FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

XYNTHA® 250 IU
XYNTHA® 500 IU
XYNTHA® 1000 IU
XYNTHA® 2000 IU

QUALITATIVE AND QUANTITATIVE COMPOSITION

For the full list of excipients

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Infusion	Available as 250, 500, 1000, or 2000 IU in single-use vials.	Polysorbate 80 (0.4 mg/vial or prefilled dual-chamber syringe), Sucrose (12 mg/vial or prefilled dual-chamber syringe), L-Histidine (6 mg/vial or prefilled dual-chamber syringe), Calcium Chloride Dihydrate (1 mg/vial or prefilled dual-chamber syringe), Sodium Chloride (72 mg/vial or prefilled dual-chamber syringe) [after reconstitution with diluent].

Xyntha is prepared by a modified process that eliminates any exogenous human- or animal-derived protein in the cell culture process, purification, or final formulation. The purification process uses a series of chromatography steps, one of which is based on affinity chromatography using a synthetic peptide affinity ligand. The process also includes a solvent-detergent viral inactivation step and a virus-retaining nanofiltration step.

The labelled potency of Xyntha is based on the European Pharmacopoeial chromogenic substrate assay, in which the Pfizer In-House Recombinant Factor VIII Potency Reference Standard has been calibrated to the WHO 7th International Standard using the one-stage clotting assay. This method of potency assignment is intended to harmonize Xyntha with clinical monitoring using a one-stage
clotting assay.

2. INDICATIONS AND CLINICAL USE

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

Geriatrics (≥ 65 years of age):
Clinical studies of Xyntha did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical

experience has not identified differences in responses between the elderly and younger patients. As with any patient receiving Xyntha, dose selection for an elderly patient should be individualized.

Pediatrics:
Xyntha is appropriate for use in children of all ages, including newborns.

3. DOSAGE AND ADMINISTRATION

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

Xyntha is appropriate for use in adults and children including newborns.

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 one 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 Xyntha therapy.

The labeled potency of Xyntha 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 Xyntha 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 2: 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, intra-abdominal 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.

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.

Inhibitors

Patients using factor VIII replacement therapy 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 factor VIII inhibitors, 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 hemophilia.

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 Xyntha.

Additional instructions are provided after **Infusion** section that detail the use of a Xyntha vial.

Prenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Whenever solution and container permite.

Xyntha Vial Kit:

Xyntha 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 Xyntha should be used as soon as possible after opening their sterile containers to minimize unnecessary exposure to room air.

Xyntha Vial Kit:

Use only the materials provided in the Xyntha kit for dissolving the Xyntha powder with the sodium chloride diluent.

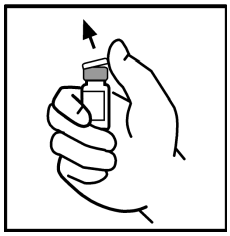
Xyntha is administered by intravenous injection after dissolving with the supplied diluent (0.9% sodium chloride) in the pre-filled syringe.

Note: If you use more than one vial of Xyntha 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.

Xyntha Vial Kit:

1. Allow the vial of freeze-dried Xyntha powder and the pre-filled diluent syringe to reach room temperature.

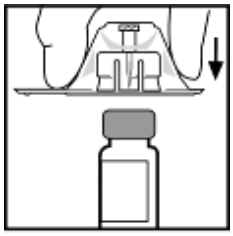
2. Remove the plastic flip-top cap from the Xyntha vial to expose the central portions of the rubber stopper.



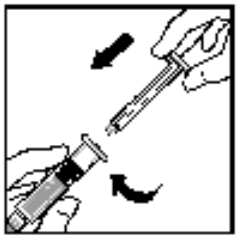
3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.

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 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.



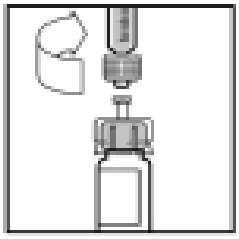
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe by pushing and turning firmly.



