PROFESSIONAL INFORMATION FOR OCTANINE® F

Scheduling status | S4 |

Proprietary name (and dosage form)

OCTANINE® F 250 (powder and solvent for solution for injection)

OCTANINE® F 500 (powder and solvent for solution for injection)

OCTANINE® F 1000 (powder and solvent for solution for injection)

Composition per vial

OCTANINE® F 250: Contains 250 IU human coagulation factor IX and 25 IU heparin per vial corresponding to approximately 2 mg protein.

It is to be reconstituted with the supplied 5 ml water for injection (Ph. Eur.), then containing approximately 50* IU factor IX/ ml.

OCTANINE® F 500: Contains 500 IU human coagulation factor IX and 50 IU heparin per vial corresponding to approximately 4 mg protein.

It is to be reconstituted with the supplied 5 ml water for injection (Ph. Eur.), then containing approximately 100* IU factor IX/ ml.

OCTANINE® F 1000: Contains 1 000 IU human coagulation factor IX and 100 IU heparin per vial corresponding to approximately 8 mg protein.

It is to be reconstituted with the supplied 10 ml water for injection (Ph. Eur.), then containing approximately 100* IU factor IX/ ml.

*according to current WHO-standard.

The potency is determined using the European Pharmacopoeia (Ph. Eur.) one stage clotting test. The specific activity of **OCTANINE® F** is approximately ≥ 50 IU/mg protein.

OCTANINE® F does not contain any microbial or preserving agents.

Other ingredients

Powder: heparin (≤ 0,15 IU/IU F IX per 1 ml), sodium chloride, sodium citrate, arginine hydrochloride and lysine hydrochloride.

Solvent: water for injection (Ph. Eur.).

Pharmacological classification

A 30.3 Biologicals (Blood fractions)

Pharmacological action

Pharmacodynamics

Pharmacotherapeutic group: antihaemorrhagics: blood coagulation factor IX - ATC-code: B02BD04.

Factor IX is a single chain glycoprotein with a molecular mass of about 68 000 Dalton. It is a vitamin K dependent coagulation factor that is synthesised in the liver.

Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results immediately in the conversion of prothrombin into thrombin, which then converts fibrinogen into fibrin and a clot is formed.

Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma level of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Pharmacokinetics

For **OCTANINE® F** the following results were achieved in pharmacokinetic study with 13 haemophilia B patients over 12 years of age (mean age 28 years, range 12 – 61 years).

N = 13	***Median***	***Mean***	***SD***	***Minimum***	***Maximum***
Incremental Recovery (IU x dl^{-1} x IU^{-1} x kg)	1,2	1,3	0,5	0,8	2,4
AUC$_{norm}$ (IU x dl^{-1} x h x IU^{-1} x kg)	32,4	37,7	13,0	24,5	64,0
Half-life (h)	27,8	29,1	5,2	22,0	36,8
MRT (h)	39,4	40,0	7,3	30,2	51,6
Clearance (ml x h^{-1} x kg)	3,1	2,9	0,9	1,6	4,1

AUC = area under curve

MRT = mean residence time

SD = Standard deviation

The incremental recovery was also tested in a second study. The meta-analysis of all recovery assessments (n = 19) resulted in a mean recovery of 1,1 IU x dl-1 x IU-1 x kg. There was no difference in incremental recovery when tested after three and six month's treatment.

Indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

Contraindications

OCTANINE® F is contraindicated in patients with

- hypersensitivity to the active substance or to any of the excipients of OCTANINE® F
- known allergy related reduction of thrombocytes during heparin treatment (heparin induced thrombocytopenia [HIT] type II)

Warnings and Special precautions

Hypersensitivity:

Allergic type hypersentivity reactions are possible with **OCTANINE® F**. It contains traces of human proteins other than factor IX and heparin (see **"Contraindications"** and **"Side effects"**).

OCTANINE® F should be discontinued immediately, if symptoms of hypersensitivity occur and the physician should be contacted. Patients should be informed of early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis (see **"Side-effects"**).

In case of shock, the standard medical treatment for shock should be implemented.

Inhibitors:

After repeated treatment with **OCTANINE® F**, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

There have been reports in literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor (see **"Side effects"**). It should be noted that patients with factor IX inhibitors might be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX concentrates, the initial administration of **OCTANINE® F** should, according to the treating physician's judgement, be performed under medicinal observation where adequate medical care for allergic reactions could be provided.

Thromboembolism:

Because of the potential risk of thromboembolic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with

appropriate biological testing when administrating **OCTANINE® F** to:

- patients with liver disease,
- patients post-operatively,
- neonates or
- patients at risk of thrombotic phenomena or disseminated intravascular coagulation (DIC).

In each of these situations, the benefit of treatment with **OCTANINE® F** should be weighed against the risk of these complications.

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Transmissible agents

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), and for the non-enveloped hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) (see **"Pregnancy and lactation"**) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/ repeated receipt of human plasma-derived factor IX concentrates.
It is strongly recommended that every time that **OCTANINE® F** 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.

Patients on a controlled sodium diet:

OCTANINE® F contains up to 3 mmol (or 69 mg) sodium for 1 vial **OCTANINE® F 250** or **500** and up to 6 mmol (or 138 mg) sodium for 1 vial **OCTANINE® F 1000** per dose. It has to be taken into consideration by patients on a controlled sodium diet.

Paediatric population

The listed warnings and precautions apply both to adults and children.

Effects on ability to drive and use machines

OCTANINE® F has no influence on the ability to drive and use machines.

