PRODUCT MONOGRAPH

OCTAPLASMA™

Solvent Detergent (S/D) Treated Human Plasma
Liquid: 200 mL
Prescription Medication, Plasma Substitute: Blood Plasma
ATC code: B05AX03

Manufactured by:

Octapharma Pharmazeutika Produktionsges m.b.H.
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and

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Manufactured for:

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OCTAPLASMA™

Solvent Detergent (S/D) Treated Human Plasma
Solution for Infusion

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Injection	Solvent Detergent (S/D) Treated Human Plasma Per 200 mL: Human plasma proteins 9.0-14.0 g (45-70 mg/mL)	*For a complete listing see* DOSAGE FORMS, COMPOSITION AND PACKAGING *section.*

DESCRIPTION

OCTAPLASMA is solvent detergent (S/D) treated human plasma (45-70 mg/mL human plasma proteins). During the manufacturing process, OCTAPLASMA is treated with a combination of 1 % Tri(n-butyl)-phosphate (TNBP) and 1 % Octoxynol. These S/D reagents are removed by castor oil extraction (TNBP) and subsequent solid phase extraction (Octoxynol) before sterile filtration. After sterile filtration, 200 mL OCTAPLASMA is filled into sterile, plasticised polyvinyl chloride (PVC) blood bags that are over-wrapped with a polyamide/polyethylene film. The coagulation activity values are close to the corresponding values for normal human single-donor fresh-frozen plasma (FFP) and a minimum of 0.5 IU/mL is obtained for all clotting factors. However, as a result of the S/D treatment and purification, the content of lipids and lipoproteins is reduced. This is of no relevance for the indications for OCTAPLASMA. OCTAPLASMA has similar pharmacokinetic properties as normal FFP.
Precautions against viral transmission include: selection of plasma donors, screening of donations and plasma pool, as well as quality control measurements of the final product. As with any blood product, a potential problem is the transmission of blood borne pathogens including those of hitherto unknown origin. When medicinal products prepared from human blood or plasma are given to a patient, the transmission of infectious agents cannot be totally excluded. This applies also to hitherto unknown pathogens. This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases (see WARNINGS AND PRECAUTIONS section).

INDICATIONS AND CLINICAL USE

OCTAPLASMA is indicated for:

- Complex deficiencies of coagulation factors such as consumption coagulopathy e.g. disseminated intravascular coagulation (DIC) or coagulopathy due to severe hepatic failure, massive transfusion, or repeated large volume plasma exchange (especially in patients with impaired liver function).
- OCTAPLASMA may be used for emergency substitution therapy in coagulation factor deficiencies, when situations, e.g. haemorrhage, do not allow a precise laboratory diagnosis, or when a specific coagulation factor concentrate is not available.
- Rapid reversal of effects of oral anticoagulants when vitamin K is insufficient in emergency situations, or in patients with impaired liver function.

The efficacy of in patients with Thrombotic Thrombocytopenic Purpura has not been studied sufficiently, therefore, the clinical experience in these patients is limited.
OCTAPLASMA should be administered under the supervision of a qualified health professional who is experienced in the use of anticoagulation agents and in the management of coagulation disorders. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Geriatrics (> 65 years of age):

No data are available.

Pediatrics (< 16 years of age):

OCTAPLASMA was evaluated in 50 pediatric patients (age range 0-16 years) in a post-marketing study. (See CLINICAL TRIALS, Table 6). The product should only be administered to these individuals if the likely benefits clearly outweigh potential risks.

CONTRAINDICATIONS

Contraindications for OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) are as follows:
Absolute contra-indications:

- IgA deficiency with documented antibodies against IgA.
- severe deficiencies of protein S.

Relative contra-indications:

- IgA deficiency, plasma protein allergy, previous reaction to FFP or OCTAPLASMA, pulmonary oedema, and manifest or latent cardiac decompensation.
- OCTAPLASMA is contraindicated for patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering to the patient (see WARNINGS AND PRECAUTIONS - General).

General

Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections.

When medicinal products prepared from human plasma are administered, infectious disease due to the transmission of infective agents cannot be totally excluded. Like other plasma products, OCTAPLASMA carries the possibility for transmission of blood-borne viral agents, and theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent. This applies also to pathogens of hitherto unknown origin.

To reduce the risk of transmission of infective agents, stringent controls are applied to the selection and screening of donors for hepatitis B, hepatitis C and HIV infection. The plasma pools are also tested for HBsAg, anti-HIV 1/2, HBV-NAT, HIV-NAT, HCV-NAT, HAV-NAT, HEV-NAT and parvovirus B19-NAT and only those found negative or below a given cut-off limit (parvovirus B19) are used for manufacturing.

S/D treatment is not effective against non-enveloped viruses, including parvovirus B19 and HAV.

Transmission of HAV may occur following transfusion with OCTAPLASMA. It is, however greatly reduced by accepting only plasma pools found negative for HAV by a NAT test and by the presence of justified limits for neutralizing antibodies towards HAV.

Transmission of parvovirus B19 may occur following transfusion of OCTAPLASMA. However plasma pools are tested for the presence of justified limits for neutralizing antibodies towards parvovirus B19 and the parvovirus B 19– NAT. This combination may limit the risk of infection, although no laboratory or clinical studies have been performed to show that it is sufficient to prevent infection.

However, as with FFP, the transmission of parvovirus B19 or HAV by OCTAPLASMA cannot be totally excluded. In immunocompromised patients, in patients with haematological disorders

of high red cell turnover and in pregnant women, parvovirus B19 infections could lead to aplastic crises and hydrops fetalis with subsequent foetal loss, respectively. Therefore, OCTAPLASMA should only be administered to these patients if strongly indicated. A possible risk of infection should be weighed against the benefit of the inactivation of enveloped viruses such as HIV, HBV and HCV. Appropriate vaccination (e.g. against HAV) for patients in regular receipt of OCTAPLASMA should be considered. Infusion of OCTAPLASMA may give rise to specific coagulation factor antibodies.

Five cases of possible transmission of vCJD, or the causative agent of this disease, by non-leukocyte-depleted red blood cell concentrates (n=4) and a low-purity coagulation factor concentrate to a haemophiliac (n=1) have been reported in the literature [1, 2, 3, 4, 5]. The possibility of transmission of the vCJD agent by S/D plasma cannot be completely ruled-out. At present, the vCJD agent cannot be routinely detected in blood. However, the hypothesis of the B-lymphocytes and follicular dendritic cells, in particular, acting as potential blood borne carriers of the prion protein and their role in neuroinvasion, suggests that leukocyte depletion during processing of blood products and plasma-derivatives will reduce the possibility of transmitting vCJD [6]. Thus, leukocyte depletion of cellular blood components has been adopted by some countries as a measure to reduce the hypothetical risk of vCJD transmission. OCTAPLASMA undergoes multiple size exclusion filtration steps resulting in complete leukocyte removal without activating the leukocytes, and both this particular measure and the down-stream processing have demonstrated a potential to clear prions using an animal model of the agent causing vCJD [7]. Additionally, a column has been included into the production process of OCTAPLASMA in order to specifically remove prions. This safety measure is considered effective for removing the infectious agent causing vCJD, if present in plasma [8]. No animal material is used in the production of OCTAPLASMA.

