PRODUCT MONOGRAPH

octaplex®

Human Prothrombin Complex, freeze dried
Powder and solvent for solution for injection

One vial of octaplex® for solution for injection contains:		
	octaplex® 500 in 20 mL	octaplex® 1000 in 40 mL
Human Coagulation Factor II	280-760 IU	560 – 1520 IU
Human Coagulation Factor VII	180-480 IU	360 – 960 IU
Human Coagulation Factor IX	500 IU	1000 IU
Human Coagulation Factor X	360-600 IU	720 – 1200 IU
Protein C	260-620 IU	520 – 1240 IU
Protein S	240-640 IU	480 – 1280 IU

Prescription Medication
ATC code: B02BD01

Manufactured by:

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

Date of Revision:

<APRIL 28; 2014>

Octapharma S.A.S.
70-72 Rue Du Maréchal Foch, BP-33
F-67381 Lingolsheim, France

Octapharma Produktionsgesellschaft Deutschland m.b.H.
Wolfgang-Marguerre-Allee 1
D-31832 Springe, Germany

Manufactured for:

Octapharma Canada, Inc.
308-214 King St W
Toronto, ON M5H 3S6, Canada

Control No: 174693 **Date of Approval: August 25, 2014**

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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Per 20 mL vial:
<table><tr><td>Human Coagulation Factor II</td><td>280-760 IU</td></tr><tr><td>Human Coagulation Factor VII</td><td>180-480 IU</td></tr><tr><td>Human Coagulation Factor IX</td><td>500 IU</td></tr><tr><td>Human Coagulation Factor X</td><td>360-600 IU</td></tr><tr><td>Protein C</td><td>260-620 IU</td></tr><tr><td>Protein S</td><td>240-640 IU</td></tr></table>Per 40 mL vial:
<table><tr><td>Human Coagulation Factor II</td><td>560 – 1520 IU</td></tr><tr><td>Human Coagulation Factor VII</td><td>360 – 960 IU</td></tr><tr><td>Human Coagulation Factor IX</td><td>1000 IU</td></tr><tr><td>Human Coagulation Factor X</td><td>720 – 1200 IU</td></tr><tr><td>Protein C</td><td>520 – 1240 IU</td></tr><tr><td>Protein S</td><td>480 – 1280 IU</td></tr></table>Factor IX specific activity is ≥ 0.6 IU/ mg proteins.</td><td>Heparin (80-310 IU / 20 mL vial; 160-620 IU / 40 mL vial)

Sodium Citrate (17.0 – 27.0 mmol/L)

Solvent (Water for Injection 20 mL/ 40 mL)

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</td></tr>
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DESCRIPTION

octaplex® is a human prothrombin complex (PCC) containing the coagulation factors II, VII, IX, and X and Proteins C and S in the amounts listed in the table above.

The octaplex® manufacturing process has the capability to reduce viruses by way of a solvent/detergent (S/D) viral inactivation process and a virus removal nanofiltration step. The capacity to remove prions has been assessed in a three-step approach for the process: QAE-Sephadex A-50, S/D + DEAE Sepharose FF Chromatography and Nanofiltration. The preparation complies with the monograph on Human Prothrombin Complex (freeze-dried) of the

European Pharmacopoeia (2005:0554). Other 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 with PCC preparations 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

octaplex® is indicated for:

- Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

Human prothrombin complex concentrates (PCCs) contain the coagulation factors II, VII, IX and X. In principle, they are indicated for prophylaxis and treatment of acquired deficiencies of one or more of these factors.

In acquired deficiencies, PCCs have been used for the reversal of oral anticoagulation due to overdose or in case of emergency surgical interventions; in bleedings due to vitamin K deficiency; and for the treatment of bleeding disorders after major liver surgery, in severe liver diseases or oesophageal varices [1-4].

For the reversal of oral anticoagulant therapy, the administration of PCCs is indicated only when the desired increase in prothrombin complex factor activity cannot efficiently or adequately be achieved through other therapeutic measures. PCC is not indicated in cases where the prothrombin time can be normalised in time by discontinuing oral anticoagulants or by vitamin K administration. Overdose of oral anticoagulants or reversal of such therapy in case of emergency situations, liver cirrhosis and neonatal vitamin K deficiency are frequent causes of acquired prothrombin complex factor deficiencies [2]. There are no data available regarding the use of octaplex® in children.

Bleeding episodes are common adverse events of oral anticoagulant therapy that frequently depend on the duration and intensity of treatment. Major bleeding events, particularly intracerebral haemorrhages, are serious complications that require the rapid reversal of anticoagulation. Urgent correction of the coagulation defect is also indicated when emergency surgery is necessary. In addition to vitamin K supplementation, the administration of PCCs is the most effective measure for the rapid reversal of the anticoagulation therapy. Due to the time-consuming administration and increased risk of volume overload, the administration of fresh frozen plasma (FFP) is less advisable in such instances. However, the application of PCCs

requires a precautious risk-benefit evaluation, including an estimation of contraindications and repeated laboratory monitoring for dose adjustment [5].

In patients with acquired deficiency of the vitamin K dependent coagulation factors (*e.g.* as induced by treatment with vitamin K antagonists), octaplex® should only be used when rapid correction of prothrombin complex levels is necessary, such as major bleeding or emergency surgery. In other cases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient.

octaplex® should be administered under the supervision of a qualified health professional that 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):

Many of the patients in clinical trials with octaplex® were over the age of 65. There is no evidence to suggest that use in the geriatric population is associated with differences in safety or effectiveness.

Paediatrics (6-16 years of age):

No data are available.

No data are available regarding the use of octaplex® in case of perinatal bleeding due to vitamin K deficiency in the newborn or due to deficiency of factors of the prothrombin complex.

CONTRAINDICATIONS

- octaplex® 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.

- Since octaplex® contains up to 310 IU of heparin, it should not be given to patients suffering from heparin-induced thrombocytopenia type II or with known allergies to heparin. Even if the antibody against the heparin-protein complex cannot be demonstrated, the administration of octaplex® may cause a booster effect with an immediate generation of the antibody.

- octaplex® is contraindicated in those rare cases where an individual has an immunoglobulin A (IgA) deficiency, with known antibodies against IgA.

- octaplex® should not be used in patients with recent myocardial infarction, with a high risk of thrombosis or with angina pectoris with the exception of life-threatening bleeds due to overdose of oral anticoagulants, or when an emergency surgical procedure is indicated in patients on vitamin K antagonists and an INR (International normalised ratio) > 3.

- In patients suffering from disseminated intravascular coagulation (DIC), the administration of octaplex® is principally not recommended because of the pro-coagulant capacity of the product. However, for life-threatening events when the substitution by FFP is not sufficient enough or if FFP cannot be given because of a threat of hypervolaemia, octaplex® might be used after interrupting the cause of DIC. Under these circumstances it is important to administer antithrombin (AT) and heparin before the administration of a PCC.

- In patients treated for coagulation disorders because of chronic liver disease or because of liver transplantation, AT levels should be monitored and an AT concentrate should be given concomitantly if an AT deficiency is present [1,3,7]. No clinical data are available for octaplex® for the treatment of bleeding disorders because of liver parenchyme disorders or oesophageal varices or because of major liver surgery. For these indications, treatment with FFP is preferable and octaplex® cannot be recommended.

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

It is strongly recommended that every time that octaplex® is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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. The measures taken are considered effective for enveloped viruses such as Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV). The measures taken may be of limited value against non-enveloped viruses such as Hepatitis A Virus (HAV) or parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red cell production (*e.g.* haemolytic anaemia). Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections.
The prion issue is more complicated to address. The prion of major concern is the one causing

vCJD, and so far, no prion protein has been found in the plasma from even clinical cases of this disease. The capacity to remove prions has been assessed in a three-step approach for the process with an actual removal log of 7.76 $\log_{10}$:

- Step A: Cryoprecipitation and Capture of the Prothrombin Complex by QAE-Sephadex A-50
- Step B: Step S/D + DEAE Sepharose FF Chromatography
- Step C: Nanofiltration

The studies were performed with PrPSc (hamster-adapted scrapie 263K).

