APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

XYNTHA® 500 IU Injection

XYNTHA® 1000 IU Injection

SODIUM CHLORIDE DILUENT FOR XYNTHA® INJECTION

Antihaemophilic Factor (Recombinant), Plasma/ Albumin-free

Powder and solvent for solution for intravenous (IV) injection

COMPOSITION:

Each single-use vial contains nominally 500 IU or 1000 IU of moroctocog alfa (recombinant coagulation factor VIII) per vial.

After reconstitution with the accompanying 4 ml Sodium Chloride 9 mg/ ml (0,9 %) solution for injection:

XYNTHA 500 IU contains approximately 500 IU/4 ml (125 IU/ml)

XYNTHA 1000 IU contains approximately 1000 IU/4 ml (250 IU/ml)

Potency (IU) is determined using the European Pharmacopoeial chromogenic assay against World Health Organization (WHO) international standard. The specific activity of XYNTHA Antihaemophilic Factor (Recombinant) is 5 500 to 9 900 IU mg protein.

XYNTHA is not purified from human blood and contains no preservatives or added animal or human components in the final formulation.

Excipients:

Calcium Chloride Dihydrate; Polysorbate 80; Sucrose; Sodium Chloride; L-Histidine

PHARMACOLOGICAL CLASSIFICATION:

A 8.1 (Coagulants, haemostatics)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties :

Mechanism of action:

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. Factor VIII activity is greatly reduced in patients with haemophilia A and therefore replacement therapy is necessary. The administration of moroctocog alfa increases plasma levels of factor VIII activity and can temporarily correct the coagulation defect in these patients.

Moroctocog alfa (AF-CC) is a glycoprotein with an approximate molecular mass of 170 000 Da consisting of 1438 amino acids. Antihaemophilic Factor (Recombinant) is a recombinant DNA-based therapeutic which has functional characteristics comparable to those of endogenous factor VIII.

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a hemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation.

Hemophilia A is an X chromosome-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in 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 tendency.

Pharmacokinetic properties:

The pharmacokinetic parameters for moroctocog alfa (AF-CC) were determined at baseline and followed-up in 25 previously treated patients (≥12 years) after repeated administration of moroctocog alfa (AF-CC) for six months. No time-dependent changes in the pharmacokinetic properties of moroctocog alfa (AF-CC) were observed (Table 1).

Table 1: Mean factor VIII pharmacokinetic parameters for 25 ptps following a rapid infusion of moroctocog alfa (AF-CC) at a dose of 50 IU/kg

Parameter	C_{max} (IU/ml)	AUC_T (hr*IU/ml)	Half-life (hr)	AUC_∞ (hr*IU/ml)	Clearance (ml/hr/kg)	Mean Residence Time (hr)	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; AUCt = area under the plasma concentration-time curve from zero to the last measurable concentration; Cmax = peak concentration; SD=standard deviation; Vss=volume of distribution at steady-state

Reference: Table 16.20, CSR-66997

Table 2 shows the pharmacokinetic parameters of nine children, four aged 14 or 15 years of age, who are also included in the summary for the adults above, along with five children aged 3,7 to 5,8 years after moroctocog alfa (AF-CC) administration. Compared with adults, the half-life of factor VIII after moroctocog alfa (AF-CC) is shorter in children and clearance (based on body weight) is approximately 40 % higher in children.

Table 2: Mean ± fVIII pharmacokinetic parameters in previously treated paediatric patients with haemophilia a after 50 IU/kg moroctocog alfa (AF-CC)

Parameter	Young Children (n=5)	Adolescents (n=4)
Age [(min – max) yr]	3,7 – 5,8	14 - 15
Cmax (IU/ml)	0,78 ± 0,34	0,97 ± 0,21
AUC_{∞} (IU.hr/ml)	12,2 ± 6,50	8,5 ± 4,0
t½ (hr)	8,3 ± 2,7	6,9 ± 2,4
CL (ml/hr/kg)	6,29 ± 4,87	6,62 ± 2,16
Vss (ml/kg)	66,9 ± 55,6	67,1 ± 13,6
Recovery (IU/dl/IU/kg)	1,52 ± 0,69	1,95 ± 0,41

Abbreviations: AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; Cmax = peak concentration; t½ = half life; CL = clearance; Vss=volume of distribution at steady-state

INDICATIONS:

XYNTHA is indicated for the control and prevention of haemorrhagic episodes and for surgical prophylaxis in patients with haemophilia A (congenital factor VIII deficiency or classic haemophilia).

XYNTHA does not contain von Willebrand factor and hence is not indicated in Von Willebrand's disease.

CONTRAINDICATIONS:

XYNTHA is contraindicated in patients with a known history of hypersensitivity to any of the constituents of the preparation and in patients with a known history of hypersensitivity to hamster proteins.

