

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

OCTAPLAS® ▼

Solution for infusion

2. Qualitative and quantitative composition

Active Ingredients

Human plasma proteins 45 - 70 mg/ml

For excipients, see 6.1.

3. Pharmaceutical form

Solution for infusion.

4. Clinical particulars

4.1 Therapeutic indications

Indications for Octaplas are identical to those for fresh frozen plasma (FFP):

- Complex deficiencies of coagulation factors such as coagulopathy due to severe hepatic failure or massive transfusion.
- Substitution therapy in coagulation factor deficiencies, in emergency situations, when a specific coagulation factor concentrate, e.g. factor V or factor XI, is not available or when a precise laboratory diagnosis is not possible.
- Reversal of the effect on fibrinolysis and rapid reversal of effects of oral anticoagulants (coumarin or indanedione type), when vitamin K is insufficient due to impaired liver function or in emergency situations.
- Thrombotic thrombocytopenic purpura (TTP), usually in conjunction with plasma exchange.
- In intensive plasma exchange procedures, Octaplas should only be used to correct the coagulation abnormality when abnormal haemorrhage occurs.

4.2 Posology and method of administration

Dosage:

The dosage depends upon the clinical situation and underlying disorder, but 12-15 ml Octaplas/kg body weight (≈25%) is a generally accepted starting dose. It is important to monitor the response, both clinically and with measurement of prothrombin time (PT), partial thromboplastin time (PTT) and/or specific coagulation factor assays.

Dosage for coagulation factor deficiencies:

An adequate haemostatic effect in minor and moderate haemorrhages or surgery in coagulation factor deficient patients is normally achieved after the infusion of 5-20 ml Octaplas/kg body weight (10-33 %).

In the event of major haemorrhage or surgery the expert advice of a haematologist should be sought.

Dosage for TTP and haemorrhages in intensive plasma exchange:

In TTP patients the whole plasma volume exchanged should be replaced with Octaplas.

For the treatment of haemorrhages in intensive plasma exchange procedures the expert advice of a haematologist should be sought.

Method of administration:

Administration of Octaplas must be based on ABO-blood group compatibility. In emergency cases, Octaplas blood group AB can be regarded as universal plasma since it can be given to all patients.

Octaplas must be administered by intravenous infusion immediately after thawing as described in section 6.6, using an infusion set with a filter. An aseptic technique must be used throughout the infusion.

Due to the risk of citrate toxicity, the infusion rate should not exceed 0.020-0.025 mmol citrate/kg body weight/min equal to ≤ 1 ml Octaplas/kg body weight/min. Toxic effects of citrate can be minimised by giving calcium gluconate i.v. into another vein.

4.3 Contra-indications

Contra-indications for Octaplas are identical to those for FFP:

IgA deficiency with documented antibodies against IgA.

4.4 Special warning and precautions for use

Octaplas should be used with caution under the following conditions:

- IgA deficiency.
- Plasma protein allergy.
- Previous reactions to FFP.
- Manifest or latent cardiac decompensation.
- Pulmonary oedema.

Octaplas should not be used as volume expander in patients where no coagulation factor deficiency has been documented.

Octaplas should not be used in cases of bleeding caused by von Willebrand's Disease (vWD) or other coagulation factor deficiencies where a specific factor concentrate is available for use.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature.

The risk of transmission of infective agents is however reduced by:

- Selection of donors by a medical interview and screening of individual donations and plasma pools for the three major pathogenic viruses HIV, HCV, HBV.
- Testing of each plasma pool for HCV genomic material.
- Inactivation/removal procedures included in the production process that have been validated using model viruses and are considered effective for HIV, HCV and HBV. The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as HAV and Parvovirus B19. Transmission of Parvovirus B19 has been reported after the use of S/D-treated plasma in spite of the presence of neutralising antibodies.
- Parvovirus B19 may seriously affect seronegative pregnant women or immunocompromised individuals or patients with increased red cell turn over, therefore Octaplas should only be administered to these patients if strongly indicated.

A maximum of 1520 single donations are used for the manufacture of Octaplas.

Octaplas is produced from plasma pools containing a specified minimum antibody level which has been shown to have neutralising effect against HAV. A possible risk of infection by non-enveloped viruses should be weighed against the benefit of the inactivation of lipid-enveloped viruses such as HIV, HBV and HCV by the SD treatment.

