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AGENZIA ITALIANA DEL FARMACO

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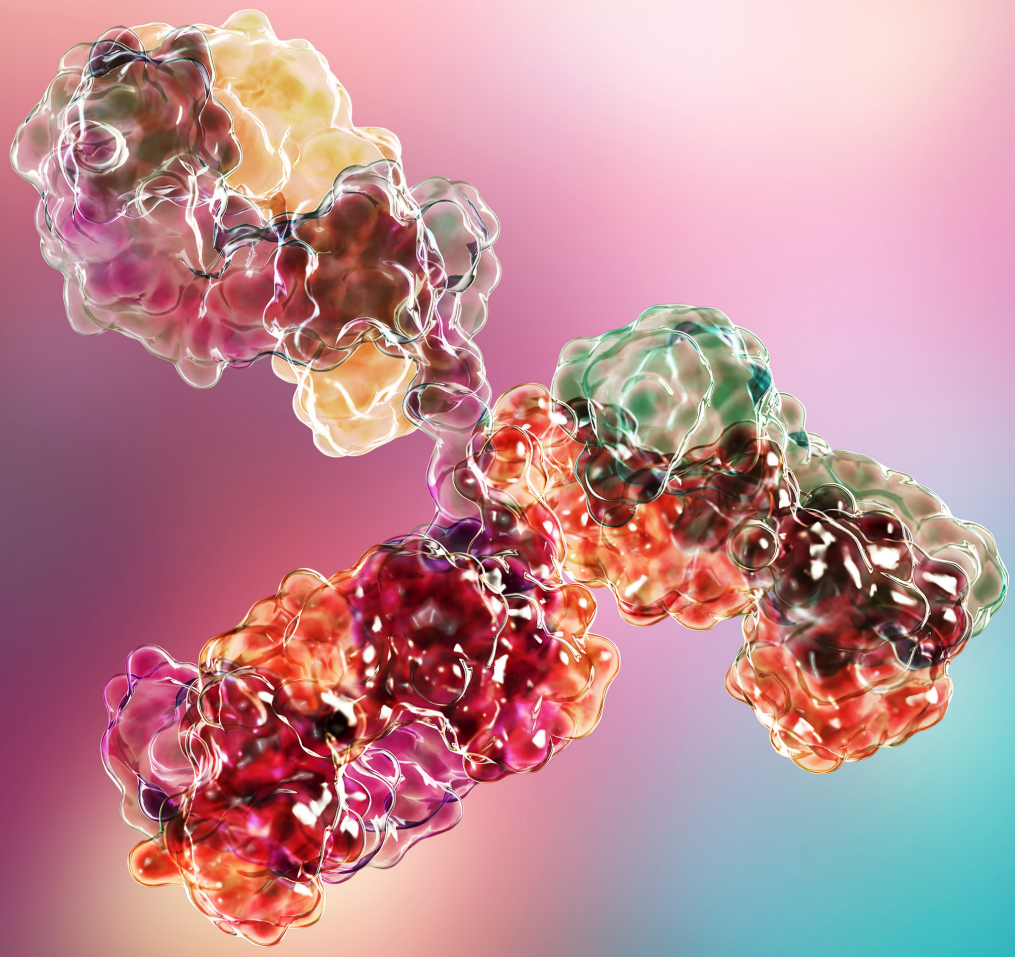
Istituto Superiore di Sanità

GUIDELINES ON THE USE OF HUMAN IMMUNOGLOBULINS IN CASE OF SHORTAGES



GITMO

SIdEM Società Italiana di Emaferesi e Manipolazione Cellulare

SIE Società Italiana di Ematologia

CHARITAS SAPIENTIA
SOCIETA' ITALIANA DI FARMACIA OSPEDALIERA E DEI SERVIZI FARMACEUTICI DELLE AZIENDE SANITARIE

SIMTI

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SOCIETÀ ITALIANA DI NEUROLOGIA

GUIDELINES ON THE USE OF HUMAN IMMUNOGLOBULINS IN CASE OF SHORTAGES

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ACRONYMNS AND ABBREVIATIONS

AIFA	Agenzia Italiana del FArmaco (Italian Medicines Agency)
ATC	Anatomical Therapeutic Chemical classification system
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CLL	Chronic Lymphocytic Leukemia
CMV	CytoMegaloVirus
CNS	Centro Nazionale Sangue (Italian National Blood Centre)
GBS	Guillain-Barré Syndrome
HSCT	Hematopoietic Stem Cell Transplantation
IG	ImmunoGlobulin
IMIG	IntraMuscular ImmunoGlobulin
IVIG	IntraVenous ImmunoGlobulin
SCIG	SubCutaneous ImmunoGlobulin
ITP	Primary Immune Thrombocytopenia
MM	Multiple Myeloma
MMN	Multifocal Motor Neuropathy
MoH	Ministry of Health
PDMP/s	Plasma-Derived Medicinal Product/s
PID	Primary Immunodeficiency Disease
PSAF	Proven Specific Antibody Failure
RCS	Regional Coordination Structures for transfusion activities
RSV	Respiratory Syncytial Virus
SID	Secondary Immunodeficiency Disease
SIMTI	Società Italiana di Medicina Trasfusionale e Immunoematologia (Italian Society of Transfusion Medicine and Immunohaematology)
SPCs	Summary of Product Characteristics

PREFACE

Plasma-Derived Medicinal Products (PDMPs) are pharmaceutical specialties produced through the industrial manufacturing processes of plasma. In Italy, plasma is collected from voluntary non-remunerated donors, through productive apheresis procedures or from whole blood donations, through separation from other blood components. PDMPs play a key role, and sometimes a non-replaceable role in the treatment of many acute and chronic clinical conditions.

