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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Octagam, Immune Globulin Intravenous (Human), safely and effectively. See full prescribing information for Octagam.

Octagam [Immune Globulin Intravenous (Human)]
5% Liquid Preparation
Initial U.S. Approval: 2004

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin intravenous (IGIV) products, including Octagam 5% liquid. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with IGIV products, including Octagam 5% liquid. Renal dysfunction and acute renal failure occur more commonly with IGIV products containing sucrose. Octagam 5% liquid does not contain sucrose.**

For patients at risk of thrombosis, renal dysfunction or acute renal failure administer Octagam 5% liquid at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

RECENT MAJOR CHANGES

Warnings and Precautions – Thrombosis (5.5) 10/2013

INDICATIONS AND USAGE

- Octagam is an immune globulin intravenous (human), 5% liquid, indicated for treatment of primary humoral immunodeficiency (PI) (1).

DOSAGE AND ADMINISTRATION

Intravenous use only (2).

Indication	Dose	Initial Infusion rate	Maintenance infusion rate (if tolerated)
PI	300-600 mg/kg Every 3-4 weeks	0.5 mg/kg/min	3.33 mg/kg/min

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Octagam 5% liquid if renal function deteriorates (2.4).
- For patients at risk of renal dysfunction or thrombotic events, administer Octagam 5% liquid at the minimum infusion rate practicable (2.4).

DOSAGE FORMS AND STRENGTHS

Octagam 5% liquid is supplied in 1.0 g, 2.5 g, 5 g , 10 g or 25 g single use bottles (3, 16).

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4)
- Patients with acute hypersensitivity reaction to corn (4)

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions. (5.1)
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure. (5.2)
- Falsely elevated blood glucose readings may occur during and after the infusion of Octagam 5% liquid with some glucometer and test strip systems. (5.3)
- Hyperproteinemia, increased serum viscosity and hyponatremia occur in patients receiving IGIV therapy. (5.4)
- Thrombosis may occur following treatment with immune globulin products, including Octagam 5% liquid. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. (5.5)
- Aseptic Meningitis Syndrome has been reported with Octagam 5% liquid and other IGIV treatments, especially with high doses or rapid infusion. (5.6)
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. (5.7)
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI). (5.8)
- The product is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent. (5.9)

ADVERSE REACTIONS

Most common adverse reactions with an incidence of > 5% during a clinical trial were headache and nausea. (6.1). **To report SUSPECTED ADVERSE REACTIONS, contact Octapharma at 1-866-766-4860 or FDA at 1-800-FDA-1088 or** *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- The passive transfer of antibodies may confound the results of serological testing (7).
- The passive transfer of antibodies may interfere with the response to live viral vaccines (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: no human or animal data. Use only if clearly needed (8.1).
- In patients over age 65 or in any person at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Octagam 5% liquid at the minimum infusion rate practicable (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: October 2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

Octagam

Immune Globulin Intravenous (Human),

5% Liquid Preparation

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

Thrombosis may occur with immune globulin intravenous (IGIV) products, including Octagam 5% liquid. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. *(See WARNING and PRECAUTIONS [5.5], PATIENT COUNSELING INFORMATION [17])*

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients who receive IGIV products, including Octagam 5% liquid. Patients predisposed to renal dysfunction include those with a degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV product containing sucrose. Octagam 5% liquid does not contain sucrose.

For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Octagam 5% liquid at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. *(See DOSAGE and ADMINISTRATION [2.4.], WARNINGS and PRECAUTIONS [5.5]*

1 INDICATIONS AND USAGE

1.1 Primary Humoral Immunodeficiency Diseases (PI)

Octagam is an immune globulin intravenous (human) 5% liquid indicated for treatment of primary humoral immunodeficiency (PI), such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

2 DOSAGE AND ADMINISTRATION

For intravenously use only

2.1 Preparation and handling

- Octagam 5% liquid should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid and/or discoloration is observed.
- Octagam 5% liquid must not be mixed with other medicinal products or administered simultaneously with other intravenous preparation in the same infusion set. Do not mix with immune globulin intravenous (IGIV) products from other manufacturers.
- Do not freeze. Solutions that have been frozen should not be used.
- Octagam 5% liquid bottle is for single use only. Octagam 5% liquid contains no preservative. Any bottle that has been entered should be used promptly. Partially used bottles should be discarded.
- Content of Octagam 5% liquid bottles may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling.
- Do not use after expiration date.
- Octagam 5% liquid should not be diluted.

