PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Proctaplex®

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

Coagulation factors (human)

ATC code: B02BD01

Manufactured by:
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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.3 Reconstitution	01/2024
4 Dosage and Administration, 4.4 Administration	01/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

octaplex® (Human Prothrombin Complex) is indicated for:

- The 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.

1.1 Pediatrics

Paediatrics

No data are available to Health Canada for pediatric use.

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.

1.2 Geriatrics

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.

2 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- 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. No clinical data are available for octaplex® for the treatment of bleeding disorders because of liver parenchymal disorders or oesophageal varices or because of major liver surgery therefore octaplex® cannot be recommended in these patients.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Patients being treated with Vitamin K antagonist (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding (see 7 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 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 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 post-operative patients, to neonates, or to patients at risk of thromboembolic events or disseminated intravascular coagulation (see 7 WARNINGS AND PRECAUTIONS).

4.2 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.

Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Table 2 Parenteral Products

Strength	Vial Size	Volume of Solvent to be Added to Vial	Approximate Available Volume	Concentration per mL
500 IU	30 mL	20 mL	20 mL	25 IU/mL FIX
1000 IU	50 mL	40 mL	40 mL	

IU = International units; FIX = Human Coagulation Factor IX

octaplex® is provided with a transfer device for reconstitution of the lyophilized powder in solvent (sterile Water for Injection (sWFI)).

octaplex® is for single use only. Do not re-use any of the components.

Inspect all components for physical integrity prior to use. Do not use products or components that appear damaged or broken.

Reconstitute octaplex® using aseptic technique for the procedure described below.
The product reconstitutes quickly (1 to 5 minutes) at room temperature (20°C to 25°C). As octaplex® contains no preservatives, the solution should be administered immediately after reconstitution, or within 8 hours, provided sterility is maintained. The reconstituted solution can be stored for up to 8 hours at room temperature (20°C to 25°C).

The reconstituted solution should be clear, colourless or 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 preparation and reconstitution:

1. Ensure that the lyophilized powder and solvent vials are at room temperature (20°C to 25°C). This temperature should be maintained during reconstitution. If the octaplex® powder and water for injection (WFI) are not already at room temperature, warm up the closed vials to room temperature. 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 or warming beyond 30°C.

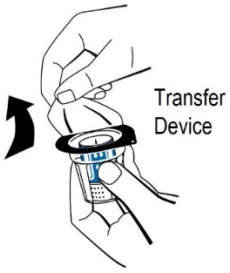

Figure 1

2. Remove the flip caps of the lyophilized powder and solvent vials and disinfect the rubber stoppers with an alcohol swab and allow to dry.

3. Open the transfer device package by peeling off the lid (*Figure 1*). To maintain sterility, do not remove the transfer device from the blister package and do not touch the spike.

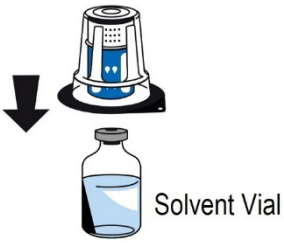

Figure 2

4. Place the solvent vial on a flat, even, clean surface and hold it firmly. Without removing the blister package, place the blue part of the transfer device on top of the solvent vial and press straight and firmly down, in one swift motion, until it snaps into place (*Figure 2*). Do not twist while attaching.

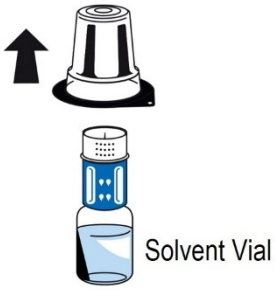

Figure 3

5. While holding onto the solvent vial, carefully remove the blister package from the transfer device by pulling vertically upwards. Make sure to leave the transfer device attached firmly to the solvent vial (*Figure 3*).