XYNTHA has not been studied in patients with a known history of hypersensitivity to hamster proteins.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity:

Allergic type hypersensitivity reactions are possible with XYNTHA. Patients should be informed of the early signs of hypersensitivity (including hives, generalized urticaria, tightness of the chest, wheezing, and hypotension) and anaphylaxis (see SIDE EFFECTS).

If allergic or anaphylactic reactions occur, administration of XYNTHA should be stopped immediately, and appropriate medical management should be given, which may include treatment for shock. Patients should be advised to discontinue use of the product and contact their physician and/ or seek immediate emergency care, depending on the type/severity of the reaction, if any of these symptoms occur.

Activity-neutralizing antibodies (inhibitors): Activity-neutralizing antibodies (inhibitors) may develop in patients receiving coagulation factor VIII-containing products. As with all coagulation factor VIII products, patients should be monitored for the development of inhibitors that should be titrated in Bethesda Units (BUs) using appropriate biological testing. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present (see SIDE EFFECTS). These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified BUs using the Bethesda assay. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Inhibitors are common in previously untreated patients and have been observed in previously treated patients on factor VIII products.

. When prescribing XYNTHA it is important to titrate and monitor each patient's factor level in order to ensure an adequate therapeutic response. (see SIDE EFFECTS).

It is recommended that, whenever possible, every time that XYNTHA is administered to patients, the name and batch number of the product is documented.
Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Effects on ability to drive and use machines

There are no indications that XYNTHA may impair the ability to drive or operate machines.

INTERACTIONS:

No formal drug interactions studies have been conducted with XYNTHA.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Treatment with XYNTHA should be initiated under the supervision of a medical practitioner experienced in the treatment of haemophilia A.

XYNTHA is appropriate for use in adults and children of all ages including newborns. The labelled potency of XYNTHA is based on the European Pharmacopoeial chromogenic substrate assay in which the Wyeth manufacturing potency standard has been calibrated using a one-stage clotting assay.

Clinical data support the use of the one-stage clotting assay for monitoring XYNTHA therapy.
With recombinant factor VIII products, clinical monitoring using the chromogenic assay typically yields results which are higher than the results obtained with the one-stage clotting assay.

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 specific treatment may be required.

Precise monitoring of the replacement therapy by means of coagulation analysis (plasma factor VIII activity assay) is recommended, particularly for surgical intervention.

One international unit (IU) of factor VIII activity corresponds approximately to the quantity of factor VIII in one ml of normal human plasma. The calculation of the required dosage factor VIII is based upon the empirical finding that 1 International Unit (IU) of factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl per IU/kg administered. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (% of normal or IU/dl) x 0,5 (IU/kg per IU/dl)

Dosing for Bleeding and Surgery:

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

Type of Haemorrhage	**Factor VIII** **Level Required (% or IU/dl)**	**Frequency of Doses (h)/** **Duration of Therapy (d)**
Minor Early haemarthrosis, 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 haemorrhage.
Moderate Haemorrhages into the muscles. Mild trauma capitis. Minor operations, including tooth extraction. Haemorrhages into the oral cavity.	30 – 60	Repeat infusion every 12 – 24 hours for 3 – 4 days or until adequate wound healing. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major Gastro-intestinal bleeding. Intracranial, intra-abdominal or intrathoracic haemorrhages. Fractures. Major operations.	60 – 100	Repeat infusion every 8 – 24 hours until threat is resolved or until adequate wound healing in the case of surgery, then therapy for at least another 7 days.

Dosage for Prophylaxis:

XYNTHA has been administered prophylactically in a pivotal clinical trial in adolescent and adult previously treated patients at a dose of 30 ± 5 IU/kg given 3 times weekly during the 6-month study period.

Inhibitors:

Patients using XYNTHA should be monitored for the development of factor VIII inhibitors. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present.

In patients with high levels of inhibitor (eg, above 10 Bethesda Units, BU's), factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.

Method of Administration:

XYNTHA is administered by intravenous (IV) infusion after reconstitution of the lyophilized powder for injection with the pre-filled diluent (0,9 % Sodium Chloride) syringe. The reconstituted solution should be used within 3 hours.

XYNTHA should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.

XYNTHA, 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 XYNTHA®, including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations above be followed closely.

XYNTHA should not be mixed with other medicinal products. In the absence of incompatibility studies, reconstituted XYNTHA should not be administered in the same tubing or container with other medicinal products. Treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

Infusion kit components supplied in this carton are compatible with XYNTHA for administration. Components other than those provided have not been tested for compatibility.

SIDE-EFFECTS:

Side Effects to XYNTHA are listed in the table below. The information in this section is supported by the following studies: 300, 301, 306, 307, 310, 311 and 4432.