2.2 Treatment of Primary Humoral Immunodeficiency

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

The dose of Octagam 5% liquid for replacement therapy in primary humoral immunodeficiency diseases is 300 to 600 mg/kg body weight (6-12 ml/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical responses.

If a patient is at risk of measles exposure (ie., outbreak in US or travel to endemic areas outside of the US) and receives a dose of less than 400 mg/kg every 3 to 4 weeks, the dose should be increased to at least 400 mg/kg. If a patient has been exposed to measles, this dose should be administered as soon as possible after exposure.

2.3 Missed Doses

If a patient on regular treatment missed a dose, the missed dose should be administered as soon as possible, and then treatment should continue as before.

2.4 Administration

Octagam 5% liquid should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid and/or discoloration is observed.

Octagam 5% liquid should be at room temperature during administration. Only administer intravenously.

Any bottle that has been opened should be used promptly. Partially used bottles should be discarded.

Octagam 5% liquid is not supplied with an infusion set. If an in-line filter is used the pore size should be 0.2 – 200 microns.

Do not use a needle of larger than 16 gauge to prevent the possibility of coring. Insert needle only once, within the stopper area delineated (by the raised ring for penetration). The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

Rate of Administration

It is recommended that Octagam 5% liquid be initially infused at infusion rates stated below, at least until the physician has had adequate experience with a given patient.

Infusion rates: 0.5 mg/kg/min (30 mg/kg/hr for the first 30 minutes; if tolerated, advance to 1 mg/kg/min (60 mg/kg/hr) for the second 30 minutes; and if further tolerated, advance to 2 mg/kg/min (120 mg/kg/hr) for the third 30 minutes. Thereafter the infusion can be maintained at a rate up to, but not exceeding, 3.33 mg/kg/min (200 mg/kg/hr).

For patients judged to be at risk for developing renal dysfunction, administer Octagam 5% liquid at the minimum infusion rate practicable, not to exceed 0.07 ml/kg (3.3 mg/kg)/minute (200 mg/kg/hour).

Table 1

Rate of Administration	mg/kg/min (mg/kg/hour)	ml/kg/min
first 30 min	0.5 (30)	0.01
next 30 min	1.0 (60)	0.02
next 30 min	2.0 (120)	0.04
Maximum	< 3.33 (< 200)	< 0.07

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

Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Octagam 5% liquid if renal function deteriorates.

For patients at risk of renal dysfunction or thromboembolic events, administer Octagam 5% liquid at the minimum infusion rate practicable.

Incompatibilities

Octagam 5% liquid must not be mixed with other medicinal products or administered simultaneously with other intravenous preparations in the same infusion set.

Shelf-life

Octagam 5% liquid may be stored for 24 months at +2°C to + 25°C (36°F to 77°F) from the date of manufacture.

Special Precautions for Storage

Do not freeze. Frozen product should not be used.

Do not use after expiration date.

3 DOSAGE FORMS AND STRENGTHS

Octagam 5% liquid is supplied in 1.0 g, 2.5 g, 5 g, 10 g or 25 g single use bottles *(See How Supplied/Storage and Handling [16]).*

4 CONTRAINDICATIONS

Octagam 5% liquid is contraindicated in patients who have acute severe hypersensitivity reactions to human immunoglobulin.

Octagam 5% liquid contains trace amounts of IgA (not more than 0.2 mg/ml in a 5% solution). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity *(See Description [11]).*

Octagam 5% liquid is contraindicated in patients with acute hypersensitivity reaction to corn. Octagam 5% liquid contains maltose, a disaccharide sugar which is derived from corn. Patients known to have corn allergies should avoid using Octagam 5% liquid.

