SUMMARY OF BASIS FOR APPROVAL

1.0 GENERAL INFORMATION

Licensed Product Name:	Albumin (Human) 5% and 25%
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: 125154/0

2.0 INDICATIONS FOR USE

Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.
The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient.

3.0 DOSAGE AND ROUTE OF ADMINISTRATION

Albumin (Human) 5% is a solution for intravenous infusion, supplied in the dosage strength of 50 g human albumin/L. The following pack sizes are supplied: 100 mL (5 g), 250 mL (12.5 g) and 500 mL (25 g).

Albumin (Human) 25% is a solution for intravenous infusion, supplied in the dosage strength of 250 g human albumin/L. The following pack sizes are supplied: 50 mL (12.5 g) and 100 mL (25 g).

Albumin (Human) contains protein, of which ≥ 96% is albumin. The preparation is [redacted] N-acetyl-DL-tryptophan and caprylic acid [redacted] and the [redacted] are present in a range of 0.064-0.096 mmol/g protein in the final container. The solution contains 130-160 mmol sodium per liter and the potassium content does not exceed 2 mmol per liter. The concentration of the albumin preparation, dosage and the infusion-rate should be adjusted to the patient's individual requirements.

The dose required depends on the size of the patient, the severity of trauma or illness and on continuing fluid and protein losses. Measures of adequacy of circulating volume and not plasma albumin levels should be used to determine the dose required.
If human albumin is to be administered, hemodynamic monitoring should be preformed regularly; this may include:

- arterial blood pressure and pulse rate
- central venous pressure
- pulmonary artery occlusion pressure

- urine output
- electrolytes
- hematocrit/hemoglobin

4.0 MANUFACTURING, CHEMISTRY, AND CONTROLS:

Overview of Manufacturing Process

Albumin (Human) is a sterile, liquid preparation of albumin derived from large pools of human plasma. All units of plasma used in the manufacture of Albumin (Human) are provided by FDA-approved blood establishments only.

The product is manufactured by the Cohn-Oncley cold ethanol fractionation process followed by ultra- and dia-filtration. The manufacturing process includes heat treatment of bulk as well as in final containers at +60 ± 0.5°C for 10-11 hours. The sterile bulk solution is aseptically filled into sterile, pyrogen-free glass bottles. The bottles are closed with rubber stoppers and sealed with crimp-caps. Each vial is subject to visual inspection prior to labelling and packaging.

The viral safety of the finished product is achieved through a combination of process steps including Cohn fractionation (Precipitation of Fraction I+II+III, Precipitation of Fraction IV, Precipitation of Fraction V) and final container pasteurization.

Validation of Assays Used for Albumin (Human) - Final Container Product

The quantitative assays to characterize the final product were performed according to the requirements of the USP and CFR respectively, or if not described there methods from other Pharmacopoeias were applied, e.g. the European Pharmacopoeia (EP). The scope for validations is given in the ICH guidelines. International standards (WHO) were used for calibration whenever available.

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

[redacted]
Total Protein by [redacted]
Protein [redacted]
[redacted]
Sodium, Potassium by [redacted]
Test for Sterility by [redacted]
Pyrogen Testing (CFR) [redacted]

[redacted]
N-Acetyl-DL-Tryptophan by [redacted]
Caprylic Acid by [redacted]
[redacted]

Validation of Manufacturing

The validation of the Albumin (Human) manufacturing process was carried out in [redacted] and [redacted] Critical process parameters and acceptance criteria were defined based on the results from previous validation studies and extensive experience with the production process.

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 evaluated. All results are consistent and within the established limits.

Validation of Viral Safety

The Albumin (Human) manufacturing process includes a number of different steps which can clear viruses that may be present in the starting plasma and thereby ensure the viral safety of the finished product. The capacity of these steps to clear viruses has been validated with a panel of both relevant and model viruses. With respect to enveloped viruses, viral clearance is achieved by final container pasteurization with additional clearance by Cohn fractionation. Non-enveloped viruses are primarily removed by Cohn fractionation, but the final container pasteurization also contributes to the overall clearance.

Table 1. Viral reduction factors during Albumin (Human) 5% manufacturing

Production steps		Viral reduction factor [$\log_{10}$]					
		Enveloped viruses			Non-enveloped viruses		
		PRV	SBV	HIV-1	REO 3	PPV	HAV
Cohn fractionation*	Precipitation of Fraction IV	> 5.50	> 6.02	> 7.08	> 7.84	6.29	> 7.45
Pasteurization final container		> 8.07	> 8.67	> 7.89	6.53	3.69	4.67
Global reduction factor		**> 13.57**	**> 14.69**	**> 14.97**	**> 14.37**	**9.98**	**> 12.12**

* Due to the similar mode of action of the individual process steps only precipitation of Fraction IV was used to calculate the global reduction factor.