Interactions

No interactions of human coagulation factor IX concentrate (OCTANINE® F) with other medicinal products are known.

Incompatibilities

OCTANINE® F must not be mixed with other medicinal products.

Only the provided injection/treatment human infusion sets should be used because treatment failure can occur as a result of human coagulation factor IX adsorption to the internal surface or some injection/infusion equipment.

Pregnancy and lactation

Animal reproduction studies have not been conducted with **OCTANINE® F**. Based on the rare occurrence of haemophilia B in women, experience regarding the use of **OCTANINE® F** during pregnancy and breastfeeding is not available. Therefore, **OCTANINE® F** should be used during pregnancy and lactation only if clearly indicated.

Parvovirus B19 infection may be serious for pregnant women (fetal infection) (see **"Warnings and Special precautions"**).

Dosage and directions for use:

The dosage and duration of the substitution therapy depends on:

- the severity of factor IX deficiency
- the location and extent of the bleeding and
- the patient's clinical condition.

One International unit (IU) of factor IX activity is equivalent to the quantity of factor IX in 1 ml of normal human plasma.

On demand treatment

The calculation of the required dosage of factor IX is based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity by 1 % of normal activity.

The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 0,8

The quantity to be administered and the frequency of application should always be oriented to the clinical effectiveness in the individual case. Factor IX products rarely required to be more than once daily.

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery.

Degree of Haemorrhage/ Type of surgical procedure	Factor IX level required (%) (IU/dl)	Frequency (hours) of doses/ Duration (days) of therapy
Haemorrhage:		
Early haemarthrosis, muscle bleed or oral bleed.	20 to 40	Repeat every 24 hours. At least 1 day, until bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleed or haematoma.	30 to 60	Repeat infusion every 24 hours for 3 to 4 days or more until pain and disability are resolved.
Life-threatening bleeds	60 to 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery:		
Minor surgery – including tooth extraction.	30 to 60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80 to 100 (pre-/ post-operative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30 % to 60 % (IU/dl).

Continuous infusion:

During the course of treatment, appropriate determination of factor IX level is advised to guide the dose to be administered and the frequency of repeated infusion. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable. Individual patients may vary in their response to factor IX, achieving different levels for in-vivo recovery and demonstrating different half-lives.

Prophylaxis:

For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 30 IU of factor IX per kg body weight given twice a week. The dosage should be adapted according to the individual response.

In some cases especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Paediatric population

There are insufficient data to recommend the use of OCTANINE® F in children less than 6 years of age. There are no clinical studies performed in children less than 12 years of age or in previously untreated patients (PUPs), (see “Side effects”). In children between 6 and 12 of age, recovery and half-life should be performed, in order to adjust the individual dosage.

Patients should be monitored for the development of antibodies against factor IX (inhibitors). If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed (Bethesda test) to determine if a factor IX inhibitor is present. If the inhibitor is presented at levels less than 10 Bethesda Units (BU) per ml, administration of additional coagulation factor IX may neutralise the inhibitor. In patients with inhibitor titres above 10 BU or with high anamnestic responses, the use of (activated) prothrombin complex concentrates (PCC) or activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.

Method of administration

Dissolve the **OCTANINE® F** as described under “Instructions for use/handling” and inject slowly intravenously. It is recommended not to administer more than 2 to 3 ml per minute.

Instructions for use/handling:

Please read all the instructions and follow them carefully.

During the procedure below, sterility must be maintained.

Do not use after expiry date given on the label.

The product reconstitutes quickly at room temperature to a clear or slightly pearly opalescent solution.

Do not use solution that are cloudy or have deposits.

After reconstitution the solution must be used immediately.

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

Use only the injection set provided. The use of other injection/infusion equipment can cause additional risks and treatment failure. (see **“Interactions”**).

Instructions for reconstitution

1. Warm the solvent (water for injection) and the concentrate in the closed vials up to 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 stopper or the caps of the vials. The temperature of the water bath should not exceed 37 °C.
2. Remove the caps from the concentrate 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 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 concentrate vial and quickly perforate the centre of the concentrate vial rubber stopper with the needle. The vacuum inside the concentrate vial draws in the water.
5. Remove the double-ended needle with the empty water vial from the concentrate vial, then slowly rotate the concentrate vial until the concentrate is completely dissolved. **OCTANINE® F** dissolves quickly at room temperature to a clear solution.

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 particular matter and discoloration prior to administration. Do not use if the concentrate fails to dissolve completely or an aggregate is formed.

Instructions for injection

As a precautionary measure, the patient's pulse rate should be measured before and during the **OCTANINE® F** injection. If a marked increase in the pulse rate occurs the injection speed must be reduced or the administration must be interrupted.

1. After the concentrate has been reconstituted in the manner described above, remove the protective cover from the filter needle and perforate the rubber stopper of the concentrate vial.
2. Remove the cap of the filter needle and attached the syringe.
3. Turn the vial with the attached syringe upside-down and draw the solution up into the syringe.
4. Disinfect the intended injection site with an alcohol swab.
5. Remove the filter needle from the syringe and attached the butterfly infusion needle to the syringe instead.

6. Inject the solution intravenously at a slow speed of 2 to 3 ml per minute.

Patients using more than one vial of **OCTANINE® F** concentrate per one treatment may use the same butterfly infusion needle and syringe again.

The filter needle is for single use only. Always use a filter needle when drawing up the preparation into a syringe.

