For the use only of a Registered Medical Practitioner (Hematologist) or a Hospital or a Laboratory.

Moroctocog alfa (AF-CC) (r-DNA origin)

XYNTHOPHILIA®

1. GENERIC NAME

Moroctocog alfa (AF-CC) (r-DNA origin)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single use vial contains either 250 IU, 500 IU, 1000 IU, or 2000 IU of Moroctocog alfa (AF-CC) (r-DNA origin).

List of Excipients

The excipients are polysorbate 80 (0.4 mg/vial), sucrose (12 mg/vial), L-Histidine (6 mg/vial), calcium chloride dihydrate (1 mg/vial), sodium chloride (36 mg/vial) [after reconstitution with diluent].

3. DOSAGE FORM AND STRENGTH

250 IU, 500 IU, 1000 IU, or 2000 IU Lyophilized powder for reconstitution in a vial and one pre-filled diluent syringe.

All strengths/presentations mentioned in this document might not be available in the market.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Moroctocog alfa (AF-CC) (r-DNA origin), Antihemophilic Factor (Recombinant) [BDDrFVIII], indicated for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia).

4.2 Posology and method of administration

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

Posology

Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Individual patients may vary in their response to factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives. Doses administered should be titrated to the patient's clinical response. In the presence of an inhibitor, higher doses or appropriate alternative treatment may be required.

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

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current World Health Organization (WHO) international standard for factor VIII activity. 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 corresponds approximately to the quantity of factor VIII in 1 mL of normal human plasma. The calculation of the required dosage of factor VIII is based upon the empirical finding that, on average, 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Clinical data support the use of the one-stage clotting assay for monitoring Moroctocog alfa (AF-CC) (r-DNA origin) therapy.

The labelled potency of Moroctocog alfa (AF-CC) (r-DNA origin) is based on the European Pharmacopoeia chromogenic substrate assay in which the Pfizer In-House Recombinant Factor VIII Potency Reference Standard has been calibrated using a one-stage clotting assay. This method of potency assignment is intended to harmonize Moroctocog alfa (AF-CC) (r-DNA origin) with clinical monitoring using a one-stage clotting assay.

Precise monitoring of the replacement therapy by means of plasma factor VIII activity assay should be considered, particularly for surgical intervention.

Dosing for Bleeding and Surgery:

In the case of the following hemorrhagic events, consideration should be given to maintaining the factor VIII activity at or above the plasma levels (in % of normal or in IU/dL) for the indicated period, as outlined in the following table.

Table 1: Maintenance of Factor VIII Activity for Various Hemorrhagic Events

Type of Hemorrhage	**Factor VIII Level Required (% or IU/dL)**	**Frequency of Doses (h)/Duration of Therapy (d)**
Minor Early hemarthrosis, superficial muscle or soft tissue and oral bleeds	20-40	Repeat every 12 to 24 hours as necessary until resolved. At least 1 day, depending upon the severity of the hemorrhage.
Moderate Hemorrhages into muscles. Mild head trauma capitus. Minor operations including tooth extraction. Hemorrhages into the oral cavity.	30-60	Repeat infusion every 12 - 24 hours for 3 - 4 days or until adequate hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major Gastrointestinal bleeding. Intracranial, intraabdominal or intrathoracic hemorrhages. Fractures. Major operations.	60-100	Repeat infusion every 8 - 24 hours until threat is resolved or in the case of surgery, until adequate local hemostasis is achieved, then continue therapy for at least another 7 days.

Prophylaxis

For long-term prophylaxis against bleeding in patients with severe hemophilia 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 Moroctocog alfa (AF-CC) (r-DNA origin) (see section 5.3).

Moroctocog alfa (AF-CC) (r-DNA origin) is appropriate for use in children of all ages, including newborns.

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.

Moroctocog alfa (AF-CC) (r-DNA origin) 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.

For reconstitution instructions prior to administration, see section 8.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2.

Known allergic reaction to hamster protein.

4.4 Special warnings and precautions for use

Traceability

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

It is strongly recommended that every time Moroctocog alfa (AF-CC) (r-DNA origin) 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.

Hypersensitivity

Allergic type hypersensitivity reactions have been observed with Moroctocog alfa (AF-CC) (r-DNA origin). 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, generalized urticaria, tightness of the chest, wheezing, and 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 hemophilia 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 patients with inhibitors (especially high level inhibitors, above 5 Bethesda units (BU)/mL), factor VIII therapy may not be effective, and other therapeutic options should be considered.

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 hemophilia and factor VIII inhibitors.