At national and international levels, current data on PDMPs demand confirm a constant increase in the use of polyvalent immunoglobulins (both for intravenous and subcutaneous use), which are today the driver of the production of a quite various range of medicinal products derived from plasma. In recent years, their use has continued to grow, progressively leading to a potential imbalance between availability and demand. In addition to the existing supply issues, also the Covid-19 pandemic has been negatively impacting plasma collection, especially in non-European countries. This further influenced the global production of PDMPs, whose distribution is defined according to market logics that inevitably trigger competitive dynamics between countries.

In case of partial availability of these products, it is possible to operate complementarily according to three strategic lines: i) the increase of plasma collection for toll fractionation; ii) a stronger collaboration with the health personnel in charge of triage; iii) the increase of production yields through the improvement of industrial technology. While on one hand, the commitment of the Italian Blood System (including the Associations and Federations of voluntary blood donors) can guarantee high levels of self-sufficiency not observed in other European and extra-European countries with comparable socio-economic conditions; on the other hand, the technological development made by the fractionation companies has actually increased the availability of products. Therefore, the aspect to be improved is the management of the appropriateness of clinical use or, in any case, to adapt the prioritisation strategy of the products in case of their partial or total unavailability.

This document was written with the purpose to provide recommendations to face a possible shortage of strategic and life-saving products such as human immunoglobulins in medical therapy.

We are grateful to all the professionals who contributed with methodological accuracy to the discussion, which was extremely useful to produce the present document.

Nicola Magrini — General Director AIFA

Vincenzo De Angelis — General Director CNS

INTRODUCTION

In the last year, following the COVID-19 pandemic, the imbalance between the availability of and the demand for the use of immunoglobulins for human use (IG) has worsened. This trend was already progressively increasing in the last decade due to the continuous approval of new indications for use, the increasingly widespread off-label use (even in the absence of solid scientific bases) and the substantial uncertainty regarding the duration of treatment (with particular reference to neurological diseases associated with immune disorders).

The Italian Medicines Agency (AIFA) and the Italian National Blood Centre (CNS) - with the involvement of the Ministry of Health (MoH), the Regional Blood Centres (RBC), the Permanent Conference for relations between the State, the Regions and the Autonomous Provinces, Donor Associations, Patient Associations and Organisations, Companies producing PDMPs and Farmindustria - have therefore defined several activities aimed to monitor and manage the possible shortages as well as to maximise the appropriateness of clinical-therapeutic use of IGs.

These activities include the implementation of a Working Group on the availability of IGs which takes advantages of the cooperation of all the aforementioned stakeholders. The main task of this group is to deal with the issue of the supply of PDMPs with a coordinated and preventive approach to ensure both the availability of these products and the therapeutic continuity to patients.

Furthermore, at the CNS a multidisciplinary working group has been established with representatives of the following scientific societies: Italian Society of Haemapheresis and Cell Manipulation - SidEM, Italian Society of Transfusion Medicine and Immunohaematology - SIMTI, Italian Society of Haematology - SIE, Italian Society of Neurology - SIN, Italian Society of Hospital Pharmacies - SIFO and the Italian Group of bone marrow transplantation and haematopoietic stem cells – GITMO. All these actors contributed to the drafting of this document.

In addition, the AIFA STC has deemed opportune the definition and provision of general guidelines as reference document for the appropriate use of IGs in several indications. In particular, it is recommended that the prescription takes place exclusively in compliance with the indications authorised and those reimbursed pursuant to Law 648/96, where priority use is guaranteed in indications for which therapeutic alternatives are not available and where the dosages can be optimised. Attention is drawn to the fact that the Regions and Autonomous Provinces define themselves the plans for the management of shortages with local control of IGs prescriptions and a real-time monitoring of the availability. Based on the availability of IGs at national and regional levels, it is proposed to adopt various specific management strategies. Furthermore, the main criteria for guaranteeing an appropriate use of IGs in shortage contexts are proposed, divided by therapeutic area and pathological condition.

BACKGROUND

Preparations with IGs have been used for therapeutic purposes since the early Fifties, in particular for Primary ImmunoDeficiencies (PID). With plasma fractionation, about 30 years ago, treatment with IntraVenous (IV) IGs has become an important therapeutic option and, since 2007, both soluble IG preparations for SubCutaneous / IntraMuscular infusion (SC / IM) and for IV use have been available in Italy. The IGs are prepared using human plasma pools resulting in significant idiotypic diversity and thus guaranteeing a greater antibody coverage to the recipient. These preparations contain structurally and functionally intact IG with normal half-life and physiological proportions of subclasses (95% monomeric IgG, small quantities of dimers and a variable quantity of IgA and IgM). The half-life of most of IGs preparations is 18-32 days, although there is considerable individual variability. The dose and treatment schedule depend on the indication. In particular, in replacement therapy it may be necessary to individualise the dosage for each patient in relation to the pharmacokinetic and clinical response.

Over the years, IGs have had extensive use. Additionally to PID replacement therapy, IGs are used also in the treatment of autoimmune diseases or systemic inflammatory processes. In clinical practice, IGs are used much more extensively than authorised indications and there is a wide range of clinical conditions for which IVIGs have been used off-label and without adequate scientific documentation of efficacy (Kivity 2010; Katz 2011; Perez 2017). A recent review conducted by the EMTm (European and Mediterranean Initiative in Transfusion Medicine) analysed the evolution of the use of IGs from 2004 to today, finding a progressive increase in the use of these products, mainly in relation to "doubtful indications" (up to 40%) in the absence of solid scientific evidence (Brand, 2021; Farrugia, 2021).

In recent years, worldwide, due to the continuous approval of new indications for use, the increasingly widespread off-label use and the substantial uncertainty regarding the duration of treatment (with particular reference to neurological diseases associated with disorders immunity), the use of IGs has continued to grow, progressively leading to a potential imbalance between availability and demand.

Furthermore, in the last year, following the COVID-19 epidemic, the shortage of IGs for human use has further worsened (Hartmann, 2020), imposing the need to implement a series of activities, shared with all stakeholders, aimed at monitoring and managing the shortage and maximising the appropriateness of clinical-therapeutic use.

