

**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, 1.27 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 moroctocog 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:

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

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

### 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 (see section 5.2)..

### 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**

#### Traceability

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

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.

#### 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 pro-coagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

### 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).

### 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 1.27 mmol (29 mg) sodium per vial or pre-filled syringe, equivalent to 1.5% of the WHO recommended maximum daily intake (RDI) of 2 g sodium for an adult. Depending on body weight of the patient and posology of ReFacto AF, patients could receive multiple vials or pre-filled syringes. This should be taken into consideration if the patient is on a low salt 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. If such inhibitors occur, the condition may 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ) and uncommon ( $\geq 1/1,000$  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 765 subjects.

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

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

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

#### Paediatric population

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 studies that included both previously treated adults and previously treated children and adolescents (n=18, aged 12-16 years in a study and n=49, aged 7-16 years in a supporting study), with a tendency for higher frequencies of adverse reactions in children aged 7-16 years as compared to adults. Additional safety experience in children has been accrued through studies that encompassed both previously treated (n=18 aged <6 years and n=19 aged 6 to <12 years) and previously untreated (n=23 aged <6 years) patients and which supports a safety profile similar with that observed in adult patients.

#### 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: antihemorrhagics, blood coagulation factor VIII; ATC code: B02BD02.

ReFacto AF contains B-domain deleted recombinant coagulation factor VIII (moroctocog 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.

## Clinical efficacy

The data in the table below relates to PUP and PTP data from ReFacto AF studies in patients <12 years.

### Consumption and efficacy results in paediatric population

	<b>PTPs &lt;6 years</b>	<b>PTPs 6 to &lt;12 years</b>	<b>PUPs &lt;6 years</b>
Dose by weight (IU/kg) per prophylaxis infusion <sup>a</sup> median (min, max)	N=14 36 IU/kg (28, 51)	N=13 32 IU/kg (21, 49)	N=22 46 IU/kg (17,161)
Total ABR all subjects <sup>b</sup> median (min, max)	--	--	N=23 3.17 (0.0, 39.5)
Total ABR for subjects who reported following an On Demand regimen at Baseline <sup>c</sup> median (min, max)	N=5 41.47 (1.6, 50.6)	N=9 25.22 (0.0, 46.6)	--
Total ABR for subjects who reported following a Prophylaxis regimen at Baseline <sup>c</sup> median (min, max)	N=13 1.99 (0.0, 11.2)	N=9 5.55 (0.0, 13.0)	--
Dose by weight (IU/kg) per bleeding episode for bleed treatment median (min, max)	N=13 35 IU/kg (28, 86)	N=14 33 IU/kg (17, 229)	N=21 55 IU/kg (11, 221)
% of bleeds treated successfully with ≤ 2 infusions	98.7%	98.8%	96.7%

<sup>a</sup> The dose and frequency of ReFacto AF prescribed throughout the study were at the investigator's discretion as per local standard of care.

<sup>b</sup> Subjects in the PUP study were not required to follow a regular continuous prophylaxis treatment; however, with the exception of one subject (with only on demand (OD) treatment) the majority of subjects took regular prophylaxis infusions. Several began with OD infusions but switched to prophylaxis treatment during their participation, and some had only sporadic prophylaxis infusions.

<sup>c</sup> Subjects in the PTP study reported their FVIII treatment modality (prophylaxis or on demand) at baseline and were not required to maintain this modality as a condition of study participation. The dose and frequency of ReFacto AF prescribed throughout the study were at the investigator's discretion as per local standard of care.

Abbreviations: ABR = annualised bleeding rate

Of note, annualised bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

## 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.

Pharmacokinetic parameter estimates for ReFacto in previously treated patients with haemophilia A			
PK parameter	Mean	SD	Median
AUC <sub>t</sub> (IU·h/mL)	19.9	4.9	19.9
t <sub>1/2</sub> (h)	14.8	5.6	12.7
CL (mL/h·kg)	2.4	0.75	2.3
MRT (h)	20.2	7.4	18.0
recovery (IU/dl increase in FVIII:C per IU/kg FVIII given)	2.4	0.38	2.5

Abbreviations: AUC<sub>t</sub> = area under the plasma concentration-time curve from zero to the last measurable concentration; t<sub>1/2</sub> = 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<sub>t</sub> and AUC<sub>∞</sub> (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<sub>t</sub> and AUC<sub>∞</sub>, 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.

