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 - 25°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 (chlorobutyl or bromobutyl rubber), and a flip off cap
– one disposable syringe, one double ended needle, one filter needle, one injection needle, and two alcohol swabs

The available pack sizes differ in the amount of human blood coagulation factor VIII/ solvent:
250 IU/vial: reconstitution with 5 ml
500 IU/vial: reconstitution with 10 ml
1000 IU/vial: reconstitution with 10 ml

Not all pack sizes may be marketed.

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

7 NAME AND ADDRESS OF PHARMACEUTICAL COMPANY

7.1 Product registration holder

Pharmaniaga Marketing Sdn Bhd (198401005734)
No. 7, Lorong Keluli 1B, Kaw. Perindustrian Bukit Raja Selatan, Seksyen 7, 40000 Shah Alam, Selangor Darul Ehsan, Malaysia

7.2 Manufacturer

Octapharma AB, 112 75 Stockholm, Sweden

8 DATE OF REVISION OF THE TEXT

July 2022

9 LEGAL CATEGORY

For prescription only.

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Octanate 50 IU/ml Powder and solvent for solution for injection
Octanate 100 IU/ml Powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Octanate 50 IU/ml
Each vial contains nominally either 250 IU or 500 IU human coagulation factor VIII.
The product contains approximately 50 IU* per ml human coagulation factor VIII when reconstituted with the supplied solvent (5 ml for 250 IU/vial and 10 ml for 500 IU/vial).
The product contains approximately ≤ 30 IU per ml von Willebrand factor (VWF:RCo).

Octanate 100 IU/ml
Each vial contains nominally 1000 IU human coagulation factor VIII.
The product contains approximately 100 IU* per ml human coagulation factor VIII when reconstituted with 10 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 specific activity is ≥ 100 IU/mg protein.
Produced from the plasma of human donors.
Excipient with known effect:
250 IU/vial: less than 1 mmol sodium (23 mg) per dose, i.e. essentially `sodium-free`
500 IU/vial: Sodium up to 1.75 mmol (40 mg) per dose
1000 IU/vial: Sodium up to 1.75 mmol (40 mg) per dose
Sodium concentration after reconstitution: 125 – 175 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 solid.
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.

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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 preferably 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) × desired factor VIII rise (%) (IU/dl) × 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 less than 1 mmol sodium (23 mg) per vial, i.e. essentially `sodium-free` for 250 IU/vial and contains up to 1.75 mmol sodium (40 mg) per vial for 500 IU/vial and 1000 IU/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 observed rarely 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 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 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 medical product is important. It allows continued monitoring of the benefit/risk balance of the medical product. Healthcare professionals are asked to report any suspected adverse reactions.

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 × kg)	AUC*norm (% × h × IU-1 × kg)	Half-life (h)	MRT* (h)	Clearance (ml × h-1 × 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.