In patients with acquired deficiency of the vitamin K dependent coagulation factors (*e.g.* as induced by treatment with vitamin K antagonists), octaplex® should only be used when rapid correction of prothrombin complex levels is necessary, such as major bleeding or emergency surgery. In other cases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient. Patients receiving a vitamin K antagonist may have an underlying hypercoaguable state and infusion of prothrombin complex concentrate may exacerbate this. The long term and repeat use safety of octaplex® has not been established in controlled clinical studies.

Appropriate vaccination (hepatitis A and B) is recommended for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.

Haematologic

Treatment with plasma-derived products that contain factors II, VII, IX, and X has been associated with thrombosis and may be associated with an increased risk of DIC, thromboembolic complications including myocardial infarction. There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either acquired or congenital deficiency, are treated with human prothrombin complex, particularly with repeated dosing. The risk may be higher in treatment of isolated factor VII deficiency, since the other vitamin K dependant coagulation factors, with longer half-lives, may accumulate to levels considerably higher than normal.

Patients given human prothrombin complex should be observed closely for signs or symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, close monitoring should be exercised when administering human prothrombin complex to patients with a history of coronary heart disease, myocardial infarction, to patients with liver disease, to peri- or postoperative patients, to neonates, or to patients at risk of thromboembolic events or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment should be weighed against the risk of these complications. Where adequate, a previous administration of AT concentrate is indicated.

octaplex® contains heparin. Therefore, a sudden, allergy induced reduction of the blood platelet count below 100.000/µl or 50 % of the starting count may be rarely observed (thrombocytopenia type II). In patients not previously hypersensitive to heparin, this decrease in thrombocytes may

occur 6-14 days after the start of treatment. In patients with previous heparin hypersensitivity this reduction may happen within a few hours. The treatment with octaplex® must be stopped immediately in patients with this allergic reaction. These patients must not receive heparin containing medicinal products in the future.

In case of consumptive coagulation and hyperfibrinolysis, octaplex® should only be administered after the disruption of the consumption process by appropriate means (*e.g.* by heparin, AT, antifibrinolytics).

Immune

Replacement therapy may rarely lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response. The occurrence of inhibitor formation was evaluated in one clinical trial (LEX 201) but the rate could not be established, due to the very small number of patients in the trial (9 only).

In patients with a known predisposition to allergies, prophylactic anti-allergic medications should be considered. If allergic or anaphylactic reactions occur, the injection must be stopped immediately. Mild reactions may be controlled with glucocorticoids and/or antihistamines. For severe disorders, such as shock, the current standard medical treatment should be implemented.

Special Populations

Pregnant Women: The safety of octaplex® 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 (Triton X-100) 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 (Triton X-100). 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.

The risk of parvovirus B19 infection on pregnant woman and foetus are well known. Although no harmful effects on mother, embryo, foetus, or child were reported in the three clinical trials, octaplex® should be used during pregnancy and lactation only if the benefit outweighs the potential risk.

Nursing Women: See Pregnant Women section above.

Paediatrics: No data are available.

Geriatrics (> 65 years of age): Many of the patients in clinical trials with octaplex® were over the age of 65. There is no evidence to suggest that use in the geriatric population is associated with differences in safety or effectiveness.

Monitoring and Laboratory Tests

Prior to the treatment with octaplex®, blood coagulation should be monitored if possible using appropriate coagulation assays, at least the Quick test should be determined. When performing clotting tests, which are sensitive to heparin in patients receiving high doses of human prothrombin complex, the heparin as a constituent of the administered product must be taken into account.

In case of major surgical interventions, precise monitoring of the substitution therapy by means of coagulation assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

PCCs are known to carry a risk of thromboembolic complications and disseminated intravascular coagulation (DIC) [6,7]. Currently available high-purity FIX concentrates for the treatment of haemophilia B have been reported to have a significantly lower thrombogenic potential than PCCs [8-9]. It is generally accepted that a suitable PCC preparation should contain all of the 4 coagulation factors in a well-balanced proportion and that it also should contain protein C (PC) and protein S (PS). Additionally, the concentration of activated coagulation factors should be kept at a minimum. Some preparations also contain small amounts of antithrombin (AT) and heparin in order to reduce the thrombotic risk after treatment with PCC [10].

Other adverse drug reactions of these preparations are related to acute tolerability. Rarely, antibodies (inhibitors) against the proteins administered are seen with PCCs.

Only very few clinical ADRs have been seen with octaplex® to date. Nevertheless, all potential side effects seen for other compounds of this class are mentioned in the product monograph.

Immune system disorders: Replacement therapy may rarely lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response (see WARNINGS AND PRECAUTIONS).

Allergic or anaphylactic-type reactions and an increase in body temperature have not been observed in clinical studies with octaplex® but may rarely occur (see WARNINGS AND PRECAUTIONS).

Nervous system disorders: Headache may rarely occur.

Vascular disorders: There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see WARNINGS AND PRECAUTIONS).

General disorders and administration site conditions: Increase in body temperature has not been observed but may rarely occur.

Investigations: A transient increase in liver transaminases has been rarely observed.

While the development of antibodies (inhibitors) against coagulation factors is a common feature in haemophilia treatment, it seems to be a very rare event after the administration of the less purified PCCs. A final statement on the development of inhibitors in previously treated patients cannot be made. Data on the occurrence of inhibitors in previously untreated patients are not available.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction (ADR) 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.

Three clinical studies with octaplex® have been conducted. In total, 90 patients have been enrolled and the patients received a total of about 569,000 IU of octaplex®. Eight ADRs in 7 patients, all graded as mild, were assessed as possibly related to octaplex® treatment, *i.e.* headache occurring twice in 1 individual, a transient increase in liver transaminases (Alanin aminotransferase (ALAT), Aspartate aminotransferase (ASAT)), 3 parvovirus B19 seroconversions, an injection site burning, and an aggravation of arterial hypertension.

Body system¶	Adverse event	Severity / Causality	No. of episodes
Nervous system disorders	Headache	Mild / possible	2
Vascular Disorders	Hypertension	Mild / possible	1
General disorders and administration site conditions	Injection site burning	Mild / possible	1
Investigations	Hepatic Function Abnormal	Mild / possible	1
	Parvovirus B19 serology positive	Mild / possible	3

Study I (LEX-201)

This was a prospective, non-randomised, non-controlled, open-labelled, multi-centre study conducted in 2 experienced haemophilia treatment centres in Poland and Hungary. Previously treated patients suffering from severe prothrombin complex factor deficiencies were treated for a period of 6 months. At baseline and after 6 months of regular treatment with octaplex® a full pharmacokinetic investigation was performed including assessment of viral markers, inhibitor activity and thrombogenicity markers. After 3 months recovery including inhibitor activity and thrombogenicity markers were assessed.

Ten patients were enrolled in study LEX-201, 6 patients were suffering from haemophilia B and 4 from FVII deficiency. Out of 4 AEs reported in 3 patients, 2 were assessed as possibly related to octaplex® administration. Both events occurred in 1 patient, who experienced mild headache 2 and 8 hours after injection. After analgesic treatment, the patient recovered.

Study II (LEX-202)

This was a prospective, non-randomised, non-controlled, open-labelled, multi-centre study conducted in 6 centres in Israel and Russia. The primary objective of the study was to assess the efficacy of octaplex® in patients suffering from major bleeds or who had to undergo emergency surgical procedures during treatment with anticoagulants of coumarin or indandion type.

Twenty patients were enrolled in Study LEX-202, 10 patients were enrolled because of bleeds and 10 because of surgical interventions. In total, 4 patients experienced 8 AEs; only one, a transient increase in liver transaminases (ALAT, ASAT), was assessed as possibly related to octaplex® administration. This patient had transient increases of ALAT and ASAT 12 hours after the last octaplex® infusion. Five days after infusion the laboratory tests were back to normal.

Study III (LEX-203)

This was a prospective, non-randomised, non-controlled, open-labelled, multi-centre study conducted in 9 centres in Germany and Israel. The primary objective of the study was to investigate the efficacy of octaplex® in patients undergoing surgical or invasive procedures being under treatment with anticoagulants.

