PRODUCT MONOGRAPH

OCTAGAM® 5%

Immunoglobulin Intravenous (Human)
Solution for Infusion, 50 mg/mL
Prescription Medication, passive immunizing agent
ATC Code: JO6BA

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OCTAGAM® 5%

Immunoglobulin Intravenous (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION **Route of Administration**	**Dosage Form / Strength**	**Clinically Relevant Nonmedicinal Ingredients**
Injection	Solution for Infusion, 50, 100, 200 and 500 mL Each mL contains 50 mg protein, of which ≥ 96% is immunoglobulin G (IgG)	IgA *For a complete listing see* DOSAGE FORMS, COMPOSITION AND PACKAGING *section.*

DESCRIPTION

OCTAGAM® 5% (OCTAGAM) is a sterile liquid preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma.

It is prepared by cold-ethanol fractionation of donated human fresh frozen plasma. Viral inactivation is accomplished by a solvent detergent (S/D) method and a specific pH 4 treatment. The pH 4 treatment also reduces anti-complementary activity and aggregation of the IgG polymers. Residual S/D reagents are removed by extraction and chromatography before sterile filtration. Residual ethanol is removed via ultra-/diafiltration. The whole manufacturing process is carried out at a low pH in order to maintain the nativity of the IgG molecules.

After addition of maltose the 5% IgG solution is sterile filtered and filled into siliconized glass vials. The final product is salt free and no dilution with saline solution is needed prior to its administration.

This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases.

Therefore the following precautions against viral transmission are taken during the manufacture of OCTAGAM: selection of plasma donors, screening of donations and plasma pool, as well as

quality control measurements of the final product. As with any blood product, a potential problem is the transmission of blood borne pathogens. When medicinal products prepared from human blood or plasma are given to a patient, the transmission of infectious agents cannot be totally excluded.

INDICATIONS AND CLINICAL USE

OCTAGAM is indicated for:

Replacement Therapy

Primary Immunodeficiency (PID) Syndromes

Replacement therapy: the following PID syndromes can be treated with intravenous replacement of IgG and are considered ”well-established” indications:[0-**Error! Reference source not found.**]

- congenital agammaglobulinaemia and hypogammaglobulinaemia.
- common variable immunodeficiency.
- severe combined immunodeficiencies.

Secondary Immunodeficiency Syndromes

IgG can also be used as replacement therapy in:

- secondary hypo-gammaglobulinaemia in patients with chronic lymphocytic leukaemia (CLL),[**Error! Reference source not found.**,**Error! Reference source not found.**] or multiple myeloma (MM) with recurrent infections.[**Error! Reference source not found.**]
- children with congenital AIDS who have bacterial infections.[**Error! Reference source not found.-Error! Reference source not found.**]

OCTAGAM should be administered under the supervision of a qualified health professional who is experienced in the use of immunizing agents and in the management of immunodeficiency syndromes. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

CONTRAINDICATIONS

Contraindications for OCTAGAM are as follows:

- OCTAGAM is contraindicated for patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- 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. OCTAGAM is also contraindicated in those rare cases where an individual has an immunoglobulin A (IgA) deficiency, with known antibodies against IgA.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses. Therefore, caution should be exercised when prescribing and administeriung immunoglobulins.
- In general the risk factors for thromboembolic events include: obesity, advance age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisations, severely hypovolemic patients, diseases which increase blood viscosity, hypercoagulable conditions, use of estrogens, indwelling central vascular catheters, and cardiovascular risk factors.
- Thrombosis may occur even in the absence of known risk factors.
- In the manufacturing process of OCTAGAM measures have been implemented to reduce the possible content of procoagulant factors. Furthermore a sensitive batch release test has been implemented (thrombin generation assay (TGA)), to detect increased thromboembolic potential.

  (see WARNINGS AND PRECAUTIONS – Thromboembolic events)

As with other IGIV formulations, this product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering to the patient (see WARNINGS AND PRECAUTIONS - General).

General

Products made from human plasma may contain infectious agents, such as viruses and theoretically, the variant Creutzfeld-Jakob disease (vCJD) agent, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infections agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections.

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. The viral safety of Octagam is ensured through a number of steps, such as the virus removal by cold-ethanol fractionation and solvent/detergent treatment which inactivates enveloped viruses such as HIV, hepatitis B (HBV) and hepatitis C (HCV) virus. In addition, prolonged pH4 incubation at 37°C inactivates both enveloped and non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19. However, as with all products prepared from human blood or plasma, the risk of transmission of infectious agents cannot be fully excluded.

OCTAGAM should be inspected visually for particulate matter and discolouration prior to administration. Do not use non-homogenous solutions, or those that have a deposit. Any remaining fraction should be discarded. OCTAGAM should be warmed up to room or body temperature before use.

Assure that patients are not volume depleted prior to the initiation of the infusion of OCTAGAM.

Certain severe adverse drug reactions may be related to the rate of infusion. Patients naive to immunoglobulin G (IgG) usually experience a higher frequency of minor events than those well maintained on regular therapy. The recommended infusion rate given under "Dosage and Administration" must be closely followed and patients must be closely monitored and carefully observed for any symptoms throughout the infusion period, and for one hour after the first infusion. In case of adverse reactions either the rate of administration must be reduced or the infusion stopped until symptoms disappear.

Patients should be observed for at least 20 minutes after administration. In case of shock, treatment should follow the guidelines for shock therapy.

Human IGIV should not be mixed with other medicinal products. A separate intravenous line should be used for the infusion. Do not use the product after expiry date.

Thromboembolic events

There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses.
Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. The drug product should be administered at the minimum concentration available and at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration.
Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia / markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity assessed appropriately (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Risk factors for thromboembolic adverse events include: obesity, advanced age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisation, severely hypovolemic patients, diseases which increase blood viscosity, hypercoagulable conditions, use of estrogens, indwelling central vascular catheters, and cardiovascular risk factors.[**Error! Reference source not found.-Error! Reference source not found.**]
The potential risks and benefits of IGIV treatment should be weighed against those of alternative therapies for all patients for whom Octagam 5% administration is being considered.
In the manufacturing process of Octagam measures have been implemented to reduce the possible content of procoagulant factors. Furthermore a sensitive batch release test has been implemented (thrombin generation assay (TGA), to detect increased thromboembolic potential to ensure the quality and therefore the safe use of Octagam.

Renal

Cases of acute renal failure have been reported in patients receiving IGIV therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medications, or over the age of 65. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.[**Error! Reference source not found.**]

In all patients, IGIV administration requires: adequate hydration prior to the initiation of the infusion of IGIV, monitoring of urine output, blood urea nitrogen (BUN), monitoring of serum creatinine levels, and avoidance of concomitant use of loop diuretics. In addition, the product should be administered at the minimum concentration and infusion-rate practicable. In case of renal impairment, IGIV discontinuation should be considered.[**Error! Reference source not found.-Error! Reference source not found.**]

Haematologic

IGIV products, including OCTAGAM, can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, haemolysis.[21-23] Haemolytic anaemia can develop subsequent to IGIV therapy due to enhanced red blood cells (RBC) sequestration (see ADVERSE REACTIONS) [24]. IGIV recipients should be monitored for clinical signs and symptoms of haemolysis (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Neurological System

A condition called aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with infusions of IVIGs, including OCTAGAM. AMS usually begins within several hours to two days following treatment. The signs include severe headache (migraine-like), neck stiffness, drowsiness, fever, inability to stand bright light, painful eye movements, and nausea and vomiting. The condition usually reverses without ill effects when treatment is

stopped. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Patients with a history of migraine appear to be more susceptible to AMS. Preventive measures to avoid the occurrence of aseptic meningitis include careful risk/benefit evaluation in patients with history of migraine, premedication with analgesics with or without caffeine, proper hydration and maintenance of good fluid intake throughout treatment, and slow infusion rates.

