1 NAME OF THE MEDICINAL PRODUCT

XYNTHA

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XYNTHA is supplied as a white to off-white powder in the following dosages:

- 250 IU
- 500 IU
- 1000 IU
- 2000 IU

3 PHARMACEUTICAL FORM

Powder and solvent for solution for intravenous (IV) injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1.1 Control of Bleeding Episodes in Hemophilia A

XYNTHA Antihemophilic Factor (Recombinant), Plasma/Albumin-Free is indicated for the control and prevention of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia).

4.1.2 Routine and Surgical Prophylaxis in Patients with Hemophilia A

XYNTHA Antihemophilic Factor (Recombinant), Plasma/Albumin-Free is indicated for routine and surgical prophylaxis in patients with hemophilia A.

XYNTHA is appropriate for use in children of all ages, including newborns.

XYNTHA does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.

4.2 Posology and method of administration

For Intravenous Use After Reconstitution

- Treatment with XYNTHA Antihemophilic Factor (Recombinant), Plasma/Albumin-Free should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.

- 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. Doses administered should be titrated to the patient's clinical response. In the presence of an inhibitor, higher doses may be required.

- One International Unit (IU) of factor VIII activity corresponds approximately to the quantity of factor VIII in one milliliter (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 approximately 2 IU/dL. The required dosage is determined using the following formula:

The expected *in vivo* peak increase in factor VIII level expressed as IU/dL (or % normal) can be estimated using the following formulas:

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

OR

IU/dL (or % of normal) = Total Dose (IU)/body weight (kg) x 2 [IU/dL]/[IU/kg]

The labeled potency of XYNTHA is based on the European Pharmacopoeia chromogenic substrate assay, in which the Wyeth manufacturing standard has been calibrated using a one-stage clotting assay. This method of potency assignment is intended to harmonize XYNTHA with clinical monitoring using a one-stage clotting assay.

4.2.1 Control of Bleeding Episodes

In the case of the following bleeding 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.

The following chart can be used to guide dosing in bleeding episodes:

Type of Bleeding Episode	**Factor VIII Level Required (IU/dL or % of normal)**	**Frequency of Doses (h)/ Duration of Therapy (d)**
Minor Early hemarthrosis, minor muscle or oral bleeds.	20–40	Repeat every 12–24 hours as necessary, until resolved. At least 1 day, depending upon the severity of the bleeding episode.
Moderate Bleeding into muscles. Mild head trauma. Bleeding into the oral cavity.	30–60	Repeat infusion every 12–24 hours for 3–4 days or until adequate local hemostasis is achieved.
Major Gastrointestinal bleeding. Intracranial, intra-abdominal or intrathoracic bleeding. Fractures.	60–100	Repeat infusion every 8–24 hours until bleeding is resolved.

4.2.2 Routine and Surgical Prophylaxis in Patients with Hemophilia A

In the case of the following bleeding 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. Monitoring of replacement therapy by means of plasma factor VIII activity is recommended, particularly for surgical intervention.

The following chart can be used to guide dosing in surgery:

Type of Surgery	**Factor VIII Level Required (IU/dL or % of normal)**	**Frequency of Doses (h)/ Duration of Therapy (d)**
Minor Minor operations, including tooth extraction.	30–60	Repeat infusion every 12–24 hours for 3–4 days or until adequate local hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major Major operations.	60–100	Repeat infusion every 8–24 hours until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved.

Dosage for prophylaxis

XYNTHA has been administered prophylactically in a pivotal clinical trial in previously treated adolescent and adults at a dose of 30 ± 5 IU/kg given 3 times weekly.

The recommended starting regimen in children (<12 years) is 25 ± 5 IU/kg of XYNTHA administered every other day. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group (see section 5.2 Pharmacodynamic properties).

Adjust the dosing regimen (dose or frequency) based on the patient's clinical response.

4.2.3 Instructions for Use

XYNTHA is administered by IV infusion after reconstitution of the freeze-dried powder with the supplied pre-filled diluent (0.9% Sodium Chloride solution) syringe.