Sixty patients were enrolled in the study and 56 patients were analysed per protocol. A total of 126 AEs were documented in 40 patients. Most AEs were related to the underlying diseases and the clinical status of the patients, and only 3 events were assessed as possibly related to study treatment: a parovirus B19 seroconversion, an injection site burning, and an aggravation of arterial hypertension.

Relative Frequency of Adverse Drug Reactions

Due to the small number of patient enrolled in clinical trials and the low number of ADRs no meaningful statement on the relative frequency can be made for each potential ADR.

Less Common Clinical Trial Adverse Drug Reactions

Due to the small number of patient enrolled in clinical trials and the low number of ADRs no meaningful statement on the relative frequency can be made for each potential ADR.

Abnormal Haematologic and Clinical Chemistry Findings

During the pharmacokinetic investigation in LEX-201 laboratory markers for coagulation activation and fibrinolysis were monitored (*i.e.* prothrombin fragment F1+2, thrombin-antithrombin III complex, fibrin monomers, d-dimers plasma levels, Prothrombin time (PT) and Activated partial thromboplastin time (aPTT)). No pattern of elevated markers was seen that could have been induced by the administration of octaplex®.

In LEX-202, one patient had transient increases of ALAT and ASAT 12 hours after the last octaplex® infusion. Five days after infusion the laboratory tests were back to normal. Otherwise, safety laboratory findings were not altered by octaplex® injections.

In LEX-203, a slight decrease over time could be seen for haematological parameters (haematokrit, haemoglobin, blood cell count). Due to the main inclusion criteria for this study being the preparation of a surgical intervention or to control bleedings and the patient population studied (patients under oral anticoagulant therapy), almost all patients showed abnormal haematological values at baseline and during the subsequent sampling period. None of the clinical chemistry parameters seemed to be affected by the study medication.

Post-Market Adverse Drug Reactions

In course of a self-sufficiency programme, octaplex® is used in Norway produced from Norwegian plasma for several FVII deficient patients and for a large number of patients in whom a rapid reversal of oral anticoagulant therapy was required. No ADRs have been reported, neither to the Norwegian health authority nor to the company.

Within the framework of post-marketing surveillance, 2 ADRs have been reported so far.

A 80-year-old patient with an INR of 7.8 and an acute bleed received 4,000 IU of octaplex®. One day later, he developed a peripheral ischemia and a transient ischemic attack.

The second case concerns a patient who received octaplex® and red blood concentrate and developed restlessness, nausea and urticaria. Investigations revealed that the patient had HLA antibodies with a wide specificity. The reporter considered the causal relationship to octaplex® as unlikely.

There have been no spontaneously reported cases in the post-marketing period that changed the risk/benefit ratio of the product.

DRUG INTERACTIONS

Overview

Human prothrombin complex products neutralise the effect of vitamin K antagonist treatment, but no interactions with other medicinal products are known. Nonetheless, octaplex® should not be mixed with other medication during injection.

Interference with biological testing:

When performing clotting tests, which are sensitive to heparin in patients receiving high doses of human prothrombin complex, the heparin as a constituent of the administered product must be taken into account.

Components used in the packaging of octaplex® are latex-free.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Classical dose-response studies were not performed due to the human origin of the product. Dose recommendations for single factor deficiencies are based on the required level, on the body weight (BW) of the patient and the activity increase per unit of the respective factor administered. For acquired deficiencies, dosing should also be individualised and preferably be accompanied by laboratory analysis of global and single coagulation parameters.

- Because of the risk of thromboembolic complications, close monitoring should be exercised when administering human prothrombin complex to patients with a history of coronary heart disease, myocardial infarction, to patients with liver disease, to peri- or postoperative patients,

to neonates, or to patients at risk of thromboembolic events or disseminated intravascular coagulation (see WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

Only general dosage guidelines are given below. Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of the bleeding and on the patient's clinical condition.

The amount and the frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adapted to the different circulating half-life of the different coagulation factors in the prothrombin complex.

Individual dosage requirements can only be identified on the basis of regular determinations of the individual plasma levels of the coagulation factors of interest, or on global tests of the prothrombin complex levels (prothrombin time, INR), and continuous monitoring of the clinical condition of the patient.

In case of major surgical interventions precise monitoring of the substitution therapy by means of coagulation assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

Acquired deficiencies

Bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment:

The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (mL/kg body weight of the reconstituted product) required for normalisation of INR (≤ 1.2 within 1 hour) at different initial INR levels are given.

Table 1: Approximate Doses of octaplex® Required for Normalization of INR

Initial INR	2 – 2.5	2.5 – 3	3 – 3.5	> 3.5
Approximate dose* (mL octaplex®/kg body weight)	0.9 –1.3	1.3 – 1.6	1.6 – 1.9	> 1.9

* The single dose should not exceed 3.000 IU (120 mL octaplex®).

The correction of the vitamin K antagonist induced impairment of haemostasis persists for approximately 6-8 hours. However, the effects of vitamin K, if administered simultaneously, are usually achieved within 4-6 hours. Thus, repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.

As these recommendations are empirical and recovery and the duration of effect may vary, monitoring of INR treatment is mandatory.

Missed Dose

Acquired deficiencies:

Not applicable because in acquired deficiencies octaplex® is administered in a hospital setting by health care professionals.

Administration

octaplex® should be administered intravenously.

Please read all the instructions and follow them carefully.

During the procedure described below, aseptic technique must be maintained.

The product reconstitutes quickly at room temperature.

The solution should be colourless to slightly blue. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discolouration prior to administration. A blue colour is not interpreted as discolouration.

Instructions for reconstitution:

Fig. 1

1. If the octaplex® powder and water for injection (WFI) are not already at room temperature, warm up the closed vials to room temperature (maximum 37°C). This temperature should be maintained during reconstitution. If a water bath is used to warm the WFI, care should be taken to ensure the water does not come into contact with the rubber stopper or closure system of the vials.

2. Remove the flip caps from the octaplex® vial and the WFI vial and clean the rubber stoppers with an alcohol swab.

Fig. 2

3. Peel away the lid of the outer package of the Mix2Vial™ transfer set. Place the WFI vial on an even surface and hold the vial firmly. Push the blue plastic cannula of the Mix2Vial™ firmly through the rubber stopper of the WFI vial in one swift motion (Fig. 1). While holding onto the WFI vial, carefully remove the outer package from the Mix2Vial™, being careful to leave the Mix2Vial™ attached firmly to the WFI vial (Fig. 2).

Fig. 3

4. With the octaplex® vial held firmly on an even surface, quickly invert the WFI vial (with the Mix2Vial™ attached), push the transparent plastic cannula end of the Mix2Vial™ firmly through the stopper of the octaplex® vial and hold the downward pressure (Fig. 3). The WFI will be drawn into the octaplex® vial by vacuum.

Fig. 4

5. With both vials still attached, slowly rotate the octaplex® vial to ensure the product is fully dissolved to a clear or slightly opalescent solution. Once the contents of the octaplex® vial are dissolved, firmly hold both the transparent and blue parts of the Mix2Vial™. Unscrew the Mix2Vial™ into two separate pieces with the vials still attached (Fig. 4) and discard the empty WFI vial and the blue part of the Mix2Vial™.

Instructions for injection:

As a precautionary measure, the patient's pulse rate should be measured before and during the injection. If a marked increase in the pulse rate occurs, the injection speed must be reduced or the administration must be interrupted.

1. After octaplex® has been reconstituted, attach a plastic sterile disposable syringe to the transparent part of Mix2Vial™. Invert the system and draw the reconstituted octaplex® into the syringe.

2. Once the octaplex® solution has been transferred into the syringe, firmly hold the barrel of the syringe (keeping it facing down) and detach the Mix2Vial™ from the syringe. Discard the Mix2Vial™ (transparent plastic part) and the empty octaplex® vial.

3. Disinfect the injection site with an alcohol swab and attach the syringe to a suitable infusion needle.

   Alternatively, octaplex® can be administered using an IV line. Ideally, a new, clean IV line should be used. Otherwise, the IV line must first be 'cleaned' of other products by flushing it with a saline or dextrose 5% solution. octaplex® should not be mixed with any other product (including saline or dextrose 5% solution) in the IV line.

4. Using an aseptic technique, inject the octaplex® solution intravenously at an initial rate of 1 mL per minute, followed by 2-3 mL per minute, if appropriate. A pump can be used to regulate and control the injection rate when administering octaplex®.