5 WARNINGS AND PRECAUTIONS

5.1 Sensitivity

Severe hypersensitivity reactions may occur [1] *(See Contraindications [4]).* In case of hypersensitivity, Octagam 5% liquid infusion should be immediately discontinued and appropriate treatment instituted. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction. IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactoid reactions when administered Octagam 5% liquid *(See Contraindications [4]).* Patients known to have corn allergies should avoid using Octagam 5% liquid *(See Contraindications [4]).*

5.2 Renal Failure

Assure that patients are not volume depleted prior to the initiation of the infusion of Octagam 5% liquid.

Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure. Renal function, including a measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of Octagam 5% liquid and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. *(See Patient Counseling Information [17])*

For patients judged to be at risk for developing renal dysfunction and/or at risk of developing thrombotic events, it may be prudent to reduce the amount of product infused per unit time by infusing Octagam 5% liquid at a maximum rate less than 0.07 ml/kg (3.3 mg/kg)/minute (200 mg/kg/hour) *(See Boxed Warning, and Dosage and Administration [2.4]).*

5.3 Blood Glucose Monitoring

Blood Glucose Testing [2]: 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 5% liquid as glucose. This has resulted 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 5% liquid, 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.

5.4 Hyperproteinemia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV therapy. The hyponatremia is likely to be a pseudohyponatremia as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. Distinguishing true hyponatremia from pseudohyponatremia is clinically critical, as treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a disposition to thromboembolic events [3].

5.5 Thrombotic events

Thrombosis may occur following treatment with immune globulin products, including Octagam 5% liquid. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer Octagam 5% liquid at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [4],[5],[6]. *(See Boxed Warning, Dosage and Administration [2.4], Patient Counseling Information [17]).*

5.6 Aseptic meningitis syndrome

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IGIV treatment and rapid infusion. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu mm, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. It appears that patients with a history of migraine may be more susceptible. [7] *(See Patient Counseling Information [17]).*

5.7 Hemolysis

IGIV products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis [8]. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration *[See Adverse Reactions]* [9]. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done *(See Patient Counseling Information [17]).*

5.8 Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV [10]. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1-6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions *(See Patient Counseling Information [17]).*

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

5.9 General

Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Octapharma. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient *(See Patient Counseling Information [17]).*

5.10 Laboratory Tests

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done.

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

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

6 ADVERSE REACTIONS

6.1 Adverse Drug Reaction Overview

The most serious adverse reactions observed with Octagam 5% liquid treatment have been immediate anaphylactic reactions, aseptic meningitis, and hemolytic anemia.

The most common adverse reactions observed with Octagam 5% liquid treatment during clinical trial (> 5%) were headache and nausea.

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.

The clinical trial database includes a multi-center, open-label, single arm study in 46 children and adults with PI. Subjects participated in the study for a mean of 346 days and received 300 to 450 mg/kg every 21 days or 400 to 600 mg/kg every 28 days. Infusions were initiated at a rate of 30 mg/kg/hour for the first 30 minutes, and, if tolerated, could be advanced to a maximum tolerated rate not exceeding 200 mg/kg/hour. Over half of the subjects were male (n=28; 61%), and more than half were on the 28-day infusion schedule (n=27; 59%). The mean age of subjects was 31.5 years.

Six subjects experienced a total of 12 SAEs (abdominal pain (2 occurrences), cardiac arrest, pneumonia, cellulitis, coxsackie viral infection, renal calculus (2 occurrences), blood culture positive, ketonuria, gastroenteritis, and colitis pseudomembranous). Eleven of the 12 SAEs were not suspected to be related to study drug; the other SAE was noted before the subject began receiving the next scheduled infusion, and it was not temporally related to the previous infusion.

Pre-medications were used in 165 (25.2%) out of 654 infusions and in 14 (30.4%) out of 46 patients. Infusions were slowed or interrupted in 9 out of 489 infusions (1.84%) without pre-medication and in 10 out of 165 infusions (6.06%) with pre-medication. Five out of 32 (15.63%) patients who never received any pre-medication had at least one slowed or interrupted infusion, whereas 9 out of 14 (64.29%) patients who received pre-medication at least once also had a slowed or interrupted infusion.

Six of the 46 subjects in the trial (13%) were withdrawn from the study: 2 on the subjects' request; 1 because of investigator's decision (non-compliance); 1 because of loss to follow-up; 1 death (cardiac arrest, not suspected to be related to study drug); and 1 by error of the study coordinator.