In a ReFacto AF study of 19 PUPs, the recovery at the beginning of the study in the 17 children aged 28 days to less than 2 years was 1.32 ± 0.65 IU/dl per IU/kg and in the 2 children aged 2 to <6 years were 1.7 and 1.8 IU/dl per IU/kg. Except in cases where inhibitors were detected, the mean recovery was stable over time (6 visits during a 2-year period) and individual values ranged from 0 (in presence of inhibitor) to 2.7 IU/dl per IU/kg.

In a study of 37 paediatric PTPs, the pharmacokinetic parameters of ReFacto AF observed after a 50 IU/kg dose are shown in the table below.

Mean ± SD FVIII Pharmacokinetic Parameters after Single 50 IU/kg Dose in Paediatric PTPs		
PK parameter	Number of subjects	Mean <sup>a</sup> ± SD
Recovery, IU/dl per IU/kg		
Aged <6 years	17	1.7 ± 0.4
Aged 6 to <12 years	19	2.1 ± 0.8
C <sub>max</sub> , IU/mL <sup>b</sup>	19	0.9 (45)
AUC <sub>inf</sub> , IU·h/mL <sup>b</sup>	14	9.9 (41)
t <sub>1/2</sub> , h <sup>b</sup>	14	9.1 ± 1.9
CL, mL/h/kg <sup>b</sup>	14	4.4 (30)
V <sub>ss</sub> , mL/kg <sup>b</sup>	14	56.4 (15)

<sup>a</sup> Geometric mean (geometric CV%) for all, except for arithmetic mean ±SD for incremental recovery and t<sub>1/2</sub>.

<sup>b</sup> Patients aged 6 to <12 years only.

Abbreviations: C<sub>max</sub> = maximum observed plasma concentration; CV = coefficient of variation; AUC<sub>inf</sub> = area under the plasma concentration-time profile from time zero extrapolated to infinite time; t<sub>1/2</sub> = terminal half-life; CL = clearance; V<sub>ss</sub> = steady-state volume of distribution.

### 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 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 discolouration 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 Europe MA EEIG  
Boulevard de la Plaine 17  
1050 Bruxelles  
Belgium

## **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 of the biological active substance

Pfizer Ireland Pharmaceuticals  
Grange Castle Business Park  
Clondalkin  
Dublin 22  
Ireland

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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

moroctocog alfa  
(recombinant human coagulation factor VIII)

#### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 vial: 250 IU moroctocog alfa (approx. 62.5 IU/ml after reconstitution).

1 vial: 500 IU moroctocog alfa (approx. 125 IU/ml after reconstitution)

1 vial: 1000 IU moroctocog alfa (approx. 250 IU/ml after reconstitution)

1 vial: 2000 IU moroctocog 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 moroctocog alfa

1 vial with 500 IU moroctocog alfa

1 vial with 1000 IU moroctocog alfa

1 vial with 2000 IU moroctocog 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 APPROPRIATE**

Discard any remaining reconstituted solution

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

Pfizer Europe MA EEIG  
Boulevard de la Plaine 17  
1050 Bruxelles  
Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/103/001  
EU/1/99/103/002  
EU/1/99/103/003  
EU/1/99/103/004

**13. MANUFACTURER'S BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

ReFacto AF 250  
ReFacto AF 500  
ReFacto AF 1000  
ReFacto AF 2000

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**REFACTO AF VIAL LABEL**

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

ReFacto AF 250 IU powder for solution for injection

ReFacto AF 500 IU powder for solution for injection

ReFacto AF 1000 IU powder for solution for injection

ReFacto AF 2000 IU powder 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**

**6. OTHER**

Store in a refrigerator

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**REFACTO AF SOLVENT PRE-FILLED SYRINGE LABEL**

**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

Moroctocog alfa  
(recombinant human coagulation factor VIII)

#### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

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

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

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

1 pre-filled syringe: 3000 IU moroctocog 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**

Pfizer Europe MA EEIG  
Boulevard de la Plaine 17  
1050 Bruxelles  
Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

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

**13. MANUFACTURER'S BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

ReFacto AF 250  
ReFacto AF 500  
ReFacto AF 1000  
ReFacto AF 2000  
ReFacto AF 3000

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**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**

## Package leaflet: Information for the user

**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**

moroctocog 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 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**

After reconstitution, ReFacto AF contains 1.27 mmol (or 29 mg) sodium (main component of cooking/table salt) per vial. This is equivalent to 1.5% of the recommended maximum daily dietary intake of sodium for an adult. Depending on your body weight and your dose of ReFacto AF, you could receive multiple vials. This should be taken into consideration if you are on a low salt 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.