Incompatibility:

octaplex® should not be mixed with other medication in the same injection set.

OVERDOSAGE

The use of high doses of human prothrombin complex products has been associated with instances of myocardial infarction, disseminated intravascular coagulation (DIC), venous thrombosis and pulmonary embolism. Therefore, in case of overdose, the risk of development of thromboembolic complications or DIC is enhanced.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The coagulation factors II, VII, IX and X, which are synthesised in the liver with the help of vitamin K, are commonly called the Prothrombin Complex. FII, FIX and FX are components of the intrinsic coagulation pathway, FVII is a component of the extrinsic pathway. These factors are synthesised in the liver in a vitamin K dependent way. Together they form the prothrombin complex. If one or more of these factors is deficient, the blood coagulation is impaired to such an extent that, depending on coagulation analysis, appropriate substitution therapy may be necessary.

The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K dependent coagulation factors, and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors. octaplex® contains, in addition to FII, FVII, FIX and FX, therapeutically effective concentrations of Protein C and Protein S, inhibitory enzymes of the coagulation pathway [11]. Like the prothrombin complex factors, they are synthesised in the liver.

Acquired deficiency of the vitamin K dependant coagulation factors occurs during treatment with vitamin K antagonists. If the deficiency becomes severe, a severe bleeding tendency results, characterised by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage. Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K dependant coagulation factors and a clinical bleeding tendency which, however, is often complex due to a simultaneous ongoing low-grade intravascular coagulation, low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

The same mechanism of action applies for bleedings due to vitamin K deficiency, caused by disorders in vitamin K resorption because of biliary tract or pancreas disorders, persisting diarrhoea or massive antibiotic therapy. Therefore, octaplex® can also be recommended for this indication.

Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue factor-factor VIIa complex activates coagulation factors X and IX, whereby factor IXa and Xa are formed. With further activation of the coagulation cascade, prothrombin (factor II) is activated and transformed to thrombin. By the action of thrombin, fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also of vital importance for platelet function as a part of the primary haemostasis.

Pharmacodynamics

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors IX, II, VII, and X in combination. ATC code: B02BD01. (see also Part II: DETAILED PHARMACOLOGY - Human Pharmacodynamics)

Classical dose-response studies were not performed due to the human origin of the product. (see ACTION AND CLINICAL PHARMACOLOGY – Mechanism of Action)

Pharmacokinetics

Please see Part II: DETAILED PHARMACOLOGY - Human Pharmacokinetics.

Absorption, Distribution, Metabolism, and Excretion

octaplex® is administered intravenously and therefore immediately available in the organism.

The coagulation factors contained in octaplex® are most likely removed by the hepatic reticuloendothelial system followed by degradation to individual amino acids by the normal intracellular processes of proteolytic hydrolysis.

STORAGE AND STABILITY

2 years shelf-life. After reconstitution the solution is to be used immediately. However, if it is not administered immediately, the reconstituted solution can be stored for up to 8 hours at +2°C to +25°C, provided sterility of the stored product is maintained.

Store at room temperature (+2°C to +25°C). Do not freeze.

Protect from exposure to light.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Powder and solvent for solution for injection.

octaplex® nominally contains the components listed in the following table.

Table 2: octaplex® Composition

Name of ingredient	octaplex® 500 IU Quantity per vial (20mL)	octaplex® 1000 IU Quantity per vial (40mL)	octaplex® Quantity per mL reconstituted solution
Total protein:	260 - 820 mg	520 - 1640 mg	13 - 41 mg/mL
Active substances			
Human coagulation factor II	280 - 760 IU	560 - 1520 IU	14 - 38 IU/ mL
Human coagulation factor VII	180 - 480 IU	360 - 960 IU	9 - 24 IU/ mL
Human coagulation factor IX	500 IU	1000 IU	25 IU/ mL
Human coagulation factor X	360 - 600 IU	720 - 1200 IU	18 - 30 IU/ mL
Further active ingredients			
Protein C	260 - 620 IU	520 - 1240	13 - 31 IU/ mL
Protein S	240 - 640 IU	480 - 1280	12 - 32 IU/ mL
Excipients			
Heparin	80 – 310 IU	160 - 620 IU	4 – 15.5 IU/ mL
Sodium Citrate	17.0 – 27.0 mmol/L		

Factor IX specific activity is ≥ 0.6 IU/ mg proteins.
Further excipient: Solvent (Water for Injection)
Small amounts of the S/D reagents TNBP (≤5 µg/ml) and Polysorbate 80 (≤ 50 µg/ml) may remain in the finished product. These substances are added during the manufacturing process because of their capacity to inactivate lipid-enveloped viruses.

Nature and Contents of Kit:

Package sizes::

octaplex® 500 in 20 mL
Powder in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium).
20 mL of solvent in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium).
Mix2Vial™ transfer set with integrated filter.

octaplex® 1000 in 40 mL
Powder in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium).
40 mL of solvent in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium).
Mix2Vial™ transfer set with integrated filter.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- Proper name: octaplex®
- Chemical name: Human Prothrombin Complex
- Molecular formula and molecular mass: not applicable
- Structural formula: not applicable
- Physicochemical properties: A detailed table, listing the octaplex® content, can be found in *PART I: HEALTH PROFESSIONAL INFORMATION – DOSAGE FORMS, COMPOSITION AND PACKAGING*

Pharmaceutical Standard

The preparation complies with the monograph on Human Prothrombin Complex (freeze-dried) of the European Pharmacopoeia (2005:0554). Doses of specific factors are expressed in WHO International Units (IU).

Product Characteristics

octaplex® is a human prothrombin complex (PCC) containing the coagulation factors II, VII, IX, and X and Proteins C and S in the amounts listed in Table 2. octaplex® is manufactured by chromatographic purification of cryo-poor plasma. Two specific virus inactivations and virus removals are included in the manufacturing process (see PHARMACEUTICAL INFORMATION – Viral Inactivation). The plasma used for the manufacture of octaplex® is obtained from collection centres that are inspected by Octapharma and are US FDA licensed. All operations and procedures of the plasma centres are reviewed with particular emphasis on donor selection, plasma testing, and proper documentation. Seroconversion rates for each centre are routinely obtained and monitored.

Each batch of octaplex® is made from a maximum of 2,000 kg of Cryopoor plasma from a maximum of 11,430 single donations. The single donations are tested and must be HBsAg-, anti-HCV-, and anti-HIV-1/2-negative. Single donations are also tested and must be negative for Syphilis. The test interval is complying with US regulations. Further, only donations that are tested negative for HIV and HCV by Polymerase Chain Reaction (PCR) in minipools are accepted, and depending upon the donation centre, these donations may be tested for Parvovirus B 19 by PCR in minipools. Additionally, the plasma pool used for the production of octaplex® is tested for HCV and Parvovirus B19 by PCR (Polymerase Chain Reaction) techniques and re-tested for HBsAg and anti- HIV-1/2. During the production process, the product is tested for

HAV by PCR. Only preparations, which are negative in all these tests, are used for further manufacture.

The preparation complies with the monograph on Human Prothrombin Complex (freeze-dried) of the European Pharmacopoeia (2005:0554). octaplex® is a further development of "PPSB Prothrombinkomplex human 250/500", the previous generation of PCC marketed by Octapharma.

Viral Inactivation

The 3 major requirements to prevent virus transmissions in general are all met by octaplex®:

1) reduction or elimination of plasma pool contamination with infectious agents, by selecting and testing source plasma (see PHARMACEUTICAL INFORMATION – Product Characteristics);

2) ensuring that accidental contamination of plasma pools by donors with silent infections will not lead to infection in the patients, by testing the capacity of the production process to remove or inactivate viruses; and

3) testing the product at appropriate stages of production for absence of detectable viral markers.

octaplex® is virus reduced by the way of a solvent/detergent (S/D) two steps viral inactivation process and a viral removal nanofiltration step. The S/D treatment was validated with lipid enveloped viruses (PRV, SBV, and HIV-1). The nanofiltration step was validated with lipid-enveloped viruses (HIV-1, SBV, PRV, BVDV) and non lipid-enveloped viruses (HAVand PPV).