All adverse events in trial OCTA-06, irrespective of the causality assessment, reported by at least 5% of subjects during the 12-months treatment are given in the table below.

Table 2: Subjects and Infusions with at least one Adverse Event *Irrespective of Causality* (Study OCTA-06)

	Octagam 5% liquid	
	No. of subjects (%)	No. of infusions (%)
Total	46 (100%)	654 (100%)
Nasal congestion	24 (52%)	39 (6%)
Sinusitis NOS	23 (50%)	45 (7%)
Headache NOS	22 (48%)	62 (9%)
Cough	20 (43%)	46 (7%)
Sore throat NOS	16 (35%)	25 (4%)
Fever	15 (33%)	19 (3%)
Vomiting NOS	12 (26%)	15 (2%)
Diarrhoea NOS	11 (24%)	22 (3%)
Bronchitis NOS	10 (22%)	14 (2%)
Abdominal pain upper	9 (20%)	11 (2%)
Arthralgia	9 (20%)	15 (2%)
Nasopharyngitis	8 (17%)	14 (2%)
Rhinorrhoea	8 (17%)	9 (1%)
Upper respiratory tract infection NOS	8 (17%)	13 (2%)
Fatigue	7 (15%)	9 (1%)
Nausea	7 (15%)	8 (1%)
Pain in limb	7 (15%)	10 (2%)
Sinus congestion	7 (15%)	9 (1%)
Back pain	5 (11%)	10 (2%)
Injection site reaction NOS	5 (11%)	11 (2%)
Wheezing	5 (11%)	8 (1%)
Asthma NOS	4 (9%)	5 (0.8%)
Asthma aggravated	4 (9%)	10 (2%)
Chest pain NEC	4 (9%)	4 (0.6%)
Conjunctivitis NEC	4 (9%)	4 (0.6%)
Dyspepsia	4 (9%)	5 (0.8%)
Earache	4 (9%)	6 (0.9%)
Ecchymosis	4 (9%)	7 (1%)
Fungal infection NOS	4 (9%)	4 (0.6%)
Injection site pain	4 (9%)	4 (0.6%)
Insomnia NEC	4 (9%)	4 (0.6%)
Sinusitis acute NOS	4 (9%)	8 (1%)
Urinary tract infection NOS	4 (9%)	8 (1%)
Vaginal candidiasis	4 (9%)	7 (1%)
Abdominal pain NOS	3 (7%)	3 (0.5%)
Dizziness (exc vertigo)	3 (7%)	4 (0.6%)
Dyspnoea NOS	3 (7%)	3 (0.5%)
Epistaxis	3 (7%)	5 (0.8%)
Eye discharge	3 (7%)	3 (0.5%)
Eye irritation	3 (7%)	3 (0.5%)
Hypertension NOS	3 (7%)	5 (0.8%)
Otitis media NOS	3 (7%)	4 (0.6%)
Pain NOS	3 (7%)	4 (0.6%)
Postnasal drip	3 (7%)	3 (0.5%)
Productive cough	3 (7%)	3 (0.5%)
Rigors	3 (7%)	4 (0.6%)
Throat irritation	3 (7%)	3 (0.5%)
Urticaria NOS	3 (7%)	8 (1%)

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The adverse reactions in trial OCTA-06 reported by at least 5% of subjects during the 12-month treatment are given in the table below.

Table 3: Subjects and Infusions with At Least One Adverse Reaction (Study OCTA-06)

	Octagam 5% liquid	
	No. of subjects (%)	No. of infusions (%)
Total	46 (100%)	654 (100%)
Headache NOS	7 (15%)	18 (3%)
Nausea	3 (7%)	4 (0.6%)

The following table provides an overview on the temporally associated adverse events (TAAEs) during and within different time-points after the end of Octagam infusion.

