SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

OCTAGAM 10%, solution for infusion

OCTAGAM 100 mg/ml, solution for infusion

[country specific]

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains:

Human normal immunoglobulin (IVIg) 100 mg

(purity of at least 95% IgG)

Each vial of 20 ml contains 2g of human normal immunoglobulin.
Each bottle of 50 ml contains 5g of human normal immunoglobulin.
Each bottle l of 60 ml contains 6g of human normal immunoglobulin.
Each bottle of 100 ml contains 10g of human normal immunoglobulin.
Each bottle of 200 ml contains 20g of human normal immunoglobulin.
Each bottle of 300 ml contains 30g of human normal immunoglobulin.

Distribution of IgG subclasses (approx. values):

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

The maximum IgA content is 400 micrograms/ml

Produced from the plasma of human donors.

Excipient(s) with known effect
This medicinal product contains 69 mg sodium per 100 ml, equivalent to 3.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 4.5 – 5.0, 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 (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and **either proven specific antibody failure (PSAF)*** or serum IgG level of <4g/l.

  *PSAF=failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

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 (in conjunction with acetylsalicylic acid; see 4.2)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

Immunomodulation in adults with:

- Active dermatomyositis treated with immunosuppressive drugs including corticosteroids, or with intolerance or contra-indications to those drugs

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 dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight and overweight patients. In overweight patients dose should be based on the physiological standard bodyweight.

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 6 g/L or within the normal reference range for the population age. Three to six months are required after the initiation of therapy for equilibration (steady-state IgG levels) 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 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.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Secondary immunodeficiencies (as defined in 4.1.)

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

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

Primary immune thrombocytopenia

There are two alternative treatment schedules:

- 0.8-1g/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 (possible repeat of dosing in case of relapse).

Kawasaki disease:

2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Chronic inflammatory demyelinating polyneuropathy (CIDP):

Starting dose: 2g/kg divided over 2-5 consecutive days.
Maintenance doses:
1 g/kg over 1-2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal Motor Neuropathy (MMN):

Starting dose: 2g/kg given over 2-5 consecutive days
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient's response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Dermatomyositis (DM):

2g/kg given divided in equal doses over 2-5 consecutive days every 4 weeks.

The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient's response and maintenance response (see Section 5.1). The dosing and intervals may have to be adapted according to the individual course of the disease.

The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of injections**
Replacement therapy		
Primary immunodeficiency syndromes	Starting dose: 0.4-0.8 g/kg Maintainance dose: 0.2-0.8 g/kg	every 3 - 4 weeks
Secondary immunodeficiencies (as defined in 4.1.)	0.2–0.4 g/kg	every 3 - 4 weeks
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	2 g/kg	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2 g/kg Maintainance dose: 1 g/kg	in divided doses over 2-5 days every 3 weeks over 1-2 days
Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 1g/kg or 2g/kg	over 2-5 consecutive days every 2-4 weeks or every 4-8 weeks over 2-5 days

Indication	Dose	Frequency of injections
Dermatomyositis (DM) in adults	2 g/kg	every 4 weeks, divided in equal doses given over 2-5 consecutive days

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.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration

For intravenous use.

Octagam 10% [100 mg/ml] should be infused intravenously at an initial rate of 0.01 mL/kg body weight per minute for 30 minutes. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.12 mL/kg body weight per minute.

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.
Patients with dermatomyositis are considered patients at increased risk for thromboembolic events (see section 4.4) and should therefore be carefully monitored and infusion rate should not exceed 0.04 ml/kg/min.

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.

4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients (see Section 4.4 and 6.1).

Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

4.4 Special warnings and precautions for use

This medicinal product contains 90 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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin by initially injecting the product slowly (0.01 to 0.02 mL/kg body weight per minute);
- 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 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 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 (see 4.5)

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.

Infusion reaction

Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) 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.

Adverse reactions may occur more frequently:

- 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
- in patients with an untreated infection or underlying chronic inflammation

Hypersensitivity
Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients
- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

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

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events (TEE) 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, dermatomyositis 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, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

Renal parameters should be assessed prior to infusion of IVIG, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

In case of renal impairment, IVIg discontinuation should be considered.

While 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 10% [100 mg/ml] contains maltose (see excipients above).

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. 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 mm^3, 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.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

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).

Neutropenia/Leukopenia
A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion-related acute lung injury (TRALI)

In patients receiving IVIg, there have been reports of non-cardiogenic pulmonary oedema [Transfusion-Related Acute Lung Injury (TRALI)], therefore, this side effect cannot be totally excluded for Octagam even though no case has been observed so far for Octagam. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing
After the administration 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.

