octapharma

CLINICAL STUDY PROTOCOL

An open-label, multicenter, Post-Marketing Requirement study to investigate the safety and tolerability of octaplas™ in the management of pediatric patients who require therapeutic plasma exchange.

Investigational Product:	octaplas™
Indication:	Therapeutic plasma exchange
Study Design:	Open-label, multicenter, Post-Marketing Requirement study
Sponsor:	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H. Oberlaaerstrasse 235, 1100, Vienna, Austria
Study Number:	LAS-213
EudraCT and/or IND Number:	BL 125416/0: Required Pediatric Assessment
Development Phase:	Phase IV
Planned Clinical Start:	Q1 2015
Planned Clinical End:	Q4 2020
Date of Protocol:	19-Oct-2018
Version:	07
Co-ordinating Investigator:	Cassandra D. Josephson, M.D. Emory University Hospital Room H183A 1364 Clifton Road, NE Atlanta, GA 30322-8110

STUDY OUTLINE

<table>
<tr><td colspan="2">Name of Sponsor/Company:
Octapharma Pharmazeutika Produktionsges.m.b.H.</td></tr>
<tr><td>Name of Investigational Product:
octaplas™</td><td>Protocol Identification Code:
LAS-213</td></tr>
<tr><td>Name of Active Ingredient:
Human Coagulation Active Plasma For Infusion, S/D treated</td><td>Date of Final Protocol:
19-Oct-2018</td></tr>
<tr><td colspan="2">Title of Study:
An open-label, multicenter, Post-Marketing Requirement study to investigate the safety and tolerability of octaplas™ in the management of pediatric patients who require therapeutic plasma exchange.</td></tr>
<tr><td colspan="2">Indication:
Pediatric patients who need therapeutic plasma exchange.</td></tr>
<tr><td colspan="2">Number of Study Center(s):
About 10-15 sites in North-America.</td></tr>
<tr><td>Study Duration:
1st quarter 2015 to 4th quarter 2020</td><td>Development Phase: IV</td></tr>
<tr><td colspan="2">Objectives:
To assess the safety and tolerability of octaplas™ in the pediatric population by monitoring serious adverse events (SAEs) adverse drug reactions (ADRs), thrombotic events (TEs), thromboembolic events (TEEs), and by measuring safety laboratory parameters.</td></tr>
<tr><td colspan="2">Study Design:
Open-label, multicenter, interventional, Post-Marketing Requirement (PMR) Phase IV study.</td></tr>
<tr><td colspan="2">Number of Patients: a minimum of 40 pediatric patients treated with octaplas™.</td></tr>
</table>

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: octaplas™	**Protocol Identification Code:** LAS-213
Name of Active Ingredient: Human Coagulation Active Plasma For Infusion, S/D treated	**Date of Final Protocol:** 19-Oct-2018

Patient Selection Criteria:

Inclusion Criteria:

1. Patients in whom therapeutic plasma exchange is required.
2. Patient is male or female ≥ 2 years to ≤ 20 years of age.
3. Patient or patient's legal representative(s)/guardian(s) has /have given voluntarily written and signed informed consent before any study-related procedure is to be performed. If children are old enough (age usually deemed by each institution) to understand the risks and benefits of the study, they should also be informed and provide their written assent.

Exclusion Criteria:

1. Patient with known homozygous congenital deficiency of Protein S.
2. Patient has a history of severe hypersensitivity reaction to plasma-derived products or to any excipient of the investigational product.
3. Patient has an already known IgA deficiency with documented antibodies against IgA.
4. Patient is currently participating in another interventional clinical study or has participated during the past 1 month prior to study inclusion. This is not applicable to non-interventional trials and does not exclude patients who have been exposed to Investigational Medicinal Product with a washout of at least 30 days from enrollment in LAS-213. Concurrent participation in a device study will be considered on a case by case basis.
5. Patient is pregnant.
6. Use of Angiotensin-Converting-Enzyme-inhibitors within 72 hours of the start of the first infusion episode or planned used of these medications while on study.

Test Product, Dose, Mode of Administration, and Batch Number(s):

octaplas™ infusion solution for IV administration, ABO blood group compatible

Name of Sponsor/Company:
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octaplas™	LAS-213
Name of Active Ingredient:	**Date of Final Protocol:**
Human Coagulation Active Plasma For Infusion, S/D treated	19-Oct-2018

Study Period and Length of Treatment:

Patients will be followed for one week (7 days) during their therapy which could consist of one or more TPE procedures. The recommended dose for a plasma exchange is 40 to 60 mL/kg. The dosing regimen might differ from the general recommendation, depending on the therapeutic treatment plan and the investigator's evaluation of the respective clinical situation (e.g. partial plasma exchange).

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):

None.

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint(s):

- Monitoring of serious adverse events (SAEs), adverse drug reactions, TEs, and TEEs caused by the octaplas™ used for plasma exchange.

Secondary Endpoint(s):

- Safety laboratory parameters (Complete Blood Count (CBC), the 'Chem 7' lab panel (Chem 7), and ionized calcium).
- Investigator's assessment of overall safety.

Summary of Study Procedures and Statistical Analysis Plan:

Study Procedures:

Screening:

At Screening, pediatric patients who require TPE will be identified and informed consent will be obtained from the patient or from the legal representative(s) or guardian(s) of the patient. If children are old enough (age usually deemed by each institution) to understand the risks and benefits of the study, they should also be informed and provide their written assent. The patient's eligibility will be reviewed based on the inclusion and exclusion criteria. A physical examination will be performed, medical history (including current relevant concomitant medications) reviewed, and demographic data will be recorded. Blood samples will be drawn to assess safety parameters (CBC and Chem 7) including the patient's ABO blood group type. A pregnancy test for females who have experienced menarche will be performed prior to enrollment.

1-Week (7-Day) Study Treatment Period:

The total treatment period will be a maximum of one week (i.e., 7 days). Within this period, TPE procedure(s) information (e.g., start and stop time of the TPE) will be documented,

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
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ionized calcium levels and the total volume (dose in mL/kg) of octaplas™ used per infusion episode for each patient will be recorded. The type of machine used for TPE will also be recorded.

Within 24 hours before each TPE procedure, vital signs will be assessed, and blood will be drawn for safety labs (CBC and Chem 7) and for ionized calcium levels. If multiple vital signs, and/or laboratory assessments are made before and after the TPE, the assessment taken most proximal to the start (pre) and after the end of the TPE (post) should be recorded in the case report form (CRF). ADRs and changes in concomitant medications will be recorded.

Follow-Up:

All SAEs, ADRs, TEs and TEEs will be recorded with start and stop dates and therapy (physical or concomitant medication) for treatment, if applicable, throughout the study period. Any other products administered concomitantly and deemed relevant by the treating physician during the study period should carefully be documented. At 24 hours after each TPE, an ionized calcium reading will be used to assess for citrate toxicity and the Investigator will provide an assessment of overall safety for the patient's treatment.

After the final follow-up for the last TPE in the 1-week (7-day) study treatment period, the clinical phase of the study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (e.g., on-going ADRs) require follow-up.

Statistical Analysis Plan:

The primary endpoint for this study is the rate of occurrence of SAEs, ADRs, TEs, and TEEs caused by the octaplas™ used for plasma exchange during the 7-day study period. All data collected will be summarized and presented descriptively to facilitate the review of population homogeneity. Additional review in specific age sub-groups will be performed if possible. No confirmatory hypothesis testing is planned. Any p-value or confidence interval presented is to be understood in the exploratory sense.

All safety parameters will be presented descriptively in full detail, by age group as well as in total. The safety assessment will include the occurrence of SAEs, ADRs, TEs and TEEs. To facilitate the detection of any possible safety signal, all ADRs will be characterized and analyzed by seriousness, severity, relation to study drug and timely relationship to study drug administration. In addition to these pre-planned categories the collected data will be examined to identify additional characteristics of interest such as e.g. particular indications for TPE, relevant concomitant medications, or Standardized MedDRA Queries (SMQs)

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covering a noticeable number of events. The rates of ADRs will be presented for such categories, together with the associated 95% confidence intervals, again per age group and in total.

Individual patient profiles or tabulations will be generated, displaying the baseline characteristics as well as all interventions, treatment details and relevant measurements on a time scale. This will facilitate the review of each individual course of treatment by a medical expert to detect any safety signal that might not be reflected in the ADR rates.

Vital sign measurements (absolute values and change from pre-TPE) will be summarized by descriptive statistics. All measurements outside age-specific thresholds will be listed and reviewed individually.

All safety laboratory data (CBC, Chem 7, and ionized calcium) will be presented descriptively per time point. All measurements outside age-specific thresholds will be listed and reviewed individually.

All data will be presented in total as well as in sub–groups reflecting the age , gender, underlying diagnosis, and/or most relevant medical history and concomitant medications as appropriate.

