

The demand for human albumin in Italy

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Introduction

Human albumin (HA) is a blood plasma protein produced in the liver. It constitutes about 60% of plasma proteins and is a physiological plasma-expander. However, its limited availability and high cost make it essential to define recommendations for its appropriate use, as an alternative to other therapeutic strategies including solutions of crystalloids and non-protein colloids.

According to all official recommendations, the choice to use albumin rather than an artificial colloid strictly depends on the clinical situation of the patient¹⁻⁶. HA is also used in all cases in which there is a contraindication to the use of non-protein colloids⁷. Based on clinical evidence, the 2009 guidance document of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)⁷ recommends the use of HA in acute conditions, which call for blood volume expansion and maintenance of adequate blood flow, as well as in some chronic conditions of low serum albumin levels. "There are some widely shared and fully agreed indications for the appropriate use of human albumin and indications that are occasionally appropriate, that is, when other criteria are fulfilled"⁷. In addition, in haemorrhagic shock HA should only

be used as a second choice [i.e. when solutions of crystalloids or non-protein colloids (first choice treatment) have already been used at maximum doses without having produced a clinically adequate response] and in cases in which non-protein colloids are contraindicated⁷.

Albumin preparations

HA is pasteurised at 60 °C for 10 hours⁸. It can be infused independently of the recipient's blood group. Preparations of 5%, 20% and 25% have been registered. The solutions of 5% HA have an osmotic pressure almost identical to that of normal plasma; the 20% and 25% solutions are hyperosmotic. All preparations contain 130-160 mEq of sodium per litre⁷.

In Italy, the medicinal product reimbursement is defined according to the therapeutic indications of the Italian Medicine Agency (AIFA) (Note 15)⁹, which identifies the medicinal products that can be funded by the National Health Service (NHS).

In Table I, a HA brief fact sheet is reported. Table II shows all packages currently on the Italian market containing HA¹⁰, their quantity of active substance, and the level of reimbursement by the NHS.

Table I - Human albumin brief fact sheet¹.

ATC ^a	B05AA01
Definition	Albumin
U/M ^b	g
Therapeutic indications	Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate. The choice of the use of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations.
NHS class ^c	A, C, H
AIFA note ^d	15
Management information	Informed consent

^a Anatomical Therapeutic Chemical Classification System. The World Health Organization system classifies all therapeutic medicinal products (MP). The purpose is to serve as a tool for MP utilization research in order to improve the quality of MP use. MPs are classified into five different levels; ^b Unit of Measure; ^c National Health Service Class. All medicinal products are divided in classes according to the level of reimbursement by the NHS. Class A includes all medicinal products at the expense of the NHS; class H includes all medicinal products distributed only by hospital pharmacies within the Regional Healthcare Services; class C refers to all medicinal products at the private out-of-pocket expense; ^d AIFA (Agenzia Italiana del Farmaco, Italian Medicine Agency) Note is a regulatory tool that defines some levels of reimbursement of medicinal products without interfering with the physician freedom to provide for prescription. However, the AIFA note must be respected by physicians to prescribe certain medicinal products at the expense of the NHS.

Table II - Products containing human albumin currently available on the Italian market.

Source: Farmadati (www.farmadati.it, accessed on 01/03/2012), processed and adapted by the Italian National Blood Centre.