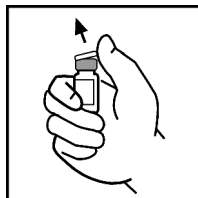
Use only the pre-filled syringe provided in the box for reconstitution. Other sterile disposable syringes may be used for administration.

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.

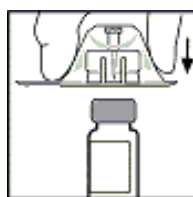
Always wash your hands before performing the following reconstitution and administration procedures. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure.

*Reconstitution:*

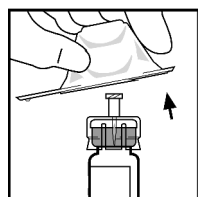
1. Allow the vial of lyophilised ReFacto AF and the pre-filled solvent syringe to reach room temperature.
2. Remove the plastic flip-top cap from the ReFacto AF vial to expose the central portion of the rubber stopper.



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.



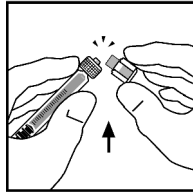
6. Lift the package away from the adapter and discard the package.



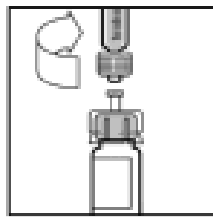
7. Attach the plunger rod to the solvent syringe by inserting the rod into the opening in the syringe stopper and pushing and turning the rod firmly until it is securely seated in the stopper.



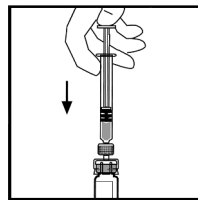
8. Break off the tamper-resistant plastic tip cap from the solvent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The cap may need to be replaced (if not administering reconstituted ReFacto AF immediately), so set it aside by placing it on its top.



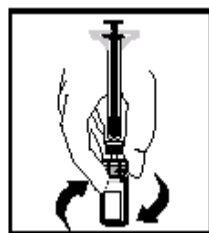
9. Place the vial on a flat surface. Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



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



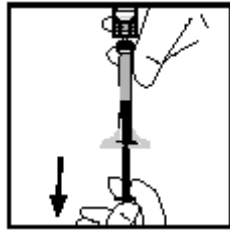
11. With the syringe still connected to the adapter, **gently** rotate the vial until the powder is dissolved.



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.



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

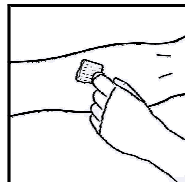
Note: If the solution is not to be used immediately, the syringe cap is to be carefully replaced. Do not touch the syringe tip or the inside of the cap.

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

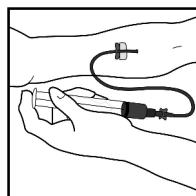
*Administration (Intravenous Infusion):*

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.
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.



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 uncommon (less than 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
- 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)

- inhibitor development for patients who have been previously treated with factor VIII products (less than 1 in 100 patients)

- 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 (see section 2 “ReFacto AF contains sodium”). 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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**This leaflet was last revised in**

Detailed information on this medicine is available on European Medicines Agency website:  
<http://www.ema.europa.eu>.

## 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**

Moroctocog 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 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**

After reconstitution, ReFacto AF contains 1.27 mmol (or 29 mg) sodium (main component of cooking/table salt) per pre-filled syringe. This is equivalent to 1.5% of the recommended maximum daily dietary intake of sodium for an adult. Depending on your body weight and your dose of ReFacto AF, you could receive multiple pre-filled syringes. This should be taken into consideration if you are on a low salt 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.