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

Dr. Wolfgang Frenzel — Wolfgang Frenzel 2018.11.04 11:52:12 +01'00' — Date

International Medical Director
on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Cassandra D. Josephson, M.D. — MD — 11/4/2018

Coordinating Investigator
Emory University Hospital
Room H183A
1364 Clifton Road, NE
Atlanta, GA 30322-8110, USA

Laurenz Trawnicek — 29-OCT-2018

Manager Biometrics
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Michael Eppolito, MBA — 24 oct 2018

Director, Clinical Operations
Octapharma USA, Inc.,
121 River street, Suite 1201
Hoboken, NJ, 07030, USA

Balazs Toth — 29 OCT 2018

Head of Corporate Drug Safety
& EU-QPPV, Drug Safety Unit
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
BW	Body Weight
CBC	Complete Blood Count
CDSU	Central Drug Safety Unit
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic case report form
FFP	Fresh Frozen Plasma
FP24	Plasma frozen within 24 hours of collection
GCP	Good Clinical Practice
HAV	Hepatitis A Virus
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PMR	Post-Marketing Requirement
RBC	Red Blood Cell
SAE(s)	Serious Adverse Event(s)
SAF	Safety Population
S/D	Solvent/Detergent
SMQ	Standardized MedDRA Query
TE	Thrombotic Event
TEE	Thromboembolic Event
TNBP	Tri(n-butyl)phosphate
TPE	Therapeutic Plasma Exchange

1 INTRODUCTION

octaplas™ is a solvent/detergent (S/D) treated and pooled human plasma prepared from units of fresh frozen plasma (FFP) pooled according to their ABO blood group. It contains the normal constituents of FFP. octaplas™ is a further development of octaplas® which is marketed in Europe since 1992. In January of 2013, octaplas™ received regulatory approval by the Food and Drug Administration for the U.S. market. For octaplas™, a new prion affinity chromatography column was implemented in the manufacturing process of the product to eliminate potential prion proteins. Furthermore, the time of S/D treatment in the manufacturing process has been shortened from 4–4.5 hours to 1–1.5 hours. These measures increase the concentration of plasmin inhibitor and slightly increases the concentration of Protein S compared with octaplas®. octaplas™ has obtained marketing authorization in Australia, Germany, Portugal, the U.K., Ireland, Belgium, Netherlands, Luxemburg, Sweden, Finland, Switzerland, Malta, and Canada. octaplas® is registered in 21 countries and octaplas™ is registered in 13 countries including the United States.

octaplas™ does not contain red blood cells (RBCs), leukocytes and platelets. The RBCs and cell fragments are removed in several filtration steps during the productions process. Therefore, adverse reactions caused by the presence of these cells (e.g., immunization against RBC antigens or febrile non-hemolytic reactions from cytokines liberated by leukocytes) are not expected to be associated with the infusion of this product.

Virus inactivation is performed using the S/D treatment method using the virus inactivating reagents 1% tri(n-butyl)phosphate (TNBP) and 1% Triton X-100 (Octoxynol). This virus inactivation procedure is effective against enveloped viruses such as Human Immunodeficiency Virus, Hepatitis B Virus and Hepatitis C Virus. The efficacy of this virus inactivation procedure has been shown in several validation studies. The S/D treatment has no effect on non-enveloped viruses such as Hepatitis A Virus (HAV) and parvovirus B19. However, the presence of neutralizing antibodies towards HAV and B19 in the starting plasma and the final product, result in immune neutralization and passive immunization which both serve to limit or prevent virus replication and thereby infection in recipients. **[1]**

The virus inactivating reagents (TNBP and Octoxynol) are removed through liquid and solid phase extraction. However toxicity studies performed in rats and dogs have shown that possible trace amounts are of no toxicological relevance to humans. Furthermore, no teratogenic, embryotoxic or mutagenic effects of TNBP and Octoxynol were observed in the toxicity studies performed.

In total, 15 prospective clinical studies and 9 retrospective studies with octaplas®/octaplas™ have been conducted. Of the 15 prospective studies, 2 were focused on safety aspects only, and of the 9 retrospective trials, 3 were mainly studying efficacy. In total, about 495 patients have been enrolled in the pro- and retrospective efficacy studies, including one observational study, and the patients were exposed to 2592 infusion episodes with octaplas®/octaplas™ or Uniplas (a plasma formulation compatible with all ABO blood groups).

octaplas™ was developed as an alternative to plasma in order to reduce the risk for a possible virus transmission. In addition, the product was developed in order to meet the request for a

standardized, cell free plasma for infusion that contains high levels or pro- and anti-coagulants, in order to improve the therapeutic efficacy and reduce adverse reactions.

1.1 Rationale for Conducting the Study

This Post-Marketing Requirement (PMR) study was requested by the Food and Drug Administration after octaplas™ received marketing approval in the United States. This PMR study is planned to be conducted in a minimum of 40 pediatric patients from ≥2 to ≤ 20 years of age who need therapeutic plasma exchange (TPE).

The study is intended to obtain additional safety information on octaplas™ in a routine clinical setting via the assessment of adverse drug reactions (ADRs), thrombotic events (TEs), and thromboembolic events (TEEs) and will be conducted in compliance with the protocol, ICH-GCP and other regulatory requirements.

1.2 Dose Rationale

octaplas™ is for intravenous use only. Please refer to the package insert of octaplas™ for further information regarding dose.

1.3 Benefit-Risk Statement

There are several benefits associated with the administration of octaplas™. octaplas™ has undergone additional steps for viral inactivation and removal. The combination of the S/D treatment and immune neutralization ensures a high degree of viral safety for this product. Antibodies against leukocytes are neutralized and removed which abolishes the risk for immune Transfusion Related Acute Lung Injury (one of the most serious complications of transfusions today); this is a very favorable feature of octaplas™ compared to plasma. As cells and cellular debris are completely removed by multiple size exclusion filtration the occurrence of adverse reactions attributable to residual blood cells, is reduced in conjunction with the use of octaplas™. The dilution effect on cytokines and allergens from the pooling of multiple units of single-donor FFP units diminishes the number and severity of adverse reactions that can occur due to the presence of allergens/soluble substances in plasma. Additionally, octaplas™ has uniform and stable levels of both pro- and anti-coagulation factors. The combination of the uniformity of these factors in octaplas™ and the consistent size of each unit could produce a more predictable hemostatic response following octaplas™ transfusion compared to standard plasma. Comprehensive biochemical studies confirmed that octaplas™ produced with the new column possesses a biochemical quality identical to its predecessor, octaplas®, with the advantage of offering an enhanced safety profile in terms of prion disease transmission such as variant Creutzfeldt-Jakob Disease.

The adverse reactions that were observed in ≥ 1% of subjects who received octaplas™ were mild and included pruritus, urticaria, nausea, headache, and paresthesia. **[2]** Serious adverse reactions that were associated with octaplas™ transfusion included anaphylactic shock, citrate toxicity and severe hypotension.

Other possible adverse reactions that may occur with the use of octaplas™ are excessive bleeding caused by hyperfibrinolysis due to lower levels of plasmin inhibitor in the product, thrombosis due to lower levels of Protein S, and citrate toxicity (hypocalcemia). The infusion rate should not exceed 1 mL/kg/min. Symptoms attributable to citrate toxicity can include fatigue, paresthesia and muscle spasms, especially in patients with liver function disorders. Because octaplas™ is made from human plasma, it may carry a risk of transmitting infectious agents such as viruses and Variant Creutzfeldt-Jakob Disease. Other adverse reactions that have been reported in the post-marketing experience include hypersensitivity reactions including anaphylactoid and allergic type of reactions, alkalosis, cardiac arrest, circulatory overload, thromboembolism, tachycardia, respiratory arrest or failure, bronchospasm, pulmonary edema, dyspnea, tachypnoea, abdominal pain, vomiting, rash, erythema, fever and/or chills, chest discomfort or pain, and seroconversions (passive transfer of antibodies).

Large volumes or fast infusion rates may induce Transfusion Associated Volume Overload that is manifested by dyspnea, hypoxia, and increasing oxygen demands. Pulmonary edema can often be seen on chest X-ray. High infusion rates may rarely cause cardiovascular effects as a result of citrate toxicity (fall in ionized calcium), especially in patients with liver function disorders. octaplas™ should be used with caution in patients with risks for thrombotic complications because of the potential for increased risk of venous thromboembolism. In order to reduce the risk for venous thromboembolism, appropriate measures should be considered in all patients at risk for thrombotic complications subjected to coagulation factor support for an extended period of time (e.g., during long-term, large-volume Therapeutic Plasma Exchange) using octaplas™.

Administration of octaplas™ must be based on ABO-blood group compatibility with the recipient. Hemolytic reactions can occur with ABO blood group mismatches. In emergency cases blood group AB can be regarded as the universal plasma since it can be given to all patients.

octaplas™ should not be used in patients with:

- Immunoglobulin A (IgA) deficiency
- Severe deficiency of Protein S
- History of hypersensitivity to FFP or to plasma-derived products including any plasma protein
- History of hypersensitivity reaction to octaplas™

2 STUDY OBJECTIVES

The primary objective is to assess the safety and tolerability of octaplas™ in the pediatric population by monitoring ADRs, TEs, TEEs, and by measuring safety laboratory parameters.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint(s)

- Monitoring of adverse drug reactions, TEs and TEEs caused by the octaplas™ used for plasma exchange.

3.1.2 Secondary Endpoint(s)

- Safety laboratory parameters (CBC, Chem 7, and ionized calcium; refer to **Section** 7.3.5.2 for definition).
- Investigator's assessment of overall safety.

3.2 Overall Study Design and Plan

An enrollment period of 5 years is planned. The study will be an open-label, multicenter, interventional, post-marketing Phase IV study in a minimum of 40 pediatric patients who need TPE.

3.2.1 Study Flow Chart

Time-Points	Screening (≤ 14 Days Prior to 1st TPE)	1-Week (7-Day) Study Treatment Period[1]			Follow-Up[10, 11]
		Within 24 Hours Before Each TPE Procedure	Study Treatment (During Each TPE Procedure)[2]	Between 30 Minutes to 3 Hours After Each TPE Procedure	24 Hours After Each TPE Procedure
Obtain Informed Consent	X				
Review of inclusion/exclusion criteria	X				
Physical examination	X				
Medical history (including relevant current concomitant medications, and blood group type (ABO) recording)	X				
Demographics	X				
Vital signs[3] (heart rate, respiratory rate, temperature, and blood pressure assessment)		X		X	
Blood draw CBC and Chem 7[4]	X	X		X	
Blood draw for ionized calcium		X	X[9]		X[8]
Record total volume of octaplas™ infused at each infusion episode			X		
Record the type of machine used for TPE (filtration or centrifugation)			X		
Record any SAEs, ADRs (including transfusion reactions), TEs, TEEs, and concomitant medications[5]			←----------Continuously----------→		
Pregnancy test for females of childbearing potential[6]	X				
Investigator's overall assessment of safety[7]					X

1. Study treatment period is a maximum of one week (7 days) and will consist of one or more TPEs. In the event that a TPE begins within the 7 day Treatment period and runs past the maximum 7 day time point, this entire TPE should be followed and all relevant TPE procedures performed (even if lasting greater than 7 days). New TPEs starting after the 7 day time point will not be considered part of the Treatment Period.
2. Subsequent treatment will be determined at the Investigator's discretion and will depend upon the clinical setting including the patient's response to treatment.
3. Vital signs will include heart rate, respiratory rate, temperature, and blood pressure assessment. If multiple vital sign assessments are taken before and/or after each TPE, the vital signs that are assessed closest before the start and after the end of each TPE should be recorded.
4. Refer to **Section** 7.3.5.2 for definition of blood test to be done. For the first TPE it is mandatory that, pre– and post–TPE samples for CBC and Chem 7 be tested. If subsequent infusion episodes are performed, pre- and post-TPE samples should be drawn unless considered not medically necessary by the Investigator (e.g., the timing of the pre-TPE sample is close to or overlaps with the timing of the post-TPE sample and it is not necessary to perform, etc.). In the event the pre- or post-TPE laboratory sample(s) are not drawn, the reason for not obtaining the sample(s) will be recorded in the case report form. These CBC and/or Chem 7

parameters may be assessed additionally at any other time point as medically indicated. If multiple laboratory assessments are made before and after the TPE, the assessment taken most proximal to the start (pre) and after the end of the infusion (post) should be recorded in the CRF.

5. For outpatients, follow-up will be done via a telephone interview to assess for any ADRs.
6. Confirmation that the subjects of child bearing potential are not pregnant must be established by a negative pregnancy test result obtained during Screening.
7. The Investigator's evaluation of overall safety will be performed 24 (+/- 2 hours) hours after each TPE procedure.
8. If it is impractical to obtain a blood sample for testing ionized calcium during the follow-up (e.g., an outpatient situation), a post-study treatment sample to test for ionized calcium may be skipped.
9. The first sample should be drawn within 90 minutes after start of the TPE.
10. The Follow-up procedures (ionized CA and Investigator's Assessment) should be performed 24 hours (+/- 2 hours) after the TPE concludes. The Follow-up procedures may be performed sooner if it is not practical to obtain these during the 24 hour post TPE period. If it is not medically feasible to obtain the Follow-up assessments, the reason must be clearly documented (e.g. patient discharged prior to 24 hours after the end of the last TPE).
11. If plasma is needed for administration during the study follow-up period, Octaplas^{TM} should be given. After the end of the follow-up, if plasma is needed, this should be provided according to institutional standard of care.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

This is an open-label, multicenter, interventional, post-marketing study in a minimum of 40 pediatric patients who need therapeutic plasma exchange (TPE). The study will be conducted at about 10-15 sites in North America.

Control Group(s)

This is an open-label study of octaplas™ to investigate its safety and tolerability in the management of pediatric patients who require TPE; there is no control group.

3.3.2 Target Parameter(s)

Safety parameters:

- Monitoring of adverse drug reactions, TEs and TEEs caused by the octaplas™ used for plasma exchange.
- Safety laboratory parameters (CBC, Chem 7, and ionized calcium).
- Investigator's assessment of overall safety.

4 STUDY POPULATION

4.1 Population Base

A minimum of 40 pediatric patients who need TPE are expected to be enrolled according to the following inclusion and exclusion criteria.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Patients in whom therapeutic plasma exchange is required.
2. Patient is male or female ≥ 2 years to ≤ 20 years of age.
3. Patient or patient's legal representative(s)/guardian(s) has / have given voluntarily written and signed informed consent before any study-related procedure is to be performed. If children are old enough (age usually deemed by each institution) to understand the risks and benefits of the study, they should also be informed and provide their written assent.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the study:

1. Patient with known homozygous congenital deficiency of Protein S.
2. Patient has a history of severe hypersensitivity reaction to plasma-derived products or to any excipient of the investigational product.
3. Patient has an already known IgA deficiency with documented antibodies against IgA.
4. Patient is currently participating in another interventional clinical study or has participated during the past 1 month prior to study inclusion. This is not applicable to non-interventional

trials and does not exclude patients who have been exposed to Investigational Medicinal Product with a washout of at least 30 days from enrollment in LAS-213. Concurrent participation in a device study will be considered on a case by case basis.

5. Patient is pregnant.
6. Use of Angiotensin-Converting-Enzyme-inhibitors within 72 hours of the start of the first infusion episode or planned used of these medications while on study.

4.2 Prior and Concomitant Therapy

Details of relevant concomitant medications will be recorded in the CRF. Relevant medications are defined as follows:

- Plasma products (e.g., octaplas™, regular plasma products, etc.) and all other blood products that are administered.
- Antifibrinolytics (**ε-**aminocaproic acid or tranexamic acid) and any other pharmaceutical pro- or anti-coagulants such as recombinant activated factor VII (rFVIIa), any of the prothrombin complex concentrates, or fibrinogen concentrates.
- Pre-transfusion medications taken to prevent allergic reactions (including steroids)
- An angiotensin-converting-enzyme (ACE) inhibitors (Lisinopril, Captopril, etc.)
- Other medications that the Investigator considers relevant to report for this trial.

Routine medications that are considered standard and/or that have little or no impact on the study data results are not to be entered into the CRF. Relevant concomitant medications or changes thereof must be recorded. If the change influences the patients' eligibility to continue in the trial, the Sponsor must be informed.

4.2.1 Permitted Concomitant Therapy

Concomitant administration of therapies not interfering with the objectives of the study is permitted.

4.2.2 Forbidden Concomitant Therapy

Angiotensin-Converting-Enzyme-inhibitors are forbidden due to the risk of potential hypotensive reactions.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

A patient may be withdrawn from the study prior to completion for any of the following reasons:

- Whenever the patient/legal representative(s)/guardian(s) decides it is in the patient's best interest to withdraw
- Whenever the Investigator decides it is in the patient's best interest to be withdrawn
- Pregnancy

For any premature patient withdrawal after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation in the CRF. Premature patient withdrawals will be included in the safety analysis.

4.3.2 Patient Replacement Policy

There is no patient replacement policy defined for this protocol. A minimum of 40 patients will be treated in this study.

4.4 Assignment of Patients to Treatment Groups

All patients enrolled in this study will be treated with octaplas™. The Investigator will inform the Sponsor of new patients enrolled by the submission of patient entry information to the Sponsor.

4.5 Relevant Protocol Deviations

If deviations from the protocol occur, the Investigator should promptly inform the Monitor and the implication of the deviation must be reviewed and discussed. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the patient and/or the trial. The documentation must be kept in the Investigator's Trial File and the Sponsor's Trial File. In case of any major protocol deviation the Investigator and the Sponsor will decide on whether the patient should be withdrawn from this study. Protocol deviations to be considered will include (but not be limited to):

- Violations of the study entry criteria
- Forbidden concomitant medication
- Significant deviations from recommended dose

4.6 Subsequent Therapy

Subsequent treatment will be based on the patient's ongoing clinical response and physician discretion per institutional standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

The reduced time of S/D treatment within the manufacturing process of octaplas® improved the concentration of plasmin inhibitor and slightly increases that for Protein S compared to its predecessor, octaplas®. The virus safety of octaplas™ was maintained as shown by virus validation studies. With a total inactivation to below the detection limit, the shortened S/D procedure has a time-safety-margin of >98.3% versus >99.5% for the predecessor product.

5.2 Packaging and Labeling

octaplas™ is delivered frozen in sterile, pyrogen-free plastic bags containing 200 mL. The bags are vacuum sealed in a clear plastic wrap and delivered in cartons of 10 units.

Each octaplas™ bag will be labeled as shown below (for blood group A).

NDC 68209-952 – 01

octaplas™ Pooled Plasma (Human), Solvent/Detergent Treated

For intravenous use only.

Rx only.

200 mL contain 9 - 14 g human plasma proteins, 0.88-1.48 g sodium citrate dihydrate, 0.06-0.24 g sodium dihydrogen phosphate dihydrate, 0.80-1.20 g glycine, ≤0.4 mg TNBP and ≤1.0 mg Octoxynol. This product contains no preservative.

