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INSTRUCTIONS FOR USE

(Summary of Product Characteristics)

1 NAME OF THE MEDICINAL PRODUCT

OCTAGAM 5%, Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)* 50 mg/ml

* corresponding to the total protein content of which at least 95% is human Immunoglobulin G

Each infusion bottle of 50 ml contains 2.5g of human normal immunoglobulin.

Each infusion bottle of 100 ml contains 5g of human normal immunoglobulin.

Distribution of IgG subclasses:

IgG_1	ca. 60 %
IgG_2	ca. 32 %
IgG_3	ca. 7 %
IgG_4	ca. 1 %

Maximum IgA content: 200 micrograms/ml

Produced from plasma of human donors.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The liquid preparation is clear to slightly opalescent and colourless to slightly yellow. The pH of the liquid preparation is 5.1 – 6.0, the osmolality is ≥ 240 mosmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production (see Section 4.4).
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
- Congenital AIDS with recurrent bacterial infections.

Immunomodulation in adults, and children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome
- Kawasaki disease

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dosage regimen is dependent on the indication.

In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response.

The following dosage regimens are given as a guideline:

Replacement therapy in primary immunodeficiency syndromes

- The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 – 6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 – 0.8 g/kg given once, followed by at least 0.2 g/kg every three to four weeks.
- The dose required to achieve a trough level of 5 – 6 g/l is of the order of 0.2 – 0.8 g/kg/month.
- The dosage interval when steady state has been reached varies from 3 – 4 weeks.
- Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels.

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections

- The recommended dose is 0.2 – 0.4 g/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation

- The recommended dose is 0.2 – 0.4 g/kg every three to four weeks. The trough levels should be maintained above 5 g/l.

Primary immune thrombocytopenia

There are two alternative treatment schedules:

- 0.8 – 1 g/kg given on day one; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for two to five days.
- The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

- 0.4 g/kg/day over 5 days.

Kawasaki disease

1.6 - 2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injection
Replacement therapy in primary immunodeficiency	- Starting dose: 0.4 - 0.8 g/kg - Thereafter: 0.2 - 0.8 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l
Congenital AIDS	0.2 - 0.4 g/kg	every 3 - 4 weeks
Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2 – 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level above 5g/l.
Immunomodulation: Primary immune thrombocytopenia	0.8 - 1.0 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2-5 days
Guillain Barré syndrome	0.4 g/kg/d	for 5 days
Kawasaki disease	1.6 - 2.0 g/kg or 2.0 g/kg	in divided doses over 2 - 5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid

Paediatric population

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

Method of administration

For intravenous use.

Human normal immunoglobulin should be infused intravenously at an initial rate of 1 ml/kg/hour for 30 minutes. If well tolerated (see Section 4.4), the rate of administration may gradually be increased to a maximum of 5 ml/kg/hour.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of Octagam 5% (see Section 4.4).

Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

4.4 Special warnings and special precautions for use

This medicinal product contains 100 mg of maltose per ml as an excipient. The interference of maltose in blood glucose assays may result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life threatening hypoglycaemia and death. Also, cases of true hypoglycaemia may go untreated if the hypoglycaemic state is masked by falsely elevated glucose readings (see Section 4.5). For acute renal failure see below.

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under Section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin by initially injecting the product slowly (1 ml/kg/hour);
- are carefully monitored for any symptoms throughout the infusion period; in particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product to Octagam 5% or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

In case of shock, standard medical treatment for shock should be implemented.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics.

This medicinal product contains not more than 0.015 mmol (or 0.35 mg) sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity).

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

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In case of renal impairment, IVIg discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products not containing such excipients may be considered.

Octagam 5% does not contain sucrose.

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

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.

AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Haemolytic anaemia

IVIg products 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 (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. (See section 4.8.)

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents

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

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

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

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

It is strongly recommended that every time that Octagam 5% is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Paediatric population

There are no specific or additional warnings or precautions applicable for the paediatric population.

4.5 Interaction with other medicinal products and other forms of interactions

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

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

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 (100 mg/ml) contained in Octagam 5% as glucose. This may result in falsely elevated glucose readings during an infusion and for a period of about 15 hours after the end of the infusion and, consequently, in the inappropriate administration of insulin, resulting in life-threatening or even fatal hypoglycemia. Also, cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings. Accordingly, when administering Octagam 5% or other parenteral maltose-containing products, the measurement of blood glucose must be done with a glucose-specific method.

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

Paediatric population

There were no specific or additional interactions observed for the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly during the third trimester. 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.

Breast-feeding

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with Octagam 5%. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

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

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to

previous administration.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also Section 4.4).

