ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

ReFacto AF 250 IU powder and solvent for solution for injection
ReFacto AF 500 IU powder and solvent for solution for injection
ReFacto AF 1000 IU powder and solvent for solution for injection
ReFacto AF 2000 IU powder and solvent for solution for injection
ReFacto AF 250 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 500 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 1000 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 2000 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 3000 IU powder and solvent for solution for injection in pre-filled syringe

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

ReFacto AF 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 62.5 IU moroctocog alfa.

ReFacto AF 500 IU powder and solvent for solution for injection
Each vial contains nominally 500 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 125 IU moroctocog alfa.

ReFacto AF 1000 IU powder and solvent for solution for injection
Each vial contains nominally 1000 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 250 IU moroctocog alfa.

ReFacto AF 2000 IU powder and solvent for solution for injection
Each vial contains nominally 2000 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 500 IU moroctocog alfa.

ReFacto AF 250 IU powder and solvent for solution for injection in pre-filled syringe
Each pre-filled syringe contains nominally 250 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 62.5 IU moroctocog alfa.

ReFacto AF 500 IU powder and solvent for solution for injection in pre-filled syringe
Each pre-filled syringe contains nominally 500 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 125 IU moroctocog alfa.

ReFacto AF 1000 IU powder and solvent for solution for injection in pre-filled syringe
Each pre-filled syringe contains nominally 1000 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 250 IU moroctocog alfa.

ReFacto AF 2000 IU powder and solvent for solution for injection in pre-filled syringe
Each pre-filled syringe contains nominally 2000 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 500 IU moroctocog alfa.

ReFacto AF 3000 IU powder and solvent for solution for injection in pre-filled syringe
Each pre-filled syringe contains nominally 3000 IU* moroctocog alfa**.
After reconstitution, each mL of solution contains approximately 750 IU moroctocog alfa.

* The potency (International Units) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ReFacto AF is 7,600-13,800 IU/mg protein.

** Human coagulation factor VIII produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Moroctocog alfa is a glycoprotein with 1438 amino acids with a sequence that is
comparable to the 90 + 80 kDa form of factor VIII (i.e. B-domain deleted) and similar post-translational modifications to those of the plasma-derived molecule.

The manufacturing process for ReFacto was modified to eliminate any exogenous human- or animal-derived protein in the cell culture process, purification, or final formulation; and at the same time the invented name was changed to ReFacto AF.

Excipient with known effect:

After reconstitution, 1.23 mmol (29 mg) sodium per vial or pre-filled syringe

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU powder and solvent for solution for injection
Powder and solvent for solution for injection
White to off-white cake/powder
Clear, colourless solvent

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection in pre-filled syringe
Powder and solvent for solution for injection in pre-filled syringe
White to off-white cake/powder in top chamber of the pre-filled syringe
Clear, colourless solvent in bottom chamber of the pre-filled syringe

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ReFacto AF is appropriate for use in adults and children of all ages, including newborns.

ReFacto AF does not contain von Willebrand factor, and hence is not indicated in von Willebrand’s disease.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia A.

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.
When monitoring patients’ factor VIII activity levels during treatment with ReFacto AF, use of the chromogenic assay is recommended. When using an in vitro thromboplastin time (aPTT)-based one-stage clotting assay for determining factor VIII activity in patients’ blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one-stage clotting assay and the chromogenic assay. Typically, one-stage clotting assay results are 20-50% lower than the chromogenic substrate assay results. The ReFacto AF laboratory standard can be used to correct for this discrepancy (see section 5.2). This is of importance particularly when changing the laboratory and/or reagents used.

**Posology**

The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of bleeding, and on the patient’s clinical condition. Doses administered should be titrated to the patient's clinical response. In the presence of an inhibitor, higher doses or appropriate specific treatment may be required.

The number of units of factor VIII administered is expressed in International Units (IUs), 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 IU (relative to an International Standard for factor VIII in plasma). One IU of factor VIII activity is equivalent to the quantity of factor VIII in one mL of normal human plasma.

Another moroctxocog alfa product approved for use outside Europe has a different manufacturing potency assigned that has been calibrated to the WHO International Standard using a one-stage clotting assay; this product is identified by the tradename XYNTHA. Due to the difference in methods used to assign product potency of XYNTHA and ReFacto AF, 1 IU of the XYNTHA product (one-stage assay calibrated) is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated). If a patient normally treated with XYNTHA is prescribed ReFacto AF, the treating physician may consider adjustment of dosing recommendations based on factor VIII recovery values.

Based on their current regimen, individuals with haemophilia A should be advised to bring an adequate supply of factor VIII product for anticipated treatment when travelling. Patients should be advised to consult with their healthcare provider prior to travel.

**On demand treatment**

The calculation of the required dose of factor VIII is based upon the empirical finding that 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dose is determined using the following formula:

\[
\text{Required units (IU)} = \text{body weight (kg)} \times \text{desired factor VIII rise (\% or IU/dl)} \times 0.5 \text{ (IU/kg per IU/dl)},
\]

where 0.5 IU/kg per IU/dl represents the reciprocal of the recovery generally observed following infusions of factor VIII.

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 levels (in % of normal or in IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

<table>
<thead>
<tr>
<th>Degree of haemorrhage/Type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20-40</td>
<td>Repeat every 12-24 hours. At least 1 day until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30-60</td>
<td>Repeat infusion every 12-24 hours for 3-4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages</td>
<td>60-100</td>
<td>Repeat infusion every 8-24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor, including tooth extraction</td>
<td>30-60</td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and post-operative)</td>
<td>80-100</td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).</td>
</tr>
</tbody>
</table>

**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 dose intervals or higher doses may be necessary.

**Paediatric population**

The need for an increased dose relative to that used for adults and older children should be anticipated when treating younger children (less than 6 years of age) with ReFacto AF. In a study of ReFacto in children less than 6 years of age, pharmacokinetic analysis revealed half-life and recovery less than that observed in older children and adults (see section 5.2). During the clinical trials, children less than 6 years of age on a prophylaxis regimen used an average dose of 50 IU/kg of ReFacto and experienced an average of 6.1 bleeding episodes per year. Older children and adults on a prophylaxis regimen used an average dose of 27 IU/kg and experienced an average of 10 bleeding episodes per year. In a clinical trial setting the mean dose per infusion of ReFacto for bleeding episodes in children less than 6 years of age was higher than the mean dose administered to older children and adults (51.3 IU/kg and 29.3 IU/kg, respectively).

**Elderly population**

Clinical studies did not include subjects aged 65 and over. In general, dose selection for an elderly patient should be individualised.
Renal or hepatic impairment

Dose adjustment for patients with renal or hepatic impairment has not been studied in clinical trials.

Method of administration

Intravenous use.

ReFacto AF is administered by intravenous infusion over several minutes after reconstitution of the lyophilised powder for injection with sodium chloride 9 mg/mL (0.9%) solution for injection (provided). The rate of administration should be determined by the patient’s comfort level. Appropriate training is recommended for non-healthcare professionals administering the product.

For reconstitution instructions prior to administration, see section 6.6.

4.3 Contraindications

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

Known allergic reaction to hamster protein.

4.4 Special warnings and special precautions for use

Hypersensitivity

Allergic type hypersensitivity reactions have been observed with ReFacto AF. The medicinal product contains traces of hamster proteins. 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 for 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 20 exposure days. Rarely inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently 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.

Reports of lack of effect

Reports of lack of effect, mainly in prophylaxis patients, have been received in the clinical trials and in the post-marketing setting for ReFacto. The reported lack of effect with ReFacto has been described as bleeding into target joints, bleeding into new joints or a subjective feeling by the patient of new onset bleeding. When prescribing ReFacto AF it is important to individually titrate and monitor each patient's factor level in order to ensure an adequate therapeutic response (see section 4.8).

It is strongly recommended that every time ReFacto AF is administered to a patient, the name on the carton and batch number of the product are recorded in order to maintain a link between the patient and the batch number of the medicinal product. Patients can affix one of the peel-off labels found on the vial or pre-filled syringe to document the batch number in their diary or for reporting any side effects.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with factor VIII 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 (see section 4.8).

Sodium content

After reconstitution this medicinal product contains 1.23 mmol (29 mg) sodium per vial or pre-filled syringe, to be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of recombinant 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, therefore no data are available on fertility. Because of 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 breast-feeding only if clearly indicated.

4.7 Effects on ability to drive and use machines

ReFacto AF 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 angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently for ReFacto, and may in some cases progress to severe anaphylaxis including shock (see section 4.4).
Trace amounts of hamster protein may be present in ReFacto AF. Very rarely, development of antibodies to hamster protein has been observed, but there were no clinical sequelae. In a study of ReFacto, twenty of 113 (18%) previously treated patients (PTPs) had an increase in anti-CHO antibody titre, without any apparent clinical effect.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with ReFacto AF (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.