Appropriate vaccination (e.g. against HAV and HBV) for patients in regular receipt of medicinal products derived from human blood or plasma should be considered.

Administration of Octaplas must be based on ABO-blood group compatibility. In emergency cases, Octaplas blood group AB can be regarded as universal plasma since it can be given to all patients.

Patients should be observed for at least 20 minutes after the administration.

In case of anaphylactic reaction or shock, the infusion must be stopped immediately. Treatment should follow the guidelines for shock therapy, see section 4.8.

Data on the use of Octaplas in premature babies are very limited, therefore, the product should only be administered to these individuals if the likely benefits clearly outweigh potential risks.

4.5 Interaction with other medicinal products and other forms of interactions

During clinical trials, Octaplas has been administered in association with various concomitant medications, and no interactions have been identified.

Incompatibilities are identical to those of FFP:

- Octaplas must not be mixed with other drugs as inactivation and precipitation may occur. The product can be mixed with red blood cells and platelets.
- To avoid the possibility of clot formation, solutions containing calcium must not be administered by the same intravenous line as Octaplas.
- Interactions with other drugs are unknown.

4.6 Pregnancy and lactation

The safety of Octaplas for use in human pregnancy has not been established in controlled clinical trials. The product should be administered to a pregnant or lactating woman only if alternative therapies are regarded inappropriate. For potential risk of parvovirus B19 transmission, see section 4.4.

4.7 Effects on ability to drive and use machines

After ambulant infusion, the patient should rest for one hour.

There are no indications that Octaplas may impair the ability to drive or to operate machines.

4.8 Undesirable effects

The following adverse reactions were reported with Octaplas during clinical trials:

- Cutaneous manifestation (rash, rash erythematous and urticaria).
- Chills/shivering with or without fever.
- Isolated fever.
- Nausea with or without vomiting.
- Local oedema.
- Pulmonary manifestation.
- Hypocalcemia.
- Anaphylactoid reaction.

The following adverse reactions are known to be associated with FFP and therefore may also occur with Octaplas:

- Acute mild allergic reaction (e.g. urticaria (hives), fever, chills, nausea, vomiting, and abdominal or back pain) due to hypersensitivity to infused proteins are common (>1/100).
- Acute severe allergic (anaphylactic or anaphylactoid) reactions (characterised by e.g. flushing of the skin, hypotension, substernal pain, bronchospasms, dyspnoea, and cardio-respiratory collapse) due to hypersensitivity to infused proteins or anti-IgA are rare (<1/1000).
- High infusion rates may cause cardiovascular effects as a result of citrate toxicity (fall in ionised calcium), especially in patients with liver function disorders.
- In the course of plasma exchange, symptoms attributable to citrate toxicity (e.g. fatigue, paresthesia, tremor, and hypocalcemia) are less common (1/100-1/1000).

- Rarely (<1/1000), incompatibility between antibodies in FFP and antigens of recipient red blood cells can result in immediate or delayed type haemolytic transfusion reactions. Therefore, administration of Octaplas must be based on ABO-blood group compatibility.
- Rarely (<1/1000), potent anti-leukocyte antibodies may be present which, as a consequence of leukocyte aggregation in pulmonary vessels, can provoke an acute pulmonary injury, a syndrome known as transfusion-related acute lung injury characterised by chills, fever, a non-productive cough, and dyspnoea.
- Rarely (<1/1000), potent specific platelet antibodies may be present which can induce a passive post-transfusional purpura (PTP) characterised by dyspnoea, rash, fever, generalised purpura, and marked thrombocytopenia.
- Since the product does not contain whole cells (red blood cells, leukocytes and platelets) the risk of immunisation is reduced.
- Infusion of Octaplas may give rise to specific coagulation factor antibodies.

Emergency measures for adverse reactions

Depending on type and severity of adverse reactions, the infusion may be discontinued and appropriate reanimation must be applied, as defined in general guidelines for shock therapy:

<u>Clinical symptoms</u>	<u>Emergency measures</u>
Subjective complaints (nausea, etc.)	Reduce infusion rate or stop administration until recovery.
Skin symptoms (flush, urticaria, etc.)	Stop administration. Antihistamines.
Tachycardia, moderate drop in pressure (below 90 mm Hg systolic)	Stop administration. Glucocorticoids i.v.
Dyspnoea Shock	Stop administration. Adrenalin 0.1-0.5 mg s.c. or i.m., high doses of glucocorticoids i.v., oxygen, volume expander, possibly increased diuresis using frusemide in case of normovolaemia, control of acid base balance and if necessary correct electrolytes.
Persistent normovolaemic shock	Dopamine dosage up to a maximum of 10 µg/kg/min, possibly in combination with noradrenalin.

