.1	4,000	0.0	-96.7
Latium	1,651,000	0.3	847,500	0.1	-48.5
Liguria	128,500	0.1	149,500	0.1	16.8
Lombardy	832,000	0.1	801,500	0.1	-3.9
Marche	113,500	0.1	177,000	0.1	56.6
Molise	62,000	0.2	62,000	0.2	0.9
Piedmont	647,500	0.1	767,500	0.2	19.1
Sardinia	670,000	0.4	666,500	0.4	0.0
Sicily	534,000	0.1	519,000	0.1	-2.3
Tuscany	128,000	0.0	1,167,000	0.3	813.5
Umbria	54,500	0.1	61,000	0.1	12.3
Veneto	132,500	0.0	105,500	0.0	-20.4
Italy	9,028,000	0.1	9,591,500	0.2	6.5

Also for this PDMP, there were considerable differences regarding utilisation from one Region to another. With the exception of Emilia- Romagna, Friuli Venezia Giulia, Latium, Lombardy, AP of Bolzano, Sicily and Veneto, all the Regions recorded significant increases in the demand.

The Region with the highest demand in 2019 was the AP of Bolzano with 1 IU *per capita*, followed by Abruzzo, Basilicata and Sardinia with 0.4 IU *per capita* (Figure 34). Figure 35 shows percentage changes compared to the Italian mean values of the standardised regional demand for 4F-PCCs as recorded by the drug Traceability system in 2019.

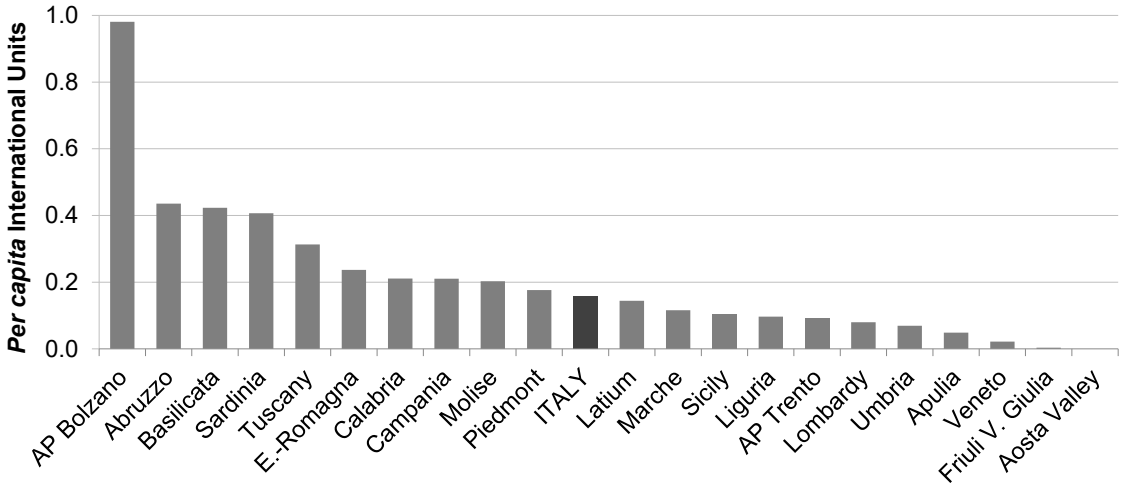

Figure 34. Total and regional demand (public and private) for 4-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2019 (adapted by the CNS on data from the Traceability information flow)

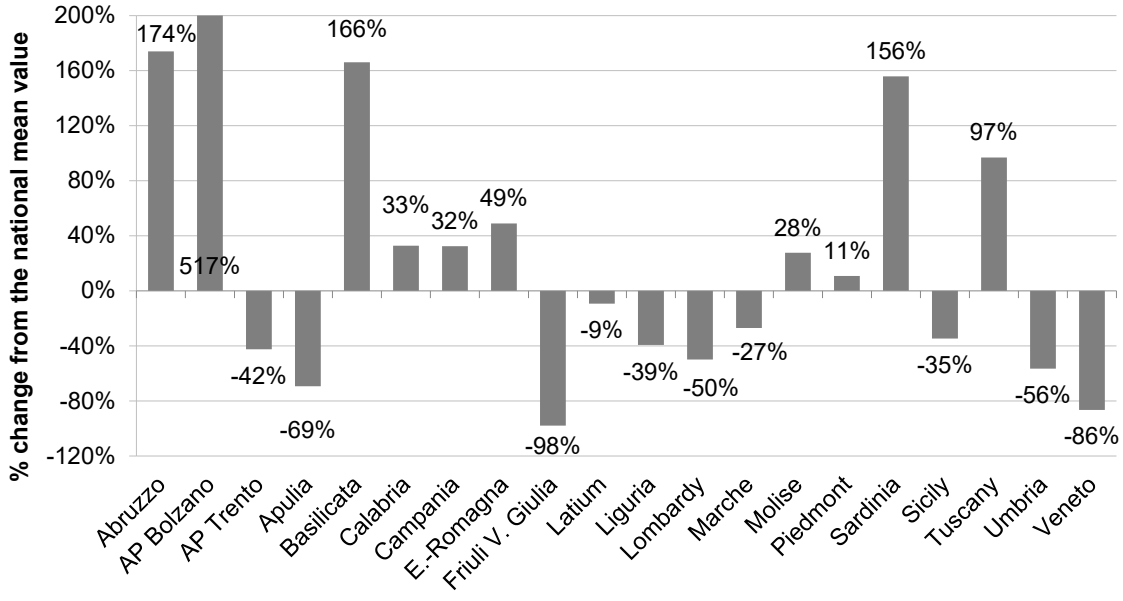

Figure 35. Percentage change from the national mean value of standardised regional demand for 4-factor prothrombin complex concentrates in 2019 (adapted by the CNS on data from the Traceability information flow)

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, 31/12/2019)

AIC code	Brand name	g	Manufacturer	NHS class
*E00178010	HAEMOCOMPLETTANP 1F 1g	1	CSL BEHRING SpA	H
040170019	RIASTAP FL POLV 1g 20mg/mL	1	CSL BEHRING SpA	C
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 2018-2019 at regional and national level.

In 2019, total fibrinogen demand showed a significant increase (+18.7%) compared to the previous year. Its volume of 43,981 g, with a standardised demand of 0.7 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 Campania, Liguria, AP of Trento and Umbria, contributed to this growth to different extents.

Figure 36 shows the regional and national standardised demand for fibrinogen in 2019. The Regions with the highest demand per 1,000 population were AP of Bolzano (1.5 g) then Umbria and Sardinia with 1.2 g. The lowest demand, between 0.2 g and 0.5 g per 1,000 population, was recorded in Molise, Liguria, Piedmont, Lombardy, Aosta Valley and the AP of Trento.

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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2018		2019		% Var 2018-2019
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,461	1.1	1,523	1.2	4.5
Aosta Valley	46	0.4	59	0.5	28.8
AP Bolzano	641	1.2	788	1.5	22.1
AP Trento	307	0.6	291	0.5	-5.3
Apulia	2,141	0.5	2,498	0.6	17.2
Basilicata	250	0.4	480	0.9	93.4
Calabria	1,446	0.7	2,182	1.1	51.6
Campania	4,785	0.8	4,319	0.7	-9.3
E.-Romagna	3,391	0.8	3,645	0.8	7.3
Friuli V. Giulia	505	0.4	1,103	0.9	118.5
Latium	3,919	0.7	5,148	0.9	31.8
Liguria	589	0.4	502	0.3	-14.4
Lombardy	3,915	0.4	4,587	0.5	16.9
Marche	956	0.6	1,030	0.7	8.2
Molise	47	0.2	73	0.2	56.8
Piedmont	1,287	0.3	1,893	0.4	47.7
Sardinia	1,654	1.0	1,936	1.2	17.7
Sicily	1,984	0.4	2,627	0.5	33.1
Tuscany	2,502	0.7	2,650	0.7	6.1
Umbria	1,069	1.2	1,047	1.2	-1.8
Veneto	4,226	0.9	5,600	1.1	32.5
Italy	37,121	0.6	43,981	0.7	18.7

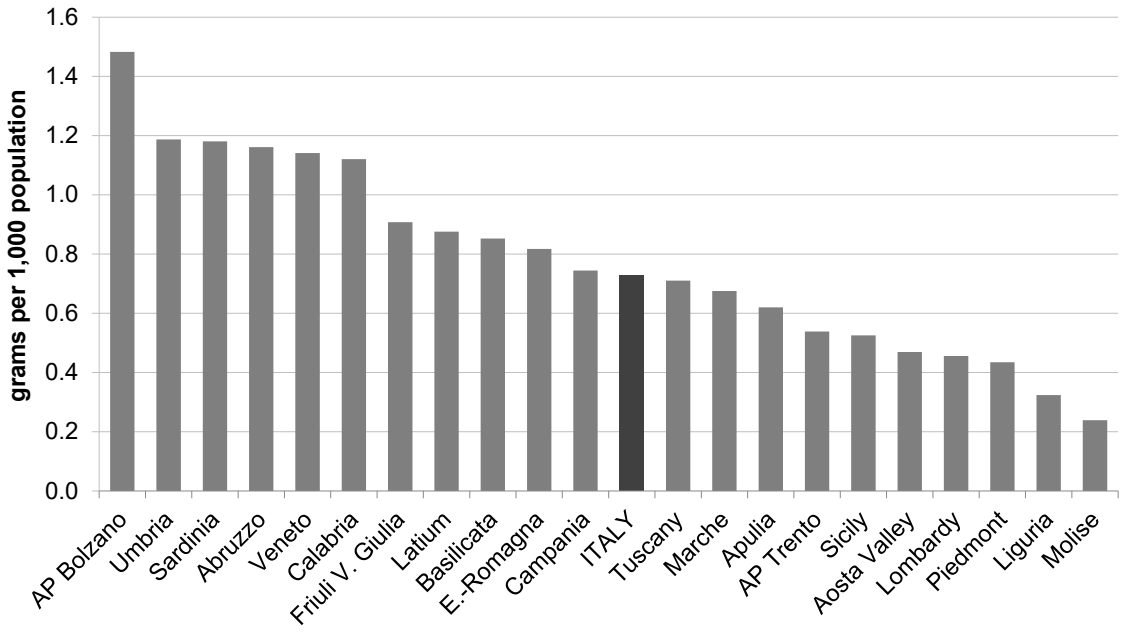

Figure 36. Total and regional demand (public and private) for fibrinogen, expressed in grams per 1,000 population, 2019 (adapted by the CNS on data from the Traceability information flow)

PART B
Other plasma-derived medicinal products

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

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

Table 36. Products containing hepatitis B immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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, 31/12/2019)

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 2018-2019, at national and at regional level.

The national demand for hepatitis B IGs for IV use, showed a downward trend (-9.5) already observed in previous years (34). The total demand in 2019 was almost 16 million IUs (0.3 IU *per capita*) (Table 38).

Table 38. Total demand (public and private) and total standardised demand for hepatitis B immunoglobulins for intravenous use, expressed in International Units and International Units *per capita*, and variations in percentage between 2018 and 2019 (adapted by the CNS on data from the Traceability information flow).

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	36,000	0.0	21,000	0.0	-41.5
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	2,819,000	0.7	1,704,500	0.4	-39.2
Basilicata	3,000	0.0	1,000	0.0	-66.4
Calabria	225,200	0.1	211,500	0.1	-5.6
Campania	5,622,800	1.0	4,370,500	0.8	-21.9
E.-Romagna	2,011,000	0.5	2,194,000	0.5	8.9
Friuli V. Giulia	42,500	0.0	375,000	0.3	782.6
Latium	923,000	0.2	465,500	0.1	-49.4
Liguria	44,000	0.0	32,000	0.0	-27.0
Lombardy	1,309,000	0.1	1,681,500	0.2	28.1
Marche	228,500	0.1	155,500	0.1	-31.7
Molise	18,000	0.1	22,000	0.1	23.4
Piedmont	860,000	0.2	657,500	0.2	-23.2
Sardinia	354,000	0.2	466,000	0.3	32.3
Sicily	439,000	0.1	297,500	0.1	-31.9
Tuscany	940,000	0.3	991,500	0.3	5.7
Umbria	8,000	0.0	-	-	-100.0
Veneto	2,002,500	0.4	2,503,500	0.5	25.0
Italy	17,885,500	0.3	16,150,000	0.3	-9.5

Campania, despite a significant decrease in its regional demand, continued to be the Region with the highest demand (0.8 IU *per capita*), equal to a quarter of the national demand, followed by Emilia-Romagna (0.5 IU), Apulia (0.4 IU), Tuscany, Friuli Venezia Giulia and Sardinia (0.3 IU).

On the other hand, the national demand for antihepatitis B SC / IM GI, shows a sharp increase, equal to + 30% of the demand recorded in 2018; the total consumption for 2019 is approximately 75 million IUs (1.3 IUs *per capita*) (Table 39) and accounted 82% of the total demand for antihepatitis B GIs.

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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow).

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	536,880	0.4	565,020	0.4	5.5
Aosta Valley	255,960	2.0	223,960	1.8	-12.1
AP Bolzano	120,200	0.2	112,160	0.2	-7.3
AP Trento	159,460	0.3	172,000	0.3	7.6
Apulia	5,603,440	1.4	6,067,860	1.5	8.8
Basilicata	259,100	0.5	294,960	0.5	14.7
Calabria	1,138,320	0.6	1,577,300	0.8	39.2
Campania	15,581,140	2.7	31,401,800	5.4	102.4
E.-Romagna	3,518,160	0.8	3,446,080	0.8	-2.2
Friuli V. Giulia	245,000	0.2	256,640	0.2	4.8
Latium	2,180,020	0.4	2,162,600	0.4	-0.5
Liguria	718,180	0.5	634,000	0.4	-11.4
Lombardy	10,434,600	1.0	10,168,380	1.0	-2.8
Marche	447,200	0.3	714,120	0.5	60.4
Molise	144,900	0.5	138,460	0.5	-3.5
Piedmont	4,672,340	1.1	4,936,840	1.1	6.1
Sardinia	3,492,000	2.1	3,397,540	2.1	-2.2
Sicily	2,584,960	0.5	3,132,700	0.6	21.8
Tuscany	2,969,280	0.8	3,375,320	0.9	13.9
Umbria	245,180	0.3	314,820	0.4	28.8
Veneto	2,579,860	0.5	2,395,600	0.5	-7.2
Italy	57,886,180	1.0	75,488,160	1.3	30.7

TETANUS IMMUNOGLOBULINS (ATC J06BB02)

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

Table 40. Products containing tetanus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019).

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 2019 the total demand for tetanus IGs was 147,042,000 IUs (2.4 IUs *per capita*), showing an increase of 11.8% compared to 2018 (Table 41).

The Regions with the highest demand, expressed as standardised volume for the resident population, were Campania (5 IUs *per capita*), and Abruzzo and Calabria (4.5 and 3.9 IUs *per capita,* respectively). In 2019, the demand increased – in some cases very significantly – in almost all Regions, with the exception of Campania (-3%), Friuli Venezia Giulia (-33%), Liguria (-3%), Lombardy (-2%), the AP of Trento (-30%), Aosta Valley (-18%) and Veneto (-3%).

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 417,500 IUs.

