EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 December 2016
EMA/CHMP/BPWP/94038/2007 Rev. 5
Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)

Draft

Revised draft agreed by the Blood Products Working Party	November 2016
Adoption by CHMP for release for consultation	15 December 2016
Start of public consultation	1 January 2017
End of consultation (deadline for comments)	31st March 2017

Guideline EMA/CHMP/BPWP/94038/2007 replaced guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) with reference number CPMP/BPWP/859/95.

Comments should be provided using this template. The completed comments form should be sent to BPWPSecretariat@ema.europa.eu

Keywords	***IVIg, human normal immunoglobulin, primary and secondary immunodeficiency syndromes, hypogammaglobulinaemia, primary immune thrombocytopenia (= idiopathic thrombocytopenic purpura (ITP)), Guillain Barré syndrome, Kawasaki disease, multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)

Table of contents

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) (EMA/CHMP/BPWP/94033/2007 rev. 2). For guidance on the clinical investigation of subcutaneous immunoglobulin products go to CHMP/BPWP/410415/2011 Rev 1and the coreSPC CPMP/BPWG/143744/2011 Rev. 1.

The QRD product information template with explanatory notes ('QRD annotated template')[1] and the convention to be followed for QRD templates[2] 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[3].

It is very useful to provide information for health professionals on posology and method of administration at the end of the package leaflet since the SmPC is not always readily available. See the QRD annotated template for further guidance on how to present such information.

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" (EMA/CHMP/BWP/360642/2010 rev. 1)[4].

Timeline history of core SmPC: The original core SmPC (CPMP/BPWP/859/95) came into operation in September 1997. First revision (CPMP/BPWP/859/95 rev.1) came into operation in December 2000. Second revision (CPMP/BPWP/859/95 rev. 2) came into operation in November 2004. EMA/CHMP/BPWP/94038/2007 rev 3 came into operation in May 2011. A minor revision in 2013 provided clarification on information to be included under the paediatric headings and guidance concerning the age range in section 4.1. This current revision (2016) encompasses the inclusion of CIDP and MMN, rewording of the secondary immunodeficiencies, correction of the dosing for Kawasaki disease and the inclusion of neutropenia/leukopenia as a side-effect.

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.

[1] http://www.ema.europa.eu/htms/human/qrd/docs/Hannotatedtemplate.pdf
[2] http://www.ema.europa.eu/htms/human/qrd/docs/convention.pdf
[3] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119001.pdf

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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, maximum IgA content]

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

Each {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.

<Excipient(s):>

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Age ranges given in this section may require modification if there are any safety issues for the excipients used for a particular product e.g. sorbitol risk for babies and young children with hereditary fructose intolerance.]

Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, and children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease.
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN),

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dose regimen is dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.
The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/l or within the normal range for the population. 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 given once followed by at least 0.2g/kg given every three to four weeks..

The dose required to achieve a trough level of 5-6 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 3-4 weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Secondary immunodeficiencies (as defined in 4.1.)
The recommended dose is 0.2-0.4 g/kg every three to four weeks.

Primary immune thrombocytopenia

There are two alternative treatment schedules:

- 0.8-1g/kg given on day one; this dose may be repeated once within 3 days.
- 0.4 g/kg given daily for two to five days.

The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day over 5 days.

Kawasaki Disease

2.0 g/kg should be administered as a single dose. ~~.~~ Patients should receive concomitant treatment with acetylsalicylic acid.

*Chronic inflammatory demyelinating polyneuropathy (CIDP)**

Starting dose: 2 g/kg divided over 2 -5 consecutive days
Maintenance doses: 1 g/kg over 1 - 2 consecutive days every 3 weeks.

Multifocal Motor Neuropathy (MMN)
Starting dose: 2 g/kg given over 2-5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.

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 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l
Secondary Immunodeficiencies (as defined in 4.1.)	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 6 g/l or within the normal range for the population
<u>Immunomodulation:</u>		
Primary immune thrombocytopenia	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 5 days
Kawasaki disease	2 g/kg	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)*	maintenance dose: 1 g/kg starting dose: 2 g/kg	every 3 weeks over 1-2 days in divided doses over 2-5 days
Multifocal Motor Neuropathy (MMN)*	maintenance dose: 1 g/kg or 2 g/kg	every 2-4 weeks or every 4-8 weeks over 2-5 days

*The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Paediatric population

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

Method of administration

For intravenous use.
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 (see section 4.4), 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 patients with antibodies against IgA..> *[The text within brackets should be selected if appropriate.]*

4.4 Special warnings and 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. In babies and young children hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they should not receive <sorbitol><fructose>-containing solutions**.**
In other patients in case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.

[*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. For acute renal failure see below.>

[*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. For acute renal failure see below.**>**

[*Product specific for products containing sucrose*:] **<**This medicinal product contains {XX} mg of sucrose per ml as an excipient. Reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, however those containing sucrose as an excipient accounted for a disproportionate share of the total number. For acute renal failure see below.>

Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate given under section 4.2 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 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 adverse reaction.
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.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

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.

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including 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 hypovolaemic 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, hypovolaemia, 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 containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain these excipients may be considered. <{(Invented) name} contains <sucrose><maltose><glucose>. (See excipients above)> <{(Invented) name} does not contain sucrose, maltose or glucose.>

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

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.
AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

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 (Coombs' 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. (See section 4.8.)

<Neutropenia/Leukopenia>
A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIgs. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days. <In XXX, this was not associated with an increased risk of infections in particular in patients with primary immunodeficiency>.

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 antibodies for example the direct antiglobulin test (DAT, direct 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 (EMA/CHMP/BWP/360642/2010 rev. 1).]

Paediatric population

[Product specific]

<The listed warnings and precautions apply both to adults and children.>

4.5 Interactions with other medicinal products and other forms of interaction

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 medicinal 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 listed interactions apply both to adults and children.>

4.6 Fertility, 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. IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are expected.

Breast-feeding

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

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

The ability to drive and operate machines may be impaired by some adverse reactions associated with {(Invented) name}. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions such as chills, headache, dizziness, 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 and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also Section 4.4).

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 (EMA/CHMP/BWP/360642/2010 rev. 1).]

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).
Frequencies have 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), not known (cannot be estimated from the available data).

<Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.>

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

MedDRA System Organ Class (SOC) According to the sequence: http://www.ema.europa.eu/htms/human/qrd/docs/HappendixII.doc	**Adverse reaction**	**Frequency**
		{<very common, common, uncommon, rare, very rare.>}

Description of selected adverse reactions

[Product specific]

Paediatric population

[Product specific]

<Frequency, type and severity of adverse reactions in children are <expected to be> the same as in adults.>

<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 cardiac or 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. In case of a full waiver or any deferral, include the standard statement in 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]

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 and colourless or pale yellow.
Solutions that are cloudy or have deposits should not be used.
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]

10. DATE OF REVISION OF THE TEXT

[Product specific]

<Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu>