

**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: .....

-----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: [XX/XXXX]

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## 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 ABO-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 thawing procedure should not take more than 30 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 ABO 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.fda.gov/medwatch](http://www.fda.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  $\geq 1\%$  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  $\geq 1\%$  of subjects in order of severity:

<b><i>Nervous system disorders</i></b> Headache, paresthesia
<b><i>Gastrointestinal disorders</i></b> Nausea
<b><i>Skin and subcutaneous tissue disorders</i></b> 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.

<b><i>Blood system disorders</i></b> Hyperfibrinolysis
<b><i>Immune system disorders</i></b> Hypersensitivity reactions including anaphylactoid and allergic type of reactions
<b><i>Metabolic and nutritional disorders</i></b> Alkalosis
<b><i>Cardiovascular disorders</i></b> Cardiac arrest, circulatory overload, thromboembolism, tachycardia
<b><i>Respiratory, thoracic and mediastinal disorders</i></b> Respiratory arrest or failure, bronchospasm, pulmonary edema, dyspnea, tachypnoea
<b><i>Gastrointestinal disorders</i></b> Abdominal pain, vomiting
<b><i>Skin and subcutaneous tissue disorders</i></b> Rash, erythema
<b><i>General disorders and administration site conditions</i></b> Fever and/or chills, chest discomfort or pain
<b><i>Investigations</i></b> Seroconversions (passive transfer of antibodies)
<b><i>Injury, poisoning and procedural complications</i></b> 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 alpha<sub>2</sub>-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 alpha<sub>2</sub>-antiplasmin, which are labile to S/D treatment, are controlled to ensure levels in the final product of  $\geq 0.4$  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

<u>Component</u>	<u>Quantity per 200 mL dose</u>
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  $\leq 2.5 \log_{10}$  IU/mL.

Each lot of Octaplas is manufactured from pooled plasma of a single AB0 blood group (A, B, AB, or O). 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<sub>2</sub>. After filtration through a 1  $\mu$ m 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<sup>Sc</sup>). 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  $\leq -18^\circ\text{C}$  (-0.4°F). The finished product is tested for coagulation factors II, V, VII, VIII, 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 [ $\log_{10}$ ]	$\geq 6.18$	$\geq 5.03$	$\geq 5.31$	$\geq 5.12$
Global Reduction Factor	$\geq 6.18$	$\geq 5.03$	$\geq 5.31$	$\geq 5.12$

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  $\geq 0.4$  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  $\mu\text{g/mL}$  for TNBP and 5.0  $\mu\text{g/mL}$  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  $>50 \times 10^9/L$  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  $32.6 \pm 9.1$  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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13. Williamson, L. M., et al. "A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation." *Transfusion* 39.11-12 (1999): 1227-34.
14. Haubelt, H., et al. "Effects of solvent/detergent-treated plasma and fresh-frozen plasma on haemostasis and fibrinolysis in complex coagulopathy following open- heart surgery." *Vox Sang* 82.1 (2002): 9-14.

## 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.

<u>NDC Number</u>	<u>NDC Number</u>	<u>Blood group</u>
<b>Octapharma Pharmazeutika Produktionsges.m.b.H</b>	<b>Octapharma AB</b>	
67467-952 - 01	68209-952 - 01	Blood group A
67467-952 - 02	68209-952 - 02	Blood group B
67467-952 - 03	68209-952 - 03	Blood group AB
67467-952 - 04	68209-952 - 04	Blood group 0

### Storage and Handling

- Store at ≤-18°C (-0.4°F) protected from light.
- Thaw product according to instructions in section 2.2.
- Use thawed product within 12 hr. if stored at 2 - 4°C (35.6°F to 39.2°F) or within 3 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

U.S. License No. 1646

**Distributed by:**

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