APPROVED PROFESSIONAL INFORMATION FOR OCTAPLEX® 500 IU

SCHEDULING STATUS S4

1. NAME OF MEDICINE

OCTAPLEX® 500 IU (Powder and solvent for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OCTAPLEX is presented as a powder and solvent for solution for infusion containing human prothrombin complex**. OCTAPLEX** nominally contains**:**

Name of ingredient	**OCTAPLEX Quantity per vial (IU)**	**OCTAPLEX 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:

- tri-sodium citrate dehydrate**:** 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

OCTAPLEX consists of a bluish-white lyophilised powder and a clear, colourless solvent (water for injection) for reconstitution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OCTAPLEX is indicated for:

- treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.
- treatment of bleeding and perioperative prophylaxis in congenital deficiency of the vitamin K dependent coagulation factors II and X 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 **OCTAPLEX**. 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 (International Normalised Ratio) 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**/ kg body weight)	0,9 – 1,3	1,3 – 1,6	1,6 – 1,9	> 1,9

* Multiple doses are allowed if the INR is not corrected to the desired level with a previous dose.

The single dose should not exceed 3 000 IU (120 ml **OCTAPLEX**). The INR should be monitored after each dose. 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

OCTAPLEX should 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.

Full instructions for reconstitution are provided in section 6.6.

4.3 Contraindications

OCTAPLEX is contraindicated in:

- patients with hypersensitivity to the active substance or any of the excipients or residues of the manufacturing process in **OCTAPLEX.**
- patients with 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

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** 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.

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

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.

Viral safety:

Standard measures to prevent infections resulting from the use of **OCTAPLEX,** medicine prepared from human blood or plasma are implemented.

The standard measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

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

Appropriate vaccination (e.g. against HBV and HAV) for patients in regular receipt of medicinal products derived from human blood or plasma such as **OCTAPLEX s**hould be considered.

There is a risk of thrombosis or disseminated intravascular coagulation when patients are treated with human prothrombin complex particularly with repeated dosing Patients given **OCTAPLEX** should be observed closely for signs or symptoms of intravascular coagulation or thrombosis. Because of the risk of thrombo-embolic complications, close monitoring should be exercised when administering **OCTAPLEX** to:

- patients with a history of coronary heart disease,
- patients with liver disease,

- peri- or postoperative patients,
- neonates or
- 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.
In patients with disseminated intravascular coagulation, it may, under certain circumstances, be necessary to substitute the coagulation factors of the prothrombin complex. This substitution may, however, only be carried out after termination of the consumptive state by appropriate means.

Reversing vitamin K antagonists exposes patients to the thromboembolic risk of the underlying disease. Resumption of anticoagulation should be carefully considered as soon as possible.
No data are available regarding the use of **OCTAPLEX** in case of perinatal bleeding due to vitamin K deficiency in the new-born.

OCTAPLEX contains 75 - 125 mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other medicines and other forms of interaction

OCTAPLEX products neutralises the effect of vitamin K antagonist treatment. 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 **OCTAPLEX**, the heparin as a constituent of the **OCTAPLEX** must be taken into account.

4.6 Fertility, pregnancy and lactation

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

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

Clinical studies/trials reported side effects

Side effects observed with the highest frequency in clinical trials were hypersensitivity and allergic type of reactions even though observed only rarely.

Immune system disorders:

Hypersensitivity or allergic type of reactions (which may include angioedema, injection site reactions, chills, flushing, urticaria, headache, changes in blood pressure, anxiety, nausea, vomiting, sweating, tachycardia, dyspnoea, or bronchospasm) may rarely occur (≥ 1/10 000 to < 1/1 000). In some cases, these reactions may progress to severe anaphylaxis.

Vascular disorders:

There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see "**4.4 Special warnings and precautions for use**").

Investigations:

A transient increase in liver transaminases has been rarely observed (≥ 1/10 000 to < 1/1 000).

Post-marketing reported side effects:

The following adverse reactions have been reported during post-marketing use of **OCTAPLEX**. 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.

Adverse Reactions Reported During 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 events[$], 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

Fever, chills

[$] Including myocardial infarction, cerebral infarction, ischemic stroke, (pulmonary) embolism, deep vein thrombosis, peripheral thrombosis or ischemia.

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 showing this allergic reaction. These patients must not receive heparin containing medicinal products in the future.

