เอกสารกำกับยา

XYNTHA™

1. Name of the Medicinal Product

XYNTHA 250 IU powder and solvent for solution for injection
XYNTHA 500 IU powder and solvent for solution for injection
XYNTHA 1,000 IU powder and solvent for solution for injection
XYNTHA 2,000 IU powder and solvent for solution for injection

2. Qualitative and Quantitative Composition

XYNTHA 250 IU powder and solvent for solution for injection
Antihemophilic Factor (Recombinant) freeze-dried is supplied in kits that include single-use vials that contain nominally 250 IU moroctocog alfa per vial.

XYNTHA 500 IU powder and solvent for solution for injection
Antihemophilic Factor (Recombinant) freeze-dried is supplied in kits that include single-use vials that contain nominally 500 IU moroctocog alfa per vial.

XYNTHA 1,000 IU powder and solvent for solution for injection
Antihemophilic Factor (Recombinant) freeze-dried is supplied in kits that include single-use vials that contain nominally 1,000 IU moroctocog alfa per vial.

XYNTHA 2,000 IU powder and solvent for solution for injection
Antihemophilic Factor (Recombinant) freeze-dried is supplied in kits that include single-use vials that contain nominally 2,000 IU moroctocog alfa per vial.

Actual factor VIII activity in IU is stated on the label of each XYNTHA Antihemophilic Factor (Recombinant) vial.

In addition, each XYNTHA Antihemophilic Factor (Recombinant) 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 package insert.

3. Pharmaceutical Form

Powder and solvent for solution for intravenous (IV) injection

White to off-white cake. Upon reconstitution, XYNTHA appears as a clear to slightly opalescent, colorless solution.

4. Clinical Particulars

4.1 Therapeutic indications

XYNTHA, Antihemophilic factor (Recombinant), is indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

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

4.2 Posology and method of administration

For intravenous use after reconstitution only.

Dose

- 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.
- 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.

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

Dosage (International Units) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)
or
IU/dL (or % of normal) = Total Dose (IU)/body weight (kg) x 2 [IU/dL]/[IU/kg]

On-demand treatment and Control of Bleeding Episodes

A guide for dosing XYNTHA for on-demand treatment and control of bleeding episodes is provided in Table 1. Maintain the plasma factor VIII activity at or above the levels (in % of normal or in IU/dL) outlined in Table 1 for the indicated period.

Table 1: Dosing for On-demand treatment and Control of Bleeding Episodes

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy
Minor Early hemarthrosis, minor muscle or oral bleeds.	20-40	12-24	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	12-24	3-4 days or until adequate local hemostasis is achieved.
Major Gastrointestinal bleeding. Intracranial, intra-abdominal or intrathoracic bleeding.	60-100	8-24	Until bleeding is resolved.

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy
Fractures.			

Perioperative Management

A guide for dosing XYNTHA during surgery (perioperative management) is provided in Table 2. Maintain the plasma factor VIII activity level at or above the level (in % of normal or in IU/dL) outlined in Table 2 for the indicated period. Monitor the replacement therapy by means of plasma factor VIII activity.

Table 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor			
Minor operations, including tooth extraction.	30-60	12-24	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	8-24	Until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved.

Routine Prophylaxis

- Adults and adolescents (≥12 years): The recommended starting regimen is 30 IU/kg of XYNTHA administered 3 times weekly.

- Children (<12 years): The recommended starting regimen is 25 IU/kg of XYNTHA administered every other day. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group (see section 5.1 Pharmacodynamic properties - Clinical studies)
- Adjust the dosing regimen (dose or frequency) based on the patient's clinical response.

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.

Reconstitution

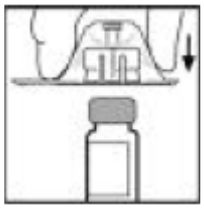
1. Allow the XYNTHA vial and the prefilled diluent syringe to reach room temperature.

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.

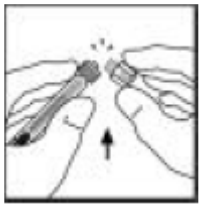
4. Peel back the cover from the clear plastic vial adapter package. **Do not remove the adapter from the package.**

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.



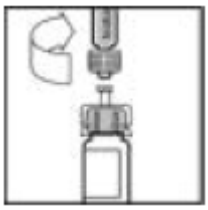
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

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.