Sensitivity

OCTAGAM contains maltose, a disaccharide sugar, which is derived from corn. Anaphylactoid/anaphylactic reactions have been reported in association with infusion of other maltose/corn starch related products. Patients known to have corn allergies should either avoid using OCTAGAM or be closely observed for signs and symptoms of acute hypersensitivity reactions.[25,26]

In case of hypersensitivity, OCTAGAM infusion should be immediately discontinued and appropriate treatment applied.

Transfusion-related acute lung injury (TRALI) has been rarely reported after treatment with IGIV products.

Special Populations

Pregnant Women: The safety of OCTAGAM for use in human pregnancy and during lactation has not been established in controlled clinical trials and therefore 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. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Nursing Women: See *Pregnant Women* section above.

Paediatrics: No specific data is available.

Geriatrics (≥ 65 years of age): Overdose is possible in overweight patients. Cases of acute renal failure have been reported in patients receiving IGIV therapy. In most cases, additional risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, or concomitant nephrotoxic medications.

Monitoring and Laboratory Tests

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 contained in OCTAGAM as glucose. This has resulted in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycaemia. Also, cases of true hypoglycaemia may go untreated if the hypoglycaemic state is masked by falsely elevated glucose readings. Accordingly, when administering OCTAGAM or other parenteral maltose-containing products, the measurement of blood glucose must be done with a glucose-specific method. Due to the potential for falsely elevated glucose readings, only testing systems that are

glucose-specific, should be used to test or monitor blood glucose levels in patients receiving maltose-containing parenteral products, including OCTAGAM. 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.[27-29]

Urine Glucose Testing: About 5% of intravenously administered maltose is excreted via the urine as glucose or maltose.[27] Having this in mind, interferences with both urine test methods can be expected.

Drug/Laboratory Test Interactions: IgG administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella and varicella for at least six weeks, and possibly up to three months. In some cases, where large doses are given this period may be as long as one year.

After injection of IGIV, the transitory rise in the various passively transferred antibodies may result in misleading positive results in serological tests, e.g. CMV serology, Coombs Test, etc.

If signs and/or symptoms of haemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done [see WARNINGS AND PRECAUTIONS].

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [see WARNINGS AND PRECAUTIONS].

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In general, various minor allergic and hypersensitivity type of reactions and headache, chills, myalgia such as back or chest pain, fever, cutaneous reactions, and nausea may occasionally occur. Reactions to intravenous immunoglobulins tend to be related to the dose and the rate of infusion.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study OCTA-06

This was a multiple-dose, open-label, multi-center study in patients with PID.[30] The objectives were to assess the safety, pharmacokinetics, and therapeutic efficacy of OCTAGAM as replacement therapy in PID. Forty-six patients received 654 infusions of OCTAGAM (either 400–600 mg/kg every 28 days or 300–450 mg/kg every 21 days) for 12 months.

Nineteen patients (41%) experienced 71 treatment-related AEs (ADRs). The most common ADR was headache NOS (7 patients, 15%; 18 events). The only other ADR that was reported by more than 2 patients was nausea (3 patients, 7%).

ADRs to OCTAGAM were reported in association with 6% of the infusions. These included headache, injection site reaction, arthralgia, hypertension, palpitations, pruritus, pain in limb, and hypotension. The number of drug-related AEs per patient was approximately constant across all infusions.

Abnormal Hematologic and Clinical Chemistry Findings

In Study OCTA-06, seven patients (15%) had a total of 28 clinically significant serum chemistry abnormalities. For AST, ALT, LDH and bilirubin, a laboratory value was considered clinically significant if it was >2.5 times the upper normal limit (ULN); a serum creatinine value was considered clinically significant if it was > ULN (i.e., any value above the ULN). Three patients (7%) had 3 incidences of AST >2.5 times ULN and 4 patients (9%) had 25 incidences of serum creatinine > ULN. All 4 patients had relatively stable creatinine levels throughout the study. Thus, the clinically significant creatinine values do not appear to be indicative of acute renal dysfunction. No patients experienced clinically significant abnormalities of ALT, LDH, or bilirubin.

Post-Market Adverse Drug Reactions

The following ADRs have been identified during post-approval use of OCTAGAM (any strength). Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

System Organ Class (MedDRA Terminology)	Reported ADRs
Blood and lymphatic system disorders	leucopenia; 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

System Organ Class (MedDRA Terminology)	Reported ADRs
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 tissue disorders	back pain; arthralgia; myalgia
Renal and urinary disorders	renal failure acute
General disorders and administration site conditions	fatigue; pyrexia; injection site reaction; chills; chest pain; hot flush; flushing; hyperhidrosis; malaise
Investigations	hepatic enzyme increased; blood glucose false positive

Thromboembolic events, such as myocardial infarction, stroke, pulmonary embolism, and deep vein thromboses, have been reported, and may be serious or even fatal depending on the site and type of thrombosis.

Cases of aseptic meningitis have been reported; however, no fatal cases have been observed.

Acute renal failure has been observed. In most cases it was mild, but may be serious in elderly patients, patients with diabetes, and patients with pre-existing renal disease.

Haemolytic anaemia / haemolysis have been observed. In most cases it is mild and self-limited.

DRUG INTERACTIONS

Overview

No formal studies of drug interactions have been performed.

Human IGIV should not be mixed with other medicinal products, including IGIV from other manufacturers. A separate intravenous line should be used for the infusion. Interactions with other drugs are unknown.

The infusion line may be flushed before and after administration of OCTAGAM with either normal saline or 5% dextrose in water.

IgG administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella and varicella for at least six weeks, and possibly up to three months. In some cases, where large doses are given, this period may be as long as one year.

Components used in the packaging of OCTAGAM are latex-free.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

OCTAGAM contains maltose which can be misinterpreted as glucose by certain types of blood glucose testing systems (for example, by systems based on GDH-PQQ or glucose-dye-oxidoreductase methods). Due to the potential for falsely elevated glucose readings, only testing systems that are glucose-specific, should be used to test or monitor blood glucose levels in patients receiving maltose-containing parenteral products, including OCTAGAM.
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 (see WARNINGS AND PRECAUTIONS).[27,29,31]

After injection of IGIV, the transitory rise in the various passively transferred antibodies may result in misleading positive results in serological tests, e.g. CMV serology, Coombs Test, etc.

DOSAGE AND ADMINISTRATION

Dosing Considerations

As there are significant differences in the half-life of IgG among patients with primary immunodeficiencies, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

Risk factors should be identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medications, or over the age of 65.