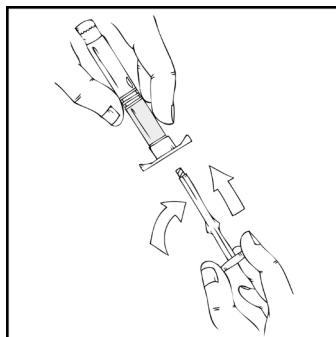
**Note:** If you need to use more than one pre-filled syringe of ReFacto AF per infusion, each syringe should be reconstituted according to the specific directions. A separate 10 cc or larger luer lock syringe (not included in this kit) may be used to draw back the reconstituted contents of each syringe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

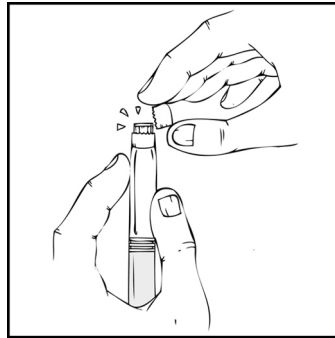
### Reconstitution

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).



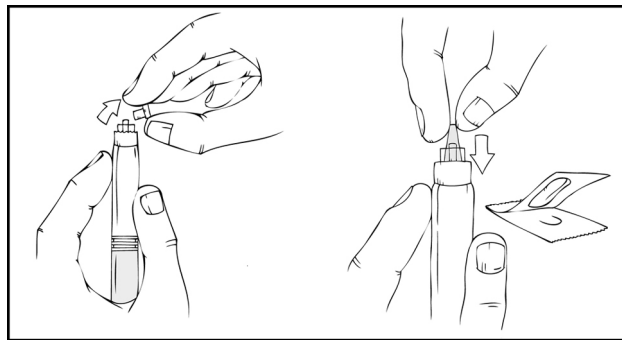
Throughout the reconstitution process, it is important to keep the ReFacto AF pre-filled syringe upright (with the white powder above the clear solution) to prevent possible leakage.

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.



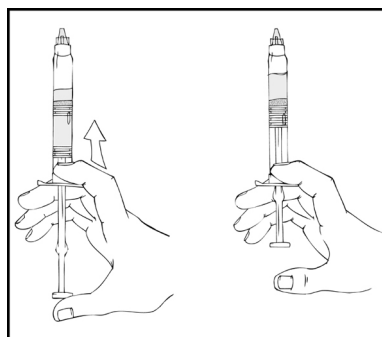
5. Remove the protective blue vented sterile cap from its packaging.

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.

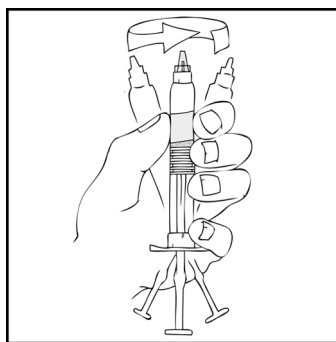


6. **Gently and slowly** advance the plunger rod by pushing until the two plungers inside the pre-filled syringe meet, and all of the solvent is transferred to the top chamber containing the ReFacto AF powder.

**Note:** To prevent the escape of fluid from the tip of the syringe, do not push the plunger rod with excessive force.

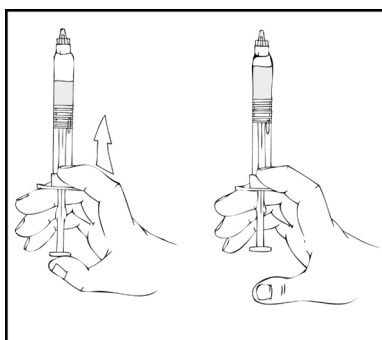


7. With the ReFacto AF pre-filled syringe remaining upright, swirl **gently** several times until the powder is dissolved.



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.

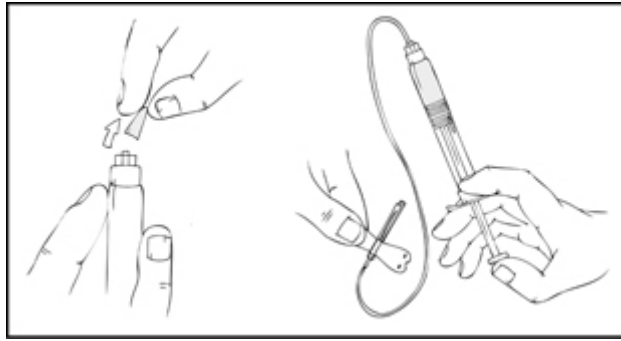
### **Administration (Intravenous Infusion)**

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.