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) and uncommon (≥ 1/1,000 to < 1/100). The table lists adverse reactions reported in the clinical trials with ReFacto or ReFacto AF. The frequencies are based on all causality treatment emergent adverse events in pooled clinical trials with 655 subjects (554 PTPs, 101 previously untreated patients (PUPs)).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common ≥ 1/10</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥ 1/1,000 to &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>FVIII inhibition (PUPs)*</td>
<td>FVIII inhibition (PTPs)**</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Anaphylactic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td>Neuropathy peripheral; somnolence; dysgeusia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td>Angina pectoris; tachycardia; palpitations</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Haemorrhage; haematoma</td>
<td></td>
<td>Hypotension; thrombophlebitis; flushing</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td></td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea; vomiting; abdominal pain; nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria; rash; pruritus</td>
<td></td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>Chills; catheter site related reaction</td>
<td>Asthenia; injection site reaction; injection site pain; injection site inflammation</td>
</tr>
<tr>
<td>Investigations</td>
<td>Antibody test positive; Anti-factor VIII antibody test positive</td>
<td></td>
<td>Aspartate aminotransferase increased; alanine aminotransferase increased; blood bilirubin increased; blood creatinine phosphokinase increased</td>
</tr>
</tbody>
</table>

* Only applicable to PUPs
** Only applicable to PTPs
Paediatric population

One event of cyst in an 11-year old patient and one event described as confusion in a 13-year old patient have been reported as possibly related to ReFacto AF treatment.

Safety of ReFacto AF was evaluated in previously treated children and adolescents (n=18, age 12-16 years in a study and n=49, age 7-16 years in a supporting study). Although a limited number of children have been studied, there is a tendency for higher frequencies of adverse reactions in children aged 7-16 years as compared to adults. Clinical trials evaluating use of ReFacto AF in children less than 6 years of age are ongoing.

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 the national reporting system listed in Appendix V.

4.9 Overdose

No symptoms of overdose have been reported with recombinant coagulation factor VIII products.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII; ATC code: B02BD02.

ReFacto AF contains B-domain deleted recombinant coagulation factor VIII (morocctocog alfa). It is a glycoprotein with an approximate molecular mass of 170,000 Da consisting of 1438 amino acids. ReFacto AF has functional characteristics comparable to those of endogenous factor VIII. Factor VIII activity is greatly reduced in patients with haemophilia A, and, therefore, replacement therapy is necessary.

When infused into a haemophiliac patient, factor VIII binds to the von Willebrand factor present 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 is 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.

Factor VIII inhibition

Within a pooled dataset of 554 PTPs treated with ReFacto (1 clinical study) or ReFacto AF (5 clinical studies), there were 8 (1.4%) confirmed factor VIII inhibitor cases (1 high-titre (≥ 5 BU/mL), 7 low-titre (< 5 BU/mL)).
In a clinical study with ReFacto AF in previously treated patients (PTPs) (factor VIII:C ≤ 2%), the incidence of factor VIII inhibitors was the primary safety endpoint. Two clinically silent, low-titre, transient inhibitors were observed in 94 patients with a median exposure of 76 exposure days (ED, range 1-92), corresponding to 2.2% of the 89 patients with at least 50 ED. In a supporting study of ReFacto AF, 1 de novo and 2 recurrent inhibitors (all low-titre, central laboratory determination) were observed in 110 patients (PTPs) (factor VIII:C ≤ 2%); median exposure of 58 ED (range 5-140) and 98 patients had at least 50 ED to ReFacto AF. Ninety-eight (98) of the original 110 patients continued treatment in a second supportive study and had subsequent extended exposure to ReFacto AF with a median of 169 additional ED (range 9-425). One (1) additional low-titre de novo inhibitor was observed.

In a clinical study of PTPs with haemophilia A (factor VIII:C ≤ 2%) undergoing major surgery, 1 low-titre inhibitor was observed in 30 patients who received treatment with ReFacto AF.

In a clinical study with ReFacto in PTPs (factor VIII:C < 2%), 1 high-titre inhibitor was observed in 113 patients.

**Immune Tolerance Induction**

Data on immune tolerance induction (ITI) have been collected in patients with haemophilia A who had developed inhibitors to factor VIII. As part of the pivotal trial with ReFacto in PUPs, ITI data from 25 patients were reviewed (15 with high titres, 10 with low titres). Of these 25 patients, 20 had a decrease in inhibitor titres to < 0.6 BU/mL, of whom initially 11 of 15 had high titres (≥ 5 BU/mL) and 9 of 10 had low titres. Out of 6 patients who developed low titre inhibitors but did not receive ITI, 5 had similar titre decreases. No long-term outcome is available.

**5.2 Pharmacokinetic properties**

Pharmacokinetic properties of ReFacto, derived from a cross-over study of ReFacto and a plasma-derived FVIII concentrate, using the chromogenic substrate assay (see section 4.2), in 18 previously treated patients are listed in the table below.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_t (IU·h/mL)</td>
<td>19.9</td>
<td>4.9</td>
<td>19.9</td>
</tr>
<tr>
<td>t_1/2 (h)</td>
<td>14.8</td>
<td>5.6</td>
<td>12.7</td>
</tr>
<tr>
<td>CL (mL/h·kg)</td>
<td>2.4</td>
<td>0.75</td>
<td>2.3</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>20.2</td>
<td>7.4</td>
<td>18.0</td>
</tr>
<tr>
<td>recovery (IU/dl increase in FVIII:C per IU/kg FVIII given)</td>
<td>2.4</td>
<td>0.38</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Abbreviations: AUC_t = area under the plasma concentration-time curve from zero to the last measurable concentration; t_1/2 = half-life; CL = clearance; FVIII:C = FVIII activity; MRT = mean residence time

In a study in which the potency of ReFacto AF, ReFacto and FVIII activity in patient plasma were measured using the chromogenic substrate assay, ReFacto AF was shown to be bioequivalent to ReFacto. The ratios of geometric least-square means of ReFacto AF-to-ReFacto were 100.6%, 99.5% and 98.1% for recovery, AUC_t and AUC∞ (area under the plasma concentration curve from time zero to infinity), respectively. The corresponding 90% confidence intervals about the ratios of ReFacto AF to ReFacto geometric means were within the bioequivalence window of 80% to 125%, demonstrating bioequivalence of ReFacto AF to ReFacto.

In a cross-over pharmacokinetic study, the pharmacokinetic parameters for ReFacto AF were determined at baseline and followed up in 25 previously treated patients (≥ 12 years) after repeated administration of ReFacto AF for six months. The ratios of geometric least-square means of month 6-to-baseline pharmacokinetic were 107%, 100% and 104% for recovery, AUC_t and AUC∞, respectively. The corresponding 90% confidence intervals about the ratios of month 6-to-baseline for
the above pharmacokinetic parameters were within the equivalence window of 80% to 125%. This indicates no time-dependent changes in the pharmacokinetic properties of ReFacto AF.

In the same study, in which the drug potency of ReFacto AF and a full-length recombinant factor VIII (FLrFVIII) comparator, and the FVIII activity measured in patient plasma samples were all determined using the same one-stage clotting assay at a central laboratory, ReFacto AF was shown to be pharmacokinetically equivalent to FLrFVIII in 30 previously treated patients (≥ 12 years) using the standard bioequivalence approach.

In PUPs, pharmacokinetic parameters of ReFacto were evaluated using the chromogenic assay. These patients (n=59; median age 10 ± 8.3 months) had a mean recovery at Week 0 of 1.5 ± 0.6 IU/dl per IU/kg (range 0.2 to 2.8 IU/dl per IU/kg) which was lower than that obtained in PTPs treated with ReFacto at Week 0 with a mean recovery of 2.4 ± 0.4 IU/dl per IU/kg (range 1.1 to 3.8 IU/dl per IU/kg). In the PUPs, the mean recovery was stable over time (5 visits during a 2-year period) and ranged from 1.5 to 1.8 IU/dl per IU/kg. Population pharmacokinetic modeling using data from 44 PUPs led to a mean estimated half-life of 8.0 ± 2.2 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

No investigations on carcinogenic potential or toxicity to reproduction have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Calcium chloride dihydrate
L-Histidine
Polysorbate 80
Sodium chloride

Solvent
Sodium chloride
Water for injections

6.2 Incompatibilities

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

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

6.3 Shelf life

3 years.

The product may be removed from refrigerated storage for one single period of maximum 3 months at room temperature (up to 25°C). At the end of this period of room temperature storage, the product must not be returned to refrigerated storage, but is to be used or discarded.
After reconstitution

Chemical and physical in-use stability has been demonstrated for 3 hours at temperatures up to 25°C.

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU powder and solvent for solution for injection
The product does not contain a preservative, and the reconstituted product should be used immediately, or within 3 hours after reconstitution. Other in-use storage times and conditions are the responsibility of the user.

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection in pre-filled syringe
The product does not contain a preservative, and the reconstituted product should be used immediately, or within 3 hours after reconstitution or removal of the grey tip cap. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU powder and solvent for solution for injection
ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection in pre-filled syringe
Store and transport refrigerated (2°C - 8°C). Do not freeze.