The AIFA STC also deemed it appropriate to provide general guidelines to refer to the appropriate use of IGs in the various indications.

It should be reiterated that, with a view to a global and shared approach to tackle the shortage of IGs and more generally of PDMPs, the activities described above cannot be separated from policies aimed at supporting plasma collection and a constant commitment to improvement of industrial technologies that allow to increase production yields.

USING IMMUNOGLOBULINS: A FRAMEWORK

Pharmaceutical specialties based on immunoglobulins, authorised and reimbursed indications in Italy

IGs are available as a sterile preparation of concentrated antibodies extracted from the plasma of healthy donors. There are a number of preparations authorised for sale available as preparations for both IV and SC / IM administration.

Appendix 1 shows the pharmaceutical specialties (ATC J06BA) distributed in 2021 with the respective indications (as in the paragraph 4.1 of the Summary of Product Characteristics - SPC).

The main authorised indications [1] for **IVIGs** concern:

- Replacement therapy in adults, children and adolescents for:
  - Primary immunodeficiency syndromes with impaired antibody production.
  - Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l.
    * PSAF = inability to produce an increase of at least 2 times in the titre of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen.
- Immunomodulation in adults, children and adolescents for:
  - Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts.
  - Guillain-Barré Syndrome (GBS).
  - Kawasaki disease (in conjunction with acetylsalicylic acid).
  - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
  - Multifocal Motor Neuropathy (MMN).

IVIGs are included in the list of medicines of consolidated use in neurology for the following indications:

- Myasthenic crisis, as an alternative to plasmapheresis.
- Rapidly worsening forms of myasthenia gravis and in the flare-up phases of the disease, when rapid improvement in muscle strength is required to minimize the risk of bulbar palsy or respiratory failure.
- In the initial stages of myasthenia gravis, waiting for the effect of cortisone and/or immunosuppressive therapy.
- As a preparation for thymectomy, in patients with myasthenia gravis not sufficiently compensated by specific basic therapies.
- In patients with myasthenia gravis who are not responsive to steroid and/or immunosuppressive drug therapies or who have contraindications to their use.

[1] Individual products still on the market may have indications that are not fully harmonized, for a complete list see Appendix 1.

SC /IM IGs are mostly authorised for replacement therapy in adults in case of:

- PID syndromes with impaired antibody production.
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukemia (CLL) who have not responded to or in whom antibiotic prophylaxis is contraindicated.
- Hypogammaglobulinemia and recurrent bacterial infections in patients with multiple myeloma (MM).
- Hypogammaglobulinaemia in patients undergoing or having undergone allogeneic haematopoietic stem cell transplantation (HSCT).

Hizentra® (CSL BEHRING GMBH) is also authorised for the treatment of patients with CIDP.

IGs are included in the complementary list of essential medicines WHO[2] for the treatment of PID (IVIG or SCIG) and Kawasaky disease (SCIG).

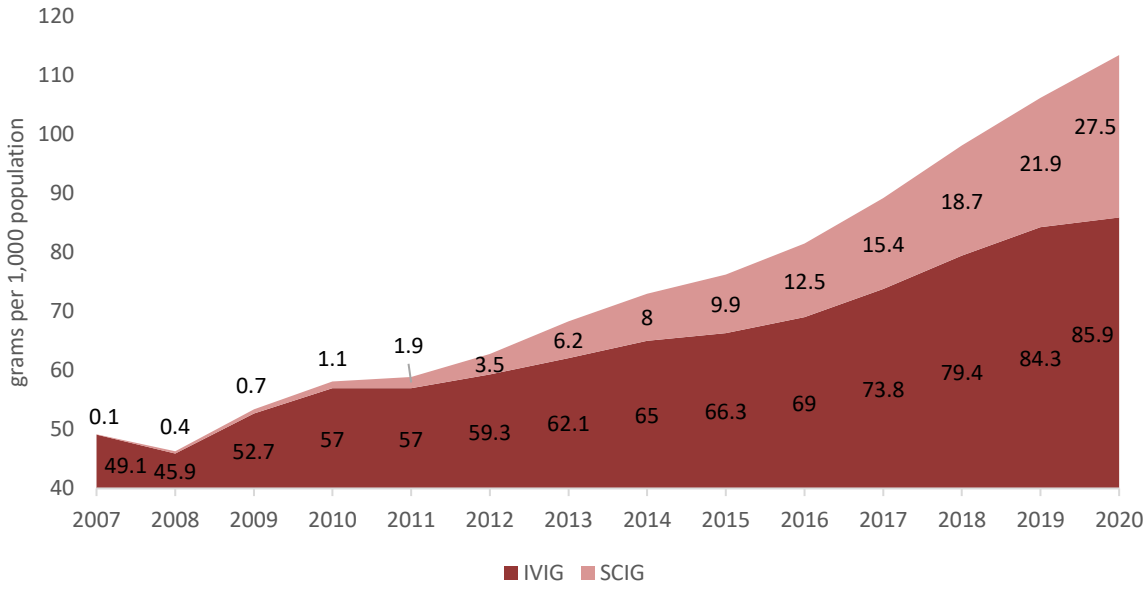
[2] "WHO Model list of essential medicines – 21st list, 2019".
Available at: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06. Latest consultation October 15th 2021.

Data on consumption and expenditure of immunoglobulins in Italy

The total demand for IGs has recorded a continuous increase in recent years, equal to approximately + 7% in the year 2020, compared to the previous year. In detail, the demand for IVIG has grown by about 2% in the last year and the demand for subcutaneous formulations has recorded an increase of about 25%.

In recent years, the trend of the total demand for IGs (grams per 1,000 population units), according the formulation, is shown in Figure 1.