Individuals who receive infusion of blood or plasma products may develop signs and/or symptoms of some viral infections. In the interest of the patient, it is recommended that, whenever possible, every time that OCTAPLASMA is administered to them, the name and batch number of the product is recorded.

Cardiovascular

High dosages of OCTAPLASMA or high infusion rates may induce hypervolaemia, pulmonary oedema, and/or cardiac failure. High infusion rates may cause symptoms attributable to citrate toxicity (fall in ionised calcium) e.g. fatigue, paresthaesia, tremor and hypocalcaemia, especially in patients with liver function disorders.

Gastrointestinal

The infusion should be discontinued if subjective complaints (e.g. nausea) cannot be mitigated by a reduction of the infusion rate.

Hematologic

OCTAPLASMA should not be used to correct hyperfibrinolysis caused by a deficiency of the plasmin inhibitor, alpha2-antiplasmin, as dilution with S/D treated plasma (which contains low levels of alpha2-antiplasmin) may further reduce alpha2-antiplasmin levels. Special attention

must be paid to signs of excessive bleeding tendency in patients likely to require massive transfusions e.g. in liver transplantation or other conditions with complex disturbances of haemostasis.

An increased incidence of thromboembolic events has been described in patients receiving large volumes of S/D treated plasma. In patients considered at risk for such complications, OCTAPLASMA should only be used if the benefit exceeds the risk of thromboembolic events. Appropriate protection against thromboembolism should be employed when indicated, and patients should be monitored for thromboembolic events [9].

In extensive plasma exchange procedures, OCTAPLASMA should only be used to correct the coagulation abnormality when abnormal haemorrhage occurs.

Immune

Administration of OCTAPLASMA must be based on ABO-blood group specificity, otherwise incompatibility reactions between antibodies contained in OCTAPLASMA and antigens on the recipient's red blood cells can result in immediate or delayed type haemolytic transfusion reactions.

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

Special Populations

Pregnant Women:

The safety of OCTAPLASMA for use in human pregnancy and during lactation has not been established in controlled clinical trials.

A study of the embryotoxic and teratogenic properties of TNBP and Octoxynol was carried out in rats and rabbits at dose levels of 50 to 900 µg/kg BM/day for TNBP and 250 to 4,500 µg/kg BM/day for Octoxynol. No test was made of the fertility and breeding efficiency, or the peri- and post-natal development since there was no evidence of any effect on the reproductive organs by the substances. In rats, some malformations occurred, but these were of a type commonly occurring in control animals of this species. No malformations were seen in the rabbits. Pre-natal development was not affected in the rats, although in the high-dose group in the rabbit, the resorption rate was slightly increased and body weight of the foetus was moderately and significantly decreased.

Although no harmful effects on mother, embryo, foetus, or child are to be expected, OCTAPLASMA should be used during pregnancy and lactation only if the benefit outweighs the potential risk.

Nursing Women:

See Pregnant Women section above.

Pediatrics (< 16 years of age):

OCTAPLASMA was evaluated in 50 pediatric patients (age range 0-16 years) in a post-marketing study. The product should only be administered to these individuals if the likely benefits clearly outweigh potential risks.

Geriatrics (> 65 years of age):

No data are available.

Monitoring and Laboratory Tests

It is important to monitor the response of the patients coagulation factor levels, both clinically and with measurement of prothrombin time (PT), partial thromboplastin time (PTT) and/or specific coagulation factor assays.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

High dosages of OCTAPLASMA or increased infusion rates may induce hypervolaemia, pulmonary oedema and/or cardiac failure. In the course of plasma exchange, symptoms attributable to citrate toxicity (e.g. fatigue, paresthaesia, tremor and hypocalcaemia) may occur.

Administration of OCTAPLASMA must be based on ABO-blood group specificity, otherwise incompatibility reactions between antibodies contained in OCTAPLASMA and antigens on the recipient's red blood cells can result in immediate or delayed type haemolytic transfusion reactions.

Table 1 provides an overview on ADRs that have rarely been reported during the use of OCTAPLASMA during its post-approval use. As these reactions are reported voluntarily from a population of uncertain size, a reliable estimation of frequency cannot be established.

Table 1 : Adverse Reactions that were reported for OCTAPLASMA during its Post-Marketing Use

System Organ Class	Reaction
Blood and lymphatic system disorders	haemolytic anaemia
Immune system disorders	anaphylactic shock anaphylactic reaction anaphylactoid reaction hypersensitivity
Metabolic and nutritional disorders	citrate toxicity alkalosis
Psychiatric disorders	Agitation
Cardiac disorders	cardiac arrest arrhythmia transfusion-related circulatory overload tachycardia
Vascular disorders	Thromboembolism circulatory collapse hypertension

System Organ Class	Reaction
	hypotension flushing haemorrhagic diathesis
Respiratory, thoracic and mediastinal disorders	pulmonary haemorrhage acute pulmonary oedema bronchospasm dyspnoea respiratory arrest or failure
Gastrointestinal disorders	vomiting nausea
Skin and subcutaneous tissue disorders	urticaria rash (erythematous) pruritus hyperhidrosis
General disorders and administration site conditions	chest pain chills pyrexia localised oedema application site reaction
Investigations	antibody test positive
Injury, poisoning and procedural complications	haemolytic transfusion reaction

Transfusion-related acute lung injury (TRALI), which is a severe and rather frequent adverse reaction known from the use of FFP [10], has not been observed with OCTAPLASMA.

The following adverse reactions have not been reported with OCTAPLASMA but were observed with FFP and therefore may also occur with OCTAPLASMA:

- 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 characterized by chills, fever, a non-productive cough, and dyspnea.

- Rarely (<1/1000), potent specific platelet antibodies may be present which can induce a passive post-transfusion purpura (PTP) characterized by dyspnea, rash, fever, generalized purpura, and marked thrombocytopenia.

Management of Severe Adverse Reactions
The infusion should be discontinued if subjective complaints (e.g. nausea) cannot be mitigated by a reduction of the infusion rate. In case of skin reactions or tachycardia accompanied by a

drop in blood pressure, or in case of respiratory problems with or without shock, infusion should be stopped immediately.

In Table 2 the different measures are specified for the different clinical symptoms.