Table 4: Overview on TAAEs Occurring During and Over a Specified Number of Hours after the End of Infusion, *Irrespective of Causality* (Study OCTA-06)

Total # of infusions (N=654)	Time-Points		
	24 hrs	48 hrs	72 hrs
Total # of TAAEs	172	183	189
Proportion of infusions with TAAEs	26.3%	28.0%	28.9%
Upper bound 1 sided 97.5% CI for proportion of TAAEs	29.7%	31.4%	32.4%

All temporally associated adverse events (TAAEs) in trial OCTA-06, irrespective of the causality assessment, reported by at least 5% of subjects within 72 hours after the end of the infusion are given in the table below.

Table 5: TAAEs During and Over 72 Hours After End of Infusion, *Irrespective of Causality* (Study OCTA-06)

TAAE	Subjects (%) n=46	Infusion (%) N=654
Headache NOS	15 (32.6%)	28 (4.3%)
Sinusitis NOS	12 (26.1%)	13 (2.0%)
Nasal congestion	10 (21.7%)	11 (1.7%)
Arthralgia	7 (15.2%)	10 (1.5%)
Cough	7 (15.2%)	7 (1.1%)
Injection site reaction NOS	5 (10.9%)	11 (1.7%)
Sore throat NOS	5 (10.9%)	5 (0.8%)
Vomiting NOS	5 (10.9%)	5 (0.8%)
Back pain	4 (8.7%)	6 (0.9%)
Diarrhoea NOS	4 (8.7%)	5 (0.8%)
Ecchymosis	4 (8.7%)	5 (0.8%)
Injection site pain	4 (8.7%)	4 (0.6%)
Nausea	4 (8.7%)	5 (0.8%)
Upper respiratory tract infection NOS	4 (8.7%)	5 (0.8%)
Wheezing	4 (8.7%)	6 (0.9%)
Asthma aggravated	3 (6.5%)	4 (0.6%)
Eye irritation	3 (6.5%)	3 (0.5%)
Fungal infection NOS	3 (6.5%)	3 (0.5%)
Pain in limb	3 (6.5%)	5 (0.8%)
Rhinorrhoea	3 (6.5%)	3 (0.5%)
Urinary tract infection NOS	3 (6.5%)	3 (0.5%)

The subset of drug related temporally associated adverse events (TAAEs) in trial OCTA-06 reported by at least 5% of subjects within 72 hours after the end of the infusion is given in the table below.

Table 6: *Drug-Related* TAAEs During and Over 72 Hours After End of Infusion (Study OCTA-06)

TAAE	Subjects (%) n=46	Infusion (%) N=654
Headache NOS	6 (13.0%)	15 (2.3%)
Nausea	3 (6.5%)	4 (0.6%)

Laboratory Abnormalities

Standard clinical laboratory evaluations were performed Study OCTA-06. Three subjects (7%) had incidences of AST (>2.5 x ULN) which were all assessed as clinically non-significant. Four subjects (9%) had incidences of serum creatinine increases being stable throughout the course of the study. Therefore, these observations were not regarded as indicative of acute renal dysfunction.

6.3 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Octagam 5% liquid Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Octagam 5% liquid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to Octagam 5% liquid.

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   Fatigue, injection site reaction, pyrexia, chills, chest pain, hot flush, flushing, hyperhidrosis, malaise
Investigations   Hepatic enzymes increased, blood glucose false positive

General

The following adverse reactions have been identified during post-approval use of IGIV products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to IGIV products.

Respiratory   Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular   Cardiac arrest, thromboembolism, vascular collapse, hypotension
Neurological   Coma, loss of consciousness, seizures, tremor
Integumentary   Steven-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
Hematologic   Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
General / Body as a Whole   Pyrexia, rigors
Musculoskeletal   Back pain
Gastrointestinal   Hepatic dysfunction, abdominal pain

7 DRUG INTERACTIONS

Admixtures of Octagam 5% liquid with other drugs and intravenous solutions have not been evaluated. It is recommended that Octagam 5% liquid be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with IGIVs from other manufacturers.

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

Various passively transferred antibodies in immunoglobulin preparations can confound the results of serological testing.

Antibodies in Octagam 5% liquid may interfere with the response to live viral vaccines, such as measles, mumps, and rubella. Physicians should be informed of recent therapy with IGIVs, so that administration of live viral vaccines, if indicated, can be appropriately delayed 3 or more months from the time of IGIV administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Octagam 5% liquid. It is also not known whether Octagam 5% liquid can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Octagam 5% liquid should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

Octagam 5% liquid has not been evaluated in nursing mothers.

