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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON CORE SmPC FOR HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg) (CPMP/BPWG/859/95 rev. 3)

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KEYWORDS	IVIg, human normal immunoglobulin, primary immunodeficiency syndromes, hypogammaglobulinaemia, idiopathic thrombocytopenic purpura (ITP), Guillain Barré syndrome, Kawasaki disease

EXECUTIVE SUMMARY

This Guideline describes the information to be included in the Summary of Product Characteristics (SmPC) for human normal immunoglobulins for intravenous administration.

1. INTRODUCTION (BACKGROUND)

The purpose of this core SmPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of Product Characteristics (SmPC) for a human normal immunoglobulin for intravenous administration (IVIg). This guideline should be read in conjunction with the Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev. 2).

The QRD Product Information template with explanatory notes* and the convention to be followed for QRD templates** provide general guidance on format and text and should be read in conjunction with the core SmPC and the Guideline on Summary of Product Characteristics.

In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the "Note for Guidance on the Warning on Transmissible Agents in SmPCs and Package Leaflets for plasma-derived medicinal products" (CPMP/BPWG/BWP/561/03).***

2. SCOPE

This core SmPC covers human normal immunoglobulin for intravenous administration defined by the European Pharmacopoeia monograph 0918. It does not apply to products intentionally prepared to contain fragments or chemically modified IgG.

3. LEGAL BASIS

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

* (http://www.emea.eu.int/htms/human/qrd/qrdplt/H01a%20EN%20NOTE%20SPC-II-lab-pl%20v6.pdf)
** (http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconventionv6.pdf)
*** (http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf)

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

[Product specific information on quantitative composition. Include: IgG subclasses, human protein content and minimum content of IgG (e.g. human protein x g/l of which at least y% is IgG), maximum IgA content]

One ml contains:
Human normal immunoglobulin……..{X} mg
(purity of at least {XX}% IgG)

One {container e.g. vial} of {xx} ml contains: X g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
IgG1 ..... {XX.X}%
IgG2 ..... {XX.X}%
IgG3 ..... {XX.X}%
IgG4 ..... {XX.X}%

The maximum IgA content is {x} micrograms/ml.

Produced from the plasma of human donors.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in:

Primary immunodeficiency syndromes with failure of antibody production.

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.

Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.

Children and adolescents with congenital AIDS and recurrent bacterial infections.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT)

Immunomodulation

Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.

Guillain Barré syndrome.

Kawasaki disease.

[For product specific auto-immune indications (e.g. multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbations) and other product specific indications – see Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) CPMP/BPWG/388/95 rev. 2]

4.2 Posology and method of administration

Posology

The dose and dosage regimen is dependent on the indication.

In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes
The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4-6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4-0.8 g/kg followed by at least 0.2 g/kg/month given in divided doses every one to four weeks.

The dose required to achieve a trough level of 6 g/l is of the order of 0.2-0.8 g/kg/month. The dosage interval when steady state has been reached varies from 2-4 weeks.
Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels (>6 – 9 g/l).

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation; children and adolescents with congenital AIDS and recurrent bacterial infections
The recommended dose is 0.2-0.4 g/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation
The recommended dose is 0.2-0.4 g/kg every three to four weeks. The trough levels should be maintained above 5g/l.

Idiopathic Thrombocytopenic Purpura
For the treatment of an acute episode, 0.8-1g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs.>

Guillain Barré syndrome
0.4 g/kg/day for 3 to 7 days.

Kawasaki Disease
1.6-2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injections
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg	every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Children and adolescents with AIDS	0.2 - 0.4 g/kg	every 3 - 4 weeks
Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2 - 0.4 g/kg	every 3 - 4 weeks
Immunomodulation:		
Idiopathic Thrombocytopenic Purpura	0.8 - 1 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2 - 5 days
Guillain Barré syndrome	0.4 g /kg/d	for 3 -7 days
Kawasaki disease	1.6 - 2 g/kg or 2 g/kg	in several doses for 2 - 5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid
Paediatric population	See above	See above

Paediatric population

As the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions, the posology in children is not considered to be different to that of adults.

Method of administration

Human normal immunoglobulin should be infused intravenously at an initial rate of {indicate product specific rate} ml/kg/hr for {indicate product specific infusion time} hr. If well tolerated, the rate of administration may gradually be increased to a maximum of {indicate product specific increased rate} ml/kg/hr.

4.3 Contraindications

[Product specific contraindications, for example:] <Fructose intolerance (see section 4.4).>
Hypersensitivity to the active substance or to any of the excipients (see section 4.4).
Hypersensitivity to human immunoglobulins <, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA.> *[The text within brackets should be selected if appropriate]*

4.4 Special warnings and special precautions for use

[In addition to the text below, include any additional product specific precautions and warnings (e.g. those relating to excipients present in the product).]

