Immune Globulin Intravenous (Human) 5%
Solvent/Detergent Treated

OCTAGAM®

U.S. License No.

Rx only

DESCRIPTION

Immune Globulin Intravenous (Human) [IGIV], OCTAGAM, is a solvent/detergent treated, sterile, 5% liquid preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. All units of human plasma used in the manufacture of OCTAGAM 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 nonreactive (negative).

The product is manufactured by the Cohn-Oncley cold ethanol fractionation process followed by ultrafiltration and chromatography. The manufacturing process includes treatment with an organic solvent/detergent (S/D) mixture composed of tri-n-butyl phosphate (TNBP) and Triton X-100. The OCTAGAM manufacturing process provides a significant viral reduction in *in vitro* studies (table 1). These reductions are achieved through a combination of process steps including Cohn fractionation, S/D treatment and pH 4 treatment.

Table 1: In vitro reduction factor during OCTAGAM manufacturing

Production step	In vitro reduction factor [$\log_{10}$]					
	Enveloped viruses			Non-enveloped viruses		
	HIV-1	PRV	SBV	MEV	PPV	SV40
*Cohn fractionation	≥5.5	≥7.3	≥6.4	≥4.9	≥7.8	≥5.5
S/D treatment	≥6.0	≥8.4	≥7.8	Not applicable (non-enveloped viruses)		
pH4 treatment	≥8.6	≥7.7	≥8.9	≥6.2	2.4	1.2
Global reduction factor	≥20.1	≥23.4	≥23.1	≥11.1	≥10.2	≥6.7

*Removal of fraction I+III.

HIV-1: Human Immunodeficiency Virus - 1
PRV: Pseudorabies Virus
SBV: Sindbis Virus
MEV: Mouse Encephalomyelitis Virus
PPV: Porcine Parvovirus
SV40: Simian Vacuolating 40 Virus

The composition of OCTAGAM is as follows:

Component	**Quantity/ml**	
Protein, of which ≥ 96% is human normal immunoglobulin G	50	mg
Maltose	100	mg
Triton X-100	≤ 5	mcg
TNBP	≤ 1	mcg
IgA	≤ 0.1	mg
IgM	≤ 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 contains ≤ 3% aggregates, ≥ 90% monomers and dimers and ≤ 3% fragments.

The sodium content of the final solution is = 30 mmol/l and the pH is between 5.1 and 6.0.[1] The osmolality is 310 - 380 mosmol/kg.

The manufacturing process for OCTAGAM isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact.[2] OCTAGAM contains the IgG antibody activities present in the donor population. IgG subclasses are fully represented with the following approximate percents of total IgG[3]: IgG_1 is 65%, IgG_2 is 30%, IgG_3 is 3% and IgG_4 is 2%.

OCTAGAM contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins.

OCTAGAM contains no preservative and no sucrose.

CLINICAL PHARMACOLOGY

Peak levels of IgG are reached immediately after infusion of OCTAGAM. 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.[4]

Studies show that the apparent half-life of OCTAGAM is approximately 40 days in immunodeficient patients.

Previous studies reported endogenous IgG half-life values of 25 to 30 days.[5]

The main pharmacokinetic parameters of OCTAGAM, measured as total IgG in study OCTA-06 are displayed below:

Table 2: PK Parameters of OCTAGAM 5% (Study OCTA-06)

	OCTAGAM 5%			
	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 lgG can vary considerably from person to person. In particular, high concentrations of lgG 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.[6-8]

In an open-label, multicenter study, 46 patients (including 10 patients between the ages of 2 and 12, and one 15 years old) with Primary Immune Deficiency (PID) received OCTAGAM individualized doses of 300 - 600 mg/kg every 3 or 4 weeks for 12 months.

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). On average, 0.4 days of hospitalization per patient were documented, and for 5.2 days patients were absent from work or school. The mean number of visits to a physician or emergency room was also very low (n=2).

