

## PRODUCT MONOGRAPH

### octaplex<sup>®</sup>

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

One vial of octaplex <sup>®</sup> for solution for injection contains:		
	octaplex <sup>®</sup> 500 in 20 ml	octaplex <sup>®</sup> 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:

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Date of Revision:

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**Control No: 208004**

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## octaplex<sup>®</sup>

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

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients	
Intravenous injection	Powder and solvent for solution for injection/ Per 20 ml vial:	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)	
		<i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>	
	Human Coagulation Factor II	280-760 IU	
	Human Coagulation Factor VII	180-480 IU	
	Human Coagulation Factor IX	500 IU	
	Human Coagulation Factor X	360-600 IU	
	Protein C	260-620 IU	
	Protein S	240-640 IU	
		Per 40 ml vial:	
	Human Coagulation Factor II	560 – 1520 IU	
	Human Coagulation Factor VII	360 – 960 IU	
	Human Coagulation Factor IX	1000 IU	
Human Coagulation Factor X	720 – 1200 IU		
Protein C	520 – 1240 IU		
Protein S	480 – 1280 IU		
	Factor IX specific activity is $\geq 0.6$ IU/ mg proteins.		

#### DESCRIPTION

octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 precautionous 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> may cause a booster effect with an immediate generation of the antibody.
- octaplex<sup>®</sup> is contraindicated in those rare cases where an individual has an immunoglobulin A (IgA) deficiency, with known antibodies against IgA.
- octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sub>10</sub>:

- 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<sup>®</sup> 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 hypercoagulable state and infusion of prothrombin complex concentrate may exacerbate this. The long term and repeat use safety of octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> 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 may rarely occur.* These may include angioedema, injection site reactions, chills, flushing, urticaria, headache, drop in blood pressure, anxiety, nausea, vomiting, sweating, tachycardia, dyspnoea, or bronchospasm. In rare cases, these reactions may progress to severe anaphylaxis (see WARNINGS AND PRECAUTIONS).

*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 been rarely observed.

*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<sup>®</sup> have been conducted. In total, 90 patients have been enrolled and the patients received a total of about 569,000 IU of octaplex<sup>®</sup>. Eight ADRs in 7 patients, all graded as mild, were assessed as possibly related to octaplex<sup>®</sup> 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.

<b>Body system¶</b>	<b>Adverse event</b>	<b>Severity / Causality</b>	<b>No. of episodes</b>
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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> administration. This patient had transient increases of ALAT and ASAT 12 hours after the last octaplex<sup>®</sup> 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<sup>®</sup> 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 parvovirus 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<sup>®</sup>.

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

The following adverse reactions have been reported during the global post-marketing use of Octaplex. The frequency of such adverse reactions cannot be reliably estimated due to the voluntary nature of such reports and causality of which cannot be clearly established.

Adverse Reactions Reported During the global Post-Marketing Use of Octaplex

*Immune system disorders*

Anaphylactic shock, anaphylactic reaction, hypersensitivity

*Nervous system disorders*

Tremor

*Cardiac disorders*

Cardiac arrest, tachycardia

*Vascular disorders*

Thromboembolic event, circulatory collapse, hypotension, hypertension

*Respiratory, thoracic and mediastinal disorders*

Dyspnoea, respiratory failure

*Gastrointestinal disorders*

Nausea

*Skin and subcutaneous tissue disorders*

Urticaria, rash

*General disorders and administration site conditions*

Pyrexia, chills

Lack of efficacy is mentioned as listed/expected adverse experience.

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<sup>®</sup> 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<sup>®</sup> 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 ( $\leq 1.2$  within 1 hour) at different initial INR levels are given.

**Table 1: Approximate Doses of octaplex<sup>®</sup> Required for Normalization of INR**

<b>Initial INR</b>	2 – 2.5	2.5 – 3	3 – 3.5	> 3.5
<b>Approximate dose* (ml octaplex<sup>®</sup>/kg body weight)</b>	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<sup>®</sup>).

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<sup>®</sup> is administered in a hospital setting by health care professionals.

## Administration

octaplex<sup>®</sup> 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<sup>®</sup> 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.

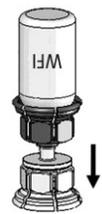


2. Remove the flip caps from the octaplex<sup>®</sup> vial and the WFI vial and clean the rubber stoppers with an alcohol swab.



Fig. 2

3. Peel away the lid of the outer package of the Mix2Via<sup>™</sup> transfer set. Place the WFI vial on an even surface and hold the vial firmly. Push the blue plastic cannula of the Mix2Via<sup>™</sup> 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 Mix2Via<sup>™</sup>, being careful to leave the Mix2Via<sup>™</sup> attached firmly to the WFI vial (Fig. 2).



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



Fig. 3



Fig. 4

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

### 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<sup>®</sup> has been reconstituted, attach a plastic sterile disposable syringe to the transparent part of Mix2Vial<sup>™</sup>. Invert the system and draw the reconstituted octaplex<sup>®</sup> into the syringe.
2. Once the octaplex<sup>®</sup> solution has been transferred into the syringe, firmly hold the barrel of the syringe (keeping it facing down) and detach the Mix2Vial<sup>™</sup> from the syringe. Discard the Mix2Vial<sup>™</sup> (transparent plastic part) and the empty octaplex<sup>®</sup> vial.
3. Disinfect the injection site with an alcohol swab and attach the syringe to a suitable infusion needle.

Alternatively, octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>.

**Incompatibility:**

octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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: antihæmorrhagics, 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<sup>®</sup> is administered intravenously and therefore immediately available in the organism.

The coagulation factors contained in octaplex<sup>®</sup> 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**

3 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<sup>®</sup> nominally contains the components listed in the following table.

**Table 2: octaplex<sup>®</sup> Composition**

Name of ingredient	octaplex <sup>®</sup> 500 IU Quantity per vial (20ml)	octaplex <sup>®</sup> 1000 IU Quantity per vial (40ml)	octaplex <sup>®</sup> Quantity per mL reconstituted solution
Total protein:	260 - 820 mg	520 - 1640 mg	13 - 41 mg/ml
<i>Active substances</i>			
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
<i>Further active ingredients</i>			
Protein C	260 - 620 IU	520 - 1240 IU	13 - 31 IU/ ml
Protein S	240 - 640 IU	480 - 1280 IU	12 - 32 IU/ ml
<i>Excipients</i>			
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  $\geq 0.6$  IU/ mg proteins.

Further excipient: Solvent (Water for Injection)

Small amounts of the S/D reagents TNBP ( $\leq 50$  µg/ml) and Polysorbate 80 ( $\leq 50$  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<sup>®</sup> 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).

Mix2Via<sup>™</sup> transfer set with integrated filter.

##### octaplex<sup>®</sup> 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).

Mix2Via<sup>™</sup> transfer set with integrated filter.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

- Proper name: octaplex<sup>®</sup>
- Chemical name: Human Prothrombin Complex
- Molecular formula and molecular mass: not applicable
- Structural formula: not applicable
- Physicochemical properties: A detailed table, listing the octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> is obtained from collection centres that are inspected by national health authorities and audited by Octapharma. 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<sup>®</sup> 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 national 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>:

- 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<sup>®</sup> 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 (HAV and PPV).

## CLINICAL TRIALS

### Efficacy and Safety Studies

#### Study demographics and trial design

Three clinical studies with octaplex<sup>®</sup> have been conducted. In total, 90 patients have been enrolled and the patients received a total of about 569,000 IU of octaplex<sup>®</sup>. 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> cannot be recommended.

#### b) Congenital Deficiencies

The pharmacokinetic characteristics of octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> treatment.

Six AEs in 5 patients, all graded as mild, were assessed as possibly related to octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> - also without giving rise to suspect increased thrombogenicity.
- The clinical trials did not provide evidence for increased thrombogenicity.

octaplex<sup>®</sup> 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<sup>®</sup> (LEX-201) demonstrating the absence of immunogenicity. However, the immunogenicity of octaplex<sup>®</sup> 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<sup>®</sup>.