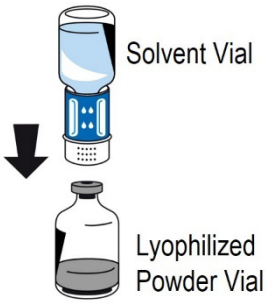

Figure 4

6. Place the lyophilized powder vial on a flat, clean surface and hold it firmly. Take the solvent vial with the attached transfer device and turn it upside down. Place the white part of the transfer device connector on top of the powder vial and press firmly down, in one swift motion, until it snaps into place (*Figure 4*). Do not twist while attaching. The solvent will flow automatically into the powder vial.

Note:

The transfer device must be attached to the solvent vial first and then to the lyophilized powder vial. Otherwise, loss of vacuum occurs, and transfer of the solvent does not take place. If the solvent is not completely transferred to the lyophilized powder vial during this process, contact your blood bank.

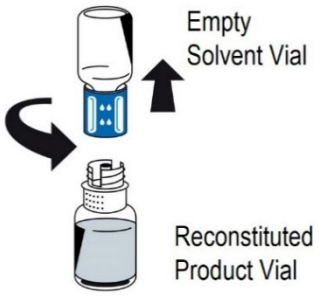

Figure 5

7. With both vials still attached, gently swirl the product vial until the product is fully dissolved. To avoid foam formation, do not shake the vial. octaplex® dissolves quickly at room temperature (20°C to 25°C) and is a clear solution that may be colourless to slightly blue. Unscrew the transfer device counterclockwise into two parts (*Figure 5*). Do not touch the luer lock connector.

8. Dispose of the empty solvent vial together with the blue part of the transfer device.

After reconstitution the solution must 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.

If the same patient is to receive more than one vial, you may pool the contents of multiple vials, provided sterility is maintained. The transfer device is for single use only. Use a separate unused transfer device for the reconstitution of each product vial. Always use the transfer device provided with the product packaging for optimal reconstitution results.

4.4 Administration

Instructions for injection:

octaplex® is for intravenous use after reconstitution only.

Do not mix with other medicinal products. Administer octaplex® through a separate infusion line. The infusion line may be flushed with normal saline or dextrose 5% solution before and after administration of octaplex®.

Instructions for Infusion:

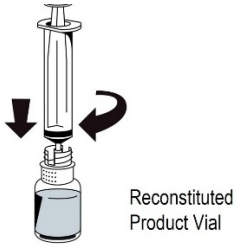

Figure 6

1. Attach a syringe to the luer lock outlet on the white part of the transfer device (*Figure 6*).

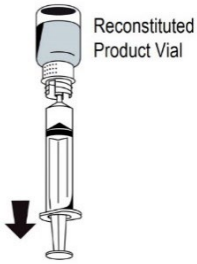

Figure 7

2. Turn the vial upside down and draw the solution into the syringe (*Figure 7*).

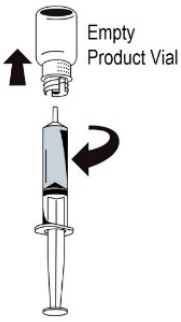

Figure 8

3. Once the solution has been transferred, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and remove the syringe from the transfer device (*Figure 8*).

4. Dispose of the white part of the transfer device together with the empty vial.

5. Attach a suitable administration set to the luer adapter of the syringe.

6. Disinfect the intended injection site appropriately.

7. 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®. No blood should enter the syringe due to the risk of fibrin clot formation.

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

Incompatibilities

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

Shelf-life

octaplex® has a shelf-life of 3 years. Chemical and physical in-use stability has been demonstrated for up to 8 hours at 25°C.
From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Special Precautions for Storage

Do not store above 25°C. Do not freeze. Store in the original package in order to protect from light. Please see 11 STORAGE, STABILITY AND DISPOSAL.

4.5 Missed Dose

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

5 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 the case of an 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To ensure the traceability of biologic products health professionals should record the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3 Dosage Forms, Strengths, Composition and Packaging

<table>
<tr><th>Route of Administration</th><th>Dosage Form / Strength/Composition</th><th>Non-medicinal Ingredients</th></tr>
<tr><td>Intravenous injection</td><td>Powder and solvent for solution for injection/
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)</td></tr>
</table>

Small amounts of the solvent/detergent (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. 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 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 7 WARNINGS AND PRECAUTIONS).