Table 3: Summary of Secondary Efficacy Variables

Variable	Subjects N	%	Total Days or Visits	Total Subject Years	Days or Visits/Subject/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

INDICATIONS AND USAGE

Primary Immune Deficiency Diseases

OCTAGAM is indicated for the treatment of primary immune deficient diseases, such as: congenital agammaglobulinemia and hypogammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

This indication was supported by a study in 46 patients who received a total of 654 infusions.

CONTRAINDICATIONS

Intolerance to homologous immunoglobulins, especially in very rare cases of immunoglobulin A (IgA) deficiency, when the patient has IgE mediated antibodies to IgA.

WARNINGS

Immune Globulin intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death[16]. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as stabilizer accounted for a disproportionate share of the total number.

OCTAGAM does not contain sucrose.

See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Immune Globulin Intravenous (Human), OCTAGAM, should only be administered intravenously. Other routes of administration have not been evaluated.

OCTAGAM should be given at the infusion rate under DOSAGE AND ADMINISTRATION at least until the physician has had adequate experience with a given patient.

Immediate anaphylactic and hypersensitivity reactions are a rare possibility.[9]

Epinephrine should be available for treatment of any acute anaphylactoid reactions.

OCTAGAM contains only trace amounts of IgA (≤ 0.1 mg/ml in a 5% solution). Nonetheless, it should not be given to patients with IgE mediated antibodies to IgA or selective IgA deficiencies.[10]

OCTAGAM is made from human plasma of US origin. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. 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

(Tel. no. 1-800-826-6905). The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

PRECAUTIONS

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. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and 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.[11-13]

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, and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. [14-18]

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing OCTAGAM at a maximum rate less than 0.07 ml/kg (3.3 mg/kg)/minute (200 mg/kg/hour).

Assure that patients are not volume depleted prior to the initiation of the infusion of OCTAGAM.

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.[19-22] Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration [see Adverse Reactions].[23] IGIV recipients should be monitored for clinical signs and symptoms of hemolysis.

Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV.[24] 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.

Thrombotic Events

Thrombotic events have been reported in association with IGIV [see Adverse Reactions].[25-27] Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity.

The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. 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.

Laboratory Tests

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

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

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

Information for Patients

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

Drug Interactions

Antibodies in OCTAGAM 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.

See **Dosage and Administration** Section.

Pregnancy Category C

Animal reproduction studies have not been performed with OCTAGAM. It is also not known whether OCTAGAM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. OCTAGAM should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

In general, reported adverse reactions to OCTAGAM in patients with either congenital or acquired immunodeficiencies are similar in kind and frequency to other IGIV products. Various minor reactions, such as headache, chills, backache, chest pain, fever, allergic reactions, arthralgia, dizziness, changes in blood pressure, cutaneous reactions and/or nausea and vomiting may occasionally occur. Reactions to intravenous immunoglobulins tend to be related to the rate of infusion.

Cases of reversible aseptic meningitis and migraine and isolated cases of reversible hemolytic anemia and reversible increases in liver function tests have been observed with OCTAGAM.

Immediate anaphylactic and hypersensitivity reactions are a remote possibility. Epinephrine should be available for treatment of any acute anaphylactoid reaction. (See Warnings).

Postmarketing

The following adverse reactions have been identified and reported during the post-approval use of IGIV products:

Respiratory Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated 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

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction, or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently**.**

Primary Immunodeficiency Diseases

All adverse event in trial OCTA-06, irrespective of the causality assessment, reported by at least 15% of subjects during the 12-months treatment are given in the table below.

Table 4: Subjects with at least one Adverse Event *Irrespective of Causality* (Study OCTA-06)

	OCTAGAM 5% No. of subjects: 46	
	No. of subjects	Percentage of all subjects
Nasal congestion	24	52%
Sinusitis NOS	23	50%
Headache NOS	22	48%
Cough	20	44%
Sore throat NOS	16	35%
Fever	15	33%
Vomiting NOS	12	26%
Diarrhoea NOS	11	24%
Bronchitis NOS	10	22%
Abdominal pain upper	9	20%
Arthralgia	9	20%
Nasopharyngitis	8	17%
Rhinorrhoea	8	17%
Upper respiratory tract infection NOS	8	17%
Fatigue	7	15%
Nausea	7	15%
Pain in limb	7	15%
Sinus congestion	7	15%

The severity of the adverse events is displayed below.