CLINICAL TRIALS

Efficacy and Safety Studies

Study demographics and trial design

Three clinical studies with octaplex® have been conducted. In total, 90 patients have been enrolled and the patients received a total of about 569,000 IU of octaplex®. All studies used an open design and no control group, which is an acceptable approach, bearing in mind the type of indications.

Table 3: Summary of Patient Demographics for Clinical Trials LEX-201, LEX-202, and LEX-203

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n =number)	Mean age (Range)	Gender
LEX-201	Prospective, non-randomised, non-controlled, open-labelled, multi-centre study	single or multiple IV doses of 26 IU FIX/kg (median dose/exposure day)	haemophilia B: n=6 FVII deficiency: n=4	20.6 (11-67)	10 male
LEX-202	Prospective, non-randomised, non-controlled, open-labelled, multi-centre study	single IV doses of 14 to 44 IU FIX/kg	n=20	68.0 (43-83)	11 male; 9 female
LEX-203	Prospective, non-randomised, open-labelled, multi-centre study	Single or multiple IV doses over a few days, median dose at first infusion was 41 IU FIX/kg	n = 60	67.1 (24-93)	33 male 27 female

Overall Efficacy

a) Acquired Deficiencies

Based on the efficacy results from LEX-202 it can be concluded that with a single octaplex® treatment the detrimental effects of oral anticoagulants of coumarin or indandion type in patients affected by bleeding episodes or in patients undergoing surgical interventions could be reversed fast and effectively: PT was raised within 10 to 30 minutes significantly to around 55% and the INR was reduced in the same time period to about 1.5. Recovery, as another marker for efficacy, was approximately 1.1 to 1.7% IU/kg BW for FII, FIX, FX, PC, and PS (total and free); for FVII recovery was 0.7% IU/kg BW.

In LEX-203, the clinical efficacy of octaplex® administered in appropriate doses was demonstrated conclusively: 51 of 56 patients who finished the study according to protocol showed a clinical response as pre-defined by the study protocol. Furthermore, 4 of those patients who were considered as non-responders based on the protocol definition can be regarded as responders from a clinical point of view, as the difference between expected and actual PT value

was only minimal and the clinical efficacy of treatment with octaplex® was assessed as excellent. Even in the remaining patient the clinical response was adequate. All patients in LEX-203 showed an excellent clinical response, in particular, no complications during surgeries caused by uncontrollable bleedings have been observed after octaplex® treatment.

The same mechanism of action applies for bleedings due to vitamin K deficiency, caused by disorders in vitamin K resorption because of biliary tract or pancreas disorders, persisting diarrhoea or massive antibiotic therapy.

No clinical data are available for octaplex® for the treatment of bleeding disorders because of liver parenchyme disorders or oesophageal varices or because of major liver surgery. For these indications, the treatment with FFP is preferable and octaplex® cannot be recommended.

b) Congenital Deficiencies

The pharmacokinetic characteristics of octaplex® are in the range of what is reported for other PCCs and present a favourable picture of the efficacy of the product [13]. From these data it can be assumed that the physiological function of the proteins is not altered and a normal efficacy of the preparation can be expected. However, study LEX-201 was conducted in only 9 patients. Due to the small study population, the efficacy and safety of octaplex® on patients with congenital deficiencies could not be established.

Overall Safety

a) Acute Tolerability

In the 3 clinical studies, a total of 90 patients received 569,000 IU of octaplex®. One hundred and thirty-eight (138) AEs were reported in 47 patients. Out of these 138 AEs, only 6 were assessed as possibly related to octaplex® treatment.

Six AEs in 5 patients, all graded as mild, were assessed as possibly related to octaplex® treatment, *i.e.* headache occurring twice in 1 individual, a transient increase in liver transaminases (ALAT, ASAT), a parvovirus B19 infection, injection site burning, and an aggravation of arterial hypertension.

b) Thrombogenicity

Activated clotting factors (FVIIa, FIXa or FXa), lack of inhibiting proteins (PC or PS, heparin and/or AT), overload with FII and FX compared to FIX and the predisposition of patients have been suggested to cause thrombotic events [14-15].

- The *in vitro* properties are favourable: The proportion of the coagulation factors to each other is almost physiological (*i.e.* FX and FII are not elevated compared to FIX) and there is a substantial content of the physiological inhibitors PC and PS. Furthermore, the content of activated factors is low; and the FVIIa content could be substantially reduced compared to the predecessor preparation. In addition, octaplex® contains heparin to safeguard against thrombogenic events, which is standard for this kind of preparation [11].

- A Wessler stasis model has been performed with octaplex® - also without giving rise to suspect increased thrombogenicity.

- The clinical trials did not provide evidence for increased thrombogenicity.

octaplex® does not contain AT. However, especially in patients treated for coagulation disorders because of chronic liver disease or because of liver transplantation, AT levels should be monitored and a AT concentrate should be given concomitantly if an AT deficiency is present [1,3,7].

c) Immunogenicity

While the development of antibodies (inhibitors) against coagulation factors is a common feature in haemophilia treatment, it seems to be a very rare event after the administration of the less purified PCCs.

Nevertheless, the production process may include steps, which induce antigenicity resulting in increased inhibitor formation in patients that had been previously treated. For this reason, a study with a treatment phase of least 6 months, with inhibitor monitoring and a repeated pharmacokinetic analysis after 3 to 6 months should be performed in previously treated patients. This kind of study has been performed for octaplex® (LEX-201) demonstrating the absence of immunogenicity. However, the immunogenicity of octaplex® was evaluated in only one clinical study (LEX-201) and could not be fully established due to the limited population size (9 patients) of the study.

d) Viral Safety

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.

In LEX-201, no viral seroconversion was observed. Viral markers were measured at baseline, after 3 and 6 months and 6-12 weeks after the last administration of octaplex®.

In LEX-202, viral safety was investigated by patient screening for anti-HAV and anti-parvovirus B19 at baseline and, if applicable, after octaplex® treatment. Of 11 patients who tested negative for anti-parvovirus B19 at baseline, 2 patients were found to be positive in the course of the study. The patients did not develop symptoms of an infection. The patients who were anti-HAV negative at baseline remained negative during the course of the study.

In LEX-203, viral markers (anti-HAV and anti-parvovirus B19) were determined for all patients 3 weeks after last octaplex® treatment. None of the patients was positive for anti-HAV at any of the time points measured. In one patient a parvovirus B19 test, which was negative before infusion, was positive after 21 days. For this patient IgM antibodies of 7 U/mL and IgG of 1.0 U/mL (borderline value) were measured.

e) Deaths

In total, 5 deaths have been reported during clinical trials, and all cases were unrelated to octaplex® treatment, as assessed by the responsible investigators.

DETAILED PHARMACOLOGY

Animal Pharmacology

octaplex® is comprised of human plasma coagulation factors. Animal pharmacology studies were not conducted.

Human Pharmacokinetics

The assessment of pharmacokinetic parameters was one of the main objectives of LEX 201. Half-life and recovery are regarded as the main surrogate endpoints for the assessment of efficacy of coagulation factors [12]. A precise evaluation of pharmacokinetics is only possible in individuals lacking the factor in question, hence in patients with congenital deficiency of any of the prothrombin factors.

The pharmacokinetic properties of octaplex® were assessed in 6 haemophilia B patients and in 4 FVII deficient patients in LEX-201. FII and FX deficient patients were not tested. Apart from 2 FVII deficient patients, all had a repetitive pharmacokinetic analysis after 6 months treatment with octaplex®. 1 FVII deficient patient withdrew consent during the baseline kinetics, therefore, only recovery could be assessed. The other patient did not return for the 6-month visit. Samples for FIX pharmacokinetics were taken at baseline and after 10, 30 and 60 minutes and after 3, 6, 9, 12, 24, 32, 48 and 72 hours. For FVII, sampling was done at baseline and after 5, 10, 30, 45, and 60 minutes and after 2, 3, 6, 9, 12, and 24 hours.

Ranges of recovery and half-life are shown in the following table. Because of the low number of patient per group, no mean values are presented.