Patients should follow the specific reconstitution and administration procedures provided by their physicians. The procedures below are provided as general guidelines for the reconstitution and administration of XYNTHA.

4.2.4 Preparation and Reconstitution

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 minimize unnecessary exposure to the atmosphere.

Note: If you use more than one vial of XYNTHA per infusion, each vial should be reconstituted as per the following instructions. The diluent syringe should be removed, leaving the vial adapter in place, and a separate, single large luer lock syringe may be used to draw back the reconstituted contents of each of the individual vials. 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.

Reconstitution

1. Allow the vials of freeze-dried XYNTHA and the pre-filled diluent syringe to reach room temperature.

2. Remove the plastic flip-top cap from the XYNTHA vial to expose the central portions 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 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 package, place the vial adapter over the vial and press down firmly on the package until the adapter spike penetrates 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 plunger 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. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted XYNTHA

immediately), so place the cap on its top on a clean surface in a spot where it would be least likely to become environmentally 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 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 XYNTHA vial.

11. Without removing the syringe, **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 opalescent and colorless. If it is not, the solution should be discarded and a new kit should be used.

12. Invert the vial and slowly draw the solution into the syringe.

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.

The reconstituted solution may be stored at room temperature prior to administration, but should be administered within 3 hours of reconstitution.

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 in section 4.2 Posology and method of administration be followed closely.

4.2.5 Administration

XYNTHA is administered by IV infusion after reconstitution with the supplied pre-filled diluent (0.9% Sodium Chloride solution, 4 mL) syringe. Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

XYNTHA should be administered using the infusion set provided in this kit and the pre-filled diluent syringe provided, or a single sterile disposable plastic 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 provided.

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

3. Remove the protective needle cover and perform venipuncture. Insert the needle on the infusion set tubing into the vein, and remove the tourniquet. The reconstituted XYNTHA product should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level. As with any intravenous administration, always verify proper needle placement.

Reconstituted XYNTHA should not be administered in the same tubing or container with other medicinal products.

After infusing XYNTHA, remove the infusion set and discard. The amount of drug product left in the infusion set will not affect treatment.

Note: Dispose of all unused solution, the empty vial(s), and other used medical supplies in an appropriate container for throwing away medical waste that might hurt others if not handled properly.

Pediatric population

Safety of XYNTHA was studied in previously treated children and adolescents (n=18, 12-16 years of age in a pivotal study and n=49, 7-16 years of age in a supporting study). In a pivotal

study, adverse event data from patients who were ≤16 years of age were compared with data from those over 16 years of age. Eighteen (18) patients were ≤16 years of age and 76 were >16 years of age. Extent of exposure was similar for patients in the two age groups. Treatment emergent adverse events were similar in severity and incidence in the two age groups.

XYNTHA may be used in the same manner as predecessor product ReFacto, because it is biochemically comparable to predecessor product ReFacto and has demonstrated similar pharmacokinetic characteristics with predecessor product ReFacto. Safety and efficacy of predecessor product ReFacto has been studied both in previously treated children and adolescents (n=31, 5-18 years of age) and in previously untreated neonates, infants, and children (n=101, ages <1-52 months). Clinical data derived from completed studies with moroctocog alfa (AF-CC) in PTP (ReFacto AF*: n=37, 18 patients <6 and 19 patients 6 to <12 years of age; XYNTHA: n=51, 46 patients <6 and 5 patients 6 to <16 years of age) and PUP (ReFacto AF: n=23 patients <6 years of age) demonstrated a safety profile similar to that of the predecessor product ReFacto. See also section 5.2 Pharmacokinetic properties.

** ReFacto AF is another moroctocog alfa (AF-CC) product approved in Europe where the labeled potency is based on the European Pharmacopoeia chromogenic substrate assay, in which the manufacturing potency standard has been calibrated to the WHO 8th International Standard (IS) using the chromogenic substrate assay, while the XYNTHA potency assignment is aligned to the WHO 8th IS using a one-stage clotting assay.*

Elderly population

Clinical studies of XYNTHA did not include subjects 65 years of age and over. In general, dose selection for an elderly patient should be individualized.