Figure 1. Total demand for intravenous and subcutaneous/intramuscular immunoglobulins in Italy. Years 2007 – 2020. Adapted by the Italian National Blood Centre, Italian National Institute of Health on data from the Ministry of Health.



Total expenditure of IGs has been subject to a steady increase over the last few years (Table 1). The percentage change in expenditure between 2018 and 2020 was more than +20% (21.9%). In particular, in this period, it was the SC /IM IGs that recorded the most evident increase in expenditure, equal to approximately 38%.

Table 1. Total expenditure of immunoglobulins for intravenous and subcutaneous/intramuscular use in Italy. Years 2018 – 2020. Adapted by the Italian National Blood Centre, Italian National Institute of Health on data from the Ministry of Health.

Year	Estimate of SCIG expediture (€)	Estimate of IVIG expediture (€)	Estimate of TOTAL IG expenditure (€)
2018	55,267,833	48,312,904	**103,580,737**
2019	64,278,470	43,271,802	**107,550,272**
2020	76,321,719	49,960,817	**126,282,536**

GENERAL STRATEGIES TO TACKLE SHORTAGES OF IMMUNOGLOBULINS

As mentioned in the introduction, due to the several new indications, the increasingly widespread off-label use and the substantial uncertainty regarding the duration of treatment (with particular reference to neurological diseases associated with immune disorders), in recent years, the use of IGs has continued to grow, progressively leading to a potential imbalance between availability and demand. Some countries, in particular Canada[3], United Kingdom[4] and France[5], have been preparing plans to manage shortages.

Similarly, to what has already happened in these countries, with particular reference to the recommendations adopted in Canada, a series of general guidelines are provided below to ensure the appropriateness of use of human IGs in a context of shortage:

- prescription exclusively in compliance with the indications authorised and admitted for reimbursement pursuant to Law 648/96;
- priority use in indications for which therapeutic alternatives are not available (and preferential use of therapeutic alternatives, where available);
- use of the lowest effective dosage for the shortest time necessary to ensure clinical efficacy.

In consideration also of the wide regional variability in IGs consumption, it is desirable that the individual Regions and Autonomous Provinces adopt plans for the management of shortages that also provide forms of local control of IGs prescriptions and real-time monitoring of the availability, in order to best allocate the therapeutic resources available.

Based on the availability of IGs at national and regional level, it is proposed to adopt various specific strategies, as detailed below.

[3]"The National Plan of Management of Shortages of Immunoglobulin Products (Ig)" – Interim Guidance; 2020-07-07. Available at: https://www.nacblood.ca/resources/shortages-plan/The%20National%20Plan%20for%20Management%20of%20Shortages%20of%20Immunoglobulin%20Products%20(Ig)%20%20Interim%20Guidance_July%2027%202020.Published.pdf Latest consultation October 15th, 2021.

[4]"Intravenous Immunoglobulin Use" Whittington Health. Available at: https://www.whittington.nhs.uk/document.ashx?id=6073 Latest consultation October 15th, 2021.

[5]"Utilisation des immunoglobulines humaines polyvalentes (Ig) dans un contexte de tensions d'approvisionnement : point sur les actions mises en œuvre" Available at: https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Utilisation-des-immunoglobulines-humaines-polyvalentes-Ig-dans-un-contexte-de-tensions-d-approvisionnement-point-sur-les-actions-mises-en-aeuvre-Point-d-Information. Latest consultation October 15th, 2021.

INVENTORY PHASE ACTIVITY AND ALLOCATION CRITERIA ACCORDING TO IMMUNOGLOBULINS AVAILABILITY

The following table shows the IG management criteria based on the availability.

Table 2. Inventory phase activity and IGs allocation criteria (adapted from: Canadian Blood Services and National Advisory Committee on Blood and Blood Products. The National Plan of Management of Shortages of Immunoglobulin Products – Interim Guidance. 2020-07-27).

Inventory level	Description and activities
Green	IG supply/inventory meets demand. • Follow jurisdictional best practice recommendations for use of IG (indications, optimal use guides, modality of administration, and doses). • Use the lowest IG dose for the shortest duration required to achieve the desired outcome. • For ongoing therapy, ensure the achievement of measurable clinical outcomes; IG should not be continued in patients with no demonstrable benefit. • Prior to starting Ig treatment, consider use of all other safe, effective, and accessible alternative therapies. • Where use is indicated, confirm that use aligns with the patient's goals of care. • Use a dose calculator based on adjusted body weight, and track Ig levels to adjust dose, as appropriate.

Green Advisory Phase	Ig supply/inventory levels are reduced or there are signs that short-term demand may outstrip capacity. **Reduce use by 10 to 20%:**
	• Continue to follow all the actions outlined in Green phase.
	• Round down IG treatment doses and frequency. Re-assess all patients that are already on treatment to find the minimal effective dose and optimize the treatment for each individual.
	• Review stocking practices and maintain the minimum inventory level required.
	• Reduce the refill volume for patients on home infusion products
	• Consider the use of alternative therapies.
	• Consider increasing availability of alternative therapies
	• Initiate actions to prepare for the potential escalation to Amber and Red phase by:
	  ○ Identifying patients that can be switched to SCIG (in the event of an IVIG shortage) or IVIG (in the event of an SCIG shortage), or other alternative therapies.
	  ○ Initiating local and provincial processes to support an adjudication process in the event of a red phase advisory.

Amber	IG supply/inventory levels are low for a short or prolonged period. **Reduce use by 20 to 50%:**
	• Continue to follow all the actions outlined in Green phase and Green Advisory phase.
	• Limit Ig use to clinical circumstances when there are:
	  ○ No viable alternatives; **and/or**
	  ○ the condition is life-threatening or there is a risk for irreversible disability as identified in the table below.
	• Use the lowest IG dose for the shortest duration required to achieve the desired outcome.
	• Implement screening of all IG orders within the hospital transfusion service/blood bank.