Table 41. Total demand (public and private) and total standardised demand, expressed in International Units and International Units *per capita*, for tetanus immunoglobulins and variations in percentage between 2018 and 2019 (adapted by the CNS on data from the Traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	4,858,000	3.7	5,867,750	4.5	21.1
Aosta Valley	470,500	3.7	382,750	3.0	-18.3
AP Bolzano	483,500	0.9	742,500	1.4	52.6
AP Trento	738,000	1.4	518,500	1.0	-29.9
Apulia	7,579,750	1.9	8,131,250	2.0	7.8
Basilicata	1,452,000	2.6	2,064,750	3.7	43.3
Calabria	5,684,250	2.9	7,551,500	3.9	33.5
Campania	29,976,750	5.1	29,078,750	5.0	-2.6
E.-Romagna	7,566,750	1.7	7,702,250	1.7	1.6
Friuli V. Giulia	511,500	0.4	341,500	0.3	-33.2
Latium	10,599,750	1.8	12,572,250	2.1	19.0
Liguria	4,673,000	3.0	4,498,500	2.9	-3.3
Lombardy	18,492,500	1.8	18,100,250	1.8	-2.4
Marche	3,952,000	2.6	5,245,250	3.4	33.3
Molise	649,000	2.1	868,250	2.8	35.0
Piedmont	4,906,000	1.1	5,921,250	1.4	21.2
Sardinia	3,419,250	2.1	4,966,750	3.0	46.0
Sicily	9,208,000	1.8	12,792,500	2.6	39.7
Tuscany	8,562,750	2.3	13,360,500	3.6	56.3
Umbria	1,732,000	2.0	2,258,500	2.6	30.8
Veneto	3,784,500	0.8	3,659,000	0.7	-3.3
Not specified Region	2,472,500	NA	417,500	NA	NA
Italy	131,772,250	2.2	147,042,000	2.4	11.8

ANTI-D (RH) IMMUNOGLOBULINS (ATC J06BB01)

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

Table 42. Products containing anti-D (Rh) immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 2018 and 2019 remained broadly stable and stood at 116,867,750 IUs in 2019 (1.9 IUs *per capita*), with the highest peak in the AP of Bolzano and the lowest level in Sardinia (4.3 and 0.9 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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,451,000	1.9	2,599,500	2.0	6.4
Aosta Valley	325,500	2.6	262,500	2.1	-19.0
AP Bolzano	2,113,500	4.0	2,303,750	4.3	8.3
AP Trento	2,195,000	4.1	1,534,250	2.8	-30.3
Apulia	6,394,500	1.6	5,779,500	1.4	-9.2
Basilicata	999,000	1.8	1,266,875	2.3	27.8
Calabria	2,346,000	1.2	2,548,000	1.3	9.1
Campania	9,922,000	1.7	9,308,875	1.6	-5.8
E.-Romagna	10,171,750	2.3	10,829,250	2.4	6.3
Friuli V. Giulia	3,988,750	3.3	1,520,250	1.3	-61.9
Latium	12,868,750	2.2	10,749,000	1.8	-16.2
Liguria	3,031,500	1.9	2,751,000	1.8	-8.9
Lombardy	24,328,250	2.4	21,195,625	2.1	-13.1

Region	2018		2019		% Var 2018-2019
	IU	IU *per capita*	IU	IU *per capita*	
Marche	3,145,500	2.1	3,225,000	2.1	3.0
Molise	392,750	1.3	443,500	1.5	14.0
Piedmont	8,965,625	2.0	9,797,750	2.2	9.8
Sardinia	1,485,000	0.9	1,403,000	0.9	-5.0
Sicily	7,960,500	1.6	7,498,500	1.5	-5.3
Tuscany	2,242,500	0.6	7,510,750	2.0	235.6
Umbria	1,356,000	1.5	1,396,500	1.6	3.3
Veneto	10,324,000	2.1	12,944,375	2.6	25.4
Italy	117,007,375	1.9	116,867,750	1.9	0.1

CYTOMEGALOVIRUS IMMUNOGLOBULINS (ATC J06BB09)

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

Table 44. Products containing cytomegalovirus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

AIC code	Brand name	U	Manufacturer	NHS class
26167015	CYTOTECT BIOTEST*EV 10mL 500U	500	BIOTEST PHARMA GmbH	H
26167027	CYTOTECT BIOTEST*EV 20mL 1000U	1000	BIOTEST PHARMA GmbH	H
26167041	CYTOTECT BIOTEST*EV 10mL1000U	1000	BIOTEST PHARMA GmbH	H
46731016	CYTOMEGATECT*EV 10mL100U	1000	BIOTEST PHARMA GmbH	H
26167039	CYTOTECT BIOTEST*EV 50mL 2500U	2500	BIOTEST PHARMA GmbH	H
26167054	CYTOTECT BIOTEST*EV 50mL 5000U	5000	BIOTEST PHARMA GmbH	H
46731028	CYTOMEGATECT*EV 50mL 100U	5000	BIOTEST PHARMA GmbH	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 2018-2019, at national and regional levels.

Table 45. Total demand (public and private) and total standardised demand for cytomegalovirus immunoglobulins products, expressed in References preparation Unit of the Paul-Erlich Institute and in References preparation Unit of the Paul-Erlich Institute *per capita*, and variations in percentages between 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	U	U *per capita*	U	U *per capita*	
Abruzzo	313,000	0.2	210,000	0.2	-32.7
Aosta Valley	-	-	17,000	0.1	100.0
AP Bolzano	-	-	18,000	0.0	100.0
AP Trento	-	-	-	0.0	NA
Apulia	429,000	0.1	646,000	0.2	51.3
Basilicata	120,000	0.2	165,000	0.3	38.5
Calabria	40,000	0.0	255,000	0.1	540.6
Campania	380,000	0.1	334,000	0.1	-11.7
E.-Romagna	2,330,000	0.5	2,682,000	0.6	14.9
Friuli V. Giulia	4,000	0.0	1,266,000	1.0	31,558.3
Latium	1,142,000	0.2	956,000	0.2	-16.0
Liguria	9,000	0.0	2,000	0.0	-77.7
Lombardy	2,184,000	0.2	2,046,000	0.2	-6.5
Marche	456,000	0.3	480,000	0.3	5.7

Region	2018		2019		% Var 2018-2019
	U	U *per capita*	U	U *per capita*	
Molise	-	-	-	0.0	NA
Piedmont	2,466,000	0.6	2,158,000	0.5	-12.1
Sardinia	-	-	-	0.0	NA
Sicily	535,000	0.1	937,000	0.2	76.1
Tuscany	257,000	0.1	132,000	0.0	-48.5
Umbria	43,000	0.0	40,000	0.0	-6.7
Veneto	3,625,000	0.7	3,146,000	0.6	-13.2
Italy	14,333,000	0.2	15,490,000	0.3	8.3

During the period under examination, the CMV IGs national demand increased by 8% compared to the previous year and stood at 15,490,000 U. However, the national average showed strong fluctuations and trends varied from one Region to another; Friuli Venezia Giulia was the Region with the highest standardized demand (1 U *per capita*), followed by Emilia-Romagna and Veneto (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 (35-37).

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

Table 46. Products containing specific varicella/zoster immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 2018-2019, at national and regional levels. The national demand for IG anti-Var showed a sharp decline (-51,7%). Total demand in 2019 was 86,625 IUs (1.4 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 2018 and 2019 (adapted by the CNS on data from the Product Quality and Pharmacrime Office - AIFA)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	1,125	0.9	1,500	1.1	33.7
Aosta Valley	4,875	38.6	1,750	13.9	-63.9
AP Bolzano	-	-	625	1.2	100.0
AP Trento	6,000	11.1	1,000	1.8	-83.4
Apulia	3,750	0.9	2,125	0.5	-43.1
Basilicata	-	-	-	-	NA
Calabria	125	0.1	375	0.2	201.5
Campania	6,125	1.1	2,625	0.5	-57.0
Emilia-Romagna	27,875	6.3	11,625	2.6	-58.4
Friuli V. Giulia	6,750	5.6	3,625	3.0	-46.3
Latium	13,750	2.3	3,750	0.6	-72.6
Liguria	4,500	2.9	4,000	2.6	-10.7

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Lombardy	66,625	6.6	35,375	3.5	-47.0
Marche	14,750	9.6	5,500	3.6	-62.6
Molise	-	-	-	-	NA
Piedmont	1,250	0.3	1,750	0.4	40.6
Sardinia	250	0.2	125	0.1	-49.7
Sicily	-	-	-	-	NA
Tuscany	5,375	1.4	1,375	0.4	-74.4
Umbria	8,000	9.0	3,125	3.5	-60.8
Veneto	8,500	1.7	6,375	1.3	-25.0
Italy	179,625	3.0	86,625	1.4	-51.7

RABIES IMMUNOGLOBULINS (ATC J06BB05)

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

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

Table 48. Products containing rabies immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 2019, the total demand for rabies IGs, recorded in ten Regions, showed a remarkable increase compared to 2018 (+67%). The total demand amounted to 185,550 IUs (3.1 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 2018 and 2019 (adapted by the CNS on data from theProduct Quality and Pharmacrime Office – AIFA)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop.	IU	IU per 1,000 pop.	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	4,500	35.8	100.0
AP Bolzano	3,450	6.5	5,550	10.4	59.8
AP Trento	3,000	5.6	3,000	5.5	-0.2
Apulia	600	0.1	3,150	0.8	427.5
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	10,350	2.3	16,650	3.7	60.6
Friuli V. Giulia	30,300	24.9	-	-	-100.0
Latium	1,500	0.3	1,500	0.3	0.3
Liguria	-	-	-	-	NA
Lombardy	22,350	2.2	14,850	1.5	-33.7
Marche	1,500	1.0	1,500	1.0	0.4
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop.	IU	IU per 1,000 pop.	
Tuscany	9,000	2.4	5,700	1.5	-36.5
Umbria	-	-	-	-	NA
Veneto	29,100	5.9	129,150	26.3	343.7
Italy	111,150	1.8	185,550	3.1	67.3

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

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

Table 50. Products containing local haemostatics-combinations currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 ingredient is expressed in mL and mL per 1,000 population (Table 51). Those products in the form of "medicated gelatin sponges" that cannot be expressed in mL no standardisation is performed and demand is calculated according to the number of packs sold (Table 52). In 2019, the total demand for local haemostatics-combinations reached a volume of about 263,712 mL (4.4 mL per 1,000 population), recording a notable increase (+63%) compared to the volume of 2018 (Table 51). In 2019, the total demand for local haemostatics-combinations, expressed in number of gelatin sponges, amounted to 36,824 sponges, recording an increase compared to 2018 (+9%) (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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	6,272	4.8	7,602	5.8	21.5
Aosta Valley	520	4.1	708	5.6	36.7
AP Bolzano	1,928	3.7	2,282	4.3	17.6
AP Trento	1,838	3.4	2,936	5.4	59.4
Apulia	10,386	2.6	16,950	4.2	64.0
Basilicata	3,440	6.1	3,112	5.5	-8.9
Calabria	4,970	2.5	4,996	2.6	1.0
Campania	23,086	4.0	38,774	6.7	68.7
Emilia-Romagna	7,686	1.7	12,382	2.8	60.9
Friuli V. Giulia	2,522	2.1	4,264	3.5	69.1
Latium	11,330	1.9	22,768	3.9	101.6
Liguria	3,226	2.1	4,556	2.9	41.8
Lombardy	24,320	2.4	52,497	5.2	115.3
Marche	2,844	1.9	4,826	3.2	70.4
Molise	428	1.4	876	2.9	106.6
Piedmont	9,506	2.2	16,001	3.7	69.1
Sardinia	4,670	2.8	5,906	3.6	27.1
Sicily	12,288	2.4	16,886	3.4	38.2
Tuscany	11,266	3.0	16,019	4.3	42.5
Umbria	2,358	2.7	4,384	5.0	86.5
Veneto	17,406	3.5	24,987	5.1	43.5
Not specified Regions	118	-	-	-	NA
Italy	162,408*	2.7	263,712	4.4	62.7

* Values update October 2020.

Table 52. Total demand (public and private) for local haemostatics-combinations, expressed in number of gelatin sponges, and variations in percentage between 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018	2019	% Var 2018-2019
Abruzzo	1,111	1,395	25.9
Aosta Valley	248	259	4.9
AP Bolzano	484	398	-18.3
AP Trento	132	178	34.5
Apulia	2,110	1,959	-6.7
Basilicata	1,200	931	-21.8
Calabria	2,324	2,170	-6.2
Campania	3,960	4,953	25.6
Emilia-Romagna	1,169	1,531	30.8
Friuli V. Giulia	54	743	1,276.3
Latium	2,761	2,146	-22.0
Liguria	559	481	-13.6
Lombardy	6,455	5,309	-18.0
Marche	1,253	1,697	36.0
Molise	24	36	51.4
Piedmont	3,421	2,799	-17.8
Sardinia	764	601	-20.9
Sicily	2,490	2,523	1.9
Tuscany	9	3,122	34,657.0
Umbria	881	947	7.8
Veneto	2,410	2,646	9.8
Italy	33,819	36,824	9.1

COAGULATION FACTOR VII (ATC B02BD05)

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

Table 53. Products containing Factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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

Quantification of the demand

In 2019, the total demand and the total standardised national demand for FVII was approximately 5.9 million IUs showing a decrease of 16% compared to 2018 (Table 54).

Despite this, a substantial increases were recorded in Calabria (+480%), Basilicata (+138%) and Emilia-Romagna (+123%). In 2019, 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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	321,600	244.5	113,400	86.5	-64.6
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	351,000	86.7	253,200	62.8	-27.5
Basilicata	57,600	101.6	136,200	242.0	138.2
Calabria	15,600	8.0	90,000	46.2	479.8
Campania	457,800	78.6	403,800	69.6	-11.4
E.-Romagna	256,800	57.7	573,600	128.6	123.0
Friuli V. Giulia	-	-	-	-	NA
Latium	2,946,000	499.6	1,798,200	305.9	-38.8
Liguria	15,000	9.6	4,800	3.1	-67.9
Lombardy	1,738,800	173.3	1,728,600	171.8	-0.8
Marche	1,200	0.8	1,200	0.8	0.4
Molise	570,000	1.847.7	270,000	883.5	-52.2
Piedmont	201,600	46.1	238,800	54.8	19.0
Sardinia	-	-	-	-	NA
Sicily	191,400	38.1	285,600	57.1	50.0
Tuscany	-	-	28,800	7.7	100.0
Umbria	-	-	4,800	5.4	100.0
Veneto	38,400	7.8	62,400	12.7	62.5
Italy	7,162,800	118.4	5,993,400	99.3	-16.2

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

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

Table 55. Products containing recombinant activated Factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 2018-2019, at national and regional level. The total demand for rFVIIa recorded in 2019 was 77,710 mg (1.3 mg per 1,000 population) with, an increase of about 26% compared to 2018.

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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Abruzzo	314	0.2	381	0.3	21.7
Aosta Valley	10	0.1	23	0.2	131.0
AP Bolzano	124	0.2	101	0.2	-19.1
AP Trento	21	0.0	20	0.0	-5.0
Apulia	6,584	1.6	9,422	2.3	43.8
Basilicata	137	0.2	43	0.1	-68.4
Calabria	6,108	3.1	7,267	3.7	19.6
Campania	6,479	1.1	10,021	1.7	55.3
E.-Romagna	3,224	0.7	2,569	0.6	-20.4
Friuli V. Giulia	22	0.0	10,900	9.0	49,458.4
Latium	4,432	0.8	3,560	0.6	-19.4
Liguria	1,014	0.7	337	0.2	-66.6

Region	2018		2019		% Var 2018-2019
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Lombardy	8,936	0.9	10,626	1.1	18.6
Marche	1,237	0.8	1,775	1.2	44.1
Molise	74	0.2	383	1.3	422.4
Piedmont	5,696	1.3	2,171	0.5	-61.7
Sardinia	483	0.3	21	0.0	-95.6
Sicily	6,922	1.4	4,648	0.9	-32.5
Tuscany	-	-	4,539	1.2	100.0
Umbria	719	0.8	436	0.5	-39.2
Veneto	9,375	1.9	8,467	1.7	-9.7
Italy	61,911	1.0	77,710	1.3	25.8

FACTOR VIII INHIBITOR BYPASSING ACTIVITY (ATC B02BD03)

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

Table 57. Products containing Factor VIII inhibitor bypassing activity currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 2018-2019 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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	FU	FU *per capita*	FU	FU *per capita*	
Abruzzo	1,687,000	1.3	1,497,000	1.1	-11.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	16,000	0.0	-	-	-100.0
AP Trento	131,000	0.2	-	-	-100.0
Apulia	470,000	0.1	164,000	0.0	-64.9
Basilicata	-	-	-	-	NA
Calabria	1,604,000	0.8	527,000	0.3	-67.0
Campania	6,073,000	1.0	2,000,000	0.3	-66.9
E.-Romagna	1,660,000	0.4	671,000	0.2	-59.6
Friuli V. Giulia	600,000	0.5	616,000	0.5	2.7
Latium	675,000	0.1	687,000	0.1	2.1
Liguria	352,000	0.2	7,000	0.0	-98.0
Lombardy	2,926,000	0.3	1,037,000	0.1	-64.6
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	1,546,000	0.4	285,000	0.1	-81.5
Sardinia	356,000	0.2	86,000	0.1	-75.7
Sicily	934,000	0.2	1,480,000	0.3	59.3
Tuscany	-	-	854,000,0	0.2	100.0
Umbria	-	-	-	-	NA
Veneto	225,000	0.0	85,000	0.0	-62.2
Italy	19,255,000	0.3	9,996,000	0.2	-48.0

In 2019, the national demand for aPCCs showed a significant decrease (-48%) compared to 2018, with some regional variations. Its total volume was 9,996,000 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 ingredient they contain expressed in milligrams (mg).

Table 59. Products containing alpha-1-proteinase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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
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 2019, the total demand for alpha-1-antitrypsin was 46,694 g (0.8 g per 1,000 population) recording a significant upward trend compared to the previous year (+ 63%) (Table 60).

