PRODUCT INFORMATION

OCTAGAM®

NAME OF DRUG

OCTAGAM® Normal Intravenous Immunoglobulin 50 mg/mL Solution for Infusion.

DESCRIPTION

OCTAGAM® contains human normal immunoglobulin G (IgG) ≥ 95%, with a broad spectrum of antibodies against infectious agents. The Immunoglobulin A (IgA) content is ≤ 0.2mg/mL. It is composed of the following distribution of IgG subclasses:

IgG_1	approx. 65%
IgG_2	approx. 29%
IgG_3	approx. 4%
IgG_4	approx. 2%

OCTAGAM® contains ≤ 3 % polymers. Monomer and dimer is ≥ 90 %.

OCTAGAM® contains all the IgG activities, which are present in the normal population. It is prepared from pooled material from more than 3500 donors.

Quantitative composition

1 mL of solution contains:

Protein, of which at least 95% is	
Human Normal Immunoglobulin G	50 mg
Maltose	100 mg
Tributyl phosphate	≤ 1 microgram
Octoxinol 9	≤ 5 microgram
Water for Injections	1 mL
IgA	≤ 0.2 mg

PHARMACOLOGY

Pharmacodynamic properties

ATC code: J06B A02

OCTAGAM® has a distribution of IgG subclasses, which are closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

The mechanism of action in idiopathic thrombocytopenic purpura is not fully elucidated. The IgG molecules have not been chemically or enzymatically modified.

OCTAGAM® has a broad spectrum of antibodies against various infectious agents (e.g. antibody titer for streptococcus and hepatitis B-antigen is established at 3 times the initial

plasma pool), corresponding to those pathogens endemic in Australia, Europe and North America.

Pharmacokinetic properties

Human normal immunoglobulin is completely bioavailable in the recipient's circulation after intravenous administration. The steady state pharmacokinetics of OCTAGAM® were studied in two open uncontrolled trials in patients with Primary Immunodeficiency. Administration at 3 or 4 weekly intervals for periods of up to 6 months resulted in maintenance of serum total IgG concentrations above 4 g/L. Mean volume of distribution was 3.7 ± 1.4L and mean clearance was measured as 0.073 ± 0.02 L/day. Half-life was measured as 35.9 (± 1.4) and 40.7 (± 17.0) days in the two studies. Half life may vary from patient to patient, in particular in primary immunodeficiency.

IgG and IgG-complexes are broken down in cells of the reticulo-endothelial system.

CLINICAL TRIALS

In an open-labelled, multicentre study, 46 patients with Primary Immune Deficiency (PID) received OCTAGAM® individualized doses of 0.3 – 0.6 g/kg every 3 or 4 weeks for 12 months.

For the primary endpoint, which was the number of episodes of serious infections, the observed rate was 0.1 infections per patient per year (5 infections over 43.5 patient-years). On average, 0.4 days of hospitalization per patient were documented, and for 5.2 days patients were absent from work or school. The mean number of visits to a physician or emergency room was also very low (n=2).

Summary of Secondary Efficacy Variables

Variable	**Subjects N**	**%**	**Total Days or Visits**	**Total Subject Years**	**Days or Visits/Subject/Year Estimate**
Work/School Days Missed	30	65	241	43.5	5.5
Days in Hospital	4	9	16	43.5	0.4
Visits to Physician/ER	27	59	92	43.5	2.1

In an open-labelled single-center study, 17 adolescent patients with PID received OCTAGAM® individualized doses of 0.2 to 0.4 g/kg every 3 weeks for a 6 months period. All patients were previously treated with IGIV preparations.

Trough levels continuously increased under OCTAGAM® treatment and reached a plateau after the 4th treatment.

The clinical efficacy was assessed as good, as the number of days with infections or fever, and the number of days out of school were low (mean number of days out of school: 7 per patient; mean no. of days with fever: 3 per patient; mean no. of days with infections: 29 per patient). No severe infections leading to hospitalization were observed.

In an open-labelled single-center study, 19 patients with Immune Thrombocytopenic Purpura (ITP) received OCTAGAM® 1 g/kg for 2 consecutive days. At baseline, 13 patients had a platelet count $\leq 20 \times 10^9$/L. In 16 patients platelet counts rose above 50×10^9/L. In the remaining patients treatment resulted in arrest of bleeding, although platelet count remained below 50×10^9/L. No excessive bleeding was observed in any of the 7 patients during splenectomy.

In the same study, 22 patients with Chronic Lymphocytic Leukemia (CLL) received OCTAGAM® 0.4 g/kg every 4 weeks for 6 consecutive courses. Prior to OCTAGAM® treatment, serum IgG levels were < 7 g/L in 17 patients. Monthly infusions resulted in a substantial increase in serum IgG in 13 out of 17 patients. During the treatment period 32 suspected infections were noted (before treatment: 47), most of them mild. Twelve episodes needed aggressive therapy (before treatment: 32). Twelve patients did not report any infections at all.

INDICATIONS

Replacement therapy

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

- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

- Children with congenital Acquired Immune Deficiency Syndrome (AIDS) who have repeated bacterial infections.