Red	There is a critical and prolonged Ig shortage. **Reduce use by over 50%:**
	• Limit IG use to clinical circumstances when there are:
	  ○ No viable alternatives; **and/or**
	  ○ the condition is life-threatening or there is a risk for irreversible disability as identified in the table below.
	• Have each case and dose approved by a formally established peer committee as per local jurisdictional guidance.
	• File a written copy of the decision in the patient's medical record and send another copy to Transfusion Medicine Services (blood bank).

It is essential that, in conditions of important and critical shortage, serious pathological conditions will be prioritised when no therapeutic alternatives are available. In Italy, the latest recommendations of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) on the correct use of blood components and PDMPs date back to 2008; in particular, a list of clinical conditions in which the routine use of IVIG is not recommended and a list of inappropriate indications for the use of IVIGs are included.

CRITERIA FOR RECOGNISED IMMUNOGLOBULIN INDICATIONS IN CASE OF SHORTAGES

The main criteria for ensuring an appropriate and priority use of IGs in contexts of shortage are listed below, divided by therapeutic area and pathological condition. (adapted from: *Canadian Blood Services and National Advisory Committee on Blood and Blood Products. The National Plan of Management of Shortages of Immunoglobulin Products – Interim Guidance. 2020-7-27*).

The list of conditions and guidance is comprehensive but not exhaustive. There may be other clinical circumstances in which a condition is life-threatening (or there is a risk for irreversible disability) and all other therapeutic options have failed, are counter-indicated or not tolerated. In these circumstances, the IGs can be considered in amber and/or red phases. If in red phase, on a review case-by-case basis these requests will be approved during a specific clinical evaluation process. These indications were developed for use during an IG shortage and should not to be interpreted as a clinical practice guideline. It is a framework to guide clinical decisions and triage in the event of an Amber or Red phase being declared, when there are not enough IGs available for all patients; in any case, it will be reviewed and updated during the development of the IGs Shortages Plan.

LEGEND

	IG supply/inventory levels are low for a short or prolonged period. **Reduce use by 20 to 50%:**
	• Continue to follow all the actions outlined in Green phase and Green Advisory phase.
	• Limit Ig use to clinical circumstances when there are:
	  ○ No viable alternatives;
	  and/or
	  ○ the condition is life-threatening or there is a risk for irreversible disability as identified in the table below.
	• Use the lowest IG dose for the shortest duration required to achieve the desired outcome.
	Implement screening of all IG orders within the hospital transfusion service/blood bank.

	There is a critical and prolonged Ig shortage. **Reduce use by over 50%:**
	• Limit IG use to clinical circumstances when there are:
	  ○ No viable alternatives;
	  and/or
	  ○ the condition is life-threatening or there is a risk for irreversible disability as identified in the table below.
	• Have each case and dose approved by a formally established peer committee as per local jurisdictional guidance.
	File a written copy of the decision in the patient's medical record and send another copy to Transfusion Medicine Services (blood bank).

A) DERMATOLOGY

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CASE OF SHORTAGES	
Bullous dermatitis (e.g.- pemphigus vulgaris, bullous, pemphigoid)	🟡 Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated 🟡 First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	🔴 Do not use
Pyoderma gangrenosum	🟡 Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated 🟡 First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	🔴 Do not use
Scleromyxedema	🟡 Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated 🟡 First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	🔴 Do not use
Stevens-Johnson syndrome and toxic epidermal necrolysis	🟡 Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated 🟡 First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	🔴 Do not use

B) HAEMATOLOGY

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CASE OF SHORTAGES	
Acquired coagulation factor inhibitors	🟡🔴 Should be considered only after adjunctive therapies (such as steroids) in urgent situations, as decided by experts at a haemophilia treatment centre	
Allogeneic haematopoietic stem cell transplant	🟡🔴 In cases of hypogammaglobulinemia, acquired post-haematopoietic stem cell transplant (HSCT). See immunology section	
Autoimmune haemolytic anemia (AIHA)	🟡🔴 In cases of failure to first-line treatment, contraindication or intolerance of other therapeutic options in life-threatening cases	
Autoimmune neutropenia	🟡 In cases of failure, contraindication or intolerance to other therapeutic options	🔴 In cases of failure, contraindication or intolerance to other therapeutic options **AND one of the following:** 🔴 For severe, active infections 🔴 A history of severe infections that responded positively to treatment
Catastrophic antiphospholipid syndrome	🟡🔴 In cases of severe disease and failure, contraindication or intolerance to other therapeutic options [1].	
Fetal and neonatal alloimmune thrombocytopenia (FNAIT)	🟡🔴 Treatment for mothers during pregnancy: permitted for use, maximum dose not to exceed 1 g/kg/week 🟡🔴 Treatment for newborns: if there is potentially fatal bleeding or a platelet count below 30 x 10^9/L, when a platelet transfusion (whether selected for human platelet antigen [HPA] or not) is not possible	

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CASE OF SHORTAGES	
Haemolytic disease of the fetus and newborn (HDFN)	🟡 Should be given only in consultation with neonatology and transfusion medicine: ○ Treatment for pregnant mothers: when there is a high risk AND intrauterine transfusion is contraindicated ○ Treatment for newborns: in cases of hyperbilirubinemia due to maternal alloimmunization if phototherapy fails	🔴 Should be given only in consultation with neonatology and transfusion medicine: ○ Treatment for pregnant mothers: when there is a high risk AND intrauterine transfusion is contraindicated ○ Treatment for newborns: in cases of hyperbilirubinemia due to maternal alloimmunization if phototherapy fails and exchange transfusion cannot be done in a reasonable timeframe.
Hyperhaemolysis syndrome	🟡🔴 In cases of severe disease and failure, contraindication or intolerance to other therapeutic options [1].	
Immune thrombocytopenia, acute	🟡 Failure, contraindication or intolerance to steroids and anti-D Ig (if patient is Rh(D)-positive). Also consider early use of thrombopoietin receptor agonist or rituximab, **AND one of the following:** ○ When platelet count is <10 x 10^9/L ○ When <30 x 10^9/L and there is moderate to severe bleeding ○ Before urgent surgery and there is a need to rapidly raise the platelet count ○ There is life-threatening bleeding 🟡 Dose: Maximum of 1g/kg x 1 dose	🔴 Failure, contraindication or intolerance to steroids and anti-D Ig (if patient is Rh(D)-positive). Also consider early use of thrombopoietin receptor agonist or rituximab, **AND one of the following:** ○ When the platelet count is <30 x 10^9/L and there is moderate to severe bleeding ○ Before urgent surgery and there is a need to rapidly raise the platelet count ○ There is life-threatening bleeding 🔴 Dose: Maximum 1g/kg x 1 dose