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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	889	0.7	1,647	1.3	85.8
Aosta Valley	1,042	8.3	972	7.7	-6.3
AP Bolzano	1,883	3.6	2,677	5.0	41.2
AP Trento	474	0.9	626	1.2	31.8
Apulia	1,014	0.3	1,328	0.3	31.6
Basilicata	-	-	3	0.0	100.0
Calabria	282	0.1	832	0.4	196.5
Campania	3,484	0.6	5,729	1.0	65.2
E.-Romagna	1,701	0.4	2,338	0.5	37.2
Friuli V.Giulia	490	0.4	2,200	1.8	349.1
Latium	1,266	0.2	2,621	0.4	107.7
Liguria	1,279	0.8	1,356	0.9	6.5
Lombardy	6,078	0.6	9,290	0.9	52.5
Marche	295	0.2	276	0.2	-6.0
Molise	36	0.1	78	0.3	118.7
Piedmont	2,182	0.5	3,340	0.8	53.8
Sardinia	1,182	0.7	2,953	1.8	151.1

Region	2018		2019		% Var 2018-2019
	g	g per 1,000 pop	g	g per 1,000 pop	
Sicily	957	0.2	2,339	0.5	145.7
Tuscany	422	0.1	2,017	0.5	378.9
Umbria	168	0.2	189	0.2	12.8
Veneto	3,581	0.7	3,883	0.8	8.4
Italy	28,705	0.5	46,694	0.8	63.0

With the exception of Marche and Aosta Valley, all the Regions had a growing trend; in particular in Tuscany, Friuli Venezia Giulia and Calabria the demand exceeded by far the value recorded in the previous year (+378%, +349% and +196%, 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).

PLASMA-DERIVED C1-ESTERASE INHIBITOR (ATC B06AC01)

Human C1 esterase inhibitor is a heat-labile plasma protein that inhibits the uncontrolled activation of the classical complement pathway (in particular that of C1 esterase) the deficiency of which is responsible for hereditary angio-oedema. The mean concentration of the C1 inhibitor in plasma is approximately 0.2 g/L (40). Table 61 shows the brand names of medicinal products containing human C1 esterase inhibitor currently on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 61. Products containing human C1 esterase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 2019, the total demand for C1 esterase inhibitor was 13,064,500 IUs (216 IUs per 1,000 population), recording an increase of 10.6% (Table 62) compared to 2018.

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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	288,000	219.0	224,500	171.2	-21.8
Aosta Valley	164,500	1,303.5	129,500	1,030.5	-20.9
AP Bolzano	42,000	79.6	50,000	94.1	18.3
AP Trento	6,000	11.1	18,500	34.2	207.6
Apulia	1,049,000	259.1	858,000	213.0	-17.8
Basilicata	48,000	84.6	56,000	99.5	17.5
Calabria	462,000	236.1	871,500	447.6	89.6
Campania	1,688,000	289.7	1,856,500	320.0	10.5
E.-Romagna	439,000	98.6	554,500	124.3	26.1
Friuli V. Giulia	6,500	5.3	18,000	14.8	177.0
Latium	910,000	154.3	2,085,000	354.6	129.8
Liguria	134,500	86.4	29,000	18.7	-78.4
Lombardy	1,613,000	160.7	1,800,000	178.9	11.3
Marche	301,000	196.5	236,000	154.7	-21.3
Molise	3,500	11.3	10,500	34.4	202.8

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Piedmont	646,500	147.7	639,500	146.8	-0.6
Sardinia	650,000	394.4	576,000	351.3	-10.9
Sicily	1,708,000	339.8	1,219,000	243.8	-28.2
Tuscany	124,500	33.3	592,500	158.9	376.8
Umbria	310,500	351.0	276,000	312.9	-10.8
Veneto	1,237,000	252.2	964,000	196.5	-22.1
Italy	11,831,500	195.6	13,064,500	216.4	10.6

An exceptional variability in standardised regional demands was observed, with maximum volumes in the Aosta Valley, Calabria and Latium (1,030, 448 e 355 IUs per 1,000 population, respectively) and minimum volumes in Friuli Venezia Giulia, Molise, Liguria and the AP of Trento (range: 14-34 IUs per 1,000 population). In Piedmont the demand can be considered as stable, while in Abruzzo, Liguria, Marche, Apulia, Sardinia, Sicily, Umbria, Aosta Valley 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 ingredient they contain expressed in IUs.

Table 63. Products containing coagulation Factor X currently available on the Italian market (adapted by the CNS on data from Farmadati and theProduct Quality and Pharmacrime Office- AIFA, 31/12/2019)

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 2019 the demand was for 36,000 IUs (3.6 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 2018 and 2019 (adapted by the CNS on data from Product Quality and Pharmacrime Office-AIFA)

Region	2018		2019		Var % 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Lombardy	78,000	7.8	36,000	3.6	-54.0
Italy	78,000	1.3	36,000	0.6	-53.8

COAGULATION FACTOR XI (ATC B02BD)

Factor XI (FXI), also known as plasma thromboplastin antecedent (PTA) or Rosenthal Factor, is a plasma glycoprotein responsible for activating FIX (42).

Congenital FXI deficiency causes an inherited recessive autosomal haemorrhagic disorder characterised by reduced FXI levels and activity, which causes moderate bleeding generally following trauma or surgery. The prevalence of homozygous forms is estimated at 1/1,000,000; in specific ethnic groups there is a significantly higher prevalence of severe forms (43).

Table 65 shows the brand names of medicinal products containing FXI currently on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 65. Products containing recombinant coagulation Factor XI currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

AIC code	Brand name	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 2019, the demand for FXI was 23,000 IUs (0.4 IU per 1,000 population) (Table 66) significantly lower than 2018. 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 2018 and 2019 (adapted by the CNS on data from theProduct Quality and Pharmacrime Office-AIFA)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	5,000	1.2	3,450*	0.9	-30.7
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	-	-	2,606*	0.6	100.0
Friuli V. Giulia	17,000	14.0	11,730*	9.7	-31.0
Latium	-	-	2,608*	0.4	100.0
Liguria	-	-	-	-	NA
Lombardy	10,000	1.0	-	-	-100.0
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	1,000	0.2	-	-	-100.0
Sardinia	-	-	-	-	NA

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Sicily	-	-	2,606*	0.5	100.0
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	-	-	-	-	NA
Italy	33,000	0.5	23,000	0.4	-30.2

*estimated values

COAGULATION FACTOR XIII (ATC B02BD07)

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

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

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

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

Table 67. Products containing plasma-derived coagulation Factor XIII distributed in Italy (adapted by the CNS on data from Farmadati, 31/12/2019)

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, 31/12/2019)

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

Quantification of the demand

In 2019, the total demand for FXIII was 745,750 IUs (12 IUs per 1,000 population) and less than half, equal to 330,750 IUs (5.5 IUs per 1,000 population), was for pdFXIII. The latter recorded an increase of 8% compared to 2018 (Table 69).

In 2019, there was no utilisation of FXIII in some Regions. The highest demand for Factor XIII of plasma origin is in Emilia-Romagna, in the AP of Trento and Veneto (24 IUs for the first one and 18 IUs per 1,000 population for the other two Regions).

While in Abruzzo, Basilicata, Calabria, Liguria and Sicily 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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow and theProduct Quality and Pharmacrime Office-AIFA)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	9,000	16.7	9,750	18.0	8.1
Apulia	9,750	2.4	-	-	-100.0
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	106,750	24.0	107,250	24.0	0.3
Friuli V. Giulia	-	-	-	-	NA
Latium	46,250	7.8	44,750	7.6	-3.0
Liguria	2,000	1.3	-	-	-100.0
Lombardy	48,750	4.9	42,500	4.2	-13.0
Marche	15,250	10.0	12,750	8.4	-16.0
Molise	-	-	-	-	NA
Piedmont	15,750	3.6	11,250	2.6	-28.3
Sardinia	-	-	4,000	2.4	100.0
Sicily	-	-	-	-	NA
Tuscany	-	-	11,000	2.9	100.0
Umbria	-	-	-	-	NA
Veneto	53,500	10.9	87,500	17.8	63.5
Italy	307,000	5.1	330,750	5.5	8.0

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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow and theProduct Quality and Pharmacrime office, AIFA)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	65,000	49.4	75,000	57.2	15.7
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	40,000	70.5	30,000	53.3	-24.4
Calabria	122,500	62.6	135,000	69.3	10.7
Campania	-	-	-	-	NA
E.-Romagna	-	-	10,000	2.2	100.0
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	40,000	25.7	55,000	35.5	38.1
Lombardy	65,000	6.5	52,500	5.2	-19.4
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	70,000	16.0	30,000	6.9	-57.0
Sardinia	-	-	-	-	NA
Sicily	-	-	2,500	0.5	100.0
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	17,500	3.6	25,000	5.1	42.8
Italy	420,000	6.9	415,000	6.9	-1.0

PROTEIN C (ATC B01AD12)

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

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

Table 71. Products containing protein C currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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 2019, the national demand for protein C stood at a volume of 702,500 IUs (11.6 IUs per 1,000 population) with a decrease of 17% compared to 2018 (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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	7,000,0	5.3	100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	35,000	8.6	3,000	0.7	-91.4
Basilicata	-	-	-	-	NA
Calabria	62,500	31.9	132,500	68.0	113.0
Campania	163,500	28.1	127,500	22.0	-21.7
E.-Romagna	-	-	8,000,0	1.8	100.0
Friuli V. Giulia	-	-	-	-	NA
Latium	161,000	27.3	139,500	23.7	-13.1
Liguria	39,500	25.4	25,000	16.1	-36.5
Lombardy	240,000	23.9	78,000	7.8	-67.6
Marche	28,000	18.3	15,000	9.8	-46.2
Molise	-	-	-	-	NA
Piedmont	2,500	0.6	-	-	-100.0
Sardinia	14,500	8.8	34,000	20.7	135.7
Sicily	64,000	12.7	62,000	12.4	-2.6
Tuscany	-	-	40,000,0	10.7	100.0
Umbria	30,000	33.9	-	-	-100.0
Veneto	8,000	1.6	31,000	6.3	287.4
Italy	848,500	14.0	702,500	11.6	-17.0

The highest regional demand was recorded in Calabria, Latium and Campania, with 68, 24 e 22 IUs per 1,000 population respectively.

The lowest regional demand was in Apulia, Emilia-Romagna, Abruzzo and Veneto with volumes between 0.7 and 6.3 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*™)[2] and products with an albumin content of between 85 and 90% (*Umanserum*™).

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

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

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

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

Table 73. Products containing other plasma protein fractions currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2019)

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

Quantification of the demand

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

Table 74 shows the utilisation of *Plasmasafe*™ and *Octaplas*™, while Table 75 illustrates the data related to *Umanserum*™, the demand for which, in 2019, recorded an increase of 9%, and a total volume of 7,680,000 mL.

The national demand for solvent/detergent-treated plasma in 2019 decreased by 10% compared to 2018, with remarkable decreases at regional level in Abruzzo (-100%) and in Tuscany (-41.5%). High increases in demand were instead recorded in Sardinia (+ 1,156%) and Umbria (+ 652%).

[2] *Plasmagrade*® represents an AIC copy of *Plasmasafe*®, assigned to the national plasma.

Table 74. Total demand (public and private) and total standardised demand for solvent/detergent-treated plasma (excluding Umanserum™), expressed in millilitres and millilitres per 1,000 population, and variations in percentage between 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	16,000	12.2	-	-	-100.0
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	10,000	18.5	10,000	18.5	-0.2
Apulia	3,495,000	863.3	3,050,400	757.1	-12.3
Basilicata	630,000	1,110.9	496,000	881.2	-20.7
Calabria	894,000	456.9	957,000	491.5	7.6
Campania	5,616,000	963.8	4,730,000	815.3	-15.4
E.-Romagna	619,400	139.1	401,200	90.0	-35.3
Friuli V. Giulia	12,000	9.9	32,000	26.3	166.7
Latium	4,507,800	735.6	4,925,200	837.7	13.9
Liguria	666,800	428.3	776,000	500.4	16.9
Lombardy	504,000	50.2	406,000	40.4	-19.6
Marche	1,592,000	1,039.3	1,804,000	1182.7	13.8
Molise	388,400	1,259.0	468,200	1532.0	21.7
Piedmont	4,468,000	1,021.1	3,508,000	805.3	-21.1
Sardinia	8,000	4.9	100,000	61.0	1,156.5
Sicily	4,325,800	860.5	4,391,800	878.4	2.1
Tuscany	2,164,400	579.2	1,263,600	338.8	-41.5
Umbria	4,000	4.5	30,000	34.0	652.2
Veneto	3,571,800	728.2	2,726,000	555.7	-23.7
Italy	33,493,400	550.9	30,075,400	498.3	-9.6

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 2018 and 2019 (adapted by the CNS on data from the Traceability information flow)

Region	2018		2019		% Var 2018-2019
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	3,953,750	976.7	3,992,500	990.9	1.5
Basilicata	86,250	152.1	110,000	195.4	28.5
Calabria	222,500	113.7	215,000	110.4	-2.9
Campania	-	-	-	-	NA
E.-Romagna	-	-	-	-	NA
Friuli V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	-	-	-	-	NA
Lombardy	-	-	25,000	2.5	100.0
Marche	-	-	-	-	NA
Molise	-	-	2,500	8.2	100.0
Piedmont	87,500	20.0	-	-	-100.0
Sardinia	-	-	-	-	NA
Sicily	2,705,250	538.1	3,010,000	602.0	11.9
Tuscany	-	-	300,000	80.4	100.0
Umbria	-	-	25,000	28.3	100.0
Veneto	5,000	1.0	-	-	-100.0
Italy	7,060,250	116.7	7,680,000	127.2	9.0

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 Venezia Giulia, Liguria, the AP of Bolzano, the AP of Trento, Umbria, Veneto (Leading Region), and Aosta Valley;
- the Plasma/Plasma-Derived Interregional Grouping (*Raggruppamento Interregionale Plasma e Plasmaderivati*, RIPP) 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.

Plasma for fractionation

Since the year 2000, the amount of plasma collected nationwide (Figure 37) has steadily increased, going from a total of 462,805 kilograms sent for fractionation in the year 2000 to 858,900 kilograms in 2019, with a percentage increase over the entire period considered, by 85.6%.

The mean annual rate of change over the period considered was 3.3%, with two peak growth periods between the years 2004-2006 and 2008-2010.

From the year 2008 there was a steady decline in the annual rate of change (Figure 38) which, in 2014, reached the lowest value for the entire period considered (-1.1%) due to the decrease in the collection of recovered plasma. The variation in percentage between 2018 and 2019 was 1.7%.

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

In 2019, the Regions participating in the LPS agreement collected about one third of the plasma sent for fractionation for a share equal to 247,074 kilograms, those adhering to the RIPP 221,071 kilograms, those of the NAIP 198,143 kilograms and those of the PlaNet 192,612 kilograms, equal respectively to 29%, 26%, 23% and 22% of the national total (Figure 39).