AIC ^a code	Name of medicinal product	g ^b	Manufacturer	NHS class ^c
034611032	ALBUMINA GRIFOLS*1FL 100ML 5%	5	Grifols Italia SpA	C
036176016	ALBUMINA LFB*FL 50ML 200MG/ML	10	Lab.Français di Fract. Biotech	A
028989046	PLASBUMIN*EV 1FL 50ML 20%	10	Kedrion 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
029251030	ALBUTEIN*IV FL 50ML 200G/L	10	Alpha Therapeutic Italia SpA	A
010317028	ALBUMINA UM.IMMUNO*50ML 20%+S.	10	Baxter SpA	A
011544020	ALBUMINA UM.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
034611018	ALBUMINA GRIFOLS*1FL 50ML 20%	10	Grifols Italia SpA	A
038747034	OCTALBIN*IV 50ML 200MG/ML	10	Octapharma Italy SpA	A
034611069	ALBUMINA GRIFOLS*50ML 25G/100ML	12.5	Grifols Italia SpA	A
036504076	ALBUREX*INFUS 1FL 50ML 25%	12.5	CSL Behring GmbH	A
021111087	UMANALBUMIN*INF FL 50ML 250G/L	12.5	Kedrion SpA	A
022515136	ALBITAL*1FL 50ML 25G/100ML+SET	12.5	Kedrion SpA	A
010317042	ALBUMINA UM.IMMUNO*50ML 25%+S.	12.5	Kedrion SpA	A
029251042	ALBUTEIN*IV FL 50ML 25%	12.5	Alpha Therapeutic Italia SpA	A
037566092	ALBUMINA BAXTER*1FL 50ML 250G/L	12.5	Baxter SpA	A
029251016	ALBUTEIN*IV FL 250ML 50G/L	12.5	Alpha Therapeutic Italia SpA	C
034611044	ALBUMINA GRIFOLS*1FL 250ML 5%	12.5	Grifols Italia SpA	C
039073010	ALBIOMIN*INF 250ML 50G/L 5%	12.5	Biotest Italia Srl	C
021111051	UMANALBUMIN*FL 250ML 5%	12.5	Kedrion SpA	C
036504037	ALBUREX*INFUS 1FL 250ML 5%	12.5	CSL Behring GmbH	C
037566015	ALBUMINA BAXTER*1FL 250ML 50G/L	12.5	Baxter SpA	C
036504064	ALBUREX*INFUS 1FL 100ML 20%	20	CSL Behring GmbH	A
028989059	PLASBUMIN*EV 1FL 100ML 20%	20	Kedrion 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
021111101	UMANALBUMIN*EV FL 100ML 200G/L	20	Kedrion SpA	A
037566078	ALBUMINA BAXTER*1FL 100ML 200G/L	20	Baxter SpA	A
038747046	OCTALBIN*IV 100ML 200MG/ML	20	Octapharma Italy SpA	A
034611020	ALBUMINA GRIFOLS*1FL 100ML 20%	20	Grifols Italia SpA	A
029251028	ALBUTEIN*IV FL 500ML 50G/L	25	Alpha Therapeutic Italia SpA	C
034611057	ALBUMINA GRIFOLS*1FL 500ML 5%	25	Grifols Italia SpA	C
038109017	FLEXBUMIN*24SACCHE 50ML 200G/L	240	Baxter SpA	H
038109031	FLEXBUMIN*12SACCHE 100ML200G/L	240	Baxter SpA	H

^a AIC, *Autorizzazione Immissione in Commercio*, Marketing authorisation. The AIFA is in charge of releasing the AIC Code, which identifies each medicinal products package on the national market¹⁰; ^b grams of human albumin contained in the medicinal product; ^c National Health Service Class. All medicinal products are divided in classes according to the level of reimbursement by the NHS. Class A includes all medicinal products at the expense of the NHS; class H includes all medicinal products distributed only by hospital pharmacies within the Regional Healthcare Services; class C refers to all medicinal products at the private out-of-pocket expense.

Quantification and characterisation of human albumin demand

Tables III and IV show both the total (public and private) and total standardised demand for HA expressed in grams and in grams per 1,000 population, respectively, in the period 2007-2011 at the national and regional levels¹¹.

The data analysed did not consider the use of the product Umanserum® (Kedrion SpA, Castelvechio Pascoli, Lucca, Italy). That product is classified as human plasma protein within the Anatomical Therapeutic Chemical Classification (ATC) system, despite its 90% albumin composition.

Table III - Quantification of total (public and private) demand for human albumin (expressed in grams) in Italy and Italian regions, from 2007 to 2011.

Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre.