Table 1: Side Effects by System Organ Class and Frequency Category and in Order of Decreasing Medical Seriousness within Each Frequency Category and System Organ Class – Per Patient Denominator

System Organ Class	**Very Common** **≥ 1/10**	**Common** **≥ 1/100** **to < 1/10**	**Uncommon** **≥ 1/1 000 to <** **1/100**
Blood and Lymphatic Disorders	Factor VIII inhibition *(PUPs)	Factor VIII 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	Cough		Dyspnoea

System Organ Class	**Very Common** **≥ 1/10**	**Common** **≥ 1/100** **to < 1/10**	**Uncommon** **≥ 1/1 000 to <** **1/100**
Mediastinal Disorders			
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 positiveLiver function test abnormal	Blood creatinine phosphokinase increased

*PUP's – Previously untreated patients

** PTP's- Previously treated patients

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

Patients with haemophilia A may develop neutralizing antibodies (inhibitors) to XYNTHA. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialized haemophilia centre be contacted

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

In a safety and efficacy clinical study with XYNTHA in previously treated patients (PTPs, study 310), the incidence of factor VIII inhibitors was the primary safety endpoint. Two clinically silent, low-titre, transient inhibitors were observed in 94 patients with a median exposure of 76 exposure days (ED, range 1 - 92), corresponding to 2,2 % of the 89 patients with at least 50 ED. In a supporting study of ReFacto AF (study 306), 1 *de novo* and 2 recurrent inhibitors (all low-titre, central laboratory determination) were observed in 110 patients; median exposure of 58 ED (range 5 - 140) and 98 patients had at least 50 ED to ReFacto AF. Ninety-eight (98) of the original 110 patients continued treatment in a second supportive study (307) and had subsequent extended exposure to XYNTHA with a median of 169 additional ED (range 9 - 425). One (1) additional low-titre *de novo* inhibitor was observed. The frequency of inhibitors observed in these studies is within the expected range.

In a Bayesian statistical analysis, results from Study 310 were used to update PTP results from prior supporting studies. Two out of 89 subjects (who completed ≥ 50 exposure days) developed an inhibitor during the course of study 310. The observation of 2 inhibitors in 89 subjects who completed ≥ 50 exposure days was consistent with a 95 % probability that the inhibitor formation rate with XYNTHA is less than 4,17 % using a Bayesian analysis.

In a clinical study of PTPs with hemophilia A (factor VIII ≤ 2%) undergoing major surgery (study 311), 1 inhibitor was observed in 30 patients who received treatment with XYNTHA.

In a clinical study with XYNTHA in PTPs (study 300), 1 inhibitor was observed in 113 patients. Also, there have been spontaneous post-marketing reports of high-titre inhibitors involving PTPs.

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 XYNTHA 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.

Trace amounts of hamster protein may be present in XYNTHA. Development of antibodies to hamster protein has been observed in clinical studies, but there were no associated clinical sequelae. In clinical trials of PTPs receiving XYNTHA 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 XYNTHA) antibody titer, without any apparent clinical effect. In a study of XYNTHA for surgical prophylaxis (study 311) 1 of 30 (3 %) patients developed a lab increase for antibody to CHO. Twenty (20) of 113 (18 %) PTPs receiving XYNTHA manufactured by the previous process (study 300) had an increase in anti-CHO antibody titer, without any apparent clinical effect.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No symptoms of overdose have been reported with XYNTHA.

IDENTIFICATION:

XYNTHA 500 IU: 10 ml glass vials containing white caked lyophilised powder.

XYNTHA 1000 IU: 10 ml glass vials containing white caked lyophilised powder.

Reconstituted solution: Clear and colourless solution essentially free from visible particulate matter.

PRESENTATION:

XYNTHA 500 IU & 1 000 IU are available as white sterile, lyophilized powder packaged in 10 ml colourless glass vials with a stopper and flip-off seal and 4ml of solvent in a pre-filled syringe with a plunger stopper, a tip-cap and a sterile vial adapter reconstitution device, a sterile infusion set, alcohol swabs, a plaster and a gauze pad.

STORAGE INSTRUCTIONS:

- XYNTHA should be stored between 2 and 8 °C, in a refrigerator.

- XYNTHA may be stored at or below 25 °C for a single period up to 3 monthsThe product may not be returned to refrigerated storage after storage at room temperature.
- Record date removed from refrigerator.
- The reconstituted solution may be stored at room temperature prior to administration, but should be used within 3 hours of reconstitution.
- Freezing should be avoided in order to prevent damage to the pre-filled diluent syringe.
- Store all medicines out of reach of children.

REGISTRATION NUMBERS:

XYNTHA 500 IU	: 35/8.1/0067
XYNTHA1000 IU	: 35/8.1/0068
SODIUM CHLORIDE DILUENT FOR XYNTHA INJECTION	: 35/34/0069

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION:

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