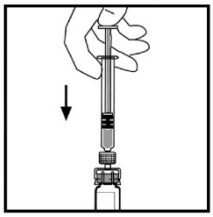
7. Break off the tamper-resistant, plastic-tip cap from the diluent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if the dissolved Xyntha 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 Xyntha vial.

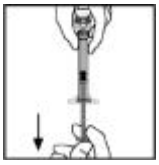


11. With the syringe still connected to the adapter, gently swirl the contents of the vial until the powder is dissolved.

    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 Xyntha, 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 counterclockwise. 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.

Xyntha should be infused within 3 hours after dissolving. The dissolved solution may be stored at room temperature prior to infusion.

Infusion (Intravenous Injection)

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 DOSAGE AND ADMINISTRATION section be followed closely.

Note: The tubing of the infusion set included with Xyntha vial kit does not contain DEHP.

Xyntha Vial kit:

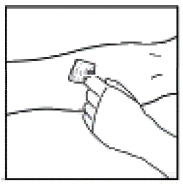
You should inject Xyntha as instructed by your hemophilia doctor or nurse. Once you learn how to self-infuse, you can follow the instructions in this insert.

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

Xyntha 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 provided 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 provided in the kit.



3. Insert the needle on the infusion set tubing into the vein, and remove the tourniquet. Infuse the reconstituted Xyntha product over several minutes. Your comfort level should determine the rate of infusion.

3. After injecting Xyntha, 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 Xyntha. 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.

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.

The reconstituted Xyntha solution does not contain a preservative and should be used within 3 hours of reconstitution.

4. CONTRAINDICATIONS

XYNTHA is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster proteins.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible with XYNTHA. Inform patients of the early signs or symptoms of hypersensitivity reactions (including hives [rash with itching], generalized urticaria, chest tightness, wheezing, and hypotension) and anaphylaxis. Discontinue XYNTHA if hypersensitivity symptoms occur and administer appropriate emergency treatment.

XYNTHA contains trace amounts of hamster proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.2 Neutralizing Antibodies

Inhibitors have been reported following administration of XYNTHA. Monitor patients for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor VIII inhibitor concentration to determine if a factor VIII inhibitor is present [*see Warnings and Precautions (5.3)*].

5.3 Monitoring Laboratory Tests

- Use individual factor VIII values for recovery and, if clinically indicated, other pharmacokinetic characteristics to guide dosing and administration.
- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm that adequate factor VIII levels have been achieved and are maintained, when clinically indicated ~~[*see Dosage and Administration (2)*].~~
- Monitor for development of factor VIII inhibitors. Perform assay to determine if factor VIII inhibitor is present when expected factor VIII activity plasma levels are not attained, or when bleeding is not controlled with the expected dose of XYNTHA. Use Bethesda Units (BU) to titer inhibitors.

6. ADVERSE REACTIONS

The most common adverse reactions (≥10%) with XYNTHA in adult and pediatric previously treated patients (PTPs) were headache, arthralgia, pyrexia, and cough.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
XYNTHA was evaluated in five completed clinical studies (N=178), comprising four studies with adult and pediatric PTPs.
The safety and efficacy of XYNTHA was evaluated in two completed pivotal studies. In the first study (n=94), safety and efficacy were examined in PTPs with severe to moderately severe hemophilia A (factor VIII activity in plasma [FVIII:C] ≤2%) who received XYNTHA for routine prophylaxis and on-

demand treatment. Ninety-four subjects received at least one dose of XYNTHA, resulting in a total of 6,775 infusions [*see Clinical Studies (14)*]. The second study (n=30) examined the use of XYNTHA for surgical prophylaxis in PTPs with severe to moderately severe hemophilia A (FVIII:C ≤2%) who required elective major surgery and were expected to receive XYNTHA replacement therapy for at least 6 days post-surgery. All subjects received at least one dose of XYNTHA, resulting in 1,161 infusions. One subject received XYNTHA for a pre-surgery pharmacokinetic assessment only and did not undergo surgery [*see Clinical Studies (14)*].

