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

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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), measles pre/post-exposure prophylaxis***

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

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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. 4). For guidance on the clinical investigation of subcutaneous immunoglobulin products refer to CHMP/BPWP/410415/2011 Rev 1 and the core SmPC CPMP/BPWG/143744/2011 Rev. 1.

The Quality Review of Documents (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 this core SmPC and the Guideline on summary of product characteristics[3].

This core SmPC has been prepared on the basis of SmPCs of authorised medicinal products and taking into account the published scientific literature. Any marketing authorisation application or variation of a marketing authorisation for a human normal immunoglobulin should be accompanied by the required data particulars, documents, literature and/or justification for the application to be valid.

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. The first revision (CPMP/BPWP/859/95 rev.1) came into operation in December 2000. The 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. Revision 5 encompassed the inclusion of multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), the rewording of the secondary immunodeficiencies, correction of the dosing for Kawasaki disease and the inclusion of neutropenia/leukopenia and Transfusion-related acute lung injury as a side-effect.

This revision 6 is to include the indication of measles pre/post-exposure prophylaxis for susceptible persons in whom active immunisation is contraindicated or not advised.

[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

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 IVIg.

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.

4. References

Letter to Immune Globulin (Human) Licensed Manufacturers: Option to Lower Lot Release Specification for Required Measles Antibody Potency Testing. Nov 5, 2018: https://www.fda.gov/media/118428/download

WHO: Manual for the Laboratory-based Surveillance of Measles, Rubella, and Congenital Rubella Syndrome: Chapter 9. Laboratory testing for determination of population immune status: https://www.who.int/immunization/monitoring_surveillance/burden/laboratory/Chapter_9.pdf?ua=1

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

<▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.> [For medicinal products subject to additional monitoring ONLY]

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Human normal immunoglobulin (IVIg)

2.2 Qualitative and quantitative composition

*[*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}%

<Minimum level anti-measles IgG is {x} IU/mL>

The maximum IgA content is {x} micrograms/mL. Produced from the plasma of human donors.

<Excipient(s) with known effect*:*>
<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, children, and adolescents (0–18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production
  Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial 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

<Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post exposure prophylaxis and active immunisation.>

Immunomodulation in adults, 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 (in conjunction with acetylsalicylic acid; see 4.2)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

4.2 Posology and method of administration

IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

Posology

The dose and dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on body weight may require adjustment in underweight or overweight patients. [*Product specific specify recommendation*].

The following dose regimens are given as guidance.

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 reference range for the population age. 3–6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) to occur. The recommended starting dose is 0.4–0.8 g/kg given once followed by at least 0.2g/kg given every 3–4 weeks.

The dose required to achieve a trough level of IgG 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 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.

Replacement therapy in secondary immunodeficiencies (as defined in 4.1.)
The recommended dose is 0.2–0.4 g/kg every 3-4 weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection.

Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

<*Measles pre-/post exposure prophylaxis*>

Post-exposure prophylaxis
If a susceptible patient has been exposed to measles, a dose of 0.4 g/kg given as soon as possible and within 6 days of exposure should provide a serum level > 240 mIU/mL of measles antibodies for at least 2 weeks. Serum levels should be checked after 2 weeks and documented. A further dose of 0.4 g/kg possibly to be repeated once after 2 weeks may be necessary to maintain the serum level > 240 mIU/mL.

If a PID/SID patient has been exposed to measles and regularly receives IVIg infusions, it should be considered to administer an extra dose of IVIg as soon as possible and within 6 days of exposure. A dose of 0.4 g/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least 2 weeks.

Pre-exposure prophylaxis
If a PID/SID patient is at risk of future measles exposure and receives an IVIg maintenance dose of less than 0.53 g/kg every 3–4 weeks, this dose should be increased once to 0.53 g/kg. This should provide a serum level of >240 mIU/mL of measles antibodies for at least 22 days after infusion**.**

Immunomodulation in:

Primary immune thrombocytopenia

There are two alternative treatment schedules:
- 0.8–1 g/kg given on day 1; this dose may be repeated once within 3 days.
- 0.4 g/kg given daily for 2–5 days. The treatment can be repeated, if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

Kawasaki Disease

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

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Starting dose: 2 g/kg divided over 2 –5 consecutive days
Maintenance doses:
1 g/kg divided over 1–2 consecutive days every 3 weeks.
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 physician's 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.

