Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Octanate 500 IU powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Octanate 100 IU/ml contains nominally 500 IU human coagulation factor VIII per vial.
The product contains approximately 100 IU* per ml human coagulation factor VIII when reconstituted with 5 ml of solvent.
The product contains approximately ≤ 60 IU per ml von Willebrand factor (VWF:RCo).

* The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The mean specific activity of Octanate LV is ≥ 100 IU/mg protein.
Produced from the plasma of human donors.
Excipient with known effect:
Sodium up to 1.75 mmol (40 mg) per dose
Sodium concentration after reconstitution: 250 – 350 mmol/l

For the 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 mass.
The solvent is a clear, colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)
Octanate can be used for all age groups.
This preparation does not contain von Willebrand factor in pharmacologically effective quantities and is therefore not indicated in von Willebrand's disease.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.
Treatment monitoring
During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. 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.

Posology

The dose and duration of the substitution therapy depend on the severity of the 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 concentrate 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 one ml of normal human plasma.

On-demand treatment

The calculation of the required dosage of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1.5 % to 2 % of normal activity. The required dosage is determined using the following formula:

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

The amount to be administered and the frequency of administration 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 (%) (IU/dl)**	**Frequency of doses (hours) / Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat every 12 to 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 12 to 24 hours for 3 to 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- 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%.

Prophylaxis

For long-term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days.

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

Continuous infusion
Prior to surgery, a pharmacokinetic analysis should be performed to obtain an estimate of clearance.
The initial infusion rate can be calculated as follows: Clearance x desired steady state level = infusion rate (IU/kg/hr).
After the initial 24 hours of continuous infusion, the clearance should be calculated again every day using the steady state equation with the measured level and the known rate of infusion.Paediatric population

A clinical study which was conducted in 15 patients of 6 years of age or less did not identify any special dosage requirements for children.
For both treatment and prophylaxis, the posology is the same in adults and children.

Method of administration

Intravenous use.
It is recommended not to administer more than 2 - 3 ml per minute.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions are possible with Octanate. The product contains traces of human proteins other than factor VIII. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

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

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days, but continues throughout life although the risk is uncommon
The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.
In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII 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 haemophilia and factor VIII inhibitors.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

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 virus 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 (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. hemolytic 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 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.
This medicinal product contains up to 1.75 mmol sodium (40 mg) per vial, equivalent to 2% of the WHO recommended maximum intake of 2 g sodium for an adult.

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angiooedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, chest tightness, tingling, vomiting, wheezing) have been observedrarly, and may in some cases progress to severe anaphylaxis (including shock).
On rare occasions, fever has been observed.
Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Octanate LV see section 5.1. 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.
For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).
Frequencies have been evaluated according to the following convention: 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).

MedDRA Standard System Organ Class	Adverse Reaction	Frequency
Immune system disorders	Hypersensitivity reaction Anaphylactic shock	Rare Very rare
General disorders and administration site conditions	Pyrexia	Rare
Blood and lymphatic system disorders	FVIII inhibition	Uncommon (PTPs)* Very common (PUPs)*
Investigations	Anti factor VIII antibody positive	Rare

*** Frequency is based on studies with all FVIII products which included patients with severe haemophilia A.**
PTPs = previously-treated patients, PUPs = previously-untreated patients

Paediatric population

Frequency, type and severity of adverse reactions in children are the same as in adults.

Reporting of suspected adverse reactions
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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

No case of overdose has 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 into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation.
Activated factor VIII acts as a cofactor 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. 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 results 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.
Of note, annualized bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

Previously untreated patients

<≤The development of antibodies to FVIII occurs mainly in previously untreated patients (PUPs). In a prospective, open-label study assessing the immunogenicity of Octanate in PUPs, 51 patients were included. 20 patients were primarily treated on demand and 31 patients were treated prophylactically. 44 patients met the criteria for assessing immunogenicity (i.e. >50 EDs and FVIII:C<1%). Inhibitors disappeared during regular Octanate treatment without a change in dose or treatment frequency in two out of five patients with inhibitors (one with a high-titer and one with a low-titer inhibitor). All inhibitors were detected in patients treated on-demand. Mean times to high-titer and low-titer inhibitor development were 10 EDs (range 3-19) and 48 ED, respectively.