Immunomodulatory effect

- Idiopathic thrombocytopenic purpura, in adults or children with a high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome
- Kawasaki disease.

Allogeneic bone marrow transplantation

CONTRAINDICATIONS

Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA. OCTAGAM® is contraindicated in any patient who has a history of an allergic reaction to any human immunoglobulin preparation or to any constituent of OCTAGAM®.

WARNINGS

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of hiterto unknown nature and theoretically to Creutzfeld-Jacob Disease (CJD) agents . The risk of transmission of infective agents is however reduced by:

i) selection of donors by a medical interview and screening of donations for the three major pathogenic viruses, HIV, HCV, HBV
ii) testing of plasma pools for HCV genomic material
iii) removal/inactivation procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV and HBV.

The manufacturing process for OCTAGAM® includes two viral inactivation steps – solvent/detergent treatment followed by an incubation step at low pH at 37°C for 24-26 hours. Viral removal and inactivation procedures performed during the manufacturing process may be of limited value against non-enveloped viruses such as hepatitis A virus or parvovirus B19.

The manufacturing process was investigated for the capacity to decrease the amount of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents. The manufacturing process of OCTAGAM® has been shown to decrease the amount of this experimental model agent. The TSE reduction step is the precipitation and separation of fraction I+III.

Vaccination for patients in receipt of medicinal products made from human plasma should be considered where appropriate.

In the interest of patients, it is recommended that, the name and batch number of OCTAGAM® is registered before administration.

PRECAUTIONS

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate must be closely followed (see ***Administration***). Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Certain adverse reactions may occur more frequently

- in cases 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 treatment has been stopped for more than eight weeks.

Hypersensitivity and anaphylactic reactions
True hypersensitivity reactions are rare. They can occur in cases of IgA deficiency with anti-IgA antibodies. Rarely, human normal immunoglobulin can induce a fall in blood pressure with an anaphylactic reaction, even in patients who have tolerated previous treatment with human normal immunoglobulin.

Potential complications can often be avoided by ensuring:
i) that patients are not sensitive to human normal immunoglobulin by first injecting the product slowly (1 mL/kg/hour);
ii) 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 intravenous Immunoglobulin (Human) (IVIg) product or when treatment has been stopped for more than eight weeks, 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.

Renal dysfunction
Cases of renal dysfunction, acute renal failure, osmotic nephrosis and death 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, sepsis, overweight, concomitant nephrotoxic medicinal products or age over 65.

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing OCTAGAM® at a maximum rate less than 0.2 g/kg/hour.

In all patients, intravenous immunglobulin administration requires:

i) adequate hydration prior to the initiation of the infusion of IVIg
ii) monitoring of urine output;
iii) monitoring of serum creatinine levels and
iv) avoidance of concomitant use of loop diuretics

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 addition, OCTAGAM® should be administered at the minimum concentration and infusion-rate practicable.

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, the current medical standards for shock treatment should be observed.

Thromboembolic events

Arterial and venous thromboembolic events have been reported in association with OCTAGAM®, particularly in those with known risk factors (see **ADVERSE REACTIONS**). The pathogenesis of thromboembolic events associated with IVIg´s is assumed to be multifactorial. A relative increase in blood viscosity from the high influx of immunoglobin and/or the presence of procoagulant factors in the immunoglobulin solution are two possible mechanisms. There was an increased rate of thromboembolic events reported in 2010 associated with OCTAGAM®. The unexpected presence of factor XIa appeared to be the main cause for the thromboembolic events. Corrective measures in the manufacturing process of OCTAGAM® have been implemented. Arterial thromboembolic events included myocardial infarction and stroke. Most arterial thromboembolic events occurred during OCTAGAM® infusion or within the first 24 hours post infusion. Venous thromboembolic events included deep vein thromboses and pulmonary embolism. Most venous thromboembolic events occurred within 72 hours post OCTAGAM® infusion.

Caution should be exercised in prescribing and infusing IVIg in patients with pre-existing risk factors for arterial and venous thromboembolic events such as obesity, smoking, a history of atherosclerosis/vascular disease or thrombotic events, hypertension, diabetes, hyperlipidaemia, multiple cardiovascular risk factors, advanced age, impaired cardiac output, pregnancy and the puerperium, oestrogen-containing hormone replacement therapy or oral contraceptive, acquired or inhertited thrombophilic disorders, prolonged periods of immobilisation, hypovolemia, surgery, central venous catheterisation, active malignancy and/or known or suspected hyperviscosity.

The potential risks and benefits of IVIg´s, including OCTAGAM® should be weighed against those of alternative therapies for all patients for whom IVIg administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronaemia/markedly high triglycerides, or monoclonal gammopathies. Patients should be monitored closely for

signs and symptoms of thromboembolism, particularly during and for 72 hours after OCTAGAM® infusion. Rapid rates of IVIg infusion may be a risk factor for thromboembolic events. The recommended infusion rate should not be exceeded. For patients judged to be a risk of developing thromboembolic events, administer OCTAGAM® at the minimum rate of infusion practible. The decision to take antithrombotic prophylactic measures is a clinical decision that requires a careful assessment of individual patients underlying risk factors.

