INSTRUCTIONS FOR USE
(Summary of Product Characteristics)

1 NAME OF THE MEDICINAL PRODUCT

OCTAGAM®

50 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains:

Human normal immunoglobulin* 50 mg
* corresponding to the total protein content of which at least 95% is human Immunoglobulin G

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

Each vial of 20 ml contains 1g of human normal immunoglobulin.
Each bottle of 50 ml contains 2.5g of human normal immunoglobulin.
Each bottle of 100 ml contains 5g of human normal immunoglobulin.
Each bottle of 200 ml contains 10g of human normal immunoglobulin.

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

4.1.1 Replacement therapy in:

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

- Myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections
- Children with congenital AIDS and recurrent infections.

4.1.2 Immunomodulation:

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

4.1.3 Allogeneic bone marrow transplantation

4.2 Posology and method of administration

4.2.1 Posology

The dose and dosage regimen is dependant on the indication.

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

The following dosage regimens are given as a guideline:

Replacement therapy in primary immunodeficiency syndromes:

- The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4.0 – 6.0 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 - 0.8 g/kg, followed by at least 0.2 g/kg every three weeks.
- The dose required to achieve a trough level of 6.0 g/l is of the order of 0.2 - 0.8 g/kg/month.
- The dosage interval when steady state has been reached varies from 2 to 4 weeks.
- Trough levels should be measured in order to adjust the dose and dosage interval.

Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections:

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

Idiopathic Thrombocytopenic Purpura:

- For the treatment of an acute episode, 0.8-1.0 g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for two to five days.
- The treatment can be repeated if relapse occurs.

Guillain Barré syndrome:

- 0.4g/kg/day for 3 to 7 days. Experience in children is limited.

Kawasaki disease:

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

Allogeneic Bone Marrow Transplantation:

- Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant. For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored.
- The starting dose is normally 0.5 g/kg/week, starting seven days before transplantation and for up to 3 months after transplantation.
- In the case of persistent lack of antibody production, dosage of 0.5 g/kg/month is recommended until antibody level returns to normal.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injection
Replacement therapy in primary immunodeficiency	- Starting dose: 0.4 - 0.8 g/kg - Thereafter: 0.2 - 0.8 g/kg	every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Children with AIDS	0.2 - 0.4 g/kg	every 3 - 4 weeks
Immunomodulation:		
Idiopathic Thrombocytopenic Purpura	0.8 - 1.0 g/kg or	on day 1, possibly repeated once within 3 days
	0.4 g/kg/day	for 2-5 days
Guillain Barré syndrome	0.4 g/kg/day	for 3-7 days
Kawasaki syndrome	1.6 - 2.0 g/kg or	in several doses for 2 - 5 days in association with acetylsalicylic acid
	2.0 g/kg	in one dose in association with acetylsalicylic acid
Allogeneic bone marrow transplantation:		
- treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg	every week from day -7 up to 3 months after transplantation
- Persistent lack of antibody production	0.5 g/kg	every month until IgG levels return to normal

4.2.2 Method of administration

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

4.3 Contraindications

Hypersensitivity to any of the components of Octagam.

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

4.4 Special warnings and special precautions for use

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

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- in patients with hypo- or agammaglobulinaemia, with or without IgA deficiency
- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion

True hypersensitivity reactions are rare. They can occur in very seldom cases of IgA deficiency with anti-IgA antibodies.

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

Potential complications can often be avoided by ensuring:

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

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

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

In case of renal impairment, IVIg discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of

many of the licensed IVIg products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered.