8.4 Pediatric Use

Octagam 5% liquid was evaluated in 11 pediatric subjects (age range 6 – 16 years). There were no obvious differences observed between adults and pediatric subjects with respect to pharmacokinetics, efficacy and safety. No pediatric specific dose requirements were necessary to achieve the desired serum IgG levels.

8.5 Geriatric Use

Patients > 65 years of age may be at increased risk for developing certain adverse reactions such as thromboembolic events and acute renal failure *(See Boxed Warning, Warnings and Precautions [5]).* In the clinical trial only 4 geriatric patients (> 65 years) were enrolled, a number insufficient to determine whether geriatric patients respond differently from younger subjects. In these 4 patients no particular issues were observed.

10 OVERDOSAGE

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

11 DESCRIPTION

Immune Globulin Intravenous (Human), Octagam 5% liquid, is a solvent/detergent (S/D)-treated, sterile preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. Octagam 5% liquid is a solution for infusion which must be administered intravenously.

All units of human plasma used in the manufacture of Octagam 5% liquid are provided by FDA-approved blood establishments only, and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV-1 and found to be non-reactive (negative).

The product is manufactured by the cold ethanol fractionation process followed by ultrafiltration and chromatography. The manufacturing process includes treatment with an organic S/D mixture composed of tri-n-butyl phosphate (TNBP) and Triton X-100 (Octoxynol). The Octagam 5% liquid manufacturing process provides a significant viral reduction in *in vitro* studies (table 7). These reductions are achieved through a combination of process steps including cold ethanol fractionation, S/D treatment and pH 4 treatment.

Table 7: In vitro reduction factor during Octagam 5% liquid manufacturing

Production step	In vitro reduction factor [$\log_{10}$]				
	Enveloped viruses			Non-enveloped viruses	
	HIV-1	PRV	SBV	MEV	PPV
Cold ethanol fractionation	≥ 4.81	≥ 6.28	≥ 7.13	≥ 7.13	≥ 6.53
S/D treatment	≥ 4.93	5.23	≥ 6.77	Not applicable	
pH4 treatment	≥ 4.33	≥ 6.71	6.71	5.07	< 1*
Global reduction factor	≥ 14.07	≥18.22	≥ 20.61	≥ 12.20	≥ 6.53

*not calculated for global LRF

HIV-1: Human Immunodeficiency Virus - 1

PRV: Pseudorabies Virus

SBV: Sindbis Virus

MEV: Mouse Encephalomyelitis Virus

PPV: Porcine Parvovirus

11.1 Composition

The composition of Octagam 5% liquid is shown in table 8 as follows:

Table 8 : Composition

Component	Quantity/ml
Protein, of which not less than 96% is human normal immunoglobulin G	50 mg
Maltose	100 mg
Triton X-100	not more than 5 mcg
TNBP	not more than 1 mcg
IgA	not more than 0.2 mg
IgM	not more than 0.1 mg
Water for Injection	ad.

This preparation contains approximately 50 mg of protein per ml (5%) of which not less than 96% is human normal immunoglobulin G. Octagam 5% liquid contains not more than 3% aggregates, not less than 90% monomers and dimers and not more than 3% fragments.
The sodium content of the final solution is not more than 30 mmol/l and the pH is between 5.1 and 6.0. The osmolality is 310 - 380 mosmol/kg.
The manufacturing process for Octagam 5% liquid isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. Octagam 5% liquid contains the IgG antibody activities present in the donor population. IgG subclasses are fully represented with the following approximate percents of total IgG: IgG_1 is 65%, IgG_2 is 30%, IgG_3 is 3% and IgG_4 is 2%.
Octagam 5% liquid contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins.
Octagam 5% liquid contains no preservative and no sucrose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Octagam 5% liquid supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria or their toxins. The mechanism of action in PI has not been fully elucidated.

12.2 Pharmacodynamics

Octagam 5% liquid 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 5% liquid which is prepared from pooled material from not less than 1000 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. Standard pharmacodynamic studies were not performed.

