Proposed English Professional information for Octanate

Scheduling status

S4

Proprietary name (and dosage form)

OCTANATE® 500 (powder for solution for injection)

OCTANATE® 1 000 (powder for solution for injection)

Composition:

a) Strength per vial:

OCTANATE® 500: Contains 500 IU human coagulation factor VIII.
To be reconstituted with the supplied 10 ml water for injections (Ph. Eur.), then containing approximately 50 IU/ml human coagulation factor VIII.

OCTANATE® 1 000: Contains 1 000 IU human coagulation factor VIII.
To be reconstituted with the supplied 10 ml water for injections (Ph. Eur.), then containing approximately 100 IU/ml human coagulation factor VIII.

b) Specific Activity: ≥ 100 IU/mg protein

The potency (IU) is determined using the European Pharmacopoeia (Ph. Eur.) chromogenic assay against the World Health Organisation (WHO) international standard.

Other ingredients:

Powder: calcium hydrochloride, glycine, sodium chloride and sodium citrate.

Solvent: water for injections (Ph. Eur.)

OCTANATE® does not contain any antimicrobial or preserving agents.

Pharmacological classification

A 30.3 Biologicals (Blood fractions)

Pharmacological action

Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics: 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 into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. FVIII is an endogenous glycoprotein responsible for the coagulation activity and haemostasis.

Activated factor VIII acts as a cofactor for 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.

Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C 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 VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

The average normal plasma activity of factor VIII is designated 100 % and a factor VIII concentration of 25 % of normal is required for haemostasis. Patients with a severe haemophilia have a factor VIII concentration of less than 1 % of normal and frequently experience bleeding even in the absence of trauma. Patients with factor VIII concentration between 1 and 5 % (moderate haemophilia) experience less bleeding and patients with a factor VIII concentration greater than 5 % (mild haemophilia) usually experience bleeding only after obvious trauma.

Von Willebrand's disease is characterised by abnormalities of von Willebrand factor (vWF), a large multimeric molecule which is bound to factor VIII. Von Willebrand factor is necessary for platelet adhesion to subendothelial tissue. Due to low level of the carrier protein, vWF, factor VIII levels are also diminished.

Pharmacokinetic properties

Human plasma coagulation factor VIII (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous factor VIII. After injection of the product, approximately two thirds to three-quarters of the factor VIII remain in the circulation. The level of factor VIII activity reached in the plasma should be between 80 % and 120 % of the predicted factor VIII activity.

Plasma factor VIII activity decreases by a two-phase exponential decay. In the initial phase, distribution between the intravascular and other compartments (body fluids) occurs with a half-life of elimination from the plasma of 3 to 6 hours. In the subsequent slower phase (which probably reflects the consumption of factor VIII), the half-life varies between 8 to 20 hours, with an average of 12 hours. This corresponds to the true biological half-life.

For **OCTANATE®** the following results were achieved in pharmacokinetic studies with 10 and 14 patients, respectively:

	Recovery (% x IU^{-1} x kg)	***AUC* norm (% x h x IU^{-1} x kg)***	***Half-life (h)***	***MRT* (h)***	***Clearance (ml x h^{-1} x kg)***
Study 1, n = 10 Mean ± SD*	*2,4 + 0,36*	*45,5 + 17,2*	*14,3 + 4,01*	*19,6 + 6,05*	*2,6 + 1,21*
Study 2, n = 14 Mean ± SD*	*2,4 + 0,25*	*33,4 + 8,50*	*12,6 + 3,03*	*16,6 + 3,73*	*3,2 + 0,88*

AUC = area under curve,*

MRT = mean residence time,*

SD = Standard deviation.*

Indications

Treatment and prophylaxis of bleeding in patients with:

- haemophilia A (congenital factor VIII deficiency)
- acquired factor VIII deficiency
- haemophilia with antibodies against factor VIII

Contraindications

Caution is advised in patients with hypersensitivity to the active substance or to any of the excipients. Factor VIII concentrate should not be used to correct factor IX deficiency (haemophilia B, Christmas disease).

