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.

6.4 Special precautions for storage
Store at 2°C – 8°C. Do not freeze.
Keep the vials 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
Powder in a vial (type I glass), with a stopper (halobutyl rubber), and a flip off cap; solvent in a vial (type I glass), with a stopper (halobutyl 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:
OCTANATE 250 IU: reconstitution with 5 ml of solvent
OCTANATE 500 IU: reconstitution with 10 ml of solvent
OCTANATE 1000 IU: reconstitution with 10 ml of solvent
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. MARKETING AUTHORISATION HOLDER
Marketing authorisation holder and Manufacturer:
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna
Austria

Distributed in Lebanon by: MPC
phone +961.1.545544
www.MPC-pharma.com
Reg. numbers: 208373/02 (250 IU), 208374/02 (500 IU), 208375/02 (1000 IU)

8. DATE OF REVISION OF THE TEXT
May 2010

9. LEGAL CATEGORY
For prescription only.

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INSTRUCTION FOR USE
(Summary of Product Characteristics)

1. NAME OF THE MEDICINAL PRODUCT
OCTANATE 250, 250 IU powder and solvent for solution for injection
OCTANATE 500, 500 IU powder and solvent for solution for injection
OCTANATE 1000, 1000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE 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.

OCTANATE 1000 IU is presented as powder and solvent for solution for injection containing nominally 1000 IU human coagulation factor VIII per vial.

The product contains approximately 100 IU* per ml human coagulation factor VIII when reconstituted with 10 ml of solvent.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free" for 1 vial OCTANATE 250 IU and up to 1.75 mmol sodium (40 mg) per dose for 1 vial OCTANATE 500 IU and 1000 IU, respectively. To be taken into consideration by patients on a controlled sodium diet.

For a full list of excipients, see section 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 prevention of bleeding episodes in patients with hemophilia A (congenital or acquired FVIII deficiency), including previously treated patients (PTPs), previously untreated patients (PUPs) and patients undergoing major and minor surgical procedures; and for the treatment of inhibitors by Immune Tolerance Induction (ITI).

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

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

The amount and frequency of administration should always be adjusted according to the clinical effectiveness in the individual patient.
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 3-4 days or more until pain and disability are resolved.
Life threatening haemorrhages	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor including tooth extraction	30 – 60	Every 24 hours, at least 1 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%.

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. In the case of major surgical interventions in particular, a 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 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.
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.
In an interim analysis of the ongoing clinical trial AVI-403, 4 out of 39 (10.3%) PUP patients treated with OCTANATE® developed inhibitors. Detection of inhibitors with a titer above 5 BU occurred at 3, 6 and 19 EDs in 3 patients treated on demand. One other PUP developed a transient, low-titer inhibitor of 2.1 BU at ED 48. Two of these subjects underwent ITI in an attempt to eradicate the inhibitors; the other subject's inhibitor disappeared autonomously without modification to his continuing on-demand treatment. (see section 4.8).
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. 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 patients with haemophilia. See also 4.4.
Interim data of an ongoing investigator initiated study to systematically document patients undergoing ITI therapy with OCTANATE® are available. The OCTANATE® dosing regime is case-dependent, under the direction of the treating center for each individual. Low responders (inhibitors < 5 BU) generally receive 50–100 IU FVIII/kg daily, or every second day, and high responders (inhibitors ≥ 5 BU) 100–150 IU/kg every 12 hours. Inhibitor titers are measured up to twice weekly for the initial 3 months and thereafter once per 3-month scheduled visit at the treatment center for the duration of therapy. Over 36 months, the outcome of ITI therapy is determined according to 3 sequential criteria, including inhibitor titre (> 0.6 BU for ≥ 2 consecutive determinations), recovery (≥ 66% of 1.5% per IU/kg for ≥ 2 consecutive determinations) and half life (FVIII t1/2 of ≥ 6 hours). Data from 41 subjects enrolled at the time of the second interim analysis of this ongoing study show that 19 subjects have completed the study (i.e. have been tolerized, have reached 36 months, or have been withdrawn by the Investigator). Of these, 15 (78.9%) have been successfully tolerized, 1 (5.3%) achieved a partial response and 3 (15.8%) failed.

Method of administration
Dissolve the preparation as described under 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.

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 VIII. 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 of shock should be implemented.
– The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication of the treatment 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 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 test. See also 4.8. Undesirable effects
– 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 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 (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, 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.

4.5 Interaction with other medicinal products and other forms of interaction
No interactions of human coagulation factor VIII products with other medicinal products.

4.6 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
No effects on ability to drive and use machines have been observed.

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4.8 Undesirable effects
– 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 infrequently, and may in some cases progress to severe anaphylaxis (including shock).
– On rare occasions, fever has been observed.
– Patients with haemophilia A may develop antibodies (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.
In an interim analysis of the ongoing clinical trial AVI-403, 4 out of 39 (10.3%) PUP patients treated with OCTANATE® developed inhibitors. Detection of inhibitors with a titer above 5 BU occurred at 3, 6 and 19 EDs in 3 patients treated on demand. One other PUP developed a transient, low-titer inhibitor of 2.1 BU at ED 48. Two of these subjects underwent ITI in an attempt to eradicate the inhibitors; the other subject's inhibitor disappeared autonomously without modification to his continuing on-demand treatment. In 35 PUPs had a baseline FVIII activity < 1% and 4 PUPs had ≤ 2% FVIII:C. All PUPs were planned to be treated on-demand. During the study, 12 PUPs underwent 14 surgical procedures. The median age at the first exposure was 7 months (range 3 days to 67 months). The median number of exposure days in the clinical trial was 100 (range 1–553). 34 of 39 patients had more than 20 exposure days.

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	

rare (>=1/10,000, <1/1,000)
very rare (<1/10,000), including isolated reports

– For information on viral safety see 4.4.

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.

5.2 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-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 (% × 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.
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