4.3 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.

4.4 Special warnings and precautions for use

Hypersensitivity

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity (including hives, generalized urticaria, tightness of the chest, wheezing, and hypotension) and anaphylaxis (see section 4.8 Undesirable 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 also section 4.8 Undesirable effects.

These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in BUs using the Bethesda assay. The risk of developing inhibitors is correlated to the exposure to anti-hemophilic 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 (PUPs) and have been observed in previously treated patients (PTPs) on factor VIII products.

Reports of lack of effect, mainly in prophylaxis patients, have been received in the clinical trials and in the post-marketing setting for the predecessor product, 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 XYNTHA it is important to titrate and monitor each patient's factor level in order to ensure an adequate therapeutic response. See also section 4.2. Posology and method of administration and section 4.8 Undesirable 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of recombinant coagulation factor VIII products with other medicinal products are known.

4.6 Pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with XYNTHA. Based on the rare occurrence of hemophilia A in women, experience regarding the use of factor VIII during pregnancy is not available. Therefore, XYNTHA should be administered to pregnant women only if clearly indicated.

Lactation

Animal reproduction studies have not been conducted with XYNTHA. It is not known whether this drug is excreted into human milk. Based on the rare occurrence of hemophilia A in women, experience regarding the use of factor VIII products during breastfeeding is not available. Therefore, XYNTHA should be administered to lactating women only if clearly indicated.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

Adverse reactions 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, 313, 4432, 4433 and 4434.

Adverse drug reaction (ADR)s by System Organ Class (SOC) and Council of International Organizations of Medical Sciences (CIOMS) frequency category listed in order of decreasing medical seriousness within each frequency category and SOC (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 system 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		Hemorrhage; hematoma	Hypotension; thrombophlebitis; flushing
Respiratory, thoracic and mediastinal disorders	Cough		Dyspnea
Gastrointestinal disorders		Diarrhea; 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 positive; human anti-mouse antibody positive[a]; liver function test abnormal	Blood creatinine phosphokinase increased

Abbreviations: PTPs=previously treated patients; PUPs=previously untreated patients.
[a] ReFacto only

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalized urticaria, headache, hives, hypotension,

lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently for XYNTHA, and may in some cases progress to severe anaphylaxis (including shock).

Inhibitor development

Patients with hemophilia A may develop neutralizing antibodies (inhibitors) to factor VIII. See also sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use. As with all coagulation factor VIII products, patients are to be monitored for the development of inhibitors that are quantified in BUs using the Nijmegen modification of the Bethesda assay. 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 center be contacted.

The risk of developing inhibitors is correlated to the exposure to anti-hemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in PTPs 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.

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 a new onset bleeding. In order to ensure an adequate therapeutic response, it is important TO INDIVIDUALLY TITRATE AND MONITOR each patient’s dose of XYNTHA, particularly when initiating treatment with XYNTHA.

Factor VIII inhibition

Previously treated patients (PTPs)

Within a pooled dataset of 641 PTPs treated with ReFacto (1 clinical study) or moroctocog alfa (AF-CC) (XYNTHA and ReFacto AF) (7 clinical studies), there were 11 (1.7%) confirmed factor VIII inhibitor cases (1 high-titre (≥5 BU/mL), 10 low-titre (<5 BU/mL)).

In a pivotal phase 3 study (study 310), in which PTPs with hemophilia A received XYNTHA for routine prophylaxis and on-demand treatment, 94 subjects received at least one dose of XYNTHA resulting in a total of 6775 infusions. In this study, the incidence of factor VIII inhibitors was the primary safety endpoint. Two patients with low titre, transient inhibitors were observed in these 94 patients (2.1%). In a supporting study (study 306), 1 *de novo* and 2 recurrent inhibitors (all low-titre, central laboratory determination) were observed in 110 patients; median exposure of 58 exposure days (ED) (range 5-140) and 98 patients had at least 50 ED. 98 of the original 110 patients continued treatment in a second supportive study (307) and had subsequent extended exposure with a median of 169 additional ED (range 9-

425). 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 (2 out of 94 subjects developed an inhibitor, 89 had 50 or more exposure days) were used to update PTP results from prior supporting studies, where one *de novo* and two recurrent inhibitors were observed in 110 subjects, and 1 inhibitor was observed in 113 subjects. This Bayesian analysis indicates that the population (true) inhibitor rate 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-titre persistent inhibitor and one transient false-positive inhibitor were reported.