For a list of excipients (non-medicinal ingredients), see Table 3 above.

Nature and contents of container

Powder and solvent for solution for injection.

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).
- Transfer device 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).
- Transfer device with integrated filter.

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

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

This product is prepared from large pools of human plasma. Thus, there is a possibility it may contain causative agents of viral or other undetermined diseases.

General

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. There are no data available regarding the use of octaplex® in pediatric patients.

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.

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; and
- Step C: Nanofiltration.

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

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. 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.

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.

Vascular disorders: There is a risk of thromboembolic episodes following the administration of human prothrombin complex.

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.

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.

Cardiovascular

Thromboembolic events

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.

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, and 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 post-operative 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.

Haematologic

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.

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).

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 an AT concentrate should be given concomitantly if an AT deficiency is present.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of octaplex® for use in human pregnancy and during lactation has not been established in 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.

7.1.2 Breast-feeding

See Pregnant Women section above.

7.1.3 Pediatrics

Pediatrics: No data are available; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In clinical trials 51 out of 90 patients treated with octaplex® were over the age of 65 and 20 were over the age of 75. There is no evidence to suggest that use in the geriatric population is associated with differences in safety or effectiveness.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Parvovirus B19 seroconversions were the most common adverse reaction observed with an incidence rate of 3.3% (3/90) in clinical trials.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Three clinical studies with octaplex® have been conducted (LEX-201, LEX-202 and LEX-203) See section 10.3 and 14.1 for details on the clinical trials. 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.

Table 4 Clinical Trial Adverse Reactions

MedDRA Standard System Organ Class	**Adverse event**	**Severity / Causality**	**No. of episodes**	**No. of episodes/ no. of patients treated with Octaplex (%)**
Nervous system disorders	Headache	Mild / possible	2	2/90 (2.2%)
Vascular Disorders	Hypertension	Mild / possible	1	1/90 (1.1%)
General disorders and administration site conditions	Injection site burning	Mild / possible	1	1/90 (1.1%)
Investigations	Hepatic Function Abnormal	Mild / possible	1	1/90 (1.1%)
	Parvovirus B19 serology positive	Mild / possible	3	3/90 (3.3%)

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

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

Relative Frequency of Adverse Drug Reactions

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

8.3 Less Common Clinical Trial Adverse Reactions

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 (haematocrit, 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.

8.5 Post-Market Adverse 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 a listed/expected adverse experience.

9 DRUG INTERACTIONS

9.2 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 medications during injection.

9.3 Drug-Behavioural Interactions

No drug behavioural interactions are known.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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.

10 CLINICAL PHARMACOLOGY

10.1 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. 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 pancreatic disorders, persisting diarrhoea, or massive antibiotic therapy.

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.

10.2 Pharmacodynamics

octaplex® contains in addition to FII, FVII, FIX and FX therapeutically effective concentrations of PC and PS, inhibitory enzymes of the coagulation pathway. 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®.

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.

10.3 Pharmacokinetics

Table 5 Summary of patient demographics for clinical trials in congenital deficiency of the prothrombin complex coagulation factors

Study #	study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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

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. 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 of treatment with octaplex®. One 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 6 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.

Table 7 Plasma half-life ranges

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).

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.

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.

11 STORAGE, STABILITY AND DISPOSAL

Store the product between 2°C to 25°C. Do not freeze.

Protect from exposure to light.

Unopened vials have a shelf-life of up to 3 years. 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.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 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 – 6 DOSAGE FORMS; STRENGTHS, 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 3 octaplex® is manufactured by chromatographic purification of cryo-poor plasma. Two specific viral inactivation steps, and a viral removal step are included in the manufacturing process (see 13 PHARMACEUTICAL INFORMATION). The plasma used for the manufacture of octaplex® 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® is made from a maximum of 2,000 kg of Cryo-poor 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 complies 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® is tested for HCV and Parvovirus B19 by PCR 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 13 PHARMACEUTICAL INFORMATION);

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-step 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).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Acquired Deficiency of the Prothrombin Complex Coagulation Factors