Store at ≤–18°C (–0.4°F) protected from light. Thawed product should be used immediately and must not be refrozen. Do not use product that is cloudy or has deposits. Unused product must be discarded.

Caution: New Drug--Limited by Federal (or United States) law to investigational use

Exp. Date:

Lot No.:

U.S. License No. 1646

Manufactured by:
Octapharma AB
Elersvägen 40
SE-112 75, Sweden

Distributed by:

Octapharma USA Inc.
Hoboken, NJ 07030
866-766-4860

5.3 Conditions for Storage and Use

The shelf-life of octaplas™ is 36 months when stored at ≤ –18°C (≤ –0.4°F) and protected from light. After thawing, the product must be used within 24 hours when stored at 1-6°C (33.8°F to 42.8°F) or within 8 hours when stored at room temperature (20 to 25°C or 68°F to 77°F). See package insert in **Appendix 1**.

The Investigator/authorized personnel at the site will ensure that the product is stored in appropriate conditions with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

octaplas™, ABO blood group specific, will be given as replacement fluid during TPE and administered per institutional standard of care. It will be used in lieu of FFP during the treatment period.

The total octaplas™ volume infused and time details of each infusion episode will be recorded.

Patients will be followed for one week (7 days) during their therapy which could consist of one or more TPE procedures. The recommended dose is a total plasma volume between 40 to 60 mL/kg, as prescribed by the treating physician. The dosing regimen might differ from the general recommendation, depending on the therapeutic treatment plan and the investigator's evaluation of the respective clinical situation (e.g. plasma exchange). The infusion rate of octaplas™ should not exceed 0.020-0.025 mmol/kg BW (body weight)/min, which is equal to <1 mL/kg BW/min.

5.5 Preparation and Method of Administration

octaplas™ will be used per the approved labeling for the product (see **Appendix 1**). octaplas™ will be administered based on ABO-blood group specificity. In urgent cases, or in circumstances that no same blood group is available (type A octaplas™ for type A recipient), the patient can be administered octaplas™ that is compatible to the recipient's blood group (e.g. type AB octaplas™ can be administered to a type A recipient).

All attempts should be made to ensure adequate octaplas™ blood-type specific inventory is available to meet patient orders. Shipment requests to Octapharma should coincide to meet these needs and should be issued promptly, taking into consideration processing and shipment time.

During the study treatment period, the hierarchy of plasma choice is:

1. octaplas™ blood group specific
2. octaplas™ blood group compatible
3. FFP

Further, if plasma is needed during the TPE follow-up period, octaplas™ should be administered.

5.6 Blinding, Emergency Envelopes and Breaking the Study Blind

Not applicable. This is an open-label study.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

octaplas™ will be dispensed per the institutional standard of care, in accordance with the package insert, as prescribed by the treating physician.

5.7.2 Assessment of Treatment Compliance

Having in mind the setting and the fact that study drug administrations will exclusively take place at the investigational site, full compliance is expected.

6 STUDY CONDUCT

6.1 Study Procedures

6.1.1 Screening

The following will take place during Screening:

- Obtaining voluntarily given, written (signed and dated) informed consent by the patient or the patient's legal representative(s)/guardian(s). If children are old enough (age usually deemed by each institution) to understand the risks and benefits of the study, they should also be informed and provide their written assent.
- Review of inclusion and exclusion criteria.
- Perform physical examination.
- Review medical history including current concomitant medication(s), and blood group type (ABO).
- Record demographic data (height, body weight (BW), gender, date of birth, race).
- Blood sample(s)[1] will be drawn for the following safety laboratory parameters: CBC and Chem 7 (refer to **Section** 7.3.5.2 for definition).
- Pregnancy testing for females of childbearing potential will be performed. Confirmation that the subject is not pregnant must be established by a negative pregnancy test result.

6.1.2 1-Week (7-Day) Study Treatment Period

The total treatment period of the study will be a maximum of one week (i.e., 7 days). Within this period, TPE procedures are to be documented.

The following will take place within 24 hours before each TPE:

- Vital signs (heart rate, respiratory rate, temperature, and blood pressure assessment) assessed.
- Blood sample(s) will be drawn for the following safety laboratory parameters: CBC, Chem 7 and ionized calcium (refer to **Section** 7.3.5.2 for definition)[2].
- If multiple vital signs, and/or laboratory assessments are made before the TPE, the assessment taken most proximal to the start (pre) of the TPE should be recorded in the CRF.

[1] The following blood volume limits for sampling are recommended, if an Investigator decides to deviate from these, this should be justified: NIH Clinical Center Guidelines for Blood Drawn for Research Purposes in the Clinical Center (M95-9) rev 06/05/2009: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

[2] For the first TPE it is mandatory that, pre– and post–TPE samples for CBC and Chem 7 be tested. If subsequent infusion episodes are performed, pre- and post-TPE samples should be drawn unless considered not medically necessary by the Investigator (e.g., the timing of the pre-TPE sample is close to or overlaps with the timing of the post-TPE sample and it is not necessary to perform, etc.). In the event the pre- or post-TPE laboratory sample(s) are not drawn, the reason for not obtaining the sample(s) will be recorded in the case report form. These CBC and/or Chem 7 parameters may be assessed additionally at any other time point as medically indicated.

The following will take place during each TPE:

- Review and documentation of data regarding any changes in concomitant medications.
- The actual timing and total volume of octaplas™ infused will be recorded.
- Blood sample(s) will be drawn for the following safety laboratory parameter: ionized calcium[3]
- Any SAEs, ADRs (refer to **Section 7.3.2** for definitions), TEs, TEEs, as well as concomitant medications.
- Record the type of machine used for TPE (filtration or centrifugation).

The following will take place between 30 minutes and 3 hours after each TPE:

- Vital signs (heart rate, respiratory rate, temperature, and blood pressure assessment) assessed.
- Blood sample(s) will be drawn for the following safety laboratory parameters: CBC and Chem 7 (refer to **Section** 7.3.5.2 for definition).
- Any SAEs, ADRs (refer to **Section 7.3.2** for definitions), TEs, TEEs, as well as concomitant medications.

6.1.3 Follow-Up

24 (+/- 2 hours) hours after each TPE, the following will be collected:

- Any SAEs, ADRs (refer to **Section** 7.3.2 for definitions), TEs, TEEs, as well as concomitant medications.
- Blood sample(s) will be drawn for ionized calcium levels to assess for citrate toxicity. If it is impractical to obtain a blood sample for testing ionized calcium during the follow-up (e.g. an outpatient situation), this lab assessment may be skipped.

After each TPE the Investigator will provide an overall Assessment of Safety observed for each patient by indicating his or her opinion of one of the following 3 categories best describing the patient's experience with treatment while on study:

- Excellent: defined as the treatment was well tolerated by the patient,
- Moderate: defined as ADR(s) were observed, but easily resolved or not clinically significant,
- Poor: defined as ADR(s) were observed requiring significant medical intervention.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

Treatment up to one week (7 days) maximum will be documented. 24 hours (+/- 2 hours) after the last TPE, the final follow-up will be performed to identify and record any SAEs, ADRs, TEs,

[3] At least one blood sample should be drawn within 90 minutes after start of each TPE. All subsequent samples should also be reported in the CRF.

TEEs, as well as concomitant medications and Investigator's overall safety assessment. This visit will also be the study completion visit.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed, when all patients have completed the last follow-up evaluation after the last TPE during study treatment period (max 1 week, 7 days).

The estimated start of this trial is 1st quarter 2015. The estimated end for this study is 4th quarter 2020.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Furthermore, the Investigator should promptly inform the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

Should the study be prematurely terminated, all study materials (completed, partially completed and blank CRFs, etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Background / Baseline Information

The following assessments will be performed upon enrollment:

- Physical examination (refer to **Section** 7.3.6 for definition).
- Medical history including current concomitant medications.
- Demographic data including height, body weight (BW), gender, date of birth, and race.
- Vital signs (heart rate, respiratory rate, temperature and blood pressure measurement)
- Blood group (ABO) determination.
- Safety laboratory parameters (CBC, Chem 7, and ionized calcium; refer to **Section** 7.3.5.2 for definition).
- Pregnancy testing will be performed for females of childbearing potential.

7.2 Efficacy Assessments

Due to the small sample size with different age groups efficacy will not be measured.

7.3 Safety Assessments

7.3.1 Relevant Drug Safety Information

Any of the following drug safety information shall be collected:

- Serious adverse events (SAEs)
- Adverse drug reactions (ADRs)
- Adverse events that fall into the category of TEs and TEEs (definitions and reporting requirements see **Sections 7.3.2** and **7.3.3**).
- Post-treatment related safety reports, pregnancies, drug overdose, interaction, abuse, misuse, and medication error (see **Section** 7.3.7).

Non-serious adverse events (AEs) observed during the trial will not be captured in the case report form (except for TEs, TEEs).

Post-treatment the Investigator will provide an overall Assessment of Safety observed for each patient by indicating his or her opinion of one of the following 3 categories best describing the patient's experience with treatment while on study:

- Excellent: defined as the treatment was well tolerated by the patient,
- Moderate: defined as ADR(s) were observed, but easily resolved or not clinically significant,
- Poor: Defined as ADR(s) were observed requiring significant medical intervention.