Table 2: Symptoms and Treatment of Adverse Reactions

Clinical Symptoms	Emergency Measures
Subjective complaints (nausea, etc.)	Reduce infusion rate; if unsuccessful stop administration until recovery.
Skin symptoms (flush, urticaria, etc.)	Stop administration. Administer antihistamines intravenously.
Tachycardia Moderate drop in blood pressure (below 90 mm Hg systolic)	Stop administration. Administer hydrocortisone i.v.
Dyspnoea Shock	Stop administration. Administer adrenaline (epinephrine) s.c. or i.m.; hydrocortisone i.v.; oxygen, volume expander; possibly increase diuresis using furosemide in case of normovolaemia, control of acid base balance; if necessary correct electrolytes.
Persistent normovolaemic shock	Dopamine hydrochloride, possibly in combination with noradrenaline (norepinephrine).
Cardiac or respiratory arrest	Resuscitation.

The following guidance (see Table 3) applies to specific adverse reactions, which may be associated with OCTAPLASMA:

Table 3: Guidance for Specific Adverse Reactions

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 OCTAPLASMA infused.
Haemolytic transfusion reaction	Stop administration. Increase 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 furosemide, sodium bicarbonate; dialysis in case of anuria. If applicable, symptomatic treatment of shock.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Six clinical studies with OCTAPLASMA have been conducted by Octapharma. In total, 229 patients have been enrolled, and the patients were exposed to a total number of about 1,200 treatment courses with OCTAPLASMA.

For a comprehensive overview of all clinical studies performed with OCTAPLASMA please refer to Table 6 under PART II: CLINICAL **TRIALS**.

Relative Frequency of Adverse Drug Reactions

The frequency of adverse drug reactions observed in clinical studies is shown in Table 4 below. The safety information derives from about 230 patients enrolled in 6 clinical studies.

Table 4: Overview of OCTAPLASMA Adverse Reactions Observed in Clinical Studies

System Organ Class	Common (> 1/100 <1/10)	Uncommon (> 1/1000 <1/100)
Immune system disorders		anaphylactic reaction
Metabolism and nutrition disorders		hypocalcaemia
Nervous system disorders		paraesthesia
Vascular disorders		hypotension
Respiratory, thoracic and mediastinal disorders		bronchospasm cough respiratory arrest or failure
Gastrointestinal disorders	nausea	vomiting
Skin and subcutaneous tissue disorders	rash pruritus	urticaria
General disorders and administration site conditions	pyrexia chills	oedema

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Please refer to Table 4 above.

Abnormal Hematologic and Clinical Chemistry Findings

High infusion rates may cause symptoms attributable to citrate toxicity (fall in ionised calcium) e.g. hypocalcaemia, fatigue, paresthaesia, and tremor, especially in patients with liver function disorders.

OCTAPLASMA contains low levels of alpha2-antiplasmin and should therefore not be used to correct hyperfibrinolysis caused by a deficiency of the plasmin inhibitor. Special attention must be paid to signs of excessive bleeding tendency in patients likely to require massive transfusions e.g. in liver transplantation or other conditions with complex disturbances of haemostasis.

Post-Market Adverse Drug Reactions

Since the introduction of OCTAPLASMA in Europe in 1992, more than 9.3 million units of OCTAPLASMA have been infused into approximately3.1 million patients. For more detailed information of reported adverse reactions please refer to Table 1PART I: ADVERSE REACTIONS, Adverse Drug Reaction Overview

DRUG INTERACTIONS

Overview

No formal studies of drug interactions have been performed and interactions with other drugs are unknown.

OCTAPLASMA must not be mixed with other drugs as inactivation and precipitation may occur. To avoid the possibility of clot formation, solutions containing calcium must not be administered by the same intravenous line as OCTAPLASMA.

Due to the risk of activation/inactivation of OCTAPLASMA, the concomitant administration of other blood products should be avoided as much as possible, except for emergency situations. However, the product can be mixed with red blood cells and platelets.

OCTAPLASMA administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella and varicella for at least six weeks, and possibly up to three months. In some cases, where large doses are given, this period may be as long as one year.

Drug-Drug Interactions

Interactions with other drugs have not been established. During clinical trials, OCTAPLASMA has been administered in association with various concomitant medications, and no interactions have been identified.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interference with serological testing

Passive transmission of plasma components from OCTAPLASMA (e.g. β-human chorionic gonadotropin; β-HCG) may result in misleading laboratory results in the recipient. For example, a false-positive pregnancy test result has been reported following passive transmission of ß-HCG.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage depends upon the clinical situation and underlying disorder. The volume and frequency of plasma exchanges vary depending on the individual patient, the clinical situation, and the preferred regimen of treatment. In the event of major haemorrhage or surgery, the expert advice of a haematologist should be sought.

Recommended Dose and Dosage Adjustment

The volume and frequency of plasma exchanges vary depending on the individual patient, the clinical situation, and the preferred regimen of treatment. The volume of the plasma exchange in most therapeutic procedures is usually equivalent to the plasma volume of the patient. A part of the exchanged plasma volume should be replaced with OCTAPLASMA in order to prevent haemostatic disorders associated with a decreased level of coagulation factors (especially in patients with impaired liver function).

The dosage depends upon the clinical situation and underlying disorder, but 12-15 mL OCTAPLASMA/kg body weight is a generally accepted starting dose (this should increase the patient's plasma coagulation factor levels by approximately 25%). 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.

An adequate haemostatic effect in minor and moderate haemorrhages or surgery is normally achieved after the infusion of 5-20 mL OCTAPLASMA/kg body weight (this should increase the patient's plasma coagulation factor levels by approximately 10-33%). In the event of major haemorrhage or surgery the expert advice of a haematologist should be sought.

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. Due to the risk of citrate toxicity, the infusion rate should not exceed 0.020-0.025 mmol citrate/kg body weight/min,

which equals to 1 mL OCTAPLASMA/kg body weight/min. Toxic effects of citrate can be minimised by giving calcium gluconate i.v. into another vein. Patients should be observed for at least 20 minutes after the administration.

Missed Dose

Not applicable because OCTAPLASMA is administered in a hospital setting by health care professionals.

Administration

Administration of OCTAPLASMA must be based on ABO-blood group specificity. In emergency cases, OCTAPLASMA blood group AB can be regarded as universal plasma since it can be given to all patients. OCTAPLASMA must be administered by intravenous infusion after thawing using an infusion set with a filter. Aseptic technique must be used throughout the infusion.

Parenteral Products

There are several options for thawing frozen OCTAPLASMA:

- Using a water bath:
  Thaw in the outer wrapper for not less than 30 minutes in a circulating water bath at +30°C to +37°C. 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. Temperature in the water bath must never exceed +37 °C and should not be lower than +30 °C. The thawing time depends on the number of bags in the water bath. If more plasma bags are thawed in parallel, the thawing time can be prolonged, but should not be longer than 60 minutes.