Assure that patients are not volume depleted prior to the initiation of the infusion of OCTAGAM. Patients should be observed for at least 20 minutes after administration.

Patients should have adequate hydration prior to the infusion of Octagam 5%. In patients at risk, IVIG products should be administered at the minimum rate of infusion and dose practicable.

Recommended Dose and Dosage Adjustment

Replacement therapy in Primary Immunodeficiencies: Monthly doses of at least 100 mg/kg are recommended. The aim of treatment is to maintain the IgG at levels greater than 500 mg/dL, or at a trough level of 350 mg/dL above baseline. A common practice is to start at 0.4 g/kg at monthly intervals but give an extra dose at onset of therapy. After 3 months the pre-infusion IgG level is assessed and adjusted to a dose that maintains a trough level of 500 mg/dL.[32]

The OCTAGAM dose administered in clinical trials was 0.3 - 0.6 g/kg every 3 – 4 weeks.

Replacement therapy in Secondary Immunodeficiencies: The recommended dose is 0.2 - 0.4g/kg body weight every 3 – 4 weeks.

Measles Exposure

Guidance for measles post-exposure prophylaxis has been provided by the National Advisory Committee on Immunization (NACI) and should be consulted. [40]

Individuals already receiving replacement IVIg at 400 mg/kg body weight or higher every month are considered protected against measles if the last dose of IVIG was received within three weeks prior to measles exposure. For patients receiving a dose below 400 mg/kg and/or when interval since last infusion is longer than 3 weeks administration of a single dose of 400 mg/kg bodyweight as soon as possible and within 6 days of exposure is recommended.

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Missed Dose

Not applicable because OCTAGAM is administered in a hospital setting by health care professionals.

Dose Adjustment

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 0.07 ml/kg (3.3 mg/kg)/minute (200 mg/kg/hour).

Administration

It is recommended that initially a 5% solution be infused at a rate of 30 mg/kg/hour for the first 30 minutes; if tolerated, advanced to 60 mg/kg/hour for the second 30 minutes; and if tolerated, advanced to 120 mg/kg/hour for the third 30 minutes. Thereafter the infusion could be maintained at a rate up to, but not exceeding, 200 mg/kg/hour.

Rate of Administration	mg/kg/hour	mL/kg/min
first 30 min	30	0.01
next 30 min	60	0.02
next 30 min	120	0.04
maximum	<200	<0.07

Certain severe adverse drug reactions may be related to the rate of infusion. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Parenteral Products

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

Assure that patients are not volume depleted prior to the initiation of the infusion of OCTAGAM. Patients should be observed for at least 20 minutes after administration.

OCTAGAM should be inspected visually for particulate matter and discolouration prior to administration. Do not use non-homogenous solutions, or those that have a deposit. Because of the possibility of bacterial contamination, any remaining contents must be discarded. OCTAGAM should be warmed up to room or body temperature before use.

Filtration of OCTAGAM is not required.

Precautions:

Human IGIV should not be mixed with other medicinal products. A separate intravenous line should be used for the infusion. Do not use the product after expiry date.

Shelf-life:

Store at +2 °C to +25 °C until the indicated expiry date.

Special Precautions for Storage:

Protect from light.

Do not freeze. Do not use after expiry date.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison control Centre.

Overdose may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with impaired renal function.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Results of *in vitro* studies suggest that OCTAGAM preparations may provide passive, IgG-mediated protection against candida, *H. influenzae* and *pneumococci*, which can be especially important in patients with primary or secondary gammaglobulin deficiency.

Pharmacodynamics

OCTAGAM contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against various infectious agents reflecting the IgG activity found in the donor population. OCTAGAM which is prepared from pooled material from not less than 3500 donors, has an IgG subclass distribution similar to that of native human plasma. Adequate doses of IGIV can restore abnormally low IgG level to the normal range.[4,33,34]

Pharmacokinetics

Several clinical studies were specifically designed to examine the pharmacokinetics of OCTAGAM after single or repeated doses. In one further study IgG plasma levels were assessed as an efficacy criterion and in another study trough levels were investigated.

Table 1 provides an overview of the pharmacokinetic parameters of OCTAGAM. The reported half-lives ranged from 36 to 40 days. Several factors such as the endogenous production, the actual catabolism rate, the underlying disease or inter-patient variability help to explain the wide range observed for terminal half-lives.

Table 1: Pharmacokinetic Studies with OCTAGAM

Study No. (Protocol) Design	No. of Patients Age Gender	Diagnosis Inclusion/ Exclusion Criteria	Treatment Dose Regimen	Pharmacokinetics Data

Study No. (Protocol) Design	No. of Patients Age Gender	Diagnosis Inclusion/ Exclusion Criteria	Treatment Dose Regimen	Pharmacokinetics Data
OCTA-06 Open label	14 Patients 10 to 70 years 8 males 6 females	Primary immunodeficiency disease, IGIV therapy at steady dose for ≥ 3 months, trough serum IgG level ≥ 400 mg/dL above baseline, no history of anaphylactic reactions to blood or blood-derived products, no demonstrable antibodies to IgA	Octagam 5% 400-600 mg/kg IV every 21 or 28 days for 12 months	$t_{½}$ 40.7 ± 17.0 Days C_{max} 16.7 mg/mL AUC 7,022 ± 1,179 mg*h/mL
X (GAM-04) Open label	17 patients 10 to 17 years 15 males 2 females	Primary immuno-deficiency syndromes; IgG titre ≤ 3 g/L; no history of anaphylactic reactions to immunoglobulins	Octagam 5% 200 to 400 mg/kg IV every 3 weeks for 6 months	$t_{½}$ 35.9 ± 10.8 Days $C_{ss\ max}$ 11.1 ± 1.9 g/L AUC_{ss} 160.1 ± 43.6 g • day/L Clearance 0.07 ± 0.02 L/day Volume of distribution: 3.7 ± 1.4 L
I (None) Open label	12 patients 22 to 66 years 4 males 8 females	Primary, severe hypogamma-globulinemia, under treatment with IgG so plasma concentration > 4 g/L, no increased liver enzymes, no HIV	Single dose of Octagam 5% 400 mg/kg IV	$t_{½}$ 30.7 days ± 4.0

After intravenous infusion, peak levels of OCTAGAM are obtained within 30 minutes. Due to the distribution of IGIV between intra-and extravascular compartments, serum IgG levels drop by about 40 to 50% during the first week following intravenous administration.[35]

High concentrations of IGIV and hyper-metabolism associated with fever and infection may shorten the half-life.[35]

For detailed data on efficacy, please refer to section PART II – CLINICAL TRIALS.

Special Populations and Conditions

No specific pharmacokinetic studies have been performed in patients at increased risk, such as elderly subjects or patients with renal or hepatic impairment.

STORAGE AND STABILITY

Store at +2 °C to +25 °C until the indicated expiry date. Do not freeze.

Protect from exposure to light.

Do not use after expiry date. Because of the possibility of bacterial contamination, any remaining contents must be discarded.

Human IGIV should not be mixed with other medicinal products. A separate intravenous line should be used for the infusion.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

OCTAGAM is a 50 mg/mL solution for intravenous infusion.