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CASE OF SHORTAGES
Immune thrombocytopenia, chronic	Failure, contraindication or intolerance to steroids and anti-D Ig (if patient is Rh (D)-positive) Alternative therapies (immunomodulators, thrombopoietin receptor agonist, rituximab) should be considered **AND one of the following:** ○ When the platelet count is <30 x 10^9/L and there is moderate to severe bleeding ○ Before urgent surgery and there is a need to rapidly raise the platelet count ○ There is life-threatening bleeding Dose: Maximum 1g/kg x 1 dose
Immune thrombocytopenia during pregnancy	Failure, contraindication or intolerance to steroids **AND one of the following:** ○ When the platelet count is <30 x 10^9/L and / or moderate to severe bleeding ○ In preparation for delivery to reach a platelet count ≥ 50 x 10^9/L in cases of failure, contraindication or intolerance to steroids ○ There is life-threatening bleeding
Post-transfusion purpura	In cases of moderate to severe bleeding if plasma exchange is not feasible
Red cell aplasia caused by parvovirus B19	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options [1].

1. For chronic conditions, when immunoglobulins are administered as maintenance treatment, try to find the minimal effective dose and optimize the treatment for each individual during Amber and Red phases.

C) IMMUNOLOGY

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CASE OF SHORTAGES
Primary or secondary immunodeficiencies known to be associated with hypogammaglobulinemia or dysgammaglobulinemia for which IG is necessary[2]	🟡🔴 Preferential use 🟡🔴 Should be based on the expert opinion of the physician, depending on the severity and frequency of infections and presence of additional immune dysregulation (e.g. autoimmunity, hyperinflammation) 🟡🔴 For maintenance treatment, target IgG levels should be lowered to minimum clinically effective target (e.g., 5-7 g/L on Day 28 in adult patients with hypogammaglobulinemia on IVIg) 🟡🔴 Increase or decrease target IgG on a case by case basis (i.e., based on factors such as clinical conditions or age)

2. Preferential use should be made of SCIG for appropriate indications if available when there is an IVIG shortage.

D) INFECTIOUS DISEASES

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CONDITIONS OF SHORTAGES
Enterovirus meningoencephalitis	In severe cases in immunocompromised patients
Infectious gastroenterocolitis (such as C. difficile enterocolitis or rotavirus gastroenteritis in immunocompromised patients)	Do not use
Invasive group A streptococcal disease or staphylococcal disease	For severe invasive group A Streptococcal disease associated with haemodynamic compromise or Streptococcal or Staphylococcal toxic shock syndrome IVIG is recommended in addition to surgical intervention, antibiotic therapy and other supportive measures
Lower respiratory tract infections caused by CMV or RSV in immunocompromised patients	Do not use; preferential use should be made of specific antivirals +/- specific hyperimmune globulin (for CMV)
Neonatal sepsis	In severe cases in cases of failure, contraindication or intolerance to other therapeutic options Should not be used for prophylaxis
Measles post-exposure prophylaxis	In pregnant women, infants and immune compromised/deficient individuals if IM injection is not an option because of weight 30 kg or greater or inability to receive IM injection

E) NEUROLOGY

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CONDITIONS OF SHORTAGES	
Acute disseminated encephalomyelitis (ADEM)	🟡🔴 In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]	
Autoimmune Encephalitis	🟡🔴 In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]	
Chronic inflammatory demyelinating polyneuropathy (CIDP)[2]	🟡🔴 Consider steroids and/or plasma exchange whenever possible 🟡🔴 Initial and maintenance treatment in cases of failure, contraindication or intolerance to other forms of immunosuppressive therapy[1]	
Graves' ophthalmopathy	🟡🔴 In cases of vision-threatening severe disease with failure, contraindications or intolerance to other therapeutic options	
Guillain-Barré syndrome (GBS) or variants including Miller Fisher syndrome	🟡 Preferential use for initial treatment of GBS if plasma exchange not available or feasible. 🟡 A second course of IVIG may be considered in patients with clearly demonstrated secondary deterioration, only after assessment by a specialist.	🔴 In cases of failure, contraindication or intolerance to plasma exchange **OR** in cases where plasma exchange is not available.
Lambert-Eaton myasthenic syndrome (LEMS)	🟡🔴 In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1].	
Multifocal motor neuropathy (MMN)[2]	🟡🔴 For front-line therapy[1].	
Myasthenia gravis (MG)	🟡 In cases of severe exacerbation, myasthenic crisis or in preparation for urgent or semi-urgent surgery	🔴 In cases of severe exacerbation, myasthenic crisis or in preparation for urgent or semi-urgent surgery with failure, contraindication, intolerance or lack of

		availability of plasma exchange or other therapeutic options
Opsoclonus-myoclonus syndrome	🟡🔴	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)	🟡🔴	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Rasmussen's encephalitis	🟡🔴	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Refractory epilepsy	🟡🔴	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Relapsing-remitting multiple sclerosis	🟡🔴	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Stiff person syndrome (SPS)	🟡🔴	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]

1. For chronic conditions, when IGs are administered as maintenance treatment, try to find the minimal effective dose and optimize the treatment for each individual during Amber and Red phases.
2. Preferential use should be made of SCIG for appropriate indications if available when there is an IVIG shortage.