- Using a dry tempering system such as the SAHARA-III:
  Place the OCTAPLASMA bags on the agitation plate according to the manufacturer instructions and thaw plasma using the fast tempering function. When +37°C blood component temperature is indicated on the temperature display terminate the tempering process and remove the bags.
  During thawing of plasma using a system such as the SAHARA-III tempering system it is recommended to use the protocol printer to record the course of the blood component temperature and error messages in event of failure.

Other thawing systems for frozen OCTAPLASMA can be used on the condition that the methods are validated for that purpose.

Allow the content of the bag to warm to approximately +37 °C before infusion. The temperature of OCTAPLASMA must not exceed +37 °C. Remove the outer wrapper and examine the bag for cracks or leaks.

Avoid shaking.

Do not use solutions that are cloudy or have deposits.

Precautions:

Interactions with other drugs are unknown. OCTAPLASMA must not be mixed with other drugs as inactivation and precipitation may occur. To avoid the possibility of clot formation, solutions containing calcium must not be administered by the same intravenous line as OCTAPLASMA.

Due to the risk of activation/inactivation of OCTAPLASMA, the concomitant administration of other blood products should be avoided as much as possible, except for emergency situations. However, the product can be mixed with red blood cells and platelets.

Special Precautions for Storage:

Protect from light.

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

OVERDOSAGE

Overdose may lead to hypervolaemia and thereby pulmonary oedema and/or cardiac failure. In such cases, OCTAPLASMA transfusion should be stopped immediately. General measures such as the administration of furosemide can be considered, if clinically appropriate

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) is a virus inactivated frozen human plasma and is assumed to be active on a species-specific basis.

Pharmacodynamics

For detailed information please refer to PART II: DETAILED PHARMACOLOGY, Human Pharmacodynamics.

Pharmacokinetics

During one clinical study pharmacokinetic data of coagulation factors after treatment with OCTAPLASMA reconstituted as lyophylisate have been collected from eight patients suffering from hereditary coagulation factor deficiencies [7]. All patients received a single OCTAPLASMA infusion of an average of 580 mL (range 400 to 1,600 mL). The dose administered was expected to achieve and maintain a plasma concentration of 10% to 20% of normal of the deficient coagulation factor. The pharmacokinetic results are shown in Table 5.

Table 5: Pharmacokinetic results

Parameter (Unit)	FVII [range] (n=2)	FX [range] (n=2)	FXI [mean, range] (n=4)
Vd (mL/kg)	33 – 48	23 – 49	52 (45 – 57)
CL (mL/kg/h)	4.7 – 7.9	0.3 – 0.8	0.9 (0.6 – 1.3)
MRT (h)	7 – 8	60 – 80	62 (42 – 92)
T ½ (h)	4 – 5	41 – 58	44 (28 – 65)
Recovery (%/IU/kg)	1.8 – 2.9	2.0 – 4.1	1.8 (1.7 – 1.8)

Vd volume of distribution; CL clearance; MRT mean residence time; T ½ half life; IU international unit.

These pharmacokinetics parameters after OCTAPLASMA administration were within the kinetic profile of coagulation factors after administration of FFP [21-23]. No pharmacokinetic results are available for the remaining coagulation factors.

Absorption:

OCTAPLASMA is administered intravenously and therefore immediately available in the organism.

Distribution, Metabolism and Excretion:
OCTAPLASMA is a virus inactivated frozen human plasma and is assumed to be active on a species-specific basis. Human plasma may cause severe toxic reactions in animals and is not tolerated at dosages approaching those generally used in humans. Routine pharmacology testing in laboratory animals is not considered to add any relevant information for the safety and efficacy of OCTAPLASMA in the clinical use.

Two contaminants derived from the manufacturing process, namely Tri(n-butyl)phosphate (TNBP) and Octoxynol, might be present in the final product (see DETAILED PHARMACOLOGY – Animal Pharmacology and TOXICOLOGY). A program of studies has been carried out to assess the pharmacokinetic profile of TNBP and Octoxynol. After i.v. administration in rats, TNBP disappeared rapidly from the plasma with an elimination half-life of approximately 20 min. TNBP was not found at any time in the urine and only very small amounts were detectable in the faeces. Concomitantly administered Octoxynol could not be detected in the plasma, the urine or the faeces [24].

Special Populations and Conditions

No specific pharmacokinetic studies have been performed in patients at increased risk, such as elderly subjects or patients with renal or hepatic impairment.

STORAGE AND STABILITY

The shelf life of OCTAPLASMA is 48 months when stored at ≤ -18 °C.

Protect from exposure to light.

After thawing OCTAPLASMA can be stored for up to 24 hours at +2-8 °C or for up to 8 hours at room temperature (+20 - 25°C) before use [19]. Do not use solutions that are cloudy or have deposits.

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

SPECIAL HANDLING INSTRUCTIONS

Any unused product or waste material should be disposed of in accordance with local requirements for blood products.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) is supplied frozen in bags of 200 mL containing 45-70 mg/mL Human Plasma Proteins.

Nature and Contents of Container:

Each 200 mL of OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) contains Human plasma proteins (9.0-14.0 g), Sodium citrate dihydrate (0.88-1.48 g), Sodium dihydrogenphosphate dihydrate (0.06-0.24 g), Glycine (0.80-1.20 g), TNBP (< 2.0 mcg/mL), Octoxynol (< 5.0 mcg/mL).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- Proper name: OCTAPLASMA, Solvent Detergent (S/D) Treated Human Plasma
- Chemical name: Human Plasma
- Molecular formula and molecular mass: not applicable
- Structural formula: not applicable
- Physicochemical properties: The total protein concentration is 45-70 mg/mL. The protein distribution is within the normal range of human plasma.

Product Characteristics

During the manufacturing process, OCTAPLASMA is treated with a combination of 1 % Tri(nbutyl)- phosphate (TNBP) and 1 % Octoxynol. These S/D reagents are removed by castor oil extraction (TNBP) and subsequent solid phase extraction (Octoxynol) before sterile filtration. After sterile filtration, 200 mL OCTAPLASMA is filled into sterile, pyrogen-free, plasticised polyvinyl chloride (PVC) blood bags that are over-wrapped with a polyamide/polyethylene film.

Viral Inactivation

To reduce the risk of transmission of infective agents, stringent controls are applied to the selection and screening of donors for hepatitis B, hepatitis C and HIV infection. The plasma pools are also tested for HBsAg, anti-HIV-1/2, HBV-NAT, HIV-NAT, HCV-NAT, HAV-NAT, HEV-NAT and parvovirus B19- NAT and only those found negative or below a given cut-off limit (parvovirus B19) are used for manufacturing. To improve the viral safety of OCTAPLASMA compared to FFP, virus inactivation using the S/D method has been included in the OCTAPLASMA manufacturing process. The S/D method has been shown to inactivate the enveloped viruses (such as HIV, HBV and HCV) in a rapid and complete manner.