Region	2007	2008	2009	2010	2011
Abruzzo	767,233	656,680	474,073	621,610	802,783
Aosta Valley	46,310	42,120	54,433	61,000	74,480
AP Bolzano	127,905	151,450	117,190	129,185	116,570
AP Trento	107,775	111,515	105,053	109,410	123,475
Apulia	3,704,368	3,391,618	3,127,333	3,720,655	3,762,990
Basilicata	422,548	347,925	382,328	340,135	354,735
Calabria	1,554,720	1,383,343	1,060,593	1,349,995	1,466,588
Campania	4,236,933	4,251,565	4,046,508	4,718,073	4,328,273
Emilia-Romagna	2,312,148	1,890,008	1,978,340	2,197,143	2,254,210
FVG	334,063	341,523	310,613	322,620	340,380
Lazio	4,277,350	3,344,238	2,080,035	3,635,510	4,036,993
Liguria	703,850	610,943	693,430	722,610	806,700
Lombardy	4,262,056	4,074,680	3,599,115	4,571,805	5,517,158
Marche	601,035	593,305	581,510	606,268	571,033
Molise	316,170	187,608	89,530	188,425	191,583
Piedmont	2,277,888	2,045,165	2,184,080	2,164,280	1,659,628
Sardinia	1,819,443	1,599,365	1,361,930	1,724,790	2,046,890
Sicily	2,829,260	2,473,290	2,133,165	2,523,743	2,929,808
Tuscany	2,144,575	1,985,165	2,255,585	2,323,878	2,493,200
Umbria	291,165	307,743	337,185	437,530	464,650
Veneto	2,114,780	2,388,168	2,106,845	2,192,670	2,029,680
Other*	1,400,825	142,110	104,633	78,810	70,858
Italy	36,652,396	32,319,523	29,183,503	34,740,143	36,442,660

Legend AP: Autonomous Province; FVG: Friuli-Venezia Giulia; Other*: movements of medicinal products not univocally defined.**Table IV** - Quantification of total (public and private) standardised demand for human albumin (expressed in grams per 1,000 population) in Italy and Italian regions, from 2007 to 2011. Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre.

Region	2007	2008	2009	2010	2011
Abruzzo	585.8	496	355.2	464.3	598
Aosta Valley	371	334.3	428.4	477.1	580.8
AP Bolzano	262.3	306.6	234.9	256.6	229.6
AP Trento	212.6	217.2	202.1	208.5	233.2
Apulia	910.2	832	766.6	911	919.8
Basilicata	714.6	588.7	647.4	577.6	603.8
Calabria	778.1	689	528	671.9	729.1
Campania	731.7	731.6	696.1	810	741.9
Emilia-Romagna	547.5	442	456.1	499.9	508.6
FVG	275.5	279.5	252.3	261.4	275.4
Latium	778.6	601.4	369.7	639.8	704.7
Liguria	437.8	379.5	429.4	447.2	499
Lombardy	446.5	422.6	369.4	465.3	556.3
Marche	391.3	382	370.5	388.7	364.8
Molise	987.8	584.7	279.1	588.4	599.1
Piedmont	523.3	464.7	492.7	486.8	372.3
Sardinia	1,096.4	960.2	815.0	1,031.3	1,221.7
Sicily	564	491.7	423.4	500.4	580
Tuscany	589.5	539.9	608.3	623	664.9
Umbria	333.5	347.9	377.1	485.7	512.6
Veneto	443	494.2	431.2	446.4	411
Other*	na	na	na	na	na
Italy	619.8	542.1	486	575.7	601.1

Legend AP: Autonomous Province; FVG: Friuli-Venezia Giulia; Other*: movements of medicinal products not univocally defined; na: not assessable.

The absolute demand for HA decreased slightly (−1%) in the period 2007-2011. In 2011, the total demand was 36,442,660 grams and the total standardised demand was 601 grams per 1,000 population (Figure 1).

A decreasing trend in the national standardised demand (−3%,) was recorded in almost all Regions and Autonomous Provinces (AP) (henceforth referred to as "Regions"). In contrast, the standardised demand per 1,000 population grew significantly in Aosta Valley, Umbria and Lombardy over the period (+57%, +54%,

and +25%, respectively. Data not shown). In 2011, the highest regional demands, standardised per 1,000 population, were recorded in Sardinia, Apulia and Campania with 1,222, 920 and 742 grams (Figure 1) and a percentage change from the national mean value of +103%, +53%, and +23% (Figure 2), respectively.

It is important to note that the above-mentioned Regions recorded almost one third of the national albumin demand (28%) although their combined population represents less than a fifth of the entire Italian population (19.1%).

