PRODUCT MONOGRAPH

OCTAGAM® 10%

Immune Globulin Intravenous (Human)
Solution for Infusion, 100 mg/mL
Prescription Medication, passive immunizing agent
Presentation sizes: 20 mL, 50 mL, 100 mL and 200 mL
ATC Code: JO6BA

Manufactured by:

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OCTAGAM® 10%

Immune Globulin Intravenous (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Injection	Solution for Infusion, 20, 50, 100 and 200 mL Each mL contains 100 mg protein, of which ≥ 96% is immunoglobulin G (IgG)	IgA *For a complete listing see* DOSAGE FORMS, COMPOSITION AND PACKAGING *section.*

DESCRIPTION

OCTAGAM® 10% 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 10% 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 (see WARNINGS AND PRECAUTIONS section).

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 10% is indicated for:

Immune thrombocytopenic purpura (ITP) patients at high risk of bleeding or prior to surgery to correct the platelet count. Clinical data on pediatric patients (< 18 years old) is limited. (See CLINICAL TRIAL section).

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 administering 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 infectious 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.[1-5] The potential risks

and benefits of IGIV treatment should be weighed against those of alternative therapies for all patients for whom OCTAGAM 10% 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.[6]

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.[7-10]

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.[11-13] Haemolytic anaemia can develop subsequent to IGIV therapy due to enhanced red blood cells (RBC) sequestration (see ADVERSE REACTIONS)[14]. 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.[15]

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. The number of elderly patients studied in clinical trials is limited.

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.[16,17]

Urine Glucose Testing: About 5% of intravenously administered maltose is excreted via the urine as glucose or maltose.[16] 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 chylomicronaemia/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.[18] The objectives were to assess the safety, pharmacokinetics, and therapeutic efficacy of OCTAGAM 5% as replacement therapy in PID. Forty-six patients received 654 infusions of OCTAGAM 5% (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 5% 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.

Study GAM10-02

This was a prospective, open-label, single-arm, multi-center study 116 subjects with newly diagnosed or chronic ITP. Subjects received OCTAGAM 10% at a dose of 2 g/kg, administered daily as two 1 g/kg doses, given intravenously on 2 consecutive days. Fifty-four (47%) subjects received OCTAGAM 10% at the maximum infusion rate allowed (12 mg/kg/min [0.12 mL/kg/min]).

Of the 238 temporally associated AEs reported for 92 subjects, the investigators judged 129 (54%) (in 62 patients) to be at least possibly related to the infusion of OCTAGAM 10%. Most of the AEs related to the infusion of OCTAGAM 10% were mild (n=105, 81%), 24 were moderate, and none was severe. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (25% of subjects), pyrexia (15% of subjects), and increased heart rate (11% of subjects).

Abnormal Haematologic and Clinical Chemistry Findings

In the ITP study (GAM10-02), there were no significant changes in haematological parameters (haemoglobin, haematocrit, red and white blood cells) over the study period, other than platelets.

Five patients had clinically relevant, transient increases in ASAT and ALAT. These changes were judged to be possibly related to OCTAGAM 10% in 2 patients and unrelated in 3 patients.

Nine patients had a negative direct Coombs test at baseline but subsequently became positive after treatment. Of these, haemolysis was documented in a single patient but was judged by the investigator to be unrelated to the study drug. In this individual patient, an episode of severe bleeding unrelated to study drug may have caused or contributed to aggravation of the ITP-related anaemia that was pre-existing at study enrolment*;* the remaining 8 patients had no clinical signs of haemolysis.

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 edema; face edema
Psychiatric disorders	agitation

System Organ Class (MedDRA Terminology)	Reported ADRs
Nervous system disorders	headache; cerebrovascular accident; meningitis aseptic; migraine; dizziness; paraesthesia
Cardiac disorders	myocardial infarction; tachycardia; palpitations; cyanosis
Vascular disorders	thrombosis; peripheral circulatory failure; hypotension; hypertension
Respiratory, thoracic and mediastinal disorders	respiratory failure; pulmonary embolism; pulmonary edema; 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 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.