In a clinical study (study 4433) in pediatric (n=37, <12 years of age) PTPs (FVIII:C <1%) receiving moroctocog alfa (AF-CC) (ReFacto AF), the percentage of patients with clinically significant inhibitor development was the primary safety outcome. No patient met the protocol-defined criteria of clinically significant FVIII inhibition. Transient, low-titre FVIII inhibitor development was observed in 2 patients (<6 years of age). Both patients showed a dip in recovery at the same visit (ED 10–15), the inhibitor test was positive, with subsequent return to expected recovery. Neither patient experienced any clinical manifestation of FVIII inhibition and did not receive specific treatment for the event.

Enrolled PTP patients (N=37) were treated with ReFacto AF at a dose and frequency prescribed by the patient's treating physicians as per local standard of care. Median annualized bleeding rate (ABR) was 38.50 (min to max = 0.0, 50.6) for on-demand regimen (N=14) and 3.67 (min to max = 0.0, 13.0) for prophylaxis regimen (N=22) patients. The majority of the first infusions were rated as "Excellent" (88.7%). The incidence rate of less-than-expected therapeutic effect (LETE) following on-demand treatment was 0.00% (no LETE bleeds from 804 bleeding episodes). The incidence rate of LETE following 2457 prophylaxis infusions was 0.08% (2 LETE bleeds with no confounding factors).

In a clinical study (study 313) in pediatric (6 months to <16 years) PTPs (≥20 ED) with hemophilia A (factor VIII:C ≤2%), 1 low-titre, clinically silent inhibitor was observed in 49 patients at risk in the study for developing an inhibitor.

In a clinical trial with the predecessor product ReFacto (study 300), 1 of 113 (0.9%) previously heavily treated patients who were evaluated for efficacy in bleeding episodes developed a high-titre 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-titre inhibitor at 98 exposure days, which was confirmed at 2 BU/mL at the central laboratory at 113 exposure days. After 18 months on continued treatment, the inhibitor level rose to nearly 13 BU/mL and a bleeding episode failed to respond to treatment.

Laboratory increases in anti-factor VIII antibody titres, in the absence of inhibitor development, have been observed in clinical trials. In a study of PTPs for routine treatment and prevention of bleeding episodes (study 310) and in a study of PTPs for surgical prophylaxis (study 311), 1 of 94 (1%) patients, and 1 of 30 (3%) patients, respectively, developed anti-factor VIII 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 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 titre, without any apparent clinical effect. In a study 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 the predecessor product ReFacto (study 300) had an increase in anti-CHO antibody titre, without any apparent clinical effect.

Previously untreated patients (PUPs)

In a clinical trial (study 301), 32 out of 101 (32%) PUPs treated with ReFacto developed inhibitors: 16 out of 101 (16%) with a titre >5 BU/mL and 16 out of 101 (16%) with a titre ≤5 BU/mL. 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 titre of <0.6 BU/mL at their latest available test after IT. In addition, IT treatment was started in 10 of the 16 low titre (≤5 BU/mL) patients, 9 of whom had titre <0.6 BU/mL 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 titre <0.6 BU/mL for their latest value. There have been spontaneous post-marketing reports of high-titre inhibitors developing in PTPs.

In a clinical study (study 4434) PUPs (<6 years of age, n=23) treated with moroctocog alfa (AF-CC) (ReFacto AF), there were 8 patients (34.8%) with FVIII inhibitors (4 patients with high titres >5 BU/mL and 4 patients with low titres ≤5 BU/mL). Five (21.7%) of these patients met the protocol-defined criteria of clinically significant FVIII inhibitors with positive inhibitor at 2 consecutive blood draws and the need to administer alternative hemostatic products and/or low FVIII recovery levels and lack of efficacy.