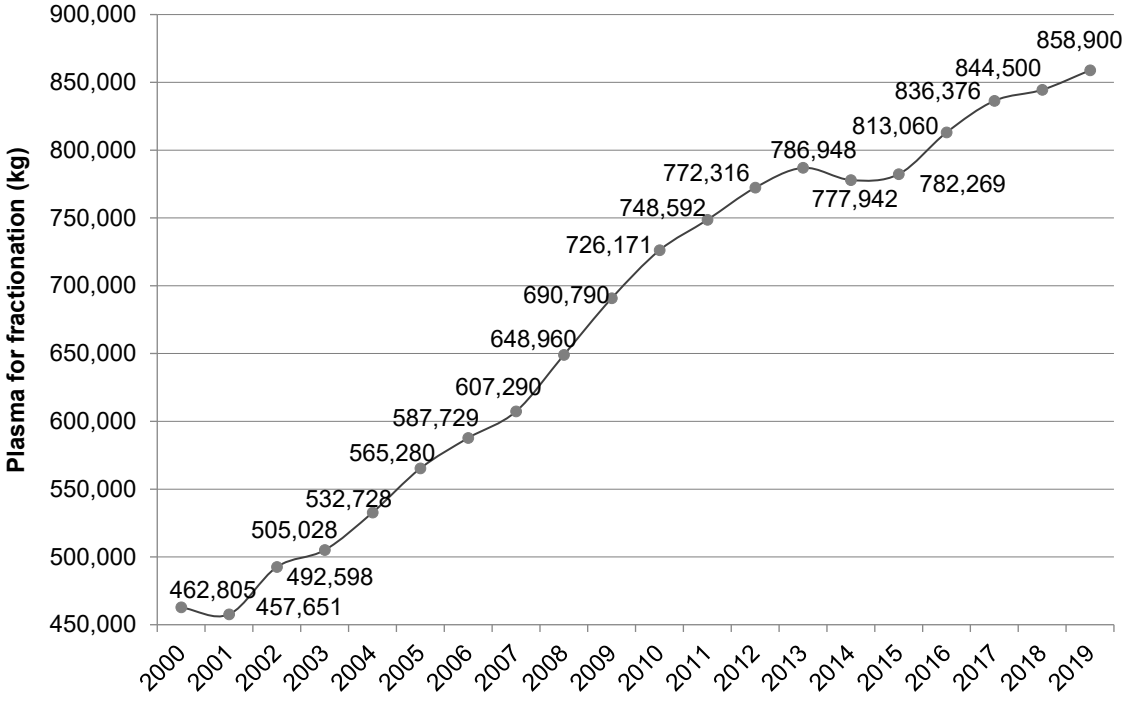

Figure 37. Plasma sent for fractionation 2000-2019 (adapted by the CNS on Kedrion and CSL Behring data, January 2021)

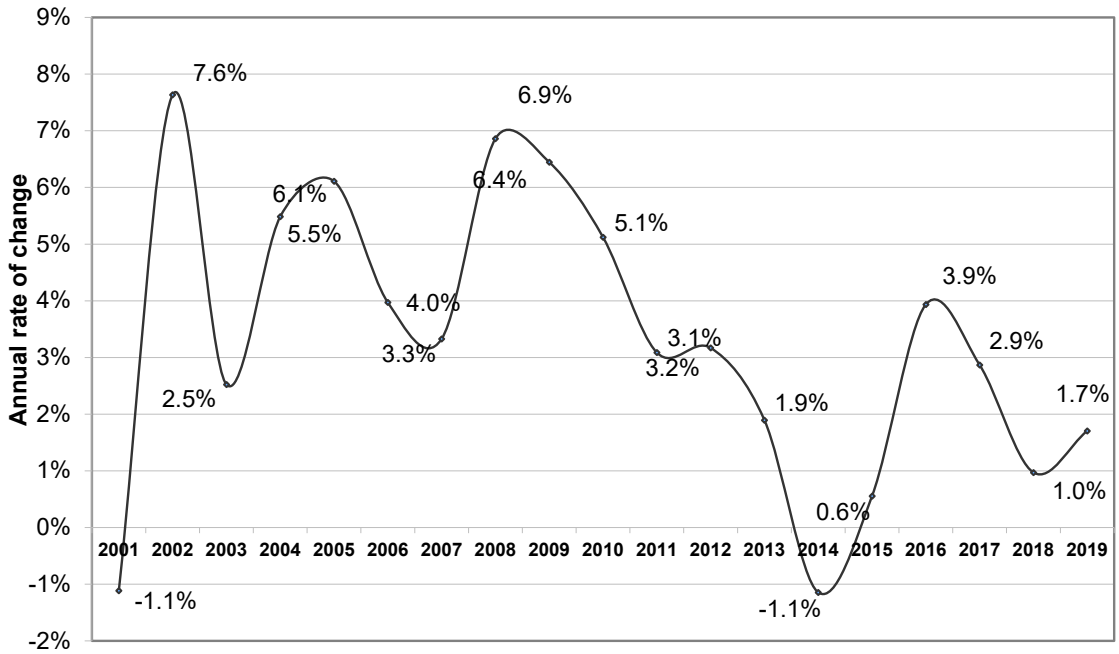

Figure 38. Annual rate of change in the amount of plasma for fractionation, from 2001 to 2019 (adapted by the CNS on Kedrion and CSL Behring data, January 2021)

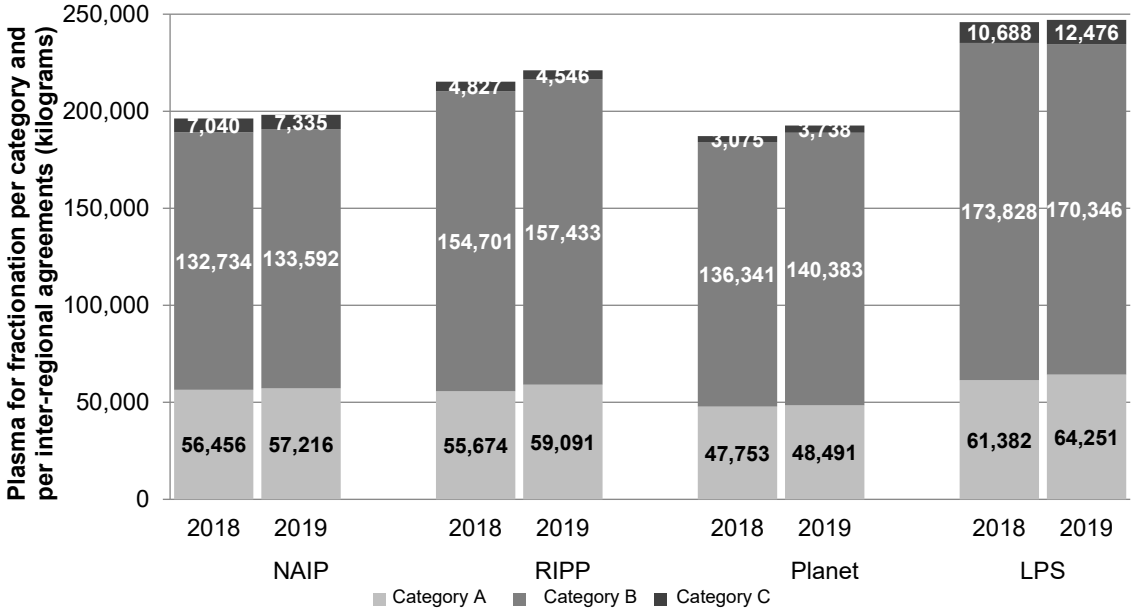

Figure 39. Total amount of plasma for fractionation by category under interregional agreements (kilograms), 2018-2019 (adapted by the CNS on data provided by Kedrion and CSL Behring, January 2021)

As regards the amount of plasma sent for fractionation in 2019, for the resident population, the NAIP Regions sent 17.0 kilograms of plasma per 1,000 population (almost comparable to the 2018 volume for the same Regions), the LPS Regions 15.4 kilograms, the RIPP Regions 14.3 kilograms and the PlaNet Regions 11.2 kilograms per 1,000 population (Figure 40).

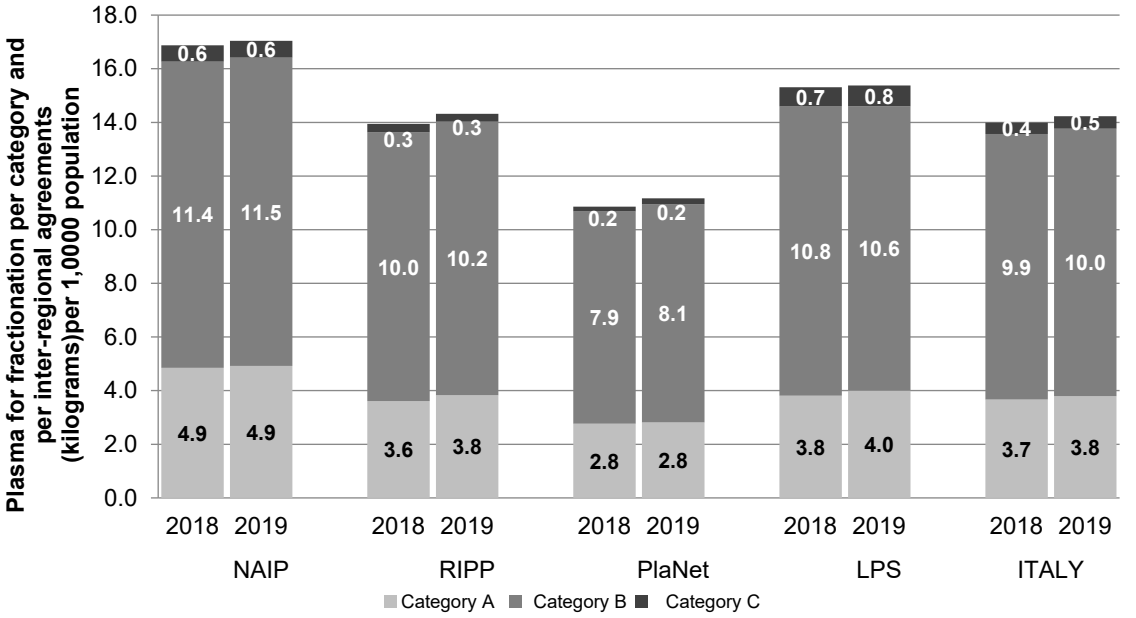

Figure 40. Total amount of plasma for fractionation by categoryunder interregional agreements (kilograms per 1,000 population), 2018-2019 (adapted by the CNS on data provided by Kedrion and CSL Behring, January 2021)

In 2019, although the national volume stood at 14.2 kilograms per 1,000 population (14.0 in 2018), with regional contributions in volumes differing greatly one from another. In point of fact, the best performance was achieded by Friuli Venezia Giulia with 23.6 kilograms per 1,000 population, followed by Marche with 22.9 and Emilia-Romagna with 20.9, while the lowest volumes, albeit with increasing values compared to 2018, were recorded in Calabria, Latium and Campania with 9.3, 7.7 and 6 kilograms per 1,000 population, respectively (Figure 41).

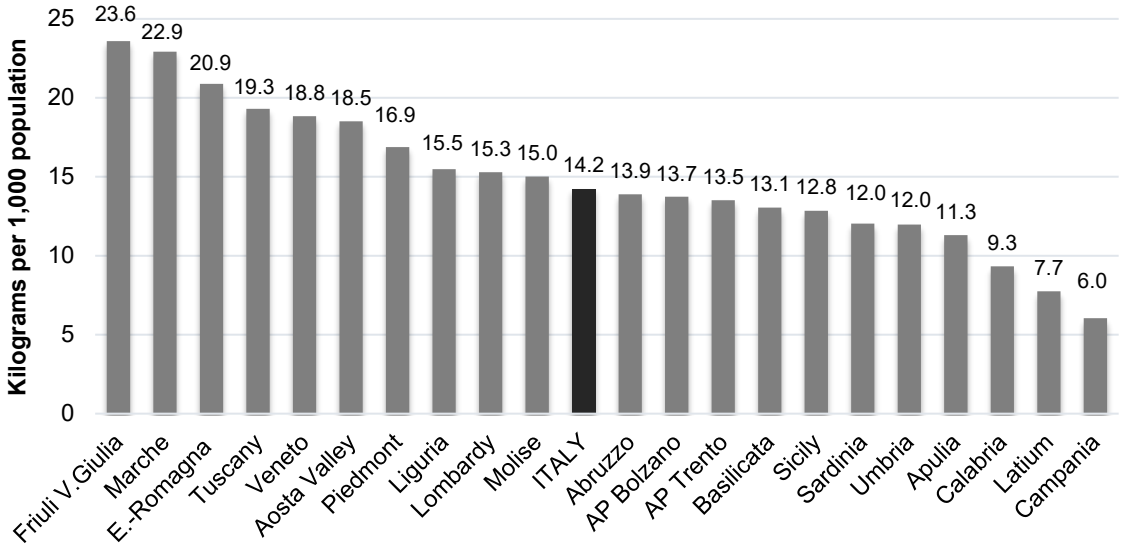

Figure 41.Total amount of plasma (kilograms per 1,000 population) for fractionation by Region, year 2019 (adapted by the CNS on data provided by Kedrion and CSL Behring, January 2021)

Supply of PDMPs from toll fractionation

In 2019, the total quantity of plasma sent for fractionation by the Italian Regions was 858,900 kilograms (Table 76); of these, 27% (229,050 kilograms) was apheresis plasma (category A), 70% (601,755 kilograms) recovered plasma (category B) and the remaining 3% (28,095 kilograms) plasma intended solely for the recovery of non-labile proteins (category C). The percentages of all three categories of plasma sent for fractionation varied from one regional area to another and from one consortium to another. In particular, the percentages of apheresis plasma (category A) for fractionation varied from 25.2% sent by PlaNet consortium to 28.9% sent by NAIP, while the percentage of plasma intended solely for the recovery of non-labile proteins (category C) varied from 2.0% sent by PlaNet 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 2019 (from July 2018 to June 2019). 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 15,000 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 2019 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 2018-2019 classified by Region and plasma category (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	A	%	B	%	C	%	Tot. Fract.	Total per 1,000 pop
Abruzzo	5,141	1.1	12,947	3.4	134	-22.5	18,221	13.9
Aosta Valley	816	-15.4	1,511	-1.5	-	-	2,327	18.5
AP Bolzano	1,375	10.7	5,920	-2.1	-	-	7,295	13.7
AP Trento	536	-11.7	6,776	2.3	-	-	7,312	13.5
Basilicata	1,462	-13.1	5,311	11.9	573	-28.1	7,347	13.1
Friuli V. Giulia	13,348	11.0	14,568	-2.1	747	983.1	28,663	23.6
Liguria	6,264	6.6	17,744	-1.8	-	-100.0	24,008	15.5
Umbria	1,710	28.7	8,850	0.4	-	-	10,560	12.0
Veneto	26,565	-3.9	59,965	0.8	5,881	-1.6	92,410	18.8
NAIP	**57,216**	**1.3**	**133,592**	**0.6**	**7,335**	**4.2**	**198,143**	**17.0**
Apulia	6,168	6.2	37,797	1.8	1,590	-24.9	45,555	11.3
Calabria	1,105	33.2	17,021	4.1	34	129.2	18,159	9.3
Emilia-Romagna	37,446	10.4	52,778	1.4	2,895	12.0	93,119	20.9
Sicily	14,373	-4.9	49,837	1.4	28	-74.3	64,238	12.8
RIPP	**59,091**	**6.1**	**157,433**	**1.8**	**4,546**	**-5.8**	**221,071**	**14.3**
Campania	762	102.1	32,632	7.8	1,669	26.7	35,063	6.0
Latium	4,604	6.6	39,197	2.3	1,728	8.1	45,530	7.7
Marche	13,824	-0.7	21,139	-2.5	-	-	34,962	22.9
Molise	892	19.1	3,698	6.6	-	-	4,590	15.0
Tuscany	28,409	0.1	43,570	2.8	-	-	71,980	19.3
Ministry of Defence	-	-	147	-36.2	341	113.8	488	-
PlaNet	**48,491**	**1.5**	**140,383**	**3.0**	**3,738**	**21.5**	**192,612**	**16.8**
Lombardy	42,695	2.6	101,845	-5.7	9,267	75.4	153,807	15.3
Piedmont	20,730	9.1	50,167	-0.1	2,632	-0.5	73,530	16.9
Sardinia	826	4.5	18,335	17.7	577	-79.1	19,738	12.0
LPS	**64,251**	**4.7**	**170,346**	**-2.0**	**12,476**	**16.7**	**247,074**	**15.4**
ITALY	**229,050**	**3.5**	**601,755**	**0.7**	**28,095**	**9.6**	**858,900**	**14.2**

Table 77. Potential supply of toll fractionated PDMPs based on the amount of plasma sent for fractionation from July 2018 to June 2019 and the yields provided by the fractionation industry – year 2019 (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	2nd semester 2018	1st semester 2019	TOTAL	Albumin	Human Immunoglobulin	Factor VIII	Factor VIII / vW Factor	FIX / 3F-PCC	Antithrombin	Fibrinogen
	kg	kg	kg	g	g	UI	UI	UI	UI	g
Abruzzo	8,851	8,804	17,655	441,374	86,509	1,606,602	529,649	-	-	683
Aosta Valley	1,214	1,282	2,496	62,394	12,229	227,115	74,873	-	-	97
AP Bolzano	3,824	3,627	7,451	186,269	36,509	678,019	223,523	-	-	288
AP Trento	3,824	3,644	7,468	186,698	36,593	679,581	224,038	-	-	289
Basilicata	3,484	3,518	7,002	175,055	34,311	637,199	210,066	-	-	271
Friuli V. Giulia	13,541	13,839	27,380	684,498	134,162	2,491,573	821,398	-	-	1,059
Liguria	11,995	11,970	23,965	599,128	117,429	2,180,826	718,954	-	-	927
Umbria	5,157	5,004	10,161	254,017	49,787	924,623	304,821	-	-	393
Veneto	46,530	45,874	92,405	2,310,115	452,783	8,408,820	2,772,138	-	-	3,575
NAIP	**98,420**	**97,562**	**195,982**	**4,899,549**	**960,312**	**17,834,358**	**5,879,459**	**-**	**-**	**7,581**
Apulia	22,388	22,298	44,686	1,161,837	178,744	5,591,740	-	6,524,160	6,121,985	-
Calabria	8,665	9,473	18,138	471,600	72,554	2,355,259	-	2,648,217	2,484,971	-
Emilia-Romagna	44,152	46,558	90,710	2,358,454	362,839	11,450,170	-	13,243,625	12,427,237	-
Sicily	33,190	32,706	65,896	1,713,290	263,583	8,560,136	-	9,620,784	9,027,722	-
RIPP	**108,395**	**111,035**	**219,430**	**5,705,181**	**877,720**	**27,957,305**	**-**	**32,036,786**	**30,061,916**	**-**
Campania	16,679	16,654	33,333	866,657	133,332	4,164,799	-	4,866,614	4,566,618	-
Latium	22,048	22,447	44,495	1,156,857	177,978	5,567,734	-	6,496,199	6,095,748	-
Marche	17,341	18,296	35,637	926,574	142,550	4,632,869	-	5,203,068	4,882,331	-
Molise	2,005	2,351	4,356	113,246	17,422	566,230	-	635,920	596,720	-
Tuscany	35,002	35,409	70,411	1,830,691	281,645	9,153,456	-	10,280,035	9,646,334	-
Ministry of Defence	187	235	421	10,955	1,685	22,463	-	61,517	57,725	-
PlaNet	**93,261**	**95,392**	**188,653**	**4,904,981**	**754,612**	**24,107,551**	**-**	**27,543,354**	**25,845,476**	**-**
Lombardy	76,249	77,804	154,053	4,005,390	616,214	19,104,115	-	22,491,807	21,105,326	-
Piedmont	35,390	36,547	71,937	1,870,368	287,749	9,026,677	-	10,502,834	9,855,399	-
Sardinia	9,775	9,165	18,940	492,429	75,758	2,256,954	-	2,765,181	2,594,724	-
LPS	**121,414**	**123,516**	**244,930**	**6,368,187**	**979,721**	**30,387,746**	**-**	**35,759,822**	**33,555,449**	**-**
Italy	**421,490**	**427,505**	**848,995**	**21,877,898**	**3,572,365**	**100,286,960**	**5,879,459**	**95,339,962**	**89,462,841**	**7,581**