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

Side effects

- Hypersensitivity or allergic reactions (which may include angiodema, burning and stinging at the injection site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently in patients treated with factor IX containing products. In some cases, these reactions have progressed to severe anaphylaxis, and they have occured in close temporal association with development of factor IX inhibitors (see also “Special precautions“).
- Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patiens with factor IX inhibitors and a history of allergic reaction.
- On rare occasions, fever has been observed.
- Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor X. As the use of OCTANINE® F in previously untreated patients (PUPs) has not been established in clinical trials, the antibody development of these patients should be analysed with an appropriate test (Bethesda test). There are insufficient data to recommend the use of OCTANINE® F in previously untreated patients.
- There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity

factor IX products has been associated with instances of

- myocardial infaction
- disseminated intravascular coagulation
- venous thrombosis and
- pulmonary embolism

The use of high purity factor IX products such as OCTANINE® F is rarely associated with such adverse reactions.

Description of selected adverse reactions

Due to the amount of heparin contained a sudden, allergy induced reduction of the blood platelet count below 100 000/µl or 50 % of the starting count may be observed (thrombocytopenia type II) in rare cases. In patients not previously hypersensitive to heparin, this decrease in thromocytes may occur (6 - 14) days after the start of treatment. In patients with a previous heparin sensitivity, this reduction may set in a few hours after treatment.

This severe form of blood platelet reduction may be accompanied by, or result in, arterial and venous thrombosis, thromboembolism, severe clotting disorders (consumptive coagulopathy), skin necrosis in the area of injection, flea bite-like bleeding (petechial haemorrhages), purpura and tarry stool.

If the specified allergic reactions are observed, the injections with OCTANINE® F should be stopped immediately. The patient should be advised not to use any heparin containing medicinal products in the future. Because of this rarely occurring heparin induced effect on the blood platelets, the patient's blood platelet count should be monitored closely, especially at the initiation of treatment.

Frequencies of side effects have been evaluated according to the following convention:

Very common (>1/10); common (>1/100 <1/10); uncommon (>1/1000 <1/100);
rare (>1/10000 <1/1000); very rare (<1/10000), including isolated reports.

System Organ Class	Rare	Very rare
Immune system disorders	hypersensitivity reaction	anaphylactic shock
Vascular disorders		thrombo-embolic event
Renal and urinary disorders		nephrotic syndrome
General disorders and administration site conditions		heparin induced thrombocytopenia, pyrexia
Investigations		anti-factor IX antibody positive

Known symptoms of overdosage and particulars of treatment

No cases of overdose with **OCTANINE® F** have been reported.

Identification

OCTANINE® F 250:

Lyophilised powder: A white or pale yellow powder or friable solid.

Reconstituted solution: Clear to slightly opalescent and colourless.

OCTANINE® F 500:

Lyophilised powder: A white or pale yellow powder or friable solid.

Reconstituted solution: Clear to slightly opalescent and colourless.

OCTANINE® F 1000:

Lyophilised powder: A white or pale yellow powder or friable solid.

Reconstituted solution: Clear to slightly opalescent and colourless.

Presentation

OCTANINE® F comes as a combination package consisting of two cartons held together with a cellophane strip.

1 carton contains the powder for solution for injection. The powder for solution for injection is supplied in a labelled 30 ml type 1 glass vial (Ph. Eur./USP), which are closed

with a type I chlorobutyl rubber stopper (Ph. Eur./USP) and sealed with a 20 mm blue aluminium flip-off cap.

1 carton contains the solvent water for injection. The water for injection (5 ml for water for injection (Ph. Eur.) for **OCTANINE® F 250** and **500**, 10 ml for water for injection (Ph. Eur.) for **OCTANINE® F 1000**) is supplied in labelled 10 ml type I glass vials (Ph. Eur.) quality, which are closed chlorobutyl rubber stoppers of type 1 (Ph. Eur.) and sealed with a 20 mm blue flip-off cap.

The package also contains the following medical devices:

- 1 disposable syringe
- 1 double-ended needle
- 1 filter needle
- 1 butterfly
- 2 alcohol swabs

Storage instructions

Store and transport at or below 25 ºC. Protect from light and do not freeze.

Use immediately after reconstitution.

Do not use after expiry date.

KEEP OUT OF THE REACH OF CHILDREN.

Registration numbers:

OCTANINE® F 250: 37/30.3/0645

OCTANINE® F 500: 37/30.3/0646

OCTANINE® F 1000: 37/30.3/0647

Name and Business Address of the Holder of the Certificate of Registration

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Date of publication of package insert

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PROFESSIONELE INLIGTING VIR OCTANINE® FF

Skeduleringstatus | S4 |

Eiendomsnaam (en doseervorm)

OCTANINE® F 250 (poeier en oplosmiddel vir oplossing vir inspuiting)

OCTANINE® F 500 (poeier en oplosmiddel vir oplossing vir inspuiting)

OCTANINE® F 1000 (poeier en oplosmiddel vir oplossing vir inspuiting)

Samestelling

OCTANINE® F 250: Bevat 250 IE mens-stollingsfaktor IX en 25 IE heparien per flessie wat ooreenstem met ongeveer 2 mg proteïen.

Dit moet met die voorsiende 5 ml water vir inspuiting (Ph Eur.) hersaamgestel word, wat dan ongeveer 50* IE faktor IX/ ml bevat.

OCTANINE® F 500: Bevat 500 IE mens-stollingsfaktor IX en 50 IE heparien per flessie wat ooreenstem met ongeveer 4 mg proteïen.

Dit moet met die voorsiende 5 ml water vir inspuiting (Ph Eur.) hersaamgestel word, wat dan ongeveer 100* IE faktor IX/ ml bevat.

