

SUMMARY OF PRODUCT CHARACTERISTICS

Human normal immunoglobulin for intravenous administration (IVIg)

1 NAME OF THE MEDICINAL PRODUCT

OCTAGAM 10%

OCTAGAM 100 mg/ml

[country specific]

solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Active ingredients

Human normal immunoglobulin (IVIg)

2.2 Quantitative composition:

1 ml solution contains:

Protein	100 mg
of which $\geq 95\%$ is human Immunoglobulin G	
IgA	≤ 0.4 mg
IgM	≤ 0.3 mg

Distribution of IgG subclasses:

IgG ₁	ca. 60%
IgG ₂	ca. 32%
IgG ₃	ca. 7%
IgG ₄	ca. 1%

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The liquid preparation is clear to slightly opalescent and colourless to slightly yellow. The pH of the liquid preparation is 4.5 – 5.0, the osmolality is ≥ 240 mosmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

4.1.1 Replacement therapy in:

- Primary immunodeficiency syndromes such as:
 - congenital agammaglobulinaemia and hypogammaglobulinaemia
 - common variable immunodeficiency

- severe combined immunodeficiency
- Wiskott Aldrich syndrome
- Myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
- Children with congenital AIDS and recurrent infections.

4.1.2 Immunomodulation

- Idiopathic thrombocytopenic purpura (ITP) in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome
- Kawasaki disease

4.1.3 Allogeneic bone marrow transplantation

4.2 Posology and method of administration

4.2.1 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 to 4 weeks.
- Trough levels should be measured in order to adjust the dose and dosage interval.

Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia 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 - 1 g/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 g/kg should be administered in divided doses over two to five days or 2 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 the 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 injection
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/day	on day 1, possibly repeated once within 3 days for 2-5 days
Guillain Barré syndrome	0.4 g/kg/day	for 3-7 days
Kawasaki syndrome	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

Indication	Dose	Frequency of injection
- Persistent lack of antibody production	0.5 g/kg	every month until IgG levels return to normal

4.2.2 Method of administration

Octagam 10% [100 mg/ml] should be infused intravenously at an initial rate of 0.01 to 0.02 mL/kg body weight per minute for 30 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.12 mL/kg/ body weight per minute.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of Octagam 10% [100 mg/ml].

Hypersensitivity to homologous immunoglobulins, especially in the very rare cases of IgA deficiency when the patient has antibodies against IgA.

4.4 Special warnings and 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 agammaglobulinaemia, 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 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 (0.01 to 0.02 mL/kg body weight per minute);
- 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 to Octagam 10% [100 mg/ml] 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.

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 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 not containing such excipients 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 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.

Some types of blood glucose testing systems may falsely interpret the maltose (90 mg/ml) contained in Octagam 10% [100 mg/ml] as glucose. This may result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin and cases of true hypoglycaemia may go untreated if the hypoglycaemic state is masked by falsely elevated glucose readings. For further details see Section 4.5.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV.

The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

There is a reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that Octagam 10% [100 mg/ml] is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interactions

In order to infuse any product that may remain in the infusion tubing at the end of the infusion the tubing may be flushed with either 0.9% saline or 5% dextrose solution.

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 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 or D may interfere with some serological tests for red cell allo-antibodies, for example the antiglobulin test (e.g. Coombs Test).

Blood Glucose Testing

Some types of blood glucose testing systems (for example, those based on the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods) falsely interpret the maltose (90 mg/ml) contained in Octagam 10% [100 mg/ml] as glucose. This may result in falsely elevated glucose readings during an infusion and for a period of about 15 hours after the end of the infusion and, consequently, in the inappropriate administration of insulin, resulting in life-threatening or even fatal hypoglycemia. Also, cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings. Accordingly, when administering Octagam 10% [100 mg/ml] or other parenteral maltose- containing products, the measurement of blood glucose must be done with a glucose-specific method.

The product information of the blood glucose testing system, including that of the test strips, should be carefully reviewed to determine if the system is appropriate for use with maltose-containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

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

In general, various allergic and hypersensitivity type of reactions and headache, chills, back pain, chest pain, fever, cutaneous reactions, vomiting, arthralgia, low blood pressure and nausea may occasionally occur. Reactions to intravenous immunoglobulins tend to be related to the dose and the rate of infusion.