Table 78. Potential supply of solvent/detergent-treated plasma based on the amount of plasma sent for fractionation from July 2018 to June 2019 and the yields provided by the fractionation industry – year 2019 (adapted by the CNS on data provided by Kedrion)

Region	2nd semester 2018 kg	1st semester 2019 kg	Total kg	Solvent/detergent-treated plasma mL
Abruzzo	-	-	-	-
Aosta Valley	-	-	-	-
AP Bolzano	-	-	-	-
AP Trento	-	-	-	-
Apulia	-	-	-	-
Basilicata	-	-	-	-
Calabria	-	-	-	-
Campania	994	2,357	3,351	3,085,981
E.-Romagna	-	-	-	-
Friuli V. Giulia	-	-	-	-
Latium	1,240	1,350	2,590	2,385,356
Liguria	-	-	-	-
Lombardy	-	-	-	-
Marche	1,057	1,321	2,378	2,189,817
Molise	461	275	737	678,422
Piedmont	2,059	2,619	4,678	4,308,642
Sardinia	-	-	-	-
Sicily	379	950	1,329	1,223,555
Tuscany	-	-	-	-
Umbria	-	-	-	-
Veneto	-	-	-	-
Ministry of Defence	-	-	-	-
Italy	**6,191**	**8,871**	**15,062**	**13,871,774**

Table 79. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs classified by Region for the year 2019 (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	480,200	83,500	8,040	60,000	380,000	30,000	715,000	1,360,000	870	-
Aosta Valley	54,600	21,925	1,500	-	10,000	-	80,000	192,000	50	-
AP Bolzano	152,170	40,200	2,160	352,000	820,000	26,000	432,000	202,000	-	-
AP Trento	156,700	45,550	2,160	17,000	40,000	-	379,000	199,000	130	-
Basilicata	231,300	18,410	960	52,000	-	10,000	340,000	928,000	280	-
Friuli V. Giulia	475,000	107,700	480	576,000	130,000	32,000	832,000	2,624,000	1,100	-
Liguria	619,500	162,775	3,900	992,000	400,000	64,000	816,000	2,432,000	500	86,000
Umbria	477,100	65,800	15,340	496,000	220,000	20,000	586,000	786,000	970	-
Veneto	2,110,200	434,455	41,080	10,962,000	1,770,000	663,000	3,992,000	5,927,000	1,560	2,636,000
NAIP	**4,756,770**	**980,315**	**75,620**	**13,507,000**	**3,770,000**	**845,000**	**8,172,000**	**14,650,000**	**5,460**	**2,722,000**
Apulia	1,315,160	235,830	20	4,191,000	-	83,000	1,541,000	7,198,000	-	82,000
Calabria	684,130	81,235	-	507,000	-	58,000	400,500	8,708,000	-	-
E.-Romagna	2,253,900	369,105	-	2,881,000	-	298,000	3,346,000	1,878,000	-	-
Sicily	2,449,000	228,260	-	1,017,000	-	172,000	2,922,500	16,442,000	-	1,812,200
RIPP	**6,702,190**	**914,430**	**20**	**8,596,000**	**-**	**611,000**	**8,210,000**	**34,226,000**	**-**	**1,894,200**
Campania	1,057,000	120,500	3,088	3,846,000	-	-	1,656,000	5,512,000	-	4,480,000
Latium	1,141,090	176,095	-	4,712,000	-	1,221,000	1,748,500	7,591,000	-	3,273,200
Marche	565,900	178,670	264	1,792,000	-	778,000	1,286,000	2,907,000	-	1,804,000
Molise	93,000	7,760	-	200,000	-	-	246,000	882,000	-	468,200
Tuscany	1,165,390	284,643	3,624	3,582,000	-	1,157,000	2,512,500	6,375,000	-	-
Ministry of Defence	3,550	-	-	-	-	-	-	-	-	-
PlaNet	**4,025,930**	**767,668**	**6,976**	**14,132,000**	**-**	**3,156,000**	**7,449,000**	**23,267,000**	**-**	**10,025,400**
Lombardy	4,262,470	553,335	2,164	12,447,000	-	556,000	6,053,000	6,182,000	-	404,000
Piedmont	1,261,800	350,000	-	10,127,000	-	211,000	3,092,000	6,395,000	-	3,508,000
Sardinia	977,950	73,545	-	869,000	-	-	1,697,000	1,836,000	-	52,000
LPS	**6,502,220**	**976,880**	**2,164**	**23,443,000**	**-**	**767,000**	**10,842,000**	**14,413,000**	**-**	**3,964,000**

ANALYSIS OF SELF-SUFFICIENCY

Albumin

In 2019, the Italian NHS demand for albumin accounted for 81% of the total. The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, was 76% (+3% compared to 2018) equal to the effective self-sufficiency, when considered as the ratio between the actual supply of toll fractionation and the NHS demand (Table 80).

The Regions that in 2019 achieved effective self-sufficiency – more than 90% – were Friuli Venezia Giulia, Liguria, AP of Trento, Umbria, Aosta Valley, Veneto, Emilia-Romagna, and Marche.

Table 80. Regional and national self-sufficiency in albumin, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	788,006	701,548	441,374	480,200	63	68
Aosta Valley	54,740	54,600	62,394	54,600	114	100
AP Bolzano	170,735	169,795	186,269	152,170	110	90
AP Trento	169,975	162,240	186,698	156,700	115	97
Basilicata	374,618	363,488	175,055	231,300	48	64
Friuli V. Giulia	485,748	477,593	684,498	475,000	143	99
Liguria	681,253	659,405	599,128	619,500	91	94
Umbria	487,178	484,293	254,017	477,100	52	99
Veneto	2,331,200	2,159,910	2,310,115	2,110,200	107	98
NAIP	**5,543,451**	**5,232,870**	**4,899,549**	**4,756,770**	**94**	**91**
Apulia	2,149,115	1,752,153	1,161,837	1,315,160	66	75
Calabria	1,177,356	1,069,775	471,600	684,130	44	64
E.-Romagna	2,719,348	2,402,518	2,358,454	2,253,900	98	94
Sicily	3,593,925	2,905,195	1,713,290	2,449,000	59	84
RIPP	**9,639,743**	**8,129,640**	**5,705,181**	**6,702,190**	**70**	**82**
Campania	4,868,173	3,950,680	866,657	1,057,000	22	27
Latium	3,640,838	2,028,313	1,156,857	1,141,090	57	56
Marche	677,360	575,925	926,574	565,900	161	98
Molise	215,810	114,638	113,246	93,000	99	81
Tuscany	1,418,978	1,350,705	1,830,691	1,165,390	136	86
Min. of Def.	-	-	10,955	3,550	-	-
PlaNet	**10,821,158**	**8,020,260**	**4,904,981**	**4,025,930**	**61**	**50**
Lombardy	6,558,565	4,778,565	4,005,390	4,262,470	84	89
Piedmont	1,524,778	1,396,435	1,870,368	1,261,800	134	90
Sardinia	1,406,075	1,360,215	492,429	977,950	36	72
LPS	**9,489,418**	**7,535,215**	**6,368,187**	**6,502,220**	**85**	**86**
Italy	**35,493,769**	**28,917,985**	**21,877,898**	**21,987,110**	**76**	**76**

The Regions that mostly benefitted from interregional compensation in 2019 were: Umbria (99% effective self-sufficiency compared to the potential 52%) and Basilicata (64% compared to 48%) for NAIP, Sardinia (72% compared to 36%) for LPS; Calabria (effective self-sufficiency 64% compared to the potential 44%) and Sicily (effective self-sufficiency 84% compared to the potential 59%) for the RIPP consortium.

The Regions that remained farthest from the goal of effective self-sufficiency were Campania, Latium Basilicata and Calabria, with percentages ranging between 27 and 64% of the NHS demand met by the toll fractionation supply.

Normal human immunoglobulins

In 2019, the NHS demand for normal IGs accounted for 92% of the total demand (Table 81).

Table 81. Regional and national self-sufficiency in human immunoglobulins, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	123,896	123,421	86,509	91,540	70	74
Aosta Valley	24,098	24,098	12,229	23,425	51	97
AP Bolzano	46,847	46,847	36,509	42,360	78	90
AP Trento	51,816	51,816	36,593	47,710	71	92
Basilicata	35,573	35,573	34,311	19,370	96	54
Friuli V. Giulia	117,266	117,266	134,162	108,180	114	92
Liguria	238,587	236,917	117,429	166,675	50	70
Umbria	101,526	101,526	49,787	81,140	49	80
Veneto	586,903	563,623	452,783	475,535	80	84
NAIP	**1,326,511**	**1,301,086**	**960,312**	**1,055,935**	**74**	**81**
Apulia	464,367	443,009	178,744	235,850	40	53
Calabria	118,200	118,165	72,554	81,235	61	69
E.-Romagna	506,953	506,048	362,839	369,105	72	73
Sicily	348,393	339,790	263,583	228,260	78	67
RIPP	**1,437,912**	**1,407,012**	**877,720**	**914,450**	**62**	**65**
Campania	448,300	419,804	133,332	123,588	32	29
Latium	671,547	499,671	177,978	176,095	36	35
Marche	217,951	217,715	142,550	178,934	65	82
Molise	45,059	11,219	17,422	7,760	155	69
Tuscany	682,203	645,008	281,645	288,267	44	45
Min. of Def.	-	-	1,685	-	NA	NA
PlaNet	**2,065,060**	**1,793,418**	**754,612**	**774,644**	**42**	**43**
Lombardy	953,728	792,582	616,214	555,499	78	70
Piedmont	526,250	524,248	287,749	350,000	55	67
Sardinia	99,427	99,257	75,758	73,545	76	74
LPS	**1,579,405**	**1,416,087**	**979,721**	**979,044**	**69**	**69**
Italy	**6,408,888**	**5,917,603**	**3,572,365**	**3,724,073**	**60**	**63**

The national potential self-sufficiency, espressed by the ratio of the potential supply to the NHS demand, in 2019 was 60%, where effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to NHS demand, was 63%.

The only Region to achieve effective self-sufficiency in IGs in 2019 – more than 90% – was Friuli Venezia Giulia, AP of Trento and Aosta Valley while the Regions that achieved the lowest effective self-sufficiency were Campania (29%), Latium (35%), Tuscany (45%).

Normal human immunoglobulins for subcutaneous use

In 2019, the NHS demand for immunoglobulins for subcutaneous / intramuscular use represented approximately 99% of the total demand (Table 82).

Table 82. Regional and national self-sufficiency in human immunoglobulin for subcutaneous use, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	32,252	32,212	86,509	8,040	269	25
Aosta Valley	2,163	2,163	12,229	1,500	565	69
AP Bolzano	4,151	4,151	36,509	2,160	880	52
AP Trento	5,386	5,386	36,593	2,160	679	40
Basilicata	11,480	11,480	34,311	960	299	8
Friuli V. Giulia	5,008	5,008	134,162	480	2,679	10
Liguria	45,487	45,487	117,429	3,900	258	9
Umbria	32,231	32,231	49,787	15,340	154	48
Veneto	118,001	118,001	452,783	41,080	384	35
NAIP	**256,159**	**256,119**	**960,312**	**75,620**	**375**	**30**
Apulia	119,373	119,373	178,744	20	150	0
Calabria	34,748	34,748	72,554	-	209	0
E.-Romagna	109,782	109,782	362,839	-	331	0
Sicily	88,861	88,841	263,583	-	297	0
RIPP	**352,765**	**352,745**	**877,720**	**20**	**249**	**0**
Campania	113,749	113,749	133,332	3,088	117	3
Latium	186,314	186,314	177,978	-	96	0
Marche	26,846	26,730	142,550	264	533	1
Molise	3,459	3,459	17,422	-	504	0
Tuscany	170,137	169,957	281,645	3,624	166	2
Min. of Def.			1,685		NA	NA
PlaNet	**500,505**	**500,209**	**754,612**	**6,976**	**151**	**1**
Lombardy	107,879	98,924	616,214	2,164	623	2
Piedmont	97,821	97,821	287,749	-	294	0
Sardinia	7,397	7,397	75,758	-	1,024	0
LPS	**213,097**	**204,142**	**979,721**	**2,164**	**480**	**1**
Italy	**1,322,527**	**1,313,216**	**3,572,365**	**84,780**	**272**	**6**

The effective self-sufficiency, regarded as the ratio between the actual supply of the processing account and the NHS demand, was 6%.

No Region in 2019 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 2019, the NHS demand for IV IGs accounted for 91% of the total demand (Table 83).

Table 83. Regional and national self-sufficiency in human immunoglobulin for for intravenous use, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	91,644	91,209	86,509	83,500	95	92
Aosta Valley	21,935	21,935	12,229	21,925	56	100
AP Bolzano	42,696	42,696	36,509	40,200	86	94
AP Trento	46,430	46,430	36,593	45,550	79	98
Basilicata	24,093	24,093	34,311	18,410	142	76
Friuli V. Giulia	112,258	112,258	134,162	107,700	120	96
Liguria	193,100	191,430	117,429	162,775	61	85
Umbria	69,295	69,295	49,787	65,800	72	95
Veneto	468,902	445,622	452,783	434,455	102	97
NAIP	**1,070,352**	**1,044,967**	**960,312**	**980,315**	**92**	**94**
Apulia	344,993	323,636	178,744	235,830	55	73
Calabria	83,452	83,417	72,554	81,235	87	97
E.-Romagna	397,171	396,266	362,839	369,105	92	93
Sicily	259,532	250,949	263,583	228,260	105	91
RIPP	**1,085,147**	**1,054,267**	**877,720**	**914,430**	**83**	**87**
Campania	334,551	306,055	133,332	120,500	44	39
Latium	485,232	313,357	177,978	176,095	57	56
Marche	191,105	190,985	142,550	178,670	75	94
Molise	41,600	7,760	17,422	7,760	225	100
Tuscany	512,067	475,052	281,645	284,643	59	60
Min. of Def.	-	-	1,685	-	-	NA
PlaNet	**1,564,555**	**1,293,209**	**754,612**	**767,668**	**58**	**59**
Lombardy	845,848	693,658	616,214	553,335	89	80
Piedmont	428,430	426,427	287,749	350,000	67	82
Sardinia	92,030	91,860	75,758	73,545	82	80
LPS	**1,366,308**	**1,211,945**	**979,721**	**976,880**	**81**	**81**
Italy	**5,086,361**	**4,604,387**	**3,572,365**	**3,639,293**	**78**	**79**

The national potential self-sufficiency, espressed by the ratio of the potential supply to NHS demand, in 2019 was 78% (77% in 2018). Effective self-sufficiency, assumed as the ratio of the actual supply of toll fractionation to NHS demand, was 79%, against 74% in 2018.

The Regions that in 2019 achieved effective self-sufficiency (more than 90%) were Abruzzo, Friuli Venezia Giulia, the AP of Bolzano, the 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% (39%).

Antithrombin

NHS demand for AT compared to national total demand dropped from 94% in 2011 to 89% in 2019. Effective self-sufficiency recorded a value of 82% in 2019, significantly lower than the potential self-sufficiency (85%) (Table 84).