Aseptic meningitis syndrome

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently 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 two days following IVIg treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu.mm., predominantly from the granulocytic series, and elevated protein levels up to several g/L. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. It appears that patients with a history of migraine may be more susceptible.

Haemolysis

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 and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration (see **ADVERSE REACTIONS**). IVIg recipients should be monitored for clinical signs and symptoms of haemolysis.

In patients with a normal acid base compensatory mechanism, the acid load delivered by the largest dose of the preparation would be neutralised by the buffering capacity of whole blood alone, even if the dose were to be infused instantaneously. In patients with limited or compromised acid base compensatory mechanisms including neonates, consideration should be given to the effect of the additional acid load that the preparation might present.

Use in children

Effects of OCTAGAM® on the immune system of the newborn have not been studied.

Use in Pregnancy

The safety of OCTAGAM® in human pregnancy has not been established in controlled clinical trials and therefore it should only be given with caution to pregnant woman 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.

Use in Lactation

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate. (see ***Use in Pregnancy*****)**

Live attenuated vaccines
Immunoglobulin administration may impair for a period of at least six weeks and up to three months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella.

After administration of this product, an interval of three months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to one 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 patient's 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 (e.g. Coombs Test), reticulocyte count and haptoglobin.

OCTAGAM® contains maltose, which could interfere with blood and urinary glucose tests.

Effects on ability to drive and use machines

There is no indication that immunoglobulins may impair the ability to drive and use machines.

ADVERSE REACTIONS

The following ADRs have been identified in clinical trials with OCTAGAM® (5% or 10%). Within each frequency grouping, undesirable effects are presented in the internationally agreed order.

MedDRA Coded	**Common >1% - <10%**	**Uncommon >0.1% - <1%**
Immune system disorders	hypersensitivity	
Nervous system disorders	headache	dizziness
Cardiac disorders	tachycardia	
Vascular disorders	hypertension	hypotension
Gastrointestinal disorders	nausea vomiting	
Skin and subcutaneous tissue disorders	eczema	
Musculoskeletal and connective tissue disorders		back pain
General disorders and administration site conditions	fever fatigue chills	chest pain hot flush

MedDRA Coded	Common >1% - <10%	Uncommon >0.1% - <1%
	injection site reaction	
Investigations	hepatic enzymes increased	

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.

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.

In addition to the ADRs listed in the table above, the following ADRs have also been identified during post-approval use of OCTAGAM® (5% or 10%). Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Blood and lymphatic system disorders Leucopoenia, haemolytic anaemia
Immune system disorders Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, angioneurotic oedema, face oedema
Metabolic and nutritional disorders Fluid overload
Psychiatric disorders Agitation
Nervous system disorders Cerebrovascular accident, meningitis aseptic, migraine, paraesthesia, seizures
Cardiac disorders Myocardial infarction, palpitations, cyanosis
Vascular disorders Cardiac arrest, thromboembolism, peripheral circulatory failure
Respiratory, thoracic and mediastinal disorders Respiratory failure, pulmonary embolism, pulmonary oedema, bronchospasm, dyspnoea, cough
Gastrointestinal disorders Diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders Urticaria, rash, rash erythematous, dermatitis, pruritus, alopecia
Musculoskeletal and connective tissue disorders Arthralgia, myalgia, pain in extremity
Renal and urinary disorders Renal failure acute

General disorders and administration site conditions Flushing, hyperhidrosis, malaise
Investigations Blood glucose false positive

For information on viral safety, see **WARNINGS**.

DOSAGE AND ADMINISTRATION

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 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 immunoglobulin G (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 depending on the circumstances (e.g. active infection) followed by 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 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, repeated on day three if necessary, 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. Patients should receive concomitant treatment with acetylsalicylic acid.

Allogeneic Bone Marrow Transplantation:

Intravenous immunoglobulin treatment may 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.

OCTAGAM® should be infused intravenously at an initial rate of 1 mL/kg/hour for 30 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 5 mL/kg/hour for the remainder of the infusion.

OCTAGAM® should be brought to room or body temperature before administration.

Any unused product must be disposed of, since OCTAGAM® contains no antimicrobial agent. Product is for single use in one patient only.

OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

PRESENTATION

Incompatibilities

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

Storage

Shelf life is 2 years.
Store below 25°C.
Do not freeze.
Protect from light.
Do not use after expiry date.

Instructions for use/handling

OCTAGAM® contains no antimicrobial agent. It must, therefore, be used immediately after opening; any remaining contents must be discarded.
Keep out of the reach of children.

Instructions for use/handling

Do not use non-homogenous solutions, or those, which have a deposit. Any unused product or waste material should be disposed of in accordance with local requirements.

Pack

The primary container is made of type II glass closed with bromobutyl rubber stopper. Each container contains 50 mg/mL solution for infusion.

1 injection vial with 20 mL
1 infusion bottle with 50 mL
1 infusion bottle with 100 mL
1 infusion bottle with 200 mL

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Date of Approval

04 August 2011

Date of Most Recent Amendment

06 March 2006