Keep the product 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

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection
250 IU, 500 IU, 1000 IU or 2000 IU powder in a 10 mL vial (type 1 glass) with a stopper (butyl) and a flip-off seal (aluminum) and 4 mL of solvent in a pre-filled syringe (type 1 glass) with a plunger stopper (butyl), a tip-cap (butyl) and a sterile vial adapter reconstitution device, a sterile infusion set, alcohol swabs, a plaster and a gauze pad.

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection in pre-filled syringe
250 IU, 500 IU, 1000 IU, 2000 IU or 3000 IU lyophilised powder in top chamber and 4 mL of solvent in bottom chamber of the pre-filled syringe (type 1 glass) with butyl rubber plungers and closure, one plunger rod for assembly, a polypropylene vented sterile cap, a sterile infusion set, alcohol swabs, a plaster and a gauze pad.

Pack size of 1.

6.6 Special precautions for disposal and other handling

ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU powder and solvent for solution for injection
The vial of lyophilised product powder for injection must be reconstituted with the supplied solvent [sodium chloride 9 mg/mL (0.9%) solution] from the pre-filled syringe using the sterile vial adapter reconstitution device. The vial should be gently rotated until all of the powder is dissolved. Please see package leaflet, section 3, for additional information on reconstitution and administration.

After reconstitution, the solution is drawn back into the syringe. The solution will be clear or slightly opalescent and colourless. The solution is to be discarded if visible particulate matter or discoloration is observed.
ReFacto AF 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection in pre-filled syringe

The lyophilised powder in the top chamber of the pre-filled syringe must be reconstituted with the solvent [sodium chloride 9 mg/mL (0.9%) solution] in the bottom chamber of the pre-filled syringe. The pre-filled syringe should be gently rotated until all of the powder is dissolved. Please see package leaflet, section 3, for additional information on reconstitution and administration.

After reconstitution, the solution will be clear or slightly opalescent and colourless. The solution is to be discarded if visible particulate matter or discolouration is observed.

The product, when reconstituted, contains polysorbate-80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). This is to be considered during the preparation and administration of the product, including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations in section 6.3 be followed closely.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/99/103/001
EU/1/99/103/002
EU/1/99/103/003
EU/1/99/103/004
EU/1/99/103/009
EU/1/99/103/006
EU/1/99/103/007
EU/1/99/103/008
EU/1/99/103/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 April 1999
Date of latest renewal: 15 April 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency [http://www.ema.europa.eu/].
ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Swedish Orphan Biovitrum AB (publ)
Strandbergsgatan 49
SE-11276 Stockholm
Sweden

Name and address of the manufacturer responsible for batch release

Wyeth Farma S.A
Autovia del Norte A-1 Km 23
Desvio Algete Km 1
28700 San Sebastian de los Reyes
Madrid
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

• At the request of the European Medicines Agency;
• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

REFACTO AF OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ReFacto AF 250 IU powder and solvent for solution for injection
ReFacto AF 500 IU powder and solvent for solution for injection
ReFacto AF 1000 IU powder and solvent for solution for injection
ReFacto AF 2000 IU powder and solvent for solution for injection
Morocotocog alfa
(recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU morocotocog alfa (approx. 62.5 IU/ml after reconstitution).
1 vial: 500 IU morocotocog alfa (approx. 125 IU/ml after reconstitution)
1 vial: 1000 IU morocotocog alfa (approx. 250 IU/ml after reconstitution)
1 vial: 2000 IU morocotocog alfa (approx. 500 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Sucrose,
calcium chloride dihydrate,
L-histidine,
polysorbate 80,
sodium chloride
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
1 vial with 250 IU morocotocog alfa
1 vial with 500 IU morocotocog alfa
1 vial with 1000 IU morocotocog alfa
1 vial with 2000 IU morocotocog alfa
1 pre-filled syringe with 4 ml solvent
1 vial adapter
1 sterile infusion set
2 alcohol swabs
1 plaster
1 gauze
5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Intravenous use, after reconstitution.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
Do not use after expiry date.

Use immediately or within 3 hours of reconstitution.

9. **SPECIAL STORAGE CONDITIONS**

Store and transport at 2°C – 8°C.
Do not freeze

Keep the vial in the original package in order to protect from light.

ReFacto AF can be stored at room temperature (up to 25°C) for a single period up to 3 months. The product may not be returned to refrigerated storage after storage at room temperature.

Date removed from the refrigerator:

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPLICABLE**

Discard any remaining reconstituted solution

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom
<table>
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<th>MARKETING AUTHORISATION NUMBER(S)</th>
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| GENERAL CLASSIFICATION FOR SUPPLY |  

| INSTRUCTIONS ON USE |  

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<th>INFORMATION IN BRAILLE</th>
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<td>ReFacto AF 250</td>
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<td>ReFacto AF 500</td>
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<td>ReFacto AF 1000</td>
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<td>ReFacto AF 2000</td>
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### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

#### REFACTO AF VIAL LABEL

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<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tr>
<td>ReFacto AF 250 IU powder for solution for injection</td>
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<tr>
<td>ReFacto AF 500 IU powder for solution for injection</td>
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<tr>
<td>ReFacto AF 1000 IU powder for solution for injection</td>
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<tr>
<td>ReFacto AF 2000 IU powder for solution for injection</td>
</tr>
<tr>
<td>Moroctocog alfa</td>
</tr>
<tr>
<td>(recombinant human coagulation factor VIII)</td>
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<tr>
<td>IV use</td>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<th>3. EXPIRY DATE</th>
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<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tr>
<th>6. OTHER</th>
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<tbody>
<tr>
<td>Store in a refrigerator</td>
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<td>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</td>
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<tr>
<td>REFACTO AF SOLVENT PRE-FILLED SYRINGE LABEL</td>
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</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

   Solvent for ReFacto AF

2. **METHOD OF ADMINISTRATION**

   IV use, after reconstitution.

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

   Contains 4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection

6. **OTHER**

   Store in a refrigerator
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ReFacto AF 250 IU powder and solvent for solution for injection in pre-filled syringe

ReFacto AF 500 IU powder and solvent for solution for injection in pre-filled syringe

ReFacto AF 1000 IU powder and solvent for solution for injection in pre-filled syringe

ReFacto AF 2000 IU powder and solvent for solution for injection in pre-filled syringe

ReFacto AF 3000 IU powder and solvent for solution for injection in pre-filled syringe

Morocctocog alfa
(recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe: 250 IU morocctocog alfa (approx. 62.5 IU/ml after reconstitution).

1 pre-filled syringe: 500 IU morocctocog alfa (approx. 125 IU/ml after reconstitution)

1 pre-filled syringe: 1000 IU morocctocog alfa (approx. 250 IU/ml after reconstitution)

1 pre-filled syringe: 2000 IU morocctocog alfa (approx. 500 IU/ml after reconstitution)

1 pre-filled syringe: 3000 IU morocctocog alfa (approx. 750 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

See the package leaflet for further information
Sucrose,
calcium chloride dihydrate,
L-histidine,
polysorbate 80,
sodium chloride

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in pre-filled syringe FuseNGo

1 pre filled syringe (250 IU powder in top chamber and 4 ml solvent in bottom chamber)
1 pre filled syringe (500 IU powder in top chamber and 4 ml solvent in bottom chamber)
1 pre filled syringe (1000 IU powder in top chamber and 4 ml solvent in bottom chamber)
1 pre filled syringe (2000 IU powder in top chamber and 4 ml solvent in bottom chamber)
1 pre filled syringe (3000 IU powder in top chamber and 4 ml solvent in bottom chamber)
1 plunger rod
1 sterile infusion set
2 alcohol swabs
1 plaster
1 gauze
1 vented sterile cap

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use, single use administration only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately or within 3 hours of reconstitution or after removing the grey rubber tip cap from the syringe

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C – 8°C).
Do not freeze
Keep in the original package in order to protect from light.
ReFacto AF can be stored at room temperature (up to 25°C) for a single period up to 3 months. The product may not be returned to refrigerated storage after storage at room temperature.
Date removed from the refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
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<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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<th>15. INSTRUCTIONS ON USE</th>
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<th>16. INFORMATION IN BRAILLE</th>
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<tr>
<td>ReFacto AF 250</td>
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<td>ReFacto AF 500</td>
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<tr>
<td>ReFacto AF 1000</td>
</tr>
<tr>
<td>ReFacto AF 2000</td>
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<tr>
<td>ReFacto AF 3000</td>
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</table>
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ReFacto AF 250 IU powder and solvent for solution for injection
ReFacto AF 500 IU powder and solvent for solution for injection
ReFacto AF 1000 IU powder and solvent for solution for injection
ReFacto AF 2000 IU powder and solvent for solution for injection
ReFacto AF 3000 IU powder and solvent for solution for injection

Moroctocog alfa
(recombinant human coagulation factor VIII)
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU moroctocog alfa for single IV use
500 IU moroctocog alfa for single IV use
1000 IU moroctocog alfa for single IV use
2000 IU moroctocog alfa for single IV use
3000 IU moroctocog alfa for single IV use

6. OTHER

Store in a refrigerator
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What ReFacto AF is and what it is used for
2. What you need to know before you use ReFacto AF
3. How to use ReFacto AF
4. Possible side effects
5. How to store ReFacto AF
6. Contents of the pack and other information

1. What ReFacto AF is and what it is used for

ReFacto AF contains the active substance moroctocog alfa, human coagulation factor VIII. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn factor VIII deficiency), it is missing or not working properly.