Table 84. Regional and national self-sufficiency in antithrombin, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	1,408,500	1,360,000	-	1,360,000	-	100
Aosta Valley	192,000	192,000	-	192,000	-	100
AP Bolzano	202,000	202,000	-	202,000	-	100
AP Trento	200,000	199,000	-	199,000	-	100
Basilicata	1,170,000	1,170,000	-	928,000	-	79
FVG	2,634,000	2,624,000	-	2,624,000	-	100
Liguria	2,508,500	2,472,000	-	2,432,000	-	98
Umbria	786,000	786,000	-	786,000	-	100
Veneto	6,002,500	5,927,000	-	5,927,000	-	100
NAIP	**15,103,500**	**14,932,000**	**-**	**14,650,000**	**-**	**98**
Apulia	8,360,500	7,388,000	6,121,985	7,198,000	83	97
Calabria	10,402,500	9,103,000	2,484,971	8,708,000	27	96
E.-Romagna	2,732,000	1,898,000	12,427,237	1,878,000	655	99
Sicily	17,292,500	16,906,000	9,027,722	16,442,000	53	97
RIPP	**38,787,500**	**35,295,000**	**30,061,916**	**34,226,000**	**85**	**97**
Campania	16,209,000	14,835,000	4,566,618	5,512,000	31	37
Latium	20,023,500	14,660,000	6,095,748	7,591,000	42	52
Marche	2,917,000	2,907,000	4,882,331	2,907,000	168	100
Molise	972,000	882,000	596,720	882,000	68	100
Tuscany	6,400,500	6,395,000	9,646,334	6,375,000	151	100
Min. of Def.	-	-	57,725	-	NA	NA
PlaNet	**46,522,000**	**39,679,000**	**25,845,476**	**23,267,000**	**65**	**59**
Lombardy	8,671,500	7,178,500	21,105,326	6,182,000	294	86
Piedmont	6,898,000	6,395,000	9,855,399	6,395,000	154	100
Sardinia	1,984,000	1,981,000	2,594,724	1,836,000	131	93
LPS	**17,553,500**	**15,554,500**	**33,555,449**	**14,413,000**	**216**	**93**
Italy	**117,966,500**	**105,460,500**	**89,462,841**	**86,556,000**	**85**	**82**

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 2019, except for Basilicata, Campania, Latium and Lombardy. The Regions that mostly benefitted from interregional compensation in 2019 were Calabria (96% effective *vs.* 27% potential self-sufficiency), Sicily (97% effective *vs.* 53% potential), and Molise (100% effective *vs.* 68% potential self-sufficiency). The farthest Regions from the objective of effective self-sufficiency were Campania (37%) and Latium (52%).

Coagulation Factor VIII

In 2019, 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 2019, 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. Regional and national self-sufficiency in plasma-derived Factor VIII, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	60,000	60,000	1,606,602	60,000	2,678	100
Aosta Valley	-	-	227,115	-	NA	NA
AP Bolzano	352,000	352,000	678,019	352,000	193	100
AP Trento	17,000	17,000	679,581	17,000	3,998	100
Basilicata	52,000	52,000	637,199	52,000	1,225	100
FVG	576,000	576,000	2,491,573	576,000	433	100
Liguria	992,000	992,000	2,180,826	992,000	220	100
Umbria	496,000	496,000	924,623	496,000	186	100
Veneto	10,962,000	10,962,000	8,408,820	10,962,000	77	100
NAIP	**13,507,000**	**13,507,000**	**17,834,358**	**13,507,000**	**132**	**100**
Apulia	4,543,000	4,543,000	5,591,740	4,191,000	123	92
Calabria	507,000	507,000	2,355,259	507,000	465	100
E.-Romagna	2,881,000	2,881,000	11,450,170	2,881,000	397	100
Sicily	1,017,000	1,017,000	8,560,136	1,017,000	842	100
RIPP	**8,948,000**	**8,948,000**	**27,957,305**	**8,596,000**	**312**	**96**
Campania	3,846,000	3,846,000	4,164,799	3,846,000	108	100
Latium	4,713,000	4,712,000	5,567,734	4,712,000	118	100
Marche	1,792,000	1,792,000	4,632,869	1,792,000	259	100
Molise	200,000	200,000	566,230	200,000	283	100
Tuscany	3,582,000	3,582,000	9,153,456	3,582,000	256	100
Min. of Def.	-	-	22,463	-	NA	NA
PlaNet	**14,133,000**	**14,132,000**	**24,107,551**	**14,132,000**	**171**	**100**
Lombardy	12,987,000	12,987,000	19,104,115	12,447,000	147	96
Piedmont	10,127,000	10,127,000	9,026,677	10,127,000	89	100
Sardinia	869,000	869,000	2,256,954	869,000	260	100
LPS	**23,983,000**	**23,983,000**	**30,387,746**	**23,443,000**	**127**	**98**
Italy	**60,571,000**	**60,570,000**	**100,286,960**	**59,678,000**	**166**	**99**

Table 86. Regional and national self-sufficiencyin plasma-derived Factor VIII and von Willebrand Factor in combination, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	2,517,000	2,517,000	529,649	380,000	21	15
Aosta Valley	10,000	10,000	74,873	10,000	749	100
AP Bolzano	874,000	874,000	223,523	820,000	26	94
AP Trento	111,000	111,000	224,038	40,000	202	36
Basilicata	40,000	40,000	210,066	-	525	0
FVG	183,000	183,000	821,398	130,000	449	71
Liguria	409,000	409,000	718,954	400,000	176	98
Umbria	945,000	945,000	304,821	220,000	32	23
Veneto	2,579,500	2,579,500	2,772,138	1,770,000	107	69
NAIP	**7,668,500**	**7,668,500**	**5,879,459**	**3,770,000**	**77**	**49**
Apulia	6,741,500	6,672,500	-	-	-	-
Calabria	1,107,500	858,500	-	-	-	-
E.-Romagna	3,019,250	3,011,500	-	-	-	-
Sicily	4,307,000	4,219,000	-	-	-	-
RIPP	**15,175,250**	**14,761,500**	**-**	**-**	**-**	**-**

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Campania	4,226,500	4,225,000	-	-	-	-
Latium	9,065,500	8,665,500	-	-	-	-
Marche	539,000	539,000	-	-	-	-
Molise	405,000	204,000	-	-	-	-
Tuscany	2,275,000	2,269,000	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	**16,511,000**	**15,902,500**	**-**	**-**	**-**	**-**
Lombardy	5,937,000	5,706,750	-	-	-	-
Piedmont	3,671,000	3,629,500	-	-	-	-
Sardinia	1,526,000	1,526,000	-	-	-	-
LPS	**11,134,000**	**10,862,250**	**-**	**-**	**-**	**-**
Italy	**50,488,750**	**49,194,750**	**5,879,459**	**3,770,000**	**12**	**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 (96% of the NHS demand), as in 2018. The regional self-sufficiency still bore significant differences with a range, varying from 81 to 100% confirming the need of improvement in the inter-regional exchange and compensation mechanisms (Table 87).

Table 87. Regional and national self- sufficiency in plasma-derived Factor IX and 3-factor prothrombin complex concentrates, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	745,000	745,000	-	745,000	-	100
Aosta Valley	80,000	80,000	-	80,000	-	100
AP Bolzano	458,000	458,000	-	458,000	-	100
AP Trento	379,000	379,000	-	379,000	-	100
Basilicata	350,000	350,000	-	350,000	-	100
FVG	864,000	864,000	-	864,000	-	100
Liguria	1,117,000	880,000	-	880,000	-	100
Umbria	739,500	739,500	-	606,000	-	82
Veneto	4,767,500	4,742,000	-	4,655,000	-	98
NAIP	**9,500,000**	**9,237,500**	**-**	**9,017,000**	**-**	**98**
Apulia	2,321,000	1,624,000	6,524,160	1,624,000	402	100
Calabria	462,500	458,500	2,648,217	458,500	578	100
E.-Romagna	4,052,000	3,744,000	13,243,625	3,644,000	354	97
Sicily	3,345,000	3,129,000	9,620,784	3,094,500	307	99
RIPP	**10,180,500**	**8,955,500**	**32,036,786**	**8,821,000**	**358**	**98**

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Campania	2,210,500	2,040,000	4,866,614	1,656,000	239	81
Latium	3,279,000	3,215,500	6,496,199	2,969,500	202	92
Marche	2,064,000	2,064,000	5,203,068	2,064,000	252	100
Molise	260,500	246,000	635,920	246,000	259	100
Tuscany	4,545,500	3,671,500	10,280,035	3,669,500	280	100
Min. of Def.	-	-	61,517	-	NA	NA
PlaNet	**12,359,500**	**11,237,000**	**27,543,354**	**10,605,000**	**245**	**94**
Lombardy	7,731,300	7,441,000	22,491,807	6,609,000	302	89
Piedmont	3,494,500	3,310,000	10,502,834	3,303,000	317	100
Sardinia	1,697,000	1,697,000	2,765,181	1,697,000	163	100
LPS	**12,922,800**	**12,448,000**	**35,759,822**	**11,609,000**	**287**	**93**
Italy	**44,962,800**	**41,878,000**	**95,339,962**	**40,052,000**	**228**	**96**

Fibrinogen

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

In 2019, the potential self-sufficiency in RiaSTAP was equal to 94% (Table 88).

However, effective self-sufficiency of 68% was achieved, showing possible room for improvement in the interregional compensation policies. All NAIP Regions, except for Basilicata and AP of Bolzano, achieved effective self-sufficiency equal to 100%.

Table 88. Regional and national self-sufficiency in fibrinogen, 2019

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	870	870	683	870	79	100
Aosta Valley	50	50	97	50	193	100
AP Bolzano	-	-	288	-	-	-
AP Trento	130	130	289	130	222	100
Basilicata	480	480	271	280	56	58
Friuli V. G.	1,103	1,100	1,059	1,100	96	100
Liguria	500	500	927	500	185	100
Umbria	970	970	393	970	41	100
Veneto	1,560	1,560	3,575	1,560	229	100
NAIP	**5,663**	**5,660**	**7,581**	**5,460**	**134**	**96**
Apulia	20	20	-	-	-	-
Calabria	-	-	-	-	-	-
E.-Romagna	50	40	-	-	-	-
Sicily	19	19	-	-	-	-
RIPP	**89**	**79**	**-**	**-**	**-**	**-**

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Campania	252	252	-	-	-	-
Latium	3	-	-	-	-	-
Marche	-	-	-	-	-	-
Molise	-	-	-	-	-	-
Tuscany	-	-	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	**255**	**252**	**-**	**-**	**-**	**-**
Lombardy	341	247	-	-	-	-
Piedmont	1,301	1,297	-	-	-	-
Sardinia	554	550	-	-	-	-
LPS	**2,196**	**2,094**	**-**	**-**	**-**	**-**
Italy	**8,203**	**8,085**	**7,581**	**5,460**	**94**	**68**

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

Table 89. Regional and national self-sufficiency in solvent/detergent virus-inactivated plasma, 2019

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	496,000	496,000	-	-	-	-
Friuli V. G.	32,000	32,000	-	-	-	-
Liguria	776,000	776,000	-	86,000	-	11
Umbria	30,000	30,000	-	-	-	-
Veneto	2,726,000	2,636,000		2,636,000	-	100
NAIP	**4,070,000**	**3,980,000**	**-**	**2,722,000**	**-**	**68**

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	mL	mL	mL	mL	%	%
Apulia	3,050,400	3,050,400	-	82,000	-	3
Calabria	957,000	957,000	-	-	-	-
E.-Romagna	401,200	401,200	-	-	-	-
Sicily	4,391,800	4,391,800	1,223,555	1,812,200	28	41
RIPP	**8,800,400**	**8,800,400**	**1,223,555**	**1,894,200**	**14**	**22**
Campania	4,730,000	4,688,000	3,085,981	4,480,000	66	96
Latium	4,925,200	4,775,200	2,385,356	3,273,200	50	69
Marche	1,804,000	1,804,000	2,189,817	1,804,000	121	100
Molise	468,200	468,200	678,422	468,200	145	100
Tuscany	1,263,600	1,263,600	-	-	-	-
Min. of Def.	-	-	-	-	-	-
PlaNet	**13,191,000**	**12,999,000**	**8,339,577**	**10,025,400**	**64**	**77**
Lombardy	406,000	406,000	-	404,000	-	100
Piedmont	3,508,000	3,508,000	4,308,642	3,508,000	123	100
Sardinia	100,000	100,000	-	52,000	-	52
LPS	**4,014,000**	**4,014,000**	**4,308,642**	**3,964,000**	**107**	**99**
Italy	**30,075,400**	**29,793,400**	**13,871,774**	**18,605,600**	**47**	**62**

For the Regions that used S/D plasma produced by toll fractionation, effective regional self-sufficiency ranged from 3% in Apulia to 100% in Veneto, Marche, Molise, Lombardy and Piedmont.

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

EXPENDITURE FOR PLASMA-DERIVED AND RECOMBINANT MEDICINAL PRODUCTS

This chapter describes the pharmaceutical expenditure incurred by the NHS for the purchase of the following medicinal products on the 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 2019, 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 2019, expenditure for the purchase of the aforementioned PDMPs was approximately 170,1 million euros (2.8 euro *per capita*) recording a decrease, compared to 2018, of approximately 1 million euros (-0.6%), thus confirming the trend observed in the previous years (17, 34). 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 456,3 million euros (7.6 euros *per capita*). The Regions with the highest *per capita* expenditure were Calabria with 12.3 euros *per capita* spent, Lazio and Campania with 10.3 euros *per capita*. The expenditure for recombinant factors increased compared to 2018 (+11%).

Table 93 shows the expenditure incurred in 2019 for the purchase of Emicizumab.

In 2019, as regards all the other PDMPs (Tables 94-97), the total expenditure was approximately 112,6 million euros, equal to around 1.86 euros *per capita* of which approximately 40 million for the purchase of specific immunoglobulins, a cost comparable to that of 2018 (Table 94), in regard to the *per capita* expenditure (0.66) (Table 95).

The other MPDs (Tables 96-97), recorded a marked increase in expenditure compared to the previous year (+19.7%), in particular as regards local haemostats (+71%), alpha-1 proteinase (+50%), the other plasma protein fractions (+23%) and the human C1 esterase inhibitor (+ 19%). On the other hand, a decrease in expenditure was recorded for protein C (-16%) and for activated prothrombin complex concentrates (-30%).