The following marketed dosage forms are available:

1 infusion bottle with 50 mL
1 infusion bottle with 100 mL
1 infusion bottle with 200 mL
1 infusion bottle with 500 mL

Nature and Contents of Container:

Each 50 mg/mL of OCTAGAM contains the active ingredients: Immunoglobulin Intravenous (Human), one millilitre (mL) of solution contains 50 mg of protein of which ≥ 96% is gammaglobulin. Each package contains 1 glass bottle of OCTAGAM ready to use and the package leaflet.

Quantitative composition:	**Per mL**
Human normal immunoglobulin G (IgG)	50 mg
Maltose	100 mg
Triton X-100	5 µg
TNBP	1 µg
Water for injections	1 mL
IgA	≤ 0.2 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- Proper name: OCTAGAM® 5%, Immunoglobulin Intravenous (Human)
- Chemical name: Immunoglobulin G (Human)
- Molecular formula and molecular mass: not applicable
- Structural formula: not applicable
- Physicochemical properties: The molecular weights range from 146 to 170 kD. Immunoglobulins have a common structure with four polypeptide chains. Two heavy chains and two non-glycosylated light chains. Human IgG is divided in four subclasses IgG_1, IgG_2, IgG_3 and IgG_4 due to minor differences in the amino sequence. The isoelectric point varies between 5.0 and 9.5

Pharmaceutical Standard

WHO. ATC 02 J06BA / Immunoglobulin G (Human)

Product Characteristics

OCTAGAM is prepared by cold-ethanol fractionation of donated human fresh frozen plasma. Each preparation is made from a pool of at least 3,500 donations of human fresh frozen plasma. Viral inactivation is accomplished by a solvent detergent (S/D) method and a specific pH 4 treatment. The pH 4 treatment also reduces anti-complementary activity and aggregation of the IgG polymers. Residual S/D reagents are removed by oil extraction (TNBP) and C18 chromatography (Triton X-100) before sterile filtration. Residual ethanol is removed via ultra-/diafiltration. A second ultra-/diafiltration step removes all ions such as sodium and increases the protein content to approximately 5%. The whole manufacturing process is carried out at a low pH in order to maintain the nativity of the IgG molecules.

After addition of maltose the 5% IgG solution is sterile filtered and filled into siliconized glass vials. The final product is salt free and no dilution with saline solution is needed prior to its administration.

The final product is examined for HBsAg and HIV-1/2 antibodies. Only preparations negative in all of these tests are released by Octapharma's Quality Control Department.

Viral Inactivation

OCTAGAM is double virus inactivated. Two established processes are incorporated into the manufacturing process, namely the S/D method and a specific pH4 treatment.

The S/D method, developed by the New York Blood Center, has been validated using both real and model viruses and in various chimpanzee tests. Among others, the effective inactivation of experimentally added HIV viruses, hepatitis non-A, non-B viruses (Hutchinson strain), HBV and HCV has been demonstrated.

CLINICAL TRIALS

Efficacy and Safety Studies

Study demographics and trial design

Twelve clinical studies have been conducted by Octapharma using OCTAGAM. Of these 4 studies were completed in patients with PID. In total, 373 patients were enrolled.

Most studies used an open design and had no control group, which is an acceptable approach, bearing in mind that the treatment with IGIV can be regarded as well established in the treatment of PID.

Studies in PID

Table 2 summarizes the 4 clinical studies that have been completed in patients with PID.

Table 2: Results of Clinical Studies in PID Patients

Study No. (Protocol) Design	Dosage, route of administration and duration	Number of Subjects Gender (Age range)	Primary Endpoint	Associated value and statistical significance for drug at specific dosages
OCTA-06 Open label	Octagam 5% 400-600 mg/kg IV every 28 days or 300 to 450 mg/kg IV every 21 days for 12 months	46 patients 28 male, 18 female (6 to 74 years)	Primary = serious infections per year Secondary = days work/school missed, hospitalizations, physician/ER visits, other infections	Serious infection rate = 0.115 infections/patient/year (98% confidence interval 0.033 - 0.279). Numbers of days patients missed work/school, were hospitalized, and visited physician or ER were each 1.5% or fewer of study days.

Study No. (Protocol) Design	Dosage, route of administration and duration	Number of Subjects Gender (Age range)	Primary Endpoint	Associated value and statistical significance for drug at specific dosages
X (GAM-04) Open label	Octagam 5% 200 to 400 mg/kg IV every 3 weeks for 6 months	17 patients 15 male, 2 female (10 to 17 years)	Number of days out of school, with infections, on antibiotics, and in hospital; frequency and type of infections	Type and severity of infections similar to normal population; no severe infections leading to hospitalization; low number of days out of school, with infection, and with fever
V (GAM/III/D) Open label	Octagam 5% 300 mg/kg IV monthly for 6 months	10 patients 7 male, 3 female (2.5 to 9 years)	Trough levels of IgG and subclasses after third injection, number and severity of infections	Effective in maintaining trough levels and reducing incidence of infections; no severe infection and 5 patients completely free of infection
I (None) Open label	Single dose of Octagam 5% 400 mg/kg IV	12 patients 4 male, 8 female (20 to 66 years)	Serum levels and half-life of IgG and IgG subclasses	Significant increase in IgG; half-life comparable to other products (30.7 ± 4.0 days)

AE = adverse event, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IV = intravenous, PCR = polymerase chain reaction, ER = emergency room, IgA = immunoglobulin A, IgG = immunoglobulin G, IGIV = intravenous immunoglobulin, PID = primary immunodeficiency disease

Safety data from clinical trials can be found in section PART I – ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions.

DETAILED PHARMACOLOGY

Non-clinical Pharmacology Studies

OCTAGAM is a preparation of human native immunoglobulins mainly to be used as replacement at normal physiological levels. Hence, the standard pharmacodynamic studies generally carried out for new substances in commonly used species are not applicable to this product.

It is clear from literature data available that no pharmacodynamic effects have to be expected from trace amounts of TNBP and Triton X-100.

Non-clinical Pharmacokinetic Studies

Pharmacokinetic studies with human proteins in animals are not predictive of the situation in humans: as a foreign protein the human material is more rapidly eliminated in animals than in man. Therefore no regular pharmacokinetic study was run for OCTAGAM.

A pharmacokinetic study was carried out in rats which were given TNBP + Triton X-100 (300 + 1,500 µg/kg) intravenously. The levels of TNBP and Triton X-100 in the plasma, urine and feces were determined.

The elimination half-life to TNBP was approximately 20 minutes. The substance could be detected in the urine, and very small amounts were excreted via the feces. Triton X-100 was neither detected in plasma nor in urine of feces.

According to published data the plasma half-life for TNBP in rats is 1.3 hours. Absorption and metabolism studies in rats and dogs indicate that 90% of ingested alkylphenol ethoxylates (p.e. Triton X-100) are excreted within 72 hours.

Human Pharmacokinetics

Several clinical studies were specifically designed to examine the pharmacokinetics of OCTAGAM after single or repeated doses. In 1 further study IgG plasma levels were assessed as an efficacy criterion and in another study trough levels were investigated.