Reports of lack of effect

Reports of lack of effect, mainly in prophylaxis patients, have been received during the clinical trials and post-marketing setting. The lack of effect and/or low factor VIII recovery has been reported in patients with inhibitors but also in patients who had no evidence of inhibitors. The lack of effect has been described as bleeding into target joints, bleeding into new joints , other bleeding or a subjective feeling by the patient of new onset bleeding. In order to ensure an adequate therapeutic response, it is important TO INDIVIDUALLY TITRATE AND MONITOR each patient's dose of Moroctocog alfa (AF-CC) (r-DNA origin), particularly when initiating treatment with Moroctocog alfa (AF-CC) (r-DNA origin) (see section 4.2. and section 4.4).

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).

4.5 Drugs interactions

No interactions of Moroctocog alfa (AF-CC) (r-DNA origin) with other medicinal products have been reported.

4.6 Use in special populations

Animal reproduction studies have not been conducted with factor VIII, therefore no data are available on fertility. Because of the rare occurrence of hemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, Moroctocog alfa (AF-CC) (r-DNA origin) should be used during pregnancy and breast-feeding only if clearly indicated.

4.7 Effects on ability to drive and use machines

Moroctocog alfa (AF-CC) (r-DNA origin) has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Table 2 Undesirable effects of Moroctocog alfa (AF-CC) (r-DNA origin) observed in clinical trials

System Organ Class (disorder)	Very Common ≥10%	Common ≥1%	Uncommon ≥0.1% and <1%	Rare ≥0.01% and <0.1%	Very Rare <0.01%
Immune system disorders					Anaphylactoid reaction

Cardiac disorders					Angina pectoris, Tachycardia, Palpitations*
Investigations				Lab increase for antibody to Mouse IgG (ReFacto only), Lab increase of FVIII antibody, Lab increase for antibody to CHO protein,	CPK increased, Increased aspartate aminotransferase, Increased alanine aminotransferase*, Increased bilirubin
Nervous system disorders				Headache, Dizziness	Neuropathy*, Perspiration increased, Somnolence, Taste altered
Metabolism and nutrition disorders					Anorexia
Musculoskeletal and connective tissue disorders				Arthralgia	Myalgia
Vascular disorders				Hemorrhage, Hematoma	Flushing*, Thrombophlebitis,* Hypotension, Vasodilation
Respiratory, thoracic & mediastinal disorders				Cough	Dyspnea
Gastrointestinal disorders				Vomiting*, Nausea, Diarrhea, Abdominal pain	
Skin and subcutaneous tissue disorders				Rash	Pruritus, Urticaria
General disorder & administration site conditions				Pyrexia, Chills, Catheter site related reaction	Asthenia, Injection site pain, Injection site reaction, Injection site inflammation*
Factor VIII	FVIII	FVIII			

Inhibition†	Inhibition in PUPS	Inhibition in PTPS			

Adverse reaction frequencies are calculated on an event per infusion basis
(*) = These adverse reactions were totalled from adverse events and hemophilia events across all studies regardless of relatedness to study drug.
All other adverse reactions were totalled across all studies from study drug-related adverse events and hemophilia events ONLY.
For the adverse reaction frequencies, surgical patients receiving continuous infusion (CI), any day CI is administered is considered one infusion.
(†) = Frequency for the Adverse Reaction Factor VIII inhibition is expressed on a per patient basis

The most frequently reported treatment-emergent adverse reaction, on a per infusion basis, was vomiting. Most adverse reactions reported were considered mild or moderate in severity.

In addition, as with any intravenous protein product, allergic type hypersensitivity reactions are possible. Manifestations of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

Patients with hemophilia A may develop neutralizing antibodies (inhibitors) to factor VIII. As with all coagulation factor VIII products, patients are to be monitored for the development of inhibitors that are quantified in Bethesda Units (BUs) using either the Bethesda assay or Bethesda assay with the Nijmegen modification. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response or an unexpectedly low yield of plasma factor VIII activity. In such cases, it is recommended that a specialized hemophilia centre be contacted.

If any reaction takes place that is thought to be related to the administration of Moroctocog alfa (AF-CC) (r-DNA origin), the rate of infusion should be decreased or the infusion stopped, as dictated by the response of the patient.