Heamolytic anemia / 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).[16,17]

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

Patients should have adequate hydration prior to the infusion of OCTAGAM 10%. In patients at risk, OCTAGAM 10% should be administered at the minimum rate of infusion and dose practicable.
Risk factors should be identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medications, or over the age of 65.

Patients should be observed for at least 20 minutes after administration.

Recommended Dose and Dosage Adjustment

Immune modulatory treatment in ITP: OCTAGAM 10% to be administered at a total dose of 2 g/kg, divided into two doses of 1 g/kg (10mL/kg) given on two consecutive days. Treatment can be repeated if relapse occurs.

Missed Dose

A missed dose should be administered as soon as possible.

Administration

Treatment of ITP:

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

It is recommended that OCTAGAM 10% should be intravenously administered initially at a rate of 1 mg/kg per minute (0.01 mL/kg per minute) for the first 30 minutes. If well-tolerated, the rate may be gradually increased to a maximum of 12 mg/kg per minute (0.12 mL/kg per minute). If side effects occur, the rate may be reduced, or the infusion interrupted until symptoms subside. The infusion may then be resumed at the rate, which is comfortable for the patient. Caution should be exercised when OCTAGAM 10% is administered for the first time.

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.

Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue OCTAGAM 10% liquid if renal function deteriorates.

For patients at risk of renal dysfunction or thromboembolic events, administer OCTAGAM 10% liquid at the minimum infusion rate practicable.

Parenteral Products

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 +8 °C for 23 months from the date of manufacture. Within this shelf-life the product may be stored up to 9 months at ≤ 25°C. After the storage at ≤ 25°C the product must be used or discarded.

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

The mechanism of action of IGIVs in the treatment of ITP is not fully understood. One possible mechanism may be the inhibition of the elimination of autoantibody-reacted platelets from the blood circulation by IgG-induced Fc-receptor blockade of phagocytes. Another proposed mechanism is the down-regulation of platelet autoantibody-producing B cells by anti-idiotypic antibodies in IGIV. [19,20]

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.[21-23]

Pharmacokinetics

The pharmacokinetics of OCTAGAM has not been formally studied in ITP patients.

Several clinical studies were specifically designed to examine the pharmacokinetics of OCTAGAM 5% after single or repeated doses in Primary Immune Deficiency patients.

Table 1 provides an overview of these studies. 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 5% in PID patients

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 5% are obtained within 30 minutes in Primary Immune Deficiency patients. 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.[24]

High concentrations of IGIV and hyper-metabolism associated with fever and infection may shorten the half-life.[24]

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 +8 °C for 23 months from the date of manufacture. Within this shelf-life the product may be stored up to 9 months at ≤ 25°C. After the storage at ≤ 25°C the product must be used or discarded.

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 10% is a 100 mg/mL solution for intravenous infusion.

The following marketed dosage forms are available:

1 infusion bottle with 20 mL – 2 g protein

1 infusion bottle with 50 mL – 5 g protein

1 infusion bottle with 100 mL – 10 g protein

1 infusion bottle with 200 mL – 20 g protein

Nature and Contents of Container:

Each 100 mg/mL of OCTAGAM 10% contains the active ingredients: Immune Globulin Intravenous (Human), one millilitre (mL) of solution contains 100 mg of protein of which ≥ 96% is gammaglobulin. Each package contains 1 glass bottle of OCTAGAM 10% ready to use and the package leaflet.

Quantitative composition:	**per mL**
Human normal immunoglobulin G (IgG)	100 mg
Maltose	90 mg
Triton X-100	5 µg
TNBP	1 µg
Water for injections	1 mL
IgA	≤ 0.4 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- Proper name: OCTAGAM® 10%, Immune Globulin 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 10%. 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 10% 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

Table 2 summarizes the clinical study that has been completed in patients with ITP.

Table 2: Results of Clinical Studies in ITP Patients

Study No. (Protocol) Design	Dosage, route of administration and duration	Number of Subjects Gender (Age range)	Primary Endpoint	Results
GAM10-02 Open label	Octagam 10% 1g/kg per day on 2 consecutive days, given IV	116 patients 42 male, 74 female (17–88 years)	Response rate: Increase in platelet count to $\geq 50 \times 10^9$/L within 7 days after treatment	Overall response rate of 80%.

