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Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CORE SPC FOR HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg) (CPMP/BPWG/859/95 rev. 2)

Rev. 1

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This revision updates sections 4.4 and 4.8 with respect to thromboembolic events. The opportunity is also taken to update 4.4 and 4.8 with respect to the warning on transmissible agents, and 4.4 for treatment of shock.

CORE SPC
FOR
HUMAN NORMAL IMMUNOGLOBULIN
FOR INTRAVENOUS ADMINISTRATION (IVIg)

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 SPC 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 "Guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products"(CPMP/BPWG/BWP/561/03).****

This core SPC 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.

* *(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

{(Trade) name of product <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.]
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<u><Replacement therapy in:</u>

Primary immunodeficiency syndromes such as:
- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections

Children with congenital AIDS and recurrent infections>

<u><Immunomodulation</u>

<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>>

<u><Allogeneic bone marrow transplantation.></u>

[Other product specific indications]

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 every three 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 in order to adjust the dose and dosage interval.

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections
The recommended dose is 0.2-0.4 g/kg every three to four weeks.>

<<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.
Experience in children is limited.>

<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.>>

<Allogeneic Bone Marrow Transplantation:
Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant.
For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The starting dose is normally 0.5 g/kg/week, starting seven days before transplantation and for up to 3 months after transplantation.
In case of persistent lack of antibody production, dosage of 0.5 g/kg/month is recommended until antibody level returns to normal.>

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 with AIDS	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>>
<Allogeneic bone marrow transplantation:		
- treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg	every week from day -7 up to 3 months after transplantation.
- persistent lack of antibody production	0.5 g/kg	every month until antibody levels return to normal>

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

Hypersensitivity to any of the components.
Hypersensitivity to homologous 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

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.

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.

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);
- that patients 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;
- that the glucose content ({x} g/g of IgG) is taken into account in case of latent diabetes (where transient glycosuria could appear), diabetes, or in patients on a low sugar diet.

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).

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 a stabiliser 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.

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

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.

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.

[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).]

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.

Interference with serological testing
After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients 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 (e.g. Coombs test), reticulocyte count and haptoglobin .

4.6 Pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

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).]

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.

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.

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

This medicinal product must not be mixed with other medicinal products.

[Product specific]

6.3 Shelf-life

[Product specific]

6.4 Special precautions for storage

[Product specific]

6.5 Nature and contents of container

[Product specific]

6.6 Instructions for use and handling and disposal

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

7. MARKETING AUTHORISATION HOLDER

{Name and address}

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]