Important information on some of the ingredients of Octagam 10% [100 mg/ml]
This medicinal product contains 69 mg sodium per 100 ml, equivalent to 3.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

(Falsely) raised erythrocyte sedimentation rate

In patients who are receiving IVIG as a therapy, the erythrocyte sedimentation rate (ESR) may falsely be increased (noninflammatory rise).

Circulatory (volume) overload

Circulatory (volume) overload can occur when the volume of the infused IVIG (or any other blood or plasma-derived product) and other coincidental infusions cause acute hypervolaemia and acute pulmonary oedema.

Local injection site reactions:
Local reactions at the injection site have been identified which might include extravasation, infusion site erythema, infusion site pruritus, and similar symptoms.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interaction with other medicinal products and other forms of interactions

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 medicinal 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.

Loop diuretics
Avoidance of concomitant use of loop diuretics

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 (90 mg/ml) contained in Octagam 10% [100 mg/ml] 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 10% [100 mg/ml] 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
The listed interactions apply both to adults and children.

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 human milk. No negative effects on the breastfed newborns/infants are anticipated.

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

OCTAGAM 10% [100 mg/ml] has no or negligible influence on the ability to drive and use machines. However, 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

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion.
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

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).

Within each Organ Class, adverse reactions are presented in order of decreasing seriousness.

Frequency of adverse drug reactions in clinical studies with Octagam:

MedDRA System Organ Classification (SOC) according to the sequence:	**Adverse Reaction**	**Frequency per patient**	**Frequency per infusion**
Blood and lymphatic system disorders	anaemia, leukopenia, lymphopenia	uncommon	uncommon
Immune system disorders (see section 4.4)	hypersensitivity	common	common
Eye disorders	vision blurred	uncommon	uncommon
Nervous system disorders	headache	very common	common
	dizziness	common	uncommon
	paresthesia, tremor	uncommon	uncommon
	cerebrovascular accident (See 4.4), hypoaesthesia, cerebral infarction	uncommon	rare
Cardiac disorders	tachycardia	common	uncommon
Vascular disorders	hypertension	common	common
	thrombosis (see 4.4)	uncommon	rare
Gastrointestinal disorders	nausea	common	common
	vomiting	common	uncommon
Musculoskeletal and connective tissue disorders	myalgia, pain in extremity	common	uncommon
	back pain, arthralgia, muscle spasms	uncommon	uncommon
Respiratory, thoracic and mediastinal disorders	dyspnoea	uncommon	uncommon
	pulmonary embolism (See 4.4)	uncommon	rare
General disorders and administration site conditions	fever	common	common
	fatigue, injection site reaction, chills	common	uncommon
	chest pain, asthenia, peripheral swelling, malaise	uncommon	uncommon
Investigations	hepatic enzymes increased, Coombs test positive	common	uncommon
	hemoglobin decreased	uncommon	uncommon

The following reactions have been reported from post-marketing experience with Octagam

Frequencies for post-marketing reported reactions cannot be estimated from the available data.

MedDRA System Organ Classification (SOC) according to the sequence:	**Adverse Reaction (Preferred Term Level)**	**Frequency**
Blood and lymphatic system disorders	haemolytic anaemia	not known
Immune system disorders (see section 4.4)	anaphylactic shock; anaphylactic reaction; anaphylactoid reaction; angioedema; face oedema	not known not known not known not known not known
Metabolic and nutritional disorders	fluid overload (pseudo)hyponatraemia	not known not known
Psychiatric disorders	confusional state	not known

	agitation anxiety nervousness	not known not known not known
Nervous system disorders	meningitis aseptic; loss of consciousness; speech disorder; migraine; photophobia;	not known not known not known not known not known
Eye disorders	visual impairment	not known
Cardiac disorders	myocardial infarction (see 4.4); angina pectoris; bradycardia; palpitations; cyanosis	not known not known not known not known not known
Vascular disorders	circulatory collapse; peripheral circulatory failure; phlebitis; hypotension; pallor	not known not known not known not known not known
Respiratory, thoracic and mediastinal disorders	respiratory failure; pulmonary oedema; bronchospasm; hypoxia; cough	not known not known not known not known not known
Gastrointestinal disorders	diarrhoea; abdominal pain	not known not known
Skin and subcutaneous tissue disorders	skin exfoliation; urticaria; rash; rash erythematous; dermatitis; pruritus; alopecia erythema	not known not known not known not known not known not known not known not known
Musculoskeletal and connective tissue disorders	neck pain; muscular weakness; musculoskeletal stiffness	not known not known not known
Renal and urinary disorders	renal failure acute (see 4.4) ; renal pain	not known not known
General disorders and administration site conditions	oedema; influenza like illness hot flush; flushing; feeling cold; feeling hot; hyperhidrosis; chest discomfort; lethargy; burning sensation;	not known not known not known not known not known not known not known not known not known not known
Investigations	blood glucose false positive (see 4.4)	not known

Description of selected adverse reactions

For description of selected adverse events, such as hypersensitivity reactions, thromboembolism, acute renal failure, aseptic meningitis syndrome and haemolytic anaemia, see Section 4.4

Paediatric population

In clinical studies with Octagam 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC-Code: J06BA02

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 usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G-subclasses closely proportional to that in naive 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.