OCTANINE® F 1000: Bevat 1 000 IE mens-stollingsfaktor IX en 100 IE heparien per flessie wat ooreenstem met ongeveer 8 mg proteïen.

Dit moet met die voorsiende 10 ml water vir inspuiting (Ph Eur.) hersaamgestel word, wat dan ongeveer 100* IE faktor IX/ ml bevat.

*volgens die huidige WGO-standaard

Die sterkte (IE) word bepaal deur die Europese Farmakopieë (Ph. Eur.) se een-stadium stollingstoets. Die spesifieke aktiwiteit van **OCTANINE® F** is ongeveer ≥ 50 IE/mg proteïen.

OCTANINE® F bevat geen antimikrobiese- of preserveermiddels nie.

Ander bestanddele:

Poeier: heparien (≤ 0,15 IE/IE F IX per 1 ml), natriumchloried, natriumsitraat, arginienhidrochloried en lisienhidrochloried.

Oplosmiddel: water vir inspuiting (Ph. Eur.).

Farmakologiese klassifikasie

A 30.3 Biologiese middels (Bloedfraksies)

Farmakologiese werking

Farmakodinamika:

Farmakoterapeutiese groep: antihemorrage: bloedstollingsfaktor IX - ATC-kode: B02BD04.

Faktor IX is ‘n enkelketting glikoproteïen met ‘n molekulêre massa van ongeveer 68 000 Dalton. Dit is ‘n vitamien K-afhanklike stollingsfaktor wat in die lewer gesintetiseer word. Faktor IX word geaktiveer deur faktor XIa in the intrinsieke stollingspad en die faktor VII/ weefselfaktorkompleks in die ekstrinsieke pad. Geaktiveerde faktor IX, in kombinasie met geaktiveerde faktor VIII, aktiveer faktor X. Geaktiveerde faktor X sit protrombien om in trombien, wat dan weer fibrinogeen in fibrien omsit en ‘n stolsel vorm.

Hemofilie B is ‘n geslags-gekoppelde oorerflike bloedstollingversteuring as gevolg van verlaagde vlakke van faktor IX en het oordadige bloeding in die gewrigte, spiere of interne organe tot gevolg wat of spontaan, of as gevolg van per abuise of chirurgiese trauma plaasvind. Die plasmavlak van faktor IX word verhoog deur vervangingsbehandeling en kan daardeur tydelike regstelling van die faktorgebrek of die regstelling van bloedingsneigings, in staat stel.

Farmakokinetika:

Die volgende resultate is met **OCTANINE® F** in ‘n farmakokinetiese studie met 13 hemofilie B pasiënte ouer as 12 jaar (gemiddelde ouderdom 28 jaar, verspreiding 12 – 61 jaar) bereik.

N = 13	*Mediaan*	*Gemiddeld*	*SA*	*Minimum*	*Maksimum*
Toenemende herstel (IE x dl^{-1} x IE^{-1} x kg)	1,2	1,3	0,5	0,8	2,4
AOK$_{norm}$ (IE x dl^{-1} x u x IE^{-1} x kg)	32,4	37,7	13,0	24,5	64,0
Halfleeftyd (u)	27,8	29,1	5,2	22,0	36,8
GVT (u)	39,4	40,0	7,3	30,2	51,6
Opruiming (ml x u^{-1} x kg)	3,1	2,9	0,9	1,6	4,1

AOK = area onder kurwe,

GVT = gemiddelde verblyftyd

SA = standaardafwyking

u = uur

Die toenemende herstel was ook in ‘n tweede studie getoets. Die meta-analise van al die herstel waardebepalings (n = 19) het tot ‘n gemiddelde herstel van 1,1 IE x dl-1 x IE-1 x kg gelei. Daar was geen verskil in die toenemende herstel wanneer dit na drie en ses maande se behandeling getoets is nie.

Indikasies

Behandeling en voorkoming van bloeding by pasiënte met hemofilie B (kongenitale faktor IX-gebrek).

Kontra-indikasies

OCTANINE® F is teenaangedui by pasiënte met:

• hipersensitiwiteit teenoor die aktiewe bestanddeel of enige ander bestanddele van **OCTANINE® F**

• bekende allergie-verwante verlaging van trombosiete tydens heparienbehandeling (heparien geïnduseerde trombositopenie [HIT] tipe II).

Waarskuwings en Spesiale voorsorgmaatreëls

Hipersensitiwiteit:

Allergiese tipe hipersensitiwiteitsreaksies is moontlik met **OCTANINE® F**. Dit bevat spoorhoeveelhede van mensproteïene buiten faktor IX en heparien. (sien **"Kontra-indikasies"** en **"Newe-effekte"**)

Indien simptome van hipersensitiwiteit voorkom, behoort **OCTANINE® F** dadelik gestaak te word en die dokter gekontak te word. Pasiënte behoort van die eerste tekens van hipersensitiwiteitsreaksies ingelig te word, insluitend galbulte, algemene urtikarie, benoudheid van die bors, hyg, hipotensie en anafilakse (sien **"Newe-effekte"**).

In geval van skok, moet die standaard mediese behandeling vir skok toegepas word.

Inhibeerders:

Na herhaaldelike behandeling met **OCTANINE® F**, behoort pasiënte gemoniteer te word vir die ontwikkeling van neutraliserende teenliggame (inhibeerders) wat in Bethesda Eenhede (BE) bepaal moet word, deur gebruik te maak van geskikte biologiese toetsing.