Table 8 Summary of patient demographics for clinical trials in acquired deficiency of the prothrombin complex coagulation factors

Study #	study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
LEX-202	Prospective, non-randomised, non-controlled, open-labelled, multi-centre study	single IV doses of 14 to 44 IU FIX/kg	n=20 anticoagulated patients with major bleeds or emergency surgery	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 anti-coagulated patients undergoing surgical interventions	67.1 (24-93)	33 male; 27 female

IV= intravenous

Efficacy and safety of octaplex® were assessed in two multicentre studies (LEX-202 and LEX-203). In total, 80 anticoagulated patients were enrolled who were suffering from major bleeds or who had to undergo emergency surgery. The studies used an open design and no control group.

Efficacy

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 indandione 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.

14.4 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.

All patients in study LEX-201, except patients no. 05 (no post-injection result) and 08 (only the 3-month follow-up result available), have been tested for Inhibitor activity by Bethesda assay at baseline and at 3 and 6 months. All patients were tested negative for these markers at all occasions.

16 NON-CLINICAL 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.

In a local tolerance study in rabbits (New Zealand White), octaplex® demonstrated excellent tolerability for intravenous infusion, the route of administration intended for clinical use. In animal experiments in rabbits (New Zealand White), octaplex® did not show any thrombogenic effects.

The excipients are porcine heparin and sodium citrate (Ph. Eur/USP). Considering the low concentration of these excipients, they are not expected to cause adverse effects following slow intravenous infusion of octaplex®.

octaplex® contains residual amounts of tri-n-butyl phosphate (TNBP; ≤ 5 µg/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. A pharmacokinetic animal study shows that negligible amounts of TNBP are expected in human plasma. Based on the results of animal toxicity studies following single and repeated intravenous administration, a therapeutic window (ratio) for humans of at least 290 can be calculated. Studies in rats and rabbits showed that TNBP has no teratogenic effects.

In summary, from a toxicological perspective, there are no restrictions on the safe use of octaplex®.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

octaplex®
Human Prothrombin Complex

Read this carefully before you start taking octaplex® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about octaplex®.

Serious Warnings and Precautions
As you are treated with Vitamin K antagonist (VKA) therapy you have an underlying disease state that predispose you to thromboembolic events especially if you have a history of thromboembolic events. Your doctor should carefully consider resumption of anticoagulation as soon as the risk of thromboembolic events outweighs the risk of acute bleeding (see WARNINGS AND PRECAUTIONS - Cardiovascular). 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).

What is octaplex® 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.

How does octaplex® work?
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.

What are the ingredients in octaplex®?
Medicinal ingredients:
Human Coagulation Factor II, VII, IX and X, and Proteins C and S.

Non-medicinal ingredients:
Heparin, sodium citrate, solvent (Water for Injection)

octaplex® comes in the following dosage forms:
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 20mL/40 mL of solvent and a transfer device with integrated filter.

Do not use octaplex® if:
- if you are allergic to the drug or one of the ingredients of this product (listed in section 6).

- if you are allergic to heparin or if heparin has ever caused a reduction in the level of platelets in your blood.
- if you have IgA deficiency with known antibodies against IgA.
- if you recently had a heart attack, or have a high risk of blood clots, or if you have coronary artery disease, or chronic liver disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take octaplex®. Talk about any health conditions or problems you may have, including:

- 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; or
- You are allergic to the active substance or to any of the nonmedicinal ingredients.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with octaplex®:
There is no known drug interaction to octaplex®.

How to take octaplex®:
ocataplex® should be administered under the supervision of a qualified Health Care Professional. Your Health Care Professional will prepare octaplex® for intravenous administration.
Any unused product or waste material should be disposed of immediately in accordance with local requirements.

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

If you think you, or a person you are caring for, have taken too much octaplex®, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using octaplex®?
These are not all the possible side effects you may have when taking octaplex®. If you experience any side effects not listed here, tell your healthcare professional.
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.

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.

There is a risk of blood clots in your vessels.

Increase of body temperature has been observed.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
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.

If you want more information about octaplex®:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.octapharma.ca, or by calling 1-888-438-0488.

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