Enrolled PUP patients (N=23) were treated with ReFacto AF at a dose and frequency prescribed by the patient's treating physicians as per local standard of care. During the study, 21 (91.3%), 22 (95.7%), and 7 (30.4%) patients had at least 1 on-demand, prophylaxis, or preventive infusion, respectively. Median ABR during the study, regardless of regimen, was 3.17 (min to max = 0.0 to 39.5). The majority (99/149, 66.4%) of the first infusions to treat a bleed were rated as "Excellent" (34.2%) or "Good" (32.2%). The incidence rate of LETE following on-demand treatment was 0.00% (no LETE bleeds from 150 bleeding episodes). The incidence rate of LETE following 1752 prophylaxis infusions was 0.11% (2 LETE bleeds with no confounding factors).

4.9 Overdose

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

4.10 Abuse and dependence

Antihemophilic Factor (Recombinant), Plasma/Albumin-Free has no potential for abuse. There is no evidence of dependence with Antihemophilic Factor (Recombinant), Plasma/Albumin-Free.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antihemorrhagics: Blood Coagulation Factor VIII

ATC code: B02BD02

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 hemophilia A, and therefore replacement therapy is necessary. The administration of XYNTHA increases plasma levels of factor VIII activity and can temporarily correct the coagulation defect in these patients.

XYNTHA, recombinant coagulation factor VIII is a glycoprotein with an approximate molecular mass of 170,000 Da, consisting of 1,438 amino acids, which does not contain the non-functional B-domain. XYNTHA is a recombinant DNA-based substance that 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.

Clinical trials data on efficacy

Immune tolerance induction

Data on immune tolerance induction (ITI) have been collected in patients with hemophilia 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 (see section 4.8 Undesirable effects). 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 (<5 BU/mL). Out of 6 patients who developed low titre inhibitors in this study but did not receive ITI, 5 had similar titre decreases. No long-term outcome is available.

Pivotal data with XYNTHA

In a pivotal phase 3 study (Study 3082B2-310WW/CSR 66997), the efficacy of XYNTHA was evaluated in routine prophylaxis and on-demand treatment. Prophylaxis was to be initiated at a dose of 30 IU/kg given 3 times per week. The on-demand treatment dosing

regimen was to be determined by the investigator. Ninety-four (94) PTPs with moderately severe or severe hemophilia A (factor VIII:C ≤2%) received at least 1 dose of XYNTHA and were included in the intent-to-treat (ITT) population. Eighty-nine (89) patients accrued at least 50 exposure days (EDs) to XYNTHA in the study.

Of the 94 patients in the ITT population, 30 patients with factor VIII:C ≤1% also participated in the double-blind, randomized, crossover PK period of the study and were included in the per-protocol population for analyses of pharmacokinetic equivalence versus another rFVIII product, Advate®, and full PK characterization. The results of these analyses showed that XYNTHA is pharmacokinetically equivalent to Advate®, and the pharmacokinetic profile of XYNTHA remained stable after 6 months of repeated use.

Intent-to-treat analysis of clinical efficacy variables in the open-label safety and efficacy period yielded similarly positive outcomes. All 94 patients received XYNTHA for routine prophylaxis; the median dose administered was 30.2 IU/kg (range 6.8 to 76.9 IU/kg). Most patients (57/94; 60.6%) reported no spontaneous bleeding while on routine prophylaxis. The median annualized bleeding rate (ABR) for all bleeding episodes was 1.9 (mean 3.9, range 0 to 42.1), indicating effective prevention of bleeding in the study population. Fifty-three (53) of 94 patients received XYNTHA for on-demand treatment; the median dose administered was 30.6 IU/kg (range 6.4 to 74.4 IU/kg). The majority of bleeding episodes (173/187; 92.5%) resolved with 1 or 2 infusions. This outcome was not restricted to any particular bleeding location, as similar efficacy was seen in bleeding occurring in joints, soft tissues/muscles, and other sites. A wide range of doses was used to initiate treatment of bleeding; however, the distribution of doses used to initiate treatment of bleeding was similar regardless of location of bleeding. Patients rated the majority of infusions used to initiate treatment of bleeding as either excellent or good (132/187; 70.6%). The incidence of less-than-expected therapeutic effect (LETE) occurred at a rate of 0.4% (25/6404 prophylactic infusions) when XYNTHA was administered for prophylaxis and 0.5% (1/187 bleeding episodes) when administered for on-demand treatment.