From its mode of action it is clear that the S/D method has no effect on non-enveloped viruses such as HAV and parvovirus B19. Thus, there is an increased risk of transmitting these viruses by pooling of plasma. However, the presence of justified limits for neutralising antibodies towards HAV and parvovirus B19 in the starting plasma and the final product, result in immune neutralisation and passive immunisation which both serve to limit or prevent virus replication in vivo and thereby infection in patients.

Five cases of possible transmission of vCJD, or the causative agent of this disease, by non-leukocyte-depleted red blood cell concentrates (n=4) and a low-purity coagulation factor concentrate to a haemophiliac (n=1) have been reported in the literature [1-5]The possibility of transmission of the vCJD agent by S/D plasma cannot be completely ruled-out. At present, the vCJD agent cannot be routinely detected in blood. However, the hypothesis of the B-lymphocytes and follicular dendritic cells, in particular, acting as a potential blood borne carriers of the prion protein and their role in neuroinvasion suggests that leukocyte depletion during processing of blood products and plasma derivatives will reduce the possibility of transmitting vCJD [6]. Thus, leukocyte depletion of cellular blood components has been adopted by some countries as a measure to reduce the hypothetical risk of vCJD transmission. OCTAPLASMA undergoes multiple size exclusion filtration steps resulting in complete leukocyte removal without activating the leukocytes, and both this particular measure and the down-stream processing have demonstrated a potential to clear prions using an animal model of the agent causing vCJD [7]. Additionally, a column has been included into the production process of OCTAPLASMA in order to specifically remove prions. This safety measure is considered effective for removing the infectious agent causing vCJD, if present in plasma [8]. No animal material is used in the production of OCTAPLASMA.

Transmission of HAV may occur following transfusion with OCTAPLASMA. It is, however greatly reduced by accepting only plasma pools found negative for HAV by a NAT test and by the presence of neutralizing antibodies towards HAV (anti-HAV IgG with a minimum level of 0.6 IU/mL).

Transmission of parvovirus B19 may occur following transfusion of OCTAPLASMA. However plasma pools are tested for the presence of neutralizing antibodies towards parvovirus B19 (antiparvovirus B19 IgG with a minimum level of 11 IU/mL is acceptable) and the parvovirus B 19– NAT (an upper limit of 10.0 IU/µl is acceptable). This combination may limit the risk of infection, although no laboratory or clinical studies have been performed to show that it is sufficient to prevent infection. However, as with FFP, the transmission of parvovirus B19 or HAV by OCTAPLASMA cannot be totally excluded. In immunocompromised patients, in patients with haematological disorders of high red cell turnover and in pregnant women, parvovirus B19 infections could lead to aplastic crises and hydrops fetalis with subsequent foetal loss, respectively. Therefore, OCTAPLASMA should only be administered to these patients if strongly indicated. A possible risk of infection should be weighed against the benefit of the inactivation of enveloped viruses such as HIV, HBV and HCV. Appropriate vaccination (e.g. against HAV) for patients in regular receipt of OCTAPLASMA should be considered. Infusion of OCTAPLASMA may give rise to specific coagulation factor antibodies.

CLINICAL TRIALS

Efficacy and Safety Studies

Study demographics and trial design

Four clinical studies (Studies Nos. 1 to 4) and 7 post-authorisation studies (Studies Nos. 5 to 11) with OCTAPLASMA have been conducted by Octapharma. All these studies used an open design, which is an acceptable approach for a compound of this class.

Study results

Based on the experience gathered during the clinical development phase and the post-marketing period, it can be concluded that OCTAPLASMA is efficacious and has a satisfying safety profile. In the 4 clinical studies (n=91 patients) a total of 6 AEs (in 4 patients) were assessed as related to OCTAPLASMA treatment.

Table 6 provides a comprehensive overview of clinical studies performed with OCTAPLASMA including those which were initiated as post-marketing studies.

Table 6: Overview of OCTAPLASMA clinical studies

Study No. Protocol No. [Ref]	Number of Patients, Gender	Diagnosis, Inclusion / Exclusion Criteria	Treatment Dose Regimen Study Design	Evaluation Criteria	Results (Efficacy)	Results (Safety)
1 [11]	30 patients 21 male, 9 female	Intensive care patients with DIC requiring plasma therapy for the treatment of severe coagulopathy;	OCTAPLASMA, lyophylised, given i.v., mean dose 377 mL Open label	PT, fibrinogen, ATIII, aPTT, PC, D-dimers; vital signs	PT, fibrinogen, antithrombin III increased significantly; aPTT, PC, D-dimers were not significantly different from baseline	No AEs;
2 [12]	11 patients 5 male, 6 female	Hereditary or acquired isolated or combined coagulation factor deficiency;	OCTAPLASMA, lyophylised, given i.v., mean dose 580 mL; Open label	Pharmacokinetics; stopping or prevention of bleeding; AE monitoring;	Overall efficacy rated as good in all patients;	3 AEs in 2 patients; no dropout due to AEs, no serious and/or unexpected AEs;
3 19/PLAS/IV/91 [13]	66 patients OCTAPLASMA: n = 20 15 male, 5 female No plasma: n = 26 FFP: n = 20	Patients with open heart surgery requiring plasma therapy;	OCTAPLASMA, lyophylised, given i.v., mean dose 700 mL Open label	Blood loss, coagulation and haematological lab parameters; AE monitoring	OCTAPLASMA and FFP comparable in terms of blood loss and coag. parameters	1 mild unrelated AE; no dropout due to AEs, no serious and/or unexpected AEs;
4 LAS-1-03-UK [14-16]	55 patients OCTAPLASMA: n=30 18 male, 12 female FFP: n=25	Patients suffering from coagulopathy due to LD (n=24), LT (n=28) or TTP (n=3)	OCTAPLASMA, 200 mL bags given i.v. LD: mean dose 13 mL/kg; LT: mean dose 44 mL/kg TTP: up to 3 litres per day for 14 days; prospective, randomized	Maintenance of coag. factors in LD and LT; platelet count in TTP; adverse vent monitoring;	No relevant changes in coag. factors, but PC, fibrinogen and PTT improved in both groups; similar degrees of correction of prolonged INR and PTT seen with both OCTAPLASMA and FFP; TTP patients attained platelet counts of > 50 x 10^9/l by day 10, and remained in stable remission 1 year later;	7 AEs in 5 patients; only 2 AEs in 1 patient related to OCTAPLASMA treatment; 2 deaths unrelated to study treatment during study period, 9 further deaths outside formal study period;