Table 4: Recovery and half-life of FVII and FIX

	Recovery def 1[1] (% IU/kg-1)	**Recovery def 2[2] (%)**	**Elimination $t_{1/2}$ (hours)**
FVII[3]	0.84 - 1.24 (n=4)	35.5 - 53.4 (n=4)	5.4 - 8.3 (n=3)
FIX	0.8 - 1.42 (n=6)	38.6 - 61.0 (n=6)	28.7 - 49.1 (n=6)

[1](C_{max}-C_0) x (body weight)/dose [2](C_{max} –C_0) x (bodyweight) x (1-HCT/100)/dose [3] Recovery based upon measured potency

For FVII, recovery has been calculated according to the measured potency (and not the declared potency). This is acceptable as the preparation is filled and labelled according to FIX.

Pharmacokinetic of FII and FX could not be conducted in the clinical trials due to the lack of patients with such deficiencies.

The plasma half-life ranges are:

Coagulation factor	Half life
Factor II	48 - 60 hours
Factor VII	1.5- 6 hours
Factor IX	20 - 24 hours
Factor X	24 - 48 hours
Protein C	1.5 - 6 hours
Protein S	24 - 48 hours

The half-lives of coagulation factors may be significantly reduced in case of extended catabolic metabolism, severe liver cell damage or disseminated intravascular coagulation (DIC).

Human Pharmacodynamics

FII, FIX and FX are components of the intrinsic coagulation pathway, FVII is a component of the extrinsic pathway. These factors are synthesised in the liver in a vitamin K dependent way. Together they form the prothrombin complex. If one or more of these factors is deficient, the blood coagulation is impaired to such an extent that, depending on coagulation analysis, appropriate substitution therapy may be necessary.

octaplex® contains in addition to FII, FVII, FIX and FX therapeutically effective concentrations of PC and PS, inhibitory enzymes of the coagulation pathway [11]. Like the prothrombin complex factors they are synthesised in the liver.

Batch analyses demonstrate an almost physiological proportion of FII, FVII, FIX and FX and rather high amounts of proteins C and S in octaplex® [11].

Classical dose-response studies were not performed due to the human origin of the product. Dose recommendations for single factor deficiencies are based on the required level, on the body weight (BW) of the patient and the activity increase per unit of the respective factor administered. For acquired deficiencies, dosing should also be individualised and preferably be accompanied by laboratory analysis of global and single coagulation parameters.

TOXICOLOGY

As octaplex® is a "mixture" of human native proteins (coagulation factors), the standard pharmacodynamic and toxicity studies, generally carried out for new (chemical) substances in commonly used animal species, are not applicable to this product.
The excipients are porcine heparin and trisodium citrate hydrate. Taking into account the amount of the excipients, no adverse effects are to be expected following slow intravenous infusion of octaplex®.

octaplex® contains residual amounts of tri-n-butyl phosphate (TNBP; ≤ 5µg/ml) and polysorbate 80 (of vegetable origin; ≤ 50 µg/ml). These chemicals are used during manufacturing for inactivation of enveloped viruses and are afterwards removed by a DEAE-sepharose fast column.

The maximum single dose of 80 IU/kg octaplex® i.v. results in ≤ 16 µg/kg TNBP and ≤ 160 µg/kg polysorbate 80.

The pharmacokinetic animal study reveals, that negligible amounts of TNBP have to be expected in human plasma.
Results of single-dose toxicity studies might be relevant for TNBP in octaplex®. Based on the results of the single-dose toxicity study in rats after i.v. administration a therapeutic window (ratio) for humans of at least 290 can be calculated.

Toxicity studies in newborns as well as studies with repeated administration are of minor interest.

Genotoxicity and carcinogenicity studies are not important for a human protein containing trace amounts of virus inactivation chemicals, which is given rather as an emergency treatment.
Studies in rats and rabbits showed that there is no teratogenic effect of TNBP.
There is no special study on local tolerance. There is a lot of data from the studies on Repeat-Dose Toxicity and Development Toxicity with repeated intravenous injections.
The use of octaplex® in clinical practice for many years does not justify further tests in animals on local tolerance from the point of animal welfare.

In summary, the impact of trace amounts of TNBP and polysorbate 80 on the tolerance of octaplex® is negligible. From a toxicological point of view there are no restrictions at all for the safe use of octaplex®.

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PART III: CONSUMER INFORMATION

octaplex®
Human Prothrombin Complex

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

ABOUT THIS MEDICATION

What the medication is used for:

- Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

What it does:
The administration of octaplex® can temporarily stop bleeding in patients with deficiency of one or several of the coagulation factors II, VII, IX and X, which are commonly called the Prothrombin Complex. octaplex® will start working immediately upon injection. octaplex® should only be used when rapid correction of major bleeding or emergency surgery is warranted.

When it should not be used:

- If reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is sufficient
- octaplex® is not for patients who are hypersensitive to this drug or to any ingredient in the formulation, such as heparin, or component of the container.
- octaplex® should not be used in patients with a recent heart attack, with a high risk of blood clots, or with coronary artery disease, or chronic liver disease.

What the medicinal ingredients are:
Human Coagulation Factor II, VII, IX and X, and Proteins C and S.

What the important nonmedicinal ingredients are:
Heparin, sodium citrate, solvent (Water for Injection)

What dosage forms it comes in:
Powder and solvent for solution for injection. One package of octaplex® contains:
One powder vial containing the active ingredients (coagulation factors) and excipients, a second vial containing 20 mL/ 40 mL of diluent and a Mix2Vial™ transfer set with integrated filter.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
This product is made from human plasma, which may contain hepatitis and other viral diseases. Your doctor should discuss the risks and benefits of this product with you before giving you this product (see WARNINGS AND PRECAUTIONS - General).

BEFORE you use octaplex® 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, or liver disease.
- You are predisposed to allergies. Antihistamines and corticosteroids may be given prior to receiving this drug.
- You have not received appropriate vaccinations for hepatitis A and B. These vaccinations should be considered if you will be receiving regular/repeated treatments with this drug.
- You are allergic against heparin.
- You are pregnant or nursing. A pregnancy test is recommended before receiving octaplex®
- You will be undergoing any scheduled surgical procedures.
- You are allergic to the active substance or to any of the nonmedicinal ingredients.

INTERACTIONS WITH THIS MEDICATION

There is no known drug interaction to octaplex®. Components used in the packaging of octaplex® are latex-free.

PROPER USE OF THIS MEDICATION

Usual dose:
The dose you receive depends on your test results for prothrombin complex levels and your body weight. The dose will be given intravenously at an initial rate of 1 mL per minute and increasing to no faster than 2 – 3 mL per minute.

Overdose:
No symptoms of overdose with octaplex® have been reported.

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:
Acquired deficiencies:
Not applicable because in acquired deficiencies octaplex® is administered in a hospital setting by health care professionals.

Administration
octaplex® should be administered under the supervision of a qualified health professional.
octaplex® should be administered intravenously. Please read all the instructions and follow them carefully. During the procedure described below, aseptic technique must be maintained. The product reconstitutes quickly at room temperature. The solution

should be colourless to slightly blue. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discolouration prior to administration. A blue colour is not interpreted as discolouration.

Instructions for Reconstitution:

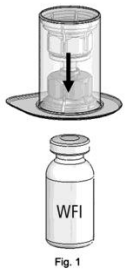
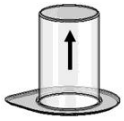


Fig. 1

1. If the octaplex® powder and water for injection (WFI) are not already at room temperature, warm up the closed vials to room temperature (maximum 37°C). This temperature should be maintained during reconstitution. If a water bath is used to warm the WFI, care should be taken to ensure the water does not come into contact with the rubber stopper or closure system of the vials.



2. Remove the flip caps from the octaplex® vial and the WFI vial and clean the rubber stoppers with an alcohol swab.

Fig. 2

3. Peel away the lid of the outer package of the Mix2Vial™ transfer set. Place the WFI vial on an even surface and hold the vial firmly. Take the Mix2Vial™ together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial™ firmly through the rubber stopper of the WFI vial in one swift motion (Fig. 1). While holding onto the WFI vial, carefully remove the outer package from the Mix2Vial™, being careful to leave the Mix2Vial™ attached firmly to the WFI vial (Fig. 2).