The lack of effect is generally considered a listed/ expected adverse experience for any drug. Cases of lack of effect have been reported for **OCTAPLEX.**

Replacement therapy may rarely (≥ 1/10 000 to < 1/1 000) 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Adverse drug reaction and product quality reporting form, found online under SAHPRA's E-Services: https://www.sahpra.org.za/ e-Library/GLF-CEM PV-06A.

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

A 30.3 Biologicals (Blood fractions)

Pharmacotherapeutic group: antihaemorrhagics, 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.

The 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. 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.

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Heparin: 0.2 – 0.5 IU/IU FIX

Tri-sodium citrate dihydrate

Solvent:

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf-life

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.

6.4 Special precautions for storage

*Powder and solvent***:** Store at or below 25 °C. Do not freeze. Store in the original package in order to protect from light.

Reconstituted solution: can be stored for 8 hours at or below 25 °C.

6.5 Nature and contents of containers

One package of OCTAPLEX contains:

- Powder in a clear and colourless 30 ml vial (type I glass) with a grey stopper (halobutyl rubber) and a blue flip off cap (aluminium).
- Solvent (water for injection) in a colourless 20 ml vial (type I or type II glass) with a grey stopper (halobutyl rubber) and a blue flip off cap (aluminium)
- 1 Transfer set

6.6 Special precautions for disposal and other handling

Please read all the instructions and follow them carefully.

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 **OCTAPLEX** 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 cap from the powder vial and the solvent vial and disinfect the rubber stopper 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).

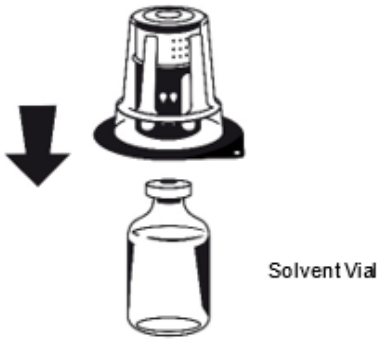


Fig. 1

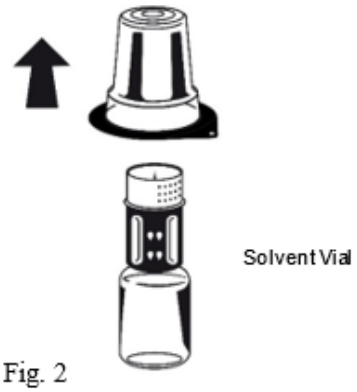


Fig. 2

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.

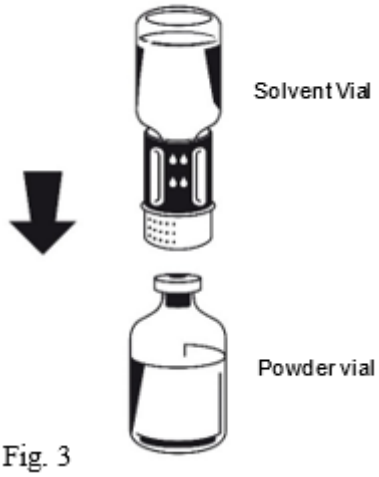


Fig. 3

5. With both vials still attached, gently swirl the powder vial until the product is dissolved. OCTAPLEX 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®.

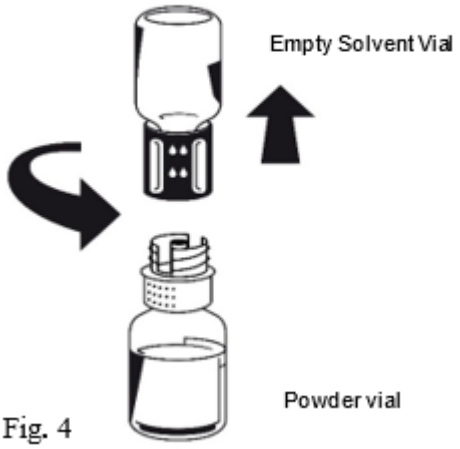


Fig. 4

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

Instructions for infusion:

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 luer lock 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. HOLDER OF CERTIFICATE OF REGISTRATION

OCTAPHARMA SA (Pty) Ltd.

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8. REGISTRATION NUMBER

52/30.3/0357

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Authorisation: 24 March 2020

Renewal: 26 November 2025

10. DATE OF REVISION OF THE TEXT

08 February 2026