ReFacto AF is used for the treatment and prevention of bleeding (prophylaxis) in adults and children of all ages (including newborns) with haemophilia A.

2. What you need to know before you use ReFacto AF

Do not use ReFacto AF

- if you are allergic to moroctocog alfa or any of the other ingredients of this medicine (listed in section 6).

- if you are allergic to hamster proteins.

If you are unsure about this, ask your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before using ReFacto AF

- if you experience allergic reactions. Some of the signs of allergic reactions are difficulty in breathing, shortness of breath, swelling, hives, itching, tightness of the chest, wheezing, and low blood pressure. Anaphylaxis is a severe allergic reaction that can cause difficulty in swallowing and/or breathing, red or swollen face and/or hands. If any of these signs occur, stop the infusion
immediately and contact a doctor or seek immediate emergency care. In case of severe allergic reactions, alternative therapy must be considered.

- the formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If your or your child’s bleeding is not being controlled with ReFacto AF, tell your doctor immediately.

- if your bleeding does not stop as expected and contact your doctor or seek immediate emergency care.

Other medicines and ReFacto AF

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines

ReFacto AF has no influence on the ability to drive or use machines.

ReFacto AF contains sodium

ReFacto AF contains 1.23 mmol (or 29 mg) sodium per vial of reconstituted powder. Inform your doctor if you are on a controlled sodium diet.

3. How to use ReFacto AF

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Treatment with ReFacto AF should be started by a doctor who is experienced in the care of patients with haemophilia A. Your doctor will decide the dose of ReFacto AF you will receive. This dose and duration will depend upon your individual needs for replacement factor VIII therapy. ReFacto AF is given by injection into a vein lasting several minutes. Patients or their carers can give injections of ReFacto AF, provided that they have been trained appropriately.

During your treatment, your doctor may decide to change the dose of ReFacto AF you receive. Consult with your health care provider before you travel. You should bring enough of your factor VIII product for anticipated treatment when travelling.

It is recommended that every time you use ReFacto AF, you record the name on the carton and batch number of the product. You can use one of the peel-off labels found on the vial to document the batch number in your diary or for reporting any side effects.

Reconstitution and administration

The procedures below are provided as guidelines for the reconstitution and administration of ReFacto AF. Patients should follow the specific reconstitution and administration procedures provided by their doctors.
Use only the pre-filled syringe provided in the box for reconstitution. Other sterile disposable syringes may be used for administration.

ReFacto AF is administered by intravenous (IV) infusion after reconstitution of the lyophilised powder for injection with the supplied solvent [sodium chloride 9 mg/ml (0.9%) solution] syringe. ReFacto AF should not be mixed with other infusion solutions.

Always wash your hands before performing the following reconstitution and administration procedures. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure.

Reconstitution:

1. Allow the vial of lyophilised ReFacto AF and the pre-filled solvent syringe to reach room temperature.

2. Remove the plastic flip-top cap from the ReFacto AF vial to expose the central portion of the rubber stopper.

3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.

4. Peel back the lid from the clear plastic vial adapter package. Do not remove the adapter from the package.

5. Place the vial on a flat surface. While holding the adapter package, place the vial adapter over the vial. Press down firmly on the package until the adapter snaps into place on top of the vial, with the adapter spike penetrating the vial stopper.

6. Lift the package away from the adapter and discard the package.

7. Attach the plunger rod to the solvent syringe by inserting the rod into the opening in the syringe stopper and pushing and turning the rod firmly until it is securely seated in the stopper.
8. Break off the tamper-resistant plastic tip cap from the solvent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The cap may need to be replaced (if not administering reconstituted ReFacto AF immediately), so set it aside by placing it on its top.

9. Place the vial on a flat surface. Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.

10. Slowly depress the plunger rod to inject all the solvent into the ReFacto AF vial.

11. With the syringe still connected to the adapter, gently rotate the vial until the powder is dissolved.

12. The final solution must be inspected visually for particulate matter before administration. The solution will appear clear to slightly opalescent and colourless.

Note: If you use more than one vial of ReFacto AF per infusion, each vial should be reconstituted as per the previous instructions. The solvent syringe should be removed, leaving the vial adapter in place, and a single large luer lock syringe may be used to draw back the reconstituted contents of each of the individual vials.
13. Ensuring that the syringe plunger rod is still fully depressed, invert the vial. Slowly draw back all the solution through the vial adapter into the syringe.

![Syringe plunger rod being depressed](image1.png)

14. Detach the syringe from the vial adapter by gently pulling and turning the syringe counterclockwise. Discard the vial with the adapter attached.

   Note: If the solution is not to be used immediately, the syringe cap is to be carefully replaced. Do not touch the syringe tip or the inside of the cap.

ReFacto AF must be used within 3 hours of reconstitution. The reconstituted solution may be stored at room temperature prior to administration.

*Administration (Intravenous Infusion):*

ReFacto AF should be administered using the infusion set provided in this kit and the pre-filled solvent syringe provided or a single sterile disposable plastic luer lock syringe.

1. Attach the syringe to the luer end of the infusion set tubing.

   ![Syringe attached to infusion set](image2.png)

2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab provided in the kit.

3. Insert the needle on the infusion set tubing into the vein as instructed by your doctor, and remove the tourniquet. Remove any air in the infusion set tubing by drawing back on the syringe. The reconstituted product is to be injected intravenously over several minutes. Your doctor may change your recommended infusion rate to make the infusion more comfortable.

![Infusion set tubing](image3.png)

Please dispose of all unused solution, the empty vial(s) and the used needles and syringes in an appropriate container for throwing away of medical waste as these materials may hurt others if not disposed of properly.

**If you use more ReFacto AF than you should**

Check with your doctor or pharmacist.
If you stop using ReFacto AF

Do not stop using ReFacto AF without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If severe, sudden allergic reactions (anaphylactic) occur, the infusion must be stopped immediately. You must contact your doctor immediately if you have any of the following early symptoms of allergic reactions:
- rash, hives, wheals, generalised itching
- swelling of lips and tongue
- difficulty in breathing, wheezing, tightness in the chest
- general feeling of being unwell
- dizziness and loss of consciousness

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment. Severe, sudden allergic (anaphylactic) reactions are uncommon (may affect up to 1 in 100 people).

Inhibitor development

For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients); however patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is around 1 in 100 patients. If this happens, your or your child’s medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
- inhibitor development for patients who have never been previously treated with factor VIII products
- headache
- cough
- joint pain
- fever

Common side effects (may affect up to 1 in 10 people)
- bleeding
- inhibitor development for patients who have been previously treated with factor VIII products (around 1 in 100 people)
- dizziness
- decreased appetite, diarrhoea, vomiting, stomach pain, nausea
- hives, rash, itching
- muscular pain
- chills, catheter site reaction
- certain blood tests may show an increase in antibodies to factor VIII
**Uncommon side effects** (may affect up to 1 in 100 people)
- severe allergic reaction
- numbness, sleepiness, altered taste
- chest pain, rapid heart beat, palpitations
- low blood pressure, pain and redness of veins associated with a blood clot, flushing
- shortness of breath
- excessive sweating
- weakness, injection site reactions including pain
- slight increase in heart enzymes
- increased liver enzymes, increased bilirubin

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. **How to store ReFacto AF**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and vial label after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C – 8°C). Do not freeze, in order to prevent damage to the pre-filled solvent syringe.

For your convenience, the medicine can be removed from such storage for one single period of maximum 3 months at room temperature (up to 25°C). At the end of this room temperature storage period, the product must not be put back in the refrigerator, but must be used or discarded. Record on the outer carton the date ReFacto AF is removed from the refrigerator and set at room temperature (up to 25°C). Keep the vial in the outer carton in order to protect from light.

Use the reconstituted solution within 3 hours of reconstitution.

The solution will be clear to slightly opalescent and colourless. Do not use this medicine if you notice that it is cloudy or contains visible particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. **Contents of the pack and other information**

**What ReFacto AF contains**

- The active substance is moroctocog alfa (recombinant coagulation factor VIII). Each vial of ReFacto AF contains nominally 250, 500, 1000, or 2000 IU of moroctocog alfa.

- The other ingredients are sucrose, calcium chloride dihydrate, L-histidine, polysorbate 80 and sodium chloride. A solvent [sodium chloride 9 mg/ml (0.9%) solution for injection] is also supplied for reconstitution.