In a clinical trial (Study 301), 32 out of 101 (32%) previously untreated patients treated with Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process developed inhibitors: 16 out of 101 (16%) with a titer >5 Bethesda Units (BU) and 16 out of 101 (16%) with a titer ≤5 BU. The median number of exposure days prior to inhibitor development in these patients was 12 days (range 3 - 49 days). Of the 16 high responder patients, 15 received immune tolerance (IT) treatment. Eleven (11) of the high responders had a titer of <0.6 BU at their latest available test after IT. In addition, IT treatment was started in 10 of the 16 low titer (≤5 BU) patients, 9 of whom had titer <0.6 BU for their latest value. Therefore, IT had an overall efficacy of 80% (20/25), 73% for high-responders and 90% for low-responders. Five (5) of the 6 remaining low responder patients who did not receive IT also had a titer <0.6 BU for their latest value.

In a clinical trial of Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process, one of 113 (0.9%) previously heavily treated patients who were evaluated for efficacy in bleeding episodes developed a high titer inhibitor. Inhibitor development in this patient occurred in the same time frame as the development of monoclonal gammopathy of uncertain significance. The patient was noted initially at a local laboratory to have a treatment-emergent low titer inhibitor at 98 exposure days, which was confirmed at 2 BU at the central laboratory at 113 exposure days. After 18 months on

continued treatment with Moroctocog alfa (AF-CC) (r-DNA origin), the inhibitor level rose to nearly 13 BU and a bleeding episode failed to respond to Moroctocog alfa (AF-CC) (r-DNA origin) treatment.

In a pivotal phase 3 study, in which previously treated patients (PTPs) with hemophilia A received Moroctocog alfa (AF-CC) (r-DNA origin) for routine prophylaxis and on-demand treatment, 94 subjects received at least one dose of Moroctocog alfa (AF-CC) (r-DNA origin) resulting in a total of 6775 infusions. In this study, the incidence of FVIII inhibitors to Moroctocog alfa (AF-CC) (r-DNA origin) was the primary safety endpoint. Two patients with low titer, transient inhibitors were observed in these 94 patients (2.1%). In a Bayesian statistical analysis, results from this study (two out of 94 subjects developed an inhibitor, 89 had 50 or more exposure days to Moroctocog alfa (AF-CC) (r-DNA origin) were used to update PTP results from prior supporting studies of Moroctocog alfa (AF-CC) (r-DNA origin). This Bayesian analysis indicates that the population (true) inhibitor rate for Moroctocog alfa (AF-CC) (r-DNA origin) was below a predefined acceptable value of 4.4%; the estimate of the 95% upper limit of the true inhibitor rate was 4.07%.

In a pivotal phase 3 study for surgical prophylaxis in patients with hemophilia A (study 311), one low titer persistent inhibitor and one transient false-positive inhibitor were reported.

There have been spontaneous post-marketing reports of high titer inhibitors developing in previously treated patients.

Laboratory increases in anti-FVIII antibody titers, in the absence of inhibitor development, have been observed in clinical trials. In a study of PTPs receiving Moroctocog alfa (AF-CC) (r-DNA origin) for routine treatment and prevention of bleeding episodes (study 310) and for surgical prophylaxis (study 311), 1 of 94 (1%) patients, and 1 of 30 (3%) patients, respectively, developed anti-FVIII antibodies; these patients did not develop an inhibitor. The clinical significance of these antibodies, in the absence of an inhibitor, is unclear.

In clinical trials of PTPs receiving Moroctocog alfa (AF-CC) (r-DNA origin) for routine treatment and prevention of bleeding episodes, 0 of 94 (0%) patients in study 310, and 3 of 110 (3%) patients in study 306/307, developed a lab increase in anti-CHO (Chinese hamster ovary, the cell line which is the source of factor VIII for Moroctocog alfa (AF-CC) (r-DNA origin) antibody titer, without any apparent clinical effect. In a study of Moroctocog alfa (AF-CC) (r-DNA origin) for surgical prophylaxis (study 311) 1 of 30 (3%) patients developed a lab increase for antibody to CHO. Twenty of 113 (18%) previously treated patients (PTPs) had an increase in anti-CHO (Chinese hamster ovary, the cell line which is the source of factor VIII for Moroctocog alfa (AF-CC) (r-DNA origin) antibody titer, without any apparent clinical effect.

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.

4.9 Overdose

No symptoms of overdose have been reported with Moroctocog alfa (AF-CC) (r-DNA origin).

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

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

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

When infused into a hemophiliac patient, factor VIII binds to the von Willebrand factor present in the patient's circulation.