Daar is literatuurverslae wat 'n korrelasie tussen die voorkoms van faktor IX-inhibeerder en allergiese reaksies aandui. Daarom, behoort pasiënte wat allergiese reaksies ondervind geëvalueer te word vir die teenwoordigheid van 'n inhibeerder (sien **"Newe-effekte"**).

Daar moet kennis geneem word dat pasiënte met faktor IX-inhibeerders 'n verhoogde risiko vir anafilakse mag hê met 'n daaropvolgende uitdaging met faktor IX.

As gevolg van die risiko van allergiese reaksies met faktor IX-konsentrate behoort die aanvanklike toediening van **OCTANINE® F** volgens die behandelende dokter se oordeel onder mediese waarneming waar voldoende mediese sorg vir allergiese reaksies voorsien kan word, uitgevoer te word.

Trombo-embolisme:

As gevolg van die risiko van trombo-emboliese komplikasies, behoort kliniese waarneming vir eerste tekens van trombotiese of verbruikskoagulopatie met geskikte biologiese toetsing ingestel te word, wanneer **OCTANINE® F** toegedien word aan:

- pasiënte met lewersiekte
- post-operatiewe pasiënte
- neonate, of
- pasiënte met ‘n risiko van trombotiese fenomena of dissemineerde intravaskulêre koagulasie (DIK)

In elkeen van hierdie gevalle, behoort die voordeel van die behandeling met **OCTANINE® F** opgeweeg te word teen die risiko van hierdie komplikasies.

Kateter-verwante komplikasies

Indien ‘n sentrale veneuse toegangstoestel (SVTT) benodig word behoort die risiko van SVTT-verwante komplikasies insluitend lokale infeksies, bakteremie en kateterplek trombose in ag geneem te word.

Oordraagbare agente

Standaard maatstawwe, om infeksies wat voortspruit uit die gebruik van medisinale produkte wat voorberei word vanaf mensbloed of -plasma te voorkom, sluit in:

- selektering van skenkers
- sifting van individuele skenkings en plasmapoel vir spesifieke merkers van infeksie en
- die insluiting van doeltreffende vervaardigingstappe vir inaktivering/verwydering van virusse

Ten spyte hiervan, wanneer medisinale produkte wat uit mensbloed of -plasma berei is, toegedien word, kan aansteeklike siektes weens die oordra van aansteeklike agense nie

heeltemal uitgesluit word nie. Dit geld ook vir onbekende virusse of tevoorskynkomende virusse en ander patogene.
Die maatstawwe word doeltreffend beskou vir omhulde virusse soos mens-immuungebrekvirus
(MIV), hepatitis B virus (HBV) en hepatitis C virus (HCV) en vir die nie-omhulde hepatitis A virus (HAV).
Die maatstawwe kan van beperkte waarde wees teen nie-omhulde virusse soos parvovirus B19. Parvovirus B19 infeksie kan ernstig wees vir swanger vroue (fetale infeksie) (sien **"Swangerskap en laktasie"**) en vir individue met 'n immuumgebrek of verhoogde eritropoïese (bv. hemolitiese anemie).
Geskikte inenting (hepatitis A en B) moet oorweeg word vir paiënte wat gereeld/ herhaaldelik faktor IX-konsentrate afkomstig van mensplasma ontvang.
Daar word ten sterkste aanbeveel dat, die naam en lotnommer van **OCTANINE® F** aangeteken word elke keer wat dit aan hulle toegedien word om te verseker dat 'n skakel tussen die pasiënt en die produklot gehandhaaf word.

Pasiënte op 'n gekontroleerde natriumdieet:
OCTANINE® F bevat tot en met 3 mmol (of 69 mg) natrium vir 1 flessie **OCTANINE® F 250** of **500** en tot en met 6 mmol (of 138 mg) natrium vir 1 flessie **OCTANINE® F** 1000 per dosis. Dit moet in aanmerking geneem word by pasiënte op 'n gekontroleerde natriumdieet.

Pediatriese populasie
Die gelyste waarskuwings en voorsorgmaatreëls is van toepassing op beide volwassenes en kinders.

Effekte op vermoë om te bestuur en masjiene te gebruik
OCTANINE® F het geen invloed op die vermoë om te bestuur en masjinerie te gebruik nie.

Interaksies

Geen interaksies van mens-stollingsfaktor IX-konsentraat (OCTANINE® F) met ander medisinale produkte is bekend nie.

Onverenigbaarhede

OCTANINE® F moet nie met ander medisinale produkte gemeng word nie.

Slegs die voorsiende inspuiting/behandeling mens-infusiestelle behoort gebruik te word want mislukking in behandeling kan voorkom as gevolg van adsorpsie van ensstollingsfaktor IX aan die interne oppervlak van sommige inspuiting-/infusietoerusting.

Swangerskap en laktasie

Diervoortplantingstudies is nie met **OCTANINE® F** uitgevoer nie. Gebaseer op die seldsame voorkoms van hemofilie B in vroue, is ondervinding aangaande die gebruik van **OCTANINE® F** tydens swangerskap en borsvoeding nie beskikbaar nie. Daarom behoort **OCTANINE® F** slegs tydens swangerskap en borsvoeding gebruik te word indien dit ongetwyfeld aangedui is.

Parvovirus B19 infeksie kan ernstig wees vir swanger vroue (fetale infeksie) (sien **"Waarskuwings en Spesiale voorsorgmaatreëls"**).

Dosis en gebruiksaanwysings

Die dosis en duur van die vervangingsbehandeling hang af van:

- die erns van faktor IX-gebrek,
- die plek en omvang van die bloeding en
- die pasiënt se kliniese toestand.