7.3.2 Adverse Events and Adverse Drug Reactions

7.3.2.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to a medicinal product related to any dose. The phrase "response to a medicinal product" means that a causal relationship between the medicinal product and an ADR carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Withdrawal due to ADR: Is a patient whose treatment with a medicinal product is discontinued because of an ADR. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection

The condition of the patient will be monitored throughout the study. ADRs will be elicited using a standard non-leading question such as "How have you been since the last evaluation?" If children or adolescent patients are unable to adequately understand and respond to this question, the information will be obtained from the patient's guardian and/or Investigator or study nurse.

Any ADR or above defined AE which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms, which represent a

single syndrome or diagnosis, the latter should be recorded in the CRF. The Investigator responsible will grade the severity of all ADRs/AEs (mild, moderate or severe), the seriousness (non-serious or serious) and causality, as defined below (**Sections 7.3.2.3, 7.3.2.4**, and **7.3.3**). The Sponsor is responsible to assess the expectedness of each ADR/AE (expected or unexpected), as defined below (**Section 7.3.2.4**).

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and followed-up until they have returned to normal and/or an adequate explanation is available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of the medicinal product are not considered as ADRs/AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The Investigator responsible should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the patients' ADRs/AEs.

7.3.2.3 Severity

The intensity/severity of all ADRs/AEs will be graded as follows:

- mild: an ADR/AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities;
- moderate: an ADR/AE which is sufficiently discomforting to interfere with the patient's routine activities;
- severe: an ADR/AE which is incapacitating and prevents the pursuit of the patient's routine activities.

Grading of an ADR/AE is up to the medical judgment of the Investigator and will be decided on a case by case basis.

7.3.2.4 Causality

The following causality definitions should be used for classification of each AE:

Probable: Event or laboratory test abnormality, with reasonable time relationship to drug intake.
Unlikely to be attributed to disease or other drugs.
Response to withdrawal clinically reasonable.
Re-challenge not required.

Possible: Event or laboratory test abnormality, with reasonable time relationship to drug intake.
Could also be explained by disease or other drugs.
Information on drug withdrawal may be lacking or unclear.

Unlikely: Event or laboratory test abnormality does not follow a reasonable time relationship to drug intake.
Could also be explained by the patient's clinical state or by environmental factors or other therapies administered.

Not related: Reports for which sufficient information exists to conclude that the etiology is unrelated to the IMP.

Unclassified: Reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

The following causality definitions should be used for classification of each ADR:

Probable: Reports or laboratory test abnormality, with reasonable time relationship to drug intake
Unlikely to be attributed to disease or other drugs
Response to withdrawal clinically reasonable
Re-challenge not required.

Possible: Reports or laboratory test abnormality, with reasonable time relationship to drug intake
Could also be explained by disease or other drugs
Information on drug withdrawal may be lacking or unclear.

Classification of ADRs:

ADRs will be classified by the Sponsor as either expected or unexpected:

- expected: an adverse event that is listed in the current edition of the Investigator's Brochure.
- unexpected: an adverse event that is not listed in the current edition of the Investigator's Brochure, or that differs because of greater severity or greater specificity.

7.3.2.5 Outcome

The outcome of all reported ADRs has to be documented as follows:

1. recovered, resolved
2. recovering, resolving
3. not recovered, not resolved
4. recovered, resolved with sequelae
5. fatal
6. unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after treatment with medicinal product ended, and without respect of being considered treatment-related or not.

7.3.2.6 Action(s) Taken

ADRs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the Investigator must be documented:

a) in general
   - none
   - medication (other than medicinal product) or other (e.g., physical) therapy started
   - test performed
   - other (to be specified)

b) on medicinal product
   - none
   - product withdrawn
   - dose reduced
   - dose increased

The responsible Investigator will follow-up each ADR until it is resolved or until the medical condition of the patient is stable and all relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events

A **serious** AE is any untoward medical occurrence at any dose:

- results in death,
- is life-threatening (this implies that the patient was at an immediate risk of death at the time of the event, and not a hypothetical situation of what could or would have happened if, for example, no treatment had been administered),
- requires in-patient hospitalization or prolongation of existing in-patient hospitalization (hospitalization does not refer to the treatment of an ADR/AE on an out-patient status or to hospitalization because of study-related procedures (e.g., infusion at two consecutive days) or because of an elective surgical procedure for which the date had been scheduled earlier),
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event (e.g. suspected transmission of an infectious agent, or other reactions that should be reported in an expedited manner although they did not immediately result in one of the above seriousness criteria).

Medical judgment should be exercised in deciding whether an ADR/AE is serious in other situations: Important ADRs/AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

SAE reporting timelines

All SAEs after the first administration of Octaplas™ are to be reported by telephone or e-mail immediately to the Clinical Project Manager or designee. Contact details will be communicated at the study initiation visit.

An Octapharma "Serious Adverse Event Report" must be completed and submitted within 24 hours after recognition of the event.

All SAEs should additionally be reported to:

Octapharma's Corporate Drug Safety Unit:
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: +43 1 61032-9949
E-mail: cdsu@octapharma.com
24 hours emergency telephone number: +1 (844) 338-7317 or +43 1 40 80 500

7.3.4 TEs and TEEs

To allow continuous monitoring of the product's safety all TEs and TEEs and other safety information as defined below must be documented and reported to Octapharma. All TEs and TEEs will be reported regardless of severity or relatedness to the product.

The following list includes diagnoses and symptoms of possible TEs and TEEs that could be expected to be reported:

Acute myocardial infarction
- Increased heart enzymes*
- ECG signs of myocardial infarction*
- Angina pectoris*
- Acute coronary syndrome*
- Chest pain or pressure*
- Cardiac arrest**

(Ischemic) Stroke

Transient ischemic attack

Cerebrovascular accident
- Vision or speech disorders*
- Unilateral paresis/weakness
- Movement disorders*
- Dysphasia*
- Sudden severe headache*

Deep vein thrombosis
- Pain or tenderness in leg(s)*
- Pain in calf/calves*
- Swelling calf/calves/lower legs*

Pulmonary embolism

Unexplained shortness of breath*
Sudden chest pain getting worse with a deep breath, coughing, or chest movement*
Cyanosis*

Thrombophlebitis
Infusion site thrombosis
* Possible sign or symptom of TEE
** May be outcome of TEE

To determine/confirm a TE or TEE the following adjudicators will be involved:

Adjudicator 1 (Investigator)

On the corresponding safety reporting form of the CRF, the Investigator is specifically asked if the reported event is a TE or TEE in his/her opinion.

Adjudicator 2 (Octapharma Central Drug Safety Unit, CDSU)

Once a TEE/TE is recorded on the CRF, the event will be forwarded to Octapharma's Drug Safety Unit who will process the TEE/TE in routine manner (including assessments of expectedness, causality, seriousness, TEE/TE classification of event).

Adjudicator 3 (Independent Data Monitoring Committee, IDMC)

The IDMC will receive anonymized case reports and/or lists of all reported adverse reactions. Serious cases, probably or possibly related and suspected TEEs/TEs (as determined by Adjudicator 1 and/or Adjudicator 2) will be reviewed on an ad-hoc basis; other cases like ADRs and not related SAEs will be reviewed on a quarterly basis. The IDMC will then vote on all new cases (simple majority), record their judgment and return their decisions back to data management.

In case, the adjudicators disagree, the following scheme will be applied (Table 1):

Table 1: Scheme of Decision for Adjudicators

Determined as TEE/TE by Adjudicator 1?	Determined as TEE/TE by Adjudicator 2?	Determined as TEE/TE by Adjudicator 3?	Determined as TEE/TE in database?
yes	no	no	yes
yes	yes	no	yes
no	yes	no	yes
no	no	yes	yes
no	yes	yes	yes
yes	no	yes	yes

7.3.5 Laboratory Tests

7.3.5.1 Determination of Blood Group

Blood samples will be drawn at Screening for determination of the patient's ABO blood group type compatibility.

7.3.5.2 Safety Laboratory Parameters

The following safety laboratory parameters will be assessed. Before each TPE and after each TPE, blood samples will be drawn for CBC and Chem 7. Within 24 hours before the first TPE procedure, during the TPE and at follow-up, ionized calcium levels will be assessed for citrate toxicity.

- Chem 7 panel:
  - Blood Urea Nitrogen
  - CO_2 (bicarbonate)
  - Serum Chloride
  - Serum Creatinine
  - Glucose
  - Serum Potassium
  - Serum Sodium
- CBC:
  - White Blood Cell
  - Red Blood Cell
  - Hemoglobin
  - Hematocrit
  - Mean Corpuscular Volume
  - Mean Corpuscular Hemoglobin
  - Mean Corpuscular Hemoglobin Concentration
  - Red Cell Distribution Width
- Ionized calcium

7.3.5.3 Pregnancy Testing

Pregnancy testing will be done at Screening for females of childbearing potential. Confirmation that the subject is not pregnant must be established by a negative pregnancy test result obtained during Screening.

7.3.6 Vital Signs and Physical Examination

Vital signs data (heart rate, respiratory rate, temperature, and blood pressure assessment) will be collected before and after each TPE.

Physical examination data (dermatological and lymphatic system, head, eyes, ears, nose, throat, respiratory tract, cardiovascular and gastrointestinal system, musculoskeletal system, neurological system, and endocrinological disorders) will be collected at Screening.