Cardiac or respiratory arrest

Resuscitation.

The following guidance applies to specific adverse reactions which may be associated with Octaplas:

Clinical symptoms

Emergency measures

Citrate toxicity (fall in ionised calcium)

Reduce infusion rate or stop administration until recovery. Calcium gluconate 10 % i.v. at a dose of 10 ml/l Octaplas infused.

Haemolytic transfusion reaction

Stop administration. Increased diuresis (maintain urine flow rates above 100 ml/hour in adults for at least 18-24 hours) using i.v. electrolytes and mannitol (e.g. mannitol 15 %, 125 ml/hour) or frusemide, sodium bicarbonate, dialysis in case of anuria. If applicable, symptomatic treatment of shock.

4.9 Overdose

- High dosages or infusion rates may induce hypervolaemia, pulmonary oedema and/or cardiac failure.
- High infusion rates may cause cardiovascular effects as a result of citrate toxicity (fall in ionised calcium), especially in patients with liver function disorders.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions, ATC code: B05A A.

Octaplas possesses the same clinical activity as normal human FFP. After SD treatment and subsequent removal of the SD reagents, the plasma protein content and distribution in Octaplas remain at comparable levels to those in FFP, i.e. 45-70 mg/ml.

The coagulation activity values are close to the corresponding values for normal human FFP and a minimum of 0.5 IU/ml is obtained for each coagulation factor.

The finished product is tested for coagulation factors V, VIII, XI.

However, as a result of the SD treatment and purification, the content in lipids and lipoproteins is reduced. This is of no relevance within the indications for Octaplas.

5.2 Pharmacokinetic properties

Octaplas has similar pharmacokinetic properties as FFP.

5.3 Preclinical safety data

Virus inactivation is carried out by the SD method, using 1 % Tri (N-Butyl) Phosphate (TNBP) and 1 % Triton X-100. These SD reagents are removed during the purification process. The maximum amounts of TNBP and Triton X-100 in the finished product are 2 µg/ml and 5 µg/ml, respectively.

Pharmacological and toxicological studies in animals indicate that these residual levels should present no clinical problem for the indications and dosages specified.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium citrate dihydrate, Sodium dihydrogenphosphate dihydrate, Glycine, TNBP, Triton X-100

6.2 Incompatibilities

Octaplas should not be mixed with other medicinal products as inactivation and precipitation may occur.

6.3 Shelf-life

The shelf-life of Octaplas is two years when stored at ≤ -30 °C and protected from light.

Once the bag has been opened, the product must be used immediately, within one hour after thawing.

6.4 Special precautions for storage

Octaplas frozen product should be stored and transported according to temperature and conditions as mentioned above (see section 6.3).

6.5 Nature and contents of container

Octaplas is filled into sterile, pyrogen-free, plasticised polyvinyl chloride blood bags which are over-wrapped with a polyamide/polyethylene film.

Bags of 200 ml.

6.6 Instructions for use and handling

Octaplas should be transported and stored at ≤ -30 °C.

Do not use after the expiry date given on the label.

Thaw in the outer wrapper in a water bath with good circulation at +30 to +37 °C. It is important to prevent water from contaminating the entry port.

Temperature in the water bath must never exceed +37 °C and should not be lower

than +30 °C. Allow the content of the bag to warm to approximately +37 °C before infusion. The temperature of Octaplas must not exceed +37 °C. The thawing procedure should not take more than 30 minutes.

Remove the outer wrapper and examine the bag for cracks or leaks.

Avoid shaking.

Do not use solutions which are cloudy or have deposits.

Storage of Octaplas for more than one hour after thawing may result in loss of activity of coagulation factors. To obtain the best yield of coagulation factors, Octaplas should be used immediately, within one hour after thawing. Octaplas stored for more than one hour after thawing should not be used to correct deficiencies of especially the labile coagulation factors.

Thawed Octaplas must not be refrozen. Unused product must be discarded.

7. Marketing authorisation holder

Octapharma Limited
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8. Marketing authorisation number

PL 10673/0009

9. Date of first authorisation/renewal of the authorisation

05 March 1998

10. Date of revision of the text

21 December 2000