- After reconstitution with the supplied solvent [sodium chloride 9 mg/ml (0.9%) solution], each vial contains 62.5, 125, 250, or 500 IU, respectively (based on the strength of moroctocog alfa,
i.e., 250, 500, 1000, or 2000 IU), of moroctocog alfa per 1 ml of the prepared solution for injection.

**What ReFacto AF looks like and contents of the pack**

ReFacto AF is provided as a powder for injection in a glass vial and a solvent is provided in a pre-filled syringe.

The contents of the pack are:
- one vial of moroctocog alfa 250, 500, 1000, or 2000 IU powder
- one pre-filled syringe of solvent, 4 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection for reconstitution, with one plunger rod
- one sterile vial adapter reconstitution device
- one sterile infusion set
- two alcohol swabs
- one plaster
- one gauze pad

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Detailed information on this medicine is available on European Medicines Agency website:
Package leaflet: Information for the user

ReFacto AF 250 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 500 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 1000 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 2000 IU powder and solvent for solution for injection in pre-filled syringe
ReFacto AF 3000 IU powder and solvent for solution for injection in pre-filled syringe

Morocctocog alfa (recombinant human coagulation factor VIII)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What ReFacto AF is and what it is used for
2. What you need to know before you use ReFacto AF
3. How to use ReFacto AF
4. Possible side effects
5. How to store ReFacto AF
6. Contents of the pack and other information

1. What ReFacto AF is and what it is used for

ReFacto AF contains the active substance morocctocog alfa, human coagulation factor VIII. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn factor VIII deficiency), it is missing or not working properly.

ReFacto AF is used for the treatment and prevention of bleeding (prophylaxis) in adults and children of all ages (including newborns) with haemophilia A.

2. What you need to know before you use ReFacto AF

Do not use ReFacto AF

- if you are allergic to morocctocog alfa or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to hamster proteins.

If you are unsure about this, ask your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before using ReFacto AF
- if you experience allergic reactions. Some of the signs of allergic reactions are difficulty in breathing, shortness of breath, swelling, hives, itching, tightness of the chest, wheezing, and low
blood pressure. Anaphylaxis is a severe allergic reaction that can cause difficulty in swallowing and/or breathing, red or swollen face and/or hands. If any of these signs occur, stop the infusion immediately and contact a doctor or seek immediate emergency care. In case of severe allergic reactions, alternative therapy must be considered.

- the formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If your or your child’s bleeding is not being controlled with ReFacto AF, tell your doctor immediately.

- if your bleeding does not stop as expected and contact your doctor or seek immediate emergency care.

Other medicines and ReFacto AF

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines

ReFacto AF has no influence on the ability to drive or use machines.

ReFacto AF contains sodium

ReFacto AF contains 1.23 mmol (or 29 mg) sodium per pre-filled syringe of reconstituted powder. Inform your doctor if you are on a controlled sodium diet.

3. How to use ReFacto AF

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Treatment with ReFacto AF should be started by a doctor who is experienced in the care of patients with haemophilia A. Your doctor will decide the dose of ReFacto AF you will receive. This dose and duration will depend upon your individual needs for replacement factor VIII therapy. ReFacto AF is given by injection into a vein lasting several minutes. Patients or their carers can give injections of ReFacto AF, provided that they have been trained appropriately.

During your treatment, your doctor may decide to change the dose of ReFacto AF you receive. Consult with your health care provider before you travel. You should bring enough of your factor VIII product for anticipated treatment when travelling.

It is recommended that every time you use ReFacto AF, you record the name on the carton and batch number of the product. You can use one of the peel-off labels found on the pre-filled syringe to document the batch number in your diary or for reporting any side effects.

Reconstitution and administration

The procedures below are provided as guidelines for the reconstitution and administration of ReFacto AF provided in a pre-filled syringe. Patients should follow the specific reconstitution and administration procedures provided by their doctors.
ReFacto AF is administered by intravenous (IV) infusion after reconstitution. The pre-filled syringe consists of 2 chambers, one chamber contains the ReFacto AF lyophilised powder and the other chamber contains the solvent [sodium chloride 9 mg/ml (0.9%) solution]. For the purposes of these instructions, this device will be referred to as a pre-filled syringe.

Use only the pre-filled syringe provided in the box for reconstitution. Other sterile disposable syringes may be used for administration.

ReFacto AF should not be mixed with other infusion solutions.

**Note:** If you need to use more than one pre-filled syringe of ReFacto AF per infusion, each syringe should be reconstituted according to the specific directions. A separate 10 cc or larger luer lock syringe (not included in this kit) may be used to draw back the reconstituted contents of each syringe (see Additional Instructions)

**Preparation**

1. Always wash your hands before performing the following procedures.
2. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure.
3. All components used in the reconstitution and administration of this product should be used as soon as possible after opening their sterile containers, to minimise unnecessary exposure to the air.

**Reconstitution**

1. Allow the pre-filled syringe to reach room temperature.
2. Remove the contents of the ReFacto AF pre-filled syringe kit and place on a clean surface, making sure you have all the supplies you will need.
3. Grasp the plunger rod as shown in the following diagram. Screw the plunger rod firmly into the opening in the finger rest of the ReFacto AF pre-filled syringe by pushing and turning clockwise firmly until resistance is felt (approximately 2 turns).

Throughout the reconstitution process, it is important to keep the ReFacto AF pre-filled syringe upright (with the white powder above the clear solution) to prevent possible leakage.
4. Holding the pre-filled syringe upright, remove the white tamper-evident seal by bending the seal right to left (or a gentle rocking motion) to break the perforation of the cap and expose the grey rubber tip cap of the ReFacto AF pre-filled syringe.

5. Remove the protective blue vented sterile cap from its packaging.

Whilst continuing to hold the ReFacto AF pre-filled syringe upright, remove the grey rubber tip cap and replace it with the protective blue vented cap. This vented cap has tiny holes that allow air to escape in order to prevent pressure build-up. Avoid touching the open end of the syringe or the protective blue vented cap.

6. **Gently and slowly** advance the plunger rod by pushing until the two plungers inside the pre-filled syringe meet, and all of the solvent is transferred to the top chamber containing the ReFacto AF powder.

**Note:** To prevent the escape of fluid from the tip of the syringe, do not push the plunger rod with excessive force.
7. With the ReFacto AF pre-filled syringe remaining upright, swirl **gently** several times until the powder is dissolved.

Look at the final solution to check for particulate matter or discolouration. The solution should appear clear to slightly opalescent and colourless. Discard the pre-filled syringe if visible particulate matter or discolouration is observed.

8. Continuing to hold the ReFacto AF pre-filled syringe in an upright position, slowly advance the plunger rod until most, but not all, of the air is removed from the (top) chamber.

ReFacto AF should be infused within 3 hours after either reconstitution or removal of the grey tip cap from the pre-filled syringe.

If you are not going to use the ReFacto AF solution immediately, you should store the syringe in an upright position, with the protective blue vented cap on the pre-filled syringe until you are ready to infuse. The reconstituted solution may be stored at room temperature for up to 3 hours. If you have not used it within 3 hours, throw it away.

**Administration (Intravenous Infusion)**

Your doctor or other healthcare professional should teach you how to infuse ReFacto AF. Once you learn how to self-infuse, you can follow the instructions in this Package Leaflet.

ReFacto AF is administered by intravenous (IV) infusion after reconstitution of the powder with the solvent (0.9% sodium chloride). Once reconstituted, ReFacto AF should be inspected for particulate matter and discoloration prior to administration.

ReFacto AF should be administered using the infusion set included in the kit, unless otherwise advised by your doctor or other healthcare professional.
1. Remove the protective blue vented cap and firmly attach the intravenous infusion set provided onto the ReFacto AF pre-filled syringe.

2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab provided in the kit.

3. Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein, as instructed by your doctor or other healthcare professional. Remove the tourniquet. The reconstituted ReFacto AF product should be injected intravenously over several minutes. Your doctor may change your recommended infusion rate to make the infusion more comfortable. Discuss your intravenous infusion procedure with your doctor or other healthcare professional. Do not attempt self-infusion unless properly trained.

Reconstituted ReFacto AF must not be administered in the same tubing or container with other medicinal products.
4. After infusing ReFacto AF, remove the infusion set and discard. The amount of drug product left in the infusion set will not affect your treatment.

**Note:** Please dispose of all unused solution, the empty pre-filled syringe, and the used medical supplies in an appropriate container for throwing away medical waste, as these materials may hurt others if not disposed of properly.

It is recommended to record the lot number from the ReFacto AF pre-filled syringe label every time you use ReFacto AF. You can use the peel-off label found on the ReFacto AF pre-filled syringe to record the lot number.

**Additional Instructions:**

**Multiple ReFacto AF in Pre-filled Syringe Reconstitution to a 10 cc or Larger Luer Lock Syringe (10 cc or larger luer lock syringes not provided)**

The instructions below are for the use of multiple ReFacto AF pre-filled syringe kits with a 10 cc or larger luer lock syringe.