7.3.7 Other Relevant Safety Information

Post study related safety reports: Any ADR (i.e., any adverse event with a suspected causal relationship to the medicinal product) which occurs after the completion of the study should be reported by the Investigator. The usual procedure for reporting post marketing safety information should be followed, but relation to the clinical study should be stated on the report.

If the Investigator becomes aware that a patient has died within 4 weeks after the last administration of the product, this should be reported as well, without being considered treatment related or not.

Pregnancies: Every effort will be made to avoid a pregnancy during the use of the product.

Pregnancies occurring during the study (fetal exposure to the product) need to be reported.

In case of pregnancy during the study, the Investigator is asked to complete the pregnancy notification form and to send it (by email or fax) to the Clinical Project Manager/designee.

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

Overdose, interaction, abuse, misuse, and medication error:

The following safety relevant information should be reported as an ADR or, if the reaction fulfils one of the criteria for seriousness, as a serious ADR.

Drug overdose: An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than that specified in the protocol, and higher than the known therapeutic dose and of clinical relevance. The reaction must be clearly identified as an overdose. Due to the study design, no overdose is expected.

Interaction: A drug interaction is a situation in which a substance/medicinal product affects the activity of the study drug, i.e., the effects are increased or decreased, or they produce an effect that none of the products exhibits on its own. The reaction must be clearly identified as drug interaction.

Abuse: An abuse is the deliberate use of a medicinal product that may lead to addiction accompanied by harmful physical or psychological effects. This is not relevant for the medicinal product but may be applicable for concomitant medications.

Misuse: Misuse is the deliberate administration or use of the medicinal product outside its described indication or outside the current state of the art medical practice (off-label-use). The reaction must be clearly identified as misuse.

Medication error: Medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging and instructions for use/labeling. The reaction must be clearly identified as a medication error. Due to the study design, no medication error should happen.

7.4 Appropriateness of Measurements

Only standardized measurements that are widely used and generally recognized as reliable, accurate, and relevant will be used in this study.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the CRF must be supported by source data in the patient records with the exceptions listed in **Section 8.1.2**.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s) and regulatory inspection(s), by providing direct access to source data/records.

8.1.2 Case Report Forms

The Sponsor will provide the CRFs in paper or electronic format. They will be reviewed against source documentation at each monitoring visit. The Investigator should allocate sufficient time and space for the review and correction process.

For each patient enrolled, an electronic CRF /eCRF) must be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff (e.g. research nurse) will be responsible for entering all of the patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry, as defined in applicable SOPs. The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must appear on the delegation of authority log.

If any errors in the eCRFs are found during the data review process discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management. The programmed checks fire automatically once an eCRF page is saved within the system. The output of the programmed checks is referred to as 'discrepancies'. Discrepancies are generated by the input of illogical eCRF data. The purpose of these objects is to clarify the use, context, or insertion of illogical or missing data with the site or designee.

All discrepancies (programmed and manual) will be submitted to the site personnel or monitor for the site within the EDC system. Once the site responds to a discrepancy, Data Management or the monitor will review the new or changed data to ensure an appropriate response and close the

discrepancy within the system. The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

8.1.3 Changes to Case Report Form Data

Errors occurring on the EDC system can only be corrected by the investigator(s) or other site personnel. An audit trail documents all changes to the data over the entire study period. If data is changed as a result of a query, a comment must be supplied within the query's text, stating the reason for the change, prior to closing. The study monitor should provide guidance to investigators and the investigators' designated representatives on making such corrections. In addition, any changes to a previously saved eCRF page that has not had a query generated will need to have a reason specified for the data change. This is handled within the EDC system and relevant prompts appear once any changes are made.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management for incomplete or ambiguous resolutions. If the query response provided confirms the data as correct, the discrepancy will be closed based on the query response. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed, and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the investigator prior to database lock.

All corrections on a CRF and on the source documents must be made in a way that does not obscure the original data. The correct data must be inserted, dated and initialed/authorized by trial site personnel. If reason for the change is not obvious, then a reason should be given. The Principal Investigator must, at a minimum, sign the final CRF page to attest to the accuracy and completeness of all the data. Once the data have been entered into the database, they will be checked and any discrepancies will be raised and returned to the Investigator for resolution. Data will be monitored and tabulated in accordance with the Data Management Plan.

8.2 Information of Investigators

An Investigator's Brochure will be handed out to the Investigator before the start of the study. This Brochure contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the medicinal product under evaluation and the respective benefit-risk ratio.

The Investigator's Brochure will be updated by the Sponsor at regular intervals and in case new information concerning the medicinal product becomes available.

The Investigator will be kept informed of important data that relate to the safe use of the product as the study proceeds.

8.3 Responsibilities

The Investigator is accountable for the conduct of the clinical study. If any responsibilities are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant study-related duties.

The Investigator may authorize site staff (e.g., sub-investigators, nurses) to enter study data into the CRF. This must be documented in the "Delegation of Authority Log", filled in and signed by the Investigator responsible.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (copies of the protocol, study approval letters, all original informed consent/assent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of recognized experts in the field of immunology, pediatrics and/or clinical care who are not actively recruiting patients.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification or termination of the study. A study specific Standard Operating Procedure will define in detail the composition, responsibilities and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

9.1 Determination of Sample Size

A minimum of 40 pediatric patients are planned to be enrolled.

The purpose of this study is to assess safety and tolerability of octaplas™ in the pediatric population by monitoring ADRs and safety laboratory parameters. The sample size of at least 40 pediatric patients is not derived from statistical considerations of power, but to gather enough clinical evidence to obtain a sound and meaningful medical assessment for patients ≥ 2 and ≤ 20 years of age.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the descriptive and explorative analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

All data collected will be summarized and presented descriptively to facilitate the review of population homogeneity and general patterns. Additional review in specific age sub-groups will be performed if possible. No confirmatory hypothesis testing is planned. Any p-value or confidence interval presented is to be understood in the exploratory sense.

All safety parameters will be presented descriptively in full detail, by age group as well as in total. The safety assessment will include the occurrence of all SAEs ADRs, TEs, and TEEs. To facilitate the detection of any possible safety signal, all ADRs will be characterized and analyzed by seriousness, severity, relation to study drug and timely relationship to study drug administration. In addition to these pre-planned categories the collected data will be examined to identify additional characteristics of interest such as e.g. particular indications for TPE, relevant concomitant medications, or SMQs covering a noticeable number of events. The rates of ADRs will be presented for such categories, together with the associated 95% confidence intervals, again per age group and in total.

Individual patient profiles or tabulations will be generated, displaying the baseline characteristics as well as all interventions, treatment details and measurements on a time scale. This will facilitate the review of each individual course of treatment by a medical expert to detect any safety signal that might not be reflected in the ADR rates.

9.2.1 Population for Analysis

The safety population (SAF) will include all patients who received at least one infusion of octaplas™.

The full analysis set (FAS) is defined according to the intent-to-treat (ITT) principle and will include all patients of the SAF with any information available on the primary endpoint; these are all treated patients monitored for SAEs, ADRs, TEs and TEEs after start of the TPE, and it is thus expected that this population will coincide with the SAF.

The per-protocol population will include all patients who have completed the infusion episode(s) and the final examination without major protocol deviations that would have an effect on the

evaluation of the primary endpoint. Examples of protocol deviations to be considered in this respect would be dosing errors, the use of prohibited concomitant medications, or the occurrence of completely unrelated medical events that require an interruption of the study procedures. The final decision regarding inclusion/exclusion of patients from the analysis sets will be taken by a panel including the Clinical Project Manager, the study statistician and a medical expert during a data review meeting before database lock. The decisions taken will be based on a review of complete data listings, and documented before the database is locked and the analysis is performed.

9.2.2 Efficacy Analysis Plan

Efficacy will not be assessed.

9.2.3 Safety Analysis Plan

The occurrence of SAEs, ADRs, TEs and TEEs will be reported. All these events will be characterized and analyzed by seriousness, severity, relation to study drug, and timely relationship to study drug administration.

Vital sign measurements *(*absolute values and change from pre-TPE*)* will be summarized by descriptive statistics. All measurements outside age-specific thresholds will be listed and reviewed individually.

All safety laboratory data – absolute values as well as changes from baseline – will be presented descriptively per time point. All measurements outside age-specific thresholds will be listed and reviewed individually.

All data will be presented in total as well as in sub–groups reflecting age , gender, underlying diagnosis and/or most relevant medical history and concomitant medications as appropriate.

9.2.4 Handling of Missing Data

In general, missing data will not be imputed; for calculations concerning the body weight, in particular the administered doses per kg, the latest available body weight measurement will be used.

9.3 Randomization / Stratification / Code Release

Not applicable. This is an open-label study.

9.4 Interim Analysis (if Applicable)

Not planned.

10 ETHICAL / REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical / Regulatory Framework

The study protocol and any subsequent amendment(s) will be submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines and country and local regulations.

The submission for regulatory approval will be made by the Sponsor or designated third party, e.g. Contract Research Organization (CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study approval letter must be available before any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g., CRO) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent/Assent

The Investigator will obtain a freely given written consent from each patient's legal representatives or guardians after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient's legal representatives or guardians, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

If children are old enough (age usually deemed by each institution) to understand the risks and benefits of the study, they should also be informed and provide their written assent.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-Ordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC/IRB and/or competent authority responsible as required by applicable regulations. IEC/IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the medicinal product, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patients' Data

The Investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient number. Documents not for submission to the Sponsor, i.e., the confidential subject identification code list, original consent forms and source records will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the medicinal product have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and Sponsor's Standard Operating Procedures) will be prepared by the Sponsor after the completion of the study. The Co-Ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee.