5.2 Pharmacodynamic properties

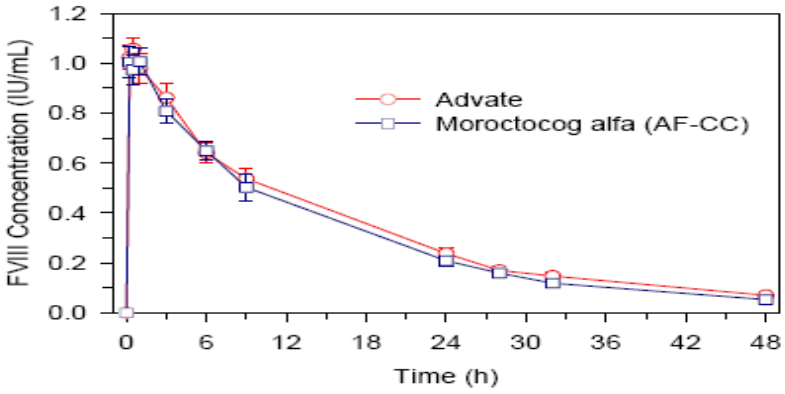
Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin, and a clot is formed. Hemophilia A is a sex-linked hereditary disorder 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.

5.3 Pharmacokinetic properties

One Stage Assay

In a pivotal cross-over pharmacokinetic study, Moroctocog alfa (AF-CC) (r-DNA origin) was shown to be bioequivalent to another recombinant factor VIII product (rFVIII, Advate®) in 30 previously treated patients (PTPs) (≥12 years) using the one-stage clotting assay. The ratios of geometric least square means of Moroctocog alfa (AF-CC) (r-DNA origin) - to-Advate® were 100%, 89.8% and 88.0% for K-value, AUC_t and AUC_∞, respectively. The corresponding 90% confidence intervals about the ratios of Moroctocog alfa (AF-CC) (r-DNA origin) to Advate® geometric means were within the bioequivalence window of 80% to 125%, demonstrating bioequivalence of Moroctocog alfa (AF-CC) (r-DNA origin) to Advate®.

Figure 1: Moroctocog alfa (AF-CC) (r-DNA origin) vs. Advate



In the same study, the pharmacokinetic parameters for Moroctocog alfa (AF-CC) (r-DNA origin) were determined at baseline and followed-up in 25 PTPs (≥12 years) after repeated administration of Moroctocog alfa (AF-CC) (r-DNA origin) for six months. At baseline, following a single 2-minute intravenous infusion of 50 IU/kg dose of Moroctocog alfa (AF-CC) (r-DNA origin), plasma FVIII:C increased sharply with a mean (±SD) C_{max} of 1.12 (±0.19) IU/mL. Thereafter, the decline of FVIII:C exhibited biphasic disposition characteristics. In the initial phase, the activity dropped at a rate consistent with relatively rapid but limited distribution into extravascular space. The mean (±SD) steady-state volume of distribution was 65.1 (±35.1) mL/kg. During the terminal phase, the rate of decline in FVIII:C was slower than the initial phase with a mean (±SD) terminal elimination half-life of 11.8 (±5.1) hours. A comparable pharmacokinetic profile was obtained after repeated use 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. No time-dependent changes in the pharmacokinetic properties of Moroctocog alfa (AF-CC) (r-DNA origin) were observed (Table 3).

Table 3 Mean Factor VIII Pharmacokinetic Parameters for 25 PTPs following a rapid Infusion of Moroctocog alfa (AF-CC) (r-DNA origin) at a Dose of 50 IU/kg

Parameter	C_{max} (IU/mL)	AUC_t (h*IU/mL)	Half-life (h)	AUC_∞ (hr*IU/mL	Clearance (ml/hr/kg)	Mean Residence Time (h)	V_{ss} (mL/kg)	Recovery (IU/dL/IU/kg)
Baseline								
Mean	1.12	13.3	11.8	14.2	4.21	16.3	65.1	2.23
SD	0.19	5.2	5.1	5.5	2.08	5.9	35.1	0.39
Min	0.59	4.1	6.4	4.7	2.00	7.9	34.8	1.19
Max	1.41	23.6	33.9	25.0	10.63	40.0	195.1	2.83
Month 6								

Mean	1.24	13.3	11.8	15.0	4.04	19.5	67.4	2.47
SD	0.42	6.7	6.2	7.5	1.87	16.1	32.6	0.84
Min	0.65	5.0	5.8	5.3	1.19	7.6	18.5	1.29
Max	2.60	41.0	32.6	14.8	9.45	89.2	168.8	5.20

Abbreviations: AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from zero to the last measurable concentration; C_{max} = peak concentration; SD=standard deviation; V_{ss}=volume of distribution at steady-state

In a pivotal phase III study (Study 311) for surgical prophylaxis, Moroctocog alfa (AF-CC) (r-DNA origin) pharmacokinetics were evaluated during the perioperative management of patients with hemophilia A who were undergoing major surgery. At the baseline visit, all patients received a single dose of Moroctocog alfa (AF-CC) (r-DNA origin) of approximately 50 IU/kg. Plasma samples were analyzed for FVIII activity using a validated one-stage (OS) clotting method. Recovery data are available for a total of 30 patients; the mean (±standard deviation [SD]) K-value was 2.11(±0.43) IU/dL per IU/kg, and the mean (±SD) *in vivo* recovery value was 101.0% (±20%).