According to original trial design and endpoint definition the clinical response (i.e. increase in platelets to at least 50×10^9/L within 7 days) was 82% in *chronic* ITP patients.

The results of Study GAM10-02 were re-analysed post-hoc after using the following revised definitions of “clinical response”.

Definition of "Clinical Response"	# (%) of chronic ITP patients with "Clinical Response"
Standard efficacy endpoint: •Increase of platelet count to ≥50 x 10^9/L within 7 days	53/65 (81.5%)
Additional Post Hoc analyses conducted outside the original study design showed the following results:	
Post Hoc re-analysis 1: • Increase of platelet count to ≥50x10^9/L within 7 days • No prohibited medication • No start or increase in dose of Etamsylate during first 7 days • No withdrawal from the study within the first 7 days • Regression of bleeding	49/65 (75.4%)
Post Hoc re-analysis 2: • Increase of platelet count to ≥50x10^9/L within 7 days • No prohibited medication • No Etamsylate* • No withdrawal from the study within the first 7 days • Regression of bleeding	37/66 (56.1%)

* Etamsylate is a synthetic haemostatic drug that was used exclusively in study sites in Poland and the Czech Republic. It was not a forbidden therapy in Study GAM10-02 and has no effect on platelet counts. A sub-analysis did not show a confounding effect on bleeds (39% of subjects who received Etamsylate had no bleeds at study day 3 versus 63% of subjects who did not receive Etamsylate).

In Study GAM10-02, 14 subjects experienced SAEs. All SAEs except one (headache) were unrelated to study drug. Five out of 14 subjects were ITP recurrences. Two patients were hospitalised for reasons other than ITP and thrombocytopenia was detected by routine laboratory testing. In 8 subjects ITP recurrences were reported as non-serious AEs. Only one case of ITP recurrence led to study withdrawal. 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 for 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 faeces were determined.

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

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

The pharmacokinetics of OCTAGAM has not been formally studied in ITP patients.

Pharmacokinetic studies performed in patients suffering from primary immunodeficiency (PID) have shown that OCTAGAM 5% is immediately and completely bioavailable in the recipients' circulation after intravenous administration. OCTAGAM 5%, like other IgG products is distributed rapidly between plasma and extravascular fluids. After approximately 3 to 5 days, equilibrium is reached between the intravascular and extravascular compartments. OCTAGAM 5% has a mean half-life of about 40 days when measured in PID patients. However, the half-life may vary from patient to patient.[24-26]

Human Pharmacodynamics

The mode of action of IVIG in autoimmune diseases is not well understood, although several mechanisms have been proposed.[27-29]

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, therefore, focused on 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. TNBP and Triton X-100 are used as S/D reagents for virus inactivation. A program of studies has been carried out to assess the toxicological effect of these compounds. In addition, a study on local tolerance of OCTAGAM 10% was performed.

Single Dose Toxicity

The acute toxicity of TNBP + Triton X-100 in a mixture ratio of 1 + 5 was carried out in rats using i.v. injection, the intended route of administration to humans. The lowest toxic dose of this mixture was 10 mg/kg BW. The picture of toxicity after a single i.v. 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 i.v. 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 i.v. 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 7^{th} or 8^{th} 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 substance-related 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.

Local Tolerance

A study with i.v. (10 mL/animal within 60 minutes), intra-arterial (10 mL/animal within 10 minutes) and paravenous (0.5 mL/animal as bolus injection) administration of OCTAGAM 10% was performed in 4 rabbits per group. Isotonic saline was given correspondingly to each animal at the contra-lateral site and served as a negative control. Animals were observed for 72 hours. Thereafter rabbits were sacrificed and histological evaluation was performed.
OCTAGAM 10% was well tolerated after i.v. and intra-arterial administration, and showed a borderline irritative effect comparable to that on the control ear after paravenous injection.

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 mutagenicity studies already described.

Immunotoxicity

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

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PART III: CONSUMER INFORMATION

OCTAGAM 10%
[Immune Globulin Intravenous (Human)]

This leaflet is part III of a three-part "Product Monograph" published when OCTAGAM 10% 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 10%. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

OCTAGAM 10% is used for:
Immune thrombocytopenic purpura (ITP) patients at high risk of bleeding or prior to surgery to correct the platelet count.