In LEX-202, viral safety was investigated by patient screening for anti-HAV and anti-parvovirus B19 at baseline and, if applicable, after octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> treatment, as assessed by the responsible investigators.

## **DETAILED PHARMACOLOGY**

### **Animal Pharmacology**

octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. 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**

	<b>Recovery def 1<sup>1</sup></b> <b>(% IU/kg-1)</b>	<b>Recovery def 2<sup>2</sup></b> <b>(%)</b>	<b>Elimination t<sub>1/2</sub></b> <b>(hours)</b>
FVII <sup>3</sup>	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)

<sup>1</sup> $(C_{\max}-C_0) \times (\text{body weight})/\text{dose}$  <sup>2</sup> $(C_{\max}-C_0) \times (\text{bodyweight}) \times (1-\text{HCT}/100)/\text{dose}$  <sup>3</sup> 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:

<b>Coagulation factor</b>	<b>Half life</b>
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<sup>®</sup> 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<sup>®</sup> [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<sup>®</sup> 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<sup>®</sup>.

octaplex<sup>®</sup> contains residual amounts of tri-n-butyl phosphate (TNBP;  $\leq 5\mu\text{g/ml}$ ) and polysorbate 80 (of vegetable origin;  $\leq 50\mu\text{g/ml}$ ). 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<sup>®</sup> i.v. results in  $\leq 16\mu\text{g/kg}$  TNBP and  $\leq 160\mu\text{g/kg}$  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<sup>®</sup>. 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<sup>®</sup> 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<sup>®</sup> is negligible. From a toxicological point of view there are no restrictions at all for the safe use of octaplex<sup>®</sup>.

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## PART III: CONSUMER INFORMATION

### octaplex<sup>®</sup> Human Prothrombin Complex

This leaflet is part III of a three-part "Product Monograph" published when octaplex<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> 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<sup>®</sup> will start working immediately upon injection. octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>™</sup> 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<sup>®</sup> 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<sup>®</sup>.
- 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<sup>®</sup>. Components used in the packaging of octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> is administered in a hospital setting by health care professionals.

##### Administration

octaplex<sup>®</sup> should be administered under the supervision of a qualified health professional.

octaplex<sup>®</sup> 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:**



1. If the octaplex<sup>®</sup> 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<sup>®</sup> vial and the WFI vial and clean the rubber stoppers with an alcohol swab.



3. Peel away the lid of the outer package of the Mix2Vial<sup>™</sup> transfer set. Place the WFI vial on an even surface and hold the vial firmly. Take the Mix2Vial<sup>™</sup> together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial<sup>™</sup> 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<sup>™</sup>, being careful to leave the Mix2Vial<sup>™</sup> attached firmly to the WFI vial (Fig. 2).



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



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



**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<sup>®</sup> has been reconstituted, attach a plastic sterile disposable syringe to the transparent part of Mix2Vial<sup>™</sup>. Invert the system and draw the reconstituted octaplex<sup>®</sup> into the syringe.
2. Once the octaplex<sup>®</sup> solution has been transferred into the syringe, firmly hold the barrel of the syringe (keeping it facing down) and detach the Mix2Vial<sup>™</sup> from the syringe. Discard the Mix2Vial<sup>™</sup> (transparent plastic part) and the empty octaplex<sup>®</sup> vial.
3. Disinfect the injection site with an alcohol swab and attach the syringe to a suitable infusion needle. Alternatively, octaplex<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Side effects may include:

- Allergic or allergic-type reactions: early signs include hives, swelling of the face or tongue, injection site reactions, chills, rapid reddening of neck/ facial region, headache, tightness of the chest, wheezing, drop in blood pressure, anxiety, nausea, vomiting, sweating, increased heart rate, 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. 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 fever headache	X	X	X

Very rarely	thromboembolic complications		X	X
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*This is not a complete list of side effects. For any unexpected effects while taking octaplex<sup>®</sup>, 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<sup>®</sup> 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:

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- Report online at [www.healthcanada.gc.ca/medeffect](http://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](http://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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