1. Reconstitute all ReFacto AF pre-filled syringes according to instructions shown above in the reconstitution directions (see Reconstitution and Administration).

   Holding the ReFacto AF pre-filled syringe in an upright position, slowly advance the plunger rod until most, but not all, of the air is removed from the drug product chamber.

2. Remove the luer-to-luer syringe connector from its package (luer-to-luer syringe connectors are not provided).
3. Connect a sterile 10 cc or larger luer lock syringe to one opening (port) in the syringe connector and the ReFacto AF pre-filled syringe to the remaining open port on the opposite end.

4. With the ReFacto AF pre-filled syringe on top, slowly depress the plunger rod until the contents empty into the 10 cc or larger luer lock syringe.

5. Remove the empty ReFacto AF pre-filled syringe and repeat procedures 3 and 4 above for any additional reconstituted syringes.

6. Remove the luer-to-luer syringe connector from the 10 cc or larger luer lock syringe and attach the infusion set, as described above in the directions for administration of the pre-filled syringe [see Administration (Intravenous Infusion)].

**Note:** Please dispose of all unused solution, the empty pre-filled syringe, and the used medical supplies in an appropriate container for throwing away medical waste, as these materials may hurt others if not disposed of properly.

If you use more ReFacto AF than you should

Check with your doctor or pharmacist.

If you stop using ReFacto AF
Do not stop using ReFacto AF without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If severe, sudden allergic reactions (anaphylactic) occur, the infusion must be stopped immediately. You must contact your doctor immediately if you have any of the following early symptoms of allergic reactions:

- rash, hives, wheals, generalised itching
- swelling of lips and tongue
- difficulty in breathing, wheezing, tightness in the chest
- general feeling of being unwell
- dizziness and loss of consciousness

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment. Severe, sudden allergic (anaphylactic) reactions are uncommon (may affect up to 1 in 100 people).

Inhibitor development

For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients); however patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is around 1 in 100 patients. If this happens, your or your child’s medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
- inhibitor development for patients who have never been previously treated with factor VIII products
- headache
- cough
- joint pain
- fever

Common side effects (may affect up to 1 in 10 people)
- bleeding
- inhibitor development for patients who have been previously treated with factor VIII products (around 1 in 100 people)
- dizziness
- decreased appetite, diarrhoea, vomiting, stomach pain, nausea
- hives, rash, itching
- muscular pain
- chills, catheter site reaction
- certain blood tests may show an increase in antibodies to factor VIII

Uncommon side effects (may affect up to 1 in 100 people)
- severe allergic reaction
- numbness, sleepiness, altered taste
- chest pain, rapid heart beat, palpitations
• low blood pressure, pain and redness of veins associated with a blood clot, flushing
• shortness of breath
• excessive sweating
• weakness, injection site reactions including pain
• slight increase in heart enzymes
• increased liver enzymes, increased bilirubin

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ReFacto AF

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and pre-filled syringe label after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C – 8°C). Do not freeze, in order to prevent damage to the pre-filled syringe.

For your convenience, the medicine can be removed from such storage for one single period of maximum 3 months at room temperature (up to 25°C). At the end of this room temperature storage period, the product must not be put back in the refrigerator, but must be used or discarded. Record on the outer carton the date ReFacto AF pre-filled syringe is removed from the refrigerator and set at room temperature (up to 25°C).

Keep the pre-filled syringe in the outer carton in order to protect from light.

Use the reconstituted solution within 3 hours of reconstitution or removal of the grey tip cap.

The solution will be clear to slightly opalescent and colourless. Do not use this medicine if you notice that it is cloudy or contains visible particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ReFacto AF contains

- The active substance is moroctocog alfa (recombinant coagulation factor VIII). Each pre-filled syringe of ReFacto AF contains nominally 250, 500, 1000, 2000, or 3000 IU of moroctocog alfa.
  A solvent [sodium chloride 9 mg/ml (0.9%) solution for injection] is included within the ReFacto AF pre-filled syringe for reconstituting moroctocog alfa.

- The other ingredients are sucrose, calcium chloride dihydrate, L-histidine, polysorbate 80 and sodium chloride.

- After reconstitution with the supplied solvent [sodium chloride 9 mg/ml (0.9%) solution], the prepared solution for injection contains either 62.5, 125, 250, 500 or 750 IU of moroctocog alfa.
per ml, respectively (based on the strength of moroctocog alfa, i.e., 250, 500, 1000, 2000, or 3000 IU).

What ReFacto AF looks like and contents of the pack

ReFacto AF is provided as a powder and solvent for solution for injection in a pre-filled syringe that contains the ReFacto AF powder in the top chamber and the solvent [sodium chloride 9 mg/ml (0.9%) solution] in the bottom chamber.

The contents of the pack are:
- one pre-filled syringe containing moroctocog alfa 250, 500, 1000, 2000, or 3000 IU powder and solvent, 4 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection for reconstitution
- one plunger rod
- one protective blue vented sterile cap
- one sterile infusion set
- two alcohol swabs
- one plaster
- one gauze pad

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Detailed information on this medicine is available on European Medicines Agency website:  
ANNEX IV

SCIENTIFIC CONCLUSIONS
Scientific conclusions

Treatment of congenital haemophilia is currently based on prophylactic or on-demand replacement therapy with coagulation factor VIII (FVIII). FVIII replacement therapy can be generally categorised into two broad classes of products; plasma derived (pdFVIII) and recombinant (rFVIII) FVIII. A wide range of individual pdFVIII and rFVIII products are authorised for use in the European Union.

A major complication of FVIII therapy is the occurrence of IgG alloantibodies (inhibitors) that neutralise FVIII activity, causing loss of bleeding control. Treatment of patients who have developed inhibitors requires careful individual management and can be resistant to therapy.

Treatment with both pdFVIII and rFVIII can lead to development of inhibitors (tested with the Nijmegen method of the Bethesda assay and defined as ≥0.6 Bethesda units (BU) for “a low titre” inhibitor and >5 BU for a “hightitre” inhibitor).

The occurrence of inhibitor development in haemophilia A patients receiving FVIII products mostly occurs in previously-untreated patients (PUPs) or minimally treated patients (MTPs) who are still within the first 50 days of exposure (EDs) to the treatment. Inhibitors are less likely to occur in previously-treated patients (PTPs).

The known risk factors for inhibitor development can be grouped into patient and treatment-related factors:

- Patient-related risk factors include type of F8 gene mutation, severity of haemophilia, ethnicity, family history of inhibitor development and possibly HLA-DR (Human Leukocyte Antigen D Related) constitution.

- Treatment-related factors include intensity of exposure, number of exposure days (EDs), on demand treatment posing a greater risk than prophylaxis, particularly in the context of danger signals such as trauma or surgery, and young age at first treatment poses a higher risk.

Whether there are significant differences in the risk of inhibitor development between different types of FVIII replacement product remains an area of uncertainty. Differences between products in each FVIII class and consequently differential risks between individual products, are biologically plausible. The pdFVIII class consists of products with or without Von Willebrand Factor (VWF), and those with VWF contain a range of VWF levels. Some experimental studies have suggested a role for VWF in protecting FVIII epitopes from recognition by the antigen-presenting cells, thereby reducing immunogenicity, although this remains theoretical. VWF is not present in rFVIII, but there is significant heterogeneity within the rFVIII class for instance due to the different manufacturing processes used, with a wide range of products from different manufacturers produced over the past 20 years. These different manufacturing processes (including the different cell lines used to engineer the rFVIII products) can in theory lead to differential immunogenicity.

In May 2016, an open-label, randomised controlled trial aimed at addressing the incidence of inhibitors between the two classes (pdFVIII vs. rFVIII products) was published in the New England Journal of Medicine. This trial, known as the SIPPET study (“Survey of Inhibitors in Plasma-Product Exposed Toddlers”) was conducted to evaluate the relative risk of inhibitors in patients treated with pdFVIII compared to rFVIII. It found that patients treated with rFVIII products had an 87% higher incidence of all inhibitors than those treated with pdFVIII (which contained VWF) (hazard ratio, 1.87; 95% CI, 1.17 to 2.96).

On 6 July 2016 Paul-Ehrlich-Institut Germany initiated a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the potential impact of the results of the SIPPET study on the marketing authorisations of relevant FVIII products.

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and to issue a recommendation on whether these should be maintained, varied, suspended or revoked and whether any risk minimisation measures should be implemented. The referral focuses on the risk of inhibitor development in PUPs.

Further to the recent publication on the SIPPET study, the MAHs were requested to assess the potential impact of the results of this study and other relevant safety data on inhibitor development in PUPs on the MA of their FVIII product including consideration on risk minimisation measures.

The lead authors of the SIPPET study were also invited to respond to a list of questions regarding the study methods and findings and to present their conclusions at the February 2017 PRAC plenary meeting. Information submitted by the lead authors of the SIPPET study during the course of the referral was also taken into consideration by PRAC in reaching its conclusion.