A pivotal phase 3 study (study 311) for surgical prophylaxis in patients with hemophilia A included PTPs with severe or moderately severe (factor VIII:C ≤2%) hemophilia A undergoing major surgical procedures who received XYNTHA. Thirty (30) patients were treated with XYNTHA and comprised the ITT population; 29 patients underwent major surgery and completed the study. Thirty (30) subjects were assigned to receive XYNTHA by bolus injection (BI; 22 patients) or by continuous infusion (CI; 8 patients) at the physician's discretion to support surgical hemostasis followed by inpatient and outpatient postoperative care. One subject assigned to CI received XYNTHA for a pre-surgery pharmacokinetic assessment only and subsequently elected not to undergo surgery. The 22 patients treated by BI received a total of 942 infusions (ranging from 16 to 72 infusions per patient) for a cumulative total dose of 2,037,386 IU of XYNTHA over 682 cumulative total exposure days (EDs) (ranging from 15 to 40 EDs per patient). The 8 patients assigned to treatment by CI, including 1 patient who received only 1 dose for PK assessment, received a total dose of 529,977 IU of XYNTHA over 204 total EDs (range 1 to 37 EDs per patient).

Of the 29 patients who underwent surgery, 25 were included in the efficacy evaluable population. Major surgical procedures for the 25 efficacy evaluable subjects were 11 total knee replacements, 1 hip replacement, 5 synovectomies, 1 left ulnar nerve transposition release, 1 ventral hernia repair/scar revision, 1 knee arthroscopy, 1 revision and debridement of the knee after a total knee replacement, 1 hip arthroplasty revision, 1 stapes replacement, 1

ankle arthrodesis, and 1 pseudotumor excision. For the 25 surgical subjects, investigator's ratings of the efficacy at the end of surgery and at the end of the initial postoperative period were excellent or good for all assessments, intraoperative blood loss was reported as normal or absent for all procedures. Thirteen of the 25 evaluable patients had blood loss in the postoperative period, and in 10 cases the postoperative blood loss was rated normal. In 3 cases, the postoperative blood loss was rated abnormal: 1 due to hemorrhage following surgical trauma to the epigastric artery, 1 due to an 800 mL blood loss after hip replacement surgery, and 1 after an elbow synovectomy where the blood loss could not be measured by the investigator.

Additional data with XYNTHA in pediatric population <16 years of age

The safety and efficacy of XYNTHA, and factor VIII:C pharmacokinetics after XYNTHA in children <16 years of age with moderately severe to severe hemophilia A (factor VIII:C ≤2%) were evaluated in an open-label study that compared (1) the efficacy of routine prophylaxis to on-demand treatment in a cohort of pediatric subjects <6 years of age, and (2) compared two routine prophylaxis regimens in a cohort of children <16 years of age.

51 subjects with at least 20 prior EDs to factor VIII products were enrolled and included in the ITT population. 50 subjects received at least 1 dose of XYNTHA, and 41 subjects completed the study.

9 pediatric subjects <6 years of age received on-demand treatment with XYNTHA at a median dose of 24 IU per kg for a 6-month period followed by routine prophylaxis regimen at a dose of 25 IU/kg every other day (EOD) for 12 months for 8 of these subjects. The median ABR observed during the on-demand treatment period was 34.0 (mean 47.0, range 0 to 92.4) compared to 0.6 (mean 1.5, range 0 to 6.2) while on the routine prophylaxis regimen (p=0.0040) (Table 1).