Do not use unless a factor VIII deficiency has been verified.

OCTANATE® should not be the only product used for the treatment of disseminated intravascular coagulation (DIC).

Warnings and Special precautions

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. **OCTANATE®** contains traces of human proteins other than factor VIII. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, and tightness of chest, wheezing, hypotension and anaphylaxis.

If these allergic or anaphylactic reactions occur, patients should be advised to discontinue **OCTANATE®** immediately and contact their physician.

In case of shock, standard medical treatment of shock should be implemented (see "**Side effects**").

The formation of neutralising antibodies, inhibitors, to factor VIII is a known complication in the treatment of individuals with haemophilia A. These inhibitors are IgG immunoglobulins directed against the factor VIII procoagulant activity, which are qualified in modified Bethesda Units (BU) per ml of plasma. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with human coagulation factor VIII should be carefully monitored for the development of inhibitory antibodies by appropriate clinical observations and laboratory tests.
There have been reports in the literature showing a relationship between the occurrence of a factor VIII inhibitor and allergic reactions. Therefore, if allergic reactions occur, the patient should be examined for the presence of an inhibitor. Patients with factor VIII inhibitors may be at an increased risk of anaphylaxis with subsequent treatment with factor VIII. Consequently, the first administration of factor VIII should, according to the treating physician's judgement, be performed under medical supervision where appropriate medical care for allergic reactions can be provided.

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) 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 VIII products.

It is strongly recommended that every time that **OCTANATE®** 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.

Effects on ability to drive and use machines

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

Patients on a controlled sodium diet:

OCTANATE® contains less than 1 mmol sodium (23 mg) per dose, i.e. up to 1,75 mmol sodium (40 mg) per dose for 1 vial **OCTANATE® 500** and **1000**, respectively. It has to be taken into consideration by patients on a controlled sodium diet.

Interactions

There are no known interactions of **OCTANATE®** with other medicinal products.

Incompatibilities

In the absence of compatibility studies, **OCTANATE®** must not be mixed with other medicinal products (see **"Dosage and Directions for use")**

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

Pregnancy and lactation

No animal reproductive and lactation studies have been conducted with **OCTANATE®**. The safety of **OCTANATE®** for use in human pregnancy has not been established. Reproduction studies in animals have not been conducted with **OCTANATE®** and it should therefore be administered to a pregnant or lactating woman only if clearly indicated (see "**Warnings** and **Special precautions**").

Dosage and directions for use:

Special warnings:

OCTANATE® must be administered slowly and intravenously.

If allergic or anaphylactic reactions occur, stop the injection immediately.

Measures to treat anaphylaxis, including adrenaline and corticosteroids, must be at hand when administering.

Do not use turbid or incompletely dissolved solutions.

Incompatibilities:

OCTANATE® must not be mixed with other medicinal products (see "**Interactions"**).

Dosage:

The dosage and duration of the substitution therapy depends on:

- the severity of the disorder of the haemostatic function,
- the location and extent of the bleeding, type of surgery and
- 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 of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body mass raises the plasma factor VIII activity 1,5 % to 2 % of normal.

The required dosage is determined using the following formula:

Required units = body mass (kg) x desired factor VIII rise (%) x 0,5

Important: The amount to be administered and the frequency of application 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 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 VIII level required (%)***	***Frequency (hours) of doses/ Duration (days) of therapy***
Haemorrhage:		
Early haemarthrosis, muscle bleed or oral bleed.	20 to 40	Repeat every 12 to 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 8 to 24 hours until threat is resolved.
Life-threatening bleeds such as head surgery, throat bleed, severe abdominal bleed	60 to 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor – including tooth extraction.	30 to 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	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 VIII activity of 30 % to 60 %

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

In the case of major surgical interventions in particular, a precise monitoring of the substituent 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* recover and demonstrating different half-lives.

For long term prophylaxis against bleeding in patients with severe haemophilia A, doses of 20 to 60 IU of Factor VIII per kg body mass should be given at intervals of 2 to 3 days. In some

cases, especially in younger patients, shorter application intervals or higher doses may be necessary.

There are insufficient data to recommend the use of **OCTANATE®** in children less than 6 years of age.

Patients should be monitored for the development of factor VIII inhibitors. If the expected factor VIII 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 VIII inhibitor is present. If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml, administration of additional human coagulation factor VIII may neutralise the inhibitor. In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) 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.

Method of administration

Dissolve the **OCTANATE®** 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 and handling instructions:

OCTANATE® – Instructions for Home treatment

- **Please read all the instructions and follow them carefully.**
- **Do not use Octanate after expiry date given on the label.**
- **During the procedure described below, sterility must be maintained.**
- **Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration.**

- **The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.**
- **Use the prepared solution immediately, to prevent microbial contamination.**
- **Only use the infusion set provided. The use of other injection/infusion equipment can cause additional risks and treatment failure.**

<u>Instructions for preparing the solution</u>:

1. Do not use the product directly from the refrigerator. Allow the solvent and the powder in the closed vials to reach room temperature.

2. Remove the flip off caps from both vials and clean the rubber stoppers with one of the provided alcohol swabs.

3. The transfer set is depicted in Fig. 1. Place the solvent vial on an even surface and hold it firmly. Take the transfer set and turn it upside down. Place the blue part of the transfer set on top of the solvent vial and press firmly down until it snaps (Fig. 2 + 3). Do not twist while attaching.

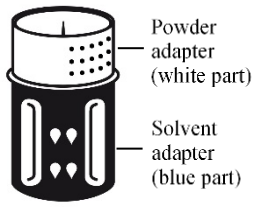


Fig. 1

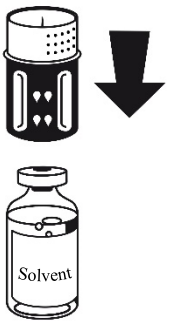


Fig. 2



Fig. 3

4. Place the powder vial on an even surface and hold it firmly. Take the solvent vial with the attached transfer set and turn it upside down. Place the white part on top of the powder vial and press firmly down until it snaps (Fig. 4). Do not twist while attaching. The solvent flows automatically into the powder vial.

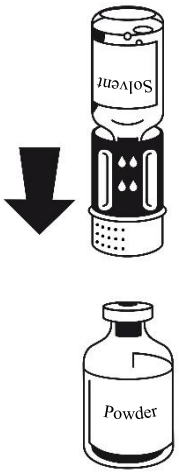


Fig. 4

5. With both vials still attached, gently swirl the powder vial until the product is dissolved.
The dissolving is completed in less than 10 minutes at room temperature. Slight foaming might occur during preparation. Unscrew the transfer set into two parts (Fig. 5). Foaming will disappear.

Dispose the empty solvent vial with the blue part of the transfer set.

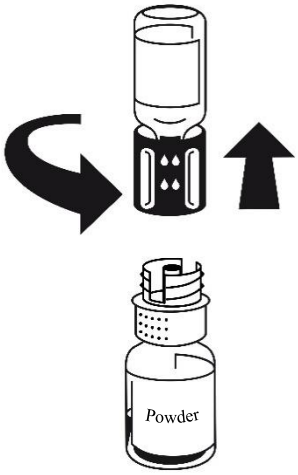


Fig. 5

Instructions for injection

As a precaution, your pulse rate should be taken before and during the injection. If a marked increase in your pulse rate occurs, reduce the injection speed or interrupt the administration for a short time.

1. Attach the syringe to the white part of the transfer set. Turn the vial upside down and draw the solution into the syringe (Fig. 6).
The solution should be clear or slightly opalescent.

Once the solution has been transferred, firmly hold the plunger of the syringe (keeping it facing down) and remove the syringe from the transfer set (Fig. 7). Dispose the empty vial together with the white part of the transfer set.