Table 5: Severity of Adverse Events *Irrespective of Causality* (Study OCTA-06)

	OCTAGAM 5%
	No. of events with severity statement: 484
Mild	351 (72%)
Moderate	124 (26%)
Severe	9 (2%)

The subset of drug related adverse events in trial OCTA-06 reported by at least 3% of subjects during the 12-month treatment is given in the table below.

Table 6: Subjects with At Least One *Drug Related* Adverse Event (Study OCTA-06)

	OCTAGAM 5% No. of subjects: 46	
	No. of subjects	Percentage of all subjects
Headache NOS	7	15%
Nausea	3	7%
Back pain	2	4%
Chest pain NEC	2	4%
Injection site reaction NOS	2	4%
Rigors	2	4%

DOSAGE AND ADMINISTRATION

Primary Immunodeficiency Diseases

As there are significant differences in the half-life of IgG among patients with primary 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 usual dose of OCTAGAM for replacement therapy in primary immunodeficiency diseases is 300 to 600 mg/kg body weight administered every 3 to 4 weeks. Doses may be adjusted over time to achieve the desired trough levels and clinical responses.

Rate of Administration

It is recommended that a 5% solution be initially infused at a rate of 30 mg/kg/hour for the first 30 minutes; if tolerated, advance to 60 mg/kg/hour for the second 30 minutes; and if further tolerated, advance to 120 mg/kg/hour for the third 30 minutes. Thereafter the infusion can be maintained at a rate up to, but not exceeding, 200 mg/kg/hour.

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing OCTAGAM at a maximum rate less than 0.07 ml/kg (3.3 mg/kg)/minute (200 mg/kg/hour).

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.

Rate of Administration	mg/kg/hour	ml/kg/min
first 30 min	30	0.01
next 30 min	60	0.02
next 30 min	120	0.04
maximum	<200	<0.07

Drug Interactions

Admixtures of OCTAGAM with other drugs and intravenous solutions have not been evaluated. It is recommended that OCTAGAM 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.

Various passively transferred antibodies in immunoglobulin preparations can confound the results of serological testing.[28]

OCTAGAM contains maltose which could interfere with blood and urine glucose tests.

Administration

OCTAGAM should be at room temperature during administration.

Any vial that has been entered should be used promptly. Partially used vials should be discarded.

Parenteral drug products should be inspected visually for turbidity and discoloration prior to administration, whenever solution and container permit. Do not use if turbid and/or discoloration is observed.

HOW SUPPLIED

OCTAGAM is supplied in 1.0 g, 2.5 g, 5 g or 10 g single use bottles

NDC Number	Size	Grams Protein
67467 – 843 - 01	**20 ml**	**1.0**
67467 – 843 - 02	**50 ml**	**2.5**
67467 – 843 - 03	**100 ml**	**5.0**
67467 – 843 - 04	**200 ml**	**10.0**

OCTAGAM is not supplied with an infusion set. If an infusion set is used (not mandatory), the filter size must be 0.2 – 200 microns.

STORAGE

OCTAGAM may be stored for 24 months at +2 °C to +8 °C (36 °F to 46 °F) or may be stored at temperatures not to exceed +25 °C (77 °F) for up to 18 months from the date of manufacture.

Do not use after expiration date.

CAUTION

U.S. federal law prohibits dispensing without prescription.