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 2019

Region	Albumin		Human Immunoglobulin intravenous use		Factor VIII		Total	
	€	€ *pro capite*	€	€ *pro capite*	€	€ *pro capite*	€	€ *pro capite*
Abruzzo	586,573	0.45	380,081	0.29	0	0	966,654	0.74
Aosta Valley	0	0.00	429	0.00	0	0	429	0.00
AP Bolzano	42,974	0.08	110,289	0.21	0	0	153,263	0.29
AP Trento	21,408	0.04	47,696	0.09	0	0	69,104	0.13
Basilicata	378,857	0.67	387,645	0.69	0	0	766,502	1.36
Friuli V. G.	8,761	0.01	355,161	0.29	0	0	363,923	0.30
Liguria	119,844	0.08	1,330,758	0.86	0	0	1,450,602	0.94
Umbria	26,192	0.03	175,803	0.20	0	0	201,995	0.23
Veneto	189,975	0.04	841,619	0.17	0	0	1,031,594	0.21
NAIP	**1,374,584**	**0.12**	**3,629,481**	**0.31**	**0**	**0**	**5,004,065**	**0.43**
						0		
Apulia	1,569,502	0.39	4,425,492	1.10	154,880	0.04	6,149,874	1.53
Calabria	1,397,444	0.72	126,813	0.07	0	0	1,524,258	0.78
E.-Romagna	379,176	0.09	1,523,030	0.34	0	0	1,902,207	0.43
Sicily	1,456,054	0.29	1,660,747	0.33	0	0	3,116,801	0.62
RIPP	**4,802,176**	**0.31**	**7,736,083**	**0.50**	**154,880**	**0.01**	**12,693,140**	**0.82**
Campania	7,793,330	1.34	7,775,293	1.34	0	0	15,568,622	2.68
Latium	2,510,790	0.43	4,947,633	0.84	0	0	7,458,423	1.27
Marche	22,169	0.01	626,630	0.41	0	0	648,800	0.43
Molise	84,572	0.28	0	0.00	0	0	84,572	0.28
Tuscany	385,164	0.10	8,325,637	2.23	0	0	8,710,802	2.34
Min. of Def.	-	-	-	-	0	0	NA	NA
PlaNet	**10,796,026**	**0.63**	**21,675,193**	**1.26**	**0**	**0**	**32,471,219**	**1.88**
Lombardy	1,721,507	0.17	6,110,383	0.61	219,780	0.02	8,051,670	0.80
Piedmont	301,077	0.07	3,328,875	0.76	0	0	3,629,952	0.83
Sardinia	907,012	0.55	791,786	0.48	0	0	1,698,797	1.04
LPS	**2,929,595**	**0.18**	**10,231,044**	**0.64**	**219,780**	**0.01**	**13,380,419**	**0.83**
Italy	**19,902,381**	**0.33**	**43,271,802**	**0.72**	**374,660**	**0.01**	**63,548,843**	**1.05**

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 2019

Region	SC/Ig		FVIII/vWF		FIX		CCP3		AT		Fibrinogen		Total	
	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*	€	€ *pc*
Abruzzo	1,283,911	0.98	1,197,893	0.91	-	-	-	-	-	-	287,320	0.22	2,769,125	2.1
Aosta Valley	34,362	0.27	-	-	-	-	-	-	-	-	3,960	0.03	38,322	0.3
AP Bolzano	109,013	0.21	29,938	0.06	-	-	-	-	-	-	346,575	0.65	485,526	0.9
AP Trento	195,119	0.36	39,831	0.07	-	-	-	-	-	-	70,985	0.13	305,936	0.6
Basilicata	558,503	0.99	22,440	0.04	-	-	-	-	31,678	0.06	88,000	0.16	700,621	1.2
FVG	238,353	0.20	31,224	0.03	-	-	-	-	-	-	-	-	269,577	0.2
Liguria	1,995,456	1.29	4,950	0.00	-	-	-	-	4,840	0.00	880	0.00	2,006,126	1.3
Umbria	922,665	1.05	368,782	0.42	58,740	0.07	-	-	-	-	33,880	0.04	1,384,067	1.6
Veneto	4,604,677	0.94	384,503	0.08	47,520	0.01	246	0.00	-	-	1,777,600	0.36	6,814,546	1.4
NAIP	**9,942,061**	**0.86**	**2,079,561**	**0.18**	**106,260**	**0.01**	**246**	**0.00**	**36,518**	**0.00**	**2,609,200**	**0.22**	**14,773,846**	**1.3**
Apulia	6,278,647	1.56	3,311,504	0.82	-	-	-	-	20,064	0.00	1,099,120	0.27	10,709,336	2.7
Calabria	1,880,876	0.97	472,320	0.24	-	-	-	-	42,147	0.02	960,080	0.49	3,355,422	1.7
E.-Romagna	5,747,998	1.29	1,652,266	0.37	-	-	26,290	0.01	5,308	0.00	1,599,400	0.36	9,031,261	2.0
Sicily	4,662,887	0.93	2,246,675	0.45	-	-	8,918	0.00	55,552	0.01	1,155,880	0.23	8,129,912	1.6
RIPP	**18,570,407**	**1.20**	**7,682,765**	**0.50**	**-**	**-**	**35,208**	**0.00**	**123,070**	**0.01**	**4,814,480**	**0.31**	**31,225,930**	**2.0**
Campania	5,697,178	0.98	2,015,458	0.35	-	-	88,704	0.02	1,005,019	0.17	1,900,360	0.33	10,706,719	1.8
Latium	9,346,608	1.59	4,487,665	0.76	82,496	0.01	17,460	0.00	757,373	0.13	2,263,800	0.39	16,955,401	2.9
Marche	1,414,600	0.93	270,818	0.18	-	-	-	-	-	-	453,200	0.30	2,138,618	1.4
Molise	187,034	0.61	112,332	0.37	-	-	-	-	-	-	32,120	0.11	331,486	1.1
Tuscany	8,523,511	2.29	1,156,155	0.31	-	-	462	0.00	2,402	0.00	1,166,000	0.31	10,848,531	2.9
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	-	-	NA
PlaNet	**25,168,932**	**1.46**	**8,042,427**	**0.47**	**82,496**	**0.00**	**106,626**	**0.01**	**1,764,794**	**0.10**	**5,815,480**	**0.34**	**40,980,755**	**2.4**
Lombardy	5,067,885	0.50	3,190,297	0.32	439,069	0.04	-	-	155,188	0.02	1,976,920	0.20	10,829,358	1.1
Piedmont	5,186,439	1.19	1,638,321	0.38	2,926	0.00	-	-	-	-	829,400	0.19	7,657,086	1.8
Sardinia	342,746	0.21	738,285	0.45	-	-	-	-	15,472	0.01	850,080	0.52	1,946,582	1.2
LPS	**10,597,070**	**0.66**	**5,566,903**	**0.35**	**441,995**	**0.03**	**-**	**-**	**170,660**	**0.01**	**3,656,400**	**0.23**	**20,433,027**	**1.3**
Italy	**64,278,470**	**1.06**	**23,371,655**	**0.39**	**630,750**	**0.01**	**142,080**	**0.00**	**2,095,042**	**0.03**	**16,895,560**	**0.28**	**107,413,557**	**1.8**

Table 92. Estimate of the total expenditure and the total *per capita* expenditure for recombinant Factors VII, VIII, IX and XIII in 2019

Region	rFVIIa		rFVIII		rFIX		rFXIII		Total	
	€	€ *pc*	€	€ *pc*	€ *pc*	€ *pc*	€	€ *pc*	€	€ *pc*
Abruzzo	246,623	0.19	8,558,376	6.53	2,780,894	2.12	465,726	0.36	12,051,618	9.2
Aosta Valley	14,888	0.12	583,810	4.65	-	-	-	-	598,698	4.8
AP Bolzano	65,378	0.12	1,508,616	2.84	3,034	0.01	-	-	1,577,027	3.0
AP Trento	12,946	0.02	2,197,447	4.06	332,569	0.61	-	-	2,542,962	4.7
Basilicata	27,834	0.05	4,798,815	8.53	232,907	0.41	186,290	0.33	5,245,846	9.3
FVG	7,262,727	5.98	2,123,837	1.75	1,355,406	1.12	-	-	10,741,970	8.8
Liguria	105,510	0.07	7,459,627	4.81	3,560,168	2.30	341,532	0.22	11,466,838	7.4
Umbria	282,223	0.32	3,788,564	4.30	562,057	0.64	-	-	4,632,844	5.3
Veneto	5,480,711	1.12	18,706,236	3.81	4,072,884	0.83	155,242	0.03	28,415,073	5.8
NAIP	**13,498,841**	**1.16**	**49,725,327**	**4.28**	**12,899,918**	**1.11**	**1,148,791**	**0.10**	**77,272,876**	**6.6**
Apulia	6,116,321	1.52	24,755,311	6.14	8,792,855	2.18	-	-	39,664,487	9.8
Calabria	4,698,115	2.41	16,414,993	8.43	2,036,152	1.05	838,307	0.43	23,987,567	12.3
E.-Romagna	1,660,975	0.37	22,533,766	5.05	6,194,791	1.39	62,097	0.01	30,451,629	6.8
Sicily	3,006,070	0.60	30,920,248	6.18	4,678,075	0.94	15,524	0.00	38,619,918	7.7
RIPP	**15,481,482**	**1.00**	**94,624,319**	**6.13**	**21,701,872**	**1.41**	**915,928**	**0.06**	**132,723,600**	**8.6**
Campania	6,465,250	1.11	45,924,552	7.92	7,084,028	1.22	-	-	59,473,830	10.3
Latium	1,827,337	0.31	53,178,147	9.05	5,545,570	0.94	-	-	60,551,054	10.3
Marche	1,148,966	0.75	5,710,245	3.74	1,377,238	0.90	-	-	8,236,449	5.4
Molise	240,149	0.79	1,310,136	4.29	-	-	-	-	1,550,285	5.1
Tuscany	2,938,105	0.79	13,436,384	3.60	6,515,619	1.75	-	-	22,890,109	6.1
Min. of Def.	-	-	-	-	-	-	-	-	-	-
PlaNet	**12,619,808**	**0.73**	**119,559,464**	**6.93**	**20,522,455**	**1.19**	**-**	**-**	**152,701,727**	**8.9**
Lombardy	6,181,728	0.61	41,638,068	4.14	11,064,279	1.10	326,008	0.03	59,210,084	5.9
Piedmont	1,390,993	0.32	20,025,436	4.60	5,423,100	1.24	186,290	0.04	27,025,819	6.2
Sardinia	13,593	0.01	7,203,607	4.39	124,282	0.08	-	-	7,341,483	4.5
LPS	**7,586,314**	**0.47**	**68,867,112**	**4.29**	**16,611,661**	**1.03**	**512,299**	**0.03**	**93,577,386**	**5.8**
Italy	**49,186,445**	**0.81**	**332,776,222**	**5.51**	**71,735,905**	**1.19**	**2,577,017**	**0.04**	**456,275,590**	**7.6**

Table 93. Estimate of the total expenditure and the total *per capita* expenditure for Emicizumab in 2019

Region	Emicizumab	
	€	€ *pc*
Abruzzo	480,296	0.37
Aosta Valley	-	-
AP Bolzano	225,004	0.42
AP Trento	-	-
Basilicata	-	-
Friuli V. Giulia.	30,289	0.02
Liguria	-	-
Umbria	250,966	0.28
Veneto	1,350,022	0.28
NAIP	**2,336,576**	**0.20**
Apulia	419,718	0.10
Calabria	1,047,132	0.54
E.-Romagna	718,281	0.16
Sicily	1,224,539	0.24
RIPP	**3,409,671**	**0.22**
Campania	2,044,505	0.35
Latium	339,669	0.06
Marche	454,334	0.30
Molise	-	-
Tuscany	1,549,064	0.42
Min. of Def.	-	-
PlaNet	**4,387,573**	**0.25**
Lombardy	3,571,933	0.36
Piedmont	2,764,949	0.63
Sardinia	-	-
LPS	**6,336,882**	**0.39**
Italy	**16,470,702**	**0.27**

Table 94. Estimate of total expenditure incurred by the National Health Service for the purchase on the market of specific immunoglobulins in 2019

Region	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs	Rabies IGs	Total
Abruzzo	262,233	3,904	253,932	50,058	40,397	645	-	611,167
Aosta Valley	63,188	-	17,853	5,704	3,512	0	3,234	93,491
AP Bolzano	31,220	-	29,820	45,394	3,902	2,107	3,989	116,431
AP Trento	76,288	-	21,885	33,253	-	1,289	2,156	134,872
Basilicata	130,450	253	91,732	15,914	35,265	-	-	273,615
Friuli V. Giulia	106,127	56,051	14,776	-	254,474	8,822	-	440,250
Liguria	239,187	4,928	195,152	48,930	434	2,006	-	490,637
Umbria	105,017	-	100,497	27,277	8,670	3,728	-	245,188
Veneto	977,531	309,271	179,129	261,155	588,864	11,454	92,816	2,420,219
NAIP	**1,991,240**	**374,406**	**904,775**	**487,686**	**935,517**	**30,050**	**102,194**	**4,825,869**
Apulia	2,475,509	369,148	371,421	93,233	119,772	3,223	2,264	3,434,570
Calabria	622,211	68,292	350,100	60,370	48,917	173	-	1,150,064
E.-Romagna	763,856	261,624	351,566	210,734	561,903	17,987	11,966	2,179,636
Sicily	1,671,280	3,438	621,014	118,427	190,977	-		2,605,135
RIPP	**5,532,856**	**702,501**	**1,694,101**	**482,764**	**921,570**	**21,383**	**14,230**	**9,369,405**
Campania	7,953,420	513,927	1,291,808	85,954	63,861	1,289	-	9,910,259
Latium	958,791	87,827	508,991	185,291	36,415	2,486	1,078	1,780,881
Marche	277,689	13,766	231,297	64,981	98,924	7,932	1,078	695,667
Molise	69,731	7,018	37,085	10,858	-	-	-	124,692
Tuscany	726,821	114,301	601,346	148,310	28,582	2,251	4,096	1,625,707
Min. of Def.		-	-	-	-	-		
PlaNet	**9,986,453**	**736,840**	**2,670,526**	**495,394**	**227,781**	**13,959**	**6,252**	**14,137,205**
Lombardy	4,770,943	355,720	544,551	403,569	335,394	28,853	10,672	6,449,702
Piedmont	2,210,436	91,567	245,254	192,157	419,851	1,295	-	3,160,559
Sardinia	1,659,265	77,198	221,303	29,129	-	-	-	1,986,895
LPS	**8,640,644**	**524,485**	**1,011,107**	**624,855**	**755,245**	**30,148**	**10,672**	**11,597,156**
Not specified region	-	-	21,691	-	-	-	-	21,691
Italy	**26,151,194**	**2,338,232**	**6,302,202**	**2,090,699**	**2,840,113**	**95,540**	**133,349**	**39,951,327**

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 2019

Regione	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs*	Rabies IGs*	Totale
Abruzzo	0.20	0.00	0.19	0.04	0.03	0.49	-	0.47
Aosta Valley	0.50	-	0.14	0.05	0.03	-	25.73	0.74
AP Bolzano	0.06	-	0.06	0.09	0.01	3.97	7.51	0.22
AP Trento	0.14	-	0.04	0.06	-	2.38	3.98	0.25
Basilicata	0.23	0.00	0.16	0.03	0.06	-	-	0.49
Friuli V. Giulia	0.09	0.05	0.01	-	0.21	7.26	-	0.36
Liguria	0.15	0.00	0.13	0.03	0.00	1.29	-	0.32
Umbria	0.12	-	0.11	0.03	0.01	4.23	-	0.28
Veneto	0.20	0.06	0.04	0.05	0.12	2.33	18.92	0.49
NAIP	**0.17**	**0.03**	**0.08**	**0.04**	**0.08**	**2.58**	**8.79**	**0.42**
Apulia	0.61	0.09	0.09	0.02	0.03	0.80	0.56	0.85
Calabria	0.32	0.04	0.18	0.03	0.03	0.09	-	0.59
E.-Romagna	0.17	0.06	0.08	0.05	0.13	4.03	2.68	0.49
Sicily	0.33	0.00	0.12	0.02	0.04	-	-	0.52
RIPP	**0.36**	**0.05**	**0.11**	**0.03**	**0.06**	**1.39**	**0.92**	**0.61**
Campania	1.37	0.09	0.22	0.01	0.01	0.22	-	1.71
Latium	0.16	0.01	0.09	0.03	0.01	0.42	0.18	0.30
Marche	0.18	0.01	0.15	0.04	0.06	5.20	0.71	0.46
Molise	0.23	0.02	0.12	0.04	-	-	-	0.41
Tuscany	0.19	0.03	0.16	0.04	0.01	0.60	1.10	0.44
Min. of Def.	-	-	-	-	-	-	-	-
PlaNet	**0.58**	**0.04**	**0.15**	**0.03**	**0.01**	**0.81**	**0.36**	**0.82**
Lombardy	0.47	0.04	0.05	0.04	0.03	2.87	1.06	0.64
Piedmont	0.51	0.02	0.06	0.04	0.10	0.30	-	0.73
Sardinia	1.01	0.05	0.13	0.02	-	-	-	1.21
LPS	**0.54**	**0.03**	**0.06**	**0.04**	**0.05**	**1.88**	**0.66**	**0.72**
Italy	**0.43**	**0.04**	**0.10**	**0.03**	**0.05**	**1.58**	**2.21**	**0.66**