Across all studies, safety was evaluated in 72 pediatric PTPs <17 years of age (46 subjects <6 years of age (4 subjects were 0 to <2 years of age), 4 subjects 6 to <12 years of age, and 22 adolescents, 12 to <17 years of age). A total of 13,109 infusions of XYNTHA were administered with a median dose per infusion of 28 IU/kg (min-max: 6-108 IU/kg).

Across all studies, the most common adverse reactions (≥10%) with XYNTHA in adult and pediatric PTPs were headache (24%), arthralgia (23%), pyrexia (23%), and cough (12%). Other adverse reactions reported in ≥5% of subjects were: diarrhea (8%), vomiting (8%), and asthenia (6%).

6.2 Immunogenicity

There is a potential for immunogenicity with therapeutic proteins. The development of factor VIII inhibitors with XYNTHA was evaluated in 167 adult and pediatric PTPs with at least 50 exposure days (EDs). Laboratory-based assessments for FVIII inhibitor (partial Nijmegen modification of the Bethesda inhibitor assay) were conducted in the clinical studies. The criterion for a positive FVIII result test result was ≥0.6 BU/mL. Across all studies, 4 subjects developed factor VIII inhibitors (2.4%).

The completed clinical studies for XYNTHA examined 178 subjects (30 for surgical prophylaxis) who had previously been treated with factor VIII (PTPs). In the first safety and efficacy study, factor VIII inhibitors were detected in two of 89 subjects (2.2%) who completed ≥50 EDs. In a Bayesian statistical analysis, results from this study were used to update PTP results from a prior supporting study using XYNTHA manufactured at the initial facility (with one *de novo* and two recurrent inhibitors observed in 110 subjects) and the experience with predecessor product (with one inhibitor observed in 113 subjects). The Bayesian analysis indicated that the population inhibitor rate for XYNTHA, an estimate of the 95% upper limit of the true inhibitor rate, was 4.17%.

None of the PTPs developed anti-CHO (Chinese hamster ovary) or anti-TN8.2 antibodies. One PTP developed anti-FVIII antibodies; but, this subject did not develop an inhibitor.

In the surgery study, one low titer persistent inhibitor and one transient false-positive inhibitor were reported. In this study, one surgical subject developed anti-CHO cell antibodies with no associated allergic reaction. One subject developed anti-FVIII antibodies; but, this subject did not develop an inhibitor.

Across all studies, immunogenicity was evaluated in 64 pediatric PTPs <17 years of age with at least 50 EDs (43 children <6 years of age, 4 subjects <12 years of age, and 17 adolescents, 12 to <17 years of age). Of these, 2 pediatric subjects developed an inhibitor.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody, including neutralizing antibody, positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of antibodies to XYNTHA with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following postmarketing adverse reaction has been reported for XYNTHA:

Inadequate therapeutic response

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

It is not known whether XYNTHA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with XYNTHA.

There is no information available on the effect of factor VIII replacement therapy on labor and delivery. XYNTHA should be used only if clinically indicated.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of XYNTHA in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XYNTHA and any potential adverse effects on the breastfed child from XYNTHA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy with XYNTHA were evaluated in clinical studies in 68 pediatric subjects <17 years of age (18 subjects aged 12 to <17 years, 50 subjects aged ≤12 years). There were no apparent differences in the efficacy and safety in pediatric subjects as compared to adults [*see Adverse Reactions (6.1) and Clinical Studies (14)*].

8.5 Geriatric Use

Clinical studies of XYNTHA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy

11 DESCRIPTION

The active ingredient in XYNTHA, Antihemophilic Factor (Recombinant), is a recombinant antihemophilic factor (rAHF), also called coagulation factor VIII, which is produced by recombinant DNA technology. It is secreted by a genetically engineered Chinese hamster ovary (CHO) cell line. The cell line is grown in a chemically defined cell culture medium that contains recombinant insulin, but does not contain any materials derived from human or animal sources.

The rAHF in XYNTHA is a purified glycoprotein, with an approximate molecular mass of 170 kDa consisting of 1,438 amino acids, which does not contain the B-domain.[13] The amino acid sequence of the rAHF is comparable to the 90 + 80 kDa form of human coagulation factor VIII.

