INSTRUCTIONS FOR USE

(Summary of product characteristics)

1 NAME OF THE MEDICINAL PRODUCT

OCTANATE 250 IU powder and solvent for solution for injection

Human Coagulation Factor VIII, freeze-dried

OCTANATE 500 IU powder and solvent for solution for injection

Human Coagulation Factor VIII, freeze-dried

2 COMPOSITION

OCTANATE 250 IU is presented as powder and solvent for solution for injection containing nominally 250 IU human coagulation factor VIII per vial.

The product contains approximately 50 IU* per ml human coagulation factor VIII when reconstituted with 5 ml of solvent.

OCTANATE 500 IU is presented as powder and solvent for solution for injection containing nominally 500 IU human coagulation factor VIII per vial.

The product contains approximately 50 IU* per ml human coagulation factor VIII when reconstituted with 10 ml of solvent.

For excipients, see 6.1.

*The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The mean specific activity of OCTANATE is ≥ 100 IU/mg protein.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

A white or pale yellow powder or friable solid.

The solvent is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

4.2 Posology and method of administration

Posology

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia. The dosage and duration of the substitution therapy depend on the severity of factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII 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 VIII in plasma). One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in 1 ml of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that one International Unit (IU) factor VIII per kg of body weight raises the plasma factor VIII activity by 1.5% to 2%. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) (IU/dl) x 0.5 IU/kg

The amount to be administered and the frequency of administrations should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given factor VIII level in the corresponding period of treatment. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage / Type of surgical procedure	Factor VIII level required (%) (IU/dl)	Frequency of doses (hours) and duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleed or oral bleeding	20 – 40	Repeat every 12 to 24 hours. At least 1 day, until bleeding (or pain) is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleed or haematoma	30 – 60	Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and restriction to movement are resolved.
Life threatening bleeds such as head injuries, throat bleed, or severe gastro-intestinal bleeding	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor such as e.g. tooth extractions	30 – 60	Every 24 hours, at least one day, until healing is achieved.
Major	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 24 hours until adequate wound healing; then therapy for at least another 7 days to maintain a FVIII activity of 30% to 60% .

Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

During the course of treatment, appropriate determination of factor VIII level 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 VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

For long term prophylaxis against bleeds in patients with severe haemophilia A, dose of 20 to 60 IU of factor VIII per kg body weight should be given at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Patients should be monitored for the development of factor VIII inhibitors. If the expected factor VIII activity plasma levels are note attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. If inhibitors are present at levels less than 10 Bethesda Units per ml, administration of additional human factor VIII may neutralise the inhibitors. In patients with inhibitor titres above 10 Bethesda Units per ml, the use of (activated) prothrombin complex concentrate or recombinant 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.

There is insufficient data available relating to the administration of OCTANATE® in children younger than 6 years of age. See also 4.4.

Method of administration

Dissolve the preparation as described at 6.6. OCTANATE® should be administered via the intravenous route at a rate of 2 to 3 ml / min.

4.3 Contra-indications

Absolute contra-indication:

- known allergic reactions to constituents in the preparation.

4.4 Special warnings and special precautions for use

As with any intravenous protein product, allergic type of hypersensitivity reactions are possible. Patients should be informed of the possible early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

If these symptoms occur, patients should be advised to discontinue use of the product immediately and contact their physician.

In case of severe circulatory reactions, the current medical standards for shock-treatment are to be observed.

When medicinal products prepared from human plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. This also applies to unknown or emerging viruses, other pathogens and theoretically to Crutzfeld-Jacob Disease (CJD) agents. The risk of transmission is however reduced by:

- Careful selection of donors and screening of donations for the three major pathogenic viruses HIV, HCV, HBV;
- Testing plasma pools for HCV genomic material using PCR;
- Introduction of validated procedures for inactivating and removing viruses in the production process (in the case of OCTANATE®, the solvent detergent (S/D) process and heat-treatment of the lyophilisate at 100 °C for 30 min). According to the current state of knowledge, none of the virus inactivation procedures used during the production of plasma derivatives are able to totally inactivate parvovirus B19 .

Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma derived F VIII concentrates is recommended.

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are IgG immungloblins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma. The risk of developing inhibitors is correlated to the period of exposure to factor VIII treatment, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. See also 4.8.

OCTANATE® should be used with caution in chidren less than 6 years because there is insufficient clinical experience available.