*[Product specific for products containing fructose/sorbitol]***<THIS MEDICINAL PRODUCT CONTAINS {XX} MG OF <SORBITOL><FRUCTOSE> PER ML AS AN EXCIPIENT. PATIENTS WITH RARE HEREDITARY PROBLEMS OF FRUCTOSE INTOLERANCE SHOULD NOT TAKE THIS MEDICINE. SPECIAL PRECAUTIONS SHOULD BE TAKEN WITH BABIES AND YOUNG CHILDREN BECAUSE THIS FRUCTOSE INTOLERANCE MAY NOT YET BE DIAGNOSED AND MAY BE FATAL.**

[*Product specific for products containing maltose*:] **<THIS MEDICINAL PRODUCT CONTAINS {XX} MG OF MALTOSE PER ML AS AN EXCIPIENT. THE INTERFERENCE OF MALTOSE IN BLOOD GLUCOSE ASSAYS MAY RESULT IN FALSELY ELEVATED GLUCOSE READINGS AND, CONSEQUENTLY, IN THE INAPPROPRIATE ADMINISTRATION OF INSULIN, RESULTING IN LIFE-THREATENING HYPOGLYCAEMIA AND DEATH. ALSO, CASES OF TRUE HYPOGLYCAEMIA MAY GO UNTREATED IF THE HYPOGLYCAEMIC STATE IS MASKED BY FALSELY ELEVATED GLUCOSE READINGS.>**

[*Product specific for products containing glucose*:] <This medicinal product contains {XX} mg of glucose per ml as an excipient. This should be taken into account in case of latent diabetes (where transient glycosuria could appear), diabetes, or in patients on a low sugar diet.>

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "4.2 Method of administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.
Certain adverse reactions may occur more frequently

- in case of high rate of infusion
- in patients with hypo- or agammaglobulinemia with or without IgA deficiency
- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin by initially injecting the product slowly ({specify the product specific rate} ml/kg/min);
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration;

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect.
In case of shock, standard medical treatment for shock should be implemented.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics.

<u>Hypersensitivity</u>
True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies.
Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

<u>Thromboembolism</u>

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In case of renal impairment, IVIg discontinuation should be considered.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose as an excipient accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered. [*Product specific depending on whether the product contains sucrose*:] <{(Invented) name} contains {XX} mg of sucrose per ml as an excipient.> <{(Invented) name} does not contain sucrose.>

In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coomb's test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis.

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies for example the antiglobulin test (Coombs test).

Transmissible agents

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]

Paediatric population

[Product specific. The text to be inserted here should be in line with the Paediatric regulation and the SmPC guideline]

4.5 Interactions with other medicinal products and other forms of interactions

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After

administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Paediatric population

[*Product specific: The text to be inserted here should be in line with the Paediatric regulation and the SmPC guideline.*]

4.6 Pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Lactation

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

[Any relevant product specific information should be added.]

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.
Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]

b. Tabulated summary of adverse reactions

The summary table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).
Frequencies has been evaluated according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

<Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.>

Frequency of Adverse Drug Reactions (ADRs) in clinical studies with {Product name}

MedDRA System Organ Class (SOC)	MedDRA preferred term	ADR frequency category
		{<Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).>}

c. Description of selected adverse reactions

[Product specific]

<d. Paediatric population>

[Product specific. The text to be inserted here should be in line with the Paediatric regulation and the SmPC guideline.]

<e. Other special population(s)>

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02
Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

[Product specific: Clinical study results can be briefly summarised here]

Paediatric population

[Product specific: The text should be in line with the Paediatric regulation and the SmPC guideline.]

5.2 Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and

extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments.
Human normal immunoglobulin has a half-life of about *{insert product specific half-life}* days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Paediatric population
[Product specific: The text should be in line with the Paediatric regulation and the SmPC guideline.]

5.3 Preclinical safety data

[Product specific]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific. Where applicable, the amount of albumin added as a stabiliser should be stated (Ph. Eur. labelling requirement).]

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

[Product specific]

6.3 Shelf-life

[Product specific: reference should be made to the SmPC guideline for stability at different temporary storage conditions.]

6.4 Special precautions for storage

[Product specific]

6.5 Nature and contents of container

[Product specific]

6.6 Special precautions for disposal <and other handling>

[Product specific]
The product should be brought to room or body temperature before use.
<Total reconstitution should be obtained within *[product specific time].*>
<Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.> The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[Product specific]

8. MARKETING AUTHORISATION NUMBER(S)

[Product specific]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Product specific]

Information related to the authorisation:

Paediatric Investigational Plan

[Product specific: The text should be in line with the Paediatric regulation and the SmPC guideline.]

10. DATE OF REVISION OF THE TEXT

[Product specific]