The format of this leaflet has been defined by the MOH and its content has been checked and approved 7.2013

INSTRUCTION FOR USE

(Summary of Product Characteristics)

1 NAME OF THE MEDICINAL PRODUCT

OCTANINE F 500 IU, 500 IU powder and solvent for solution for injection
OCTANINE F 1000 IU, 1000 IU powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- OCTANINE F 500 IU is presented as a powder and solvent for solution for injection containing nominally 500 IU human coagulation factor IX per vial.

The product contains approximately 100 IU/ml human coagulation factor IX when reconstituted with 5 ml water for injections (Ph.Eur.).

- OCTANINE F 1000 IU is presented as a powder and solvent for solution for injection containing nominally 1000 IU human coagulation factor IX per vial.

The product contains approximately 100 IU/ml human coagulation factor IX when reconstituted with 10 ml water for injections (Ph.Eur.).

OCTANINE F is produced from plasma of human donors.
The potency (IU) is determined using the European Pharmacopoeia one stage clotting test, in comparison with an international standard from the World Health Organisation (WHO). The specific activity of OCTANINE F is approximately ≥ 100 IU/mg protein.

This medicinal product contains up to 3 mmol (or 69 mg) sodium for 1 vial OCTANINE F 500 IU and up to 6 mmol (or 138 mg) sodium for 1 vial OCTANINE F 1000 IU per dose. To be taken into consideration by patients on a controlled sodium diet.
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 pale yellow also appearing as a friable solid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

Posology

The dosage and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

On demand treatment
The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).
One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma. The calculation of the required dosage of factor IX is based on the empirical finding that 1 International Unit (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 amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. Factor IX products rarely require to be administered 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 of doses (hours) / Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 - 60	Repeat infusion every 24 hours for 3 - 4 days or more until pain and acute disability are resolved.
Life-threatening haemorrhages	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor Surgery including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major Surgery	80 – 100 (pre-/post-operative)	Repeat infusion every 8-24 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).

During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. 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 of 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 40 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

In the study conducted in 25 children under 6 years of age, the median dose administered per exposure day was similar for prophylaxis and treatment of bleeding, i.e. 35 to 40 IU/kg BW.

Patients should be monitored for the development of 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 to determine if a factor IX inhibitor is present. In patients with high levels of inhibitor, factor IX therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.
See also 4.4.

There is not enough data available to recommend continuous infusion of Octanine F in surgical procedures.

Method of administration

Dissolve the preparation as described at 6.6. The product should be administered via the intravenous route. It is recommended not to administer more than 2 - 3 ml per minute.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Known allergy related reduction of thrombocytes during Heparin treatment (HIT type II).

4.4 Special warnings and precautions for use

- As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of human proteins other than factor IX and heparin (see also sections 4.3 and 4.8). Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.
  In case of shock, standard medical -treatment for shock should be implemented.
- Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal

products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped 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) 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.
- After repeated treatment with human coagulation factor IX products, 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 the 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. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX. Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.
- Since the use of factor IX complex products has historically been associated with the development of thromboembolic complications (the risk being higher in low purity preparations) the use of factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC). Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with OCTANINE F should be weighed against the risk of these complications.
- Up to now, not enough results have been obtained from ongoing studies on surgeries performed under continuous perfusion with OCTANINE F.
- 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.
- This medicinal product contains up to 3 mmol (or 69 mg) sodium for 1 vial OCTANINE F 500 IU and up to 6 mmol (or 138 mg) sodium for 1 vial OCTANINE F 1000 IU per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor IX products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during

pregnancy and breast-feeding is not available. Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

rare (≥1/10,000 to <1/1,000
very rare (<1/10,000), including isolated reports

- Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion 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 occurred in close temporal association with development of factor IX inhibitors (see also 4.4).

- Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. A study in 25 children with Haemophilia B was conducted, thereof 6 patients were previously untreated and had a median no. of exposure days to OCTANINE F of 38 (range 8-90). All patients had a factor IX inhibitor level of <0.4 BU at baseline. No inhibitor was observed during the study.
- Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.
- On rare occasions, fever has been observed.
- 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 infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high

purity factor IX is rarely associated with such side effects.

- 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 thrombocytes may occur 6-14 days after the start of treatment. In patients with a previous heparin hypersensitivity 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 disorder (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.

- For safety with respect to transmissible agents, see 4.4.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: 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 and it 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. Activated factor X converts prothrombin into thrombin. Thrombin 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 levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Paedriatric population

A study in 25 children below 6 years of age was conducted. Thereof, 6 patients were previously untreated. The recovery after administration of >25 IU of OCTANINE F/kg body

weight was investigated during the first 3 months of treatment and after 12-24 months. The incremental recovery (geometric mean ± s.d., one-stage assay, actual potency) was calculated to be 0.8±1.4 and 0.9±1.3 %/IU/kg at the 1st and the 2nd assessment, respectively.

5.2 Pharmacokinetic properties

For OCTANINE F the following results were achieved in one 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/dl]/[IU/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 the 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/dl]/[IU/kg].

5.3 Preclinical safety data

Human plasma coagulation factor IX (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous factor IX.
Animal studies are limited and show no additional risks to those already mentioned in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Heparin,
Sodium chloride,
Sodium citrate dihydrate,
Arginine hydrochloride,
Lysine hydrochloride

Solvent:
water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

6.3 Shelf life

2 years

Chemical and physical in use stability has been demonstrated for 72 hours at 25°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

OCTANINE F comes as a combination package consisting of two cartons held together with a plastic film.

OCTANINE F 500 IU:
Carton 1: powder in a 30 ml vial, with a stopper and a flip off cap; package leaflet.
+
Carton 2: 5 ml of solvent (water for injections), with a stopper and a flip off cap.

OCTANINE F 1000 IU:
Carton 1: powder in a 30 ml vial, with a stopper and a flip off cap; package leaflet.
+
Carton 2: 10 ml of solvent (water for injections), with a stopper and a flip off cap.

Carton 2 also contains the following medical devices:

- 1 disposable syringe
- 1 transfer set (1 double-ended needle and 1filter needle)
- 1 infusion set (butterfly)
- 2 alcohol swabs

6.6 Special precautions for disposal and other handling

Please read all the instructions and follow them carefully.
During the procedure described below, sterility must be maintained.
Do not use after expiry date given on the label and carton.
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.

Instructions for reconstitution:

1. Warm the solvent (water for injections) 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 stoppers 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 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 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.

Reconstituted products should be inspected visually for particulate matter and discolouration prior to administration.

If the concentrate fails to dissolve completely or an aggregate is formed, do not use the preparation.
The reconstituted solution must be used on one occasion only.

Instructions for injection:

As a precautionary measure, the patients pulse rate should be measured before and during the factor IX 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 attach the 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. Remove the filter needle from the syringe and attach the butterfly infusion needle to the syringe instead.
6. Insert the butterfly infusion needle into the chosen vein.

7. If you have used a tourniquet to make the vein easier to see, this tourniquet should be released before you start injecting the factor IX. Monitor your pulse rate before and during the injection.
8. Inject the solution intravenously at a slow speed of 2 - 3 ml per minute.

Patients using more than one vial of OCTANINE F concentrate for 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 product or waste material should be disposed of in accordance with local requirements.

7 NAME AND ADDRESS OF PHARMACEUTICAL COMPANY

7.1 Manufacturers

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna
Austria

Octapharma S.A.
70 - 72 Rue du Maréchal Foch
BP 33, F - 67381 Lingolsheim
France

7.2 Registration holder

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

8. DATE OF (PARTIAL) REVISION OF THE TEXT

2011-02-23

9. LEGAL CATEGORY

For prescription only.