Product Approval Information
Summary Basis of Approval
OCTAGAM® 5%

I. General Information

Licensed Product Name:	Immune Globulin Intravenous (Human) 5%
Proprietary Product Name:	OCTAGAM®
Other Name:	n.a.
Name and Address of Sponsor:	OCTAPHARMA Pharmazeutika Produktionsges. m. b. H. Oberlaaer Strasse 235 A – 1100 Vienna, Austria
Biologics License Application (BLA) Tracking Number:	STN 125062
Date of Submission:	June 14, 2002
Date of Filing:	August 14, 2002
Review Designation:	
Date of Licensure:	

II. Indications for Use

OCTAGAM, a liquid, room temperature storable IGIV, 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.

OCTAGAM is especially useful when high levels or rapid elevation of circulating IgG are desired or when intramuscular injections are contraindicated (e.g., small muscle mass).

III. Dosage Form, Route of Administration, and Recommended Dosage

OCTAGAM 5% is a solution for intravenous infusion, supplied in the dosage strength of 50 mg human normal immunoglobulin G / ml.
The following pack sizes are supplied: 20 ml, 50 ml, 100 ml and 200 ml.

OCTAGAM contains protein, of which ≥ 96% is normal immunoglobulin G derived from human plasma.

Fc function, as measured by the European Pharmacopoeial compendial method, was ≥80% at the time of release.

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.

OCTAGAM is recommended to be infused at a rate of 30 mg/kg/hour for the first 30 minutes; if tolerated, advanced to 60 mg/kg/hour for the second 30 minutes; and if tolerated, advanced to 120 mg/kg/hour for the third 30 minutes. Thereafter the infusion could be maintained at a rate up to, but not exceeding, 200 mg/kg/hour.

IV. Manufacturing, Chemistry, and Controls

Overview of Manufacturing Process

OCTAGAM, is a solvent/detergent and pH 4 treated, sterile, 5% liquid preparation of highly purified immunoglobulin G (IgG) derived from pools of human plasma of at least 1000 donors. (21 CFR, § 640.102)

The crude intermediate, Fr. II paste, is manufactured by the Cohn-Oncley cold ethanol fractionation process. Thereafter, this intermediate is purified by several filtrations, ultrafiltration, liquid phase extraction and solid phase extraction steps. The sterile bulk solution is aseptically filled into siliconized, sterile, pyrogen-free glass bottles. The bottles are closed with rubber stoppers and overseals. Each vial undergoes visual inspection before being labelled and packed.

The viral safety of the finished product is achieved through a combination of process steps including Cohn fractionation (separation of fraction I+III), solvent/detergent treatment (mixture of tri-n-butyl phosphate and Triton X-100) and low pH treatment (pH 4).

Validation of Assays Used for OCTAGAM 5% - Final Container Product

The quantitative assays to characterize final product were performed according to the

requirements of the USP and CFR respectively, or if not mentioned there other Pharmacopoeias were applied, e.g. the European Pharmacopoeia (EP).
The scope for validations is given in the ICH guidelines. In case of a specific guide its requirements were utilized. Whenever available international standards (WHO) were used for calibration.

The following test methods on final container product were validated for the determination of required quality attributes:

Protein Composition by cellulose acetate electrophoresis (USP)
pH-value (USP)
Osmolality (USP)
Chloride by potentiometry
Sodium, Potassium by Flame-Photometry (EP)
Aluminum by AAS
Maltose by HPLC
Molecular Weight Distribution of Immunoglobulin by HPLC (EP)
Tri-n-butylphosphate (TNBP) with GC
Octoxynol 9 (Triton X-100) with HPLC
Anti-Diphteria IgG by Toxin Neutralization
Anti-Measles Virus IgG by Virus Neutralization
Anti-Polio Type 1 IgG by Virus Neutralization Anti- Hepatitis B-surface-antigen by ELISA
Prekallikrein Activator by Chromogenic Substrate Assay (EP)
Total Protein by Kinetic Nephelometry (EP)
IgM Concentration by Kinetic Nephelometry
IgG-concentration by Kinetic Nephelometry
IgA Content with Radial Immunodiffusion
Anti-A and anti-B-Hemagglutinins (EP)
Irregular anti-D Antibodies by indirect Coombs-method

Validations according to specific guidelines:

Bacterial Endotoxins by Limulus Amebocyte Lysate Test, chromogenic method (USP)
Test for Sterility by Membrane Filtration Method (USP)
Pyrogen Testing (CFR)

Validation of Manufacturing

The validation of the OCTAGAM manufacturing process was carried out in 2001. Critical process parameters and acceptance criteria were defined based on the results from previous validation studies and extensive experience with the production process.