Study No. Protocol No. [Ref]	Number of Patients, Gender	Diagnosis, Inclusion / Exclusion Criteria	Treatment Dose Regimen Study Design	Evaluation Criteria	Results (Efficacy)	Results (Safety)
5 LAS-1-02-D	67 patients OCTAPLASMA: n = 36 FFP: n = 31;	Intensive care patients following heart surgery requiring plasma therapy;	OCTAPLASMA 200 mL bags, given i.v.; total dose 600 mL; FFP 600 mL; Open label	F1+2, PAP, D-dimers, PC, PT, aPTT, fibrinogen, FVIII; AT, PS, free PS and PI, TI; prophylaxis and stop of bleeds; AE monitoring; vital signs;	stat. significant differences in PS and PI after FFP compared to OCTAPLASMA; correlation between change of TI and change of PAP after 60 min. stat. significant for OCTAPLASMA; change of PI, and change of PAP after 60 min. stat. significant for FFP	No AEs or thrombotic complications during and after infusion of both products; 14 patients died during study (4 in OCTAPLASMA and 10 in FFP group); all cases not related to the trial drugs.
6 PVI/B001	OCTAPLASMA: n = 894 age 8 days to 96 years; RBCC: n=11,749 platelet concentrate: n = 1,711	Any patient requiring plasma therapy;	Plasma Viro-Inactivé (PVI) (=OCTAPLASMA), 200 mL bags; to be given i.v. according to physician's prescription; Open label	AE monitoring;	(Not applicable)	No AEs for OCTAPLASMA; RBCC: 485 AEs; platelet concentrate: 142 AEs;
7 PVI/B002	55 neonates age 0 to 7 days;	Any patient requiring plasma therapy;	Plasma Viro-Inactivé (PVI) (=OCTAPLASMA), 200 mL bags; to be given i.v. acc. to physician's prescription; Open label	AE monitoring;	(Not applicable)	No AEs;
8 PVI/B003	5 patients age 43 to 79 years, 2 males, 3 females	Rh-negative patients requiring plasma therapy irrespective of their anti-D status;	Plasma Viro-Inactivé (PVI) (=OCTAPLASMA), 200 mL bags; to be given i.v. acc. to physician's prescription; Open label	Anti-D status at baseline and at weeks 1, 8, and 6 months after OCTAPLASMA administration;	No anti-D immunisation related to OCTAPLASMA administration;	No AEs;
9 PVI/B004	23 patients	Anti-HAV and/or anti-parvovirus B19 negative patients requiring plasma therapy;	Plasma Viro-Inactivé (PVI) (=OCTAPLASMA), 200 mL bags; to be given i.v. according to physician's prescription; Open label	HAV IgG antibodies, HAV PCR, parvovirus B19 IgG antibodies, parvovirus B19 PCR;	HAV: In 14 patients evaluable passive immunisation against HAV; B19: in 4 out of the 9 patients evaluable for B19, passive immunisation;	HAV PCR during follow-up all negative; B19: in 1 patient seroconversion observed.

Study No. Protocol No. [Ref]	Number of Patients, Gender	Diagnosis, Inclusion / Exclusion Criteria	Treatment Dose Regimen Study Design	Evaluation Criteria	Results (Efficacy)	Results (Safety)
10 [17]	Total: 610 adults and 198 children; OCTAPLASMA: 119 adults and 63 children; Available for viral markers: n = 343 (194 transfused)	Any patient with extracorporeal surgery;	OCTAPLASMA 200 mL bags, given i.v. acc. to physician's prescription, mean dose: 7.5 bags; other blood products: platelet concentrates, fresh whole blood, SAGMAN red cells; Open label	Irregular red blood cell antibody screening; anti-HAV IgG, HBsAg, anti-HBc, anti-HCV IgG, anti-HIV-1/2, anti-HTLV IgG, anti-CMV IgG, anti- B19 IgG, PCR testing (HAV, B19).	(Not applicable)	No definite viral infections seen for OCTAPLASMA; no irregular antibodies;
11 LAS-212	50 patients: 37 neonates /infants (0 to 2 years old) 13 children and adolescents (> 2 to 16 years old)	Cardiac surgery (n=40), liver transplantation and/or with liver dysfunction (n=5), sepsis-related coagulopathy (n=4) hypoxic encephalopathy (n=1)	OCTAPLASMA 200 mL bags Dose depended on the age and body weight (BW) of the patient and on the clinical setting. Open-label, multicenter, single arm, post-marketing study	Safety assessment was prospectively defined as excellent (treatment was well tolerated by the patient), moderate (ADRs were observed, but easily resolved or not clinically significant), or poor (ADRs were observed requiring significant medical intervention)	Hemostatic parameters as measured by international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), thromboelastography (TEG) or thromboelastometry (TEM) were within the expected ranges following use of OCTAPLASMA	Overall safety in this study was assessed by investigators as 'excellent' for all 50 patients. No AEs related to OCTAPLASMA, no hyperfibrinolytic events or treatment-related thromboembolic events.

DETAILED PHARMACOLOGY

Animal Pharmacology

OCTAPLASMA is a virus inactivated frozen human plasma and is assumed to be active on a species-specific basis. Human plasma may cause severe toxic reactions in animals and is not tolerated at dosages approaching those generally used in humans. Routine pharmacology testing in laboratory animals is not considered to add any relevant information for the safety and efficacy of OCTAPLASMA in the clinical use.

The level of impurities putatively present in the end product is controlled by the manufacturing process itself, specifications for the raw materials and in process controls, as well as by the final product specification. Two contaminants derived from the manufacturing process, namely TNBP and Octoxynol, may be present in the final product at levels not exceeding 2.0 mcg/mL for TNBP and 5.0 mcg/mL for Octoxynol. A program of studies has been carried out to assess the pharmacokinetic profile of TNBP and Octoxynol. It should be borne in mind that the exposure to TNBP and Octoxynol may be large in patients undergoing therapeutic plasmapheresis. After i.v. administration in rats, TNBP disappeared rapidly from the plasma with an elimination half-life of approximately 20 min. TNBP was not found at any time in the urine and only very small amounts were detectable in the faeces. Concomitantly administered Octoxynol could not be detected in the plasma, the urine or the faeces [24].

Animal Pharmacokinetics and Metabolism

A pharmacokinetic study was carried out by the applicant in rats, which were given 300 mcg of TNBP/kg + 1,500 mcg of Octoxynol/kg BM i.v. The plasma half-life for TNBP was approximately 20 minutes, Octoxynol was not detected.

According to published data [25] the plasma half-life for TNBP in rats after intravenous administration of 5 mg/kg is 1.3 hours. The main excretion route is via the urine, small amounts are excreted via faeces and the breathing air (CO2).