What it does:
The mechanism of action therapy is not fully understood, but includes modulatory effects of the immune system.

When it should not be used:
OCTAGAM 10% 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:
Immune Globulin Intravenous (Human), 10%

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

What dosage forms it comes in:
OCTAGAM 10% is a 100 mg/mL solution for intravenous infusion and comes in the following dosage forms:
1 infusion bottle with 20 mL
1 infusion bottle with 50 mL
1 infusion bottle with 100 mL
1 infusion bottle with 200 mL

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

As with all Immune Globulin 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 10% 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 thromboembolism 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 10% 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 10% 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 10%.
OCTAGAM 10% 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 10% with either normal saline or 5% dextrose in water.
Components used in the packaging of OCTAGAM 10% are latex-free.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will determine the dose(s) of OCTAGAM 10% 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 10%:
Immune modulatory treatment in ITP – 2 g/kg divided into two doses of 1 g/kg (10 mL/kg) given on two consecutive days. Treatment can be repeated if relapse occurs.
Filtration of OCTAGAM 10% 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 10%, contact your doctor or pharmacist.

HOW TO STORE IT

Store refrigerated (+2 °C to +8 °C) for up to 23 months. Within this shelf-life the product may be stored up to 9 months at ≤ 25°C. After the storage at ≤ 25°C the product must be used or discarded.

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.healthcanda.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

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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PARTIE III : RENSEIGNEMENTS POUR LE CONSOMMATEUR

OCTAGAM 10 %

[Immunoglobuline intraveineuse (humaine)]

Le présent dépliant constitue la troisième et dernière partie de la monographie de produit publiée à la suite de l'approbation de la vente au Canada d'OCTAGAM 10% et est destiné aux consommateurs. Comme ce dépliant est un résumé, il ne contient pas tous les renseignements sur OCTAGAM 10%. Pour toute question au sujet de ce médicament, communiquez avec votre médecin ou un pharmacien.

AU SUJET DE CE MÉDICAMENT

Emploi du médicament :

OCTAGAM 10% est utilisé dans les cas suivants :

Patients atteints d'un

Purpura thrombopénique immunologique (PTI) présentant un risque hémorragique élevé, ou avant une intervention chirurgicale afin de corriger la numération plaquettaire.

Effet du médicament :

Le mécanisme d'action du médicament n'est pas parfaitement connu, mais possède un effet modulateur du système immunitaire.

Situations dans lesquelles il ne faut pas l'utiliser :

Ne pas utiliser OCTAGAM 10% si :

- Vous présentez des antécédents de réaction allergique à une préparation contenant des immunoglobulines humaines.
- Vous présentez un déficit en immunoglobulines A (IgA), avec présence connue d'anticorps anti-IgA.
- Vous êtes allergique à l'un des composants de la préparation.

Ingrédients médicinaux :

Immunoglobuline intraveineuse (humaine), 10 %

Ingrédients non médicinaux importants :

Maltose, Triton X-100, TNBP, eau pour injection, IgA

Forme posologique :

OCTAGAM 10% est une solution à 100 mg/ml pour perfusion intraveineuse disponible sous différentes formes posologiques :

1 flacon de perfusion de 20 ml
1 flacon de perfusion de 50 ml
1 flacon de perfusion de 100 ml
1 flacon de perfusion de 200 ml

MISES EN GARDE ET PRÉCAUTIONS

Sérieuses mises en garde et précautions

Comme toutes les formulations d'immunoglobuline intraveineuse, ce produit est fabriqué à partir de plasma humain, lequel peut contenir des agents infectieux tels que des virus de l'hépatite et d'autres maladies virales. Des mesures rigoureuses sont appliquées lors de la collecte de plasma humain et de la fabrication des produits à base de plasma humain afin d'en assurer l'innocuité virale. Dans le cas particulier d'OCTAGAM 10%, l'innocuité virale a été améliorée en intégrant deux étapes d'inactivation/de retrait des virus lors du processus de fabrication. Votre médecin doit discuter avec vous des risques et des bienfaits de ce produit avant de vous l'administrer.