Table 3 provides an overview of the pharmacokinetic parameters of OCTAGAM. The reported half-lives ranged from 36 to 40 days. Several factors such as the endogenous production, the actual catabolism rate, the underlying disease or inter-patient variability help to explain the wide range observed for terminal half-lives.

No specific pharmacokinetic studies have been performed in patients at increased risk, such as elderly subjects or patients with renal or hepatic impairment.

Table 3: Human Pharmacokinetic Studies with OCTAGAM

Study No. (Protocol) Design	No. of Patients Age Gender	Diagnosis Inclusion/ Exclusion Criteria	Treatment Dose Regimen	Pharmacokinetics Data
OCTA-06 Open	14 Patients 10 to 70 years 8 males 6 females	Primary immunodeficiency disease, IGIV therapy at steady dose for ≥ 3 months, trough serum IgG level ≥ 400 mg/dL above baseline, no history of anaphylactic reactions to blood or blood-derived products, no demonstrable antibodies to IgA	Octagam 5% 400-600 mg/kg IV every 21 or 28 days for 12 months	$t_{½}$ 40.7 ± 17.0 Days C_{max} 16.7 mg/mL AUC 7,022 ± 1,179 mg*h/mL
X (GAM-04) Open	17 patients 10 to 17 years 15 males 2 females	Primary immuno-deficiency syndromes; IgG titre ≤ 3 g/L; no history of anaphylactic reactions to immunoglobulins	Octagam 5% 200 to 400 mg/kg IV every 3 weeks for 6 months	$t_{½}$ 35.9 ± 10.8 Days $C_{ss\ max}$ 11.1 ± 1.9 g/L AUC_{ss} 160.1 ± 43.6 g • day/L Clearance 0.07 ± 0.02 L/day Volume of distribution: 3.7 ± 1.4 L
I (None) Open	12 patients 22 to 66 years 4 males 8 females	Primary, severe hypogamma-globulinaemia, under treatment with IgG so plasma concentration > 4 g/L, no increased liver enzymes, no HIV	Single dose of Octagam 5% 400 mg/kg IV	$t_{½}$ 30.7 days ± 4.0

ITP = Immune thrombocytopenic purpura; CCL = Chronic lymphocytic leukemia
PAPS = Primary antiphospholipid syndrome; MM = Multiple myeloma

Pivotal Multiple Dose Pharmacokinetic Studies

In the pivotal US pharmacokinetics study, Study OCTA-06, a subset of 14 patients aged between 10 and 70 years with PID underwent pharmacokinetic assessment as part of the protocol.[30] Patients received infusions of OCTAGAM (400 to 600 mg/kg IV) every 3 to 4 weeks for 12 months. Pharmacokinetic analysis of total IgG, IgG subclasses and selected antigen-specific antibodies were performed on these patients. Pharmacokinetic samples were collected at baseline and after the 5th month of treatment (after the 5th infusion for patients on a 28-day infusion schedule, and after the 7th infusion for patients on a 21-day infusion schedule).

For patients on the 21-day infusion schedule, the mean total IgG concentration at 15 minutes post-infusion was 1,453.3 mg/dL; the mean concentration decreased steadily to a value of 768.8 at 28 days post-infusion, a decrease of approximately 47%. For patients on the 28-day infusion schedule, the mean total IgG concentration 15 minutes post-infusion was 1,762.5 mg/dL; the

mean concentration decreased steadily to a value of 789.4 at 28 days post-infusion, a decrease of approximately 55%. For all post-infusion time points except 21 days post-infusion, total IgG levels were higher for patients on the 28-day infusion schedule than those on the 21-day infusion schedule. The decreases in IgG subclass levels generally followed a trend similar to that observed for the Total IgG levels.

Table 4: Serum Levels of Total IgG (mg/dL) Over Time for Octa-06

	Infusion Schedule			
	21-Day		**28-Day**	
Time Post Infusion	**Mean**	**S.D.**	**Mean**	**S.D.**
15 min	1,453.3 (n=6)	293.7	1,762.5 (n=8)	308.8
28 days	768.8 (n=6)	183.1	789.4 (n=8)	134.2

For Total IgG, the mean C_{max} was 1,661 mg/dL, the mean T_{max} was 0.3 days, the mean AUC was 29,258 day•mg/dL, and the estimated serum half-life was 40.7 days. There were 2 patients for whom T_{max} was much higher than for the other patients. Patient 06/16 had a T_{max} of 0.9 days, and Patient 06/33 had a T_{max} of 2.9 days; the next highest value for T_{max} was 0.04 days (approximately 1 hour). Thus, it is appears that these 2 patients were responsible for the seemingly high value of T_{max} for total IgG reported above. For IgG subclasses 1, 2, and 3, the mean T_{max} was approximately 0.08 days (approximately 2 hours); for IgG subclass 4, the mean T_{max} was 0.7 days (approximately 16 hours). The reason for this apparent delay in the time to reach C_{max} for IgG_4 is not known. The mean estimated serum half-lives for IgG_1 and IgG_3 were approximately 26-27 days, and the mean estimated serum half-lives for IgG_2 and IgG_4 were approximately 38-40 days. The reason for this noticeable difference is not known.

In Study X, which is also pivotal in terms of pharmacokinetics, 16 of 17 patients (10 to 17 years old) with PID syndromes were investigated (1 dropped out prematurely, and was not included in the pharmacokinetic analysis). During the treatment period, patients received 9 cycles of OCTAGAM 200 to 400 mg/kg every 3 weeks. In addition to the baseline sample, 2 samples were obtained before and after each administration. After the last infusion of OCTAGAM several pharmacokinetic samples were taken over 3 weeks.

During the treatment period, the average C_{max} in steady state ($C_{ss\ max}$) was 11.1 ± 1.9 g/L; the average trough level ($C_{ss\ min}$) was 6.2 ± 1.8 g/L. The average difference between the trough level and the maximal level after infusion was 4.9 ± 0.9 g/L.

Terminal half-life of total IgG was 35.9 ± 10.8 days with a median of 34.0 days. The half-lives of the sub-classes (mean and standard deviation) were 36.3 ± 9.2 days (median 37.8) for IgG_1,37.1 ± 13.9 days (median 32.1) for IgG_2, 28.6 ± 10.4 days (median 27.6) for IgG_3 and 15.6 ± 4.5 days (median 16.4) for IgG_4. The volume of distribution for the total IgG was 3.7 ± 1.4 L and the total body clearance was 0.07 ± 0.02 L/day.

Single Dose Pharmacokinetic Studies

Study I included 12 adult patients with primary hypogammaglobulinemia. Single doses were given to assess the pharmacokinetics and tolerability of OCTAGAM 400 mg/kg. The mean IgG half-life of 30.7 ± 4.0 days was similar to that of other IGIV products. The mean IgG concentration before the infusion was 8.9 ± 2.5 g/L. After the infusion, serum IgG reached a peak of 17.6 ± 2.3 g/L at day 2, which then slowly declined within 28 days. Regarding IgG subclasses, the IgG_1, IgG_2 and IgG_3 levels increased significantly after OCTAGAM infusion. A half-life could not be calculated for IgG_4.

