SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Octaplex 500 IU
powder and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Octaplex 500 IU is presented as a powder and solvent for solution for infusion containing human prothrombin complex. Octaplex 500 IU nominally contains:

Name of ingredient	**Octaplex 500 IU Quantity per vial (IU)**	**Octaplex 500 IU Quantity after reconstitution with 20 ml of Water for Injections (IU/ml)**
Active substances		
Human coagulation factor II	280 - 760	14 - 38
Human coagulation factor VII	180 - 480	9 - 24
Human coagulation factor IX	500	25
Human coagulation factor X	360 - 600	18 - 30
Further active ingredients		
Protein C	260 - 620	13 - 31
Protein S	240 - 640	12 - 32

The total protein content per vial is 260 - 820 mg. The specific activity of the product is ≥ 0.6 IU/mg proteins, expressed as factor IX activity.

Excipients known to have a recognised action or effect: sodium (75 - 125 mg per vial), heparin (100 - 250 IU per vial, corresponding to 0.2 - 0.5 IU/IU FIX).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.
The powder is white or slightly colored
powder or friable solid, very hygroscopic .
The solvent is a clear and colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- 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.

- Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor product is not available.

4.2 Posology and method of administration

Posology

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 (see section 5.2). 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).

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.

Initial INR	2 – 2.5	2.5 – 3	3 – 3.5	> 3.5
Approximate dose* (mL Octaplex 500 IU /kg body weight)	0.9 –1.3	1.3 – 1.6	1.6 – 1.9	> 1.9

*The single dose should not exceed 3000 IU (120 mL Octaplex 500 IU).

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 during treatment is mandatory.

Bleeding and perioperative prophylaxis in congenital deficiency of the vitamin K dependent coagulation factors II and X when specific coagulation factor product is not available:

The calculated required dosage for treatment is based on the empirical finding that approximately 1 IU of factor II or X per kg body weight raises the plasma factor II or X activity by 0.02 and 0.017 IU/mL, respectively.

The dose of a specific factor administered is expressed in International Units (IU), which are related to the current WHO standard for each factor. The activity in plasma of a specific coagulation factor is expressed either as a percentage (relative to normal plasma) or in International Units (relative to the international standard for the specific coagulation factor).

One International Unit (IU) of a coagulation factor activity is equivalent to the quantity in one mL of normal human plasma.

For example, the calculation of the required dosage of factor X is based on the empirical finding that 1 International Unit (IU) of factor X per kg body weight raises the plasma factor X activity by 0.017 IU/mL. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor X rise (IU/mL) x 59

where 59 (mL/kg) is the reciprocal of the estimated recovery.

Required dosage for factor II:

Required units = body weight (kg) x desired factor II rise (IU/mL) x 50

If the individual recovery is known, that value should be used for calculation.

Method of administration
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Octaplex 500 IU must be administered intravenously. The infusion should start at a speed of 1 mL per minute, followed by 2-3 mL per minute, using an aseptic technique.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergy to heparin or history of heparin induced thrombocytopenia.
- Individuals who have IgA deficiency with known antibodies against IgA.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of the vitamin K dependent coagulation factors (e.g. as induced by treatment with vitamin K antagonists), Octaplex 500 IU 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.

If allergic or anaphylactic-type reactions occur, the infusion should be stopped immediately. In case of shock, standard medical treatment for shock should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses.

Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

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) and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

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

It is strongly recommended that every time Octaplex 500 IU 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.

There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency are treated with human prothrombin complex particularly with repeated dosing. 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, 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.

No data are available regarding the use of Octaplex 500 IU in case of perinatal bleeding due to vitamin K deficiency in the new-born.

Octaplex 500 IU contains 75 – 125 mg sodium per vial, equivalent to 3.8 – 6.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

In congenital deficiency of any of the vitamin K dependent factors, specific coagulation factor product should be used when available.

4.5 Interaction with other medicinal products and other forms of interaction

Human prothrombin complex products neutralise the effect of vitamin K antagonist treatment, but no interactions with other medicinal products are known.

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.

4.6 Fertility, pregnancy and lactation

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

Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of Safety Profile

Replacement therapy may 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.