There are no pharmacokinetic studies for Octoxynol in the literature. However, the very similar nonoxynol-9 is excreted (within 7 days) via the faeces 52-78%, the urine 20-39% and the breathing air (CO2) 0-1.2% in rats after oral and intraperitoneal administration [26].

Human Pharmacokinetics

During one clinical study pharmacokinetic data of coagulation factors after treatment with OCTAPLASMA reconstituted as lyophylisate have been collected from eight patients suffering from hereditary coagulation factor deficiencies [12]. All patients received a single OCTAPLASMA infusion of an average of 580 mL (range 400 to 1,600 mL). The dose administered was expected to achieve and maintain a plasma concentration of 10% to 20% of normal of the deficient coagulation factor. The pharmacokinetic results are shown in the Table 7.

Table 7: Pharmacokinetic parameters after administration of OCTAPLASMA

Patient No.	Coagulation Factor	Vd (mL/kg)	Cl (mL/h/kg)	MRT (h)	Terminal t½ (h)	Maximal Increase (IU/mL)	Recovery (%/IU/kg)
05	VII	33.22	4.65	7.87	4.94	0.20	2.9
07	VII	48.37	7.92	6.75	4.23	0.15	1.8
01	X	48.64	0.82	60.1	40.63	0.20	2.0
09	X	22.65	0.27	80.1	57.80	0.26	4.1
06	XI	57.49	0.61	92.4	65.11	0.13	1.7
08	XI	51.52	1.25	42.3	28.35	0.15	1.8
10	XI	56.08	0.91	61.5	42.68	0.15	1.7
11	XI	44.58	0.77	52.5	39.75	0.15	1.8

Vd = volume of distribution; Cl=clearance; MRT=mean residence time; tl/2= half-life

These pharmacokinetics parameters after OCTAPLASMA administration were within the kinetic profile of coagulation factors after administration of FFP [21-23]. No pharmacokinetic results are available for the remaining coagulation factors.

Human Pharmacodynamics

The total protein concentration is 45-70 mg/mL. The protein distribution is within the normal range of human plasma, please refer to Table 8 below. Protein S and Plasmin inhibitor levels have been found to be below the range for normal human plasma. The final product release limits are ≤ 0.3 IU/ml and ≤ 2.0 U/ml, respectively.

After S/D treatment and subsequent removal of S/D reagents, the plasma protein content and distribution in OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) remain at comparable levels to those in normal fresh frozen plasma (see Table 8).

Table 8: Plasma Protein Levels in OCTAPLASMA Compared to Single-Donor Fresh-Frozen Plasma [20]

Parameters	OCTAPLASMA (n=12) Mean (min-max)	Reference ranges FFP
Total protein [mg/mL]	55 (54-57)	48-64
Albumin [mg/mL]	32 (30-34)	28-41
Fibrinogen [mg/mL]	2.5 (2.4-2.6)	1.45-3.85
IgG [mg/mL]	9.65 (9.15-10.10)	6.60-14.50
IgA [mg/mL]	2.00 (1.80-2.05)	0.75-4.20
IgM [mg/mL]	1.25 (1.20-1.30)	0.40-3.10
Factor V [IU/mL]	0.78 (0.75-0.84)	0.54-1.45
Factor VII [IU/mL]	1.08 (0.90-1.17)	0.62-1.65

Parameters	OCTAPLASMA (n=12) Mean (min-max)	Reference ranges FFP
Factor X [IU/mL]	0.78 (0.75-0.80)	0.68-1.48
Factor XI [IU/mL]	0.99 (0.91-1.04)	0.42-1.44
Protein C [IU/mL]	0.85 (0.81-0.87)	0.58-1.64
Protein S [IU/mL]	0.64 (0.55-0.71)	0.56-1.68
Plasmin inhibitor [IU/mL]	0.23 (0.20-0.27)	0.72-1.32

12 consecutive batches OCTAPLASMA were investigated; mean (minimum-maximum) values are presented; FFP, single-donor fresh-frozen plasma

One clinical study aimed to investigate the pharmacodynamics of OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) has been performed. [12].

Five male and six female patients, included for hereditary, acquired, isolated or combined coagulation deficiency, received lyophilised OCTAPLASMA as a single, i.v. injection. Thereof, 2 patients each had a factor VII or factor X, and 4 patients a factor XI deficiency. Two patients received OCTAPLASMA lyophylisate for ongoing bleeding, one for plasmapheresis and eight for prevention of bleeding before an invasive procedure. Bleeding was stopped in the two patients with ongoing bleeding. In the nine other patients, plasmapheresis and surgical procedures were uneventful, with no abnormal bleeding. The overall effectiveness of OCTAPLASMA as rated by the investigator was good in all patients.

Two patients experienced a total of three adverse events (AEs), consisting of an anaphylactoid reaction and urticaria with pruritus. These AEs resolved with an antihistaminic and both patients recovered. No patient dropped out of the study for safety reasons. No serious and/or unexpected AEs occurred. No adverse laboratory findings were observed for haematology, blood biochemistry and viral safety parameters.

TOXICOLOGY

OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) is a virus inactivated frozen human plasma and is assumed to be active on a species-specific basis. Human plasma may cause severe toxic reactions in animals and is not tolerated at dosages approaching those generally used in humans. Routine toxicology testing in laboratory animals is not considered to add any relevant information for the safety and efficacy of OCTAPLASMA in the clinical use.

Studies were conducted to evaluate the effects of the materials used for viral inactivation by the S/D method [1% Tri(N-Butyl) Phosphate (TNBP) and 1% Octoxynol]. After purification, the maximum amounts of TNBP and Octoxynol in the finished product are 2.0 mcg/mL and 5.0 mcg/mL, respectively. Pharmacological and toxicological studies in animals indicate that these residual levels should present no clinical problem for the indications and dosages specified.

Based on preclinical data it is not possible to give information on the total quantity of OCTAPLASMA that can be administrated before any adverse effects of the S/D components are likely to become apparent.

However, “therapeutic windows” might be calculated for humans: according to acute intravenous toxicity tests in rats the lowest toxic sum dose of TNBP and Octoxynol (1:5) was 10,000 mcg/kg For a single dose of 20 mL/kg OCTAPLASMA containing < 140 mcg/kg TNBP and Octoxynol at the ratio 2+5 this window is ≥ 71.4.

- For a transfusion period of 5x20 mL/kg per day the window is ≥ 14.3.
- For a 3-day treatment with 5x20 mL/kg per day the window is ≥ 4.8.

These calculations, however, neglect the rapid metabolism of these compounds. As a consequence, greater safety margins might be assumed for repeated administration of OCTAPLASMA.

Mutagenic Potential

The mutagenicity investigations of TNBP and Octoxynol performed by the applicant and available in the literature [27-29] likewise give no indication of mutagenic properties.

Reproductive Toxicity

A study of the embryotoxic and teratogenic properties of TNBP and Octoxynol was carried out in rats and rabbits at dose levels.