Octanate is being assessed for induction of immune tolerance induction (ITI) therapy in an ongoing observational clinical study. In an interim analysis of the 69 patients so far treated with Octanate via ITI, 49 patients have completed the study. In the patients where the inhibitor was successfully eliminated, the monthly bleeding rates were significantly reduced.

5.2 Pharmacokinetic properties

Human plasma coagulation factor VIII (from the powder) 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-quarter of the factor VIII remain in the circulation. The level of factor VIII activity reached in the plasma should be between 80% - 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 for two pharmacokinetic studies with 10 and 14 haemophilia A 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 the curve,
MRT* = mean residence time,
SD* = standard deviation

5.3 Preclinical safety data

Toxicological data available on tri-n-butylphosphate (TNBP) and polysorbate 80 (tween 80), the solvent/detergent reagents used in the SD method of viral inactivation during manufacture of Octanate, although limited for the latter, indicate that adverse effects are unlikely at the anticipated human exposures.
Even doses of several times the recommended human dosage per kilogram body weight of these reagents show no toxic effects on laboratory animals. No mutagenic potential was observed for either of the two substances.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

- Sodium citrate
- Sodium chloride
- Calcium chloride
- Glycine

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

6.3 Shelf life

2 years
The reconstituted solution must be used immediately and for single use only.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vials in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 package Octanate contains:

- Powder in a vial (type I glass), with a stopper (bromobutyl rubber), and a flip off cap
- solvent in a vial (type I glass), with a stopper (bromobutyl rubber), and a flip off cap
- 1 equipment pack for intravenous injection (1 transfer set, 1 infusion set, 1 disposable syringe)
- 2 alcohol swabs

6.6 Special precautions for disposal and other handling

- 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.

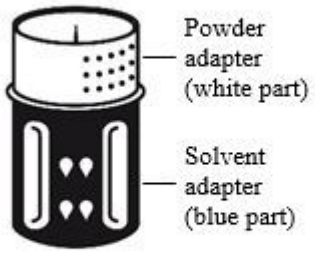

Fig. 1

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.

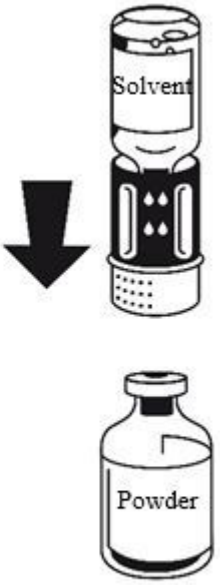

Fig. 4

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.

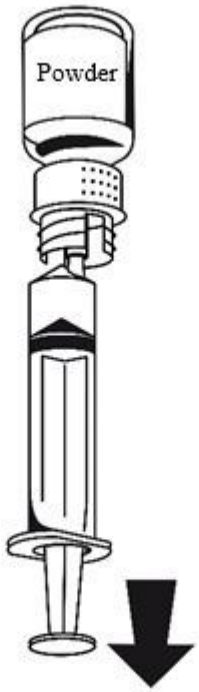

Fig. 6

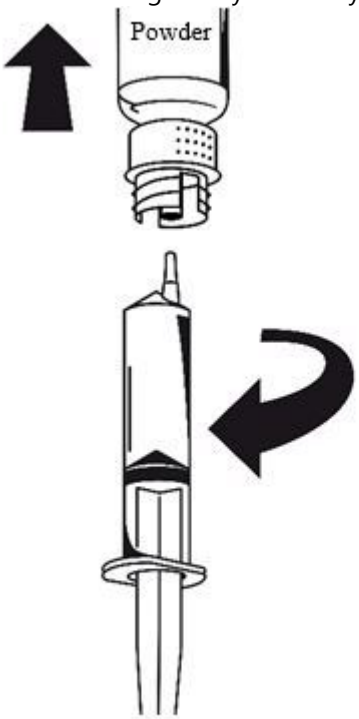

Fig. 7

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 mak
the vein easier to see, this tourniquet should be released before you start injectin
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 sam
injection needle and syringe again. The transfer set is for single use only.

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

7 MARKETING AUTHORISATION HOLDER

Octapharma (IP)
Lennikse Baan 451
Anderlecht
Brussels-Capital Region
1070
Belgium

8 MARKETING AUTHORISATION NUMBER

PA2219/004/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th May 2018
Date of last renewal: 13th October 2019

10 DATE OF REVISION OF THE TEXT

October 2025