Mise en garde : événements thromboemboliques

- Des événements thromboemboliques tels que crise cardiaque, accident vasculaire cérébral et obstruction d'une veine profonde (p. ex. dans un mollet) ou d'un vaisseau sanguin dans un poumon (embolie pulmonaire) peuvent se produire avec l'administration d'immunoglobuline humaine par voie intraveineuse (IgIV).
- Des événements thromboemboliques surviennent plus fréquemment chez les patients qui présentent des facteurs de risque thromboembolique préexistants en lien avec l'administration d'IgIV.
- En général, les facteurs de risque thromboembolique comprennent l'obésité, un âge avancé, l'hypertension, le diabète sucré, la survenue antérieure d'une crise cardiaque, d'un accident vasculaire cérébral ou de l'obstruction d'une veine profonde ou autre, de longues périodes d'immobilisations et la prise de certaines hormones (p. ex. la pilule).
- Une thrombose peut survenir même en l'absence de facteurs de risque connus.
- Dans le cas particulier d'OCTAGAM 10 %, des mesures additionnelles ont été prises pour réduire les risques d'événements thromboemboliques et pour garantir la qualité, et donc l'innocuité d'OCTAGAM. Néanmoins, les patients qui présentent des facteurs de risque connus devraient s'assurer d'un apport hydrique équilibré ; par ailleurs le produit devrait être administré à vitesse lente.

AVANT d'utiliser OCTAGAM 10%, adressez-vous à votre médecin ou à un pharmacien si :

- Vous avez récemment présenté des problèmes cardiaques ou des caillots sanguins.
- Vous êtes enceinte ou allaitez.
- Vous présentez les facteurs de risque suivants : néphropathie, diabète, déshydratation sévère, surpoids, prise de médicaments néphrotoxiques, ou si vous avez plus de 65 ans.
- Vous êtes allergique à la substance active ou à l'un des ingrédients non médicinaux.
- Vous avez des antécédents d'allergie à des produits contenant du maïs.
- Vous utilisez un appareil de mesure de la glycémie ou de la glycosurie car le maltose contenu dans ce produit peut

interférer avec les mesures.

INTERACTIONS AVEC CE MÉDICAMENT

Il n'existe aucune interaction médicamenteuse connue avec OCTAGAM 10%. L'administration d'OCTAGAM 10% peut ralentir la protection offerte par les vaccins à virus vivant atténué contre la rougeole, les oreillons, la rubéole et la varicelle pendant au moins six semaines, et jusqu'à 3 mois ou plus.
La tubulure de perfusion peut être rincée avant et après l'administration d'OCTAGAM 10% à l'aide d'une solution physiologique salée ou d'une solution de dextrose (5 %) et d'eau.
Les composants utilisés dans l'emballage d'OCTAGAM 10% ne contiennent pas de latex.

UTILISATION CONVENABLE DU MÉDICAMENT

Dose habituelle :
Votre médecin déterminera la(les) dose(s) d'OCTAGAM 10% qui vous sera (seront) administrée(s) sous forme de perfusion (injection lente dans une veine). La dose que vous recevrez dépendra de votre situation clinique et de votre maladie, mais les doses suivantes correspondent aux doses initiales d'OCTAGAM 10% généralement acceptées :

Traitement immunomodulateur en cas de PTI – 2 g/kg répartis en deux doses de 1 g/kg (10 ml/kg) administrées deux jours consécutifs.
Le traitement peut être renouvelé en cas de rechute.
Il n'est pas nécessaire de filtrer OCTAGAM 10%.

Surdosage :
Un surdosage est possible chez les patients en surpoids, âgés ou en cas d'insuffisance rénale.

En cas de surdosage du médicament, contacter immédiatement un médecin, le service des urgences de l'hôpital ou le centre antipoison régional, même en l'absence de symptômes.

Dose oubliée :
Sans objet.