Een Internasionale eenheid (IE) van faktor IX-aktiwiteit is gelykstaande aan die hoeveelheid faktor IX in 1 ml van normale mensplasma.

Op aanvraag behandeling

Die berekening van die aanbevole dosis van faktor IX is gebaseer op die empiriese bevinding dat 1 IE faktor IX per kg liggaamsgewig die plasma faktor IX-aktiwiteit met 1 % van normale aktiwiteit verhoog.

Die aanbevole dosis is bepaal deur die volgende formule te gebruik:

Anbevole eenhede = liggaamsgewig (kg) x verlangde faktor IX verhoging (%) (IE/dl) x 0, 8

Die hoeveelheid wat toegedien moet word en die frekwensie van die toediening behoort altyd tot die kliniese doeltreffendheid in die individuele geval georïenteerd te wees.

Faktor IX- produkte vereis selde om meer as een keer per dag toegedien te word.

In die geval van die volgende hemorragiese voorvalle behoort die faktor IX-aktiwiteit nie onder die gegewe plasma-aktiwiteitsvlak (in % van normaal) in die oorstemmende periode te daal nie. Die volgende tabel kan gebruik word om leiding te gee in die dosis in bloedingsepisodes en chirurgie.

Graad van hemorrage/ Tipe chirurgiese prosedure	***Faktor IX-vlakvereiste (%) (IE/dl)***	***Frekwensie (uur) van dosisse/ Duur (dae) van terapie***
Hemorrage:		
Vroeë hemartrose, spierbloeding of mondbloeding.	20 to 40	Herhaal elke 24 uur. Ten minste 1 dag, totdat bloedingsepisode soos aangedui deur pyn uit die weg geruim is en genesing bereik is.
Meer omvattende hemartrose, spierbloeding of hematoom.	30 to 60	Herhaal infusie elke 24 uur vir 3 tot 4 dae of meer totdat pyn en ongeskiktheid uit die weg geruim is.
Lewensbedreigende bloedings	60 to 100	Herhaal elke 8 tot 24 uur todat bedreiging verby is.

Chirurgie:		
Geringe chirurgie – insluitend tandekstraksie.	30 to 60	Every 24 hours, at least 1 day, until healing is achieved.
Ernstige chirurgie	80 to 100 (pre-/ post-operative)	Herhaal infusie elke 8 tot 24 uur tot voldoende wondgenesing, dan behandeling vir ten minste nog 7 dae om ‘n faktor IX-aktiwiteit van 30 % tot 60 % (IE/dl) te handhaaf.

Volgehoue infusie:
Tydens die verloop van behandeling, word geskikte bepaling van faktor IX-vlak aangeraai om leiding te gee in die dosis wat toegedien moet word en die frekwensie vir die herhaling van die infusie. In die geval van ernstige chirurgiese ingrepe is presiese monitering van die vervangingsbehandeling deur stollingsanalise (plasma faktor IX-aktiwiteit) veral onmisbaar. Individuele pasiënte mag verskil in hul reaksie teenoor factor IX deur verskillende vlakke van in-vivo herstel te bereik en verskillende halfleeftye te demonstreer.

Profilakse:
Vir langtermyn profilakse teen bloeding by pasiënte met ernstige hemofilie B is die dosis gewoonlik 20 tot 30 IE van faktor IX per kg liggaamsgewig twee keer ‘n week gegee. Die dosis behoort aangepas te word na aanleiding van die individuele respons.
In sommige gevalle, veral by jonger pasiënte, mag korter dosisintervalle of hoër dosisse nodig wees.

Pediatriese populasie
Daar is onvoldoende data om die gebruik van **OCTANINE® F** by kinders jonger as 6 jaar aan te beveel. Daar is geen kliniese studies in kinders jonger as 12 jarige ouderdom of in vorige onbehandelde pasiënte (VOP’e), uitgevoer nie (sien **“Newe-effekte”**). Herstel en halfleeftyd behoort by kinders tussen 6 en 12 jaar uitgevoer te word ten einde die individuele dosis aan te pas.
Pasiënte behoort gemoniteer te word vir die ontwikkeling van teeliggame teen faktor IX (inhibeerders). As die verwagte faktor IX aktiwiteitsplasmavlakke nie bereik word nie of indien bloeding nie beheer word met die geskikte dosis nie, behoort ‘n toets gedoen te word (Bethesda toets) om te bepaal of ‘n faktor IX inhibeerder teenwoordig is. Indien die inhibeerder teenwoordig is teen vlakke van 10 Bethesda Eenhede (BE) per ml, kan

die toediening van addisionele stollingsfaktor IX die inhibeerder neutraliseer. By pasiënte met inhibeerder titers bokant 10 BE of met hoë anamnestiese reaksies, moet die gebruik van (geaktiveerde) protrombienkompleks konsentrate (PKK) of geaktiveerde faktor VII (rFVIIa) preparate oorweeg word. Hierdie behandelings behoort deur die geneesheer met ondervinding in die sorg van pasiënte met hemofilie gelei te word.

Metode van toediening

Los **OCTANINE® F** op soos beskryf onder “Instruksies vir gebruik/hantering” en spuit stadig intraveneus in. Daar word aanbeveel om nie meer as 2 tot 3 ml per minuut toe te dien nie.

Instruksies vir gebruik/hantering:

Lees asseblief die instruksies en volg hulle noukeurig.

Tydens die prosedure moet steriliteit gehandhaaf word.

Moet nie na die vervaldatum wat op die etiket is gebruik nie.