TABLE 1 ANNUALIZED BLEEDING RATE IN SUBJECTS RECEIVING ON-DEMAND AND PROPHYLAXIS TREATMENT

	On-Demand Number of bleeds = 363 N = 9 (ITT population)		Routine Prophylaxis (25 IU/kg EOD Regimen) Number of bleeds = 10 N = 8 (ITT population)	
	Median	Mean (SD)	Median	Mean (SD)
Bleed type				
Overall	34.0	47.0 (32.2)	0.6	1.5 (2.2)
Traumatic	31.8	37.9 (31.6)	0.0	0.8 (1.3)
Spontaneous	7.6	9.1 (9.2)	0.0	0.6 (1.3)
Bleed location				
Joint	17.5	26.2 (21.1)	0.0	0.5 (1.3)
Soft tissue/Muscle	16.5	21.2 (15.3)	0.0	0.7 (1.1)
Other	1.1	2.2 (2.4)	0.0	0.3 (0.5)

Abbreviations: ABR=annualized bleed rate; EOD=every other day; ITT=intent to treat; N= number of subjects with ABR data included for each regimen; SD=standard deviation

42 pediatric subjects <16 years of age received either routine prophylaxis dosing regimen 45 IU/kg twice per week or 25 IU/kg every other day for 12 months before crossing over to receive the alternate regimen, and 35 subjects provided data for both regimens. Because the

90% confidence interval (CI) for the difference of (0.03, 2.22) was inside the prospectively defined equivalence limit of (−3.3), equivalent efficacy was established with respect to ABR for both regimens (mean±SD 3.3±5.3 compared to 2.2±4.1).

A total of 838 OD infusions were administered to treat the 562 bleeding episodes. The majority of bleeding episodes (518/562; 92.2%) resolved with 1 or 2 infusions. A total 526 (93.6%) bleeding episodes treated with study drug were rated "Excellent" or "Good" in their response to initial treatment (i.e., first infusion).

The incidence of LETE occurred at a rate of 0.16% (18/10927 prophylactic infusions) when XYNTHA was administered for prophylaxis and no occurrence when administered for on-demand treatment.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters for XYNTHA were determined at baseline and followed-up in 25 PTPs (≥12 years) after repeated administration of XYNTHA for six months. These patients received a single infusion of 50 IU/kg of XYNTHA. No time-dependent changes in the pharmacokinetic properties of XYNTHA were observed (Table 2).

TABLE 2 PHARMACOKINETIC PARAMETER ESTIMATES FOR XYNTHA AT BASELINE AND MONTH 6 IN PREVIOUSLY TREATED PATIENTS WITH HEMOPHILIA A

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*	42.0	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
Reference: Table 16.20, CSR-66997
*A patient with a very long half-life (75.7 hr) had been excluded.

Table 3 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 XYNTHA administration. Compared with adults, the half-life of XYNTHA is shorter in children and clearance (based on body weight) is approximately 40% higher in children.

TABLE 3 MEAN ± FACTOR VIII PHARMACOKINETIC PARAMETERS IN PREVIOUSLY TREATED PEDIATRIC PATIENTS WITH HEMOPHILIA A AFTER 50 IU/kg XYNTHA		
Parameter	Young Children (n=5)	Adolescents (n=4)
Age [(min – max) yr]	3.7 – 5.8	14 – 15
C_{max} (IU/mL)	0.78 ± 0.34	0.97 ± 0.21
AUC_{∞} (IU.hr/mL)	12.2 ± 6.50	8.5 ± 4.0
$t_{½}$ (hr)	8.3 ± 2.7	6.9 ± 2.4
CL (mL/hr/kg)	6.29 ± 4.87	6.62 ± 2.16
V_{ss} (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; C_{max}=peak concentration; t½=terminal half-life; CL=clearance; V_{ss}=volume of distribution at steady-state

Table 4 presents pharmacokinetic data from the clinical study (4433) on PTPs.