It was shown that the pharmacokinetics of immunoglobulins follow 2-phase decay curves with an α- and a β-phase. The rapid α-phase represents a re-distribution of IgG to various body compartments and the slower β-phase represents the catabolism of the protein.

The half-lives calculated for total IgG and the relevant IgG subclasses were similar to what is reported for other preparations. The weakness of the study is the fact that all patients received another IGIV brand about 1 week prior to OCTAGAM treatment and a carry-over effect cannot be excluded. However, in a later study (Study X) these results were confirmed and therefore the conclusions drawn from this study are valid.

Human Pharmacodynamics

IGIVs contain mainly IgG with a broad spectrum of antibodies against various infectious agents.

OCTAGAM contains all the IgG activities that are present in the normal population. It is prepared from material from at least 3,500 donors. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to normal range.

Results of *in vitro* studies suggest that OCTAGAM preparations may provide passive, IgG-mediated protection against candida, *H. influenzae* and *pneumococci*, which can be especially important in patients with primary or secondary gammaglobulin deficiency.

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

In vitro investigations give evidence that different mechanisms are responsible for the clinical effects of IGIV in many diseases with auto-immune pathogenesis, such as the induction of cytokines, soluble cytokine receptors and cytokine receptor antagonist with anti-inflammatory properties. Furthermore, *in vitro* studies have shown phagocytic cell stimulation by IGIV, inhibition of complement-mediated red cell lysis and down-modulation of lymphocyte proliferation and ROS (reactive oxygen species) generation from monocytes.[36-38] In HIV-1 infected patients, IGIV administration has been shown to down-modulate an increased tumour necrosis factor alpha (TNF-α) activity. All these effects may contribute to the immunomodulating effects of IGIV preparations. In a pig-to-human *ex vivo* perfusion model of kidney xeno-transplantation, OCTAGAM was shown to prolong kidney survival when added to the human blood perfusate. This effect may be mediated by modulation of complement

activation. The results of this study give evidence that IGIV may be useful to dampen hyper-acute rejection.[39]

TOXICOLOGY

Animal Toxicity Studies

IgG is a normal constituent of the human organism. In animals, single dose toxicity testing is of no relevance since the high doses required would result in IgG overload. Repeated dose toxicity testing, and embryo-foetal toxicity studies with immunoglobulin preparations are impracticable due to the induction of, and the interference with antibodies. Effects of the preparation on the immune system of new-born animals have not been studied.

Since the clinical experience does not provide any evidence of tumorigenic or mutagenic effects of IgG, experimental studies, particularly in heterologous species, are not considered to be necessary.

The preclinical evaluation of OCTAGAM was, therefore, limited to the evaluation of its safety with respect to impurities that are derived from the manufacturing process. The level of impurities is controlled by the manufacturing process specifications on raw materials, by in-process controls, and by the final product specification. The two contaminants resulting from the manufacturing process are TNBP and Triton X-100, used as S/D reagents for virus inactivation. A program of studies has been carried out to assess the toxicological effect of these compounds.

Single Dose Toxicity

The acute toxicity of TNBP + Triton X-100 in a mixture ratio of 1 + 5 was carried out in rats using IV injection, the proposed route of administration to humans. The picture of toxicity after a single IV injection was essentially characterized by ataxia, dyspnoea, reduced motility, reduced muscular tonus, tonic convulsions, abdominal or lateral position, and mydriasis. No pathological changes caused by the substances were revealed during dissection of the animals that died prematurely or those which survived. There was no evidence of a gender-specific susceptibility.

After a single intra-peritoneal application of TNBP + Triton X-100 in the ratio of 1 + 20, but also of the individual substances, the picture of toxicity corresponded to that after IV injection. There were no differences in sensitivity between mature and newborn rats after a single intra-peritoneal administration of TNBP + Triton X-100 (1 + 5).

Repeated Dose Toxicity

TNBP and Triton X-100 were administered daily by IV injection to rats and dogs for a period of 13 weeks. Three dose levels were used for each species.

Rat: 12 µg TNBP/kg + 60 µg Triton X-100/kg

60 µg TNBP/kg + 300 µg Triton X-100/kg

300 µg TNBP/kg + 1,500 µg Triton X-100/kg

Dog: 13 µg TNBP/kg + 65 µg Triton X-100/kg

50 µg TNBP/kg + 250 µg Triton X-100/kg

500 µg TNBP/kg + 2,500 µg Triton X-100/kg

At the low dose, no signs of local or systemic intolerance reactions were observed. With the medium and high doses, local damage was observed at the injection sites including discoloration, induration and necrosis in the rats, and swollen and/or indurated veins in the dogs. Within both species, an injection of the higher dose was not possible after the 7th or 8th week.

These local intolerance findings have no clinical relevance for the use of OCTAGAM in humans, since the final product contains only a maximum of one sixth of the locally toxic concentration used in the animal experiment. Furthermore, these findings were observed under extreme conditions, i.e. a daily administration for 13 weeks. Due to the fast dilution of OCTAGAM in the circulation, there is a further dilution factor during clinical use of more than a thousand fold.

There were no systemic changes caused by the substances in the rats. No differences compared with the control group were detected in dogs, apart from slight haematological changes, i.e., reduced haematocrit, haemoglobin and erythrocytes, and an increased erythrocyte sedimentation rate.

The literature contains reports of *in vitro* tests in which Triton X-100 was tested for its cytotoxic effects on human fibroblasts. Triton X-100 was shown to be moderately toxic. An obvious reduction in the toxicity of Triton X-100 in human fibroblast cultures could be observed with increasing serum protein content.

In the subchronic *in vivo* tests described above and also in the tests for cytotoxicity included in the pilot tests for the mutagenicity studies, no evidence of toxicologically significant cell damage was observed.

In vitro, Triton X-100 inhibits enzyme activity in the cell-free system. The IC50 was in the region of 25 ppm. Due to the rapid dilution of the residual amounts of Triton X-100 in OCTAGAM when infused *in vivo*, these *in vitro* findings appear to be toxicologically not relevant.

There is no evidence that the residual amounts of TNBP or Triton X-100 in the doses likely to be administered during the clinical use of OCTAGAM would affect the blood or blood components in patients.

Reproductive Toxicity

A study of the embryotoxic and teratogenic properties of TNBP and Triton X-100 was carried out in rats and rabbits.

Rat: 100 µg TNBP/kg + 500 µg Triton X-100/kg

300 µg TNBP/kg + 1,500 µg Triton X-100/kg

900 µg TNBP/kg + 4,500 µg Triton X-100/kg

Rabbit: 50 µg TNBP/kg + 250 µg Triton X-100/kg

150 µg TNBP/kg + 750 µg Triton X-100/kg

400 µg TNBP/kg + 2,250 µg Triton X-100/kg

No test was made on the fertility and breeding efficiency, or the peri- or post-natal development since there was no evidence of any effect on the reproductive organs by the substances.

In rats, some malformations occurred, but these were of a type commonly occurring in control animals of this species. No malformations were seen in rabbits.

Pre-natal development was not affected in rats. In the high-dose group in rabbits, the resorption rate was slightly increased and the foetus weights reduced.