OCTANINE® F se hersamestelling tot ‘n helder of effense pêrel melkagtige oplossing is vinnig by kamertemperatuur.

Na hersamestelling moet die oplossing dadelik gebruik word.

Moet nie oplossings wat troebel is of afsaksels het, gebruik nie.

Enige ongebruikte produk of afvalmateriaal moet volgens plaaslike riglyne weggedoen word.

Gebruik slegs die inspuitingstel wat voorsien is. Die gebruik van ‘n ander spuit-/infusietoerusting kan addisionele risiko’s en mislukking in behandeling veroorsaak (sien **“Interaksies”**).

Instruksies vir hersamestelling:

1. Verwarm die oplosmiddel (water vir inspuiting) en die konsentraat in die geslote flessies, tot kamertemperatuur. Hierdie temperatuur behoort gehandhaaf te word tydens die hersamestelling. Indien ‘n waterbad gebruik word vir verwarming, moet sorg geneem word om te voorkom dat water in kontak met die rubberstoppers of die doppies van die flessies kom. Die temperatuur van die waterbad moet nie 37 °C oorskry nie.
2. Verwyder die doppies van die konsentraatflessie en die waterflessie en maak die rubberstoppers skoon met ‘n alkoholpluisie.
3. Verwyder die beskermende omhulsel van die kort kant van die dubbel-einde naald en maak seker dat die punt van die blootgestelde naald nie geraak word nie. Perforeer

dan die middel van die waterflessie se rubberstopper met die naald wat vertikaal gehou word. Om te verseker dat die vloeistof van die waterflessie volledig opgetrek word moet die naald op so ‘n wyse in die rubberstopper gesteek word dat dit net die stopper binnedring en sigbaar in die flessie is.

4. Verwyder die beskermende omhulsel van die ander, lang kant van die dubbel-einde naald en maak seker om nie die blootgestelde punt van die naald te raak nie. Hou die waterflessie onderstebo bokant die regop konsentraatflessie en perforeer vinnig die middel van die konsentraatflessie se rubberstopper met die naald. Die vakuum binne die konsentraatflessie trek die water in.
5. Verwyder die dubbel-einde naald met die leë waterflessie van die konsentraatflessie en roteer die konsentraatflessie stadig totdat dit volledig opgelos het. OCTANINE® F los vinnig op tot ‘n helder oplossing by kamertemperatuur.

Die oplossing behoort helder of effens melkagtig te wees. Moet nie oplossings wat troebel is of afsaksels het gebruik nie. Hersaamgestelde produkte moet voor toediening vir sigbare deeltjies en verkleuring nagegaan word. Moet nie gebruik nie indien die konsentraat faal om volledig op te los, of ‘n aggregaat vorm.

Instruksies vir inspuiting:

As ‘n voorsorgmaatreël moet die pasiënt se polsslag geneem word voor en tydens die inspuiting. Indien daar ‘n merkbare verhoging in die polsslag vookom moet die inspuitingstempo verlaag word of die toediening moet onderbreek word.

1. Nadat die konsentraat op bogenoemde wyse hersaamgestel is, verwyder die beskermende omhulsel van die filternaald en perforeer die rubberstopper van die konsentraatflessie.
2. Verwyder die doppie van die filternaald en heg die spuit aan.
3. Draai die flessie met die aangehegte spuit onderstebo en trek die oplossing in die spuit op.
4. Ontsmet die voorgenome inspuitingsplek met ‘n alkoholpluisie.
5. Verwyder die filternaald van die spuit en heg instede die vlinder-infusienaald aan die spuit.
6. Spuit die oplossing intraveneus in teen ‘n stadige tempo van 2 tot 3 ml per minuut.

Pasiënte wat meer as een flessie OCTANINE® F-konsentraat per een behandeling gebruik kan dieselfde vlinder-infusiemnaald en spuit weer gebruik.
Die filternaald is vir eenmalige gebruik. Gebruik altyd die filternaald wanneer die preparaat in die spuit opgetrek word.

Enige ongebruikte oplossingproduk of afvalmateriaal moet volgens die plaaslike riglyne vir weggedoen word.

Newe-effekte

- Hipersensitiwiteitsreaksies of allergiese reaksies (wat angio-edeem, brandende en steekgevoel by die inspuitingsplek, koue rillings, gloede, algemene urtikaria, hoofpyn, galbulte, hipotensie, letargie, naarheid, rusteloosheid, tagikardie, benoudheid van die bors, tinteling, braking, hyg kan insluit) is selde by pasiënte wat met factor IX-bevattende produkte behandel word waargeneem. In sommige gevalle het hierdie reaksies tot ernstige anafilakse gevorder en het hulle in nou temporale assosiasie met die ontwikkeling van faktor IX inhibeerders (sien **"Spesiale voorsorgmaatreëls"**) voorgekom.
- Nefrotiese sindroom is aangemeld na immuuntoleransie induksie poging in hemofilie B pasiënte met faktor IX-inhibeerders en 'n geskiedenis van allergiese reaksie.
- In seldsame gevalle is koors waargeneem.
- Pasiënte met hemofilie B kan neutraliserende teenliggame (inhibeerders) teenoor faktor IX ontwikkel. Aangesien die gebruik van **OCTANINE® F** by voorheen onbehandelde pasiënte (VOP's) nie in kliniese proewe vasgestel is nie, behoort die ontwikkeling van teenliggame by hierdie pasiënte geanaliseer te word met 'n geskikte toets (Bethesda toets). Daar is onvoldoende data om die gebruik van **OCTANINE® F** by voorheen onbehandelde pasiënte aan te beveel.
- Daar is 'n potensiële risiko van trombo-emboliese episodes na die toediening van faktor IX-produkte met 'n hoër risiko vir lae suiwerheid preparate. Die gebruik van lae suiwerheid faktor IX-produkte is geassosieer met gevalle van:
    - miokardiale infarksie,
    - dessemineerde intravaskulêre koagulasie,
    - veneuse trombose en
    - pulmonêre embolisme.