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

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.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1-6 hrs after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support. IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

In all patients, IVIg administration requires:

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

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

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

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 are made from human blood or plasma, it may carry a risk for transmitting infectious agents, e.g.. viruses, pathogens and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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 is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products

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

Live attenuated vaccines

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

Interference with serological testing

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

Passive transmission of antibodies to erythrocyte antigens, e. g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

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 may result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Also, cases of true hypoglycemia may go untreated if the hypoglycemic 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.
The product information of the blood glucose testing system, including that of the test strips, should be carefully reviewed to determine if the system is appropriate for use with maltose-containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

4.6 Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy on the foetus or the neonate are to be expected. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

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

MedDRA 8.1 Coded	Common ≥1% - <10%	Uncommon ≥0.1% - <1%	Rare ≥0.01% - <0.1%	Very Rare < 0.01%
Blood and lymphatic system disorders				leukopenia; haemolytic anaemia
Immune system disorders	hypersensitivity			anaphylactic shock; anaphylactic reaction; anaphylactoid reaction; angioneurotic oedema; face oedema
Metabolic and nutritional disorders				fluid overload
Psychiatric disorders				agitation
Nervous system disorders	headache			cerebrovascular accident; meningitis aseptic; migraine; dizziness; paraesthesia
Cardiac disorders				myocardial infarction; tachycardia; palpitations; cyanosis
Vascular disorders			hypotension	thrombosis; peripheral circulatory failure; 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 pain in extremity
Renal and urinary disorders				renal failure acute
General disorders and administration site conditions	pyrexia; fatigue; injection site reaction	chills; chest pain hot flush		flushing; hyperhidrosis; malaise
Investigations			hepatic enzymes increased	blood glucose false positive blood creatinine increased

Rarely Octagam may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting

infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. For safety with respect to transmissible agents, see 4.4.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC-Code: J06 BA02

Human normal immunoglobulin contains mainly ≥ 95 % immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

IgA content is ≤ 0.2 mg/ml.

Opsonisation and neutralisation of microbes and toxins has been documented.

Human normal immunoglobulin contains all the IgG activities which are present in the normal population.

It is prepared from pooled plasma from not fewer than 3500 donations.

Human normal immunoglobulin has a distribution of IgG-subclasses:

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

which are closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG level to the normal range.

The mechanism of action in idiopathic thrombocytopenic purpura is not fully elucidated.

The IgG-molecules have not been chemically or enzymatically modified. The antibody activities are fully functional. Octagam contains ≤ 3.0 % polymers. Monomer and dimer is ≥ 90 %.

Human normal immunoglobulin has a broad spectrum of antibodies against various infectious agents (e.g. antibody titer for steptococcus and hepatitis B-antigen is established at 3 times the initial plasma pool), corresponding to those pathogens endemic in Europe and North America.

5.2 Pharmacokinetic properties

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

Human normal immunoglobulin has a half life of about 40 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

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

5.3 Preclinical safety data

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

Virus inactivation by the SD method is carried out with TNBP and Octoxynol (Triton X-100). The maximum permitted amounts in the final product are ≤ 1 µg/ml TNBP and ≤ 5 µg/ml Octoxynol. In the doses in which Octagam is administered, these substances have been found to have no toxic effects in animal tests concerning acute and chronic toxicity, teratogenicity and embryotoxicity.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose	100 mg/ml
Water for injections	ad 1ml

6.2 Incompatibilities

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

6.3 Shelflife

2 years

6.4 Special precautions for storage

Store below 25°C.
Do not freeze.
Keep container in the outer carton in order to protect from light.
Do not use after expiry date.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Any remaining contents must be discarded.

6.5 Nature and contents of container

Package size	*Contents*	*Container*
OCTAGAM 1 g	20 ml	30 ml injection vial
OCTAGAM 2.5 g	50 ml	70 ml infusion bottle
OCTAGAM 5 g	100 ml	100 ml infusion bottle
OCTAGAM 10 g	200 ml	250 ml infusion bottle

Not all pack sizes may be marketed.

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

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

6.6 Special precautions for disposal and other handling

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

The solution should be clear to slightly opalescent and colourless to slightly yellow.

Do not use solutions that are cloudy or have deposits.

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

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

7 NAME AND ADDRESS OF PHARMACEUTICAL COMPANY

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8 DATE OF REVISION OF THE TEXT

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9 LEGAL CATEGORY

For prescription only.