The purification process uses a series of chromatography steps, one of which is based on affinity chromatography using a patented synthetic peptide affinity ligand.[14] The process also includes a solvent-detergent viral inactivation step and a virus-retaining nanofiltration step.

The potency expressed in International Units (IU) is determined using the chromogenic assay of the European Pharmacopoeia. The Wyeth manufacturing reference standard for potency has been calibrated against the World Health Organization (WHO) International Standard for factor VIII activity using the one-stage clotting assay. The specific activity of XYNTHA is 5,500 to 9,900 IU per milligram of protein.

XYNTHA is formulated as a sterile, nonpyrogenic, no preservative, lyophilized powder preparation for intravenous injection. Each single-use vial contains nominally 250, 500, 1000, or 2000 IU of XYNTHA. Upon reconstitution, the product is a clear to slightly opalescent, colorless solution that contains sodium chloride, sucrose, L-histidine, calcium chloride, and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XYNTHA temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

12.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia. Determination of aPTT is a conventional *in vitro* assay for biological activity of factor VIII. Treatment with XYNTHA normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

The pharmacokinetic parameters of XYNTHA in 30 PTPs 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA are summarized in Table 3.

In addition, 25 of the same subjects later received a single infusion of 50 IU/kg of XYNTHA for a 6-month follow-up pharmacokinetic study. The parameters were comparable between baseline and 6 months, indicating no time-dependent changes in the pharmacokinetics of XYNTHA.

In a separate study, 8 of 30 subjects at least 12 years old with hemophilia A undergoing elective major surgery received a single 50 IU/kg infusion of XYNTHA. The pharmacokinetic parameters in these subjects are also summarized in Table 3.

Table 3: Mean ± SD XYNTHA Pharmacokinetic Parameters in Previously Treated Patients with Hemophilia A after Single 50 IU/kg Dose			
Parameter	**Initial Visit (n = 30)**	**Month 6 (n = 25)**	**Pre-surgery (n=8)**
C_{max} (IU/mL)	1.08 ± 0.22	1.24 ± 0.42	1.08 ± 0.24
AUC_{∞} (IU•hr/mL)	13.5 ± 5.6	15.0 ± 7.5	16.0 ± 5.2
$t_{1/2}$ (hr)	11.2 ± 5.0	11.8 ± 6.2*	16.7 ± 5.4
CL (mL/hr/kg)	4.51 ± 2.23	4.04 ± 1.87	3.48 ± 1.25
Vss (mL/kg)	66.1 ± 33.0	67.4 ± 32.6	69.0 ± 20.1
Recovery (IU/dL per IU/kg)	2.15 ± 0.44	2.47 ± 0.84	2.17 ± 0.47

Abbreviations: AUC_{∞} = area under the plasma concentration-time curve from zero to infinity; C_{max} = peak concentration; $t_{1/2}$ = plasma elimination half-life; CL = clearance; n = number of subjects; SD = standard deviation; Vss = volume of distribution at steady-state.
*One subject was excluded from the calculation due to lack of a well-defined terminal phase.

Table 4 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 3.7-5.8 years after single 50 IU/kg doses of XYNTHA. Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximately 40% higher in children.

Table 4: Mean ± SD XYNTHA Pharmacokinetic Parameters in Previously Treated Pediatric Patients with Hemophilia A after Single 50 IU/kg Dose		
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
$t_{1/2}$ (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 per IU/kg)	1.52 ± 0.69	1.95 ± 0.41

Abbreviations: AUC_{∞} = area under the plasma concentration-time curve from zero to infinity; C_{max} = peak concentration; $t_{1/2}$ = plasma elimination half-life; CL = clearance; n = number of subjects; SD = standard deviation; Vss = volume of distribution at steady-state.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 with respect to its biochemical and physicochemical properties, as well as its nonclinical *in vivo* pharmacology and toxicology. By inference, predecessor product and XYNTHA would be expected to have equivalent mutagenic and carcinogenic potential. The predecessor product 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.