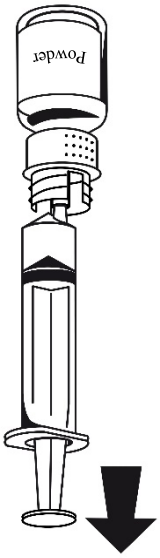


Fig. 6

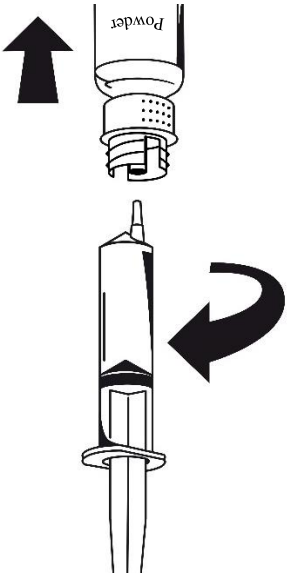


Fig. 7

2. Clean the chosen injection site with one of the provided alcohol swabs.
3. Attach the provided infusion set to the syringe
4. Insert the injection needle into the chosen vein. If you have used a tourniquet to make the vein easier to see, this tourniquet should be released before you start injecting **OCTANATE®**.
5. No blood must flow into the syringe due to the risk of formation of fibrin clots.
6. Inject the solution into the vein at a slow speed, not faster than 2 - 3 ml per minute.

If you use more than one vial of **OCTANATE®** powder for one treatment, you may use the same infusion set and syringe again. The transfer set is for single use only.

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

If you use more OCTANATE® than you should

No symptoms of overdose with human coagulation factor VIII have been reported. However, the recommend dosage should not be exceeded.

If you forget to use OCTANATE®

Do not take a double dose to make up for a forgotten dose. Proceed with the next dose immediately and continue as advised by your doctor or pharmacist.

Side effects

- Allergic reactions or anaphylactic reactions are observed in rare cases. Indications for an increased sensitivity can vary from burning and or stinging at the injection site, hives, hypotension, lethargy, restlessness, tachycardia, tingling, chills, nausea, vomiting, generalised urticaria, tightness of the chest, shortness of breath, wheezing, flushing, headache, angioedema and may in some cases progress to severe anaphylaxis including anaphylactic shock.

  If allergic or anaphylactic reactions occur, the injection must be stopped immediately and a physician consulted. Light reactions may be controlled with glucocorticoides and/or anthistamines. Severe circulatory disorders should be treated according to the current specific guidelines of shock therapy.
- On rare occasions, fever has been observed.
- Other side effects include angio-oedema, flushing, headache, light-headedness and visual disturbances
- Patients with haemophilia A may develop antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest as an insufficient clinical response. Treatment of such patients requires the expertise of a specialised haemophilia centre.

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 ,000); very rare (<1/10 000), not known (cannot be estimated from the available data).

System Organ Class	Rare	Very rare
Immune system disorders	hypersensitivity reaction	anaphylactic shock
General disorders and administration site conditions	fever	
Investigations	Factor VIII antibodies in blood	

Known symptoms of overdosage and particulars of treatment

No cases of overdose with **OCTANATE®** have been reported. No symptoms of overdose are known. Treatment is supportive and symptomatic.

Identification

OCTANATE® 500:

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

Reconstituted solution: Clear to slightly opalescent and colourless.

OCTANATE® 1 000:

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

Reconstituted solution: Clear to slightly opalescent and colourless.

Presentation

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

1 carton contains the powder for solution for injection supplied in a labelled 30 ml vial of glass type 1 (Ph. Eur.) closed with a bromobutyl rubber stopper of type 1 (Ph. Eur.) and sealed with a 20 mm blue aluminium flip-off cap.

1 carton contains the solvent water for injections (Ph. Eur.), 10 ml for **OCTANATE® 500** and **OCTANATE® 1 000**. It is supplied in labelled 10 ml glass vials of type 1 (Ph. Eur.) quality closed with bromobutyl 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 transfer set
- 1 infusion set
- 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 turbid or incompletely dissolved solutions.

KEEP OUT OF REACH OF CHILDREN.

Registration numbers:

OCTANATE® 500: 36/30.3/0345

OCTANATE® 1 000: 36/30.3/0346

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

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