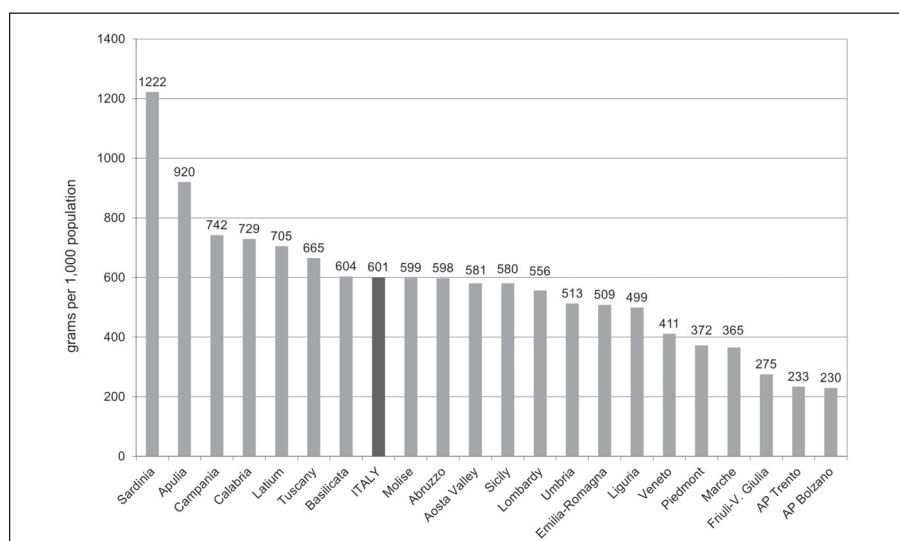


Figure 1 - Quantification of total (public and private) standardised demand for albumin, expressed in grams per 1,000 population, in Italy and Italian Regions, year 2011. Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre. **Legend** AP: Autonomous Province; Friuli-V. Giulia: Friuli-Venezia Giulia.

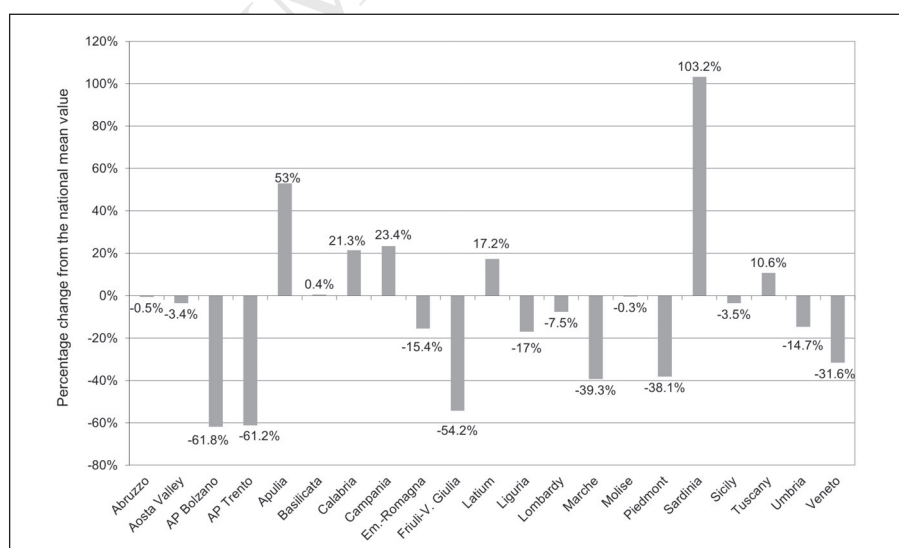


Figure 2 - Percentage change from the national mean value of standardised regional demand for human albumin (grams per 1,000 population) in 2011. Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre. **Legend** AP: Autonomous Province; Em.-Romagna: Emilia-Romagna; Friuli-V. Giulia: Friuli-Venezia Giulia.

The lowest standardised demands were recorded in three Regions (Friuli-Venezia Giulia and APs of Trento and Bolzano) with a percentage change from the national mean utilisation of -54% , -61% , and -62% (Figure 2), respectively. These data highlight the regional differences in the usage of HA.

In order to assess whether the utilisation trend is determined by a particular segment of the demand, usages were also divided per distribution channel (pharmacies open to the public, public healthcare facilities, private healthcare facilities).