Clinical discussion

Published observational studies

The responses of MAHs referred to a range of published observational studies (the CANAL, RODIN, FranceCoag, UKHCDO, amongst others) which have sought to evaluate any differential risks of inhibitor development between the classes of pdFVIII and rFVIII, as well as any differential risk of inhibitor development between products within the rFVIII class.

These studies have yielded different results and suffer from the limitations of observational studies, and in particular from possible selection bias. The risk of inhibitor development is multifactorial (aside from any putative product-specific risk), and such studies have not always been able to collect information on relevant covariates and to adjust the analyses accordingly; residual confounding is inevitably a significant uncertainty. Furthermore, over time there have been changes in manufacturing process of individual products and changes in treatment regimens between centres, hence “like for like” comparisons between products is not always possible. These factors make control of such studies and interpretation of the results challenging.

The CANAL study² found no evidence of a class difference, including pdFVIII products with considerable quantities of von Willebrand factor; for ‘clinically relevant’ inhibitors the adjusted hazard ratio was 0.7 (95% CI 0.4-1.1), and for high titre inhibitors (≥5 BU) was 0.8 (95% CI 0.4-1.3).

The RODIN/Pednet study³ also found no evidence of a class difference in inhibitor risk between all pdFVIII vs all rFVIII; for ‘clinically relevant’ inhibitors the adjusted hazard ratio was 0.96 (95% CI 0.62-1.49), and for high titre inhibitors (≥5 BU/ml) was 0.95 (95% CI 0.56-1.61). However, the study found evidence of an increased risk of inhibitors (all and high titre) for 2nd generation rFVIII octocog alfa (Kogenate FS/Helixate NexGen) compared with 3rd generation rFVIII octocog alfa (which was driven solely by data for Advate).

Similar to RODIN/Pednet, the UKHCDO study found a significant increased risk of inhibitors (all and high titre) for Kogenate FS/Helixate NexGen (2nd generation rFVIII) compared to Advate (3rd generation rFVIII). Although this became non-significant when UK patients (also included in the RODIN/Pednet study were excluded. There was also evidence for an increased risk with Refacto AF (another 3rd generation rFVIII) vs Advate, but only for all inhibitor development. Like the UKHCDO study, the FranceCoag study also found no statistically significant increased risk for any rFVIII products vs Advate when French patients (also in the RODIN/Pednet study) were excluded.

Prior to the current referral, it was noted that PRAC had already considered the implications of the RODIN/Pednet, the UKHCDO and the FranceCoag studies for the EU marketing authorisations for FVIII products. In 2013, PRAC had concluded that the RODIN/Pednet findings were not sufficiently

² http://www.bloodjournal.org/content/109/11/4648.full.pdf
robust to support a conclusion that Kogenate FS/Helixate NexGen was associated with an increased risk of developing factor VIII inhibitors compared with other products. In 2016, PRAC had considered the findings of meta-analysis of all three studies (RODIN/Pednet, UKHCD0 and FranceCoag studies), and again concluded that the currently available evidence does not confirm that Kogenate Bayer/Helixate NexGen is associated with an increased risk of factor VIII inhibitors, compared with other recombinant factor VIII products in PUPs.

MAH-sponsored studies

The MAHs provided an analysis of low and high titre inhibitor development in PUPs with severe haemophilia A (FVIII < 1%) from all clinical trials and observational studies conducted with their products, along with critical discussion on the limitations of these studies.

The data came from a very wide range of heterogenous studies across products and over time. Many of these studies were small and not specifically designed to evaluate the inhibitor risk in PUPs with severe haemophilia A. The studies were mostly single arm and do not provide data to perform comparative analysis (either between pdFVIII and rFVIII as a class comparison, or within the rFVIII class). However, the general estimates of inhibitor rates from these studies for individual products are broadly in line with the findings from large observational studies.

Of the larger and more relevant studies for pdFVIII products, inhibitor rates observed (often not stated if high or low titre) ranged from 3.5 to 33%, with most around 10-25%. However, in many cases little information was provided on the methods, patient populations and nature of the inhibitors to assess the information in the context of more recent published data. For most rFVIII products, newer and more relevant information from clinical trials in PUPs is available. Inhibitor rates in these studies range from 15 to 38% for all inhibitors and 9 to 22.6% for high titre inhibitors; i.e. within the range of ‘very common’.

The PRAC also considered interim results submitted by the MAHs from ongoing studies from CSL (CRD019_5001) and Bayer (Leopold KIDS, 13400, part B.).

Furthermore, the PRAC examined clinical trials and the scientific literature for de novo inhibitors in PTPs. The analysis demonstrated that the frequency of inhibitor development is much lower in PTPs compared to PUPs. The available data showed that in many studies including the EUHASS registry (Iorio A, 2017; Fischer K, 2015) the frequency could be classified as “uncommon”.

The SIPPET study

The SIPPET study was an open-label, randomized, multi-centre, multi-national trial investigating the incidence of neutralising allo-antibodies in patients with severe congenital haemophilia A (plasma FVIII concentration <1%) with either the use of pdFVIII or rFVIII concentrates. Eligible patients (<6 years, male, severe haemophilia A, no previous treatment with any FVIII concentrate or only minimal treatment with blood components) were included from 42 sites. The primary and secondary outcomes assessed in the study were the incidence of all inhibitors (≥0.4 BU/ml) and the incidence of high-titre inhibitors (≥5 BU/ml), respectively.

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Inhibitors developed in 76 patients, 50 of whom had high-titre inhibitors (≥5 BU). Inhibitors developed in 29 of the 125 patients treated with pdFVIII (20 patients had high-titre inhibitors) and in 47 of the 126 patients treated with rFVIII (30 patients had high-titre inhibitors). The cumulative incidence of all inhibitors was 26.8% (95% confidence interval [CI], 18.4 to 35.2) with pdFVIII and 44.5% (95% CI, 34.7 to 54.3) with rFVIII; the cumulative incidence of high-titre inhibitors was 18.6% (95% CI, 11.2 to 26.0) and 28.4% (95% CI, 19.6 to 37.2), respectively. In Cox regression models for the primary end point of all inhibitors, rFVIII was associated with an 87% higher incidence than pdFVIII (hazard ratio, 1.87; 95% CI, 1.17 to 2.96). This association was consistently observed in multivariable analysis. For high-titre inhibitors, the hazard ratio was 1.69 (95% CI, 0.96 to 2.98).

Ad hoc expert group meeting

The PRAC considered the views expressed by experts during an ad-hoc meeting. The expert group was of the view that the relevant available data sources have been considered. The expert group suggested that further data are needed to establish if there are clinically relevant differences in frequency of inhibitor development between different factor VIII products and that, in principle, such data should be collected separately for individual products, as degree of immunogenicity will be difficult to generalise across the classes of products (i.e. recombinant vs. plasma-derived).

The experts also agreed that the degree of immunogenicity of different products was adequately described overall with the amendments to the SmPC proposed by the PRAC highlighting the clinical relevance of inhibitor development (in particular low compared to high titre inhibitors), as well as the frequency of ‘very common’ in PUPs and ‘uncommon’ in PTPs. The experts also suggested studies which could further characterise the immunogenic properties of the factor VIII medicinal products (e.g. mechanistic, observational studies).

Discussion

The PRAC considered that as a prospective randomised trial, the SIPPET study avoided many of the design limitations of the observational and registry-based studies undertaken so far to evaluate the risk of inhibitor development in PUPs. However the PRAC is of the view that there are uncertainties with regards to the findings of the SIPPET study which preclude the conclusion that there is a higher risk of inhibitor development in PUPs treated with rFVIII products than pdFVIII products studied in this clinical trial, as detailed below:

• The SIPPET analysis does not allow for product-specific conclusions to be made as it relates only to a small number of certain FVIII products. The study was not designed and powered to generate sufficient product-specific data and, therefore, to draw any conclusions on the risk of inhibitor development for individual products. In particular, only 13 patients (10% of the FVIII arm) received a third generation rFVIII product. However, despite the lack of robust evidence to support differential risks between rFVIII products, differential risks cannot be excluded, as this is a heterogeneous product class with differences in composition and formulations. Therefore, there is a high degree of uncertainty around extrapolating the SIPPET findings to the entire rFVIII class, particularly for more recently-authorised rFVIII products which were not included in the SIPPET trial.

• The SIPPET study has methodological limitations, with particular uncertainty around whether the randomisation process (block size of 2) may have introduced a selection bias in the study.

• There were also deviations from the final protocol and statistical analysis plan. The statistical concerns include the fact that no pre-specified primary analysis has been published and the fact that the study was stopped early following the publication of the RODIN study indicating that Kogenate FS might be associated with an increased risk of inhibitor formation. Although this could not have been prevented, an early termination of an open label trial raises the possibility of investigator bias and inflation of the probability of detecting an effect that is not present.
Treatment regimens in EU are different from those in the SIPPET study. The relevance for clinical practice in the EU (and therefore for the products subject to this procedure) is therefore questioned. It is uncertain whether the findings of SIPPET can be extrapolated to the risk of inhibitors in PUPs in current clinical practice in the EU as treatment modality and intensity have been suggested as risk factors for inhibitor development in previous studies. Importantly, the EU SmPCs do not include modified prophylaxis (as defined in the SIPPET study) as an authorised posology, and the impact of the apparent imbalance in the unspecified other combinations of treatment modality on the SIPPET findings is unclear. Therefore, it remains uncertain whether the same differential risk of inhibitor development observed in the SIPPET study would be apparent in patient populations treated in routine care in other countries where the modality of treatment (i.e. primary prophylaxis) is different from that in the study. The additional points of clarification provided by the SIPPET authors do not fully resolve this uncertainty.