12.3 Pharmacokinetics

Peak levels of IgG are reached immediately after infusion of Octagam 5% liquid. It has been shown that after infusion, exogenous IgG is distributed relatively rapidly between plasma and extravascular fluid until approximately half is partitioned in the extravascular space. Therefore a rapid initial drop in serum IgG is expected [11].
Studies show that the apparent half-life of Octagam 5% liquid is approximately 40 days in immunodeficient patients.
The main pharmacokinetic parameters of Octagam 5% liquid measured as total IgG in study OCTA-06 are displayed below:
In the pharmacokinetic study, a subset of 14 patients aged between 10 and 70 years with PI underwent pharmacokinetic assessments. Patients received infusions of Octagam 5% liquid (300 to 600 mg/kg) every 3 (n=6) to 4 (n=8) weeks for 12 months. Pharmacokinetic samples were collected at baseline and after the 5th month of treatment. After the infusion, blood samples were taken until day 28 (for patients on a 21 day schedule, the interval was extended to 4 weeks for the pharmacokinetic study).

Table 9: PK Parameters of Octagam 5% liquid (Study OCTA-06)

	Octagam 5% liquid			
	N	Mean	SD	Median
Cmax (mg/mL)	14	16.7	3.2	16.4
AUC (mg*h/mL)	14	7022	1179	7103
T1/2 (days)	14	40.7	17.0	36.3
Trough IgG Level 21 Day Infusion Schedule (mg/dL)	19	881.6	151.5	859
Trough IgG Level 28 Day Infusion Schedule (mg/dL)	25	763.5	156.8	760

The half-life of IgG can vary considerably from person to person. In particular, high concentrations of IgG and hypermetabolism associated with fever and infection have been seen to coincide with a shortened half-life of IgG. Longer half-lives are often seen with immunodeficient patients [12].

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies were conducted on carcinogenesis, mutagenesis, or impairment of fertility with Octagam 5% liquid. Repeated-dose toxicity studies and the genotoxic studies gave no evidence of carcinogenic properties of TNBP and Octoxynol [13], [14].
The results of *in vitro* and *in vivo* genotoxicity studies for TNBP and Octoxynol were negative. The results of studies on the embryotoxic and teratogenic properties of TNBP and Octoxynol in rats and rabbits at a wide range of i.v. doses were also negative.

13.2 Animal Toxicology and/or Pharmacology

No studies were conducted on non-clinical pharmacology, toxicology, local tolerance or pharmacokinetics with Octagam 5% liquid.
A variety of single-dose toxicity studies were performed for TNBP and Octoxynol alone or in combination. The lowest toxic dose of TNBP + Octoxynol (1+5) was 10,000 mcg/kg BM in rats after intravenous administration. Studies on 13-week toxicity were performed for combinations of TNBP + Octoxynol in a broad dose range intravenously in dogs and rats. In these studies the lowest toxic dose for rats was local 60 mcg TNBP/kg +300 mcg Octoxynol/kg BM i.v. (concentration: 0.0006% and 0.003%, respectively) and systemic 300 mcg TNBP/kg + 1,500 mcg Octoxynol/kg BM i.v. (concentration: 0.003% and 0.015%, respectively). The lowest toxic dose for dogs was local 50 mcg TNBP/kg + 250 mcg Octoxynol/kg BM i.v. (concentration: 0.005% and 0.025%, respectively) and systemic 500 mcg TNBP/kg + 2,500 mcg Octoxynol/kg BM i.v. (concentration: 0.05% and 0.25%, respectively).
Local tolerance of TNBP and Octoxynol was evaluated from the experiments on repeat-dose toxicity (rats, dogs) and on developmental toxicity (rats, rabbits). In these animal studies the lowest dose exerting local adverse reactions was 50 + 250 mcg/kg BM (TNBP + Octoxynol; daily injections) in dogs. At this dose 4 out of 6 dogs were affected starting in week 7 of treatment.
A pharmacokinetic study was carried out in rats given 300 mcg of TNBP/kg and 1,500 mcg Octoxynol/kg BM i.v. The plasma half-life for TNBP was approximately 20 minutes. Octoxynol was not detected.