Multifocal Motor Neuropathy (MMN)

Starting dose: 2 g/kg divided 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 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 physician's 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.
The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of infusions
Replacement therapy:		
Primary immunodeficiency syndromes	Starting dose: 0.4 – 0.8 g/kg Maintenance dose: 0.2 – 0.8 g/kg	every 3 – 4 weeks
Secondary Immunodeficiencies (as defined in 4.1.)	0.2 – 0.4 g/kg	every 3 – 4 weeks
Measles pre/post exposure prophylaxis:		
Post-exposure prophylaxis in susceptible patients	0.4 g/kg	As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/mL
Post-exposure prophylaxis in PID/SID patients	0.4 g/kg	In addition to maintenance therapy, given as an extra dose within 6 days of exposure
Pre-exposure prophylaxis in PID/SID patients	0.53 g/kg	If a patient receives a maintenance dose of less than 0.53 g/kg every 3–4 weeks, this dose should be increased once to at least 0.53 g/kg.
Immunomodulation:		
Primary immune thrombocytopenia	0.8 – 1g/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 acetylsalicyli

		c acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg	in divided doses over 2–5 days every 3 weeks in divided doses over 1–2 days
Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg or 2 g/kg	 in divided doses 2–5 consecutive days every 2–4 weeks or every 4–8 weeks in divided doses over 2–5 days

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 must be adjusted to the clinical outcome of the above-mentioned conditions.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

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. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. 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

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients (see sections 4.4 and 6.1). *[Product specific contraindications]*.

Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

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).]

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use
Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin by initially administering 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 a controlled healthcare setting in order to detect potential adverse signs and to ensure that emergency treatment can be administered immediately should problems occur. All other patients should be observed for at least 20 minutes after administration.

In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the IVIg infusion
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics (see 4.5).

In case of adverse reaction, either the infusion rate must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Infusion-related reaction
Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) 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.

Adverse reactions may occur more frequently
- 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
- in patients with an active infection or underlying chronic inflammation

Hypersensitivity

Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients:
- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

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.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While 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.>

Aseptic meningitis syndrome (AMS)

AMS has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid (CSF) 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.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced 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 IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion-related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion-related acute lung injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours after a transfusion, often within 1–2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing

After the administration 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]

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.

Loop diuretics
Avoidance of concomitant use of loop diuretics

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. 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

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 breast-feeding mothers. Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.

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

<{Invented name} has <no or negligible influence> <minor influence> <moderate influence> <major influence> on the ability to drive and use machines.> [describe effects where applicable.]

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

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.>

Source of the safety database (e.g. from clinical trials, post-authorisation safety studies and/or spontaneous reporting)

MedDRA System Organ	**Adverse reaction**	**Frequency per patient**	**Frequency per infusion**
Class (SOC)			
		{<very common, common, uncommon, rare, very rare.>}	{<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 infants, elderly patients or patients with cardiac or renal impairment (see section 4.4.).

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 donors. 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.
[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

Absorption

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution

It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3–5 days equilibrium is reached between the intra- and extravascular compartments.

Elimination

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]

[Measles pre-/post exposure prophylaxis] (see references)

No clinical studies have been performed in susceptible patients regarding *Measles pre-/post exposure prophylaxis.*

<Product name> meets the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard. The dosing is based on pharmacokinetic calculations, which take body weight, blood volume and half-life of immunoglobulins into consideration. These calculations predict a:

- Serum titre at 13.5 days = 270 mIU/mL (dose: 0.4 g/kg) This provides a safety margin more than double that of the WHO protective titre of 120 mIU/mL
- Serum titre at 22 days (t1/2) = 180 mIU/mL (dose: 0.4 g/kg)
- Serum titre at 22 days (t1/2) = 238.5 mIU/mL (dose: 0.53 g/kg –pre-exposure prophylaxis)

5.3 Preclinical safety data

[Product specific]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific. (Ph. Eur. labelling requirement)]

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, nor with any other IVIg 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 <, and on the website of {name of Member State Agency (link)}>.>