Clinical Studies

In a prospective, open-label, multicentre phase III trial, the efficacy and safety of Octagam 10% [100 mg/ml] was studied in patients suffering from idiopathic (immune) thrombocytopenic purpura (ITP). Octagam 10% [100 mg/ml] was infused on 2 consecutive days at a dose of 1 gram/kg/day, and patients were observed for a period of 21 days and at a follow-up visit on Day 63 post-infusion. Haematology parameters were assessed on Days 2 to 7, 14 and 21.

A total of 116 subjects were included in the analysis; 66 were subjects with chronic ITP, 49 were newly-diagnosed, and 1 subject was incorrectly enrolled in the study (had no ITP) and was therefore excluded from the efficacy analysis.

The overall response rate in the full analysis set was 80% (95% confidence interval: 73% to 87%). Clinical response rates were similar in the 2 cohorts: 82% in the chronic ITP

cohort and 78% in the newly diagnosed cohort. In subjects with a response, the median time to platelet response was 2 days, with a range of 1 to 6 days.

The overall maximum infusion rate was 0.12 ml/kg/min. In the group of subjects in which a maximum infusion rate of 0.12 mL/kg/min was allowed (n=90), a median maximum infusion rate of 0.12 mL/kg/min (mean 0.10 mL/kg/min) was achieved. Overall, 55% of subjects experienced a drug-related AE, with a similar incidence in the chronic ITP and newly-diagnosed ITP cohort. All of the drug-related AEs were mild or moderate in intensity, and all of them resolved. The most common AEs were headache, increased heart rate (alterations in pulse rate of as little as > 10 beats/min were to be reported), and pyrexia. Drug-related infusional AEs during or within 1 hour of infusions given at rates of ≤ 0.08 ml/kg/min occurred in 32 of 116 subjects (28%), while only 6 of 54 subjects (11%) had such AEs at a rate of 0.12 ml/kg/min (if AE onset was after the end of the infusion, the last rate applied was assigned to the AE). There was no case of haemolysis related to the study drug. Pre-treatment to alleviate infusion-related intolerability was not given except in 1 subject.

Chronic inflammatory demyelinating polyneuropathy (CIDP):

A retrospective study included data from 46 patients with chronic inflammatory demyelinating polyneuropathy (CIDP), who had been treated with Octagam 5%. The analysis of efficacy included 24 patients, with 11 untreated patients (group 1) and 13 patients who had received no immunoglobulins in the 12 weeks before the start of therapy with Octagam 5% (group 2). Group 3 contained 13 other patients who had been pretreated with immunoglobulins (immunoglobulins administered within 12 weeks before the start of administration of Octagam 5%). The treatment was regarded as effective if the ONLS (Overall Neuropathy Limitations Scale) was reduced by at least one point within 4 months of the start of treatment. In groups 1 and 2, the score was significantly reduced in 41.7% of the patients (p=0.02). Only 3 of the 13 patients (23.08%) in group 3 (pretreated with IVIg) exhibited an improvement in ONLS; 10 patients remained stable. No more marked improvement in the ONLS was to be expected for the patients pretreated with IVIg.
The mean age of the patients examined was 65 years, which is greater than in other CIDP studies. In patients older than 65 years, the response rate was lower than in younger patients. This is in accordance with published data.

Dermatomyositis (DM):

In a prospective, double-blind, randomized placebo-controlled, multicenter study a total of 95 adult patients (mean age 53 years, range 22-79 years; 75% female) with dermatomyositis were enrolled.
In the First Period (16 weeks), subjects received either 2 g/kg Octagam 10% or placebo every 4 weeks for 4 infusion cycles.

Subjects could remain on their previous DM medication (maximum dosing, e.g. for corticosteroids: 20mg/day prednisone equivalent) if they were on stable dosing prior to enrolment. During the First Period concomitant DM medication dosing had to be kept stable and about 93% of subjects received corticosteroids (with appr. 50% receiving ≤10mg/day prednisone equivalent).