TABLE 4 MEAN ± SD FVIII PHARMACOKINETIC PARAMETERS AFTER SINGLE 50 IU/kg DOSE IN PEDIATRIC PTPs		
PK parameter	Number of patients	Mean[a] ± SD
Recovery, IU/dl per IU/kg Aged <6 years Aged 6 to <12 years	 17 19	 1.7 ± 0.4 2.1 ± 0.8
C_{max}, IU/mL[b]	19	0.9 (45)
AUC_{inf}, IU h/mL[b]	14	9.9 (41)
$t_{1/2}$, h[b]	14	9.1 ± 1.9
CL, mL/h/kg[b]	14	4.4 (30)
Vss, mL/kg[b]	14	56.4 (15)

[a] Geometric mean (geometric CV%) for all, except for arithmetic mean ± SD for incremental recovery and $t_{1/2}$
[b] Patients aged 6 to <12 years only.
Abbreviations: C_{max} = maximum observed plasma concentration; CV = coefficient of variation; AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time; $t_{1/2}$ = terminal half-life; CL = clearance; Vss = steady-state volume of distribution.

In a ReFacto AF study (4434) 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.

5.3 Preclinical safety data

No studies have been conducted with XYNTHA to assess its mutagenic or carcinogenic potential. XYNTHA has been shown to be comparable to the predecessor product ReFacto with respect to its biochemical and physicochemical properties, as well as its non-clinical *in vivo* pharmacology and toxicology. By inference, predecessor product ReFacto and XYNTHA would be expected to have equivalent mutagenic and carcinogenic potential. The predecessor product ReFacto has been shown to be nongenotoxic in the mouse micronucleus assay. No studies have been conducted in animals to assess impairment of fertility or fetal development.

In preclinical studies, XYNTHA was used to safely and effectively restore hemostasis. XYNTHA demonstrated a toxicological profile that was similar to the toxicological profile observed with the predecessor product ReFacto, which had in turn been shown to

demonstrate a similar toxicological profile to a plasma-derived factor VIII product when tested in repeated dose toxicology studies in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine, sucrose, sodium chloride, calcium chloride dihydrate, polysorbate 80

6.2 Incompatibilities

In the absence of incompatibility studies, reconstituted XYNTHA should not be administered in the same tubing or container with other medicinal products. Infusion kit components supplied in this carton are compatible with XYNTHA for administration.

6.3 Shelf-life

Refer to date of expiry indicated on the outer packaging.

6.4 Special precautions for storage

Product as packaged for sale:

- Store XYNTHA under refrigeration at a temperature of 2° to 8°C (36° to 46°F) for up to 36 months from the date of manufacture until the expiration date stated on the label. Within the expiration date, XYNTHA may also be stored at room temperature not to exceed 25°C (77°F) for up to 3 months. After room temperature storage, XYNTHA can be returned to the refrigerator until the expiration date. Do not store XYNTHA at room temperature and return it to the refrigerator more than once.
- The starting date at room temperature storage should be clearly recorded in the space provided on the outer carton. At the end of the 3-month period, the product must be used immediately, discarded, or returned to refrigerated storage. The diluent syringe may be stored at 2° to 25°C (36° to 77°F).
- Do not use XYNTHA after the expiration date.
- Do not freeze to prevent damage to the prefilled diluent syringe.
- During storage, avoid prolonged exposure of XYNTHA vial to light.

Product after reconstitution:

Administer XYNTHA within 3 hours after reconstitution. The reconstituted solution may be stored at room temperature prior to administration.

6.5 Nature and contents of container

XYNTHA™ Antihemophilic Factor (Recombinant), Plasma/Albumin-Free is supplied in kits that include single-use (Freeze-Dried) vials that contain nominally 250, 500, 1000, or 2000 IU per vial.

In addition, each XYNTHA Antihemophilic Factor (Recombinant), Plasma/Albumin-Free kit contains: one pre-filled diluent syringe containing 4 mL 0.9% Sodium Chloride with plunger

rod for assembly, one vial adapter, one sterile infusion set, two alcohol swabs, one bandage, one gauze, and one package insert.

Actual factor VIII activity in IU is stated on the label of each XYNTHA Antihemophilic Factor (Recombinant), Plasma/Albumin-Free vial.

7 PRODUCT OWNER

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