SUMMARY OF PRODUCT CHARACTERISTICS
(INSTRUCTIONS FOR USE)

1. NAME OF THE MEDICINAL PRODUCT

Octaplex 500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Octaplex is presented as a powder and solvent for solution for injection 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: sodium (75 - 125 mg per vial), heparin (100 - 250 IU per vial, corresponding to 0.2 - 0.5 IU/IU FIX).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white or slightly coloured.
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.

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/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.

Method of administration
Dissolve the product as described at 6.6. 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- 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 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, other pathogens and theoretically to Creutzfeld-Jacob Desease (CJD) agents.

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

It is strongly recommended that every time 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 (hepatitis A and B) is recommended for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.

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.

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 medicinal products and other forms of interactions

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 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

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 section 4.4).

Investigations:

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

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.

For safety with respect to transmissible agents, see 4.4.

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.

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.

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.

Efficacy in Clinical Studies

Study demographics and trial design

Five clinical studies with octaplex® have been conducted. In total, 349 patients have been enrolled and the patients received a total of about 993,000 IU of octaplex®.

Summary of Patient Demographics for Clinical Trials LEX-201, LEX-202, LEX-203, LEX-205 and LEX-206

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n =number)**	**Mean age (Range)**	**Gender**
LEX-201	Prospective, non-randomised, non-controlled, open-labelled, multi-centre study	single or multiple IV doses of 26 IU FIX/kg (median dose/exposure day)	haemophilia B: n=6 FVII deficiency: n=4	20.6 (11-67)	10 male
LEX-202	Prospective, non-randomised, non-controlled, open-labelled, multi-centre study	single IV doses of 14 to 44 IU FIX/kg	n=20	68.0 (43-83)	11 male 9 female
LEX-203	Prospective, non-randomised, open-labelled, multi-centre study	single or multiple IV doses over a few days, median dose at first infusion was 41 IU FIX/kg	n = 60	67.1 (24-93)	33 male 27 female
LEX-205	Prospective, randomised, active-controlled, multi-centre study	single IV infusion of either octaplex dose (mL/kg = $\ln(INR_0/1.4) / 0.52$) or FFP dose	Overall: n = 200 octaplex: n = 97 FFP: n = 103	Overall: 66.6 (18-98) octaplex: 65.5 (29-89) FFP: 67.6 (18-98)	137 male 63 female
LEX-206	Prospective, randomised, open-labelled, multi-centre study	single IV dose of either 25 IU FIX/kg or 40 IU FIX/kg	n = 59	76.4 (49-92)	42 male 17 female

Overall 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 indandion type in patients affected by bleeding episodes or in patients undergoing surgical interventions could be reversed fast and effectively: PT was raised within 10 to 30 minutes significantly to around 55% and the INR was reduced in the same time period to about 1.5. Recovery, as another marker for efficacy, was approximately 1.1 to 1.7% IU/kg BW for FII, FIX, FX, PC, and PS (total and free); for FVII recovery was 0.7% IU/kg BW.

In LEX-203, the clinical efficacy of octaplex® administered in appropriate doses was demonstrated conclusively: 51 of 56 patients who finished the study according to protocol showed a clinical response as pre-defined by the study protocol. Furthermore, 4 of those patients who were considered as non-responders based on the protocol definition can be regarded as responders from a clinical point of view, as the difference between expected and actual PT value was only minimal and the clinical efficacy of treatment with octaplex® was assessed as excellent. Even in the remaining patient the clinical response was adequate. All patients in LEX-203 showed an excellent clinical response, in particular, no complications during surgeries caused by uncontrollable bleedings have been observed after octaplex® treatment.

In LEX-205, the non-inferiority of octaplex® in comparison with fresh frozen plasma (FFP) was demonstrated. During the entire study, INR response (i.e. correction of patient's INR to <1.5, 15 minutes after the end of first infusion) was achieved by 74 of 97 (76%) octaplex®-treated patients and by 31 of 103 (30%) FFP-treated patients.

Non-inferiority of octaplex® could also be shown for the second co-primary variable, i.e. the number of units (mean ± SD) of red blood cells (RBC) transfusion required. For the 41 octaplex®-treated patients 0.4 ± 2.4 RBC units and for the 42 FFP-treated patients 0.3 ± 0.8 RBC units were needed, in the period up to the interim analysis. In the subsequent period, 0.2 ± 0.5 RBC units were required for 56 octaplex®-treated patients and 0.0 ± 0.1 units for 61 FFP-treated patients, again supporting non-inferiority of octaplex® in comparison with FFP. Superiority of octaplex® over FFP could be demonstrated for secondary endpoints, such as the mean changes in prothrombin time and in levels of FII, FVII, FIX and FX. The safety assessment did not reveal any overall difference in safety between the two treatments or raise any concern about the safety of the treatment with octaplex®.

In LEX-206, octaplex® infusion resulted in rapid reversal of INR in all patients with intracranial haemorrhage. The high octaplex® dose (40 IU/kg) brought a benefit over the standard dose in terms of amplitude of INR decrease within the first 10 minutes after infusion. Haematoma volume, clinical status, global outcome, overall clinical response, and quality of life were similar between the high dose and the standard dose of Octaplex administered. The mean infusion speed applied in the study was 14 mL/min (range 4-43). As expected, infusion speed did not impact its efficacy.