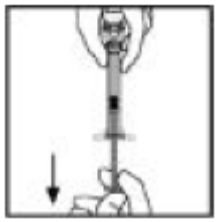


10. Slowly depress the plunger rod to inject all the diluent into the XYNTHA vial.

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.**

Administration

For 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.

4.3 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.

4.4 Special warnings and precautions for use

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.

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 Monitoring Laboratory Tests below).

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 section 4.2 Posology and method of administration).
- 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

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.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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 section 5.1 Pharmacodynamics properties – Clinical studies). 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 section 5.1 Pharmacodynamics properties – Clinical studies).

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%).

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 6 to <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.

Post-marketing 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 post-marketing adverse reaction has been reported for XYNTHA: Inadequate therapeutic response

4.9 Overdose

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Antihemorrhagics: Blood Coagulation Factor VIII

ATC code: B02BD02

Mechanism of Action

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

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.

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, and routine prophylaxis in PTPs with hemophilia A. These completed clinical studies for XYNTHA examined 174 PTP subjects, 94 from the first study, and 50 from a second study, for on-demand treatment and routine prophylaxis and 30 from a third study 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

On-demand treatment in adolescents and adults

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 sub-study. Twenty-five (25/30) of these subjects with FVIII:C ≤1% completed both the first (PK1) and the second (PK2) pharmacokinetic assessments (see section 5.2 Pharmacokinetic properties).

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 3). 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 3: 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 $\leq$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 ($\leq$12 years of age) with severe to moderately severe hemophilia A (FVIII:C $\leq$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).

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[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 5).

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 5).

Table 5: Summary of Annualized Bleeding Rate During Routine Prophylaxis Treatment with XYNTHA

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

Table 5: Summary of Annualized Bleeding Rate During Routine Prophylaxis Treatment with XYNTHA

Age Category (years)	Number of Subjects	% Reduction from OD	Statistic	Treated Total Routine Prophylaxis ABR	Treated Spontaneous Routine Prophylaxis ABR	Treated Traumatic Routine Prophylaxis ABR
≥17	76	89%	Mean±SD	3.2±4.70	1.6±2.88	1.6±3.42
			Median (Min-Max)	1.9 (0.0-23.3)	0.0 (0.0-13.7)	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).

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 section 4.8 Undesirable effects).

In comparison to the pharmacokinetic parameters reported in adults, children have shorter half-lives, larger volumes of distribution and lower recovery of factor VIII after XYNTHA administration. The clearance (based on per kg body weight) is approximately 40% higher in children. Higher or more frequent doses may be required to account for the observed differences in pharmacokinetic parameters (see section 5.2 Pharmacokinetic properties).

5.2 Pharmacokinetic properties

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 6.

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 6.

Table 6: 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
V_{ss} (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;

V_{ss} = volume of distribution at steady-state.

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

Table 7 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 7: 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
V_{ss} (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; V_{ss} = volume of distribution at steady-state.

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.

5.3 Preclinical safety data

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.

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.

6. Pharmaceutical Particulars

6.1 List of excipients

Powder

Polysorbate 80

Sucrose

L-Histidine

Calcium Chloride Dihydrate

Sodium Chloride (after reconstitution with diluent)

Solvent

Sodium chloride

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Please see details on the carton.

6.4 Special precautions for storage

XYNTHA Antihemophilic Factor (Recombinant) should be stored under refrigeration at a temperature

of 2º to 8ºC. XYNTHA vial may also be stored at room temperature not to exceed 25ºC for up to 3 months. The diluent syringe should be stored at 2º to 25ºC 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. After room temperature storage, the product can be returned to refrigerated storage until the expiration date. Do not store XYNTHA vial at room temperature and return it to refrigerated storage more than once. Do not use XYNTHA vial after the expiry date on the label.

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

6.5 Nature and contents of container

250 IU, 500 IU, 1,000 IU or 2,000 IU powder in a 10 mL vial (type 1 glass) with a stopper (Chlorobutyl) and a Crimp seal (aluminum) and a sterile vial adapter reconstitution device, a sterile infusion set, alcohol swabs, a plaster and a gauze pad.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorization Holder

Pfizer (Thailand) Limited

8. Marketing Authorization Numbers

9. Date of Authorization

10. Date of Revision of the Text

17 February 2021

LPD Revision No.: 1.3

LPD Date: February 17, 2021

Country: Thailand