Die gebruik van hoë gesuiwerde faktor IX-produkte soos OCTANINE® F word selde met sulke nadelige reaksies geassosieer.

Beskrywing van uitgesoekte nadelige reaksies:
As gevolg van die hoeveelheid heparien wat **OCTANINE® F** bevat, kan 'n skielike allergie geïnduseerde daling in bloedplaatjietelling laer as 100 000/µl of 50 % van die begintelling (trombositopenie tipe II) in seldsame gevalle waargeneem word. By pasiënte wat nie voorheen hipersensitief was teenoor heparien nie, kan die daling in trombosiete binne

6 - 14 dae na die aanvang van behandeling voorkom.
By pasiënte met vorige hepariensensitiwiteit kan hierdie daling binne ‘n paar uur na aanvang van behandeling, ontwikkel.
Hierdie ernstige vorm van bloedplaatjie afname kan vergesel word deur, of lei tot, arteriële en veneuse trombose, trombo-embolisme, ernstige stollingsversteurings (verbruikskoagulopatie), velnekrose in die area van die toedieningsplek, vlooibytagtige bloeding (stippelbloeding), purpura en teeragtige stoelgange.
Die behandeling met **OCTANINE® F** moet onmiddellik gestaak word indien hierdie spesifieke allergiese reaksies waargeneem word. Die pasiënt moet ingelig word om nie heparien-bevattende medisinale produkte in die toekoms te gebruik nie. As gevolg van hierdie seldsame voorkoms van heparien geïnduseerde effek op die bloedplaatjies behoort die pasiënt se bloedplaatjietelling streng gemoniteer te word, veral met aanvang van behandeling.

Frekwensies van newe-effekte is volgens die volgende konvensie geëvalueer:
Baie algemeen (>1/10); algemeen (>1/100 <1/10); ongewoon (>1/1000 <1/100); seldsaam (>1/10000 <1/1000); baie seldsaam (<1/10000), insluitend geïsoleerde verslae.

Stelselorgaanklas	Seldsaam	Baie seldsaam
Immuunsisteem versteurings	hipersensitiwiteitsreaksie	anafilaktiese skok
Vaskulêre versteurings		Trombo-emboliese voorval
Renale en urinêre versteurings		nefrotiese sindroom
Algemene versteuring en toedieningsplek toestande		heparien geïnduseerde trombositopenie, koors
Ondersoeke		anti-faktor IX-teenliggaam positief

Bekende simptome van oordosering en besonderhede van die behandeling daarvan

Geen gevalle van oordosis met **OCTANINE® F** is aangemeld nie.

Identifikasie

OCTANINE® F 250:

Gevriesdroogte poeier: ‘n Wit of bleekgeel poeier of bros vastestof.

Hersaamgestelde oplossing: Helder tot effens melkagtig en kleurloos.

OCTANINE® F 500:

Gevriesdroogte poeier: ‘n Wit of bleekgeel poeier of bros vastestof.

Hersaamgestelde oplossing: Helder tot effens melkagtig en kleurloos.

OCTANINE® F 1000:

Gevriesdroogte poeier: ‘n Wit of bleekgeel poeier of bros vastestof.

Hersaamgestelde oplossing: Helder tot effens melkagtig en kleurloos.

Aanbieding

OCTANINE® F kom as ‘n kombinasie verpakking, bestaande uit twee kartonne wat met ‘n selofaanstrokie aanmekaar vasgemaak is.

1 karton bevat die poeier vir oplossing. Die poeier vir oplossing word voorsien in ‘n geëtiketeerde 30 ml tipe I glasflessie (Ph. Eur./USP) wat gesluit word met ‘n tipe I chlorobutyl rubberstopper (Ph. Eur./USP) en geseël met ‘n 20 mm blou aluminium afknipdoppie;

1 karton bevat die oplosmiddel water vir inspuiting. Die water vir inspuiting 5 ml water vir inspuiting (Ph. Eur.) vir **OCTANINE® F 250** en **500**, 10 ml water vir inspuiting vir **OCTANINE® F 1000** word voorsien in 10 ml tipe I glasflessies (Ph. Eur.) wat met tipe I chlorobutiel rubberstoppers (Ph. Eur.) gesluit word en geseël word met ‘n 20 mm blou afknipdoppie.

Die verpakking bevat ook die volgende mediese toestelle:

- 1 wegdoenbare spuit
- 1 dubbel-einde naald
- 1 filternaald

- 1 vlinder-infusienaald
- 2 alkoholpluisies

Bergingsinstruksies

Bewaar en vervoer by of benede 25 ºC. Beskerm teen lig en moet nie vries nie.

Die hersaamgestelde oplossing moet onmiddelik gebruik word. Moet nie na die vervaldatum gebruik nie.

HOU BUITE BEREIK VAN KINDERS.

Registrasienommers

OCTANINE® F 250: 37/30.3/0645

OCTANINE® F 500: 37/30.3/0646

OCTANINE® F 1000: 37/30.3/0647

Naam en Besigheidsadres van die Houer van die Registrasiesertifikaat

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Gebou # 3

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