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Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration

Draft

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This guideline replaces guideline on core SPC for human normal immunoglobulin for subcutaneous and intramuscular administration with reference number CPMP/BPWG/282/00

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

Keywords	*human normal immunoglobulin, primary immunodeficiency syndromes, hypogammaglobulinaemia, hepatitis A prophylaxis, immunomodulation*

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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 subcutaneous and/or intramuscular 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 subcutaneous and/or intramuscular administration. The choice of text will depend on whether the product is for both subcutaneous and intramuscular administration or only one of these routes. This guideline should be read in conjunction with the current version of the Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular administration (EMA/CHMP/BPWP/410415/2011 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)[4].

Timeline history of core SmPC: The original core SPC (CPMP/BPWG/282/00) came into operation in January 2003.

2. Scope

This core SmPC covers human normal immunoglobulin for subcutaneous and intramuscular administration defined by the European Pharmacopoeia monograph 0338. 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/enterprise/sectors/pharmaceuticals/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

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (<SCIg> <and> <IMIg>)

[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

<Antibodies to Hepatitis A at least (x) IU/ml>

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):>
<Sodium content: >

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[Product specific, including osmolality]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications for subcutaneous administration (SCIg)

Replacement therapy in adults and children and adolescents (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 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.

Indications for intramuscular administration (IMIg)

[Product specific for SC/IMIg with a minimum antibody content for HAV of 100 IU/ml:]

<- Hepatitis A prophylaxis in travellers who present less than 2 weeks before possible exposure, preferably in combination with vaccination.

For long term hepatitis A prophylaxis, active immunisation is recommended.

- Hepatitis A prophylaxis in persons exposed less than 2 weeks previously.>

[For product specific immunomodulatory indications - see current version of the Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular Administration EMA/CHMP/BPWP/410415/2011 rev 1. These product specific indications should state in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.]

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.

Replacement therapy

The product should be administered via the subcutaneous route.

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

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l. A loading dose of at least 0.2 to 0.5 g/kg ({XX} to {YY} ml/kg) body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals (approximately once per week) to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg. Each single dose may need to be injected at different anatomic sites.

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 dose and aim for higher trough levels.

<Hepatitis A prophylaxis

The product should be administered via the intramuscular route.

To achieve a minimum protective level of 10 mIU/ml with an IMIg with a minimum antibody content for HAV of 100 IU/ml, the following dosing is recommended:

- **Short term Hepatitis A prophylaxis** in travellers who present less than 2 weeks before possible exposure.

  For stays in endemic areas of less than 3 months: 0.17 ml/kg body weight (preferably given in combination with vaccination).

- **Hepatitis A prophylaxis** in persons exposed less than 2 weeks previously: 0.17 ml/kg body weight.>

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 in replacement therapy indications.

Method of administration

For subcutaneous use <only>.
Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. The patient must be instructed in the use of a syringe driver, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

{(Invented) name} may be injected into sites such as abdomen, thigh, upper arm, and lateral hip.
It is recommended to use an initial administration speed of {XX} ml/h/pump.
The infusion speed can be enhanced by {YY} ml/h/pump every subsequent infusion. The recommended maximum speed is {ZZ} ml/h/pump. More than one pump can be used simultaneously. The infusion site should be changed every 5-15 ml. Doses over 15 ml should be divided and injected into 2 or more sites.
The recommended maximum number of infusion sites is {X}.

<**Intramuscular injection** must be given by a physician or nurse.>

4.3 Contraindications

[Product specific contraindications]
Hypersensitivity to the active substance or to any of the excipients (see section 4.4).
{(Invented) name} must not be given intravascularly.
It must also not be administered intramuscularly in case of severe thrombocytopenia and in other disorders of haemostasis.

4.4 Special warnings and precautions for use

If {(Invented) name} is accidentally administered into a blood vessel patients could develop shock.

[Excipients: include any product specific precautions and warnings relating to excipients present in the product.]

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 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.

Hypersensitivity

True allergic reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be switched to {(Invented) name} only under close medical supervision.

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.

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 naïve 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.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired of inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity). Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms. Patients should be sufficiently hydrated before use of immunoglobulins.

<Important information about some of the ingredients of {(Invented) name}
<Product>.
This medicine contains up to {XXX} mg ({YY} mmol) sodium per dose (bodyweight 75 kg) if the maximal daily dose (XX g = YY ml) is applied. This should be taken into consideration in patients on a controlled sodium diet.>

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 SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010).]

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. SCIg 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 to be 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

{(Invented) name} has no or negligible influence on the ability to drive and use 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.

Local reactions at infusion sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash.

[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 SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010).]

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

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration, ATC code: J06BA01

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.

[Product specific for products with immunomodulatory indications:] <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

Following subcutaneous administration of {(Invented) name}, peak serum levels are achieved after approximately {X} days.

In a clinical trial with {(Invented) name} (n = {XX}), the subjects achieved sustained trough levels (median {XX} g/l) over a period of {YY} weeks when receiving median weekly doses of {ZZ} g/kg.

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).]
<Sodium>

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]*.>
< Products should be inspected visually for particulate matter and discoloration prior to administration.>.
Solutions that are cloudy or have deposits should not be used. (see also section 3 “Pharmaceutical Form”).

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>