EFFETS SECONDAIRES ET MESURES À PRENDRE

Parmi les effets secondaires, citons les frissons, la fièvre, les céphalées, les douleurs musculaires comme les douleurs rachidiennes ou thoraciques, les bouffées vasomotrices, les nausées, les réactions allergiques (comme les modifications de pression artérielle, les difficultés respiratoires, la coloration bleue de la peau ou des muqueuses, la tachycardie), les étourdissements, la fatigue, la somnolence, les réactions cutanées (comme les éruptions transitoires, les démangeaisons et l'urticaire), méningite transitoire (méningite aseptique réversible), diminution transitoire des globules rouges (anémie hémolytique réversible /hémolyse) les douleurs abdominales, les diarrhées et les vomissements.
Les symptômes suivants peuvent indiquer la survenue d'événements thrombo-emboliques : oppression ou douleurs thoraciques, troubles de la vision ou de l'élocution, hémiplégie/hémiparésie, troubles du mouvement, douleur ou endolorissement dans la (les) jambe(s) ou le(s) mollet(s), œdème au niveau du (des) mollet(s) ou de la partie inférieure de la (des) jambe(s), ou cyanose. Consulter votre médecin en cas d'apparition d'un ou plusieurs de ces symptômes.

EFFETS SECONDAIRES GRAVES, FRÉQUENCE D'APPARITION ET MESURES À PRENDRE

Symptôme/effet		Consultez votre médecin ou un pharmacien		Cessez de prendre le médicament et appelez votre médecin ou un pharmacien
		Dans les cas graves seulement	Dans tous les cas	
Fréquent	réaction de type allergique		T	T
	céphalées	T		T
	nausées	T		T
	fièvre	T		
Rare	réactions cutanées comme l'urticaire		T	T
	douleurs rachidiennes ou thoraciques		T	T
	frissons		T	T
Très rare	choc		T	T
	œdème de la langue ou du visage		T	T
	migraine		T	T
	étourdisse-ments	T		T
	douleurs cardiaques		T	T
	palpitations		T	T
	diminution ou augmentation de la pression artérielle		T	T
	difficultés respiratoires ou toux		T	T
	vomissements		T	T
	diarrhées		T	T
	douleurs abdominales		T	T

Cette liste des effets secondaires n'est pas exhaustive. Si des effets inattendus surviennent pendant le traitement par OCTAGAM 10%, communiquez avec votre médecin ou un pharmacien.

CONSERVATION DU MÉDICAMENT

À conserver au réfrigérateur (entre +2°C et +8°C) pendant 23 mois au maximum. Pendant cette période, le produit peut être conservé à une température ≤ 25°C pendant 9 mois au maximum. À l'issue de cette période, le produit doit être utilisé ou éliminé. Réchauffer le produit à température ambiante ou corporelle avant utilisation. Ne pas congeler. Ne pas exposer le médicament au soleil. Éliminer toute solution restante après utilisation. Ne pas utiliser le produit au-delà de la date de péremption.

Garder hors de la portée des enfants.

DÉCLARATION DES EFFETS SECONDAIRES PRÉSUMÉS

Pour informer le Programme Canada Vigilance de toute réaction indésirable suspecte associée à l'utilisation de médicaments, vous pouvez choisir entre les options suivantes

- Déclaration en ligne à l'adresse www.healthcanda.gc.ca/medeffect
- Appel sans frais : 1-866-234-2345
- Envoi d'un formulaire de déclaration au Programme Canada Vigilance :
  - Par fax sans frais : 1-866-678-6789
  - Par courrier : Programme Canada Vigilance, Santé Canada

Des étiquettes pré-affranchies, le formulaire de déclaration à Canada Vigilance et les instructions à suivre pour rendre compte de réactions indésirables sont disponibles sur le site Internet de MedEffect™ à l'adresse www.healthcanada.gc.ca/medeffect.

REMARQUE : Pour des informations concernant la prise en charge de réactions indésirables, contacter votre médecin. Le Programme Canada Vigilance ne dispense pas de conseils d'ordre médical

POUR DE PLUS AMPLES RENSEIGNEMENTS

Le présent feuillet ainsi que la monographie de produit intégrale préparés pour les professionnels de la santé peuvent être obtenus à l'adresse suivante : http://www.octapharma.com, ou en communiquant avec Octapharma Canada Inc. au 1-888-438-0488

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