4. With the octaplex® vial held firmly on an even surface, quickly invert the WFI vial (with the Mix2Vial™ attached), push the transparent plastic cannula end of the Mix2Vial™ firmly through the stopper of the octaplex® vial, and hold the downward pressure (Fig. 3). The WFI will be drawn into the octaplex® vial by vacuum.

Fig. 3

Fig. 4

5. With both vials still attached, slowly rotate the octaplex® vial to ensure the product is fully dissolved to a clear or slightly opalescent solution. Once the contents of the octaplex® vial are dissolved, firmly hold both the transparent and blue parts of the Mix2Vial™. Unscrew the Mix2Vial™ into two separate pieces with the vials still attached (Fig. 4) and discard the empty WFI vial and the blue part of the Mix2Vial™.

Instructions for Injection:

As a precautionary measure, the patient's pulse rate should be measured before and during the injection. If a marked increase in the pulse rate occurs, the injection speed must be reduced or the administration must be interrupted.

1. After octaplex® has been reconstituted, attach a plastic sterile disposable syringe to the transparent part of Mix2Vial™. Invert the system and draw the reconstituted octaplex® into the syringe.
2. Once the octaplex® solution has been transferred into the syringe, firmly hold the barrel of the syringe (keeping it facing down) and detach the Mix2Vial™ from the syringe. Discard the Mix2Vial™ (transparent plastic part) and the empty octaplex® vial.
3. Disinfect the injection site with an alcohol swab and attach the syringe to a suitable infusion needle. Alternatively, octaplex® can be administered using an IV line. Ideally, a new, clean IV line should be used. Otherwise, the IV line must first be 'cleaned' of other products by flushing it with a saline or dextrose 5% solution. octaplex® should not be mixed with any other product (including saline or dextrose 5% solution) in the IV line.
4. Using an aseptic technique, inject the octaplex® solution intravenously at an initial rate of 1 mL per minute, followed by 2-3 mL per minute, if appropriate. A pump can be used to regulate and control the injection rate when administering octaplex®.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Headaches may rarely occur.
- Allergic or allergic-type reactions: early signs include hives, increase in body temperature, generalised hives, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, discontinue the administration immediately and contact your physician. In case of shock, the current medical standards for treatment of shock are to be observed. No case of allergic or anaphylactic reaction was reported under octaplex® treatment so far; therefore the incidence is expected to be very low.
- Immune system disorders: Replacement therapy may rarely lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response. A final statement on the development of inhibitors in previously treated patients cannot be made.

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	
Rarely	allergic type of reactions		X	X
	fever		X	X
	headache	X		

Very rarely	thromboembolic complications		X	X

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

HOW TO STORE IT

Store protected from light at +2°C to +25°C. Do not freeze. After reconstitution as recommended (see *Instructions for reconstitution*), octaplex® should be administered immediately. However, if it is not administered immediately, the reconstituted solution can be stored for up to 8 hours at +2°C to +25°C, provided sterility of the stored product is maintained. Any solution remaining should be discarded.

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 Octapharma Canada Inc.,
at: 1-888-438-0488

This leaflet was prepared by Octapharma Pharmazeutika Produktionsges.m.b.H

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PARTIE III : RENSEIGNEMENTS POUR LE CONSOMMATEUR

octaplex®
Complexe Prothrombique Humain

Le présent dépliant constitue la troisième et dernière partie de la monographie de produit publiée à la suite de l'approbation de la vente au Canada de octaplex® et est destiné aux consommateurs. Comme ce dépliant est un résumé, il ne contient pas tous les renseignements sur octaplex®. Pour toute question au sujet de ce médicament, communiquez avec votre médecin ou un pharmacien.

AU SUJET DE CE MÉDICAMENT

Emploi du médicament :

- Traitement des hémorragies ou prophylaxie péropératoire des hémorragies associées aux déficits du complexe prothromobique de facteurs de coagulation causées, à titre d'exemple, par un traitement par des antagonistes de la vitamine K, ou correction rapide d'un déficit secondaire à un surdosage d'antagonistes de la vitamine K.

Effet du médicament :
L'administration d' octaplex® peut faire cesser temporairement les hémorragies chez les patients présentant un déficit d'un ou plusieurs facteurs de coagulation (II, VII, IX ou X), lesquels sont souvent regroupés sous le nom de complexe prothrombique. octaplex® commencera à agir immédiatement dès l'injection. octaplex® ne doit être utilisé que dans les cas de correction rapide d'hémorragies majeures ou dans les cas d'interventions chirurgicales d'urgence.

Situations dans lesquelles il ne faut pas l'utiliser :

- Lorsqu'une réduction de la dose de l'antagoniste de la vitamine K et/ou l'administration de la vitamine K est suffisante.
- octaplex® n'est pas destiné aux patients qui présentent une hypersensibilité à ce médicament ou à tout ingrédient de la préparation, tels l'héparine ou un composant du contenant.
- octaplex® ne doit pas être utilisé chez les patients qui ont eu une crise cardiaque récente, qui présentent un risque élevé de survenue de caillots sanguins, ou qui sont atteints d'une coronaropathie ou d'une maladie hépatique chronique.

Ingrédients médicinaux :
Facteurs de coagulation humains II, VII, IX et X, et protéines C et S.

Ingrédients non médicinaux importants :
Héparine, citrate de sodium, diluant (eau pour injections)

Forme posologique :
Poudre et diluant pour la solution d'injection. Un emballage d' octaplex® contient :
Un flacon de la poudre contenant les principes actifs (facteurs de coagulation) et les excipients, un second flacon contenant 20 mL/ 40 mL de diluant et un ensemble de transfert Mix2Vial™ avec filtre intégré.

MISES EN GARDE ET PRÉCAUTIONS

Sérieuses mises en garde et précautions
Ce produit est fabriqué à partir de plasma humain; il peut contenir une hépatite ou d'autres maladies virales. Votre médecin doit discuter avec vous des risques et des bienfaits de ce produit avant de vous l'administrer (voir MISES EN GARDE ET PRÉCAUTIONS - Général).

AVANT d'utiliser octaplex®, adressez-vous à votre médecin ou à un pharmacien si :

- Vous avez eu récemment une crise cardiaque, vous présentez un risque élevé de survenue de caillots sanguins, ou vous êtes atteint d'une coronaropathie ou une maladie hépatique.
- Vous êtes prédisposé aux allergies. Il est possible que vous deviez recevoir des antihistaminiques et des corticostéroïdes avant de prendre ce médicament.
- Vous n'avez pas reçu les vaccins appropriés contre l'hépatite A et l'hépatite B. Il faut considérer recevoir ces vaccins si les traitements par ce médicament sont réguliers et répétés.
- Vous êtes allergique aux héparines.
- Vous êtes enceinte ou allaitez. Il est recommandé de passer un test de grossesse avant de recevoir octaplex®.
- Vous devez subir des procédures chirurgicales.
- Vous êtes allergique à la substance active ou à l'un des ingrédients non médicinaux.

INTERACTIONS AVEC CE MÉDICAMENT

Il n'existe pas d'interactions médicamenteuses connues avec octaplex®. Les composants compris dans l'emballage d' octaplex® ne contiennent pas de latex.

UTILISATION CONVENABLE DU MÉDICAMENT

Dose habituelle :
La dose que vous recevez dépend des résultats aux épreuves mesurant les concentrations du complexe prothrombique, de même que de votre poids corporel. La dose sera administrée par voie intraveineuse à une vitesse initiale de 1 mL par minute, puis sera augmentée à une vitesse n'excédant pas 2-3 mL par minute.

Surdosage :
Aucun symptôme de surdosage lié à octaplex® n'a été signalé.

En case de surdosage, communiquez immédiatement avec un professionnel de la santé, l'urgence d'un centre hospitalier ou le centre antipoison de votre région, même en l'absence de symptômes.

Dose oubliée :
Déficits acquis :

Ne s'applique pas : dans les cas de déficits acquis, octaplex® est administré à l'hôpital et par des professionnels de la santé.