Allergic or anaphylactic-type reactions may rarely occur (≥ 1/10,000 to < 1/1,000) including severe anaphylactic reactions.

Increase in body temperature has been observed very rarely (<1/10,000).

There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see section 4.4).

Tabulated list of adverse reactions of Octaplex

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been based on clinical trial data, according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) or not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	Adverse reactions	Frequency
Psychiatric Disorders	Anxiety	uncommon
Vascular disorders	Deep vein thrombosis	common
	Thrombosis	uncommon
	Hypertension	uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	uncommon
	Bronchospasm	uncommon
	Hemoptysis	uncommon
	Epistaxis	uncommon
General disorders and administration site conditions	Injection site burning	uncommon
Investigations	Fibrin D-dimer increased	uncommon
	Blood thrombin increased	uncommon
	Hepatic Function Abnormal	uncommon
Injury, poisoning and procedural complications	Thrombosis in device	uncommon

The following adverse reactions have been reported during post-marketing use of Octaplex 500 IU. Because post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not possible to reliably estimate the frequency of these reactions.

Immune system disorders Anaphylactic shock, hypersensitivity
Nervous system disorders Tremor
Cardiac disorders Cardiac arrest, tachycardia
Vascular disorders Circulatory collapse, hypotension
Respiratory, thoracic and mediastinal disorders Dyspnoea, respiratory failure
Gastrointestinal disorders Nausea
Skin and subcutaneous tissue disorders Urticaria, rash
General disorders and administration site conditions Chills

Octaplex 500 IU 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 500 IU must be stopped immediately in patients showing this allergic reaction. These patients must not receive heparin containing medicinal products in the future.

For safety with respect to transmissible agents, see 4.4.

Paediatric population
No data is available regarding the use of Octaplex in paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factors IX, II, VII, and X in combination, ATC code: B02BD01.

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.

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.

Isolated severe deficiency of factor VII leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis. Isolated deficiency of factor IX is one of the classical haemophilias (haemophilia B). Isolated deficiency of factor II or factor X is very rare but in severe form they cause a bleeding tendency similar to that seen in classical haemophilia.

Acquired deficiency of the vitamin K dependent 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 dependent 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 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.

5.2 Pharmacokinetic properties

The plasma half-life ranges are:

Coagulation factor	half-life
Factor II	48 - 60 hours
Factor VII	1.5- 6 hours
Factor IX	20 - 24 hours
Factor X	24 - 48 hours

Octaplex 500 IU is administered intravenously and therefore immediately available in the organism.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Heparin: 5-12.5 IU/ml
sodium citrate

Solvent:
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 8 hours at +2°C to +25°C.

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at 2°C to 25°C.
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

One package of Octaplex 500 IU contains:

- Powder in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 20 mL of Water for Injections in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 1 Nextaro® transfer device.

6.6 Instructions for use , handling and disposal

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 clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.

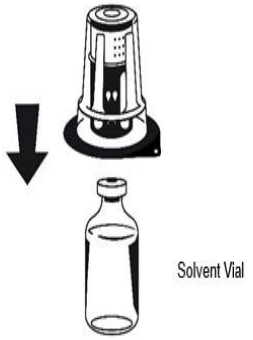
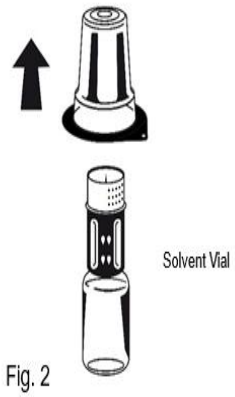
After reconstitution the solution must be used immediately.

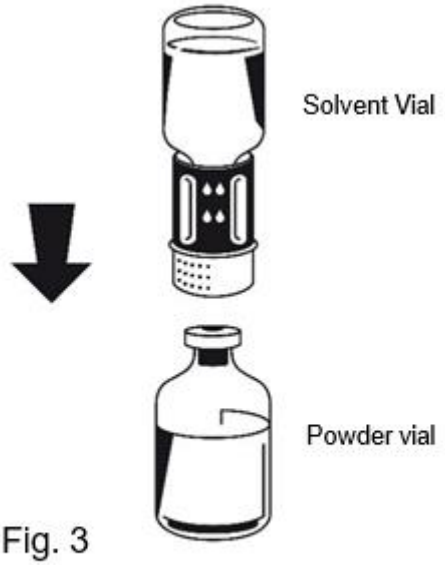
Any unused product or waste material should be disposed of in accordance with local requirements.