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. For safety with respect to transmissible agents, see Section 4.4.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

The frequencies given in the following table are derived from clinical studies that were conducted with Octagam 5% (columns named „common" and „uncommon") and from postmarketing experience with Octagam 5% (column named „very rare"). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA 8.1 Coded	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Very Rare < 1/10,000
Blood and lymphatic system disorders			leukopenia; haemolytic anaemia
Immune system disorders	hypersensitivity		anaphylactic shock; anaphylactic reaction; anaphylactoid reaction; angioneurotic oedema; face oedema
Psychiatric disorders			agitation
Nervous system disorders	headache		cerebrovascular accident; meningitis aseptic; migraine; dizziness; paraesthesia
Cardiac disorders			myocardial infarction; tachycardia; palpitations; cyanosis
Vascular disorders			thrombosis; peripheral circulatory failure; hypotension; hypertension
Respiratory, thoracic and mediastinal disorders			respiratory failure; pulmonary embolism; pulmonary oedema; bronchospasm; dyspnoea; cough
Gastrointestinal disorders	nausea		vomiting; diarrhoea; abdominal pain
Skin and subcutaneous tissue disorders		eczema	urticaria; rash; rash erythematous; dermatitis; pruritus; alopecia
Musculoskeletal and connective tissue disorders		back pain	arthralgia; myalgia
Renal and urinary disorders			renal failure acute
General disorders and administration site conditions	fever; fatigue; injection site reaction	chills; chest pain	hot flush; flushing; hyperhidrosis; malaise
Investigations			hepatic enzymes increased; blood glucose false positive

Description of selected adverse reactions

For description of selected adverse events, see Section 4.4

Paediatric population

In clinical studies with Octagam 5% most adverse reactions observed in children were graded as mild and many of them responded to simple measurements such as reduction of the infusion rate or temporary discontinuation of the infusion. With respect to the type of adverse reaction, all were recognised for IVIG preparations. The most frequent adverse reaction observed in the paediatric population was headache.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration

ATC-Code: J06B A02

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population.

It is prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G-subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low Immunoglobulin G levels to the normal range.

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

Paediatric population

A prospective open-label phase III study was performed with Octagam 5% in 17 children/adolescent patients (median age 14.0 years, range 10.5 to 16.8) suffering from primary immunodeficiency disorders. Patients were treated for a period of 6 months. The clinical efficacy was satisfying, as the number of days with infections or fever, and the number of days out of school were low, and the type and severity of infections was comparable to those observed in the normal population. No severe infections leading to hospitalisation were observed. It is also noteworthy that the number of infectious episodes was lower, when IgG plasma levels were maintained around 6 g/l than when the IgG plasma levels were around 4 g/l.

5.2 Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments.

Human normal immunoglobulin has an average half life ranging from 26 to 41 days, as measured in immunodeficient patients. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

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

Paediatric population

A prospective open-label phase III study was performed with Octagam 5% in 17 children/adolescent patients (median age 14.0 years, range 10.5 to 16.8) suffering from primary immunodeficiency disorders. Patients were treated for a period of 6 months.

During the treatment period, the average Cmax in steady state was 11.1 ± 1.9 g/l; the average trough level was 6.2 ± 1.8 g/l. The terminal half-life of total IgG was 36 ± 11 days with a median of 34 days. 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.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body. Studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction in animals are impracticable due to induction of and interference by developing antibodies to heterologous proteins. Since clinical experience provides no evidence for carcinogenic or mutagenic potential of immunoglobulins, no experimental studies in heterologous species were performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

The product should be stored and transported at +2°C to +25°C.

Do not freeze.

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

Do not use after expiry date.

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

Keep out of the reach of children.

6.5 Nature and contents of container

The infusion bottles are made of glass type II, Ph.Eur. closed with bromobutyl rubber stoppers.

Pack sizes:

1 infusion bottle with 2.5 g (50 ml)

1 infusion bottle with 5 g (100 ml)

Components used in the packaging of Octagam 5% are latex-free.

6.6 Special precautions for disposal and other handling

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

Do not use non-homogenous solutions, or those which have a deposit.

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

7 NAME AND ADDRESS OF PHARMACEUTICAL COMPANY

7.1 Marketing authorisation holder

Pharmaniaga Marketing Sdn Bhd (198401005734)

No. 7, Lorong Keluli 1B,

Kaw. Perindustrian Bukit Raja Selatan,

Seksyen 7, 40000 Shah Alam,

Selangor Darul Ehsan, Malaysia.

Manufacturer

Octapharma S.A.S.

72 rue du Maréchal Foch

F-67380 Lingolsheim, France

8 DATE OF REVISION OF THE TEXT

May 2020

9 LEGAL CATEGORY

Controlled Medicine.

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