This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

Octapharma carries general liability insurance to cover any potential damage or injury occurring to a patient directly associated with their participation in the study.

The Investigator is responsible for dispensing the study product according to this protocol, and for its secure storage and safe handling throughout the study.

14 REFERENCES

1. Rollag H, Solheim BG, Svennevig JL: Viral safety of blood derivatives by immune neutralization. Vox Sang 1998; 74 Suppl 1: 213-217.
2. octaplas™. Annotated prescribing information. Octapharma. Hoboken, New Jersey, USA.

15 APPENDICES

15.1 Appendix 1: octaplas™ Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Octaplas safely and effectively. See full prescribing information for Octaplas.

Octaplas, Pooled Plasma (Human), Solvent/Detergent Treated
Solution for Intravenous Infusion
Initial U.S. Approval: 2013

----------INDICATIONS AND USAGE----------
Octaplas is a solvent/ detergent (S/D) treated, pooled human plasma indicated for

- Replacement of multiple coagulation factors in patients with acquired deficiencies
  - due to liver disease
  - undergoing cardiac surgery or liver transplant
- Plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)

----------DOSAGE AND ADMINISTRATION----------
For intravenous use only.
Administer Octaplas based on AB0-blood group compatibility.

Indication	Dosage
Replacement of multiple coagulation factors in patients with acquired deficiencies	10 to 15 milliliters per kg, Adjust the dose based on the desired clinical response
Plasma exchange in patients with TTP	1 to 1.5 plasma volumes (40 to 60 milliliters per kg)

----------DOSAGE FORMS AND STRENGTHS----------
Solution for infusion containing 45 to 70 mg human plasma protein per mL in a 200 mL volume. (3)

----------CONTRAINDICATIONS----------

- IgA deficiency
- Severe deficiency of Protein S
- History of hypersensitivity to fresh frozen plasma (FFP) or to plasma-derived products including any plasma protein
- History of hypersensitivity reaction to Octaplas

----------WARNINGS AND PRECAUTIONS----------

- Transfusion reactions can occur with AB0 blood group mismatches (5.1)
- High infusion rates can induce hypervolemia with consequent pulmonary edema or cardiac failure (5.2)
- Excessive bleedings due to hyperfibrinolysis can occur due to low levels of alpha2-antiplasmin (5.3)
- Thrombosis can occur due to low levels of Protein S (5.4)
- Citrate toxicity can occur with volumes exceeding one milliliter of Octaplas per kg per minute (5.5)
- Octaplas is made from human blood; therefore, may carry the risk of transmitting infectious agents, e.g., viruses and theoretically, the variant Creutzfeldt-Jakob disease and Creutzfeldt-Jakob disease agent (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reactions observed in ≥ 1% of patients included pruritis, urticaria, nausea, headache, paresthesia (6).

Serious adverse reactions seen in clinical trials were anaphylactic shock, citrate toxicity and severe hypotension.

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).

See 17 for PATIENT COUNSELING INFORMATION
Revised: [March 2015]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Octaplas is a solvent / detergent (S/D) treated, pooled human plasma indicated for:

- Replacement of multiple coagulation factors in patients with acquired deficiencies
  - due to liver disease
  - undergoing cardiac surgery and liver transplant
- Plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)

2 DOSAGE AND ADMINISTRATION

For intravenous use only
Administer Octaplas based on AB0-blood group compatibility.

2.1 Dose

Replacement of coagulation factors in patients with acquired deficiencies due to liver disease or undergoing cardiac surgery or liver transplant

Initially infuse of 10 to 15 mL Octaplas per kilogram body weight. This should increase the patient's plasma coagulation factor levels by approximately 15-25%. If hemostasis is not achieved, use higher doses.

Adjust dose based on desired clinical response.

Monitor response, including measurement of activated partial thromboplastin time (aPTT), prothrombin time (PT), and/or specific coagulation factors.

Plasma exchange in patients with TTP.

Completely replace plasma volume removed during plasmapheresis with Octaplas. Generally, 1 to 1.5 plasma volumes corresponds to 40 to 60 milliliters per kg.[1,2]

2.2 Administration

Administer Octaplas after thawing using an infusion set with a filter.

Octaplas should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid.

Avoid shaking.

Steps for Thawing:

- For water bath:
  - Thaw in the outer wrapper for up to 30 minutes in a circulating water bath at +30°C to +37°C (86°F to 98.6°F). An overwrap bag may be used to provide further protection of contents if appropriate.
  - Prevent water from contaminating the entry port.
  - The minimum thawing time is 30 minutes at 37°C (98.6°F). The thawing time depends on the number of bags in the water bath. If more than one plasma bag is thawed in the same water bath, then the thawing time can be prolonged, but should not exceed 60 minutes.

- For dry tempering system:
  - Place the Octaplas bags between the heating plates according to the manufacturer's instructions.
  - Thaw plasma following manufacturer directions between +30°C to +37°C (86°F to 98.6°F). Remove the product when the thawing process is completed. The thawing process may be monitored and recorded using the thawing device printer or barcode scanner recommended by the device manufacturer.
  - Monitor the thawing process and record using the thawing device printer or barcode scanner recommended by the device manufacturer.

Do not freeze Octaplas. Discard unused product.

3 DOSAGE FORMS AND STRENGTHS

Solution for infusion containing 45 to 70 mg human plasma proteins per mL in a 200 mL volume.

4 CONTRAINDICATIONS

Do not use Octaplas in patients with:

- IgA deficiency
- Severe deficiency of Protein S
- History of hypersensitivity to fresh frozen plasma (FFP) or to plasma-derived products including any plasma protein
- History of hypersensitivity reaction to Octaplas

5 WARNINGS AND PRECAUTIONS

5.1 Transfusion reactions

Transfusion reactions can occur with AB0 blood group mismatches. Administration of Octaplas must be based on ABO-blood group compatibility.

5.2 Hypervolemia

High infusion rates can induce hypervolemia with consequent pulmonary edema or cardiac failure. Monitor patients for signs and symptoms of pulmonary edema or cardiac failure and institute appropriate management.

5.3 Hyperfibrinolysis

Excessive bleeding due to hyperfibrinolysis can occur due to low levels of alpha2-antiplasmin (also named plasmin inhibitor). Monitor for signs of excessive bleeding in patients undergoing liver transplantation.

5.4 Thrombosis

Thrombosis can occur due to low levels of Protein S. Monitor for signs and symptoms of thrombosis in patients at risk.

5.5 Citrate Toxicity

Citrate toxicity can occur with volumes exceeding one milliliter of Octaplas per kg per minute. The infusion rate should not exceed 0.020-0.025 mmol citrate per kilogram per minute (i.e., less than one milliliter Octaplas per kg per minute). Symptoms attributable to citrate toxicity (hypocalcaemia) include e.g., fatigue, paresthesia and muscle spasms, especially in patients with liver function disorders. Administer calcium gluconate intravenously into another vein in order to minimize citrate toxicity.

5.6 Infection Risk from Human Plasma

Because Octaplas is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Octapharma [1-866-766-4860] or FDA at 1-800-FDA-1088 or www.fea.gov/medwatch. *See Description (11)*

6 ADVERSE REACTIONS

Serious adverse reactions seen in clinical trials were anaphylactic shock, citrate toxicity and severe hypotension.

The most common adverse reactions observed in ≥ 1% of subjects included pruritis, urticaria, nausea, headache, and paresthesia.

6.1 Clinical Trials Experience

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

Adverse reactions observed in clinical trials derive from 9 clinical trials. The mean dose administered ranged from 6 to 15 milliliters/kg body weight; when used in plasma exchange the dose was between 15 to 75 milliliters/kg. Two of the studies were conducted in healthy volunteers (n=90).

In total, 359 subjects received about 600 transfusion episodes in these trials.

The following table shows the adverse reactions observed in ≥ 1% of subjects in order of severity:

Nervous system disorders
Headache, paresthesia
Gastrointestinal disorders
Nausea
Skin and subcutaneous tissue disorders
Pruritis, urticaria

6.2 Post-Marketing Experience

Because post-marketing 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.

Blood system disorders Hyperfibrinolysis
Immune system disorders Hypersensitivity reactions including anaphylactoid and allergic type of reactions
Metabolic and nutritional disorders Alkalosis
Cardiovascular disorders Cardiac arrest, circulatory overload, thromboembolism, tachycardia
Respiratory, thoracic and mediastinal disorders Respiratory arrest or failure, bronchospasm, pulmonary edema, dyspnea, tachypnoea
Gastrointestinal disorders Abdominal pain, vomiting
Skin and subcutaneous tissue disorders Rash, erythema
General disorders and administration site conditions Fever and/or chills, chest discomfort or pain
Investigations Seroconversions (passive transfer of antibodies)
Injury, poisoning and procedural complications Citrate toxicity

7 DRUG INTERACTIONS

Do not inject drugs containing calcium in the same intravenous line with Octaplas because precipitants may block the line.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

Efficacy and safety of Octaplas in labor or delivery is unknown.

8.3 Nursing Mothers

Efficacy and safety of Octaplas in lactating women is unknown.