Having considered the abovementioned results from SIPPET, the published literature and all the information submitted by the MAHs, as well as the views expressed by experts expressed at the ad-hoc expert meeting, the PRAC concluded that:

- Inhibitor development is an identified risk with both pdFVIII and rFVIII products. Although the clinical studies for some individual products have identified limited numbers of cases of inhibitor development, these tend to be small studies with methodological limitations, or studies not adequately designed to evaluate this risk.

- The FVIII products are heterogenous, and the plausibility of different rates of inhibitor development between individual products cannot be excluded.

- Individual studies have identified a wide range of inhibitor development across products, but the direct comparability of study results is questionable based on diversity of study methods and patient populations over time.

- The SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products. Due to heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies that have evaluated only class effects to individual products; and particularly to products (including more recently authorised products) which are not included in such studies.

- Finally, the PRAC noted that to date most studies evaluating a differential risk of inhibitor development between classes of FVIII products suffer from a variety of potential methodological limitations and based on the available data considered there is no clear and consistent evidence to suggest differences in relative risk between classes of FVIII products. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAH responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between the rFVIII and pdFVIII product classes.

In view of the above, the PRAC recommended the following updates of sections 4.4, 4.8 and 5.1 of the SmPC as well as sections 2 and 4 of the Package Leaflet for the FVIII products indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) as follows:

- The section 4.4 of the SmPC should be amended to include a warning on the clinical importance of monitoring patients for FVIII inhibitor development (in particular warning on the clinical consequences of low compared to high titre inhibitors).

- With regards to sections 4.8 and 5.1 of the SmPC, the PRAC noted that several FVIII products currently include reference to data from study results which do not allow for a definite conclusion on the inhibitor risk for individual products. As the evidence suggests that all human
FVIII products carry a risk of inhibitor development such statements should be removed. The available data supports a frequency of FVIII inhibitor development within the frequency of ‘very common’ and ‘uncommon’, for PUPs and PTPs respectively, therefore the PRAC recommends that the SmPCs should be aligned with these frequencies unless justified by product specific data. For products for which section 4.2 contains the following statement for PUPs:

"<Previously untreated patients. The safety and efficacy of {Invented) name} in previously untreated patients have not yet been established. No data are available. >), the above frequency for PUPs should not be implemented. In relation to section 5.1, any reference to inhibitor development studies in PUPs and PTPs should be deleted unless the studies were conducted in compliance with a Paediatric Investigation Plan or the studies provide robust evidence of a frequency of inhibitors in PUP which is less than ‘very common’ or for PTPs which is different from ‘uncommon’ (as laid down in the attachments of the PRAC AR).

Further to the assessment of the totality of the responses submitted by the MAH for susoctocog alfa (Obizur), the PRAC is of the opinion that the outcome of this article 31 referral procedure does not apply to this product in view of the indication of Obizur (acquired haemophilia A due to inhibitory antibodies to endogenous FVIII) and the different target population.

Benefit –risk balance

Based on the current evidence from the SIPPET study, as well as data from the individual clinical trials and observational studies included in the MAH responses, and the views expressed by the experts of the ad-hoc expert meeting, the PRAC agreed that the current evidence does not provide clear and consistent evidence of any statistically and clinically meaningful differences in inhibitor risk between rFVIII and pdFVIII products. No conclusions can be drawn on any role of VWF in protecting against inhibitor development.

Given these are heterogeneous products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies.

Individual studies have identified a wide range of inhibitor frequency in PUPs across products, and the SIPPET study was not designed to differentiate between individual products in each class. Due to very different study methods and patient populations that have been studied over time, and inconsistent findings across studies, the PRAC found that the totality of evidence does not support a conclusion that recombinant factor VIII medicines, as a class, poses a greater risk of inhibitor development than the class derived from plasma.

Besides, the PRAC noted that several FVIII products currently include in their product information reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products. As the evidence suggests that all human FVIII products carry a risk of inhibitor development, within the frequency of ‘very common’ and ‘uncommon’ for PUPs and PTPs respectively, the PRAC recommends that the SmPCs should be aligned with these frequencies unless justified by product specific data.

In view of the above, the PRAC concluded that the benefit-risk balance of Factor VIII products indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency), remains favourable subject to the changes to the product information agreed (section 4.4, 4.8 and 5.1 of the SmPC).

Re-examination procedure

Following the adoption of the PRAC recommendation during the May 2017 PRAC meeting, the MAH LFB Biomedicaments expressed their disagreement with the initial PRAC recommendation.

Given the detailed grounds provided by the MAH, the PRAC carried out a new assessment of the available data in the context of the re-examination.
PRAC discussion on grounds for re-examination

The SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products. Due to heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies that have evaluated only class effects to individual products; and particularly to products (including more recently authorised products) which are not included in such studies. The findings from the SIPPET study, as well as those from the individual clinical trials and observational studies, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between the rFVIII and pdFVIII product classes.

Overall, the PRAC maintains its conclusions that standardised information on the frequency for FVIII products in PUP and PTP should be reflected in section 4.8 of the SmPC, unless another frequency range for a specific medicinal product is demonstrated by robust clinical studies for which the results would be summarised in section 5.1.

Expert consultation

The PRAC consulted an ad-hoc expert meeting on some of the aspects that formed part of the detailed grounds submitted by LFB Biomedicaments.

Overall, the expert group supported the PRAC initial conclusions and agreed that the proposed product information provides an adequate level of information to appropriately communicate to prescribers and patients about the risk of inhibitor development. No additional communication, on risk factors for inhibitor development beyond the product information or any additional risk minimisation measures was recommended.

The group also agreed that specific data about frequency of inhibitors for each product should not be included in the SmPC as the available studies are not adequately powered to draw precise conclusions on the absolute frequency for each product or on the relative frequency of inhibitors between products.

The experts emphasized that collaboration between academia, industry and regulators should be encouraged to collect harmonised data through registries.

PRAC conclusions

In conclusion, further to the initial assessment and the re-examination procedure, PRAC maintains its conclusion that the benefit-risk balance of the human plasma derived and recombinant coagulation Factor VIII containing medicinal products remains favourable subject to the agreed changes to the product information (section 4.4, 4.8 and 5.1 of the SmPC).

The PRAC adopted a recommendation on 01 September 2017 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for human plasma derived and recombinant coagulation factor VIII containing medicinal products (see Annex I and Annex A).

- The PRAC considered the totality of the data submitted with regards to the risk of inhibitor development for the classes of recombinant and plasma derived FVIII products, in previously untreated patients (PUPs). This included published literature (SIPPET study6), data generated in individual clinical trials and a range of observational studies submitted by the marketing

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authorisation holders, including the data generated in large multicentre cohort studies, data submitted by the national competent authorities of the EU Member States as well as responses provided by the Authors of the SIPPET study. PRAC also considered grounds submitted by LFB Biomedicaments as basis for their request for re-examination of the PRAC recommendation and the views of two experts meetings held on 22 February and 3 August 2017.

- The PRAC noted that the SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products in total. Due to the heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies evaluating only class effects to individual products; and particularly to the products that are not included in such studies.

- The PRAC also considered that studies conducted to date suffer from a variety of methodological limitations and, on balance, there is no clear and consistent evidence to suggest differences in relative risks between FVIII product classes based on available data. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAH responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between rFVIII and pdFVIII product classes. Given these are heterogenous products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies.

- The PRAC noted that the efficacy and safety of Factor VIII products as indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A have been established. Based on the available data, the PRAC considered that SmPC updates for the FVIII products are warranted: section 4.4 should be amended to include a warning on the clinical importance of monitoring patients for FVIII inhibitor development. With regards to sections 4.8 and 5.1, the PRAC noted that several FVIII products currently include reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products. Results of clinical studies not sufficiently robust (e.g. suffering from methodological limitations) should not be reflected in the product information on FVIII products. The PRAC recommended changes to the product information accordingly. Besides, as the evidence suggests that all human FVIII products carry a risk of inhibitor development, within the frequency of ‘very common’ and ‘uncommon’, for PUPs and PTPs respectively, the PRAC recommended that the product information of these products should be aligned with these frequencies unless justified by product specific data.

Therefore, the PRAC concluded that the benefit-risk balance of the human plasma derived and recombinant coagulation Factor VIII containing medicinal products remains favourable and recommended the variations to the terms of the marketing authorisations.

**CHMP opinion**

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.