14 CLINICAL STUDIES

In an open-label, multicenter study, 46 patients (including 10 patients between the ages of 6 and 12, and one 15 years old) with primary humoral immunodeficiency (PI) received Octagam 5% liquid individualized doses of 300 - 600 mg/kg every 3 or 4 weeks for 12 months. Six patients discontinued the study prematurely.
Eligible patients had to meet the following key inclusion criteria: aged 3 years or older; had a PI that had as a significant component hypogammaglobulinemia or antibody deficiency; had been receiving IGIV replacement therapy at a steady dose for at least 3 months prior to study entry and had maintained a trough level of at least 320 mg/dL above baseline serum IgG levels.
Patients were excluded if they had a history of severe reactions to blood or any blood-derived product; if they had a selective IgA deficiency or demonstrable antibodies to IgA; if they received blood or any blood product or derivative other than a commercially available IGIV within 3 months prior to study entry; if they had hepatic function abnormalities or a positive direct Coombs test at screening; if they had a pre-existing renal impairment, a history of drug or alcohol abuse in the previous 12 months or acquired medical condition known to cause secondary immune deficiency; if they were receiving long-term daily treatment with steroids at a dose of at least 1 mg/kg/day; if they had a requirement for pre-medication for IGIV infusion other than aspirin, acetaminophen, or other non-steroidal anti-inflammatory drug, or antihistamine; and if the received immunosuppressive or immunomodulatory drugs.
The primary efficacy endpoint was the number of episodes of serious infections/patient/year. Serious infection included pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscesses or bacterial or viral meningitis. Secondary efficacy variables were: the number of days of work/school missed; the number and days of hospitalizations; the number of visits to physicians for acute problems and/or visits to hospital emergency rooms; and the number of other infections documented by radiograph and fever.
For the primary endpoint, which was the number of episodes of serious infections, the observed rate was 0.1 infections per patient per year (5 infections over 43.5 patient-years).

Table 10: Summary of Secondary Efficacy Variables

Variable	Subjects N	Subjects %	Total Days or Visits	Total Subject Years	Days or Visits/Subj./Year Estimate
Work/School Days Missed	30	65	241	43.5	5.5
Days in Hospital	4	9	16	43.5	0.4
Visits to Physician/ER	27	59	92	43.5	2.1

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16 HOW SUPPLIED/STORAGE AND HANDLING

Octagam 5% liquid is supplied in 1.0 g, 2.5 g, 5 g, 10 g or 25 g single use bottles.

NDC Number	Size	Grams Protein
68982 – 840 – 01	**20 ml**	**1.0**
68982 – 840 – 02	**50 ml**	**2.5**
68982 – 840 – 03	**100 ml**	**5.0**
68982 – 840 – 04	**200 ml**	**10.0**
68982 – 840 – 05*	**500 ml**	**25.0**

*manufacturing site Octapharma Vienna only

Octagam 5% liquid is not supplied with an infusion set. If a filtered infusion set is used (not mandatory), the filter size must be 0.2 – 200 microns.
Components used in the packaging of Octagam 5% liquid are latex-free.
Octagam 5% liquid may be stored for 24 months at +2°C to + 25°C (36°F to 77°F) from the date of manufacture.
Do not use after expiration date.
Do not freeze. Frozen product should not be used.
Any unused product or waste material should be disposed of in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Inform patients of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should contact their physicians immediately.

Inform patients to also immediately report the following to their physician:

- signs and symptoms of renal failures, such as decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath
- signs and symptoms of aseptic meningitis, such as headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting
- signs and symptoms of hemolysis, such as fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine
- signs and symptoms of TRALI, such as severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, fever. TRALI typically occurs within 1 to 6 hours following transfusion.

Thrombosis

Instruct patients to immediately report symptoms of thrombosis, These symptoms may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.

Inform patients that Octagam 5% liquid is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses, and, theoretically, the CJD agent). Inform patients that the risk Octagam 5% liquid may transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing the donated plasma for certain virus infections and by inactivating and/or removing certain viruses during manufacturing.

Inform patients that administration of IgG may interfere with the response to live viral vaccines such as measles, mumps and rubella. Inform patients to notify their immunizing physician of therapy with Octagam 5% liquid.

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