Manufactured by: OCTAPHARMA Pharmazeutika
Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Distributed by: Octapharma USA, Inc.
13800 Coppermine Road
Herndon, Virginia 20170
1-800-826-6905

Revision date: March 2004

REFERENCES

1. Bergstroem J,.Hultman E. Normal Plasma-Sodium Values. *Lancet* 1962.
2. Buchacher A, Biesert L, Helmich B. [Requirements to a 4th generation IGIV - Characteristics of Octagam; product overview]. *HAMOSTASEOLOGIE.* 1996;16:74-7.
3. Shakib F, Stanworth DR, Drew R, Catty D. A quantitative study of the distribution of IgG sub-classes in a group of normal human sera. *J.Immunol.Methods* 1975;8:17-28.
4. Waldmann TA,.Strober W. Metabolism of immunoglobulins. *Prog.Allergy* 1969;13:1-110.
5. Eibl MM,.Wedgwood RJ. Intravenous immunoglobulin: a review. *Immunodefic.Rev.* 1989;1 Suppl:1-42.
6. Lever AM, Yap PL, Cuthbertson B, Wootton R, Webster AD. Increased half-life of gammaglobulin after prolonged intravenous replacement therapy. *Clin Exp.Immunol* 1987;67:441-6.
7. Morell A, Riesen W. Structure, function and catabolism of immunoglobulins. pp 17-26. 1981.
8. Stiehm ER. Standard and special human immune serum globulins as therapeutic agents. *Pediatrics* 1979;63:301-19.
9. Duhem C, Dicato MA, Ries F. Side-effects of intravenous immune globulins. *Clin.Exp.Immunol.* 1994;97 Suppl 1:79-83.
10. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. *N.Engl.J Med.* 1986;314:560-4.
11. Casteels-Van Daele, Wijndaele L, Brock P, Kruger M, Gillis P. Aseptic meningitis associated with high dose intravenous immunoglobulin therapy [letter; comment]. *J.Neurol.Neurosurg.Psychiatry* 1992;55:980-1.
12. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors [see comments]. *Ann Intern.Med.* 1994;121:259-62.
13. Watson JD, Gibson J, Joshua DE, Kronenberg H. Aseptic meningitis associated with high dose intravenous immunoglobulin therapy. *J.Neurol.Neurosurg.Psychiatry* 1991;54:275-6.
14. Ahsan N. Intravenous immunoglobulin induced-nephropathy: a complication of IVIG therapy. *J Nephrol.* 1998;11:157-61.
15. Brannagan TH, Nagle KJ, Lange DJ, Rowland LP. Complications of intravenous immune globulin treatment in neurologic disease. *Neurology* 1996;47:674-7.
16. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. *J Am.Soc.Nephrol.* 1997;8:1788-94.

17. Misbah SA,.Chapel HM. Adverse effects of intravenous immunoglobulin. *Drug Saf.* 1993;9:254-62.

18. Schifferli JA. High-dose intravenous immunoglobulin treatment and renal function. In Dominioni L, Nydegger UE, eds. *Intravenous immunoglobulins today & tomorrow*, pp 27-33. London: Royal Society of Medicine Services Ltd., 1992.

19. Ahsan N, Palmer BF, Wheeler D, Greenlee-RG J, Toto RD. Intravenous immunoglobulin-induced osmotic nephrosis. *Arch.Intern.Med.* 1994;154:1985-7.

20. Copelan EA, Strohm PL, Kennedy MS, Tutschka PJ. Hemolysis following intravenous immune globulin therapy. *Transfusion* 1986;26:410-2.

21. Reinhart WH,.Berchtold PE. Effect of high-dose intravenous immunoglobulin therapy on blood rheology. *Lancet* 1992;339:662-4.

22. Thomas MJ, Misbah SA, Chapel HM, Jones M, Elrington G, Newsom DJ. Hemolysis after high-dose intravenous Ig [letter]. *Blood* 1993;82:3789.

23. Kessary-Shoham H., Levy Y, Shoenfeld Y, Lorber M, Gershon H. In vivo administration of intravenous immunoglobulin (IVIg) can lead to enhanced erythrocyte sequestration. *JOURNAL OF AUTOIMMUNITY.* 1999;13:129-35.

24. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001;41:264-8.

25. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994;44:223-6.

26. Wolberg AS, Kon RH, Monroe DM, Hoffman M. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. *Am.J Hematol.* 2000;65:30-4.

27. Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986;2:217-8.

28. Siber GR, Werner BG, Halsey NA, Reid R, Almeido HJ, Garrett SC *et al*. Interference of immune globulin with measles and rubella immunization. *J Pediatr.* 1993;122:204-11.