Genotoxicity

TNBP and Triton X-100 (1+ 5) were tested in vitro (Ames test, HPRT test) and in vivo (rats; chromosomal analysis, micronucleus test). The SCE test (in vitro) and the micronucleus test in mice were performed for TNBP alone. No indication of mutagenic properties was observed.

There are also no reports on mutagenicity of TNBP or Triton X-100 in the literature.

Carcinogenicity

No evidence of a carcinogenic potential of TNBP + Triton X-100 was observed in the subacute toxicity and mutagenesis studies already described. No specific studies were carried out since the therapeutic administration to humans is carried out in intervals of several weeks only and hence TNBP and Triton X-100 are passed to humans in correspondingly small quantities.

Immunotoxicity

The toxicological studies performed by the applicant gave no indication of sensitising properties of TNBP and/or Triton X-100 and this is in accordance with the existing literature.

REFERENCES

1. Committee for Proprietary Medicinal Products. Guidelines to Assess Efficacy and Safety of Normal Intravenous Immunoglobulin Products for Marketing Authorisations (CPMP/388/95). Feb. 1996.

2. Committee for Proprietary Medicinal Products. Note for Guidance on Core SPC for Human Normal Immunoglobulin (I.V.) (CPMP/859/95). Mar. 1997.

3. Keller T, McGrath K, Newland A, et al: Indications for use of intravenous immunoglobulin. Recommendations of the Australasian Society of Blood Transfusion consensus symposium. Med.J.Aust. 1993;159:204-206.

4. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N.Engl.J.Med. 1988;319:902-907.

5. Griffiths H, Brennan V, Lea J, et al: Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood 1989;73:366-368.

6. Chapel HM, Hargreaves R, Lee M, et al: Intravenous immunoglobulin therapy in patients with multiple myeloma. Immunodeficiency 1993;4:77-78.

7. AnonymousRecommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins for persons with altered immunocompetence. MMWR.Morb.Mortal.Wkly.Rep. 1993;42:1-18.

8. Calvelli TA, Rubinstein A: Intravenous gamma-globulin in infant acquired immunodeficiency syndrome. Pediatr.Infect.Dis. 1986;5:S207-S210.

9. Hague RA, Yap PL, Mok JY, et al: Intravenous immunoglobulin in HIV infection: evidence for the efficacy of treatment. Arch.Dis.Child 1989;64:1146-1150.

10. Mofenson LM, Moye J, Jr.: Intravenous immune globulin for the prevention of infections in children with symptomatic human immunodeficiency virus infection. Pediatr.Res. 1993;33:S80-S87.

11. Dalakas MC: High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology 1994;44:223-226.

12. Harkness K, Howell SJ, Davies-Jones GA: Encephalopathy associated with intravenous immunoglobulin treatment for Guillain-Barre syndrome. J.Neurol.Neurosurg.Psychiatry 1996;60:586-

13. Reinhart WH, Berchtold PE: Effect of high-dose intravenous immunoglobulin therapy on blood rheology. Lancet 1992;339:662-664.

14. Silbert PL, Knezevic WV, Bridge DT: Cerebral infarction complicating intravenous immunoglobulin therapy for polyneuritis cranialis. Neurology 1992;42:257-258.

15. Woodruff RK, Grigg AP, Firkin FC, et al: Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. Lancet 1986;2:217-218.

16. Shah S, Vervan M: Use of i.v. immune globulin and occurrence of associated acute renal failure and thrombosis. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2005;62:720-725.

17. Ahsan N: Intravenous immunoglobulin induced-nephropathy: a complication of IVIG therapy. J Nephrol 1998;11:157-161.

18. Brannagan TH, III, Nagle KJ, Lange DJ, et al: Complications of intravenous immune globulin treatment in neurologic disease. Neurology 1996;47:674-677.

19. Cayco AV, Perazella MA, Hayslett JP: Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. J Am Soc.Nephrol 1997;8:1788-1794.

20. Schifferli JA: High-dose intravenous immunoglobulin treatment and renal function; in Dominioni L, Nydegger UE (eds): Intravenous immunoglobulins today & tomorrow. London, Royal Society of Medicine Services Ltd., 1992, pp 27-33.

21. Copelan EA, Strohm PL, Kennedy MS, et al: Hemolysis following intravenous immune globulin therapy. Transfusion 1986;26:410-412.

22. Thomas MJ, Misbah SA, Chapel HM, et al: Hemolysis after high-dose intravenous Ig. Blood 1993;82:3789-

23. Wilson JR, Bhoopalam H, Fisher M: Hemolytic anemia associated with intravenous immunoglobulin. Muscle Nerve 1997;20:1142-1145.

24. Kessary-Shoham H, Levy Y, Shoenfeld Y, et al: In vivo administration of intravenous immunoglobulin (IVIg) can lead to enhanced erythrocyte sequestration. J.Autoimmun. 1999;13:129-135.

25. Enokibori M, Kuge M, Mori K: Anaphylactoid reaction to maltose 5% solution during spinal anaesthesia. Can.J Anaesth. 1998;45:52-55.

26. Guharoy SR, Barajas M: Probable anaphylactic reaction to corn-derived dextrose solution. Vet.Hum.Toxicol. 1991;33:609-610.

27. Kannan S, Rowland CH, Hockings GI, et al: Intragam can interfere with blood glucose monitoring. Med J Aust. 2004;180:251-252.

28. Medicines and Healthcare Products Regulatory Agency: Medical Device Alert. 16-4-2003; http://www.mhra.gov.uk

29. Roche Diagnostics: Accu-Chek test strips package insert. 2005; www.accu-chek.com/us

30. Ochs HD, Pinciaro PJ, The Octagam Study Group: Octagam((R)) 5%, an intravenous IgG product, is efficacious and well tolerated in subjects with primary immunodeficiency diseases. J Clin Immunol 2004;24:309-314.

31. Medicines and Healthcare Products Regulatory Agency: Medical Device Alert. 16-4-2003; http://www.mhra.gov.uk

32. Stiehm RE: Conventional Therapy of Primary Immunodeficiency Diseases; in Ochs H, Smith CI, Puck JM (eds): Primary Immunodeficiency Diseases: a Molecular and Genetic Approach. New York, Oxford Univ. Press, 1999, pp 448-458.

33. Cunningham-Rundles C, Siegal FP, Smithwick EM, et al: Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. Ann.Intern.Med. 1984;101:435-439.

34. Nolte MT, Pirofsky B, Gerritz GA, et al: Intravenous immunoglobulin therapy for antibody deficiency. Clin.Exp.Immunol. 1979;36:237-243.

35. Morell A, Schurch B, Ryser D, et al: In vivo behaviour of gamma globulin preparations. Vox Sang. 1980;38:272-283.

36. Aukrust P, Froland SS, Liabakk NB, et al: Release of cytokines, soluble cytokine receptors, and interleukin-1 receptor antagonist after intravenous immunoglobulin administration in vivo. Blood 1994;84:2136-2143.

37. Aukrust P, Muller F, Nordoy I, et al: Modulation of lymphocyte and monocyte activity after intravenous immunoglobulin administration in vivo. Clin.Exp.Immunol. 1997;107:50-56.