Chromogenic Assay

The labeled potency of Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process is based on the European Pharmacopoeia chromogenic substrate assay in which the Pfizer In-House Recombinant Factor VIII Potency Reference Standard has been calibrated to the WHO International Standard using the chromogenic substrate assay.

In a crossover pharmacokinetic study of eighteen (18) previously treated patients using the chromogenic assay, the circulating mean half-life for Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process was 14.8 ± 5.6 hours (ranged from 7.6 - 28.5 hours), which was not statistically significantly different from plasma-derived Antihemophilic Factor (Human), (pdAHF), which had a mean half-life of 13.7 ± 3.7 hours (ranged from 8.8 - 25.1 hours). Mean incremental recovery (K-value) of Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process in plasma was 2.4 ± 0.4 IU/dL per IU/kg (ranged from 1.9 - 3.3 IU/dL per IU/kg). This was comparable to the mean incremental recovery observed in plasma for pdAHF which was 2.3 ± 0.3 IU/dL per IU/kg (ranged from 1.7 - 2.9 IU/dL per IU/kg).

In additional clinical studies using Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process, pharmacokinetic parameters measured using the chromogenic assay were determined for previously treated patients (PTPs) and previously untreated patients (PUPs). In PTPs (n=101; median age 26 ± 12 years), Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process had a recovery at Week 0 of 2.4 ± 0.4 IU/dL per IU/kg (range 1.1 to 3.8 IU/dL per IU/kg). In measurements over 4 years of use (Month 3 [n=90], Month 6 [n=87], Month 12 [n=88], Month 24 [n=70], Month 36 [n=64] and Month 48 [n=52]), the mean incremental recovery was reproducible and ranged from 2.3 to 2.5 IU/dL per IU/kg. A subset of 37 study subjects had evaluable pharmacokinetic profiles at both baseline and Month 12. The 90% confidence intervals for the ratios of the mean values of Month 12-to-baseline AUC_T, AUC_∞, and K-value were well within the bioequivalence window of 80% to 125%, demonstrating the stability of these pharmacokinetic parameters over 1 year. In PUPs (n=59; median age 10 ± 8.3 months),

Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process 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). The mean incremental recovery for PUPs was stable over time (5 visits during a 2-year period) and ranged from 1.5 to 1.8 IU/dL per IU/kg of Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process. Population pharmacokinetic modeling using data from 44 PUPs led to a mean estimated half-life of Moroctocog alfa (AF-CC) (r-DNA origin) manufactured by the previous process in PUPs of 8.0 ± 2.2 hours.

Table 4: Mean Factor VIII Pharmacokinetic Parameters for 37 PTPS with Both Baseline and Month 12 Pharmacokinetic Profiles Following a Rapid Infusion of Moroctocog alfa (AF-CC) (r-DNA origin) Manufactured by the Previous Process at a Dose of 50 IU/kg

Parameter	C_{max} (IU/ml)	AUC_T (hr*IU/ml)	Half-life (hr)	$AUC_{\square}$ (hr*IU/ml)	Clearance (ml/hr/kg)		Mean Residence Time (hr)	V_{ss} (ml/kg)	K-value (IU/dL/IU/kg)
Baseline									
Mean	1.17	13.6	10.6	15.4	3.53		15.0	50.9	2.34
SD	0.24	3.4	2.5	4.5	1.03		3.4	13.0	0.49
Min	0.55	6.0	6.8	7.6	1.78		9.8	36.9	1.10
Max	1.90	21.1	17.2	28.1	6.60		24.7	99.0	3.80
Month 6									
Mean	1.20	14.0	11.4	16.5	3.37		16.1	51.1	2.40
SD	0.29	4.7	3.5	5.7	1.08		4.6	11.4	0.58
Min	0.84	7.8	6.6	8.8	1.49		9.7	21.3	1.67
Max	2.31	32.4	20.1	33.5	5.66		27.8	83.2	4.61

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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.