* 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 2019

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	88,210	1,832,777	818,159	-	204,761	434,808	275,016	-	-	-	15,323	3,669,053
Aosta Valley	-	-	98,739	-	-	226,777	152,850	-	-	-	-	478,366
AP Bolzano	-	-	258,702	-	157,832	629,282	66,000	-	-	-	-	1,111,816
AP Trento	-	-	179,225	3,927	21,780	160,537	16,797	-	-	15,531	-	397,797
Basilicata	105,945	-	450,375	207,713	78,016	765	65,542	-	-	-	-	908,357
Friuli V. Giulia	-	357,496	455,033	12,584	1,184	518,606	13,460	-	38,709	-	-	1,397,070
Liguria	3,734	8,570	371,493	274,261	45,290	332,030	33,942	-	-	-	49,500	1,118,820
Umbria	3,734	-	466,624	14,732	19,136	49,832	323,030	-	-	-	-	877,087
Veneto	48,539	104,066	1,723,689	-	30,774	937,875	1,155,230	-	-	136,751	47,737	4,184,660
NAIP	**250,161**	**2,302,908**	**4,822,038**	**513,217**	**558,771**	**3,290,513**	**2,101,867**	**-**	**38,709**	**152,282**	**112,560**	**14,143,027**
Apulia	192,752	198,469	1,276,594	1,651,919	15,364	325,336	1,035,378	-	11,385	-	6,567	4,713,764
Calabria	64,079	418,126	936,446	414,468	49,230	219,648	662,301	-	-	-	279,263	3,043,561
E.-Romagna	446,183	821,513	777,368	157,772	313,148	617,232	675,044	-	8,600	161,016	12,188	3,990,064
Sicily	218,752	1,817,851	1,482,996	1,427,911	88,717	617,496	1,454,324	-	8,600	-	102,300	7,218,946
RIPP	**921,766**	**3,255,958**	**4,473,404**	**3,652,070**	**466,460**	**1,779,712**	**3,827,047**	**-**	**28,585**	**161,016**	**400,318**	**18,966,335**
Campania	288,636	1,955,800	3,350,613	81,453	264,247	1,471,306	2,252,741	-	-	-	208,725	9,873,520
Latium	1,042,034	714,500	1,493,316	608,354	169,259	664,765	1,955,386	-	8,606	68,767	29,370	6,754,356
Marche	933	-	666,236	-	84,942	70,672	279,353	-	-	19,927	28,875	1,150,939
Molise	210,024	-	54,303	351	-	20,592	9,463	-	-	-	-	294,732
Tuscany	22,403	1,045,552	1,842,309	484,466	316,897	513,682	677,835	-	-	17,192	83,600	5,003,935
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**1,564,029**	**3,715,852**	**7,406,777**	**1,174,623**	**835,345**	**2,741,017**	**5,174,778**	**-**	**8,606**	**105,885**	**350,570**	**23,077,483**
Lombardy	1,298,882	1,128,930	3,046,731	3,892	73,700	2,443,173	2,122,142	19,862	-	66,422	119,948	10,323,683
Piedmont	185,287	348,926	1,588,826	-	216,552	779,255	747,040	-	-	17,582	-	3,883,469
Sardinia	-	105,290	440,711	18,590	188,000	749,832	687,424	-	-	6,252	71,060	2,267,159
LPS	**1,484,169**	**1,583,145**	**5,076,269**	**22,482**	**478,253**	**3,972,261**	**3,556,605**	**19,862**	**-**	**90,256**	**191,008**	**16,474,311**
Italy	**4,220,126**	**10,857,864**	**21,778,488**	**5,362,391**	**2,338,829**	**11,783,503**	**14,660,297**	**19,862**	**75,900**	**509,439**	**1,054,456**	**72,661,155**

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 2019

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	0.07	1.40	0.62	-	0.16	0.33	0.21	-	-	-	0.01	2.80
Aosta Valley	-	-	0.79	-	-	1.80	1.22	-	-	-	-	3.81
AP Bolzano	-	-	0.49	-	0.30	1.18	0.12	-	-	-	-	2.09
AP Trento	-	-	0.33	0.01	0.04	0.30	0.03	-	-	28.70	-	0.74
Basilicata	0.19	-	0.80	0.37	0.14	0.00	0.12	-	-	-	-	1.61
Friuli V. Giulia	-	0.29	0.37	0.01	0.00	0.43	0.01	-	31.85	-	-	1.15
Liguria	0.00	0.01	0.24	0.18	0.03	0.21	0.02	-	-	-	0.03	0.72
Umbria	0.00	-	0.53	0.02	0.02	0.06	0.37	-	-	-	-	0.99
Veneto	0.01	0.02	0.35	-	0.01	0.19	0.24	-	-	27.88	0.01	0.85
NAIP	**0.02**	**0.20**	**0.41**	**0.04**	**0.05**	**0.28**	**0.18**	**-**	**3.33**	**13.10**	**0.01**	**1.22**
Apulia	0.05	0.05	0.32	0.41	0.00	0.08	0.26	-	2.83	-	0.00	1.17
Calabria	0.03	0.21	0.48	0.21	0.03	0.11	0.34	-	-	-	0.14	1.56
E.-Romagna	0.10	0.18	0.17	0.04	0.07	0.14	0.15	-	1.93	36.11	0.00	0.89
Sicily	0.04	0.36	0.30	0.29	0.02	0.12	0.29	-	1.72	-	0.02	1.44
RIPP	**0.06**	**0.21**	**0.29**	**0.24**	**0.03**	**0.12**	**0.25**	**-**	**1.85**	**10.43**	**0.03**	**1.23**
Campania	0.05	0.34	0.58	0.01	0.05	0.25	0.39	-	-	-	0.04	1.70
Latium	0.18	0.12	0.25	0.10	0.03	0.11	0.33	-	1.46	11.70	0.00	1.15
Marche	0.00	-	0.44	-	0.06	0.05	0.18	-	-	13.06	0.02	0.75
Molise	0.69	-	0.18	0.00	-	0.07	0.03	-	-	-	-	0.96
Tuscany	0.01	0.28	0.49	0.13	0.08	0.14	0.18	-	-	4.61	0.02	1.34
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**0.09**	**0.22**	**0.43**	**0.07**	**0.05**	**0.16**	**0.30**	**-**	**0.50**	**6.14**	**0.02**	**1.34**
Lombardy	0.13	0.11	0.30	0.00	0.01	0.24	0.21	2.0	-	6.60	0.01	1.03
Piedmont	0.04	0.08	0.36	-	0.05	0.18	0.17	-	-	4.04	-	0.89
Sardinia	-	0.06	0.27	0.01	0.11	0.46	0.42	-	-	3.81	0.04	1.38
LPS	**0.09**	**0.10**	**0.32**	**0.00**	**0.03**	**0.25**	**0.22**	**1.2**	**-**	**5.62**	**0.01**	**1.03**
ITALY	**0.07**	**0.18**	**0.36**	**0.09**	**0.04**	**0.20**	**0.24**	**0.3**	**1.26**	**8.44**	**0.02**	**1.20**

* values per 1,000 population

National and Regional mean price per gram or International Unit

Tables 98-99-100 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 2.87 euros. The variability observed between Regions (range: 2.21-3.91 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 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 AP of Trento, 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 23,371,655 euros (0.51 euros per IU), and almost entirely accounted for the distribution through NHS facilities (95%) (96% in 2018) (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 35,243,482 million euros with a decrease of 14% compared to 2018, in line with the increasing availability of toll fractionation products. The mean unit price per gram at national level was 40.58 euros (range: 34.87-48.12 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 2019

Region	Mean price			Demand				Total expenditure			
	NHS facilities	Pharmacies	Total	NHS facilities		Pharmacies		NHS facilities		Pharmacies	
	€	€	€	g	%	g	%	g	%	g	%
Abruzzo	2.27	3.93	2.65	170,870	77%	50,478	23%	388,116	66%	198,456	34%
Aosta Valley	-	-	-	-	-	-	-	-	-	-	-
AP Bolzano	2.44	-	2.44	17,625	100%	-	0%	42,974	100%	-	0%
AP Trento	-	3.86	3.86	-	0%	5,540	100%	-	0%	21,408	100%
Basilicata	2.19	3.95	2.87	81,305	62%	50,883	38%	177,767	47%	201,090	53%
Friuli V. Giulia	1.98	3.90	3.38	700	27%	1,893	73%	1,383	16%	7,378	84%
Liguria	1.98	3.92	3.00	18,925	47%	20,980	53%	37,527	31%	82,317	69%
Umbria	2.09	3.93	3.64	1,125	16%	6,068	84%	2,351	9%	23,841	91%
Veneto	2.54	3.93	3.82	3,880	8%	45,830	92%	9,844	5%	180,131	95%
NAIP	**2.24**	**3.93**	**2.89**	**294,430**	**62%**	**181,670**	**38%**	**659,962**	**48%**	**714,621**	**52%**
Apulia	2.16	3.93	3.59	83,100	19%	353,893	81%	179,819	11%	1,389,683	89%
Calabria	2.21	3.91	3.62	65,000	17%	320,645	83%	143,545	10%	1,253,900	90%
E.-Romagna	2.47	3.92	2.55	140,750	95%	7,868	5%	348,325	92%	30,851	8%
Sicily	1.97	3.88	3.19	164,565	36%	291,630	64%	323,853	22%	1,132,201	78%
RIPP	**2.20**	**3.91**	**3.36**	**453,415**	**32%**	**974,035**	**68%**	**995,541**	**21%**	**3,806,635**	**79%**
Campania	1.91	3.88	2.69	1,747,955	60%	1,145,725	40%	3,346,167	43%	4,447,163	57%
Latium	2.06	3.93	2.83	521,845	59%	365,378	41%	1,076,282	43%	1,434,508	57%
Marche	2.21	-	2.21	10,025	100%	-	0%	22,169	100%	-	0%
Molise	-	3.91	3.91	-	0%	21,638	100%	-	0%	84,572	100%
Tuscany	2.04	3.90	2.08	181,090	98%	4,225	2%	368,690	96%	16,474	4%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**1.96**	**3.89**	**2.70**	**2,460,915**	**62%**	**1,536,965**	**38%**	**4,813,309**	**45%**	**5,982,717**	**55%**
Lombardy	2.15	3.92	3.34	170,810	33%	345,285	67%	367,203	21%	1,354,304	79%
Piedmont	2.13	3.94	2.24	127,025	94%	7,610	6%	271,072	90%	30,005	10%
Sardinia	1.86	3.94	2.37	288,400	75%	93,865	25%	536,914	59%	370,097	41%
LPS	**2.00**	**3.93**	**2.84**	**586,235**	**57%**	**446,760**	**43%**	**1,175,189**	**40%**	**1,754,406**	**60%**
Italy	**2.01**	**3.90**	**2.87**	**3,794,995**	**55%**	**3,139,430**	**45%**	**7,644,001**	**38%**	**12,258,380**	**62%**

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 2019

	Mean price			Demand				Total expenditure			
Region	**NHS facilities**	**Pharmacies**	**Total**	**NHS facilities**		**Pharmacies**		**NHS facilities**		**Pharmacies**	
	€	**€**	**€**	**UI**	**%**	**UI**	**%**	**UI**	**%**	**UI**	**%**
Abruzzo	0.56	-	0.56	2,137,000	100%	-	0%	1,197,893	100%	-	0%
Aosta Valley	-	-	-	-	-	-	-	-	-	-	-
AP Bolzano	0.55	-	0.55	54,000	100%	-	0%	29,938	100%	-	0%
AP Trento	0.56	-	0.56	71,000	100%	-	0%	39,831	100%	-	0%
Basilicata	0.56	-	0.56	40,000	100%	-	0%	22,440	100%	-	0%
Friuli V. Giulia	0.55	0.60	0.59	14,000	26%	39,000	74%	7,700	25%	23,524	75%
Liguria	0.55	-	0.55	9,000	100%	-	0%	4,950	100%	-	0%
Umbria	0.51	-	0.51	725,000	100%	-	0%	368,782	100%	-	0%
Veneto	0.47	-	0.47	809,500	100%	-	0%	384,503	100%	-	0%
NAIP	**0.53**	**0.60**	**0.53**	**3,859,500**	**99%**	**39,000**	**1%**	**2,056,037**	**99%**	**23,524**	**1%**
Apulia	0.50	-	0.50	6,672,500	100%	-	0%	3,311,504	100%	-	0%
Calabria	0.55	0.59	0.55	826,000	96%	32,500	4%	453,072	96%	19,248	4%
E.-Romagna	0.55	-	0.55	3,011,500	100%	-	0%	1,652,266	100%	-	0%
Sicily	0.53	0.53	0.53	3,937,000	93%	282,000	7%	2,096,173	93%	150,502	7%
RIPP	**0.52**	**0.54**	**0.52**	**14,447,000**	**98%**	**314,500**	**2%**	**7,513,015**	**98%**	**169,750**	**2%**
Campania	0.48	-	0.48	4,225,000	100%	-	0%	2,015,458	100%	-	0%
Latium	0.52	0.60	0.52	8,597,000	99%	68,500	1%	4,446,438	99%	41,227	1%
Marche	0.50	-	0.50	539,000	100%	-	0%	270,818	100%	-	0%
Molise	0.55	-	0.55	204,000	100%	-	0%	112,332	100%	-	0%
Tuscany	0.51	-	0.51	2,269,000	100%	-	0%	1,156,155	100%	-	0%
Min. of Def.	-	-	-	-	-	-	-	-	-	-	-
PlaNet	**0.51**	**0.60**	**0.51**	**15,834,000**	**100%**	**68,500**	**0%**	**8,001,200**	**99%**	**41,227**	**1%**
Lombardy	0.54	0.60	0.56	4,119,500	72%	1,587,250	28%	2,235,693	70%	954,603	30%
Piedmont	0.45	-	0.45	3,629,500	100%	-	0%	1,638,321	100%	-	0%
Sardinia	0.48	-	0.48	1,526,000	100%	-	0%	738,285	100%	-	0%
LPS	**0.50**	**0.60**	**0.51**	**9,275,000**	**85%**	**1,587,250**	**15%**	**4,612,300**	**83%**	**954,603**	**17%**
Italy	**0.51**	**0.59**	**0.51**	**43,415,500**	**96%**	**2,009,250**	**4%**	**22,182,551**	**95%**	**1,189,104**	**5%**

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 2019

Region	Mean price per gram (€) NHS facilities	Total demand (g) NHS facilities	Total expenditure NHS facilities*
Abruzzo	47.12	7,247	341,458
Aosta Valley	42.89	10	429
AP Bolzano	42.03	2,379	99,958
AP Trento	40.48	600	24,288
Basilicata	40.68	2,298	93,488
Friuli V. Giulia	47.70	720	34,346
Liguria	43.07	26,270	1,131,372
Umbria	46.16	3,130	144,481
Veneto	43.08	2,795	120,406
NAIP	**43.79**	**45,449**	**1,990,226**
Apulia	47.14	80,026	3,772,114
Calabria	45.23	1,507	68,156
E.-Romagna	48.12	21,073	1,014,049
Sicily	46.06	6,344	292,215
RIPP	**47.24**	**108,950**	**5,146,535**
Campania	34.87	156,795	5,467,451
Latium	35.21	134,974	4,752,116
Marche	44.21	10,235	452,445
Molise	-	-	-
Tuscany	41.70	181,104	7,551,543
Min. of Def.	-	-	-
PlaNet	**37.72**	**483,109**	**18,223,556**
Lombardy	43.15	138,994	5,998,006
Piedmont	42.02	73,610	3,093,374
Sardinia	43.23	18,315	791,786
LPS	**42.80**	**230,919**	**9,883,166**
Italy	**40.58**	**868,426**	**35,243,482**

* The value does not include *Pentaglobin*™,

FINAL CONSIDERATIONS

The national demand for albumin was still particularly high and confirmed the increase observed in 2018 (588 grams per 1,000 population).

An increased demand was observed in particular in Latium (+13%), Calabria (+9%) and Sicily (+8%). The Regions with the highest standardised demand per 1,000 population were Sardinia, Campania and Sicily with standardised volumes of 857, 839 and 718 grams, respectively.

About 9% of the national demand was distributed through public pharmacies, reaching a quantity of approximately 3,139 kilograms, The pharmacy channel was particularly used in Calabria and Campania where it accounts respectively for 27 and 24% of the regional demands.

The growth trend of the demand for IG was confirmed in the two-year period 2018-2019: +8% of the demand for IG; + 17% 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 Liguria, with around 192, 183 and 154 grams respectively.

The demand for AT has increased slightly (+2%) in 2019 like the demand of 4F-PCCs (+ 6,5%), while the demand for 3F-PCCs remained almost stable (-0,7%).

As regards the haemophilia A treatment, on one hand, the demand for pdFVIII (alone and in combination with vWF) significantly decreased (-8%); on the other, there was an evident increase in the demand for rFVIII (+ 9%) in particular as regards drugs with extended half-life FVIII (+ 56%).

The consumption of Emicizumab also increased significantly (+ 800%) and this was probably associated with the decrease in the demand for the activated prothrombin complex (-48%).

Concerning the haemophilia B treatment, the clinical use of extended half-life FIX progressively replaced the demand for pdFIX.

The total volume of plasma sent by Regions for fractionation increased 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 23.6 sent by Friuli Venezia Giulia, with an average volume of 14.2 kilograms per 1,000 population.

The level of albumin self-sufficiency stood at, around 76% (72% in 2018), As regards IGs, on the other hand, self-sufficiency in human immunoglobulin for intravenous and subcutaneous/intramuscolar use achieved at national level was 63%, while self-sufficiency in IV IG reached 79%; self-sufficiency for SC / IM IG was only 6%.

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 118 million euros, in line with the costs estimated by the contracts in force in 2019; yet a roughly additional 3 million euros had to be taken into account for the processing of solvent/detergent virus-inactivated plasma, for a total of about 121million euros.

The estimate of the expenditure incurred by the NHS in 2019 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 170,1 million euros. An additional 112 million euros were used for the purchase of all the other PDMPs.

The cost of purchasing Emicizumab was 16,5 million euros.

The expenditure associated to recombinant products was about 456,3 million euros. The total expenditure for medicinal products described in this report was around 2.5% of the total NHS pharmaceutical expenditure recorded in 2019 (54).

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Serie Rapporti ISTISAN
numero di settembre 2021

Stampato in proprio
Servizio Comunicazione Scientifica – Istituto Superiore di Sanità

Roma, settembre 2021