F) RHEUMATOLOGY

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CASE OF SHORTAGES
Dermatomyositis	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome)	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Juvenile dermatomyositis	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Kawasaki disease	First line therapy Following the initial dose, maximum one additional dose may be given if there is ongoing inflammation
Macrophage activation syndrome (MAS)	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]
Polymyositis	In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[1]

1. For chronic conditions, when IGs are administered as maintenance treatment, try to find the minimal effective dose and optimize the treatment for each individual during Amber and Red phases.

G) ORGAN TRANSPLANT

CONDITION	CRITERIA FOR ENSURING APPROPRIATE AND PRIORITY USE OF IGs IN CASE OF SHORTAGES	
Heart, lungs, liver, kidneys, pancreas **(humoral rejection or pre- transplant HLA/ABO desensitization)**	🟡 May be used as part of combination therapy with immunosuppressive therapy and/or plasmapheresis in selected cases.	🔴 As part of combination therapy with immunosuppressive therapy and/or plasmapheresis, evaluated on a case-by-case basis by a peer committee 🔴 For post-transplant treatment only, not new initiation of pre-transplantation desensitization protocol 🔴 Consult with transplant team required regarding potential delay in initiation of new transplants

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APPENDIX 1. PREPARATIONS WITH HUMAN IMMUNOGLOBULINS (J06BA) AND AUTHORISED INDICATIONS

[Source: Farmadati and Banca Dati AIFA; latest update 31/12/2021]

*** Prescription of hospital centers or specialists (internist, infectious disease specialist, haematologist, immunologist)**

§ Prescription of hospital centers or specialists (internist, infectious disease specialist, haematologist, immunologist, neurologist)

SC/IM IG

IV IG

ATC	**J06BA01**
Specialty	**CUTAQUIG**
Administration	Subcutaneous
Company	OCTAPHARMA Italy S.p.A
Class	RNRL*
	C(nn)
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) in: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). • Hypogammaglobulinaemia and recurrent bacterial infections in patients with Chronic Lymphocytic Leukemia (CLL), where prophylactic antibiotics have failed or are contraindicated. • Hypogammaglobulinemia and recurrent bacterial infections in patients with Multiple Myeloma (MM). • Hypogammaglobulinemia in patients before and after Haematopoietic Stem Cell Transplantation (HSCT).

ATC	**J06BA01**
Specialty	**CUVITRU**
Administration	Subcutaneous
Company	TAKEDA Italy S.p.A
Class	RNRL*
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) in: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). • Hypogammaglobulinaemia and recurrent bacterial infections in patients with Chronic Lymphocytic Leukemia (CLL), where prophylactic antibiotics have failed or are contraindicated. • Hypogammaglobulinemia and recurrent bacterial infections in patients with Multiple Myeloma (MM). • Hypogammaglobulinemia in patients before and after Haematopoietic Stem Cell Transplantation (HSCT).

ATC	**J06BA02**
Specialty	**FLEBOGAMMA**
Administration	Intravenous
Company	INSTITUTO GRIFOLS S.A
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4). • Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukemia who have failed to respond to antibiotic prophylaxis. • Hypogammaglobulinaemia and recurrent bacterial infections in patients with plateau phase multiple myeloma who have failed to respond to pneumococcal immunization. • Hypogammaglobulinemia in patients who have undergone Haematopoietic Stem Cell Transplantation (HSCT). • Congenital AIDS with recurrent bacterial infections. Immunomodulation in adults, children and adolescents (2-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease.

ATC	**J06BA02**
Specialty	**FLEBOGAMMA DIF**
Administration	Intravenous
Company	INSTITUTO GRIFOLS S.A
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen.

Follow

Immunomodulation in adults, children and adolescent patients (2-18 years) for:

- Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts.
- Guillain-Barré syndrome.
- Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2).
- Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN).

ATC	**J06BA02**
Specialty	**GAMMAGARD**
Administration	Intravenous
Company	BAXALTA INNOVATIONS GMBH
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4). • Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukemia who have failed to respond to antibiotic prophylaxis. • Hypogammaglobulinaemia and recurrent bacterial infections in patients with plateau phase multiple myeloma who have failed to respond to pneumococcal immunization. • Hypogammaglobulinemia in patients who have undergone Haematopoietic Stem Cell Transplantation (HSCT). • Congenital AIDS with recurrent bacterial infections. Immunomodulation in adults, children and adolescents (0-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease.

ATC	**J06BA02**
Specialty	**GAMTEN**
Administration	Intravenous
Company	OCTAPHARMA ITALY S.p.A
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (0-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN).

ATC	**J06BA02**
Specialty	**GAMUNEX**
Administration	Intravenous
Company	GRIFOLS DEUTSCHLAND GMBH
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen.

Follow

Immunomodulation in adults, children and adolescent patients (0-18 years) for:
- Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts.
- Guillain-Barré syndrome.
- Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2).
- Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN).

ATC	**J06BA02**
Specialty	**GLOBIGA**
Administration	Intravenous
Company	OCTAPHARMA ITALY S.p.A
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (0-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN).

ATC	**J06BA01**
Specialty	**HIZENTRA**
Administration	Subcutaneous
Company	CSL BEHRING GMBH
Class	RNRL§
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0 to 18 years) in case of: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). • Secondary Immunodeficiency Syndromes (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4g / L. * PSFA = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulatory therapy in adults, children and adolescents (0-18 years): • Hizentra is indicated for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance treatment after stabilization with intravenous immunoglobulin (IVIG).

ATC	**J06BA01**
Specialty	**HYQVIA**
Administration	Subcutaneous
Company	BAXALTA INNOVATIONS GMBH
Class	RNRL*
	H
Indication (SPC 4.1)	HyQvia is indicated for replacement therapy in adults, children and adolescent patients (0 to 18 years) for the treatment of: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG level <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen.