7. DESCRIPTION

Each single use vial contains either 250 IU, 500 IU, 1000 IU, or 2000 IU of Moroctocog alfa (AF-CC) (r-DNA origin) Lyophilized powder for reconstitution in a vial and one prefilled diluent syringe.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

In the absence of incompatibility studies, reconstituted Moroctocog alfa (AF-CC) (r-DNA origin) should not be administered in the same tubing or container with other medicinal products. Infusion kit components supplied in this carton are compatible with Moroctocog alfa (AF-CC) (r-DNA origin) for administration.

8.2 Shelf-life

36 months

8.3 Packaging information

Nature and Contents of Container

Moroctocog alfa (AF-CC) (r-DNA origin), Antihemophilic Factor (Recombinant) freeze-dried is supplied in kits that include single-use vials that contain nominally 250 IU, 500 IU, 1000 IU, or 2000 IU per vial. Actual factor VIII activity in IU is stated on the label of each Moroctocog alfa (AF-CC) (r-DNA origin), Antihemophilic Factor (Recombinant) vial.

In addition, each Moroctocog alfa (AF-CC) (r-DNA origin) Antihemophilic Factor (Recombinant) kit contains: 1 pre-filled diluent syringe containing 4 mL of 0.9% Sodium Chloride solution for injection with plunger rod for assembly, 1 vial adapter, 1 sterile infusion set, 2 alcohol swabs, 1 bandage, 1 gauze, and 1 package insert.

Moroctocog alfa (AF-CC) (r-DNA origin), Antihemophilic Factor (Recombinant) can also be supplied in a pack presentation kit containing: 3 vials of Moroctocog Alfa (AF-CC) (r-DNA origin) lyophilized powder for reconstitution, 3 labeled pre-filled diluent syringes containing each 4 mL of 0.9% Sodium Chloride solution for injection, 3 vial adapters and 1 package insert.

Not all strengths/pack Presentation may be marketed.

8.4 Storage and handling instructions

Moroctocog alfa (AF-CC) (r-DNA origin) (AF-CC), Antihemophilic Factor (Recombinant) should be stored under refrigeration at a temperature of 2°C to 8°C. Moroctocog alfa (AF-CC) (r-DNA origin) vial may also be stored at room temperature not to exceed 25°C for up to 3 months. The diluent syringe should be stored at 2°C to 25°C and should not be used subsequent to expiration of the Moroctocog alfa (AF-CC) (r-DNA origin) drug product. The patient should write in the space provided on the outer carton the date the product was placed at room temperature. After room temperature storage, the product can be returned to refrigerated storage until the expiration date. Do not store Moroctocog alfa (AF-CC) (r-DNA origin) vial at room temperature and return it to refrigerated storage more than once. Do not use Moroctocog alfa (AF-CC) (r-DNA origin) vial after the expiry date on the label.

Product after Reconstitution: The reconstituted solution may be stored at room temperature prior to administration. The product does not contain a preservative and should be used within 3 hours.

Special Precaution for Use/Handling/Disposal

Freezing should be avoided to prevent damage to the pre-filled diluent syringe. During storage, avoid prolonged exposure of Moroctocog alfa (AF-CC) (r-DNA origin) vial to light.

Administration

Patients should follow the specific reconstitution and administration procedures provided by their physicians. For instructions, patients should follow the recommendations in the below **Administration** and **Reconstitution** sections. The procedures below are provided as general guidelines for the reconstitution and administration of Moroctocog alfa (AF-CC) (r-DNA origin).

Additional instructions are provided after **Infusion** section that detail the use of a Moroctocog alfa (AF-CC) (r-DNA origin) vial [see Combined Use of a Moroctocog alfa (AF-CC) (r-DNA origin) Vial Kit].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Moroctocog alfa (AF-CC) (r-DNA origin) Vial Kit:

Moroctocog alfa (AF-CC) (r-DNA origin) is administered by IV infusion after reconstitution of the lyophilized powder with the supplied pre-filled diluent (0.9% Sodium Chloride solution) syringe.

Reconstitution

Always wash your hands before performing the following procedures. Use germ-free methods during the preparation procedures.

All components used in the mixing and injection of Moroctocog alfa (AF-CC) (r-DNA origin) should be used as soon as possible after opening their sterile containers to minimize unnecessary exposure to room air.