The manufacturing process of OCTAGAM follows the Cohn fractionation process. After cryo-precipitation the Factor IX complex may optionally be mass-captured from the supernatant. Those options have been validated and compared.
Based on the results, reproducibility of the manufacturing process through to the final product could be demonstrated with consistent quality. In-process controls and final

container test results obtained from these validation batches have been compared. All results are consistent and within the established limits.

In 2003, identical equipment (a chromatography column and the ultra/diafiltration units) dedicated for US plasma only was introduced. Hence, the manufacturing process was revalidated. Data from the revalidation confirmed the initial validation results, which have been obtained in 2001.

Validation of Viral Safety

The OCTAGAM manufacturing process includes a number of different steps which can remove or inactivate any potential virus load in the starting plasma, and so ensure the viral safety of the finished product. The efficacy of these steps has been validated with a panel of both actual and model viruses. With regards to enveloped viruses, viral clearance is achieved primarily by solvent/detergent (S/D) treatment with tri-n-butyl phosphate (TNBP) and Triton X-100, with additional clearance by pH 4 treatment and Cohn fractionation. With regards to non-enveloped viruses, Cohn fractionation is the most significant step, but the pH 4 treatment also contributes to the overall clearance.

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

Stability Studies of Final Container Product

Stability data for the final container of 3 consecutive production batches of OCTAGAM, produced in 1998 were submitted including all filling sizes:
20 ml/1g, 50 ml/2.5g, 100 ml/5g, 200 ml/10g.
In accordance to ICH guidelines the samples had been stored at +5 °C and at +25 °C/60 % RH with testing up to 36 months.
The product was also stored at +30 °C/70 % RH with testing up to 36 months and at +40 °C/75 % RH with testing up to 6 months to cover possible temperature deviations that might occur during shipping.
Photostability studies were carried out at +25 °C/60 % RH with testing up to 12 months.

Furthermore samples were stored in inverted position at +25 °C/60 % RH with testing up to 36 months to investigate a possible impact of stopper contact on the product.
Tests included clarity, coloration, immunoelectrophoresis, pH, osmolality, CAF-electrophoresis, molecular size distribution, anticomplementary activity, prekallikrein activator, IgG content, IgA content, IgM content, Anti-streptolysin O antibodies, aluminum, maltose, HBsAg antibodies, HAV antibodies, Parvo B 19 antibodies, sterility, pyrogens, F_c function, CMV antibodies, endotoxins, SDS-PAGE.
The above study confirms the stability of the product when maintained at +5°C and +25°C/60 % RH as defined in the corresponding specification.
In addition, prolonged exposure of inverted samples to +25°C/60 % RH indicates the stability of OCTAGAM and also demonstrates compatibility of the drug with the container/closure system.
Under accelerated conditions at +40°C/75 % RH the finished product was stable up to 3 months. The ICH guideline for stability of new drugs was confirmed since all test results at +30°C/70 % RH meet the specification up to 12 months.
Photostability studies of the final containers did not show any degradation at all.
The combined data demonstrate a product that is stable at both refrigerated and controlled room temperature conditions. Thereby the data support the proposed shelf life and storage conditions.

Shelf Life and Storage Conditions of Final Container Product

On the basis of stability data provided for the final product, the approved shelf life is 24 months if stored at +2°C to +8°C (36°F to 46°F), and 18 months if stored at $\leq$ +25 °C (77°F). Protection from light is ensured by the outer carton.

The date of manufacture is defined as the date of final sterile filtration of the formulated drug product.

Labeling

The labeling of OCTAGAM is composed of a package insert, bottle labels and carton labels.
The outer carton label and the bottle label state the name of drug, NDC code, strength, route of administration, prescription status, composition, storage conditions, expiry date, lot number, manufacturer and distributor.