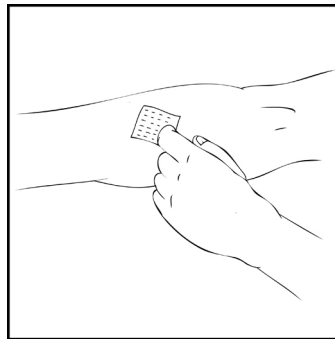
ReFacto AF is administered by intravenous (IV) infusion after reconstitution of the powder with the solvent (0.9% sodium chloride). Once reconstituted, ReFacto AF should be inspected for particulate matter and discolouration prior to administration.

ReFacto AF should be administered using the infusion set included in the kit, unless otherwise advised by your doctor or other healthcare professional.

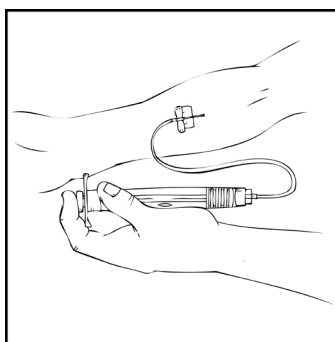
1. Remove the protective blue vented cap and firmly attach the intravenous infusion set provided onto the ReFacto AF pre-filled syringe.



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



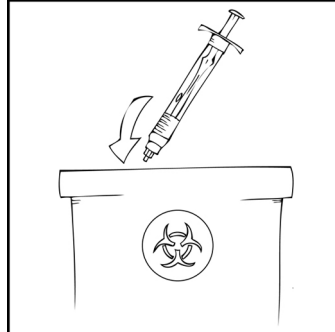
3. Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein, as instructed by your doctor or other healthcare professional. Remove the tourniquet. The reconstituted ReFacto AF product should be injected intravenously over several minutes. Your doctor 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.

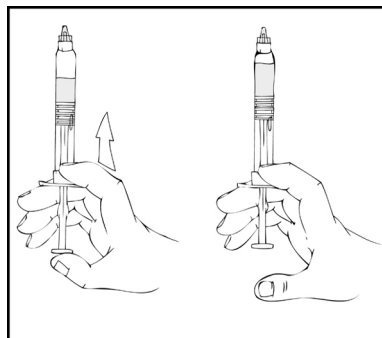
**Additional Instructions:**

**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.

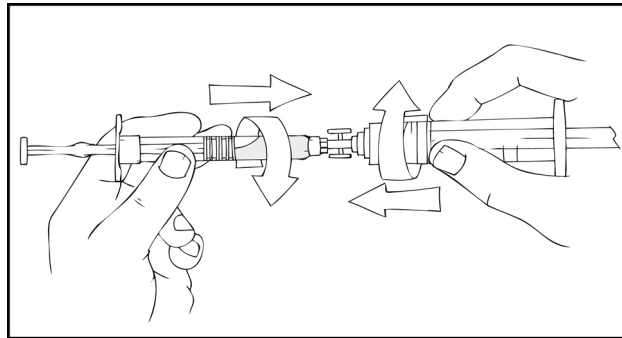
1. Reconstitute all ReFacto AF pre-filled syringes according to instructions shown above in the reconstitution directions (see Reconstitution and Administration).

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.

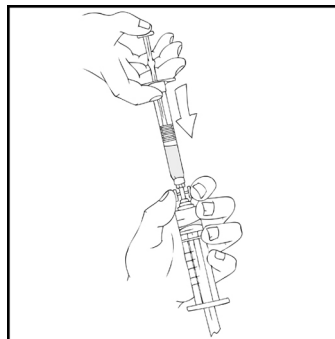


2. Remove the luer-to-luer syringe connector from its package (luer-to-luer syringe connectors are not provided).

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.

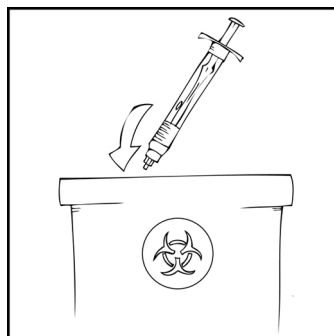


4. With the ReFacto AF pre-filled syringe on top, slowly depress the plunger rod until the contents empty into the 10 cc or larger luer lock syringe.



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 uncommon (less than 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
- 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)

- inhibitor development for patients who have been previously treated with factor VIII products (less than 1 in 100 patients)
- 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 (see section 2 “ReFacto AF contains sodium”).
- 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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