13.2 Animal Toxicology and/or Pharmacology

Preclinical studies evaluating XYNTHA in hemophilia A dogs without inhibitors demonstrated safe and effective restoration of hemostasis. XYNTHA demonstrated a toxicological profile that was similar to the toxicological profile observed with the predecessor product. Toxicity associated with XYNTHA was primarily associated with anti-FVIII neutralizing antibody generation first detectable at 15 days of repeat dosing in high (approximately 735 IU/kg/day) level-dosed, non-human primates.

14 CLINICAL STUDIES

Three completed multicenter, open-label studies support the analysis of safety and efficacy of XYNTHA in on-demand treatment and control of bleeding episodes and perioperative management. These completed clinical studies for XYNTHA examined 174 PTP subjects, 94 for on-demand treatment and routine prophylaxis and 30 for surgical prophylaxis. Subjects with severe to moderately severe hemophilia A (FVIII:C ≤2%) and no history of FVIII inhibitors were eligible for the trials.

On-demand treatment and Control of Bleeding Episodes

Ninety-four (94) subjects, 12 years of age and older received XYNTHA in a routine prophylaxis treatment regimen with on-demand treatment administered as clinically indicated. All 94 subjects were treated with at least one dose and all are included in the intent-to-treat (ITT) population. Eighty-nine (89) subjects accrued ≥50 EDs. Median age for the 94 treated subjects was 24 years (mean 28 and min-max: 12-60 years).

Of these 94 subjects, 30 evaluable subjects participated in a randomized crossover pharmacokinetics substudy. Twenty-five (25/30) of these subjects with FVIII:C ≤1% completed both the first (PK1) and the second (PK2) pharmacokinetic assessments [*see Clinical Pharmacology (12.3)*].[16]

Fifty-three subjects (53/94) received XYNTHA on-demand treatment for a total of 187 bleeding episodes. Seven of these bleeding episodes occurred in subjects prior to switching to a prophylaxis treatment regimen. One hundred ten of 180 bleeds (110/180 or 61%) occurred ≤48 hours after the last dose and 39% (70/180 bleeds) occurred >48 hours after the last dose. The majority of bleeds reported to occur ≤48 hours after the last prophylaxis dose were traumatic (64/110 bleeds or 58%). Forty-two bleeds (42/70 or 60%) reported to occur >48 hours after the last prophylaxis dose were spontaneous. The on-demand treatment dosing regimen was determined by the investigator. The median dose for on-demand treatment was 31 IU/kg (min-max: 6-74 IU/kg) and the median exposure per subject was 3 days (min-max: 1-26).

The majority of bleeding episodes (173/187 or 93%) resolved with 1 or 2 infusions (Table 5). One hundred thirty-two of 187 bleeding episodes (132/187 or 71%) treated with XYNTHA were rated excellent or good in their response to initial treatment, 45 (24%) were rated moderate. Five (3%) were rated no response, and 5 (3%) were not rated.

Table 5: Summary of Response to Infusions to Treat New Bleeding Episode by Number of Infusions Needed for Resolution						
	Number of Infusions (%)					
Response to 1st Infusion	1	2	3	4	>4	Total Number of Bleeds
Excellent[a]	42 (95.5)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	44
Good[b]	69 (78.4)	16 (18.2)	3 (3.4)	0 (0.0)	0 (0.0)	88
Moderate[c]	24 (53.3)	16 (35.6)	2 (4.4)	0 (0.0)	3 (6.7)	45
No Response[d]	0 (0.0)	0 (0.0)	2 (40.0)	2 (40.0)	1 (20.0)	5
Not Assessed	4 (80.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	5[e]
Total	139 (74.3)	34 (18.2)	7 (3.7)	3 (1.6)	4 (2.1)	187

[a] *Excellent:* Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered.
[b] *Good*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.
[c] *Moderate:* Probable or slight improvement starting after 8 hours following the infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.
[d] *No Response:* No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens.
[e] Includes one infusion with commercial FVIII that occurred before routine prophylaxis began.