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

MedDRA 8.1 Coded	Common ≥1% - <10%	Uncommon ≥0.1% - <1%	Very Rare < 0.01%
Blood and lymphatic system disorders			leukopenia; haemolytic anaemia
Immune system disorders	hypersensitivity		anaphylactic shock; anaphylactic reaction; anaphylactoid reaction; angioneurotic oedema; face oedema
Psychiatric disorders			agitation
Nervous system disorders	headache		cerebrovascular accident; meningitis aseptic; migraine; dizziness; paraesthesia
Cardiac disorders			myocardial infarction; tachycardia; palpitations; cyanosis
Vascular disorders			thrombosis; peripheral circulatory failure; hypotension; hypertension
Respiratory, thoracic and mediastinal disorders			respiratory failure; pulmonary embolism; pulmonary oedema; bronchospasm; dyspnoea; cough
Gastrointestinal disorders	nausea		vomiting; diarrhoea; abdominal pain
Skin and subcutaneous tissue disorders		eczema;	urticaria; rash; rash erythematous; dermatitis; pruritus; alopecia
Musculoskeletal and connective		back pain	arthralgia;

tissue disorders			myalgia
Renal and urinary disorders			renal failure acute
General disorders and administration site conditions	fever; fatigue; injection site reaction	chills; chest pain	hot flush; flushing; hyperhidrosis; malaise
Investigations			hepatic enzymes increased; blood glucose false positive

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.

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.

Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. For safety with respect to transmissible agents, see 4.4.

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: J06B A02

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 prepared from pooled plasma from not fewer than 3500 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 level to the normal range.

The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Clinical Studies

In a prospective, open-label, multicentre phase III trial, the efficacy and safety of Octagam 10% [100 mg/ml] was studied in patients suffering from idiopathic (immune) thrombocytopenic purpura (ITP). Octagam 10% [100 mg/ml] was infused on 2 consecutive days at a dose of 1 gram/kg/day, and patients were observed for a period of 21 days and at a follow-up visit on Day 63 post-infusion. Haematology parameters were assessed on Days 2 to 7, 14 and 21.

A total of 31 subjects were included in the analysis; 15 were subjects with chronic ITP, 15 were newly-diagnosed, and 1 subject was incorrectly enrolled in the study (had no ITP) and was therefore excluded from the efficacy analysis.

In total, 25 subjects (83%) showed a clinical response. A higher clinical response rate was seen in the newly-diagnosed cohort (93%) than in the chronic ITP cohort (73%). In subjects with a response, the median time to platelet response was 2 days, with a range of 1 to 5 days.

In 24 subjects (77%), Octagam 10% [100 mg/ml] was given at the maximum allowed infusion rate of 0.06 mL/kg/min. Following a Protocol Amendment, 2 patients of the presented analysis received the product at a rate of 0.08 mL/kg/min which was uneventful in both cases. In the continuation of this on-going study, 22 subjects have been treated with the maximum allowed infusion rate of 0.12 mL/kg/min.

In 9 of 62 infusions (14.5%) treatment-related infusional AE were observed. The most common drug-related AE was headache, followed by tachycardia and pyrexia. There was no case of haemolysis related to the study drug. Pre-treatment to alleviate infusion-related intolerability was not given.

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 an average half life ranging from 26 to 41 days, as measured in immunodeficient patients. 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

Immunoglobulins are normal constituents of the human body. In animals, acute toxicity testing is of no relevance because of the excessive dose required. Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable. Effects of the product on the immune system of the newborn have not been studied.

Virus inactivation by solvent/detergent treatment is carried out with Tri-n-butyl phosphate (TNBP) and Octoxynol (Triton X-100). The maximum permitted amounts in the final product are 1 µg/ml TNBP and 5 µg/ml Octoxynol. In the doses in which Octagam 10% [100 mg/ml] is administered, these substances have been found to have no toxic effects in animal tests concerning acute and chronic toxicity, teratogenicity and embryotoxicity.

Since clinical experience provides no hint for tumorigenic or mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose
Water for injections

6.2 Incompatibilities

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

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Keep the container in the outer carton in order to protect from light.

Do not freeze.

Do not use after expiry date.

Because of the possibility of bacterial contamination, any remaining contents must be discarded.

Within its shelf-life, the product may be stored below 25 °C for up to 3 months, without being refrigerated again during this period, and must be withdrawn if not used after this.

6.5 Nature and contents of container

<i>Package size</i>	<i>Contents</i>	<i>Container</i>
Octagam 20 ml	2 g	30 ml injection vial
Octagam 50 ml	5 g	70 ml infusion bottle
Octagam 100 ml	10 g	100 ml infusion bottle
Octagam 200 ml	20 g	250 ml infusion bottle

Not all pack sizes may be marketed.

The primary container is made of type II glass closed with bromobutyl rubber stopper.

Components used in the packaging of Octagam 10% [100 mg/ml] are latex-free.

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use.

The solution should be clear or slightly opalescent.

Do not use solutions that are cloudy or have deposits.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

To be completed nationally

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

Date of last renewal:

10 DATE OF REVISION OF THE TEXT

April 2008

11 LEGAL CATEGORY

For prescription only.