ATC	**J06BA02**
Specialty	**IGVENA**
Administration	Intravenous
Company	Kedrion S.p.A.
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (2-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN).

ATC	**J06BA02**
Specialty	**INTRATECT**
Administration	Intravenous
Company	BIOTEST PHARMA GMBH
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen.

Follow

Immunomodulation in adults, children and adolescent patients (2-18 years) for:
- Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts.
- Guillain-Barré syndrome.
- Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2).
- Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN).

ATC	**J06BA02**
Specialty	**IQYMUNE**
Administration	Intravenous
Company	LABORATOIRE FRANÇAIS DU FRACTIONNEMENT ET DES BIOTECHNOLOGIES
Class	OSP
	C(nn)
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (2-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN).

ATC	**J06BA01**
Specialty	**KEYCUTE**
Administration	Subcutaneous
Company	KEDRION S.p.A.
Class	RNRL*
	H
Indication (SPC 4.1)	Replacement therapy in adults in case of: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). • Hypogammaglobulinaemia and recurrent bacterial infections in patients with Chronic Lymphocytic Leukemia (CLL), where prophylactic antibiotics have failed or are contraindicated. • Hypogammaglobulinemia and recurrent bacterial infections in patients with Multiple Myeloma (MM). • Hypogammaglobulinemia in patients before and after Haematopoietic Stem Cell Transplantation (HSCT).

ATC	**J06BA02**
Specialty	**KIOVIG**
Administration	Intravenous
Company	BAXTER AG
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (2-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). Multifocal Motor Neuropathy (MMN).

ATC	**J06BA01**
Specialty	**NAXIGLO**
Administration	Subcutaneous
Company	KEDRION S.p.A
Class	RNRL*
	H
Indication (SPC 4.1)	Replacement therapy in adults in case of: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). • Hypogammaglobulinaemia and recurrent bacterial infections in patients with Chronic Lymphocytic Leukemia (CLL), where prophylactic antibiotics have failed or are contraindicated. • Hypogammaglobulinemia and recurrent bacterial infections in patients with Multiple Myeloma (MM). • Hypogammaglobulinemia in patients before and after Haematopoietic Stem Cell Transplantation (HSCT).

ATC	**J06BA02**
Specialty	**OCTAGAM**
Administration	Intravenous
Company	OCTAPHARMA ITALY S.p.A
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (2-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). Multifocal Motor Neuropathy (MMN).

ATC	**J06BA01**
Specialty	**OCTANORM**
Administration	Subcutaneous
Company	OCTAPHARMA ITALY S.p.A
Class	RNRL*
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) in case of: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). • Hypogammaglobulinaemia and recurrent bacterial infections in patients with Chronic Lymphocytic Leukemia (CLL), where prophylactic antibiotics have failed or are contraindicated. • Hypogammaglobulinemia and recurrent bacterial infections in patients with Multiple Myeloma (MM). • Hypogammaglobulinemia in patients before and after Haematopoietic Stem Cell Transplantation (HSCT).

ATC	**J06BA02**
Specialty	**PENTAGLOBIN**
Administration	Intravenous
Company	BIOTEST PHARMA GMBH
Class	OSP
	C
Indication (SPC 4.1)	Supportive care of severe bacterial infections in association with antibiotic therapy. Immunoglobulin replacement therapy in immunosuppressed patients and in patients with severe secondary antibody deficiency syndrome.

ATC	**J06BA02**
Specialty	**PLITAGAMMA**
Administration	Intravenous
Company	INSTITUTO GRIFOLS S.A
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) in case of: • Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).

Follow

- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukemia who have failed to respond to antibiotic prophylaxis.
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with plateau phase multiple myeloma who have failed to respond to pneumococcal immunization.
- Hypogammaglobulinemia in patients who have undergone Haematopoietic Stem Cell Transplantation (HSCT).
- Congenital AIDS with recurrent bacterial infections.

Immunomodulation in adults, children and adolescents (2-18 years) for:

- Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery to restore platelet counts.
- Guillain-Barré syndrome.
- Kawasaki disease.

ATC	**J06BA02**
Specialty	**PRIVIGEN**
Administration	Intravenous
Company	CSL BEHRING GMBH
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (0-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (2-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN).

ATC	**J06BA01**
Specialty	**SUBCUVIA (GU 113/2020; sold until 31/10/2020)**
Administration	Subcutaneous/Intramuscular
Company	BAXALTA INNOVATIONS GMBH
Class	RNRL*
	H
Indication (SPC 4.1)	Replacement therapy in adult and children patients with primary immunodeficiency syndromes, such as: • Congenital agammaglobulinemia and hypogammaglobulinemia. • Common variable immunodeficiency. • Severe combined immunodeficiency. • IgG subclass deficiency with recurrent infections. Replacement therapy for myeloma or chronic lymphocytic leukemia with secondary severe hypogammaglobulinemia and recurrent infections.

ATC	**J06BA02**
Specialty	**VENITAL**
Administration	Intravenous
Company	KEDRION S.p.A
Class	OSP
	H
Indication (SPC 4.1)	Replacement therapy in adults, children and adolescent patients (2-18 years) for: • Primary immunodeficiency syndromes (PID) with impaired antibody production. • Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and demonstrated inability to produce specific antibodies (PSAF) * or serum IgG levels <4 g / l. * PSAF = inability to produce an increase of at least 2 times in the titer of IgG antibodies to pneumococcal polysaccharide vaccines containing the polypeptide antigen. Immunomodulation in adults, children and adolescent patients (2-18 years) for: • Primary Immune Thrombocytopenia (ITP), in patients at high risk of bleeding or before surgery, to restore platelet counts. • Guillain-Barré syndrome. • Kawasaki disease (concomitantly with acetylsalicylic acid; see 4.2). • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN).