HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XYNTHA® safely and effectively. See full prescribing information for XYNTHA®.

 $XYNTHA^{\circledast} \ [Antihemophilic\ Factor\ (Recombinant),\ Plasma/Albumin-Freel$

For Intravenous Injection - Lyophilized Powder for Solution

Initial U.S. Approval: 2008

- INDICATIONS AND USAGE -

XYNTHA is a recombinant antihemophilic factor indicated for:

- Control and prevention of bleeding episodes in patients with hemophilia A (1.1)
- Surgical prophylaxis in patients with hemophilia A (1.2)

XYNTHA is not indicated in patients with von Willebrand's disease.

- DOSAGE AND ADMINISTRATION -

For intravenous use after reconstitution only (2)

• 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)

where IU = International Unit

 Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician. (2.1, 2.2)

- DOSAGE FORMS AND STRENGTHS -

XYNTHA is available as lyophilized powder in single-use vials of 250, 500, 1000, or 2000 IU. (3)

- CONTRAINDICATIONS -

Do not use in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster proteins.

WARNINGS AND PRECAUTIONS -

- Anaphylaxis and severe hypersensitivity reactions are possible. Patients may develop hypersensitivity to hamster protein, which is present in trace amounts in XYNTHA. Should such reactions occur, discontinue treatment with the product and administer appropriate treatment. (5.1)
- Development of activity-neutralizing antibodies has been detected in patients receiving factor VIII-containing products, including XYNTHA. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor VIII inhibitor concentration. (5.2, 5.3, 6.2)

- ADVERSE REACTIONS -

The most common adverse reactions (≥ 5%) with XYNTHA were headache, pyrexia, nausea, vomiting, diarrhea, and asthenia.

Two patients (n=89), previously treated with factor VIII, developed inhibitors during the safety and efficacy clinical study. (6.2)

In the surgery study (n=30), one low titer persistent inhibitor and one transient false-positive inhibitor were reported. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

- USE IN SPECIFIC POPULATIONS -

Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Control and Prevention 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).

1.2 Surgical Prophylaxis in Patients with Hemophilia A

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

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

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution.

- Initiate treatment with XYNTHA 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. Titrate the administered doses to the patient's clinical response. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- One International Unit (IU) of factor VIII activity corresponds approximately to the quantity of factor VIII in one milliliter 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.² 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 % 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 [see Clinical Pharmacology (12.3)].

2.1 Control and Prevention 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 / Duration of Therapy		
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.		

2.2 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 / Duration of Therapy		
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.		

2.3 Instructions for Use

Administer XYNTHA by intravenous infusion after reconstitution of the lyophilized powder with the supplied prefilled diluent (0.9% Sodium Chloride solution) syringe.

Patients should follow the specific reconstitution and administration procedures provided by their physician. Instructions are provided in the FDA-approved patient labeling [see Patient Counseling Information (17)]. The procedures below are general guidelines for the preparation, reconstitution and administration of XYNTHA.

For additional instructions on the use of a XYNTHA vial and a XYNTHA SOLOFUSE, see Use of a XYNTHA Vial Kit and a XYNTHA SOLOFUSETM Kit section below [see Dosage and Administration (2.6)].

2.4 Preparation and Reconstitution

Preparation

- 1. Always wash hands before performing the following procedures.
- 2. Use aseptic technique during the reconstitution procedures.
- 3. Use all components in the reconstitution and administration of this product as soon as possible after opening their sterile containers to minimize unnecessary exposure to the atmosphere.

Note:

- If the patient uses more than one vial of XYNTHA per infusion, reconstitute each vial according to the following instructions. Remove the diluent syringe, leaving the vial adapter in place. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of each vial. Do not detach the diluent syringe or the large luer lock syringe until ready to attach the large luer lock syringe to the next vial adapter.
- If the patient uses one vial of XYNTHA with one XYNTHA SOLOFUSETM for the infusion, reconstitute the vial and the syringe according to the instructions for each respective product kit. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of the vial and the syringe. [See Dosage and Administration (2.6)]

Reconstitution

- 1. Allow the XYNTHA vial and the prefilled 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 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 XYNTHA vial on a flat surface. While holding the adapter package, place the vial adapter over the XYNTHA 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 XYNTHA vial, with the adapter attached, 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 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 XYNTHA 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, discard the solution and use a new kit.

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



13. Detach the syringe from the vial adapter by gently pulling and turning the syringe counterclockwise. Discard the empty XYNTHA vial with the adapter attached.

Note:

- If the solution is not used immediately, carefully replace the syringe cap. Do not touch the syringe tip or the inside of the cap.
- Store the reconstituted solution at room temperature prior to administration, but use within 3 hours after 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. The tubing of the infusion set included with this kit does not contain DEHP.

2.5 Administration

Administer XYNTHA by intravenous infusion after reconstitution only.

Inspect the final XYNTHA solution visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear to slightly opalescent and colorless. If it is not, discard the solution and use a new kit.

Use the tubing and the prefilled diluent syringe provided in this kit or a single sterile disposable plastic syringe. Do not administer XYNTHA in the same tubing or container with other medicinal products.

- 1. Attach the syringe to the luer end of the infusion set tubing provided.
- 2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab provided in the kit.



- 3. Remove the protective needle cover and perform venipuncture. Insert the needle on the infusion set tubing into the vein, and remove the tourniquet. Verify proper needle placement.
- 4. Inject the reconstituted XYNTHA product intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.



5. After infusing XYNTHA, remove and discard the infusion set. 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.

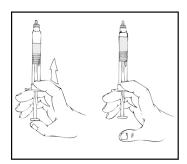
2.6 Use of a XYNTHA Vial Kit with a XYNTHA SOLOFUSETM Kit

These instructions are for the use of only one XYNTHA Vial Kit with one XYNTHA SOLOFUSETM Kit. For further information, please contact the Medical Information Department at Wyeth Pharmaceuticals, 1-800-438-1985.

- 1. Reconstitute the XYNTHA vial using the instructions described in Preparation and Reconstitution [see Dosage and Administration (2.4)].
- 2. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the XYNTHA vial with the vial adapter in place.



3. Reconstitute the XYNTHA SOLOFUSETM using the instructions included with the product kit, remembering to remove most, but not all, of the air from the drug product chamber.



4. After removing the protective blue vented cap, connect the XYNTHA SOLOFUSETM to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.



5. Slowly depress the plunger rod of the XYNTHA SOLOFUSETM until the contents empty into the XYNTHA vial. The plunger rod may move back slightly after release.



6. Detach and discard the empty XYNTHA SOLOFUSETM from the vial adapter.

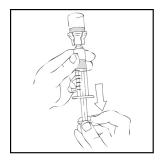
Note: If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.



7. Connect a sterile 10 milliliter or larger luer lock syringe to the vial adapter. Inject some air into the vial to make withdrawing the vial contents easier.



8. Invert the vial and slowly draw the solution into the large luer lock syringe.



- 9. Detach the syringe from the vial adapter by gently turning and pulling the syringe counterclockwise. Discard the vial with the adapter attached.
- 10. Attach the infusion set to the large luer lock syringe as directed [see Dosage and Administration (2.5)].

3 DOSAGE FORMS AND STRENGTHS

XYNTHA is available as a white to off-white lyophilized powder in the following nominal dosages:

- 250 International Units
- 500 International Units
- 1000 International Units
- 2000 International Units

Each XYNTHA vial has the actual recombinant factor VIII (rFVIII) potency in International Units stated on the label.

4 CONTRAINDICATIONS

Do not use 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 Anaphylaxis and Hypersensitivity Reactions

Allergic type hypersensitivity reactions are possible. 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. Advise patients to discontinue use of the product and to contact their physician if these symptoms occur. [See Patient Counseling Information (17)]

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

Patients using coagulation factor VIII products, including XYNTHA, should be monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of XYNTHA. 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 Warnings and Precautions (5.3)]. 4,5,6,7,8,9,10,11,12

5.3 Monitoring: Laboratory Tests

The clinical response to XYNTHA may vary. If bleeding is not controlled with the recommended dose, determine the plasma level of factor VIII and administer a sufficient dose of XYNTHA to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, suspect the presence of an inhibitor (neutralizing antibodies) [see Warnings and Precautions (5.2)] and perform appropriate testing as follows:

- 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

Overall, the most common adverse reactions ($\geq 5\%$) with XYNTHA were headache, pyrexia, nausea, vomiting, diarrhea, and asthenia.

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 two clinical studies (N=124). In the first study (n=94), safety and efficacy were examined in previously treated patients (PTPs) with hemophilia A (factor VIII activity in plasma [FVIII:C] \leq 2%]who received XYNTHA for routine prophylaxis and ondemand treatment. Ninety-four patients 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 previously treated patients with severe or moderately severe hemophilia A ([FVIII:C] \leq 2%) who required elective major surgery and were expected to receive XYNTHA replacement therapy for at least 6 days post-surgery. All patients received at least one dose of XYNTHA, resulting in 1161 infusions. One patient received XYNTHA for a pre-surgery pharmacokinetic assessment only and did not undergo surgery. [see Clinical Studies (14)].

The most frequently reported adverse reaction in PTP patients was headache (24% of subjects). Other adverse reactions reported in \geq 5% of patients were: nausea (6%), diarrhea (5%), asthenia (5%), and pyrexia (5%).

The most frequently reported adverse reaction in surgical patients was pyrexia (43%). Other adverse reactions reported in \geq 5% of patients were: headache (13%), nausea (13%), and vomiting (7%).

6.2 Immunogenicity Information

There is a potential for immunogenicity with therapeutic proteins. The clinical studies for XYNTHA examined 94 patients who had previously been treated with factor VIII (PTPs) and 30 surgical patients. In the safety and efficacy study, two subjects with inhibitors were observed in 89 subjects (2.2%) who completed \geq 50 exposure days. 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 patients) 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 patient 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 patient developed anti-CHO cell antibodies with no associated allergic reaction. One patient developed anti-FVIII antibodies; but, this patient did not develop an inhibitor.

Overall, no allergic manifestation to any immune response was observed during the study.

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 reactions have been reported for XYNTHA:

Hypersensitivity Reactions Anaphylaxis Inhibitor Development Inadequate therapeutic response

7 DRUG INTERACTIONS

None known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with XYNTHA. It is not known whether XYNTHA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. XYNTHA should be given to a pregnant woman only if clinically indicated.

8.2 Labor and Delivery

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.

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if XYNTHA is administered to nursing mothers. XYNTHA should be given to nursing mothers only if clinically indicated.

8.4 Pediatric Use

Pharmacokinetics of XYNTHA was studied in 7 previously treated patients 12-16 years of age. Pharmacokinetic parameters in these patients were similar to those obtained for adults after a dose of 50 IU/kg. For these 7 patients, the mean (\pm SD) C_{max} and AUC_{∞} were 1.09 ± 0.21 IU/mL and 11.5 ± 5.2 IU·h/mL, respectively. The mean clearance and plasma half-life values were 5.23 ± 2.36 mL/h/kg and 8.03 ± 2.44 hours (range 3.52-10.6 hours), respectively. The mean K-value and *in vivo* recoveries were 2.18 ± 0.41 IU/dL per IU/kg and $112 \pm 23\%$, respectively.

8.5 Geriatric Use

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

11 DESCRIPTION

The active ingredient in XYNTHA, Antihemophilic Factor (Recombinant), Plasma/Albumin-Free, 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. 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

In a randomized crossover clinical study, 30 previously treated patients (PTP) 12-60 years old received a single infusion of 50 IU/kg of XYNTHA followed by a full-length recombinant FVIII (FLrFVIII) or a single infusion of FLrFVIII followed by XYNTHA. The one-stage clotting assay method was used to determine the concentrations of these two products in blood. XYNTHA was shown to be pharmacokinetically equivalent to FLrFVIII as the 90% confidence intervals for XYNTHA-to-FLrFVIII ratios of the mean values of C_{max} and AUC_{∞} were within pre-established limits of 80% to 125%. The pharmacokinetic parameters of XYNTHA in these patients are summarized in Table 1.

In addition, 25 of the same patients 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 pharmacokinetic properties of XYNTHA; the 90% confidence intervals for XYNTHA 6 month-to-baseline ratios of the mean values of C_{max} and AUC_{∞} were within pre-established limits of 80% to 125%.

In a separate study investigating the efficacy of XYNTHA in patients with hemophilia A undergoing elective major surgery, 8 of 30 patients (≥ 12 years) who received a single 50 IU/kg infusion of XYNTHA as part of their presurgery evaluation participated in a pharmacokinetic evaluation. The pharmacokinetic parameters in these patients also are summarized in Table 1.

Table 1: 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	$11.8 \pm 6.2*$	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	
K-value	2.15 ± 0.44	2.47 ± 0.84	2.17 ± 0.47	
(IU/dL per IU/kg)				
In vivo Recovery (%)	103 ± 21	116 ± 40	104 ± 22	

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

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

Safety and Efficacy Study

In an open label safety and efficacy study (n=94), subjects received XYNTHA in a routine prophylaxis treatment regimen with on-demand treatment administered as clinically indicated.

^{*}One subject was excluded from the calculation due to lack of a well-defined terminal phase.

All 94 subjects were treated with at least one dose and all are included in the intent-to-treat (ITT) population. All subjects had been previously treated (previously treated patients or PTPs) with factor VIII. Eighty-nine (89) subjects accrued ≥ 50 exposure days. Median age for the 94 treated subjects was 24 years (mean 27.7 and range 12-60 years). All subjects had ≥ 150 previous exposure days with baseline FVIII activity level of $\leq 2\%$.

For routine prophylaxis, XYNTHA was administered at a dose of 30 ± 5 IU/kg 3 times a week with provisions for dose escalation based on pre-specified criteria. Seven dose escalations were prescribed for 6 subjects during the course of the study. Forty-three subjects (43/94 or 45.7%) reported no bleeding while on routine prophylaxis. The median annualized bleeding rate (ABR) for all bleeding episodes was 1.9 (mean 3.9, range 0-42.1).

Fifty-three subjects (53/94) received XYNTHA on-demand treatment for a total of 187 bleeding episodes (see Table 2). 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 61.1%) occurred \leq 48 hours after the last dose and 38.9% (70/180 bleeds) occurred > 48 hours after the last dose. The majority of bleeds reported to occur \leq 48 hours after the last prophylaxis dose were traumatic (64/110 bleeds or 58.2%). 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 30.6 IU/kg (range 6.4 to 74.4 IU/kg).

Table 2: Time Interval Between Last Prophylaxis Dose of XYNTHA and Start of Bleed											
≤ 24	4 hrs	> 24 5	$> 24 \le 48 \text{ hrs}$ $> 48 \le 72 \text{ hrs}$ $> 72 \text{ hrs}$		$3 \le 72 \text{ hrs}$ > 72 hrs		> 48 ≤ 72 hrs		Unknown ^a		Total Bleeding Episodes
Spon	Traum	Spon	Traum	Spon	Traum	Spon	Traum	Spon	Traum		
13	20	33	44	24	12	18	16	3	4	187	

^a Bleeds with unknown start time or bleeds in which previous prophylaxis dose was before the start of the safety and efficacy period of the study. Abbreviations: Spon = spontaneous new bleed; Traum = new bleed due to trauma; hrs = hours.

The majority of bleeding episodes (173/187 or 92.5%) resolved with 1 or 2 infusions. Subjects rated the outcomes of infusions on a pre-specified four (4) point hemostatic efficacy scale. One hundred thirty-two of 187 bleeding episodes (132/187 or 70.6%) treated with XYNTHA were rated excellent or good in their response to initial treatment, 45 (24.1%) were rated moderate. Five (2.7%) were rated no response, and 5 (2.7%) were not rated.

Table 3: Summary of Response to Infusions to Treat New Bleeding Episode by Number of Infusions Needed for Resolution

Number of Infusions (%)							
Response to 1 st Infusion	1	2	3	4	>4	Total Number of Bleeds	
Excellent	42 (95.5)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	44	
Good	69 (78.4)	16 (18.2)	3 (3.4)	0(0.0)	0(0.0)	88	
Moderate	24 (53.3)	16 (35.6)	2 (4.4)	0(0.0)	3 (6.7)	45	
No Response	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 ^a	
Total	139 (74.3)	34 (18.2)	7 (3.7)	3 (1.6)	4 (2.1)	187	

^a Includes 1 infusion with commercial FVIII that occurred before routine prophylaxis began.

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

Surgical Prophylaxis Study

In an open-label study (n=30) for surgical prophylaxis in subjects with hemophilia A, XYNTHA was administered to 25 efficacy-evaluable PTPs with severe or moderately severe (FVIII:C ≤ 2%) hemophilia A 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).

The results of the hemostatic efficacy ratings for these subjects are presented in Table 4. 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 4: Summary of Hemostatic Efficacy						
Time of Hemostatic Efficacy Assessment	Excellent	Good	Number of subjects			
End of surgery	18 (72%)	7 (28%)	25			
End of initial postoperative period ^a	23 (92%)	2 (8%)	25			

^a Conclusion of initial postoperative period is date of discharge or postoperative Day 6, whichever occurs later.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XYNTHA® is supplied in kits that include single-use vials containing nominally 250, 500, 1000, or 2000 International Units lyophilized powder per vial:

250 International Units Kit: NDC 58394-012-01

500 International Units Kit: NDC 58394-013-01

1000 International Units Kit: NDC 58394-014-01

2000 International Units Kit: NDC 58394-015-01

Each XYNTHA Vial Kit contains: one prefilled 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 pad, and one package insert.

Actual factor VIII activity in International Units is stated on the label of each XYNTHA vial.

16.2 Storage and Handling

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 also may 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.
- Clearly record the starting date at room temperature storage in the space provided on the outer carton. At the end of the 3-month period, immediately use, discard, or return the product 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. (Freezing may damage the prefilled diluent syringe.)

• During storage, avoid prolonged exposure of XYNTHA vial to light.

Product After Reconstitution:

• Store the reconstituted solution at room temperature prior to administration. Remember to administer XYNTHA within 3 hours after reconstitution.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Advise the patients of the following

- Tell their healthcare provider about any adverse reactions or problems that concern them when taking XYNTHA.
- Allergic-type hypersensitivity reactions are possible. Discuss the early signs of
 hypersensitivity reactions (including hives [rash with itching], generalized urticaria,
 tightness of the chest, wheezing, hypotension) and anaphylaxis. Advise patients to
 discontinue use of the product, call their healthcare provider, and go to the emergency
 department if these symptoms occur.
- Tell their healthcare provider if they experience a lack of a clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Tell their healthcare provider if they become pregnant or intend to become pregnant during therapy.
- Notify their healthcare provider if they are breastfeeding.
- Consult their healthcare provider prior to travel and to bring an adequate supply of XYNTHA, based on their current regimen, for anticipated treatment when traveling.

FDA-Approved Patient Labeling

Patient Information

XYNTHA[®]/**ZIN**-tha/

[Antihemophilic Factor (Recombinant), Plasma/Albumin-Free]

Please read this patient information carefully before using XYNTHA and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical problems or your treatment.

What is XYNTHA?

XYNTHA is an injectable medicine that is used to help control and prevent bleeding in people with hemophilia A. Hemophilia A is also called classic hemophilia.

XYNTHA is not used to treat von Willebrand's disease.

What should I tell my healthcare provider before using XYNTHA?

Tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or planning to become pregnant. It is not known if XYNTHA may harm your unborn baby.
- are breastfeeding. It is not known if XYNTHA passes into your milk and if it can harm your baby.

Tell your healthcare provider about all of the medicines you take, including all prescription and non-prescription medicines, such as over-the-counter medicines, supplements, or herbal remedies.

How should I infuse XYNTHA?

Step-by-step instructions for infusing with XYNTHA are provided at the end of this leaflet.

The steps listed below are general guidelines for using XYNTHA. Always follow any specific instructions from your healthcare provider. If you are unsure of the procedures, please call your healthcare provider before using.

Call your healthcare provider right away if bleeding is not controlled after using XYNTHA. Your body can make antibodies against XYNTHA (called "inhibitors") that may stop XYNTHA from working properly. Your healthcare provider may need to take blood tests from time to time to monitor for inhibitors.

Call your healthcare provider right away if you take more than the dose you should take.

Talk to your healthcare provider before traveling. Plan to bring enough XYNTHA for your treatment during this time.

What are the possible or reasonably likely side effects of XYNTHA?

Common side effects of XYNTHA are

- headache
- fever
- nausea
- vomiting
- diarrhea
- weakness

Call your healthcare provider or go to the emergency department right away if you have any of the following symptoms because these may be signs of a serious allergic reaction:

- wheezing
- difficulty breathing
- chest tightness
- turning blue (look at lips and gums)
- fast heartbeat
- swelling of the face
- faintness
- rash
- hives

Talk to your healthcare provider about any side effect that bothers you or that does not go away. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XYNTHA?

Store XYNTHA in the refrigerator at 36° to 46°F (2° to 8°C). Store the diluent syringe at 36° to 77°F (2° to 25°C).

Do not freeze.

Protect from light.

XYNTHA can last at room temperature (below 77°F) for up to 3 months. If you store XYNTHA at room temperature, carefully write down the date you put XYNTHA at room temperature, so you will know when to either put it back in the refrigerator, use it immediately, or throw it away. There is a space on the carton for you to write the date.

If stored at room temperature, XYNTHA can be returned <u>one time</u> to the refrigerator until the expiration date. Do not store at room temperature and return it to the refrigerator more than once. Throw away any unused XYNTHA after the expiration date.

Infuse XYNTHA within 3 hours of reconstitution. You can keep the reconstituted solution at room temperature before infusion, but if you have not used it in 3 hours, throw it away.

Do not use reconstituted XYNTHA if it is not clear to slightly opalescent and colorless.

Dispose of all materials, whether reconstituted or not, in an appropriate medical waste container.

What else should I know about XYNTHA?

Medicines are sometimes prescribed for purposes other than those listed here. Talk to your healthcare provider if you have any concerns. You can ask your healthcare provider for information about XYNTHA that was written for healthcare professionals.

Do not share XYNTHA with other people, even if they have the same symptoms that you have.

Instructions for Use

XYNTHA®/ZIN-tha/ [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free]

XYNTHA is supplied as a lyophilized powder. Before you can infuse it (intravenous injection), you must reconstitute the powder by mixing it with the liquid diluent supplied. The liquid diluent is 0.9% sodium chloride.

Reconstitute and infuse XYNTHA using the infusion set, diluent, syringe, and adapter provided in this kit. Please follow the directions below for the proper use of this product.

PREPARATION AND RECONSTITUTION OF XYNTHA

Preparation

- 1. Always wash your hands before doing the following steps.
- 2. Keep everything clean and germ-free while you are reconstituting XYNTHA.
- 3. Once the vials are open, finish reconstituting XYNTHA as soon as possible. This will help to keep them germ-free.
- 4. For additional instructions on the use of a XYNTHA Vial Kit and a XYNTHA SOLOFUSETM kit, see detailed information provided after the **INFUSION OF XYNTHA** section.

Reconstitution

Note: If you use more than one vial of XYNTHA for each infusion, reconstitute each vial according to steps 1 through 11.

- 1. Let the XYNTHA vial and the prefilled diluent syringe reach room temperature.
- 2. Remove the plastic flip-top cap from the XYNTHA vial to show the center part 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 XYNTHA vial on a flat surface. While holding the adapter in the package, place the vial adapter over the XYNTHA vial. Press down firmly on the package until the adapter snaps into place on top of the vial, with the adapter spike going into the vial stopper.



6. Grasp the plunger rod as shown in the picture below. Do not touch 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 reconstituted XYNTHA is not used immediately), so place the cap on its top on a clean surface in a spot where it will stay clean.



8. Lift the package cover away from the adapter and throw the package away.



9. Place the XYNTHA 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 push 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.

Look carefully at the final solution. The solution should be clear to slightly opalescent and colorless. If it is not, throw away the solution and use a new kit.

12. Make sure the syringe plunger rod is still fully pressed down, then turn over the XYNTHA vial. Slowly pull the solution into the syringe. Turn the syringe upward again and remove any air bubbles by gently tapping the syringe with your finger and slowly pushing air out of the syringe.

If you reconstituted more than one vial of XYNTHA, remove the diluent syringe from the vial adapter and leave the vial adapter attached to the XYNTHA vial. Quickly attach a separate large luer lock syringe and pull the reconstituted solution as instructed above. Repeat this procedure with each vial in turn. Do not detach the diluent syringe or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.



13. Remove the syringe from the vial adapter by gently pulling and turning the syringe counterclockwise. Throw away the empty XYNTHA vial with the adapter attached.

Note:

- If you are not using the solution right away, carefully replace the syringe cap. Do not touch the syringe tip or the inside of the cap.
- Infuse XYNTHA solution within 3 hours after reconstitution. The reconstituted solution may be kept at room temperature for up to 3 hours prior to infusion. If you have not used it in 3 hours, throw it away.

INFUSION OF XYNTHA

Your healthcare provider will teach you how to infuse XYNTHA yourself. Once you learn how to do this, you can follow the instructions in this insert.

Before XYNTHA can be infused, you must reconstitute it as instructed above in the **PREPARATION AND RECONSTITUTION OF XYNTHA** section.

After reconstitution, be sure to look carefully at the XYNTHA solution. The solution should be clear to slightly opalescent and colorless. If it is not, throw away the solution and use a new kit.

Use the infusion set included in the kit to infuse XYNTHA. Do not infuse XYNTHA in the same tubing or container with other medicines.

- 1. Attach the syringe to the luer end of the provided infusion set tubing.
- 2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab provided in the kit.



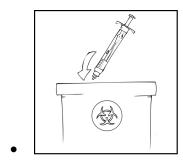
- 3. Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein as instructed by your healthcare provider. Remove the tourniquet. Verify proper needle placement.
- 4. Infuse the reconstituted XYNTHA product over several minutes. Your comfort level should determine the rate of infusion



5. After infusing XYNTHA, remove the infusion set and throw it away. The amount of liquid left in the infusion set will not affect your treatment.

Note:

• Throw away all unused solution, the empty vial(s), and other used medical supplies in an appropriate container.



• It is a good idea to record the lot number from the XYNTHA vial label every time you use XYNTHA. You can use the peel-off label found on the vial to record the lot number.

ADDITIONAL INSTRUCTIONS

XYNTHA is also supplied in kits that have both the XYNTHA powder and the diluent within single-use prefilled dual-chamber syringes, called XYNTHA SOLOFUSETM.

If you use one XYNTHA vial and one of XYNTHA SOLOFUSE™ for the infusion, reconstitute the XYNTHA vial and the XYNTHA SOLOFUSE™ according to the specific directions for that respective product kit. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of the XYNTHA vial and XYNTHA SOLOFUSE™.

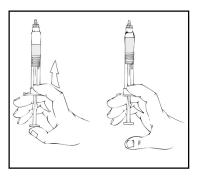
Use of a XYNTHA Vial Kit with a XYNTHA SOLOFUSETM Kit

These instructions are for the use of only one XYNTHA vial kit and one XYNTHA SOLOFUSETM Kit. For further information, please contact your healthcare provider or call the Medical Information Department at Wyeth Pharmaceuticals, 1-800-438-1985.

1. Reconstitute the XYNTHA vial using the instructions described in **PREPARATION AND RECONSTITUTION OF XYNTHA** section. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the XYNTHA vial with the vial adapter in place.



2. Reconstitute the XYNTHA SOLOFUSETM using the instructions included with the kit, remembering to remove most, but not all, of the air from the syringe.



3. After removing the protective blue vented cap, connect the XYNTHA SOLOFUSETM to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.



4. Slowly depress the plunger rod of the XYNTHA SOLOFUSETM until the contents empty into the XYNTHA vial. The plunger rod may move back slightly after release.



5. Detach the empty XYNTHA SOLOFUSETM from the vial adapter and throw it away.

If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.



6. Connect a sterile 10 milliliter or larger luer lock syringe to the vial adapter. You may want to inject some air into the XYNTHA vial to make withdrawing the vial contents easier.



7. Invert the XYNTHA vial and slowly draw the solution into the large luer lock syringe.



- 8. Detach the large luer lock syringe from the vial adapter by gently turning and pulling the syringe counterclockwise. Throw away the empty XYNTHA vial with the adapter attached.
- 9. Attach the infusion set to the large luer lock syringe as directed in the **INFUSION OF XYNTHA** section.

Note: Dispose of all unused solution and other used medical supplies in an appropriate container.







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