Moroctocog alfa (AF-CC) (r-DNA origin) Vial Kit:

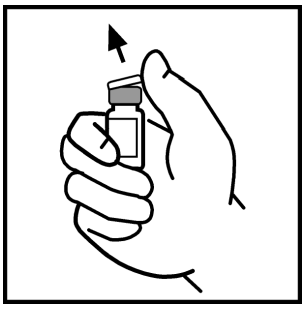
Use only the materials provided in the Moroctocog alfa (AF-CC) (r-DNA origin) kit for dissolving the Moroctocog alfa (AF-CC) (r-DNA origin) powder with the sodium chloride diluent.

Moroctocog alfa (AF-CC) (r-DNA origin) is administered by intravenous injection after dissolving with the supplied diluent (0.9% sodium chloride) in the pre-filled syringe.

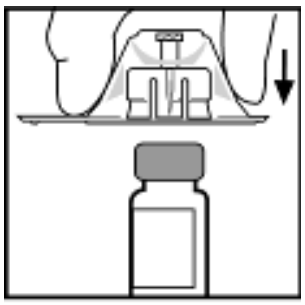
Note: If you use more than one vial of Moroctocog alfa (AF-CC) (r-DNA origin) per injection, each vial should be dissolved according to the following instructions. The empty syringe should be removed leaving the vial adapter in place, and a separate large luer lock syringe may be used to draw back the dissolved contents of each vial. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.

Moroctocog alfa (AF-CC) (r-DNA origin) Vial Kit:

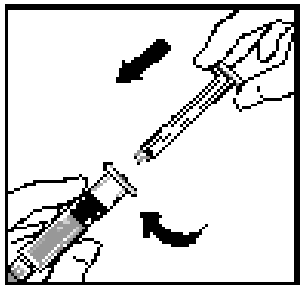
1. Allow the vial of freeze-dried Moroctocog alfa (AF-CC) (r-DNA origin) powder and the pre-filled diluent syringe to reach room temperature.
2. Remove the plastic flip-top cap from the Moroctocog alfa (AF-CC) (r-DNA origin) vial to expose the central portions of the rubber stopper.



3. Wipe the top of the vial with alcohol swab 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. If you need to use more than 1 vial to inject your prescribed dose, you must use a new alcohol swab for each vial.
4. Peel back the cover 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 in the 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.

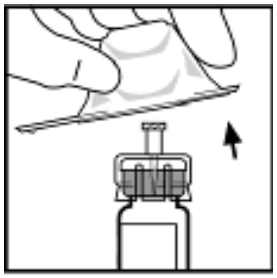


6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe by pushing and turning firmly.

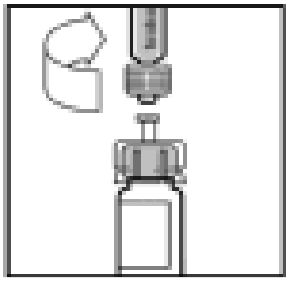


7. Break off the tamper-resistant, plastic-tip cap from the diluent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if the dissolved Moroctocog alfa (AF-CC) (r-DNA origin) is not used immediately), so place the cap on its top on a clean surface in a spot where it would be least likely to become contaminated.

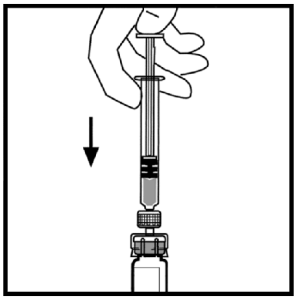
8. Lift the package away from the adapter and discard the package.



9. Place the vial on a flat surface. Connect the diluent 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 diluent into the Moroctocog alfa (AF-CC) (r-DNA origin) vial.

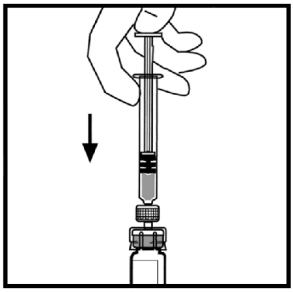


11. With the syringe still connected to the adapter, gently swirl the contents of the vial until the powder is dissolved.

Note: The final solution should be inspected visually for particulate matter before administration. The solution should be clear to slightly pearly and colorless. If it is not, the solution should be discarded and a new kit should be used.

12. Ensuring that the syringe plunger rod is still fully depressed, invert the vial. Slowly draw the solution into the syringe.

Note: If you prepared more than one vial of Moroctocog alfa (AF-CC) (r-DNA origin), remove the diluent syringe from the vial adapter, leaving the vial adapter attached to the vial. Quickly attach a separate large luer lock syringe and draw back the dissolved contents as instructed above. Repeat this procedure with each vial in turn. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.



13. 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 should be carefully replaced. Do not touch the syringe tip or the inside of the cap.