38. Aukrust P, Muller F, Svenson M, et al: Administration of intravenous immunoglobulin (IVIG) in vivo--down-regulatory effects on the IL-1 system. Clin Exp Immunol 1999;115:136-143.

39. Fiane AE, Videm V, Mellbye OJ, et al: Immunoglobulin prolongs survival of pig kidneys perfused ex vivo with human blood. Scand.J.Immunol. 1998;47:568-574.
40. Tunis MC, Salvadori MI, Dubey V, Baclic O. Updated NACI recommendations for measles post-exposure prophylaxis, CCDR 2018; volume 44-9

PART III: CONSUMER INFORMATION

OCTAGAM 5%
[Immunoglobulin Intravenous (Human)]

This leaflet is part III of a three-part "Product Monograph" published when OCTAGAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OCTAGAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
OCTAGAM is used for replacement therapy in the following:
Primary immunodeficiency (PID) syndromes
- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiencies

Secondary immunodeficiency syndromes
- secondary hypogammaglobulinaemia in patients with chronic lymphocytic leukaemia (CLL), or multiple myeloma (MM) with recurrent infections
- children with congenital AIDS who have bacterial infections

What it does:
The mechanism of action in indications other than replacement therapy is not fully understood, but includes immunomodulatory effects.
This product can help prevent infections by providing a protective role in diseases where patients suffer from a poorly functioning immune system.
When it should not be used:
OCTAGAM should not be used if:
- You have a history of an allergic reaction to any human immunoglobulin preparation.
- You have immunoglobulin A (IgA) deficiency, with known antibodies against IgA.
- You are allergic to any of the components of the preparation.

What the medicinal ingredient is:
Immunoglobulin Intravenous (Human), 5%

What the important nonmedicinal ingredients are:
Maltose, Triton X-100, TNBP, Water for Injections, IgA

What dosage forms it comes in:
OCTAGAM is a 50 mg/mL solution for intravenous infusion and comes in the following dosage forms:
1 infusion bottle with 50 mL
1 infusion bottle with 100 mL
1 infusion bottle with 200 mL
1 infusion bottle with 500 mL

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
As with all Immunoglobulin Intravenous formulations this product is made from human plasma, which may contain the infectious agents such as viruses that cause hepatitis and other viral diseases. Stringent steps are in place during the collection of human plasma and product manufacturing to ensure the viral safety of human plasma based products. In the particular case of OCTAGAM 5% viral safety has been increased by having included two steps of viral inactivation/removal in the manufacturing process. Your doctor should discuss the risks and benefits of this product with you before giving you this product.

Warning: Thromboembolic events
- Thromboembolic events such as heart attack, stroke, and obstructions of a deep vein e.g. in the calves or of a blood vessel in the lung (pulmonary embolism) may occur with administration of human immunoglobulin intravenous (IGIV) products.
- Thromboembolic events occur more commonly in patients with pre-existing risk factors for thrombo-embolism receiving IGIV products.

  In general the risk factors for thromboembolic events include: obesity; advance age; hypertension; diabetes mellitus; previous events of heart attack, stroke, and obstructions of a deep vein etc.; prolonged periods of immobilisations; intake of certain hormones (e.g. the pill);.
- Thrombosis may occur even in the absence of known risk factors.
- In the particular case of OCTAGAM 5% specific additional measures have been implemented to reduce the risk of thromboembolic events and to ensure the quality and therefore the safe use of OCTAGAM. Nevertheless, patients with known risk factors should ensure a balanced fluid intake; moreover the product needs to be administered at a slow speed.

BEFORE you use OCTAGAM talk to your doctor or pharmacist if:
- You recently have heart disease or have had blood clots.
- If you are pregnant or nursing.
- You have the following risk factors: kidney disease diabetes mellitus, seriously dehydrated, overweight, take kidney damaging medications or over the age of 65.
- You are allergic to the active substance or to any of the nonmedicinal ingredients.
- You have a history of allergy to corn products.
- You use any device to measure blood or urine glucose, as the maltose in this product may interfere with these measurements.

INTERACTIONS WITH THIS MEDICATION

There is no known drug interaction to OCTAGAM. OCTAGAM administration may slow the protection of live attenuated viral vaccines such as measles, mumps, rubella and varicella for at least six weeks, and possibly up to three months or longer.
The infusion line may be flushed before and after administration of OCTAGAM with either normal saline or 5% dextrose in water.
Components used in the packaging of OCTAGAM are latex-free.

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor will determine the dose(s) of OCTAGAM that you are to receive as an infusion, which is an injection given slowly in a vein. The dose you receive will depend on your clinical situation and disease, but the following are a generally accepted starting dose of OCTAGAM:
Primary Immunodeficiencies – Monthly doses of at least 100 mg/kg are recommended.
Secondary Immunodeficiencies – The recommended dose is 0.2 - 0.4 g/kg body weight every 3 – 4 weeks.

It is recommended that OCTAGAM be infused at a rate of 30 mg/kg/hour for the first 30 minutes; if tolerated, advanced to 60 mg/kg/hour for the second 30 minutes; and if tolerated, advanced to 120 mg/kg/hour for the third 30 minutes. Thereafter the infusion could be maintained at a rate up to, but not exceeding, 200 mg/kg/hour.
Filtration of OCTAGAM is not required.

Overdose:
Overdose is possible in patients that are overweight, elderly, or those with impaired kidney function.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Centre immediately, even if there are no symptoms.

Missed Dose:
Not applicable.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include: rigors (chills), fever, headache, muscle pain including back or chest pain, flushing, nausea, allergic reactions (such as changes in blood pressure, difficulty breathing a blue discoloration of the skin or mucous membranes, fast heart rate), dizziness, fatigue, drowsiness, skin reactions (such as rash, itching, hives), temporary meningitis (reversible aseptic meningitis), temporary decrease of red blood cells (reversible haemolytic anaemia/haemolysis), abdominal pain, diarrhoea and vomiting.
The following symptoms may be signs of thromboembolic events: chest pain or pressure, vision or speech disorder, one-sided paralysis/weakness, movement disorder, pain or tenderness in leg(s) or calf(s), swelling in calf(s) or lower leg(s) or cyanosis. If any of those symptoms occur, please talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	allergic type of reaction		T	T
	headache	T		T
	nausea	T		T
	fever	T		
Uncommon	skin reactions incl. hives		T	T
	back or chest pain		T	T
	chills		T	T
Very rare	shock		T	T
	swelling of tongue or face		T	T
	migraine		T	T
	dizziness	T		T
	heart pain		T	T
	beating of the heart		T	T
	fall or increased blood pressure		T	T
	difficulties in breathing or cough		T	T
	vomiting		T	T
	diarrhoea		T	T
	belly pain		T	T

This is not a complete list of side effects. For any unexpected effects while taking OCTAGAM, contact your doctor or pharmacist.

HOW TO STORE IT

Store refrigerated or at room temperature (+2 °C to +25 °C). Warm up to room or body temperature before use. Do not freeze. Protect from light. Discard any remaining contents after use. Do not use after expiry date.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.octapharma.com
or by contacting Octapharma Canada Inc.,
at: 1-888-438-0488

This leaflet was prepared by Octapharma Pharmazeutika Produktionsges.m.b.H

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