Table 2. Viral reduction factors during Albumin (Human) 25% manufacturing

Production steps		In vitro reduction factor [$\log_{10}$]					
		Enveloped viruses			Non-enveloped viruses		
		PRV	SBV	HIV-1	REO 3	PPV	HAV
Cohn fractionation*	Precipitation of Fraction IV	> 5.50	> 6.02	> 7.08	> 7.84	6.29	> 7.45
Pasteurization final container		> 8.67	> 8.79	> 7.23	5.36	3.22	2.45
Global reduction factor		**> 14.17**	**> 14.81**	**> 14.31**	**> 13.20**	**9.51**	**> 9.90**

* Due to the similar mode of action of the individual process steps only precipitation of Fraction IV was used to calculate the global reduction factor.

PRV: Pseudorabies Virus
SBV: Sindbis Virus
HIV-1: Human Immunodeficiency Virus - 1
Reo 3: Reovirus Type 3
PPV: Porcine Parvovirus
HAV: Hepatitis A Virus

Stability Studies of Final Container Product

Stability data for the final container of Albumin (Human) 5% comprising 24 months' data were submitted. A design for a full stability study was complied according [redacted] with filling sizes of 100 mL and 250 mL. [redacted] batches have been put on stability, [redacted] of each filling size. All vials from the [redacted] batches are stored in inverted orientation, and for comparison, vials of one batch of each filling size are stored upright at [redacted] C. Long-term [redacted] and accelerated [redacted] study conditions were applied as well.

Real-time data from the long-term studies show that all parameters remain constant up to 24 months. Furthermore, the orientation of the vials, inverted or upright, has no impact on the stability of the product.

Statistical evaluation by linear regression of [redacted] indicates that a shelf-life of 36 months can be expected when stored at + 2°C to + 25°C, as the confidence limit does not intersect the specification limit within this time. Stability data for final containers of Albumin (Human) 25% comprising 36 months data of long term studies at [redacted] C and [redacted] months data of accelerated studies at [redacted], [redacted] months data of [redacted] studies at [redacted] and 36 months data of inverted studies at [redacted] were submitted. The high stability of the product for both filling sizes of 50 mL and 100 mL was proven for each storage condition mentioned above.

Tests for Albumin (Human) stability studies included [redacted] stability and [redacted] at different time points.

In addition, conformance lots have been put on stability. For Albumin (Human) 5% [redacted] months and for Albumin (Human) 25% [redacted] months of data were presented to the FDA. This study is still ongoing and results will be submitted to the FDA on a regular basis.

A shelf life of 36 months can be guaranteed if the product is stored at + 2°C to +25°C. It is recommended to store the product protected from light.

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 36 months if stored at +2°C to +25°C (36°F to 77°F) and protected from light. 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

Labeling of Albumin (Human) 5% and Albumin (Human) 25% consists of a package insert, vial labels and carton labels.

The outer carton label and the vial 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-licensing inspection at the manufacturing site of Octapharma Pharmazeutika Produktionsgesellschaft m.b.H. in Vienna, Austria was carried out by the Agency from March 22 to 31, 2006. The observations presented in the Form 483 were resolved. 'The response information package was submitted to CBER on April 19, 2006. No further comments or questions have been raised by the Agency; thus the manufacture of Albumin (Human) complies with information given in the Biologics License Application.

5. NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY:

Since Albumin (Human) is a native albumin, 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.

6. HUMAN PHARMACOKINETICS

Albumin makes up half the normal intravascular protein mass and is responsible for 75%-80% of the plasma colloid osmotic pressure.

In a healthy person, 9-12 grams of albumin are synthesized in the liver per day. The rate of synthesis is controlled primarily by changes in the colloid osmotic pressure and the osmolality of the extravascular space. Insulin, thyroxin, and corticosteroids also stimulate the production of albumin. However, growth hormone has no significant effect on albumin synthesis. Importantly, in severe protein malnutrition, production of albumin may be decreased.

Albumin is a predominantly extravascular protein with a total mass of approximately 160 grams, despite a lower interstitial concentration compared with serum concentration. The serum concentration of albumin is about 4 grams/dL in normal individuals and the total intravascular mass is about 120 grams. Under normal circumstances, the albumin concentration in the interstitial space is half that in the intravascular space. The half-life of albumin is 17-19 days.