Pre-Licensing Inspection of Octapharma Pharmazeutika Produktionsges. m.b.H

The pre-approval inspection at the manufacturing site of Octapharma Pharmazeutika Produktionsgesellschaft m.b.H. in Vienna, Austria was carried out by the Agency from January 23 to February 04, 2003. The observations presented in the Form 483 were resolved. The response information package was submitted to CBER on April 09, 2003. No further comments or questions have been raised by the Agency; thus the manufacture of OCTAGAM is considered to comply with information given in the Biologics License Application.

V. Non-Clinical Pharmacology and Toxicology

Since OCTAGAM is a native immunoglobulin, which is a normal constituent of human plasma to be used at physiological levels, the standard pharmacodynamic and toxicity studies generally carried out for new substances are not applicable to this product.

However, toxicity studies were conducted for tri-n-butyl phosphate (TNBP) and octyl phenyl-polyethylene glycol ether (Triton X-100). TNBP and Triton X-100 are used in the manufacture of OCTAGAM and are present in maximum residual amounts of ---1 and ---- 5 µg/ml, respectively. TNBP and Triton X-100 were tested in combination (1+5).
These toxicity studies were carried out in accordance with the relevant GLP guidelines valid at the time (Good Laboratory Practice Regulations issued by the EC, USA, OECD and Japan).

The usual replacement therapy with OCTAGAM in primary immunodeficiency (300 to 600 mg/kg every 3 to 4 weeks) results in maximum doses of TNBP and Triton X-100 of 12 µg/kg and 60 µg/kg, respectively, per single injection.

Single-dose toxicity studies in rats revealed intravenous doses of 1.7 mg/kg TNBP and 8.3 mg/kg Triton X-100 (sum dose= 10 mg/kg) as lowest toxic dose.
Toxic effects observed were ataxia, dyspnoea, reduced motility, reduced muscle tone, tonic convulsions, prone or lateral position and mydriasis. Autopsies revealed no substance-related pathological changes.

From these acute studies a therapeutic ratio of $\geq$ 139 was calculated:

$$\frac{\text{Lowest toxic dose in animals (10,000 µg/kg i.v.)}}{\text{Maximum human “therapeutic” dose (}\leq 12 + \leq 60 = \leq 72 \text{ µg/kg i.v.)}} = \geq 139$$

Repeat-dose toxicity studies were targeted for 13 weeks with daily intravenous treatment in rats and dogs. At 60 µg/kg TNBP + 300 µg/kg Triton X-100, rats showed first signs of local adverse reactions. At 300 µg/kg TNBP + 1,500 µg/kg Triton X-100 treatment had to be terminated after week 6 because of local side effects. Dogs showed mild local reactions after 50 µg/kg TNBP + 250 µg/kg Triton X-100. Treatment was stopped because of local adverse effects in week 8 at doses of 500 µg/kg TNBP + 2,500 µg/kg Triton X-100.
Histological examination of the injection sites revealed organised and/or recanalised thromboses, perivascular fibrosis, perivascular bleeding and fresh thromboses. No systemic changes related to the test substances were found in the rats and dogs except with the highest doses: 1 death out of 50 rats at 300 µg/kg TNBP + 1,500 µg/kg Triton X-100 i.v. and slight haematological changes in dogs at 500 µg/kg TNBP + 2,500 µg/kg Triton X-100 i.v.

The following therapeutic ratios can be calculated

rat local $\quad \frac{\text{Lowest toxic dose = 360 µg/kg}}{\text{Maximum human “therapeutic” dose } \leq 72 \text{ µg/kg}} = \geq 5$

rat systemic $\frac{\text{Lowest toxic dose = 1,800 μg/kg}}{\text{Maximum human "therapeutic" dose} \leq 72\ \mu g/kg} = \geq 25$

dog local $\frac{\text{Lowest toxic dose = 300 μg/kg}}{\text{Maximum human "therapeutic" dose} \leq 72\ \mu g/kg} = \geq 4.2$

dog systemic $\frac{\text{Lowest toxic dose = 3,000 μg/kg}}{\text{Maximum human "therapeutic" dose} \leq 72\ \mu g/kg} = \geq 42.7$

Regarding local tolerance it has to be mentioned that in the animal experiments TNBP and Triton X-100 were dissolved in water, whereas in humans these chemicals will be administered in a buffered, protein-containing solution. Furthermore, at the lowest irritating dose (dogs, 50 + 250 μg/kg/day) 4 out of 6 dogs were affected starting in week 7 of treatment. This is far beyond any therapeutic regime in patients.