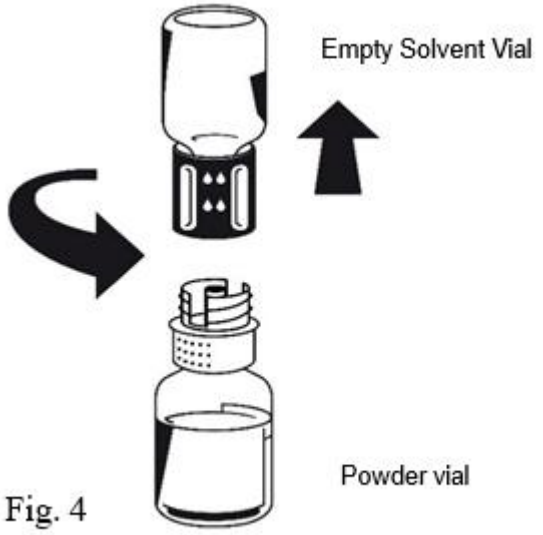
Instructions for reconstitution:

1. If necessary, allow the solvent (Water for Injections) and the powder in the closed vials to reach room temperature. This temperature should be maintained during reconstitution.
   If a water bath is used for warming, care must be taken to avoid water coming into contact with the rubber stoppers or the caps of the vials. The temperature of the water bath should not exceed 37°C.

2. Remove the flip off caps from the powder vial and the solvent vial and disinfect the rubber stoppers appropriately.

3. Peel away the lid of the outer package of the Nextaro®. Place the solvent vial on an even surface and hold it firmly. Without removing the outer package, place the blue part of the Nextaro® on top of the solvent vial and press firmly down until it snaps (Fig. 1). Do not twist while attaching! While holding onto the solvent vial, carefully remove the outer package from the Nextaro®, being careful to leave the Nextaro® attached firmly to the solvent vial (Fig. 2).	 Fig. 1  Fig. 2

4. Place the powder vial on an even surface and hold it firmly. Take the solvent vial with the attached Nextaro® and turn it upside down. Place the white part of the Nextaro® connector on top of the powder vial and press firmly down until it snaps (Fig. 3). Do not twist while attaching! The solvent flows automatically into the powder vial.	 Fig. 3

5. With both vials still attached, gently swirl the powder vial until the product is dissolved. Octaplex 500 IU dissolves quickly at room temperature to a colourless to slightly blue solution. Unscrew the Nextaro® into two parts (Fig. 4). Dispose the empty solvent vial with the blue part of the Nextaro®.	 Fig. 4

If the powder fails to dissolve completely or an aggregate is formed, do not use the preparation.

<u>Instructions for infusion:</u>

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

1. Attach a 20 ml syringe to the luerlock outlet on the white part of the Nextaro®. Turn the vial upside down and draw the solution into the syringe.

Once the solution has been transferred, firmly hold the plunger of the syringe (keeping it facing down) and remove the syringe from the Nextaro®. Dispose the Nextaro® and the empty vial.

2. Disinfect the intended injection site appropriately.

3. Inject the solution intravenously at a slow speed: Initially 1 ml per minute, not faster than 2 - 3 ml per minute.

No blood must flow into the syringe due to the risk of formation of fibrin clots. The Nextaro® is for single use only.

7. NAME AND ADDRESS OF PHARMACEUTICAL COMPANY

7.1 Manufacturer

OCTAPHARMA AG, SEIDENSTRASSE 2, CH-8853 LACHEN, SWITZERLAND

7.2 Registration holder

Dover Medical & Scientific Equipment Ltd.,
11 Hamaalot St.,
Herzliya 46583, Israel

8. MARKETING AUTHORISATION NUMBER

138 74 31775 00

Revised in December 2022 according to MoH's guidelines.