Of the 94 subjects described above, in the first completed open-label safety and efficacy study of XYNTHA, 18 were adolescent subjects 12 to <17 years of age with severe to moderately severe hemophilia A (FVIII:C ≤2%). Ten (10) of these adolescent subjects, received XYNTHA for the on-demand treatment of 66 bleeding episodes, with the majority of the bleeding episodes (63/66 or 95%) resolving with 1 or 2 infusions. The response to infusion was rated on a pre-specified 4 point hemostatic efficacy scale. Thirty-eight (38) of 66 bleeding episodes (58%) were rated excellent or good in their response to initial treatment, 24 (36%) were rated as moderate, and 4 (6%) were not rated. The median dose per on demand infusion was 47 IU/kg (min-max: 24-74).

On-demand treatment in children
Additional data for 50 subjects are available from a second safety and efficacy study of XYNTHA in children (≤12 years of age) with severe to moderately severe hemophilia A (FVIII:C ≤2%). Of the 50 subjects, 38 subjects received XYNTHA for on-demand and follow-up treatment of 562 bleeding episodes with the majority of the bleeding episodes (518/562 or 92%) resolving with 1 or 2 infusions. Of 559 bleeding episodes treated with XYNTHA with response assessments to the first infusion, 526 (94%) were rated excellent or good in their response to initial treatment and 27 (5%) were rated as moderate. The median dose per on-demand infusion was 28 IU/kg (min-max: 10-92).

Perioperative Management

In a study (n=30) for surgical prophylaxis in subjects with hemophilia A, XYNTHA was administered to 25 efficacy-evaluable PTPs undergoing major surgical procedures (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).[17] The results of the hemostatic efficacy ratings for these subjects are presented in Table 6. Investigator's ratings of 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

subjects. Thirteen of the subjects (13/25 or 52%) had blood loss in the postoperative period. The postoperative blood loss was rated as "normal" for ten of these cases while three cases were 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).

Table 6: Summary of Hemostatic Efficacy

Time of Hemostatic Efficacy Assessment	Excellent[a]	Good[b]	Number of subjects
End of surgery	18 (72%)	7 (28%)	25
End of initial postoperative period[c]	23 (92%)	2 (8%)	25

[a] *Excellent :* Achieved hemostasis comparable to that expected after similar surgery in a patient without hemophilia.
[b] *Good:* Prolonged time to hemostasis, with somewhat increased bleeding compared with that expected after similar surgery in a patient without hemophilia.
[c] End of initial postoperative period is date of discharge or postoperative Day 6, whichever occurs later.

Routine Prophylaxis

One hundred and two (102) subjects (94 subjects ≥12 years of age and 8 subjects <12 years of age) received XYNTHA for routine prophylaxis, for comparison of annualized bleeding rate (ABR) to on-demand treatment alone as a part of 2 completed studies. XYNTHA was administered for routine prophylaxis at a dose of 25 ± 5 IU/kg every other day (in subjects <12 years of age) or 30 ± 5 IU/kg administered 3 times weekly (in subjects 12 years of age or older), with provisions for dose escalation based on pre-specified criteria (over a 4-week period, 2 spontaneous bleeds into a major joint and/or target joint, or 3 or more spontaneous bleeding episodes in any location). Among these 102 subjects, 7 dose escalations were prescribed for 6 subjects.

In subjects ≥12 years, 42 subjects (42/94 or 45%) reported no bleeding while on routine prophylaxis. The mean±SD total ABR during routine prophylaxis was 4.0±6.64 with median (min-max) of 1.9 (0.0-44.2). The mean ABR for subjects during routine prophylaxis was 88% lower than the mean ABR for subjects during on-demand treatment (Table 7).

In subjects <12 years, 4 subjects (4/8 or 50%) reported no bleeding while on routine prophylaxis. The mean±SD total ABR during routine prophylaxis was 1.5±2.2 with median (min-max) of 0.6 (0.0-6.2). The mean ABR for subjects during routine prophylaxis was 97% lower than the mean ABR for subjects during on-demand treatment (Table 7).