The proportion of responders (improvement of ≥20 points on the TIS) at week 16 in the Full Analysis Set (FAS) was significantly higher in the Octagam 10% group than in the placebo group (78.72% versus 43.75%; Difference: 34.97% [95% CI: 16.70, 53.24; p=0.0008] see Table 1).

Table 1. Total Improvement Score – Proportion of Responders at Week 16

Analysis	TIS Response	Octagam 10% N=47	Placebo N=48	Difference Octagam 10% – placebo
Primary (at least minimal improvement)	Number (%) of responders	37 (78.72%)	21 (43.75%)	
	Difference in response rates			34.97
	[95% CI] p- value[a]			[16.70, 53.24] 0.0008
Secondary At least moderate improvement	Number (%) of responders	32 (68.09%)	11 (22.92%)	
	Difference in response rates			45.17
	[95% CI] p- value[a]			[27.31, 63.03] <0.0001
Secondary At least major improvement	Number (%) of responders	15 (31.91%)	4 (8.33%)	
	Difference in response rates			23.58
	[95% CI] p- value[a]			[8.13, 39.03] 0.0062

[a]Cochran-Mantel-Haenszel Test
'At least moderate improvement' defined as ≥40 points on the TIS and 'At least major improvement' defined as ≥60 points on the TIS, based on six Core Set Measures (CSM): Manual Muscle Testing MMT-8, Physician Global Disease Activity (GDA), Extramuscular Activity, Patient GDA, Health Assessment Questionnaire (HAQ), Muscle Enzymes.
CI=confidence interval; N=number of patients; TIS=total improvement score.

In the 24-week Open Label Extension (OLE) Period, 91 subjects went on to receive further 6 infusion cycles of Octagam 10% every 4 weeks. Reduction of concomitant immunosuppressive treatment was permitted during this period and in 15% of subjects corticosteroid dosing could be tapered.

For all efficacy endpoints, through Week 40, the response in the Octagam 10% group from the First Period was maintained. Subjects in the placebo group attained a similar response after switching to Octagam 10% in the Extension Period (see Table 2).

Table 2. Total Improvement Score – Proportion of Responders at Week 40

TIS Response at Week 40	Octagam 10%	Placebo/Octagam 10%	Total
Number (%) of responders			
At least minimal improvement	32/45 (71.11%)	32/46 (69.57%)	64/91 (70.33%)
95% CI	57.87; 84.35	56.27; 82.86	60.94; 79.72

A total of 664 infusion cycles with Octagam 10% were administered during the entire study. Overall, 62 subjects (65.3%) experienced 282 treatment emergent adverse event that were considered related to study drug, the majority of which were mild in intensity (207/282). During the study no patient met the criteria for intravascular haemolysis.

During the study a reduction in the maximum allowed infusion rate from 0.12 mL/kg/min to 0.04 mL/kg/min was implemented. For both the placebo-controlled period and the entire study, exposure-adjusted incidence rates for thromboembolic events were consistently lower in the 'After reduction' analyses, (1.54 per 100 patient months before and 0.54 after

reduction for the entire study). It is therefore recommended to use the lowest possible infusion rate in DM patients with risk factors (see also Section 4.4).

Paediatric population

No specific studies in the paediatric population were performed with Octagam 10%.

However, 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. For Octagam 10%, no formal pharmacokinetic data in immunodeficient patients have been obtained.

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

Paediatric population

No specific studies in the paediatric population were performed with Octagam 10%.

However, 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 C_{max} 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, nor with any other IVIg products.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

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

The product may be removed from the refrigerator for a single period of up to 9 months (without exceeding the expiry date) and stored at a temperature ≤ 25°C. At the end of this period, the product should not be refrigerated again and should be disposed of. The date at which the product was taken out of the refrigerator should be recorded on the outer carton.

6.5 Nature and contents of container

Pack sizes:

2 g	in	20 ml
5 g	in	50 ml
6 g	in	60 ml
10 g	in	100 ml
20 g	in	200 ml
3 x 10 g	in	3 x 100 ml
3 x 20 g	in	3 x 200 ml
30 g	in	300 ml

Not all pack sizes may be marketed.

20 ml of solution in a 30 ml vial.

50 ml of solution in a 70 ml bottle.

60 ml of solution in a 70 ml bottle.

100 ml of solution in a 100 ml bottle.

200 ml of solution in a 250 ml bottle.

300 ml of solution in a 300 ml bottle.

The vials/bottles are made of type II glass closed with bromobutyl rubber stoppers.

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 or pale yellow.

Solutions that are cloudy or have deposits should be not used.

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

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

7 MARKETING AUTHORISATION HOLDER

To be completed nationally

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

Date of last renewal:

10 DATE OF REVISION OF THE TEXT

11 LEGAL CATEGORY

For prescription only.