Figure 3 shows the percentage distribution, on a regional basis, of the use of the above-mentioned distribution channels and the related amount of HA expressed in grams per 1,000 population in 2011. From this analysis it emerged that although pharmacies open to the public are an important distribution channel only in Campania, Calabria, Apulia, Sicily, Molise, and Latium, where in 2011 270, 231, 262, 90, 91, and 87 grams per 1,000 population were distributed respectively, nevertheless they significantly influenced the national share of demand related to this distribution channel.

The Regions of Campania, Apulia and Calabria account for the largest quantity of HA distribution through the channel of pharmacies open to the public. Indeed, the Region of Campania with 270 grams, the Region of Puglia with 262 grams and the Region of Calabria with 231 grams per 1,000 population recorded a deviation compared to the national mean value (83

grams per 1,000 population) of $+324\%$, $+314\%$, and $+277\%$, respectively.

As regards the distribution by public healthcare facilities, there was a decreasing trend initially and then a recovery in 2011 for most Regions (data not reported here), with the exception of Regions where demand was stable (Lombardy, Piedmont and Veneto) and Regions with increasing trends in the period 2007-2011 (Umbria and Aosta Valley). Among the six Regions with a percentage change above the national mean value in 2011 (422 grams per 1,000 population), Sardinia and Tuscany recorded values of 157% and 49% with 1084 and 627 grams per 1,000 population, respectively.

As far as the distribution by private healthcare facilities is concerned, decreasing trends were also documented initially with recovery in 2010 (data not reported here). A particularly substantial usage was recorded in some Regions such as Latium, Molise and Lombardy with a deviation compared to the national mean value of $+153\%$, $+128\%$, and $+68\%$, respectively. However, this difference is likely to be due to the specific healthcare organisation of these Regions, where private hospitals play a particularly significant role.

Figure 4 shows the comparison between Italy, some European and extra-European Countries for albumin demand per 1,000 population. Italy is at the top of the ranking with a *per capita* consumption three times higher than other Countries with equal socio-economic levels¹².

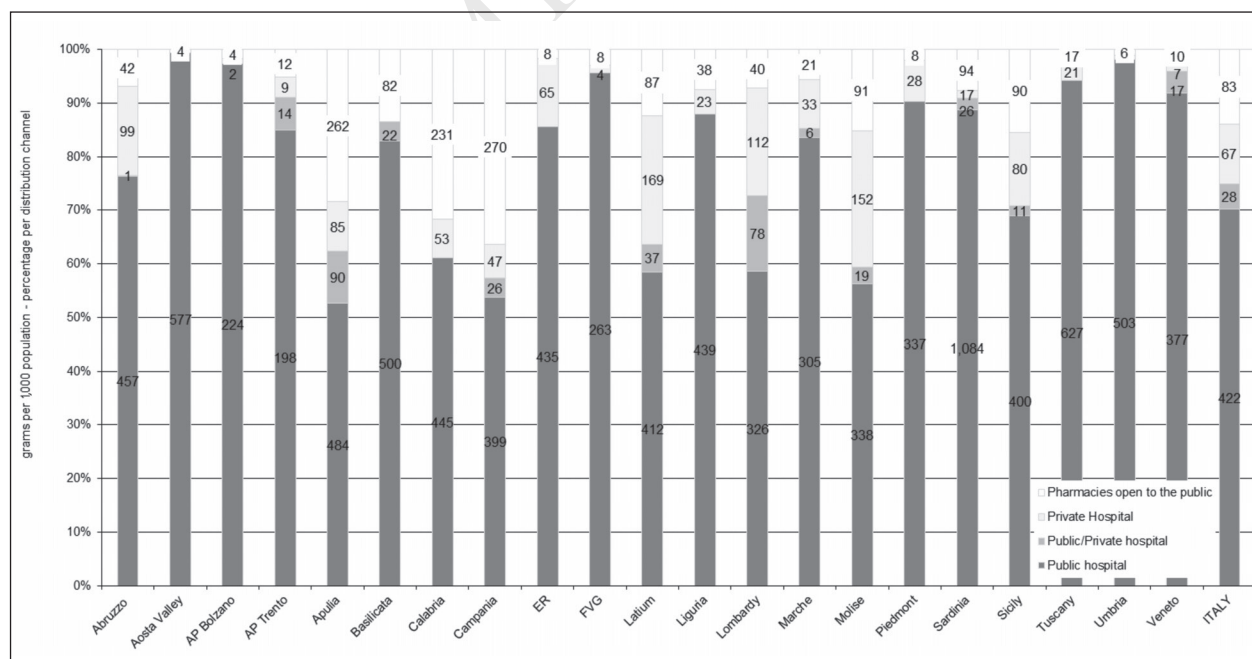


Figure 3 - Regional demand for human albumin, in grams per 1,000 population, by distribution channel, year 2011.

Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre.

Legend AP: Autonomous Province; Em.-Romagna: Emilia-Romagna; Friuli-V. Giulia: Friuli-Venezia Giulia.

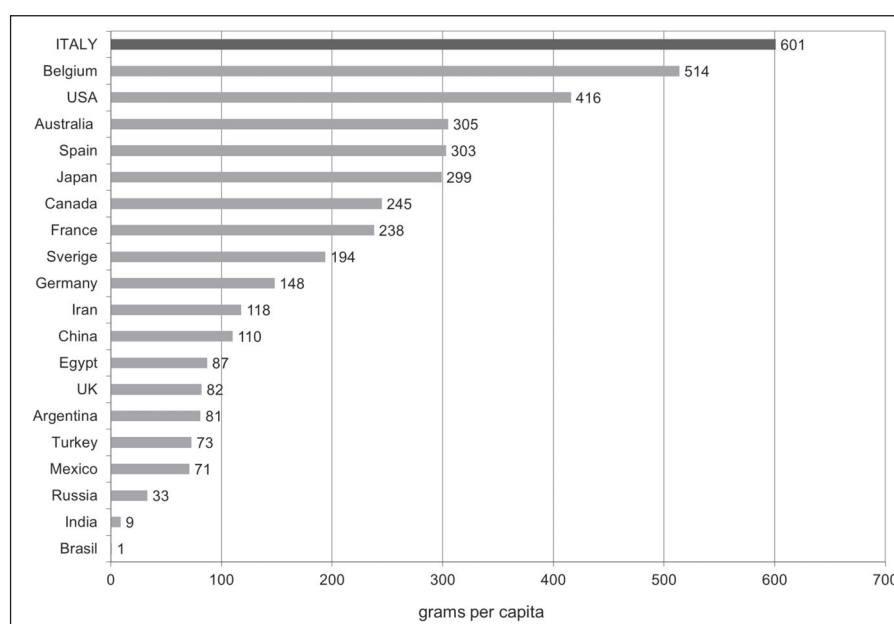


Figure 4 - Demand for albumin (expressed in grams per 1,000 population) in some European and extra-European Countries.

Sources for Italy (2011): medicinal product traceability, processed and adapted by the Italian National Blood Centre; sources for European and extra-European Countries (2010): Robert P, 2010¹².

These data are worthy of attention if considered in relation to the variability observed at the regional level. In 2011, some Regions (Sardinia, Apulia and Campania) recorded peaks up to six times (or even more) higher than those reported in 2010 in other Regions or in European and extra-European Countries. In fact, in France, Germany and the United Kingdom the mean demand for HA was 238, 148 and 82 grams per 1,000 population, respectively.

Conclusions

Appropriate use of plasma-derived medicinal products is a strategic goal of all policies aimed at the achievement of national self-sufficiency. HA and polyvalent immunoglobulin for intravascular administration are the driving products with regard to national planning of plasma collection. Therefore, the definition of their appropriate demand has a key role in determining both national needs and self-sufficiency levels to be achieved.

Currently, there are no internationally recognised and/or shared references related to the HA *per capita* utilisation that could be considered as indicative of an appropriate use. However, benchmarking national data between Italy and other countries, which are comparable at socio-economic level, provides a clear indication on the unusual Italian propensity to use this medicinal product and should induce a careful consideration of a possible inappropriate usage of HA in many Italian Regions, also including those where an important portion

of this product is being distributed in pharmacies open to the public.

Keywords: human albumin, albumin infusion, plasma-derived medicinal product, analysis of demand, albumin preparation.

The Authors declare no conflicts of interest.

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