Table 7: Summary of Annualized Bleeding Rate During Routine Prophylaxis Treatment with XYNTHA

Age Category (years)	Number of Subjects	% Reduction from OD	Treated Total Routine Prophylaxis ABR Mean ± SD Median (Min-Max)	Treated Spontaneous Routine Prophylaxis ABR Mean ± SD Median (Min-Max)	Treated Traumatic Routine Prophylaxis ABR Mean ± SD Median (Min-Max)
0 to <12	8	97%	1.5 ± 2.20 0.6 (0.0-6.2)	0.6 ± 1.31 0.0 (0.0-3.7)	0.9 ± 1.30 0.0 (0.0-3.2)
≥12	94[a]	88%	4.0 ± 6.64 1.9 (0.0-44.2)	2.0 ± 4.25 0.0 (0.0-32.1)	2.0 ± 4.10 0.0 (0.0-23.3)
12 to <17	18[b]	84%	7.3 ± 11.37 3.0 (0.0-44.2)	3.3 ± 7.73 0.0 (0.0-32.1)	4.0 ± 5.94 1.9 (0.0-19.6)
≥17	76	89%	3.2 ± 4.70 1.9 (0.0-23.3)	1.6 ± 2.88 0.0 (0.0-13.7)	1.6 ± 3.42 0.0 (0.0-23.3)

OD = on demand; ABR = annualized bleeding rate; SD = standard deviation, Min = minimum, Max = maximum.
[a]The treated total ABR mean ± SD during prophylaxis for the 93 subjects aged ≥12 years (outlier removed), was 3.6 ± 5.18 with median (min-max) of 1.9 (0.0-23.3). The spontaneous treated ABR mean ± SD was 1.6 ± 2.87 with median (min-max) of 0.0 (0.0-13.7). The traumatic ABR mean ± SD was 1.9 ± 3.99 with median (min-max) of 0.0 (0.0-23.3).
[b]The treated total ABR mean ± SD during prophylaxis for the 17 adolescents (outlier removed), was 5.2 ± 6.90 with median (min-max) of 2.0 (0.0-21.4). The spontaneous ABR mean ± SD was 1.6 ± 2.94 with median (min-max) of 0.0 (0.0-11.6). The traumatic ABR mean ± SD was 3.5 ± 5.77 with median (min-max) of 1.9 (0.0-19.6).

STORAGE AND STABILITY

Xyntha Antihemophilic Factor (Recombinant), Plasma/Albumin-Free should be stored under refrigeration at a temperature of 2° to 8°C. Xyntha vial may be stored outside of the refrigerator at temperatures up to a maximum of 25ºC for a single period of up to 3 months, after which it should not be refrigerated again. Xyntha should be discarded if not used within 3 months after removal from the refrigerator. The diluent syringe should be stored at 2° to 25°C (36° to 77° F) and should not be used subsequent to expiration of the Xyntha drug product. The patient should write in the space provided on the outer carton the date the product was placed at room temperature. . Do not use Xyntha after the expiry date on the label.

Xyntha Vial Kit:

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 HANDLING INSTRUCTIONS

- Do not use XYNTHA after the expiration date.

- Freezing should be avoided to prevent damage to the pre-filled diluent syringe.
- During storage, avoid prolonged exposure of Xyntha vial to light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Xyntha Vial Kit:

Xyntha, Antihemophilic Factor (Recombinant), Plasma/Albumin-Free (freeze-dried) is supplied in kits that include single-use vials that contain nominally 250, 500, 1000, or 2000 IU per vial. Actual factor VIII activity in IU is stated on the label of each Xyntha Antihemophilic Factor (Recombinant), Plasma/Albumin-Free 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.

REGISTRATION NUMBERS OF THE DRUG

Xyntha 250 IU: 137 78 31591
Xyntha 500 IU: 137 78 31592
Xyntha 1000 IU: 137 78 31593
Xyntha 2000 IU: 137 78 31594

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