Toxicity studies of TNBP + Triton X-100 on reproduction in rats (up to 900 + 4,500 µg/kg i.v.) and rabbits (up to 450 + 2,250 µg/kg i.v.) showed no indications of embryotoxic or teratogenic properties.

In vitro and *in vivo* (up to 5 + 25 mg/kg i.v.) studies showed no indications that TNBP + Triton X-100 has any mutagenic properties.

Subchronic toxicity and mutagenicity studies gave no indications that the combination of TNBP and Triton X-100 has carcinogenic properties. Therefore the applicant conducted no special studies.

In conclusion, no toxicological effects of TNBP and Triton X-100 have been observed when OCTAGAM is administered at the dose levels given above. Hence, from a toxicological point of view, OCTAGAM can be administered to humans without toxic effects from TNBP and Triton X-100.

VI Human Pharmacokinetics

A pharmacokinetic analysis was done as part of the Phase III, pivotal clinical trial (Study OCTA-06). Pharmacokinetic analyses of total IgG, IgG subclasses, and selected antigen-specific antibodies were performed on a subset of 14 patients at baseline and 5 months after start of treatment with OCTAGAM. Trough levels were assessed in all patients.

In the subset analysis, for patients on the 21-day infusion schedule, the mean total IgG concentration at 15 minutes post-infusion was 1,453.3 mg/dl (14.5 g/l), which decreased by approximately 47% by 28 days post-infusion to 768.8 mg/dl (7.7 g/l). For patients on the 28-day infusion schedule, the mean total IgG concentration at 15 minutes post-infusion was 1,762.5 mg/dl (17.6 g/l), which decreased approximately 55% by 28 days post-infusion to 789.4 mg/dl (7.9 g/l). The decreases in IgG subclass levels generally followed a trend similar to that observed for the total IgG levels. The pharmacokinetic behavior of the total IgG levels and IgG subclass

levels followed similar patterns and did not indicate accumulation or metabolism induction in patients with PID.

Trough levels of IgG at Months 6, 10, and 12 were above 400 mg/dl in all patients. Mean trough levels at these visits were between 882 and 964 mg/dl for patients on the 21-day infusion schedule (baseline mean 986 mg/dl) and between 764 and 852 mg/dl for patients on the 28-day infusion schedule (baseline mean 883 mg/dl). Mean trough levels were therefore maintained above the recommended concentration of 500 mg/dl.

VII Clinical Microbiology

There is no clinical microbiology evaluation for OCTAGAM as it is not an anti-infective product.

VIII Clinical Summary

The pivotal study to demonstrate the safety and efficacy of OCTAGAM was the US study (OCTA-06). Other studies were conducted outside of the US and were provided as supportive data (see Safety).

Study OCTA-06 was a multiple-dose, open-label, multi-center study in patients with PID. The study was conducted at 9 centers in the US from May 2000 to December 2001. The objectives were to assess the safety, pharmacokinetics, and therapeutic efficacy of OCTAGAM as replacement therapy in PID.

Eligible patients were to be 3 years or older, have a PID that had as a significant component hypogammaglobulinemia or antibody deficiency (for example, common variable immunodeficiency, X-linked agammaglobulinemia, and hyper IgM syndrome), had received 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 400 mg/dl (changed during the study to 320 mg/dl) above baseline serum IgG levels. Patients with a history of anaphylactic reactions to blood or blood-derived products, or with demonstrable antibodies to IgA were to be excluded.

The planned sample size was 40 patients. Patients were to participate in the study for 12 months and receive 13 to 17 infusions based on dose intervals of either 21 or 28 days (depending on a patient's infusion schedule and trough IgG history prior to study entry). Patients were to receive 300 to 450 mg/kg every 21 days or 400 to 600 mg/kg every 28 days.

Safety data (adverse events [AEs]; vital signs; effects on hepatic, renal, hematologic function; transmission of hepatitis B, hepatitis C, and HIV) were assessed periodically. During and after each OCTAGAM infusion and at follow-up, the Investigator was to assess AEs. A 2-sided 90% confidence interval (CI) for the overall AE rate was calculated by using the normal approximation. If the upper bound of the CI was > 40%, the safety of OCTAGAM was to be considered unacceptable.