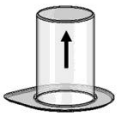
Administration

L'administration d' octaplex® doit être effectuée sous la surveillance d'un professionnel de santé qualifié.
octaplex® doit être administré par voie intraveineuse. Veuillez lire toutes les directives et les suivre attentivement. Au cours de la procédure décrite ci-dessous, il faut avoir recours à des techniques aseptiques. La reconstitution du produit s'effectue rapidement à température ambiante. La reconstitution doit donner une solution incolore à légèrement bleutée. Ne pas utiliser de solution trouble ou contenant un dépôt. Une inspection visuelle du produit reconstitué doit être réalisée avant administration afin de détecter toute particule et/ou décoloration. Une couleur bleutée n'est pas considérée comme une décoloration.

Instructions pour la reconstitution:

Fig. 1

1. Si la poudre d'octaplex® et l'eau pour injection ne sont pas à température ambiante, laisser les flacons fermés atteindre la température ambiante (maximum 37°C). Cette température doit être maintenue lors de la reconstitution. Si l'eau pour injection est réchauffée au bain-marie, veiller à ce que l'eau n'entre pas en contact avec le bouchon en caoutchouc ou le système de fermeture des flacons.



2. Retirer l'opercule des flacons d'octaplex® et d'eau pour injection puis nettoyer le bouchon en caoutchouc à l'aide d'une compresse imbibée d'alcool.

Fig. 2

3. Retirer le couvercle de l'emballage externe de l'ensemble de transfert du Mix2Vial™. Placer le flacon d'eau pour injection sur une surface plane et le tenir fermement. Prendre le Mix2Vial™ avec son emballage externe et le retourner. Pousser la canule de plastique bleue du Mix2Vial™ fermement à travers le bouchon de caoutchouc du flacon d'eau pour injection (fig. 1). Tout en tenant bien le flacon de WFI, retirer avec soin l'emballage externe du Mix2Vial™ en faisant bien attention de laisser le Mix2Vial™ attaché fermement au flacon d'eau pour injection (fig. 2).

Fig. 3

4. En tenant fermement le flacon d'octaplex® sur une surface plane, retourner rapidement le flacon d'eau pour injection (avec le Mix2Vial™ attaché) et pousser fermement le bout de la canule de plastique transparente à travers le bouchon du flacon d'octaplex® tout en maintenant la pression en tenant l'ensemble (fig. 3). L'eau pour injection sera aspirée dans le flacon d'octaplex® par la succion.

Fig. 4

5. Les deux flacons toujours attachés, faire tourner le flacon d'octaplex® doucement pour s'assurer que le produit est complètement dissout en une solution transparente ou légèrement opalescente. Une fois le contenu du flacon d'octaplex® dissout, bien tenir à la fois la partie transparente et la partie bleue du Mix2Vial™. Dévisser le Mix2Vial™ en deux pièces séparées avec les flacons toujours attachés (fig. 4) et jeter le flacon de WFI vide et la partie bleue du Mix2Vial™.

Instructions pour l'injection:

En tant que mesure préventive, le rythme cardiaque du patient devrait être mesuré avant et pendant l'injection. Si une hausse marquée du pouls survient, la vitesse d'injection doit être réduite ou l'administration doit être interrompue.

1. Après avoir reconstitué la solution d'octaplex®, attacher une seringue en plastique jetable stérile à la partie transparente du Mix2Vial™. Retourner l'installation et aspirer l'octaplex® reconstitué dans la seringue.
2. Une fois la solution d'octaplex® transférée dans la seringue, tenir fermement le cylindre de la seringue (en la maintenant orientée vers le bas) et détacher le Mix2Vial™ de la seringue. Éliminer le Mix2Vial™ (la partie de plastique transparente) et le flacon d'octaplex® vide.
3. Désinfectez le site d'injection avec un tampon alcoolisé et attachez la seringue à une aiguille appropriée pour l'infusion.
   Idéalement, une voie intraveineuse propre devrait être utilisée. Autrement, la voie doit être débarrassée au préalable de tout autre produit par rinçage avec une solution saline ou Dextrose 5%. octaplex® ne doit pas être mélangé à tout autre produit (incluant une solution saline ou Dextrose 5%) dans la voie d'infusion intraveineuse.

4. À l'aide d'une technique aseptique, injecter la solution d'octaplex® par voie intraveineuse à un débit initial de 1 ml par minute, puis augmenter à 2-3 ml par minute, si ce débit est adapté au patient. Il est possible d'utiliser une pompe afin de réguler et contrôler la vitesse d'injection lors de l'administration d'octaplex®.

EFFETS SECONDAIRES ET MESURES À PRENDRE

Les effets secondaires peuvent comprendre :

- Des céphalées occasionnelles (rares).
- Des réactions allergiques ou des réactions ressemblant à des allergies : les signes précoces comprennent l'urticaire, l'augmentation de la température corporelle, l'urticaire généralisée, l'oppression thoracique, la respiration sifflante, l'hypotension et l'anaphylaxie. Si des symptômes d'allergie apparaissent, cessez immédiatement de vous administrer le médicament et communiquez avec votre médecin. En cas de choc, les normes thérapeutiques actuelles s'appliquant au

traitement des chocs doivent être observées. Aucun cas de réaction allergique ou anaphylactique n'a été signalé jusqu'à maintenant lors d'un traitement par octaplex®; par conséquent, une faible incidence est à prévoir.

- Troubles du système immunitaire : Un traitement de remplacement peut, en de très rares occasions, entraîner la formation d'anticorps circulants, lesquels inhibent un ou plusieurs des facteurs du complexe prothrombique humain. Si de tels inhibiteurs apparaissent, la réponse clinique sera peu manifeste. On ne peut statuer de manière définitive sur l'apparition de ces inhibiteurs chez les patients qui ont été préalablement traités.

FRÉMESURES À PRENDRE				
Symptôme/effet		Consultez votre médecin ou un pharmacien		Cessez de prendre le médicament et appelez votre médecin ou un pharmacien
		Dans les cas sévères seulement	Dans tous les cas	
Rare	réactions de type allergique		X	X
	fièvre		X	X
	céphalées	X		
Très rare	complications thromboemboliques		X	X

Cette liste des effets secondaires n'est pas exhaustive. Si des effets inattendus surviennent pendant le traitement par octaplex®, communiquez avec votre médecin ou un pharmacien.

CONSERVATION DU MÉDICAMENT

Conserver à une température entre +2°C et +25°C, à l'abri de la lumière. Ne congelez pas le médicament. Après reconstitution (voir *Instructions pour la reconstitution*), octaplex® doit être utilisée immédiatement. Toutefois, si elle n'est pas utilisée immédiatement, la solution reconstituée peut être conservée pour une durée maximale de 8 heures à +2°C to +25°C, à la condition que la stérilité du produit entreposé soit maintenue. Toute solution restante doit être jetée.

DÉCLARATION DES EFFETS INDÉSIRABLES SOUPÇONNÉS

Vous pouvez déclarer les effets indésirables soupçonnés associés à l'utilisation des produits de santé au Programme Canada Vigilance de l'une des 3 façons suivantes :

- En ligne www.santecanada.gc.ca/medeffet
- Par téléphone, en composant le numéro sans frais 1-866-234-2345;
- En remplissant un formulaire de déclaration de Canada Vigilance et en le faisant parvenir
  - par télécopieur, au numéro sans frais 1-866-678-6789
  - par la poste au: Programme Canada Vigilance
    Santé Canada
    Indice postal 0701D
    Ottawa (Ontario) K1A 0K9

Les étiquettes préaffranchies, le formulaire de déclaration de Canada Vigilance ainsi que les lignes directrices concernant la déclaration d'effets indésirables sont disponibles sur le site Web de MedEffet[MC] Canada à www.santecanada.gc.ca/medeffet.

REMARQUE : Pour obtenir des renseignements relatifs à la gestion des effets secondaires, veuillez communiquer avec votre professionnel de la santé. Le Programme Canada Vigilance ne fournit pas de conseils médicaux.

POUR DE PLUS AMPLES RENSEIGNEMENTS

Le présent feuillet ainsi que la monographie de produit intégrale préparée pour les professionnels de la santé peuvent être obtenus à l'adresse suivante
http://www.octapharma.ca
ou en communiquant avec Octapharma Canada Inc.,
au 1-888-438-0488.

Le présent feuillet a été rédigé par Octapharma Pharmazeutika Produktionsges.m.b.H.

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