No test was made of the fertility and breeding efficiency, or the peri- and post-natal development since there was no evidence of any effect on the reproductive organs by the substances.

In rats, some malformations occurred, but these were of a type commonly occurring in control animals of this species. No malformations were seen in the rabbits.

Pre-natal development was not affected in the rats, although in the high-dose group in the rabbit, the resorption rate was slightly increased and body weight of the foetus was moderately and significantly decreased.

Genotoxicity

In an in vitro test in Aspergillus nidulans on the genotoxic activity at a concentration of 0.01% (corresponding to 100 mg/L) Octoxynol proved to be genotoxically inactive. Higher concentrations were in the cytotoxic range.

Carcinogenicity

No evidence of carcinogenic properties of TNBP + Octoxynol was produced in the subacute toxicity and mutagenesis studies already described. No special carcinogenic studies were carried out.

Additional Toxicology Information

No evidence of sensitising properties of TNBP + Octoxynol (ratio 1:5) was observed. No immunotoxicological reactions were observed after administration of Octoxynol.

Comparison of the doses used during the toxicological studies in animals mentioned to the human therapeutic dose may provide indications of the therapeutic ratio.

Pharmacological and toxicological studies in animals indicate that these residual levels of TNBP and Octoxynol do not represent a clinical problem for the indications and dosages specified for OCTAPLASMA [30, 31].

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PART III: CONSUMER INFORMATION

OCTAPLASMA

[Solvent detergent (S/D) treated human plasma]

This leaflet is part III of a three-part "Product Monograph" published when OCTAPLASMA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OCTAPLASMA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- Complex disorders of the blood clotting system due to severe liver failure, massive transfusion (this is the process of transferring blood or blood-based products from one person into the circulatory system of another), or repeated large volume plasma exchange. This is a removal procedure of (components of) blood plasma from the circulation (especially in patients with damaged liver function).
- OCTAPLASMA may be used for emergency therapy in clotting factor deficiencies, in special situations, e.g. when acute bleeding does not allow a precise laboratory diagnosis, or when a specific clotting factor concentrate is not available.
- Rapid conversion of the effects of oral anticoagulants (substances that prevent coagulation, i.e. they stop blood from clotting) when vitamin K is insufficient in emergency situations, or in patients with damaged liver function.

What it does:

The administration of OCTAPLASMA can temporarily stop bleeding in patients with clotting factor deficiencies in emergency situations, when vitamin K treatment is insufficient, or in patients with damaged liver function. OCTAPLASMA will start working immediately upon injection and the symptoms of bleeding should resolve.

When it should not be used:

- IgA deficiency, Servere deficiences of protein S, plasma protein allergy, previous reaction to fresh frozen plasma or OCTAPLASMA, fluid in the lungs or cardiac failure.

What the medicinal ingredient is:

Human plasma proteins

What the important nonmedicinal ingredients are:

Glycine, Octoxynol, Sodium citrate dehydrate, Sodium dihydrogenphosphate dihydrate, TNBP

What dosage forms it comes in:

OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) is supplied frozen in bags of 200 mL containing 45-70 mg/mL Human Plasma Proteins.

Each 200 mL of OCTAPLASMA (Solvent Detergent (S/D) Treated Human Plasma) contains: Human plasma proteins (9.0-14.0 g), Sodium citrate dihydrate (0.88-1.48 g), Sodium dihydrogenphosphate dihydrate (0.06-0.24 g), Glycine (0.80-1.20 g), TNBP (< 2.0 mcg/mL), Octoxynol (< 5.0 mcg/mL).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

This product is made from human plasma, which may contain infectious agents, such as viruses that cause hepatitis and other viral diseases. However, Octaplasma is treated to either remove or inactivate certain viruses. Pathogen inactivation of lipid enveloped viruses such as HIV, HBV and HCV is achieved through solvent detergent (S/D) treatment of plasma and the production process also allows immune neutralization of non-lipid enveloped viruses such as HAV and Parvovirus B19. Your doctor should discuss the risks and benefits of this product with you before giving you this product.

BEFORE you use OCTAPLASMA talk to your doctor or pharmacist if:

- You recently had a heart attack, have a high risk of blood clots, or have coronary artery disease.
- If you are pregnant or nursing. A pregnancy test is recommended before receiving OCTAPLASMA.
- You are allergic to the active substance or to any of the ingredients.
- You have a disease that causes marked fibrinolysis that is responsible for breaking down blood clots.

INTERACTIONS WITH THIS MEDICATION

There is no known drug interaction to OCTAPLASMA. OCTAPLASMA administration may slow the protection of live attenuated vaccines such as measles, mumps, rubella (also known as three-day or liberty measles) and chicken pox for at least six weeks, and possibly up to three months or longer.

PROPER USE OF THIS MEDICATION

Usual dose:

The dose you receive will depend on your clinical situation and disease, but 12-15 mL OCTAPLASMA/kg body weight is a generally accepted starting dose. The duration of administration will be determined by your doctor.

Overdose:

Overdose may lead to volume overload and thereby water in the lung and/or heart failure. In such cases, OCTAPLASMA transfusion should be stopped immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable because OCTAPLASMA is usually given in a hospital setting.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Nausea, flushing, hives, fast heart rate, drop in blood pressure, reduction or cessation of breathing, and reduction or cessation of a sufficient amount of blood flow from the heart throughout the body that may result in impaired function of internal organs.
- In the course of plasma exchange, symptoms attributable to citrate overdose (e.g. fatigue, a sensation of tingling, numbness or prickling, tremor and low calcium concentrations) may occur.
- Acute lung injury, a syndrome known as transfusion relatedacute lung injury, may occur and is characterized by chills, fever, a non-productive cough, and difficulty or shortness of breath.
- Passive post-transfusion purpura (PTP) may occur which is characterized by difficulty or shortness of breath, rash, fever, discoloration of the skin that may include a reddish purple to brown color, and marked reduction in platelets.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	allergic type of reaction		T	T
	fever and/or chills	T		T
Very Rare	Shock		T	T
	abnormal heart rate		T	T
	fall or raise in blood pressure		T	T
	breathing disorders		T	T
	vomiting		T	T
	nausea	T		T
	skin reaction		T	T

This is not a complete list of side effects. For any unexpected effects while taking OCTAPLASMA, contact your doctor or pharmacist.

HOW TO STORE IT

Store frozen at < -18 °C, protect from exposure to light. After thawing OCTAPLASMA can be stored for up to 24 hours at +2-8 °C or for up to 8 hours at room temperature (+20 – 25 °C) before use. Thawed OCTAPLASMA must not be refrozen. Unused product must be discarded.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.octapharma.ca
or by contacting the sponsor, Octapharma Canada Inc.
at: 1-888-438-0488

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