Moroctocog alfa (AF-CC) (r-DNA origin) should be infused within 3 hours after dissolving. The dissolved solution may be stored at room temperature prior to infusion.

Infusion (Intravenous Injection)

Moroctocog alfa (AF-CC) (r-DNA origin), when reconstituted, contains polysorbate-80, which is known to increase the rate of di- (2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of Moroctocog alfa (AF-CC) (r-DNA origin), including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations in section 4.2. Posology and Method of Administration section be followed closely.

Note:
Single Vial Pack Presentation Kit: The tubing of the infusion set included with Moroctocog alfa (AF-CC) (r-DNA origin) vial kit and Moroctocog alfa (AF-CC) (r-DNA origin) Solofuse kit does not contain DEHP.

Additional Pack Presentation Kit: An infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and bandages are required. These devices are not included in the Moroctocog Alfa (AF-CC) (r-DNA origin) in the additional pack presentation kit.

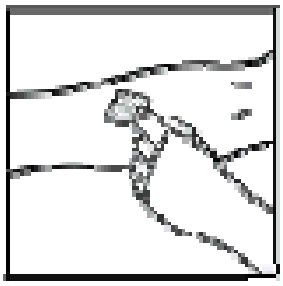
Moroctocog alfa (AF-CC) (r-DNA origin) Vial kit:

Inject Moroctocog alfa (AF-CC) (r-DNA origin) as instructed by your hemophilia doctor or nurse. Once you learn how to infuse, you can follow the instructions in this insert.

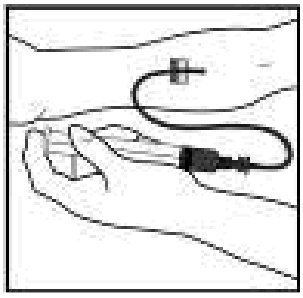
Always wash your hands before doing the following procedures. Germ-free methods should be used during injection.

Moroctocog alfa (AF-CC) (r-DNA origin) should be administered using the pre-filled diluent syringe provided or a single sterile disposable plastic luer-lock syringe. In addition, the solution should be withdrawn from the vial using the vial adapter.

1. Attach the syringe to the luer end of the infusion set tubing and perform venipuncture as instructed by your hemophilia doctor or nurse.
2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab. If you need to use more than 1 vial to inject your prescribed dose, you must use a new alcohol swab for each vial. Do not use the injection needle to withdraw the medicine from vial.



3. Insert the needle on the infusion set tubing into the vein, and remove the tourniquet. Infuse the reconstituted Moroctocog alfa (AF-CC) (r-DNA origin) product over several minutes. Your comfort level should determine the rate of infusion.



4. After injecting Moroctocog alfa (AF-CC) (r-DNA origin), remove the infusion set and discard. The amount of drug product left in the infusion set will not affect your treatment. Dispose of all unused solution, the empty vial(s), and the used needles and syringes in an appropriate sharps container used for throwing away waste that might hurt others if not handled properly.

You should record the lot number of the product every time you use Moroctocog alfa (AF-CC) (r-DNA origin). The lot number can be found on the vial label. The peel-off label on the vial may be used to record the lot number.

The reconstituted Moroctocog alfa (AF-CC) (r-DNA origin) solution does not contain a preservative and should be used within 3 hours of reconstitution.

9. PATIENT COUNSELLING INFORMATION

Advise patients comprehensively about the product including to report any adverse reactions or problems that concern them when taking Moroctocog alfa (AF-CC) (r-DNA origin) to their healthcare provider.

- Discontinue use of the product, call their healthcare provider, and go to the emergency department if any allergic-type hypersensitivity reactions occur. Inform patients of the early signs of hypersensitivity reactions (including hives [rash with itching]), generalized urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis.
- Contact their healthcare provider if they experience a lack of a clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Notify their healthcare provider if they become pregnant or intend to become pregnant during therapy, or if they are breastfeeding.
- Local irritation may occur when infusing Moroctocog alfa (AF-CC) (r-DNA origin) Solofuse.

10. DETAILS OF MANUFACTURER

Manufactured by:

Wyeth Farma, S.A. Autovía del Norte A-1
Km 23., Desvío Algete, Km 1, 28700 San
Sebastian de los Reyes, Madrid, Spain
Imported and Marketed by:

Pfizer Products India Private Limited,
The Capital- B Wing, 1802, 18th Floor, Plot No. C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

IMP-204/2017 dated 28-Sep-2017

12. DATE OF REVISION

September 2021.