8.4 Pediatric Use

Efficacy and safety of Octaplas have not been evaluated in pediatric patients.

8.5 Geriatric Use

Efficacy and safety of Octaplas have not been established in geriatric patients.

11 DESCRIPTION

Octaplas is a sterile, pyrogen free, frozen solution of solvent/detergent (S/D) treated pooled human plasma.

The active ingredient comprises plasma proteins such as albumin, immunoglobulins, other globulins, coagulation factors, complement proteins and protease inhibitors. The content and distribution of plasma proteins in Octaplas are comparable to reference ranges for healthy blood donors, except for Protein S and alpha2-antiplasmin. Within a mean total protein content of 57 mg/mL, albumin comprises ~50% and immunoglobulin classes G, A, and M comprise ~12%, ~3%, and ~1%, respectively. Protein S and alpha2-antiplasmin, which are labile to S/D treatment, are controlled to ensure levels in the final product of ≥ 0.4 International Units (IU) per mL. Plasma lipids and lipoproteins are reduced due to S/D treatment and subsequent oil and solid phase extraction.

Composition of Octaplas

Component	Quantity per 200 mL dose
Human plasma proteins	9.0 - 14.0 g
Sodium citrate dihydrate	0.88 - 1.48 g
Sodium dihydrogen-phosphate dihydrate	0.06 - 0.24 g
Glycine	0.80 - 1.20 g

Octaplas is manufactured from human plasma collected in US licensed plasma donation centers. All plasma donations are tested for viral markers in compliance with US regulation. In addition, the manufacturing plasma pool may not contain a titer of human Parvovirus B19 DNA exceeding 10.0 IU per microliter and must have a negative result in a test for human Hepatitis E Virus (HEV) RNA by NAT PCR with a sensitivity of ≤ 2.5 $\log_{10}$ IU/mL.

Each lot of Octaplas is manufactured from pooled plasma of a single AB0 blood group (A, B, AB, or 0). The manufacturing plasma pool is limited to 390 kg comprising 630-1,520 individual donors. Frozen plasma units are thawed and pooled. Sodium dihydrogen phosphate dihydrate is added as a buffer against increase in pH due to loss of CO_2. After filtration through a 1 µm pore size membrane, the plasma pool is treated with S/D reagents [1% tri(n-butyl) phosphate (TNBP) and 1% octoxynol for 1-1.5 hours at +30°C (86°F)] to inactivate enveloped viruses. The S/D reagents are removed by sequential oil and solid phase extraction procedures. Glycine is added to adjust the osmolality. Plasma with glycine is applied to a column filled with affinity ligand resin intended for selective binding of prion protein (PrP^{Sc}). The effectiveness of this step in removal of prion infectivity from the product has not been established. After sterile filtration, the product is filled into sterile polyvinyl chloride blood bags, labeled, deep-frozen and stored at a temperature of ≤ -18°C (-0.4°F). The finished product is tested for coagulation factors II, V, VII, VIII, IX, X and XI, Protein C, Protein S, alpha2-antiplasmin (also known as Plasmin Inhibitor), fibrinogen and ADAMTS13.

The S/D treatment step has been validated to effectively inactivate relevant pathogenic and model enveloped viruses as summarized in Table 1.

Table 1 Virus Reduction During Octaplas Manufacture

Production Step	Virus Reduction Factor [$\log_{10}$]			
	HIV-1	PRV	SBV	BVDV
S/D treatment [$\log_{10}$]	≥ 5.05	6.56	≥ 5.46	≥ 4.04
Global Reduction Factor	**≥ 5.05**	**6.56**	**≥ 5.46**	**≥ 4.04**

HIV-1: Human Immunodeficiency Virus – 1
PRV: Pseudorabies Virus
BVDV: Bovine Viral Diarrhea Virus
SBV: Sindbis Virus

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Octaplas replaces human plasma proteins.

12.2 Pharmacodynamics

Coagulation factor activities in the final product are controlled to obtain levels within the range of normal human plasma. Protein S and alpha2-antiplasmin, which are labile to S/D treatment, are controlled to ensure levels in the final product of ≥ 0.4 International Units (IU) per mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TNBP and Octoxynol used in the manufacturing process for viral inactivation may be present in the final product at levels not exceeding 2.0 µg/mL for TNBP and 5.0 µg/mL for Octoxynol.

Toxicity

No evidence of toxicity was observed for TNBP + Octoxynol in sub-acute toxicity studies. [3]

Mutagenicity

No evidence of mutagenicity was observed in *in vitro* or *in vivo* mutagenicity studies performed for TNBP. [4-9]

14 CLINICAL STUDIES

The Octaplas predecessor product was studied in liver disease, liver transplantation, cardiac surgery and TTP.

An open-label parallel group study was performed in surgical patients who were allocated to receive either a single infusion of Octaplas (n=20) or no plasma treatment (n=26) during open-heart surgery.[10] A historical control group of patients having received standard single-donor FFP (n=20) was used to compare the efficacy and safety. The average dose of Octaplas was 700 mL (range 200 to 3400 mL), compared with 1012 mL (range 500 to 4000 mL) for standard FFP. The choice of plasma product (Octaplas or FFP) did not appear to influence the postoperative course with respect to volume of postoperative bleeding, the need for reoperation secondary to bleeding, or the length of the postoperative hospital stay. This study was not powered to detect any difference in efficacy.

A prospective, single-blind, randomized study was designed to investigate the safety and efficacy of Octaplas compared with standard FFP in adult patients with coagulopathies due to liver disease (LD) or liver transplantation (LTX), or for the management of newly diagnosed thrombotic thrombocytopenic purpura (TTP).[11-13] In total, 55 patients were included in the study. Three patients were suffering from TTP and all received Octaplas. Of the 24 patients with LD, 11 were treated with Octaplas, and out of the 28 LTX patients, 13 received Octaplas. Within the LD and the LTX groups, patients were comparable in all clinical aspects and in the dose of plasma given. There were no relevant changes in any of the coagulation factors, but protein C and fibrinogen improved considerably in both groups, accompanied by a corresponding improvement in partial thromboplastin time (PTT) levels 24 hours after infusion. Similar degrees of correction of prolonged international normalized ratio (INR) and PTT values were achieved with both Octaplas and FFP. All 3 patients with TTP attained platelet counts of $>50x10^9$/L by Day 10. This study was not powered to detect any difference in efficacy.

A prospective, non-randomized open-label study in intensive care patients was conducted in post-operative open heart surgery patients in the surgical intensive care unit who were in need of plasma transfusion for acute bleeding or for the risk of bleeding.[14] There were a total of 67 patients, 36 who received Octaplas (600 mL) and 31 who received FFP (600 mL). Parameters measured included PT, PTT, free Protein S and plasmin inhibitor. Parameters were measured before treatment and 60 minutes after termination of plasma infusion. The decrease in PT and PTT, and the rise in free Protein S were similar between the two study arms. Plasmin inhibitor declined after Octaplas and remained unaffected by FFP. Clinical hemostasis evaluations were also similar between the two treatment regimens. This study was not powered to detect any difference in efficacy.

In a randomized, open-label, controlled study, 60 healthy adult volunteers (mean age 32.6±9.1 years) received after a standard plasmapheresis (PPh) of 600 mL plasma, an administration of 1200 mL of Octaplas or the predecessor product in a cross-over design. Coagulation factors (FI, FII, FV, FVII, FVIII, FIX, FX, and FXI) and hemostatic parameters (aPTT, PT and protein C) were assessed post-infusion at 15 minutes, 2 hours and 24 hours. The primary analysis was to demonstrate equivalence for recoveries using a 10% margin. All coagulation and hemostatic parameters met the equivalence criterion. To verify the assumption of improvement of plasmin inhibitor (PI) concentrations, a test for superiority was conducted. Statistically significant differences between treatments were found at 15 minutes (P=0.0012) and 2 hours (P=0.0190) post-transfusion for the per protocol population. Increased levels of PI post-infusion of Octaplas, as compared to the predecessor product may be attributable to the increased concentrations of PI.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

Octaplas is supplied in polyvinyl chloride blood bags containing 200 mL frozen solution and has a slightly yellow appearance.

NDC Number	Blood group
Octapharma Pharmazeutika Produktionsges.m.b.H	
68982-952 - 01	Blood group A
68982-953 - 01	Blood group B
68982-954 - 01	Blood group AB
68982-955 - 01	Blood group 0

Storage and Handling

- Store at ≤-18°C (-0.4°F) for 3 years from the date of manufacture.
- Store protected from light.
- Thaw product according to instructions in section 2.2.
- Use thawed product within 24 hr. if stored at 1 - 6°C (33.8°F to 42.8°F) or within 8 hr. if stored at 20 - 25°C (68°F to 77°F).
- Do not refreeze thawed product.
- Do not use product that is cloudy or has deposits.
- Discard product after the expiration date printed on the container label.

17 PATIENT COUNSELING INFORMATION

Inform patients to report:

- Early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, or anaphylaxis.
- Development of edema or volume overload including shortness of breath or breathing difficulties

Remind patients that Octaplas is made from human blood and may contain infectious agents that can cause disease. Report flu-like or other symptoms or viral infection.

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

Octapharma AB
Elersvägen 40
SE- 112 75, Sweden

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Distributed by:
Octapharma USA Inc.
121 River Street, Suite 1201
Hoboken, NJ 07030