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

5.2 Pharmacokinetic properties

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

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

	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](Cmax-C0) x (body weight)/dose [2](Cmax –C0) 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.

The plasma half-life ranges are:

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

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

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: 0.2 – 0.5 IU/IU FIX
Sodium citrate

Solvent:
Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years
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.

6.4 Special precautions for storage

Store at or below 30°C.
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

One package of Octaplex is available in two presentations and contains:

Presentation 1:
- 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 or type II glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 1 transfer set Nextaro®

Presentation 2:
- 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 or type II glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 1 Transfer set (1 double-ended needle and 1 filter needle)
- 1 Disposable syringe
- 1 Infusion set
- 2 Alcohol swabs

6.6 Instructions for use and 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.

Presentation 1:

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).

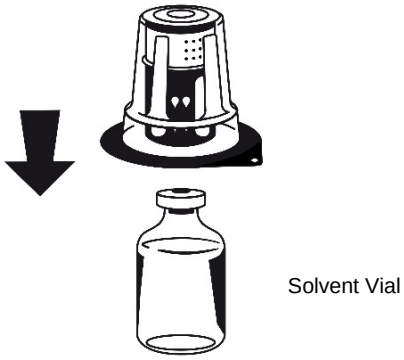


Fig. 1

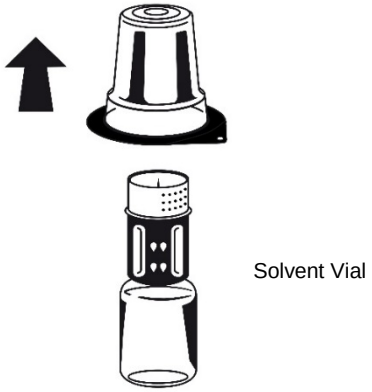
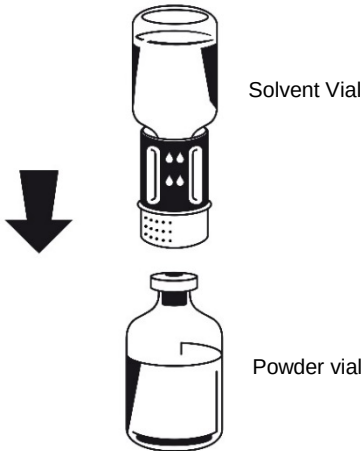


Fig. 2

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.



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®.

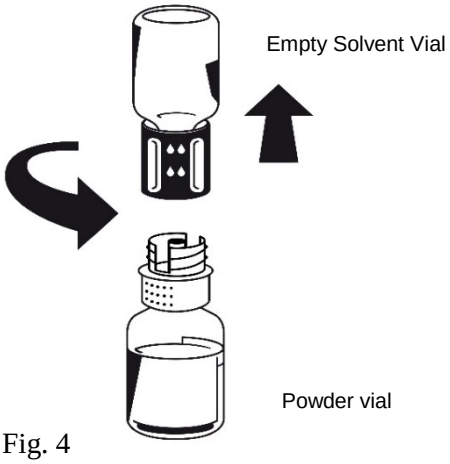


Fig. 4

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

Instructions for injection:

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

1. Attach a 20 mL (500 IU) 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.

Presentation 2:

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 caps from the powder vial and the water vial and clean the rubber stoppers with an alcohol swab.
3. Remove the protective cover from the short end of the double-ended needle, making sure not to touch the exposed tip of the needle.
   Then perforate the centre of the water vial rubber stopper with the vertically held needle.
   In order to withdraw the fluid from the water vial completely, the needle must be introduced into the rubber stopper in such a way that it just penetrates the stopper and is visible in the vial.
4. Remove the protective cover from the other, long end of the double-ended needle, making sure not to touch the exposed tip of the needle.
   Hold the water vial upside-down above the upright powder vial and quickly perforate the centre of the powder vial rubber stopper with the needle. The vacuum inside the powder vial draws in the water.
5. Remove the double-ended needle with the empty water vial from the powder vial, then slowly rotate the powder vial until it is completely dissolved. Octaplex dissolves quickly at room temperature to a colourless to slightly blue solution.

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. After the powder has been reconstituted in the manner described above, remove the protective cover from the filter needle and perforate the rubber stopper of the powder vial.
2. Remove the cap of the filter needle and attach a 20 ml syringe.
3. Turn the vial with the attached syringe upside-down and draw up the solution into the syringe.
4. Disinfect the intended injection site with an alcohol swab.
5. After removing the filter, inject the solution intravenously at a slow speed: Initially 1 ml per minute, not faster than 2 - 3 ml per minute**.**

The filter needle is for single use only. Always use a filter needle when drawing up the preparation into a syringe. No blood must flow into the syringe due to the risk of formation of fibrin clots.

7. NAME AND ADDRESS OF PHARMACEUTICAL COMPANY

7.1 Marketing Authorisation Holder

Wellchem Pharmaceuticals Pte Ltd
221, Henderson Road #04-15
Singapore 159557

7.2 Manufacturers

- Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna, Austria
- Octapharma S.A.S., Lingolsheim, France

8. DATE OF REVISION OF THE TEXT

Date of last revision: 13.07.2020