The catabolism of albumin takes place mainly in the vascular endothelium at a rate of 9-12 grams per day, or 4% of total body albumin. The rate of albumin degradation is related to its concentration. Calorie and protein deprivation also accelerate albumin catabolism. Serum levels of albumin may fall during periods of stress, trauma, or sepsis despite its long half-life. The drop may result from accelerated redistribution from the intravascular space, decreased synthesis, and increased catabolism. Injury and infection result in a decrease of serum albumin level of approximately 1-1.5 grams/dL within 3-7 days.

Clearance of proteins from the interstitium is dependent upon the lymphatic flow, which in healthy individuals is around 120 mL/h, with a protein content of about 80% of plasma. The flow of lymph itself is dependent upon interstitial fluid pressure, intrinsic pumping by the lymphatic vessels and external compression of vessels by muscle contraction, arterial pulsation, and body movement.

The distribution of exogenous albumin between body compartments has been examined by the injection of radio-labeled albumin. Over the first 2 days, there is a rapid phase of disappearance from the plasma that correlates with the transcapillary exchange rate of 4.5% per hour. The distribution half-time is about 15 hours. Then there is a slower decay of about 3.7% per day with an elimination half time of about 19 days.

7. CLINICAL MICROBIOLOGY

There is no clinical microbiology evaluation for Albumin (Human) 5% and Albumin (Human) 25% as it is not an anti-infective product.

8. CLINICAL SUMMARY

In order to obtain a marketing authorisation for Albumin (Human) 25% in the US, Octapharma conducted a clinical trial under an IND. The purpose of this study was to demonstrate that the efficacy of Albumin (Human) 25% is non-inferior to another human albumin brand (25%) licensed in the US in preventing central volume depletion after paracentesis due to cirrhotic ascites and has a comparable safety profile.

Cohort A received treatment with albumin after consecutive paracenteses (multiple dose treatment), whereas cohort B received treatment with albumin after single paracentesis (single dose treatment). Efficacy evaluation was performed only in cohort A. Planned enrolment was 50 subjects in Cohort A and 20 subjects in cohort B.

Due to the fact that the SAFE Study had resolved prior safety concerns with human albumin raised by the Cochrane Group in 1998, and the extensive post-marketing safety experience with Octapharma's albumin preparations, the study was terminated prematurely after enrollment of 17 subjects in agreement with the FDA.

Efficacy

The efficacy evaluation of efficacy was based on changes from baseline of Blood Urea Nitrogen (BUN) and serum creatinine at Day 1 in cohort A.

The changes from baseline for BUN and serum creatinine at Day 1, following the first paracentesis, were analysed with the baseline observation and the volume of ascites removed as covariates, and with treatment, centre and cohort as factors. These efficacy variables were assessed for the first paracentesis only. Non-inferiority was not formally tested. No clinically relevant differences were noted between the two treatment groups with respect to changes in BUN and creatinine levels from baseline to post-treatment. No clinically relevant changes in body weight were noted between the two treatment groups.

Due to the reduced power, no efficacy conclusions can be made. However, even though only 17 patients were available for analysis, no difference from a descriptive point of view was observed between the two treatment groups.

Safety

A total of 8 subjects in the Albumin (Human) treatment group experienced at least one adverse event (AE). The most frequently reported individual AEs were urinary tract infection, abdominal discomfort, and nausea. The majority of adverse events were mild or moderate in severity and were not considered related to study treatment. A total of 7 subjects (4 subjects in the Albumin (Human) treatment group and 3 subjects in the control group) experienced at least one serious AE.

Many subjects had abnormal laboratory measurements at various points throughout the course of the study. However, the overwhelming majority of these abnormal measurements were considered by the Investigator to be not clinically significant.

No clinically significant mean changes were noted for any vital signs parameter following study treatment. Minor fluctuations were noted in mean systolic and diastolic blood pressures. There was no indication that Albumin (Human) treatment had an orthostatic effect on blood pressure following study treatment after any paracentesis.

No clinically relevant differences were observed between the two treatment groups with respect to safety and tolerability.

9. ORPHAN DRUG CONSIDERATION

There is no orphan drug designation for Albumin (Human) 5% and Albumin (Human) 25%.

10. MARKETING HISTORY

Marketing Authorization in European Union was granted in 1990. Presently Albumin (Human) is licensed in 55 countries. Since 1992, the total amount sold world-wide of human albumin manufactured by Octapharma (any concentration) is approximately [redacted] (status May 2006).