There is no clinical experience for this product in treating von Willebrand's disease.

4.5 Interactions with other medicinal products

No interactions of human factor VIII with other medicinal products are known.

4.6 Pregnancy and lactation

No reliable data are available about the administration of OCTANATE® during pregnancy and lactation. Therefore OCTANATE® should be administered to pregnant or lactating women only if this is absolutely necessary and the benefit outweighs the risk.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Fever, hypersensitivity or allergic reactions (such as rigors, flushing, generalised urticaria, headaches, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing, angioedema, burning and stinging at the infusion site) have been observed infrequently during the administration of factor VIII preparations. The treatment required depends on the nature and severity of the reactions.

Patients with haemophilia A may develop inhibitors to factor VIII. If such inhibitors occur, the condition will manifest as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. Currently, there are no reliable data available concerning to the administration of OCTANATE® to previously unreated patients (PUPs). Therefore previously untreated patients should be carefully monitored for the formation of inhibitors using appropriate laboratory tests (Bethesda Test).

4.9 Overdose

No symptoms of overdose with OCTANATE® have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antihemorrhagics: blood coagulation factor VIII.

ATC code: B02BD02

The factor VIII/von Willebrand factor complex consists of two molecules (FVIII and vWF) with different physiological functions. When infused to a patient, factor VIII binds to vWF in the patient's circulation.

Activated factor VIII acts as a co factor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. The factor VIII activity is greatly reduced in haemophilia A patients and corresponding replacement therapy is required.

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

5.2 Pharmacokinetic properties

The following table gives a summary of the most important pharmacokinetic parameters which have been obtained in clinical studies.

Parameter	Value	Unit
Recovery	2.1 to 2.4	ml/IU/kg
AUC	1100 to 1600	% hour
Half-life	12.8 to 13.7	hour
Mean residence time	16.2 to 18.6	hour
Clearance	2.4 to 3.2	ml/hour/kg

5.3 Preclinical safety data

Factor VIII (in the concentrate) is a normal constituent of human plasma and behaves like the body's own factor VIII.

Even if multiple doses of the usually administered normal dose is given to animals, no toxicity is seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1 ml of solution contains:

Sodium citrate	2.94 mg
Calcium chloride	0.15 mg
Sodium chloride	6.6 mg
Glycine (as stabiliser)	9 mg

6.2 Incompatibilities

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

Only the provided infusion set can be used because treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some infusion sets.

6.3 Shelf life

24 months at +2 °C to + 25 °C.

6.4 Special precautions for storage

Store protected from light at a temperature of +2 °C to + 25 °C. Do not freeze.

Do not use OCTANATE after the expiry date. The reconstituted solution should be used immediately. Any unused solution must be discarded.

6.5 Nature and contents of container

1 vial with lyophilised powder (250 IU or 500 IU) glass type I (Ph. Eur)

1 vial with 5 ml or 10 ml of solvent (water for injections) glass type I (Ph. Eur).

1 infusion set consisting of:

1 disposable syringe, 1 transfer set (1 double-ended needle and 1 filter needle), 1 infusion set, 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!

Instructions for reconstitution:

1. Allow the solvent (Water for Injections) and the concentrate 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 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 vial until the concentrate is completely dissolved. Octanate dissolves quickly at room temperature to a clear solution. The reconstitution time is less than 10 minutes at room temperature.

After reconstitution with the supplied solvent, Octanate is administered intravenously. 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.

The reconstituted solution must be used immediately and on one occasion only.

Instructions for injection:

As a precautionary measure, the patient's pulse rate should be measured before and during the factor VIII 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 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 attach the injection needle to the syringe instead.

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

Patients using more than one vial of OCTANATE concentrate may use the same injection needle and syringe, but the filter needle is for single use only. Always use a filter needle when drawing up the preparation into a syringe.

Do not use OCTANATE after the expiry date. Any unused product or waste material should be disposed of in accordance with local requirements.

7 NAME AND ADDRESS OF PHARMACEUTICAL COMPANY

Marketing authorisation holder

OCTAPHARMA AG
Seidenstrasse 2
CH-8853 Lachen
Switzerland

Manufacturers

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Importeur and Distributor

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8 DATE OF REVISION OF THE TEXT

February 2016

9 PRESCRIPTION STATUS

For prescription only.

Available only in pharmacies.