The primary efficacy endpoint was the number of episodes of serious infections/patient/year, where serious infections were diagnosed based on defined criteria and included pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscesses, and bacterial or viral meningitis. To demonstrate efficacy

according to the FDA criterion, patients receiving an IGIV preparation should experience no more than 1 serious infection per patient per year.

The results showed that subjects had a serious infection rate of 0.115 infections/subject/year (98% confidence interval = 0.033 to 0.279), a rate that is much less than 1 infection/subject/year.

The rates of subjects missing work/school, being hospitalized, or visiting a physician/ER were low in subjects treated with OCTAGAM. Each occurred in ≤ 1.5% of the total days in the study. There were no other infections documented by radiograph or fever.

A pharmacokinetic analysis was conducted on a subset of 14 patients at baseline and 5 months after start of treatment. Trough levels were assessed in all patients.

Safety

Safety data deriving from 217 patients who have participated in non-US pre-marketing clinical trials, and from approximately 4,700 patients who have participated in a post-marketing survey were filed as supportive data.

In OCTA-06, 46 patients received a total of 654 infusions of OCTAGAM, with a mean total volume of infused of 8,250 ml (range: 3,553 to 18,300 ml). The majority of patients were Caucasian (94%), over half of the patients were male (61%), and over half were on the 28-day infusion schedule (59%). The mean age of patients was 32 years (range: 6 to 74 years); 11 patients were ≤16 years old.

The most common AEs were sinusitis not otherwise specified (NOS) (50%); headache NOS and nasal congestion (each 46%); cough (44%); pyrexia (33%); sore throat NOS (30%); vomiting NOS (26%); acute bronchitis NOS and diarrhea NOS (each 22%); and upper abdominal pain and arthralgia (each 20%).

Nineteen patients experienced AEs that were potentially related to OCTAGAM. The most common treatment-related AE was headache NOS (15%). The only other treatment-related AE that was reported by more than 2 patients was nausea (7%).

There was no serious AE which was suspected to be related to OCTAGAM treatment. No patient discontinued the study because of an AE.

Approximately 5% of infusions were associated with an AE suspected to be related to OCTAGAM. Overall, the number of AEs per patient decreased between infusions 1 and 16.

There was no pattern of AEs emerging after long-term treatment and no apparent withdrawal effects.

Assessments of laboratory values, vital signs, trough IgG levels, and immunology results did not indicate any safety concerns.

Although each of the supportive non-US studies was designed with different objectives and/or patient populations, the safety profile of OCTAGAM was consistent across the studies. In general, reported adverse reactions to OCTAGAM in patients with either congenital or acquired immunodeficiencies followed a known pattern seen for IGIV products. Various minor reactions, such as headache, chills, backache, chest pain, fever, allergic reactions, arthralgia, dizziness, fall in blood pressure, cutaneous reactions, nausea, and vomiting may occasionally occur. 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.

The studies in the European OCTAGAM development program have not shown any patterns of abnormalities in vital signs or laboratory parameters. There have been no reports of HIV, HCV, HBV, or HAV transmission in these studies.

Efficacy

The efficacy of OCTAGAM, at doses of between 300 and 600 mg/kg, with regard to rates of serious infection was successfully demonstrated. Three patients (6.5%) experienced a total of 5 serious infection episodes. Based on the total enrollment of 46 patients for a total of 43.54 patient-years, the estimated rate was 0.115 serious infections per patient per year, with a 98% confidence interval of 0.033 to 0.279.
Efficacy was also demonstrated by low rates of missed work/school days (1.5% of study days), hospitalization (0.1% of study days), and visits to a physician/ER (0.6% of study days).

The 3 supportive European studies in patients with PID (n= 39), despite different objectives and local regulatory considerations, had consistent results and demonstrated the efficacy of OCTAGAM as replacement therapy in PID.

IX. Post-Licensure Commitments

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X. Orphan Drug Consideration

There is no orphan drug designation for OCTAGAM.

XI. Marketing History

Marketing Authorization in European Union was granted in 1995. Presently OCTAGAM is licensed in 54 countries. Worldwide sales up to December 2003 are 19 tons.

XII. FDA Decision